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## Mechanistic Studies and Expansion of the Substrate Scope of Direct Enantioselective Alkynylation of α-Ketiminoesters Catalyzed by Adaptable (Phebox)Rhodium(III) Complexes

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**ABSTRACT:** Mechanistic studies and expansion of the substrate scope of direct enantioselective alkynylation of  $\alpha$ -ketiminoesters catalyzed by adaptable (phebox)rhodium(III) complexes are described. The mechanistic studies revealed that less acidic alkyne rather than more acidic acetic acid acted as a proton source in the catalytic cycle, and the generation of more active (acetato- $\kappa^2 O, O'$ )(alkynyl)(phebox)rhodium(III) complexes from the starting (diacetato)rhodium(III) complexes limited the overall reactivity of the reaction. These findings, as well as facile exchange of the alkynyl ligand on the (alkynyl)rhodium(III) complexes led us to use (acetato- $\kappa^2 O, O'$ )(trimethylsilylethynyl)(phebox)rhodium(III) complexes as a general precatalyst for various (alkynyl)rhodium(III) complexes. Use of the (trimethylsilylethynyl)rhodium(III) complexes as precatalyst enhanced the catalytic performance of the reactions with an  $\alpha$ -ketiminoester derived from ethyl trifluoropyruvate at a catalyst loading as low as 0.5 mol % and expanded the substrate scope to unprecedented  $\alpha$ -ketiminophosphonate and cyclic *N*-sulfonyl  $\alpha$ -ketiminoesters.

#### **1. INTRODUCTION**

Asymmetric alkynylation of imines is a highly efficient approach toward synthesizing optically active propargylamines,<sup>1</sup> a valuable intermediate for the synthesis of natural products and bioactive compounds.<sup>2</sup> Various alkynylation methodologies have been developed using stoichiometric amounts of metal reagents, such as alkyllithium and dialkylzinc.<sup>3</sup> Despite the robustness of these methodologies, however, reduced compatibility with base-labile functional groups is inevitable. In contrast, in situ catalytic generation of metal acetylide species directly from terminal alkynes is a more atom-economical way to promote nucleophilic addition to imines.<sup>4</sup> Such direct alkynylation is effective for imines derived from aldehydes using Cu(I) and Ag(I) catalysts under proton-transfer conditions.<sup>5</sup> On the other hand, direct catalytic alkynylation of imines derived from ketones (ketimines), which allows for the construction of tetrasubstituted carbon stereocenters at the propargylic position, has not been established due to the low reactivity of the ketimines and difficulty in their stereocontrol.<sup>6</sup> Some examples of Cu(I)-catalyzed enantioselective alkynylation to ketimines were recently reported,<sup>7,8</sup> but there is much room for improvement in terms of the scope of the ketimines, especially those applicable for the synthesis of  $\alpha$ , $\alpha$ disubstituted a-amino acid derivatives.9

To overcome these problems, we previously reported direct enantioselective alkynylation of  $\alpha$ -ketiminoester 2 catalyzed by (aqua)(diacetato)(phebox)Rh(III) complex 1 (Scheme 1).<sup>10,11</sup> Using  $C_2$ -symmetric indane-substituted (phebox)Rh(III) complex 1a as the optimal catalyst, the reaction provided  $\alpha$ , $\alpha$ disubstituted  $\alpha$ -amino acid derivatives 4 in high yield and enantioselectivity from a broad range of alkynes **3** with various functional groups, such as *O*-TBS, *N*-Cbz, *N*-Fmoc, acetal, tertiary alcohol, and a formyl group. The limited catalytic activity of **1a**, however, made it difficult to further reduce the catalyst loading, and the substrate scope of the electrophile was limited to  $\alpha$ -ketiminoesters derived from highly electrophilic ethyl trifluoropyruvate.

# Scheme 1. (Diacetato)rhodium(III)-Catalyzed Direct Enantioselective Alkynylation of $\alpha$ -Ketiminoesters



In the effort to improve the catalytic activity, we aimed to elucidate the reaction mechanism. Such mechanistic studies often lead to an improved catalytic performance and expansion of the substrate scope, as exemplified by seminal Pd-catalyzed cross-coupling reactions.<sup>12</sup> Few mechanistic studies have been performed on the catalytic asymmetric alkynylation of imines,<sup>13</sup> however, even well-established aldimines. We envisioned that the Rh(III)-catalyzed system would be suitable for mechanistic studies because of the high stability of (phebox)Rh(III) complexes, and that such mechanistic studies would lead to an improved reaction conditions applicable to other  $\alpha$ -ketiminoesters.

