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# Rhodium(III)-catalyzed annulation of arenes with alkynes assisted by an internal oxidizing N–O bond†

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**Rh(III)-catalyzed C–H activation of 3-aryl-dihydroisoxazoles in the coupling with diarylacetylenes has been developed under redox-neutral conditions. This reaction occurred under mild conditions with no by-product, and the N–O bond functions as an oxidizing directing group, leading to efficient synthesis of isoquinolines functionalized with a proximal secondary alcohol.**

Isoquinolines are an important class of heterocyclic compounds that exhibit important biological activity for pharmaceutical studies and have found other important applications.[1] Therefore, development of simple and mild synthetic methods to access this moiety has been increasingly explored. Of the many synthetic methods developed, the traditional routes such as Bischler–Napieralski, Pomeranz–Fritsch, and Pictet–Gams reactions are well known.[2] However, they most often require harsh reaction conditions and highly active substrates. Alternatively, transition metal catalysis offers an attractive alternative. Thus, isoquinoline synthesis *via* transition metal-catalyzed annulation between *ortho*-haloarylimines and internal alkynes has been developed as a useful method. However, a preactivated form of an arene substrate is necessary.[3] On the other hand, transition metal-catalyzed C–H bond activation has emerged as an important strategy in organic synthesis.[4] Notably, Rh(I)-catalyzed synthesis of isoquinolines *via* C–H activation of arenes, imines, or oximes under redox-neutral conditions has been reported by the groups of Jun,[5] Cheng,[6] and Bergman and Ellman,[7] where high temperature was generally necessary due to the relatively low activity of the Rh(I) catalyst. Later, Ru(II)- and Mn-catalyzed synthesis of isoquolines *via* C–H activation has also been reported.[8]

Recently, Cp*Rh(III) complexes have proved to be highly active catalysts in C–H activation of arenes, and they stand out among most frequently used catalysts in a vast number of transformations.[9] In fact, Cp*Rh(III) catalysts have been employed for the synthesis of isoquolines. In the pioneering work, Fagnou[10] and Miura[11] independently developed Rh(III)-catalyzed synthesis of isoquolines *via* oxidative coupling between aldimines and alkynes. Since Fagnou and co-workers reported redox-neutral couplings using N–O cleavage as an internal oxidant,[12] various internal oxidizing directing groups have been developed for the synthesis of isoquinoline derivatives.[13] In nearly all these syntheses, isoquinolines were produced together with a small molecule co-product. In addition, the isoquinoline products also have limited molecular complexity. Herein, we disclose a Rh(III)-catalyzed 100% atom-economical, mild synthesis of isoquinolines *via* C–H activation of 3-aryl-dihydroisoxazoles, and the coupling with internal alkynes was assisted by an internal oxidizing N–O bond.

We initiated our studies with the screening of the reaction conditions for the coupling of 3-phenyldihydroisoxazole (**1a**) with diphenylacetylene (**2a**) using $[RhCp^*Cl_2]_2$ as a catalyst at 60 °C (Table 1). Coupling using CsOAc as a base in MeOH resulted in the formation of **3aa** in 32% isolated yield (entry 1). MeCN proved unviable for this transformation (entry 2). We further screened several other solvents such as DCE, EtOH, and HFIP (entries 3–5). To our delight, product **3aa** was isolated in 76% yield when HFIP was employed (entry 5). Under these conditions, on changing the base all gave inferior results (entries 6 and 7). Thus the following conditions were eventually established for subsequent studies: $[RhCp^*Cl_2]_2$ (4 mol%), and CsOAc (30 mol%) in HFIP at 60 °C for 12 h.

With the optimal reaction conditions in hand, we first examined the scope and limitations with respect to a dihydroisoxazole substrate (Fig. 1, **1a–f**). Dihydroisoxazoles fused with various carbocycles were well-tolerated and the coupling

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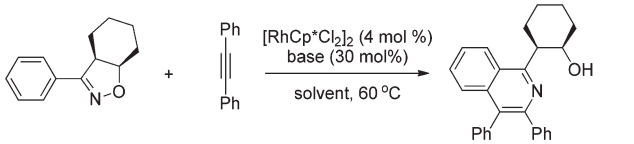
**Table 1** Optimization studies[a]




1a 2a 3aa

| Entry | Base | Solvent | Yield[b] (%) |
|---|---|---|---|
| 1 | CsOAc | MeOH | 32 |
| 2 | CsOAc | MeCN | nd |
| 3 | CsOAc | DCE | 37 |
| 4 | CsOAc | EtOH | Trace |
| 5 | CsOAc | HFIP | 76 |
| 6 | NaOAc | HFIP | 29 |
| 7 | CsOPiv | HFIP | 60 |

[a] Reaction conditions: $[RhCp^*Cl_2]_2$ (4 mol%), base (30 mol%), **1a** (0.20 mmol), and **2a** (0.24 mmol) in solvent (2 mL) at 60 °C for 12 h. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. [b] Yield of isolated product.

