An Improved Catalyst Architecture for Rhodium (III) Catalyzed C–H Activation and its Application to Pyridone Synthesis

Todd K. Hyster and **Tomislav Rovis**

Tomislav Rovis: rovis@lamar.colostate.edu

aDepartment of Chemistry, Fort Collins, CO 80523. Tel: 970-491-7208

Abstract

We have developed a method for preparing pyridones from the coupling reaction of acrylamides and alkynes with either stoichometric $Cu(OAc)_2$ or catalytic $Cu(OAc)_2$ and air as oxidants. In the course of these studies, it was found that a larger ligand, 1,3-di-tert-butylcyclopentadienyl (termed Cp^t) results in higher degrees of regioselectivity in the alkyne insertion event. The transformation tolerates a broad variety of alkynes and acrylamides. Furthermore, Cp^t and Cp^* demonstrate similar catalytic activity. This similarity allows for mechanistic studies to be undertaken which suggest a difference in mechanism between this reaction and the previously studied benzamide system.

Ligand development is a key element in the growth of organometallic catalysis. While directed C–H activation has experienced an explosion of interest in the last decade, few groups have tackled ligand development to increase reactivity and selectivity. Exceptions include Yu and co-workers who have developed a variety of amino acid based ligands to increase the reactivity,[1] regioselectivity, and enantioselectivity[2] of a transformation. Vedernikov and coworkers found 2,6 pyridinedicarboxylic acids facilitate the aerobic oxidation of 8-methylquinoline.[3] Sanford and Arnold have found carbene ligands can stabilize Pd (IV) intermediates in directed halogenations.[4] Rh (III) C–H activation, which has been used for the synthesis of a variety of heterocycles,[5] has seen very little ligand development. A prominent exception is the introduction of polyphenylated cyclopentadienyl ligand on Rh(III) by Satoh and Miura.[6]
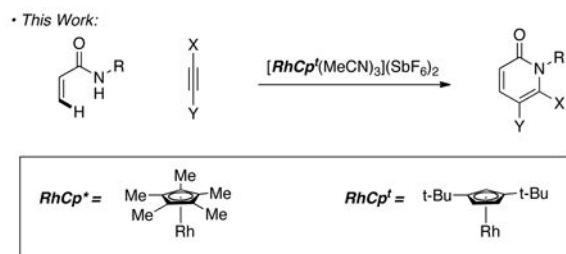

$$(1)$$
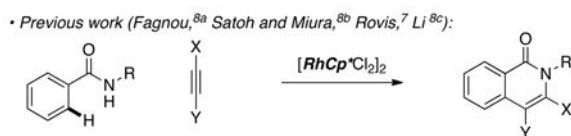
Correspondence to: Tomislav Rovis, rovis@lamar.colostate.edu.

$$(2)$$

Previously, our group[7] and others[8] employed Rh (III) C–H activation in the preparation of isoquinolones from benzamides and alkynes (eq 1). The reaction was proposed to proceed via aryl C–H activation by Rh (III) followed by alkyne insertion. As we looked to expand this reaction to the more elusive alkene sp^2 C–H activation with acrylamides in order to access pyridones, a ubiquitous scaffold in biologically relevant molecules,[9] we found low regioselectivities for the insertion of unsymmetrical alkynes (eq 2). Herein we disclose our development of a new ligand for Rh(III)-catalyzed C-H activation, which leads to significantly improved regioselectivity of alkyne insertion en route to pyridone products. We further describe a series of mechanistic studies, which shed considerable light on the mechanism of this transformation.

Building on our own work, we began our investigations in the oxidative coupling of acrylamide and alkynes.[10] Employing conditions used in our isoquinolone synthesis affords the desired pyridone **3a** in 30% yield and 7.8:1 regioselectivity (entry 1, Table 1). A brief solvent screen revealed dichloroethane to be an ideal solvent with 82% yield and identical regioselectivity (entry 2, Table 1). The desire for more mild conditions directed us to $[RhCp^*(MeCN)_3](SbF_6)_2$, a catalyst used with success by Fagnou and co-workers.[11] With this catalyst the reaction can be run at temperatures ranging from 60 °C to 110 °C with good yields but a moderate decrease in regioselectivity to 6:1. In our previous work with benzamides, the insertion of unsymmetrical alkynes universally proceeds with regioselectivities >10:1; however, with acrylamides, the selectivities are significantly lower. We speculated that a modification of the ligand might increase the selectivity of alkyne insertion. To that end, we synthesized a Rh (III) precatalyst bearing a 1,3-di-*tert*-butyl cyclopentadienyl group (Cp^t), similar to a species previously described by Jin.[12] Gratifyingly, the use of this catalyst results in an improved regioselectivity with no loss in yield (contrast Cp^* and Cp^t columns, Table 1). Stimulated by this result, we conducted a screen of various acrylamide and alkyne-coupling partners under these conditions.

