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Rhodium-Catalyzed C–H Activation/Annulation Cascade of Aryl Oximes and Propargyl Alcohols to Isoquinoline *N*-Oxides

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Abstract: A *β*-hydroxy elimination instead of common oxidization to carbonyl group in secondary propargyl alcohols was successfully developed to form 2-benzyl substituted isoquinoline *N*-oxides by a Rhodium-catalyzed C–H activation and annulation cascade, in which moderate to excellent yields (up to 92%) could be obtained under mild reaction conditions, along with good regioselectivity, broad generality and applicability.

Keywords: Isoquinoline *N*-oxides; *β*-hydroxy elimination; Rhodium; Secondary propargyl alcohols

Introduction

The *N*-oxides of isoquinoline and pyridine are important structural units widely embedded in various natural products,[1] pharmaceutical agents,[2] and chiral ligands (Figure 1).[3] Meanwhile, they are also widely used as powerful directing groups in the C–H functionalization of isoquinolines, pyridines and other natural product scaffolds.[4] However, the traditional synthesis of these *N*-oxides mainly involves the direct oxidation of parent heterocycles with a stoichiometric amount of peroxides or peracids, such as *m*-CPBA, H_2O_2, CF_3CO_3H, and $MeReO_3/H_2O_2$.[4d,5] The major limitations of them are that the parent heterocycles need to be prepared in advance and probably suffer from the overoxidation.[5] Over the past decades, transition-metal-catalyzed heteroatom-directed C–H functionalization and cycloaddition cascade reactions have become a powerful approach for the synthesis of these *N*-oxides.[5–6] Among them, oxime exhibits to be a facile precursor and can couple with alkynes,[6f] diazo compounds,[5–6] and other coupling partners[6c] to build intriguing isoquinoline or pyridine *N*-oxides. Such as,

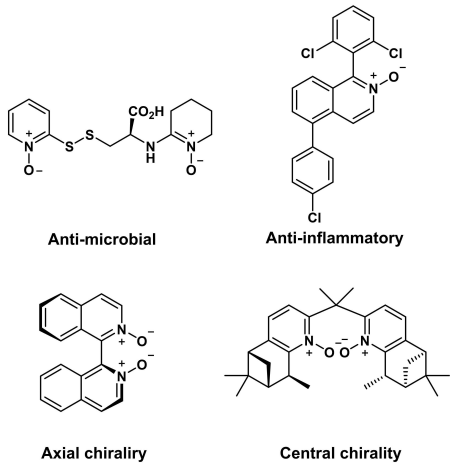
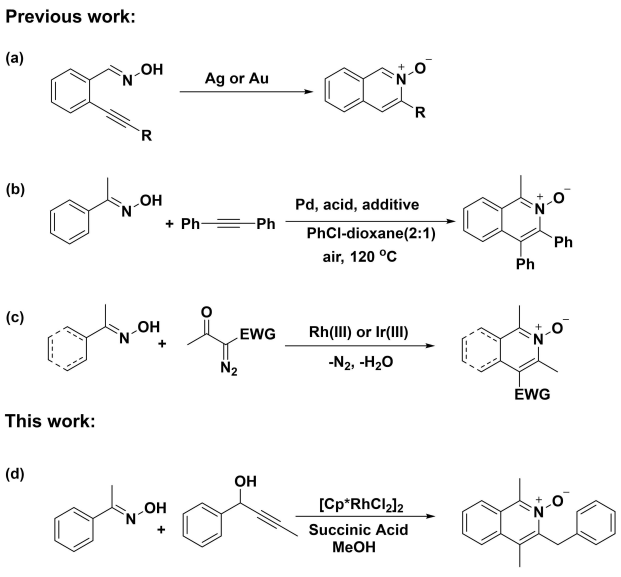


Figure 1. Representative compounds containing isoquinoline and pyridine *N*-oxides.

