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Selective Synthesis of Alkynylated Isoquinolines and Biisoquinolines *via* Rh^{III} Catalyzed C-H Activation/1,3-Diyne Strategy

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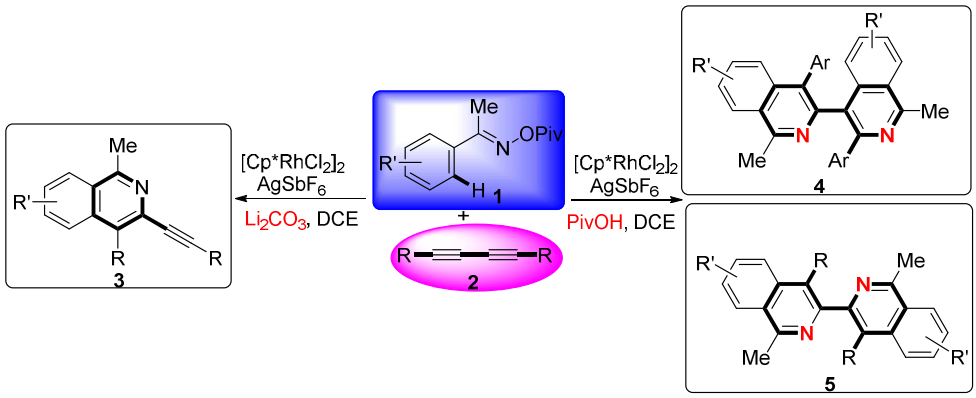
Table of Content Graphic:



Abstract: Described herein is a convenient and highly selective synthesis of alkynylated isoquinolines and biisoquinolines from various aryl ketone *O*-pivaloyloxime derivatives and 1,3-diynes *via* rhodium-catalyzed C-H bond activation. In this transformations, alkynylated isoquinolines, 3,4'- and 3,3'-biisoquinolines could be obtained respectively through changing the reaction conditions. Mechanistic investigation revealed that the C-H activation of aryl ketone *O*-pivaloyloxime was the key step to this reaction.

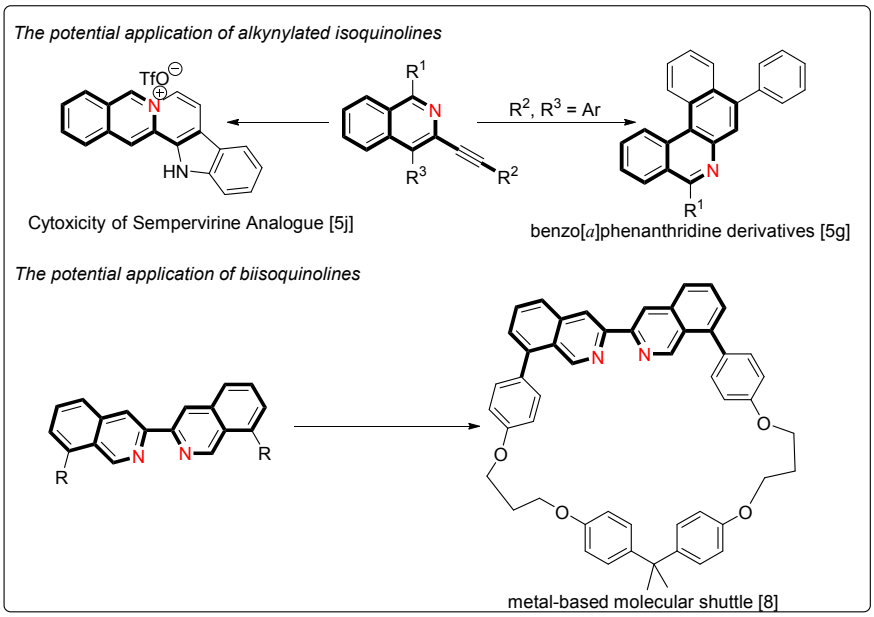
INTRODUCTION

Alkynylated isoquinolines and biisoquinolines have been recognized as an important class of heterocycles which are widely found in numerous bioactive natural products, ligands, and functional materials (Scheme 1). [1]The synthesis of isoquinoline compounds through C−H activation has also been well developed in recent decade.[2] For example, sequential C−H activation/annulation of aromatic oximes,[3] imines,[4] hydrazone,[5] azines[6] and azides[7] with internal alkynes catalyzed by Rh, Ru or Co were

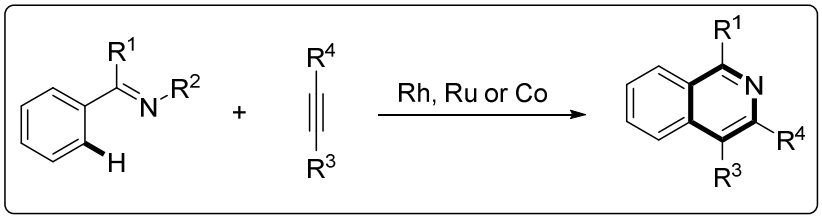
achieved to access isoquinolines (Scheme 2). However, those substrates are limited to internal alkynes. Moreover, the achievements on alkynylated isoquinolines and biisoquinolines were still less reported.[8]

1,3-Diynes have emerged as important raw materials for the synthesis of arenes and heteroarenes, since the found of Glaser coupling reaction in 1869.[9] However, there are only a few examples of synthesis of heterocycles from 1,3-diynes *via* the widely used transition-metal catalysis strategy, due to its hardly control of the chemselectivity and regioselectivity.[10] Herein, we report the selective synthesis of alkynylated isoquinolines and biisoquinolines from 1,3-diynes *via* rhodium-catalyzed C-H bond activation.

Scheme 1. The potential application of alkynylated isoquinolines and biisoquinolines.



Scheme 2. The construction of isoquinolines *via* tandem C−H activation/annulation

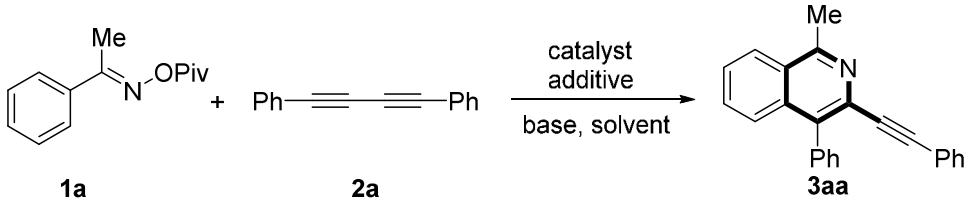


RESULTS AND DISCUSSION

In the preliminary investigation, we explored the formation of alkynylated isoquinolines which are important starting materials for the preparation of benzophenanthridines that are widely used as distributed alkaloids, DNA-chain intercalating reagents, potent antitumor and antiinfectious drugs.[11] Initially, we examined the reaction of 1-phenylethan-1-one *O*-pivaloyl oxime (**1a**) and 1,4-diphenylbuta-1,3-diyne (**2a**) in the presence of $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), NaOAc (2.0 equiv.) in DCE at 50 °C for 12 h. Gratifyingly, the desired 1-methyl-4-phenyl-3-(phenylethynyl)isoquinoline (**3aa**) was obtained in 53% yield (Table 1, entry 1). Importantly, the structure of **3aa** was confirmed by single-crystal X-ray analysis (see Supporting Information).[12a] Other catalysts were investigated. No desired product was achieved when $[RuCl_2(p\text{-cymene})]_2$, and $Pd(OAc)_2$ were used as catalysts (Table 1, entries 2 and 3). In the accordance with previous experience from our own study, the additives always significantly influence the rhodium

catalyzed C-H activation.[13] The absence of $AgSbF_6$ resulted in only 31% yield of **3aa** (Table 1, entry 4). Additives such as AgOAc, $AgBF_4$ and KPF_6 were found to be inferior for this transformation, providing **3aa** in 35%, 42%, and 33% yields, respectively (Table1, entries 5-7). No reaction was observed in the absence of a base (Table 1, entry 8). It was found that the introduction of Li_2CO_3 under otherwise identical conditions improved the yield to 86% (Table1, entry 12). Other bases such as KOAc, K_2CO_3, Na_2CO_3, K_3PO_4 were failed to give a yield better than Li_2CO_3 (Table 1, entries 9-13). It was observed that DCE was superior to $CHCl_3$, CH_2Cl_2, MeOH, *t*-AmylOH and DMF used as solvent (Table 1, entries 14-18). Lower and higher temperatures were both inferior for this reaction (Table 1, entries 19-21). Finally, the optimal reaction conditions were obtained: $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), Li_2CO_3 (2.0 equiv.) in DCE (2.0 mL) at 50 °C for 12 h.