We were pleased to find that extensive substitution on the acrylamide is tolerated for pyridone formation. Alkyl *N*-substituted acrylamides are tolerated with high yield and high regioselectivity (Table 2, entries 1, 2, 8). The syntheses of amino acid protected pyridones are important for medicinal targets.[13] The cinnamamide derived from alanine methyl ester is tolerated in the reaction, and delivers the pyridone in high yield and regioselectivity (Table 2, entry 3). Alkyl substitution on the alkene (Table 2, entries 4–7) results in high yield but

lackluster regioselectivity; however, this can be improved when Cp^t is used. The use of an acrylamide containing an enamide results in formation of pyridone exclusively with good levels of selectivity and no pyrrole formation[14] (Table 2, entry 8). Finally, a variety of aryl substitution on the double bond is accepted in all cases resulting in high selectivity using Cp* (Table 2, entries 10–12).

An investigation of the alkyne component reveals a variety of substitution patterns are tolerated. Propiolates, which had not previously been demonstrated to participate in Rh(III) C-H activation catalysis, are tolerated when excess alkyne is used resulting in pyridone formation in good yield and regioselectivity (Table 2, entry 13). Unsymmetrical alkynes with alkyl and aryl substitution engage with good yields and selectivity that can be enhanced using Cp^t (Table 2, entries 14 and 17). Protected propargyl amines and alcohols are permitted, while their unprotected counterparts result in no product formation (Table 2, entries 15 and 16). Additionally, di-alkyl alkynes with sterically different groups result in product formation in high regioselectivity whereas di-alkyl alkynes with small differences in the sterics of two groups result in much lower selectivity (Table 2, entries 19 and 20). Enynes were employed in this reaction with high levels of selectivity, which one could imagine would afford access to the products of di-alkyl alkynes with the opposite regioselectivity after olefin reduction (Table 2, entry 18).[15] In light of the propensity of terminal alkynes to dimerize, we imagined that silyl protected alkynes would render an acceptable solution. TMS protected phenylacetylene results in dimerization with a small degree of product formation. The more robust TES protected alkynes function better with moderate yield and good levels of selectivity (Table 2, entry 21). It is important to note that Cp^t does not have a beneficial effect on selectivity in the cases of TES-protected alkynes.[16]

While pyridones are a common motif, it would be advantageous to derivatize these products to access different nitrogen containing heterocycles (Scheme 1). Chloropyridine **3a″**, a potentially useful cross-coupling partner for further elaboration, can be accessed in 82% yield when pyridone **3a** is treated with $POCl_3/PCl_5$. The dihydro pyridone scaffold can be prepared in 80% yield when pyridone **3a′** is treated with L-Selectride.

Inspection of our conditions led us to realize that this process would be less acceptable for large scale reactions (Table 3). Specifically, while we felt reasonably confident that Rh catalyst loading could be decreased on scale, the use of 2 equivalents of $Cu(OAc)_2$ as a stoichiometric oxidant delivers unneeded excess copper waste. In an effort to resolve these issues, we looked to decrease the catalyst and oxidant loading. We were pleased to find that when the oxidant loading is decreased to 20 mol% and the reaction is run open to air, pyridone formation is observed in >90% yield; however, subsequent decrease in the catalyst loading to 1 mol % forms pyridone in only 15% yield. Portionwise addition of alkyne over 30 h improves the yield to 50%. This suggests an inhibitory affect by the alkyne.[17] Furthermore, an increase in the concentration of the reaction delivers higher conversions (entry 3 vs 4, Table 3) and a slightly higher Rh catalyst loading provides optimal results (entry 6, 6 mmol scale). Preliminary experiments suggest copper is not needed at all if the reaction is conducted under air in the presence of NaOAc as base (entry 7, Table 3).

