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## Rhodium(III)-Catalyzed Anti-Markovnikov Hydroamidation of Unactivated Alkenes using Dioxazolones as Amidating Reagents

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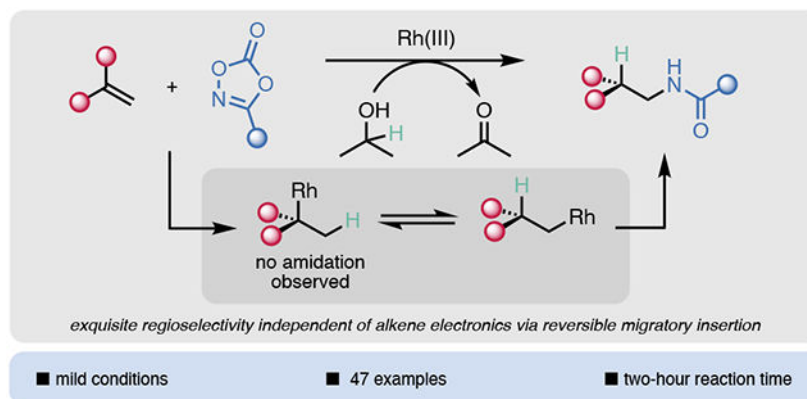
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### Abstract

The amide is one of the most prevalent functional groups in all of pharmaceuticals and for this reason, reactions that introduce the amide moiety are of particular value. Intermolecular hydroamidation of alkenes remains an underexplored method for the synthesis of amide-containing compounds. The majority of hydroamidation procedures exhibit Markovnikov regioselectivity, while current methods for anti-Markovnikov hydroamidation are somewhat limited to activated alkene substrates or radical processes. Herein, we report a general method for the intermolecular anti-Markovnikov hydroamidation of unactivated alkenes under mild conditions, utilizing Rh(III) catalysis in conjunction with dioxazolone amidating reagents and isopropanol as an environmentally friendly hydride source. The reaction tolerates a wide range of functional groups, and efficiently converts electron-deficient alkenes, styrenes, and 1,1-disubstituted alkenes, in addition to unactivated alkenes, to their corresponding linear amides. Mechanistic studies reveal a reversible rhodium hydride migratory insertion step, leading to exquisite selectivity for the anti-Markovnikov product.

### Graphical Abstract



Due to the prevalence of nitrogen within bioactive molecules,<sup>1</sup> C—N bond forming reactions are some of the most widely used in medicinal chemistry.<sup>2</sup> Among these, the

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intermolecular hydroamination of alkenes is a valuable method of introducing nitrogen-containing moieties to widely available feedstock chemicals. Both Markovnikov and anti-Markovnikov hydroamination procedures have been developed with a variety of transition metal catalysts and nitrogen sources, including asymmetric methods for the synthesis of chiral amines.<sup>3,4,5,6,7,8,9,10</sup> Recently, photoredox methodologies have also been leveraged to achieve hydroamination via the generation of radical species under mild conditions.<sup>11,12,13,14,15,16</sup> Despite impressive recent advances in hydroamination, there has been limited success diversifying the nitrogen-containing moieties that can be introduced. Most hydroamination reactions result in aliphatic amine, aryl amine, or sulfonamide products. Due to the ubiquity of the amide in bioactive molecules, hydroamidation methods are of particular interest. According to a 2006 survey of leading pharmaceutical companies, 2/3 of drug candidates contained an amide bond.<sup>17</sup> In 2020, a pharmaceutical company survey revealed that roughly one third of all reactions conducted internally were amide formation.<sup>18</sup> The vast majority of these reactions are traditional couplings of acid derivatives and amines. A complementary strategy is to unite intact amides or amide surrogates with alkenes, one of the most readily available functional groups, in a catalytic hydroamidation reaction. This latter strategy is largely unexplored, likely as a consequence of the reduced nucleophilicity of amides compared to aliphatic amines (although there are a few examples of anti-Markovnikov hydroamidation to install the specialized phthalimide moiety).<sup>13,19</sup> Recent examples, including this work, circumvent this constraint by using dioxazolones as electrophilic amide sources via metal nitrenoid formation,<sup>20,21,22,23,24</sup> or generation of an amidyl radical.<sup>25,26</sup>

