Catalytic Cycloaddition

DOI: 10.1002/ange.200702586

A Cationic Rhodium–Chiral Diene Complex as a High-Performance Catalyst for the Intramolecular Asymmetric [4+2] Cycloaddition of Alkyne-1,3-Dienes**

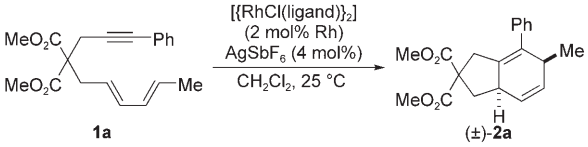
Ryo Shintani, Yuta Sannohe, Takaoki Tsuji, and Tamio Hayashi**

Dedicated to Süd-Chemie on the occasion of its 150th anniversary

The successful development of a transition-metal-catalyzed asymmetric transformation requires the achievement of both high catalytic activity and high enantioselectivity. It is therefore desirable to properly evaluate the relationship between the catalyst activity and the nature of a ligand on the transition metal in a given catalytic reaction, and develop its asymmetric variant by employing a chiral ligand with the required properties for high activity. In this context, we demonstrate herein that a rhodium–diene complex is much more active than its rhodium–bisphosphine counterpart as a catalyst for intramolecular [4+2] cycloadditions of alkyne-tethered 1,3-dienes, and that the use of a chiral diene ligand leads to the development of a highly active and enantioselective asymmetric variant of this reaction.

Since the first report by Livinghouse in 1990,[1] many rhodium(I) complexes, along with complexes of several other transition metals,[2] have been shown to catalyze intramolecular [4+2] cycloaddition reactions of alkyne-tethered 1,3-dienes. Cationic rhodium(I) complexes bearing a bisphosphine ligand such as 1,2-bis(diphenylphosphanyl)ethane (dppe)[3] or 1,4-bis(diphenylphosphanyl)butane (dppb)[4] have been utilized as highly efficient catalysts for these reactions, and some asymmetric variants using chiral bisphosphine ligands have also been developed.[5] Chung et al., on the other hand, described the use of [Rh(naphthalene)(cod)]BF_4 (cod = 1,5-cyclooctadiene) as an effective catalyst,[6] thereby demonstrating that a phosphine-free rhodium–diene complex can also show high activity for these cycloadditions.[7]

On the basis of these precedents, we initially focused on the head-to-head comparison of several ligands to quantitatively evaluate their efficiency in the rhodium-catalyzed intramolecular [4+2] cycloaddition reaction with alkyne-tethered 1,3-diene **1a** as a model substrate [Eq. (1)]. These reactions were carried out in the presence of 2 mol% of rhodium catalyst in dichloromethane at 25 °C in a reaction



(1)

calorimeter (Omnical SuperCRC), and the data were analyzed by the reaction progress kinetic analysis method developed by Blackmond.[8] The reaction catalyzed by the Rh–cod complex proceeded very fast, with 97% conversion being achieved in only 10 min (Figure 1). In contrast, the use of rhodium–bisphosphine catalysts gave much slower reactions (3–4% conversion after 10 min), thereby establishing that the Rh–cod complex is at least 20 times more active than its Rh–dppe and Rh–dppb counterparts under these conditions (Figure 1).

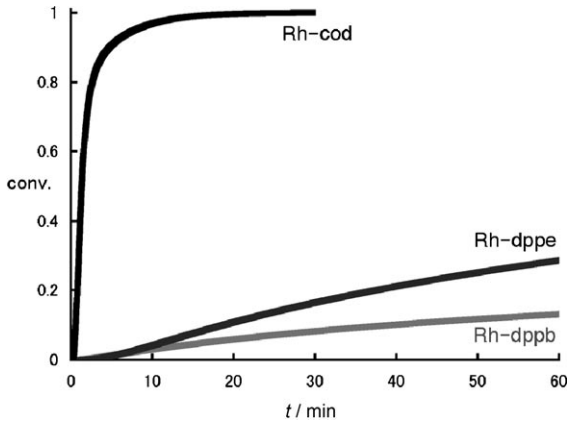


Figure 1. A plot of conversion versus time for the reaction of **1a** (initial concentration: 0.10 M) in CH_2Cl_2 (3.0 mL) in the presence of a rhodium catalyst (2.0 mM Rh) and $AgSbF_6$ (3.9 mM) at 25 °C.

