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C−H Activation Guided by Aromatic N−H Ketimines: Synthesis of Functionalized Isoquinolines Using Benzyl Azides and Alkynes

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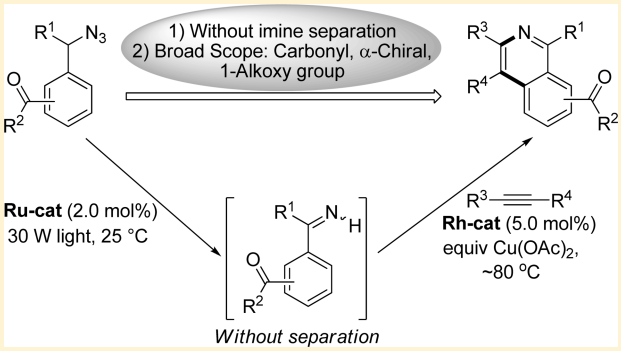
Supporting Information

ABSTRACT: Aromatic N−H ketimines were in situ generated from various benzylic azides by ruthenium catalysis for the subsequent Rh-catalyzed annulation reaction with alkynes to give the corresponding isoquinolines. In contrast to conventional synthetic methods for aromatic N−H ketimines, our protocol works under mild and neutral conditions, which enabled the synthesis of isoquinolines having various functionalities such as carbonyl, ester, alkenyl, and ether groups. In addition, the imidates generated from α-azido ethers were successfully used for the synthesis of 1-alkoxyisoquinolines.



INTRODUCTION

Metal catalyzed C−H bond activation guided by a directing group is one of the most attractive tools in organic synthesis.[1] Recently, chelation-assisted electrophilic metalation of an *ortho* C(sp^2)−H bond directed by the lone pair of a nitrogen atom offers an advanced route for the construction of azacyclic compounds.[2] Among the numerous nitrogen-containing directing groups, *N*-substituted aromatic imines have been widely employed for the synthesis of various heteroaromatic compounds.[1b,d,2] However, the substituents of the imines are usually removed in the final step to give neutral products.[3] In the viewpoint of atom economy, *N*-unsubstituted imines (N−H imines) would be more desirable over *N*-substituted ones. Recently, several reports by Miura,[4a] Glorius,[4b] Wang,[4c] Zhao,[4d,e] and Cramer[4f] have shown the unique utility and promising importance of N−H imines by using Rh-, Mn-, and Ru-catalysts for C−H bond activation and consequent annulation with alkynes, carbenes and allenes (Scheme 1). However, the significance of their work is limited by the demonstrated scope of N−H imines, which are simple and relatively stable N−H aromatic ketimines prepared by methods using strongly nucleophilic Grignard reagents or alkyllithiums.[5] Thus, alternative synthetic methods for N−H imines having various functional groups are important to extend the utilities of known reactions and to develop new ones.

Recently, we have reported a novel method for the synthesis of N−H imines from alkyl azides by using a diruthenium catalyst (**1**), which were utilized in various reactions under mild conditions.[6] Then we wondered if the seemingly unstable N−H imines can be utilized for the reactions requiring more harsh conditions. To show the versatility of our synthetic protocol for N−H imines, we selected the Rh-catalyzed synthesis of isoquinolines requiring heating and stoichiometric amount of cupric acetate as an oxidant.[7]

Isoquinolines and their derivatives have been recognized as an important class of compounds that are frequently found in numerous bioactive natural products.[8] Even though numerous processes for the synthesis of isoquinolines by imine directed C−H bond activation reactions exist,[7,9] it is hard to find practical ones to construct isoquinolines having important functional groups such as carbonyl,[8d,e] α-chiral[8f] or C-1 alkoxy-functionalities,[8g] despite of the vast prevalence of these functionalities in natural products (Figure 1). In most of the previous processes, *N*-protected imines were prepared from the corresponding carbonyl compounds; it is difficult to construct isoquinolines having carbonyl groups (Scheme 2a).[3,7] Diphenyl N−H ketimine was the sole example tested in the Rh-catalyzed reaction, while diaryl N−H ketimines and aryl *n*-butyl ketimines were tested in the Mn-catalyzed reaction for the synthesis of isoquinolines (Scheme 2b).[4a,c] The recent process using vinyl azides as the precursors of N−H imines showed a broad reaction scope; however, it is difficult to synthesize isoquinolines having a chiral or sp^2 carbon center at the C-1 position (Scheme 2c).[10]

Herein, we wish to report a new cascade synthesis of functionalized isoquinolines from various benzylic azides through Ru-catalyzed transformation into imines and Rh-catalyzed *N*-annulation with alkynes (Scheme 2d). The essential merit of our protocol is a broad scope of applicable benzylic azides, including those having carbonyl groups and α-chiral center. Furthermore, N−H imidates are available with our protocol from the corresponding α-azido ethers and applicable for the Rh-catalyzed annulation reaction with alkynes to give 1-alkoxyisoquinolines.

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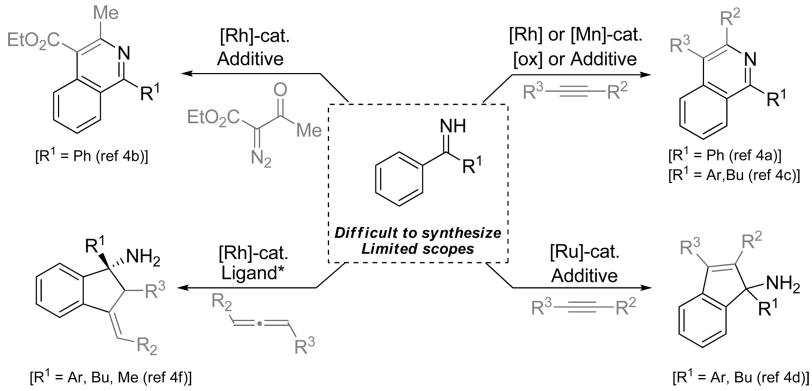
Scheme 1. N−H Imines in C−H Bond Activation Reactions



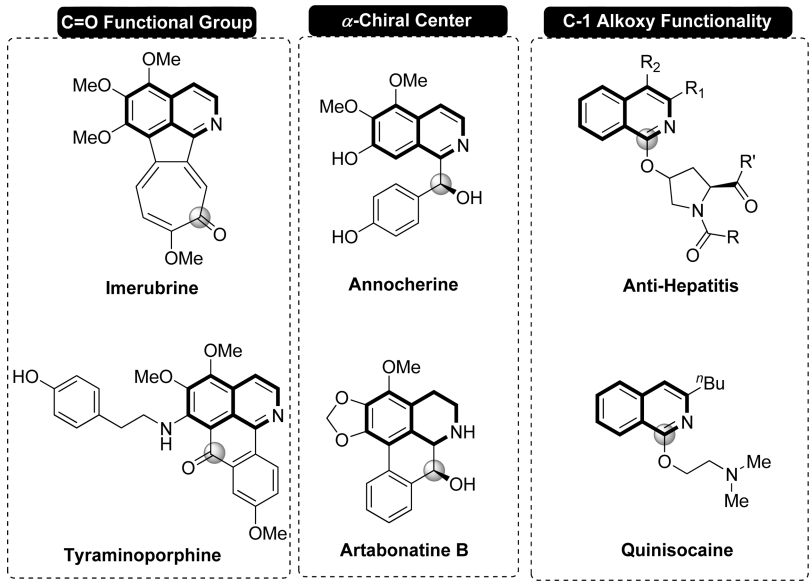
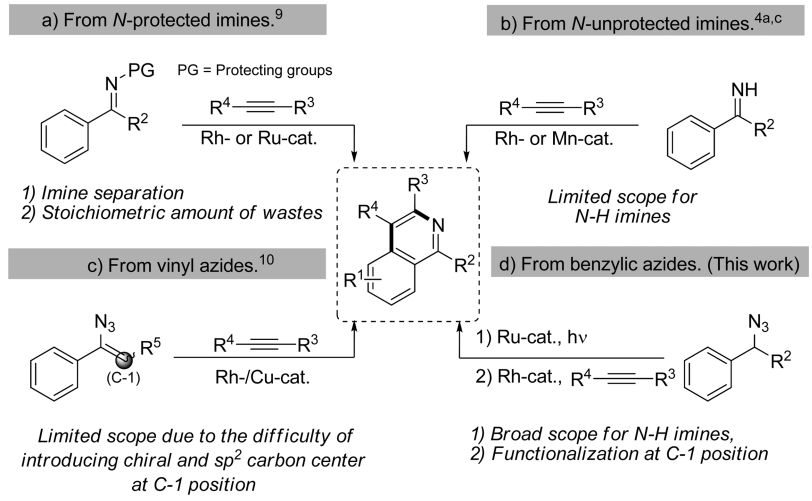


Figure 1. Natural products containing isoquinoline moieties having various functional groups.

