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DIRECT ENANTIOSELECTIVE ALKYNYLATION OF α-KETOESTERS AND α-KETIMINOESTERS CATALYZED BY [BIS(OXAZOLINE)PHENYL]RHODIUM(III) COMPLEXES

Kazuhiro Morisaki,[1] Hiroyuki Morimoto,[1] Kazushi Mashima,[2] and Takashi Ohshima[1]*

[1]Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-8582, Japan. [2]Graduate School of Engineering Science, Osaka University, Osaka 560-8603, Japan. E-mail: ohshima@phar.kyushu-u.ac.jp

Abstract – This review summarizes our studies of the direct enantioselective alkynylation of α-ketoesters and α-ketiminoesters catalyzed by [bis(oxazoline)phenyl]rhodium(III) ((phebox)Rh(III)) complexes. The reactions provide chiral α-tetrasubstituted propargyl alcohols and propargylamines under proton-transfer conditions in high yield and with high enantioselectivity. The unique nature of (phebox)Rh(III) complexes allows the reactions to occur in the presence of various functional groups, including an electrophilic aldehyde functionality. Mechanistic studies revealed that the generation of (alkynyl)Rh(III) complexes limited the overall reactivity, which led us to use (trimethylsilylethynyl)(phebox)Rh(III) complexes as efficient pre-catalysts. The use of (trimethylsilylethynyl)(phebox)Rh(III) complexes reduced catalyst loading to as low as 0.5 mol%, and expanded the substrate scope to unprecedented α-ketiminophosphonate and cyclic *N*-sulfonyl α-ketiminoesters.

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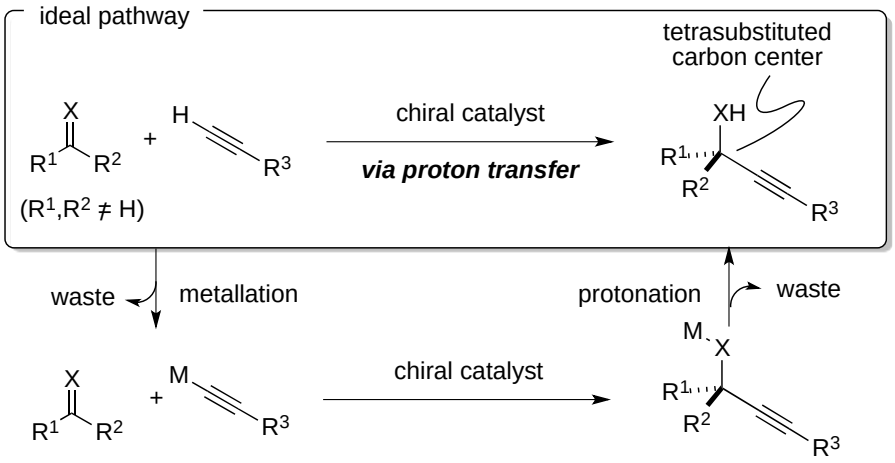
1. INTRODUCTION

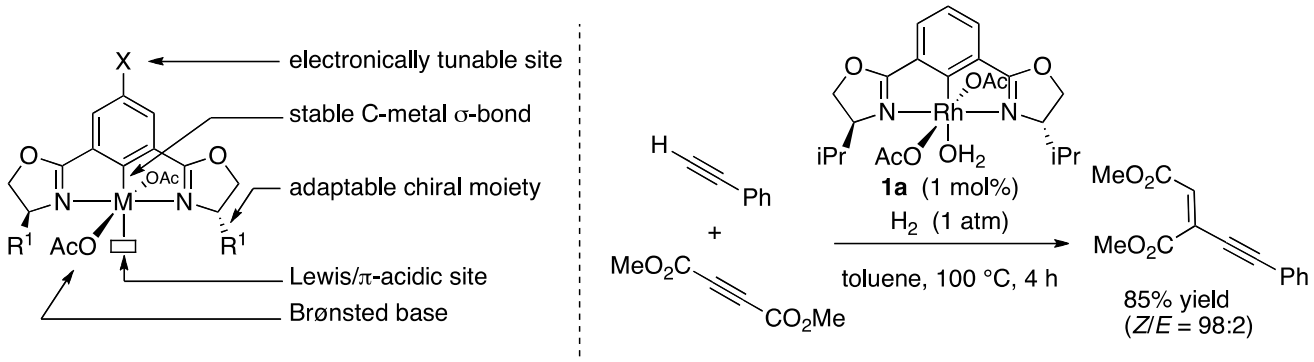
Chiral propargylic compounds, such as propargyl alcohols and propargylamines, are versatile building blocks for synthesizing various functionalized molecules.[1] Metal-assisted enantioselective alkynylation of carbonyl compounds and imines is one of the most efficient routes for synthesizing chiral propargylic compounds.[2] At the early stage of the development, stoichiometric amounts of metal reagents, such as alkyllithium and dialkylzinc, are used to increase the nucleophilicity of alkynes.[3,4] The reliability of these methodologies, however, is offset by the generation of stoichiometric amounts of unwanted waste and limited compatibility with base-labile functional groups. In contrast, in-situ catalytic generation of nucleophilic alkynylmetal species directly from terminal alkynes is a more atom-economical way of promoting the nucleophilic addition of alkynes to electrophiles.[5] Given the recent high demand for environmentally benign processes, direct catalytic enantioselective alkynylation is well explored for aldehydes[6] and aldimines.[7] On the other hand, reactions with ketones[8] and ketimines[9] are rarely reported due to their limited reactivity and difficult stereocontrol, although such reactions allow for the construction of tetrasubstituted stereogenic centers at the propargylic position (Scheme 1). In addition, while mechanistic studies often lead to improved catalytic performance and expansion of the substrate scope, few mechanistic studies have been performed on the catalytic enantioselective alkynylation of carbonyl compounds and imines.[10]



Scheme 1. Enantioselective Alkynylation of Ketones and Ketimines

To develop the ideal alkynylation reactions for ketones and ketimines, we planned to use chiral bis(oxazoline)phenyl (phebox)-ligated transition metal complexes developed by Nishiyama and coworkers (Scheme 2).[11] The phebox-metal complexes have a metal-carbon σ-bond with a phenyl backbone, which allows for modulation of the electronic properties of metal complexes and induces high stability against hydrolysis and oxidation. Additionally, similar to bis(oxazolinyl)pyridine (pybox) complexes, the chiral bis(oxazoline) moieties provide an effective steric environment for asymmetric

induction. (Aqua)(diacetato)(phebox)rhodium(III) complexes **1** are representative chiral (phebox)metal complexes that serve as efficient and multifunctional catalysts for various types of enantioselective reactions, including conjugate reduction, reductive aldol reaction, direct aldol reaction of aldehydes, diboration of terminal alkenes, and hydrosilylation.[12] These complexes also function as effective catalysts for cross-dimerization of alkynes under a hydrogen atmosphere.[13]



Scheme 2. (Phebox)metal Complexes and (Aqua)(diacetato)(phebox)Rh(III)-Catalyzed Cross-Dimerization of Alkynes

Given that (aqua)(diacetato)(phebox)rhodium(III) complexes **1** provide an effective steric environment for transforming carbonyl compounds and catalytically generate nucleophilic (alkynyl)Rh(III) species, we anticipated that **1** would effectively promote the alkynylation of ketones and ketimines. Additionally, we speculated that the adaptable nature of the (phebox)Rh(III) complexes would allow for the development of more useful catalysts by adjusting the electronic and steric environment.

2. ALKYNYLATION OF α-KETOESTERS[14]

We initiated our studies on the direct catalytic alkynylation of ethyl trifluoropyruvate (**2**) because of the importance of CF_3-containing chiral compounds as pharmaceuticals.[15] In the presence of 1.2 equivalents of phenylacetylene (**3a**), complex **1a** promoted the reaction in high enantiomeric excess, albeit in insufficient yield (Table 1, entry 1). Based on this initial result, we examined the effects of substituents on the phebox ligand. We synthesized and tested a variety of complexes with the C_2- and C_1-symmetric

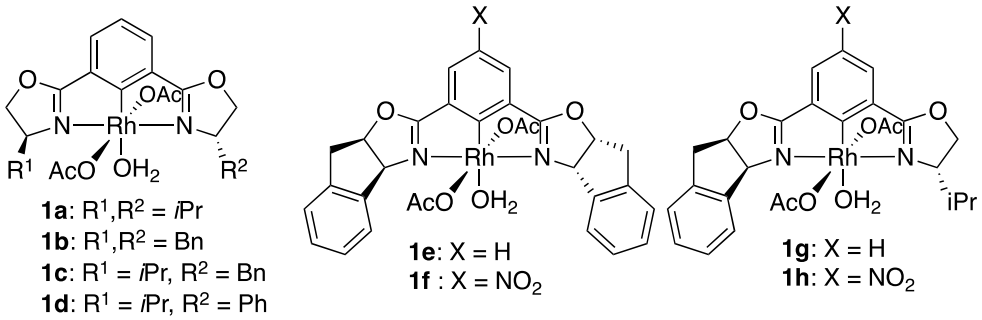
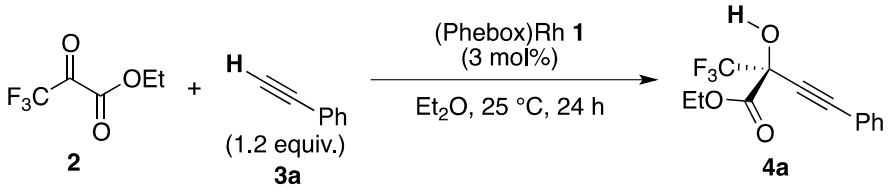


Figure 1. Structures of C_2- and C_1-Symmetric (Aqua)(diacetato)(phebox)Rh(III) Complexes

phebox ligand.[16] Although Rh complex **1d** afforded the best enantioselectivity (entry 5), **1e** and **1g** with indanyl substituents led to the best reactivity and enantioselectivity (entries 3 and 6).

