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Ruthenium-Catalyzed Highly Regioselective Cyclization of Ketoximes with Alkynes by C−H Bond Activation: A Practical Route to Synthesize Substituted Isoquinolines

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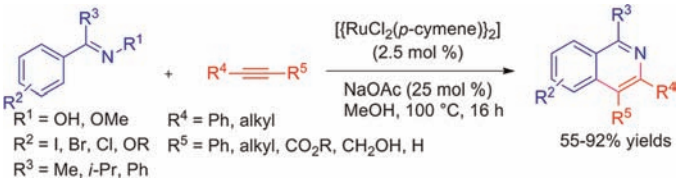
ABSTRACT



Aromatic and heteroaromatic ketoximes underwent cyclization with alkynes in the presence of a catalytic amount of [{$RuCl_2$(*p*-cymene)}$_2$] and NaOAc to give isoquinoline derivatives in good to excellent yields in a highly regioselective manner.

Isoquinoline derivatives are an important class of heterocyclic compounds.[1] This core is present in various biologically active molecules and natural products.[1] In the literature, several methods are available to synthesize isoquinoline derivatives.[2] Palladium- or nickel-catalyzed cyclization of *o*-halobenzimines with carbon−carbon π-components is one of the promising methods to synthesize isoquinoline derivatives.[3] However, in these reactions, a preactivated halogen group such as I or Br was used to activate the *ortho*-carbon of the aromatic imines.

Rhodium(I)-catalyzed chelation-assisted C−H bond activation of aromatic and alkene imines or oximes followed by alkenylation with alkynes and subsequent intramolecular electrocyclization providing isoquinolines and pyridines have been reported by the Jun, Cheng, and Ellman groups.[4,5] In these reactions, the *ortho* aromatic or alkene C−H bond was activated by imine or oxime directing groups instead of using a preactivated halogen group. Later, Fagnou et al. and Miura et al. reported a rhodium(III)-catalyzed cyclization of benzaldimines with alkynes by C−H bond activation.[6a,b] Subsequently, Cheng's group established a nice method to synthesize isoquinolinium salts from aromatic aldehydes, amines and alkynes in the presence of rhodium(III) catalysts by C−H bond activation.[6c]

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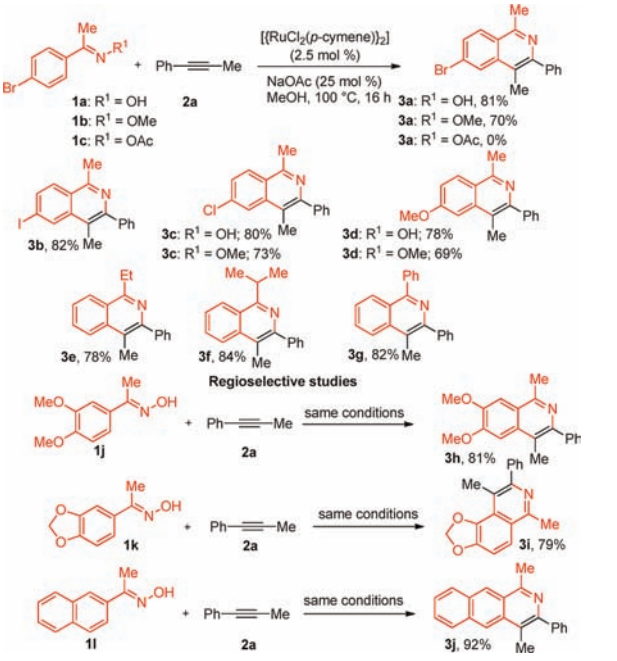
Chiba's group reported a Rh(III)-catalyzed cyclization of aryl ketone *O*-acyloximes with alkynes by C−H bond activation.[6d−f] Very recently, Rovis et al. and Li et al. demonstrated a rhodium-catalyzed cyclization of aromatic ketoximes with alkynes by C−H bond activation.[6g,h] Although several reports have been known to synthesize isoquinolines by C−H bond activation in the literature, the control of regioselectivity in the cyclization of ketoximes with unsymmetrical alkynes is still a challenging task. In all reported reactions, a mixture of regioisomeric products was observed in most of the unsymmetrical alkynes (except 1-phenyl-1-propyne). In all these reactions, only rhodium complexes were used as catalysts.

