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Ruthenium-Catalyzed Formal Dehydrative [4 + 2] Cycloaddition of Enamides and Alkynes for the Synthesis of Highly Substituted Pyridines: Reaction Development and Mechanistic Study

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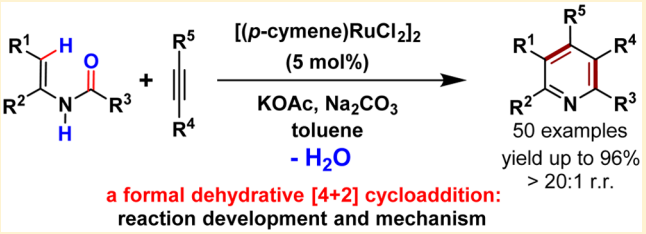
Supporting Information

ABSTRACT: Reported herein is a ruthenium-catalyzed formal dehydrative [4 + 2] cycloaddition of enamides and alkynes, representing a mild and economic protocol for the construction of highly substituted pyridines. Notably, the features of broad substrate scope, high efficiency, good functional group tolerance, and excellent regioselectivities were observed for this reaction. Density functional theory (DFT) calculations and experiments have been carried out to understand the mechanism and regiochemistry. DFT calculations suggested that this formal dehydrative [4 + 2] reaction starts with a concerted metalation deprotonation of the enamide by the acetate group in the Ru catalyst, which generates a six-membered ruthenacycle intermediate. Then alkyne inserts into the Ru−C bond of the six-membered ruthenacycle, giving rise to an eight-membered ruthenacycle intermediate. The carbonyl group (which comes originally from the enamide substrate and is coordinated to the Ru center in the eight-membered ruthenacycle intermediate) then inserts into the Ru−C bond to give an intermediate, which produces the final pyridine product through further dehydration. Alkyne insertion step is a regio-determining step and prefers to have the aryl groups of the used alkynes stay away from the catalyst in order to avoid repulsion of aryl group with the enamide moiety in the six-membered ruthenacycle and to keep the conjugation between the aryl group and the triple C−C bond of the alkynes. Consequently, the aryl groups of the used alkynes are in the β-position of the final pyridines, and the present reaction has high regioselectivity.



INTRODUCTION

Of the N-heterocycles, pyridines are among the most prevalent scaffolds found in natural products and pharmaceuticals.[1] In the last few decades, a wealth of research has focused on the construction of these heterocycles.[2] Nonetheless, access to pyridines with desirable substitution patterns often remains a challenge when traditional multicomponent approaches are applied.[3] Though classic condensation protocols are available for pyridine core construction, substituent patterns of these pyridines are largely dictated by the activating groups required for reactivity.[4] Recently, intermolecular [2 + 2 + 2] cycloadditions of nitriles and alkynes have received much attention because of broad availability of the starting materials.[5] However, this synthetic method often leads to the generation of regioisomers.[6] Novel complementary approaches to diversely substituted pyridines are still highly desirable, and several impressive reports highlight the recent advances in this field.[7]

Enamides are highly valuable building blocks in organic synthesis.[8] The importance of enamide chemistry has been highlighted by transition-metal-catalyzed coupling reactions[9] and Lewis acid-catalyzed nucleophilic addition.[10] As outlined in Scheme 1a, the Glorius[11] and Fagnou[12] groups independently revealed the Rh-catalyzed oxidative coupling of enamides with internal alkynes, producing highly substituted pyrroles. In 2013, Ackermann[13] and Wang[14] groups independently found that Ru catalyst can mediate an oxidative coupling of enamides with internal alkynes to generate pyrroles in a highly efficient manner. In addition, examples of Pd, Ag, or Cu catalyzed or promoted cross-coupling of enamides with internal alkynes have also been reported, but still focused on pyrrole synthesis.[15] To the best of our knowledge, a metal-catalyzed formal dehydrative [4 + 2] cycloaddition of enamides with alkynes to directly construct pyridines has remained elusive until now.[16] In 2007, Movassaghi et al. reported a noncatalytic method to make pyridines by using acetylenes and enamides.[17] However, a stoichiometric amount of Tf_2O and 2-chloropyridine was requested to achieve satisfied yields. We report herein a formal dehydrative [4 + 2] cycloaddition of enamides and alkynes, a new complementary process toward highly substituted pyridines, featured with excellent chemo- and regio-selectivities, broad scope, and functional group tolerance (Scheme 1b). Meanwhile, experiments and DFT calculations have been

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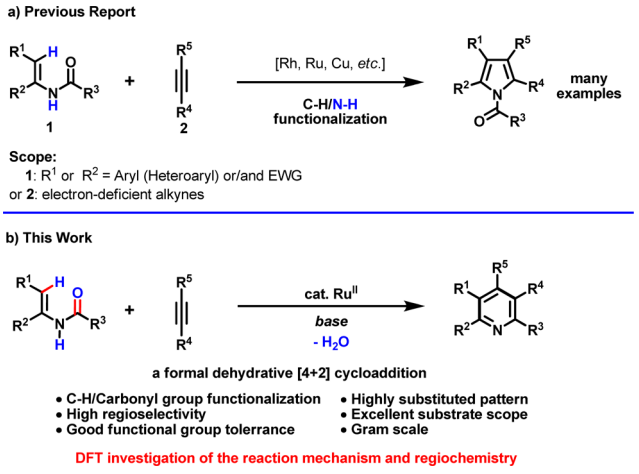
Scheme 1. Two Different Metal-Catalyzed Reactions of Enamides and Alkynes for the Synthesis of Pyrroles and Pyridines



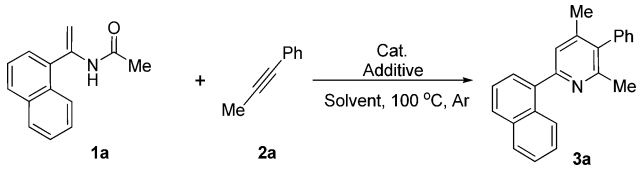
carried out to understand the reaction mechanism and regiochemistry.

