

Chiral Diene-Phosphine Tridentate Ligands for Rhodium-Catalyzed Asymmetric Cycloisomerization of 1,6-Enynes

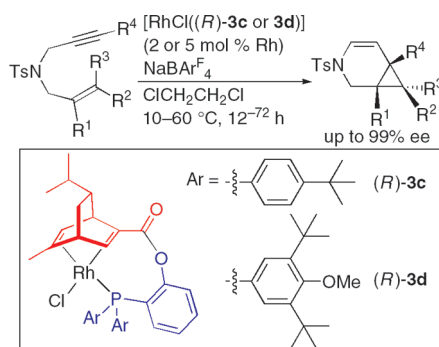
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ABSTRACT



Asymmetric cycloisomerization of nitrogen-bridged 1,6-enynes proceeded in the presence of a cationic rhodium complex coordinated with a chiral diene/phosphine tridentate ligand to give high yields of chiral 3-azabicyclo[4.1.0]heptenes with high enantioselectivity.

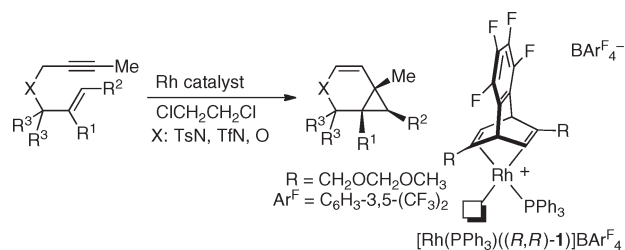
The recent development of transition-metal-catalyzed cycloisomerization of 1,*n*-enynes provides a useful methodology for the preparation of diverse polycyclic compounds in a single step.¹ Cycloisomerization of heteroatom-bridged 1,6-enynes is one of the most straightforward methods for the synthesis of bicyclo[4.1.0]heptene derivatives containing heteroatoms, such as oxygen and nitrogen, which have potential biological activities.² Although there have been several reports on the cycloisomerization catalyzed by π -acidic metals, such as Pt,³ Au,⁴ Rh,⁵ and Ir,^{6,7} asymmetric variants have not been well developed.⁸ Shibata and co-workers reported the first asymmetric cycloisomerization of nitrogen-bridged 1,6-enynes catalyzed by an iridium/bisphosphine complex under CO.⁶ A chiral bisphosphine/NHC- or a chiral monophosphine/cyclometalated NHC-platinum complex has been developed by Marinetti and co-workers.⁹ Michelet and co-workers reported that the asymmetric cycloisomerization with high enantioselectivity is catalyzed by chiral gold/bisphosphine complexes.^{10,11} Although high enantioselectivity is attained

in some catalytic systems, they are still limited in terms of substrate scope and catalyst efficiency, and thus development of a new catalytic system is desirable. In this context, we recently reported that a rhodium(I) complex coordinated with triphenylphosphine and a chiral diene ligand¹² based on a tetrafluorobenzobarrelelene (tfb) skeleton is a good catalyst for asymmetric cycloisomerization of nitrogen- and oxygen-bridged 1,6-enynes, where the active cationic rhodium species has a stereochemically controlled

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Scheme 1. A Rh/Chiral Diene-Phosphine Catalyst in Asymmetric Cycloisomerization of 1,6-Enynes



single coordination site¹³ on the rhodium center for electrophilic activation of the alkyne moiety (Scheme 1).¹⁴ The catalytic system, however, has some drawbacks as follows: (i) The oligomerization of enynes is sometimes observed, probably due to the dissociation of nonchelating triphenylphosphine. (ii) The applicable substrates are limited to enynes substituted with a methyl group at the alkyne terminus, and limited substituents of alkene moieties can

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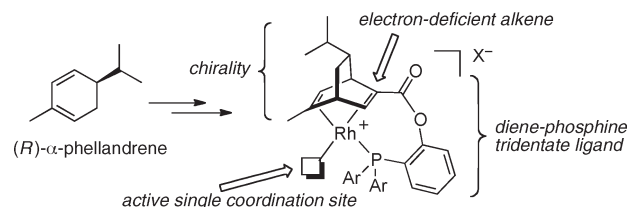
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only be applied to high yielding reactions with high enantioselectivity. (iii) The chiral tfb ligand is not readily available in an enantiopure form. To establish a more efficient and general catalytic system for cycloisomerization of 1,6-enynes, we designed new tridentate ligands for rhodium (Scheme 2).^{15,16} The designed rhodium catalysts involve characteristic features as follows: (i) A tridentate ligand, which has chelating one phosphorus atom and a chiral diene moiety, strongly coordinates to a rhodium center, and the in situ generated cationic complex provides a single vacant site on the square planar geometry of the rhodium(I) center. (ii) An electron-withdrawing character of an alkene moiety substituted with an ester group, which locates trans to the single vacant site of the cationic complex, is expected to enhance the π -acidity of rhodium toward electrophilic alkyne activation. (iii) The chiral diene framework is readily obtained from a natural product (*R*)- α -phellandrene. Here we report the development of new chiral diene-phosphine tridentate ligands for rhodium in asymmetric cycloisomerization of nitrogen-bridged 1,6-enynes giving 3-azabicyclo[4.1.0]heptene derivatives with high enantioselectivity.