Scheme 2. Metal-Catalyzed Synthesis of Isoquinolines by C−H Bond Activation



RESULTS AND DISCUSSION

First, we tested the Rh-catalyzed annulation reaction of 1-phenylethanimine (**4a**) with diphenylacetylene to give 1-methyl-3,4-diphenylisoquinoline (**5a**) (Table 1). A solution of the imine **4a** generated from (1-azidoethyl)benzene (**3a**) in the presence of the diruthenium catalyst **1**, was added to another solution of diphenylacetylene, copper acetate ($Cu(OAc)_2$), and the rhodium catalyst **2** in dimethylformamide (DMF). Copper acetate was essential, and the use of less than 1 equiv (amount of copper acetate was used with respect to diphenylacetylene)

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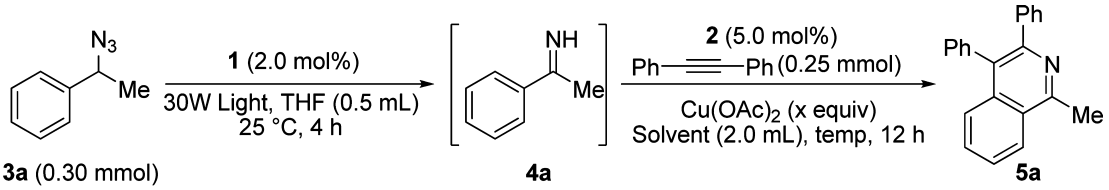
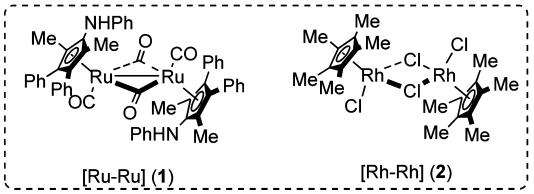
Table 1. Optimization of the Ru/Rh Tandem Catalysis



3a (0.30 mmol) **4a** **5a**



entry	$CuOAc_2$ (equiv)	solvent	temp (°C)	yield (%)[a]
1	–	THF:DMF = 1:4	90	trace
2	0.2	THF:DMF = 1:4	90	43
3	0.5	THF:DMF = 1:4	90	74
4	1.0	THF:DMF = 1:4	90	98
5	1.0	THF:DMF = 1:4	75	95
6	1.0	THF:DMF = 1:4	50	21
7	**1.0**	**THF**	**75**	**95**
8[b]	1.0	THF	75	35
9[c]	1.0	THF	75	90
10[d]	1.0	THF	75	no reaction

[a]Determined by ^{1}H NMR analysis. [b]One-pot one-step reaction. [c]One-pot two-step reaction. [d]Without using catalyst **2**.

lowered the yield of **5a** (entries 1–4). Heating (>75 °C) was needed for a satisfactory yield (entries 5 and 6). For the annulation step, tetrahydrofuran (THF) was also effective, so the use of polar solvent such as DMF was not necessary (entry 7).[11] Fortunately, the activity of **2** in the presence of **1** eliminates the extra step of unstable imine separation, although mixing all the reagents at the beginning of the reaction (one-pot one-step) gave a mixture of unreacted azide and isoquinoline product, strongly suggesting the inhibition of the activity of **1** (entry 8).[12] Notably, **5a** was obtained in about 90% when diphenylacetylene, catalyst **2** and $Cu(OAc)_2$ were added into the same reaction pot containing **4a** (one-pot two-step reaction sequence, entry 9). However, we do believe that two-pot procedure would be more reliable and reproducible as various imines were often susceptible to hydrolysis. No isoquinoline (**5a**) was formed from **4a** by using only catalyst **1** (entry 10).

Under the optimized conditions for the synthesis of isoquinoline **5a**, we explored the scope of this tandem catalytic process (Table 2). The substituent effect of the aromatic ring was not significant on the reaction efficiency; comparable results were obtained from the reactions of an electron-rich (**3b**) and an electron-poor (**3c**) substrates.[10] The C–Br bond in **3c** remained intact during the tandem catalytic process. The reaction with a dialkyl substituted alkyne was proceeded smoothly to give **5d** in 91% yield. The annulation of unsymmetrical alkynes such as 1-phenyl-1-butyne, methyl 3-phenylpropiolate, and 3-phenylprop-2-yn-1-ol were occurred regioselectively to give isoquinolines (**5e–f,h**) in good yields. Notably, (6-chlorohex-1-ynyl)benzene and silyloxy-protected 3-phenylprop-2-yn-1-ol gave **5g** and **5i** as regioisomeric mixtures (regioisomeric ratio of **5g** and **5i** was 92:8 and 95:5, respectively). 1-(1-Azidoethyl)naphthalene (**3j**) was also a successful substrate for the annulation. An azafluoranthene derivative (**5k**), the core structure of which is abundant in many natural products such as triclisine, imelutenine, and rufescine[13] was obtained in 75% yield from 9-azido-9*H*-fluorene. Various substituents such as phenyl, vinyl, alkoxymethyl, and methoxycarbonyl groups could be introduced at the C-1 position of isoquinolines (**5m–p**) in good yields, although the simple isoquinoline **5l** was formed in a poor yield probably due to the low thermal stability of the benzaldimine precursor.

Our catalyst system has turned out to be effective for the synthesis of isoquinolines containing a chiral substituent at the C-1 position, which are essential components in many natural products such as annocherine and artabonatine B.[8f] Previously, isoquinolines having α-hydroxy chiral centers were synthesized by either chiral catalysts[14a] or kinetic resolution;[14b] however, the protocols were limited to specific substrates and gave low yields. In our process, an optically active N–H imine (**7**) was synthesized without any deterioration of optical purity by the ring-opening reaction of (2*S*,3*S*)-2-methyl-3-phenyloxirane (**6**),[15] methoxymethyl ether (MOM) protection of the resulting alcohol, and Ru-catalyzed imine formation (Scheme 3). The subsequent Rh-catalyzed annulation of **7** with diphenylacetylene produced the isoquinoline **8** containing a chiral carbon substituent at the C-1 position.

Another interesting application of our protocol is the synthesis of isoquinolines having carbonyl groups such as **10a** and **10b** (Scheme 4). The corresponding imines were successfully generated from the keto azides **9a** and **9b** by the Ru-catalysis in high yields, and the Rh-catalyzed annulation proceeded with the direction of the resulting imine functionality. Notably, the unsymmetrical keto azide **9b** selectively led to the less sterically hindered regioisomer **10b**.[16]

Recently, amidines and imidoyl halides have been employed for the synthesis of 1-aminoisoquinolines[17a] and 1-haloisoquinolines,[17b] respectively. We envisioned that α-azido ethers, which can be prepared from benzyl ethers by the selective azidation at the benzylic position,[18] are precursors suitable for

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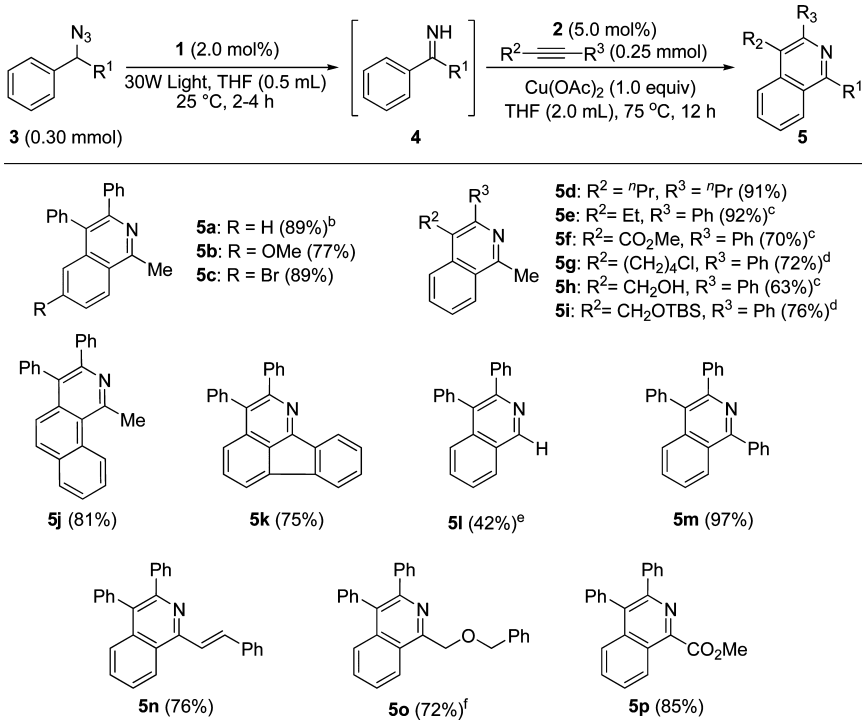
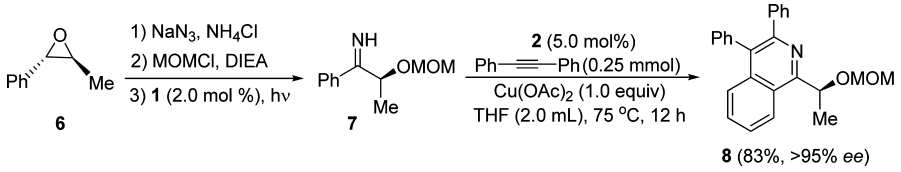
Table 2. Tandem Catalysis for the Synthesis of Isoquinolines[a]



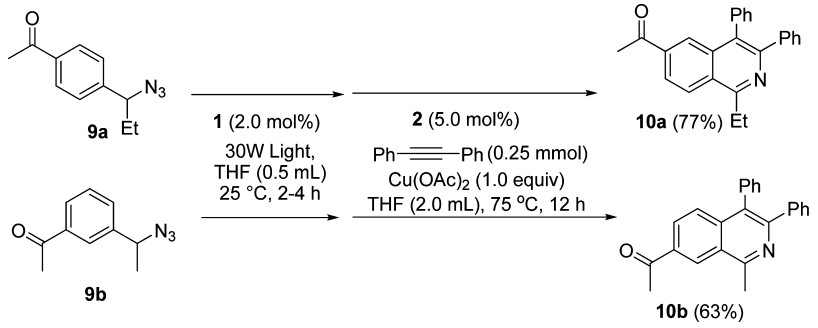
[a]A solution containing azide (**3**, 0.3 mmol), and **1** (2.0 mol %) in THF (0.5 mL) was irradiated by fluorescent light (30 W). After 2−4 h with monitoring the conversion of benzyl azide by TLC, the reaction mixture was transferred to the solution of alkynes (0.25 mmol), **2** (5.0 mol %), and $Cu(OAc)_2$ (1.0 equiv) in THF and then heated for 12 h. [b]Isolated yields were based on the amount of alkynes. [c]Only single regioisomer was obtained. [d]Two regioisomers were obtained (regioisomeric ratio of **5g** and **5i** was 92:8 and 95:5, respectively). [e]2 equiv of **3l** were used. [f]10 mol % of **2** was used.