RESULTS AND DISCUSSION

Optimization Studies. Key results of reaction condition optimization are summarized in Table 1. Model reaction of *N*-vinyl amide **1a** and alkyne **2a** was used to evaluate reaction parameters (Table 1). After testing several commonly used metal catalysts (entries 2−4), $[(p\text{-cymene})RuCl_2]_2$ was chosen to be the best due to its high catalysis efficiency (Table 1, entry 4, 76%). Encouragingly, we found that an enhanced chemical yield could be achieved by using a combination of KOAc and Na_2CO_3 (entry 12, 86%). Solvent screening disclosed that toluene was the most efficient medium for this reaction (entries 16−20). In addition, we found that the reaction temperature did not have a significant impact on the reaction yields, as demonstrated by the observations that slightly decreased or increased temperature had very close reaction yields (entries 13 and 14, 80 °C, 81%; 120 °C, 76%). Therefore, we chose the reaction conditions in entry 12 as the optimal reaction conditions (5 mol % $[(p\text{-cymene})RuCl_2]_2$ as catalyst, toluene as the solvent, and the reaction temperature of 100 °C).

Substrate Scope. With the optimized reaction conditions in hand, a series of enamides **1b−u** were examined (Table 2). **1b−g** (R^2 = phenyl group) reacted with **2a** to yield pyridines **3b−g** in moderate to excellent yields. For the syntheses of **3b−e** from **1b−e**, we found that these substrates were prone to decomposition. Therefore, 4 Å molecular sieves were added to suppress the enamide hydrolysis, and the target reactions under these new reaction conditions took place smoothly with reasonable to good yields. Substrates **1h−k** (R^2 = heterocycles) were also good substrates and gave the corresponding pyridines **3h−k** in yields. Enamides with alkenyl group on R^2 position (**1l** and **1m**) can also be used to afford their corresponding pyridine products **3l** and **3m** in good chemical yields. Additionally, enamides (**1n, 1p−s**) bearing alkyl groups on R^2 position also underwent cycloaddition to provide pyridines **3n** and **3p−s**, respectively. When **1o** (R^2 = PhCO) and multisubstituted substrates **1t−u** (R^2 = Ar and R^1 = $-(CH_2)_{(1-2)}-$) were subjected to the optimal reaction conditions, the desired pyridines **3o** and **3t−u** were obtained in useful synthetic yields. Notably, the generated pyridines **3** in all these reactions were formed with complete regioselectivity (all r.r. > 20:1). Furthermore, we tested whether acetanilides (e.g., *N*-phenylacetamide and *N*-(*p*-tolyl)acetamide) can also give pyridine products under the optimal conditions. Unfortunately, no desired pyridines products were generated for these tested acetanilides, indicating the activation of $C_{sp^2}-H$ of aromatic compounds in acetanilides is difficult under current reaction conditions.

Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	additive	solvent	yield[b]
1	none[c]	K_2CO_3	toluene	n.r.[d]
2	$Pd(OAc)_2$	K_2CO_3	toluene	n.d.[l]
3	$[Cp^*RhCl_2]_2$[k]	K_2CO_3	toluene	8%
4	$[(p\text{-cymene})RuCl_2]_2$	K_2CO_3	toluene	76%[j]
5	$[(p\text{-cymene})RuCl_2]_2$	Et_3N	toluene	Trace
6	$[(p\text{-cymene})RuCl_2]_2$	*t*-BuOK	toluene	trace
7	$[(p\text{-cymene})RuCl_2]_2$	NaOAc	toluene	65%[j]
8	$[(p\text{-cymene})RuCl_2]_2$	KOAc	toluene	81%[j]
9	$[(p\text{-cymene})RuCl_2]_2$	CsOAc	toluene	79%[j]
10	$[(p\text{-cymene})RuCl_2]_2$	Na_2CO_3	toluene	84%[j]
11	$[(p\text{-cymene})RuCl_2]_2$	Cs_2CO_3	toluene	70%[j]
12	$[(p\text{-cymene})RuCl_2]_2$	KOAc/Na_2CO_3[h]	toluene	86%[j]
13[e]	$[(p\text{-cymene})RuCl_2]_2$	KOAc/Na_2CO_3[h]	toluene	81%[j]
14[f]	$[(p\text{-cymene})RuCl_2]_2$	KOAc/Na_2CO_3[h]	toluene	76%[j]
15[g]	$[(p\text{-cymene})RuCl_2]_2$	KOAc/Na_2CO_3[h]	toluene	51%[j]
16	$[(p\text{-cymene})RuCl_2]_2$	KOAc/Na_2CO_3[h]	MeCN	41%[j]
17	$[(p\text{-cymene})RuCl_2]_2$	KOAc/Na_2CO_3[h]	dioxane	58%[j]
18	$[(p\text{-cymene})RuCl_2]_2$	KOAc/Na_2CO_3[h]	DCE	61%[j]
19[i]	$[(p\text{-cymene})RuCl_2]_2$	KOAc/Na_2CO_3[h]	*t*-AmylOH	43%[j]
20	$[(p\text{-cymene})RuCl_2]_2$	KOAc/Na_2CO_3[h]	DMF	45%[j]