Herein we describe our mechanistic studies on the rhodium(III)-catalyzed direct enantioselective alkynylation of  $\alpha$ ketiminoesters. We isolated and identified (acetato- $\kappa^2 O, O'$ )(alkynyl)(phebox)Rh(III) complexes, and found that the generation of this species determined the overall reactivity of the reaction. We also succeeded in generating this species via an alkynyl ligand exchange using (acetato- $\kappa^2 O, O'$ )(phebox)(trimethylsilylethynyl)Rh(III) complexes as a precatalyst. Use of this precatalyst improved the performance of the reaction compared with the original (diacetato)Rh(III) complexes, and allowed us to reduce the catalyst loading to as low as 0.5 mol %. In addition, by acting as precatalysts, lessreactive  $\alpha$ -ketiminophosphonates and cyclic N-sulfonyl ketiminoesters, which have not previously been reported as substrates for direct catalytic enantioselective alkynylations, afforded  $\alpha, \alpha$ -disubstituted  $\alpha$ -amino acid derivatives in good yield and enantioselectivity.

#### 2. RESULTS AND DISCUSSION

2.1 Isolation of (Alkynyl)(phebox)rhodium(III) Complexes and Identification of the Proton Source. We initiated our mechanistic studies by identifying the proton source in the catalytic cycle. We first postulated two catalytic cycles with different proton sources to close the catalytic cycle based on previous reports (Scheme 2).<sup>14,15</sup> In the first catalytic cycle (cycle 1), (aqua)(diacetato)(phebox)Rh(III) complex 1 reacted with alkynes 3 to give the corresponding (acetato- $\kappa^2 O, O'$ )(alkynyl)(phebox)Rh(III) complex 5, followed by reaction with  $\alpha$ -ketiminoester 2 to give (amido)Rh(III) intermediate 6. The resulting intermediate 6 was protonated with acetic acid, which was generated during the formation of 5, to close the catalytic cycle. In the second cycle (cycle 2), alkyne 3 acted as a proton source instead of acetic acid to give 4 and regenerate 5.

#### Scheme 2. Two Possible Catalytic Cycles



To gain further insight into the proton source, we first synthesized (alkynyl)Rh(III) complex **5**. We prepared (acetato- $\kappa^2 O, O'$ )(phenylethynyl)(phebox)Rh(III) complex **5a** in good yield by heating **1a** with phenylacetylene (**3a**) in toluene according to the reported protocol for analogous complexes

(Scheme 3, equation 1).<sup>15</sup> Complex **5a** was isolated after column chromatography, and was stable in air and moisture. Although attempts to obtain single crystal X-ray diffraction structure of **5a** were unsuccessful, related complex **7a** (equation 2) was isolated and its X-ray crystallographic structure determined (Figure 1). The acetato ligand of **7a** was coordinated to the rhodium center in a  $\kappa^2$  fashion, which is consistent with related Rh(III) complexes.<sup>15</sup>

#### Scheme 3. Isolation of (Alkynyl)rhodium(III) Complexes



Figure 1. X-ray crystallographic structure of 7a.

We then investigated the reactivity of (alkynyl)Rh(III) complex 5a to clarify the proton source acting under the reaction conditions. Treatment of stoichiometric amounts of 5a and 2 with either acetic acid or alkyne 3a would give product 4a if such reaction pathways were operative. The results shown in equations 3 and 4 suggested that the less acidic alkyne 3a (pK<sub>a</sub>) = 28.8 in DMSO) was the proton source to release the product 4a and close the catalytic cycle, while the more acidic acetic acid ( $pK_a = 12.6$  in DMSO) was not. These findings are consistent with the observation in (phebox)Rh(III)-catalyzed alkynylation of dimethyl acetylenedicarboxylate.<sup>15</sup> Although these stoichiometric studies may not completely reflect the actual catalytic reaction conditions, the conclusion that alkyne 3a acts as the proton source was further supported when 5a was used as a catalyst under the reaction conditions (equation 5 and Figure 2). Using a catalytic amount of 5a, the reaction proceeded even in the absence of acetic acid. Addition of a catalytic amount of acetic acid under the same reaction condition did not change the reaction rate,16 suggesting that the cata-

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lytic cycle 1 is not operative or not kinetically competent with the catalytic cycle 2. These results suggest that catalytic cycle 2, in which alkynes **3** act as the proton source, is operative under the reaction conditions, and support the importance of alkynes as a proton source in the transition metal-catalyzed alkynylation reactions under proton-transfer conditions.<sup>13,15</sup>



Figure 2. Reaction profiles using (alkynyl)Rh(III) complex 5a in the absence or presence of acetic acid. Conditions:  $[2]_0 = 0.25$  M,  $[3a]_0 = 0.375$  M,  $[5a]_0 = 6.3$  mM,  $[AcOH]_0 = 0$  or 6.3 mM, 29 °C.