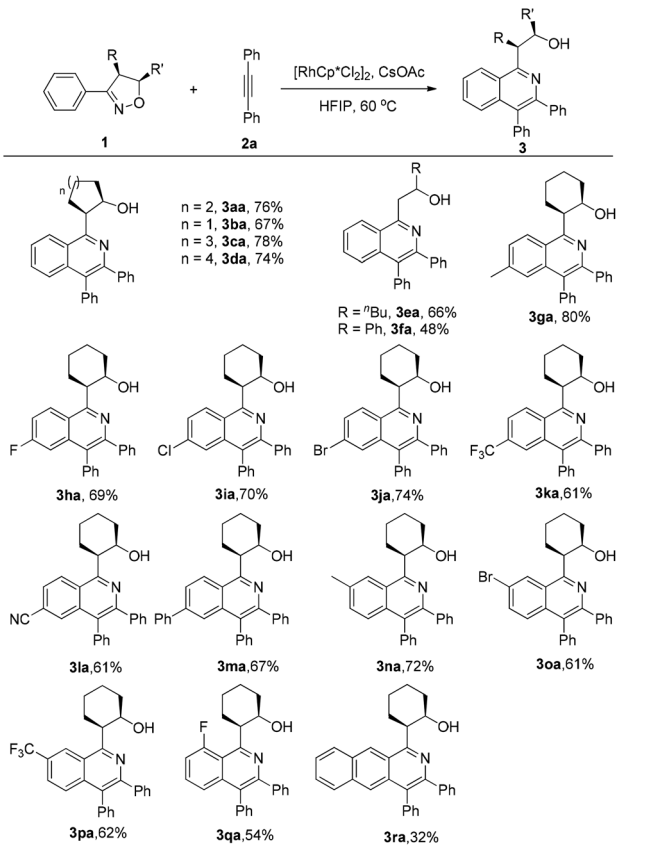



**Fig. 1** Substrate scope of dihydroisoxazole. Reaction conditions: $[RhCp^*Cl_2]_2$ (4 mol%), CsOAc (30 mol%), **1** (0.20 mmol), and **2a** (0.24 mmol) in HFIP (2 mL) at 60 °C for 12 h. Yield of the isolated product.

afforded products **3aa–da** in 67–78% isolated yields. Thus, the reaction efficiency is essentially not affected by the size of the fused ring. In the absence of any fused ring, the corresponding homobenzylic alcohol products (**3ea** and **3fa**) were obtained in 66% and 48% yields when $^n$Bu- and Ph- were introduced to the 5-position of dihydroisoxazole, respectively. Substrates bearing methyl, halo, trifluoromethyl, phenyl, and cyano groups at the *para* position of the benzene ring all reacted smoothly resulting in moderate to good yields (**3ga–ma**). Dihydroisoxazoles bearing methyl, bromo and trifluoromethyl groups at the *meta* position of the benzene ring coupled with **2a** to give the corresponding products **3na–pa** in moderate yields, and the coupling corresponds to C–H activation at the less hindered *ortho* C–H position. *ortho*-Substituted arene is also applicable as in the coupling of 2-fluorophenyl dihydroisoxazole that afforded product **3qa** in 54% yield. The desired product was isolated in only 32% yield when a 2-naphthyl ring was introduced to the dihydroisoxazole (**3ra**). Unfortunately, when heteroarene substrates such as thiophene were subjected to the standard conditions, only traces of the product were detected.

We next explored the scope of the alkyne substrate in this reaction (Fig. 2). The annulative coupling between **1a** and various symmetric diarylacetylenes bearing electron-donating or electron-withdrawing groups at the *para* or *meta* position took place to afford the corresponding products in 66–73% yields (**3ab–ag**). This reaction is also compatible with *ortho*-fluoro substituted diarylacetylene, from which product **3ah** was isolated in 71% yield. It's noted that **1a** coupling with unsymmetrical diarylacetylene **3i** displayed moderate reactivity but high regioselectivity (**3ai**). However, *ortho*-methyl substituted diarylacetylene reacted very poor, and di(2-thienyl)-acetylene, 3-hexyne, (cyclopropylethynyl)benzene, methyl 3-phenylpropiolate, and phenylacetylene all failed to undergo the desired reaction.

