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Rh-Catalyzed Enyne Cycloisomerization

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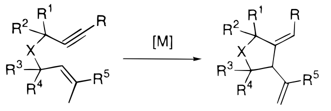
Transition metal-catalyzed carbocyclization of alkenes and alkynes is one of the most efficient methods for the synthesis of a variety of carbocyclic and heterocyclic compounds.[1] This strategy has allowed transformations of unsaturated functional groups in ways which are either difficult or impossible without the action of transition metal complexes. One excellent example is the transition metal-catalyzed cycloisomerization of 1,6-enynes which leads to the formation of 1, 4-dienes (intramolecular Alder-ene reaction)[2] (eq 1). Many transition metals have been applied to catalyze this Alder-ene type reaction.[3] Both Pd- and Ru-catalyzed Alder-ene reactions have been developed by Trost.[4] The intramolecular cycloisomerization of 1, 6-enynes has evolved into a synthetically powerful carbon−carbon bond forming process.[5] Recently, a highly selective enyne cycloisomerization has also been developed by Buchwald using an early transition metal catalyst [Cp$_2$Ti(CO)$_2$].[6] Although Pd-, Ru-, and Ti-catalyzed Alder-ene type reactions have been extensively studied, new catalytic systems are still valuable to expand the reaction scope, activity, and selectivity.



Eq1

To the best of our knowledge, no Rh-based catalyst systems have been reported for facilitating Alder-ene type reactions. Herein we report a highly effective and selective Rh-catalyzed cycloisomerization of 1, 6-enynes to form 1, 4-dienes. The following attractive features of the Rh-catalyzed Alder-ene type reaction have been revealed: (1) 1, 4-dienes are formed selectively (similar to Ru-catalyst and Ti-catalyst systems) at room temperature, (2) easy variation of the diphosphine ligand in [Rh(diphos)Cl]$_2$ allows the Rh-catalyst to be fine-tuned with respect to steric and electronic requirements of substrates, (3) cycloisomerization of enyne with an allylic ester tether gives an α-methylene γ-butyrolactone.

Recently, a variety of rhodium(I) complexes have been applied to catalyze the [4 + 2],[7] [5 + 2],[8] and Pauson−Khand[9] reactions. Metallacyclopentenes were suggested as key intermediates in these transformations.[7−9] We envisioned that a new Rh-catalyzed Alder ene reaction might be possible if β-hydride and reductive eliminations could be controlled after the formation of the metallacyclopentene intermediate. A key for this reaction is to generate a highly coordinatively unsaturated environment to bind the enyne substrate so that the formation of a metallacyclopentene can proceed smoothly. A related example of such an unsaturated compound is the Crabtree catalyst [Ir(COD)Py(PCy$_3$)]$^+$.[10] The highly coordinatively unsaturated chelating phosphine modified Rh(I)-catalyst has been applied in asymmetric hydroacylation[11] and enantioselective isomerization of allylamines.[12]

To find appropriate conditions to perform the Rh-catalyzed enyne cycloisomerization reaction, **1a** was selected as a prototypical substrate. Through systematic studies, high yield and clean transformation was achieved with a *cis*-olefin *Z*-**1a** using 10 mol % Rh-catalyst with dppb as the ligand (84% yield) (see Supporting Information). *The major advance in this study was to prepare a [Rh(dppb)Cl]$_2$ complex as the clean catalyst precursor and the cationic Rh-catalyst was prepared in situ from the reaction of [Rh(dppb)Cl]$_2$ dimer with AgSbF$_6$ in the presence of enyne substrates*. Typically, the catalytic reactions were carried out in 1,2-dichloroethane (DCE) with a 0.1 M substrate concentration at room temperature. On the basis of this important finding, a number of phosphines were tested for the enyne cycloisomerization reaction. Interestingly, the catalytic activity varies considerably by changing phosphine ligands. A Rh complex with a 1, 4-diphosphinite, BICPO,[13] is the most active isomerization catalyst. A Rh-catalyst with the chelating phosphine dppb is more active than the Rh system with the dppe ligand. Rh complexes with chelating phosphines such as dppp and dppm are inactive for the enyne isomerization reaction.

