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Synthesis of Isoquinolines via Rh(III)-Catalyzed C−H Activation Using Hydrazone as a New Oxidizing Directing Group

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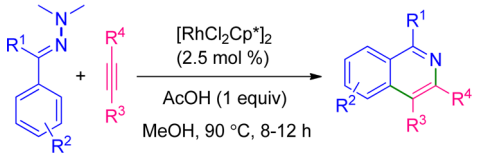
ABSTRACT



An efficient and mechanistically interesting method for the synthesis of highly substituted isoquinolines by a Rh(III)-catalyzed hydrazone directed *ortho* C−H bond activation and annulation without an external oxidant is described. This reaction is accomplished via a C−C and C−N bond formation along with N−N bond cleavage.

Isoquinoline and its derivatives are important bioactive structural motifs found in many natural products[1] and pharmaceutically relevant molecules[2] (Figure 1).[3] In addition, isoquinoline derivatives are used as chiral ligands in asymmetric synthesis[4] and as ligands for iridium complexes used as phosphorescent emitters for organic light-emitting diodes.[5] On the other hand, donor−spacer−acceptor-type compounds derived from bis(isoquinoline-*N*-oxide) are used as fluorosensors for lithium, magnesium, and calcium cations.[6] Becaused of the wide applications of isoquinolines in various fields (Figure 1), continuous efforts have been shown for the development of new methods for their synthesis.

Although many classical methods such as Bischler−Napieralski, Pomeranz−Fritsch, and Pictet−Spengler reactions are known for the synthesis of isoquinolines, most are limited by the substrate scope and harsh reaction conditions.[7] Previously, a transition-metal-catalyzed annulation reaction of *ortho*-haloarylimines with internal alkynes to form isoquinoline compounds was reported.[8,9] Recently, transition-metal-catalyzed C−H bond functionalization reactions have

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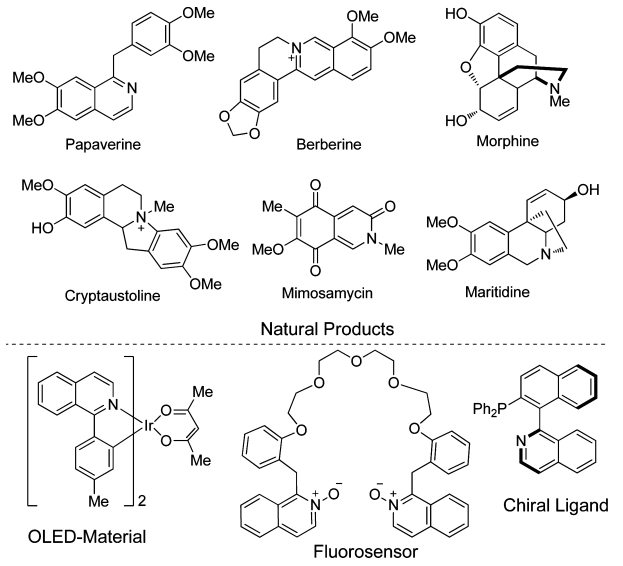

Figure 1. Isoquinoline cored natural and useful compounds.

become important for the construction of carbon−carbon and carbon−heteroatom bonds.[10] In particular, Rh- and Ru-catalyzed C−H bond activation reactions have displayed a wide scope of applications in the synthesis of heterocyclic and carbocyclic compounds[11,12] such as isoquinoline derivatives[13−15] from aromatic imines or oximes with alkynes using Rh(I) or Rh(III) as the catalysts. The synthesis of isoquinolines from oxime derivatives does not require an external oxidant;[15] the N−O bond of oxime acts as an internal oxidant in the reaction. It is important to mention that this attractive strategy for using the directing group itself as an oxidant mostly involves N−O bond (*N*-oxide, oxime, *N*-methoxyamide) cleavage for the redox process.[16] Our continuous interest in C−H bond functionalization[17] and isoquinoline synthesis[18] prompted us to explore the possibility of using other functionality (other than N−O bond) as an internal oxidant in the C−H activation reaction. Herein we report an efficient method for the synthesis of isoquinolines from arylhydrazones catalyzed by $[RhCp^*Cl_2]_2$. It is noteworthy that the hydrazone moiety has rarely been as a directing group for C−H bond activation reaction.[19]

The reaction of acetophenone *N*,*N*-dimethylhydrazone **1a** with diphenylacetylene (**2a**) in the presence of 2.5 mol % of $[RhCp^*Cl_2]_2$ and 1 equiv of AcOH in MeOH at 90 °C for 8 h gave 1-methyl-3,4-diphenylisoquinoline **3aa** in 93% isolated yield. The structure of compound **3aa** was thoroughly characterized by its ^1H and ^{13}C NMR and HRMS data. The choice of solvent and additives is very crucial for the success of the present Rh(III)-catalyzed C−H bond activation and annulation reaction. We tested various solvents such as toluene, 1,4-dioxane, 1,2-dichloroethane, THF, EtOAc, acetone, and MeCN for the reaction of **1a** with **2a** to form **3aa**, and in all cases, low or no product yields were observed (see the Supporting Information for the detailed optimization study). In the absence of acetic acid, the reaction gave only a trace of the product. The use of dichloroacetic acid or acetate salts like AgOAc, NaOAc, KOAc, and CsOAc gave product **3aa** in 17−30% yields.

