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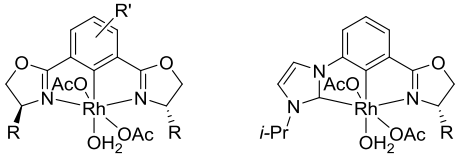
Enantioselective Direct Alkynylation of Ketones Catalyzed by Chiral CCN Pincer Rh(III) Complexes

Jun-ichi Ito,* Shino Ubukata, Shun Muraoka, Hisao Nishiyama*

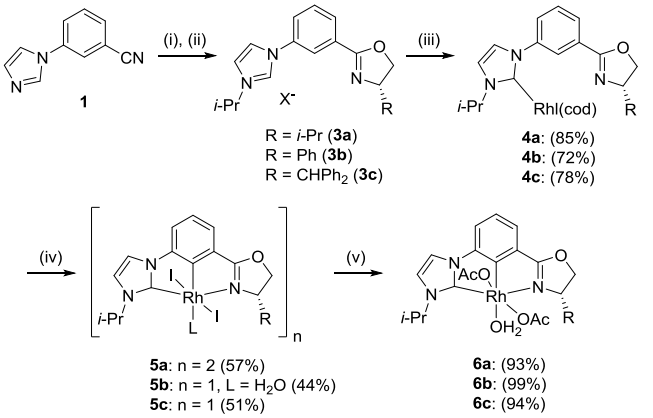
Abstract: This report describes enantioselective direct asymmetric alkynylation of ketones with new chiral CCN Rh catalysts containing N-heterocyclic carbene and oxazoline hybrid ligands. The catalytic reaction of fluoroalkyl-substituted ketones, $ArCOCF_2X$ (X = F, Cl, H), with aromatic and aliphatic alkynes yielded the corresponding chiral propargyl alcohols with high enantioselectivity. Control and kinetic experiments suggested a bis(alkynyl) Rh intermediate as the active species for the C-C bond-forming step.

Chiral propargyl alcohols are an important class of organic moiety found in natural compounds and pharmaceutical products, and are used as building blocks in organic synthesis.[1,2] Enantioselective alkynylation of ketones is one of the most efficient methods for the synthesis of chiral propargylic alcohol derivatives containing a tetra-substituted chiral carbon center. In general, metal alkynyl compounds generated in situ by terminal alkynes with stoichiometric amounts of alkyl lithium and alkyl zinc reagents have been used as nucleophiles for ketones.[3,4] Although this method is reliable and highly enantioselective for a wide range of ketones, they require excess organometallic reagents for activation of the alkyne. In terms of atom economy, direct activation of alkynes by a metal catalyst is a desirable methodology. Thus, this type of direct alkynylation of ketones has been studied extensively using both achiral and chiral catalysts based on Cu, Ag, Rh and Zn.[5,6] Few highly effective and enantioselective direct alkynylations of ketones had been reported until recently, when Wolf and co-workers described the alkynylation of a trifluoroacetopheone derivative with ynamides catalyzed by chiral Cu/amino alcohol catalysts,[7] and Liu and co-workers demonstrated alkynylation of isatin derivatives catalyzed by chiral Cu/guanidine catalysts.[8]



phebox-Rh (**I**) this work

The NCN pincer Rh(III) acetate complexes, phebox-Rh (I), have emerged as highly efficient catalysts for direct alkynylation of trifluoropyruvate and ketamine derivatives as documented by Ohshima, Mashima and co-workers.[9] Despite the many pincer catalysts available,[10] their application to other ketones is limited.[11] Given the importance of enantioselective C-C bond formation in organic synthesis, further development of new chiral catalysts is important. Since *N*-heterocyclic carbene (NHC) ligands have been widely utilized as electron-donating ancillary ligands in transition metal catalysts,[12] a chiral NHC pincer scaffold with a Rh(III) atom was expected to produce a suitable reaction field for activation of both alkynes and ketones. Thus, new CCN pincer Rh complexes were designed based on chiral oxazoline-NHC hybrid ligands. This report describes the preparation of chiral CCN pincer Rh complexes and their application to asymmetric alkynylation of activated ketones containing CF_3, CF_2Cl, and CF_2H groups.



