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Rhodium(III)-Catalyzed Heterocycle Synthesis Using an Internal Oxidant: Improved Reactivity and Mechanistic Studies

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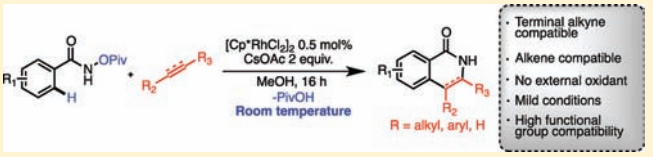
Supporting Information

ABSTRACT: Directing groups that can act as internal oxidants have recently been shown to be beneficial in metal-catalyzed heterocycle syntheses that undergo C−H functionalization. Pursuant to the rhodium(III)-catalyzed redox-neutral isoquinolone synthesis that we recently reported, we present in this article the development of a more reactive internal oxidant/directing group that can promote the formation of a wide variety of isoquinolones at room temperature while employing low catalyst loadings (0.5 mol %). In contrast to previously reported oxidative rhodium(III)-catalyzed heterocycle syntheses, the new conditions allow for the first time the use of terminal alkynes. Also, it is shown that the use of alkenes, including ethylene, instead of alkynes leads to the room temperature formation of 3,4-dihydroisoquinolones. Mechanistic investigations of this new system point to a change in the turnover limiting step of the catalytic cycle relative to the previously reported conditions. Concerted metalation−deprotonation (CMD) is now proposed to be the turnover limiting step. In addition, DFT calculations conducted on this system agree with a stepwise C−N bond reductive elimination/N−O bond oxidative addition mechanism to afford the desired heterocycle. Concepts highlighted by the calculations were found to be consistent with experimental results.

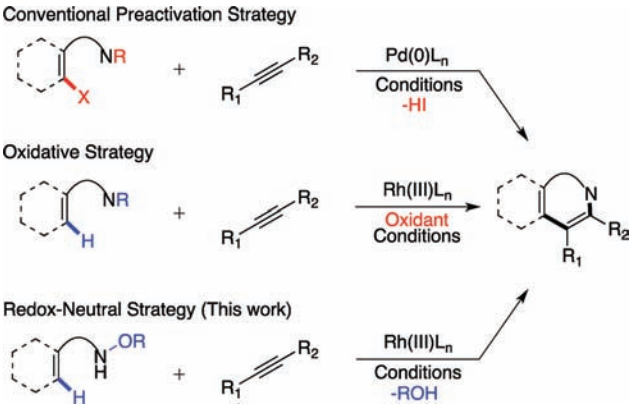


INTRODUCTION

The wealth of nitrogen-containing heterocycles in biologically active molecules has provided a driving force for chemists to develop increasingly efficient methods toward their synthesis.[1] While the construction of many heterocyclic molecules traditionally required harsh conditions, transition metal catalysis has provided advantageous alternatives. Indeed, recently developed methods now allow for mild, functional group tolerant and high yielding syntheses of several types of valuable heterocyclic compounds. Intermolecular methods involving palladium-catalyzed oxidative addition/reductive elimination steps constitute outstanding examples as they provide an effective approach to a wide variety of heterocycles through instinctive bond disconnections.[2] Pioneering work from Larock is illustrative, wherein a substrate containing both a nitrogen-containing moiety and a carbon-halide bond can undergo annulation with an alkyne (Scheme 1).[3] Although these protocols have proved to be effective, as demonstrated by their utilization in medicinal chemistry[4] and natural product syntheses,[5] they are limited by the availability of the preactivated substrates, which can be expensive or nontrivial to prepare.

To address this drawback, our group and others have recently focused on exploiting a C−H bond under oxidative conditions in place of a C−X bond, which allows the use of easily accessible starting materials.[6] The strategy typically makes use of the nitrogen-containing moiety as a directing group to effect cyclometalation at the C−H bond.[7] Then, insertion of an alkyne can be followed by C−N bond reductive elimination to yield the desired heterocycle.[8] Cp*Rh(III)L_n were found to be competent catalysts for these transformations.[9] As a result, within the last three years, methods to synthesize indoles,[6a−d] isoquinolines,[6e−g] isoquinolones,[6d,h−j] pyrroles,[6b,c,k] and pyridones[6j,l] have been developed. One common feature of all these reactions is the requisite use of internal alkynes, which give rise exclusively to disubstituted heterocycles. This limitation stems from of the use of $Cu(OAc)_2 \cdot H_2O$ as oxidant to turnover the rhodium catalyst. Dimerization occurs preferentially when terminal alkynes are employed, preventing the monosubstituted heterocycle from being formed.

Scheme 1. Heterocycle formation through Cross-Coupling/Cyclization



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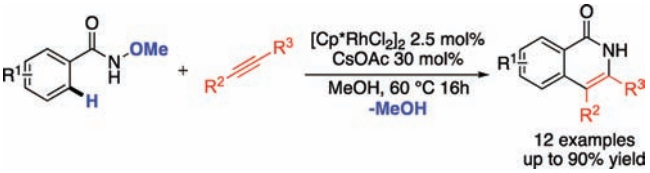
Scheme 2. External-Oxidant Free Isoquinolone Synthesis



In recent elegant reports, Satoh and Miura,[10] Glorius,[11,12] and Bergman and Ellman[13] independently demonstrated that using alkenes under very similar conditions resulted in oxidative olefination reaction.[14] These reactions demonstrate the capability of Rh(III) catalysts to insert into alkenes and then β-hydride eliminate. However, reports on the use of alkenes to form saturated heterocycles via C(sp^3)−N bond reductive elimination remain rare.[12]

We have recently reported the synthesis of isoquinolones from benzamide-type starting materials (Scheme 2).[15−17] Our initial strategy was to employ a hydroxamic acid as a strong directing group to effect the *ortho* metalation. Yu has pioneered their use as a directing group with various palladium-catalyzed C−H functionalization reactions.[18] Interestingly, we realized that when employing this directing group, no external oxidant was needed to turn over the rhodium catalyst and yield the desired isoquinolone. The N−O bond contained in the substrate was cleaved during the reaction and found to obviate the need for an external oxidant, which is an emerging concept that has been employed very recently in the context of a palladium-catalyzed C−H functionalizations by Hartwig[19] and Cui and Wu.[20] Since this isoquinolone synthesis does not require copper additives, we surmised that further development of the method could address some of the alkyne related limitations previously mentioned.