[a]Reaction conditions: **1a** (0.3 mmol, 1.0 equiv), **2a** (0.45 mmol, 1.5 equiv), cat. (5 mol %), additive (2.0 equiv), and toluene (2 mL) at 100 °C under argon atmosphere for 36 h. [b]Yield of isolated product. [c]No catalyst. [d]No reaction. [e]80 °C. [f]120 °C. [g]Air atomosphere. [h]KOAc (1.0 equiv) and Na_2CO_3 (1.0 equiv). [i]*t*-AmylOH = 2-Methyl-2-butanol. [j]Ratio of regioisomer (r.r.) > 20:1, determined by crude NMR. [k]Dichloro(pentamethylcyclopentadienyl)-rhodium(III) dimer. [l]Not detected.

Further investigation of the scope of enamides was conducted (Table 3). For enamides with R^3 = alkyl group, reactions proceeded well to afford the corresponding products in good chemical yields (**5a−f, 5i**). For enamide **4g** with R^3 = alkenyl group, the catalytic process smoothly provided tetrasubstituted **5g** in 64% yield. Pleasingly, for enamide **4h** with R^3 = difluoromethyl group, pyridine **5h** was obtained in 76% yield. When R^2 and R^3 were both phenyl groups, a moderate yield (51%) of **5j** was achieved by using an excess amount of alkyne **2a** (3.0 equiv). Lastly, *N*-methyl protected enamide **1a** was synthesized to verify the necessity of the NH group in the substrate. No desired pyridine **3a** was detected under the standard conditions, proving that the NH group is essential to the present dehydrative annulation reaction.

To further demonstrate the generality and practicability of this formal dehydrative [4 + 2] cycloaddition, we tested an array of alkynes **2**. Symmetric diarylalkynes showed good to high reactivities (Table 4, **6a**, **6e−g**). Symmetric dimethyl

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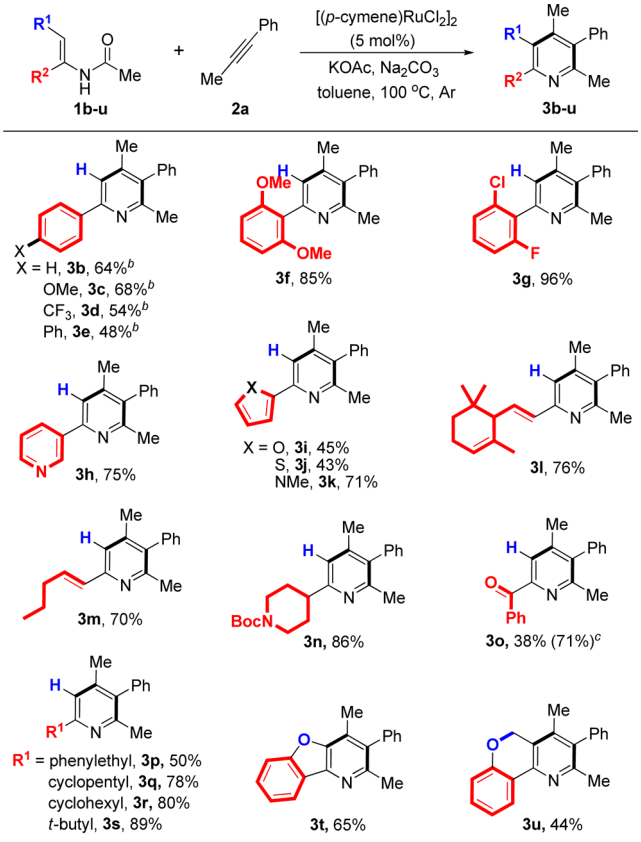
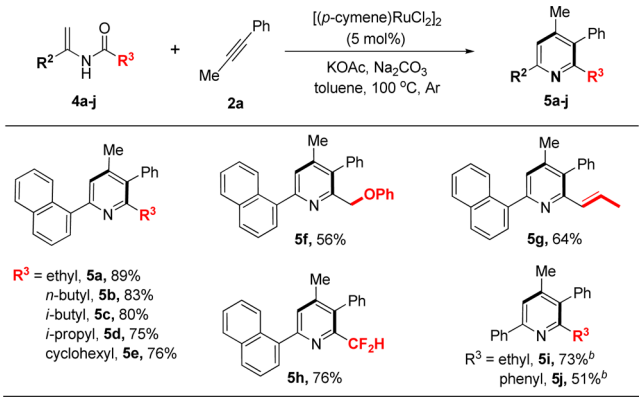
Table 2. Scope of Enamides[a]



[a]Reaction conditions: **1b–u** (0.3 mmol, 1.0 equiv), **2a** (1.5–2.0 equiv), $[(p\text{-cymene})RuCl_2]_2$ (5 mol %), Na_2CO_3 (1.0 equiv), KOAc (1.0 equiv), and toluene (2 mL) at 100 °C under argon atmosphere for 24–48 h. [b]**2a** (3.0 equiv), Na_2CO_3 (2.0 equiv), and 4 Å MS (100 mg) were used. [c]Yield based on recovery of **1**.