Scheme 1. Preparation of ligand precursors and CCN Rh complexes: (i) amino alcohol, $Zn(TFA)_2$, PhCl, 130 °C; (ii) *i*-PrI, 60 °C; (iii) $[Rh(OH)(cod)]_2$, THF; (iv) NIS, 1,4-dioxane, 80 °C; (v) AgOAc, CH_2Cl_2.

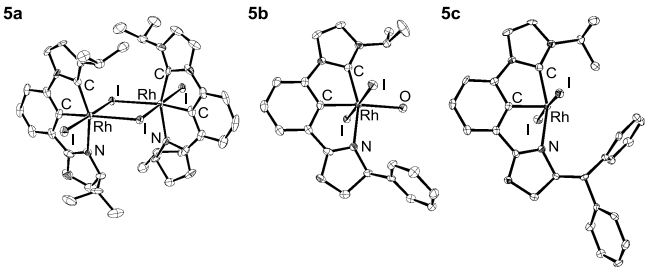


Figure 1. ORTEP diagrams of **5a–c** with 50% probability.

Preparation of ligand precursors and CCN Rh complexes are summarized in Scheme 1. The CCN ligand precursors **3a-c** were synthesized from **1**[13] by successive Zn-catalyzed oxazoline formation and *N*-alkylation of the imidazole moiety. Metalation of **3** with $[Rh(cod)(OH)]_2$ yielded NHC-Rh(I) complexes **4**. Further cyclometalation of **4** was conducted using C-H bond activation via electrophilic activation by Rh(III) species. Subsequently, *N*-iodosuccinimide (NIS) was shown to be a

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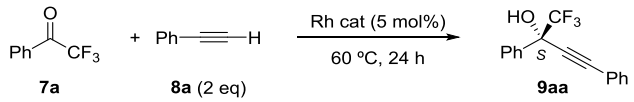
suitable oxidant for promoting cyclometalation of **4**, giving the desired CCN pincer complexes **5**. This is a new method for the preparation of pincer complexes containing NHC ligand framework. X-ray analysis revealed that **5a** possessed dimeric and pseudo-octahedral geometry, and that **5b** and **5c** had monomeric structures with pseudo-octahedral geometry and pseudo square pyramidal geometry, respectively (Figure 1).[14] Finally, the acetate complexes **6a**-**c** were prepared by treatment of **5** with AgOAc.

Table 1. Asymmetric alkynylation of trifluoroacetophenone with phenylacetylene.[a]



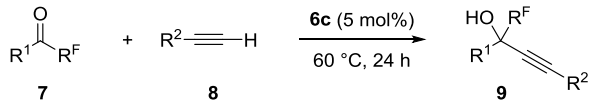
7a **8a** (2 eq) **9aa**

Entry	Catalyst	Solvent	Yield (%)	Ee (%)[b]
1	**6a**	Toluene[c]	66	86
2	**6a**	THF[c]	64	84
3	**6a**	neat	71	87
4	**6b**	neat	53	86
5	**6c**	neat	75	88
6[d]	**I-*i*pr**	neat	13	29

[a] Reaction conditions: **7a** (0.4 mmol), **8a** (1.0 mmol), Rh cat. (5 mol%), 60 °C, 24 h. [b] Determined by HPLC. [c] 2 M solution of **7a**. [d] [(*S*,*S*)-phebox-*i*-Pr]Rh(OAc)$_2$(OH$_2$) (**I-*ip***) was used.

The catalytic activity of **6a**-**c** for direct asymmetric alkynylation of trifluoroacetophenone (**7a**) with phenylacetylene (**8a**) was examined (Table 1). Reaction of **6a** in toluene at 60 °C gave the corresponding alcohol **9aa** in 64% yield with 86% ee (entry 1). Use of THF gave a similar result (entry 2). An improvement in yield was observed under neat conditions without any change in enantioselectivity (entry 3). While use of **6b** reduced the yield, **6c** increased the yield with similar enantioselectivity. The catalytic activity of the phebox-Rh complex was also investigated. However, the phebox-Rh complex **I-*ip***[15] resulted in lower yield and enantioselectivity, indicating that the NHC-oxazoline ligand system had advantages for the direct alkynylation of **7a**.

