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Rhodium-Catalyzed Oxidative Cycloaddition of Benzamides and Alkynes via C−H/N−H Activation

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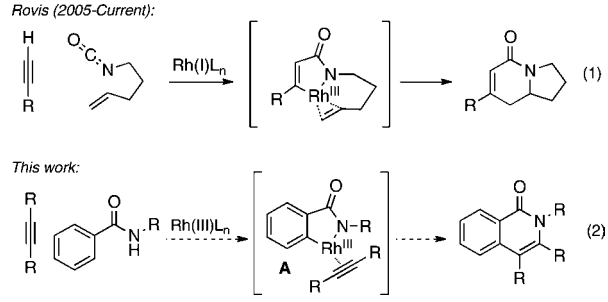
Abstract: The oxidative cycloaddition of benzamides and alkynes has been developed. The reaction utilizes Rh(III) catalysts in the presence of Cu(II) oxidants, and is proposed to proceed by N−H metalation of the amide followed by ortho C−H activation. The resultant rhodacycle undergoes alkyne insertion to form isoquinolones in good yield. The reaction is tolerant of extensive substitution on the amide, alkyne, and arene, including halides, silyl ethers, and unprotected aldehydes as substituents. Unsymmetrical alkynes proceed with excellent regioselectivity, and heteroaryl carboxamides are tolerated leading to intriguing scaffolds for medicinal chemistry. A series of competition experiments shed further light on the mechanism of the transformation and reasons for selectivity.

Introduction

Metal-catalyzed cycloadditions have proven reliable to form heterocycles[1] with rhodium playing a prominent role.[2] We have previously demonstrated that interception of rhodacyclic intermediates in a [2 + 2 + 2] cycloaddition provides access to indolizidines and quinolizidines from alkynes and alkene tethered isocyanates (eq 1).[3] Although the described [2 + 2 + 2] cycloaddition methodology tolerates a range of aryl and alkyl alkynes, benzyne does not participate in metallacycle formation. To address this limitation, we imagined accessing similar products via a C−H activation strategy. Treatment of benzamides with catalytic amounts of rhodium(III) would generate rhodacycle **A**, which would undergo alkyne insertion to provide isoquinolones (eq 2).[4]

Similar intermediates have been invoked in isoquinolone synthesis from benzotriazones and phthalimides, with concomitant extrusion of either N_2 or CO.[5] Rhodium(III) catalysis forming similar metallacycles via C−H activation is precedented, with the added advantage of using unfunctionalized arenes.[6] Excellent work by Miura and Satoh[7] revealed that benzoic acid is able to direct C−H insertion in the presence of alkynes under rhodium(III) catalysis to yield isocoumarins (eq 3). Miura and Satoh expanded on this reactivity by using mildly acidic N−H bonds as directing groups for rhodium(III) catalyzed C−H activation, which in the presence of alkynes results in the cyclized product from a C−H/N−H activation (eqs 4, 6, and 7).[8] In a spectacular application of this approach, Fagnou has demonstrated a regioselective indole synthesis by coupling *N*-aryl acetamides and alkynes under cationic rhodium(III) conditions (eq 5).[9] We envisioned using an amide as a directing group with selective formation of the isoquinolone motif, a scaffold found in a variety of natural products.[10] Herein, we provide a complete description of our development of the



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(8) (a) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2068. (b) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141. (c) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019.
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(10) For a review of isoquinolone synthesis, see: Glushkov, V. A.; Shklyaev, Y. V. *Chem. Heterocycl. Compd.* **2001**, *37*, 663.

methodology, a brief derivation of the isoquinolone scaffold, and some mechanistic insights.