Scheme 3. Synthesis of an Isoquinoline Containing a Chiral Substituent at the C-1 Position[a]



[a]DIEA = *N*,*N*-diisopropylethylamine.

Scheme 4. Synthesis of Isoquinolines Containing Carbonyl Groups



the synthesis of a wide range of 1-alkoxyisoquinolines. The transformation of azidobenzyl ethers into the corresponding imidates was tested with (azido(ethoxy)methyl)benzene (**11a**); the azidoether in THF-d_8 was illuminated with fluorescent light in the presence of **1** (8.0 mol %) at room temperature for 3 h to give the imidate **12a** in 70% yield along with benzonitrile (27%) and EtOH.[19,20] Having established the chemoselective access to various N−H imidates, we then explored the Rh-catalyzed isoquinoline synthesis (Table 3).[21,22] A solution of an imidate (2.0 equiv) in THF was transferred with a cannula into the flask containing a solution of an alkyne, the rhodium catalyst **2** (5.0 mol %), and $Cu(OAc)_2$ (1.2 equiv of copper acetate was used with respect to alkynes) in THF. 1-Alkoxyisoquinolines were obtained in 50−92% isolated yields with respect to alkynes,

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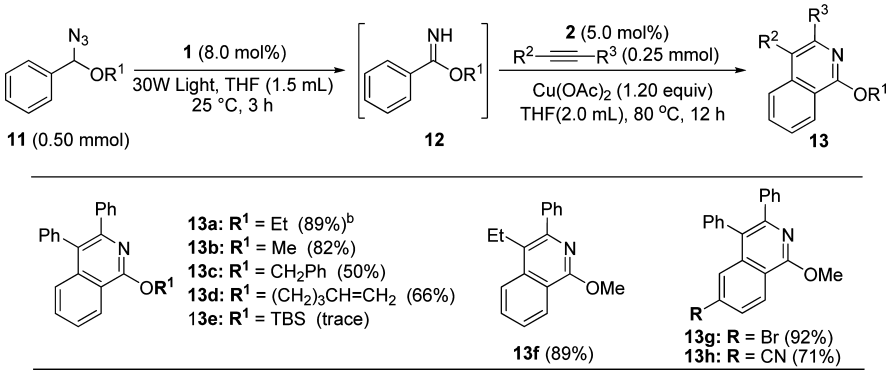
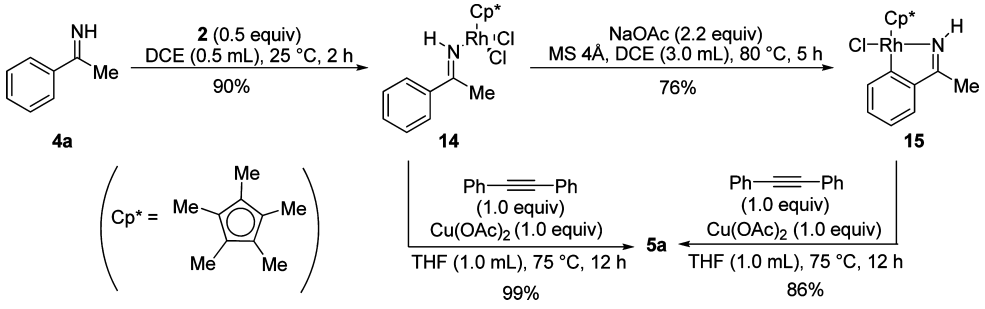
Table 3. Tandem Catalysis for the Synthesis of the 1-Alkoxy Isoquinolines[a]



[a]A solution containing α-azido ether (**11**, 0.5 mmol), and **1** (8.0 mol %) in THF (1.5 mL) was irradiated by fluorescent light (30 W). After 3 h, the reaction mixture was transferred to the solution of alkyne (0.25 mmol), **2** (5.0 mol %), and $Cu(OAc)_2$ (1.2 equiv) in THF and then heated for 12 h. [b]Isolated yield.

Scheme 5. Rhodium Intermediates for the Isoquinoline Formation

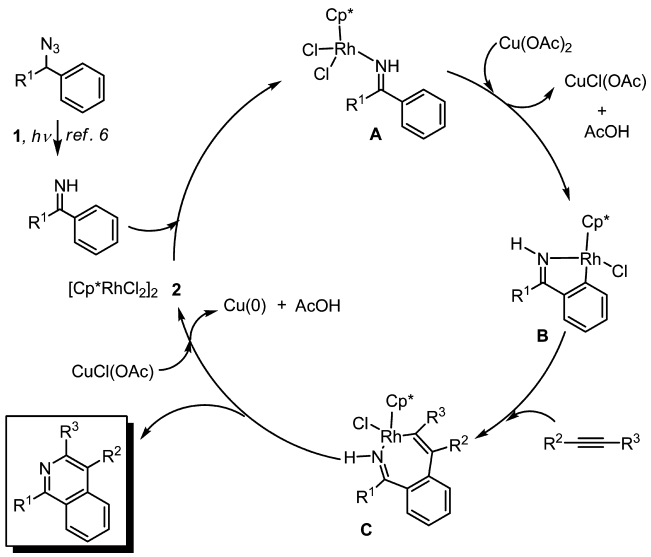


in which the alkoxy substituents contain methyl, ethyl, benzyl, and olefinic groups. However, the attempt to synthesize a siloxy derivative (**13e**) was not successful, although the imidate **12e** was formed in 61% yield. The annulation with unsymmetrical 1-phenyl-1-butyne proceeded regioselectively to give **13f** in 70% isolation yield. The high yield of isoquinoline **13g** was a noticeable result showing the compatibility of aryl bromide moiety with our catalytic system. Another noticeable result is the successful synthesis of **13h** using the corresponding imidate **12h** containing nitrile group, which cannot be afforded by the conventional acid-catalyzed synthesis of imidates using aromatic nitriles and alcohols.[23,24]

Fortunately, for the first time, we succeeded to isolate the N−H imine rhodium complex **14** from the stoichiometric reaction of the ketimine **4a** with the dirhodium complex **2** at room temperature, and the five-membered rhodacycle **15** having N−H moiety by the treatment of **14** with sodium acetate at 80 °C (Scheme 5).[25] Their molecular structures were elucidated by X-ray crystallography.[26] Interestingly, the structure of **14** shows an *anti*-geometry of the rhodium moiety and the phenyl group, which should be rearranged to a *syn*-geometry for the next C−H activation step. The intermediacy of **14** and **15** were confirmed by the formation of isoquinoline **5a** in high yield in the reaction with diphenylacetylene in the presence of cupric acetate.[25]

The reaction pathway for the formation of isoquinolines can be suggested by combining our observations and the previous reports describing the Rh-catalyzed reactions of *N*-substituted imines with alkynes (Scheme 6).[7,27] As we have reported,[6] N−H imines are formed from benzylic azides by the ruthenium catalysis involving the liberation of N_2 and [1,2]-H shift. Then the Rh-catalyzed reaction is initiated by forming the N−H imine

Scheme 6. Reaction Pathway for the Formation of Isoquinolines from Benzylic Azides and Alkynes by Tandem Ru/Rh Catalysis



rhodium complex **A**,[26] which is transformed to the rhodacycle **B** while liberating acetic acid. An alkyne is inserted in the Rh−C bond of **B** to give the seven-membered rhodacycle intermediate **C**.[27] The reductive elimination reaction of **C** gave a 3,4-disubstituted isoquinoline along with a Rh(I) species. The catalytic cycle is completed by the regeneration of the Rh(III) species by the oxidation of the Rh(I) species with Cu(II) species.

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CONCLUSION

In summary, we demonstrated the utility of N−H imines and N−H imidates under conditions requiring heating and stoichiometric amounts of oxidant for the synthesis of various isoquinolines, including those containing carbonyl groups on the aromatic ring and chiral substituents and alkoxy groups at the C-1 position. The N−H imines were generated under mild and neutral conditions from benzyl azides by a Ru-catalysis and utilized in the tandem Rh-catalyzed annulation with internal alkynes. Our demonstration will stimulate the use of N−H imines and the development of new reactions employing functional N−H imines.