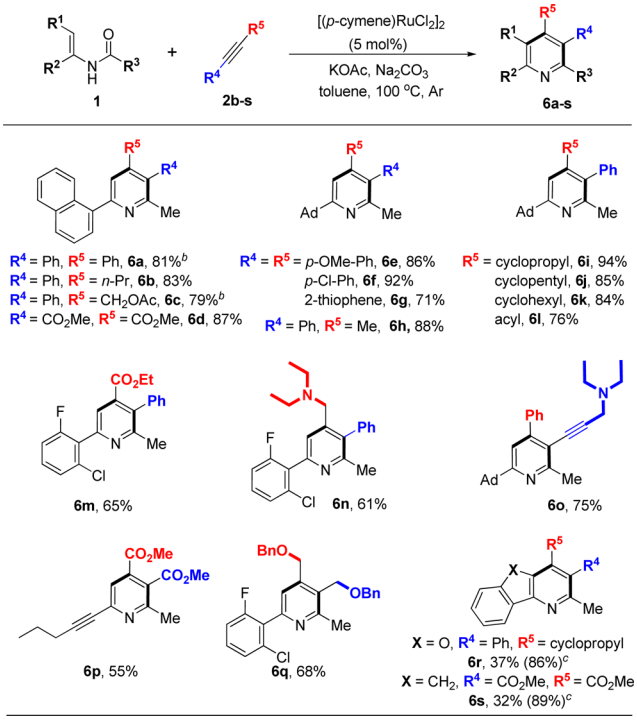
Table 3. Scope of Other Enamides[a]



[a]Reaction conditions: **4a–j** (0.3 mmol, 1.0 equiv), **2a** (1.5–2.0 equiv), $[(p\text{-cymene})RuCl_2]_2$ (5 mol %), Na_2CO_3 (1.0 equiv), KOAc (1.0 equiv), and toluene (2 mL) at 100 °C under argon atmosphere for 24–48 h. [b]**2a** (3.0 equiv), Na_2CO_3 (2.0 equiv), and 4 Å MS (100 mg) were used.

acetylenedicarboxylate afforded substituted pyridines **6d** and **6p** (87% and 55%, respectively). Symmetric dialkyl alkyne (**2q**) was also verified to be an active partner for this catalytic process (**6q**, 68%). To further understand the regioselectivity of the present reaction, a number of unsymmetric internal alkynes were investigated (Table 4). To our surprise, all unsymmetric

Table 4. Scope of Alkynes[a,d]

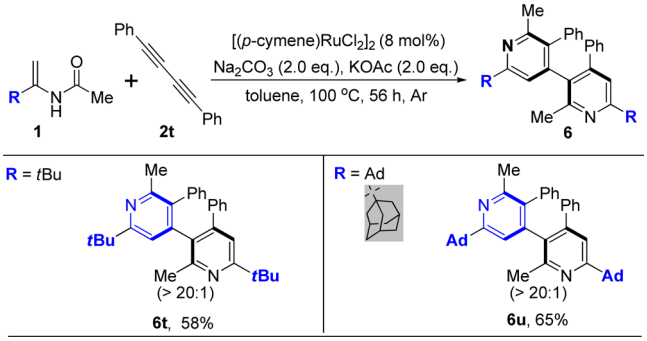


[a]Reaction conditions: **1** (0.3 mmol, 1.0 equiv), **2** (1.5–2.0 equiv), $[(p\text{-cymene})RuCl_2]_2$ (5 mol %), Na_2CO_3 (1.0 equiv), KOAc (1.0 equiv), and toluene (2 mL) at 100 °C under argon atmosphere for 24–48 h. [b]8 mol % $[(p\text{-cymene})RuCl_2]_2$ was used. [c]Yield based on recovery of **1**. [d]Ad = adamantyl.

internal alkynes underwent cyclization reaction with enamides **1** to give a single regioisomer in good yields (**6b–c**, **6h–o**). In addition, pentasubstituted pyridine derivatives (**6r** and **6s**) were also obtained in 37% and 32%, respectively. The configuration of these pyridine analogues was assigned by comparing the NMR spectra of pyridines **3c** and **5j** with ref 18 and analysis of their 2D NMR spectra (see Supporting Information).

Synthesis of Bipyridines. It is important to note that this methodology can be successfully utilized to generate highly substituted bipyridines in a facile one-pot process when diynes were used, even though a higher catalyst loading (8 mol %) and elongated reaction time (56 h) were required (Table 5). It was

Table 5. Synthesis of Bipyridines[a]



[a]**1** (0.6 mmol), 1,4-diphenylbuta-1,3-diyne (0.2 mmol), $[(p\text{-cymene})RuCl_2]_2$ (8 mol %), Na_2CO_3 (2.0 equiv), KOAc (2.0 equiv), 4 Å MS (200 mg), and toluene (2 mL) at 100 °C under argon atmosphere for 56 h.