2.2 Kinetic Experiments. To examine the kinetic aspects of the reaction, we first performed experiments to examine whether generation of (alkynyl)Rh(III) complex 5a from (diacetato)Rh(III) complex 1a is the slowest step in the catalytic cycle. Comparison of the reaction profiles of 5a with 1a revealed that the reaction proceeded much faster with 5a than with **1a** (Figure 3 (a)), suggesting that the generation of **5a** from 1a is the slowest step in the overall reaction pathway when 1a is used as a catalyst. This finding is consistent with the observation that preparation of (alkynyl)Rh(III) complexes 5 required a reaction temperature of 60 °C, while the alkynylation reactions of  $\alpha$ -ketiminoester 2 proceeded at or below room temperature. To clarify the presence of induction period using 1a as catalyst, we performed reaction progress kinetic analysis under same [e] reaction conditions (Figure 3 (b)),<sup>1</sup> and we observed non-overlapped reaction progress curves using time-scale adjustment protocol,<sup>17d</sup> in which the rate for higher initial concentration of 2 ( $[2]_0 = 0.25$  M) was faster than that for lower initial concentration of 2 ( $[2]_0 = 0.15$  M) at the time-adjusted point (t = 360 min), supporting the presence of induction period using 1a as catalyst. The observed induction period using 1a as the catalyst also suggests that the formation of active species from **1a** is the rate-limiting step at the initial stage of the reaction. Thus, when **1a** is used, the generation of **5a** from **1a** determines the overall reactivity of the reaction.



**Figure 3.** (a) Comparison of catalytic activity of Rh(III) complexes. Conditions:  $[\mathbf{2}]_0 = 0.25 \text{ M}$ ,  $[\mathbf{3a}]_0 = 0.375 \text{ M}$ ,  $[\mathbf{1a}]_0$  or  $[\mathbf{5a}]_0 = 3.8 \text{ mM}$ , room temperature. (b) Same [e] experiments for (diacetato)Rh(III) complex **1a** (time-scale was adjusted as t + 360 min for  $[\mathbf{2}]_0 = 0.15 \text{ M}$ ). Conditions:  $[\mathbf{2}]_0 = 0.25 \text{ or } 0.15 \text{ M}$ ,  $[\mathbf{3a}]_0 = 0.375 \text{ or } 0.275 \text{ M}$ ,  $[\mathbf{1a}]_0 = 6.3 \text{ mM}$ , room temperature.

We next investigated the kinetic profiles of the catalytic cycle using (alkynyl)Rh(III) complex **5a** as the catalyst.<sup>16</sup> We used 1.25 mol % of **5a** as the standard condition for the initial rate kinetic studies to accurately determine the product formation rate because the reaction was too fast with 2.5 mol % of the catalyst. The initial rate kinetic studies revealed nearly the first-order rate dependency for both the catalyst **5a** and the alkyne **3a**, suggesting that these species are involved in the turnover-limiting step of the catalytic cycle. In contrast, the kinetic profile of  $\alpha$ -ketiminoester **2** differed from that of the above species: no significant rate dependency was observed when the concentration of **2** was high (0.25–0.13 M), whereas partial rate dependency was observed when the concentration of **2** was low (0.13–0.04 M). To further confirm this kinetic

