JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis of Isoquinolines and Heterocycle-Fused Pyridines via Three-Component Cascade Reaction of Aryl Ketones, Hydroxylamine, and Alkynes

Liyao Zheng, Jia Ju, Yunhui Bin, and Ruimao Hua*

Department of Chemistry, Tsinghua University, Key Laboratory of Organic Optoelectronics & Molecular Engineering of Ministry of Education, Beijing 100084, China

Supporting Information

ABSTRACT: An efficient one-pot synthesis of isoquinolines and heterocycle-fused pyridines by three-component reaction of aryl ketones, hydroxylamine, and alkynes is developed. The reaction involves condensation of aryl ketones and hydroxylamine, rhodium(III)-catalyzed C−H bond activation of the in situ generated aryl ketone oximes, and cyclization with internal alkynes. This protocol enables rapid assembly of multisubstituted isoquinolines as well as γ-carbolines, furo[2,3-*c*]pyridines, thieno[2,3-*c*]pyridines, and benzofuro[2,3-*c*]pyridines from readily available substrates.

INTRODUCTION

Nitrogen-containing heterocyclic compounds are ubiquitous in numerous natural and synthetic bioactive molecules. Among them, isoquinolines and relative fused pyridines are important heterocycles that serve as privileged components in medical chemistry and pharmaceutical industry.[1] Furthermore, some isoquinolines are useful ligands[2] for catalytic asymmetric syntheses[2a] and electrophosphorescent complexes.[2c] Motivated by the need of high throughput screening in modern drug discovery, rapid building high capacity libraries of drug candidates from readily available building blocks is particularly attractive. Therefore, chemists continue to devise novel synthetic methodologies with minimization of substrate preactivation and maximization of product diversity.

The development of synthetic chemistry of isoquinolines gives a good illustration for this concept. Traditional routes, which are demonstrated well by several name reactions such as Bischler−Napieralski reaction, Pomeranz−Fritsch reaction, and Pictet−Gams reaction, typically need highly active substrates and harsh reaction conditions.[3] To address these issues, various metal-catalyzed cyclizations[4] were developed over the past two decades. For intramolecular approaches, highly prefunctionalized substrates, such as imine and oxime derivatives of *ortho*-alkynylaryl aldehyde were employed, thus narrowing the product diversity inherently.[4c−g] For intermolecular cyclization, Larock's group[4h,i] developed a palladium-catalyzed coupling of *o*-haloaldimines and alkynes to construct the isoquinoline skeleton, while Cheng's group[4j] reported a similar strategy using nickel-catalyzed systems. However, the use of preactivated *o*-haloaldimines as substrates still leads narrow substrate broad scope and low atom economy.

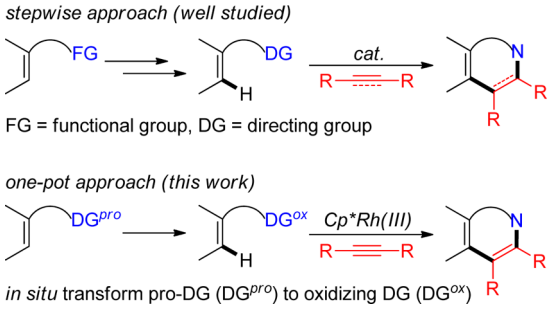
Recently, rhodium-catalyzed C−H activation has emerged as a versatile tool in heterocycle syntheses.[5] Jun[6a] and Cheng[6b] have developed Rh(I)-catalyzed systems for isoquinoline synthesis, but high temperature (130 °C or higher) was needed. In 2009, Miura[7a] and Fagnou[7b] have independently reported the Cp*Rh(III)-catalyzed isoquinoline synthesis by oxidative coupling between alkynes and imines using stoichiometric $Cu(OAc)_2$ as external oxidant. In 2010, Guimond and Fagnou[8b] reported an elegant isoquinolone synthesis using N−O bond as an internal oxidant for C−N bond formation and catalyst turnover. Shortly afterward, this "external-oxidant-free" strategy[8] was expanded by Chiba[8c] and Li[8d] for isoquinoline synthesis, where *O*-acetyl oximes and oximes are employed as oxidizing directing groups (DG^{ox}) for Rh(III)-catalyzed C−H bond activation, respectively.

In the above examples involving C−H activation for isoquinoline synthesis, directing groups with nitrogen atoms are installed in the substrates beforehand; thus, additional steps for the synthesis of the substrates are needed. For example, in Chiba's isoquinoline synthesis,[8c] the *O*-acetyl oximes need a two-step synthesis from corresponding aryl ketones, and a large amount of pyridine is used as base in both steps. With our continuing interests in alkyne involved multicomponent reactions and cascade heterocycle syntheses,[9,10] we embarked on devising cascade reactions by combination of Rh(III) catalyzed C−H activation with other reactions. We were specifically interested in generating directing groups (DGs) via in situ transformation of a preparatory functional group, namely, pro-directing groups (DG^{pro}) (Scheme 1),[11] as inspired by the concept of "prodrug". Very recently, Cheng[12] reported a one-pot three-component reaction of aryl aldehydes, methylamines, and alkynes to afford isoquinolinium salts though Cp*Rh(III)-catalyzed C−H bond activation, where stoichiometric $Cu(OAc)_2$ is used as external oxidant. Herein, we disclose a one-pot synthesis of isoquinolines by three-component reaction of aryl ketones, hydroxylamine, and

Received: May 23, 2012
Published: June 18, 2012

dx.doi.org/10.1021/jo3010414 | *J. Org. Chem.* 2012, 77, 5794−5800

Scheme 1. Strategy for Nitrogen-Containing Heterocycle Synthesis via Directed C−H Activation

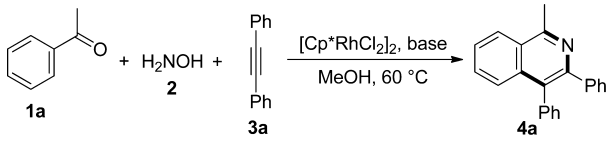


alkynes. The reaction proceeds under mild conditions in the external-oxidant-free fashion and can be expanded to synthesis of various heterocycle-fused pyridines.

RESULTS AND DISCUSSION

As a model reaction, acetophenone and 1,2-diphenylacetylene were employed as substrates, while a variety of nitrogen sources (*N*-sources) and bases were examined to optimize the reaction conditions (Table 1).