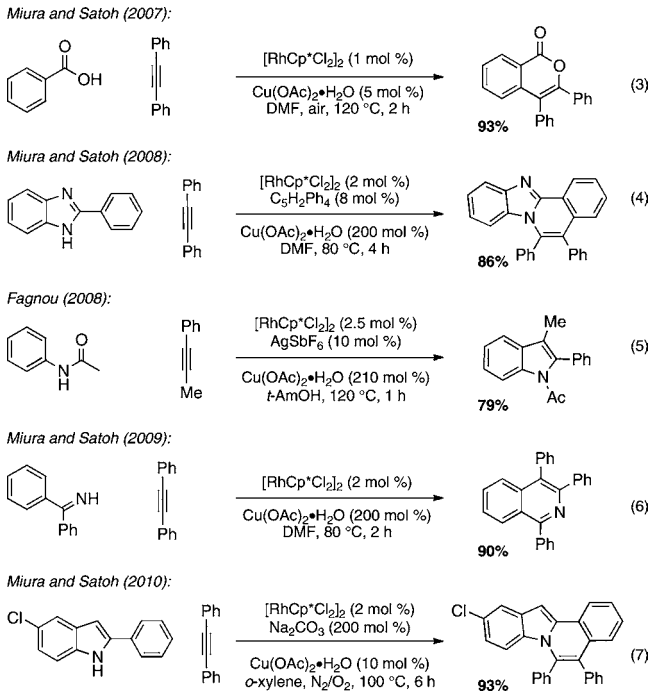
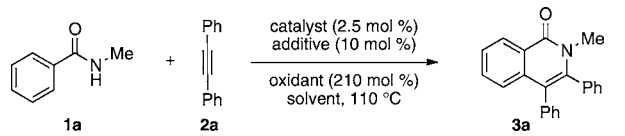


Table 1. Conditions Screen



1a 2a 3a

entry	catalyst	additive	oxidant	solvent	yield (%)
1	$[RhCp^*Cl_2]_2$	$AgSbF_6$	$Cu(OAc)_2$	PhMe	23
2	$[RhCp^*Cl_2]_2$	$AgSbF_6$	$Cu(OAc)_2$	*t*-AmOH	65
3	$[RhCp^*Cl_2]_2$	none	$Cu(OAc)_2$	*t*-AmOH	82
4	$[RhCp^*Cl_2]_2$	$AgSbF_6$	$Cu(OTf)_2$	*t*-AmOH	0
5[a]	$[RhCp^*Cl_2]_2$	$AgSbF_6$	$Cu(OTf)_2$	*t*-AmOH	65
6[b]	$[RhCp^*Cl_2]_2$	none	$Cu(OTf)_2$	*t*-AmOH	0

[a] A total of 50 mol % PivOH, and 250 mol % K_2CO_3 were added. [b] A total of 300 mol % Et_3N was added.

Results and Discussion

Initial Conditions Screen. Our studies began with *N*-methyl benzamide and diphenylacetylene. When $[RhCp^*Cl_2]_2$ is used as catalyst with $Cu(OAc)_2$ as stoichiometric oxidant and $AgSbF_6$ to sequester the halides, the desired isoquinolone product is obtained in 23% yield (Table 1). *t*-Amyl alcohol was found to be the ideal solvent for the reaction providing isoquinolone **3a** in 65% yield. Substitution of $Cu(OAc)_2$ with $Cu(OTf)_2$ resulted in the exclusive recovery of starting material. However, addition of pivalic acid and potassium carbonate to the $Cu(OTf)_2$ reaction affords **3a** in 65% yield, suggesting the oxidant is a source of carboxylate necessary for the reaction to proceed.[11] Ultimately, the exclusion of $AgSbF_6$ gave the optimal conditions with a yield of 82%. In the course of reaction optimization, we observed that, when $AgSbF_6$ was added to the reaction, a naphthalene product resulting from two C−H activations and two alkyne insertions is observed (Figure 1).[12] We speculate that the cationic rhodium is better able to coordinate an additional equivalent of alkyne resulting in a side pathway leading to the napthalene product.

