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Rh(III)-Catalyzed C−H Activation and Double Directing Group Strategy for the Regioselective Synthesis of Naphthyridinones

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Supporting Information

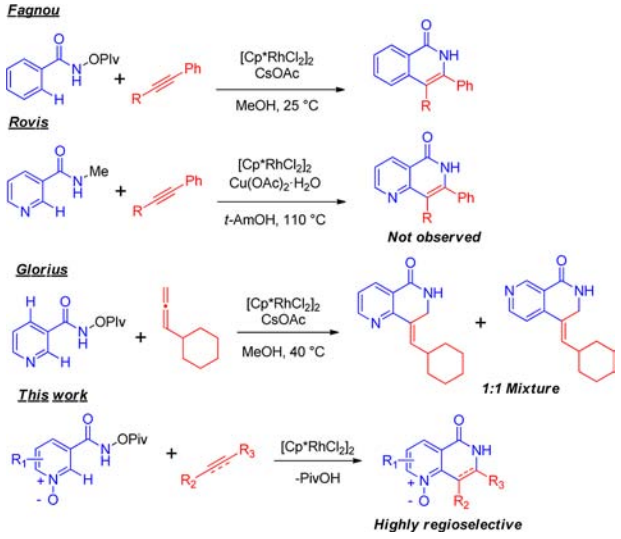
ABSTRACT: A general Rh(III)-catalyzed synthesis of naphthyridinone derivatives is described. It relies on a double-activation and directing approach leveraging nicotinamide *N*-oxides as substrates. In general, high yields and selectivities can be achieved using low catalyst loadings and mild conditions (room temperature) in the couplings with alkynes, while alkenes require slightly more elevated temperatures.

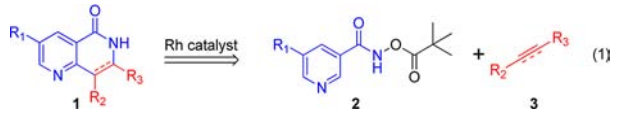
Nitrogen-containing heterocycles are ubiquitous in both natural products and pharmaceuticals; therefore, new, selective methods for their preparation are an important focus of research. Traditional methods often require harsh reaction conditions, rendering them incompatible with functionalized substrates.[1] Transition metal catalysis offers an attractive alternative. In the past decade, directed C−H activation approaches have enabled more-direct access to heterocyclic scaffolds.[2,3] Recently, Rh(III)-catalyzed [4+2] annulation reactions of aromatic carboxamides with alkynes have emerged as a powerful and efficient method to construct fused 2-pyridone heterocycles.[4] A newer strategy employs an internal, multifunctional group that both directs the metal to the desired site of C−H activation and reoxidizes it after the formation of a C−N bond, typically by cleavage of an N−O bond.[5]

The utility of this method is highlighted in the ability to rapidly access isoquinolones from rather simple starting materials. Extension of this reaction to other heterocycles was met with partial success; examples in which the parent phenyl ring has been replaced by electron-rich heterocycles (furan, thiophene, indoles) have recently been reported.[4a,5a,b] In contrast, extension of this method to pyridine derivatives has been only partially successful. Rovis observed that the reaction failed to afford any of the naphthyridinone product under the conditions studied,[4a] while Glorius reported the isolation of a 1:1 mixture of products resulting from the unselective activation of the C-2 and C-4 positions of the nicotinamide ring (Scheme 1).[5b] Li also reported a mixture of regioisomers at the 2- and 4-positions.[6] We describe herein a general solution to this problem that addresses both reactivity and selectivity challenges by employing pyridine *N*-oxides as substrates. This general and highly regioselective Rh(III)-catalyzed annulation leads to naphthyridone derivatives in high yields under mild conditions (Scheme 1).

