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Multinuclear Pd/Zn Complex-Catalyzed Asymmetric Alkylative Ring-Opening Reaction of Oxabicyclic Alkenes

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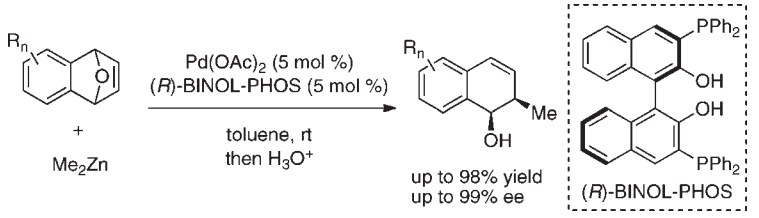
ABSTRACT



A multinuclear palladium catalyst can be used to realize the efficient catalytic asymmetric alkylative ring-opening reaction of oxabicyclic alkenes using dimethylzinc. The use of (*R*)-BINOL-PHOS bearing bisphosphine and diol moieties is essential for achieving excellent catalytic performance; the corresponding monophosphine and hydroxy-protected derivatives showed lower catalytic activities and/or enantioselectivities. The generation of Pd/Zn-multinuclear complexes is a key feature of the present catalysis.

The development of a multimetallic synergism contributes to new catalyst design as a novel and remarkably enhanced catalytic approach in organic chemistry.[1] We previously reported the BINOL scaffold for the generation of multinuclear complexes and achieved excellent catalytic performance in the Cu-catalyzed asymmetric conjugate addition of organozinc reagents to acyclic and cyclic enones.[2] The incorporation of Cu and Zn atoms in the catalyst was confirmed by ESI-MS analyses and was fundamental for the excellent catalytic performance. The present paper describes the asymmetric alkylative ring-opening reaction of oxabicyclic alkenes. As part of our ongoing studies on a new combination of transition metals and main group metals, we discovered that Pd and Zn atoms have cooperative effects in the catalyst (Figure 1). Our strategy using BINOL-PHOS ligands could be used to generate Zn-linked ligands with dialkylzinc reagents, the phosphorus moieties of which coordinate to Pd centers to form multinuclear complexes. There have been several reports on asymmetric alkylative ring-opening reactions using Pd catalyst, which can be used to achieve the highly enantioselective synthesis of optically active alcohols bearing contiguous chiral centers.[3,4] We describe here a multinuclear catalysis including Pd and Zn atoms for highly efficient asymmetric alkylative ring-opening reactions using organozinc reagents (Figure 2). The previously

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(1) (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (b) Majima, K.; Takita, R.; Okada, A.; Oshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 15837. (c) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777. (d) Takacs, J. M.; Reddy, D. S.; Moteki, S. A.; Wu, D.; Palencia, H. *J. Am. Chem. Soc.* **2004**, *126*, 4494. (e) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269. (f) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (g) Trost, B. M.; Müller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438. (h) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117 and references therein.

(2) Endo, K.; Ogawa, M.; Shibata, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 2410.

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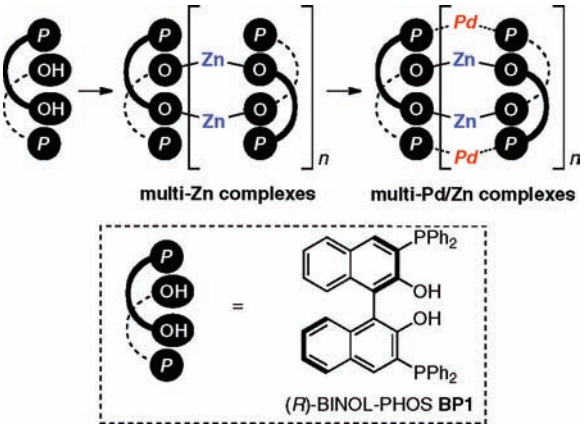