The variation in regioselectivity as a function of substrate was perhaps most puzzling (witness **3a**, **3c**, **3h**, **3i** in Table 2 compared to the corresponding reaction with N-methyl benzamide which gives >20:1 regioselectivity). The simplest explanation for this dichotomy is a change in mechanism. Pointed experiments were conducted to try to shed light on this issue.[18]
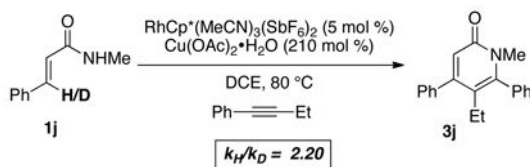

(3)

In an effort to probe whether C–H activation is the turnover-limiting step, we set out to determine the kinetic isotope effect. Using initial rates kinetics with *proteo/deutero N*-methylcinnamide a KIE value of 2.2 is observed. While this value fits with a primary kinetic isotope effect, and is within the range of KIE values found in palladium and rhodium catalyzed $^{C–H}$ activations,[19,20] we felt further evidence was required before proposing C–H activation as the turnover limiting step. If C–H insertion is the turnover-limiting step, then an increase in the acidity of the cleavable proton should have a positive effect on the rate of the reaction. Consequently we employed a competition experiment between *N*-methylcinnamamide and the *N*-methylpentafluorophenyl-cinnamamide derivative **1n**, using a 1:1:1 stoichiometry between the two amides and the alkyne. The reaction proved counter-intuitive delivering **3j** as the only observed pyridone product.

(4)

This surprising finding prompted us to conduct a Hammett study. A variety of substituted cinnamides were prepared and their incorporation in the reaction was compared to the parent cinnamide **1j**. The Hammett plot reveals a potential break, with more electron-rich and more electron-deficient systems both undergoing reaction slower than electron-neutral substrates.[21] To provide further support for this hypothesis, we conducted a kinetic isotope effect study with the two extremes of reactivity.
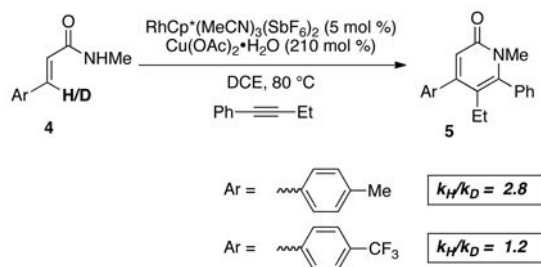
(5)

Clearly, the kinetic isotope effect data and the competition experiment described above do not uniformly support the CMD mechanism.[31] We propose the following mechanism (Scheme 2). The pre-catalyst presumably loses an acetonitrile ligand to form an acetate-ligated species. Coordination of an equivalent of acrylamide forms a cationic species **A**. This intermediate can then undergo acetate assisted C–H activation to render intermediate **B**.[22] The 5-membered rhodacycle **B** can experience a regioselective insertion of one equivalent of alkyne, with the improved regioselectivity associated with Cp^t a consequence of the extreme steric differentiation between a tert-butyl group and a hydrogen. Based of the work of Jones and co-workers, [23] it is likely that the C–Rh bond migrates to access the 7-membered rhodacycle **C**. At this point reductive elimination can occur to generate the desired pyridone and a rhodium (I) species. This species can undergo two single electron oxidations via $Cu(OAc)_2$ to render the catalytically active rhodium species. The Hammett plot and isotope effect study suggest that for electron-rich substrates, C-H activation is turnover limiting while in the case of the more acidic substrates, a subsequent step is turnover limiting, either alkyne insertion or reductive elimination.

Conclusions

We have described a new ligand for rhodium(III) C–H activation. This ligand has the benefits of increasing the regioselectivity of the alkyne insertion event, a problem common to Rh (III) C–H activation. Additionally we have found that the mechanism of the transformation is not uniform with its benzamide counterpart, and provide evidence for a distinct change in mechanism as a function of substrate electronics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Notes and references

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15. During the preparation of this manuscript Huestis/Fagnou report the use of enynes in the synthesis in indoles and pyrrole resulting in apparent reversed regioselectivity upon hydrogenation; see ref 11c.

16. Stuart/Fagnou report the use of TMS protected alkynes; see ref 11d.

17. This was observed by Stuart/Fagnou; see ref 11d.

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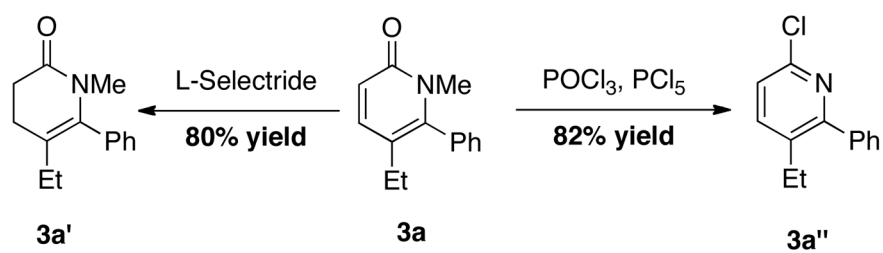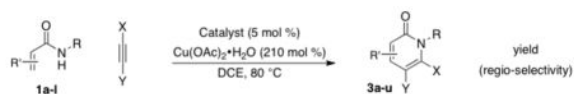
Scheme 1.
Derivatization