Most previous work on hydroamidation has yielded Markovnikov products (Scheme 1A). Early examples from Widenhoefer and Hartwig achieve hydroamidation using amide nucleophiles and unactivated alkenes, with platinum,<sup>27,28</sup> gold,<sup>29</sup> or iridium<sup>30</sup> catalysts, but high reaction temperatures and a large excess of the alkene are generally required. More recently, Buchwald demonstrated an elegant copper-catalyzed Markovnikov hydroamidation of vinylarenes, using dioxazolones and a silane hydride source.<sup>21</sup> Nickel and cobalt catalysis have also been leveraged for Markovnikov hydroamidation by S. Zhu<sup>22</sup>, Yu<sup>31</sup>, and R. Zhu.<sup>32</sup>

Although even less explored than Markovnikov-selective methods, the anti-Markovnikov hydroamidation of alkenes has also been reported (Scheme 1B). Verma disclosed a metal-free hydroamidation of styrenes with aryl amides,<sup>25</sup> and Xiao and C. Wang employed iron catalysis for the hydroamidation of allyl alcohol.<sup>33</sup> While highly enabling, these methods are unable to engage unactivated alkenes as substrates. T. Wang used *N*-aminated dihydropyridines as redox-active amidyl radical precursors to effect anti-Markovnikov hydroamidation of unactivated alkenes under photocatalytic conditions.<sup>26</sup> This work proceeds via a radical addition mechanism, leaving room for a complementary transition metal-catalyzed anti-Markovnikov hydroamidation procedure. Herein we report the anti-Markovnikov hydroamidation of unactivated alkenes, via a reversible and unselective Rh(III) hydride migratory insertion step, using dioxazolones as amide surrogates that are readily made in one or two steps from carboxylic acids, and isopropanol as an environmentally benign hydride source (Scheme 1C).

Our previous work has revealed that Rh(III) catalysts engage even simple alkenes in a variety of reactions.<sup>34,35</sup> Extensive precedent by Krische and others<sup>36,37,38,39,40,41</sup> has established that transfer hydrogenation can occur from isopropanol. We speculated that we could merge these technologies to leverage rhodium hydride species for alkene functionalization. Specifically, rhodium hydride insertion into an alkene, followed by trapping with a dioxazolone would lead to anti-Markovnikov hydroamidation products.

Through reaction optimization, we obtained high yield of the desired hydroamidation product with the conditions shown in Table 1 entry 1 (detailed optimization tables are available in the Supporting Information). Of particular note is the selection of the electron-deficient 1,2,3,4-tetramethyl-5-trifluoromethylcyclopenta-1,3-dienyl (Cp\*<sup>CF3</sup>), which outperforms the prototypical pentamethylcyclopentadienyl (Cp\*) ligand (Table 1, entry 2). Increased electron deficiency of the catalyst may aid migratory insertion into the alkene, resulting in higher reactivity.<sup>42,43</sup> Control reactions demonstrated that rhodium, *i*-PrOH, and K<sub>2</sub>CO<sub>3</sub> are all necessary components (Table 1, entries 4-6). We were pleased to observe that the hydroamidation product is still formed in synthetically useful yields when the equivalents of dioxazolone are reduced (2 equiv., 51%, Table 1, entry 7), and when the reaction is conducted without heating (55%, Table 1, entries 8). Additionally, the reaction exhibits no sensitivity to air (Table 1, entry 9).