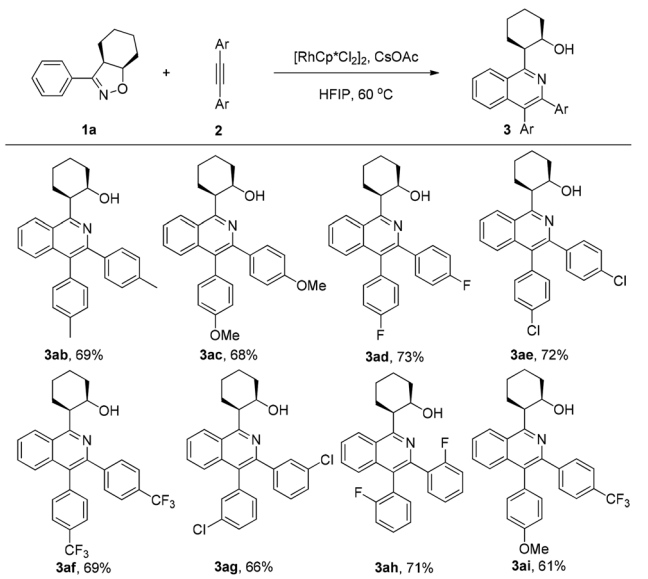
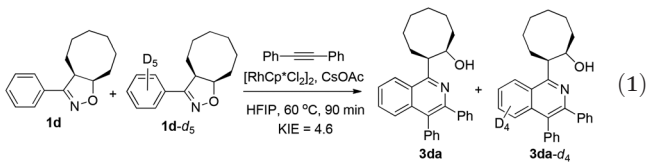
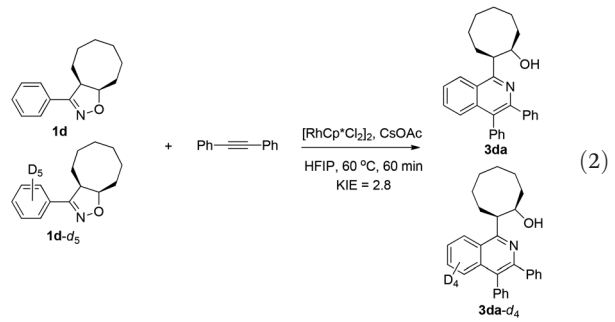



**Fig. 2** Substrate scope of alkynes. Reaction conditions: $[RhCp^*Cl_2]_2$ (4 mol%), CsOAc (30 mol%), **1a** (0.20 mmol), and alkyne (0.24 mmol) in HFIP (2 mL) at 60 °C for 12 h. Yield of the isolated product.



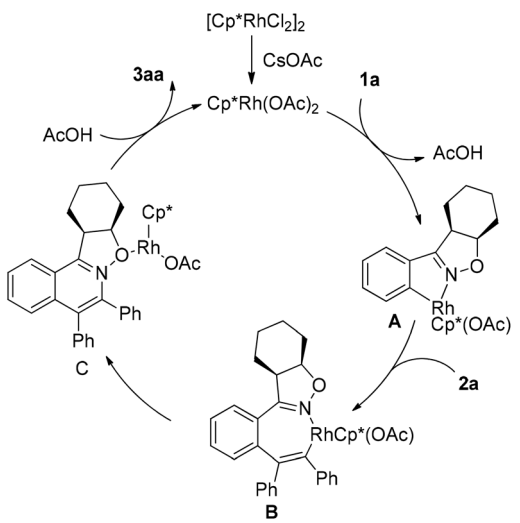

(1)




(2)

To gain preliminary insights into the reaction mechanism, the kinetic isotope effect (KIE) of this reaction has been measured. KIE values determined from an intermolecular competition (eqn (1)) and two parallel reactions of 4.6 and 2.8 were obtained at a low conversion (eqn (2)), indicating that C–H bond cleavage of **1d** is probably involved in the turnover-limiting step.

Based on these observations and literature precedents,[14] a proposed reaction mechanism is given in Scheme 1. Starting from $Cp^*Rh(OAc)_2$ as an active catalyst, coordination of **1a** to rhodium and subsequent C–H activation generates a five-membered rhodacycle **A**. Then, coordination and insertion of the alkyne **2a** into the Rh–C bond gives a seven-membered rhodacyclic intermediate **B**, which undergoes reductive elimination to afford a Rh(I) intermediate **C**. Subsequent N–O oxidative addition[15] followed by protonolysis affords product **3aa**, together with regeneration of the active Rh(III) catalyst for the next cycle.




**Scheme 1** A proposed simplified catalytic cycle.

## Conclusions

In summary, we developed Rh(III)-catalyzed C–H activation of 3-aryl-dihydroisoxazoles in the coupling with diarylacetylenes under redox-neutral conditions. This reaction is operationally simple and occurred under mild conditions with no by-product being generated, where the N–O bond functions as an oxidizing directing group, leading to efficient synthesis of isoquinolines functionalized with a proximal secondary alcohol. This system expanded the applications of Rh(III)-catalyzed C–H activation of arenes.

## Acknowledgements

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