Table 1 Optimization of the reaction conditions[a]



1a **2a** **3aa**

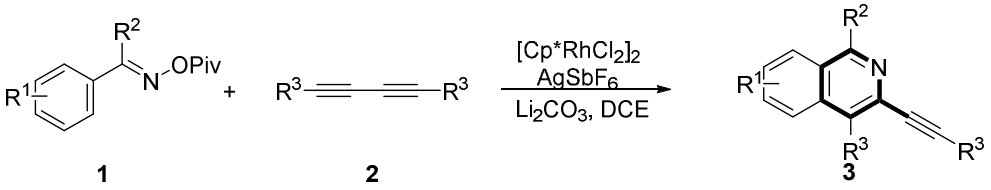
entry	catalyst	additive	base	solvent	yield (%)
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$	NaOAc	DCE	53
2	$[RuCl_2(p\text{-cymene})]_2$	$AgSbF_6$	NaOAc	DCE	N.R.
3	$Pd(OAc)_2$	$AgSbF_6$	NaOAc	DCE	N.R.
4	$[Cp^*RhCl_2]_2$	—	NaOAc	DCE	31
5	$[Cp^*RhCl_2]_2$	AgOAc	NaOAc	DCE	35
6	$[Cp^*RhCl_2]_2$	$AgBF_4$	NaOAc	DCE	42
7	$[Cp^*RhCl_2]_2$	KPF_6	NaOAc	DCE	33
8	$[Cp^*RhCl_2]_2$	$AgSbF_6$	—	DCE	N.R.
9	$[Cp^*RhCl_2]_2$	$AgSbF_6$	KOAc	DCE	48
10	$[Cp^*RhCl_2]_2$	$AgSbF_6$	K_2CO_3	DCE	43
11	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Na_2CO_3	DCE	45
12	**$[Cp^*RhCl_2]_2$**	**$AgSbF_6$**	**Li_2CO_3**	**DCE**	**86**
13	$[Cp^*RhCl_2]_2$	$AgSbF_6$	K_3PO_4	DCE	38
14	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Li_2CO_3	$CHCl_3$	54
15	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Li_2CO_3	CH_2Cl_2	67
16	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Li_2CO_3	MeOH	28
17	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Li_2CO_3	*t*-AmylOH	N.R.
18	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Li_2CO_3	DMF	N.R.
19	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Li_2CO_3	DCE	trace[b]
20	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Li_2CO_3	DCE	83[c]
21	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Li_2CO_3	DCE	trace[d]

[a]Reaction conditions: **1a** (22 mg, 0.1 mmol), **2a** (30 mg, 0.15 mmol), catalyst (5 mol%), additive (20 mol%), base (0.2 mmol), solvent (2 mL), 50 °C under air for 12 h. [b]temperature is room temperature. [c]temperature is 60 °C. [d]temperature is 100 °C.

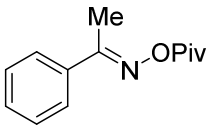
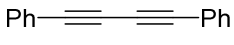
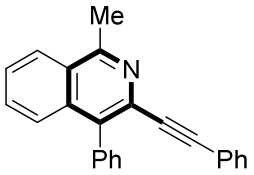
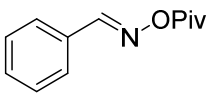
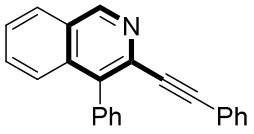
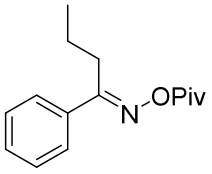
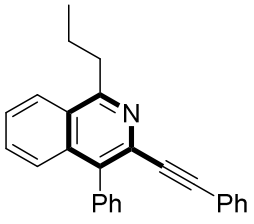
With the optimized conditions established, we began to use them for the preparation of alkynylated isoquinolines with diverse functional groups. Firstly, the reaction of

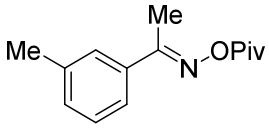
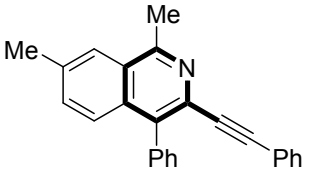
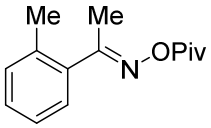
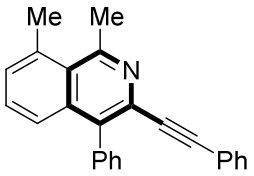
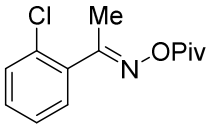
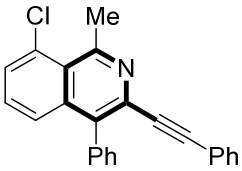
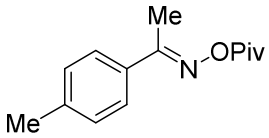
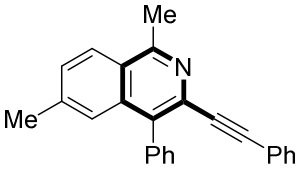
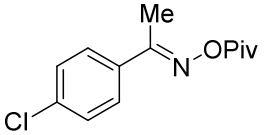
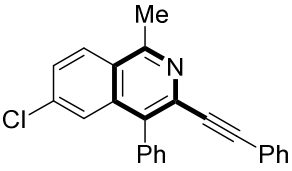
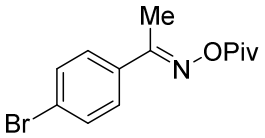
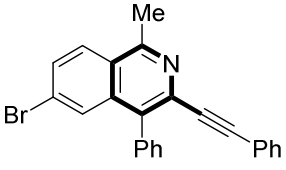
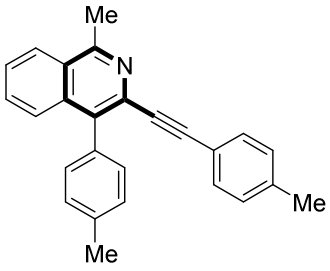
1,4-diphenylbuta-1,3-diyne **2a** with various aryl ketone/aldehyde *O*-pivaloyloxime derivatives **1** were examined. Benzaldehyde *O*-pivaloyl oxime **1b** failed to afford the products under the reaction conditions (Table 2, entry 2). 1-Phenylbutan-1-one *O*-pivaloyl oxime **1c** gave the corresponding products in lower yields compared with 1-phenylethan-1-one *O*-pivaloyl oxime **1a** (Table 2, entry 3). Aryl ketone *O*-pivaloyloxime derivatives bearing electron-donating substituents showed higher reactivity than those with electron-withdrawing groups (Table 2, entries 4-9). The steric hindrance played a key role in the reaction. *Ortho*-substituted aryl ketone *O*-pivaloyloxime derivatives generated the corresponding products in lower yields compared with *para*- and *meta*- substituted compounds (Table 2, entries 4-8). It was worth noting that the compatibility of chloride (Table 2, entries 6 and 8), bromide (Table 2, entry 9) functional groups offered a great opportunity for further functionalization. The scope of the reaction with regard to a range of the 1,3-diynes was evaluated, nextly. We were pleased to observe that both electron-rich and electron-deficient diaryl diyne gave moderate to excellent reaction yields (Table 2, entries 10-15). Remarkably, not only diaryl diynes, but also dialkyl diyne **2h** and **2i** showed good reactivity and selectivity under the identical conditions (Table 2, entry 16 and 17).

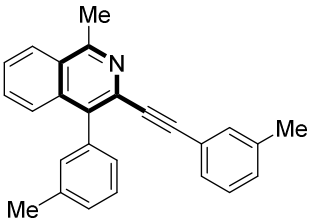
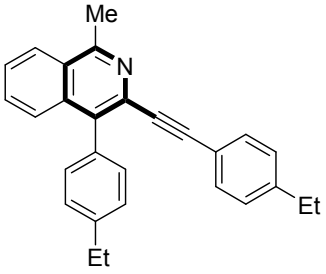
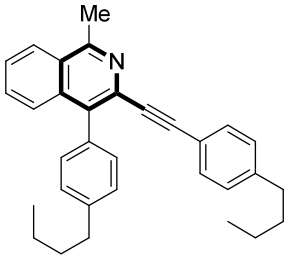
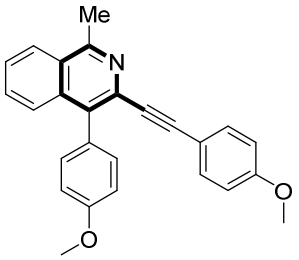
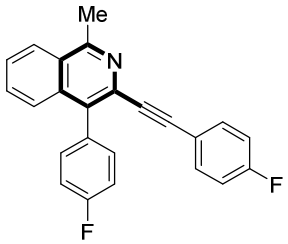
Table 2 Synthesis of alkynylated isoquinolines[a]

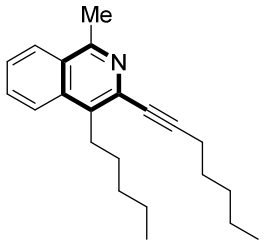
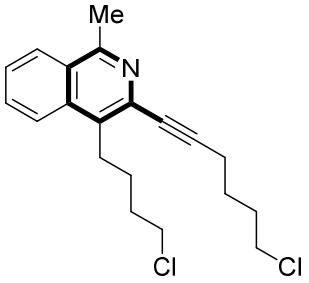


1 **2** **3**

entry	substrate **1**	substrate **2**	product	yield (%)
1	 **1a**	 **2a**	 **3aa**	86
2	 **1b**	**2a**	 **3ba**	0
3	 **1c**	**2a**	 **3ca**	59

4	 **1d**		**2a**	 **3da**	82
5	 **1e**		**2a**	 **3ea**	58
6	 **1f**		**2a**	 **3fa**	53
7	 **1g**		**2a**	 **3ga**	89
8	 **1h**		**2a**	 **3ha**	75
9	 **1i**		**2a**	 **3ia**	79
10	**1a**	R^3 = *p*-MePh **2b**		 **3ab**	78

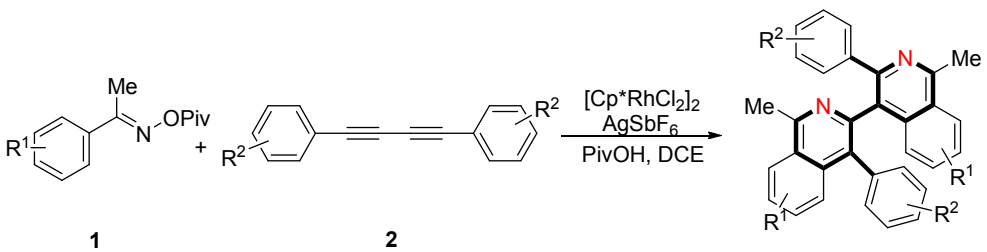
11	**1a**	R^3 = *m*-MePh **2c**	 **3ac**	82
12	**1a**	R^3 = *p*-EtPh **2d**	 **3ad**	91
13	**1a**	R^3 = *p*-*n*-BuPh **2e**	 **3ae**	85
14	**1a**	R^3 = *p*-MeOPh **2f**	 **3af**	68
15	**1a**	R^3 = *p*-FPh **2g**	 **3ag**	58

16	**1a**	R^3 = *n*-amyl **2h**	 **3ah**	90
17	**1a**	$R^3 = C_4H_6Cl$ **2i**	 **3ai**	82

[a]Reaction conditions 1: **1** (0.1 mmol), **2** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), Li_2CO_3 (0.2 mmol), DCE (2 mL), 50 °C under air for 12 h.