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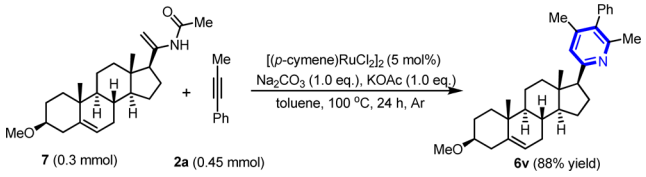
expected that two types of regioisomers can be generated from the dehydrative [4 + 2] reaction using diynes. Here only one type of regioisomers (**6t** and **6u**) was generated. This can be explained by steric reason for the formations of the second pyridines, which prefers to have the bulky *t*-Bu and Ad groups to stay away from the first-step formed pyridines, as those shown in **6t** and **6u**.

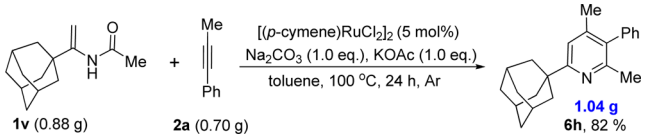
Late-stage modification was considered as a valuable method for drug optimization in medicinal chemistry. As indicated in Scheme 2, when we subjected steroid **7** to the dehydrative cycloaddition reaction conditions, pyridine **6v** was synthesized in 88% yield.

Scheme 2. Late-Stage Modification



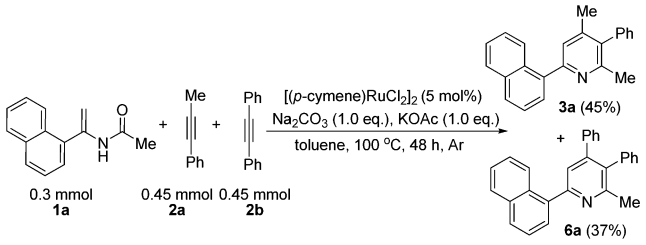
With the aim of evaluating the practicality of this catalytic process, a gram-scale experiment was performed with **1v** (0.88 g) and **2a** (0.70 g), yielding the corresponding product **6h** in 82% (Scheme 3, 1.04 g)

Scheme 3. Gram-Scale Synthesis of 6h



To understand how substituents in the used alkynes affect the reaction outcome, a competing dehydrative cyclization experiment using two alkynes **2a** and **2b** with different electronic effects to react with **1a** had been performed (Scheme 4). This investigation demonstrated that the dehydrative

Scheme 4. Intermolecular Competition between Alkynes

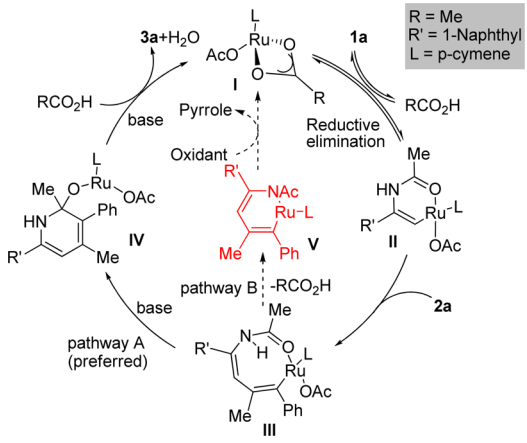


cyclization of enamides with alkynes is not sensitive to the electronic effect of the alkynes (because very close reaction yields of **3a** and **6a** were obtained).

MECHANISTIC STUDIES

Plausible Mechanism. The proposed reaction mechanism for the present formal dehydrative [4 + 2] cyclization is given in Scheme 5. First, catalytic species **I** ($Ru(p\text{-cymene})(OAc)_2$) is *in situ* formed.[19] Then metalation and deprotonation of **I** to the enamide substrate generate a six-membered ruthenacycle intermediate **II**.[20] Intermediate **III** is then formed after insertion of **2a** into Ru−C bond in **II**. Carbonly group in **III**

Scheme 5. Postulated Mechanism of the Formal Dehydrative [4 + 2] Cycloaddition



is then inserts into the Ru−C bond intramolecularly, giving intermediate **IV** (pathway A). Finally, through further dehydration process, intermediate **IV** in pathway A is converted to the pyridine product with the concomitant generation of the catalytic species **I**. The present reaction has a competing pathway related to the generation of pyrrole, even though we did not observe such product in our reaction system. This competing reaction starts from intermediate **III**, which undergoes decarboxylation to give intermediate **V** (rather than the C═O insertion into the Ru−C bond to give intermediate **IV** in the pyridine formation (pathway A). Intermediate **V** then undergoes reductive elimination and oxidation to give the final pyrrole product (Pathway B). Mechanistic study through experiments and DFT calculations presented below supports that pathway A (leading to the formation of pyridine) is the preferred one.