Table 1. Optimization of Reaction Conditions for Isoquinoline Synthesis[a]



entry	*N*-source	base (equiv)	time (h)	yield (%)[b]
1	$H_2NOMe{\cdot}HCl$	CsOAc (2.1)	12	27
2	$H_2NOH{\cdot}HCl$	CsOAc (2.1)	12	92
3	$H_2NOH{\cdot}HCl$	KOAc (2.1)	12	86
4	$H_2NOH{\cdot}HCl$	NaOAc (2.1)	12	53
5	$H_2NOH{\cdot}HCl$	K_2CO_3 (2.1)	12	79
6	$H_2NOH{\cdot}HCl$	Et_3N (2.1)	12	0
7	$H_2NOH{\cdot}HCl$	KOAc (1.5)	12	73
8	$H_2NOH{\cdot}HCl$	KOAc (1.1)	12	0
9	**$H_2NOH{\cdot}HCl$**	**KOAc (2.1)**	**18**	**93 (85[c])**
10	aq H_2NOH[d]	KOAc (0.3)	18	18
11	aq H_2NOH[d]	KOAc (1.0)	18	45
12	aq H_2NOH[d]	CsOAc (0.3)	18	64

[a]Unless otherwise noted, reactions were carried out using **1a** (0.50 mmol), **2** (1.1 equiv), and **3a** (1.1 equiv) with $[Cp^*RhCl_2]_2$ (1.0 mol %) and base in 1.0 mL of MeOH at 60 °C. [b]Yields of **4a** are based on GC by using *n*-$C_{28}H_{58}$ as internal standard. [c]Isolated yields in 2.0 mmol scale. [d]50 wt % aqueous solution, containing 1.2 equiv of H_2NOH.

Inspired by Guimond's isoquinolone synthesis[8b] using *N*-methoxyhydroxamic acids as starting materials, we first choose *N*-methoxyhydroxylamine hydrochloride as *N*-source. $[Cp^*RhCl_2]_2$ was used as precursor of catalysis, while an excess equivalent of CsOAc was added to neutralize hydrochloride and provide OAc^- to generate $Cp^*Rh(OAc)_n$ species as active catalysis. Though the condensation step proceeded smoothly to form acetophenone *N*-methoxyoximes, only trace amount of the desired isoquinoline derivative was obtained (entry 1). To our delight, simply replacing *N*-source to hydroxylamine hydrochloride gave the desired product with high yield (entry 2). Replacing base to KOAc displayed nearly the same efficiency (entry 3), while other acetates such as NaOAc (entry 4) and other potassium salts such as K_2CO_3 (entry 5) displayed lower efficiency. No desired product was detected by using organic base such as Et_3N (entry 6). Considering price and convenience in handling,[13] KOAc was chosen for further optimization. Reducing the dose of KOAc from 2.1 to 1.5 equiv gave declined activity (entry 7), while 1.1 equiv of KOAc (which is neutralized completely by 1.1 equiv of acid in $H_2NOH{\cdot}HCl$ to form HOAc) gave no desired product (entry 8). Prolonging the reaction to 18 h proved to be optimal (93% GC yield and 85% isolated yield in 2.0 mmol scale).

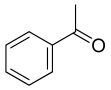
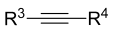
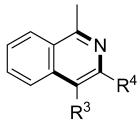
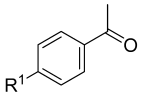
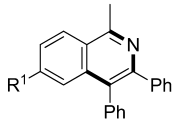
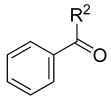
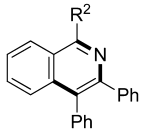
Hydroxylamine aqueous solution (50 wt %) was also employed as *N*-source for further optimization of reaction conditions, as we wished to reduce the dose of base. However, no satisfactory results were obtained in several attempts (entries 10−12). We speculated that the in situ generated HOAc favors the condensation of aryl ketones and hydroxylamine, as oxygen atom of the carbonyl group can be partly protonated by weak acid, thus increasing the electropositivity of the carbon atom of the carbonyl group to favor nucleophilic attack of H_2NOH. Additionally, increased concentration of OAc^- may favor generation of the active $Cp^*Rh(OAc)_n$ species.

By using the optimized reaction condition, the generality for the synthesis of isoquinolines was next examined (Table 2). With acetophenone as ketone substrate, a survey of the scope of alkynes revealed that both aryl and alkyl-substituted symmetric internal alkynes reacted well to afford isoquinolines **4aa** and **4ab**, respectively. Notably, asymmetric alkyne **3c** and **3d** was also applicable with good yield and high regioselectivity. Alkyne **3e** with a hydroxyl group gave corresponding isoquinoline **4ae** with high regioselectivity but low yield (44%, ca. 40% acetophenone oxime and **3e** were recovered) under the standard conditions. We speculated that the hydroxyl group could coordinate to Rh, thus reducing the activity of the catalyst. Fortunately, a much higher yield (72%) was obtained by simply increasing the catalyst loading and reaction temperature. Insertion of diarylacetylenes with electron-donating group (EDG) OMe (**3f**) or electron-withdrawing group (EWG) Cl (**3g**) as *para* substituent also proceeded smoothly. Substrates of ketones with various *para* substituents were also examined. Generally, ketones with EDGs (**1b**, **1c**) had higher reactivity than that those with EWGs (**1d**−**1f**). As the first condensation step of aryl ketones and hydroxylamine is relatively faster than subsequent steps, it is expectable that the electronic effects of the two coupling partners are matched with Li's isoquinoline synthesis,[8d] which uses ketone oximes and alkynes as coupling partners.

We next investigated the scope of R^2 group in ketone substrates **1**. By using various alkyl groups as the R^2 group, we found that yield of isoquinolines **4** was declined as increase of steric hindrance of R^2. For ethyl phenyl ketone **1g**, the efficiency was as high as that of acetophenone. However, for the ketones with isopropyl (**1h**), cyclohexyl (**1i**), or cyclopropyl (**1j**) as the R^2 group, the yield of corresponding isoquinolines **4** were unsatisfactory. This substituent effect was owing to the inactive isomer of oxime formation in the condensation step.[14] As demonstrated by Chiba et al.,[8c] the isomer of oxime with the hydroxyl group and the aryl group in the same side cannot proceed the C−H bond activation process, for the nitrogen atom can hardly direct Rh to the *ortho* site. Recent work of Chiba[15a] reveals that both of *anti*- and *syn*-isomers of oxime can

dx.doi.org/10.1021/jo3010414 | J. Org. Chem. 2012, 77, 5794−5800

Table 2. Substrate Scope of Isoquinoline Synthesis[a]