Shin group reported a pioneering silver(I)-catalyzed direct route to isoquinoline *N*-oixides *via* an intramolecular annulation from *o*-alkynylarylaldoximes

(Scheme 1a).[6h] After that, some similar strategies were also reported.[6d,e,g] Interestingly, Huang and co-workers in 2013 fulfilled a novel oxime directed C–H activation cascade with diaryl alkynes to efficiently build multisubstituted isoquinoline *N*-oxides (Scheme 1b).[6f] Besides, Glorious's group and Ramana's group independently achieved a *N*-oxide directed C–H activation of aryl oxime and further annulation with diazo compound by the Rh(III) or Ir(III) catalytic system to give the intriguing polysubstituted isoquinoline and pyridine *N*-oxides (Scheme 1c).[5–6]

Despite these progress, other readily available synthons still were highly desired. Propargyl alcohols have been applied widely as important building blocks in transition-metal-catalyzed intermolecular annulations.[7] In our continuous efforts on the development of transition metal-catalyzed C–H functionalization strategies to construct diverse drug-like heterocycles,[4e,7o,q,8] we serendipitously found an unusual aspect of secondary propargyl alcohols that could smoothly couple with aryl oximes to form 2-benzyl substituted isoquinoline *N*-oxides *via* a Rh(III)-catalyzed C–H activation and unusual *β*-hydroxy elimination cascade (Scheme 1d). To the best of our knowledge, the hydroxyl group in secondary propargyl alcohols was usually oxidized to carbonyl group, or directly reserved into the formed target heterocycles,[7g,l,m,o–u] still no related reports involved a *β*-hydroxy elimination in Rh(III)-catalyzed C–H activation and annulation cascade between oxime and secondary propargyl alcohol.[7d,h,j,u,9] Herein, we report this new finding that the secondary propargyl alcohols underwent an unprecedented *β*-hydroxy elimination instead of common oxidization to form 2-benzyl substituted isoquinoline *N*-oxides *via* Rh(III)-catalyzed C–H activation and annulation cascade with moderate to excellent yields (up to 92%) under mild reaction conditions, along with regioselectivity, broad generality and versatile applicability.

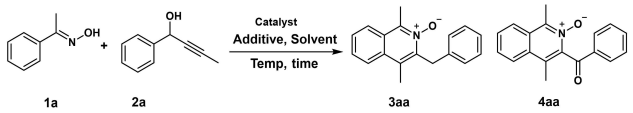


Scheme 1. Transition-metal-catalyzed Synthesis of *N*-oxides of Isoquinoline.

Results and Discussion

The explorations were firstly employed by the treatment of acetophenone oxime **1a** (0.4 mmol, 1 equiv.) and secondary propargyl alcohol **2a** (0.8 mmol, 2 equiv.) under the catalyst system consists of [Cp*Rh(CH$_3$CN)][SbF$_6$]$_2$ (8 mol%), Ag$_2$CO$_3$(100 mol%) and PivOH (0.8 mmol, 2 equiv.) in methanol (MeOH) at 90 °C for 12 h. As expected, the hydroxyl group in secondary propargyl alcohol was oxidized to carbonyl group and further reserved in the formation of heterocycle (**4aa**) with 45% yield (Table 1, entry 1). However, we surprisingly detected a new product 2-benzyl substituted isoquinoline *N*-oxide **3aa** which was suspected to undergo an unprecedented *β*-hydroxy elimination instead of oxidization when we changed this metal catalyst into [Cp*RhCl$_2$]$_2$ (Table 1, entry 2). The structures of **3aa** and **4aa** were unambiguously confirmed by their ^{1}H and ^{13}C NMR spectra, mass spectrometry data, and X-ray crystallographic analysis, respectively.[10] The new finding inspired our interest to further screen the catalysts, and the results indicated that [Ru(*p*-cymene)Cl$_2$]$_2$ and [Cp*IrCl$_2$]$_2$ could not catalyze this new transformation (Table 1, entries 3 and 4). Subsequently, we screened different additives, such as Ag$_2$CO$_3$, PivOH, AcOH, benzoic acid, phenylacetic acid, propanedioic acid, succinic acid and citric acid, and the results revealed that succinic acid was superior to other additives (Table 1, entries 5–12), providing the product **3aa** with 82% yield. Therefore, succinic acid was chose as the additive in subsequent experiments. Further investigations of different solvents indicated that MeOH was the best choice for this transformation (Table 1, entries 13–18). Besides, we also investigated the influences of reaction time and temperature to this reaction (Table 1, entries 19–23), the results demonstrated that this transformation could proceed smoothly with the yield of 85% at 90 °C for 24 h. Meanwhile, we could obtaine product **3aa** with the yield of 54% in a low [Cp*RhCl$_2$]$_2$ loading (Table 1, entry 24). Meanwhile, the molar ratios of substrates **1a** and **2a** were investigated (Table 1, entries 25–26). Besides, the controlled reaction experiment showed that the target product **3aa** could not be obtained in the absence of [Cp*RhCl$_2$]$_2$ or succinic acid (Table 1, entries 27 and 28). Briefly, the optimum result could be obtained when aryl oxime (0.4 mmol, **1a**) and secondary propargyl alcohol (0.8 mmol, **2a**) were treated in MeOH under the presence of [Cp*RhCl$_2$]$_2$ (8 mol%) as catalyst and succinic acid (2.0 equiv.) as additive at 90 °C for 12 h or 24 h.