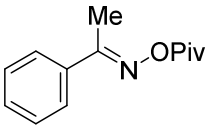
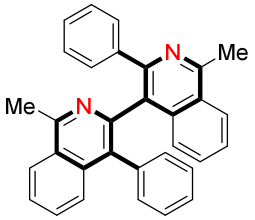
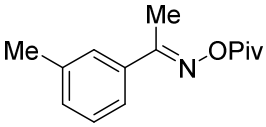
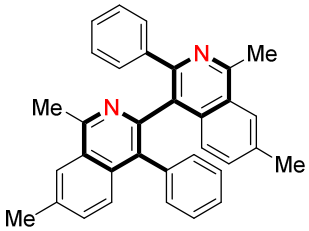
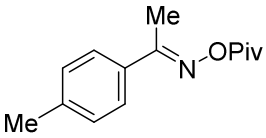
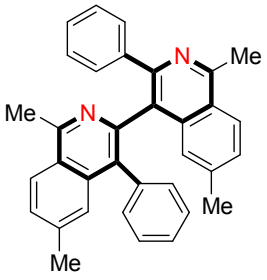
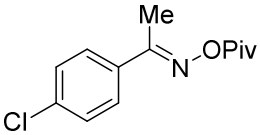
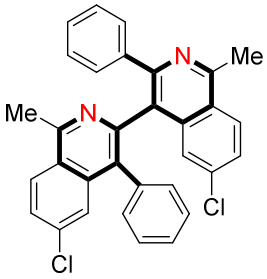
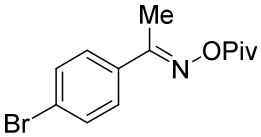
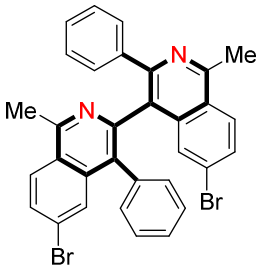
Following these results, we then investigated the preparation of biisoquinolines which were used as a building block to prepare non-sterically hindering chelates, including amacrocyclic system that was widely used in metal-based molecular shuttle.[14] Firstly, the 1-methyl-4-phenyl-3-(phenylethynyl)isoquinoline **3aa** was reacted with 1-phenylethan-1-one *O*-pivaloyl oxime **1a** under the optimized conditions. Fortunately, biisoquinoline product **4aa** was achieved in 68% yield. However, two different core structures in **4aa** were detected from the analysis of NMR spectrum which was different from the structure reported by Glorius and co-workers.[4] Then, we tried a one-pot synthesis of biisoquinolines **4.** Unforturally, the yield was almost low in the presence of Li_2CO_3 or PivONa, although the ration of **1a** and **2a** was 3:1. To our delight, we achieved the synthesis of selective biisoquinolines **4** in one pot by using conditions **2** in which trimethylacetic acid was used instead of base. Various highly selective biisoquinolines **4** were synthesized under this reaction conditions (Table 3). X-ray crystallography of **4ae** further confirmed that the structure of the product was 3,4'-biisoquinoline,[12b] which were difficult to preparation from traditional methods (see Supporting Informantion). Unfortunately, the desired product **4ah** was obtained in low yield when dialkyl diyne **2h** was used.

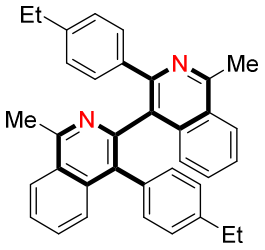
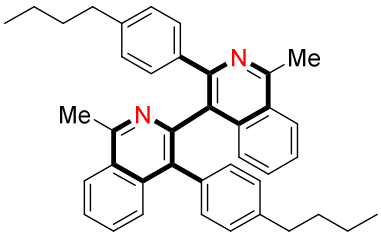
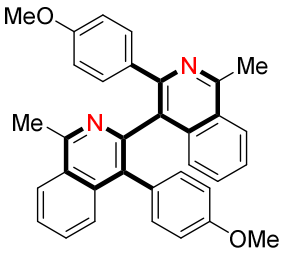
Table 3 Synthesis of 3,4'-biisoquinolines[a]



1 **2** **4**

entry	substrate **1**	sbustrate **2**	product	yield

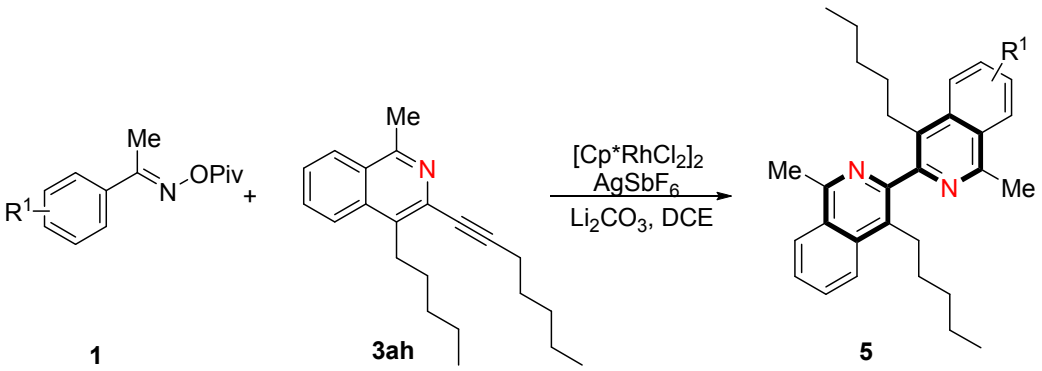
				(%)
1	 **1a**	**2a**	 **4aa**	78
2	 **1d**	**2a**	 **4da**	71
3	 **1g**	**2a**	 **4ga**	73
4	 **1h**	**2a**	 **4ha**	65
5	 **1i**	**2a**	 **4ia**	62

6	**1a**	**2d**	 **4ad**	63
7	**1a**	**2e**	 **4ae**	65
8	**1a**	**2f**	 **4af**	56

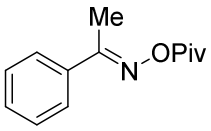
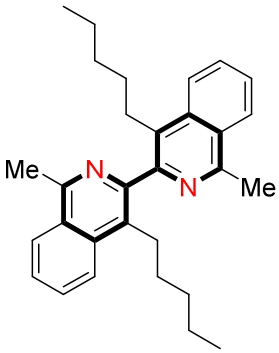
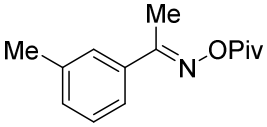
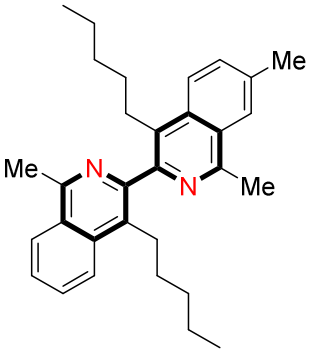
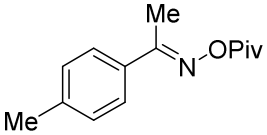
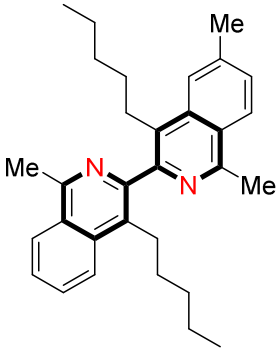
[a]Reaction conditions **2**: **1** (0.2 mmol), **2** (0.1 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), PivOH (0.2 mmol), DCE (2 mL), 50 °C under air for 12 h.