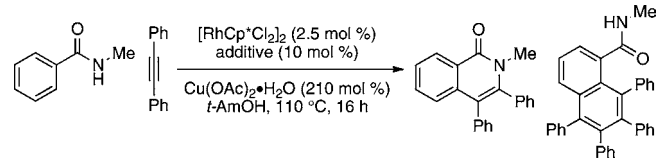
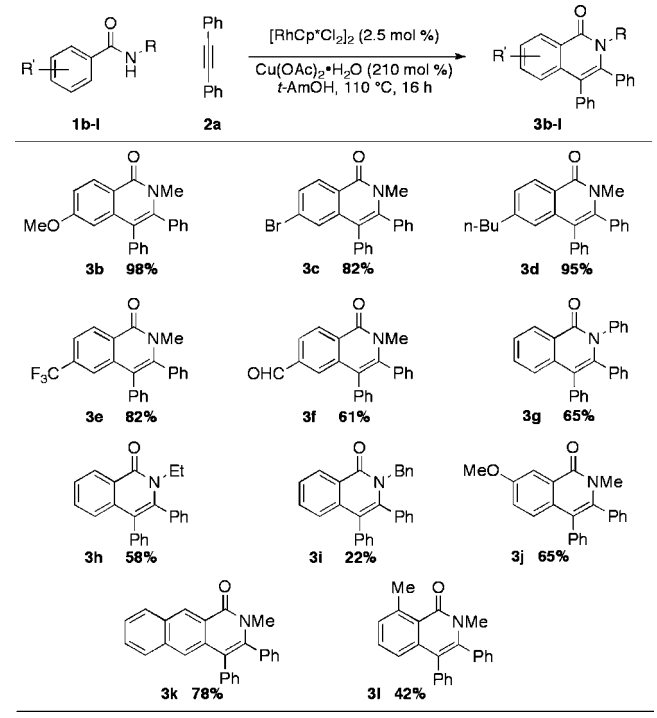


Figure 1. Additive effect.

Chart 1. Benzamide Screen



Substrate Scope. An examination of the scope revealed that electron-rich and electron-poor *N*-methyl benzamides participate in good yield (Chart 1). The reaction is tolerant of aryl bromides and unprotected aldehydes (**3c** and **3f**). The use of other substituents on nitrogen is also tolerated including *N*-ethyl, *N*-phenyl, and *N*-benzyl amides, the latter proceeding in a depressed yield.[13] It is interesting to note that we do not observe an indole product when subjecting **1g** to these reaction conditions, as per the precedent of Fagnou.[6] Apparently, benzamide C−H activation is faster than *N*-phenyl C−H activation under these neutral catalyst conditions. Substitution at the meta position is well tolerated and leads to isoquinolone products as single regioisomers (**3j** and **3k**). *ortho*-Methyl benzamide affords the isoquinolone product in slightly depressed yield.[14]

(11) This has been suggested in palladium C-H functionalization; see Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015.

(12) Similar reactivity was observed by Miura and Satoh when examining 2-aryl oxazole substrates; see ref 8c

(13) *I*-Pr and *t*-Bu benzamides provide no cycloadduct under these conditions.

(14) *N*-acyl benzyl amines do not undergo the cycloaddition under these conditions.

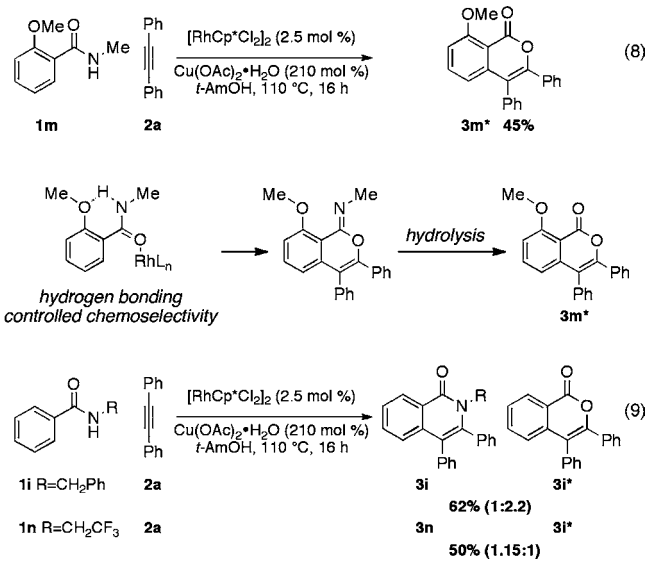
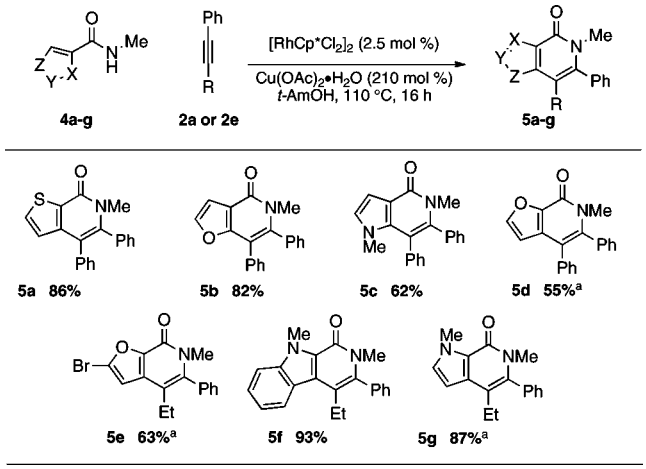


Figure 2. Competitive isocoumarin formation.