behavior of  $\alpha$ -ketiminoester 2, we conducted reaction progress kinetic analysis according to the reported procedure.<sup>17</sup> We monitored the formation of 4a using <sup>19</sup>F NMR spectroscopy to elucidate overall reaction profile under the standard conditions where  $[2]_0 = 0.25$  M,  $[3a]_0 = 0.375$  M and [e] = 0.125 M as well as a different [e] condition where  $[\mathbf{2}]_0 = 0.25$  M,  $[\mathbf{3a}]_0 =$ 0.45 M and [e] = 0.20 M. Plots of (d[4a]/dt)/[3a] versus [2] were curved lines (Figure 4 (a)), suggesting that the reaction order of [2] is complex, and the shape of the line suggests saturation kinetic behavior in [2], which is consistent with the observation in the initial rate kinetic experiments. These results suggest a change in the resting state between 5 and 6 over the reaction course, where 6 is the major form at the beginning of the reaction and 5 is the major form at the late stage of the reaction.<sup>17b</sup> The overlay of the plots under different [e] conditions in Figure 4 (a) suggests the first-order dependency for 3a, which is consistent with the results of the initial rate kinetic study.<sup>17b</sup> In addition, time-adjusted overlay of plots under same [e] conditions (Figure 4 (b))<sup>17d</sup> indicated that the catalyst **5a** is stable under the reaction conditions.



**Figure 4.** (a) Reaction progress kinetic analysis under different [*e*] conditions. Conditions:  $[\mathbf{2}]_0 = 0.25 \text{ M}$ ,  $[\mathbf{3a}]_0 = 0.375 \text{ or } 0.45 \text{ M}$ ,  $[\mathbf{5a}]_0 = 6.3 \text{ mM}$ , 29 °C. (b) Reaction progress kinetic analysis

under same [*e*] conditions (time-scale was adjusted as t + 420 s for  $[2]_0 = 0.15$  M). Conditions:  $[2]_0 = 0.25$  or 0.15 M,  $[3a]_0 = 0.375$  or 0.275 M,  $[5a]_0 = 6.3$  mM, 29 °C.

We also investigated the kinetic isotope effects<sup>18</sup> using **3a** and mono-deuterated phenylacetylene (3a-d) to determine whether deprotonation of terminal alkynes is involved in the turnover-limiting step of the catalytic cycle. We observed inverse kinetic isotope effects ( $k_{\rm H}/k_{\rm D} = 0.85$ ) when the reactions were performed independently with 3a or 3a-d (equations 6 and 7 and Figure 5).<sup>16</sup> The result suggests that  $\hat{C}$ -H bond cleavage is not involved in the turnover-limiting step because normal kinetic isotope effects  $(k_{\rm H}/k_{\rm D} > 1)$  are expected under such conditions. The observed inverse kinetic isotope effects could be due to hybridization-induced changes of the terminal carbon of the alkyne **3** from sp to  $sp^2$  in the transition state.<sup>19</sup> Based on the fact that hybridization of the carbon on alkynes changes from sp to sp<sup>2</sup> upon coordination to transition metal complexes, coordination of alkyne 3 to (amido)rhodium(III) complex 6, rather than deprotonation of the terminal alkyne 3, would be the turnover-limiting step in the overall catalytic cycle.20



**Figure 5.** Kinetic Isotope Effects. Conditions:  $[2]_0 = 0.25$  M,  $[3a]_0$  or  $[3a-d]_0 = 0.375$  M,  $[5a]_0 = 3.1$  mM, 29 °C

As the last kinetic experiments, we performed an Eyring plot analysis to determine the activation energy parameters of the catalytic cycle. Kinetic experiments using **5a** as the catalyst from -30 to 29 °C yielded two lines: one from -30 to – 10 °C and the other from -10 °C to 29 °C (Figure 6a). Each of the lines yielded the following activation parameters:  $\Delta H^{\ddagger} = 11.1 \text{ kcal mol}^{-1}$ ,  $\Delta S^{\ddagger} = -21.8 \text{ cal mol}^{-1} \text{ K}^{-1}$  and  $\Delta G^{\ddagger} = 17.8 \text{ kcal mol}^{-1}$  at 29 °C from the former line and  $\Delta H^{\ddagger} = 5.7 \text{ kcal mol}^{-1}$ ,  $\Delta S^{\ddagger} = -42.5 \text{ cal mol}^{-1} \text{ K}^{-1}$  and  $\Delta G^{\ddagger} = 18.6 \text{ kcal mol}^{-1}$  at 29 °C from the latter line.<sup>16</sup> Such non-linear behavior of the Eyring plots implies the presence of competitive rate-limiting steps in the catalytic cycle,<sup>21</sup> and we assumed that coordination of the alkynes would be the latter step ( $\Delta G^{\ddagger} = 18.6 \text{ kcal mol}^{-1}$ )

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.Cbz

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(a) -6.5

-7

-8

-9

-8.5

-9.5

-10

-10.5

-11

0.003

-11.5

(b) 5

4.8

4.6

4.4

4.2 In(kS/kR)

3.8

3.6

3.4

3.2

3

0.003

4

In(k/T)