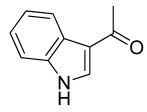
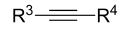
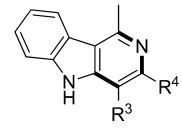
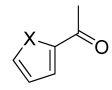
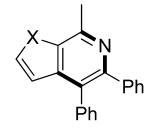
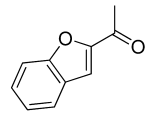
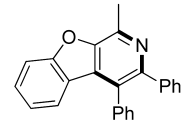
entry	ketone **1**	alkyne **3**	product **4**/yield(%)
			
1	**1a**	**3a** (R^3, R^4 = Ph)	**4aa** (85, 92[b])
2	**1a**	**3b** (R^3, R^4 = *n*-Pr)	**4ab** (80, 84[b])
3	**1a**	**3c** (R^3 = Me, R^4 = Ph)	**4ac** (81, 82[b])
4	**1a**	**3d** (R^3 = Et, R^4 = Ph)	**4ad** (74, 80[b])
5	**1a**	**3e** (R^3 = CH_2OH, R^4 = Ph)	**4ae** (72[c], 75[b,c])
6	**1a**	**3f** (R^3, R^4 = 4-MeO-C_6H_4)	**4af** (91, 92[b])
7	**1a**	**3g** (R^3, R^4 = 4-Cl-C_6H_4)	**4ag** (82, 89[b])
			
8	**1b** (R^1 = Me)	**3a**	**4ba** (83)
9	**1c** (R^1 = OMe)	**3a**	**4ca** (87)
10	**1d** (R^1 = Cl)	**3a**	**4da** (78)
11	**1e** (R^1 = Br)	**3a**	**4ea** (80)
12	**1f** (R^1 = NO_2)	**3a**	**4fa** (77)
			
13	**1g** (R^2 = Et)	**3a**	**4ga** (84, 94[b])
14	**1h** (R^2 = *i*-Pr)	**3a**	**4ha** (45, 87[d])
15	**1i** (R^2 = cyclohexyl)	**3a**	**4ia** (37, 75[d])
16	**1j** (R^2 = cyclopropyl)	**3a**	**4ja** (21, 53[d])

[a]Unless otherwise noted, reactions were carried out using **1** (2.0 mmol), **3** (1.1 equiv), and $H_2NOH{\cdot}HCI$ (1.1 equiv) with $[Cp^*RhCl_2]_2$ (1.0 mol %) and KOAc (2.1 equiv) in 10 mL of MeOH at 60 °C for 18 h. [b]**3** (2.0 mmol), **1** (1.2 equiv), $H_2NOH{\cdot}HCl$ (1.2 equiv), KOAc (2.2 equiv). [c]80 °C, 2.5 mol % $[Cp^*RhCl_2]_2$. [d]**3** (2.0 mmol), **1** (2.0 equiv), $H_2NOH{\cdot}HCl$ (2.0 equiv), KOAc (3.0 equiv).

react well under $Cu(OAc)_2/[Cp^*RhCl_2]_2$ bimetallic catalytic system[15] via iminyl copper and then iminyl rhodium species. However, in our $[Cp^*RhCl_2]_2$/KOAc catalytic system, only when these two groups were in the opposite side, the oxime group can serve as a directing group for C−H bond activation. With increase of steric hindrance of R^2, the ratio of inactive oxime isomer increased, thus resulting in declined yields. To address this issue, we changed the reactant ratio to ensure that there was enough active isomer of oxime relative to 1 equiv of alkyne. As expected, yields of **4ha**, **4ia**, and **4ja** were increased to about twice over that in the standard condition (alkyne was excess) when 2 equiv of ketones were used. It is worth noting that no rearrangement products were detected by using **1j** as substrates, while both *E* and *Z* isomers of ring-opening products were obtained in Chiba's bimetallic catalytic system.[15a] The ketone excess condition was also applied successfully to synthesize isoquinolines **4aa**−**4ag**, when expensive alkyne substrates **3a**−**3g** were used as ketone substrates to couple with much cheaper acetophenone.

We then extended this three-component reaction to various ketone substrates with heterocycles to afford heterocycle fused pyridine skeletons (Table 3).[16] By utilization of 3-acetyl indole as substrate, γ-carbolines[17] were obtained in high yield. Recently, Jiao et al.[17c] reported a Pd(II)-catalyzed γ-carboline synthesis by using *tert*-butylimines of *N*-substituted indole-3-

Table 3. Substrate Scope of Heterocycle Fused Pyridine Synthesis[a]

entry	ketone **1**	alkyne **3**	product **4**/yield(%)
			
1	**1k**	**3a** (R^3, R^4 = Ph)	**4ka** (90)
2	**1k**	**3b** (R^3, R^4 = *n*-Pr)	**4kb** (87)
3	**1k**	**3c** (R^3 = Me, R^4 = Ph)	**4kc** (82)
			
4	**1l** (X = O)	**3a**	**4la** (42)
5	**1m** (X = S)	**3a**	**4ma** (68)
			
6	**1n**	**3a**	**4na** (65)

[a]Unless otherwise noted, reactions were carried out using **1** (2.0 mmol), **3** (1.1 equiv), and $H_2NOH{\cdot}HCl$ (1.1 equiv) with $[Cp^*RhCl_2]_2$ (1.0 mol %) and KOAc (2.1 equiv) in 10 mL of MeOH at 60 °C for 18 h.

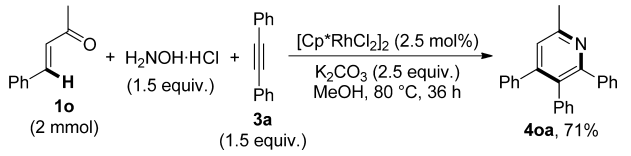
carboxaldehydes and alkynes as coupling partners. However, this approach needs additional steps for substrate synthesis and stoichiometric external oxidant for annulation. The present one-pot approach affords a rapid avenue to multisubstituted γ-carbolines from readily available building blocks. Similar to the above isoquinoline synthesis, symmetric internal alkynes with aryl or alkyl groups reacted well to afford desired γ-carbolines and unsymmetrical alkyne **1c** proceeded regioselectiviely to give **4kc** in good yield. The other isomer, though detected in thin layer chromatography and GC−MS, was too little to be isolated. The structure of **4kc** was unambiguously identified by HMBC and X-ray analysis (see the Supporting Information). Notably, the N−H bond of indole, which needs protection in Jiao's γ-carbolines system[17c] and is reactive in some Cp*Rh(III) catalyzed systems,[18] did not hinder the C−H activation process in our work. For ketones with oxygen- or sulfur-containing heterocycles, cyclization also proceeded smoothly to afford furo[2,3-*c*]pyridine **4la**, thieno[2,3-*c*]pyridine **4ma**, and benzofuro[2,3-*c*]pyridine **4na**.