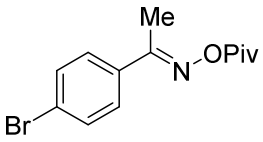
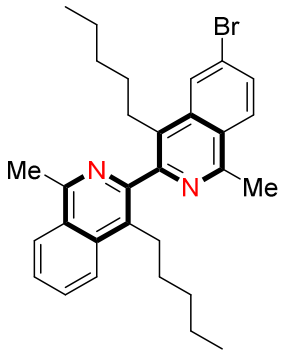
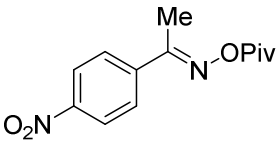
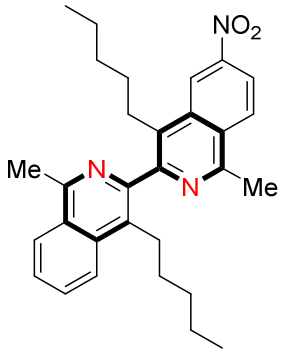
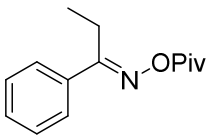
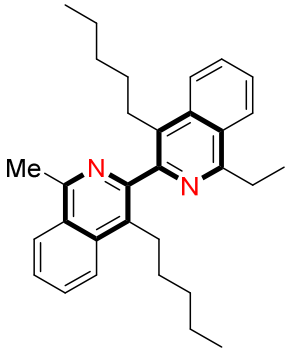
Considering the 3,4'-biisoquinoline **4ah** achieved in low yield under the reaction conditions developed above, we designed two steps to investigate the selectivity of dialkyl diyne due to its lower steric hindrance than diaryl diyne. In the first place, the 3-(hept-1-yn-1-yl)-1-methyl-4-pentylisoquinoline **3ah** was prepared under the conditions **1**. Then, **3ah** was reacted with **1a** in the prescience of $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), Li_2CO_3 (0.2 mmol). Remarkably, the biisoquinoline **5ah** which has two symmetrical core structures was obtained. The exact structure was confirmed through NMR and HRMS. By using the stepwise approach, we developed various nonsymmetrical 3,3'-biisoquinolines in moderate yields with high chemo- and regioselectivity under the same conditions as shown in **Table 4**.

Table 4 Synthesis of 3,3'-biisoquinolines[a]



1 **3ah** **5**

entry	substrate **1**	product	yield (%)
1	 **1a**	 **5ah**	53
2	 **1d**	 **5dh**	55
3	 **1g**	 **5gh**	58

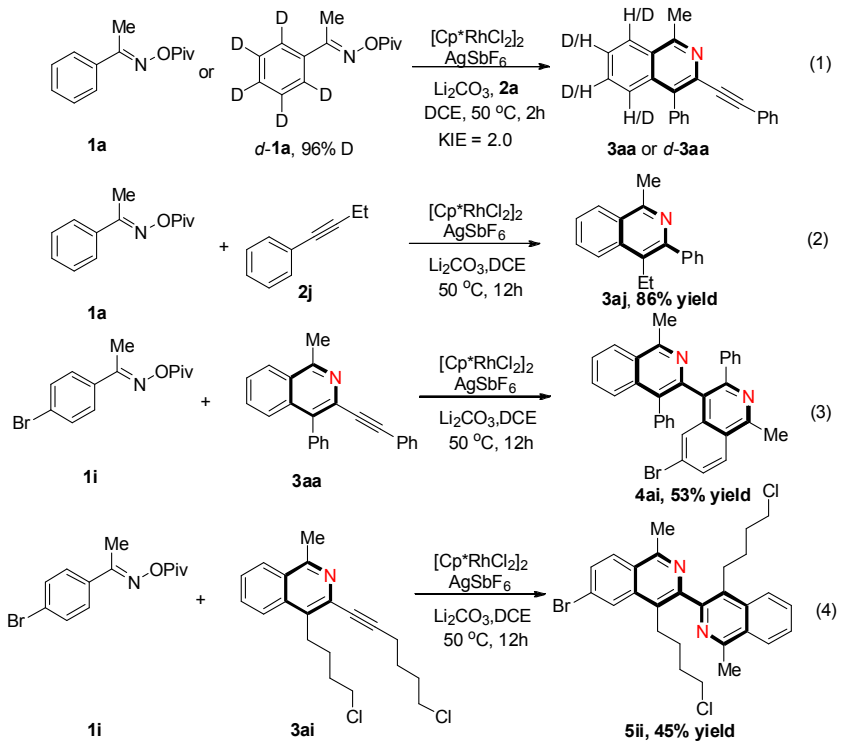
4	 **1i**	 **5ih**	49
5	 **1j**	 **5jh**	42
6	 **1k**	 **5kh**	51

[a]Reaction conditions: **1** (0.1 mmol), **3ah** (0.1 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), Li_2CO_3 (0.2 mmol), DCE (2 mL), 50 °C under air for 12 h.

To probe the preliminary mechanism of the reaction, the kinetic isotope effect of 1-phenylethan-1-one *O*-pivaloyl oxime **1a** and its pentadeuterate analogue *d*-**1a** were studied. A kinetic isotope effect (KIE) of 2.0 (k_H/k_D) was observed, demonstrated that the C-H cleavage might be involved in this transformation as rate-limiting step (Scheme 3, eq. 1). Asymmetrical alkyne, such as, but-1-yn-1-ylbenzene, was examined under the standard reaction conditions, and the desired isoquinoline was achieved in 86% yield (Scheme 3, eq. 2). According to the literatures reported by Fagnou[15b] and others,[3] the experimental evidence indicated that the reaction might go through a C-N bond formation/N-O bond cleavage process. The **3aa** and **3ai** prepared through the standard condition could be easily reacted with **1i**, giving the corresponding nonsymmetrical biisoquinolines **4ai** and **5ii** in

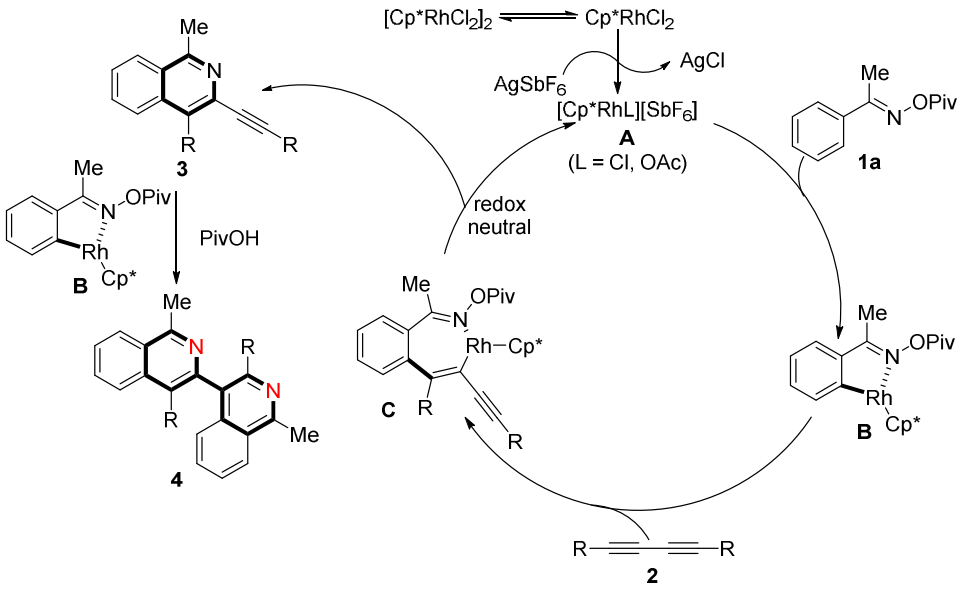
moderate yields (Scheme 3, eq. 3 and eq. 4). The fact demonstrated that the formation of biisoquinolines might process to steps.

Scheme 3. The study of mechanism.



On the basis of these results and literature precedents, [2-7, 15, 16] a plausible reaction mechanism was proposed as shown in **Scheme 4**. First, anion exchange of $[Cp^*RhCl_2]_2$ with $AgSbF_6$ afforded the reactive Rh(III) species **A**, which selectively activates the C-H of 1-phenylethan-1-one *O*-pivaloyl oxime **1a** to form the intermediate **B**. Subsequent insertion of **B** to diynes affords the seven-membered intermediate **C**. The first-step product **3** was gave by C-N bond formation and *N*-O bond cleavage of intermediate **C** *via* a redox neutral manner. And the active Rh(III) species was regenerated for the next catalytic cycle. The intermediate **B** might be reacted with product **3** to form biisoquinoline **4** in the presence of trimethylacetic acid. The formation of compound **4** may demonstrate that the order of migratory insertion is alkynyl, phenyl, isoquinolinyl, alkyl group.

Scheme 4. The proposed mechanism.



CONCLUSION

In summary, we have developed a novel method to the synthesis of alkynylated isoquinolines, 3,4'- and 3,3'-biisoquinolines with high selectivity *via* rhodium-catalyzed C-H activation/1,3-diyne strategy. Various symmetrical and asymmetrical biisoquinolines were obtained in high regioselectivity. Further studies on the application of C-H activation/1,3-diyne strategy to synthesize useful bisheterocycles were ongoing in our laboratory.

EXPERIMENTAL SECTION

General The reagents and solvents were purchased from common commercial sources and used without additional purification, if there is no special version. The starting materials of aryl ketone *O*-pivaloyloxime derivatives were prepared according to the known methods.[17] NMR spectra were recorded for ^{1}H NMR at 400 MHz, and ^{13}C NMR at 100 MHz using TMS as internal standard. The following abbreviations were used to describe peak patterns where appropriate: singlet (s), doublet (d), triplet (t), quintuplet (q), multiplet (m), doublet of doublet (dd), broad resonances (br). Mass spectroscopy data of the products were collected on an HRMS-EI-TOF instrument. UV/vis spectra were measured on SHIMADZU UV-2550.

General Procedure for Preparation of products 3

A 25 mL sealed tube with a magnetic stir bar was charged with $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), Li_2CO_3 (2.0 equiv.), **1** (0.1 mmol), diyne (0.15 mmol), DCE (2.0 mL). Then the sealed tube was sealed and heated to 50 ^{o}C with stirring for 12 h. After cooling down, the mixture was filtered through a plug of Celite, and then the residue was concentrated and purified by flash column chromatography with ethyl acetate (EA) and petroleum ether (Pet) (PE/EA = 50:1) as eluent to afford the corresponding products.

