J|A|C|S
COMMUNICATIONS

Published on Web 01/18/2007

Rhodium-Catalyzed Asymmetric Cyclodimerization of Oxa- and Azabicyclic Alkenes

Takahiro Nishimura,* Takahiro Kawamoto, Keigo Sasaki, Eiji Tsurumaki, and Tamio Hayashi*

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

Received November 27, 2006; E-mail: thayashi@kuchem.kyoto-u.ac.jp

Owing to their high and unique reactivity, oxa- and azabicyclic alkenes have been recognized as useful starting compounds for enantioselective synthesis of chiral building blocks in recent years.[1] Lautens and co-workers have developed transition-metal-catalyzed asymmetric transformations of these bicyclic alkenes, where enantioposition-selective addition of nucleophiles brings about desymmetrization of their meso structure, and subsequent ring-opening reactions provide a route to optically active compounds bearing multiple stereocenters.[2] Another important synthetic use of the oxa- and azabicyclic alkenes is the nickel-catalyzed co-dimerization with alkynes giving benzocoumarins or dihydroarenes reported by Cheng and co-workers.[3,4] This type of co-dimerization is of great interest because of the high atom efficiency.[5] Here we describe that a cationic binap−rhodium complex efficiently catalyzes asymmetric cyclodimerization of oxa- and azabicyclic alkenes, providing a new method for the construction of chiral furan and pyrrolidine derivatives with excellent enantioselectivity.

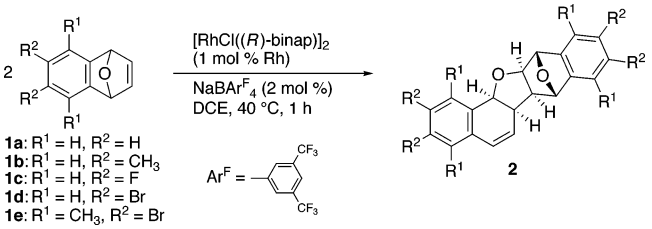
A cationic rhodium complex coordinated with binap was found to be highly effective in catalyzing the asymmetric cyclodimerization of oxabenzonorbornadienes **1**, producing high yields of polycyclic tetrahydrofuran derivatives with high enantioselectivity (Table 1). Thus, a solution of **1a**, $[RhCl((R)\text{-binap})]_2$[6] (1 mol % of Rh), and $NaBAr^F_4$ (Ar^F = 3,5-bis(trifluoromethyl)phenyl)[7] in 1,2-dichloroethane (DCE) was heated at 40 °C for 1 h. Evaporation of the solvent followed by silica gel chromatography gave a quantitative yield of (+)-tetrahydrofuran **2a** ($[\alpha]_D^{20}$ +220 (*c* 1.03, $CHCl_3$)), whose enantiomeric purity was 99% (entry 1). The presence of $NaBAr^F_4$ is essential for this reaction, indicating that a cationic rhodium complex works as an active catalytic species. A cationic rhodium complex generated from $[Rh(cod)_2]BF_4$ and (*R*)-binap can also be used, but the reaction was slower than that with the combination of $[RhCl((R)\text{-binap})]_2$ and $NaBAr^F_4$, probably due to the strong coordination ability of 1,5-cyclooctadiene which prevents the olefinic substrate from coordinating to the rhodium. Oxabenzonorbornadienes **1b**−**1e** bearing substituents on the benzene ring also gave the corresponding cyclodimerization products **2b**−**2e** in high yields with high enantioselectivity (96−99% ee) (entries 2−5). The relative and absolute configurations of **2d** were determined as depicted in Table 1 by X-ray crystallographic analysis.[8]

On the basis of high catalytic activity of the cationic rhodium complex and stereochemistry of the product, the catalytic cycle of the present cyclodimerization is speculated as shown in Scheme 1. A coordinatively unsaturated cationic binap/rhodium(I) species **A**, generated from $[RhCl((R)\text{-binap})]_2$ and $NaBAr^F_4$, undergoes the oxidative cyclization with two molecules of oxabenzonorbornadiene **1a** to form rhodacyclopentane intermediate **B**.[9] β-Oxygen elimination giving a six-membered alkoxorhodium(III) complex **C**[10] followed by reductive elimination of sp^3 C−O bond[11] from **C** produces tetrahydrofuran **2a** with regeneration of the cationic rhodium(I) **A**.

