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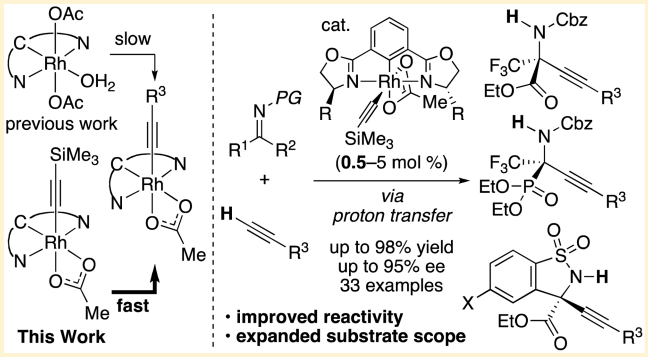
Mechanistic Studies and Expansion of the Substrate Scope of Direct Enantioselective Alkynylation of α-Ketiminoesters Catalyzed by Adaptable (Phebox)Rhodium(III) Complexes

Kazuhiro Morisaki,[†,‡] Masanao Sawa,[†,‡] Ryohei Yonesaki,[†] Hiroyuki Morimoto,[*,†] Kazushi Mashima,[§] and Takashi Ohshima[*,†]

[†]Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-8582, Japan
[§]Department of Chemistry, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka 560-8531, Japan

Supporting Information

ABSTRACT: Mechanistic studies and expansion of the substrate scope of direct enantioselective alkynylation of α-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-κ^2O,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-κ^2O,O')(trimethylsilylethynyl)(phebox)rhodium(III) complexes as a general precatalyst for various (alkynyl)rhodium(III) complexes. Use of the (trimethylsilylethynyl)rhodium(III) complexes as precatalysts enhanced the catalytic performance of the reactions with an α-ketiminoester derived from ethyl trifluoropyruvate at a catalyst loading as low as 0.5 mol % and expanded the substrate scope to unprecedented α-ketiminophosphonate and cyclic *N*-sulfonyl α-ketiminoesters.

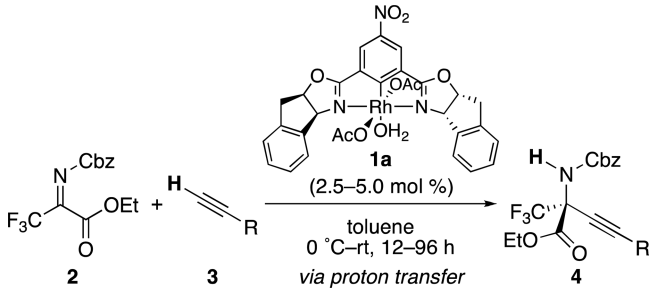


1. INTRODUCTION

Asymmetric alkynylation of imines is a highly efficient approach toward synthesizing optically active propargylamines,[1] a valuable intermediate for the synthesis of natural products and bioactive compounds.[2] Various alkynylation methodologies have been developed using stoichiometric amounts of metal reagents, such as alkyllithium and dialkylzinc.[3] 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.[4] Such direct alkynylation is effective for imines derived from aldehydes using Cu(I) and Ag(I) catalysts under proton-transfer conditions.[5] 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.[6] Some examples of Cu(I)-catalyzed enantioselective alkynylation to ketimines were recently reported,[7,8] but there is much room for improvement in terms of the scope of the ketimines, especially those applicable for the synthesis of α,α-disubstituted α-amino acid derivatives.[9]

To overcome these problems, we previously reported direct enantioselective alkynylation of α-ketiminoester **2** catalyzed by (aqua)(diacetato)(phebox)Rh(III) complex **1** (Scheme 1).[10,11] Using C_2-symmetric Indane-substituted (phebox)Rh(III) complex **1a** as the optimal catalyst, the reaction provided α,α-disubstituted α-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,

Scheme 1. (Diacetato)rhodium(III)-Catalyzed Direct Enantioselective Alkynylation of α-Ketiminoesters



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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 α-ketiminoesters derived from highly electrophilic ethyl trifluoropyruvate.

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.[12] Few mechanistic studies have been performed on the catalytic asymmetric alkynylation of imines,[13] 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 α-ketiminoesters.

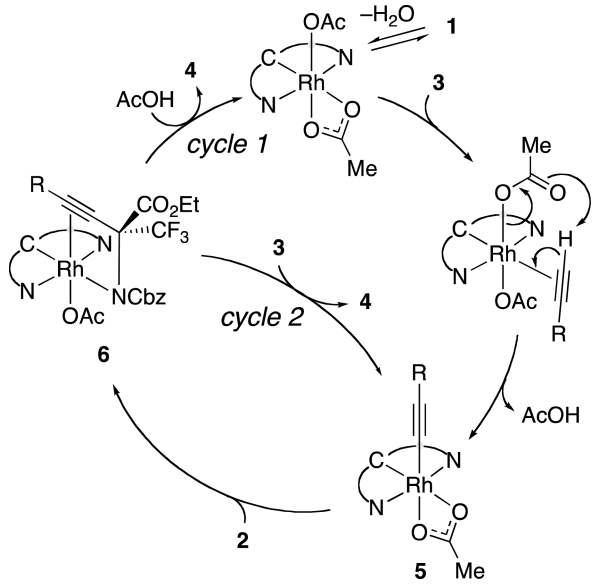
Herein we describe our mechanistic studies on the rhodium(III)-catalyzed direct enantioselective alkynylation of α-ketiminoesters. We isolated and identified (acetato-κ^2O,O')(alkynyl)(phebox)Rh(III) complexes, and found that the generation of this species determined the overall reactivity of the reaction. We also succeeded in generating this species via an alkynyl ligand exchange using (acetato-κ^2O,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, less-reactive α-ketiminophosphonates and cyclic *N*-sulfonyl ketiminoesters, which have not previously been reported as substrates for direct catalytic enantioselective alkynylations, afforded α,α-disubstituted α-amino acid derivatives in good yield and enantioselectivity.