Experimental Study of the Reaction Mechanism. To gain some mechanistic insights into the current protocol, a number of control experiments were performed, including an intermolecular kinetic isotope effect experiment and several deuterium-labeling experiments (Scheme 6). Notably, a small kinetic isotope effect was observed in the intermolecular (k_H/k_D = 2.2) competition experiment [Scheme 6, eq (a)]. Under the standard conditions and the addition of 10.0 equiv of D_2O, we found that approximately 31% deuterium was incorporated into the recovered **1a** and 8% deuterium was incorporated into product **3a** [Scheme 6, eq (b)]. Performing this reaction in the absence of alkynes **2a**, about 75% deuterium was found in the recovered **1a** [Scheme 6, eq (c)]. However, no deuterated **1a** was identified when this substrate was simply mixed with D_2O [Scheme 6, eq (d)]. Several conclusions were drawn from these experiments: the C−H metalation−deprotonation step (**1a** and **I** to **II**, Scheme 5) is reversible; this step is not involved in the rate-determining step. This was further supported by DFT calculations (see below). In the absence of base (e.g., Na_2CO_3, KOAc), no **3a** could be generated for the dehydrative cyclization reaction, suggesting that base is very critical to the success of the target reaction [Scheme 6, eq (e)]. The reason why a different base influences the reaction outcome is not clear at this current stage. Notably, addition of $Cu(OAc)_2$ provided a competing pathway and afforded undesirable pyrrole **3a′** [Scheme 6, eq (f)]. We think that the added oxidant here could significantly alter the reaction pathway shown in Scheme 5. We also investigated whether the present dehydrative

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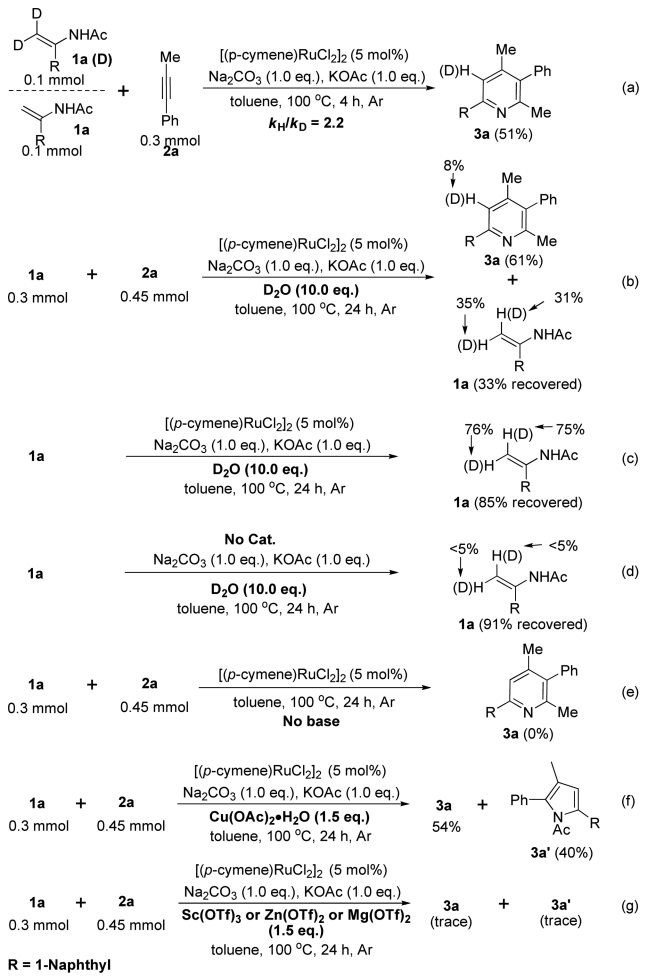
Scheme 6. Experimental Studies of Mechanism (R = 1-Naphthyl)



cyclization reaction can occur in the presence of Lewis acids such as $Sc(OTf)_3$, $Mg(OTf)_2$, or $Zn(OTf)_2$. The negative answer suggests that adding Lewis acid is detrimental for the pyridine formation reaction [Scheme 6, eq (g)].

DFT Studies of the Formal Dehydrative [4 + 2] Cycloaddition. The above mechanism was further scrutinized by DFT calculations using the M06//B3LYP calculations (geometry optimizations using B3LYP and single-point energy calculations using M06. For details, see the Supporting Information).[21] Here we use relative Gibbs free energies in the gas phase to discuss the reaction mechanism.[22] Figure 1 gives the potential energy surface of the catalytic cycle together with the competing processes related to the regiochemistry and side reaction of pyrrole formation. Figure 2 gives several key transition structures.

Figure 1a shows that the catalytic cycle begins with coordination of the enamide to the Ru center of the catalyst, giving complexes **IN1** and **IN2**. Complexes **IN1** with carbonyl coordination to Ru atom is more stable than **IN2** with alkene coordination to Ru atom. Complexes **IN1** and **IN2** are in equilibrium, and **IN2** is the reacting conformer for the followed reaction steps of the catalytic cycle.

A concerted metalation deprotonation (CMD) process by the coordinated acetate converts **IN2** to **IN3**. The computed activation free energy of the CMD process is 20.4 kcal/mol. **IN3** then releases HOAC molecule to give six-membered ruthenacycle intermediate **IN4**. Intermediate **IN4** is an 18-e complex with the coordination of carbonyl group of the enamide moiety. The incoming alkyne can replace this carbonyl group for coordination to form **IN5** and **IN5a**, both of which are also 18-e complexes (see Figure 1a,b). **IN5** and **IN5a** differ from each other by the relative orientation of the alkyne with respect to the Ru−enamide bond. The alkyne coordination to the metal center prefers to have the alkyne, its two substituents, and the Ru atom in the same plane. In **IN5**, the Ph group, which points away from the catalyst and experiences no steric hindrance, is in plane with the alkyne moiety to keep good conjugation. In contrast, in **IN5a**, the Ph group experiences repulsion from the amide moiety and has to distort to a position that does not enjoy conjugation between the Ph group and the alkyne moiety. Consequently, **IN5a** is less stable than **IN5** by 1.3 kcal/mol in terms of Gibbs energy in the gas phase.