Scheme 2. Concept of New Rh/Chiral Diene-Phosphine Catalysts



We focused on carboxylic acid (*1R,4R,7R*)-**2**,¹⁷ which is readily prepared from (*R*)- α -phellandrene, as a chiral diene framework for the synthesis of new chiral diene-monophosphine tridentate ligands (Scheme 3). The ligands were simply prepared by esterification of **2** with 2-(diarylphosphino)phenols. Thus, carboxylic acid **2** was treated with oxalyl chloride, and the resulting acid chloride was reacted

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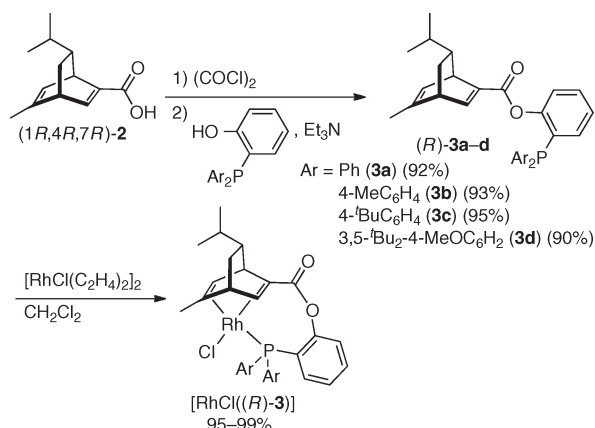
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with 2-(diarylphosphino)phenols in the presence of triethylamine to give diene-phosphine ligands **3a–d** in high yields (90–95%) bearing several substituents on the two benzene rings of the phosphino group. Rhodium complexes coordinated with the ligands **3a–d** were also prepared by the reactions with $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$, and they were isolated in high yields (95–99%) by column chromatography on silica gel.

^1H NMR (CDCl_3) of the complex $[\text{RhCl}((R)\text{-3a})]$ displayed two nonequivalent alkenic protons at 3.81 and 4.61 ppm, which are shifted from 3.28 and 7.15 ppm, respectively, of ligand $(R)\text{-3a}$. Four alkenic carbons showing the

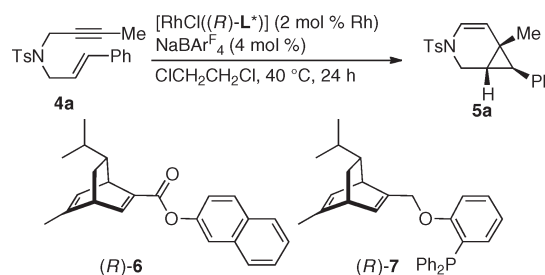
Scheme 3. Synthesis of Ligands and Their Rhodium Complexes



coupling with the rhodium center (50.4, 55.4, 84.1, and 109.1 ppm) were also observed in the ^{13}C NMR spectrum, and ^{31}P NMR displayed a doublet peak at 34.1 ppm ($^1J_{\text{Rh-P}} = 173$ Hz). These results indicate that the rhodium center is coordinated with both the diene moiety and the phosphorus atom in solution.

To evaluate the designed rhodium catalysts, the reaction of 1,6-enyne **4a** was carried out in the presence of $[\text{RhCl}((R)\text{-L}^*)]$ (2 mol %) and $\text{NaBAR}^{\text{F}}_4$ (4 mol %) ($\text{Ar}^{\text{F}} = 3,5\text{-bis(trifluoromethyl)phenyl}$) in 1,2-dichloroethane at 40 °C for 24 h (Table 1). The use of a rhodium complex coordinated with $(R)\text{-3a}$ gave a 73% yield of the cycloisomerization product **5a**, whose enantiomeric excess was 81% (entry 1). The substituent of the phosphorus atom on the ligand had a significant effect on the catalytic activity and enantioselectivity (entries 2–5). Thus, chiral ligand **3b** substituted with *p*-tolyl groups on the phosphorus atom improved both the yield and enantioselectivity of **5a** (87% yield, 82% ee) (entry 2). Ligand **3c** having a bulky *tert*-butyl group at the *para*-position displayed the highest catalytic activity and enantioselectivity to give **5a** in 90% yield with 91% ee (entry 3). High enantioselectivity was also observed by use of ligand **3d** bearing bulkier aromatic groups (3,5-di-*tert*-butyl-4-methoxyphenyl), although the reaction was slow (entry 4), and a prolonged reaction time (72 h) was required for the complete conversion of **4a** giving **5a** in 90% yield with 89% ee (entry 5). Both the yield