EXPERIMENTAL SECTION

General Information. All solvents were purified according to the standard methods before use. Synthesis of isoquinolines was performed in a flame-dried Schlenk flask under argon atmosphere. Syntheses of *N*-unsubstituted ketimines and imidates were performed using NMR tubes equipped with J-Young valves (5 mm, 400 MHz). Flash column chromatography was carried out on silica gel (230−400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on 300 or 600 MHz spectrometers. ^{1}H NMR spectra were referenced to residual peaks of $CDCl_3$ (7.26 ppm), THF-d_8 (3.58 ppm), CD_2Cl_2 (5.32 ppm) and reported as follows; chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet). Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.23 ppm), THF-d_8 (67.57 ppm) and CD_2Cl_2 (54.00 ppm). 2D NMR spectra (COESY and NOESY) were recorded on a 600 MHz spectrometer. Mass spectral data were obtained by high resolution mass spectrometer. Infrared spectra were recorded neat as thin films. All X-ray data were collected using a diffractometer equipped with a Mo X-ray tube. Collected data were corrected for absorption with SADABS based upon the Laue symmetry by using equivalent reflections. All calculations were carried out with SHELXTL programs. Ruthenium catalyst **1** was synthesized according to the literature procedure.[12] $[RhCp^*Cl_2]_2$ (**2**), anhydrous $Cu(OAc)_2$, (1*S*,2*S*)-(−)-1-phenylpropylene oxide, (*R*)-(−)-α-methoxyphenyl acetic acid, alcohols, halides, epoxides and ketones were purchased from commercial sources.

Synthesis and Characterization of Internal Alkynes. Diphenylacetylene, oct-4-yne, but-1-ynylbenzene and 3-phenylprop-2-yn-1-ol were purchased from commercial sources. *tert*-Butyldimethyl(3-phenylprop-2-ynyloxy)silane,[28a] methyl 3-phenylpropiolate[28b] and (6-chlorohex-1-ynyl)benzene[28c] were prepared according to the literature procedures.

Synthesis and Characterization of Benzylic Azides. **3a−c**, **3j−n**, and **3p** were prepared according to the literature procedures.[29] New azides **3o**, ((1*R*,2*S*)-1-azido-2-(methoxymethoxy)propyl)benzene, **9a** and **9b** were prepared by following procedures.

*Synthesis of (1-Azido-2-(benzyloxy)ethyl)benzene (**3o**).* 2-Azido-2-phenylethanol was synthesized according to the literature procedure.[29g] To a solution of 2-azido-2-phenylethanol (0.32 g, 2.0 mmol) and benzyl bromide (0.48 mL, 4.0 mmol) in dry THF (10 mL), NaH (0.10 g, 2.6 mmol) was added portion wise at 0 °C. After being stirred for 12 h at room temperature, the reaction was quenched by addition of saturated aqueous NH_4Cl solution at 0 °C. Then the crude products were extracted with EtOAc (25 mL × 3), and the combined organic layer was dried over anhydrous Na_2SO_4 and filtered through the glass filter. The filtrate was concentrated at reduced pressure, and the resulting residue was purified by column chromatography over silica-gel (*n*-hexane/EtOAc) to give **3o** as a colorless oil (Yield: 0.39 g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (d, J = 6.3 Hz, 2H), 4.65 (dd, J = 19.2, 12.1 Hz, 2H), 4.80 (t, J = 6.4 Hz, 1H), 7.34−7.44 (m, 10H); ^{13}C NMR (75 MHz, CDCl3) δ 65.4, 73.5, 74.2, 127.1, 127.7, 127.9, 128.5, 128.6, 128.8, 136.8, 137.8; IR (NaCl) ν cm^{-1} 1605, 1617, 1646, 1953, 2099, 2502, 2861, 2906, 3032, 3065, 3089; HRMS (FAB) m/z calcd for $C_{15}H_{16}N_3O$ $[M + H]^+$ 254.1293, found 254.1290.

Synthesis of ((1R,2S)-1-Azido-2-(methoxymethoxy)propyl)-benzene. (1*R*,2*S*)-1-Azido-1-phenylpropane-2-ol was prepared according to literature procedure.[15] ((1*R*,2*S*)-1-Azido-2-(methoxymethoxy)-propyl)benzene was synthesized from (1*R*,2*S*)-1-azido-1-phenylpropane-2-ol according to modified literature procedure.[29h] To a solution of (1*R*,2*S*)-1-azido-1-phenylpropane-2-ol (0.27 mg, 1.5 mmol) and DIEA (0.79 mL, 4.5 mmol) in dry CH_2Cl_2 (5.0 mL), MOMCl (0.34 mL, 4.5 mmol) was added dropwise at 0 °C. After being stirred for 12h at room temperature, the reaction was quenched by addition of saturated aqueous NH_4Cl solution at 0 °C. Then the crude products were extracted with CH_2Cl_2 (25 mL × 3) and the combined organic layer was dried over anhydrous Na_2SO_4 and filtered through a glass filter. The filtrate was concentrated at reduced pressure, and the resulting residue was purified by column chromatography over silica-gel (*n*-hexane/Et_2O) to give pale yellow oil (Yield: 0.32 g, 95%): DIEA = *N*,*N*-diisopropylethylamine, MOMCl = chloromethyl methyl ether; $[\alpha]_D^{20}$ −116.5 (*c* 0.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (d, J = 6.3 Hz, 3H), 3.24 (s, 3H), 3.88−3.96 (m, 1H), 4.55 (d, J = 6.8 Hz, 1H), 4.60 (d, J = 5.2, 1H), 4.64 (d, J = 6.8, 1H), 7.30−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.0, 55.6, 69.9, 76.3, 95.4, 127.8, 128.3, 128.7, 137.1; IR (NaCl) ν cm^{-1} 919, 1033, 1104, 1154, 1216, 1254, 1289, 1349, 1381, 1401, 1453, 1586, 1604, 1953, 2104, 2779, 2824, 2844, 2891, 2935, 3032, 3065; HRMS (FAB) m/z calcd for $C_{11}H_{16}N_3O_2$ $[M + H]^+$ 222.1243, found 222.1241.

*Synthesis of 1-(4-(1-Azidopropyl)phenyl)ethanone (**9a**).* A solution of 1-(4-propylphenyl)ethanone (1.6 g, 10 mmol), NBS (2.3 g, 13 mmol), and benzoyl peroxide (0.24 g, 0.10 mmol) in carbon tetrachloride (30 mL) was stirred at 60 °C for 12 h. After being cooled down to room temperature, the reaction mixture was filtered through a silica-pad, and concentrated at reduced pressure. The resulting residue and NaN_3 (1.3 g, 20 mmol) were dissolved in DMF (30 mL), and the solution was stirred at 60 °C for 12 h. The reaction mixture was diluted with water (25 mL), and crude products were extracted with EtOAc (30 mL × 3). The combined organic layer was washed with H_2O (25 mL) and brine (25 mL), dried over anhydrous $MgSO_4$, and filtered through a glass filter. The filtrate was concentrated, and the resulting residue was purified by column chromatography over silica-gel (*n*-hexane/CH_2Cl_2) to give **9a** as a pale yellow liquid (Yield: 1.24 g, 61%): NBS = *N*-bromosuccinimide, DMF = *N*,*N*-dimethylformamide; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 3H), 1.72−1.92 (m, 2H), 2.61 (s, 3H), 4.43 (t, J = 7.0 Hz, 1H), 7.38−7.41 (m, 2H), 7.95−7.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.7, 26.8, 29.5, 67.4, 127.2, 129.0, 137.0, 145.1, 197.7; IR (NaCl) ν cm^{-1} 1268, 1306, 1360, 1414, 1463, 1507, 1574, 1609, 1651, 1681, 2098, 2480, 2879, 2937, 2972, 3058, 3353; HRMS (EI) m/z calcd for $C_{11}H_{13}N_3O$ [M] 203.1059, found 203.1057.

*Synthesis of 1-(3-(1-Azidoethyl)phenyl)ethanone (**9b**).* To a solution of 3-acetyl-α-methylbenzyl alcohol[29i] (0.82 mL, 5.0 mmol) in dry toluene (15 mL), DPPA (1.3 mL, 6.0 mmol) was added slowly at 0 °C under argon atmosphere. After being stirred for 10 min, DBU (0.90 mL, 6.0 mmol) was added dropwise at 0 °C over 15 min. After being stirred at room temperature for 12 h, the reaction mixture was diluted with H_2O (25 mL), and crude products were extracted with CH_2Cl_2 (30 mL × 3). The combined organic layer was washed with H_2O (25 mL) and brine (25 mL), dried over anhydrous $MgSO_4$, and filtered through a glass filter. The filtrate was concentrated, and the resulting residue was purified by column chromatography over silica-gel (*n*-hexane/CH_2Cl_2) to give **9b** as colorless oil (Yield: 0.57 g, 62%): DPPA = diphenylphosphoryl azide, DBU = 1,8-Diazabicycloundec-7-ene; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (d, J = 6.8 Hz, 3H), 2.62 (s, 3H), 4.70 (q, J = 4.8 Hz, 1H), 7.46−7.56 (m, 2H), 7.88−7.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 26.6, 60.6, 126.0, 128.1, 129.1, 130.9, 137.5, 141.6, 197.7; IR (NaCl) ν cm^{-1} 1259, 1359, 1378, 1436, 1488, 1587, 1603, 1686, 2103, 2480, 2932, 2981, 3067, 3441; HRMS (EI) m/z calcd for $C_{10}H_{11}N_3O$ [M] 189.0902, found 189.0901.