We recently required efficient access to naphthyridinones such as **1** (eq 1).[7] Naphthyridinones are popular scaffolds in drug discovery; thus, new methods for their synthesis are of interest.[8]

Scheme 1. Heterocycle Synthesis via Rh(III)-Catalyzed C−H Activation with Internal Directing Group/Oxidant





We postulated that we could gain access to the desired naphthyridinones by C−H activation of functionalized nicotinamide derivatives **2** (eq 1) in the presence of an unsaturated coupling partner [norbornadiene or (trialkylsilyl)acetylene].[9]

The use of nicotinamide derivatives in the Rh(III)-catalyzed annulation with norbornadiene furnished a mixture of products resulting from C−H activation at C-2 and C-4 (Chart 1). Interestingly, the regioselectivity with regard to the C−H activation could only be influenced subtly by introducing varying substituents at the 5-position. This is in contrast to reports of excellent regioselectivity for meta-substituted substrates in the parent phenyl system.[3c,d] The use of silylalkynes provided only trace amounts of the desired product; however, 4-octyne furnished adduct **1e** in 78% yield with 1.7:1 regioselectivity.

In addition to poor selectivity, poor reaction rates were also observed, in contrast to the reasonable rates reported for the corresponding all-carbon congeners. We reasoned that employ-

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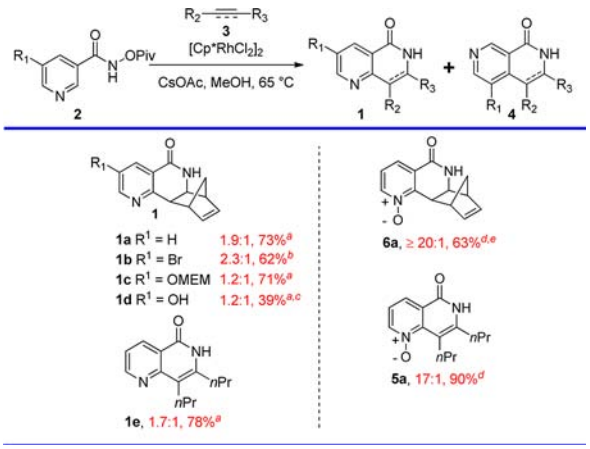
Chart 1. Rh(III)-Catalyzed Annulation of Nicotinamide Derivatives



General conditions: 1.1 equiv of norbornadiene, 2.0 equiv of CsOAc. Regioselectivity determined by ^{1}H NMR of crude reaction mixture. Isolated, combined yields. [a]Used 2.5 mol% $[Cp^*RhCl_2]_2$. [b]Used 5 mol % $[Cp^*RhCl_2]_2$. [c]Hydroxyl group was protected as TBS ether. Silyl group was deprotected during reaction. [d]Used 0.5 equiv of NaOAc and 1 mol% $[Cp^*RhCl_2]_2$. [e]Regioselectivity determined by ^{1}H NMR of isolated product.

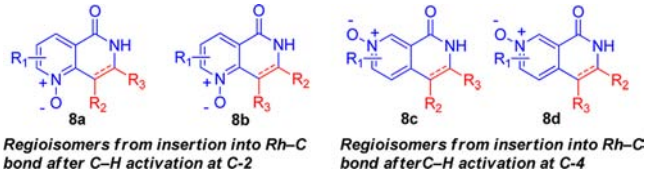
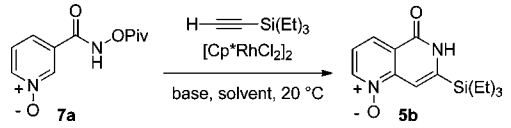


Figure 1. Potential regioisomers arising from unsymmetrical alkenes/alkynes.

Table 1. Reaction Optimization



entry	base	solvent	yield (%)[a]	regioisomeric ratio[b]
1	CsOAc	MeOH	89	23:1
2	CsOAc	2-PrOH	85	31:1
3	CsOAc	CH_3CN	88	19:1
4	CsOAc	DMF	32	NA
5	CsOAc	THF	84	NA
6	CsOAc	PhMe	85	47:1
7	CsOAc	NMP	24	23:1
8	KOAc	MeOH	85	23:1
9	**NaOAc**	**MeOH**	**89**	**23:1**
10	LiOAc	MeOH	84	23:1
11[c]	CsOAc	MeOH	85	24:1
12[d]	NaOAc	MeOH	87	23:1

General conditions: 1.1 equiv of $Si(Et)_3$-acetylene, 2.0 equiv of base, and 2 mol% $[Cp^*RhCl_2]_2$. [a]Assay yields of major regioisomer determined by HPLC. [b]Based on HPLC area percent values. [c]Used 0.5 mol% $[Cp^*RhCl_2]_2$. [d]Used 0.5 equiv of NaOAc.

ing a nicotinamide *N*-oxide not only would result in increased reaction rates due to its more electron rich nature but also should favor the desired regioselectivity. To our delight, the *N*-oxide **7a** smoothly added across norbornadiene to furnish the dihydronaphthyridinone *N*-oxide adduct **6a** in 63% yield with ≥20:1 regioselectivity favoring the regioisomer depicted. Similar results were obtained using an alkynyl coupling partner 4-octyne (Chart 1, **5a**).

