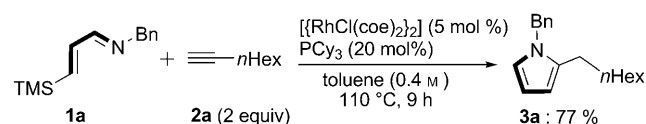


Rhodium(I)-Catalyzed [4+1] Cycloaddition Reactions of α,β -Unsaturated Imines with Terminal Alkynes for the Preparation of Pyrrole Derivatives**

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Vinylidene complexes have attracted much attention for being unique reactive intermediate and synthetically useful, and characteristic reactions have been developed using various kinds of transition-metal complexes.^[1] One of the main reactions involves the addition of heteroatom nucleophiles such as alcohols, carboxylates, and carbamates to give anti-Markovnikov addition products.^[1] However, the addition of the heteroatom of C=X bonds to the vinylidene carbon atom has rarely been achieved in spite of the high synthetic potential of the zwitterionic intermediates that are produced.^[2] Herein, we report a rhodium(I)-catalyzed [4+1] cycloaddition reaction between α,β -unsaturated imines and terminal alkynes for the preparation of synthetically useful, substituted pyrrole derivatives through the addition of the imine nitrogen atom to rhodium vinylidene intermediates.^[3]

When a mixture of β -TMS-substituted α,β -unsaturated imine **1a** and 1-octyne (**2a**) was treated with a catalytic amount of $[\text{RhCl}(\text{coe})_2]_2$ and PCy_3 in toluene at 110 °C for nine hours, pyrrole **3a** (a formal [4+1] cycloaddition product)^[4] was obtained in good yield (Scheme 1). In this reaction $[\text{RhCl}(\text{coe})_2]_2$, as well as other phosphine ligands such as PPh_3 , $\text{P}(i\text{Pr})_3$, 1,4-bis(diphenylphosphanyl)butane (dppb), and 1,1'-bis(diphenylphosphanyl)ferrocene (dppf) showed almost no activity. Also, $[\text{RhOH}(\text{cod})]_2$ (cod = 1,5-cyclooctadiene), $[\text{Rh}(\text{cod})_2]\text{BF}_4$, and $[\text{IrCl}(\text{coe})_2]_2$ in the presence of PCy_3 did not show any activity either. Meanwhile, $[\text{RhCl}(\text{coe})_2]_2/\text{PCy}_3$



Scheme 1. Rhodium(I)-catalyzed [4+1] cycloaddition reaction between α,β -unsaturated imine **1a** and terminal alkyne **2a**. Bn = benzyl, coe = cyclooctene, Cy = cyclohexyl, TMS = trimethylsilyl.

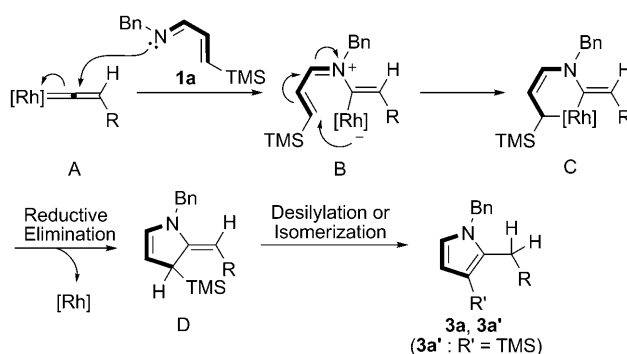
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showed somewhat lower activity compared to $[\text{RhCl}(\text{coe})_2]_2/\text{PCy}_3$.

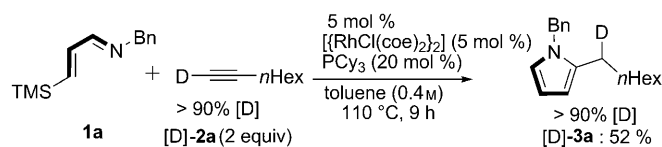
The reaction is thought to proceed by the nucleophilic addition of the nitrogen atom of the imine **1a** to the carbene carbon atom of the rhodium vinylidene complex **A**,^[5] which is generated in situ from the terminal alkyne, to afford a zwitterionic intermediate **B** (Scheme 2). This intermediate