General Procedure for Preparation of products 4

A 25 mL sealed tube with a magnetic stir bar was charged with $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), PivOH (2.0 equiv.), **1** (0.2 mmol), diyne (0.1 mmol), DCE (2.0 mL). Then the sealed tube was sealed and heated to 50 ^{o}C with stirring for 12 h. After cooling down, the mixture was filtered through a plug of Celite, and then the residue was concentrated and purified by flash column

chromatography with ethyl acetate (EA) and petroleum ether (Pet) (PE/EA = 30:1) as eluent to afford the corresponding products.

General Procedure for Preparation of products 5

A 25 mL sealed tube with a magnetic stir bar was charged with $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), Li_2CO_3 (2.0 equiv.), **3ah, 3ai** or **3aa** (0.1 mmol), **1** (0.1 mmol), DCE (2.0 mL). Then the sealed tube was sealed and heated to 50 ^oC with stirring for 12 h. After cooling down, the mixture was filtered through a plug of Celite, and then the residue was concentrated and purified by flash column chromatography with ethyl acetate (EA) and petroleum ether (Pet) (PE/EA = 30:1) as eluent to afford the corresponding products.

Isotopically labeled experiment

A 25 mL sealed tube with a magnetic stir bar was charged with $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), Li_2CO_3 (2.0 equiv.), **1a** (0.05 mmol), *d*-**1a** (0.05 mmol), diyne (0.15 mmol), DCE (2.0 mL). Then the sealed tube was sealed and heated to 50 ^oC with stirring for 2 h. After cooling down, the mixture was filtered through a plug of Celite, and then the residue was concentrated and purified by flash column chromatography with ethyl acetate (EA) and petroleum ether (Pet) as eluent to afford the corresponding products.

Characterization data of the products

1-methyl-4-phenyl-3-(phenylethynyl)isoquinoline (3aa) white solid (27 mg, 86%); mp (^oC): 205–206; ^1H NMR (400 Hz, $CDCl_3$, TMS) δ 3.06 (s, 3H), 7.25–7.27 (m, 5H), 7.51–7.56 (m, 5H), 7.61–7.66 (m, 3H), 8.18–8.20 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.7, 89.6, 92.2, 122.9, 125.8, 126.1, 126.6, 127.4, 127.9, 128.1, 128.2, 128.4, 130.4, 130.9, 131.8, 134.1, 135.1, 135.4, 136.8, 158.5. IR *v* 2926, 1610, 1556, 1505, 1447, 1397, 1262, 764 cm^{-1}; HRMS (EI) Calcd for $C_{24}H_{17}N$ (M^+) 319.1361, Found 319.1363.

4-phenyl-3-(phenylethynyl)-1-propylisoquinoline (3ca) white solid (20 mg, 59%); mp (^oC) 121–122; ^1H NMR (400 Hz, $CDCl_3$, TMS) δ 1.15 (t, 3H, *J* = 7.2 Hz), 1.97 (q, 2H, *J* = 8.0 Hz), 3.35-3.39 (m, 2H), 7.23–7.27 (m, 5H), 7.51–7.62 (m, 7H), 7.65-7.68 (m, 1H), 8.21-8.24 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 14.5, 23.7, 37.9, 89.8, 92.2, 122.9, 125.6, 125.9, 126.3, 127.3, 127.9, 128.1, 128.2, 128.3, 130.2, 130.9, 131.8, 134.3, 135.3, 135.4, 136.9, 162.3. IR *v* 2923, 2839, 1632, 1536, 1457, 1252, 746 cm^{-1}; HRMS (EI) Calcd for $C_{26}H_{21}N$ (M^+) 347.1674, Found 347.1671.

1,7-dimethyl-4-phenyl-3-(phenylethynyl)isoquinoline (3da) white solid (27 mg, 82%); mp (^oC): 138–139; ^1H NMR (400 Hz, $CDCl_3$, TMS) δ 2.58 (s, 3H), 3.03 (s, 3H), 7.25–7.27 (m, 5H), 7.45–7.47 (m, 1H), 7.52–7.58 (m, 6H), 7.95 (s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.0, 22.7, 89.7, 91.8, 123.0, 124.9, 126.0, 126.7, 127.8, 128.1(2C), 128.2, 130.9, 131.7, 132.5, 133.2, 133.3, 135.3, 136.9, 137.5, 157.8. IR *v* 2924, 2846, 1660, 1638, 1569, 1548, 1488, 1459, 865, 818, 775 cm^{-1}; HRMS (EI) Calcd for $C_{25}H_{19}N$ (M^+) 333.1517, Found 333.1519.

1,8-dimethyl-4-phenyl-3-(phenylethynyl)isoquinoline (3ea) white solid (19 mg, 58%); mp (^oC) 113–114; ^1H NMR (400 Hz, $CDCl_3$, TMS) δ 3.00 (s, 3H), 3.25 (s, 3H), 7.22–7.27 (m, 5H), 7.42–7.55 (m, 8H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 26.0, 29.6, 89.0, 92.7, 122.8, 125.1, 127.5, 127.8, 128.1, 128.2, 128.4, 129.9, 130.8, 131.2, 131.8, 133.2, 135.9, 136.5, 137.2, 137.4, 158.7. IR *v* 2846, 1611, 1521, 1457, 1290, 815, 732 cm^{-1}; HRMS (EI) Calcd for $C_{25}H_{19}N$ (M^+) 333.1517, Found 333.1520.

8-chloro-1-methyl-4-phenyl-3-(phenylethynyl)isoquinoline (3fa) white solid (19 mg, 53%); mp (^oC):

136–137; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 3.39 (s, 3H), 7.21–7.28 (m, 5H), 7.44–7.47 (m, 3H), 7.52–7.57 (m, 4H), 7.67 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 29.8, 88.7, 93.3, 122.6, 124.9, 125.8, 128.1 (2C), 128.4, 128.6, 129.9, 130.5, 130.7, 131.8, 132.7, 134.4, 135.3, 136.8, 138.3, 158.3. IR *v* 2941, 1600, 1540, 1446, 1391, 1357, 818, 758, 703 cm^{-1}; HRMS (EI) Calcd for $C_{24}H_{16}ClN$ (M^+) 353.0971, Found 353.0973.

1,6-dimethyl-4-phenyl-3-(phenylethynyl)isoquinoline (3ga) white solid (29 mg, 89%); mp (°C):119–120; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 2.45 (s, 3H), 3.03 (s, 3H), 7.24–7.27 (m, 5H), 7.41 (s, 1H), 7.44–7.46 (m, 1H), 7.50–7.57 (m, 5H), 8.08 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.1, 22.6, 89.7, 92.2, 123.0, 124.9, 125.0, 125.7, 127.8, 128.1, 128.2, 128.3, 129.5, 130.9, 131.7, 134.2, 135.0, 135.3, 137.0, 140.9, 158.2. IR *v* 2924, 1622, 1571, 1550, 1491, 1443, 1390, 1262, 733, 698 cm^{-1}; HRMS (EI) Calcd for $C_{25}H_{19}N$ (M^+) 333.1517, Found 333.1520.

6-chloro-1-methyl-4-phenyl-3-(phenylethynyl)isoquinoline (3ha) white solid (26 mg, 75%); mp (°C): 187–188; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 3.05 (s, 3H), 7.24–7.27 (m, 5H), 7.48–7.63 (m, 7H), 8.12 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.5, 88.9, 93.3, 122.6, 124.7, 125.0, 127.6, 128.2, 128.3 (2C), 128.4, 128.6, 130.7, 131.8, 134.5, 135.1, 136.0, 136.2, 137.1, 158.4. IR *v* 2921, 2818, 1628, 1544, 1346, 748 cm^{-1}; HRMS (EI) Calcd for $C_{24}H_{16}ClN$ (M^+) 353.0971, Found 353.0968.

6-bromo-1-methyl-4-phenyl-3-(phenylethynyl)isoquinoline (3ia) white solid (31 mg, 79%); mp (°C): 182–183; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 3.04 (s, 3H), 7.23–7.27 (m, 5H), 7.48–7.51 (m, 2H), 7.54–7.60 (m, 3H), 7.69–7.71 (m, 1H), 7.80 (m, 1H), 8.05 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.6, 89.2, 93.0, 122.6, 124.9, 125.6, 127.5, 128.2 (2C), 128.3, 128.4, 128.6, 130.8 (2C), 131.8, 134.3, 135.3, 136.1, 136.4, 158.6. IR *v* 2955, 2849, 1601, 1564, 1488, 1388, 742 cm^{-1}; HRMS (EI) Calcd for $C_{24}H_{16}BrN$ (M^+) 397.0466, Found 397.0466.

1-methyl-4-(p-tolyl)-3-(p-tolylethynyl)isoquinoline (3ab) white solid (27 mg, 78%); mp (°C) 103–104; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 2.33 (s, 3H), 2.50 (s, 3H), 3.10 (s, 3H), 7.06–7.08 (m, 2H), 7.18–7.21 (m, 2H), 7.35-7.37 (m, 2H), 7.40-7.42 (m, 2H), 7.62-7.65 (m, 2H), 7.70-7.72 (m, 1H), 8.18-8.20 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 21.4, 21.6, 22.6, 89.2, 92.3, 120.0, 125.8, 126.2, 126.5, 127.2, 128.8, 128.9, 130.3, 130.8, 131.7, 133.7, 134.3, 135.1, 135.2, 137.5, 138.5, 158.3. IR *v* 2928, 2856, 1663, 1630, 1553, 1515, 1475, 818, 767 cm^{-1}; HRMS (EI) Calcd for $C_{26}H_{21}N$ (M^+) 347.1674, Found 347.1676.