-7.5

H\_\_\_Cbz

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from –10 to 29 °C

from –30 to –10 °C

v = -56015x + 12655

 $R^2 = 0.99249$ 

0.0042 0.0044

y = 2076.9x - 3.6967

 $R^2 = 0.99652$ 

0.0045

4a

EtO

whereas the addition of alkynyl ligand to  $\alpha$ -ketiminoester 2 would be the former step ( $\Delta G^{\ddagger} = 17.8 \text{ kcal mol}^{-1}$ ) at room temperature, based on the results of the initial rate kinetic experiments. The large negative value of the activation entropy in the latter step ( $\Delta S^{\ddagger} = -42.5$  cal mol<sup>-1</sup> K<sup>-1</sup>) implies the association of molecules in the turnover-limiting step, which is consistent with the assumption that the coordination of alkyne 3 to (amido)Rh(III) complex 6 is the turnover-limiting step at room temperature. On the other hand, the Eyring plot for enantiomeric excesses was a single line between -30 °C and 29 °C, and yielded the following differential activation parameters:  $\Delta\Delta H^{\ddagger} = -4.1 \text{ kcal/mol}, \Delta\Delta S^{\ddagger} = -7.3 \text{ cal mol}^{-1} \text{ K}^{-1}, \text{ and } \Delta\Delta G^{\ddagger} =$ -1.9 kcal mol<sup>-1</sup> at 27 °C (Figure 6b). The result suggests that differential enthalpy is a major contributor for determining the enantioselectivity.

5a

(2.5 mol %)

toluene (0.25 M)

-30. -20. -10.

0 or 29 °C

y = -2886.1x + 2.2465

 $R^2 = 0.99588$ 

0.0036

0.0038

1/T (K<sup>-1</sup>)

0.004

0.004

3a

(1.5 equiv)

0.0032 0.0034

Figure 6. Eyring plots. (a) Effect of temperature on activation energies. (b) Effect of temperature on enantioselectivity. Conditions:  $[\mathbf{2}]_0 = 0.25 \text{ M}, [\mathbf{3a}]_0 = 0.375 \text{ M}, [\mathbf{5a}]_0 = 6.3 \text{ mM}, -30, -20,$ -10, 0 or 29 °C.

1/T (K<sup>-1</sup>)

0.0035

2.3 Additional Experiments and Proposed Mechanism. We performed additional experiments to determine the reversibility of the reaction steps. Treatment of (alkynyl)Rh(III) complex 5a with acetic acid did not yield (diacetato)Rh(III) complex 1a, but resulted in the recovery of 5a (equation 8), indicating that the formation of 5a from 1a involves at least one irreversible step. On the other hand, the dissociation of water from 1a seems reversible as the formation of 5a in the presence of additional water was slower than that in the ab-

sence of water.<sup>16</sup> In contrast, the presence of additional alkyne 3a facilitated the formation of 5a,<sup>16</sup> implying that 3a is involved in the rate-determining step in the formation of 5a. Taken together, these findings suggest that the formation of 5a involves the reversible dissociation of water from 1a, followed by an irreversible deprotonation of terminal alkyne 3, as depicted in Scheme 2, although the same process was depicted as reversible steps in a previous report.<sup>15</sup> Additionally, treatment of product 4b in the presence of (alkynyl)Rh(III) complex 5b and alkyne 3a did not form any crossover product 4a even at 60 °C (equation 9), suggesting that the formation of 4 from (amido)rhodium(III) complex 6 is irreversible after protonation of the amido ligand with terminal alkyne 3.



Finally, we performed experiments to clarify whether nonlinear effects are present when using (alkynyl)Rh(III) complex **5a** as catalyst.<sup>16</sup> We observed a liner relationship between the enantiomeric excess of (alkynyl)Rh(III) complex 5a and that of 4a, suggesting that 5a acts as monomeric species.

