Cycloaddition Reactions

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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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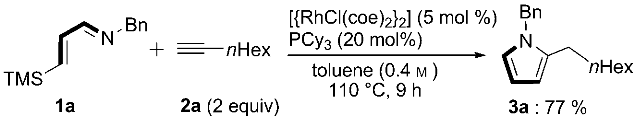
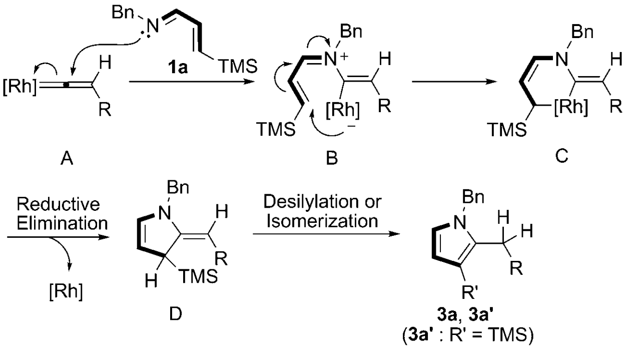
Vinylidene complexes have attracted much attention for being unique reactive intermediate and synthetically useful, and characteristic reactions have been developed using various kinds of transition-metal complexes.[1] One of the main reactions involves the addition of heteroatom nucleophiles such as 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 [{RhCl(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 [{RhCl(coe)$_2$}$_2$], as well as other phosphine ligands such as PPh$_3$, P(*i*Pr)$_3$, 1,4-bis(diphenylphosphanyl)butane (dppb), and 1,1′-bis(diphenylphosphanyl)ferrocene (dppf) showed almost no activity. Also, [{RhOH(cod)}$_2$] (cod = 1,5-cyclooctadiene), [Rh(cod)$_2$]BF$_4$, and [{IrCl(coe)$_2$}$_2$] in the presence of PCy$_3$ did not show any activity either. Meanwhile, [{RhCl(cod)$_2$}$_2$]/PCy$_3$ showed somewhat lower activity compared to [{RhCl(coe)$_2$}$_2$]/PCy$_3$.



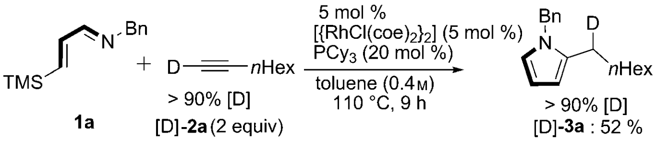
Scheme 1. Rhodium(I)-catalyzed [4+1] cycloaddition reaction between α,β-unsaturated imine **1a** and terminal alkyne **2a**. Bn = benzyl, coe = cyclooctene, Cy = cyclohexyl, TMS = trimethylsilyl.

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 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 ([D$_1$]-**2a**) gave pyrrole [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 [RhCl(=C=C(H)*n*Hex)(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.



Scheme 2. Proposed reaction mechanism.

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 ([D$_1$]-**2a**).

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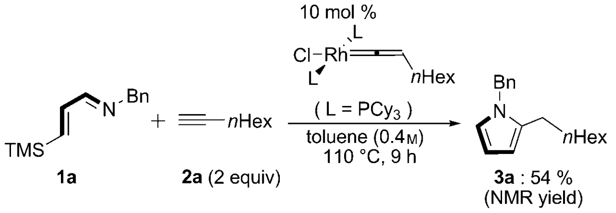
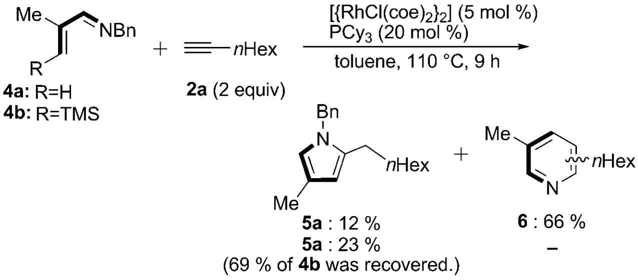


Scheme 4. [4+1] Cycloaddition reaction using the isolated rhodium vinylidene complex.

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]

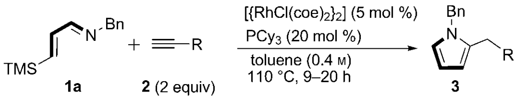
To evaluate the importance of the TMS group, a comparison of the reactions using β-nonsubstituted derivative **4a** and β-silyl-substituted α,β-unsaturated imine **4b** was carried out. When nonsubstituted imine **4a** was treated with $[\{RhCl(coe)_2\}_2]$ and PCy_3 in toluene at 110°C, the corresponding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

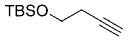
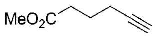
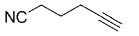
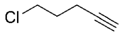
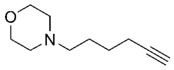


Scheme 5. [4+1] or [4+2] Cycloaddition reaction of imine **4a** and **4b**.