1-methyl-4-(m-tolyl)-3-(m-tolylethynyl)isoquinoline (3ac) light brown solid (28 mg, 82%); mp (°C): 105–106; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 2.29 (s, 3H), 2.47 (s, 3H), 3.05 (s, 3H), 7.07–7.09 (m, 3H), 7.13–7.16 (m, 1H), 7.30-7.34 (m, 3H), 7.43-7.46 (m, 1H), 7.59-7.61 (m, 2H), 7.68-7.70 (m, 1H), 8.15-8.17 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 21.2, 21.6, 22.6, 89.4, 92.5, 122.8, 125.8, 126.2, 126.5, 127.3, 128.0 (2C), 128.1, 128.6, 128.7, 129.3, 130.3, 131.5, 132.4, 134.1, 135.1, 135.4, 136.7, 137.7 (2C), 158.4. IR *v* 2919, 2855, 1603, 1569, 1544, 1488, 1442, 1390, 788, 760, 738, 689 cm^{-1}; HRMS (EI) Calcd for $C_{26}H_{21}N$ (M^+) 347.1674, Found 347.1673.

4-(4-ethylphenyl)-3-((4-ethylphenyl)ethynyl)-1-methylisoquinoline (3ad) white solid (34 mg, 91%); mp (°C): 75–76; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 1.21 (t, 3H, *J* = 8.0 Hz), 1.38 (t, 3H, *J* = 7.6 Hz), 2.62 (q, 2H, *J* = 7.6 Hz), 2.81 (q, 2H, *J* = 7.6 Hz), 3.06 (s, 3H), 7.07–7.09 (m, 2H), 7.15–7.17 (m, 2H),

7.38-7.44 (m, 4H), 7.60-7.63 (m, 2H), 7.70-7.72 (m, 1H), 8.16-8.19 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 15.3, 15.9, 22.6, 28.9, 29.7, 89.1, 92.7, 120.1, 125.8, 126.2, 126.5, 127.2, 127.7, 130.3, 130.9, 131.8, 134.0, 134.3, 135.2, 135.3, 143.9, 144.8, 158.2. IR *v* 2908, 2823, 1636, 1545 1483, 1290, 810, 736 cm^{-1}; HRMS (EI) Calcd for $C_{28}H_{25}N$ (M^+) 375.1987, Found 375.1989.

4-(4-butylphenyl)-3-((4-butylphenyl)ethynyl)-1-methylisoquinoline (3ae) white solid (37 mg, 85%); mp (°C): 67–68; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 0.91 (t, 3H, *J* = 7.6 Hz), 1.01 (t, 3H, *J* = 7.6 Hz), 1.30–1.37 (m, 2H), 1.43–1.49 (m, 2H), 1.52–1.60 (m, 2H), 1.70–1.77 (m, 2H), 2.57 (t, 2H, *J* = 7.6 Hz), 2.76 (t, 2H, *J* = 7.6 Hz), 3.04 (s, 3H), 7.04–7.06 (m, 2H), 7.14–7.16 (m, 2H), 7.35-7.37 (m, 2H), 7.40-7.42 (m, 2H), 7.58–7.61 (m, 2H), 7.68–7.70 (m, 1H), 8.15–8.17 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 13.9, 14.1, 22.3, 22.4, 22.6, 33.4, 33.9, 35.6 (2C), 89.3, 92.5, 120.1, 125.7, 126.2, 126.5, 127.2, 128.2, 130.2, 130.8, 131.7, 134.0, 134.4, 135.2, 135.3, 142.5, 143.5, 158.2. IR *v* 2950, 2928, 2856, 1660, 1587, 1548, 1510, 1433, 1266, 737 cm^{-1}; HRMS (EI) Calcd for $C_{32}H_{33}N$ (M^+) 431.2613, Found 431.2615.

4-(4-methoxyphenyl)-3-((4-methoxyphenyl)ethynyl)-1-methylisoquinoline (3af) light yellow solid (26 mg, 68%); mp (°C): 116–117; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 3.03 (s, 3H), 3.79 (s, 3H), 3.92 (s, 3H), 6.78–6.80 (m, 2H), 7.07–7.09 (m, 2H), 7.23-7.25 (m, 2H), 7.44-7.46 (m, 2H), 7.57-7.62 (m, 2H), 7.68-7.70 (m, 1H), 8.14-8.16 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.7, 55.3, 55.4, 88.7, 92.2, 113.6, 113.8, 115.1, 125.8, 126.1, 126.5, 127.1, 129.0, 130.2, 132.1, 133.3, 134.4, 134.6, 135.4, 158.2, 159.3, 159.7. IR *v* 2920, 1605, 1548, 1512, 1460, 1436, 1388, 1247, 1171, 1034, 829 cm^{-1}; HRMS (EI) Calcd for $C_{26}H_{21}NO_2$ (M^+) 379.1572, Found 379.1574.

4-(4-fluorophenyl)-3-((4-fluorophenyl)ethynyl)-1-methylisoquinoline (3ag) white solid (21 mg, 58%); mp (°C) 124–125; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 3.06 (s, 3H), 7.00–7.01 (m, 2H), 7.24–7.30 (m, 4H), 7.48–7.51 (m, 2H), 7.64–7.65 (m, 3H), 8.19–8.21 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.7, 89.0, 91.3, 115.1, 115.4, 115.5, 115.7, 118.8, 125.8, 125.9, 126.6, 127.5, 130.6, 132.5, 132.6, 133.6, 133.7, 134.1, 134.2, 135.1, 158.9, 161.4, 163.8, 163.9. IR *v* 2936, 2817, 1658, 1536, 1487, 1268, 758 cm^{-1}; HRMS (EI) Calcd for $C_{24}H_{15}F_2N$ (M^+) 355.1173, Found 355.1175.

3-(hept-1-yn-1-yl)-1-methyl-4-pentylisoquinoline (3ah) white solid (28 mg, 90%); mp (°C): 60–61; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 0.91–0.96 (m, 6H), 1.34–1.52 (m, 8H), 1.66–1.71 (m, 4H), 2.54 (t, 2H, *J* = 7.2), 2.94 (s, 3H), 3.18–3.22 (m, 2H),7.57 (t, 1H, *J* = 7.2 Hz), 7.71 (t, 1H, *J* = 7.2 Hz), 7.99 (d, 1H, *J* = 8.4 Hz), 8.11 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 14.0, 14.1, 19.8, 22.3, 22.4, 22.6, 28.4, 29.4, 30.1, 31.3, 32.2, 80.0, 93.6, 123.9, 126.3, 126.6 (2C), 130.0, 133.1, 134.7 (2C), 156.7. IR *v* 2958, 2928, 2856, 1604, 1565, 1548, 1467, 1391, 766, 741 cm^{-1}; HRMS (EI) Calcd for $C_{22}H_{29}N$ (M^+) 307.2300, Found 307.2300.

4-(4-chlorobutyl)-3-(6-chlorohex-1-yn-1-yl)-1-methylisoquinoline (3ai) light yellow oil (28 mg, 82%); ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 1.81–1.89 (m, 4H), 1.94–2.06 (m, 4H), 2.61–2.63 (m, 2H), 2.93 (s, 3H), 3.25 (t, 2H, J = 7.6 Hz), 3.60–3.65 (m, 4H), 7.57–7.61 (m, 1H), 7.70–7.74 (m, 1H), 7.98 (d, 1H, *J* = 8.4 Hz), 8.12 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 19.1, 22.5, 25.9, 27.4, 28.5, 31.8, 32.5, 44.6, 44.8, 80.6, 92.5, 123.7, 126.4, 126.7, 126.9, 130.3, 132.1, 134.5, 134.7, 157.2. IR

v 2926, 1738, 1456, 1238, 1045 cm^{-1}; HRMS (EI) Calcd for $C_{20}H_{23}Cl_2N$ (M^+) 347.1208, Found 347.1210.

1,1'-dimethyl-3',4-diphenyl-3,4'-biisoquinoline (4aa) white solid (34 mg, 78%); mp (^oC): 187–188; ^1H NMR (400 Hz, $CDCl_3$, TMS) δ 2.98 (s, 3H), 3.18 (s, 3H), 6.06–6.08 (m, 1H), 6.56–6.58 (m, 1H), 6.83–6.87 (m, 1H), 7.00–7.04 (m, 1H) 7.06–7.14 (m, 6H) 7.42–7.44 (m, 1H) 7.52–7.67 (m, 5H) 8.14–8.16 (m, 1H) 8.28–8.30 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.5, 22.7, 125.7, 126.1 (2C), 126.4 (2C), 126.5, 126.9, 127.0, 127.1, 127.3 (2C), 127.5, 129.0, 130.0, 130.2, 130.3, 130.7, 132.1, 135.7, 136.0, 137.1, 140.5, 147.0, 149.3, 157.6, 158.2. IR *v* 2923, 2851, 1694, 1612, 1485, 1442, 1386, 1271, 1147, 737 cm^{-1}; HRMS (EI) Calcd for $C_{32}H_{24}N_2$ (M^+) 436.1939, Found 436.1935.