With a general catalytic system for fused pyridines in hand, we wonder if this one-pot strategy could be expanded to pyridine synthesis.[19] (*E*)-4-Phenylbut-3-en-2-one (**1o**) was employed as ketone substrate to react with $H_2NOH{\cdot}HCl$ and alkyne **3a** under our standard $[Cp^*RhCl_2]_2$/KOAc catalytic system. However, corresponding pyridine **4oa** was obtained in very low yield (<10%). Neither elevating the reaction temperature to 80 °C nor replacing the base with CsOAc gave much favor to improve the yield. Fortunately, we found that the reaction proceed smoothly with an acceptable yield (71%) by using K_2CO_3 as the base under 80 °C, with higher catalyst loading and prolonged reaction time (Scheme 2). Although the yield was lower than that of Chiba and Li's pyridine synthesis[19c] from the oxime of **1o** (86% for **4oa**), a higher step economic procedure was achieved.

As discussed above, ketones with bulky R^2 groups carried out the annulation with lower efficiency than that of aryl methyl

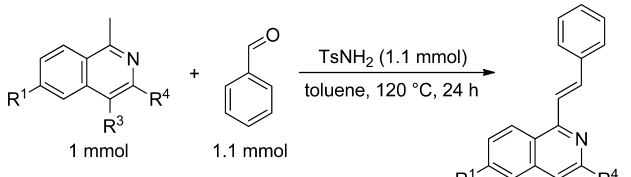
dx.doi.org/10.1021/jo3010414 | J. Org. Chem. 2012, 77, 5794−5800

Scheme 2. One-Pot Synthesis of Pyridine



ketones. We therefore sought routes to derivatize the 1-methyl isoquinolines to more complex structures. Recently, Wang et al.[20] revealed that 2-methyl quinolines can conduct addition to *N*-sulfonyl aldimines and subsequent elimination to form corresponding *trans*-alkenylazaarene under catalyst-free conditions. They also revealed that the addition−elimination processes can carry out in a one-pot procedure. Considering the similar reactivity of methyl group in 2-position of quinoline and 1-position of isoquinoline, we suggested the similar derivatization can take place for 1-methyl isoquinolines. Thus, we applied this method to some 1-methyl isoquinolines synthesized above. As expected, isoquinoline substrates **4aa**, **4ba**, and **4ac** all reacted well to obtain corresponding *trans*-alkenyl isoquinolines with highly stereoselectivity (Scheme 3).

Scheme 3. Derivatization of 1-Methyl Isoquinolines



4aa (R^1 = H, R^3, R^4 = Ph), **5a** (83%)
4ba (R^1 = Me, R^3, R^4 = Ph), **5b** (86%)
4ac (R^1 = H, R^3 = Me, R^4 = Ph), **5c** (81%)

Notably, methyl group substituted at 6-position (**4ba**) or 4-position (**4ac**) of the isoquinoline was inactive in this reaction. The highly regioselectivity was due to the nitrogen-assisted concerted process as indicated by Wang.[20] Also, stronger acidity of methyl group in the 1-position made contribution to the regioselectivity.

In summary, we have developed a versatile and straightforward route to construct multisubstituted isoquinolines and relative fused pyridine heterocycles by using readily available ketones and alkynes. The reaction proceeds efficiently via cascade reaction involving ketone−hydroxylamine condensation, C−H activation, and intermolecular cyclization in a "one-pot" and "external-oxidant-free" approach under mild conditions.

EXPERIMENTAL SECTION

General Methods. All organic starting materials are analytically pure and used without further purification. All reactions were carried out without any particular precautions to extrude moisture or oxygen. Nuclear magnetic resonance (NMR) spectra were recorded using $CDCl_3$ or DMSO-d_6 as solvent at 298 K. ^{1}H NMR (300 or 600 MHz) chemical shifts (δ) were referenced to internal standard TMS (for ^{1}H, δ = 0.00 ppm). ^{13}C NMR (75 or 150 MHz) chemical shifts were referenced to internal solvent $CDCl_3$ (for ^{13}C, δ = 77.16 ppm) or DMSO-d_6 (for ^{13}C, δ = 40.45 ppm). Gas chromatography (GC) analyses were performed on a GC instrument (capillary 25 m column). Mass spectra (MS) were obtained on a low-resolution GC−MS spectrometer with a PEG-25M column, and HRMS (ESI) experiments were performed on a high resolution magnetic sector mass spectrometer. The melting points were uncorrected. $[Cp^*RhCl_2]_2$ was prepared following a literature procedure.[21] Alkynes **1f** and **1g** were prepared by reported procedures with slight modification.[22]

Typical Experimental Procedure for Synthesis of 4. To a 25 mL tube equipped with a magnetic stirrer, 1,2-diphenylacetylene (392.1 mg, 2.2 mmol), hydroxylamine hydrochloride (152.8 mg, 2.2 mmol), $[Cp^*RhCl_2]_2$ (12.4 mg, 0.02 mmol), KOAc (412.2 mg, 4.2 mmol), acetophenone (240.4 mg, 2.0 mmol), and MeOH (10 mL) were added sequentially. The tube was sealed and stirred at 60 °C in an oil bath for 18 h. After removal of the solvent under reduced pressure, purification was performed by flash column chromatography on silica gel with petroleum ether/ethyl acetate (gradient mixture ratio from 100:0 to 75:25) as eluant to afford isoquinoline **4aa** (500.8 mg, 85%).

*1-Methyl-3,4-diphenylisoquinoline (**4aa**).*[6b] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14−8.11 (1H, m), 7.65−7.62 (1H, m), 7.52−7.49 (2H, m), 7.39−7.36 (2H, m), 7.31−7.28 (3H, m), 7.21−7.10 (5H, m), 3.04 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 149.4, 141.0, 137.6, 136.0, 131.4, 130.2, 129.9, 129.1, 128.2, 127.6, 127.1, 126.9, 126.5, 126.2, 126.1, 125.5, 22.8; GC−MS *m*/*z* (% rel. inten.) 295 (M^+, 53), 294 (100), 252 (19), 146 (14), 139 (10).

