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Cationic Rhodium(I)/Segphos-Catalyzed Cycloisomerization of 1,6- and 1,7-Diynes in the Presence of 1,2-Cyclohexanedione

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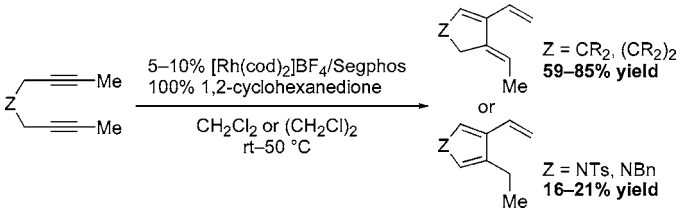
ABSTRACT



We have developed the first catalytic cycloisomerization of 1,6- and 1,7-diynes leading to trienes and vinylpyrroles by using a cationic rhodium(I)/Segphos complex (2.5–10 mol %) and 1,2-cyclohexanedione (100 mol %). 1,2-Cyclohexanedione may effectively occupy vacant coordination sites and thus promote the present cycloisomerization.

Transition-metal-catalyzed carbocyclization is one of the most efficient methods for the construction of a variety of carbocycles and heterocycles.[1,2] In particular, transition-metal-catalyzed cycloisomerization of 1,6-enynes such as the intramolecular Alder−ene reaction is an useful method for the synthesis of five-membered cyclic compounds.[3] This cycloisomerization can be catalyzed by many transition metals such as Pd,[4] Ru,[5] Ti,[6] Co,[7] Ir,[8] and Rh.[9,10] The Rh-catalyzed Alder−ene reaction has been extensively studied, and a number of highly enantioselective catalyses have been reported.[10] The proposed mechanism for the Rh-catalyzed Alder−ene reaction is outlined in Scheme 1. A 1,6-enyne

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(2) For a review on Rh-catalyzed carbocyclizations, see: Robinson, J. E. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 241.

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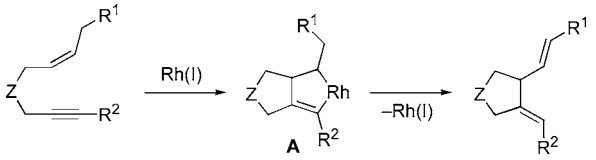
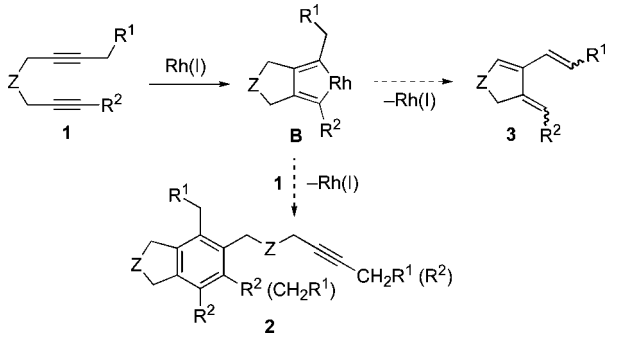
Scheme 1



reacts with a Rh(I) complex to give rhodacyclopentene intermediate **A**. β-Hydride elimination from intermediate **A** followed by reductive elimination furnishes a 1,4-diene.

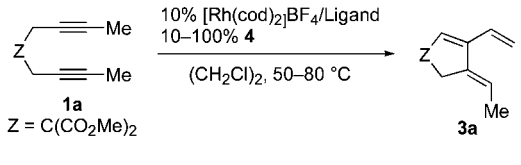
On the other hand, analogous cycloisomerization of 1,6-diynes has not been reported to date.[11,12] In general, 1,6-diyne **1** reacts with a Rh(I) complex to furnish rhodacyclopentadiene intermediate **B**, which readily reacts with diyne **1** to give homo-[2 + 2 + 2] cycloaddition product **2**.[13−16] We anticipated that the presence of another chelating ligand in addition to a bisphosphine ligand occupies vacant coordination sites, which may eliminate the occupation by diyne **1** and promote β-hydride elimination from intermediate **B**. Subsequent reductive elimination and double-bond isomerization would furnish triene **3** (Scheme 2). In this paper, we report the first cycloisomerization of 1,6- and 1,7-diynes leading to trienes and vinylpyrroles catalyzed by a cationic rhodium(I)/Segphos [(4,4′-bi-1,3-benzodioxole)-5,5′-diylbis-(diphenylphosphine)] complex in the presence of 1,2-cyclohexanedione.