2. RESULTS AND DISCUSSION

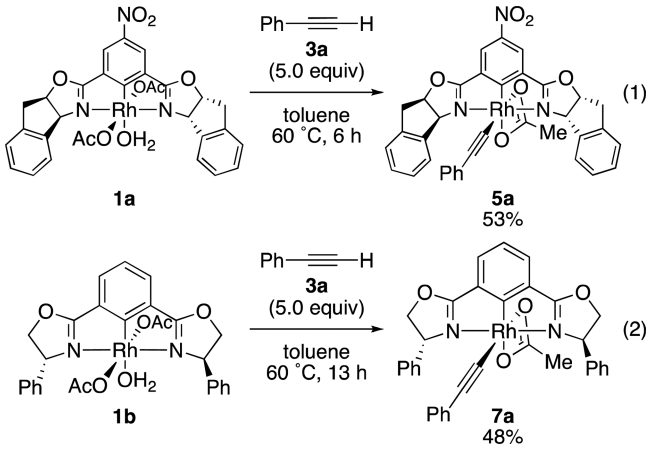
2.1. Isolation of (Alkynyl)(Phebox)Rhodium(III) Complexes and Identification of the Proton Source. We initiated our mechanistic studies by identifying the proton source in the catalytic cycle. We first postulated two catalytic cycles with different proton sources to close the catalytic cycle based on previous reports (Scheme 2).[14,15] In the first catalytic cycle (cycle 1), (aqua)(diacetato)(phebox)Rh(III) complex **1** reacted with alkynes **3** to give the corresponding (acetato-κ^2O,O')(alkynyl)(phebox)Rh(III) complex **5**, followed by reaction with α-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**.

To gain further insight into the proton source, we first synthesized (alkynyl)Rh(III) complex **5**. We prepared (acetato-κ^2O,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, eq 1).[15] 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** (Scheme 3, eq 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 κ^2 fashion, which is consistent with related Rh(III) complexes.[15]

Scheme 2. Two Possible Catalytic Cycles



Scheme 3. Isolation of (Alkynyl)Rhodium(III) Complexes



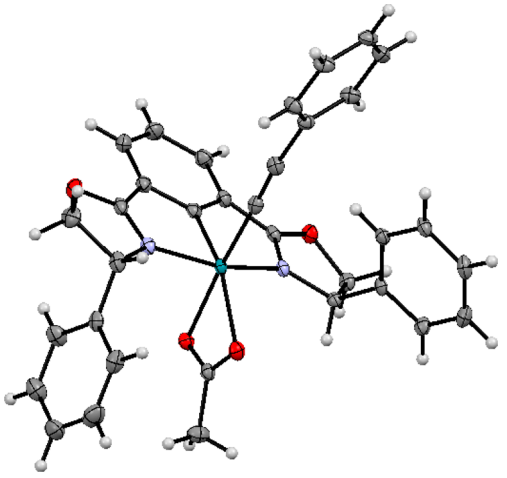


Figure 1. X-ray crystallographic structure of **7a**.

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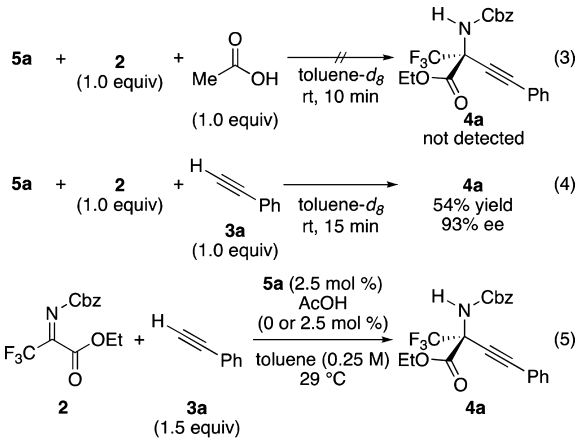
We then investigated the reactivity of (alkynyl)Rh(III) complex **5a** to clarify the proton source acting under the reaction conditions. Treatment of stoichiometric amounts of **5a** and **2** with either acetic acid or alkyne **3a** would give product **4a** if such reaction pathways were operative. The results shown in eqs 3 and 4 suggested that the less acidic alkyne **3a** (pK_a = 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.[15] 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 (eq 5 and Figure 2).

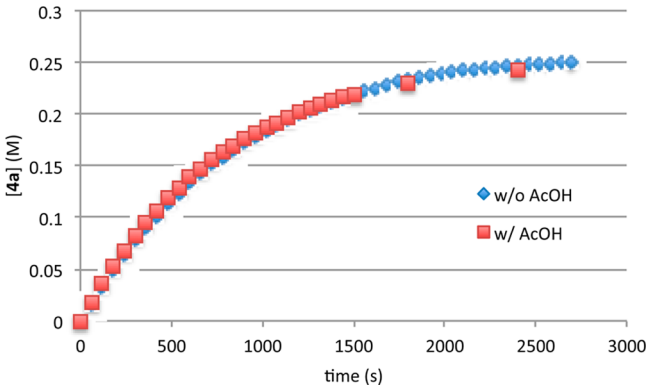


Figure 2. Reaction profiles using (alkynyl)Rh(III) complex **5a** in the absence or presence of acetic acid. Conditions: $[\mathbf{2}]_0$ = 0.25 M, $[\mathbf{3a}]_0$ = 0.375 M, $[\mathbf{5a}]_0$ = 6.3 mM, $[AcOH]_0$ = 0 or 6.3 mM, 29 °C.