In this article, we describe (1) the optimization of the internal oxidant/directing group leading to the discovery of increased reactivity which allows heterocycle formation to be performed at room temperature using low catalyst loading; (2) the expanded scope of the reaction which now enables the use of terminal alkynes and alkenes, the former yielding monosubstituted isoquinolones and the later giving saturated heterocycles while furnishing C(sp^3)−N bonds; (3) computational and experimental studies which reveal important insights about the mechanism of the redox-neutral rhodium-catalyzed isoquinolone formation; and (4) the application of these findings to the synthesis of isoquinolines.

RESULT AND DISCUSSION

Internal Oxidant Optimization. We previously reported an isoquinolone synthesis from the coupling of *N*-methoxyhydroxamic acids with alkynes.[15] Although the reaction conditions reported were mild, we questioned whether it would possible to achieve better reactivity by modifying the nature of the built-in oxidant. We reasoned that using hydroxamic acids bearing better leaving groups, or groups that could better stabilize intermediates of the catalytic cycle (Figure 1), would be beneficial to the reaction.

With this mind set, a variety of hydroxamic acid-type substrates were synthesized, each one having a different leaving group on the nitrogen. Since the reaction was known to be more challenging with internal alkynes substituted with

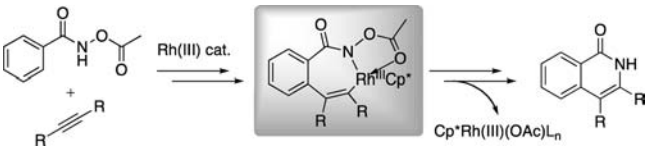


Figure 1. Proposed stabilized intermediate in the catalytic cycle.

two alkyl groups, substrate optimization was performed using both diaryl-substituted and dialkyl-substituted alkynes (Chart 1). Being uncertain about the nature of the C−N bond forming/N−O bond cleaving process, we first surveyed built-in oxidants that have very similar leaving group ability as our original directing group. However, no yield improvement was observed with the hydroxy (**1b**) or the phenoxy (**1c**) groups. We then synthesized a variety of carboxylate-type internal oxidants. Such substrates provided a major yield improvement when using 4-octyne (**2b**). Both the pivalate (**1e**) and the benzoate (**1f**) gave an almost quantitative yield with **2a** and 85% yield using **2b**. A carbonate (**1g**) and a highly hindered mesytoyl (**1h**) leaving groups also gave good yields with **2a** and **2b**. This increased reactivity could potentially be due to the better leaving group ability of the acetate and to an interaction of the carbonyl's oxygen lone pair with the rhodium catalyst (Figure 1). We believed that the N−O bond cleaving/C−N bond forming step might be facilitated by such interactions. Following this idea, substrate **1i** was synthesized in order to have the trichloroacetimide's nitrogen to act as an even stronger intramolecular sigma donor for rhodium. However, no isoquinolone was observed when this substrate was used as starting material. Nitrogen leaving groups were also tested (**1j**, **1k**), however, they were unsuccessful due to the strength of the N−N bonds in these moieties. Considering these results, the pivaloyl group was selected for further reaction development.

Next, we sought to evaluate the improved reactivity provided by the new internal oxidant (Table 1). It was found that, while keeping the temperature at 60 °C, the catalyst loading could be reduced to 0.5 mol % Rh(III) dimer without impacting the yield (Table 1, entry 2). However, lowering the Rh(III) dimer content to 0.5 mol % decreased the yield considerably (Table 1, entry 3). We were then pleased to find that running the reaction at room temperature could also provide nearly quantitative yields while using only 0.5 mol % Rh(III) (Table 1, entry 5). Lowering the catalyst loading to 0.1 mol % at this temperature resulted in an incomplete reaction affording 61% ^{1}H NMR yield after 16 h. Finally, it is noteworthy that the isoquinolone synthesis can be performed on gram-scale using 0.5 mol % Rh(III) to afford 3,4-diphenylisoquinolone in 96% isolated yield (Table 1, entry 7).

Improved Reaction Scope. With the newly found optimal internal oxidant, a reinvestigation of the scope of the isoquinolone synthesis previously reported was carried out. All the experiments were conducted with 0.5 mol % rhodium(III) dimer at room temperature. Chart 2 presents a comparison of the previously reported and newly designed conditions. With diaryl-substituted alkynes, yields remain high with both systems (Chart 2, **3a**−**c**). The electron withdrawing or donating character of the substituents on the hydroxamic acids does not seem to affect the outcome of the reaction. When a meta-subsituted starting material is employed, the corresponding isoquinolone is obtained as a single regioisomer (Chart 2, **3d**). Moreover, in