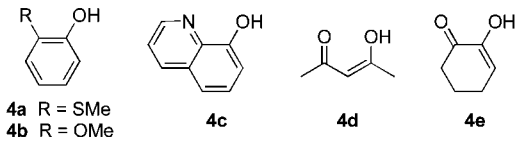
Scheme 2



The reaction of malonate-derived 1,6-diyne **1a** with a cationic Rh(I)/Segphos catalyst (10 mol %) was examined in the presence of various additional chelating ligands to promote the cycloisomerization as shown in Table 1. The use of substituted phenol derivatives **4a**−**c** bearing a coordinative sulfur, oxygen, or nitrogen substituent furnished a homo-[2 + 2 + 2] cycloaddition product as a major product, and the desired cycloisomerization product **3a** was obtained

Table 1. Optimization of Reaction Conditions for Rh(I)$^+$/Modified-BINAP-Catalyzed Cycloisomerization of **1a**[a]





entry	ligand	**4** (mol %)	condition	% yield (*E*/*Z*)[b]
1	Segphos	**4a** (100)	50 °C, 16 h	<5 (>20:1)
2	Segphos	**4b** (100)	50 °C, 16 h	0 (−)
3	Segphos	**4c** (10)	80 °C, 16 h	29 (>20:1)
4	Segphos	**4d** (100)	50 °C, 16 h	0 (−)
5[c]	Segphos	**4e** (100)	50 °C, 3 h	85 (>20:1)[d]
6	BINAP	**4e** (100)	50 °C, 3 h	24 (>20:1)
7	H_8-BINAP[e]	**4e** (100)	50 °C, 3 h	38 (>20:1)
8[c]	Segphos	**4e** (20)	50 °C, 3 h	58 (>20:1)[d]

[a] $[Rh(cod)_2]BF_4$/ligand (0.010 mmol), **4a**−**e** (0.010−0.10 mmol), **1a** (0.10 mmol), and $(CH_2Cl)_2$ (1.5 mL) were employed. [b] NMR yield. [c] $[Rh(cod)_2]BF_4$/Segphos (0.030 mmol), **4e** (0.060−0.30 mmol), **1a** (0.30 mmol), and $(CH_2Cl)_2$ (3.0 mL) were employed. [d] Isolated yield. [e] H_8-BINAP: 2,2′-bis(diphenylphosphino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl.

(9) For a recent review on Rh-catalyzed Alder−ene reactions, see: Brummond, K. M.; McCabe, J. M. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 151.

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(11) Ruthenium-catalyzed cycloisomerization of 1,6-diynols to form $\alpha,\beta,\gamma,\delta$-unsaturated ketones and aldehydes has been reported; see: (a) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4178. (b) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 11516. (c) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 4763.

(12) Rhodium-catalyzed reductive cyclization of 1,6- and 1,7-diynes has been reported; see: (a) Ojima, I.; Zhu, J.; Vidal, E. S.; Kass, D. F. *J. Am. Chem. Soc.* **1998**, *120*, 6690. (b) Muraoka, T.; Matsuda, I.; Itoh, K. *Tetrahedron Lett.* **1998**, *39*, 7325. (c) Muraoka, T.; Matsuda, I.; Itoh, K. *Organomellics* **2002**, *21*, 3650. (d) Liu, C.; Widenhoefer, R. A. *Organometallics* **2002**, *21*, 5666. (e) Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 7875.

(13) For recent reviews on [2 + 2 + 2] cycloadditions of alkynes, see: (a) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (b) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209. (c) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (d) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503.

(14) For a recent review on Rh-catalyzed [2 + 2 + 2] cycloadditions, see: Fujiwara, M.; Ojima, I. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 129.

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(16) For selected examples of cationic Rh(I)/modified-BINAP complex-catalyzed [2 + 2 + 2] cycloadditions of alkynes, see: (a) Tanaka, K.; Shirasaka, K. *Org. Lett.* **2003**, *5*, 4697. (b) Tanaka, K.; Nishida, G.; Wada, A.; Noguchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 6510. (c) Tanaka, K.; Toyoda, K.; Wada, A.; Shirasaka, K.; Hirano, M. *Chem.—Eur. J.* **2005**, *11*, 1145. (d) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586. (e) Tanaka, K.; Sagae, H.; Toyoda, K.; Noguchi, K.; Hirano, M. *J. Am. Chem. Soc.* **2007**, *129*, 1522. (f) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3951 and references cited therein.