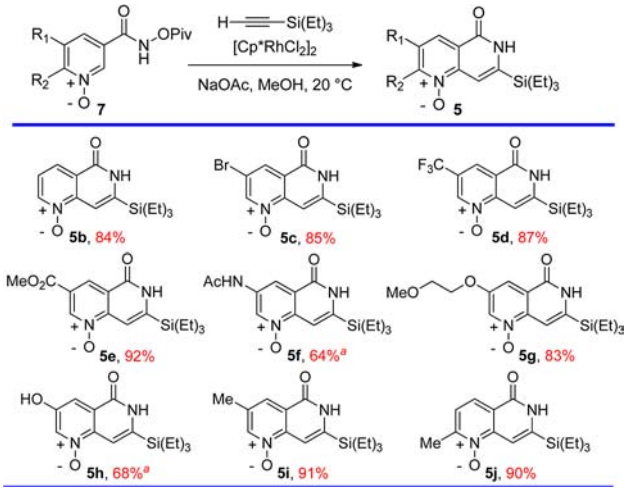
Having established proof of concept, reaction optimization was undertaken. Unlike norbornadiene or 4-octyne, unsymmetrical coupling partners could lead to the formation of four regioisomers arising from C−H activation at the 2- vs 4-positions of the ring and from alkene/alkyne insertion into the Rh−C bond (Figure 1).

To probe the global reaction selectivity while accessing value-added products, nicotinamide *N*-oxide **7a** and TES-acetylene[10] were chosen as substrates for optimization experiments.[11] The annulation took place efficiently at room temperature in the presence of CsOAc and 2 mol% rhodium catalyst and tolerated a number of different solvents with little to no impact on product yield (Table 1, entries 1−7). The exceptions were polar, aprotic solvents, which were not well tolerated and afforded the desired product in depressed yields (entries 4 and 7). Similarly, the nature of the counterion present in the exogenous base had little effect on product yields, with Cs-, K-, Na-, and LiOAc all affording similar results (entries 1, 8−10). Additional optimization demonstrated that catalyst loading could be reduced to 0.5 mol% and base stoichiometry could be reduced to 0.5 equiv (entries 11 and 12).[12]

Reaction selectivity was uniformly high in all optimization experiments, favoring **5b** as the major product. The minor isomer observed is the result of inverted alkyne insertion (e.g., **8b**) and not C−H activation at the 4-pyridyl carbon (e.g., **8d**). The methanol/sodium acetate system was selected as optimal based on product yield, selectivity, and reagent handling. With optimized reaction conditions in hand, the substrate scope was examined.

A variety of substituents on the nicotinamide core were well tolerated in the reaction (Chart 2). The electronic nature of a substituent at the 5-position of the ring had little effect on the outcome of the reaction, providing products in good yield and ≥20:1 regioselectivity in all cases. Electron-withdrawing (**5c**−**5f**)

Chart 2. Effects of *N*-Oxide Ring Substituents



General conditions: 1.1 equiv of $Si(Et)_3$-acetylene, 0.5 equiv of NaOAc, and 1 mol% $[Cp^*RhCl_2]_2$. Regioselectivity determined by ^{1}H NMR of crude reaction mixtures. Yields are isolated. [a]Reduced yields reflect difficulty in isolation. Assay yields for compounds **5f** and **5h** were 80 and 89%, respectively, as determined by ^{1}H NMR.