Table 1. Optimization of Reaction Conditions.[a]

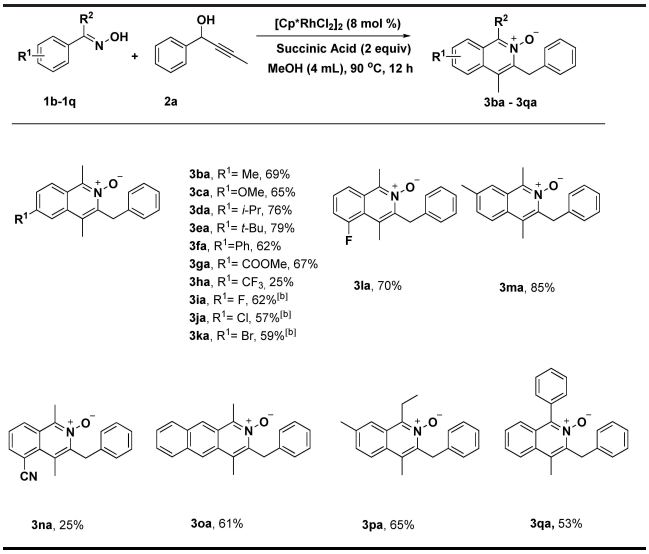


Entry	Catalyst	Additive	Yield[b] 3aa(4aa)
1	[Cp*Rh (CH$_3$CN)] [SbF$_6$]$_2$	Ag$_2$CO$_3$/PivOH	ND (45)
2	[Cp*RhCl$_2$]$_2$	Ag$_2$CO$_3$/PivOH	23 (24)
3	[RuCl$_2$(*p*-cymene)]$_2$	Ag$_2$CO$_3$/PivOH	ND
4	[Cp*IrCl$_2$]$_2$	Ag$_2$CO$_3$/PivOH	ND
5	[Cp*RhCl$_2$]$_2$	Ag$_2$CO$_3$	25
6	[Cp*RhCl$_2$]$_2$	PivOH	45
7	[Cp*RhCl$_2$]$_2$	AcOH	67
8	[Cp*RhCl$_2$]$_2$	Benzoic acid	56
9	[Cp*RhCl$_2$]$_2$	Phenylacetic acid	53
10	[Cp*RhCl$_2$]$_2$	Propandioic acid	70
11	[Cp*RhCl$_2$]$_2$	Succinic acid	82
12	[Cp*RhCl$_2$]$_2$	Citric acid	81
13[c]	[Cp*RhCl$_2$]$_2$	Succinic acid	20
14[d]	[Cp*RhCl$_2$]$_2$	Succinic acid	ND
15[e]	[Cp*RhCl$_2$]$_2$	Succinic acid	ND
16[f]	[Cp*RhCl$_2$]$_2$	Succinic acid	10
17[g]	[Cp*RhCl$_2$]$_2$	Succinic acid	ND
18[h]	[Cp*RhCl$_2$]$_2$	Succinic acid	ND
19[i]	[Cp*RhCl$_2$]$_2$	Succinic acid	35
20[j]	[Cp*RhCl$_2$]$_2$	Succinic acid	64
21[k]	[Cp*RhCl$_2$]$_2$	Succinic acid	44
22[l]	[Cp*RhCl$_2$]$_2$	Succinic acid	63
23[m]	[Cp*RhCl$_2$]$_2$	Succinic acid	85
24[n]	[Cp*RhCl$_2$]$_2$	Succinic acid	54
25[o]	[Cp*RhCl$_2$]$_2$	Succinic acid	56
26[p]	[Cp*RhCl$_2$]$_2$	Succinic acid	69
27	–	Succinic acid	ND
28	[Cp*RhCl$_2$]$_2$	–	ND

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.8 mmol), [Cp*RhCl$_2$]$_2$ (8 mol%), Succinic acid (2.0 equiv.) in MeOH (4.0 mL) at 90 °C under air for 12 h. [b] Isolated yield. [c–h] Solvent: EtOH: ethanol, DCE: dichloroethane, (CH$_3$)$_2$CO: acetone, ACN: acetonitrile, THF: tetrahydrofuran, PhMe: toluene. [i] At 60 °C. [j] At 100 °C. [k] 2 h. [l] 6 h. [m] 24 h. [n] [Cp*RhCl$_2$]$_2$ (5 mol%). [o] **1a**/**2a** = 1/1. [p] **1a**/**2a** = 1/1.5.