General Procedure for the Synthesis of Isoquinolines Using Benzylic Azides and Alkynes. In a Schlenk flask, **3** (0.30 mmol), **1** (6.3 mg, 2.0 mol %), and dry THF (0.50 mL) were charged under argon atmosphere. The reaction mixture was stirred for 2−4 h at room temperature under 30 W fluorescent light. The complete conversion was monitored by TLC. Then the reaction mixture in flask 1 was transferred to another flask containing alkyne (0.25 mmol), **2** (7.7 mg, 5.0 mol %), and $Cu(OAc)_2$ (46 mg, 0.25 mmol) through a cannula and THF (2.0 mL) was added. The reaction mixture was stirred at 75 °C for 12 h, and filtered through a silica gel pad. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by column

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chromatography over silica-gel (*n*-hexane/EtOAc or CH_2Cl_2) to give corresponding isoquinolines.

*1-Methyl-3,4-diphenylisoquinoline (**5a**).*[10] White solid (Yield: 66 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (s, 3H), 7.13−7.25 (m, 5H), 7.29−7.39 (m, 5H), 7.57−7.61 (m, 2H), 7.63−7.68 (m, 1H), 8.16−8.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 125.7, 126.3, 126.4, 126.6, 127.1, 127.2, 127.7, 128.3, 129.3, 130.0, 130.4, 131.5, 136.1, 137.7, 141.2, 149.6, 157.9.

*6-Methoxy-1-methyl-3,4-diphenylisoquinoline (**5b**).*[10] White solid (Yield: 63 mg, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01 (s, 3H), 3.72 (s, 3H), 6.91 (d, J = 2.4 Hz, 1H), 7.14−7.25 (m, 6H), 7.29−7.36 (m, 5H), 8.10 (d, J = 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 55.4, 104.6, 118.8, 122.0, 127.0, 127.2, 127.6, 127.7, 128.4, 128.7, 130.4, 131.5, 138.0, 138.2, 141.4, 150.3, 157.2, 160.7.

*6-Bromo-1-methyl-3,4-diphenylisoquinoline (**5c**).*[10] White solid (Yield: 83 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04 (s, 3H), 7.17−7.21 (m, 5H), 7.31−7.38 (m, 5H), 7.66 (dd, J = 1.8, 8.9 Hz, 1H), 7.80 (d, J = 1.8 Hz, 1H), 8.05 (d, J = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 124.8, 125.2, 127.3, 127.5, 127.6, 127.8, 128.5, 128.6, 130.2, 130.4, 131.5, 137.0, 137.6, 140.8, 150.8, 157.9.

*1-Methyl-3,4-dipropylisoquinoline (**5d**).*[10] White solid (Yield: 52 mg, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (t, J = 7.3 Hz, 3H), 1.11 (t, J = 7.3 Hz, 3H), 1.63−1.74 (m, 2H), 1.75−1.87 (m, 2H), 2.90−3.02 (m, 7H), 7.51 (ddd, J = 8.8, 6.7, 1.1 Hz, 1H), 7.66 (ddd, J = 8.7, 6.8, 1.2 Hz, 1H), 7.98 (d, J = 8.5 Hz, 1H), 8.09 (dd, J = 8.4, 0.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 14.8, 22.5, 24.0, 30.0, 37.6, 123.7, 125.4, 126.20, 126.29, 126.3, 129.5, 135.6, 151.8, 155.8.

*4-Ethyl-1-methyl-3-phenylisoquinoline (**5e**).*[3c] White solid (Yield: 57 mg, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.4 Hz, 3H), 2.97 (s, 3H), 2.99 (q, J = 7.5 Hz, 2H), 7.38−7.54 (m, 5H), 7.58 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.72 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.9, 21.8, 22.7, 124.3, 126.3, 126.5, 126.9, 127.6, 128.3, 128.7, 129.4, 130.0, 135.3, 142.1, 150.9, 156.0.

*Methyl 1-methyl-3-phenylisoquinoline-4-carboxylate (**5f**).*[10] White solid (Yield: 48 mg, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04(s, 3H), 3.73 (s, 3H), 7.37−7.49 (m, 3H), 7.60−7.65 (m, 1H), 7.70−7.77 (m, 3H), 8.00 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 52.6, 121.9, 124.9, 125.8, 126.0, 127.5, 128.6, 128.8, 131.3, 133.5, 140.5, 149.9, 160.4, 169.7.

*4-(4-Chlorobutyl)-1-methyl-3-phenylisoquinoline (**5g**).*[3c] Yellow liquid (Yield: 58 mg, 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ (Major isomer) 1.69−1.81 (m, 4H), 2.96−3.01 (m, 5H), 3.41 (t, J = 6.2 Hz, 2H), 7.39−7.51 (m, 5H), 7.55−7.61 (m, 1H), 7.70−7.75 (m, 1H), 8.04 (d, J = 8.4 Hz, 1H), 8.15 (dd, J = 8.4, 0.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (Major isomer) 22.6, 27.6, 28.2, 32.4, 44.5, 124.1, 126.43, 126.46, 126.5, 126.7, 127.6, 128.3, 129.3, 130.1, 135.3, 141.8, 151.2, 156.2; ^{1}H NMR (300 MHz, $CDCl_3$) δ (Minor isomer) 1.69−1.81 (m, 4H), 2.96−3.01 (m, 5H), 3.39 (t, J = 6.2 Hz, 2H), 7.39−7.51 (m, 5H), 7.55−7.61 (m, 1H), 7.70−7.75 (m, 1H), 8.08−8.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (Minor isomer) 22.6, 27.5, 29.8, 34.7, 44.9, 125.4, 125.6, 126.0, 126.5, 126.7, 127.6, 128.6, 129.8, 130.4, 136.1, 137.7, 150.7, 157.6. [Note: major and minor isomers were obtained as inseparable mixture in 92:8 ratio.]

*(1-Methyl-3-phenylisoquinoline-4-yl)methanol (**5h**).*[9b] Yellow solid (Yield: 39 mg, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (t, J = 4.8 Hz, 1H), 2.99 (s, 3H), 4.99 (d, J = 4.7 Hz, 2H), 7.40−7.49 (m, 3H), 7.60−7.66 (m, 3H), 7.75−7.80 (m, 1H), 8.18 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 59.6, 124.3, 124.6, 126.3, 126.9, 128.1, 128.4, 129.8 (overlapped), 130.7, 135.9, 140.6, 151.9, 158.8.

*4-((tert-Butyldimethylsilyloxy)methyl)-1-methyl-3-phenylisoquinoline (**5i**).*[9b] Pale yellow solid (Yield: 69 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ (Major isomer) 0.09 (s, 6H), 0.92 (s, 9H), 3.01 (s, 3H), 5.00 (s, 2H), 7.42−7.50 (m, 3H), 7.58−7.63 (m, 1H), 7.70−7.78 (m, 3H), 8.17 (d, J = 8.5 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (Major isomer) −5.11, 18.5, 22.9, 26.0, 60.3, 124.6, 125.1, 126.0, 126.6, 126.8, 128.0, 128.2, 130.1, 136.4, 140.8, 151.6, 158.4. [Note: major and minor isomers were obtained as inseparable mixture in 95:5 ratio.]

*1-Methyl-3,4-diphenylbenzo[h]isoquinoline (**5j**).*[10] White solid (Yield: 50 mg, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.43 (s, 3H), 7.17−7.26 (m, 5H), 7.32−7.44 (m, 5H), 7.54 (d, J = 9.1 Hz, 1H), 7.61−7.66 (m, 1H), 7.69−7.73 (m, 1H), 7.90 (dd, J = 1.4, 7.7 Hz, 1H), 8.89 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.7, 124.1, 124.4, 126.8, 127.0, 127.3, 127.4, 127.5, 127.8, 128.4, 128.9, 129.8, 130.4 (overlapped), 131.3, 131.8, 133.1, 137.4, 138.2, 140.8, 151.1, 155.6.

*2,3-Diphenylindeno[1,2,3-ij]isoquinoline (**5k**).* Pale yellow solid (Yield: 67 mg, 75%): mp 174−176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.28 (m, 5H), 7.31−7.35 (m, 3H), 7.41−7.47 (m, 4H), 7.55 (dd, J = 8.4, 0.4 Hz, 1H), 7.64 (dd, J = 8.4, 6.4 Hz, 1H), 7.79−7.85 (m, 2H), 8.16−8.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.6, 122.1, 122.7, 125.6, 125.7, 127.3, 127.4, 127.9, 128.2, 128.8, 130.0, 130.1, 130.8, 131.6, 132.7, 133.1, 137.2, 137.5, 139.3, 140.8, 141.5, 154.3, 160.2; IR (NaCl) ν cm^{-1} 3057, 3027, 1950, 1882, 1811, 1619, 1583, 1568, 1497, 1476, 1427, 1367; HRMS (EI) m/z calcd for $C_{27}H_{17}N$ [M] 355.1361, found 355.1362.