Table 1. Alkynylation Catalyzed by C_2- and C_1-Symmetric (Phebox)Rh(III) Complexes **1**

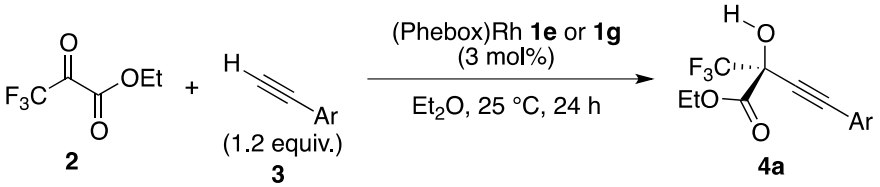


Entry	**1** (C_2)	Yield (%)[a]	Ee (%)[b]	Entry	**1** (C_1)	Yield (%)[a]	Ee (%)[b]
1	**1a**	35	88	4	**1c**	99	86
2	**1b**	87	83	5	**1d**	41	92
3	**1e**	94	91	6	**1g**	95	91

[a]Yield of the isolated product. [b]Determined by chiral HPLC analysis.

With these catalysts in hand, we investigated the substrate scope of aryl-substituted alkynes **3** (Table 2). In the presence of C_1-symmetric catalyst **1g**, phenylacetylenes with electron-donating and -withdrawing groups smoothly reacted to afford the products in high yield and with high enantioselectivity, while the same reactions using C_2-symmetric complex **1e** gave slightly inferior yields.

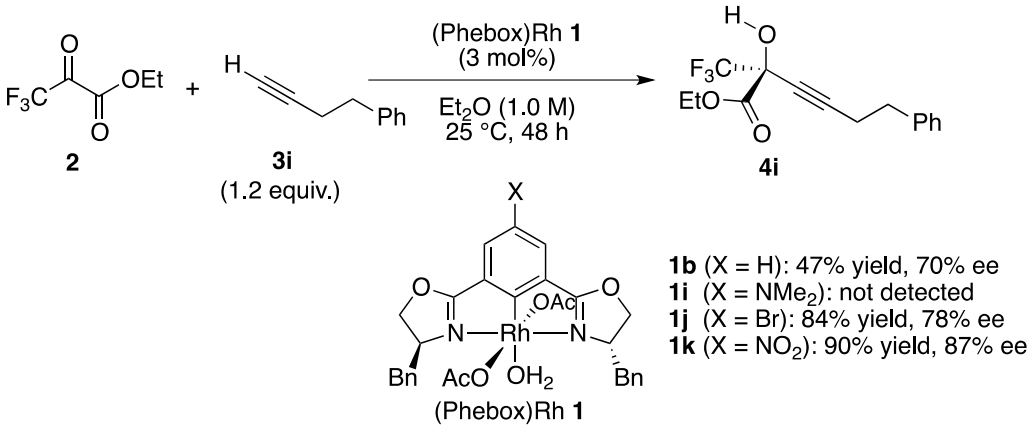
Table 2. Substrate Scope of Aryl-Substituted Alkynes and Effects of Symmetry of the Ligand



Entry	**3**	Ar	Catalyst **1e** (C_2)		Catalyst **1g** (C_1)	
			Yield (%)[a]	Ee (%)[b]	Yield (%)[a]	Ee (%)[b]
1	**3b**	4-Me-C_6H_4-	82	95	90	94
2	**3c**	3-Me-C_6H_4-	83	89	99	90
3	**3d**	2-Me-C_6H_4-	84	93	99	92
4	**3e**	4-MeO-C_6H_4-	78	80	88	90
5	**3f**	4-F-C_6H_4-	83	92	90	90
6	**3g**	4-Br-C_6H_4-	86	94	89	95
7	**3h**	4-CF_3-C_6H_4-	85	86	90	92

[a]Yield of the isolated product. [b]Determined by chiral HPLC analysis.

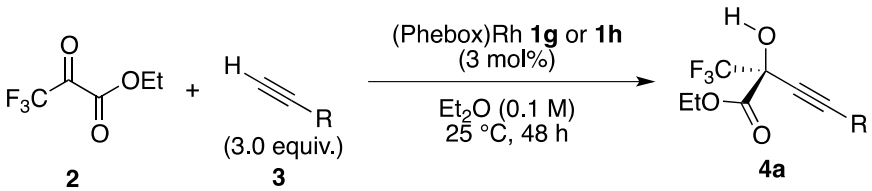
In contrast, the reaction with alkyl-substituted alkynes using complex **1g** was unsatisfactory (Scheme 3). For example, the reaction with 4-phenyl-1-butyne (**3i**) gave product **4i** in only 29% yield. To improve the reactivity, we investigated the electronic effects of the catalyst using complexes **1i**–**1k**, and found that complexes **1j** and **1k** with an electron-withdrawing group remarkably improved both the yield and enantioselectivity.[17]

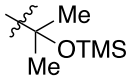


Scheme 3. Electronic Tuning of (Phebox)Rh(III) Complexes

These results led us to use the nitro-substituted C_1-symmetric Rh complex **1h** as the catalyst for the reaction with alkyl-substituted alkynes, as summarized in Table 3. A variety of alkyl-substituted alkynes

Table 3. Substrate Scope of Alkyl-Substituted Alkynes

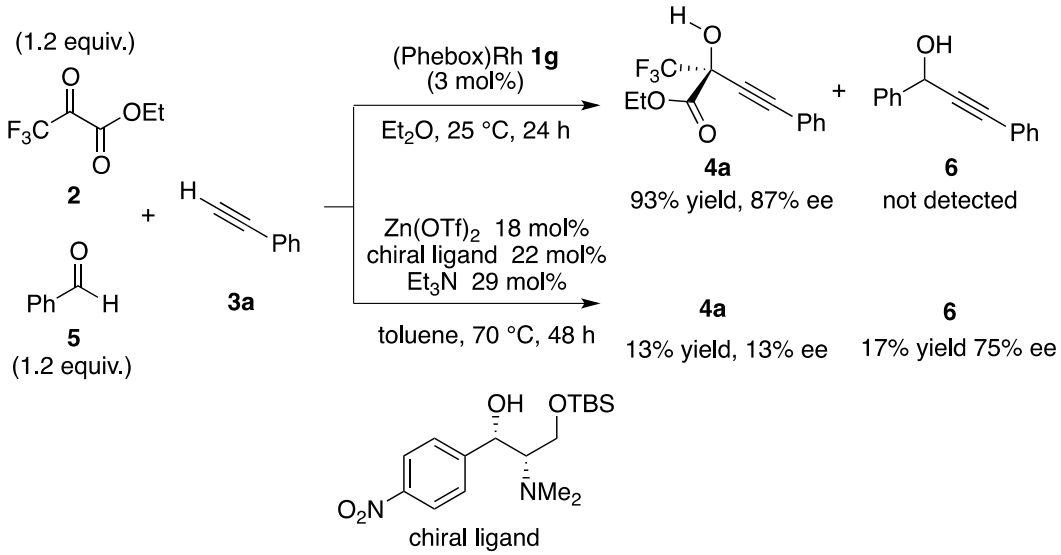


Entry	3	R	Catalyst **1g** (*para*-H)		Catalyst **1h** (*para*-NO_2)	
			Yield (%)[a]	Ee (%)[b]	Yield (%)[a]	Ee (%)[b]
1	**3i**	-CH_2CH_2Ph	82	81	91	92
2	**3j**	*n*Pr	66	85	91	93
3	**3k**	1-cyclohexenyl	85	87	93	96
4	**3l**	cyclopropyl	94	29	97	74
5	**3m**	*t*Bu	42	79	81	92
6	**3n**	TMS	52	82	72	84
7	**3o**		44	94	79	94
8	**3p**	-$CH(OEt)_2$	68	83	61	86

[a]Yield of the isolated product. [b]Determined by chiral HPLC analysis.

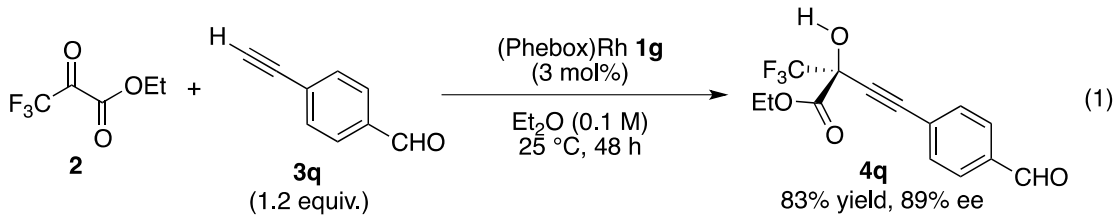
3 provided the products **4** in high yield and with high enantioselectivity, while electronically unmodified C_1-symmetric Rh(III) complex **1g** gave less satisfactory results.

In line with our interests in chemoselectivity,[18] we performed competitive experiments between α-ketoester **2** and benzaldehyde (**5**), a frequently used electrophile for alkynylation. The competitive reaction revealed that α-ketoester **2** was more reactive than aldehyde **5** under our reaction conditions (Scheme 4). Notably, other representative alkynylation conditions, such as catalytic zinc triflate with chiral amino alcohol ligand[6] and stoichiometric amounts of *n*BuLi, led to only non-selective or sluggish reactions.