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-subustituted 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]

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



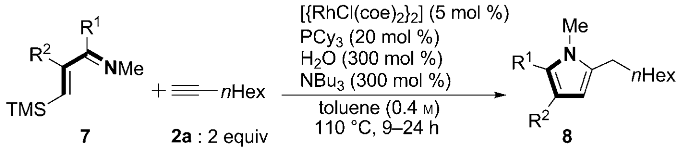
Entry	2	Alkyne	Yield of 3 [%][a]
1	**2b**	cHex—≡	56 (**3b**)
2	**2c**		71[b] (**3c**)
3	**2d**		73[c] (**3d**)
4	**2e**		70 (**3e**)
5	**2f**		75 (**3f**)
6	**2g**		66[d] (**3g**)

[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.

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, 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.



Entry	7 (*E*/*Z*)	R1	R2	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 [{RhCl(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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Keywords: α,β-unsaturated imines · cycloaddition · pyrroles · rhodium · terminal alkynes

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[1] For recent reviews on catalytic reactions through vinylidene complex intermediates, see: a) C. Bruneau, P. H. Dixneuf, *Metal Vinylidenes and Allenylidenes in Catalysis*, Wiley-VCH, Weinheim, **2008**; b) C. Bruneau, P. H. Dixneuf, *Acc. Chem. Res.* **1999**, *32*, 311–323; c) C. Bruneau, P. H. Dixneuf, *Angew. Chem.* **2006**, *118*, 2232–2260; *Angew. Chem. Int. Ed.* **2006**, *45*, 2176–2203; d) B. M. Trost, A. McClory, *Chem. Asian J.* **2008**, *3*, 164–194.

[2] For examples of the nucleophilic addition of the nitrogen atom of imines to the carbene carbon atom of vinylidene complexes, see: a) A. G. M. Barrett, J. Mortier, M. Sabat, M. A. Sturgess, *Organometallics* **1998**, *7*, 2553–2561; b) H. Fischer, F. Kirchbauer, A. Früh, M. M. Abd-Elzaher, G. Roth, C. C. Karl, M. Dede, *J. Organomet. Chem.* **2001**, *620*, 165–173; c) M. M. Abd-Elzaher, T. Froneck, G. Roth, V. Gvozdev, H. Fischer, *J. Organomet. Chem.* **2000**, *599*, 288–297; d) M. M. Abd-Elzaher, H. Fischer, *J. Organomet. Chem.* **1999**, *588*, 235–241, and references therein.

[3] For representative recent examples of rhodium(I)-catalyzed reactions involving rhodium vinylidene species, see: a) Y. Fukumoto, H. Asai, M. Shimizu, N. Chatani, *J. Am. Chem. Soc.* **2007**, *129*, 13792–13793; b) B. M. Trost, A. McClory, *Angew. Chem.* **2007**, *119*, 2120–2123; *Angew. Chem. Int. Ed.* **2007**, *46*, 2074–2077; c) Y. Chen, C. Lee, *J. Am. Chem. Soc.* **2006**, *128*, 15598–15599; d) J. M. Joo, Y. Yuan, C. Lee, *J. Am. Chem. Soc.* **2006**, *128*, 14818–14819; e) Y. Fukumoto, F. Kinashi, T. Kawahara, N. Chatani, *Org. Lett.* **2006**, *8*, 4641–4643; f) H. Kim, C. Lee, *J. Am. Chem. Soc.* **2006**, *128*, 6336–6337, and references therein.

[4] Only a few examples of [4+1] cycloaddition reactions of α,β-unsaturated imines with carbene species have been reported; a) R. Bonneau, Y. N. Romashin, M. T. H. Liu, *J. Photochem. Photobiol. A* **1999**, *126*, 31–36; b) Y. N. Romashin, M. T. H. Liu, R. Bonneau, *Chem. Commun.* **1999**, 447–448; c) Y. N. Romashin, M. T. H. Liu, W. Ma, R. A. Moss, *Tetrahedron Lett.* **1999**, *40*, 7163–7165.

[5] For an example of pyrrole synthesis utilizing the intramolecular addition of imine nitrogen atom to carbene carbon atom, see; Y. Zhang, J. W. Herndon, *Org. Lett.* **2003**, *5*, 2043–2045.