Figure 1. Design of multi-Pd/Zn-complexes.

reported ligands are expensive and somewhat difficult to synthesize; thus, a simple procedure for the synthesis of (*R*)-BINOL-PHOS (**BP1**) (3 steps without column chromatography, 65% yield from inexpensive (*R*)-BINOL) could broaden the utility of the present catalysis.[2,5]

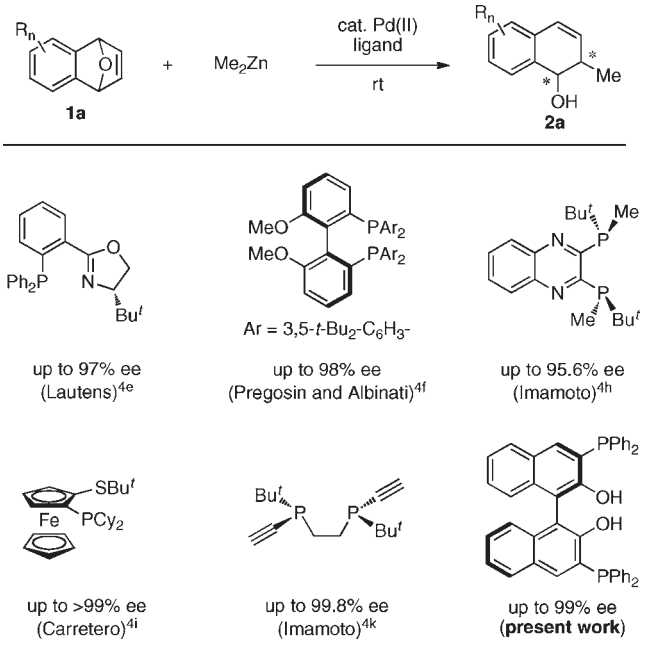
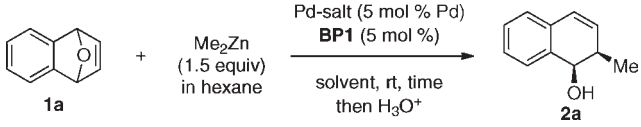


Figure 2. Representative ligands for Pd-catalyzed asymmetric alkylative ring opening of oxabicyclic alkenes.

The initial screening of reaction conditions is described in Table 1. The reaction of oxanorbornadiene **1a** and Me_2Zn (1.5 equiv) was carried out in the presence of Pd salt (5 mol %) and (*R*)-BINOL-PHOS (**BP1**) (5 mol %) at room temperature. The use of THF as a solvent gave the product **2a** in 48% yield with 56% ee (entry 1). The

(3) For reviews, see: (a) Lautens, M. *Synlett* **1993**, 177. (b) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1. (c) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48.

Table 1. Screening of Reaction Conditions



entry	Pd salt	solvent[a,b]	time (h)	yield, ee (%)[c]
1	$Pd(OAc)_2$	THF (0.1)	24	48, 56
2	$PdCl_2(CH_3CN)_2$	THF (0.1)	24	51, 57
3	$Pd(TFA)_2$	THF (0.1)	24	42, 54
4	$[Pd(allyl)Cl]_2$	THF (0.1)	24	23, 47
5	$Pd_2dba_3 \cdot CHCl_3$	THF (0.1)	24	-
6	$Pd(OAc)_2$	Et_2O (0.1)	24	-
7	$Pd(OAc)_2$	DCM (0.1)	24	63, 85
8	$Pd(OAc)_2$	DCE (0.1)	24	49, 10
9	$Pd(OAc)_2$	toluene (0.1)	24	63, 97
10	$Pd(OAc)_2$	toluene (0.2)	24	70, 97
11	**$Pd(OAc)_2$**	**toluene (0.5)**	**16**	**93, 97**
12[d]	$Pd(OAc)_2$	toluene (0.5)	24	-
13[d]	$Pd(OAc)_2$	THF (0.5)	20	47, 64
14[d]	$Pd(OAc)_2$	dioxane (0.5)	8	66, 69
15[d]	$Pd(OAc)_2$	DCM (0.5)	8	88, 69
16[d]	$Pd(OAc)_2$	DCE (0.5)	8	86, 60
17[d]	$Pd(OAc)_2$	DMF (0.5)	20	-
18[d]	$PdCl_2(CH_3CN)_2$	DCM (0.5)	24	85, 59