Chart 2. Heteroaryl Screen[a]

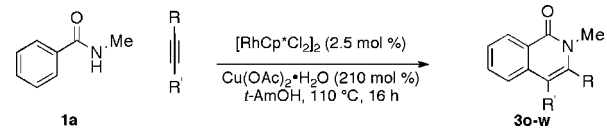


[a] Five mol % $RhCp^*(MeCN)_3(SbF_6)_2$ used as catalyst.

The examination of the benzamide scope revealed three substrates that afforded anomalous results. Whereas *ortho*-methyl benzamide produces the isoquinolone product, the corresponding *ortho*-methoxy benzamide leads to clean conversion to the isocoumarin (eq 8, Figure 2). We suggest that this dichotomy is electronic in nature and that there is an intramolecular hydrogen bond between the amide and the *ortho*-methoxy group altering the chemoselectivity of the cyclization forming an imido ester product (Figure 2). The imido ester is hydrolyzed to form the isocoumarin product *in situ* or in the workup. Furthermore, the use of the more electron-deficient benzyl or trifluoroethyl amide leads to a mixture of isoquinolone and isocoumarin products (eq 9, Figure 2).

Extension of this reaction to heteroaryl carboxamides proved successful under these reaction conditions (Chart 2).[15] With 3-heteroaryl carboxamides **4b** and **4c**, the reaction affords a single regioisomer as product resulting from C−H activation at the more activated 2-position (**5b** and **5c**, Chart 2). Thiophene and indolyl carboxamides **4a** and **4f** provide the corresponding adducts in excellent yield using the neutral catalyst. However, 2-furyl and 2-pyrrolyl carboxamides lead to low yields under the neutral precatalyst conditions.[16] This situation was rectified with the use of the more activated cationic precatalyst $[RhCp^*(MeCN)_3](SbF_6)_2$, leading to products **5d**, **5e**, and **5g** (Chart 2). The use of unsymmetrical alkynes with heteroaryl carboxamides led to products **5e**−**5g** as single regioisomers, paralleling results with those found with benzamides (Chart 2 and see below).

Table 2. Alkyne Screen



entry	alkyne	product	yield (%)	regioselectivity
1	Ar, Ar	**3o** Ar = C_6H_4OMe	94	NA
2[a]		**3p** Ar = $C_6H_4CF_3$	50	NA
3	S, S	**3q**	50	NA
4[b]	n-Bu, n-Bu	**3r**	50	NA
5	Ph, Et	**3s**	82	>19:1
6	Ph, CH_2OTBS	**3t**	67	>19:1
7	Ph, EtO, OEt	**3u**	78	>19:1
8	Ph, n-Bu	**3v**	70	10:1
9	i-Pr, Me	**3w**	64	>19:1

[a]Reaction conducted for 40 h. [b]Ag_2CO_3 used in place of $Cu(OAc)_2•H_2O$.

With respect to the alkyne substituent, the reaction shows broad substrate tolerance among internal alkynes (Table 2).[17] Electron-rich tolanes participate in excellent yield while electron-

(15) Under these conditions, *N*-methylpyridine-3-carboxamide and *N*,2-dimethyloxazole-4-carboxamide afford cycloadduct in 0% and 8% yield, respectively.

(16) For example, 2-furyl carboxamide **4d** leads to **5d** in 13% yield using the $[RhCp^*Cl_2]_2$ conditions.

(17) Terminal alkynes are not tolerated under the current reaction conditions.

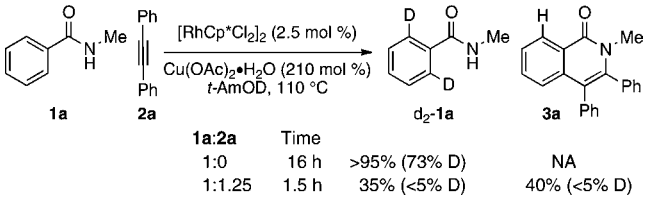


Figure 3. Reversible C−H activation.