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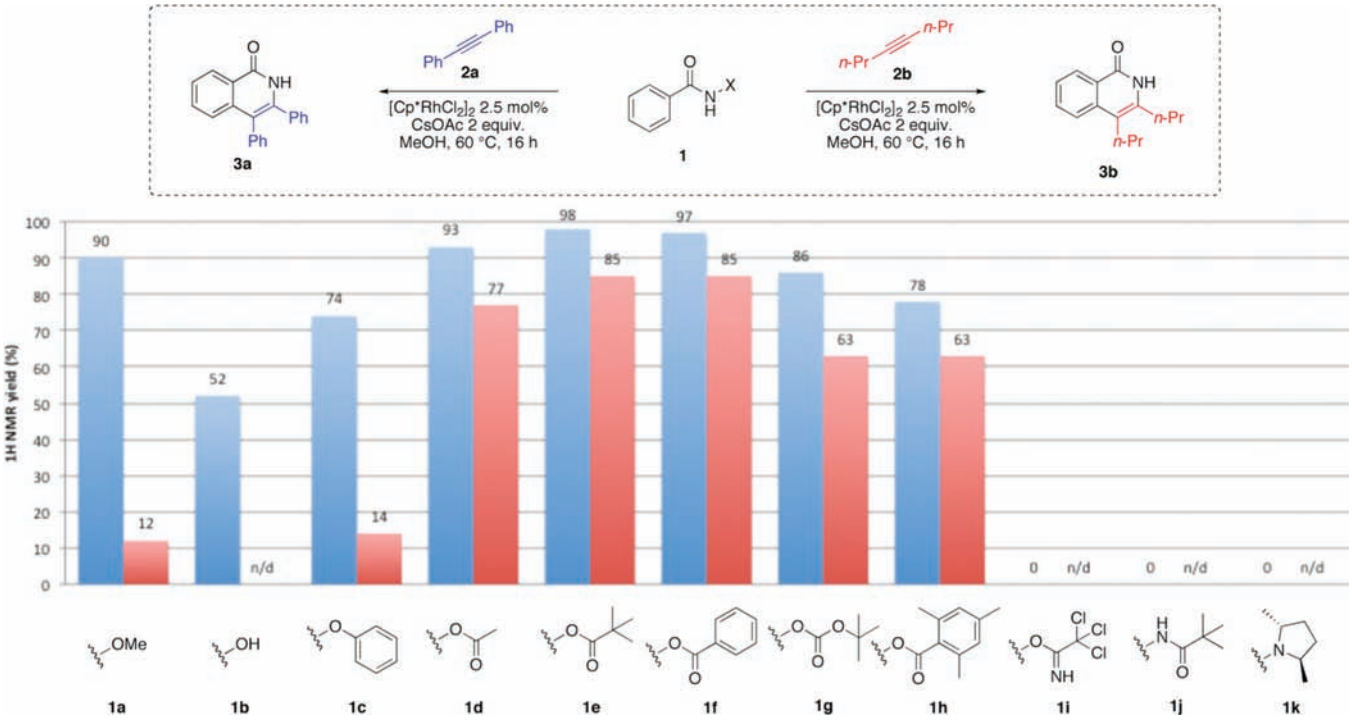
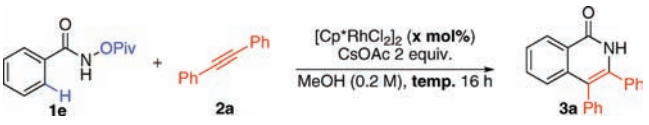
Chart 1. Internal Oxidant Optimization[a,b]



[a]Conditions: **1** (1 equiv, 0.2 mmol), **2a** or **2b** (1.1 equiv, 0.22 mmol), CsOAc (2 equiv, 0.4 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), MeOH (0.2 M), 60 °C, 16 h. [b]^{1}H NMR yield vs trimethoxybenzene as internal standard.

Table 1. Increased Reactivity Provided by the Pivalate Internal Oxidant[a]

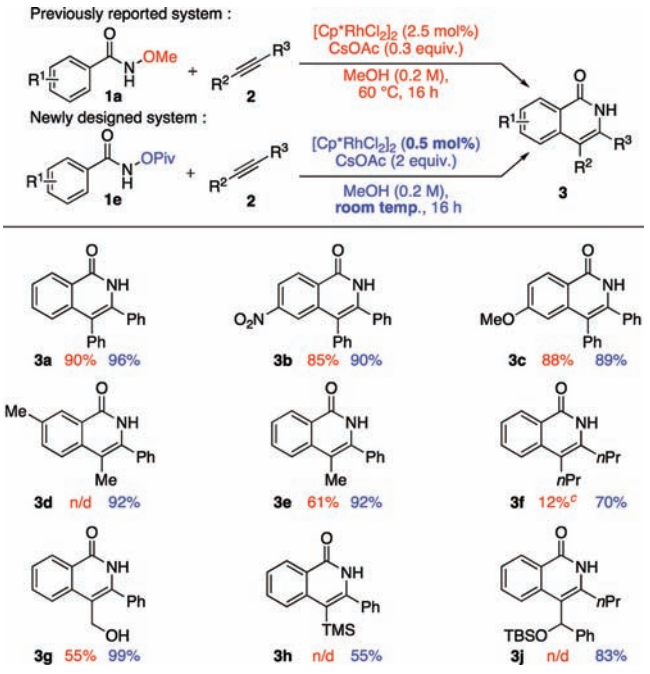


entry	temperature (°C)	catalyst loading (mol %)	^{1}H NMR yield **4a**[b]
1	60	2.5	97
2	60	0.5	99
3	60	0.05	33
4	rt	2.5	99
5	rt	0.25	99
6	rt	0.05	61
7[c]	rt	0.25	96 (isolated)

[a] Conditions: **1e** (1 equiv, 0.20 mmol), **2a** (1.1 equiv, 0.22 mmol), CsOAc (2 equiv, 0.40 mmol), $[Cp^*RhCl_2]_2$ (*x* mol %), MeOH (0.2 M), specified temperature, 16 h. [b] ^{1}H NMR yield vs trimethoxybenzene as internal standard. [c] Reaction conducted on a 1.00 g scale of **1e**.