Proposed mechanism
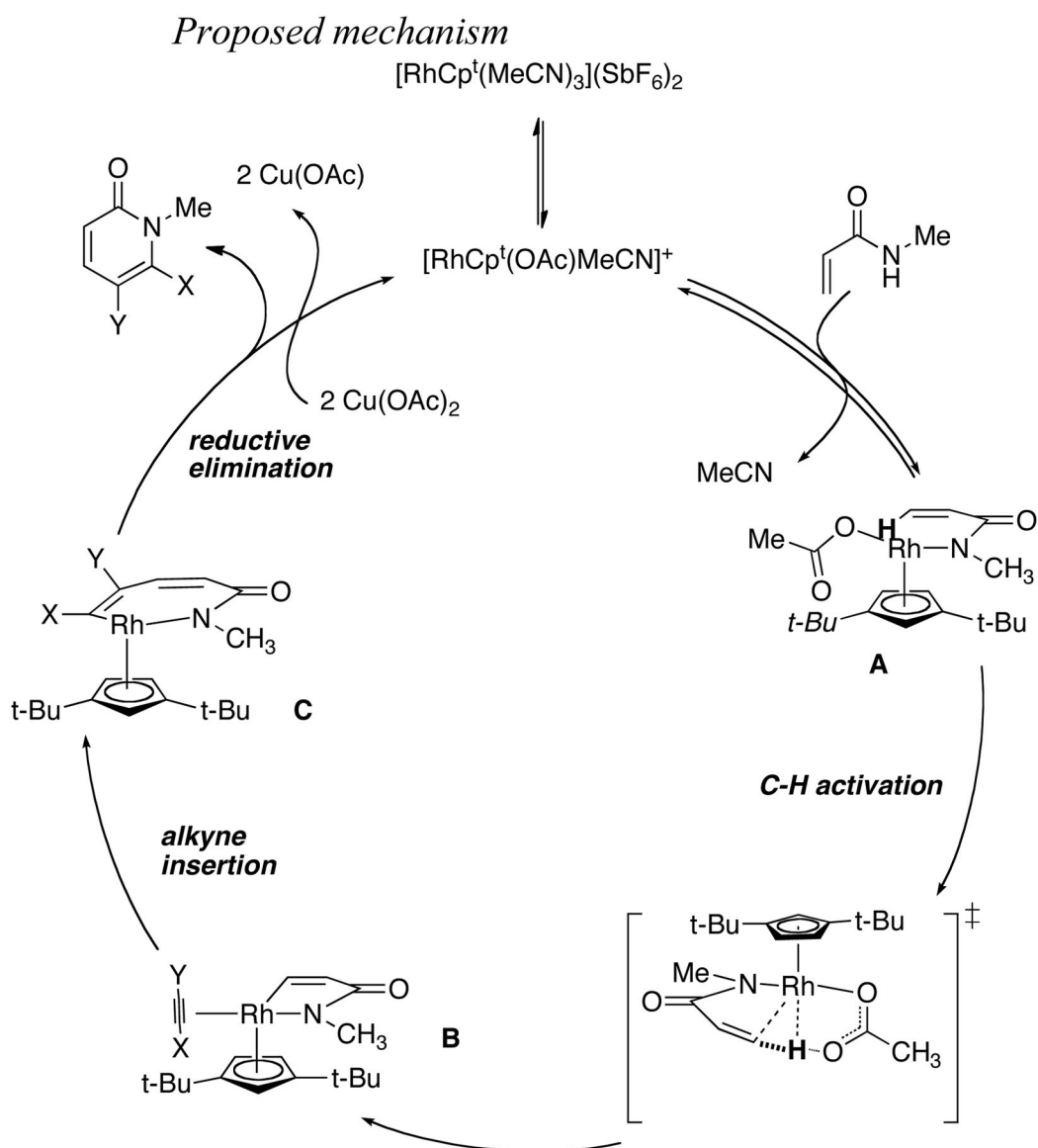
Scheme 2.
Proposed mechanism

Table 1

Optimization

entry	catalyst	temp (°C)	solvent	yield (%)	rr
1[a]	[RhCp*Cl₂]₂	110	t-AmOH	30	7.8:1
2[a]	[RhCp*Cl₂]₂	110	DCE	82	7.8:1
3	RhCp*(MeCN)₃(SbF₆)₂	110	DCE	90	6:1
4	RhCp*(MeCN)₃(SbF₆)₂	60	DCE	85	6:1
5	RhCp*(MeCN)₃(SbF₆)₂	80	DCE	90	6:1
6	RhCpᵗ(MeCN)₃(SbF₆)₂	80	DCE	86	14:1

[a]2.5 mol% Rh catalyst used.