Scheme 4. Competitive Experiments Using Equimolar Mixture of α-Ketoester **2** and Aldehyde **5**

The unique chemoselectivity of (phebox)Rh(III) complex **1g** allowed for the reaction between ketoester **2** and 4-ethynylbenzaldehyde (**3q**) to give the desired product **4q** in high yield without a protection-deprotection sequence (eq 1).



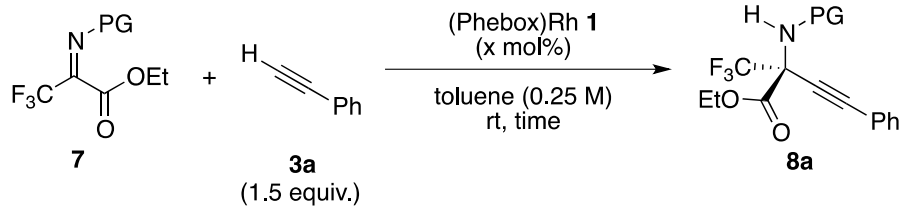
3. ALKYNYLATION OF α-KETIMINOESTERS[19]

α-Amino acids with an α-tetrasubstituted carbon stereocenter have gained much attention as a component of peptide-based drugs because they are more conformationally restricted and have better metabolic

stability than natural α-amino acids.[20] We anticipated that (phebox)rhodium(III) complexes **1** would also function as efficient catalysts for the alkynylation of α-ketiminoesters,[21] giving readily transformable α-amino acid derivatives with an α-tetrasubstituted carbon stereocenter.

We began our studies on the alkynylation of α-ketiminoesters **7** by searching for the most suitable protecting groups on the imine nitrogen atom (Table 4, entries 1–3). In the presence of 5.0 mol% of (phebox)Rh(III) complex **1a** and 1.5 equivalents of phenylacetylene (**3a**), Ts- and Cbz-protected ketiminoesters **7a** and **7b** reacted at room temperature to give the corresponding propargylamines **8a** and **8b**, respectively (entries 1 and 2). Although **7a** afforded the product with better enantioselectivity, we selected **7b** as the optimized electrophile for further investigation because of the facile deprotection of the Cbz group. We then investigated the effects of substituents on the oxazoline ring of (phebox)Rh(III) catalyst **1**, and found that C_2-symmetric catalyst **1e** was the best in terms of both reactivity and enantioselectivity (entries 4–6), in sharp contrast to the reactions with α-ketoester for which C_1-symmetric catalysts gave better results. Catalyst loading and reaction time were reduced to 2.5 mol% and 12 h, respectively (entry 7). Finally, catalyst **1f** with an electron-withdrawing nitro group at the *para* position to the rhodium metal gave the optimal result (entry 8).

Table 4. Optimization of Reaction Conditions

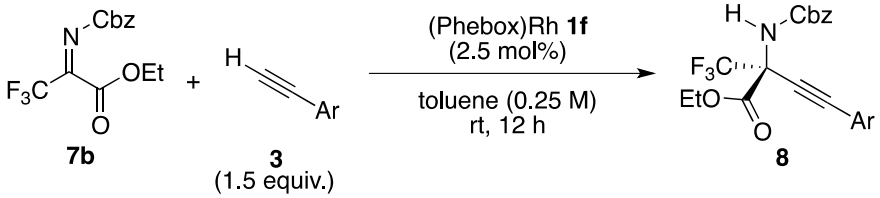


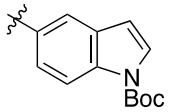
Entry	PG	7	1	x (mol%)	Time (h)	Yield (%)[a]	Ee (%)[b]
1	Ts	**7a**	**1a**	5.0	19	55	47
2	Cbz	**7b**	**1a**	5.0	24	88	44
3[c]	Boc	**7c**	**1a**	5.0	24	32	43
4	Cbz	**7b**	**1b**	5.0	24	82	50
5	Cbz	**7b**	**1e**	5.0	24	95	92
6	Cbz	**7b**	**1g**	5.0	24	96	69
7	Cbz	**7b**	**1e**	2.5	12	89	91
8	Cbz	**7b**	**1f**	2.5	12	93[d]	92

[a]Determined by ^{19}F NMR analysis of the crude mixture. [b]Determined by HPLC analysis with chiral stationary phase. [c]Reaction was performed at 70 °C. [d]Yield of isolated product.

With the optimized conditions in hand, we investigated the substrate scope of aryl-substituted alkynes (Table 5). A variety of phenylacetylene derivatives with electron-donating and -withdrawing groups afforded the products in high yield and with high enantioselectivity (entries 1–6). In addition, heterocycles and formyl and base-labile Fmoc groups were tolerated under catalytic conditions, highlighting the particularly broad functional group tolerance under our reaction conditions (entries 7–10).

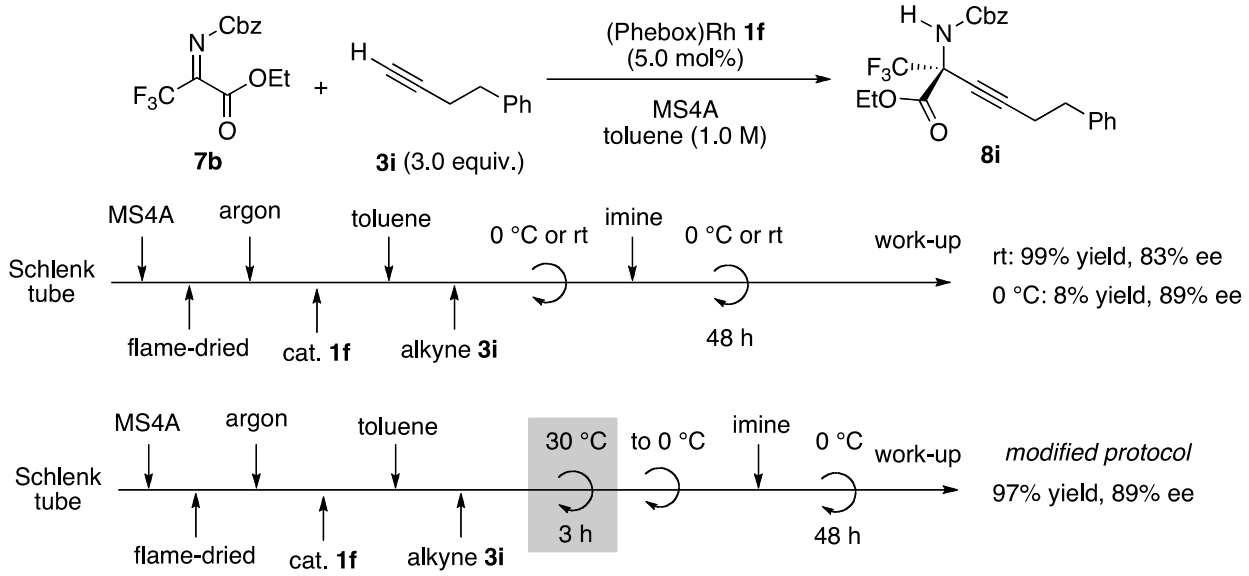
Table 5. Substrate Scope of Aryl-Substituted Alkynes



Entry	**3**	Ar	**8**	Yield (%)[a]	Ee (%)[b]
1[c]	**3a**	Ph	**8a**	91	93
2	**3b**	4-Me-C_6H_4-	**8b**	94	93
3	**3e**	4-MeO-C_6H_4-	**8e**	89	93
4	**3g**	4-Br-C_6H_4-	**8g**	92	94
5	**3h**	4-CF_3-C_6H_4-	**8h**	85	93
6	**3d**	2-Me-C_6H_4-	**8d**	96	90
7	**3r**	3-thienyl	**8r**	97	94
8[d]	**3s**		**8s**	95	95
9	**3q**	4-formyl-C_6H_4-	**8q**	>99	94
10[d,e]	**3t**	4-FmocNH-C_6H_4-	**8t**	84	92

[a]Yield of isolated product. [b]Determined by HPLC analysis with chiral stationary phase. [c]0.50 mmol of **7b** were used. [d]5.0 mol% of catalyst were used. [e]CH_2Cl_2 was used as solvent and reaction was performed for 24 h.

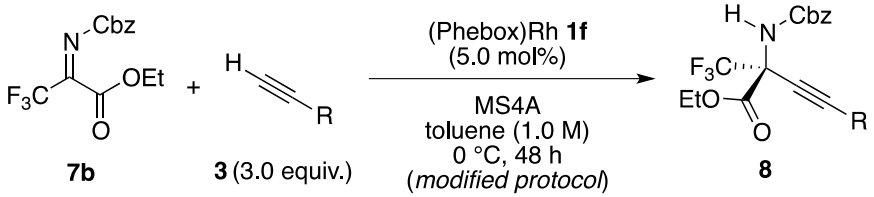
In the case of alkyl-substituted alkyne **3i**, the enantioselectivity of the product was lower than that of aryl-substituted alkynes, while the reaction smoothly proceeded at room temperature (Scheme 5). To improve the enantioselectivity, we performed the reaction at 0 °C; the reactivity was dramatically reduced, however, and even when using the optimized procedure for aryl-substituted alkynes, the product was obtained in only 8% yield. After several attempts, we finally found that the reaction smoothly proceeded at 0 °C after treating the catalyst **1f** with alkyl-substituted alkyne **3i** at 30 °C for 3 h before adding the imine **7b**. We discuss why this modification was effective later in this review.



Scheme 5. Optimization of Reaction Conditions for Alkyl-Substituted Alkynes

Under the modified reaction conditions, various alkyl-substituted alkynes afforded the product in high yield and with high enantioselectivity and broad functional group tolerance (Table 6).

