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Palladium-Catalyzed Enantioselective Ring Opening of Oxabicyclic Alkenes with Organozinc Halides

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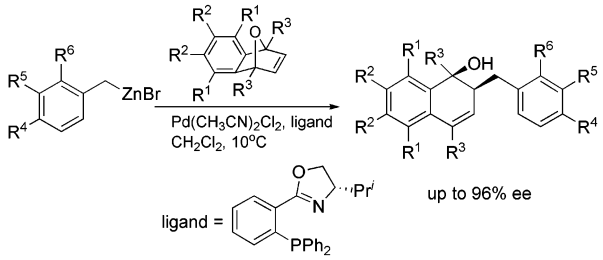
ABSTRACT



Palladium-catalyzed asymmetric ring opening of oxabenzonorbornadienes with readily available organozinc halides under mild conditions in the presence of (*S*)-Pr^i-PHOX produces the corresponding 1,2-dihydronaphth-1-ols in good yield and high enantioselectivity.

Catalytic asymmetric reactions using organozinc reagents have been well documented.[1] However, the most widely used reagents are dialkylzinc, and less attention has been paid to the use of alkylzinc halides, although they are more readily available.[2] On the other hand, ring opening of oxabicyclic compounds with a variety of nucleophiles, first reported by Caple and co-workers and developed by Luatens,[3,4] has emerged as an attractive strategy for the preparation of cyclic and acyclic compounds with multiple stereocenters.[4] Recently, Lautens reported a palladium- or copper-catalyzed addition of dialkylzinc to oxabicyclic alkenes, and excellent results were obtained.[5] However the reagents were limited to dialkylzinc. To date, there is no report on the enantioselective ring opening of oxabicyclic alkenes with organozinc

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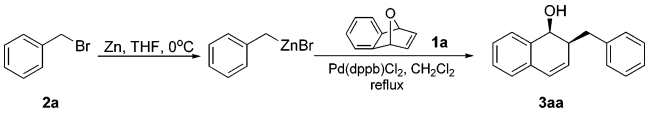
halides, although they are more versatile and more easily available.[6] We now report here the palladium-catalyzed ring opening of 7-oxabenzonorborna-diene and its derivatives with alkylzinc halides to furnish 2-alkyl-1,2-dihydro-1-naphthol in high enantiomeric excess.

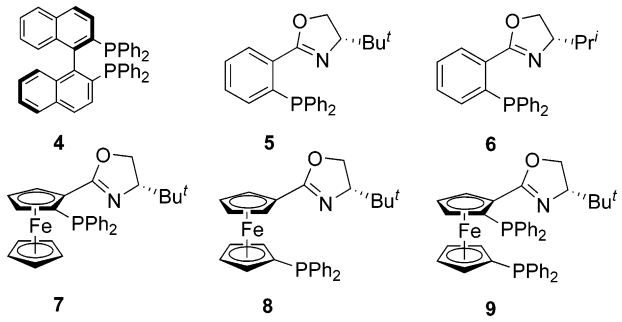
In our initial experiment, 7-oxabenzonorbornadiene (**1a**) was treated with benzylzinc bromide[7] in the presence of 5 mol % of Pd(dppb)Cl_2 in dichloromethane under reflux for 8 h to provide 2-benzyl-1,2-dihydro-1-naphthol **3aa** in 78% yield (Scheme 1). A control experiment indicated that no reaction occurred in the absence of Pd-catalyst.

Scheme 1



Encouraged by this result, we carried out an asymmetric version of the same reaction using different kinds of chiral ligands commercially available or developed by us (Scheme 2), and the results are shown in Table 1.

Scheme 2



From Table 1, it can be seen that *N*,*P*-ligands are effective, although diphosphine ligands are most often used in this ring-opening reaction.[4,5] Among them, (*S*)-Pr^i-PHOX **6**[8] gave the highest ee value with acceptable chemical yield at 10 °C (Table 1, entry 3). (*R*)-BINAP **4**, (*S*)-Bu^t-PHOX **5**,[8] and ferrocene **7**[9] gave moderate enantioselectivity (entries 1, 2, and 4), and ferrocene **8**[10] and **9**[11] gave low enantioselectivity,

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Table 1. Effect of Reaction Conditions on the Enantioselectivity of Ring Opening of **1a** with Benzylzinc Bromide[a]

