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Rhodium-Catalyzed Olefin Isomerization/ Enantioselective Intramolecular Alder-Ene Reaction Cascade

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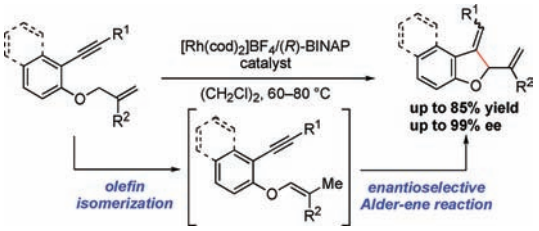
ABSTRACT



The olefin isomerization/enantioselective intramolecular Alder-ene reaction cascade was achieved by using a cationic rhodium(I)/(*R*)-BINAP complex as a catalyst. A variety of substituted dihydrobenzofurans and dihydronaphthofurans were obtained from phenol- or naphthol-linked 1,7-enynes, respectively, with good yields and ee values.

The transition-metal-catalyzed intramolecular Alder-ene reaction of 1,6-enynes is a valuable method for the construction of carbocycles and heterocycles.[1,2] The Trost group first reported an enantioselective variant of this reaction by using palladium catalysts, although the enantioselectivity was moderate.[3a] The Zhang group realized the highly enantioselective reaction by using rhodium catalysts.[3b] After these pioneering works, a number of highly efficient enantioselective reactions have been reported.[4] In these reports, 1,6-enynes, in which the propargyl group and the allyl group are connected with heteroatoms or malonates, have been most frequently

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(1) For reviews, see: (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (b) Trost, B. M. *Chem.—Eur. J.* **1998**, *4*, 2405. (c) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (d) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (e) Brummond, K. M.; McCabe, J. M. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; p 151. (f) Zhang, Z.; Zhu, G.; Tong, X.; Wang, F.; Xie, X.; Wang, J.; Jiang, L. *Curr. Org. Chem.* **2006**, *10*, 1457. (g) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268.

(2) For examples, see: (a) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. (b) Trost, B. M.; Lautens, M.; Chan, C.; Jeberatnam, D. J.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636. (c) Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; MacPherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255. (d) Sturla, S. J.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976. (e) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714. (f) Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2000**, *122*, 6490. (g) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2002**, *124*, 5025. (h) Tong, X.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 6370. (i) Tong, X.; Li, D.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 7601. (j) Fürstner, A.; Martin, R.; Majima, K. *J. Am. Chem. Soc.* **2005**, *127*, 12236. (k) Fürstner, A.; Majima, K.; Martin, R.; Krause, H.; Kattnig, E.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 1992. (l) Wang, J.; Xie, X.; Ma, F.; Peng, Z.; Zhang, L.; Zhang, Z. *Tetrahedron* **2010**, *75*, 1281.

(3) (a) Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651. (b) Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **2000**, *39*, 4104.

(4) For examples, see: (a) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249. (b) Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 8198. (c) Lei, A.; He, M.; Wu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4104. (d) Lei, A.; Waldkirch, J. P.; He, M.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4526. (e) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704. (f) Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 11472. (g) Hashmi, A. S. K.; Haufe, P.; Nass, A. R. *Adv. Synth. Catal.* **2003**, *345*, 1237. (h) Hashmi, A. S. K.; Haufe, P.; Nass, A. R.; Bats, J. W. *Adv. Synth. Catal.* **2004**, *346*, 421. (i) Mikami, K.; Kataoka, S.; Yusa, Y.; Aikawa, K. *Org. Lett.* **2004**, *6*, 3699. (j) He, M.; Lei, A.; Zhang, X. *Tetrahedron Lett.* **2005**, *46*, 1823. (k) Mikami, K.; Kataoka, S.; Aikawa, K. *Org. Lett.* **2005**, *7*, 5777. (l) Mikami, K.; Kataoka, S.; Wakabayashi, K.; Aikawa, K. *Tetrahedron Lett.* **2006**, *47*, 6361. (m) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3942. (n) Liu, F.; Liu, Q.; He, M.; Zhang, X.; Lei, A. *Org. Biomol. Chem.* **2007**, *5*, 3531. (o) Nicolaou, K. C.; Li, A.; Ellery, S. P.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6293. (p) Corkum, E. G.; Hass, M. J.; Sullivan, A. D.; Bergens, S. H. *Org. Lett.* **2011**, *13*, 3522.