Table 6. Substrate Scope of Alkyl-Substituted Alkynes

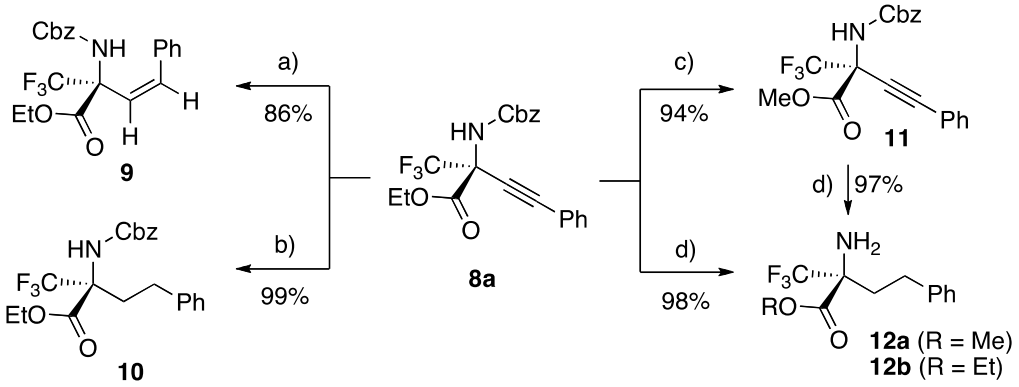


Entry	**3**	R	**8**	Yield (%)[a]	Ee (%)[b]
1	**3l**	cyclopropyl	**8l**	93	93
2	**3k**	1-cyclohexenyl	**8k**	89	93
3	**3p**	-$CH(OEt)_2$	**8p**	82	90
4	**3u**	-CH_2OTBS	**8u**	94	82
5[c]	**3v**	-CH_2NHCbz	**8v**	90	87
6[d]	**3n**	TMS	**8n**	89	79
7[d]	**3w**	-$C(Me)_2OH$	**8w**	91	88

[a]Yield of isolated product. [b]Determined by HPLC analysis with chiral stationary phase. [c]Reaction was performed with 0.50 mmol of **7b**, and 1.6 equiv. of **3v** were recovered after the reaction. [d]Reaction was performed at room temperature for 96 h.

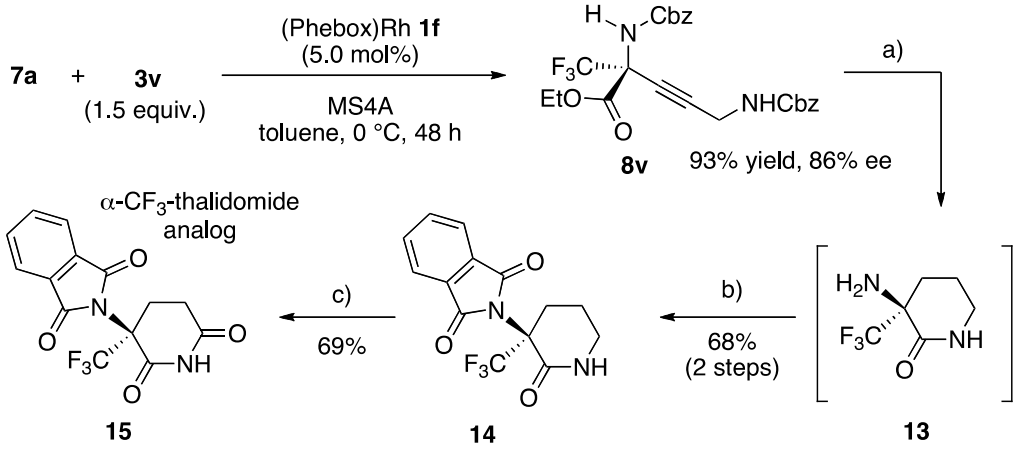
We also performed further transformation of the product **8a** (Scheme 6). The alkyne moiety can be partially and fully reduced to give **9** and **10** without affecting the Cbz group. In addition,

transesterification of **8a**[22] and deprotection of the Cbz group were performed to give **11** and **12**.



Scheme 6. Transformation of the Adduct. a) Lindlar catalyst, H_2 (1 atm), toluene (0.1 M), rt, 1.5 h; b) Pd/$CaCO_3$, H_2 (1 atm), dioxane (0.1 M), rt, 2 h; c) cat. ZnTAC24^{TM}, MeOH, reflux, 5 h; d) 10% Pd/C, H_2 (1 atm), EtOH (0.1 M), rt, 8 h.

Finally, we applied the alkynylation of α-ketiminoesters to the synthesis of **15**, α-trifluoromethylated analog of thalidomide (Scheme 7). Analog **15** was previously synthesized only in a racemic fashion via a related sequence using stoichiometric amounts of *n*BuLi.[23] We planned to reduce the alkyne moiety of **8v** while removing the two Cbz groups under hydrogenation conditions, and subsequent intermolecular amidation of ester would provide lactam **13** with a tetrasubstituted carbon stereocenter, which is the core structure of the thalidomide analog **15**. First, we conducted the reaction with reduced amounts of alkyne **3v** (1.5 equivalents). It is noteworthy that the same reaction did not proceed at all using stoichiometric amounts of *n*BuLi and LiHMDS. Next, propargylamine **8v** was smoothly converted to lactam **13**, which was transformed into **14** by treatment with phthaloyl dichloride. Finally, RuO_2-catalyzed C–H oxidation gave optically active α-trifluoromethylated thalidomide analog **15** in 44% total yield in 4 steps from the known substrates **7a** and **3v**.

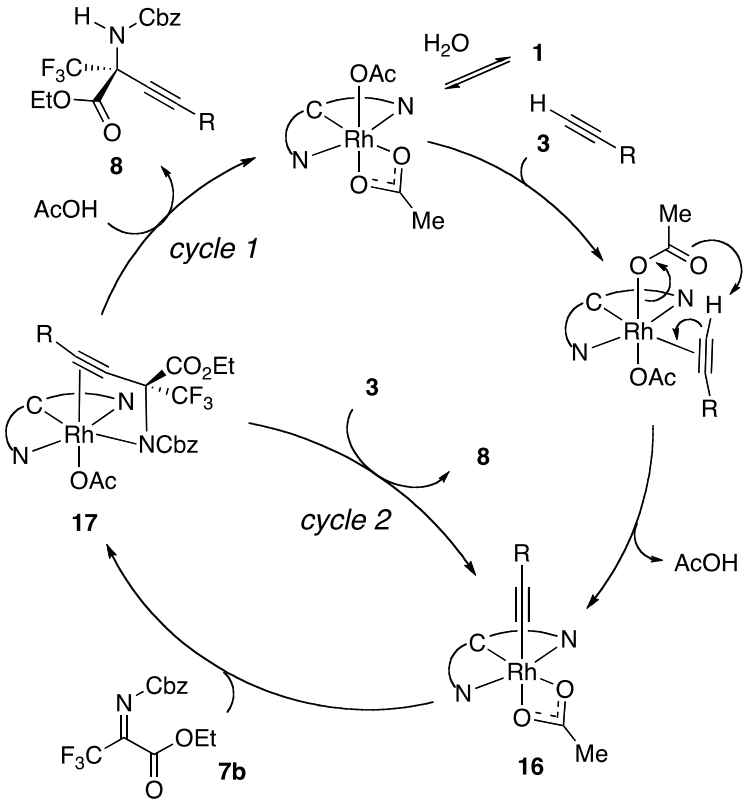


Scheme 7. Synthesis of a Thalidomide Analog. a) 10% Pd/C, H_2 (1 atm), MeOH, rt, 4 h; b) phthaloyl dichloride, DMAP, $CHCl_3$, 0 °C to reflux, 48 h; c) $RuO_2 \cdot xH_2O$, $NaIO_4$, CH_2Cl_2/H_2O, rt, 96 h.

4. MECHANISTIC STUDIES[24]

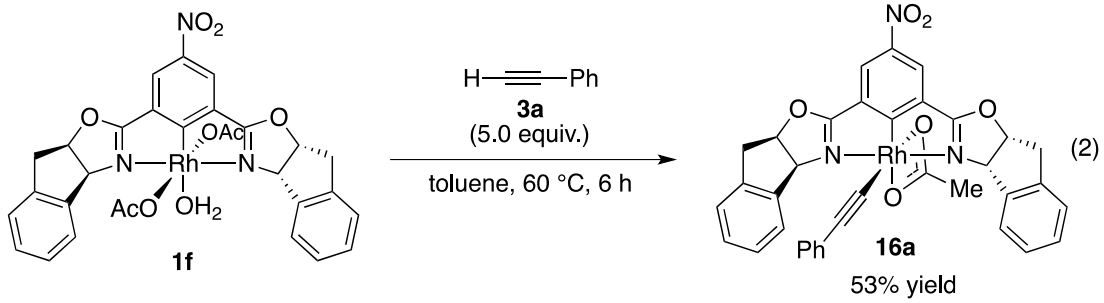
As described above, we developed a direct enantioselective alkynylation of α-ketoester and α-ketiminoesters catalyzed by (aqua)(diacetato)(phebox)rhodium(III) complexes **1**. The limited catalytic activity of **1**, however, made it difficult to further reduce catalyst loading and expand the substrate scope of the electrophiles. To gain insight into overcoming these problems, we performed the mechanistic studies, which often lead to improved catalytic performance. We thought that the Rh(III)-catalyzed system would be suitable for mechanistic studies of direct catalytic alkynylation reactions because of the high stability of (phebox)Rh(III) complexes.

We began our mechanistic studies by identifying the catalytic cycle. We first postulated two catalytic cycles based on the published precedent (Scheme 8).[13] In the first catalytic cycle (cycle 1), (aqua)(diacetato)(phebox)Rh(III) complex **1** deprotonates alkynes **3** to give the corresponding (acetato-κ^2O,O')(phenylethynyl)(phebox)Rh(III) complex **16**, followed by the reaction with imine **7b** to provide (amido)(phebox)Rh(III) complex **17**. The resulting complex **17** reacts with acetic acid, which is generated along with the deprotonation of alkynes, to complete the catalytic cycle. In the second cycle (cycle 2), terminal alkynes **3** function as proton sources to give products **8** and regenerate **16**.