Having established optimized conditions for the anti-Markovnikov hydroamidation reaction, we next examined its scope (Scheme 2). Alkenes containing a wide range of functional groups are compatible with the reaction conditions, including free and protected alcohols (**3c**, **3h**, **3j**, **3m**, **3o**, **3p**, **3q**, **3aa**, **3ac**), protected amines (**3b**, **3g**, **3i**, **4e**), and potentially sensitive leaving groups, including acetate, tosylate, and bromide (**3j**, **3o**, and **3u** respectively). Other functional groups that are tolerated include a nitrile (**3l**), Weinreb amide (**3n**), sulfone (**3r**), and epoxide (**3ad**). It is also notable that ketones (**3s**, **4l**), are preserved, even under reducing metal-hydride conditions. More complex natural products linalool (**3p**) and sclareol (**3q**) undergo hydroamidation in good yields, and, notably, the trisubstituted alkene of linalool remains untouched. Likely, the more sterically hindered alkene region is unable to undergo migratory insertion, thereby enabling selective hydroamidation of the terminal alkene. Radical hydroamidation methods exhibit opposite chemoselectivity with analogous substrates.<sup>20</sup> In addition to the aliphatic alkenes examined, the reaction also proceeds smoothly with styrenes (**3v-3x**) and electron deficient alkenes such as acrylates and vinyl sulfones (**3s**, **3y**). We are also able to isolate terminally amidated products **3z** and **3aa** from internal alkene starting materials ethyl crotonate and trans 3-penten-1-ol, albeit in lower yields. These products most likely result from an alkene chain walk mechanism that first isomerizes the double bond to the terminal position, where it then undergoes hydroamidation. Similar chain walking has been previously described for Rh(I) hydride species by Shi.<sup>44</sup>

Furthermore, we were excited to see that 1,1-disubstituted alkenes are also amenable to the hydroamidation procedure. Methacrylate derivatives (**3ab-3ae**) perform well in the method.  $\alpha$ -substituted styrenes (**3af**, **3ag**) undergo hydroamidation in moderate yields as well. Substituted methylenecyclohexanes (**3ah-3al**) also afford the desired products efficiently with moderate to excellent diastereoselectivity, but yield was found to decrease as the steric

bulk of the substituents is increased. For example, the yield and diastereomeric ratio are minorly impacted moving from phenyl to *tert*-butyl (**3ai**, **3aj**), but using significantly bulkier substrates  $\beta$ -pinene (**3ak** and (+)-longifolene (**3al**, results in a large drop in yield and significantly higher diastereomeric ratios of 4:1 and >20:1 respectively.

We also expanded the hydroamidation scope beyond the addition of an acetamide group by making use of different dioxazolones. Amides with longer linear aliphatic chains and rings of varying size were all installed efficiently (**4a**, **4b**, **4c**, **4d**, **4f**, **4g**, **4h**). *N*-phthaloyl glycine and dehydrocholic acid-derived dioxazolones (**4e**, **4i**) afford the hydroamidated products in synthetically useful yields, despite using reduced equivalents of the dioxazolone due to solubility constraints.

We next turned our attention to elucidating the mechanism (Scheme 3). A rhodium hydride species was observed by stirring  $[\text{Cp}^*\text{CF}_3\text{RhCl}_2]_2$ , isopropanol, and  $\text{K}_2\text{CO}_3$  in  $\text{DCM-}d_2$  at room temperature for one minute and taking a  $^1\text{H}$  NMR spectrum, where we observed the hydride as a triplet ( $-11.18$  ppm,  $J = 20$  Hz).<sup>45,46,47</sup> Although further experiments suggest that the observed species is not catalytically active (see SI for details), this demonstrates the formation of a rhodium hydride under these conditions. In order to test whether a rhodium hydride is mechanistically active, we performed stoichiometric experiments with  $\text{Et}_3\text{SiH}$  as a hydride source, which generate a small amount of active rhodium monohydride, as well as predominant formation of inactive rhodium dihydride species (see SI for details). Subjecting 1-decene to the standard conditions using  $\text{Et}_3\text{SiH}$  instead of isopropanol, we observe the hydroamidation product, albeit in just 6% yield. On the basis of these experiments, as well as literature on rhodium transfer hydrogenation,<sup>48</sup> we propose that rhodium hydride formation is likely the first step of the mechanism.