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 catalytic 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.[13,15]

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 3a), suggesting that the generation of **5a**

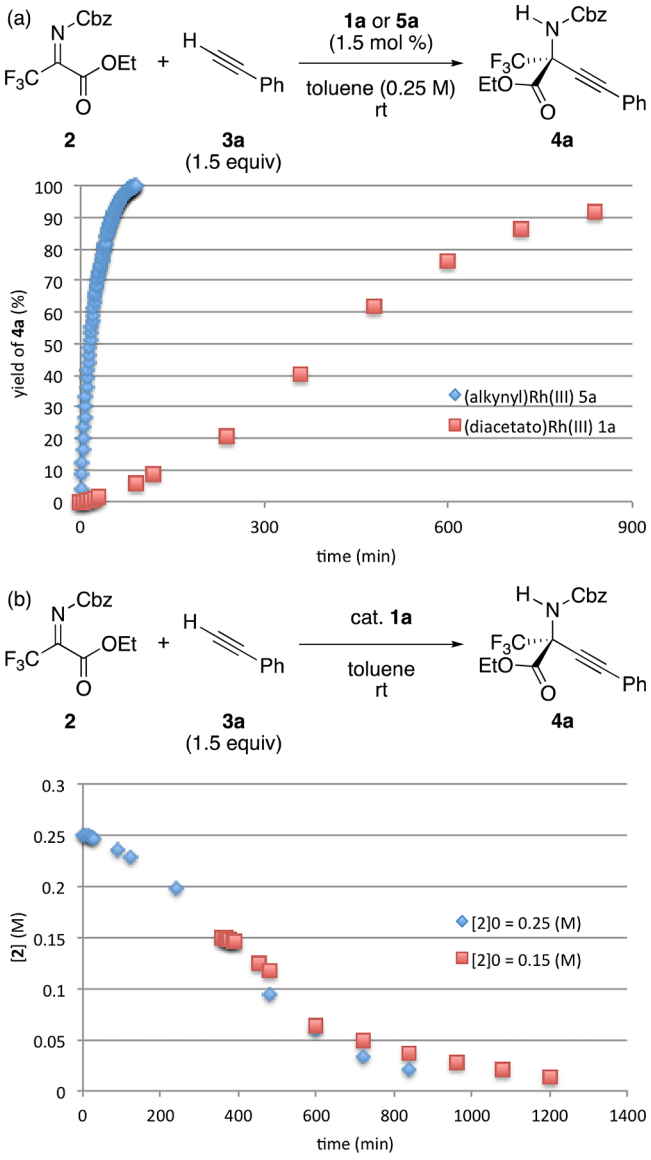


Figure 3. (a) Comparison of catalytic activity of Rh(III) complexes. Conditions: $[\mathbf{2}]_0$ = 0.25 M, $[\mathbf{3a}]_0$ = 0.375 M, $[\mathbf{1a}]_0$ or $[\mathbf{5a}]_0$ = 3.8 mM, room temperature. (b) Same [*e*] experiments for (diacetato)Rh(III) complex **1a** (time-scale was adjusted as *t*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

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 α-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 3b),[17] and we observed nonoverlapped reaction progress curves using time-scale adjustment protocol,[17d] in which the rate for higher initial concentration of **2** ($[\mathbf{2}]_0$ = 0.25 M) was faster than

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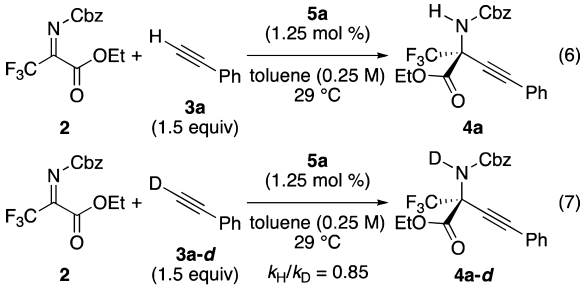
that for lower initial concentration of **2** ($[\mathbf{2}]_0$ = 0.15 M) at the time-adjusted point (t = 360 min), supporting the presence of induction period using **1a** as catalyst. The observed induction period using **1a** as the catalyst also suggests that the formation of active species from **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.

We next investigated the kinetic profiles of the catalytic cycle using (alkynyl)Rh(III) complex **5a** as the catalyst.[16] 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 α-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 α-ketiminoester **2**, we conducted reaction progress kinetic analysis according to the reported procedure.[17] We monitored the formation of **4a** using ^{19}F NMR spectroscopy to elucidate overall reaction profile under the standard conditions where $[\mathbf{2}]_0$ = 0.25 M, $[\mathbf{3a}]_0$ = 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 $(\mathrm{d}[\mathbf{4a}]/\mathrm{d}t)/[\mathbf{3a}]$ versus $[\mathbf{2}]$ were curved lines (Figure 4a), suggesting that the reaction order of $[\mathbf{2}]$ is complex, and the shape of the line suggests saturation kinetic behavior in $[\mathbf{2}]$, 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.[17b] The overlay of the plots under different $[e]$ conditions in Figure 4a suggests the first-order dependency for **3a**, which is consistent with the results of the initial rate kinetic study.[17b] In addition, time-adjusted overlay of plots under same $[e]$ conditions (Figure 4b)[17d] indicated that the catalyst **5a** is stable under the reaction conditions.