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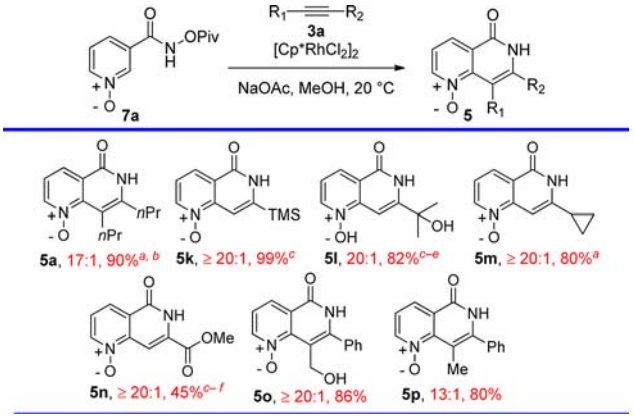
Chart 3. Reaction with Alkynes



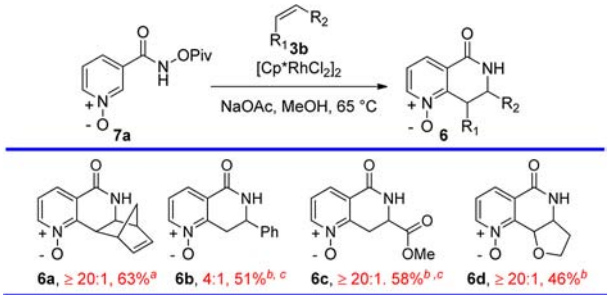
General conditions: 1.1 equiv of alkyne, 0.5 equiv of NaOAc, and 1 mol% $[Cp^*RhCl_2]_2$. Selectivity of alkyne insertion into the Rh−C bond as determined by ^{1}H NMR of crude reaction mixture. Yields are isolated. [a]Reaction at 50 °C. [b]Selectivity of C−H activation at the 2- vs 4-position on the ring. [c]1.5 equiv of alkyne. [d]2.5 mol% $[Cp^*RhCl_2]_2$. [e]Reaction at 65 °C. [f]Selectivity determined by ^{1}H NMR of isolated product.

and electron-donating substituents (**5g** and **5i**) were tolerated without impact to yields. A base-labile ester moiety (**5e**) was tolerated as was a hydroxyl (**5h**) and acetamide (**5f**) functionality. Substitution at the 6-position was also tolerated, as exemplified in **5j**, which gave 90% yield and ≥20:1 selectivity.

The reaction proved to be general for a variety of terminal and internal alkynes to afford naphthyridinone *N*-oxides (Chart 3). The regioselectivity of alkyne insertion was consistent with previous studies; sterically demanding alkyne substituents were positioned adjacent to the lactam nitrogen in the product. A variety of functional groups on the alkynyl coupling partner were tolerated, including strained rings, esters, and free hydroxyl groups. Reactions with terminal alkyne coupling partners gave yields of 45−99% and provided products in uniformly high selectivity. Internal alkynes were also acceptable substrates. Both dialkyl (**5a**) and alkyl-aryl (**5o** and **5p**) alkynes cyclized in 80−90% yield, with selectivities ranging from 13:1 to ≥20:1. In cases where the alkyne possessed a vicinal sp^2-hybridized center, that center was selectively installed adjacent to the lactam nitrogen in the product (**5n**−**5p**). Elevated temperatures were required in cases where either electron-deficient or sterically demanding coupling partners were employed (**5a** and **5l**−**5n**). At elevated temperatures, we observed a small amount of C−H activation at C-4 in the case of symmetrical alkyne 4-octyne (Chart 3, **5a**), while for unsymmetrical alkynes regioselectivity was dictated by alkyne insertion into the Rh−C bond at C-2, suggesting an interesting selectivity dichotomy based on reaction temperature.

Extending the reaction scope to include alkenes, other than norbornadiene, would offer access to the useful dihydronaphthyridinone core structure. Rewardingly, alkenes performed well in the reaction, contrary to related systems where alkenes have been challenging substrates due to competing β-hydride elimination giving rise to Heck-type adducts.[13] The conditions were further optimized for alkenes; the reactions required a slightly higher catalyst loading (2.5 mol%) in addition to heating (Chart 4). Both acyclic and strained cyclic alkenes participated, with selectivity ranging from 4:1 using styrene (**6b**) to ≥20:1 with methyl acrylate and 2,3-dihydrofuran (**6c** and **6d**). As with alkynes, vicinal sp^2 carbon centers were installed next to the