contrast to the first generation system (N-OMe), the use of alkyl-aryl disubstituted alkynes gave high yields and high regioselectivity with the sp^2 center being installed at the 3-position of the heterocycle. Interestingly, a TMS-protected alkyne was also tolerated, which constitutes a useful handle for further functionalization (Chart 2, **3h**). Additionally, while dialkyl substituted alkynes were problematic with the previously reported

Chart 2. Internal Alkyne Scope[a,b]



[a]Conditions: Previous system: **1a** (1 equiv., 0.20 mmol), **2** (1.1 equiv., 0.22 mmol), CsOAc (0.3 equiv., 0.06 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), MeOH (0.2 M), 60 °C, 16 h. New system: **1e** (1 equiv., 0.20 mmol), **2** (1.1 equiv., 0.22 mmol), CsOAc (2 equiv., 0.40 mmol), $[Cp^*RhCl_2]_2$ (0.5 mol %), MeOH (0.2 M), room temp., 16 h. [b]Isolated yields are reported. [c] ^{1}H NMR yield.

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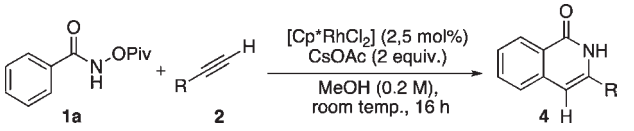
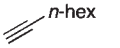
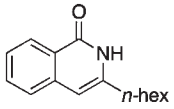
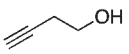
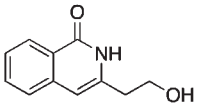
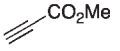
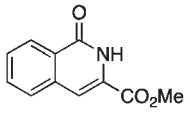
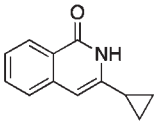
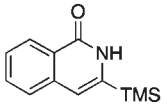
conditions, they are now well suited using the pivaloyl group as internal oxidant. When unsymmetrical dialkyl-substituted alkynes are employed, the more sterically demanding group will typically be installed at the 4-position (Chart 2, **3j**). This outcome is in agreement with previous reports on rhodium-catalyzed heterocycle formation.[6a−c,e,h]

As mentioned earlier, an important limitation encountered with the recently developed rhodium-catalyzed oxidative synthesis of nitrogen-containing heterocycles was the inability to incorporate terminal alkynes. Their use has primarily lead to alkyne dimerization (glaser coupling) due to the Cu(II) oxidant typically employed in these reactions. As a result, only disubstituted heterocycles have been synthesized using Rh(III)-catalyzed methods.[6] With the newly designed copper-free conditions, a reinvestigation of this restraint was conducted. It was found that terminal alkynes were now tolerated and give the desired monosubstituted heterocycle in moderate to high yield. In addition, the regioselectivity of their insertion is highly predictable, with the terminal end being located at the 4-position. As shown in Table 2, with yields ranging from 85% to 95%, the reaction is compatible with alkyl-substituted terminal alkynes. Performing the heterocycle formation at 60 °C also allowed for the formation of a 3-methylester monosubstituted isoquinolone (Table 2, **4c**). Moreover, we were pleased to observe that trimethylsilylacetylene is a suitable alkyne yielding an isoquinolone that can be subsequently functionalized (Table 2, **4e**). Phenylacetylene was also subjected to the reaction conditions; however, none of the desired product was observed.

With recent reports on oxidative olefinations using Cp*Rh(III)L_n as catalysts,[10−13,21] we were interested in investigating the use of alkenes under our new conditions to access the corresponding 3,4-dihydro heterocycle. The inherent challenge with this method is the formation of the C(sp^3)−N bond while avoiding the well-documented β-hydride elimination which gives rise to Heck-type products. To do so, the C−N bond forming/N−O bond cleaving step must be lower in energy than β-hydride elimination. Considering the mild reaction conditions required for the isoquinolone synthesis, we presumed that the formation of the unsaturated heterocycle could occur preferentially. Indeed, it was found that alkenes do undergo insertion followed by C−N bond formation with no product arising from β-hydride elimination (Table 3). Following the same trend as their alkyne counterparts, alkenes substituted with a vicinal sp^2 carbon center provide the 3,4-dihydroisoquinolone with the sp^2-hybridized substituent generally located at the 3-position (Table 3, entries 1 and 2). With respect to sp^3 substituted terminal alkenes, the products obtained were typically a mixture of regioisomers which were separable by flash column chromatography (Table 3, entries 5 and 6). A current limitation to the alkene scope is the poor reactivity of acyclic internal alkenes and unactivated cyclic alkenes. Both diaryl-substituted and dialkylsubstituted alkenes failed to react under our reaction conditions.[22] However, strained cyclic substrates such as norbornadiene, cyclohexadiene, and 2,3-dihydrofuran were found to react readily providing tricyclic structures (Table 3, entries 2−4). Interestingly, the unsubstituted 3,4-dihydroisoquinolone can also be synthesized at ambient pressure and ambient temperature using a balloon of ethylene (Table 3, entry 8). It is of note that 3,4-dihydroisoquinolone **6c** can undergo a retro-Diels−Alder reaction providing the unsubstituted isoquinolone **4f** in high yield (Scheme 3).[23] The scope highlights the validity of the method

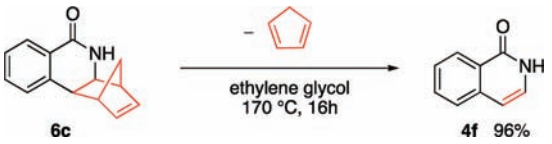
Table 2. Terminal Alkyne Scope[a]



Entry	Alkyne	Product	Yield[b]
1			**4a** 92%[c]
2			**4b** 85%[d]
3			**4c** 49%[d]
4			**4d** 95%
5			**4e** 75%

[a] Conditions: **1g** (1 equiv, 0.20 mmol), **2** (1.1 equiv, 0.22 mmol), CsOAc (2 equiv, 0.40 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), MeOH (0.2 M), room temperature, 16 h. [b] Isolated yields are reported. [c] 0.5 mol % $[Cp^*RhCl_2]_2$ was employed. [d] Reaction ran at 60 °C.