We also investigated the kinetic isotope effects[18] using **3a** and monodeuterated 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_H/k_D = 0.85) when the reactions were performed independently with **3a** or **3a**−***d*** (eqs 6 and 7 and Figure 5).[16] The result suggests that C−H bond



cleavage is not involved in the turnover-limiting step because normal kinetic isotope effects (k_H/k_D > 1) are expected under such conditions. The observed inverse kinetic isotope effects

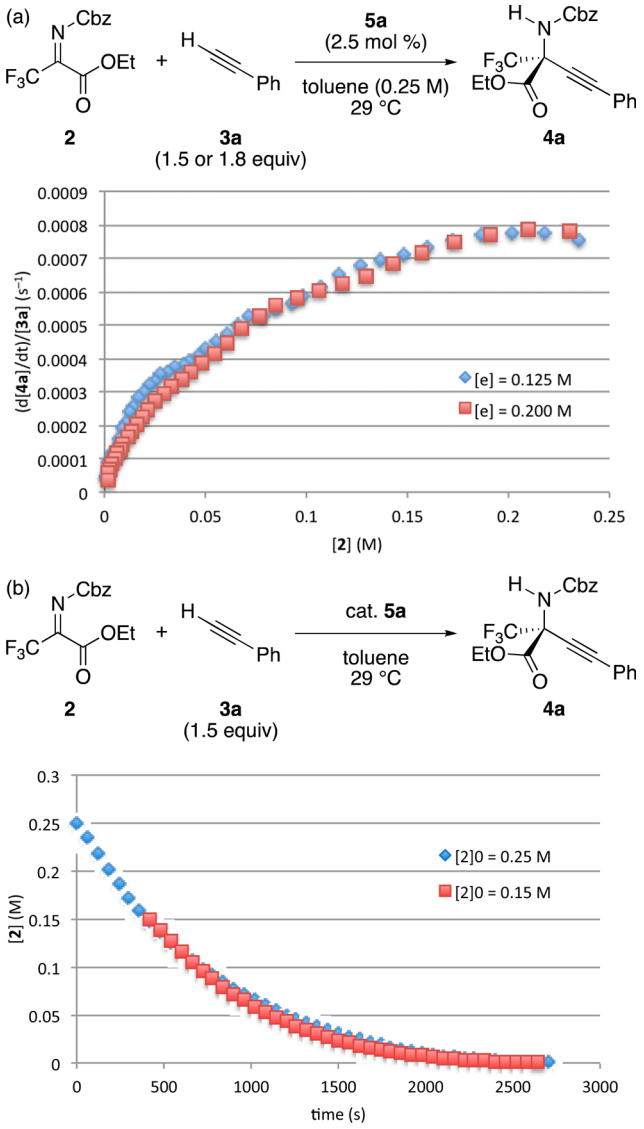


Figure 4. (a) Reaction progress kinetic analysis under different $[e]$ conditions. Conditions: $[\mathbf{2}]_0$ = 0.25 M, $[\mathbf{3a}]_0$ = 0.375 or 0.45 M, $[\mathbf{5a}]_0$ = 6.3 mM, 29 °C. (b) Reaction progress kinetic analysis under same $[e]$ conditions (time-scale was adjusted as t + 420 s for $[\mathbf{2}]_0$ = 0.15 M). Conditions: $[\mathbf{2}]_0$ = 0.25 or 0.15 M, $[\mathbf{3a}]_0$ = 0.375 or 0.275 M, $[\mathbf{5a}]_0$ = 6.3 mM, 29 °C.

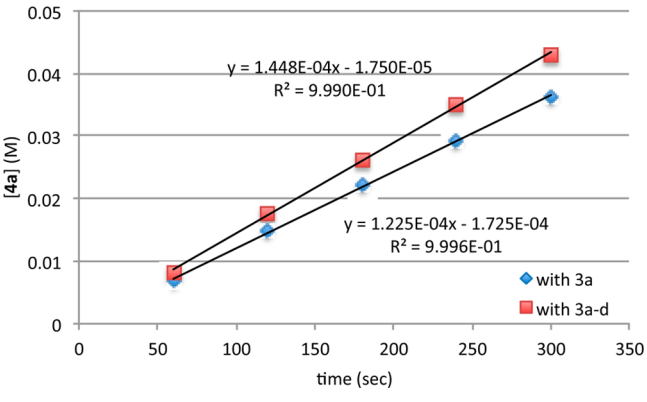


Figure 5. Kinetic isotope effects. Conditions: $[\mathbf{2}]_0$ = 0.25 M, $[\mathbf{3a}]_0$ or $[\mathbf{3a}-\boldsymbol{d}]_0$ = 0.375 M, $[\mathbf{5a}]_0$ = 3.1 mM, 29 °C.

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could be due to hybridization-induced changes of the terminal carbon of the alkyne **3** from sp to sp^2 in the transition state.[19] On the basis of the fact that hybridization of the carbon on alkynes changes from sp to sp^2 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]

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 to 29 °C (Figure 6a). Each of the lines