1,1',7,7'-tetramethyl-3',4-diphenyl-3,4'-biisoquinoline (4da) white solid (33 mg, 71%); mp (^oC): 234–235; ^1H NMR (400 Hz, $CDCl_3$, TMS) δ 2.57 (s, 3H), 2.60 (s, 3H), 2.93 (s, 3H), 3.14 (s, 3H), 6.04–6.06 (m, 1H), 6.55–6.56 (m, 1H), 6.83–6.86 (m, 1H), 6.98–7.01 (m, 1H), 7.05–7.11 (m, 6H) 7.32–7.34 (m, 1H), 7.36–7.38 (m, 1H), 7.43 (m, 2H), 7.89 (m, 1H),8.04 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 21.9, 22.0, 22.7 (2C), 124.6 (2C), 126.0, 126.3, 126.6, 126.7, 126.8, 127.2, 127.3, 127.4, 129.0, 130.3, 130.7, 131.8, 132.0, 132.1, 134.2, 135.3, 136.0, 136.1, 136.8, 141.0, 146.5, 148.7, 156.8, 157.3. IR *v* 2924, 2855, 1629, 1569, 1553, 1445, 1401, 1276, 829, 762, 741, 701 cm^{-1}; HRMS (EI) Calcd for $C_{34}H_{28}N_2$ (M^+) 464.2252, Found 464.2252.

1,1',6,6'-tetramethyl-3',4-diphenyl-3,4'-biisoquinoline (4ga) white solid (34 mg, 73%); mp (^oC): 202–203; ^1H NMR (400 Hz, $CDCl_3$, TMS) δ 2.39 (s, 3H), 2.44 (s, 3H), 2.93 (s, 3H), 3.15 (s, 3H), 6.06–6.08 (m, 1H), 6.56–6.58 (m, 1H), 6.84–6.87 (m, 1H), 7.00–7.12 (m, 7H) 7.20 (m, 1H), 7.27 (m, 1H), 7.38–7.40 (m, 1H) 7.46–7.49 (m, 1H), 8.02 (d, 1H, *J* = 8.4 Hz), 8.20 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.0, 22.2, 22.6, 22.7, 124.5, 124.8, 125.0, 125.3, 125.5, 125.6, 126.8, 126.9, 127.2 (2C), 127.4, 127.6, 128.6, 129.0, 130.3, 130.8, 131.5, 136.0, 136.3, 137.3, 140.2, 140.3, 141.0, 147.5, 149.5, 157.2, 157.7. IR *v* 2919, 2864, 1621, 1565, 1496, 1445, 1390, 1262, 732, 702 cm^{-1}; HRMS (EI) Calcd for $C_{34}H_{28}N_2$ (M^+) 464.2252, Found 464.2252.

6,6'-dichloro-1,1'-dimethyl-3',4-diphenyl-3,4'-biisoquinoline (4ha) yellow solid (33 mg, 65%); mp (^oC): 221–222; ^1H NMR (400 Hz, $CDCl_3$, TMS) δ 2.94 (s, 3H), 3.17 (s, 3H), 6.02–6.04 (m, 1H), 6.55–6.57 (m, 1H), 6.88–6.92 (m, 1H), 7.03–7.15 (m, 7H), 7.40 (m, 1H), 7.49–7.53 (m, 2H), 7.59–7.61 (m, 1H), 8.08–8.10 (m, 1H) 8.23–8.25 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.7, 22.8, 124.3, 124.8, 125.0 (2C), 126.9, 127.3, 127.4, 127.5 (2C), 127.6 (2C), 127.7, 128.1, 129.0, 130.2, 130.5, 131.7, 134.9, 136.6, 136.7, 137.1, 140.3, 147.7, 150.6, 157.9, 158.3. IR *v* 2916, 2849, 1610, 1564, 1483, 1387, 1090, 759 cm^{-1}; HRMS (EI) Calcd for $C_{32}H_{22}Cl_2N_2$ (M^+) 504.1160, Found 504.1161.

6,6'-dibromo-1,1'-dimethyl-3',4-diphenyl-3,4'-biisoquinoline (4ia) yellow solid (37 mg, 62%); mp (^oC): 191–192; ^1H NMR (400 Hz, $CDCl_3$, TMS) δ 2.96 (s, 3H), 3.16 (s, 3H), 6.04–6.06 (m, 1H), 6.56–6.58 (m, 1H), 6.89–6.93 (m, 1H), 7.05–7.15 (m, 7H) 7.58–7.59 (m, 1H), 7.66–7.68 (m, 2H), 7.73–7.76 (m, 1H), 8.01–8.03 (m, 1H) 8.15–8.17 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.5, 22.7, 124.5, 125.0, 125.4, 125.5, 126.9, 127.4, 127.5 (2C), 127.6 (2C), 127.7, 128.3, 129.0, 130.2, 130.3, 130.5, 130.8, 131.6, 134.8, 137.3, 138.2, 147.5, 150.5, 158.0, 158.4. IR *v* 2926, 2844, 1618, 1532, 1497, 1461, 1266, 1230, 1166, 732, 696 cm^{-1}; HRMS (EI) Calcd for $C_{32}H_{22}Br_2N_2$ (M^+) 592.0150, Found 592.0152.

3',4-bis(4-ethylphenyl)-1,1'-dimethyl-3,4'-biisoquinoline (4ad) white solid (31 mg, 63%); mp (^{o}C): 246–247; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 1.12–1.18 (m, 6H), 2.51–2.54 (m, 4H), 2.96 (s, 3H), 3.16 (s, 3H), 6.01–6.03 (m, 1H), 6.45–6.47 (m, 1H), 6.65–6.67 (m, 1H), 6.82–6.84 (m, 1H), 6.89–6.91 (m, 2H) 7.01–7.03 (m, 2H), 7.46–7.65 (m, 6H), 8.12–8.14 (m, 1H), 8.26–8.28 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 15.4, 15.8, 22.7 (2C), 28.5, 28.6, 125.6 (2C), 126.2, 126.4 (2C), 126.7, 126.8 (2C), 126.9, 127.8, 128.8, 129.8, 129.9, 130.2, 130.6, 132.1, 132.9, 136.3, 137.1, 138.3, 142.6, 143.1, 147.3, 149.6, 157.3, 157.9. IR *v* 2924, 1608, 1512, 1436, 1130, 752, 676 cm^{-1}; HRMS (EI) Calcd for $C_{36}H_{32}N_2$ (M^+) 492.2565, Found 492.2568.

3',4-bis(4-ethylphenyl)-1,1'-dimethyl-3,4'-biisoquinoline (4ae) white solid (36 mg, 65%); mp (^{o}C): 222–223; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 0.87–0.95 (m, 6H), 1.26–1.33 (m, 4H), 1.45–1.55 (m, 4H), 2.47–2.53 (m, 4H), 2.98 (s, 3H), 3.18 (s, 3H), 6.01–6.02 (m, 1H), 6.45–6.46 (m, 1H), 6.64–6.66 (m, 1H), 6.81–6.83 (m, 1H), 6.89–6.91 (m, 2H) 7.03–7.04 (m, 2H), 7.50–7.65 (m, 6H), 8.13–8.15 (m, 1H), 8.28–8.30 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 13.9, 14.0, 22.2, 22.6, 22.7, 26.9, 33.4, 33.6, 35.2, 35.3, 125.6 (2C), 126.0, 126.1, 126.3, 126.4 (2C), 126.8, 127.3, 127.4 (2C), 127.8, 128.8, 129.8, 129.9, 130.1, 130.6, 132.1, 132.9, 136.2, 137.1, 141.3, 141.6, 147.4, 157.2, 157.9. IR *v* 2865, 1645, 1536, 1423, 873, 733 cm^{-1}; HRMS (EI) Calcd for $C_{40}H_{40}N_2$ (M^+) 548.3191, Found 548.3189.

3',4-bis(4-methoxyphenyl)-1,1'-dimethyl-3,4'-biisoquinoline (4af) light yellow solid (28 mg, 56%); mp (^{o}C): 212–213; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 2.96 (s, 3H), 3.16 (s, 3H), 3.71 (d, 6H, *J* = 7.2 Hz), 6.07–6.10 (m, 1H), 6.37–6.40 (m, 1H), 6.45–6.48 (m, 1H), 6.56–6.59 (m, 1H), 6.61–6.64 (m, 2H), 7.08–7.10 (m, 2H), 7.45–7.65 (m, 6H), 8.11–8.13 (m, 1H), 8.26–8.28 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.7, 55.1, 55.2, 112.6, 112.8, 113.0, 125.7, 125.9, 126.2, 126.4, 126.8, 127.5, 128.1, 129.9, 130.0 (2C), 130.1, 131.5, 131.7, 131.8, 133.6, 136.4, 137.1, 140.0, 157.4, 157.9, 158.4, 158.8. IR *v* 2934, 1663, 1584, 1529, 1496, 784, 723 cm^{-1}; HRMS (EI) Calcd for $C_{34}H_{28}N_2O_2$ (M^+) 496.2151, Found 496.2148.

6'-bromo-1,1'-dimethyl-3',4-diphenyl-3,4'-biisoquinoline (4ai) light yellow solid (27 mg, 53%); mp (^{o}C): 151–152; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 2.95 (s, 3H), 3.20 (s, 3H), 6.07–6.09 (m, 1H), 6.59–6.61 (m, 1H), 6.89–6.93 (m, 1H), 7.01–7.05 (m, 1H), 7.09–7.15 (m, 6H), 7.44–7.46 (m, 1H), 7.55–7.59 (m, 1H),7.65–7.68 (m, 2H), 7.71 (m, 1H), 8.01 (d, 1H, *J* = 9.2 Hz), 8.32 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.7, 22.8, 124.5, 125.2, 125.8, 126.2, 126.6, 127.0, 127.1, 127.2, 127.3, 127.4, 127.6, 128.5, 129.1, 129.9, 130.1, 130.3, 130.6, 132.3, 135.6, 136.0, 138.4, 140.5, 146.3, 150.7, 158.0, 158.2. IR *v* 2921, 1600, 1566, 1484, 1390, 762 cm^{-1}; HRMS (EI) Calcd for $C_{32}H_{23}BrN_2$ (M^+) 514.1045, Found 514.1050.