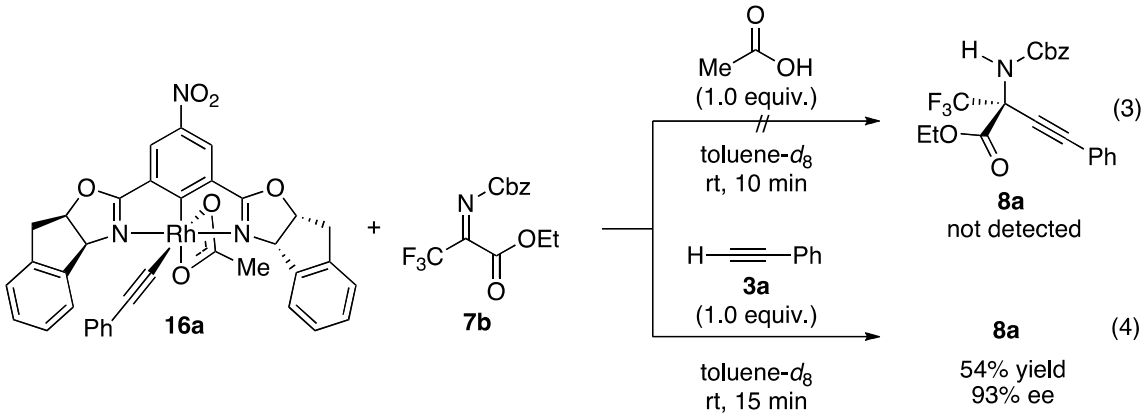


Scheme 8. Two Plausible Catalytic Cycles

To understand which catalytic cycle is operative, we prepared (acetato-κ^2O,O')(phenylethynyl)(phebox)Rh(III) complex **16a** according to the published procedure (eq 2).[13]

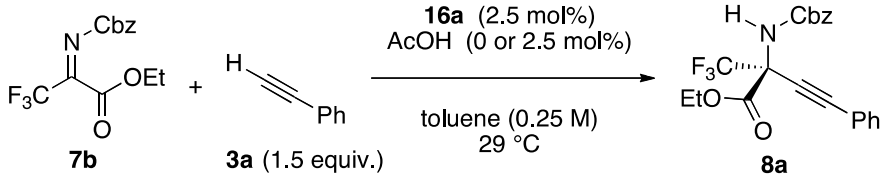


With complex **16a** in hand, we performed stoichiometric reactions (eqs 3 and 4). Treatment of a stoichiometric amount of **16a** and imine **7b** in the presence of acetic acid did not afford the product, in contrast to the result with alkynes **3a**. These results indicated that less acidic alkyne **3a** (pK$_a$ = 28.8 in DMSO) functioned as a proton source, while more acidic acetic acid (pK$_a$ = 12.6 in DMSO) did not.



This conclusion was further supported by experiments under catalytic reaction conditions (Figure 2). Using a catalytic amount of **16a**, the reaction proceeded even in the absence of acetic acid, and addition of a catalytic amount of acetic acid did not affect the reaction rate, suggesting that catalytic cycle 2 is operative under the reaction conditions.

Next, we examined whether the generation of (alkynyl)Rh(III) complex **16a** from (diacetato)Rh(III) complex **1f** is the slowest step under the reaction conditions. Comparison of the reaction progress between **1f** and **16a** revealed that the reaction proceeded much faster with **16a**, indicating that the generation of **16a** from **1f** was the slowest step in the overall reaction pathway when **1f** was used as the catalyst (Figure 3).



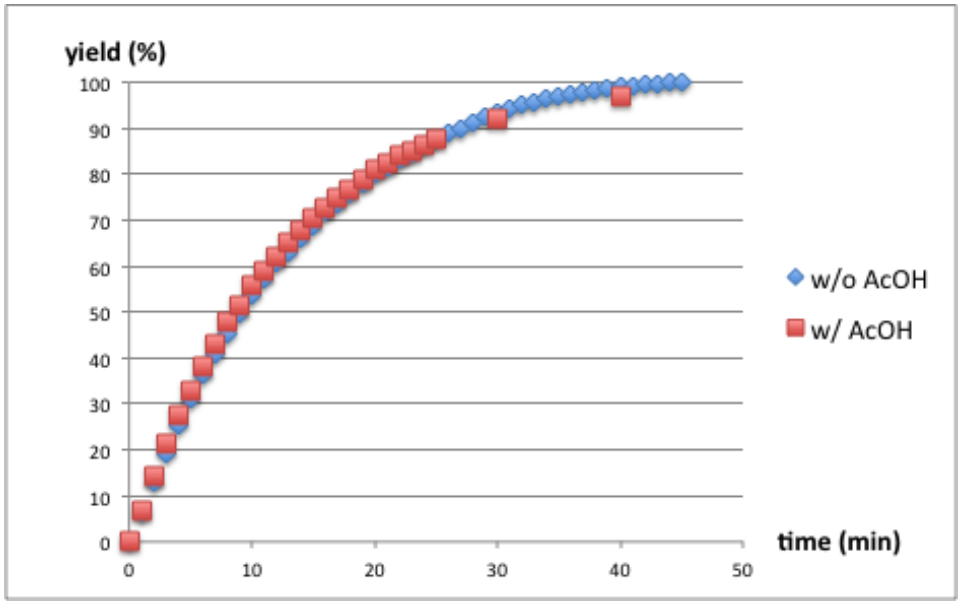
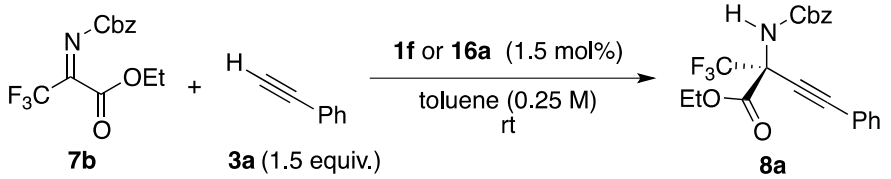


Figure 2. Reaction Profiles Using (Alkynyl)Rh(III) Complex **16a** in the Absence or Presence of Acetic Acid. Conditions: [**7a**]$_0$ = 0.25 M, [**3a**]$_0$ = 0.375 M, [**16a**]$_0$ = 6.3 mM, [AcOH]$_0$ = 0 or 6.3 mM, 29 °C.



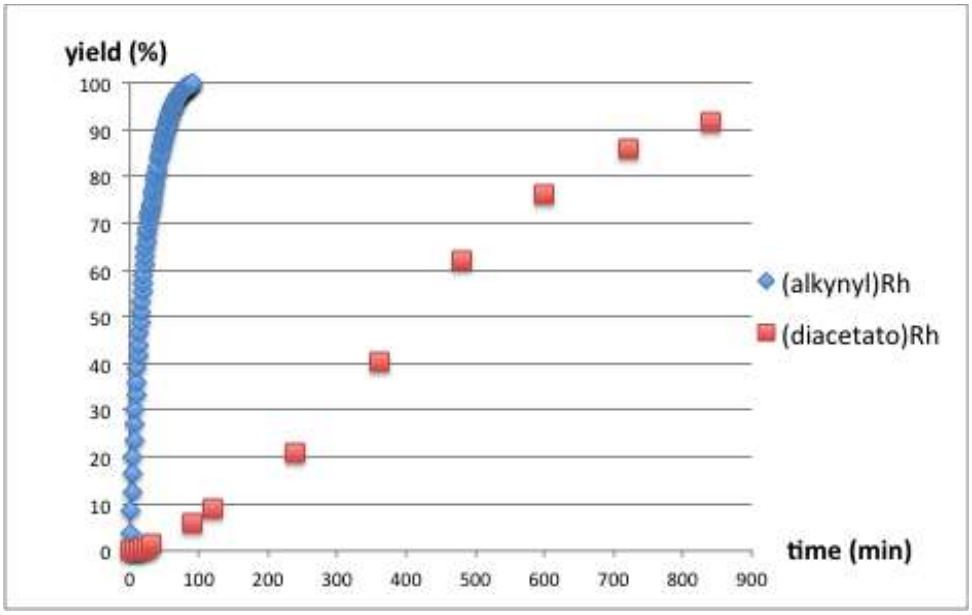


Figure 3. Comparison of Catalytic Activity of Rh(III) Complexes **1f** and **16a**. Conditions: [**7b**]$_0$ = 0.25 M, [**3a**]$_0$ = 0.375 M, [**1f**]$_0$ or [**16a**]$_0$ = 3.8 mM, room temperature.

To support the conclusions, we also performed a reaction progress kinetic analysis under the same [*e*] conditions (Figure 4).[25] We observed a non-overlapping reaction progress curve using a time-scale adjustment protocol,[26] and the results suggested that the concentration of **1f** was not stable under the reaction condition, and the formation of catalytically active species from **1f** was the rate-limiting step at the initial stage of the reaction.