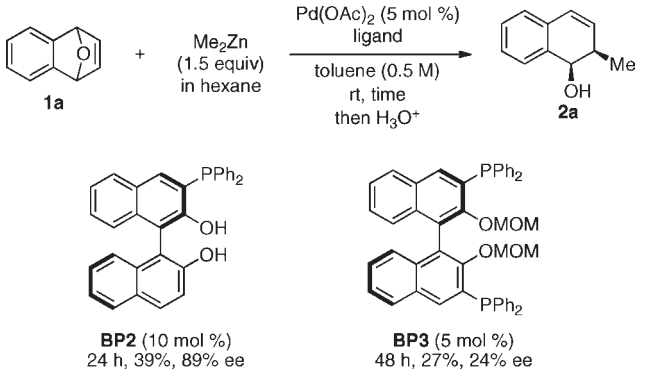
[a] The concentration of **1a** is in parentheses. [b] DCM, dichloromethane; DCE, 1,2-dichloroethane; DMF, *N*,*N*-dimethylformamide. [c] NMR yields. The enantiomeric excess was determined by chiral HPLC analyses (see Supporting Information). [d] $Zn(OTf)_2$ (5 mol %) was added.

screening of Pd(II) salts showed the comparable enantioselectivities (entries 2−4); however, Pd(0) precursor did not work at all (entry 5). Thus, $Pd(OAc)_2$ was used as the catalyst precursor for the subsequent screening of solvents. Further examination showed that toluene could be used to achieve excellent ee (entry 9). A higher concentration of **1a** in toluene improved the yield of product; 0.5 M gave the best results, and the product **2a** was obtained in 93% yield with 97% ee (entry 11). To improve the reaction rate, the use of $PdCl_2(CH_3CN)_2$ or $Pd(OAc)_2$ in the presence of a $Zn(OTf)_2$ system was examined.[4e,6] Unexpectedly, the reaction with $Zn(OTf)_2$ in toluene did not proceed at all (entry 12). Although the reaction in THF, dioxane, DCM, or DCE proceeded, the yield and enantioselectivity were lower than those in entry 11 (entries 13−16).[4c,d] The reaction

(4) (a) Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804. (b) Lautens, M.; Hiebert, S.; Renaud, J.-L. *Org. Lett.* **2000**, *2*, 1971. (c) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834. (d) Priego, J.; Mancheño, O. G.; Cabrera, S.; Arrayás, R. G.; Llamas, T.; Carretero, J. C. *Chem. Commun.* **2002**, 2512. (e) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437. (f) Dotta, P.; Kumar, P. G. A.; Pregosin, P. S.; Albinati, A.; Rizzato, S. *Organometallics* **2004**, *23*, 2295. (g) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3944. (h) Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934. (i) Cabrera, S.; Arrayás, R. G.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 17938. (j) Imamoto, T.; Kumada, A.; Yoshida, K. *Chem. Lett.* **2007**, *36*, 500. (k) Imamoto, T.; Saitoh, Y.; Koide, A.; Ogura, T.; Yoshida, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 8636. (l) Ogura, T.; Yoshida, K.; Yanagisawa, A.; Imamoto, T. *Org. Lett.* **2009**, *11*, 2245.

(5) (*R*)-BINOL (>99.0% ee) was purchased from Fuji Molecular Planning Co., Ltd. at JPY50,000/500 g.