*1-Methyl-3,4-dipropylisoquinoline (**4ab**).*[6b] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (1H, d, *J* = 8.3 Hz), 7.93 (1H, d, *J* = 8.6 Hz), 7.63−7.58 (1H, m), 7.47−7.42 (1H, m), 2.99−2.88 (7H, m), 1.86−1.60 (4H, m), 1.10−1.02 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 151.7, 135.4, 129.4, 126.2, 126.1, 126.0, 125.2, 123.6, 37.5, 29.8, 24.2, 23.8, 22.4, 14.6, 14.4; GC−MS *m*/*z* (% rel. inten.) 227 (M^+, 49), 226 (43), 212 (79), 199 (42), 198 (100), 184 (50), 182 (35), 171(61), 157 (14), 128 (23), 115 (17).

*1,4-Dimethyl-3-phenylisoquinoline (**4ac**).*[6b] White solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (1H, d, *J* = 8.2 Hz), 7.98 (1H, d, *J* = 8.2 Hz), 7.69−7.66 (1H, m), 7.57−7.52 (3H, m), 7.46−7.43 (2H, m), 7.37−7.35 (1H, m), 2.95 (3H, s), 2.56 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.9, 150.7, 141.7, 136.2, 129.9, 129.8, 128.1, 127.4, 126.2, 126.2, 126.0, 124.1, 122.1, 22.5, 15.4; GC−MS *m*/*z* (% rel. inten.) 233 (M^+, 47), 232 (100), 217 (9), 189 (5), 115 (14), 109 (8).

*4-Ethyl-1-methyl-3-phenylisoquinoline (**4ad**).*[6b] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (1H, d, *J* = 8.2 Hz), 8.04 (1H, d, *J* = 8.6 Hz), 7.70−7.65 (1H, m), 7.56−7.34 (6H, m), 3.01−2.95 (5H, m), 1.24 (3H, t, *J* = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 150.8, 141.9, 135.2, 129.8, 129.2, 128.5, 128.2, 127.4, 126.7, 126.3, 126.2, 124.1, 22.5, 21.7, 15.7; GC−MS *m*/*z* (% rel. inten.) 247 (M^+, 54), 246 (100), 232 (20), 231 (23), 230 (15), 217 (9), 189 (5), 115 (18).

*(1-Methyl-3-phenylisoquinolin-4-yl)methanol (**4ae**).*[8c] White solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (1H, d, *J* = 8.3 Hz), 8.23 (1H, d, *J* = 7.9 Hz), 7.86−7.65 (4H, m), 7.50−7.45 (3H, m), 5.36 (1H, br s), 4.84 (2H, d, *J* = 3.8 Hz), 2.92 (3H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.3, 151.2, 141.4, 136.6, 131.1, 130.7, 128.7, 128.6, 127.7, 126.8, 126.8, 126.0, 125.9, 58.6, 23.3; GC−MS *m*/*z* (% rel. inten.) 249 (M^+, 91), 248 (100), 230 (20), 220 (31), 172 (16), 143 (10), 115 (27), 102 (10), 77 (12).

*3,4-Bis(4-methoxyphenyl)-1-methylisoquinoline (**4af**).*[15b] Pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10−8.06 (1H, m), 7.67−7.64 (1H, m), 7.51−7.43 (2H, m), 7.34 (2H, d, *J* = 8.9 Hz), 7.11 (2H, d, *J* = 8.6 Hz), 6.87 (2H, d, *J* = 8.6 Hz), 6.73 (2H, d, *J* = 8.9 Hz), 3.75 (3H, s), 3.68 (3H, s), 3.01 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 158.5, 157.2, 149.0, 136.3, 133.6, 132.3, 131.5, 129.8, 129.7, 128.1, 126.1, 126.0, 125.9, 125.4, 113.7, 113.1, 55.1, 55.0, 22.7; GC−MS *m*/*z* (% rel. inten.) 355 (M^+, 81), 354 (100), 311 (19), 268 (12), 170 (9), 156 (10), 124 (11).

*3,4-Bis(4-chlorophenyl)-1-methylisoquinoline (**4ag**).*[15b] Pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18−8.14 (1H, m), 7.58−7.55 (3H, m), 7.33−7.27 (4H, m), 7.18−7.10 (4H, m), 3.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 148.2, 139.3, 135.9, 135.8, 133.5, 133.3, 132.7, 131.6, 130.3, 128.8, 128.0 (overlapped), 127.0, 126.3, 125.9, 125.7, 22.8; GC−MS *m*/*z* (% rel. inten.) 365 (M^+, 40), 364 (76), 363 (57), 362 (100), 327 (20), 164 (15), 146 (45), 125 (15).

*1,6-Dimethyl-3,4-diphenylisoquinoline (**4ba**).*[6b] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (1H, d, *J* = 8.6 Hz), 7.40−7.25 (7H, m), 7.20−7.08 (5H, m), 3.00 (3H, s), 2.35 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 149.5, 141.2, 140.1, 137.7, 136.2, 131.4, 130.2,

dx.doi.org/10.1021/jo3010414 | J. Org. Chem. 2012, 77, 5794−5800

128.7, 128.6, 128.1, 127.5, 127.0, 126.8, 125.4, 125.0, 124.5, 22.7, 22.1; GC−MS *m*/*z* (% rel. inten.) 309 (M^+, 54), 308 (100), 252 (15), 146 (17), 139 (9).

*1-Methyl-6-methoxy-3,4-diphenylisoquinoline (**4ca**).*[6b] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (1H, d, J = 9.3 Hz), 7.36−7.27 (5H, m), 7.22−7.12 (6H, m), 6.90 (1H, d, J = 2.7 Hz), 3.68 (s, 3 H), 3.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 157.0, 150.2, 141.3, 138.1, 138.0, 131.4, 130.3, 128.6, 128.3, 127.6, 127.5, 127.1, 126.9, 121.9, 118.7, 104.5, 55.2, 22.7; GC−MS *m*/*z* (% rel. inten.) 325 (M^+, 54), 324 (100), 281 (29), 155 (11), 146 (8), 139 (11).

*6-Chloro-1-methyl-3,4-diphenylisoquinoline (**4da**).*[6b] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (1H, d, J = 8.9 Hz), 7.62 (1H, d, J = 1.7 Hz), 7.44 (1H, dd, J = 8.6, 1.7 Hz), 7.37−7.30 (5H, m), 7.19−7.15 (5H, m), 3.00 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 150.6, 140.6, 137.1, 136.9, 136.3, 131.3, 130.2, 128.4 (overlapped), 127.6, 127.4, 127.4, 127.3, 127.2, 125.0, 124.4, 22.7; GC−MS *m*/*z* (% rel. inten.) 331 (M^+, 16), 330 (39), 329 (50), 328 (100), 293 (10), 252 (20), 146 (30), 139 (13).