Scheme 3. Access to unsubstituted isoquinolone via retro Diels-Alder reaction



to construct, in a minimal amount of steps, a wide variety isoquinolones having various substitution patterns while generating only pivalic acid as a byproduct.

Computational and Experimental Mechanistic Investigations. The observed increase in reactivity provided by the *O*-pivaloylhydroxamic acid directing group/internal oxidant as well as the uncertain nature of the C−N bond forming/N−O bond cleaving step of the catalytic cycle prompted us to further investigate the mechanism of this transformation. We determined in our previous communications on the subject that the first step of the catalytic cycle was likely a reversible arene rhodation.[15] We proposed that alkyne insertion was then occurring,[24] which was followed by a concerted or stepwise C−N bond forming/N−O bond cleaving step. It was also demonstrated from crossover experiments that the N−O bond cleavage happened in an intramolecular sense (Scheme 4). From

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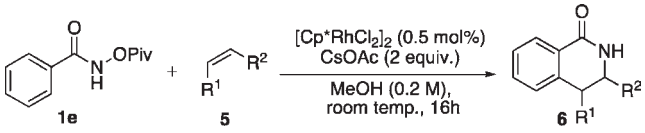
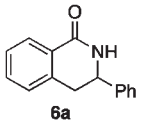
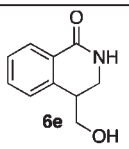
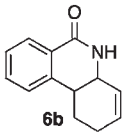
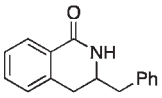
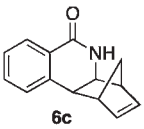
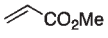
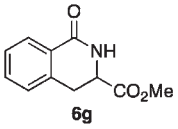
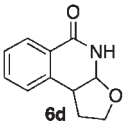
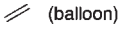
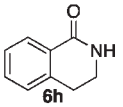
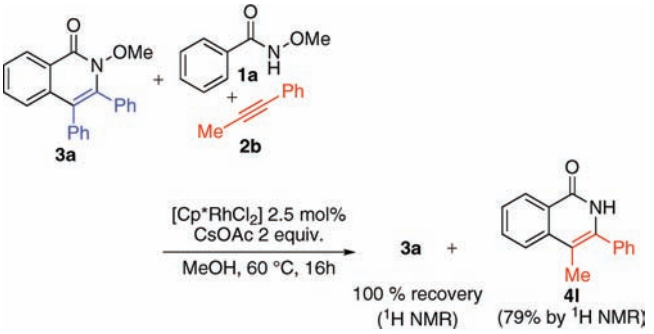
Table 3. Alkene Scope[a]



Entry	Alkene	Product	Yield[b]	Regioselectivity	Entry	Alkene	Product	Yield[b]	Regioselectivity
1		 **6a**	90%	>20:1	5		 **6e**	85%[c]	~1.3:1
2		 **6b**	77%	>20:1	6		 **6f**	85%[c]	2:1
3		 **6c**	91%	N/A	7		 **6g**	95%	1:4.5[d]
4		 **6d**	77%	>20:1	8		 **6h**	95%	N/A

[a] Conditions: **1e** (1.0 equiv, 0.20 mmol), **5** (1.1 equiv, 0.22 mmol), CsOAc (2.0 equiv, 0.40 mmol), $[Cp^*RhCl_2]_2$ (0.5 mol %), MeOH (0.2 M), room temperature, 16 h. [b] Isolated yields are reported. [c] Isolated yield of both regioisomers. [d] Inseparable mixture of regioisomer.

Scheme 4. Crossover Experiment Showing the Intramolecular Nature of the N−O Bond Cleavage



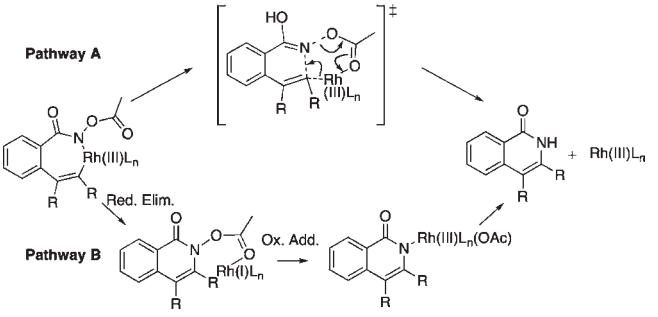


Figure 2. Mechanistic hypotheses for the C−N bond forming/N−O bond cleaving event.

this last piece of information, we reasoned that two mechanistic pathways could account for the last steps of the catalytic cycle (Figure 2). Pathway A consists of a concerted process where a highly organized six-membered cyclic transition state accounts for simultaneous C−N bond formation and N−O bond cleavage. The main characteristic of such a mechanism is that the Rh(III) catalyst remains at the +3 oxidation state throughout the entire catalytic cycle. Pathway B is a more common reductive elimination/oxidative addition process that would occur in a stepwise fashion. The C−N bond reductive elimination would yield an intermediate that would readily proceed to N−O bond oxidative addition. For such a mechanism to be operative and consistent with the experimental data,[15] the oxidative addition would have to occur faster than decoordination of the substrate from the catalyst.

Drawing inspiration from the work of Rovis on a similar system,[6h] a reaction was conducted to establish the reversibility of the cyclometalation in the presence of an alkyne (Scheme 5). Thus, the reaction of **1a** with **2a** using the standard reaction conditions in deuterated methanol was stopped before completion. Compounds **1a** and **3a** were isolated and their deuterium content was analyzed by ^1H NMR. With both recovered compounds, no deuterium incorporation was observed suggesting that cyclometalation is irreversible in presence of **2a**.