To support the experimental results of our mechanistic studies, we performed density functional theory (DFT) calculations of the key intermediates in the catalytic cycle using (alkynyl)Rh(III) complex 5' bearing an unsubstituted phebox ligand, N-methoxycarbonyl  $\alpha$ -ketiminoester 2', and alkyne 3a as a model system (Figure 7).<sup>16</sup> Migratory insertion of the phenylethynyl ligand on 5' to 2' via a six-membered transition state (TS1) showed an activation energy barrier of 20.7 kcal mol<sup>-1</sup> at 25 °C, whereas the coordination of **3a** to (amido)Rh(III) complex 6' (TS2) resulted in a transition state energy of 24.2 kcal mol<sup>-1</sup> at 25 °C. The comparable energies between TS1 and TS2 are in agreement with the presence of competitive rate-limiting steps based on the activation energies from the Eyring plot, and the higher energy in TS2 than in TS1 supports the assumption that coordination of the alkyne 3 is involved in the turnover-limiting step. In addition, deprotonation of the coordinated terminal alkyne 3 (TS3) exhibited a lower activation energy (16.7 kcal mol<sup>-1</sup> at 25 °C) than the coordination step (TS2), supporting the interpretation of the observed inverse kinetic isotope effects.



**Figure 7.** Transition state of key intermediates by DFT calculation. Gibbs energies are given at 25 °C.

On the basis of these findings, we propose the mechanism of Rh(III)-catalyzed direct alkynylation of  $\alpha$ -ketiminoester **2** shown in Scheme 4. First, (aqua)(diacetato)(phebox)Rh(III) complex **1** reacts with alkyne **3** to give (acetato- $\kappa^2 O, O'$ )(alkynyl)Rh(III) complex **5**, as illustrated in Scheme 2, and this reaction is the rate-limiting step at the initial stage of the reaction when **1** is used as the catalyst. Once **5** is generated, it reacts with  $\alpha$ -ketiminoester **2** to give (amido)Rh(III) complex **6**. After the formation of complex **6**, coordination of al-kyne **3** gives complex **8** and this coordination process is the turnover-limiting step in the catalytic cycle. Complex **8** then irreversibly releases product **4** after deprotonation of the coordinated terminal alkyne **3** with the amido ligand.

#### **Scheme 4. Proposed Reaction Mechanism**



2.4 Improvement of the Catalytic Activity Using (Trimethylsilylethynyl)rhodium(III) Complex as a Precatalyst. The mechanistic studies described above revealed that efficient generation of (alkynyl)Rh(III) complex 5 is important for improving the reactivity of the alkynylation reaction. We therefore sought to develop a better method for generating 5. We first hypothesized that complex 5a could be used as a substitute for (diacetato)Rh(III) complex 1a if exchange of the alkynyl ligand on 5a with other terminal alkynes 3 proceeded faster than the formation of 5 from 1a and 3. The alkynyl ligand exchange indeed proceeded with an aryl-substituted alkyne 3b at room temperature within 30 min to give complex 5b in good yield (equation 10). Unfortunately, this was not the case with an alkyl-substituted alkyne 3c, and no desired complex 5c was observed even at an elevated temperature (equation 11), presumably due to the thermodynamic preference of aryl-substituted (alkynyl)Rh(III) complex **5a** over alkyl-substituted (alkynyl)Rh(III) complex **5c**.



Based on these results, we aimed to develop a new precatalyst to promote the alkynyl ligand exchange with both aryland alkyl-substituted alkynes. Examination of several (phebox)Rh(III) complexes revealed that (trimethylsilylethynyl)Rh(III) complex **5d** promoted the desired ligand exchange reactions with both aryl- and alkyl-substituted alkynes (equations 12 and 13). Although alkyl-substituted alkyne **3c** showed equilibrium favorable to the starting complex **5d** under stoichiometric reaction conditions, the equilibrium could be shifted to **5c** in the presence of a large excess of **3c** under the actual catalytic reaction conditions.<sup>16</sup>



We next performed experiments to verify the utility of (trimethylsilylethynyl)Rh(III) complex **5d** as a general precatalyst for the alkynylation of  $\alpha$ -ketiminoester **2** (Scheme 5). A catalytic amount of **5d** promoted the reaction faster than **1a** with an aryl-substituted alkyne **3a**, and the catalyst loading of **5d** could be reduced to 0.5 mol % without affecting the yield or enantioselectivity (equation 14). The reaction with alkylsubstituted alkyne **3c** also gave the desired product **4c** in 96% yield and 87% ee using 2.5 mol % of **5d** at 0 °C without preactivation of catalyst at 30 °C, which was required in our previous report with 5 mol % of (diacetato)Rh(III) complex **1a** (equation 15).<sup>10</sup> Notably, the formation of trimethylsilylethynyl adduct **4d** was not detected under these catalytic reaction conditions using **5d** as the precatalyst.