*3,4-Diphenylisoquinoline (**5l**).*[30] White solid (Yield: 30 mg, 42%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17−7.25 (m, 5H), 7.33−7.39 (m, 5H), 7.60−7.69 (m, 3H), 8.03−8.06 (m, 1H), 9.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.8, 127.0, 127.2, 127.54, 127.59, 127.7, 127.8, 128.5, 130.4, 130.7, 130.8, 131.4, 136.1, 137.4, 140.9, 150.8, 151.9.

*1,3,4-Triphenylisoquinoline (**5m**).*[3c] White solid (Yield: 87 mg, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15−7.21 (m, 3H), 7.28−7.31 (m, 2H), 7.34−7.44 (m, 5H), 7.47−7.60 (m, 5H), 7.71 (d, J = 8.2 Hz, 1H), 7.82 (dd, J = 8.3, 1.6 Hz, 2H), 8.18 (d, J = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.6, 126.2, 126.7, 127.1, 127.4, 127.7 (overlapped), 128.5 (overlapped), 128.7, 129.9, 130.1, 130.4, 130.6, 131.5, 137.1, 137.7, 140.0, 141.1, 149.8, 160.0.

*(E)-3,4-Diphenyl-1-styrylisoquinoline (**5n**).*[9b] White solid (Yield: 73 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19−7.27 (m, 5H), 7.32−7.48 (m, 8H), 7.56−7.62 (m, 2H), 7.67−7.73 (m, 3H), 8.08 (d, J = 15.5 Hz, 1H), 8.15 (d, J = 15.6 Hz, 1H), 8.42−8.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.1, 124.5, 125.6, 125.5, 126.8, 127.2, 127.4, 127.71, 127.74, 128.5, 128.7, 128.9, 130.01, 130.07, 130.7, 131.6, 136.3, 137.0, 137.3, 137.9, 141.3, 150.0, 153.6.

*1-(Benzyloxymethyl)-3,4-diphenylisoquinoline (**5o**).* White solid (Yield: 72 mg, 72%): mp 91−93 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.72 (s, 2H), 5.26 (s, 2H), 7.17−7.23 (m, 5H), 7.29−7.40 (m, 10H), 7.56−7.61 (m, 2H), 7.63−7.67 (m, 1H), 8.42−8.47 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.1, 73.8, 126.0, 126.2, 126.3, 127.0, 127.2, 127.4, 127.8, 127.9, 128.2, 128.4, 128.5, 130.2, 130.5, 131.2, 131.4, 136.8, 137.5, 138.2, 140.9, 149.3, 156.3; IR (NaCl) ν cm^{-1} 1029, 1073, 1099, 1156, 1179, 1265, 1347, 1373, 1448, 1504, 1554, 1571, 1614, 1735, 1952, 2856, 2924, 3030, 3060; HRMS (FAB) m/z calcd for $C_{29}H_{24}NO$ $[M + H]^+$ 402.1858, found 402.1859.

*Methyl-3,4-diphenylisoquinoline-1-carboxylate (**5p**).*[9b] White solid (Yield: 72 mg, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (s, 3H), 7.17−7.25 (m, 5H), 7.36−7.39 (m, 5H), 7.62−7.73 (m, 3H), 8.71−8.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.2, 125.3, 126.2, 126.3, 127.6, 127.90, 127.93, 128.1, 128.5, 130.6, 130.7, 131.2, 134.0, 137.0, 137.2, 140.1, 148.6, 149.8, 166.9.

*(S)-1-(1-(Methoxymethoxy)ethyl)-3,4-diphenylisoquinoline (**8**).* White solid (Yield: 77 mg, 83%, >95% ee): mp 84−86 °C; $[\alpha]_D^{20}$ −83.7 (*c* 0.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (d, J = 6.9 Hz, 3H), 3.40 (s, 3H), 4.80 (d, J = 6.7 Hz, 1H), 4.76 (d, J = 6.7 Hz, 1H), 6.15−7.23 (m, 5H), 7.33−7.39 (m, 5H), 7.54−7.59 (m, 2H), 7.65−7.69 (m, 1H), 8.66−8.69 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 76.3, 95.4, 124.9, 125.6, 126.5, 126.6, 127.1, 127.4, 127.7, 128.42, 128.49, 129.9, 130.4, 130.6, 131.4, 131.5, 137.2, 137.7, 140.9, 149.1, 159.8; IR (NaCl) ν cm^{-1} 979, 993, 1033, 1099, 1119, 1155, 1213, 1265, 1343, 1375, 1445, 1505, 1553, 1602, 1614, 1951, 2776, 2822, 2887, 2931, 2980, 3027, 3057; HRMS (EI) m/z calcd for $C_{25}H_{23}NO_2$ [M] 369.1729, found 369.1730.

Determination of the Optical Purity of 8. The optical purity of **8** was determined by ^{1}H NMR spectroscopy after converting to the corresponding (*R*)-methoxyphenylacetic acid (MPA) ester derivative of 1-(3,4-diphenylisoquinoline-1yl)ethanol. Deprotection of methoxymethyl ether (MOM) moiety from **8** gave (*S*)-1-(3,4-diphenylisoquinoline-1yl)ethanol. The deprotection was carried out by the following procedure:[31] $BF_3{\cdot}Et_2O$ (0.14 mL, 0.55 mmol) was added dropwise to a solution of **8** (67 mg, 0.18 mmol) in dimethyl sulfide (3.5 mL) at 0 °C and the mixture was stirred for 6 h at room temperature. The reaction mixture was quenched by the saturated aqueous solution of $NaHCO_3$.

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The resulting mixture was washed with water and brine, and the organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified by column chromatography (silica gel column; *n*-hexane/Et_2O) to give 1-(3,4-diphenylisoquinoline-1yl)ethanol (Yield: 53 mg, 89%):[10] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (d, J = 6.4 Hz, 3H), 5.55 (d, J = 6.4 Hz, 1H), 5.64−5.73 (m, 1H), 7.20−7.30 (m, 5H), 7.35−7.41 (m, 5H), 7.59−7.65 (m, 2H), 7.69−7.74 (m, 1H), 8.09−8.14 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 66.1, 123.5, 124.2, 126.9, 127.0, 127.5, 127.6, 127.8, 128.5, 128.6, 130.5, 131.51, 131.57, 137.0, 137.4, 140.5, 147.9, 161.1. Then, in a dry round-bottom flask (10 mL), 1-(3,4-diphenylisoquinoline-1yl)ethanol (17 mg, 0.05 mmol), (*R*)-2-methoxy-2-phenylacetic acid (11 mg, 0.07 mmol), DCC (14 mg, 0.07 mmol), and DMPA (3.0 mg, 0.03 mmol) were added under argon atmosphere, and dissolved in dry dichloromethane (1.0 mL). The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was washed with water and brine, and the organic layer was dried over anhydrous Na_2SO_4. Then the crude product was purified by column chromatography (*n*-hexane/Et_2O) to the MPA ester as white gum (Yield: 21 mg, 89%, >95 ee): DCC = *N*,*N*′-Dicyclohexylcarbodiimide; DMAP = *N*,*N*′-Dimethylaminopyridine; $[\alpha]_D^{20}$ −60.8 (*c* 0.01, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (Major isomer) 1.76 (d, J = 6.5 Hz, 3H), 3.37 (s, 3H), 4.86 (s, 1H), 6.79 (q, J = 6.5 Hz, 1H), 7.16−7.25 (m, 8H), 7.31−7.39 (m, 8H), 7.45−7.50 (m, 2H), 8.14 (d, J = 7.8 Hz, 1H); ^{1}H NMR (300 MHz, $CDCl_3$) δ (Minor isomer) 1.90 (d, J = 6.5 Hz, 3H), 3.42 (s, 3H), 4.84 (s, 1H), 6.77 (q, J = 6.5 Hz, 1H), 7.16−7.25 (m, 8H), 7.31−7.39 (m, 8H), 7.45−7.50 (m, 2H), 7.87 (d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (Major + Minor) 19.1. 57.5, 72.0, 82.8, 124.4, 124.7, 126.7, 127.0, 127.2.127.5, 127.6, 127.7, 128.5, 128.6, 128.7, 128.8, 130.0, 130.5, 130.6, 130.9, 131.3, 131.5, 136.3, 137.0, 137.6, 140.8, 148.9, 156.5, 170.5; IR (NaCl) ν cm^{-1} 1005, 1031, 1076, 1116, 1286, 1338, 1364, 1376, 1413, 1445, 1504, 1556, 1613, 2851, 2924, 2991, 3060, 3369; HRMS (EI) m/z calcd for $C_{32}H_{27}NO_3$ [M] 473.1991, found 473.1993.