Having the optimized reaction conditions in hand, we explored the scope of the present reaction, and the results are shown in Table 1. Thus, the reaction of various acetophenone hydrazones **1b**−**i** having both electron-donating and -withdrawing groups with **2a** gave the corresponding substituted isoquinolines **3ba**−**ia** in good to excellent yields (Table 1, entries 2−9). Under the same

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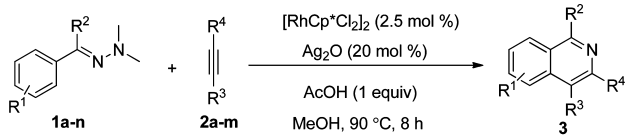
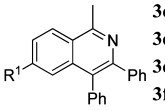
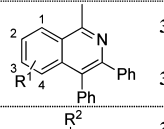
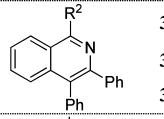
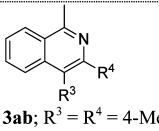
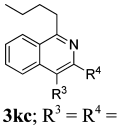
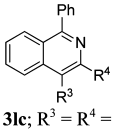
Table 1. Scope of Rh(III)-Catalyzed Isoquinoline Formation[a]



1a; R^1 = H, R^2 = Me
1b; R^1 = 4-Me, R^2 = Me
1c; R^1 = 4-OMe, R^2 = Me
1d; R^1 = 4-F, R^2 = Me
1e; R^1 = 4-Cl, R^2 = Me
1f; R^1 = 4-Br, R^2 = Me
1g; R^1 = 4-CF_3, R^2 = Me
1h; R^1 = 4-NO_2, R^2 = Me
1i; R^1 = 4-Ph, R^2 = Me
1j; R^1 = H, R^2 = Et
1k; R^1 = H, R^2 = *n*-Bu
1l; R^1 = H, R^2 = Ph
1m; R^1 = 2-Me, R^2 = Me
1n; R^1 = 3-Me, R^2 = Me

2a; R^3 = R^4 = Ph
2b; R^3 = R^4 = 4-MeC_6H_4
2c; R^3 = R^4 = 4-$OMeC_6H_4$
2d; R^3 = R^4 = 4-FC_6H_4
2e; R^3 = R^4 = 4-ClC_6H_4
2f; R^3 = R^4 = 4-BrC_6H_4
2g; R^3 = R^4 = 3-MeC_6H_4
2h; R^3 = R^4 = 2-MeC_6H_4
2i; R^3 = R^4 = 2-thiophene
2j; R^3 = R^4 = *i*-Pr
2k; R^3 = Et; R^4 = Ph
2l; R^3 = CH_2Ph, R^4 = Ph
2m; R^3 = $(CH_2)_2CH_3$, R^4 = Me

entry	1	2	time (h)	product 3		yield[b]
1	**1a**	**2a**	8		**3aa**; R^1 = H	93[c]
2	**1b**	**2a**	12		**3ba**; R^1 = Me	95
3	**1c**	**2a**	12		**3ca**; R^1 = OMe	96
4	**1d**	**2a**	12		**3da**; R^1 = F	68
5	**1e**	**2a**	12		**3ea**; R^1 = Cl	93
6	**1f**	**2a**	12		**3fa**; R^1 = Br	74
7	**1g**	**2a**	24		**3ga**; R^1 = CF_3	63
8	**1h**	**2a**	24		**3ha**; R^1 = NO_2	44
9	**1i**	**2a**	12		**3ia**; R^1 = Ph	93[c]
10	**1m**	**2a**	14		**3ma**; R^1 = 1-Me	21
11	**1n**	**2a**	24		**3na**; R^1 = 2-Me	71
12	**1j**	**2a**	12		**3ja**; R^2 = Et	95[c]
13	**1k**	**2a**	12		**3ka**; R^2 = *n*-Bu	90[c]
14	**1l**	**2a**	12		**3la**; R^2 = Ph	93[c]
15	**1a**	**2b**	16		**3ab**; R^3 = R^4 = 4-MeC_6H_4	80
16	**1a**	**2c**	16		**3ac**; R^3 = R^4 = 4-$OMeC_6H_4$	88
17	**1a**	**2d**	16		**3ad**; R^3 = R^4 = 4-FC_6H_4	80
18	**1a**	**2e**	16		**3ae**; R^3 = R^4 = 4-ClC_6H_4	82