Table 1. Rhodium-Catalyzed Cycloisomerization of **4a**^a



entry	ligand (L^*)	conversion (%) ^b	yield (%) ^b	ee (%) ^c
1	3a	82	73	81
2	3b	98	87	82
3	3c	100	90 ^d	91
4	3d	56	52	90
5 ^e	3d	100	90 ^d	89
6	1 / PPh_3 ^f	33	27	83
7	6 ^g	0	0	—
8	6 / PPh_3 ^{g,h}	25	11	41
9	7	50	49	55
10 ⁱ	3c	0	0	—

^a For detailed reaction conditions, see Supporting Information.

^b Determined by ^1H NMR. ^c Determined by HPLC. ^d Isolated yield.

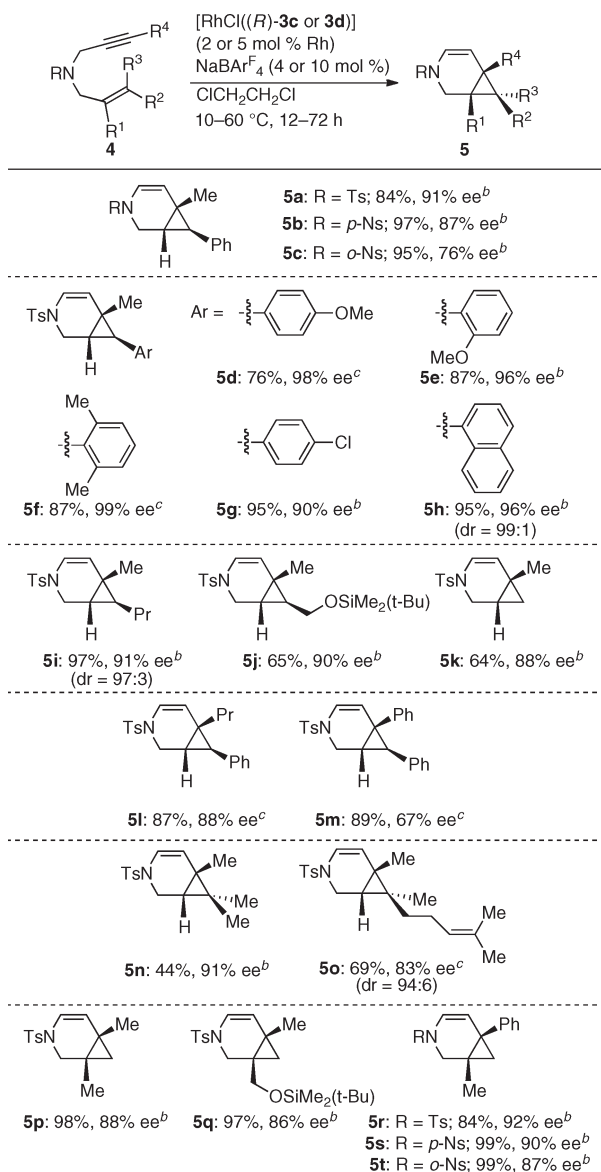
^e For 72 h. ^f $[\text{RhCl}(\text{PPh}_3)((S,S)\text{-1})]$ (2 mol %). ^g $[\text{RhCl}((R)\text{-6})]_2$ (2 mol % of Rh). ^h PPh_3 (2 mol %). ⁱ Without $\text{NaBAR}^{\text{F}}_4$.

and the ee value of **5a** obtained here are higher than those obtained with ligand **1** shown in Scheme 1.¹⁴ Thus, the reaction catalyzed by $[\text{RhCl}(\text{PPh}_3)((S,S)\text{-1})]$ (2 mol %) gave a 27% yield of **5a** with 83% ee under the same reaction conditions (entry 6). Ligand **6**,^{17b} which lacks a phosphorus group, displayed no catalytic activity (entry 7).¹⁸ The use of triphenylphosphine as a second ligand combined with ligand **6** displayed low catalytic activity and enantioselectivity (entry 8). The use of diene-phosphine ligand **7**, where an *o*-(diphenylphosphino)phenyl group is tethered by an ether functionality instead of the ester one of **3a**, gave **5a** in 49% yield 55% ee (entry 9). This result indicates that high catalytic activity of the rhodium/**3a** complex (entry 1 vs entry 9) is due to its high π -accepting ability caused by the electron-deficient alkene moiety located trans to the coordination site toward **4a**. Facile formation of the cationic rhodium species with the aid of $\text{NaBAR}^{\text{F}}_4$ was also essential in the present reaction (entry 10). The absolute configuration of **5a** obtained with $(R)\text{-3}$ was determined to be (1*S*,6*R*,7*R*)-(+ by comparison of its specific rotation with the value reported previously.¹⁴