[6] In the crude products, 3-TMS derivatives were obtained in most cases and the ratio of TMS derivative to protodesilylated derivative depended on the reaction conditions and the nature of the substrate. The protodesilylation reaction of TMS-substituted pyrrole usually proceeded smoothly during purification by column chromatography on silica gel, however, 1-benzyl-2-{(5-morpholino)pentyl}-3-(trimethylsilyl) pyrrole was isolated in the reaction of morpholino derivative **2g**.

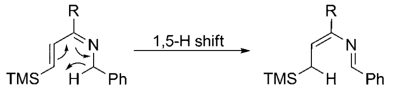
[7] The vinylidene complex was prepared according to the procedure for the preparation of similar rhodium(I) vinylidene complexes. F. J. G. Alonso, A. Höhn, J. Wolf, H. Otto, H. Werner, *Angew. Chem.* **1985**, *97*, 401–402; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 406–408, and see the Supporting Information for details.

[8] a) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2006**, *128*, 5604–5605; b) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 3645–3651; where internal alkynes were employed in most cases and only one example was reported for a terminal alkyne to give the corresponding dihydropyridine in good yield. This type of transformation was first reported by Odom and co-workers; c) C. Cao, Y. Li, Y. Shi, A. L. Odom, *Chem. Commun.* **2004**, 2002–2003.

[9] Other imines, which have methyl or phenyl group instead of a TMS group at the β position, did not give the corresponding pyrroles (or pyridines). In the case of the imine with a phenyl substituent, most of the starting material was recovered. In contrast, the imine bearing a methyl group was mostly consumed, but the reaction gave a complex mixture of unidentified products. Thus, the presence of the TMS (or silyl) group is essential for this reaction.

[10] Other silyl substituents at the β position gave the following results. PhMe$_2$Si: 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.



[12] Ketimines possessing an alkyl substituent gave very low yield, partly because they were unstable under the reaction conditions.

[13] For selected reviews, see: a) F. Bellina, R. Rossi, *Tetrahedron* **2006**, *62*, 7213–7256; b) G. Balme, *Angew. Chem.* **2004**, *116*, 6396–6399; *Angew. Chem. Int. Ed.* **2004**, *43*, 6238–6241; c) A. Fürstner, *Angew. Chem.* **2003**, *115*, 3706–3728; *Angew. Chem. Int. Ed.* **2003**, *42*, 3582–3603.

[14] a) D. Curran, J. Grimshaw, S. D. Perera, *Chem. Soc. Rev.* **1991**, *20*, 391–404; for selected examples, see: b) K. Ogawa, S. C. Rasmussen, *Macromolecules* **2006**, *39*, 1771–1778; c) A. Facchetti, A. Abbotto, L. Beverina, M. E. van der Boom, P. Dutta, G. Evmenenko, G. A. Pagani, T. J. Marks, *Chem. Mater.* **2003**, *15*, 1064–1072.

[15] For recent, representative examples of transition-metal-catalyzed pyrrole syntheses, see: a) L. Ackermann, R. Sandmann, L. T. Kaspar, *Org. Lett.* **2009**, *11*, 2031–2034; b) Y. Lu, X. Fu, H. Chen, X. Du, X. Jia, Y. Liu, *Adv. Synth. Catal.* **2009**, *351*, 129–134; c) A. V. Lygin, O. V. Larionov, V. S. Korotkov, A. de Meijere, *Chem. Eur. J.* **2009**, *15*, 227–236; d) A. S. Dudnik, A. W. Sromek, M. Rubina, J. T. Kim, A. V. Kel'in, V. Gevorgyan, *J. Am. Chem. Soc.* **2008**, *130*, 1440–1452; e) Y. Lu, B. A. Arndtsen, *Angew. Chem.* **2008**, *120*, 5510–5513; *Angew. Chem. Int. Ed.* **2008**, *47*, 5430–5433; f) Y.-F. Wang, K. K. Toh, S. Chiba, K. Narasaka, *Org. Lett.* **2008**, *10*, 5019–5022; g) S. Chiba, Y.-F. Wang, G. Lapointe, K. Narasaka, *Org. Lett.* **2008**, *10*, 313–316; h) F. M. Istrate, F. Gagosz, *Org. Lett.* **2007**, *9*, 3181–3184; i) X. Yuan, X. Xu, X. Zhou, J. Yuan, L. Mai, Y. Li, *J. Org. Chem.* **2007**, *72*, 1510–1513; j) M. R. Rivero, S. L. Buchwald, *Org. Lett.* **2007**, *9*, 973–976; k) C. V. Galliford, K. A. Scheidt, *J. Org. Chem.* **2007**, *72*, 1811–1813, and references therein.