We then sought to confirm that isopropanol is the hydride source by using isopropanol- $d_8$  in the standard reaction conditions, and we indeed saw deuterium incorporation in the product (Scheme 3A). A second interesting observation from this experiment was that deuterium is incorporated equally at both C1 and C2, leading us to hypothesize that migratory insertion of the rhodium hydride is completely unselective. Since amidation occurs exclusively at the terminal position, we posited that migratory insertion is also reversible (supported by our prior observation that chain walking may occur to form products **3z** and **3aa**).<sup>44,49</sup> To test this, we subjected terminally-deuterated 1-undecene- $d_2$  to the standard conditions (Scheme 3B). In the product we observed that some of the deuterium incorporation at C1 is transferred to C2, which further supports an unselective and reversible migratory insertion step. The exquisite terminal selectivity for amidation therefore suggests a higher barrier to amidation for the secondary alkylrhodium species.

To probe the reversibility of the alkene coordination step, we subjected 1-decene to the standard conditions with isopropanol- $d_8$ , but stopped the reaction after 30 minutes so that full conversion was not achieved (Scheme 3C). If alkene coordination is reversible, we should observe deuteration of the alkene due to migratory insertion of rhodium deuteride to form a secondary alkylrhodium species and subsequent  $\beta$ -hydride elimination (this pathway is implied by the deuteration of both C1 and C2 in Scheme 3A). Upon isolating

the unreacted alkene, we did not observe deuterium incorporation, suggesting that alkene coordination is irreversible.

Subjecting 1-decene to the reaction conditions with a 1:1 mixture of isopropanol and isopropanol- $d_8$  (Scheme 3D) results in no detectable deuterium incorporation in the product, implying a large primary KIE on the rhodium hydride-forming step and potentially on subsequent steps.<sup>50</sup>

Since the above experiments suggest that amidation is turnover-limiting, we used a competition experiment between fluoromethyl dioxazolone and methyl dioxazolone to determine whether dioxazolone coordination or nitrenoid formation is the turnover-limiting step (Scheme 3E). While methyl dioxazolone is more strongly coordinating, fluoromethyl dioxazolone is more easily activated to undergo nitrenoid formation. The product ratio of the reaction was 2.3:1 in favor of the fluorinated product, showing that the more weakly coordinating fluoromethyl dioxazolone outcompetes methyl dioxazolone. We thus conclude that dioxazolone coordination cannot be turnover limiting and that this outcompetition is a result of more facile dioxazolone activation, implying that nitrenoid formation is turnover-limiting.

On the basis of the above experiments, we propose the mechanism shown in Scheme 4. First,  $K_2CO_3$  promotes the formation of rhodium alkoxide **I** from isopropanol. This species then undergoes  $\beta$ -hydride elimination to release acetone and form rhodium hydride **II**. Irreversible coordination of an alkene results in species **III**, which can undergo reversible migratory insertion to form either alkyrhodium species **IV** or **IVa**. Since the branched regioisomer of the product is not detected, we conclude that only **IV** is amidated, while **IVa** undergoes  $\beta$ -hydride elimination back to **III**. Upon dioxazolone coordination to **IV** to form **V**, turnover-limiting N—O bond cleavage and  $CO_2$  extrusion occur, forming rhodium nitrenoid **VI**. Migratory insertion and protodemetalation of the resultant N—Rh bond release the hydroamidated product and regenerate the catalyst.