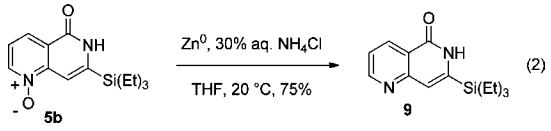
Chart 4. Reaction with Alkenes



General conditions: 1.5 equiv of alkene, 0.5 equiv of NaOAc, and 2.5 mol% $[Cp^*RhCl_2]_2$. Yields are isolated. [a]Selectivity of C−H activation at the 2- vs 4-position on the ring as determined by ^{1}H NMR of isolated product. [b]Selectivity of alkene insertion into the Rh−C bond as determined by ^{1}H NMR of crude reaction mixture. [c]Low yields reflect difficulty in isolation. Assay yields for **6b** and **6c** were 84 and 82%, respectively, for the major regioisomers as determined by ^{1}H NMR of crude reaction mixtures.

lactam nitrogen selectively. Like their alkyne counterparts, regioisomeric impurities observed with unsymmetrical alkenes were the result of inverted olefin insertion at C-2. For symmetrical norbornadiene, the minor regioisomer arose from C−H activation at C-4.

The resulting naphthyridinone *N*-oxides are smoothly reduced to the parent naphthyridinone under mild conditions, as exemplified by treatment of **5b** with Zn powder and aqueous NH_4Cl in THF to afford naphthyridinone **9** in 75% yield (eq 2).[14] Importantly, the vinylsilane functional group was preserved during the reduction, demonstrating the mild nature of the reaction conditions.



To probe the mechanism of the C−H insertion reaction, an experiment was performed in deuterated solvent. It was anticipated that the reaction proceeds via a mechanism similar to the related Rh(III)-mediated oxidative cycloaddition manifold developed by Fagnou and co-workers.[5b,d] Nicotinamide *N*-oxide **7a** was subjected to the C−H insertion reaction conditions in CD_3OD at 20 °C in the absence of alkyne [Scheme 2, (1)]. At the 2-position, 12% deuterium incorporation was observed while at the 4-position <5% was observed. Interestingly 8% deuterium incorporation was also observed at the 6-position. Performing the same reaction in the presence of an alkyne coupling partner at ambient temperature led to no deuterium incorporation in the isolated product [Scheme 2, (2)]. These results suggest the cyclometalation of **7a** under the reaction conditions is slow compared to the subsequent alkyne insertion.[15]

The postulated mechanism that gives rise to the major observed regioisomer commences with a preferred C−H activation at the 2-position of the *N*-oxide ring of **I** to afford metallocycle **II** (Scheme 2). Regioselective alkyne/alkene insertion into the Rh−C bond would then furnish intermediate **III**, followed by reductive elimination to give the naphthyridinone *N*-oxide product **IV** with concomitant N−O bond cleavage to re-oxidize the metal center. Based on the labeling experiment in the presence of the alkyne, it is proposed that

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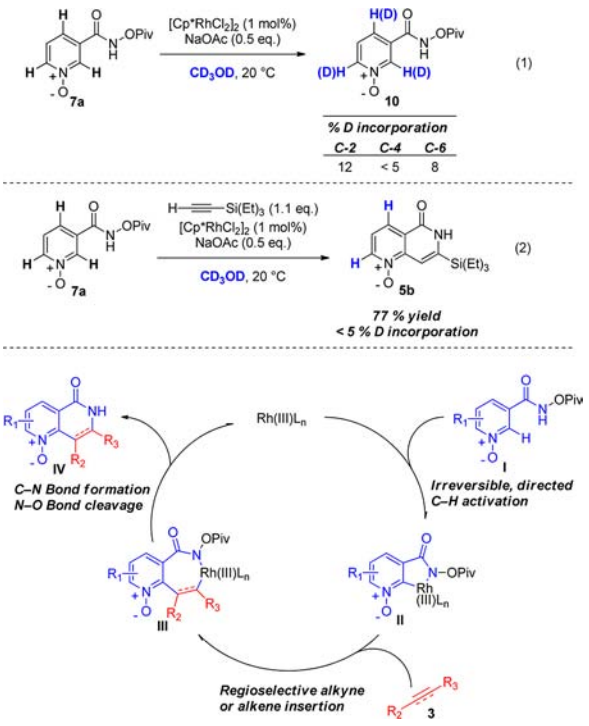
Scheme 2. Deuterium Labeling Studies and Postulated Mechanism



insertions at the 4- and 6-position are slower. To the extent they occur under the reaction conditions, they appear to lead to intermediates that are either slower in the insertion step (4-position) or unproductive (6-position).