With the optimized reaction conditions in hand, we firstly examined the scope of differently substituted aryl oximes (**1b–1q**) in the catalytic system above with propargyl alcohol **2a** (Table 2). In general, introducing an electron-donating or electron-withdrawing group into the *para* position of aryl oximes could smoothly couple with propargyl alcohol **2a** to afford the target compounds (**3ba–3ha**) in good yields. It seemed that the electron-donating groups were significantly superior to the electron-withdrawing groups especially trifluoromethyl group (**3ha**, 25%) with a lower yield. Introduction of halide substituents (–F, –Cl and –Br) to the *para* position of the benzene ring

Table 2. Substrate Scope of (Hetero)Aryl Oximes.[a]

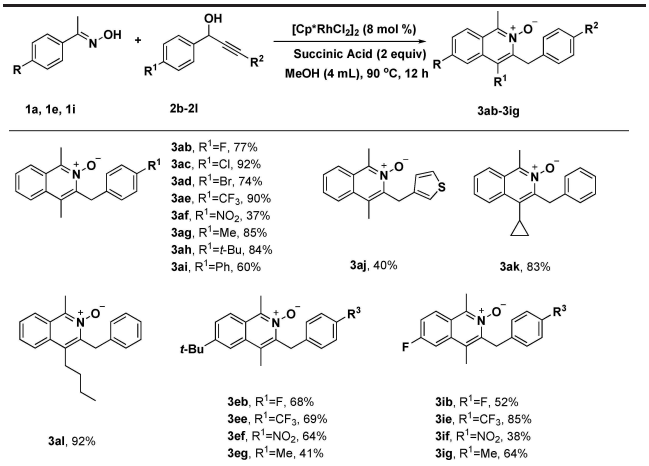


[a] Reaction conditions: **1** (0.4 mmol), **2a** (0.8 mmol), [Cp*RhCl$_2$]$_2$ (8 mol%), Succinic acid (2.0 equiv) in MeOH (4 mL) at 90 °C for 12 h.
[b] 24 h.

also could afford the target compounds with good yields when the reaction time was prolonged to 24 h (**3ia**, **3ja** and **3ka**). Surprisingly, we found an interesting regioselectivity when the electron-withdrawing groups (–F and –CN) and electron-donating group (–CH$_3$) were independently introduced into the *meta* position of the benzene ring of aryl oxime **1a**. The introduction of *m*-F and *m*-CN gave the 2-position C–H activation products **3la** and **3na**. In contrast, the C–H activation of *m*-CH$_3$ substrate took place solely at 6-position of aryl oxime to give product **3ma**. This regioselectivity is probably attributed to the C–H bond acidity or the Rh–C bond stability in the cyclorhenation step.[11] The structures of **3la**, **3ma** and **3na** were also unambiguously confirmed by an X-ray crystallographic analysis.[12] Besides, fused ring (**1o**) was integrated into aryl oximes, and the resulting substrate could also provide the corresponding *N*-oxide **3oa** in a moderate yield. Notably, other functionalized aryl oximes were compatible with the standard reaction conditions to form the corresponding target products (**3pa** and **3qa**) with good yields.

Based on the above results, we next explored the scope of propargyl alcohols (**2b-2l**, Table 3). As we expected, coupling oxime **1a** with propargyl alcohols equipping various substitutions at R^1 position (**2b–2i**) all gave the desired products in good to excellent yields (**3ab–3ai**). The thienyl substituted propargyl alcohol was also tolerant and gave product **3aj** with the yield of 40%. Subsequently, we explored the influences of other bulkier R^2 groups, such as cyclopropyl and *n*-butyl groups, and the results displayed

Table 3. Scope of Propargyl Alcohols.[a]

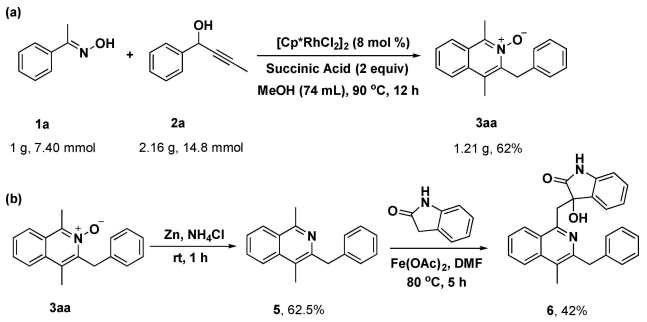


[a] Reaction conditions: **1** (0.4 mmol), **2** (0.8 mmol), $[Cp^*RhCl_2]_2$ (8 mol%), Succinic acid (2.0 equiv) in MeOH (4.0 mL) at 90 °C for 12 h.