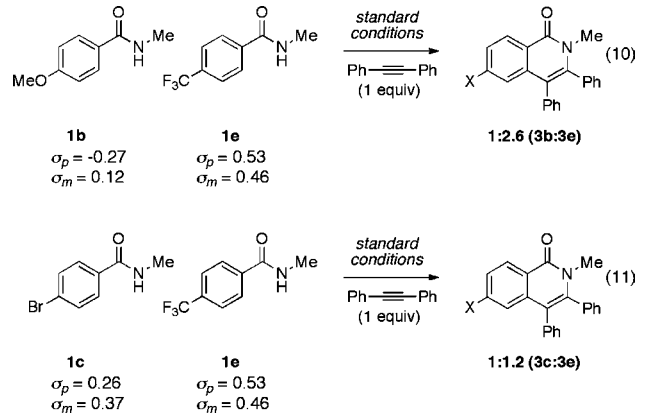


Figure 4. Benzamide competition experiments.

deficient systems are somewhat more recalcitrant (contrast entries 1 and 2, Table 2). Heteroaryl and aliphatic alkynes are also tolerated. Acetals are deprotected under the reaction conditions to yield the corresponding aldehyde (entry 7, Table 2).[18] When unsymmetrical alkynes are employed, largely a single regioisomer is observed. An unsymmetrical dialkyl alkyne also participates, with 4-methyl-2-pentyne surprisingly affording **3u** bearing the bulky isopropyl group distal to the isoquinolone nitrogen (entry 9, Table 2).

Mechanistic Studies. We conducted a series of experiments to probe the reaction mechanism. Fagnou has shown that the C−H insertion step is reversible with electron rich *N*-phenyl acetamide.[6] When our reaction is conducted in *t*-AmOD in the absence of alkyne, 73% deuterium incorporation is observed at the two ortho positions (Figure 3). If the same reaction is conducted in the presence of diphenylacetylene, no deuterium incorporation is observed in unreacted **1a**. These experiments suggest that, under the reaction conditions, the C−H insertion step is largely irreversible.[19]

Further support for this step in the mechanism was gained from a series of competition experiments. Equimolar amounts of benzamides **1b** and **1e** were subjected to the standard reaction conditions with a single equivalent of alkyne. The product formation favors isoquinolone **3e** derived from the more electron-deficient benzamide (eq 10, Figure 4). These results suggest that either N−H activation or C−H activation could be turnover limiting. In order to distinguish between these two possibilities, we also conducted a competition experiment between **1c** and **1e**, two para substituents that have disparate σ_p values but similar σ_m values. In the event, **3c** and **3e** are formed

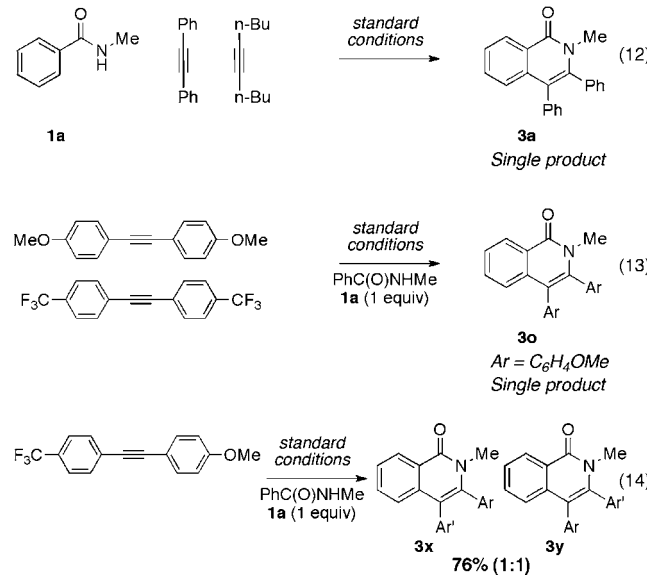


Figure 5. Alkyne competition experiments.

in nearly equal amounts consistent with the hypothesis that C−H activation is the first irreversible step (eq 11, Figure 4). If N−H activation was the first irreversible step, we should see a greater difference in product distribution given the increased acidity of amide **1e** relative to **1c**. Importantly, this suggests a mechanistic dichotomy between this manifold and Fagnou's Rh(III)-catalyzed C−H/N-H activation of N-acetyl anilides leading to indoles.[6]