Scheme 1. Effect of Ligand



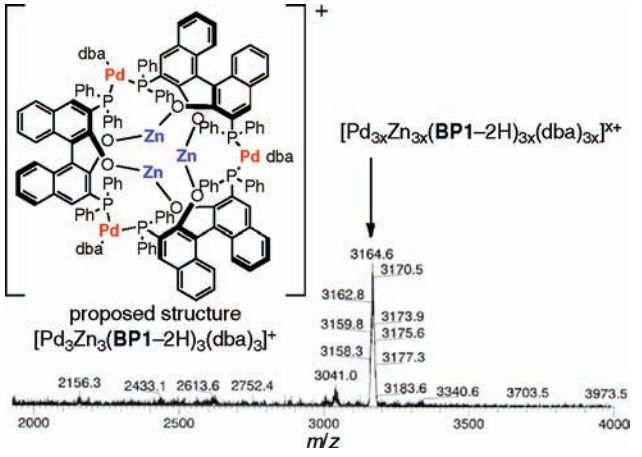


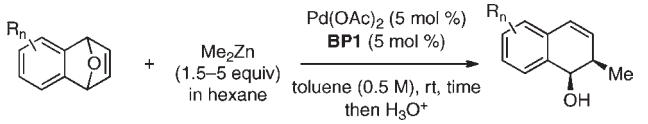
Figure 3. ESI-MS analysis of Pd/Zn-complex derived from **BP1**.

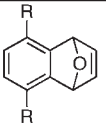
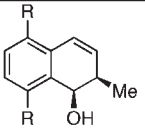
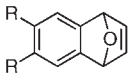
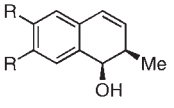
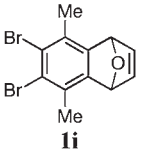
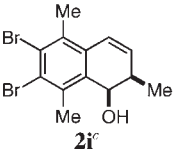
in DMF did not proceed (entry 17). The enantioselectivity with the use of $PdCl_2(CH_3CN)_2$ was less than that with $Pd(OAc)_2$ (entry 18).

The choice of ligand was important. Scheme 1 presents the excellent performance of (*R*)-BINOL-PHOS (**BP1**) with regard to catalytic activity and stereoselectivity. The reaction in the presence of monophosphine **BP2** was not complete even after 24 h and gave the product **2a** in 39% yield with a reduced enantioselectivity of 89% ee. The methoxy methyl-protected ligand **BP3** required a longer reaction time to give the corresponding product **2a** in 27% yield with 24% ee. These results clarified that the bisphosphine and diols in (*R*)-BINOL-PHOS (**BP1**) are important for realizing excellent catalytic activity and enantioselectivity.

In our previous report, ESI-MS analyses of Zn- and Cu/Zn-complexes derived from **BP1** showed the existence of a Zn_2-complex and Cu_2/Zn_2-complex.[2] Thus, ESI-MS analyses were performed for the corresponding Pd/Zn-complexes derived from **BP1**. Part of the spectrum is shown in Figure 3 (see the Supporting Information for the large spectrum). The peak found in the spectrum indicated the generation of Pd/Zn-multinuclear complex, the isotope distribution pattern of which was very complicated and unclear. Uncharacterized peaks around *m*/*z* 1500 were observed, and a major peak in the range of *m*/*z* 2000−4000 for *m*/*z* 3170.5 seems to be $[Pd_3Zn_3(\mathbf{BP1}\text{-}2H)_3(dba)_3]^+$ (exact mass 3168.3) derived from Pd precursor. In this context, the multicationic complexes, such as $[Pd_6Zn_6(\mathbf{BP1}\text{-}2H)_6(dba)_6]^{2+}$ and others, could be possible. Although we could not determine the

Table 2. Scope of Oxanorbornadienes



entry[a]	substrate	time (h)	product	yield, ee (%)[b]
				