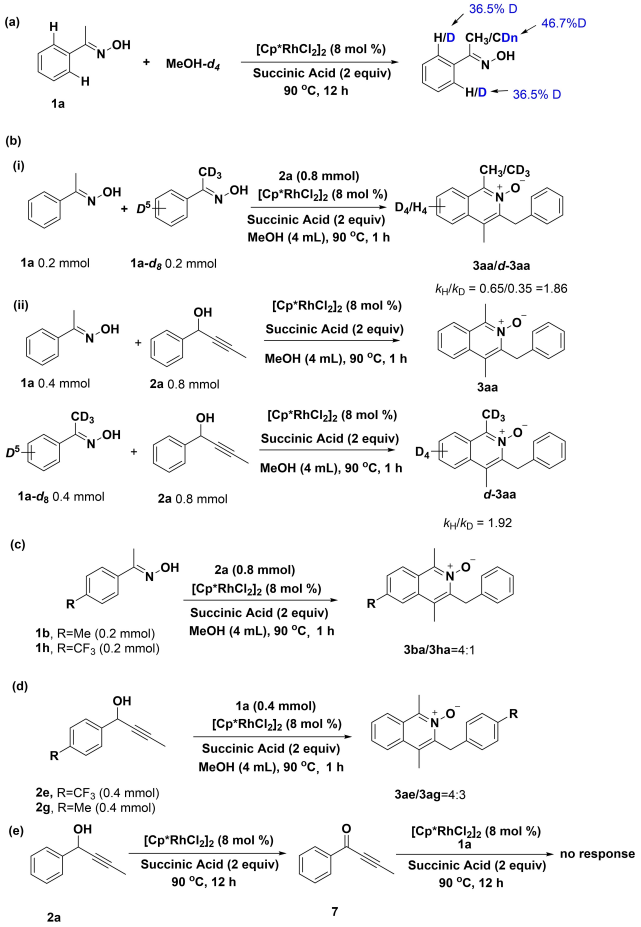
that the two substrates provided the corresponding products in excellent yields (**3 ak** and **3 al**). Similarly, 4-*tert*-butylaryl oxime (**1 e**) and 4-fluoroaryl oxime (**1 i**) were further studied with differently substituted secondary propargyl alcohols, and both could be successfully converted into target products with good yields (**3 eb**–**3 ig**).

To further assess the efficiency and potential applications of this transformation, we firstly performed a gramscale preparation, and obtained the target product **3 aa** with 62% isolated yield (Scheme 2a). In view of the potential biological value of isoquinoline core,[13] we have attempted to switch these intriguing isoquinoline *N*-oxides into isoquinoline cores. After explorations, the *N*-oxide **3 aa** was easily reduced to isoquinoline product **5** by Zn/NH_4Cl catalytic system with a good yield (Scheme 2b). Additionally, we successfully achieved alkylation and hydroxylation reaction between two different C(sp^3)–H bonds, indolin-2-ones and **5**, to get product **6** through an oxidative cross coupling reaction, and achieved regioselectivity of the C1-methyl of **5**, which may be further used for structural modification in drug discovery (Scheme 2b).

In order to gain an insight into the preliminary mechanism, we carried out several mechanistic experiments. Firstly, an H/D exchange experiment of aryl oxime **1 a** was performed to probe the reversibility of the C–H activation. A notable deuterium scrambling was observed when the reaction was performed under standard reaction conditions in CD_3OD for 12 h (Scheme 3a). The C(sp^2)–H activation of the benzene ring was reversible process with approximately 36.5% deuteration at the *ortho* positions of the aryl oxime, and 46.7% deuteration at the methyl of the aryl oxime which may be a result of the isomerization of imine and enamine. Next, the kinetic isotope effect (KIE) experiments were carried out and the results indicated that C–H cleavage may not be the rate-limiting step, as evidenced by the values of $k_H/k_D = 1.86$ (measured from the competition experiment) and $k_H/k_D = 1.92$ (measured from parallel reactions) as shown in Scheme 3b. Meanwhile, the competition experiment between the electron-donating substituted **1 b** and



Scheme 2. Gram-scale Preparation and Conversion of **3 aa**.