Table 1. Asymmetric alkynylation of ketones with alkynes.[a]



7 **8** **9**

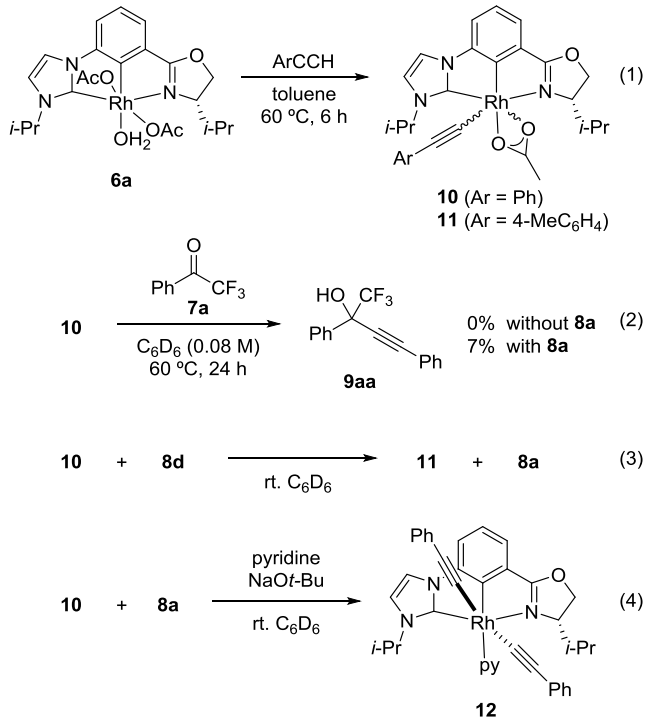
Entry	Ketone (R^1, R^F)	Alkyne (R^2)	Yield (%)	Ee (%)[b]
1	Ph, CF_3 (**7a**)	4-BrC_6H_4 (**8b**)	70	85
2[c]	Ph, CF_3 (**7a**)	4-ClC_6H_4 (**8c**)	66	87
3	Ph, CF_3 (**7a**)	4-MeC_6H_4 (**8d**)	78	91
4	Ph, CF_3 (**7a**)	4-$MeOC_6H_4$ (**8e**)	76	91
5	Ph, CF_3 (**7a**)	2-ClC_6H_4 (**8f**)	35	78
6	Ph, CF_3 (**7a**)	9-phenathrene (**8g**)	85	91
7	Ph, CF_3 (**7a**)	cyclohexyl (**8h**)	75	90
8	Ph, CF_3 (**7a**)	cyclopropyl (**8i**)	78	93
9	Ph, CF_3 (**7a**)	4-chlorobutyl (**8j**)	52	88
10	Ph, CF_3 (**7a**)	1-cyclohexenyl (**8k**)	66	88
11	4-BrC_6H_4, CF_3 (**7b**)	Ph (**8a**)	80	90
12	4-ClC_6H_4, CF_3 (**7c**)	Ph (**8a**)	78	88
13	4-MeC_6H_4, CF_3 (**7d**)	Ph (**8a**)	63	87
14	4-$MeOC_6H_4$, CF_3 (**7e**)	Ph (**8a**)	47	83
15	3-BrC_6H_4, CF_3 (**7f**)	Ph (**8a**)	80	79
16	2-thionyl, CF_3 (**7g**)	Ph (**8a**)	41	85
17	Ph, CF_2Cl (**7h**)	Ph (**8a**)	63	88
18	Ph, CF_2Cl (**7h**)	cyclohexyl (**8h**)	70	88
19	Ph, CF_2H (**7i**)	Ph (**8a**)	77	79
20	Ph, CF_2H (**7i**)	cyclohexyl (**8h**)	79	82

[a] Reaction conditions: **7** (0.4 mmol), **8** (0.8 mmol), **6c** (5 mol%), 60 °C, 24 h. [b] Determined by HPLC. [c] Reaction was performed in 8 M toluene solution.