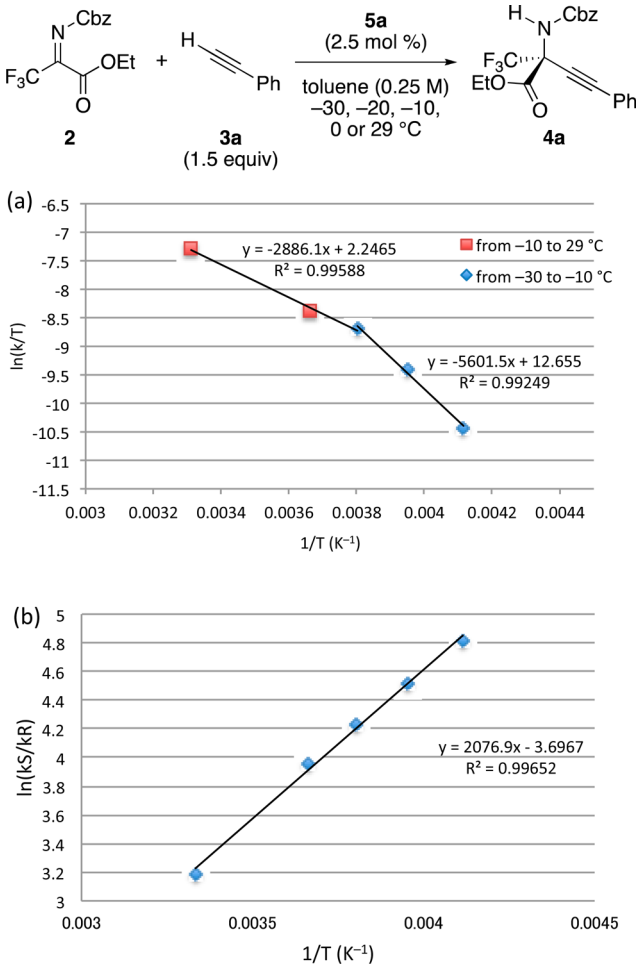
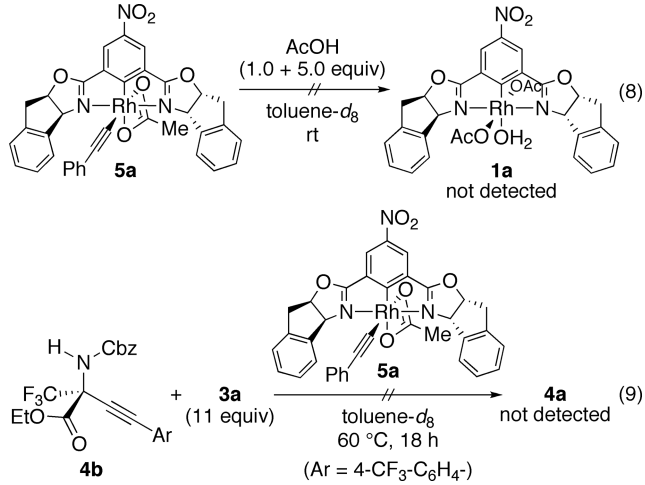


Figure 6. Eyring plots. (a) Effect of temperature on activation energies. (b) Effect of temperature on enantioselectivity. Conditions: $[\mathbf{2}]_0$ = 0.25 M, $[\mathbf{3a}]_0$ = 0.375 M, $[\mathbf{5a}]_0$ = 6.3 mM, −30, −20, −10, 0, or 29 °C.

yielded the following activation parameters: $\Delta H^{\ddagger}$ = 11.1 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −21.8 cal mol^{-1} K^{-1} and $\Delta G^{\ddagger}$ = 17.8 kcal mol^{-1} at 29 °C from the former line and $\Delta H^{\ddagger}$ = 5.7 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −42.5 cal mol^{-1} K^{-1} and $\Delta G^{\ddagger}$ = 18.6 kcal mol^{-1} at 29 °C from the latter line.[16] Such nonlinear behavior of the Eyring plots implies the presence of competitive rate-limiting steps in the catalytic cycle,[21] and we assumed that coordination of the alkynes would be the latter step ($\Delta G^{\ddagger}$ = 18.6 kcal mol^{-1}), whereas the addition of alkynyl ligand to α-ketiminoester **2** would be the former step ($\Delta G^{\ddagger}$ = 17.8 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^{-1} K^{-1}) 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 and 29 °C, and yielded the following differential activation parameters: $\Delta\Delta H^{\ddagger}$ = −4.1 kcal mol^{-1}, $\Delta\Delta S^{\ddagger}$ = −7.3 cal mol^{-1} K^{-1}, and $\Delta\Delta G^{\ddagger}$ = −1.9 kcal mol^{-1} at 27 °C (Figure 6b). The result suggests that differential enthalpy is a major contributor for determining the enantioselectivity.

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** (eq 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 absence of water.[16] In contrast, the presence of additional alkyne **3a** facilitated the formation of **5a**,[16] 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.[15] Additionally, treatment of product **4b** in the presence of (alkynyl)Rh(III) complex **5a** and alkyne **3a** did not form any crossover product **4a** even at 60 °C (eq 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.[16] 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 α-ketiminoester **2′**, and alkyne **3a** as a model system (Figure 7).[16] Migratory insertion

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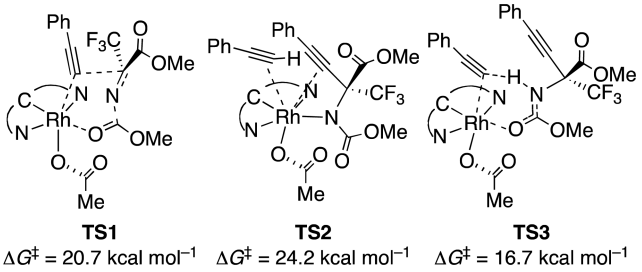
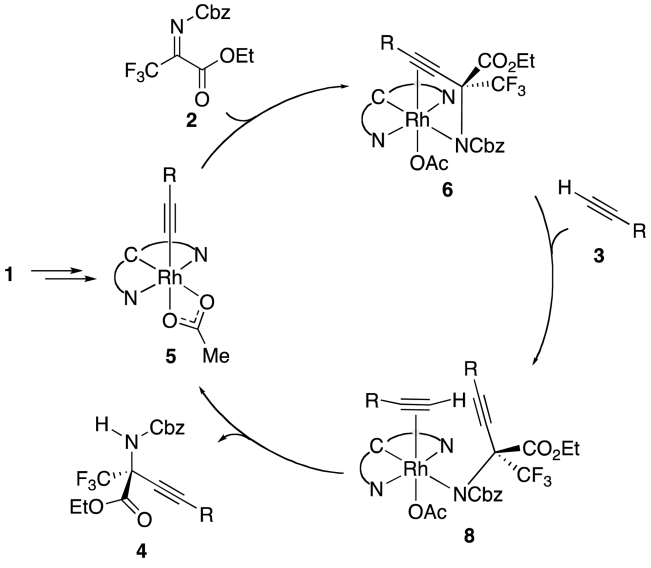


Figure 7. Transition state of key intermediates by DFT calculation. Gibbs energies are given at 25 °C.