The results of these kinetic studies suggested that the use of a chiral diene ligand[9–12] would be desirable for the development of a highly efficient asymmetric variant of this process.[13] As shown in Equation (2), the reaction of **1a** proceeded smoothly with (*S*,*S*)-Ph-bod*[10] as the ligand to

[*] Dr. R. Shintani, Y. Sannohe, T. Tsuji, Prof. Dr. T. Hayashi
Department of Chemistry
Graduate School of Science
Kyoto University
Sakyo, Kyoto 606-8502 (Japan)
Fax: (+81) 75-753-3988
E-mail: shintani@kuchem.kyoto-u.ac.jp
thayashi@kuchem.kyoto-u.ac.jp

[**] Financial support of this work was provided, in part, by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (21 COE on Kyoto University Alliance for Chemistry).

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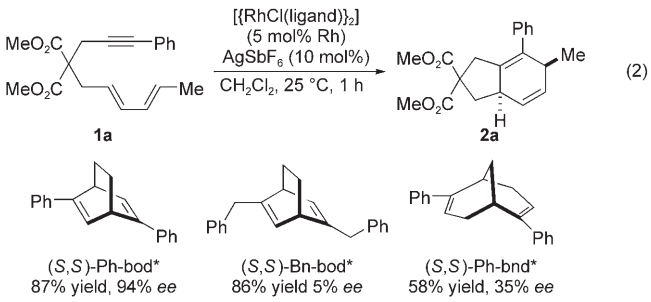


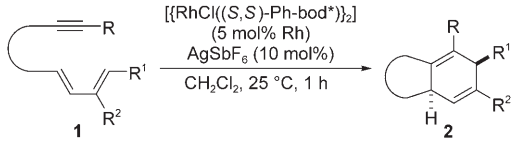
(2)

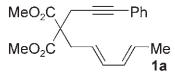
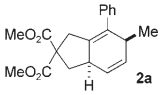
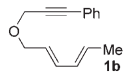
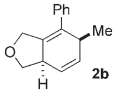
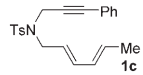
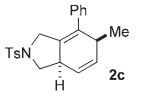
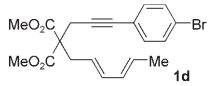
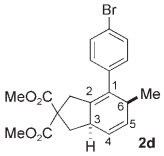
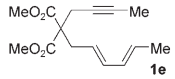
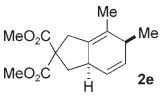
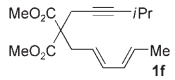
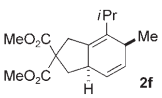
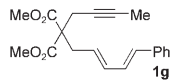
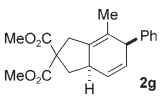
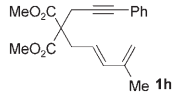
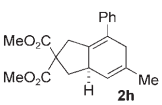
give cycloadduct **2a** in 87% yield with a high enantioselectivity of 94% *ee*.[14] A high yield of **2a** was also obtained with (*S*,*S*)-Bn-bod* as the ligand,[10,11] although the enantioselectivity was significantly lower (5% *ee*). The use of a structurally different chiral diene ligand, namely (*S*,*S*)-Ph-bnd*,[9c,d] resulted in only a moderate yield and *ee* (58% yield, 35% *ee*).