Further application to other substrates was examined using **6c**. Aromatic alkynes **8b**-**e** yielded the corresponding propargyl alcohols **9** with high enantioselectivity (entries 1-4). A bulky alkyne **8g** produced a high yield and enantioselectivity, while o-chlorophenyl acetylene **8f** decreased both yield and ee (entries 5 and 6). Aliphatic alkynes **8h**-**j** and an enyne **8k** were employed as substrates to give products with high enantioselectivity (entries 7-10). Reaction of **8a** with ketones **7b**-**f** containing phenyl derivatives provided the desired products in 47-80% yield with good to high enantioselectivity (entries 11-15). The heteroaromatic compound **7g** also was used as a substrate (entry 16). In addition, ketone **7h** containing a CF_2Cl group showed enantioselectivity similar to that of **7a** (entries 17 and 18). The CF_2H-group-substituted ketone **7i** also afforded products with good enantioselectivity (entries 19 and 20).

To gain insight into the reaction mechanism, stoichiometric reactions of the Rh complexes were examined. Previous studies showed that reaction of the Rh(III) acetate complex with a terminal alkyne gave the corresponding alkynyl complex.[9,16] Such an alkynyl complex was proposed to be an active intermediate in the alkynylation reaction. Similarly, in the present study, reaction of **6a** with **8a** gave alkynyl complex **10** in 65% yield as coordination isomers of alkynyl and acetate ligands (Scheme 2, Eq. (1)).

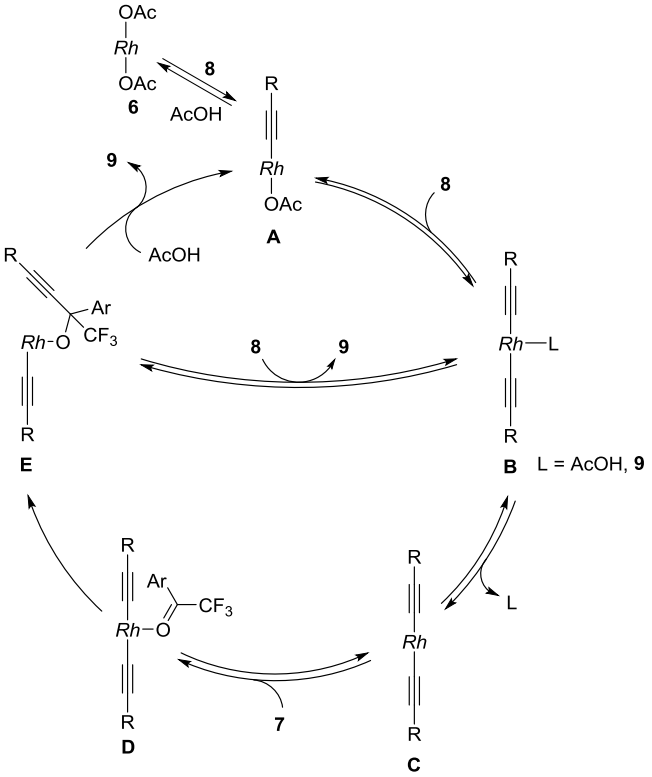
After obtaining alkynyl complex **10**, the stoichiometric reaction of **10** with 5 equiv. of **7a** was monitored in C_6D_6. However, no reaction was observed, even at 60 °C for 24 h (Scheme 2, Eq. (2)). In contrast, the corresponding reaction in the presence of 1 equiv. of **8a** resulted in the formation of **9aa** in 7% yield, as determined by ^{19}F NMR.



Scheme 2. Control experiments.