*1-(1-Ethyl-3,4-diphenylisoquinolin-6-yl)ethanone (**10a**).* White solid (Yield: 68 mg, 77%): mp 116−118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (t, J = 7.5 Hz, 3H), 2.52 (s, 3H), 3.45 (q, J = 7.5 Hz, 2H), 7.18−7.26 (m, 5H), 7.35−7.41 (m, 5H), 8.10 (dd, J = 8.7, 1.7 Hz, 1H), 8.26 (d, J = 1.2 Hz, 1H), 8.30 (d, J = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 26.8, 29.0, 124.6, 125.9, 126.9, 127.4, 127.7, 127.8, 128.4, 128.7, 130.0, 130.5, 131.5, 136.2, 137.1, 137.6, 140.8, 150.5, 162.4, 198.1; IR (NaCl) ν cm^{-1} 1370, 1384, 1413, 1446, 1496, 1549, 1572, 1601, 1688, 1729, 2854, 2874, 2932, 2971, 3029, 3058, 3084; HRMS (EI) m/z calcd for $C_{25}H_{21}NO$ [M] 351.1623, found 351.1624.

*1-(1-Methyl-3,4-diphenylisoquinolin-7-yl)ethanone (**10b**).* White solid (Yield: 53 mg, 63%): mp 200−202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.76 (s, 3H), 3.15 (s, 3H), 7.19−7.23 (m, 5H), 7.35−7.39 (m, 5H), 7.86 (d, J = 8.8 Hz, 1H), 8.10 (dd, J = 8.8, 1.7 Hz, 1H), 8.81 (d, J = 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 26.9, 125.6, 127.0, 127.4, 127.5, 127.6, 127.9, 128.2, 128.6, 129.3, 130.4, 131.4, 134.9, 137.2, 138.6, 140.6, 151.9, 159.5, 197.5; IR (NaCl) ν cm^{-1} 1389, 1421, 1485, 1506, 1556, 1582, 1611, 1681, 1734, 1811, 1819, 1881, 1891, 1947, 1959, 2921, 2957, 3027, 3056, 3084; HRMS (EI) m/z calcd for $C_{24}H_{19}NO$ [M] 337.1467, found 337.1465.

Synthesis and Characterization of Azidoethers. Azidoethers **11a−c** were prepared according to the literature procedures.[18] Unknown azidoethers including **11d, 11e, 11g**, and **11h** were prepared by following procedure.[18a] To solution of benzyl ether (5.0 mmol) and $PhI(OAc)_2$ (4.2 g, 13 mmol) in dry acetonitrile (38 mL), $TMSN_3$ (1.7 mL, 13 mmol) was added dropwise over 20 min at 0 °C under argon atmosphere. The reaction mixture was stirred at room temperature for 6 h. Volatiles were removed at reduced pressure, and the resulting residue was purified by column chromatography over silica-gel (*n*-hexane/EtOAc or CH_2Cl_2) to give corresponding azidoethers. $PhI(OAc)_2$ = (diacetoxyiodo)benzene, $TMSN_3$ = trimethylsilyl azide.

*(Azido(pent-4-enyloxy)methyl)benzene (**11d**).* Colorless oil (Yield: 0.24 g, 22%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79 (dt, J = 14.3, 6.4 Hz, 2H), 2.20 (q, J = 7.2 Hz, 2H), 3.74 (ddt, J = 84.9, 9.23, 6.3 Hz, 2H), 4.97−5.08 (m, 2H), 5.41 (s, 1H), 5.76−5.90 (m, 1H), 7.36−7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.0, 30.5, 68.6, 92.9, 115.4, 126.4, 128.9, 129.4, 137.5, 138.2; IR (NaCl) ν cm^{-1} 1235, 1288, 1372, 1453, 1494, 1643, 1739, 2105, 2877, 2938; HRMS (EI) m/z calcd for $C_{12}H_{15}N_3O$ [M] 217.1215, found 217.1218.

*(Azido(phenyl)methoxy)(tert-butyl)dimethylsilane (**11e**).* Colorless oil (Yield: 0.57 g, 43%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 3H), 0.23 (s, 3H), 0.96 (s, 9H), 5.70 (s, 1H), 7.35−7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, −4.4, 18.4, 25.8, 86.5, 125.8, 128.7, 129.0, 139.7; IR (NaCl) ν cm^{-1} 1363, 1390, 1408, 1455, 1472, 1494, 1588, 1728, 1951, 2106, 2713, 2742, 2859, 2887, 2931, 2957, 3034, 3067, 3090; HRMS (EI) m/z calcd for $C_{13}H_{21}N_3OSi$ [M] 263.1454, found 263.1453.

*1-(Azido(methoxy)methyl)-4-bromobenzene (**11g**).* Colorless oil (Yield: 0.48 g, 40%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (s, 3H), 5.32 (s, 1H), 7.30−7.34 (m, 2H), 7.51−7.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.4, 93.2, 123.4, 128.0, 131.9, 136.0; IR (NaCl) ν cm^{-1} 1335, 1404, 1486, 1593, 2106, 2833, 2935, 2956, 3001; HRMS (EI) m/z calcd for $C_8H_7BrN_3O$ $[M - H]^+$ 239.9772, found 239.9771.

*1-(Azido(methoxy)methyl)-4-benzonitrile (**11h**).* Colorless oil (Yield: 0.81 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (s, 3H), 5.39 (s, 1H), 7.56−7.58 (m, 2H), 7.69−7.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.6, 92.6, 113.2, 118.5, 127.1, 132.6, 141.8; IR (NaCl) ν cm^{-1} 1282, 1305, 1333, 1409, 1446, 1504, 1574, 1611, 1729, 1933, 2108, 2231, 2837, 2939, 3004, 3064; HRMS (FAB) m/z calcd for $C_9H_9N_4O$ $[M + H]^+$ 189.0776, found 189.0779.

General Procedure for the Synthesis of Isoquinolines Using Azidoethers and Alkynes. In a Schlenk flask, **11** (0.50 mmol), **1** (43 mg, 8.0 mol %), and dry THF (1.0 mL) were charged under argon atmosphere. The reaction mixture was stirred for 3 h at room temperature under 30 W fluorescent light. The complete conversion was monitored by TLC. Then the reaction mixture in flask 1 was transferred to another flask containing alkyne (0.25 mmol), **2** (7.7 mg, 5.0 mol %), and $Cu(OAc)_2$ (55 mg, 0.30 mmol) through a cannula and THF (2 mL) was added. The reaction mixture was stirred at 80 °C for 12 h, and then filtered through a silica gel pad. The filtrate was concentrated at reduced pressure, and the resulting residue was purified by column chromatography over silica-gel (*n*-hexane/diethyl ether) to give the corresponding isoquinolines **13a−h**.

*1-Ethoxy-3,4-diphenylisoquinoline (**13a**).* White solid (Yield: 72 mg, 89%): mp 131−133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (t, J = 7.1 Hz, 3H), 4.68 (q, J = 7.1 Hz, 2H), 7.14−7.23 (m, 5H), 7.29−7.34 (m, 3H), 7.38−7.42 (m, 2H), 7.46−7.48 (m, 1H), 7.51−7.53 (m, 2H), 8.32−8.36 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 62.1, 118.6, 124.1, 124.8, 125.5, 126.2, 127.10, 127.14, 127.5, 128.5, 130.4, 130.5, 131.9, 138.2, 138.5, 141.1, 147.0, 159.4. IR (NaCl) ν cm^{-1} 1379, 1414, 1443, 1464, 1478, 1506, 1563, 1578, 1617, 1738, 1883, 1948, 2851, 2902, 2927, 2951, 2978, 3025, 3058. HRMS (EI) m/z calcd for $C_{23}H_{19}NO$ [M] calcd 325.1467, found 325.1464.

*1-Methoxy-3,4-diphenylisoquinoline (**13b**).* White solid (Yield: 64 mg, 82%): mp 173−175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (s, 3H), 7.16−7.24 (m, 5H), 7.31−7.45 (m, 5H), 7.48−7.56 (m, 3H), 8.30−8.33 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.3, 114.2, 118.9, 119.7, 124.6, 125.6, 127.2, 127.8, 127.9, 128.9, 130.4, 131.5, 131.6, 136.6, 138.0, 140.1, 149.1, 159.4; IR (NaCl) ν cm^{-1} 1379, 1414, 1443, 1464, 1478, 1506, 1563, 1578, 1617, 1738, 1883, 1948, 2851, 2902, 2927, 2951, 2978, 3025, 3058; HRMS (EI) m/z calcd for $C_{22}H_{17}NO$ [M] 311.1310, found 311.1311.

*1-(Benzyloxy)-3,4-diphenylisoquinoline (**13c**).* White solid (Yield: 48 mg, 50%): mp 136−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (s, 2H), 7.14−7.24 (m, 6H), 7.32−7.44 (m, 8H), 7.50−7.60 (m, 4H), 8.38−8.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.9, 118.6, 124.2, 125.2, 125.6, 126.4, 127.1, 127.2, 127.6, 127.9, 128.09, 128.2, 128.5, 128.6, 128.8, 130.6, 131.8, 137.9, 138.7, 140.9, 146.9, 159.1; IR (NaCl) ν cm^{-1} 1274, 1335, 1354, 1411, 1444, 1505, 1577, 1600, 1617, 1738, 1807, 1883, 1949, 2886, 2945, 3031, 3061; HRMS (EI) m/z calcd for $C_{28}H_{21}NO$ [M] 387.1623, found 387.1620.

