ORGANIC LETTERS

2011
Vol. 13, No. 14
3674–3677

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

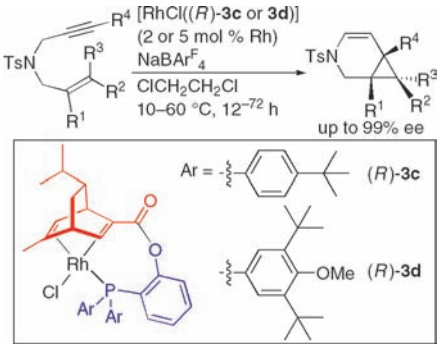
Takahiro Nishimura,* Yuko Maeda, and Tamio Hayashi*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

tnishi@kuchem.kyoto-u.ac.jp; thayashi@kuchem.kyoto-u.ac.jp

Received May 17, 2011

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.

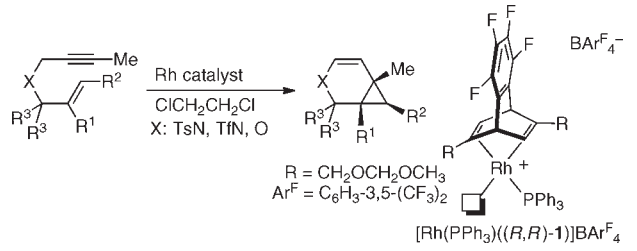
The recent development of transition-metal-catalyzed cycloisomerization of 1,n-enynes provides a useful methodology for the preparation of diverse polycyclic compounds in a single step.[1] Cycloisomerization of heteroatom-bridged 1,6-enynes is one of the most straightforward methods for the synthesis 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 bisphoshine/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/bisphoshine 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 ligand[12] based on a tetrafluorobenzobarrelene (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

(1) For reviews, see: (a) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215. (b) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431. (c) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (d) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (e) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (f) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (g) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847.

(2) Micheli, F.; Cavanni, P.; Andreotti, D.; Arban, R.; Benedetti, R.; Bertani, B.; Bettati, M.; Bettelini, L.; Bonanomi, G.; Braggio, S.; Carletti, R.; Checchia, A.; Corsi, M.; Fazzolari, E.; Fontana, S.; Marchioro, C.; Merlo-Pich, E.; Negri, M.; Oliosi, B.; Ratti, E.; Read, K. D.; Roscic, M.; Sartori, I.; Spada, S.; Tedesco, G.; Tarsi, L.; Terreni, S.; Visentini, F.; Zocchi, A.; Zonzini, L.; Di Fabio, R. *J. Med. Chem.* **2010**, *53*, 4989.

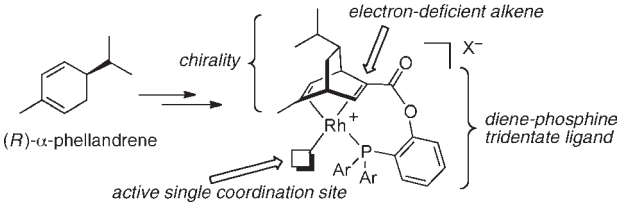
10.1021/ol2013236
Published on Web 06/21/2011

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



single coordination site[13] 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 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 (1*R*,4*R*,7*R*)-**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

(3) (a) Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567. (b) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. (c) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511. (d) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (e) Nevado, C.; Ferrer, C.; Echavarren, A. M. *Org. Lett.* **2004**, *6*, 3191. (f) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244. (g) Cho, E. J.; Kim, M.; Lee, D. *Org. Lett.* **2006**, *8*, 5413. (h) Hercouet, A.; Berrée, F.; Lin, C. H.; Toupet, L.; Carboni, B. *Org. Lett.* **2007**, *9*, 1717. (i) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306. (j) Olagnier, D.; Costes, P.; Berry, A.; Linas, M.-D.; Urrutigoity, M.; Dechy-Cabaret, O.; Benoit-Vical, F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6075. (k) Xia, J.-B.; Liu, W.-B.; Wang, T.-M. You, S.-L. *Chem.—Eur. J.* **2010**, *16*, 6442.

(4) (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. (b) Lee, S. I.; Kim, S. M.; Kim, S. Y.; Chung, Y. K. *Synlett* **2006**, 2256. (c) Lee, S. I.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, Y. K. *J. Org. Chem.* **2006**, *71*, 9366. (d) Kim, S. M.; Park, J. H.; Choi, S. Y.; Chung, Y. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6172. (e) Chen, Z.; Zhang, Y.-X.; Wang, Y.-H.; Zhu, L.-L.; Liu, H.; Li, X.-X.; Guo, L. *Org. Lett.* **2010**, *12*, 3468.

(5) Costes, P.; Weckesser, J.; Dechy-Cabaret, O.; Urrutigoïty, M.; Kalck, P. *Appl. Organomet. Chem.* **2008**, *22*, 211.