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^{-1} 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^{-1} 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^{-1} at 25 °C) than the coordination step (**TS2**), supporting the interpretation of the observed inverse kinetic isotope effects.

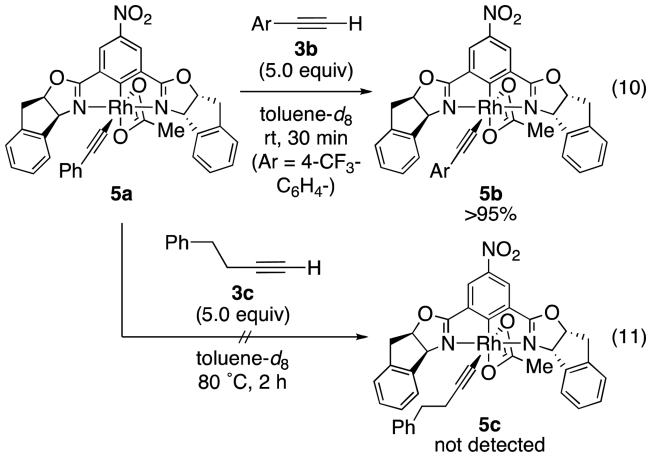
On the basis of these findings, we propose the mechanism of Rh(III)-catalyzed direct alkynylation of α-ketiminoester **2** shown in Scheme 4. First, (aqua)(diacetato)(phebox)Rh(III)

Scheme 4. Proposed Reaction Mechanism



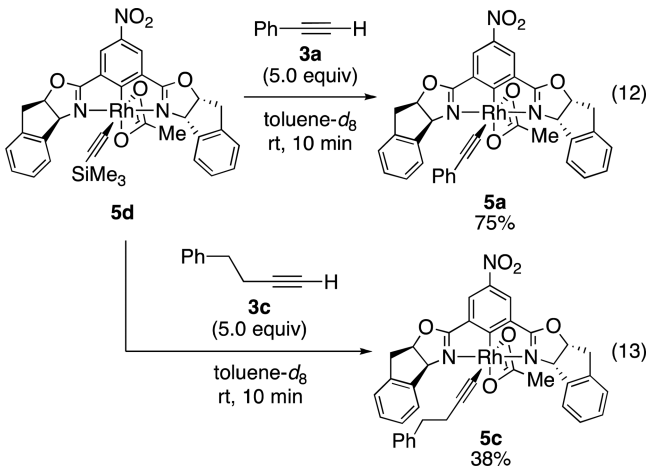
complex **1** reacts with alkyne **3** to give (acetato-κ^2O,O')-(alkynyl)Rh(III) complex **5**, as illustrated in Scheme 2, and this reaction is the rate-limiting step at the initial stage of the reaction when **1** is used as the catalyst. Once **5** is generated, it reacts with α-ketiminoester **2** to give (amido)Rh(III) complex **6**. After the formation of complex **6**, coordination of alkyne **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.

2.4. Improvement of the Catalytic Activity Using (Trimethylsilylethynyl)Rhodium(III) Complex as a Pre-catalyst. 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 (eq 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 (eq 11), presumably due to the thermodynamic preference of aryl-substituted (alkynyl)Rh(III) complex **5a** over alkyl-substituted (alkynyl)Rh(III) complex **5c**.

On the basis of these results, we aimed to develop a new precatalyst to promote the alkynyl ligand exchange with both aryl- and 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 (eqs 12 and 13). Although alkyl-substituted



alkyne **3c** showed equilibrium favorable to the starting complex **5d** under stoichiometric reaction conditions, the equilibrium

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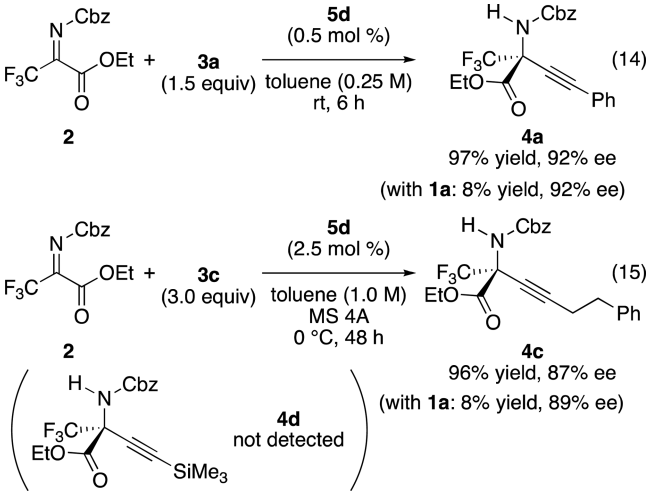
could be shifted to **5c** in the presence of a large excess of **3c** under the actual catalytic reaction conditions.[16]

We next performed experiments to verify the utility of (trimethylsilylethynyl)Rh(III) complex **5d** as a general precatalyst for the alkynylation of α-ketiminoester **2** (Scheme 5). A catalytic amount of **5d** promoted the reaction faster than

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



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 (Scheme 5, eq 14). The reaction with alkyl-substituted 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** (Scheme 5, eq 15).[10] Notably, the formation of trimethylsilylethynyl adduct **4d** was not detected under these catalytic reaction conditions using **5d** as the precatalyst.