Table 2

Pyridone Scope

Entry	Product	Cp*[b]	Cp^t[c]
1	**3a**	90% (6:1)	**86% (14:1)**
2	**3b**	85 % (5:1)	**78% (15:1)**
3	**3c**	76% (>19:1)	-
4	**3d**	98 % (5:1)	**98% (8.3:1)**
5	**3e**	85 % (3.3:1)	**82% (4.8:1)**
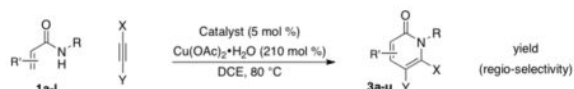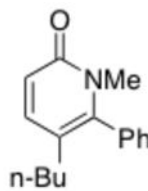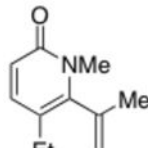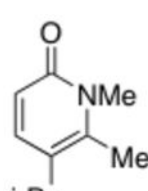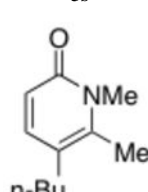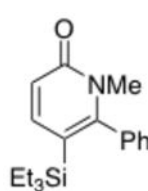
Entry	Product	Cp*[b]	Cp^t [c]
6	**3f**	75% (3.6:1)	**69% (4.6:1)**
7	**3g**	60% (3.8:1)	**82% (4.6:1)**
8	**3h**	-	**85% (>19:1)**
9	**3i**	75% (6.8:1)	**65% (>19:1)**
10	**3j**	74% (>19:1)	**78% (8.1:1)**
11[d]	**3k**	85% (>19:1)	-
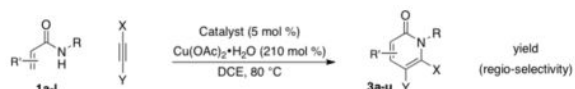
Entry	Product	Cp*[b]	Cpt[c]
12	3l	85 % (>19:1)	-
13[e]	3m	62 % (4.7:1)	**50% (>19:1)**
14	3n	78% (11:1)	-
15	3o	65% (2.5:1)	**58% (4.8:1)**
16	3p	69% (2.1:1)	**56% (7.2:1)**
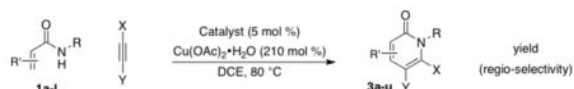
Entry	Product	Cp* [b]	Cp^t [c]
17	3q	77% (5:1)	**81 % (12.3:1)**
18	3r	60 % (4.8:1)	**79% (16:1)**
19	3s	74% (11:1)	-
20	3t	52% (1.2:1)	**60% (1:1.2)**
21[d]	3u	53% (5.8:1)	**55% (2.7:1)**

[a] Conditions: **1** (1 equiv), alkyne (1.1 equiv), rhodium catalyst, Cu(OAc)$_2$•H$_2$O in DCE at 80 °C.

[b] Cp*= Rh(C$_5$Me$_5$)(MeCN)$_3$(SbF$_6$)$_2$.
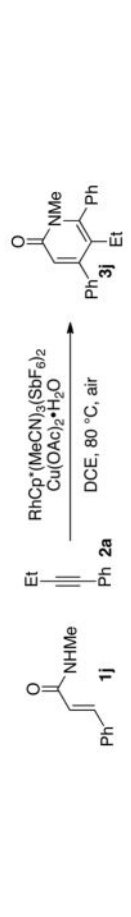
[c] Cp^t = Rh(C$_5$H$_3$(t-Bu)$_2$)(MeCN)$_3$(SbF$_6$)$_2$.

[d] 10 mol % rhodium catalyst.

*e*2 equiv alkyne.

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Table 3

Optimization for Large Scale Reactions

Entry	Scale (mmol)	Catalyst (mol %)	Conc. (M)	Cu(OAc)$_2$•H$_2$O (mol %)	GC/MS yield (%)
1	.22	5	0.3	20	86
2	.22	1	0.3	20	15
3[a]	.22	1	0.3	20	37
4[a]	.22	2.5	0.15	20	35
5[a]	.44	1	0.6	20	45
6[a]	6.22	2	0.6	20	69[b]
7[c]	.22	5	.3	0	40

[a]Portionwise addition of alkyne; see SI.

[b]Isolated yield.

[c]Reaction conducted under O$_2$ in presence of NaOAc (4 equiv).