(6) Shibata, T.; Kobayashi, Y.; Maekawa, S.; Toshida, N.; Takagi, K. *Tetrahedron* **2005**, *61*, 9018.

(7) Sim, S. H.; Lee, S. I.; Park, J. H.; Chung, Y. K. *Adv. Synth. Catal.* **2010**, *352*, 317.

(8) For a recent example of asymmetric cycloisomerization of enynes via 5-*endo* cyclization, see: Martínez, A.; García-García, P.; Fernández-Rodriíguez, M. A.; Rodríguez, F.; Sanz, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 4633.

(9) (a) Brissy, D.; Skander, M.; Retailleau, P.; Marinetti, A. *Organometallics* **2007**, *26*, 5782. (b) Brissy, D.; Skander, M.; Retailleau, P.; Frison, G.; Marinetti, A. *Organometallics* **2009**, *28*, 140. (c) Brissy, D.; Skander, M.; Jullien, H.; Retailleau, P.; Marinetti, A. *Org. Lett.* **2009**, *11*, 2137.

(10) Chao, C.-M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, 6988.

(11) For an example of gold-catalyzed asymmetric cycloisomerization for the synthesis of the triple reuptake inhibitor, see: Deschamps, N. M.; Elitzin, V. I.; Liu, B.; Mitchell, M. B.; Sharp, M. J.; Tabet, E. A. *J. Org. Chem.* **2011**, *76*, 712.

(12) For reviews of chiral diene ligands, see: (a) Shintani, R.; Hayashi, T. *Aldrichimica Acta* **2009**, *42*, 31. (b) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482.

(13) Feducia, J. A.; Campbell, A. N.; Doherty, M. Q.; Gagné, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 13290.

(14) Nishimura, T.; Kawamoto, T.; Nagaosa, M.; Kumamoto, H.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 1638.

(15) Nishimura, T.; Maeda, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7324.

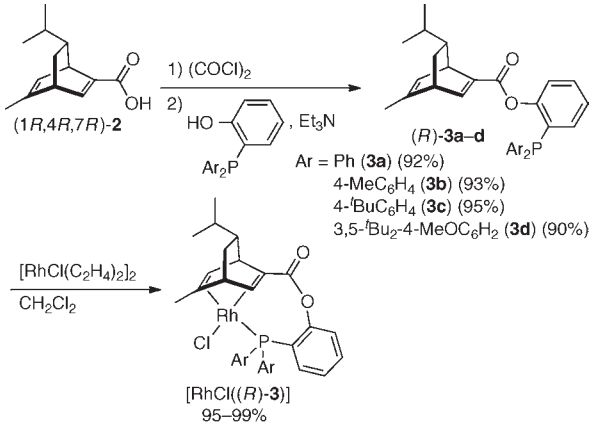
(16) For selected examples of the use of phosphine/alkene hybrid ligands in the symmetric reactions, see: (a) Maire, P.; Delbon, S.; Breher, F.; Geier, J.; Böhler, C.; Rüegger, H.; Schönberg, H.; Grützmacher, H. *Chem.—Eur. J.* **2004**, *10*, 4198. (b) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4611. (c) Kasák, P.; Arion, V. B.; Widhalm, M. *Tetrahedron: Asymmetry* **2006**, *17*, 3084. (d) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. (e) Mariz, R.; Briceño, A.; Dorta, R. *Organometallics* **2008**, *27*, 6605. (f) Štěpnička, P.; Císařová, I. *Inorg. Chem.* **2006**, *45*, 8785. (g) Stemmler, R. T.; Bolm, C. *Synlett* **2007**, 1365. (h) Minuth, T.; Boysen, M. M. K. *Org. Lett.* **2009**, *11*, 4212. (i) Liu, Z.; Du, H. *Org. Lett.* **2010**, *12*, 3054.

(17) (a) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 4387. (b) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2009**, 4815. (c) Shintani, R.; Tsutsumi, Y.; Nagaosa, M.; Nishimura, T.; Hayashi, T. *J. Am. Chem. Soc.* **2009**, *131*, 13588. (d) Shintani, R.; Soh, Y.-T.; Hayashi, T. *Org. Lett.* **2010**, *12*, 4106. (e) Shintani, R.; Hayashi, T. *Org. Lett.* **2011**, *13*, 350. (f) Pattison, G.; Piraux, G.; Lam, H. W. *J. Am. Chem. Soc.* **2010**, *132*, 14373.

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 $[RhCl(C_2H_4)_2]_2$, and they were isolated in high yields (95–99%) by column chromatography on silica gel.