Having established the utility of precatalyst **5d**, we examined the full scope of direct catalytic asymmetric alkynylation of α-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.

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 acid-sensitive 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.

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 α-ketiminoesters, which have not been previously applied to direct catalytic alkynylation reactions. We first examined Cbz-protected α-ketiminophosphonate **9**,[22] an analogue of α-ketiminoester, because optically active aminophosphonic acid derivatives can serve as transition state analogues of the corresponding amino acids and are important drug candidates.[23] We initially screened (diacetato)(phebox)-

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

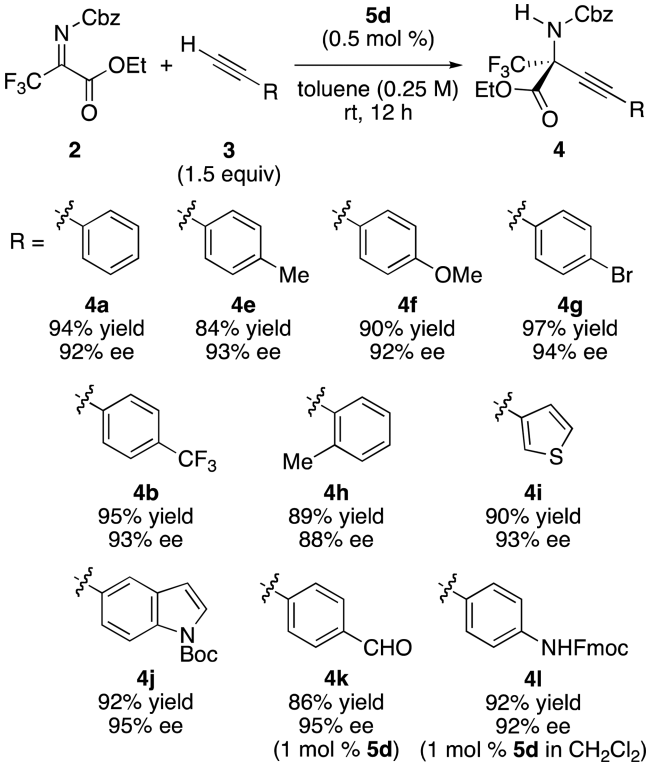
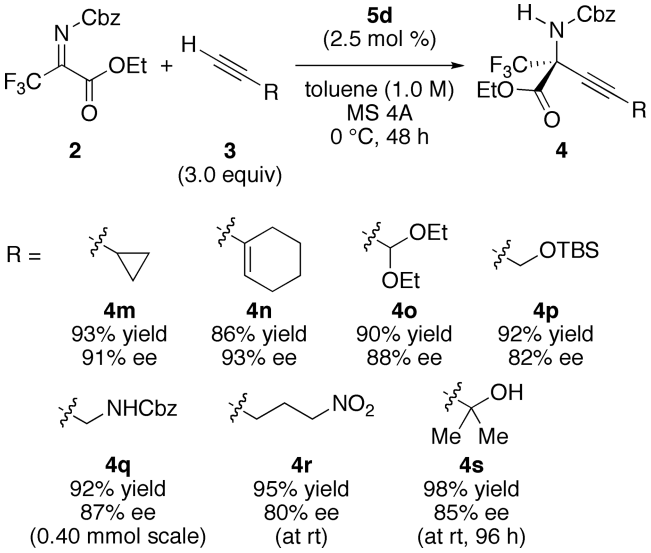


Table 2. Substrate Scope of Alkyl-Substituted Alkynes Using (Trimethylsilylethyl)Rh(III) Complex 5d



Rh(III) catalysts **1** with different substituents on bis(oxazoline) moiety for an alkynylation reaction of **9** with alkyne **3a** (Table 3),[16] 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 and 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 α-ketiminoester **2**. Indeed, we found that both

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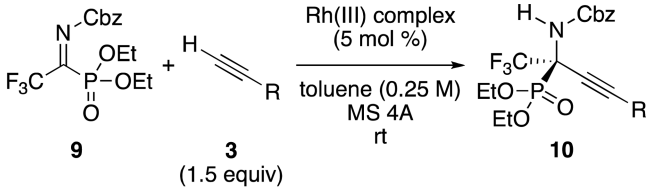
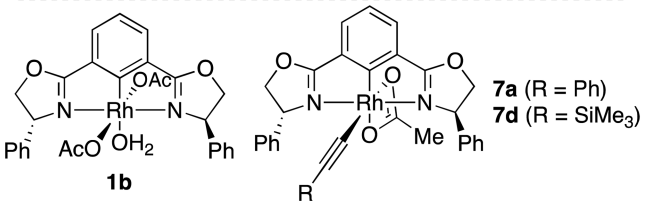
Table 3. Optimization of Catalysts and Scope of Alkynes for α-Ketiminophosphonate 9





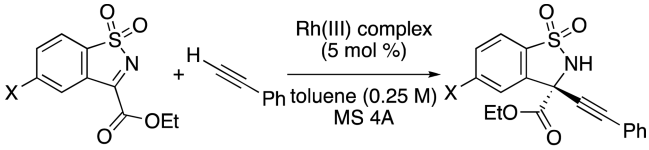
entry	R	Rh(III) complex	10	time (h)	yield (%)[a]	ee (%)[b]
1	Ph	**1a**	**10a**	24	17[c]	9
2	Ph	**1b**	**10a**	24	8[c]	87
3	Ph	**7a**	**10a**	24	>95[c]	89
4	Ph	**7d**	**10a**	18	96	88
5	4-Me-C_6H_4–	**7d**	**10b**	18	91	88
6	4-MeO-C_6H_4–	**7d**	**10c**	18	99	87
7	4-CF_3–C_6H_4–	**7d**	**10d**	18	97	88
8	2-Me-C_6H_4–	**7d**	**10e**	18	97	93
9[d]	cyclopropyl	**7d**	**10f**	24	86	80