From this point, we were intrigued to determine the turnover limiting step of the catalytic cycle. Taking into account the new system's reactivity, it was also appropriate to determine whether

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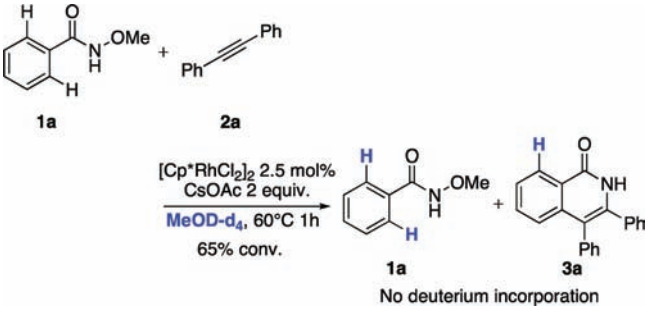
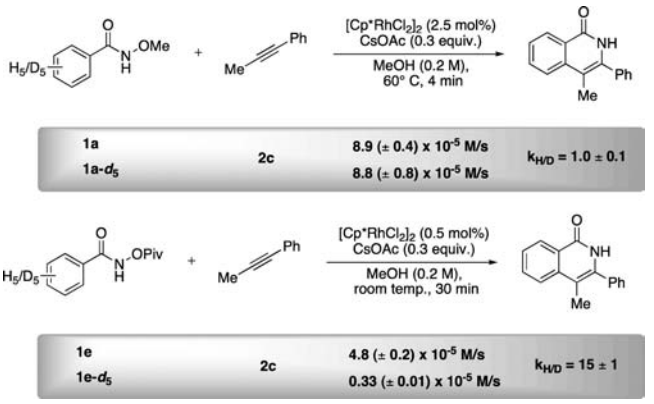
Scheme 5. Irreversibility of Alkyne Insertion



Scheme 6. DKIE Mesurements

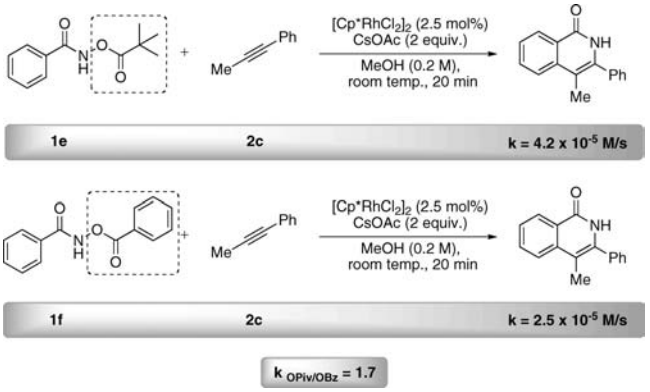


the slow step is the same with both **1a** and **1e**. To do so, we conducted deuterium kinetic isotope effect (DKIE) measurements by comparing the initial rates of both systems side by side. Scheme 6 summarizes the results of this study. No DKIE was observed with the *N*-methoxybenzamide substrate, whereas a large primary DKIE of 15 ± 1 was found with the **1e**. These results suggest that the rate-limiting step depends on the internal oxidant. With **1a**, the rate-limiting step remains uncertain, whereas the use of **1e** makes the C−H bond cleavage the slow step. The high DKIE of 15 ± 1 with **1e** can be explained by tunneling effects.[25]

To corroborate this finding, a rate study of the reaction of **1e** and **1f** with **2c** using the new conditions was conducted (Scheme 7). It was found that while the leaving group ability of benzoate is greater than that of pivalate, the reaction occurred 1.7 times faster with the latter. If the N−O bond cleavage was the turnover limiting step, one would expect the substituent with better leaving group ability to react faster. In this case, since the DKIE experiments suggest the slow step to be the C−H bond cleavage, it is reasonable to find the pivalate to be faster as it is most likely the stronger directing group.

To acquire a better understanding of the overall catalytic cycle, quantum chemical[26] density functional theory[27] (DFT) calculations were conducted for the reaction of substrate **1d** (N-OAc) with acetylene using $CpRh(OAc)_2$ as catalyst. These chemical species were selected to simplify calculations while keeping the essential features of the catalytic cycle as accurate as possible. All computations were performed using the hybrid B3LYP level functional[28,29] with a TZVP[30] basis set for all atoms except rhodium, for which a DZVP[31] basis set was used. Gibbs

Scheme 7. Rate Measurements for Subtrates with a Different Internal Oxidant



free-energy calculations were performed in both the gas phase and with a solvent correction for methanol at 298 K (please refer to Supporting Information for full computational details). The goal of this exercise was to gain insight into the currently unknown nature of the C−N bond forming/N−O bond cleaving event. Scheme 8 presents the relative Gibbs free energy for all the intermediates and transition states, while Scheme 9 shows the resultant catalytic cycle.