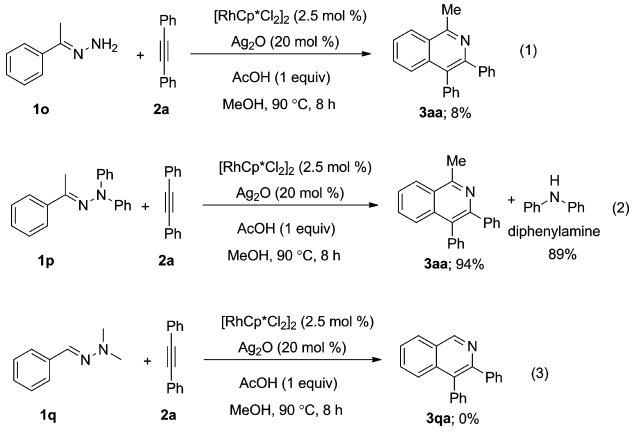
entry	1	2	time (h)	product 3	yield[b]
19	**1a**	**2f**	16	**3af**; R^3 = R^4 = 4-BrC_6H_4	63
20	**1a**	**2g**	16	**3ag**; R^3 = R^4 = 3-MeC_6H_4	82
21	**1a**	**2h**	16	**3ah**; R^3 = R^4 = 2-MeC_6H_4	35
22	**1a**	**2i**	16	**3ai**; R^3 = R^4 = 2-thiophene	30
23	**1a**	**2j**	8	**3aj**; R^3 = R^4 = *n*-Pr	93[c]
24	**1a**	**2k**	16	**3ak**; R^3 = Et, R^4 = Ph	95
25	**1a**	**2l**	16	**3al**; R^3 = CH_2Ph, R^4 = Ph	75
26	**1k**	**2c**	12	 **3kc**; R^3 = R^4 = 4-$OMeC_6H_4$	90
27	**1k**	**2f**	12	**3kf**; R^3 = R^4 = 4-BrC_6H_4	88
28	**1k**	**2j**	12	**3kj**; R^3 = R^4 = *n*-Pr	93
29	**1k**	**2k**	12	**3kk**; R^3 = Et, R^4 = Ph	92
30	**1l**	**2c**	12	 **3lc**; R^3 = R^4 = 4-$OMeC_6H_4$	91
31	**1l**	**2f**	24	**3lf**; R^3 = R^4 = 4-BrC_6H_4	88
32	**1l**	**2j**	12	**3lj**; R^3 = R^4 = *n*-Pr	90
33	**1l**	**2k**	12	**3lk**; R^3 = Et, R^4 = Ph	92
34	**1e**	**2m**	24	**3em**; R^3 = $(CH_2)_2CH_3$, R^4 = Me	86 (3:1)[d]

[a] Unless otherwise mentioned, all reactions were carried out using **1** (0.20 mmol) and **2** (0.24 mmol), AcOH (0.20 mmol), Ag_2O (0.040 mmol, 20 mol %), and $[RhCp^*Cl_2]_2$ (0.0050 mmol, 2.5 mol %) in MeOH (1 mL) at 90 °C for 8−24 h under N_2. [b] Isolated yields. [c] No Ag_2O was used. [d] Ratios of regioisomers are given in parentheses, and major isomers are shown.

conditions, electron-withdrawing substituents such as F, CF_3, or NO_2 at the para position of **1** appear to give lower product yields (entries 4, 7, and 8). 2-Methyl-substituted substrate **1m** also afforded a lower yield of expected product **3ma** presumably due to the steric hindrance of ortho substitution (entry 10). 3-Methylacetopenone hydrazone **1n** having two possible C−H bond activation sites is regioselectively functionalized at the less hindered ortho C−H bond (entry 11). In addition to acetophenone hydrazones, other alkyl aryl ketones and benzophenone hydrazones **1j**–**l** also reacted smoothly with **2a** to afford isoquinolines **3ja**–**la** in 90−95% yields (entries 12−14). To understand the scope of the present catalytic reaction, we also tested the reaction of various symmetrical and unsymmetrical alkynes with **1a**. Thus, 4-Me-, 4-OMe-, 4-F-, 4-Cl-, 4-Br-, 3-Me-, and 2-Me-substituted diphenylacetylenes (**2b**–**h**) produced respective isoquinolines in good to excellent yields (entries 15−21). Heterocyclic acetylene such as 1,2-di(thiophene-2-yl)ethyne (**2i**) also survived under the reaction conditions to produce isoquinoline **3ai**