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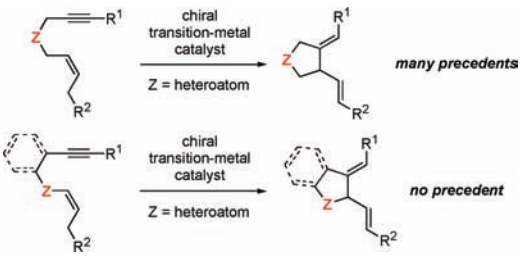
employed due to their high stability and facile preparation (Scheme 1). However, 1,6-enynes, possessing the heteroatom-substituted alkene moiety, have not been employed presumably due to their low stability and troublesome preparation (Scheme 1).

Scheme 1



On the other hand, our research group recently reported the cationic rhodium(I)/dppf complex-catalyzed olefin isomerization[5]/propargyl Claisen rearrangement cascade of ether-linked 1,6-enynes **A**, possessing the 1,1-disubstituted alkene moiety, leading to allenyl aldehydes **C** (Scheme 2).[6] In this cascade reaction, 1,5-enynes **B**, possessing the enol ether moiety, are generated in situ and subsequently undergo the propargyl Claisen rearrangement in one pot. We anticipated that if 1,7-enynes **D**, in which the CR^3R^4 moiety of **A** is replaced with the phenyl group, are employed, 1,6-enynes **E**, possessing the trisubstituted enol ether moiety, are generated in situ[7] and subsequently undergo the enantioselective intramolecular Alder-ene reaction to give enantioenriched dihydrobenzofurans **F** in one pot (Scheme 2). Although Mikami and co-workers reported the enantioselective intramolecular Alder-ene reactions of trisubstituted olefinic 1,6-enynes,[4a,e] those possessing a terminally disubstituted alkene moiety have been scarcely explored.[8] Therefore, the enantioselective transformation from **E** to **F** is challenging. Herein, we report the asymmetric synthesis of substituted dihydrobenzofurans by the cationic rhodium(I)/(*R*)-BINAP complex-catalyzed olefin isomerization/enantioselective intramolecular Alder-ene reaction cascade.[9]

The reaction of 1,7-enyne **1a** was first investigated in the presence of a cationic rhodium(I)/(*R*)-BINAP complex

Scheme 2

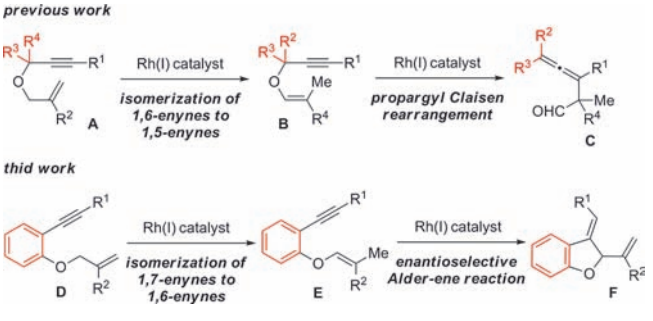
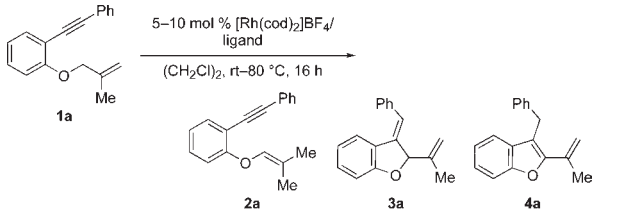


Table 1. Optimization of Reaction Conditions for Rh-Catalyzed Cascade Reaction of 1,7-Enyne **1a**[a]



				% yield[b] (% ee)		
entry	ligand	temp	conv (%)	**2a**	**3a**	**4a**
1	(*R*)-BINAP	rt	43	31	10 (97)	0
2	(*R*)-BINAP	80 °C	100	0	11 (97)	73
3	(*R*)-Segphos	80 °C	100	0	16 (96)	62
4	(*R*)-H_8−BINAP	80 °C	100	15	45 (97)	26
5	(*S,S*)-DIOP	80 °C	100	32	0	18
6	(*S,S*)-BDPP	80 °C	100	51	0	15
7[c]	(*S,S*)-Chiraphos	80 °C	100	78	0	5
8[c]	(*R,R*)-Me-Duphos	80 °C	45	43	0	0
9[c]	(*R,R*)-QuinoxP*	80 °C	98	81	0	0
10[d]	(*R*)-BINAP	70 °C	97	8	69 (98)	4

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol, 10 mol %), ligand (0.010 mmol, 10 mol %), **1a** (0.10 mmol), and $(CH_2Cl)_2$ (1.5 mL) were used. [b] Isolated yield. As **2a** and **3a** were isolated as a mixture, their yields were determined by ^{1}H NMR. [c] $[Rh(nbd)_2]BF_4$ was used. [d] $[Rh(cod)_2]BF_4$ (0.015 mmol, 5 mol %), ligand (0.015 mmol, 5 mol %), **1a** (0.30 mmol), and $(CH_2Cl)_2$ (1.5 mL) were used.