1,1'-dimethyl-4,4'-dipentyl-3,3'-biisoquinoline (5ah) white solid (22 mg, 53%); mp (^{o}C): 85–86; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 0.76 (t, 6H, *J* = 7.2 Hz), 1.16–1.19 (m, 8H), 1.66 (m, 4H), 2.76 (m, 4H), 2.99 (s, 6H), 7.63 (t, 2H, *J* = 7.6 Hz), 7.76 (t, 1H, *J* = 7.6 Hz), 8.09 (d, 1H, *J* = 8.4 Hz), 8.21 (d, 1H, *J* = 8.0 Hz); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 13.9, 22.2, 22.3, 28.8, 30.1, 32.3, 124.2, 126.3, 127.1, 128.6, 129.7, 135.7, 150.0, 155.8. IR *v* 2955, 2923, 2860, 1613, 1558, 1502, 1462, 1387, 752 cm^{-1}; HRMS (EI) Calcd for $C_{30}H_{36}N_2$ (M^+) 424.2878, Found 424.2880.

1,1',7-trimethyl-4,4'-dipentyl-3,3'-biisoquinoline (5dh) white solid (24 mg, 55%); mp (°C) 91–92; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 0.75–0.78 (m, 6H), 1.17–1.20 (m, 8H), 1.65–1.81 (m, 5H), 2.62 (s, 3H), 2.78 (m, 3H), 2.97 (d, 6H, *J* = 11.2 Hz), 7.58–7.65 (m, 2H), 7.33–7.77 (m, 1H), 7.97–8.01 (m, 2H), 8.09 (d, 1H, *J* = 8.4 Hz), 8.21 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 13.9, 21.9, 22.3 (2C), 28.8, 29.7, 30.1 (2C), 32.3 (2C), 124.1, 124.2, 125.3, 126.1, 126.2, 127.0, 127.3, 128.3, 128.5, 129.6, 131.8, 133.8, 135.7, 135.9, 149.4, 150.3, 155.1, 155.8. IR *v* 2962, 2924, 2864, 1621, 1566, 1506, 1463, 1391, 1266, 737 cm^{-1}; HRMS (EI) Calcd for $C_{31}H_{38}N_2$ (M^+) 438.3035, Found 438.3038.

1,1',6-trimethyl-4,4'-dipentyl-3,3'-biisoquinoline (5gh) white solid (25 mg, 58%); mp (°C): 95–96; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 0.75–0.78 (m, 6H), 1.18–1.19 (m, 8H), 1.65 (m, 4H), 2.62–2.82 (s, 7H), 2.97 (d, 6H, *J* = 13.2 Hz), 7.44–7.46 (m, 1H), 7.60–7.64 (m, 1H), 7.73–7.77 (m, 1H), 7.83 (m, 1H), 8.07–8.11 (m, 2H), 8.19–8.22 (m, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 13.9, 22.3 (2C), 22.4 (2C), 28.7, 28.8, 30.0, 30.1, 32.2, 32.3, 123.2, 124.2, 125.4, 126.2 (2C), 127.0, 127.9, 128.4 (2C), 129.6, 135.7, 135.9, 139.7, 150.2, 150.3, 155.5, 155.8. IR *v* 2932, 2835, 1601, 1536, 1488, 1298, 743 cm^{-1}; HRMS (EI) Calcd for $C_{31}H_{38}N_2$ (M^+) 438.3035, Found 438.3036.

6-bromo-1,1'-dimethyl-4,4'-dipentyl-3,3'-biisoquinoline (5ih) yellow solid (25 mg, 49%); mp (°C): 121–122; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 0.74–0.78 (m, 6H), 1.16–1.20 (m, 8H), 1.65 (m, 4H), 2.74 (m, 4H), 2.97 (d, 6H, *J* = 9.6 Hz), 7.61–7.65 (m, 1H), 7.69–7.71 (m, 1H), 7.74–7.77 (m, 1H), 8.05–8.09 (m, 2H), 8.20–8.22 (m, 2H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 13.9 (2C), 22.2, 22.3 (2C), 22.4, 28.7 (2C), 30.0, 30.1, 32.1, 32.2, 124.2, 124.8, 125.5, 126.3, 126.4, 126.7, 127.1, 127.8, 128.0, 128.5, 129.7, 135.6, 137.1, 149.7, 151.4, 156.0 (2C). IR *v* 2953, 2928, 1601, 1584, 1478, 1288, 721 cm^{-1}; HRMS (EI) Calcd for $C_{30}H_{35}BrN_2$ (M^+) 502.1984, Found 502.1984.

1,1'-dimethyl-6-nitro-4,4'-dipentyl-3,3'-biisoquinoline (5jh) white solid (20 mg, 42%); mp (°C) 133–134; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 0.74–0.78 (m, 6H), 1.16–1.26 (m, 8H), 1.68 (m, 4H), 2.82 (m, 3H), 2.99 (s, 3H), 3.04 (s, 3H), 7.64–7.68 (m, 1H), 7.76–7.80 (m, 1H), 8.10 (d, 1H, *J* = 8.4 Hz), 8.22 (d, 1H, *J* = 8.4 Hz), 8.37 (m, 2H), 9.02 (s, 1H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 13.8, 13.9, 22.2, 22.3, 22.4, 22.6, 28.8, 30.1, 30.5, 32.1, 32.2, 119.7, 120.8, 124.2, 126.3, 126.6, 127.2, 128.4, 128.6, 128.8, 129.9, 130.4, 135.4, 135.5, 148.0, 149.1, 152.5, 156.2, 156.3. IR *v* 2926, 2849, 1632, 1559, 1532, 1348, 742 cm^{-1}; HRMS (EI) Calcd for $C_{30}H_{35}N_3O_2$ (M^+) 469.2729, Found 469.2730.

1-ethyl-1'-methyl-4,4'-dipentyl-3,3'-biisoquinoline (5kh) light yellow solid (22 mg, 51%); mp (°C): 118–119; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 0.75–0.78 (m, 6H), 1.20 (m, 8H), 1.42–1.45 (m, 3H), 1.68 (m, 4H), 2.68–2.99 (m, 7H), 3.35–3.37 (m, 2H), 7.62–7.65 (m, 2H), 7.72–7.77 (m, 2H), 8.09 (d, 2H, *J* = 8.4 Hz), 8.20–8.26 (m, 2H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 13.9, 14.5, 22.4, 28.9, 30.1, 30.2, 32.3, 124.2, 124.4, 126.0, 126.2, 126.3, 127.1, 128.4, 128.5, 129.5, 129.6, 135.7, 136.1, 150.4, 155.8, 160.7. IR *v* 2958, 2924, 2856, 1617, 1553, 1463, 1386, 758 cm^{-1}; HRMS (EI) Calcd for $C_{31}H_{38}N_2$ (M^+) 438.3035, Found 438.3035.

6-bromo-4,4'-bis(4-chlorobutyl)-1,1'-dimethyl-3,3'-biisoquinoline (5ii) light yellow solid (24 mg, 45%); mp (°C): 145–146; ^{1}H NMR (400 Hz, $CDCl_3$, TMS) δ 1.66–1.73 (m, 6H), 1.84 (m, 3H), 2.80 (s, 3H), 2.99 (d, 6H, *J* = 9.6), 3.39 (t, 4H, *J* = 6.8 Hz), 7.65–7.69 (m, 1H), 7.72–7.75 (m, 1H), 7.77–7.81 (m, 1H), 8.09 (d, 2H, *J* = 8.8 Hz), 8.22–8.24 (m, 2H); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 22.4 (2C),

27.4, 27.5, 27.8, 27.9,32.5, 32.6, 44.5, 44.6, 124.0, 125.1, 125.5, 126.4, 126.5, 126.6, 126.9, 127.1, 127.6, 128.1, 130.0, 130.1, 135.4, 136.9, 149.7, 151.4, 156.5 (2C). IR *v* 2923, 1602, 1564, 1462, 1391, 812, 759 cm^{-1}; HRMS (EI) Calcd for $C_{28}H_{29}BrCl_2N_2$ (M^+) 542.0891, Found 542.0897.

4-ethyl-1-methyl-3-phenylisoquinoline (3aj) [15d, 18] light yellow solid (21 mg, 86%); mp (^oC): 112–113; ^1H NMR (400 Hz, $CDCl_3$, TMS) δ 1.36–1.31 (m, 3H), 3.00–3.05 (m, 5H), 7.42–7.55 (m, 5H), 7.63–7.65 (m, 1H), 7.66–7.67 (m, 1H), 8.11 (d, 1H, *J* = 8.4 Hz), 8.20 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR (100 Hz, $CDCl_3$, TMS) δ 15.7, 21.7, 22.5, 124.2, 126.2, 126.3, 126.7, 127.4, 128.2, 128.6, 129.2, 129.8, 135.2, 141.9, 150.7, 155.9.

Supporting Information

X-ray crystallography of 3aa and 4ae, UV-Vis absorption spectra, and 1H NMR, 13C NMR spectra.

This material is available free of charge *via* the Internet at http://pubs.acs.org.

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(12) (a) CCDC-1519039 contains the supplementary crystallographic data for **3aa**; (b) CCDC-1519235 contains the supplementary crystallographic data for **4ae**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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