In summary, we have developed a novel method for highly selective Rh(III)-catalyzed anti-Markovnikov hydroamidation of unactivated alkenes, proceeding via reversible migratory insertion. The reaction exhibits a broad substrate scope under mild reaction conditions. In addition to tolerating a multitude of functional groups, the reaction is amenable to different classes of olefin, including electron deficient alkenes, styrenes, and 1,1-disubstituted alkenes, with no change in regioselectivity. Modulation of the dioxazolone also allows for the introduction of a variety of amide groups. Further advantages of the method include short (two-hour) reaction times, insensitivity to air, and the use of the ubiquitous solvent isopropanol as the hydride source. It is our hope that this reaction will provide a convenient way to append the prevalent amide functionality to molecules, and will enable new and streamlined synthetic pathways.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGMENT

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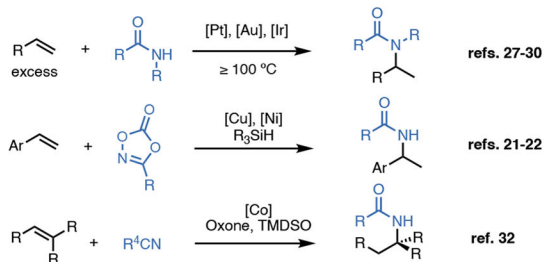
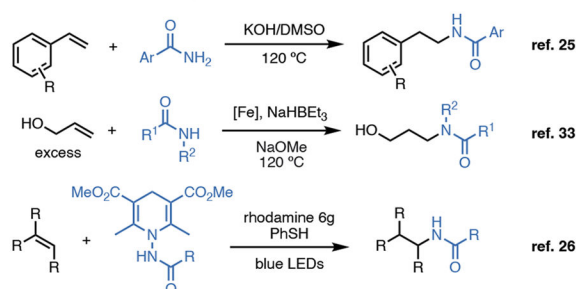
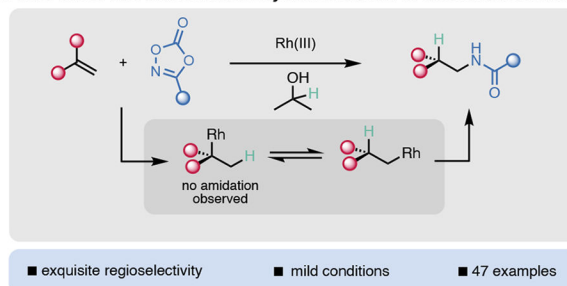
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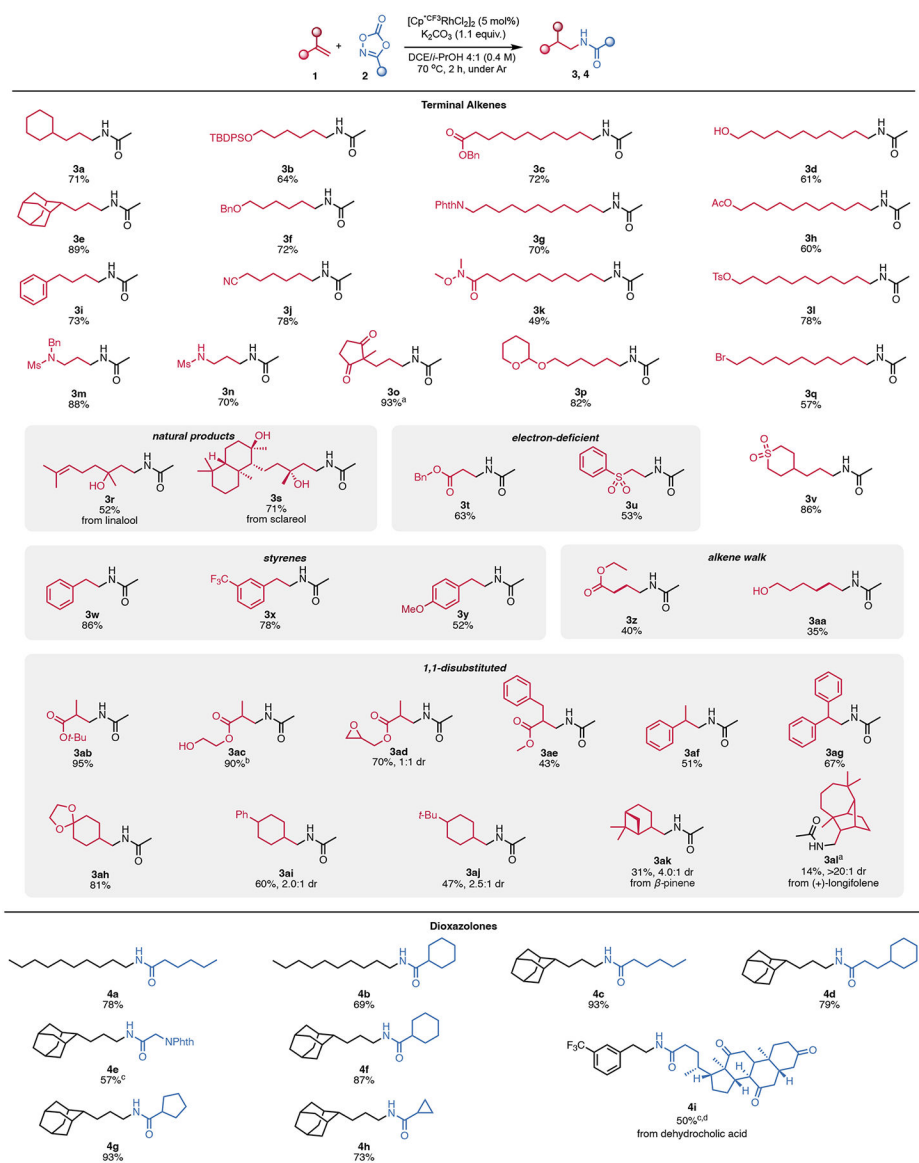
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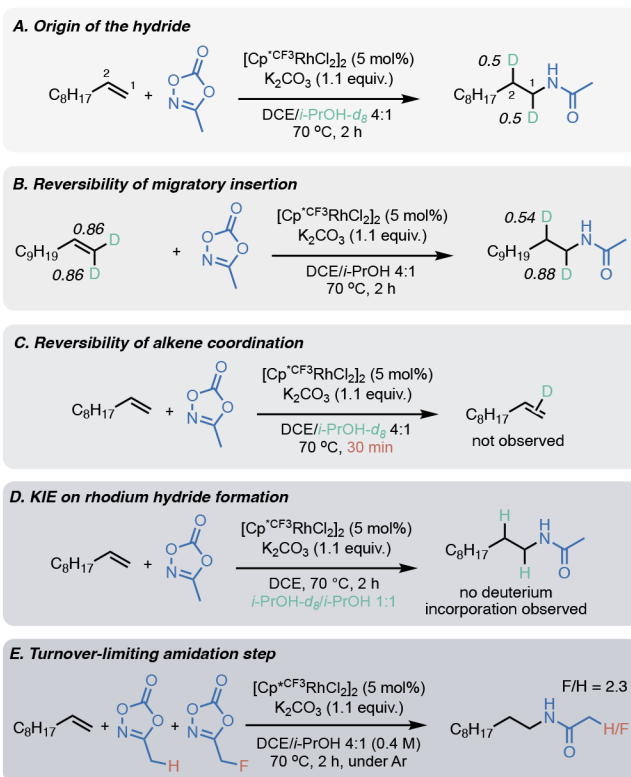