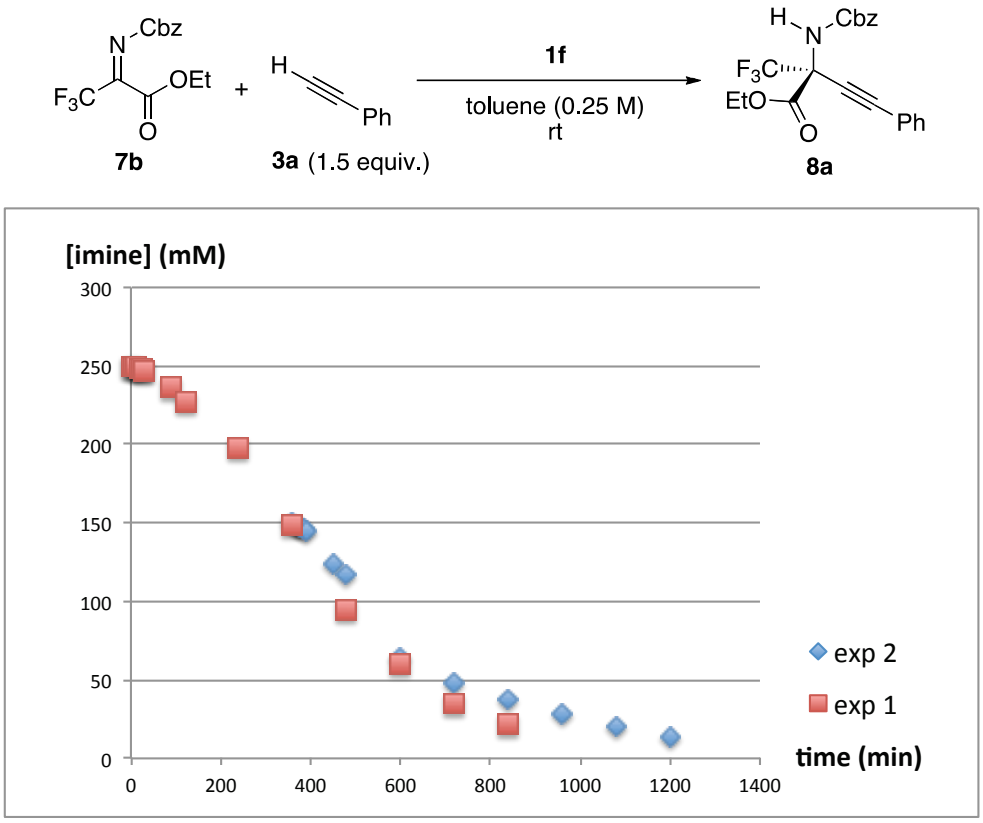
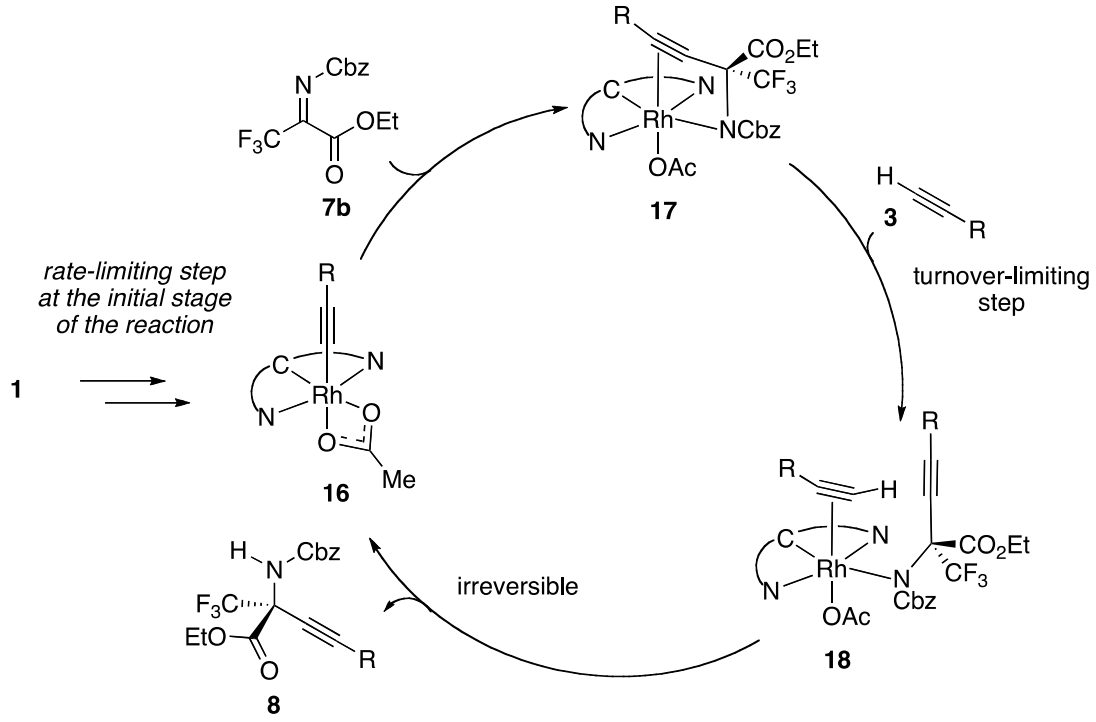


Figure 4. Same [*e*] Experiments for (Diacetato)Rh(III) Complex **1f**. Conditions: $[\mathbf{7b}]_0$ = 0.25 or 0.15 M, $[\mathbf{3a}]_0$ = 0.375 or 0.275 M, $[\mathbf{1f}]_0$ = 6.3 mM, room temperature; time-scale was adjusted as t + 360 min for $[\mathbf{7b}]_0$ = 0.15 M.

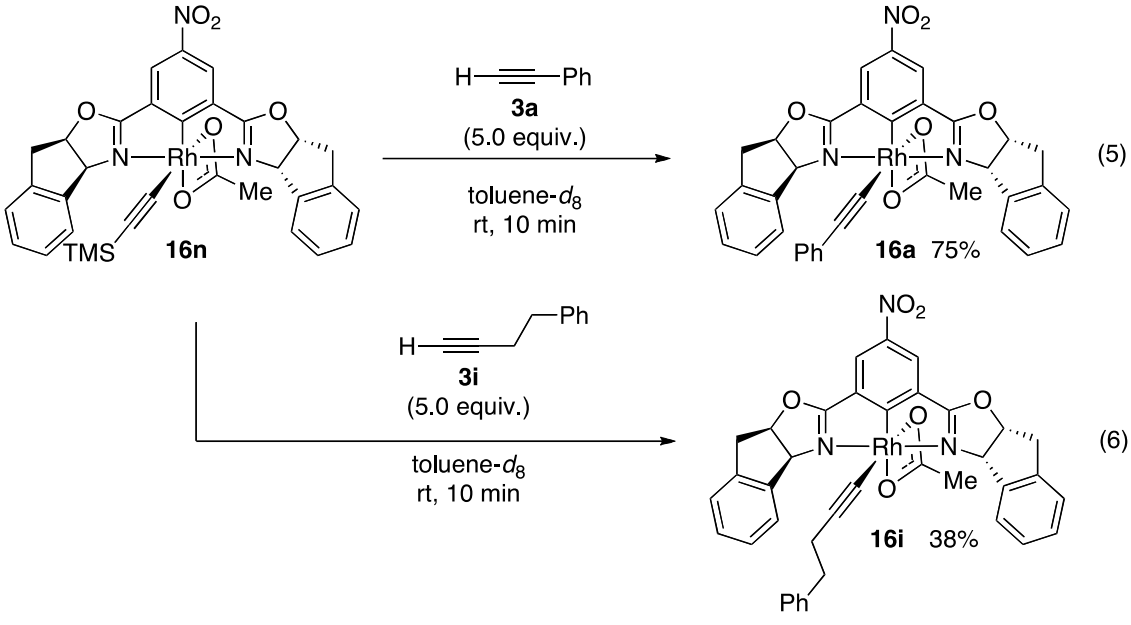
We also performed additional experiments, such as initial rate kinetic analysis, kinetic isotope effects, Eyring plot, stoichiometric reactions, and DFT calculations. On the basis of these findings, we propose the mechanism of (phebox)Rh(III)-catalyzed direct alkynylation of α-ketiminoester shown in Scheme 9. First, (aqua)(diacetato)(phebox)Rh(III) complex **1** reacted with alkyne **3** to give the corresponding (acetato-κ^2O,O')(phenylethynyl)(phebox)Rh(III) complex **16**, and this reaction is rate-limiting at the initial stage of the reaction when **1** is used as a catalyst. Once **16** is generated, it reacts with imine **7b** to give the (amido)(phebox)Rh(III) complex **17**. After **17** is generated, coordination with alkyne **3** gives complex **18** and this step is turnover-limiting in the catalytic cycle after the generation of **16**.[27] Finally complex **18** irreversibly releases product **8** and regenerates complex **16**.