The substrate scope of the present rhodium-catalyzed asymmetric cycloisomerization of nitrogen-bridged 1,6-enynes **4** was fairly broad as shown in Scheme 4. The reaction was carried out by use of $[\text{RhCl}((R)\text{-3c})]$ or $[\text{RhCl}((R)\text{-3d})]$ as a precursor of the active cationic rhodium species,

(18) The use of a chiral tetrafluorobenzobarrelene ligand substituted with a methyl and a 2-(diisopropylamido)phenyl group, which is an efficient tridentate ligand in the rhodium-catalyzed asymmetric cyclopropanation of styrene (ref 15), gave no cycloisomerization product **5a**.

Scheme 4. Rhodium-Catalyzed Cycloisomerization of 1,6-Enyne **4**^a



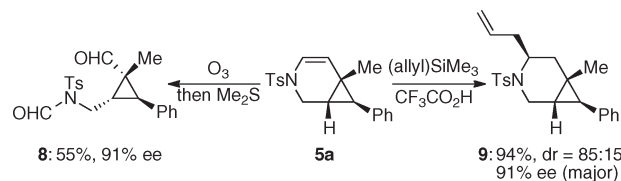
^a For detailed reaction conditions, see Table S1 in the Supporting Information. ^b Performed with [RhCl((*R*)-**3c**)]. ^c Performed with [RhCl((*R*)-**3d**)].

where the ligand, displaying high catalytic activity and enantioselectivity, was selected depending on the enynes. Asymmetric cycloisomerization can be applied to the enynes bearing not only a *p*-toluenesulfonyl group (Ts; **4a**) on the nitrogen atom but also a 4-nitrobenzenesulfonyl (*p*-Ns; **4b**) and 2-nitrobenzenesulfonyl group (*o*-Ns; **4c**) to give the corresponding bicyclic compounds **5a–5c** in high yields with 91, 87, and 76% ee, respectively. The reaction of 1,6-enynes **4d–4h** bearing aryl groups on the alkene

(19) The reaction of an oxygen-tethered analogue of **4m** under the same reaction conditions did not give the corresponding oxabicyclo[4.1.0]heptene derivative due to oligomerization of the starting 1,6-enyne.

moiety (R²) proceeded to give the corresponding bicyclic compounds **5d–5h** in high yields, the enantioselectivity ranging between 90 and 99% ee. 1,6-Enynes substituted with a propyl group (**4i**), a silyloxymethyl group (**4j**) on the alkene moiety (R²), and unsubstituted **4k** (R² = H) also gave the corresponding cycloisomerization products **5i–5k** in 64–97% yields over 88% ee. The enynes **4l** and **4m** substituted with propyl and phenyl at the alkyne terminus (R⁴) were also good substrates to give **5l** and **5m** with 88% and 67% ee, respectively.¹⁹ In the reactions of 1,6-enynes **4n** and **4o** bearing trisubstituted alkene moieties, although the yields of the cycloisomerization products were modest because of the formation of oligomeric compounds, enantioselectivities of the products were high (91% ee for **5n** and 88% ee for **5o**). High enantioselectivities were also observed in the reactions of 1,6-enynes **4p–4t** possessing an exomethylene part (R² = R³ = H) giving the corresponding products in high yields with high enantioselectivity (86–92% ee).²⁰

Scheme 5. Transformations of **5a**



The bicyclic compound **5a** obtained here with 91% ee is readily converted into functionalized compounds without loss of enantiomeric purity (Scheme 5). For example, oxidative cleavage of an alkene moiety of **5a** with ozone gave highly functionalized cyclopropane **8** in 55% yield. The allylation of **5a** by treatment with allyltrimethylsilane in the presence of trifluoroacetic acid gave allylation product **9** in 94% yield.

In summary, we have developed a rhodium-catalyzed asymmetric cycloisomerization of nitrogen-bridged 1,6-enynes giving 3-azabicyclo[4.1.0]heptenes in high yields with high enantioselectivity. The reaction was realized by use of a cationic rhodium complex coordinated with a chiral diene/phosphine tridentate ligand, which is readily prepared in an enantiopure form.

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Supporting Information Available. Experimental procedures and data for the substrates and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(20) The relative and absolute configurations of **5p** obtained with (*R*, *R*)-**3c** were determined to be (1*S*,6*S*) by X-ray crystallographic analysis (CCDC 816724).