To perform effective enyne isomerization, both dppb and BICPO have been used to prepare active Rh-catalysts. A variety of enyne substrates were converted to 1, 4-dienes in moderate to excellent yields. The results with the Rh-dppb catalyst are summarized in Table 1. In contrast to the titanium-catalyzed reaction,[6] only enyne substrates containing a *cis*-olefin are cycloisomerized. *trans*-Olefins do not react. In this catalytic system, an ether-tethered enyne gave higher reactivity than other type of enyne substrates. A *cis* fused ring system was formed exclusively when **1g** was used as the enyne. The *cis* configuration of product **2g** was assigned by a 2D NOESY study. An allylic ester (**1h**) was converted smoothly to an ene product **2h**, α-methylene-γ-butyrolactone, using the Rh-catalyst. The α-methylene-γ-butyrolactone is common in sesquterpenes and has a

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[5] (a) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625. (b) Trost, B. M.; Krische, M. J. *J. Am. Chem. Soc*, **1996**, *118*, 223 (c) Trost, B. M.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131. (d) Trost, B. M.; Haffner, C. D.; Jebaratnam, D. J.; Krische, M. J.; Thomas, A. P. *J. Am. Chem. Soc.* **1999**, *121*, 6183.

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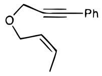
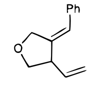
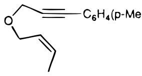
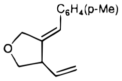
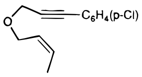
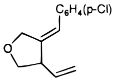
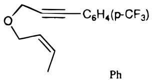
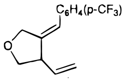
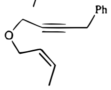
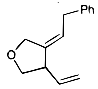
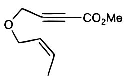
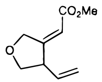
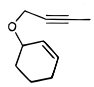
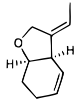
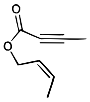
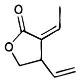
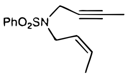
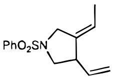
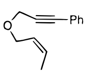
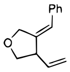
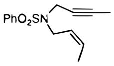
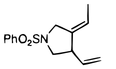
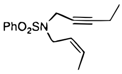
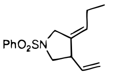
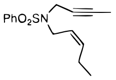
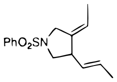
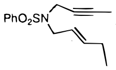
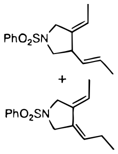
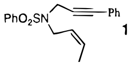
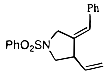
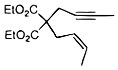
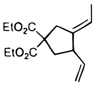
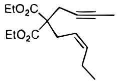
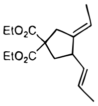
Table 1. Rhodium-Catalyzed Cycloisomerization of 1,6-Enynes[a]

entry	substrate		product		temp.	time (h)	yield (%)[b]
1		**Z-1a**		**2a**	rt	2	84
2		**1b**		**2b**	rt	12	50
3		**1c**		**2c**	rt	2	91
4		**1d**		**2d**	rt	1	80
5		**1e**		**2e**	rt	6	83
6		**1f**		**2f**	rt	12	85
7[b]		**1g**		**2g**	rt	2	85
8		**1h**		**2h**	55 °C	24	50
9		**Z-1i**		**2i**	40 °C	12	50[c]

[a] All reactions were carried out in $ClCH_2CH_2Cl$ with substrate (0.2 mmol, 0.1M)/$[Rh(dppb)Cl]_2$/$AgSbF_6$ = 1: 0.05:0.1. The catalyst $[Rh(dppb)]^+$ was prepared by adding $AgSbF_6$ to the $[Rh(dppb)C1]_2$ in the presence of substrate. [b] The stereochemistry is relative. [c] Conversion based on ^{1}H NMR (360 MHz), ene product cannot be separated from the substrate.