*6-Bromo-1-methyl-3,4-diphenylisoquinoline (**4ea**).*[15b] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (1H, d, J = 8.8 Hz), 7.80 (1H, d, J = 2.0 Hz), 7.59 (1H, dd, J = 8.8, 2.0 Hz), 7.36−7.29 (5H, m), 7.19−7.14 (5H, m), 3.01 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ157.8, 150.6, 140.6, 137.4, 136.8, 131.3, 130.3, 130.0, 128.5, 128.4, 128.3, 127.7, 127.5, 127.3, 127.2, 125.1, 124.6, 22.7; GC−MS *m*/*z* (% rel. inten.) 375 (M^+, 47), 374 (100), 373 (52), 372 (96), 293 (25), 292 (25), 252 (21), 146 (46), 139 (22).

*1-Methyl-6-nitro-3,4-diphenylisoquinoline (**4fa**).*[6b] Yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (1H, d, J = 1.7 Hz), 8.30−8.22 (2H, m), 7.41−7.35 (5H, m), 7.24−7.16 (5H, m), 3.09 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 151.5, 148.1, 139.9, 136.0, 135.7, 131.2, 130.3, 130.2, 128.7, 128.0, 127.7, 127.7, 127.6, 127.5, 122.5, 119.8, 22.9; GC−MS *m*/*z* (% rel. inten.) 340 (M^+, 69), 339 (100), 293 (53), 292 (41), 281 (14), 189 (13), 146 (25), 139 (24).

*1-Ethyl-3,4-diphenylisoquinoline (**4ga**).*[15b] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18−8.15 (1H, m), 7.65−7.61 (1H, m), 7.49−7.39 (4H, m), 7.28−7.11 (8H, m), 3.41 (2H, q, J = 7.6 Hz), 1.51 (3H, t, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 149.3, 141.2, 137.8, 136.3, 131.4, 130.4, 129.7, 128.9, 128.2, 127.6, 127.1, 126.9, 126.4, 126.4, 125.3, 125.1, 28.8, 13.9; GC−MS *m*/*z* (% rel. inten.) 309 (M^+, 55), 308 (100), 293 (13), 280 (10), 146 (10), 139 (10).

*1-Isopropyl-3,4-diphenylisoquinoline (**4ha**).*[15a] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27−8.22 (1H, m), 7.67−7.62 (1H, m), 7.49−7.45 (4H, m), 7.34−7.09 (8H, m), 4.00 (1H, septet, J = 6.5 Hz), 1.53 (6H, d, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ165.0, 148.7, 141.4, 138.2, 136.6, 131.5, 130.7, 129.5, 128.5, 128.4, 127.5, 127.2, 127.0, 126.6, 126.4, 124.9, 124.6, 31.4, 22.4; GC−MS *m*/*z* (% rel. inten.) 323 (M^+, 75), 322 (86), 308 (64), 306 (23), 296 (23), 295 (100), 280 (27), 252 (13), 202 (16), 153 (16), 146 (17), 139 (18).

*1-Cyclohexyl-3,4-diphenylisoquinoline (**4ia**).* White solid: mp 158−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26−8.23 (1H, m), 7.65−7.62 (1H, m), 7.50−7.43 (4H, m), 7.35−7.10 (8H, m), 3.67−3.57 (1H, m), 2.10−1.78 (7H, m), 1.63−1.32 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 148.8, 141.4, 138.2, 136.6, 131.5, 130.7, 129.4, 128.4 (overlapped), 127.5, 127.2, 126.9, 126.6, 126.3, 124.9, 124.6, 41.9, 32.7, 27.0, 26.4; GC−MS *m*/*z* (% rel. inten.) 363 (M^+, 45), 362 (44), 334 (11), 309 (28), 308 (100), 296 (17), 295 (76), 280 (10), 152 (12), 146 (11), 139 (8) ; HRMS (ESI) calcd for $C_{27}H_{26}N$ $[M + H]^+$ 364.2060, found 364.2065.

*1-Cyclopropyl-3,4-diphenylisoquinoline (**4ja**).*[15a] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43−8.40 (1H, m), 7.65−7.60 (1H, m), 7.52−7.45 (2H, m), 7.40−7.36 (2H, m), 7.32−7.10 (8H, m), 2.82−2.73 (1H, m), 1.42−1.37 (2H, m), 1.12−1.06 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 148.8, 141.3, 138.1, 136.2, 131.5, 130.5, 129.7, 128.4, 128.1, 127.4, 127.2, 126.9, 126.4, 126.3 (overlapped), 124.9, 13.7, 9.6; GC−MS *m*/*z* (% rel. inten.) 321 (M^+, 75), 320 (100), 243 (12), 152 (13), 146 (11), 139 (8).

*1-Methyl-3,4-diphenyl-5H-pyrido[4,3-b]indole (**4ka**).* White solid: mp 185−187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (1H, s), 8.12 (1H, d, J = 7.6 Hz), 7.40−7.18 (10H, m), 7.12−7.10 (3H, m), 3.07 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 151.5, 143.9, 140.5, 139.7, 136.2, 130.4, 130.3, 128.9, 127.6 (overlapped), 127.4, 127.1, 126.0, 122.6, 122.3, 120.7, 117.0, 111.0, 23.7; GC−MS *m*/*z* (% rel. inten.) 334 (M^+, 58), 333 (100), 318 (8), 291 (8), 167 (20), 166 (14), 159 (11); HRMS (ESI) calcd for $C_{24}H_{19}N_2$ $[M + H]^+$ 335.1543, found 335.1541.

*1-Methyl-3,4-dipropyl-5H-pyrido[4,3-b]indole (**4kb**).* White solid: mp 206−208 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (1H, br s), 8.08 (1H, d, J = 7.9 Hz), 7.48−7.38 (2H, m), 7.31−7.25 (1H, m), 2.99 (3H, s), 2.93−2.83 (4H, m), 1.85−1.63 (4H, m), 1.02−0.97 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 150.2, 144.6, 139.7, 125.7, 123.2, 122.2, 120.6, 116.4, 115.2, 111.0, 36.8, 29.5, 24.4, 23.4, 23.3, 14.5 (overlapped); GC−MS *m*/*z* (% rel. inten.) 266 (M^+, 39), 251 (64), 238 (22), 223 (40), 221 (29), 210 (100), 196 (12), 167 (11), 105 (23); HRMS (ESI) calcd for $C_{18}H_{23}N_2$ $[M + H]^+$ 267.1856, found 267.1863.