1	**1a**, R = H	16	**2a**	87, 97
2	**1b**, R = Me	15	**2b**[c]	94, 99
3	**1c**, R = OMe	18	**2c**	95, 98 (41, 96)[d]
4	**1d**, R = F	48	**2d**[c]	44, 81
				
5	**1e**, R = Me	5	**2e**[c]	96, 98
6	**1f**, R = OMe	24	**2f**[c]	85, 99
7	**1g**, R = -OCH_2O-	4	**2g**	98, 97
8	**1h**, R = F	22	**2h**	91, 98 (48, 96)[e]
9	 **1i**	48	 **2i**[c]	83, 97 (42, 89)[e]

[a] Me_2Zn (1.5 equiv in entry 1; 3 equiv in entries 2, 3, 5, 6, and 7; 5 equiv in entries 4, 8, and 9) was used. [b] Isolated yields. The enantiomeric excess was determined by chiral HPLC analyses (see Supporting Information). [c] Absolute configuration was not determined. [d] A toluene solution of 1 M Me_2Zn (3 equiv) was used. [e] A hexane solution of 1 M Me_2Zn (3 equiv) was used.

(6) The use of Et_2Zn or *n*-Bu_2Zn instead of Me_2Zn diminished the catalytic activity and stereoselectivity. The reaction of **1a** with Et_2Zn under the optimized conditions for Me_2Zn gave a trace amount of desired product; the reductive ring-opening product formed. In contrast, the reaction in the presence of $PdCl_2(CH_3CN)_2$ (5 mol %), **BP1** (5 mol %), and $Zn(OTf)_2$ (5 mol %) gave the desired product in 48% yield with 17% ee. The use of mixed reagents, Et_2Zn (1.5 equiv) and Me_2Zn (1.5 equiv), under the same reaction conditions gave the ethylated product exclusively in 31% yield with 44% ee. Furthermore, the reaction using Et_2Zn (3 equiv) gave the product in 21% yield with 13% ee. The details are under examination.

exact structures of the active complexes, we confirmed that the complex included multi-Pd and -Zn atoms.

Various types of substituted oxanorbornadienes can be used for the present asymmetric alkylative ring-opening reaction (Table 2). Since an excess amount of Me_2Zn improved the yields and enantioselectivities in the reaction of substituted oxanorbornadienes, 3−5 equiv of Me_2Zn was used. The reactions of 5,8-disubstituted compounds **1b** and **1c** gave the corresponding alcohols **2b** and **2c**, respectively, in high to excellent yields with excellent enantioselectivities (entries 2 and 3). The use of a 1 M solution of Me_2Zn in toluene diminished the yield of product **2c** to 21% with 89% ee; thus, the co-presence of hexane seems to be favorable.[7] In contrast, the reaction using 5,8-difluoro compound **1d** gave **2d** in low yield, albeit with high enantioselectivity (entry 4). The electronic effects are generally inconsequential in other cases. The reactions of 6,7-disubstituted compounds **1e**−**h** gave the corresponding products **2e**−**h** in excellent yields with excellent enantioselectivities (entries 5−8). Furthermore, the reaction of 5,6,7,8-tetrasubstituted oxabicyclic alkene **1i** gave the corresponding product **2i** in 83% yield with 97% ee (entry 9).

(7) Almost no reaction occurred in a single solvent of hexane.

In conclusion, we have demonstrated an efficient Pd-catalyzed asymmetric alkylative ring-opening reaction using the readily accessible BINOL-PHOS ligand. The incorporation of bisphosphine and diols definitely enhanced both the catalytic activity and the stereoselectivity. Therefore, Pd/Zn-multimetallic synergism based on our originally developed BINOL-PHOS plays an important role in the present reactions. The further modification of ligand architectures to achieve a pliable catalyst system for metal-catalyzed asymmetric reactions is underway in our laboratory.

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Supporting Information Available. Experimental procedure and HPLC analyses of the racemic and chiral compounds. This material is available free of charge via the Internet at http://pubs.acs.org.