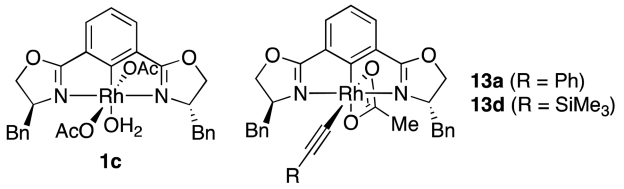
[a]Isolated yield. [b]Enantiomeric excess was determined by HPLC analysis with chiral stationary phase. [c]Determined by ^{19}F NMR analysis of the crude mixture. [d]Three equivalents of alkyne **3** was used.

(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 and 4).[16] 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**.[16] The reaction was also effective for other aryl-substituted alkynes with electron-donating or electron-withdrawing substituents and cyclopropylacetylene (entries 5–9). The absolute configuration of product **10a** was determined unambiguously by single crystal X-ray diffraction.[16]

Next, we applied the precatalyst system to cyclic *N*-sulfonyl α-ketiminoesters **11**.[24] 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 benzyl-substituted (diacetato)Rh(III) complexes **1b** and **1c** gave product **12a** in high enantioselectivity (entries 1–3).[16] The use of (phenylethynyl)Rh(III) complexes **7a** and **13a** showed improvements on reactivity (entries 4 and 5),[25] and the yields were further increased by raising the temperature to 70 °C while keeping the enantioselectivity in an acceptable level (entries 6 and 7). Further examination of related substrates **11b** (X = OMe) and **11c** (X = Cl) revealed, however, that benzyl-substituted (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 α-ketiminoesters **2** and **9** (entries 12–14).

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





entry	X	Rh(III) complex	temp	time (h)	yield (%)[a]	ee (%)[b]
1	H	**1a**	rt	45	10[c]	12
2	H	**1b**	rt	43	12[c]	92
3	H	**1c**	rt	45	14[c]	90
4	H	**7a**	rt	45	30[c]	96
5	H	**13a**	rt	45	49[c]	91
6	H	**7a**	70 °C	48	91	86
7	H	**13a**	70 °C	48	93	86
8	OMe	**7a**	70 °C	48	74	67
9	OMe	**13a**	70 °C	48	96	88
10	Cl	**7a**	70 °C	48	92	79
11	Cl	**13a**	70 °C	48	96	88
12	H	**13d**	70 °C	48	98	85
13	OMe	**13d**	70 °C	48	92	86
14	Cl	**13d**	70 °C	48	90	87

[a]Isolated yield. [b]Enantiomeric excess was determined by HPLC analysis with chiral stationary phase. [c]Determined by ^1H NMR analysis of the crude mixture.

With the optimal precatalyst **13d** in hand, we examined scope of alkynes for cyclic *N*-sulfonyl α-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.[16]

3. CONCLUSION

In summary, we present our mechanistic studies and expansion of the substrate scope of direct enantioselective alkynylation of α-ketiminoester **2** catalyzed by (aqua)(diacetato)(phebox)Rh-(III) complex **1a**. On the basis of the mechanistic analysis, (acetato-κ^2O,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-κ^2O,O')-(trimethylsilylethynyl)(phebox)Rh(III) complex **5d** as a general precatalyst that reacts with both aryl- and alkyl-substituted terminal alkynes to afford the corresponding (acetato-κ^2O,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 α-ketimino-

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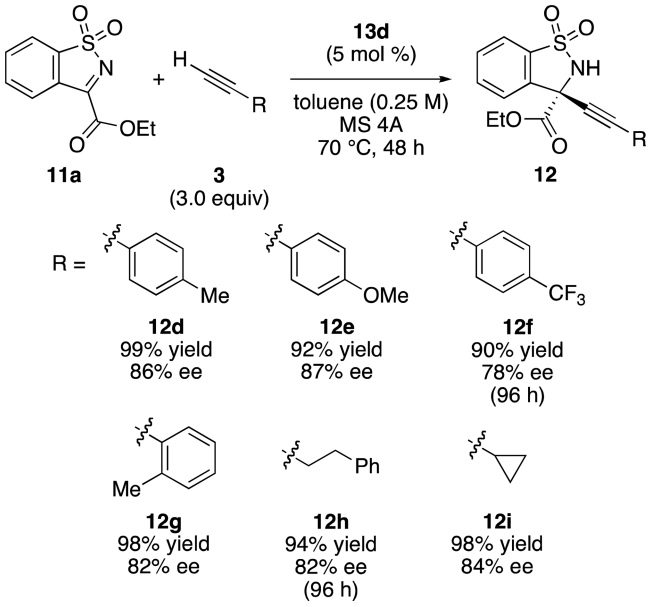
Table 5. Scope of Alkynes for Cyclic *N*-Sulfonyl α-Ketiminoester 11a



phosphonate **9** and cyclic *N*-sulfonyl α-ketiminoesters **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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01590.

Experimental procedures, characterization of compounds and computational details (PDF)
Crystallographic data for compound **7a** (CIF)
Crystallographic data for compound **10a** (CIF)
Crystallographic data for compound **14a** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*ohshima@phar.kyushu-u.ac.jp
*hmorimot@phar.kyushu-u.ac.jp

Author Contributions

‡K.M. and M.S. contributed equally.

Notes

The authors declare no competing financial interest.

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