*1,4-Dimethyl-3-phenyl-5H-pyrido[4,3-b]indole (**4kc**).* White solid: mp 315−316 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.73 (1H, s), 8.14 (1H, d, J = 7.9 Hz), 7.66−7.61 (3H, m), 7.52−7.38 (4H, m), 7.30 (1H, t, J = 7.6 Hz), 2.95 (3H, s), 2.54 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5, 150.1, 145.7, 142.0, 141.1, 130.6, 128.6, 128.0, 126.6, 122.8, 122.7, 120.9, 116.6, 112.2, 111.5, 24.2, 15.0; GC−MS *m*/*z* (% rel. inten.) 272 (M^+, 51), 271 (100), 255 (8), 135 (16), 128 (10); HRMS (ESI) calcd for $C_{19}H_{17}N_2$ $[M + H]^+$ 273.1386, found 273.1385.

*7-Methyl-4,5-diphenylfuro[2,3-c]pyridine (**4la**).*[6b] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (1H, d, J = 2.4), 7.37−7.17 (10H, m), 6.68 (1H, d, J = 2.4), 2.84 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 149.7, 147.9, 141.4, 140.6, 137.7, 134.3, 130.4, 130.2, 128.4, 127.8, 127.1, 127.1, 126.8, 106.5, 18.8; GC−MS *m*/*z* (% rel. inten.) 285 (M^+, 48), 284 (100), 241 (9), 215 (10), 213 (10), 142 (12), 127 (9).

*7-Methyl-4,5-diphenylthieno[2,3-c]pyridine (**4ma**).*[6b] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, dd, J = 5.5, 0.7), 7.37−7.17 (11H, m), 2.90 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 151.1, 145.8, 140.6, 138.4, 134.3, 131.0, 130.7, 130.4, 128.4 (overlapped), 127.8, 127.2, 127.2, 124.4, 23.8; GC−MS *m*/*z* (% rel. inten.) 301 (M^+, 54), 300 (100), 285 (4), 258 (16), 150 (11), 149 (9).

*1-Methyl-3,4-diphenylbenzofuro[2,3-c]pyridine (**4na**).*[15b] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (1H, d, J = 8.3 Hz), 7.50−7.44 (1H, m), 7.39−7.29 (7H, m), 7.23−7.18 (3H, m), 7.13−7.09 (2H, m), 2.93 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 150.6, 150.3, 141.9, 140.4, 137.3, 130.3, 130.3, 129.8, 129.3, 128.7 (overlapped), 128.3, 127.8, 127.1, 123.5, 123.2, 122.9, 112.3, 19.0; GC−MS *m*/*z* (% rel. inten.) 335 (M^+, 56), 334 (100), 263 (11), 167 (10), 152 (12).

*6-Methyl-2,3,4-triphenylpyridine (**4oa**).*[19c] White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.14 (9H, m), 7.08−6.97 (5H, m), 6.87−6.83 (2H, m), 2.68 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 157.0, 150.0, 141.1, 139.8, 138.0, 131.7, 131.6, 130.0, 129.4, 127.9, 127.7 (overlapped), 127.3, 127.3, 126.5, 123.3, 24.6; GC−MS *m*/*z* (% rel. inten.) 321 (M^+, 47), 320 (100), 304 (5), 215 (5), 159 (8), 152 (18), 146 (4), 139 (4).

Typical Experimental Procedure for Synthesis of 5. To a 25 mL tube equipped with a magnetic stirrer, **4aa** (295.4 mg, 1.0 mmol), *p*-toluenesulfonamide (188.3 mg, 1.1 mmol), benzaldehyde (116.7 mg, 1.1 mmol), and toluene (2 mL) were added sequentially. The tube was charged with N_2, sealed, and stirred at 120 °C in an oil bath for 24 h. After removal of the solvent under reduced pressure, purification was performed by flash column chromatography on silica gel with petroleum as eluant to afford **5a** (317.0 mg, 83%).

*(E)-3,4-Diphenyl-1-styrylisoquinoline (**5a**).*[8c] Yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42−8.39 (1H, m), 8.17−8.03 (2H, m), 7.70−7.64 (3H, m), 7.57−7.45 (4H, m), 7.40−7.15 (11H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 149.9, 141.2, 137.9, 137.2, 136.9, 136.2, 131.5, 130.6, 129.9, 129.9, 128.8, 128.6, 128.4, 127.6, 127.6, 127.3, 127.2, 126.7, 126.4, 125.5, 124.4, 123.0; GC−MS *m*/*z* (% rel. inten.) 383 (M^+, 100), 382 (63), 306 (17), 304 (13), 277 (7), 183 (10), 182 (9), 176 (8).

*(E)-6-Methyl-3,4-diphenyl-1-styrylisoquinoline (**5b**).* Yellow solid: mp 186−188 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (1H, d, J = 8.6

dx.doi.org/10.1021/jo3010414 | J. Org. Chem. 2012, 77, 5794−5800

Hz), 8.11 (1H, d, J = 15.5 Hz), 8.05 (1H, d, J = 15.5 Hz), 7.72−7.69 (2H, m), 7.46−7.18 (15H, m), 2.42 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 150.1, 141.4, 140.2, 138.1, 137.3, 137.2, 136.0, 131.6, 130.7, 129.5, 129.0, 128.8, 128.5, 128.4, 127.6 (overlapped), 127.3, 127.1, 125.2, 124.3, 124.0, 123.3, 22.3; GC−MS m/z (% rel. inten.) 397 (M^+, 100), 396 (52), 382 (24), 320 (13), 277 (8), 190 (9), 189 (8), 183 (10), 176 (7); HRMS (ESI) calcd for $C_{30}H_{24}N$ $[M + H]^+$ 398.1903, found 398.1905.

*(E)-4-Methyl-3-phenyl-1-styrylisoquinoline (**5c**).* Yellow solid: mp 102−104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (1H, d, J = 8.3 Hz), 8.02−7.91 (3H, m), 7.68−7.59 (5H, m), 7.53−7.44 (3H, m), 7.41−7.30 (3H, m), 7.27−7.22 (1H, m), 2.58 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 151.2, 141.7, 137.2, 136.9, 135.4, 130.3, 129.7, 128.7, 128.3, 128.0, 127.7, 127.6, 127.4, 126.4, 125.3, 124.8, 124.2, 123.2, 123.1, 15.9; GC−MS m/z (% rel. inten.) 321 (M^+, 100), 320 (74), 244 (25), 152 (14), 146 (10), 139 (8); HRMS (ESI) calcd for $C_{24}H_{20}N$ $[M + H]^+$ 322.1590, found 322.1592.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of all products, HMBC spectrum and X-ray structural details of **4kc**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ruimao@mail.tsinghua.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project was supported by the National Natural Science Foundation of China (21032004, 20972084) and the Bilateral Scientific Cooperation between Tsinghua University & K. U. Leuven. The authors thank Miss Yuan Chen, from Liaoning Normal University, for her kind English proofreading.