(10 mol %). At room temperature for 16 h, the desired dihydrobenzofuran **3a** was obtained with a high ee value (Table 1, entry 1). However, the reaction was sluggish and enol ether **2a** was generated as a major product. Although a complete conversion of **1a** was observed at 80 °C for 16 h, achiral benzofuran **4a** was generated as a major product (entry 2). The effect of chiral bisphosphine ligands (Figure 1) was then examined at 80 °C (entries 2−9), which revealed that biaryl bisphosphines are effective ligands for the formation of **3a** and **4a** (entries 2−4), and (*R*)-BINAP showed the highest reaction rate (entry 2). To suppress the formation of **4a**, the reaction conditions were carefully optimized. Gratifyingly, when the reaction was conducted using 5 mol % catalyst at 70 °C, **3a** was obtained in good yield with a high ee value (entry 10).

(5) For a recent review of the transition-metal-catalyzed olefin isomerization, see: Tanaka, K. In *Comprehensive Organometallic Chemistry III*; Crabtree, R. H., Mingos, D. M. P., Ojima, I., Eds.; Elsevier: Oxford, 2007; Vol. 10, p 71.

(6) Tanaka, K.; Okazaki, E.; Shibata, Y. *J. Am. Chem. Soc.* **2009**, *131*, 10822.

(7) In the cationic rhodium(I)/bisphosphine complex-catalyzed Alder-ene reaction of oxygen-linked 1,6-enynes, the formation of 1,5-enynes, possessing the enol ether moiety, was observed as the undesired side reaction. See: ref 3b.

(8) A single example using the 1,6-enyne possessing a terminally disubstituted alkene moiety has been reported. However, this reaction is limited to an *N*-tosylate protected amide. See: ref 4d.

(9) Recently, novel cascade reactions initiated by the transition-metal-catalyzed olefin isomerization reaction were reported. See: (a) Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2008**, *130*, 14452. (b) Terada, M.; Toda, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6354.

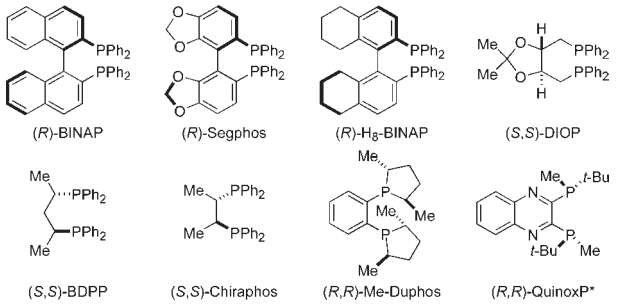


Figure 1. Structures of chiral bisphosphine ligands.

With the optimized reaction conditions in hand, we explored the scope of the cationic rhodium(I)/(*R*)-BINAP complex-catalyzed olefin isomerization/enantioselective intramolecular Alder-ene reaction cascade (Table 2). Various aryl (entries 1−4), alkenyl (entry 5), and alkyl substituents (entries 6−8) could be incorporated at the alkyne terminus. This study revealed that the electronic nature of the aromatic substituents at the alkyne terminus showed a modest impact on the product yields [electron-deficient aryl (entries 3 and 4) > electron-rich aryl (entries 1 and 2)].[10] On the other hand, the ee values of aryl-, cyclohexenyl-, and cyclohexyl-substituted products were higher than those of primary alkyl-substituted ones (entries 1−6 vs entries 7 and 8). With respect to the substituents at the alkene moiety, phenyl-substituted enyne **1i** could be transformed into the corresponding dihydrobenzofuran **3i** with a high ee value, although the product yield was low (entry 9).[11] In these reactions, the major olefin geometries were in an *E* configuration (entries 1−9). However, the products obtained from naphthyl-linked 1,7-enynes **1j** and **1k** were *Z* isomers (entries 10 and 11).[12] The absolute configuration of dihydronaphthofuran (−)-**3k** was unambiguously determined to be *S* by the anomalous dispersion method (Figure 2).

The reactions of 1,7-enynes **1l** and **1m**, possessing the 1,2-disubstituted alkene moiety, were also examined (Scheme 3). Although the desired chiral dihydrobenzofurans were not obtained at all, the corresponding benzofurans **4l** and **4m** were obtained in moderate yields.