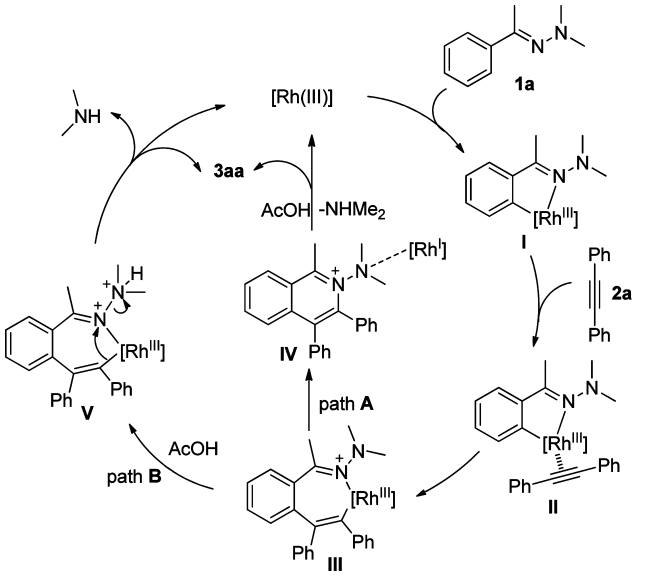
in moderate yield (entry 22). Dialkylacetylene oct-4-yne (**2j**) reacted with **1a** to give isoquinoline **3aj** in 93% yield (entry 23). Unsymmetrical alkynes **2k** and **2l** also reacted with **1a** in a highly regioselective manner to form the corresponding isoquinolines in excellent yields (entries 24 and 25). Similarly, treatment of alkynes with different keto hydrazones (1-phenylpentan-1-one and benzophenone) gave the corresponding substituted isoquinolines in excellent yields (entries 26−33). The reaction of unsymmetrical dialkylalkyne **2m** with **1e** was examined under similar reaction conditions, and regioisomeric products **3em** and **3em′** were isolated in 65 and 21% isolated yields (entry 34).

In addition to *N,N*-dimethylhydrazones, we also tested the reactivity of different *N,N*-disubstituted hydrazones. The reaction of unsubstituted acetophenone hydrazone **1o** with **2a** under standard reaction conditions gave low product yield (eq 1). On the other hand, the reaction of *N,N*-diphenylacetophenone hydrazone **1p** with **2a** gave product **3aa** and diphenylamine in 94 and 89% isolated yields (eq 2). It is surprising to mention that *N,N*-dimethylbenzaldehyde hydrazone **1q** with **2a** under similar reaction conditions did not afford the expected isoquinoline product **3qa** (eq 3). The reactivity difference of aryl ketone and benzaldehyde hydrazone toward alkyne **2a** is not yet clear.



Based on our experiment results and the known chemistry in the literature,[13−16] a possible mechanism for the present catalytic reaction is proposed in Scheme 1 by using **1a** and **2a** as the substrates. The coordination of hydrazone **1a** via the imine nitrogen to Rh^{III} and subsequent *ortho*-C−H bond activation forms a five-membered rhodacycle **I**. Regioselective coordination and insertion of alkyne **2a** in to the Rh−C bond of intermediate **II** gives a seven-membered intermediate **III**. The formation of product **3aa** from **III** can be attained in two different pathways. A C−N bond formation by reductive elimination of intermediate **III** would give *N*-(dimethylamino)isoquinolinium cation (**IV**) and a Rh^{I} species. The reduction of intermediate **IV** by the resulted Rh^{I} species releases isoquinoline product **3aa** and Rh^{III} (path **A**). Another pathway involving an AcOH-promoted intramolecular nucleophilic substitution leading to a C−N bond

Scheme 1. Proposed Mechanism for Rh(III)-Catalyzed Isoquinoline Formation



formation and N−N bond cleavage to afford product **3aa**, dimethylamine, and a Rh^{III} is also possible (path **B**). The Rh^{III} generated can then restart the catalytic reaction.

Acetic acid is crucial for the success of the present catalytic reaction. This implies that path B is likely more favorable for the present catalytic reaction. The protonation of *N,N*-dimethyl group of intermediate **V** makes it a better leaving group (Scheme 1, path B). In addition, most of the existing literature supports consecutive C−N bond formation and N−N bond cleavage (path B) over reductive elimination (path A).[15,16]

In summary, we have developed a new, efficient, regioselective method for the synthesis of substituted isoquinolines from arylhydrazones and -alkynes via a Rh(III)-catalyzed C−H activation and annulation. This reaction is accomplished through C−H bond cleavage, C−C and C−N bond formation, along with N−N bond cleavage. This new hydrazone-directed isoquinoline synthesis has the advantage of avoiding external oxidant. Detailed mechanistic studies and further application of this method to the synthesis of useful compounds are in progress.

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Supporting Information Available. General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.