It is most likely that the stereochemistry of the product **2a** is decided at the formation of rhodacyclopentane intermediate **B** (Scheme 2). Two molecules of the olefinic substrate **1a** approach the rhodium, avoiding the steric repulsions between the phenyl rings on the diphenylphosphino groups of binap[12] and oxabenzonorbornadiene moiety. Thus, the rhodacyclopentane in the **B-1** structure, which leads to (+)-enantiomer of **2a**, is formed preferentially over its diastereomeric isomer **B-2** or a meso-type rhodacyclopentane intermediate.[13]

The same type of ring-opening cyclodimerization was observed in the rhodium-catalyzed reaction of **3**, which is an aza analogue of **2a** (eq 1). Although the reactivity of **3** is lower, the reaction in toluene at 100 °C for 14 h gave 90% yield of pyrrolidine derivative **4** with 99% ee. The reaction of oxanorbornadiene **5**, which lacks the benzo moiety, proceeded in a different way to give 56% yield

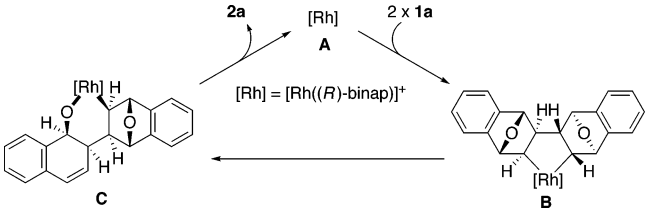
Table 1. Rhodium-Catalyzed Asymmetric Cyclodimerization of Oxabenzonorbornadiene[a]



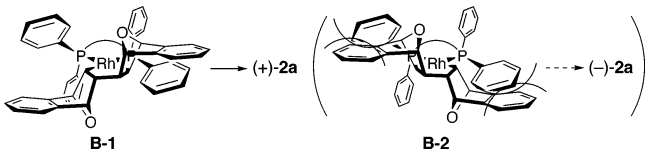
entry	substrate	product	isolated yield (%)	ee (%) of **2**[b]
1	**1a**	**2a**	99	99
2	**1b**	**2b**	99	98
3	**1c**	**2c**	99	99
4	**1d**	**2d**	99	99
5	**1e**	**2e**	92	96

[a] Reaction conditions: alkene **1** (0.40 mmol), $[RhCl((R)\text{-binap})]_2$ (0.002 mmol, 1 mol % of Rh), $NaBAr^F_4$ (0.008 mmol, 2 mol %), 1,2-dichloroethane (0.4 mL) at 40 °C for 1 h. [b] Determined by HPLC analysis with chiral stationary phase columns: Chiralcel OD−H (**2a**, **2c**−**2e**) and Chiralpak AS (**2b**).

Scheme 1. Proposed Catalytic Cycle



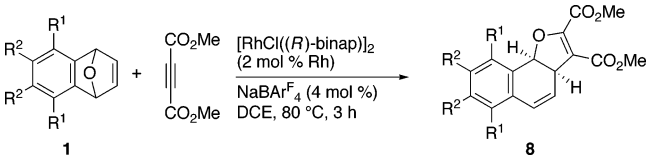
Scheme 2 [a]



[a] The binaphthalene moiety in (*R*)-binap is omitted for clarity.