The disrupted conjugation found in **IN5a** is also kept in the alkyne insertion transition state **TS2a**, but this is still absent in **TS2**. Therefore, **TS2** is favored over **TS2a** by 4.4 kcal/mol, and the alkyne insertion has an exclusive preference to give **IN6** via **TS2** (see discussion for this again).

DFT calculations indicated that alkyne insertion into the Ru−C bond via **TS2** requires an activation free energy of 14.9 kcal/mol. The carbonyl group in **IN6** is a free ligand, but it then coordinates to the Ru center, giving the eight-membered ruthenacycle intermediate **IN7**, which is set up for the followed C═O insertion into the Ru−C bond. The carbonyl insertion step, leading to **IN8** (and then more stable **IN9** with acetate as a bidentate ligand, not a monodentate ligand), needs an activation free energy of 29.0 kcal/mol and is exergonic by 5.9 kcal/mol. Protonation of **IN9** with the assistance of AcOH furnishes **IN10** and regenerates the catalytic species for the next catalytic cycle: The ligand exchange reaction (**IN9** + enamide + HOAC → **IN10** + **IN1**) for completing the catalytic cycle is exergonic by 5.3 kcal/mol. Finally, dehydration of **IN10** gives rise to the polysubstituted pyridine.

TS2 and **TS3** are very close in energy, suggesting that the alkyne insertion is reversible. But **TS2a** is higher than both **TS2** and **TS3** by more than 4 kcal/mol, indicating that the alkyne insertion is regio-determining step and the exclusive formation of product pyridine **P**, which has the Ph group in its β-position. This is consistent with the experiment observed regiochemistry.

In the pyridine formation pathway, **IN3** can be converted back to **IN1** through protonation by AcOH, which is easy and requires an activation free energy of 12.2 kcal/mol in the gas phase. This suggests that enamides' C−H metalation−deprotonation step is reversible and is the reason for the observation of deuterium incorporated enamides in eq (b) of Scheme 6.

The present reaction has a competing process leading to the formation of pyrrole (Figure 1c and the pathway B in Scheme 5). **IN6** can be converted to **IN11** by switching carbonyl coordination to amide's nitrogen coordination to the Ru atom. Then a concerted deprotonation of nitrogen atom converts **IN11** to **IN12** via **TS4**, requiring an activation free energy of 15.7 kcal/mol. **IN12** loses HOAc and uses its carbonyl group to coordinate Ru, giving **IN13**. Reductive elimination of **IN13** to give pyrrole is difficult, with a computed activation free energy of 35.9 kcal/mol (**IN12** can directly give pyrrole, but this is difficult and requires an activation free energy of 31.7 kcal/mol). This implies that pyrrole cannot be formed in the present reaction system, which agrees with the experiments. In previous experiments (together with the present investigated control

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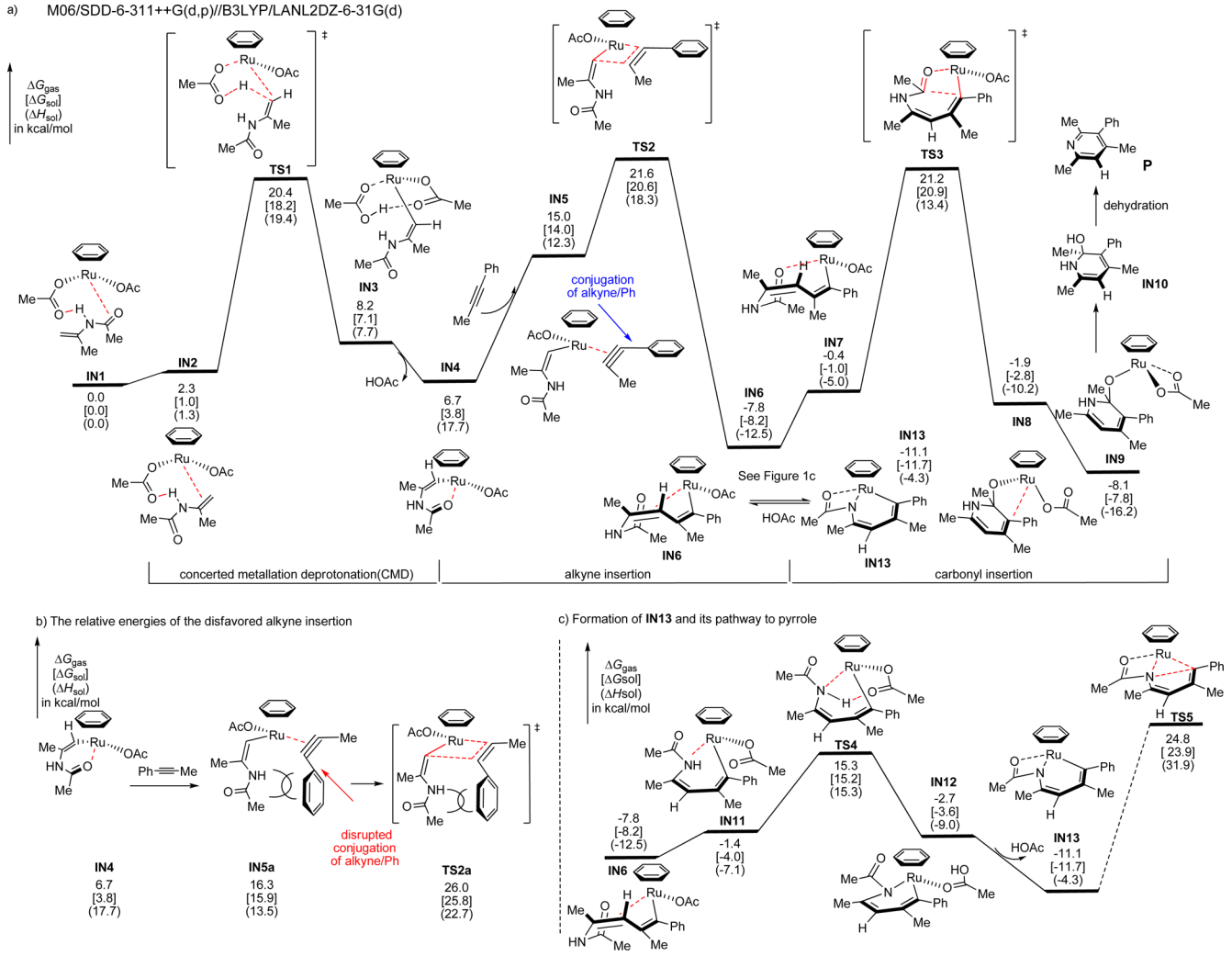