Due to the low reactivity of **10** toward **7a**, the reactivity of **10** toward another alkyne was examined. In contrast to the above, reaction of **10** with **8d** proceeded rapidly to give **11** accompanied by **8a** via alkyne exchange (Scheme 2, Eq. (3)). If this exchange reaction involved a second C-H activation of **10**,[17,18] formation of a bis(alkynyl) intermediate was expected to occur via deprotonation of an alkyne by an acetate ligand.[19] However, this intermediate could not be detected in the mixture of **10** and **8a**. For the purpose of trapping a bis(alkynyl) complex, the reaction was conducted in the presence of a base. As a result, a bis(alkynyl) complex **12** was detected upon addition of pyridine to the mixture of **8a** and **10** (Scheme 2, Eq. (4)). Further addition of NaO*t*Bu resulted in quantitative formation of **12**. The reaction of **12** with 5 equiv. of **7a** in C_6D_6 at 60 °C for 24 h gave only a trace amount of **9aa** (1%) due to the strong coordination of pyridine. However, we assume that the formation of **12** is indirect evidence for a bis(alkynyl) intermediate in the catalytic reaction. One equiv. of AcOH inhibited the catalytic reaction of **7a** and **8a** with **10**, indicating that formation of a bis(alkynyl) intermediate was hampered by AcOH. The catalytic reaction was also inhibited by the presence of the product **9aa**. In contrast, the reaction was accelerated in higher concentration of **8a**.

These catalytic reactions were also investigated using kinetic experiments of reaction of **7a** with **8a** using **10**, conducted with excess amounts of **7a** (8–20 equiv.) to render the reaction pseudo-first order (see Supporting Information). The results revealed that the decrease in the concentration of **8a** followed a pseudo-first order rate law that was independent of the **7a** concentration. Thus, the rate order in **7a** was approximately zero. In addition, the value of k_H/k_D was calculated to be 1.0 by independent experiments using **8a** and PhCCD (**8a-d**).



Scheme 3. Proposed mechanism.

The reaction mechanism shown in Scheme 3 was proposed based on control and kinetic experiments. Reaction of **6** with an alkyne produced mono(alkynyl) intermediate **A**. Successive second C-H activation of an alkyne by **A** gave bis(alkynyl) intermediate **B**. The alkyne exchange reaction of **10** implied interconversion between **A** and **B**. The value of k_H/k_D also supported an equilibrium between **A** and **B**.[20] At this point, the position of the equilibrium was shifted to **A** under the catalytic condition. Following ligand substitution of **B** with a ketone **7** gave **D.** Since **B** was an 18-electron complex, this step could proceed via a coordinatively-unsaturated intermediate **C** in a dissociation mechanism. We assumed that the formation of **C** was a rate-determining step. The insertion of a ketone into the Rh-alkynyl bond yielded intermediate **E**. Based on formation of the *S*-enantiomer, the *si*-face of **7a** was attacked by the alkynyl group in this step. Finally, protonation of **E** with AcOH or **8** yielded product **9** accompanied by **A** or **B**. During direct alkynylation of trifluoropyruvate derivatives catalyzed by phebox-Rh complex, a mono(alkynyl) complex was proposed as the active intermediate.[9] In contrast, for fluorinated acetophenone derivatives, formation of the bis(alkynyl) intermediate was required to enhance the reactivity of the metal alkynyl fragment.

In conclusion, new CCN pincer Rh complexes were synthesized via C-H bond activation. The CCN complex functioned as an efficient catalyst for asymmetric direct alkynylation of trifluoroketone derivatives with good enantioselectivity. A bis(alkynyl) intermediate was proposed as

the active species in the C-C bond forming step from the results of kinetic and control experiments.

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Keywords: asymmetric synthesis • alkynylation • ketone • rhodium • pincer ligand

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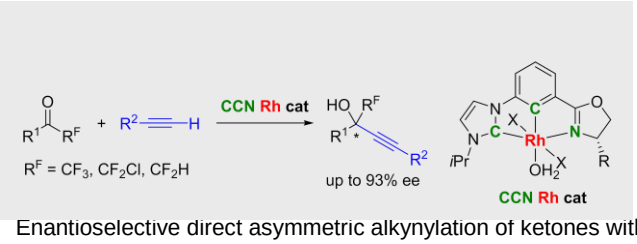

Enantioselective direct asymmetric alkynylation of ketones with new chiral CCN Rh catalysts containing N-heterocyclic carbene and oxazoline hybrid ligands was described. The catalytic reaction of fluoroalkyl-substituted ketones, $ArCOCF_2X$ (X = F, Cl, H), with aromatic and aliphatic alkynes yielded the corresponding chiral propargyl alcohols with high enantioselectivity.

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