*1-(Pent-4-enyloxy)-3,4-diphenylisoquinoline (**13d**).* White solid (Yield: 60 mg, 66%): mp 72−74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99−2.08 (m, 2H), 2.31−2.38 (m, 2H), 4.65 (t, J = 6.4 Hz, 2H), 5.00−5.14 (m, 2H), 5.87−6.00 (m, 1H), 7.15−7.24 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 30.7, 65.6, 115.2, 118.6, 124.1, 124.8, 125.6, 126.2, 127.13, 127.17, 127.6, 128.5, 130.51, 130.54, 131.9, 138.2, 138.4,

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138.6, 141.0, 147.0, 159.5; IR (NaCl) ν cm^{-1} 1363, 1414, 1444, 1506, 1578, 1617, 1641, 1738, 2104, 2361, 2951, 2976, 3028, 3063; HRMS (EI) m/z calcd for $C_{26}H_{23}NO$ [M] 365.1780, found 365.1780.

*4-Ethyl-1-methoxy-3-phenylisoquinoline (**13f**).* White solid (Yield: 59 mg, 89%): mp 112−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.3 Hz, 3H), 2.95 (q, J = 7.4 Hz, 2H), 4.09 (s, 3H), 7.36−7.59 (m, 6H), 7.70 (dt, J = 7.6, 1.3 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 8.30 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 21.5, 53.6, 119.2, 123.7, 123.9, 124.7, 126.0, 127.5, 128.1, 129.5, 130.4, 137.6, 141.9, 148.1, 158.5; IR (NaCl) ν cm^{-1} 1319, 1339, 1367, 1443, 1454, 1506, 1574, 1740, 2875, 2935, 2973, 3033, 3060; HRMS (EI) m/z calcd for $C_{18}H_{17}NO$ [M] 263.1310, found 263.1312.

*6-Bromo-1-methoxy-3,4-diphenylisoquinoline (**13g**).* White solid (Yield: 90 mg, 92%): mp 242−244 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (s, 3H), 7.17−7.21 (m, 5H), 7.34−7.40 (m, 5H), 7.60 (dd, J = 8.7, 1.9 Hz, 1H), 7.69 (d, J = 1.6 Hz, 1H), 8.18 (d, J = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.0, 117.0, 124.1, 125.8, 126.0, 127.4, 127.5, 127.6, 127.9, 128.7, 129.8, 130.4, 131.7, 137.3, 140.0, 140.6, 148.4, 159.7; IR (NaCl) ν cm^{-1} 1276, 1335, 1372, 1408, 1442, 1486, 1569, 1607, 2865, 2891, 2956, 3024, 3055, 3066, 3081; HRMS (EI) m/z calcd for $C_{22}H_{16}BrNO$ [M] 389.0415, found 389.0412.

*1-Methoxy-3,4-diphenylisoquinoline-6-carbonitrile (**13h**).* White solid (Yield: 60 mg, 71%): mp 142−144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (s, 3H), 7.18−7.22 (m, 5H), 7.38−7.42 (m, 5H), 7.67 (dd, J = 8.6, 1.4 Hz, 1H), 7.91 (d, J = 0.8 Hz, 1H), 8.41 (dd, J = 8.5, 0.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.8, 118.6, 124.1, 125.0, 125.6, 126.3, 127.1, 127.2, 127.6, 128.0, 128.5, 130.5, 131.8, 138.1, 138.5, 141.0, 146.9, 159.7; IR (NaCl) ν cm^{-1} 1321, 1340, 1378, 1427, 1460, 1479, 1602, 2839, 2905, 2942, 3003, 3075; HRMS (EI) m/z calcd for $C_{23}H_{16}N_2O$ [M] 336.1263, found 336.1260.

Synthesis of Rh-Imine Complex 14. A solution of **3a** (18 mg, 0.12 mmol) and **1** (3.0 mg, 2.0 mol %) in dry dichloroethane (0.50 mL) was stirred and illuminated under 30 W fluorescent light for 2 h at room temperature. To the reaction mixture a solution of $[Cp^*RhCl_2]_2$ (37 mg, 0.060 mmol) in dry dichloroethane (2.0 mL) was added, and the resulting mixture was stirred for 2 h at room temperature. Volatiles were removed at reduced pressure and the resulting solid was crystallized from dichloromethane/*n*-hexane (1:1) at room temperature to give microcrystalline **14** (Yield: 46 mg, 90%): mp 160 °C dec.; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.67 (s, 15H, 5Me-Cp*), 2.77 (s, 3H, Me), 7.43−7.57 (m, 5H, Ph), 9.48 (bs, 1H, N−H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 9.6 (Me-Cp*), 24.4, 94.6 (d, J = 8.3 Hz, Rh-Cp*), 126.6, 129.4, 132.3, 138.1, 182.7 (C═N); IR (NaCl) ν cm^{-1} 875, 1025, 1081, 1160, 1228, 1270, 1354, 1375, 1396, 1449, 1491, 1598, 1625 (N═H), 1681, 2916, 2966, 3297, 3495; HRMS (FAB) m/z calcd for $C_{18}H_{25}NCl_2Rh$ $[M + H]^+$ 428.0419, found 428.0422, calcd for $C_{18}H_{24}NClRh$ $[M - HCl]^+$ 392.0652, found 392.0642.

Synthesis of Rh-Imine Complex 15. In a Schlenk flask, **14** (52 mg, 0.12 mmol), NaOAc (44 mg, 0.26 mmol: NaOAc was dried at 120 °C for 24 h under a high vacuum prior to use), 4 Å molecular sieves (25 mg) and dry dichloroethane (3.0 mL) were charged under argon atmosphere. The reaction mixture was stirred for 5 h at 80 °C, and filtered through a Celite pad. The filtrate was concentrated at reduced pressure, and resulting residue was crystallized from dichloromethane/*n*-hexane (1:2) mixture at room temperature to give microcrystalline **15** (Yield: 36 mg, 76%): mp 190 °C dec ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.66 (s, 15H, 5Me-Cp*), 2.51 (d, J = 0.6 Hz, 3H, Me), 7.03 (dt, J = 7.4, 1.0 Hz, 1H), 7.23 (ddd, J = 7.6, 7.4, 1.5 Hz, 1H), 7.40 (dd, J = 7.6, 1.2 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 8.94 (bs, 1H, N−H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 9.6 (Me-Cp*), 22.7 (d, J = 2.1 Hz, Rh-Me), 99.0 (d, J = 6.5 Hz, Rh-Cp*), 122.6, 128.0, 131.9, 137.2, 146.7, 185.02 (d, J = 31.8 Hz, Rh−C(Ph)), 185.09 (N═C); IR (NaCl) ν cm^{-1} 856, 877, 1377, 1395, 1427, 1455, 1548, 1576, 1603, 1737, 2912, 2977, 3051, 3097, 3168; HRMS (EI) m/z calcd for $C_{18}H_{24}ClNRh$ $[M - H]^+$ 391.0574, found 391.0570.

Synthesis of 5a from 14. In a flame-dried Schlenk flask, **14** (52 mg, 0.12 mmol), diphenylacetylene (22 mg, 0.12 mmol) and $Cu(OAc)_2$ (22 mg, 0.12 mmol) were charged under argon atmosphere. Dry THF (1.0 mL) was added, and the reaction mixture was stirred at 75 °C for 12 h. After 12 h, the reaction mixture was cooled down to room temperature, and filtered through a silica gel pad. The filtrate was concentrated under reduced pressure, and 1,3,5-trimethoxybenzene was added as an internal standard to the crude reaction mixture to analyze it by ^{1}H NMR spectroscopy (NMR yield of **5a** was >99%).

Synthesis of 5a from 15. In a flame-dried Schlenk flask, **15** (20 mg, 0.05 mmol), diphenylacetylene (10 mg, 0.05 mmol) and $Cu(OAc)_2$ (9.1 mg, 0.05 mmol) were charged under argon atmosphere. Dry THF (1.0 mL) was added, and the reaction mixture was stirred at 75 °C for 12 h. After 12 h, the reaction mixture was cooled down to room temperature, and filtered through a silica gel pad. The filtrate was concentrated under reduced pressure, and 1,3,5-trimethoxybenzene was added as an internal standard to the crude reaction mixture to analyze it by ^{1}H NMR spectroscopy (NMR yield of **5a** was 86%).

Catalytic Activity of 14 and 15 for the Formation of 5a. To a solution of **1** (2.8 mg, 2.0 mol %) in dry THF (0.50 mL), **3a** (18 mg, 0.12 mmol) was added under argon atmosphere. The reaction mixture was illuminated with 30 W fluorescent light for 2 h. The conversion of **3a** was monitored by TLC. After complete conversion of **3a**, the reaction mixture was transferred through a cannula to another Schlenk flask containing diphenylacetylene (18 mg, 0.10 mmol), **14** or **15** (10 mol %), and $Cu(OAc)_2$ (18 mg, 0.10 mmol) under argon atmosphere. The reaction mixture was stirred at 75 °C for 12 h. After 12 h, the reaction mixture was cooled down to room temperature, and filtered through a silica gel pad. The filtrate was concentrated under a reduced pressure, and 1,3,5-trimethoxybenzene was added as an internal standard to analyze the crude reaction mixture by ^{1}H NMR spectroscopy (NMR yields of **5a** catalyzed by **14** and **15** were 99% and 86% respectively).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR data for all isoquinolines, unknown azides, and azidoethers, and the X-ray crystallographic data (CIF) for Rh-complexes **14** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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