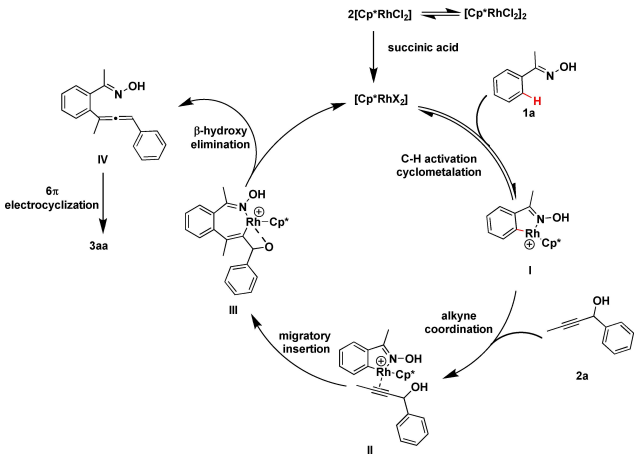
Scheme 3. Preliminary Mechanism Studies.

electron-withdrawing substituted **1 h** revealed that the transformation favored the electron-rich aryl oxime with ratio of 4/1 (Scheme 3c). Likewise, the competition experiment was also conducted between different propargyl alcohols **2 e** and **2 g**, and the result indicated that the electron-withdrawing group on the benzene ring of propargyl alcohol had a slightly better impact than the electron-donating group (Scheme 3d). Besides, we conducted the experiment of propargyl alcohol alone under standard conditions (Scheme 3e), and the results showed that propargyl alcohol may be not esterified with stoichiometric succinic acid under standard conditions.

On the basis of the preliminary mechanistic experiments and precedent literature reports,[5,7d,14] we proposed a possible mechanism (Scheme 4). Firstly, the catalyst is generated through anion exchange and further coordinates with aryl oxime **1 a** to form the five-membered rhodacyclic intermediate **I** by reversible C–H bond activation. The metal species was subsequently coordinated with propargylic alcohol **2 a** to afford the intermediate **II**, followed by regioselective insertion into Rh–C to give carbometalated intermediate **III**, and then β-hydroxy elimination affords the allene intermediate **IV**, which undergoes a 6π electrocyclization to afford the target compound **3 aa**.

Conclusion

In summary, we serendipitously found an unusual aspect of secondary propargyl alcohols that could smoothly couple with aryl oximes *via* a Rhodium-catalyzed C–H activation and β-hydroxy elimination to form a series of isoquinoline *N*-oxides. What is noteworthy is that the secondary propargyl alcohols underwent an unreported β-hydroxy elimination instead of common oxidization to carbonyl groups in this Rh-catalyzed C–H activation and annulation cascade to form 2-benzyl substituted isoquinoline *N*-oxides with mild reaction conditions and good function group tolerance.



Scheme 4. Proposed Catalytic Cycle.

Experimental Section

A pressure tube was charged with aryl oxime (**1 a**, 55 mg, 0.4 mmol) and propargyl alcohol (**2 a**, 119 mg, 0.8 mmol), $[Cp^*RhCl_2]_2$ (20 mg, 8 mol%), succinic acid (96 mg, 0.8 mmol) and MeOH (4 mL). The reaction mixture was stirred at 90 °C for 12 h. After the reaction completed, dichloromethane (DCM) 10 mL was added and the mixture was filtered through a pad of celite which was subsequently washed with DCM. Then the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using PE/EA (5:1–1:1) to afford the product **3 aa**.

Acknowledgements

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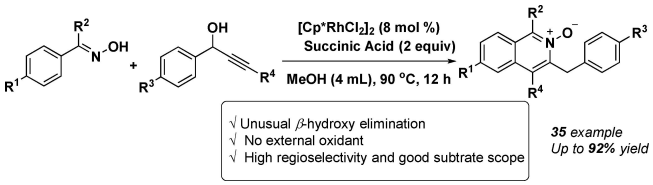
RESEARCH ARTICLE

Rhodium-Catalyzed C–H Activation/Annulation Cascade of Aryl Oximes and Propargyl Alcohols to Isoquinoline *N*-Oxides



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