Scheme 9. Proposed Reaction Mechanism

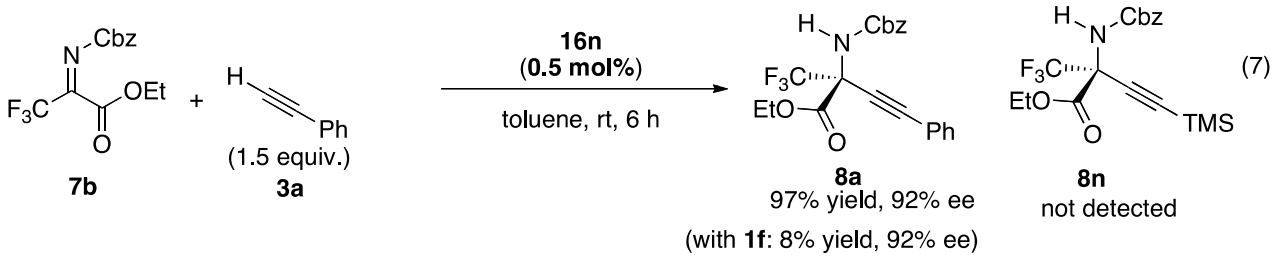
5. IMPROVEMENT OF THE CATALYTIC ACTIVITY USING MODIFIED PRECATALYST

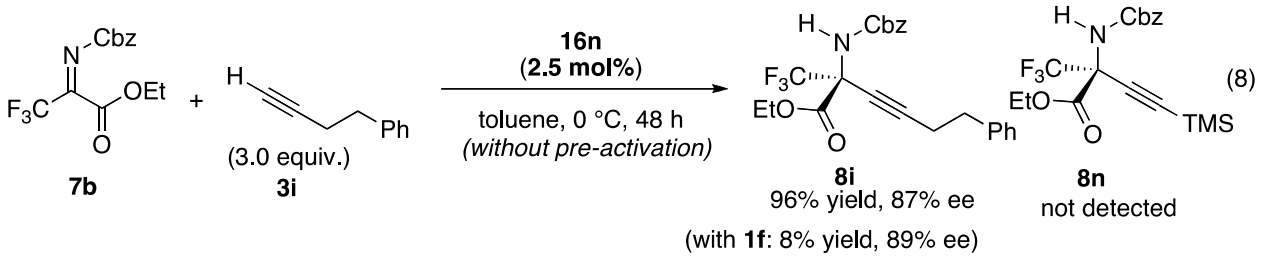
The mechanistic studies described above revealed that efficient generation of (alkynyl)Rh(III) complex **16** is important enhancing the catalytic performance. We hypothesized that (phenylethynyl)(phebox)Rh(III) complex **16a** would be a more effective catalyst if the exchange of the alkynyl ligand on **16** with various alkynes **3** proceeded faster than the generation of **16** from **1f**. Although



the alkynyl ligand exchange of **16a** proceeded with aryl-substituted alkynes, the same reaction did not proceed with alkyl-substituted alkynes **3i**. To improve the reactivity with alkyl-substituted alkynes, we examined various (alkynyl)Rh(III) complexes and found that (trimethylsilylethynyl)Rh(III) complex **16n** smoothly promoted the exchange reaction with both aryl- and alkyl-substituted alkynes (eqs 5 and 6).

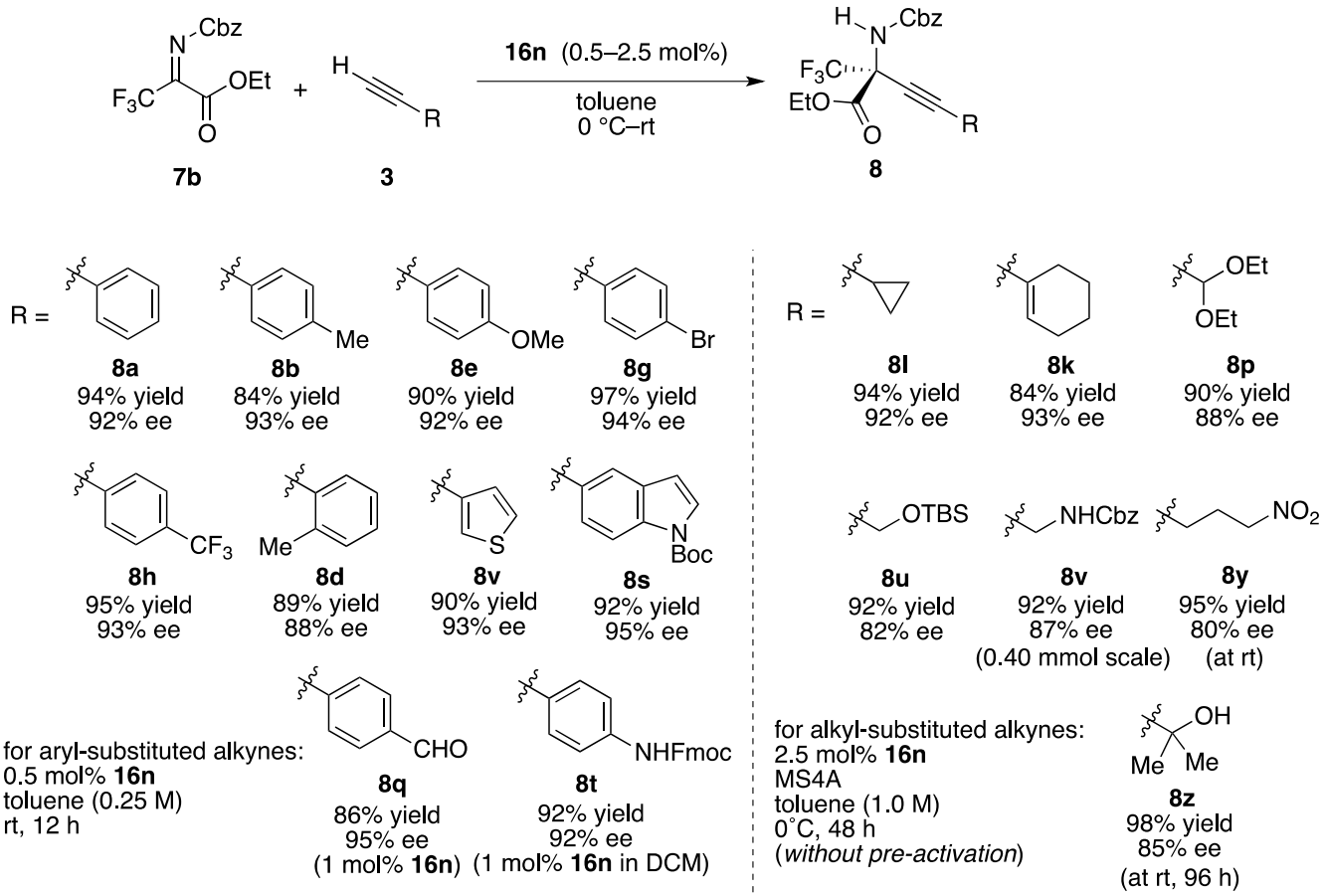
To verify the utility of (alkynyl)Rh(III) complex **16n** as a general precatalyst, we compared the reactivity of **16n** and (diacetato)Rh(III) complex **1f** (eqs 7 and 8). The use of **16n** as a catalyst allowed to reduce the catalyst loading to as low as 0.5 mol% for the reaction with aryl-substituted alkyne **3a**, while the reaction with 0.5 mol% of **1f** produced an insufficient yield. The reaction with alkyl-substituted alkynes **3i** also gave product **8i** in 96% yield and 87% ee at 0 °C without pre-activating the catalyst. It is notable that trimethylsilylacetylene adduct **8n** was not detected under the reaction conditions when **16n** was used as a catalyst.





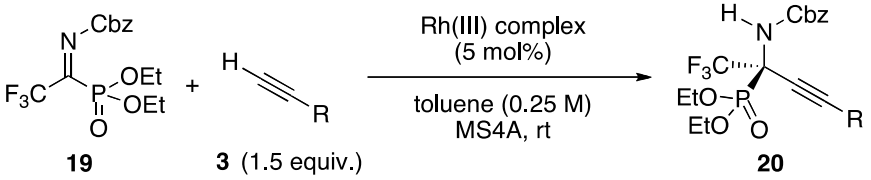
We examined the scope of the direct alkynylation of α-ketiminoesters using newly developed precatalyst **16n**. The catalyst loading was reduced to as low as 0.5 mol% for aryl-substituted alkynes and 2.5 mol% for alkyl-substituted alkynes, without a loss of functional group tolerance (Table 7).

Table 7. Substrate Scope of Alkynes Using **16n**



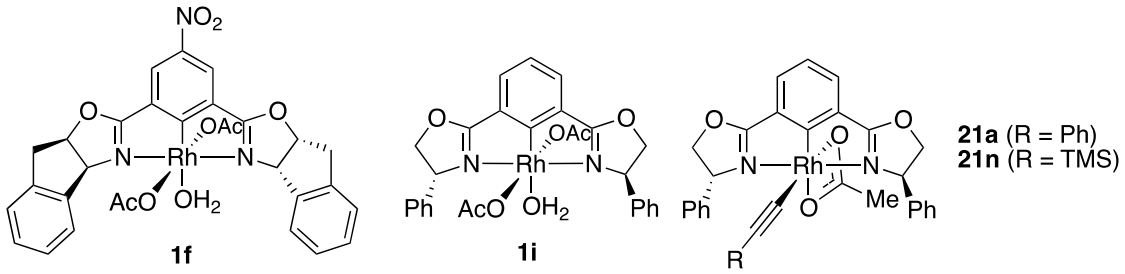
Encouraged by the results using **16n** as a precatalyst, we turned our attention to the reaction with less electrophilic α-ketiminoesters, which have not been used in direct catalytic enantioselective alkynylation. We first examined the reaction with Cbz-protected α-ketiminophosphonate **19**, because optically active α-aminophosphonic acid derivatives can serve as transition-state analogs of the corresponding amino acids.[28] We screened (aqua)(diacetato)(phebox)Rh(III) complexes **1** with various substituents on the oxazoline moiety, and found that phenyl-substituted complex **1i** had better enantioselectivity due to the flexible nature of the (phebox)Rh(III) complexes (Table 8, entries 1 and 2). Using of (phenylethynyl)- and (trimethylsilylethynyl)(phebox)Rh(III) complexes **21a** and **21n** with a phenyl substituent on the oxazoline moiety dramatically improved the reactivity to afford product **20a** in high yield and with high enantioselectivity (entries 3 and 4). The optimized reaction conditions were also effective for other aryl-substituted alkynes and cyclopropylacetylene (entries 5–9).