To learn about the subsequent steps in the catalytic cycle, we conducted a series of competition experiments between alkynes. Equimolar amounts of **1a**, 5-decyne, and diphenylacetylene afford isoquinolone **3a** as a single product (eq 12, Figure 5). A competition experiment between electron-rich (*p*-methoxy) and electron-deficient (*p*-trifluoromethyl) tolanes provides only the isoquinolone derived from the electron-rich alkyne (eq 13, Figure 5). Lastly, an unsymmetrical tolane gives two regioisomeric isoquinolones in good yield (eq 14, Figure 5). Taken together, these results suggest that more electron-rich alkynes are favored in the insertion event but the regioselectivity of insertion appears to be dictated largely by steric factors.[20]

In light of these experiments we propose the following mechanism (Figure 6). The rhodium dimer precatalyst presumably dissociates into the coordinatively unsaturated monomer, which can exchange ligands to form an acetate-ligated species with the copper oxidant. Coordination of an equivalent of benzamide then initiates either N- or O-metalation before a turnover limiting C−H activation can occur to form a 5-membered rhodacycle, with concomitant formation of acetic acid. This rhodacycle has an open coordination site which can regioselectively and irreversibly insert an equivalent of alkyne to form a 7-membered rhodacycle with an open coordination site. If this coordination site is occupied by an equivalent of alkyne, this can lead to the naphthalene side product; alternately, the rhodium can reductively eliminate to form the desired isoquinolone and generate a rhodium(I) species which can

(18) Acetic acid is generated during the course of the reaction and the Cu salt is used as its hydrate, presumably providing the necessary water and acid to lead to hydrolysis of the acetal.

(19) This deuteration experiment was also conducted on N-*t*-Bu benzamide. In the absence of alkyne, no deuterium incorporation was observed after 16 h under these conditions suggesting the sterics of the *tert*-butyl group negatively affects its ability to metalate by rhodium. This also suggests that metalation occurs on nitrogen rather than oxygen.

(20) The apparent reversed regioselectivity in product **3u** seems to contradict this model; further studies to address this dichotomy are ongoing.

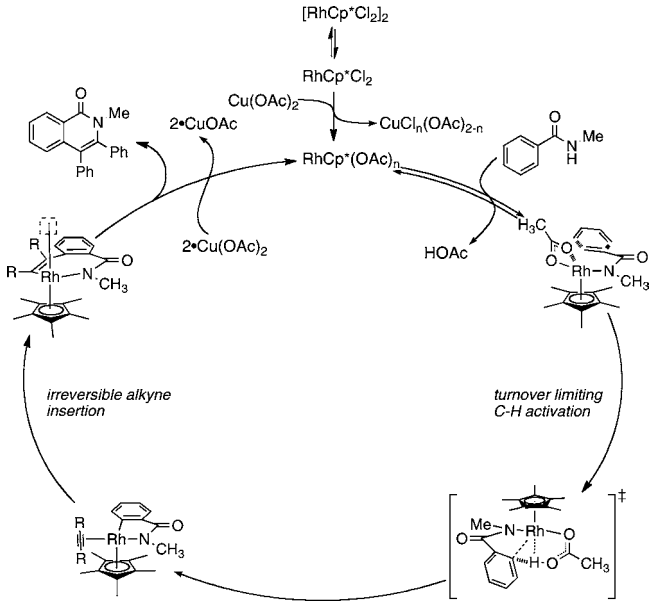


Figure 6. Proposed mechanism.

undergo oxidation to regenerate the catalytically active rhodium(III) complex.

Conclusion

In conclusion, we have developed a Rh(III) catalyzed oxidative isoquinolone synthesis using a transient 5-membered rhodacycle accessed from *ortho* C−H/N−H activation.[21] We found that heterocycles are well tolerated in the reaction allowing access to a number of unique molecular scaffolds. Additionally, unsymmetrical alkynes are tolerated in high yield and high regioselective with high functional group tolerance. The mechanism of the reaction was probed to find that C−H activation is the turnover-limiting step. A series of competition experiments shed light on this mechanism, suggesting alkyne insertion is largely governed by steric factors and alkyne coordination plays a central role in product selectivity.

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

JA103776U

(21) During the preparation and review of this manuscript, similar and complementary studies leading to isoquinolone synthesis were reported by the groups of Keith Fagnou and Masahiro Miura; see: (a) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (b) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 744.