Table 2. Rhodium-Catalyzed Cycloisomerization of 1,6-Enynes with a Phosphinite Ligands[a]

entry	substrate		product		cat. (mol%)	time (h)	yield (%)[b]
1		**1a**		**2a**	10	1.5	81
2		**1i**		**2i**	3	13	98
3		**1k**		**2k**	3	13	100
4		**1l**		**2l**	3	16	99
5[b]		**1m**		**2m** **2m′**	10	4	96[b]
6		**1n**		**2n**	10	5	98
7		**1j**		**2j**	3	16	90
8		**1o**		**2o**	3	16	89

[a] All reactions were carried out in $ClCH_2CH_2Cl$ with substrate (0.2 mmol, 0.1M). The catalyst $[Rh(BICPO)]^+$ was prepared by adding $AgSbF_6$ to the $[Rh(BICPO)Cl]_2$ after substates were introduced. [b] **2m**: **2m′** = 66:34.

wide range of biological activity.[14] This example is noteworthy because cycloisomerization of enynes with an allylic ester tether to yield *γ-butyrolactones* has not been reported in the corresponding Pd-, Ti-, or Ru-catalyzed enyne isomerizations. The cyclization of nitrogen containing substrate **Z-1i** is slow with a Rh-dppb catalyst. After 12 h at 40 °C, **Z-1i** was converted to a 1, 4-diene product **2i** in around 50% yield (entry 9, Table 1). However, both 1, 4-diene and 1, 3-diene products were obtained after an additional 12 h. So far, the enyne substrate **1j** containing a carbon tether does not cyclize with the Rh-dppb catalyst.

We demonstrated a Rh-catalyzed cycloisomerization of 1, 6-enynes to 1, 4-dienes using a 1, 4-bisphosphine as the ligand. This transformation provides an excellent complement to the previous catalyst system. However, this cyclization protocol is limited by the substrate scope in which only ether linked enyne substrates give high reactivity toward cyclization. To make this reaction more useful, we were interested in searching for a more active Rh-catalyst which can promote cyclization of a wide variety of 1, 6-enynes.

Table 2 summarizes experimental results of Rh-catalyzed cycloisomerization of 1, 6-enynes with a Rh-bisphosphinite (Rh-BICPO) catalyst.The enyne cycloisomerization reaction was performed at room temperature in $ClCH_2CH_2Cl$. *The catalyst was prepared from 1.5 mol % $[Rh(BICPO)Cl]_2$ and 3 mol % $AgSbF_6$ in the presence of substrate*. Significant improvement has been observed with the Rh-BICPO catalyst compared to results achieved with the Rh-dppb catalyst system. The increase of activity (catalyst loading lowered to 3 mol %) is found with the bisphosphinite-Rh catalyst. Cycloisomerization of an array of 1, 6-enyne substrates bearing an O, N, or C in the tether gave 1, 4-dienes in excellent yields (Table 2). Furthermore, this Rh-BICPO catalyst can promote cyclization of enynes containing either *E*- or *Z*-alkenes Rh−BICPO (entry 4, 5 in Table 2). Therefore, the substrate scope with the RhBICPO catalyst is broader than that observed with the Rh-dppb catalyst.

In conclusion, we have demonstrated a Rh-catalyzed enyne cycloisomerization to make 1, 4-dienes. Our findings illustrate that the Rh catalytic system has unique reactivity and selectivity compared to other late transition metal- and Ti-catalyzed processes. Work toward developing an asymmetric variant of the enyne cycloisomerization reaction as well as Rh-catalyzed [4 + 2] and [5 + 2] reactions is underway and will be reported in due course.

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Supporting Information Available: Spectroscopic data, experimental details and path of reaction discovery (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA994220S

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