10.1021/ja068488c CCC: $37.00

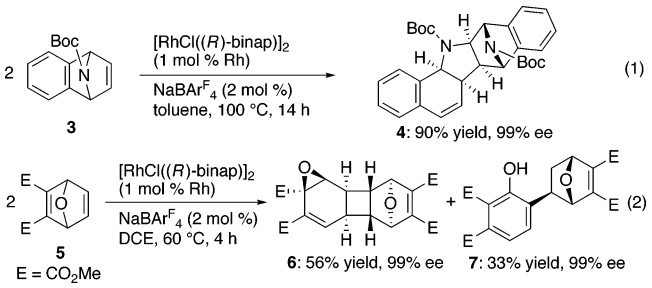
Table 2. Rhodium-Catalyzed Asymmetric Cross-Cyclodimerization of Oxabenzonorbornadiene and DMAD[a]



entry	substrate	product	isolated yield (%)	ee (%) of **8**[b]
1	**1a**	**8a**	95	99
2	**1b**	**8b**	87	98
3	**1c**	**8c**	97	99
4	**1d**	**8d**	89	99
5	**1e**	**8e**	94	87

[a] Reaction conditions: alkene **1** (0.20 mmol), dimethyl 2-butynedioate (DMAD) (0.60 mmol), $[RhCl((R)\text{-binap})]_2$ (2 mol % of Rh), $NaBAr^F_4$ (4 mol %), 1,2-dichloroethane (0.4 mL) at 80 °C for 3 h. [b] Determined by HPLC analysis with a chiral stationary phase column: Chiralcel OD−H.

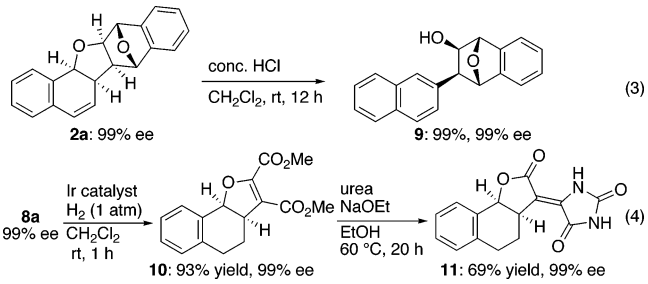
of cyclobutane **6** and 33% yield of phenol **7**, both of which have the same and high enantiomeric purity (99% ee) (eq 2).[14] Both **6** and **7** are formed probably by way of an alkoxorhodium intermediate analogous to **C**, the subsequent transformations of which are different from those in the case of **1**.[15]



The asymmetric cross-cyclodimerization of oxabenzonorbornadienes **1** with an alkyne was also successful using the cationic rhodium/binap catalyst (Table 2). Thus, treatment of **1a** with dimethyl 2-butynedioate (DMAD) (3 equiv) in the presence of $[RhCl((R)\text{-binap})]_2$ (2 mol % of Rh) and $NaBAr^F_4$ at 80 °C for 3 h gave dihydronaphthofuran **8a** in 95% yield (entry 1). It is remarkable that the enantioselectivity is extremely high (99% ee) here again. The present cross-cyclodimerization of oxabenzonorbornadiene **1a** with DMAD is one of the rare examples of [3 + 2] cycloaddition,[16] which may proceed via rhodacyclopentene in a catalytic cycle similar to the homodimerization shown in Scheme 1. Other oxabenzonorbornadienes **1b**−**1e** also gave the corresponding dihydronaphthofurans **8b**−**8e** in high yields with high enantioselectivity (entries 2−5).[17,18]

The homo- and cross-cyclodimerization products obtained here with high enantioselectivity are readily converted into some highly functionalized compounds without loss of enantiomeric purity. Two examples are shown in eqs 3 and 4. Treatment of the homodimerization product **2a** with hydrochloric acid leads to carbon−oxygen bond cleavage of the tetrahydrofuran ring, giving a quantitative yield of alcohol **9** (99% ee). Exposure of dihydronaphthofuran **8a** to hydrogen in the presence of iridium catalyst $[Ir(cod)(PCy_3)(py)]PF_6$[19] brought about selective hydrogenation of the double bond in the dihydronaphthalene moiety. On treatment of the resulting **10** with sodium ethoxide in ethanol in the presence of urea, the dihydrofuran ring was isomerized into lactone to give hydantoin **11** (99% ee), which has potential biological activity.[20]