(10) In the reactions of **1c** and **1d**, the formation of the corresponding benzofurans was suppressed.

(11) The corresponding benzofuran **4i** was also generated in ca. 13% yield.

(12) Importantly, the benzene or naphthalene linkage in 1,7-enynes is necessary to gain high product yield. The reaction of ethylene-linked 1,7-enyne **1n** proceeded in low yield, although the product **3n** could not be isolated in a pure form due to the formation of an unidentified mixture of byproduct. In addition, the reaction of tosylamide-linked 1,7-enyne **1o** was sluggish.

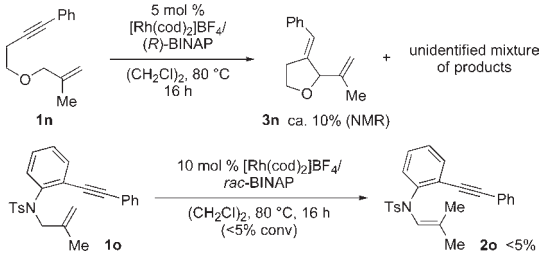
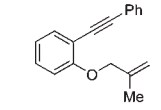
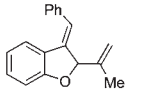
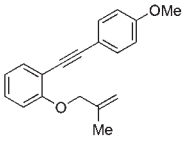
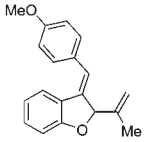
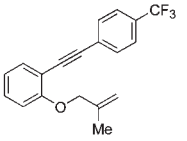
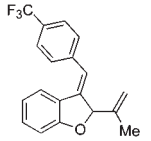
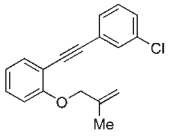
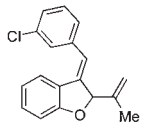
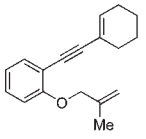
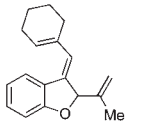
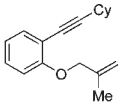
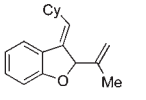
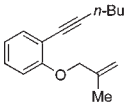
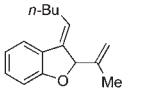
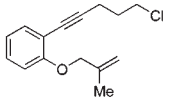
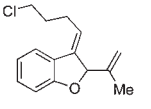
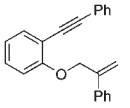
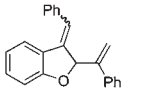
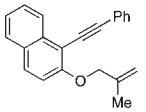
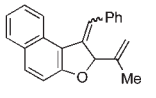
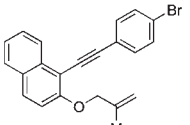
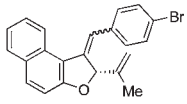


Table 2. Rh-Catalyzed Olefin Isomerization/Enantioselective Intramolecular Alder-Ene Reaction Cascade of 1,7-Enynes **1a**−**k**[a]

entry	1	conditions	product % yield[b] (% ee)
1	 **1a**	70 °C 16 h	 (−)-**3a** 69[c] (98)
2[d]	 **1b**	70 °C 48 h	 (+)-**3b** 69[e] (97)
3	 **1c**	70 °C 16 h	 (−)-**3c** 76 (98)
4	 **1d**	70 °C 48 h	 (−)-**3d** 85 (97)
5	 **1e**	70 °C 16 h	 (−)-**3e** 68 (98)
6	 **1f**	60 °C 24 h	 (−)-**3f** 81 (99)
7	 **1g**	60 °C 72 h	 (−)-**3g** 66 (88)
8	 **1h**	70 °C 48 h	 (−)-**3h** 69 (86)
9[d]	 **1i**	80 °C 72 h	 (−)-**3i** 23 (94) *E*/*Z* = 94:6
10	 **1j**	60 °C 16 h	 (−)-**3j** 60 (98) *E*/*Z* = 9:91
11	 **1k**	60 °C 16 h	 (*S*)-(−)-**3k** 72 (97) *E*/*Z* = 7:93

[a] Reactions were conducted using $[Rh(cod)_2]BF_4$ (0.015 mmol, 5 mol %), (*R*)-BINAP (0.015 mmol, 5 mol %), and **1a**−**k** (0.30 mmol) in $(CH_2Cl)_2$ (1.5 mL). [b] Isolated yield. [c] Isolated as a mixture of **2a** and **3a**. Pure **2a** and **3a** were isolated by GPC. [d] Catalyst: 10 mol %. [e] Isolated as a mixture of **3b** and **4b**. Pure **3b** was isolated by GPC.