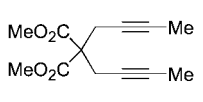
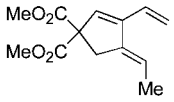
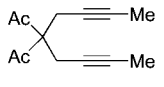
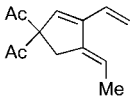
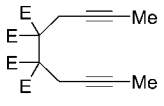
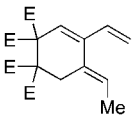
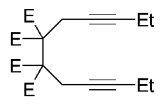
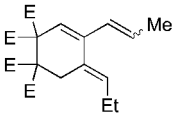
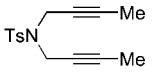
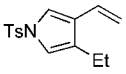
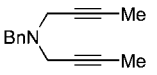
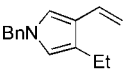
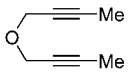
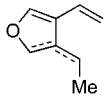
in low yield or not at all (entries 1−3).[17] Next, enolizable 1,3- and 1,2-diketones were examined (entries 4 and 5). Although the use of acetylacetone (**4d**) was not effective (entry 4), the use of 1,2-cyclohexanedione (**4e**) furnished **3a** in high yield (entry 5). Among the modified-BINAP ligands examined (entries 5−7), Segphos was clearly the ligand of choice (entry 5). The amount of **4e** significantly affected the yield of **3a**. Decreasing the amount of **4e** lowered the yield of **3a** and increased the yield of the homo-[2 + 2 + 2] cycloaddition product (entry 8).

We explored the scope of this process by employing the above optimal reaction conditions as shown in Table 2. Not only malonate-derived 1,6-diyne **1a** (entry 1) but also acetylacetone-derived 1,6-diyne (**1b**, entry 4) and 1,7-diyne **1c** (entry 5) could participate in this reaction.[18] The reaction could be carried out using 5 mol % of Rh with only a slight erosion of the yield of **3a**, but the use of 2.5 mol % of Rh significantly lowered the yield of **3a** (entries 2 and 3). Although the cycloisomerization of internal diyne **1d** possessing an ethyl group at the alkyne termini proceeded in moderate yield, an *E*/*Z* mixture was obtained (entry 6). Nitrogen-linked 1,6-diynes **1e** and **1f** furnished vinylpyrroles **5e** and **5f**, although their yields were low due to the formation of homo-[2 + 2 + 2] cycloaddition products as major products (entries 7 and 8). Unfortunately, because oxygen-linked 1,6-diyne **1g** showed high reactivity toward the homo-[2 + 2 + 2] cycloaddition, the expected cycloisomerization product **3g** or **5g** could not be obtained (entry 9).

A possible mechanism for the cycloisomerization of 1,6- and 1,7-diynes is shown in Scheme 3. The cationic Rh(I)/Segphos complex reacts with 1,2-cyclohexanedione (**4e**) furnishing Rh(I) complex **C**. Diyne **1** reacts with complex **C**, providing rhodacyclopentadiene intermediate **D**. β-Hydride elimination and double-bond isomerization form triene **3** or pyrrole **5**.

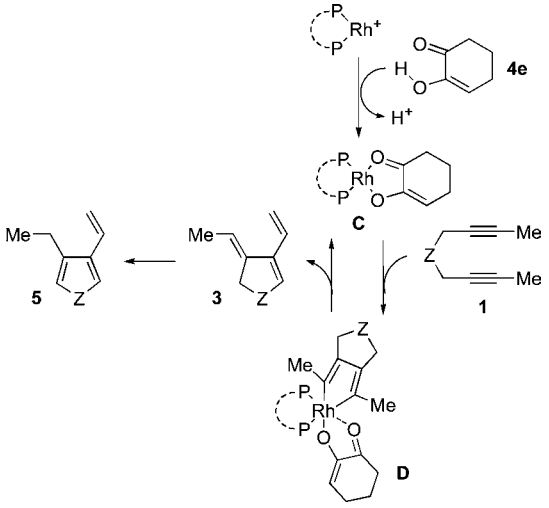
Finally, the reaction of 1,6-enyne **6a** bearing a geminally disubstituted alkene moiety in the presence of [Rh(cod)$_2$]-BF$_4$/H$_8$-BINAP (10 mol %)[19] and **4e** (100 mol %) at 100 °C was examined as shown in Scheme 4. Although the reaction