■ REFERENCES

(1) (a) Joule, J. A.; Mills, K., *Heterocyclic Chemistry*, 5th ed.; Wiley-Blackwell: West Sussex, United Kingdom, 2010. (b) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications*, 2nd ed.; Wiley-VCH GmbH & Co. KGaA: Weinheim, Germany, 2003. (c) Croisy-Delcey, M.; Croisy, A.; Carrez, D.; Huel, C.; Chiaroni, A.; Ducrot, P.; Bisagni, E.; Jin, L.; Leclercq, G. *Bioorg. Med. Chem.* **2000**, *8*, 2629. (d) van Muilwijk-Koezen, J. E.; Timmerman, H.; van der Goot, H.; Menge, W. M. P. B.; Frijtag von Drabbe Künzel, J.; de Groote, M.; IJzerman, A. P. *J. Med. Chem.* **2000**, *43*, 2227. (e) Reux, B.; Nevalainen, T.; Raitio, K. H.; Koskinen, A. M. P. *Bioorg. Med. Chem.* **2009**, *17*, 4441. (f) Chen, Y.; Sajjad, M.; Wang, Y.; Batt, C.; Nabi, H. A.; Pandey, R. K. *ACS Med. Chem. Lett.* **2011**, *2*, 136.

(2) (a) Chen, C.; Li, X.; Schreiber, S.-L. *J. Am. Chem. Soc.* **2003**, *125*, 10174. (b) Lim, C. W.; Tissot, O.; Mattison, A.; Hooper, M. W.; Brown, J. M.; Cowley, A. R.; Hulmes, D. I.; Blacker, A. J. *Org. Process Res. Dev.* **2003**, *7*, 379. (c) Su, Y. J.; Huang, H. L.; Li, C. L.; Chien, C. H.; Tao, Y. T.; Chou, P. T.; Datta, S.; Liu, R. S. *Adv. Mater.* **2003**, *15*, 884. (d) Durola, F.; Sauvage, J.-P.; Wenger, O. S. *Chem. Commun.* **2006**, 171.

(3) Li, J.-J.; Corey, E. J. *Name Reactions in Heterocyclic Chemistry*; John Wiley & Sons. Inc.: Hoboken, NJ, 2005, pp 375.

(4) For reviews, see: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (c) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937. For intramolecular cyclization examples, see: (d) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437. (e) Niu, Y.-N.; Yan, Z.-Y.; Gao, G.-L.; Wang, H.-L.; Shu, X.-Z.; Ji, K.-G.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 2893. (f) Yu, X.; Wu, J. *J. Comb. Chem.* **2009**, *11*, 895. (g) Gao, H.; Zhang, J. *Adv. Synth. Catal.* **2009**, *351*, 85. For intermolecular cyclization examples, see: (h) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (i) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042. (j) Korivi, R. P.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 5179.

(5) For reviews, see: (a) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874. (b) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (e) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (f) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814.

(6) (a) Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759. (b) Parthasarathy, K.; Cheng, C.-H. *J. Org. Chem.* **2009**, *74*, 9359.

(7) For Rh(III)-catalyzed isoquinoline syntheses using $Cu(OAc)_2$ as external oxidants, see: (a) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141. (b) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050.

(8) For a highlight, see: (a) Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1977. For selected examples, see: (b) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (c) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (d) Zhang, X.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A.; Li, X. *Adv. Synth. Catal.* **2011**, *353*, 719. (e) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (f) Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, DOI: 10.1002/anie.201201273.

(9) For a monograph, see: (a) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. For reviews, see: (b) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. (c) D'Souza, D. M.; Mueller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095. (d) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083.

(10) (a) Huang, Q.; Hua, R. *Adv. Synth. Catal.* **2007**, *349*, 849. (b) Qi, C.; Zheng, Q.; Hua, R. *Tetrahedron* **2009**, *65*, 1316. (c) Wu, B.; Hua, R. *Tetrahedron Lett.* **2010**, *51*, 6433. (d) Su, J.; Ju, J.; Hua, R. *Curr. Org. Synth.* **2012**, *9*, 273.

(11) Acyl group itself can also serve as a directing group for Rh(III)-catalyzed C−H activation; see: (a) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064. (b) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 4169. (c) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2154. (d) Schröder, N; Wencel-Delord, J; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298. Though aryl ketones can coupled with alkenes and alkynes in the above works, high temperature (120 °C or higher) was needed. In our mild conditions, even if the acyl group can chelate Rh, the ketone−hydroxylamine condensation proceeds relatively faster and the resulting oxime is a more effective ligand. In fact, no ketone−alkyne coupled product was detected for each entry in GC−MS.

(12) Jayakumar, J.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 197.

(13) CsOAc is very sensitive to moisture.

(14) The inactive oxime isomer could not transform to the other isomer under our standard condition.

(15) (a) Too, P. C.; Chua, S. H.; Wong, S. H.; Chiba, S. *J. Org. Chem.* **2011**, *76*, 6159. (b) Wang, Y.-F.; Toh, K. K.; Lee, J.-Y.; Chiba, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 5927.

(16) For recent examples, see: (a) Huang, Z.; Hu, Y.; Zhou, Y.; Shi, D. *ACS Comb. Sci.* **2011**, *13*, 45. (b) Yang, D.; Burugupalli, S.; Daniel, D.; Chen, Y. *J. Org. Chem.* **2012**, *77*, 4466.

(17) (a) Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, 3, 3083. (b) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9318. (c) Ding, S.; Shi, Z.; Cui, Y.; Jiao, N. *Org. Lett.* **2010**, *12*, 1540.

(18) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068.

(19) For Rh-catalyzed pyridine syntheses from α,β-unsaturated ketoximes and alkynes, see: (a) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, *10*, 325. (b) Hyster, T. K.; Rovis, T.

Chem. Commun. **2011**, *47*, 11846. (c) Too, P. C.; Noji, T.; Lim, Y. J.; Li, X.; Chiba, S. *Synlett* **2011**, 2789. (d) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2012**, *77*, 2501.

(20) Yan, Y.; Xu, K.; Fang, Y.; Wang, Z. *J. Org. Chem.* **2011**, *76*, 6849.

(21) Fujita, K; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 2785.

(22) Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 3199. The reactions were conducted in 5 mmol scale (based on iodobenzenes) in MeCN, with reduced dose of catalyst and base (1 mol % $PdCl_2(PPh_3)_2$, 2 mol % CuI, and 3.0 equiv of DBU).