Figure 1. (a) DFT computed energy surface, (b) disfavored alkyne insertion intermediate and transition state, and (c) disfavored pathway to pyrrole.

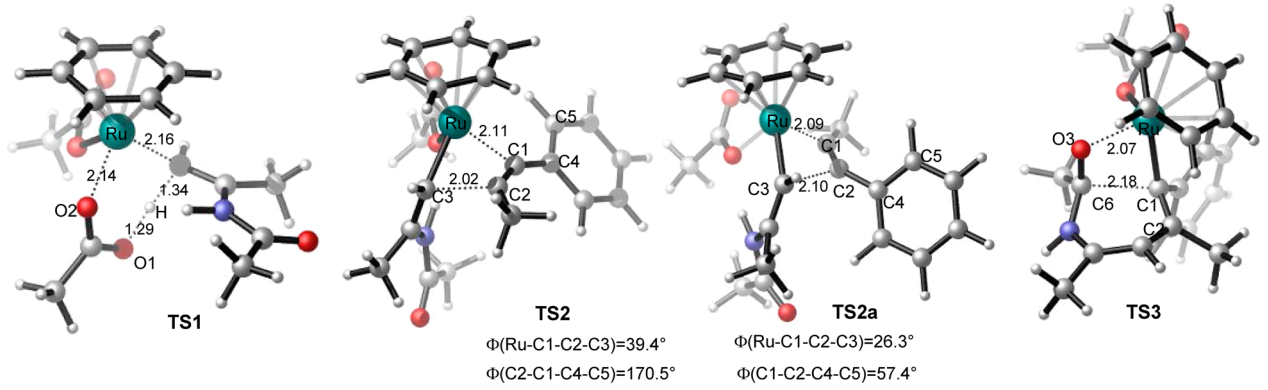

Figure 2. DFT computed key transition structure (distances in Å).

experiment eq (f) in Scheme 6), the added oxidants could alter the whole reaction process to give pyrrole,[13,14] but the reasons for this change are not known at this moment.

Since **IN13** can be easily generated from **IN6**, the pyridine formation process shown in Figure 1a can have this species as the intermediate. **IN13** is lower in energy than **IN6**, suggesting that the most difficult step in the pyridine formation is from **IN13** to **IN6** and then to **TS3**. Therefore, the formal dehydrative [4 + 2] reaction requires an overall activation free energy of 32.3 kcal/mol in the gas phase (from **IN13** to **TS3**). The overall activation free energy of the present reaction is 32.6 kcal/mol in solution.[23]

CONCLUSIONS

In summary, we have developed a new and efficient Ru-catalyzed formal dehydrative [4 + 2] cycloaddition of enamides and alkynes for synthesis of highly substituted pyridines. The generality of such an intermolecular annulation is demonstrated

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by a wide scope with respect to both enamides and alkynes. The mechanism and regioselectivity of this reaction have been scrutinized by experiments and DFT calculations. DFT calculation results indicated that the reaction starts from a CMD process of enamides by the acetate group in the catalyst, generating a six-membered ruthenacycle intermediate. Then alkyne insertion into Ru−C bond of the six-membered ruthenacycle intermediate gives an eight-membered ruthenacycle intermediate, which undergoes carbonyl insertion and dehydration to give the final pyridines (Figure 1a). The high regiochemistry of the present formal dehydrative [4 + 2] cycloaddition is determined by the alkyne insertion step, which prefers to avoid steric repulsion of aryl group with the enamide moiety in the six-membered ruthenacycle and to have a good conjugation between the aryl group and the triple bond of the alkyne substrates, in the alkyne insertion transition state. Consequently, the aryl group of the used alkynes is in the β-position of the final pyridine products.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, NMR spectra of the products, DFT data, and complete ref 21. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06400.

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Notes

The authors declare no competing financial interest.

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