Recently, a less-expensive ruthenium catalyst has been widely used in the cyclization reaction because of its remarkable regioselectivity and the low cost of the metal.[7,8] To the best of our knowledge, there is no report discussing the complete regioselective synthesis of isoquinolines by cyclization of ketoximes with unsymmetrical alkynes. Herein, we report a highly regioselective cyclization of aromatic and heteroaromatic ketoximes with substituted alkynes in the presence of catalytic amount of $[\{RuCl_2(p\text{-cymene})\}_2]$ and NaOAc to afford highly substituted isoquinoline derivatives in good to excellent yields. The present catalytic reaction was compatible with various sensitive functional groups substituted unsymmetrical internal as well as terminal alkynes. In all cases, the corresponding isoquinoline derivatives were observed in a highly regioselective manner. It is important to note that terminal alkynes were also compatible for the present reaction. The proposed mechanism of the cyclization reaction was strongly supported by isolation of a key five-membered ruthenacycle intermediate. Experimental evidence was also provided to support the proposed mechanism.

A variety of aromatic ketoximes **1** was compatible for the present cyclization reaction (Scheme 1). When 4-bromoacetophenone oxime (**1a**) was treated with an unsymmetrical alkyne, 1-phenyl-1-propyne (**2a**), in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ (2.5 mol %) and NaOAc (25 mol %) in MeOH at 100 °C for 16 h, an isoquinoline derivative **3a** was observed in 81% isolated yield in a highly

Scheme 1. Substituted Ketoximes Scope



regioselective manner (Scheme 1). The cyclization of *o*-methyl 4-bromoacetophenone oxime (**1b**) and *o*-acetyl 4-bromoacetophenone oxime (**1c**) with **2a** under similar reaction conditions was also examined. In case of *o*-methyl oxime **1b**, the corresponding cyclization product **3a** was observed in 70% yield, whereas no cyclization product **3a** was observed in case of *o*-acetyl oxime **1c** (for optimization studies, see the Supporting Information). The cyclization of 4-iodoacetophenone oxime **1d**, 4-chloroacetophenone oxime **1e**, and 4-methoxyacetophenone oxime **1f** with 1-phenyl-1-propyne (**2a**) gave isoquinoline derivatives **3b**−**d** in excellent yields with very high regioselectivity. The effect of changing the methyl group in acetophenone oxime to some other groups such as ethyl, isopropyl, and phenyl was also investigated. Thus, propiophenone oxime **1g**, isobutyrophenone oxime **1h**, and benzophenone oxime **1i** efficiently underwent cyclization with **2a** to provide isoquinoline derivatives **3e**−**g** in 78%, 84%, and 82% yields, respectively. Next, the regioselectivity of unsymmetrical aromatic ketoximes **1j**−**l** with an unsymmetrical alkyne, 1-phenyl-1-propyne (**2a**), was examined. Thus, 3,4-dimethoxyacetophenone oxime **1j** reacted with **2a** regioselectively to afford **3h** in 81% yield. In the substrate **1j**, there are two *ortho* aromatic C−H bonds for cyclization. Regioselectively, the cyclization takes place at the less hindered C−H bond of **1j** moiety exclusively. In contrast, 3,4-methylenedioxy acetophenone oxime **1k** reacted with **2a** to produce a reverse regioselective product **3i** exclusively in 79% yield. In **1k** also, there are two *ortho* aromatic C−H bonds for cyclization. However, oxidative cyclization takes place at the sterically hindered C−H bond of **1k** moiety predominately. As like **1j**, 2-acetonaphthone oxime **1l** also underwent cyclization regioselectively with **2a** at the less substituted C−H bond of **1l**