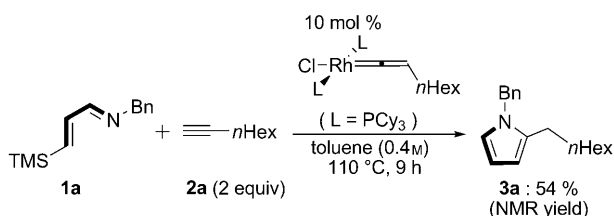
Scheme 2. Proposed reaction mechanism.

further undergoes intramolecular cyclization to generate metalacyclic intermediate **C**. Finally, reductive elimination proceeds to give the pyrrole **3a** via enamine **D** through olefin isomerization and desilylation^[6] with regeneration of the catalyst. The reaction of imine **1a** with 1-deuterio-1-octyne ($[\text{D}_1]$ -**2a**) gave pyrrole $[\text{D}_1]$ -**3a** wherein deuterium (90% incorporation) was introduced onto the carbon atom adjacent to the pyrrole ring (Scheme 3). Furthermore, the isolated vinylidene complex $[\text{RhCl}(\text{C}=\text{C}(\text{H})n\text{Hex})(\text{PCy}_3)_2]$ ^[7] also catalyzed the reaction under similar reaction conditions (Scheme 4). These results are consistent with the proposed mechanism shown in Scheme 2. Thus, by utilizing the rhodium vinylidene complex, a novel [4+1] cycloaddition was realized where the α,β -unsaturated imine and terminal alkyne carbon atom constitute the pyrrole ring through a zwitterionic intermediate.

Recently, Colby, Bergman, and Ellman reported an apparently similar combination of reactants and reagents to



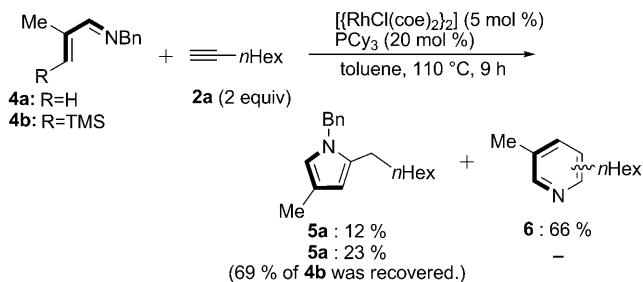
Scheme 3. [4+1] Cycloaddition reaction using 1-deuterio-1-octyne ($[\text{D}_1]$ -**2a**).



Scheme 4. [4+1] Cycloaddition reaction using the isolated rhodium vinylidene complex.

give dihydropyridines instead of pyrroles.^[8] In their reaction, C–H bond activation took place at the β position to the imine moiety, and subsequent alkyne insertion gave 1,3,5-azatrienes, which underwent thermal electrocyclization and gave dihydropyridines.^[8]

To evaluate the importance of the TMS group, a comparison of the reactions using β -nonsubstituted derivative **4a** and β -silyl-substituted α,β -unsaturated imine **4b** was carried out. When nonsubstituted imine **4a** was treated with $[\{\text{RhCl}(\text{coe})_2\}_2]$ and PCy_3 in toluene at 110 °C, the corresponding pyrrole **5a** was obtained in only 12% yield and pyridines **6** were obtained as the major products (Scheme 5). In contrast,



Scheme 5. [4+1] or [4+2] Cycloaddition reaction of imine **4a** and **4b**.

imine **4b**, which has a TMS group at the β position, gave pyrrole **5a** as the only isolable product, albeit in low yield. The TMS group is assumed to inhibit the C–H activation reaction at the β position to the imine moiety.^[9,10]

The reaction of imine **1a** with several terminal alkyne derivatives was examined under the optimized reaction conditions (Table 1). The reaction proceeded smoothly with alkynes possessing a functional group such as silyl ether or methoxycarbonyl group to give 2-substituted pyrroles in good yield (Table 1, entries 2 and 3). Notably, alkynes with a more sensitive functional group such as nitrile, chloro, or amino groups also reacted with **1a** to give the corresponding functionalized pyrroles in good yield (Table 1, entries 4–6).^[6]

Next, we carried out the reaction using several imine derivatives which have a Me substituent on the nitrogen atom instead of a Bn group:^[11] to do this we employed 1-octyne as the alkyne counterpart (Table 2). In these cases, the yield of pyrrole derivatives was somewhat improved by carrying out the reaction in the presence of three equivalents each of NBU_3 and H_2O to suppress side reactions. Imine **7a**, which is derived from phenyl ketone, gave pyrrole **8a** in good yield (Table 2, entry 1). Ketimines **7b–7e** with alkenyl, alkynyl, or heteroaryl substituents were also employed and gave the corresponding 2,5-disubstituted pyrroles in reasonable yield (Table 2,

Table 1: [4+1] Cycloaddition reactions of imine **1a** with several alkynes.