**A. Markovnikov hydroamidation****B. Anti-Markovnikov hydroamidation****C. This work: anti-Markovnikov hydroamidation of unactivated alkenes**

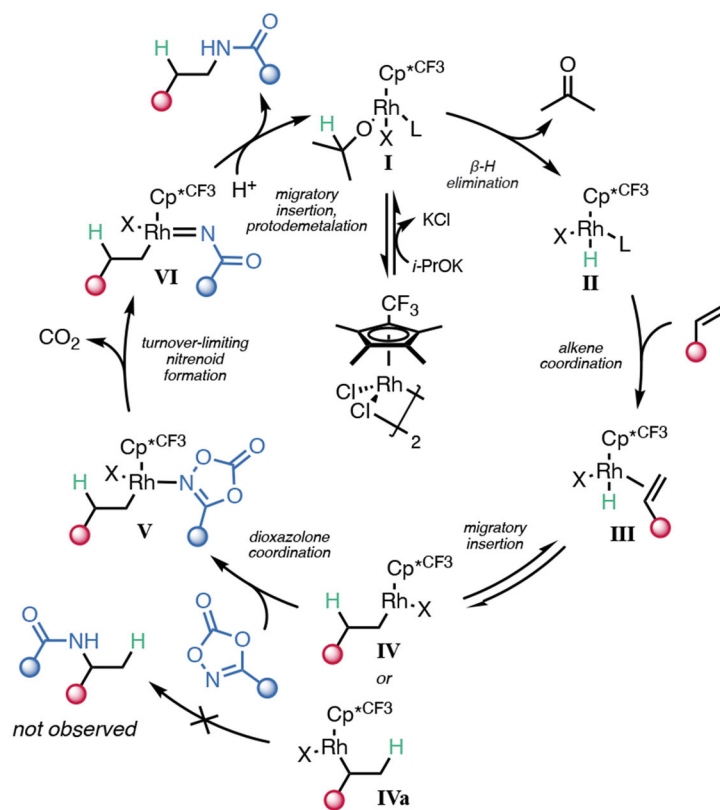
Scheme 1. Previous work on hydroamidation of alkenes

**Scheme 2. Hydroamidation scope**

Unless otherwise noted, we report isolated yields of reactions run on 0.1 mmol scale using five equivalents of dioxazolone. <sup>a</sup> The NMR yield is reported. <sup>b</sup> The free alcohol was TMS-protected in the starting material. <sup>c</sup> With 2.5 equivalents of dioxazolone. <sup>d</sup> 0.05 mmol scale. Ac = acetyl, Bn = benzyl, Phth = phthaloyl, Ms = methanesulfonyl, TBDPS = *tert*-butyldiphenylsilyl, Ts = *para*-toluenesulfonyl.



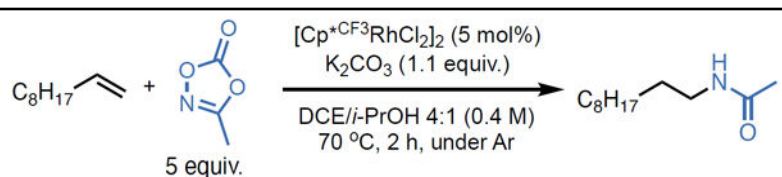
Scheme 3. Mechanistic studies



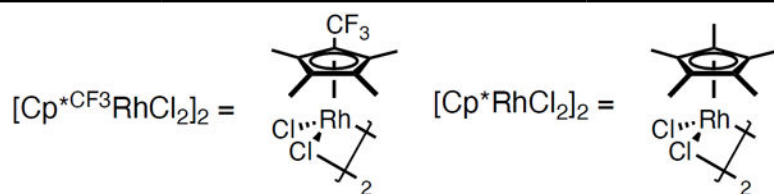
Scheme 4. Proposed mechanism

Table 1.

Optimized reaction conditions and controls



Entry	Deviation from Standard Conditions	Yield (%) <sup>a</sup>
1	none	79
2	$[Cp^*RhCl_2]_2$	37
3	no Rh	—
4	no <i>i</i> -PrOH	—
5	no $K_2CO_3$	—
6	2 equiv. dioxazolone	51
7	22 °C	55
8	under air	80



Optimization was performed on 0.1 mmol scale, using 1-decene and methyl dioxazolone (5 equiv.) in DCE/*i*-PrOH. <sup>a</sup>Yields were determined by <sup>1</sup>H NMR of the unpurified reaction mixture, with mesitylene as internal standard.