Substrates with an oxygen or nitrogen atom in the tether can be employed with high efficiency (90–96% yield, 91–97% *ee*; Table 1, entries 2 and 3) in this reaction, with (*S*,*S*)-Ph-bod* as the ligand, and various substitution patterns on the alkyne and the 1,3-diene are also tolerated, with the corresponding cycloadducts being isolated in high yield and with high *ee* values (87–95% yield, 83–99% *ee*; Table 1, entries 4–8). The absolute configuration of cycloadduct **2d** (Table 1, entry 4) was established as (3*R*,6*S*) by X-ray crystallographic analysis.[15]

A proposed catalytic cycle for this process with substrate **1a** is shown in Figure 2.[1] Initial coordination of **1a** to a cationic Rh^{I}–(*S*,*S*)-Ph-bod* complex leads to oxidative cyclization to form rhodacyclopentene intermediate **A**, which undergoes a suprafacial 1,3-allylic migration of rhodium to give rhodacycloheptadiene species **B**. Reductive elimination of the [4+2] cycloadduct **2a** from intermediate **B** then regenerates the cationic rhodium(I) complex. On the basis of this mechanism, the stereo-determining step is the formation of rhodacyclopentene **A** and the observed stereochemical outcome can therefore be rationalized as shown in Figure 3. The rhodacyclopentene has a (3*S*,4*R*) configuration rather than a (3*R*,4*S*) configuration (complex **A′**) to avoid steric repulsion between the propenyl group at the 4-position and the phenyl group on the olefin of the (*S*,*S*)-Ph-bod*

Table 1: The rhodium-catalyzed asymmetric [4+2] cycloaddition of alkyne-tethered 1,3-dienes **1**.



Entry	Substrate	Product	Yield [%]	*ee* [%]
1	 **1a**	 **2a**	87	94
2[a]	 **1b**	 **2b**	90	97
3	 **1c**	 **2c**	96	91
4	 **1d**	 **2d**	87	95
5	 **1e**	 **2e**	89	97
6[a]	 **1f**	 **2f**	95	>99
7	 **1g**	 **2g**	89	87
8[a]	 **1h**	 **2h**	92	83

[a] The reaction was conducted at 0 °C.

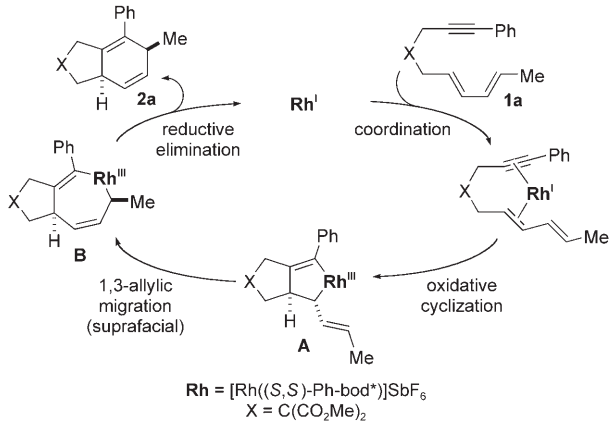


Figure 2. Proposed catalytic cycle for the asymmetric [4+2] cycloaddition of **1a** catalyzed by Rh–(*S*,*S*)-Ph-bod*.

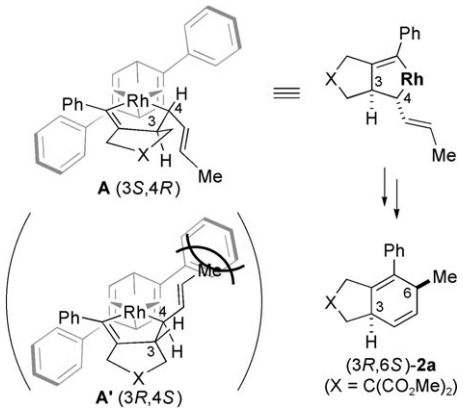
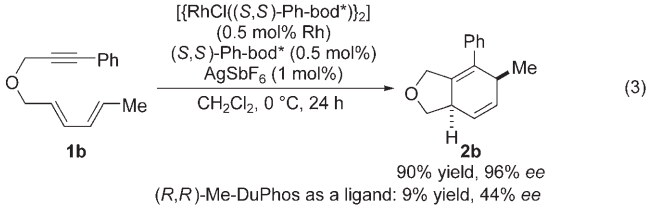


Figure 3. Rationale for the stereochemical outcome of the asymmetric [4+2] cycloaddition of **1a** catalyzed by Rh–(*S*,*S*)-Ph-bod*.

ligand. This intermediate gives (3*R*,6*S*)-**2a** by a stereospecific 1,3-allylic migration of rhodium and subsequent reductive elimination.