Entry	2	Alkyne	Yield of 3 [%] ^[a]
1	2b	cHex-C≡CH	56 (3b)
2	2c	TBSO-CH ₂ -C≡CH	71 ^[b] (3c)
3	2d	MeO ₂ C-CH ₂ -C≡CH	73 ^[c] (3d)
4	2e	NC-CH ₂ -C≡CH	70 (3e)
5	2f	Cl-CH ₂ -C≡CH	75 (3f)
6	2g	4-(2-(dimethylamino)ethoxy)-1-butyne	66 ^[d] (3g)

[a] Yield of isolated product. [b] 15% of **1a** was recovered. [c] 13% of **1a** was recovered. [d] 24% yield of **3g** and 42% yield of its 3-TMS derivative were obtained. TBS = *tert*-butyldimethylsilyl.

entries 2–5).^[12] Furthermore, even trisubstituted pyrrole **8f** could be obtained by using ketimine **7f** (Table 2, entry 6). The preparation of substituted pyrroles is important because of their high utility as medicinal agents^[13] and functional materials^[14] etc., and this approach would be a concise method for the preparation of such pyrroles in a catalytic manner.^[15]

In summary, we have developed a novel rhodium(I)-catalyzed intermolecular [4+1] cycloaddition reaction of α,β -unsaturated imines with terminal alkynes by utilizing the addition of the imine nitrogen atom to the rhodium vinylidene complex. This reaction demonstrates another utility of the rhodium vinylidene complex as a reactive species. Also, the reaction could be a useful method for the preparation of substituted pyrroles with high tolerance of functional groups. Efforts are currently underway to expand the scope of this reaction and to clarify the mechanism more explicitly.

Table 2: [4+1] Cycloaddition reactions of several imines with 1-octyne.

Reaction scheme showing the synthesis of pyrrole **8** from ketimine **7** and alkyne **2a** (2 equiv). Conditions: $[\text{RhCl}(\text{coe})_2]_2$ (5 mol %), PCy_3 (20 mol %), H_2O (300 mol %), NBU_3 (300 mol %), toluene (0.4 M), 110°C , 9–24 h.

Entry	7 (E/Z)	R ¹	R ²	Yield of 8 [%] ^[a]
1	7a (1:3)	Ph	H	72 (8a)
2 ^[b]	7b ^[e]	C=C(Me) ₂	H	64 (8b)
3	7c ^[f]	propynyl	H	50 (8c)
4 ^[b]	7d (1:1)	2-furyl	H	53 (8d)
5 ^[b]	7e (1:4)	2-thienyl	H	62 (8e)
6 ^[c,d]	7f (1:2.5)	Ph	Me	56 (8f)

[a] Yield of isolated product. [b] 3 equivalents of 1-octyne were used. [c] The reaction was carried out without NBU_3 at 1.0 M. [d] 17% of imine **7f** was recovered. [e] Geometry of imine **7b** was mostly *E*. [f] Geometry of imine **7c** could not be determined (but was mostly one isomer).

Experimental Section

General procedure: A degassed solution of α,β -unsaturated imine (0.2 mmol) and terminal alkyne (0.40 mmol) in toluene (0.5 mL,

0.4 M) was added to $[\text{RhCl}(\text{coe})_2]_2$ (0.01 mmol, 10 mol % at Rh atom) and PCy_3 (0.04 mmol, 20 mol %). The reaction mixture was kept in a closed system and was stirred for 9–24 h at 110 °C before the solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography on silica gel to give the corresponding pyrrole derivative.

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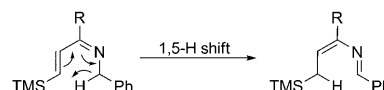
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- [10] Other silyl substituents at the β position gave the following results. PhMe_2Si : 65 % (recovery 5 %); TBS: 15 % (recovery 58 %). Bulkier silyl group retarded the reaction.
- [11] When ketimines with a benzyl group on the nitrogen atom were used as substrates, corresponding pyrroles were obtained in low yield because of the competitive 1,5-hydride shift.



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