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Scheme 5. Comparison of Reactivity of (Trimethylsilylethynyl)Rh(III) Complex 5d with (Diacetato)Rh(III) Complex 1a



Having established the utility of precatalyst **5d**, we examined the full scope of direct catalytic asymmetric alkynylation of  $\alpha$ -ketiminoester **2**. The catalyst loading was reduced to as low as 0.5 mol % with aryl-substituted alkynes **3** without decreasing the yield or enantioselectivity (Table 1). A variety of functional groups were tolerated, including electron-donating and electron-withdrawing substituents, heterocycles, and formyl and base-sensitive Fmoc groups.

Table 1. Substrate Scope of Aryl-Substituted Alkynes Using (Trimethylsilylethyl)Rh(III) Complex 5d



Alkyl-substituted terminal alkynes also gave the corresponding propargylamines **4** in high yield and enantioselectivity in the presence of 2.5 mol % of **5d** (Table 2). An acidsensitive acetal group and a base-sensitive TBS group were compatible under the reaction conditions. The reaction also proceeded smoothly with alkynes **3r** and **3s** bearing acidic protons.

 Table 2. Substrate Scope of Alkyl-Substituted Alkynes

 Using (Trimethylsilylethyl)Rh(III) Complex 5d



2.5 Expansion of the Substrate Scope Using the Precatalysts. Encouraged by the results using 5d as the precatalyst, we turned our attention to expanding the substrate scope to less reactive  $\alpha$ -ketiminoesters, which have not been previously applied to direct catalytic alkynylation reactions. We first examined Cbz-protected  $\alpha$ -ketiminophosphonate 9,<sup>22</sup> an analog of  $\alpha$ -ketiminoester, because optically active aminophosphonic acid derivatives can serve as transition state analogs of the corresponding amino acids and are important drug candidates.<sup>23</sup> We initially screened (diacetato)(phebox)Rh(III) catalysts 1 with different substituents on bis(oxazoline) moiety for an alkynylation reaction of **9** with alkyne **3a** (Table 3),<sup>16</sup> and found that phenyl-substituted (diacetato)(phebox)Rh(III) complex 1b showed better enantioselectivity thanks to the adaptable nature of the (phebox)Rh(III) complexes for different substrates (entries 1-2). Although the reactivity of these (diacetato)Rh(III) complexes 1 was low presumably due to slow generation of the active (alkynyl)Rh(III) species, we anticipated that the use of (alkynyl)Rh(III) complexes could improve the reactivity based on the results from the above study for  $\alpha$ ketiminoester 2. Indeed, we found that both (phenylethynyl)Rh(III) complex 7a and (trimethylsilylethynyl)Rh(III) precatalyst 7d promoted the reaction smoothly at room temperature to give the desired product 10a in high yield and enantioselectivity (entries 3-4).<sup>16</sup> The reaction using corresponding (diacetato)Rh(III) complex 1b as the catalyst proceeded only sluggishly (entry 2), demonstrating the advantage of using precatalyst 7d over (diacetato)Rh(III) complex 1b.<sup>16</sup> The reaction was also effective for other arylsubstituted alkynes with electron-donating or electronwithdrawing substituents and cyclopropylacetylene (entries 5-9). The absolute configuration of product 10a was determined unambiguously by single crystal X-ray diffraction.<sup>16</sup>

# Table 3. Optimization of Catalysts and Scope of Alkynes for α-Ketiminophosphonate 9

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entry	R	Rh(III)	10	time	yield	ee
		complex		(h)	$(\%)^{a}$	$(\%)^{b}$
1	Ph	1a	10a	24	$17^c$	9
2	Ph	1b	10a	24	8 <sup>c</sup>	87
3	Ph	7a	10a	24	>95 <sup>c</sup>	89
4	Ph	7d	10a	18	96	88
5	4-Me-C <sub>6</sub> H <sub>4</sub> -	7d	10b	18	91	88
6	4-MeO-C <sub>6</sub> H <sub>4</sub> -	7d	10c	18	99	87
7	$4-CF_{3}-C_{6}H_{4}-$	7d	10d	18	97	88
8	2-Me-C <sub>6</sub> H <sub>4</sub> -	7d	10e	18	97	93
9 <sup>d</sup>	cyclopropyl	7d	10f	24	86	80

"Isolated yield. <sup>b</sup>Enantiomeric excess was determined by HPLC analysis with chiral stationary phase. <sup>c</sup>Determined by <sup>1</sup>H NMR analysis of the crude mixture. <sup>d</sup>3.0 equiv of alkyne **3** was used.