In conclusion, a Rh(III)-catalyzed C−H activation of nicotinamide *N*-oxides in the presence of alkenes or alkynes to afford naphthyridinone *N*-oxide or dihydronaphthyridinone *N*-oxide products has been realized. The reaction proceeds with nearly perfect regioselectivity on the pyridine and high regioselectivity for the olefin insertion.[16] Furthermore, the reaction proceeds under mild conditions with relatively low catalyst loadings (1 mol% for alkyne, 2.5 mol% for alkenes). Additional mechanistic and computational studies to fully rationalize the observed products are planned and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) General overviews: (a) Bull, J. A.; Mousseau, J. J.; Guillaume, P.; Charrette, A. B. *Chem. Rev.* **2012**, *112*, 2642. (b) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications*, 3rd ed.; Wiley-VCH: Weinheim, Germany, 2012.

(2) Recent reviews: (a) Patureau, F. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1977. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (c) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *43*, 814.

(3) (a) Umeda, N.; Tsurgi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019. (b) Fukutani, T.; Umeda, M.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141. (c) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645.

(4) (a) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (b) Hyster, T. K.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1606. (c) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050.

(5) (a) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (b) Wang, H.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 7318. (c) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592. (d) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (e) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (f) Ye, B.; Cramer, N. *J. Am. Chem. Soc.* **2013**, *135*, 636. (g) Xu, X.; Liu, Y.; Park, C. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9372.

(6) Song, G.; Gong, X.; Li, X. *J. Org. Chem.* **2011**, *76*, 7583.

(7) Fang, Y.-Q.; Bio, M. M.; Hansen, K. B.; Potter, M. S.; Clausen, A. *J. Am. Chem. Soc.* **2010**, *132*, 15525.

(8) (a) Johnson, D. S.; Chung, C.; Fay, L. K.; Favor, D. A.; Repine, J. T.; White, A. D.; Akunne, H. C.; Fitzgerald, L.; Nicholls, K.; Snyder, B. J.; Whetzel, S. Z.; Zhang, L.; Serpa, K. A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2621. (b) Siu, T.; Kozina, E. S.; Jung, J.; Altman, M. D.; Rush, T.; Dinsmore, C. J.; Young, J. R.; Rosenstein, C.; Chan, G.; Mathur, A.; Bachman, E.; Mo, J.-R.; Xu, L.; Bouthillette, M.; Marshall, C. G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7421. (c) Li, Y.; Rossi, M. A.; Liang, J.; Siu, T.; Hu, E.; Cosford, N.; Prasit, P.; Barnett, S. F.; Defeo-Jones, D.; Jones, R. E.; Robinson, R. G.; Leander, K.; Huber, H. E.; Mittal, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 834.

(9) Pd-catalyzed C−H activations of pyridine *N*-oxides: (a) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (b) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 1820. (c) Kanyiva, K. S.; Nako, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872.

(10) The use of terminal alkynes is known to be problematic in similar systems that employ external oxidants (typically Cu(II)) due to alkyne dimerization (Glaser coupling).

(11) This would allow access to the desired naphthyridinone motif upon protonolysis of the silyl group and reduction of the pyridine *N*-oxide.

(12) The $(CH_3CN)_3Cp^*Rh(III)SbF_6$ catalyst was equally effective at promoting the transformation as $[Cp^*Rh(III)Cl_2]_2$ at the same catalyst loading.

(13) (a) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7094. (b) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 5776. (c) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407. (d) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982. (e) Patureau, F. W.; Besset, T. *Angew. Chem., Int. Ed.* **2010**, *50*, 1064. (f) Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 540.

(14) Aoyagi, Y.; Abe, T.; Ohta, A. *Synthesis* **1997**, 891.

(15) The presence of different reaction pathways in the absence and presence of coupling partner cannot be ruled out and is the subject of further studies.

(16) After completion of this research, a single example of regioselective functionalization of a nicotinamide was reported in closely related chemistry: Presset, M.; Oehlreich, D.; Rombouts, F.; Molander, G. A. *Org. Lett.* **2013**, *15*, 1528.