Table 8. Direct Catalytic Enantioselective Alkynylation of α-Ketiminophosphonate **19**



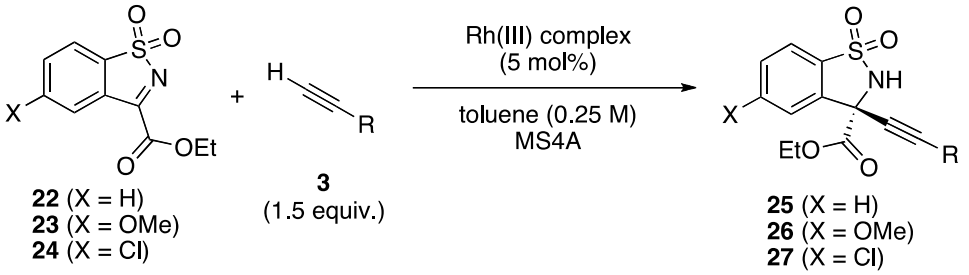
Entry	**3**	R	Rh(III) Complex	**20**	Time (h)	Yield (%)[a]	Ee (%)[b]
1	**3a**	Ph	**1f**	**20a**	24	17[c]	9
2	**3a**	Ph	**1i**	**20a**	24	8[c]	87
3	**3a**	Ph	**21a**	**20a**	24	>95[c]	89
4	**3a**	Ph	**21n**	**20a**	18	96	88
5	**3b**	4-Me-C_6H_4-	**21n**	**20b**	18	91	88
6	**3e**	4-MeO-C_6H_4-	**21n**	**20e**	18	99	87
7	**3h**	4-CF_3-C_6H_4-	**21n**	**20h**	18	97	88
8	**3d**	2-Me-C_6H_4-	**21n**	**20d**	18	97	93
9[d]	**3l**	cyclopropyl	**21n**	**20l**	18	86	80

[a]Yield of isolated product. [b]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** were used.



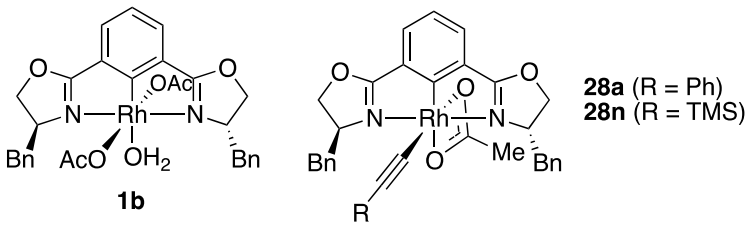
We then applied the reaction conditions to cyclic *N*-sulfonyl α-ketiminoesters, which provide α-tetrasubstituted chiral sultam derivatives (Table 9).[29] With unsubstituted electrophile **22** (X= H), we first screened a series of (diacetato)Rh(III) complexes **1** and found that benzyl-substituted (diacetato)Rh(III) complex **1b** afforded product **25a** with high enantioselectivity (entry 2). The use of (phenylethynyl)Rh(III) complex **28a** improved the reactivity (entry 3), and the yield was further improved by increasing the temperature to 70 °C, while the enantioselectivity was maintained at an acceptable level (entry 4). Finally, (trimethylsilylethynyl)Rh(III) complex **28n** had comparable reactivity as expected (entry 5), and under the optimized reaction conditions the products were obtained in high yield and with high enantioselectivity (entries 6–13).

Table 9. Direct Catalytic Enantioselective Alkynylation of Cyclic *N*-Sulfonyl α-Ketiminoesters



Entry	X	R	Rh(III)	Temp	Time (h)	Product	Yield (%)[a]	Ee (%)[b]
1	H	Ph	**1f**	rt	45	**25a**	10[c]	12
2	H	Ph	**1b**	rt	45	**25a**	14[c]	90
3	H	Ph	**28a**	rt	45	**25a**	49[c]	91
4	H	Ph	**28a**	70 °C	48	**25a**	93	86
5	H	Ph	**28n**	70 °C	48	**25a**	98	85
6	OMe	Ph	**28n**	70 °C	48	**26a**	92	86
7	Cl	Ph	**28n**	70 °C	48	**27a**	90	87
8	H	4-Me-C_6H_4-	**28n**	70 °C	48	**25b**	89	86
9	H	4-MeO-C_6H_4-	**28n**	70 °C	48	**25e**	92	87
10	H	4-CF_3-C_6H_4-	**28n**	70 °C	48	**25h**	90	78
11	H	2-Me-C_6H_4-	**28n**	70 °C	48	**25d**	98	82
12	H	$PhCH_2CH_2$-	**28n**	70 °C	48	**25i**	94	82
13	H	cyclopropyl	**28n**	70 °C	48	**25l**	98	84

[a]Yield of isolated product. [b]Determined by HPLC analysis with chiral stationary phase. [c]Determined by ^{1}H NMR analysis of the crude mixture.



6. CONCLUSION

In summary, we developed a direct enantioselective alkynylation reaction of α-ketoesters and α-ketiminoesters catalyzed by (phebox)rhodium(III) complexes. Enantioenriched propargyl alcohols and propargylamines with a tetrasubstituted stereogenic center at the propargylic position were obtained in high yield and with high enantioselectivity with both aryl- and alkyl-substituted alkynes under proton transfer conditions. The catalytic system was compatible with a wide range of functional groups, including electrophilic formyl groups, and allowed for the development of an efficient method to access

enantioenriched α-CF_3-substituted thalidomide analogs. We also successfully elucidated the reaction mechanism and expanded the substrate scope. Mechanistic studies revealed that generation of the (alkynyl)(phebox)Rh(III) complex from the (diacetato)(phebox)Rh(III) complex determined the overall reaction rate in the initial stages of the reaction. These results, along with the observed facile exchange of the alkynyl ligand on the (alkynyl)(phebox)Rh(III) complexes, led us to use (trimethylsilylethynyl)(phebox)Rh(III) complexes that react with both aryl- and alkyl-substituted alkynes to give the corresponding (alkynyl)(phebox)Rh(III) complexes. The new catalytic system with (trimethylsilylethynyl)(phebox)Rh(III) precatalysts exhibited enhanced catalytic performance, reduced catalyst loading to as low as 0.5 mol%, and expanded the substrate scope of the reaction with α-ketiminophosphonate and cyclic *N*-sulfonyl α-ketiminoesters.

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Kazuhiro Morisaki was born in 1989 in Nagasaki, Japan. He received his bachelor's degree in 2012 from Kyushu University under the supervision of Professor Takashi Ohshima and is now pursuing his Ph.D. degree in the same research group. He received Kyushu University Student Award (2014) and is a recipient of JSPS Research Fellowship for Young Scientists (2014-2016). His research interests include development of highly atom-economical and environmentally benign catalytic processes.

Hiroyuki Morimoto was born in 1981 in Hiroshima, Japan. He received his bachelor's degree in 2004, and Ph.D. degree in 2009 from The University of Tokyo under the supervision of Professor Masakatsu Shibasaki. After a postdoctoral fellow in the University of Illinois at Urbana-Champaign with Professor John F. Hartwig (2009-2010), he returned to Japan and joined Professor Ohshima's group in Kyushu University as an assistant professor. He has received Inoue Research Award for Young Scientists (2012) and Takasago International Corporation Award in Synthetic Organic Chemistry, Japan (2012). His research interests include development of atom-economical and environmentally benign catalytic reactions.

Kazushi Mashima was born in 1957 in Niigata, Japan. In 1983, he became an Assistant Professor at the Institute for Molecular Science, Okazaki National Institutes before receiving his PhD degree from Osaka University in 1985. After working as an Assistant Professor at the Faculty of Engineering, Kyoto University and the Faculty of Science, Osaka University, he was promoted to Associate Professor at the Faculty (now Graduate School) of Engineering Science, Osaka University in 1994, and then to full Professor at the Graduate School of Engineering Science, Osaka University in 2003. He worked with Professor M. A. Bennett as a post-doctoral fellow at the Australian National University in 1992 and Professor W. A. Herrmann as an Alexander von Humboldt fellow at the Technisch Universität München in 1993. He received the Progress Award in Synthetic Organic Chemistry, Japan, in 1994; the BCSJ Award (the best paper award of Bull. Chem. Soc. Jpn.) in 2000; The Chemical Society of Japan Award for Creative Work for 2008; The 9th Green and Sustainable Chemistry Award by the Ministry of Education, Culture, Sports, Science, and Technology in 2010; and The Award of the Society of Polymer Science, Japan in 2010. He is a head of the program of Grant-in-Aid for Scientific Research on Innovative Areas (2015-2019), MEXT, Japan, "Precise Formation of a Catalyst Having a Specified Filed for Use in Extremely Difficult Substrate Conversion Reactions". His current research interests include organometallic chemistry for metal-catalyzed organic transformations, including direct amination of alcoholic substrates.

Takashi Ohshima was born in 1968 in Ehime, Japan. He received his bachelor's degree from The University of Tokyo in 1991 under the direction of Professor Masaji Ohno and received his PhD. degree from The University of Tokyo in 1996 under the direction of Professor Masakatsu Shibasaki. On the following year, he joined Otsuka Pharmaceutical Co., Ltd. After two years as a postdoctoral fellow at The Scripps Research Institute with Professor K. C. Nicolaou (1997-1999), he returned to Japan as an assistant professor in The University of Tokyo. He was appointed as Associate Professor of Osaka University in 2005. In 2010, he was promoted to a full professor of Kyushu University. He has received the Fujisawa Award in Synthetic Organic Chemistry (2001), The Pharmaceutical Society of Japan Award for Young Scientists (2004), The Japanese Society for Process Chemistry Award for Excellence (2008, 2014, and 2016), Green Sustainable Chemistry Award with MEXT Award (2010), Asian Core Program Lectureship Award (2012 from China, 2013 from Korea, 2015 from Singapore), and The Pharmaceutical Society of Japan Award for Divisional Scientific Promotions (2014). His research interests include development of new catalysis, natural product synthesis, green and sustainable chemistry, and medicinal chemistry.