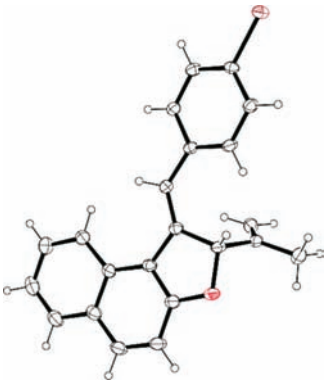
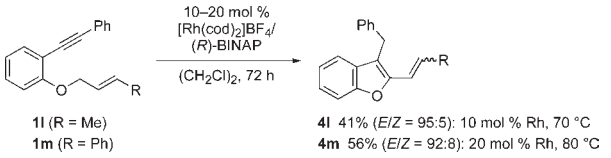


Figure 2. ORTEP diagram of (*S*)-(−)-**3k** with ellipsoids at 30% probability.

Scheme 3



We propose the following mechanism (Scheme 4). In the first step, the olefin isomerization[13] proceeds to afford 1,6-enyne **2**. Enyne **2** reacts with rhodium to afford rhodacyclopentene **G**. β-Hydride elimination followed by reductive elimination affords dihydrobenzofuran (*E*)-**3**. In the case of dihydronaphthofurans, *Z* isomers were obtained presumably through the rhodium-catalyzed isomerization of *E* isomers in order to release the steric hindrance.[14] Subsequent rhodium-catalyzed olefin isomerization affords benzofuran **4**.[15]

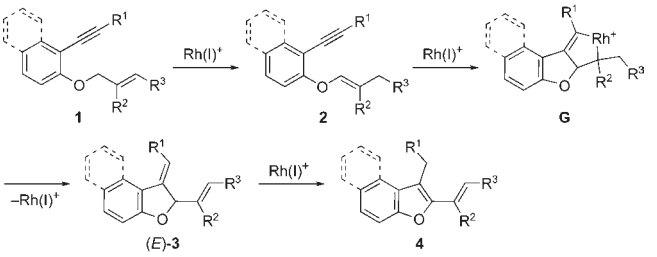
Indeed, isolated **2a** was transformed into **3a** and **4a** at 70 °C in the presence of the cationic rhodium(I)/(*R*)-BINAP catalyst (Scheme 5). Furthermore, heating of **3a** in $(CH_2Cl)_2$ in the absence of the Rh catalyst did not furnish **4a** (Scheme 6).

(13) For the cationic rhodium(I)/bisphosphine complex-catalyzed isomerization of allyl ethers to enol ethers, see: (a) Fatig, T.; Soulié, J.; Lallemand, J.-Y.; Mercier, F.; Mathey, F. *Tetrahedron* **2000**, *56*, 101. (b) Hiroya, K.; Kurihara, Y.; Ogasawara, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2287.

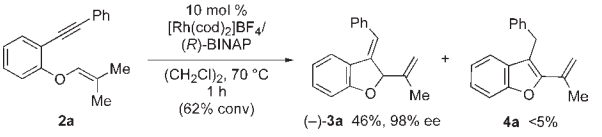
(14) For the cationic rhodium(I)/bisphosphine complex-catalyzed *E*/*Z* isomerization of alkenes, see: Tanaka, K.; Shoji, T.; Hirano, M. *Eur. J. Org. Chem.* **2007**, 2687.

(15) For the cationic rhodium(I)/bisphosphine complex-catalyzed isomerization of α-alkylidenecycloalkanones to cycloalkenones, see: Takeishi, K.; Sugishima, K.; Sasaki, K.; Tanaka, K. *Chem.—Eur. J.* **2004**, *10*, 5681.

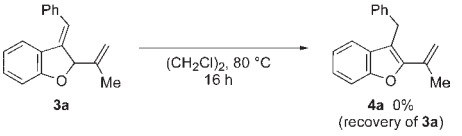
Scheme 4



Scheme 5



Scheme 6



In conclusion, the olefin isomerization/enantioselective intramolecular Alder-ene reaction cascade was achieved by using a cationic rhodium(I)/(*R*)-BINAP complex as a catalyst. A variety of substituted dihydrobenzofurans and dihydronaphthofurans were obtained from phenol- or naphthol-linked 1,7-enynes, respectively, with good yields and ee values. Further utilization of the cationic rhodium(I) complex for various cascade reactions is underway in our laboratory.

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Supporting Information Available. Experimental procedures, compound characterization data, and an X-ray crystallographic information file. This material is available free of charge via the Internet at http://pubs.acs.org.