In summary, we have realized a new type of catalytic asymmetric [3 + 2] cycloaddition reactions. High enantioselectivity (up to 99% ee) was observed in both homo- and cross-cyclodimerization of oxabicyclic alkenes by use of a cationic rhodium/(*R*)-binap catalyst.



Acknowledgment. This work has been supported in part by a Grant-in-Aid for Scientific Research, the Ministry of Education, Culture, Sports, Science and Technology, Japan (Priority Areas "Advanced Molecular Transformations of Carbon Resources").

Supporting Information Available: Experimental procedures and spectroscopic and analytical data for the substrates and products (PDF) and X-ray data files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Fagnou, K. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; Chapter 10. (b) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48. (c) Lautens, M.; Fagnou, K.; Taylor, M.; Rovis, T. *J. Organomet. Chem.* **2001**, *624*, 259.
(2) (a) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650. (b) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170. (c) Lautens, M.; Fagnou, K. *Tetrahedron* **2001**, *57*, 5067. (d) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884. (e) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437. (f) Cho, Y.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837 and references therein.
(3) (a) Rayabarapu, D. K.; Sambaiah, T.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1286. (b) Rayabarapu, D. K.; Cheng, C.-H. *Pure Appl. Chem.* **2002**, *74*, 69. (c) Rayabarapu, D. K.; Cheng, C.-H. *Chem.—Eur. J.* **2003**, *9*, 3164.
(4) Pd-catalyzed deoxygenative dimerization of oxabicyclic alkenes: Shih, H.-T.; Shih, H.-H.; Cheng, C.-H. *Org. Lett.* **2001**, *3*, 811.
(5) (a) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259. (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.
(6) Binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.
(7) (a) Nishida, H.; Takada, N.; Yoshimura, M.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600. (b) Brookhart, M.; Grant, B.; Volpe, A. F., Jr. *Organometallics* **1992**, *11*, 3920.
(8) The Flack parameter is 0.035(13) with this absolute configuration. See Supporting Information.
(9) For an example of rhodium-catalyzed asymmetric [2 + 2] cycloaddition, see: Shibata, T.; Takami, K.; Kawachi, A. *Org. Lett.* **2006**, *8*, 1343 and references therein.
(10) This type of β-oxygen elimination has been reported in the nickel-catalyzed cyclization (ref 3).
(11) A carbon−oxygen bond formation on the rhodium center is quite rare. Bernard, K. A.; Churchill, M. R.; Janik, T. S.; Atwood, J. D. *Organometallics* **1990**, *9*, 12.
(12) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T. *Organometallics* **1993**, *12*, 4188 and references therein.
(13) The products formed via meso-type or endo-cyclized rhodacyclopentane intermediates were not observed.
(14) A small amount of a dihydrofuran derivative (4%) formed via the similar pathway to **2** was also detected by ^1H NMR.
(15) A plausible reaction pathway for the formation of these products is shown in Supporting Information.
(16) (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (c) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (d) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.
(17) The structure of **8e** including its absolute configuration was determined by X-ray analysis. See Supporting Information.
(18) The cross-cyclodimerization was not observed with 4-octyne or diphenylacetylene.
(19) Crabtree, R. H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *135*, 395.
(20) (a) Lehmann, J. *Arch. Pharm.* **1984**, *317*, 459. (b) Brown, M. L.; Zha, C. C.; Van Dyke, C. C.; Brown, G. B.; Brouillette, W. J. *J. Med. Chem.* **1999**, *42*, 1537.

JA068488C