The catalytic cycle starts from $CpRh(OAc)_2$ (**I**), which is first coordinated to **1d** with concomitant loss of acetic acid. Next, based on mechanistic investigations of closely related systems[6b,32] and our large primary DKIE, we assumed that C−H bond cleavage would occur via a concerted metalation−deprotonation (CMD) transition state (TS). This step affords intermediate **III**, where acetic acid is still bound to rhodium. The Gibbs free energy of the CMD TS is 20.5 kcal mol^{-1}, which is the highest barrier reached in the catalytic cycle.[33,34] Calculations were also conducted with nondeprotonated **1d** bound to Rh(III) prior to the CMD step. However, a high CMD TS energy of 34.7 kcal mol^{-1} (Scheme 8, red line) was found with this cationic complex for the CMD process. This pathway was consequently ruled out. This calculation however reveals the importance of substrate deprotonation for allowing a low-barrier catalytic cycle. Continuing with the lowest energy pathway, the acetic acid ligand dissociates from intermediate **III** to give intermediate **IV** and then acetylene coordinates to Rh(III) to yield intermediate **V**. From this point, insertion of acetylene in the Rh−C bond can occur to give intermediate **VI**, a process where the TS energy is 11.4 kcal mol^{-1}. Then, reductive elimination via TS3 ($\Delta G^{\ddagger}$ is −0.2 kcal mol^{-1}) allows the C−N bond formation and delivers intermediate **VII**. The low barrier energy for the reductive elimination step would explain its kinetic irrelevance under the new reaction conditions. Subsequently, a fast oxidative addition occurs via TS4 to form intermediate **VIII**, which is finally protonated by acetic acid. This last step yields the desired isoquinolone and regenerates the catalyst. Calculations were also attempted to find the lowest energy pathway of a concerted process analogous to pathway A presented in Figure 2, but no low energy pathway was found to match the experimental data. Consequently, we propose pathway B as being operative in the catalytic cycle. The low energy barrier calculated for the N−O bond oxidative addition correlates well with the

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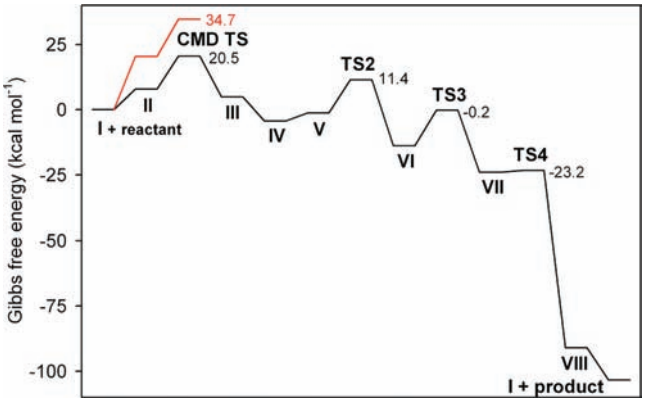
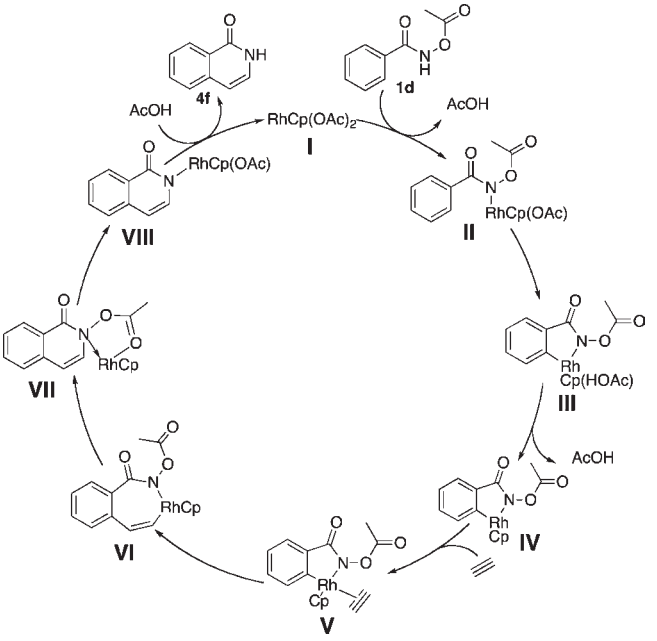
Scheme 8. Free Energy Diagram ($\Delta G^{\ddagger}_{298K}$, kcal·mol^{-1} in Methanol) for the Relevant Intermediates, Transition States and Products for the Reaction of 1d with Acetylene[a]



[a] The neutral and cationic pathway energies are shown in black and red, respectively.

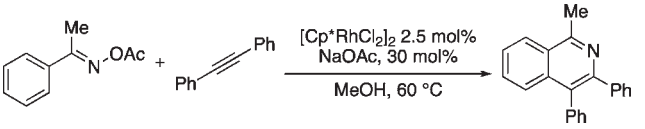
Scheme 9. DFT Calculated Catalytic Cycle



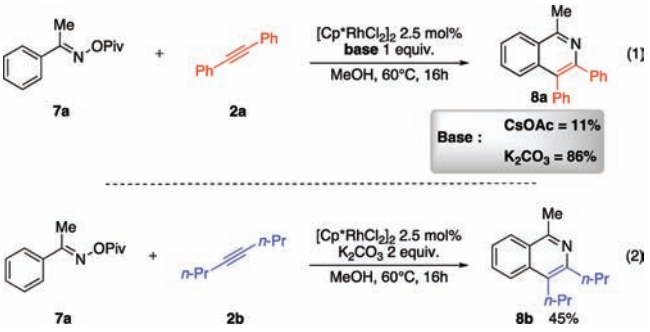
experimental evidence showing that the cleavage of the N−O bond happens intramolecularly on the substrate on which the C−N bond is formed. It is also of note that a cationic pathway, where the substrate's directing group is not deprotonated (acting as an L ligand), is considerably higher in energy than a similar pathway where the complex is neutral.

Isoquinoline Synthesis. With the development of a mild and robust redox-neutral isoquinolone synthesis, we sought to elaborate on this strategy in order to make it compatible with other heterocycle syntheses. Possessing a somewhat similar structure, we targeted the isoquinoline motif as a potential candidate. Although an excellent communication from Chiba recently reported this extension (Scheme 10),[35]

Scheme 10. Chiba's Work with Isoquinolines



Scheme 11. Base Effect in Isoquinoline Synthesis



we were curious to see if the preference for a neutral complex, that is, a complex where the substrate's directing group acts as an X ligand on rhodium throughout the catalytic cycle, was still valid in this system. A series of experiments were conducted to test this hypothesis.