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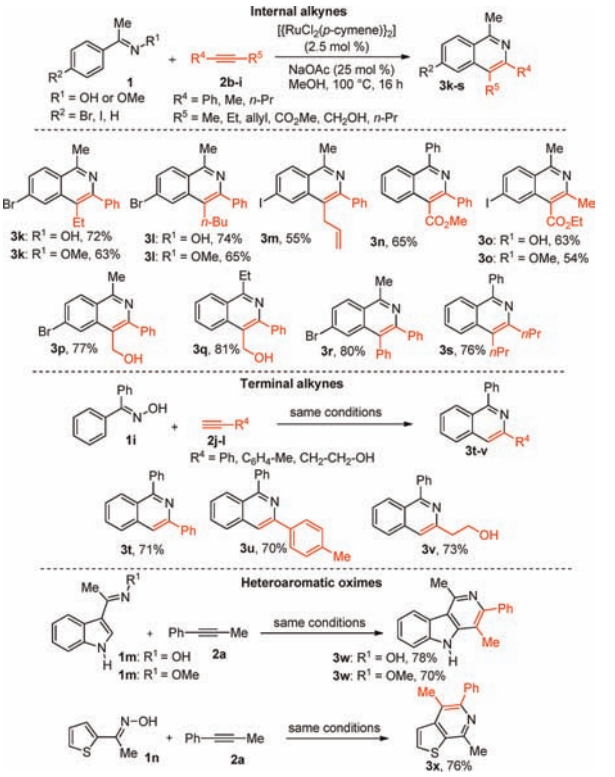
Scheme 2. Unsymmetrical Alkynes Scope

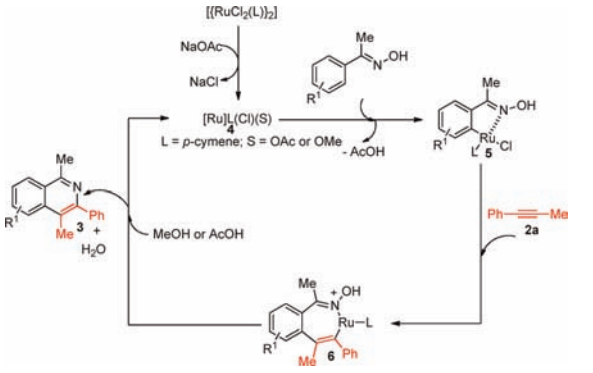


to give **3j** in excellent 92% yield. The cyclization reaction of various substituted *o*-methyl oximes with **2a** was also tested. Thus, the reaction of *o*-methyl 4-chloroacetophenone oxime and *o*-methyl 4-methoxyacetophenone oxime with **2a** produced corresponding cyclization products **3c** and **3d** in 73% and 69% yields, respectively. It is important to note that cyclization of substituted *o*-methyl oximes with alkynes affording isoquinoline derivatives is unprecedented in the literature.