^{1}H NMR ($CDCl_3$) of the complex [RhCl((*R*)-**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*)-**3a**. Four alkenic carbons showing the

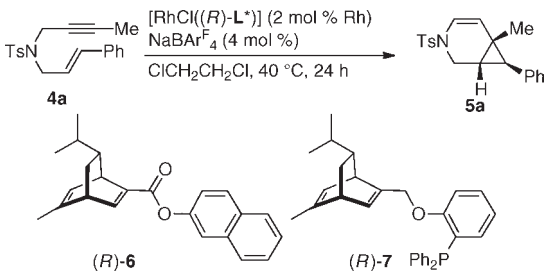
Scheme 3. Synthesis of Ligands and Their Rhodium Complexes



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 ($^1J_{Rh-P}$ = 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 [RhCl((*R*)-**L***)] (2 mol %) and $NaBAr^F_4$ (4 mol %) (Ar^F = 3,5-bis(trifluoromethyl)phenyl) in 1,2-dichloroethane at 40 °C for 24 h (Table 1). The use of a rhodium complex coordinated with (*R*)-**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	–

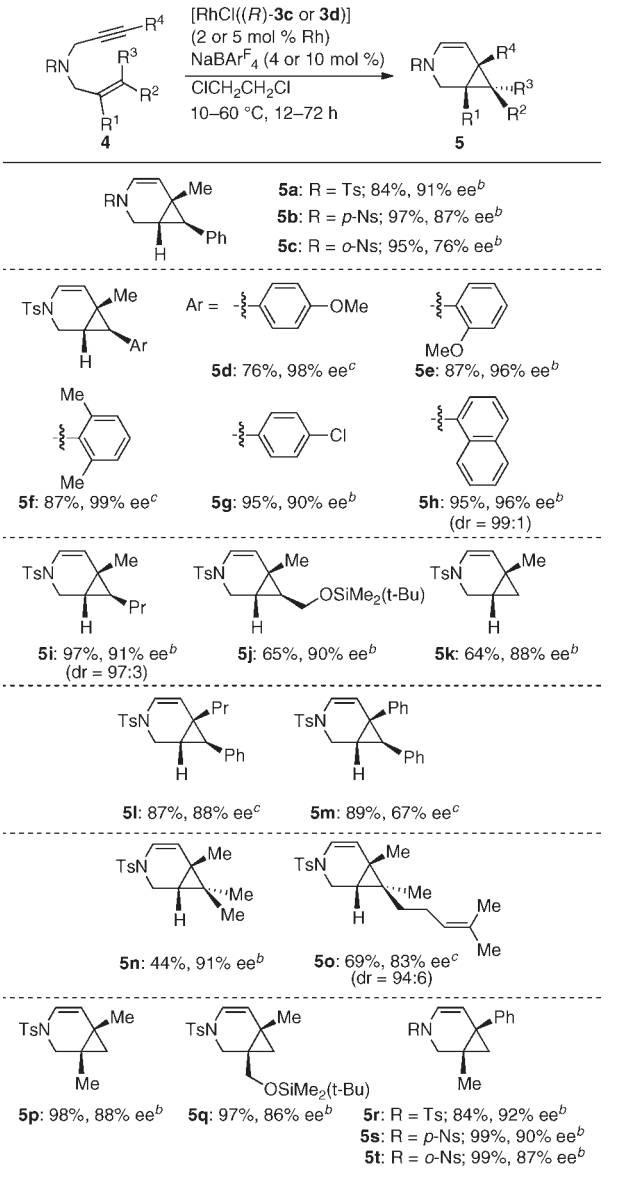
[a] For detailed reaction conditions, see Supporting Information. [b] Determined by ^{1}H NMR. [c] Determined by HPLC. [d] Isolated yield. [e] For 72 h. [f] [RhCl(PPh_3)((*S,S*)-**1**)] (2 mol %). [g] [RhCl((*R*)-**6**)]$_2$ (2 mol % of Rh). [h] PPh_3 (2 mol %). [i] Without $NaBAr^F_4$.

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 [RhCl(PPh_3)((*S,S*)-**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 $NaBAr^F_4$ was also essential in the present reaction (entry 10). The absolute configuration of **5a** obtained with (*R*)-**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 [RhCl((*R*)-**3c**)] or [RhCl((*R*)-**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-catalyed asymmetric cyclopropanation of styrene (ref 15), gave no cycloisomerization product **5a**.

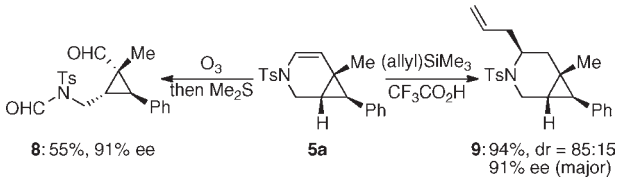
Scheme 4. Rhodium-Catalyzed Cycloisomerization of 1,6-Enyne **4**[a]



[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 moiety (R^2) 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 (R^2), and unsubstituted **4k** (R^2 = 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 (R^4) 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 (R^2 = R^3 = 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.

Acknowledgment. This work has been supported by a Grant-in-Aid for Scientific Research (19105002 and 22750090) from the MEXT, Japan.

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.

(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.

(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).