Next, we applied the precatalyst system to cyclic N-sulfonyl  $\alpha$ -ketiminoesters 11.<sup>24</sup> With unsubstituted electrophile 11a (X = H), we first screened a series of (diacetato)Rh(III) complexes 1 (Table 4) and found that both phenyl-and benzylsubstituted (diacetato)Rh(III) complexes 1b and 1c gave product 12a in high enantioselectivity (entries 1-3).<sup>16</sup> The use of (phenylethynyl)Rh(III) complexes 7a and 13a showed improvements on reactivity (entries 4-5),<sup>25</sup> and the yields were further increased by raising the temperature to 70 °C while keeping the enantioselectivity in an acceptable level (entries 6–7). Further examination of related substrates 11b (X = OMe) and 11c (X = Cl) revealed, however, that benzylsubstituted (phebox)Rh(III) complex 13a gave higher enantioselectivity (entries 8-11), and we chose 13a as the optimal catalyst. At last, the use of (trimethylsilylethynyl)Rh(III) complex 13d showed comparable reactivity as expected from the above studies for  $\alpha$ -ketiminoesters **2** and **9** (entries 12–14).

Table 4. Optimization of Catalysts for Cyclic *N*-Sulfonyl α-Ketiminoesters 11



<sup>&</sup>lt;sup>*a*</sup>Isolated yield. <sup>*b*</sup>Enantiomeric excess was determined by HPLC analysis with chiral stationary phase. <sup>*c*</sup>Determined by <sup>1</sup>H NMR analysis of the crude mixture.

With the optimal precatalyst **13d** in hand, we examined scope of alkynes for cyclic *N*-sulfonyl  $\alpha$ -ketiminoester **11a**, and the corresponding sultam derivatives **12** with tetrasubstituted carbon stereocenter were obtained in high yield and enantioselectivity for both aryl- and alkyl-substituted alkynes **3** (Table 5). The absolute configuration of **12a** was determined by single crystal X-ray analysis after derivatization to the corresponding amide.<sup>16</sup>

Table 5. Scope of Alkynes for Cyclic N-Sulfonyl  $\alpha$ -Ketiminoester 11a

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#### **3. CONCLUSION**

In summary, we present our mechanistic studies and expansion of the substrate scope of direct enantioselective alkynylation of  $\alpha$ -ketiminoester 2 catalyzed by (aqua)(diacetato)(phebox)Rh(III) complex 1a. Based on the mechanistic analysis, (acetato- $\kappa^{=}O.O'$ )(alkynyl)(phebox)Rh(III) complex **5a** was more active than 1a and generation of 5a from 1a determined the overall reactivity. This information, as well as the observed facile exchange of alkynyl ligand on the (alkynyl)rhodium(III) complexes, led us to synthesize (acetato- $\kappa^{=}O,O'$ )(trimethylsilylethynyl)(phebox)Rh(III) complex 5d as a general precatalyst that reacts with both aryl- and alkylsubstituted terminal alkynes to afford the corresponding (acetato- $\kappa^{=}O,O'$ )(alkynyl)(phebox)Rh(III) complexes. The new catalytic system reduced catalyst loading without loss of reactivity, enantioselectivity, or functional group tolerance. The precatalysts were also effective for less reactive aketiminophosphonate 9 and cyclic N-sulfonyl αketiminoesters 11, both of which could be applied in the direct catalytic enantioselective alkynylation for the first time. These successful applications were realized owing to the adaptable nature of (phebox)Rh(III) complexes for each substrate. Although preparation of the (alkynyl)Rh(III) complexes is not optimal and needs to be improved, we hope the information revealed from our study could shed light on the future studies on direct catalytic alkynylation of imines.

(96 h)

#### ASSOCIATED CONTENT

#### Supporting Information

Supporting Information Available: Experimental procedures, characterization of compounds and computational details (PDF). 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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(25) Limited improvements on reactivity using (alkynyl)Rh(III) complexes in the case of substrate **11a** may be due to the innate reactivity of **11a** compared with other  $\alpha$ ketiminoesters **2** and **9**. Even in this case, however, the use of (alkynyl)Rh(III) complexes was superior over (diacetato)Rh(III) complexes because of the difficulty in separation of the starting material **11** and product **12**; while the (alkynyl)Rh(III) complexes promoted the reactions to full conversion, (diacetato)Rh(III) complexes were not able to achieve full conversion under identical reaction conditions.