The high efficiency of the present catalysis with (*S*,*S*)-Ph-bod* as the ligand is highlighted by the reaction of **1b** at a lower catalyst loading [Eq. (3)]. This reaction proceeds

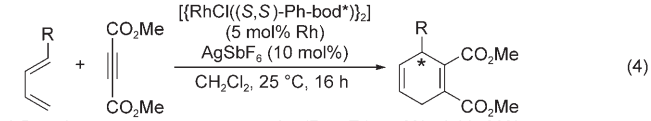


(3)

90% yield, 96% *ee*
(*R*,*R*)-Me-DuPhos as a ligand: 9% yield, 44% *ee*

smoothly in the presence of only 0.5 mol% of the Rh–(*S*,*S*)-Ph-bod* catalyst at 0°C to give cycloadduct **2b** in 90% yield and with 96% *ee*. In comparison, (*R*,*R*)-Me-DuPhos, which is the best chiral bisphosphine ligand for this reaction reported to date,[5b] affords **2b** in a very sluggish reaction with only 9% yield and 44% *ee* with the same catalyst loading.

The present catalyst system also allows us to carry out intermolecular reactions between 1,3-dienes and alkynes.[6] Thus, the reaction of *trans*-1,3-hexadiene with dimethyl acetylenedicarboxylate proceeds smoothly in the presence of 5 mol% of the Rh–(*S*,*S*)-Ph-bod* catalyst at 25°C to give 1,4-cyclohexadiene **3a** in 72% yield and with 83% *ee* [Eq. (4)].[16] Similarly, *trans*-1,3-decadiene gives the corresponding cycloadduct **3b** with 87% *ee*.



(4)

3a (R = Et): 72% yield, 83% *ee*
3b (R = *n*Hex): 48% yield, 87% *ee*

In summary, we have established that a rhodium–diene catalyst is much more active than its rhodium–bisphosphine counterpart for the intramolecular [4+2] cycloaddition of alkyne-tethered 1,3-dienes, and we have developed a highly active and enantioselective asymmetric variant by employing a chiral diene ligand. This catalyst system can also be applied to the intermolecular cycloaddition of 1,3-dienes and alkynes with high efficiency.

Experimental Section

A solution of alkyne-tethered 1,3-diene **1** (0.20 mmol) in CH_2Cl_2 (1.7 mL) was added to a mixture of [{RhCl((*S*,*S*)-Ph-bod*)}$_2$] (4.0 mg, 10 μmol Rh) and $AgSbF_6$ (6.9 mg, 20 μmol) in CH_2Cl_2 (0.3 mL). The resulting mixture was stirred for 1 h at 25°C and was then passed through a pad of silica gel with Et_2O as eluent. After removal of the solvent under vacuum, the residue was chromatographed on silica gel with EtOAc/hexane as eluent to afford compound **2**.

Received: June 13, 2007
Published online: August 23, 2007

Keywords: asymmetric catalysis · cycloaddition · diene ligands · enantioselectivity · rhodium

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[13] A single example of intramolecular [4+2] cycloaddition catalyzed by a rhodium–chiral diene catalyst with low enantioselectivity has been reported (26% *ee*; reference [5c]). High enantio-

selectivities were obtained in the presence of a chiral bisphosphine ligand.
[14] The *ee* value of **2a** stays the same at low and complete conversion of **1a**, thereby indicating that the (*S*,*S*)-Ph-bod* ligand remains bound to the rhodium center throughout the reaction.
[15] CCDC-648192 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[16] Similar examples using (*S*)-binap as a ligand (up to 82% *ee*) were reported at the 87th Annual Meeting of the Chemical Society of Japan: D. Fujiwara, A. Kawachi, T. Shibata, **2006**, presentation no. 3D6-16.