Table 2. Rh(I)$^+$/Segphos-Catalyzed Cycloisomerization of 1,6- and 1,7-Diynes **1** in the Presence of **4e**[a]

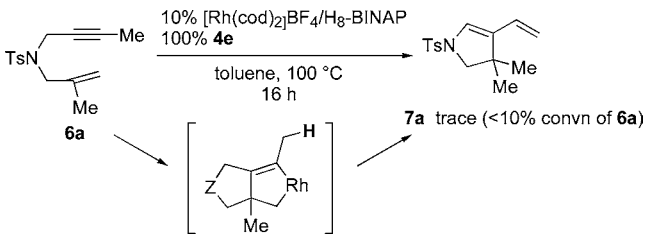
entry	diyne	product	% yield (*E*/*Z*)[b]
			
1	**1a**	**3a**	85 (>20:1)
2[c]	**1a**	**3a**	80 (>20:1)
3[d]	**1a**	**3a**	51 (>20:1)[e]
			
4[f]	**1b**	**3b**	70 (>20:1)
			
5	**1c** E = CO_2Et	**3c**	68 (>20:1)
			
6	**1d** E = CO_2Et	**3d**	59 (3:1)
			
7[g]	**1e**	**5e**	21 (–)
			
8[g]	**1f**	**5f**	16 (–)
			
9	**1g**	**3g** or **5g**	<5 (–)

[a] Reactions were conducted using [Rh(cod)$_2$]BF$_4$/Segphos (0.030 mmol, 10 mol %), **4e** (0.30 mmol, 100 mol %), **1** (0.30 mmol), and $(CH_2Cl)_2$ (3.0 mL) at 50 °C for 3 h. [b] Isolated yield. [c] Catalyst: 5 mol %. [d] Catalyst: 2.5 mol %. Reaction time: 24 h. [e] Diyne **1a** was recovered in 13% yield. [f] At rt. [g] In CH_2Cl_2 at 40 °C.

Scheme 3



Scheme 4

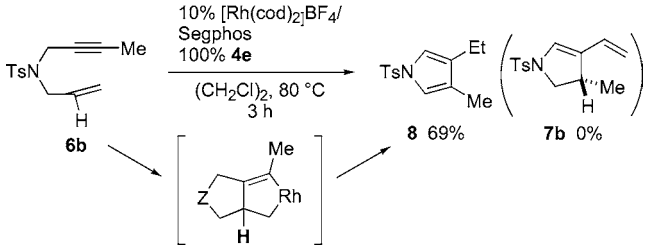


(17) No reaction was observed using 100 mol % of **4c** at 80 °C for 16 h.

was sluggish, the formation of similar cycloisomerization product **7a** presumably through β-hydride elimination of a propargylic hydrogen was observed.

The reaction of 1,6-enyne **6b** bearing a monosubstituted alkene moiety was also examined as shown in Scheme 5. In

Scheme 5



this case, cycloisomerization presumably through β-hydride elimination of a vinylic hydrogen proceeded to give pyrrole **8** in good yield, but cycloisomerization product **7b** was not generated at all.

In conclusion, we have developed the first cycloisomerization of 1,6- and 1,7-diynes leading to trienes and vinylpyrroles catalyzed by a cationic rhodium(I)/Segphos complex in the presence of 1,2-cyclohexanedione. Further utilization of 1,2-cyclohexanedione in transition-metal catalysis is currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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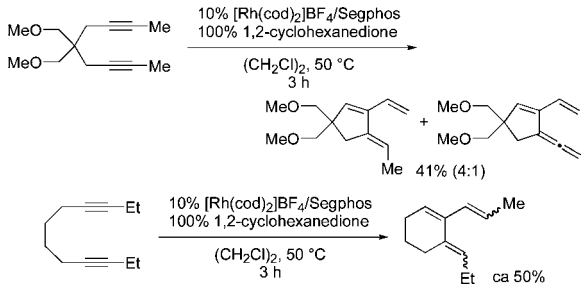
(18) Although the cycloisomerization of 1,3-dimethoxypropane-derived 1,6-diyne and 3,9-dodecadiyne proceeded, the products could not be isolated in a pure form due to the formation of an inseparable allene byproduct or inseparable olefinic isomers.



(19) $[Rh(cod)_2]BF_4/H_8$-BINAP was used as a catalyst due to low solubility of $[Rh(cod)_2]BF_4$/Segphos in toluene.