For further understanding the regioselectivity of the present reaction, cyclization of ketoximes **1** with various unsymmetrical alkynes was examined under similar reaction conditions (Scheme 2). Unsymmetrical alkynes 1-phenyl-1-butyne (**2b**), 1-phenyl-1-hexyne (**2c**), and 1-phenyl-4-penten-1-yne (**2d**) reacted with 4-bromoacetophenone oxime **1a** or 4-iodoacetophenone oxime **1d** regioselectively to afford **3k**−**m** in 72%, 74%, and 55% yields, respectively (Scheme 2). Surprisingly, bulky benzophenone oxime **1i** reacted efficiently with methyl phenylpropiolate (**2e**) to provide the corresponding isoquinoline derivative **3n** in 65% yield (Scheme 2). Ethyl 2-butynoate (**2f**) also reacted efficiently with 4-iodoacetophenone oxime **1d** to afford isoquinoline derivative **3o** in 63% yield in a highly regioselective manner. Interestingly, 3-phenyl-2-propyn-1-ol (**2g**) also efficiently participated in the cyclization reaction with 4-bromoacetophenone oxime **1a** and propiophenone oxime **1g** to give the corresponding isoquinoline derivatives **3p** and **3q** in 77% and 81% yields, respectively, in a highly regioselective manner. Also, *o*-methyl 4-bromoacetophenone oxime **1b** and *o*-methyl 4-iodoacetophenone oxime underwent cyclization reaction with 1-phenyl-1-butyne (**2b**), 1-phenyl-1-hexyne (**2c**) and ethyl 2-butynoate (**2f**) to provide the corresponding isoquinoline derivatives **3k**, **3l** and **3o** in 63%, 65% and 54% yields, respectively. The catalytic reaction was also tested with symmetrical alkynes. Thus, diphenyl acetylene (**2h**) and 3-hexyne (**2i**) underwent cyclization with 4-bromoacetophenone oxime **1a** or benzophenone oxime **1i** to afford isoquinoline derivatives **3r** and **3s** in 80% and 76% yields, respectively.

Terminal alkynes were also compatible for the present cyclization reaction (Scheme 2). Thus, phenylacetylene (**2j**) reacted efficiently with **1i** to give isoquinoline derivative **3t** in 71% yield in a highly regioselective manner. Similarly, 4-methyl phenylacetylene (**2k**) and pent-4-yn-1-ol (**2l**) also efficiently participated in the cyclization reaction with **1i** to afford the corresponding isoquinoline derivatives **3u** and **3v** in 70% and 73% yields, respectively, in a highly regioselective manner. In the reaction, highly substituted carbon of terminal alkyne was connected to the nitrogen atom of oxime **1i** and terminal carbon of alkyne was attached to the *ortho* carbon of oxime **1i**. The catalytic reaction was also tested with heteroaromatic oximes **1m** and **1n** (Scheme 2). Treatment of 3-acetylindole oxime **1m** with **2a** under the optimized reaction conditions gave isoquinoline derivative **3w** in 78% yield in a highly regioselective manner. The *o*-methyl 3-acetylindole oxime also underwent cyclization reaction with **2a** to provide **3w** in 70% yield. 2-Acetylthiophene oxime **1n** reacted with **2a** regioselectively to afford the corresponding cyclization product **3x** in 76% yield.

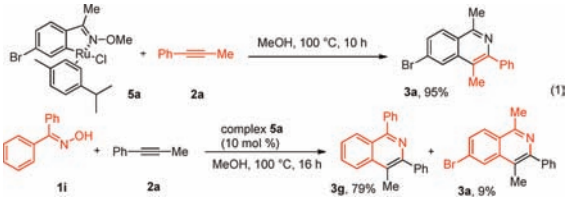
Scheme 3. Proposed Mechanism



On the basis of the known metal-catalyzed C−H bond activation,[4−8] a reasonable mechanism is proposed to account for the present cyclization reaction in Scheme 3. The dissociation of dimeric form of ruthenium complex to monomer followed by ligand exchange with NaOAc gives a ruthenium acetate species **4** to initiate the catalytic reaction. Coordination of the nitrogen atom of oxime **1** to the ruthenium acetate species **4** followed by acetate accelerated *ortho*-metalation affords a five-membered metalacycle

intermediate **5**.[9] Coordinative regioselective insertion of alkyne **2** into the Ru−carbon bond of intermediate **5** provides a seven-membered intermediate **6**. Subsequent C−N bond formation and N−O bond cleavage of intermediate **6** in the presence of MeOH or AcOH affords product **3** and regenerates the active ruthenium species **4** for the next catalytic cycle.[6g,h,7f,9,10] The exact reason for high regioselectivity is not very clear in the reaction. The phenyl group of alkyne **2** might coordinates intramolecularly with ruthenium metal in intermediate **6** and stabilizes it. This may be the reason for the high regioselectivity.