From the outset, we reacted **7a** with **2a** under conditions very similar to the ones we initially developed for the isoquinolone synthesis. The thought behind using **7a** as starting material was to have weakly acidic protons on the methyl *alpha* to the oxime moiety. Thus, deprotonation would provide a neutral Rh(III) complex throughout the catalytic cycle. From this experiment, we were pleased to observe that **8a** was formed in an 11% ^{1}H NMR yield. Changing the base from CsOAc to the stronger K_2CO_3 increased the yield of **8a** to 86% (Scheme 11, eq 1).

Next, **7a** was reacted with the more challenging alkyne **2b** using K_2CO_3 as base (Scheme 11, eq 2). This time, a lower yield of 45% was obtained.[36] Trying to improve this moderate yield, we embarked on the screening of other internal oxidants. Interestingly, when *O*-mesitoylacetophenone oxime (**7b**) was employed as starting material, a further investigation of the crude reaction mixture's ^{1}H NMR spectrum revealed that an almost quantitative amount of ester **9** was produced (Scheme 12). If the reaction would proceed as expected, the corresponding benzoate should be observed in place of the methyl ester. The only way a quantitative amount of ester **9** can be produced is by basic methanolysis of **7b**, which would concomitantly afford the free acetophenone oxime. This interesting finding led us to question whether the simple free oxime could be the actual competent starting material in these isoquinolines syntheses. Thus, oxime **7c** was reacted with **2a** and **2b** in the standard reaction conditions (Scheme 12, eqs 2 and 3). The ^{1}H NMR yields obtained were found to be essentialy the same as the ones obtained using the acyl protectected oximes. This finding confirms that the free oxime is the active starting material. It should consequently simplify the preparation of the substrates undergoing this type of reaction.

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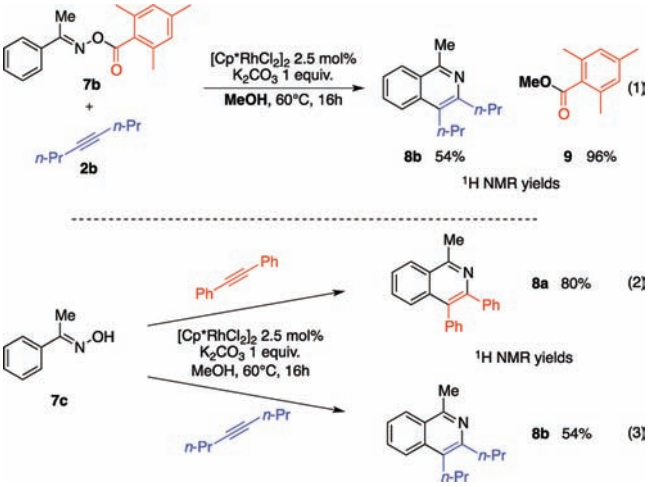
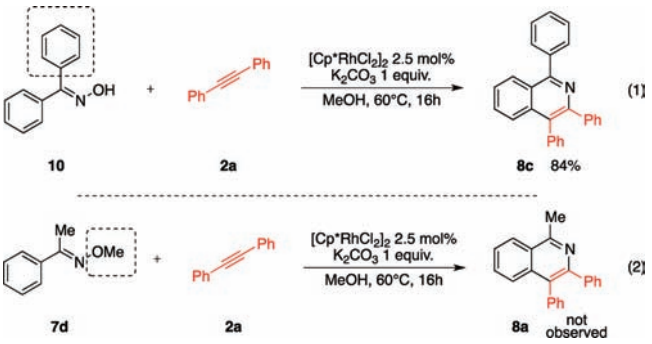
Scheme 12. Observation of a Methylester Side-Product



Scheme 13. Control Experiments



Control experiments were then conducted to verify whether deprotonation of the starting material to obtain a neutral Rh(III) complex was indeed important with this system and, if so, to reveal where the deprotonation occurs. Thus, oxime **10** was first reacted with **2a** in the standard reaction conditions (Scheme 13, eq 1). A ^{1}H NMR yield of 84% was obtained for this reaction, indicating that, in contrast with our initial assumption, deprotonation *alpha* to the oxime was not essential to undergo the desired transformation. Subsequently, a reaction of *O*-methyloxime **7d** with **2a** was run (Scheme 13, eq 2). From this experiment, no desired isoquinoline was observed. These results are consistent with deprotonation of the oxime oxygen as an important step in the reaction. These findings are also in good agreement with the computational experiments done on the isoquinolone system where it was shown that a deprotonated substrate bound to rhodium lowers the energy barriers of the CMD TS by providing a neutral Rh(III) complex.

CONCLUSION

In conclusion, through empirical screening of a variety of internal oxidants, we have developed a mild rhodium(III)-catalyzed isoquinolone and 3,4-dihydroisoquinolone synthesis. The reaction is a rare example of an aromatic C−H bond functionalization reaction run at room temperature. It can also provide high yields with catalyst loadings as low as 0.5 mol %. Additionally, we have circumvented the limitations associated with the oxidative heterocycle syntheses reported recently where exclusively internal alkynes were tolerated. Indeed, the overall redox-neutral strategy presented herein allowed us to use terminal alkynes as well as alkenes to access isoquinolones with various substitution patterns. Mechanistic insights revealed a change in the rate-limiting step depending on the internal oxidant used. In addition, DFT calculations were conducted, which shed light on the reductive C−N bond forming and oxidative N−O bond cleaving steps. These calculations also revealed the importance of substrate deprotonation throughout the catalytic cycle. This concept was shown to be readily applicable to rhodium(III)-catalyzed isoquinoline synthesis. We believe that these findings will prove valuable in the design of novel rhodium(III)-catalyzed heterocycle syntheses and in the promotion of reaction conditions that avoid the use of wasteful metal oxidants.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
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