The proposed mechanism in Scheme 3 is strongly supported by the isolation of key ruthenacycle intermediate **5a** (eq 1). When *o*-methyl 4-bromoacetophenone oxime (**1b**) was treated with stoichiometric amount of [{$RuCl_2$(*p*-cymene)}$_2$] and NaOAc in MeOH at 100 °C for 16 h, a five-membered ruthenacycle intermediate **5a** was observed in 69% yield (eq 1). The structure of complex **5a** was determined by single crystal X-ray diffraction (see the Supporting Information). Subsequently, when intermediate **5a** was treated with alkyne **2a** in the presence of MeOH at 100 °C for 10 h, an isoquinoline derivative **3a** was obtained in 95% yield. In the present cyclization reaction of oximes **1** with alkynes **2**, only catalytic amount of NaOAc (25 mol %) was used. However, a stoichiometric amount of NaOAc (1.2 equiv) is crucial for the acetate mediated *ortho*-metalation.[9] It is likely that during the C−N bond formation of intermediate **6**, MeOH protonates OH group of intermediate **6** and regenerates the active ruthenium methoxide catalyst **4** for next catalytic cycle (assuming that due to the intramolecular coordination of the nitrogen to ruthenium in intermediate **6**, the OH group at the nitrogen side in intermediate **6** could be basic character). This assumption is strongly supported by the following experimental evidence. Treatment of benzophenone oxime (**1i**) with 1-phenyl-1-propyne (**2a**) in the presence of a catalytic amount of complex **5a** (10 mol %) in MeOH at 100 °C for 16 h gave isoquinoline derivatives **3g** in 79% and **3a** in 9% yields, respectively (Scheme 1). In the cyclization reaction, NaOAc was not used. This result clearly reveals that in the cyclization reaction, NaOAc provides the OAc^- source to the ruthenium species to initiate the *ortho*-metalation of the first catalytic cycle. In the subsequent catalytic cycles, MeOH protonates the OH of intermediate **6** and regenerates the active ruthenium methoxide **4** for the next *ortho*-metalation.



On the basis of these studies, the cyclization reaction of some of the substituted oximes **1** with alkynes **2** was examined in the absence of NaOAc and only in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (2.5 mol %) in MeOH at 100 °C for 16 h. The observed results showed that some reactions such as propiophenone oxime **1g** and isobutyrophenone oxime **1h** with 1-phenyl-1-propyne (**2a**) gave the corresponding isoquinoline derivatives **3e** and **3f** in excellent 79% and 82% isolated yields, respectively, even in the absence of NaOAc (Scheme 1). But, in other oximes such as benzophenone oxime **1i** and 2-acetonaphthone oxime **1l** with **2a**, isoquinoline derivatives **3g** and **3j** were observed only in 25% and 62% yields, respectively (Scheme 1). In the remaining reactions such as benzophenone oxime **1i** with methyl phenylpropiolate (**2e**) or phenylacetylene (**2j**), cyclization compounds **3n** and **3t** were observed only in very low 25% and 10% yields, respectively (Scheme 2). In the reaction of benzophenone oxime **1i** with 3-hexyne (**2i**), no cyclization compound **3s** was observed (Scheme 2). Based on these observations, we conclude that OAc^- anion is an efficient base to initiate the catalytic reaction when compared to Cl^- anion, which is present in the ruthenium catalyst.

In conclusion, we have demonstrated a ruthenium-catalyzed regioselective cyclization of substituted aromatic and heteroaromatic ketoximes with internal as well as terminal alkynes in the presence of catalytic amount of NaOAc to afford isoquinoline derivatives in good to excellent yields. Further extension of cyclization of substituted aldoximes with other π-components and a detailed mechanistic investigation are in progress.

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Supporting Information Available. General experimental procedure, CIF information, 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.

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