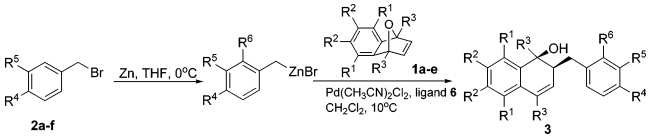
entry	ligand	yield (%)[b]	ee (%)[c]
1	**4**	46	47
2	**5**	66	66
3	**6**	64	90
4	**7**	70	66
5	**8**	80	6
6	**9**	85	2
7[d]	**6**	13	84
8[e]	**6**	98	78

[a] All reactions run at 10 °C with ratio of **1a**/BnZnBr/Pd$(CH_3CN)_2Cl_2$/ligand = 1:1.5:0.05:0.05. [b] Isolated yield based on oxabicyclic alkene. [c] Determined by HPLC. [d] The reaction runs at −20 °C. [e] The reaction runs at reflux.

although the chemical yield was higher (entries 5 and 6). Temperature effect was also significant, with a lower enantioselectivity being given at temperatures either lower or higher than 10 °C. However, the yield was higher if the reaction proceeded at higher temperature (entries 7 and 8).

To extend the scope of substrate, other substituted benzylzinc bromides were investigated. In almost all cases, substituted benzylzinc bromides reacted with **1a** smoothly to provide corresponding 2-benzyl-1,2-dihydro-1-naphthol with high ee values (Table 2, entries 1−4 and 6−10), while

Table 2. Enantioselective Ring Opening of Oxabicyclic Alkenes with Benzylzinc Bromide[a]



entry	R^1, R^2, R^3	R^4, R^5, R^6		yield (%)[b]	ee (%)[c,d]
1	H, H, H	H, H, H	**3aa**	64	90
2	H, H, H	Br, H, H	**3ab**	70	96
3	H, H, H	F, H, H	**3ac**	57	90
4	H, H, H	Me, H, H	**3ad**	65	87
5	H, H, H	H, OMe, H	**3ae**	44	76
6	H, H, H	Cl, Cl, H	**3af**	53	89
7	H, H, H	H, Br, H	**3ag**	35	95
8	H, H, H	H, H, Br	**3ah**	76	93
9	H, H, H	H, H, OMe	**3ai**	49	94
10	H, H, H	H, H, Me	**3aj**	20	88
11	Me, H, H	Br, H, H	**3bb**	76	95
12	H, Me, H	Br, H, H	**3cb**	72	90
13	H, Br, H	Br, H, H	**3db**	52	81
14	H, H, Me	Br, H, H	**3eb**	52	64

[a] All reactions run at 10 °C with ratio of **1a**/BnZnBr/Pd$(CH_3CN)_2Cl_2$/ligand = 1:1.5:0.05:0.05. [b] Isolated yield based on oxabicyclic alkenes. [c] Determined by HPLC. [d] Rotation sign is (+) for all products.

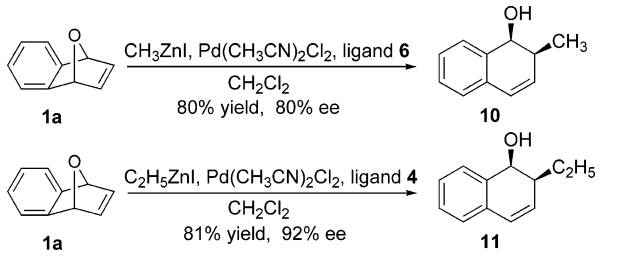
the yield varied from 20% (entry 10) to 76% (entry 8) despite the position of substituents. When 4-bromobenzylzinc bromide was used, product **3ab** was given with 70% yield and

96% ee (Table 2, entry 2), which increased to 99% after one single recrystallization from diethyl ether. Ring opening of oxabenzonorbornadienes bearing substituents at various positions with 4-bromobenzylzinc bromide also provided the corresponding products in high enantioselectivity (entries 11−13), except that derived from dimethylfuran, which gave the product containing quaternary chiral carbon **3eb** in 64% ee (entry 14). Addition of 4-bromobenzyl-zinc bromide to 5,8-dimethyl derivative **1b** delivered the corresponding adduct **3bb** with 95% ee (entry 11).

The relative and absolute configuration of adduct **3ab** was unequivocally demonstrated by single-crystal X-ray analysis (see Supporting Information). Configuration of it was assigned as (*S*,*S*), and the hydroxyl group and benzyl group are in a *syn*-substituted pattern.

Not only benzylzinc bromide but also methyl- and ethylzinc iodide are suitable reagents in this ring-opening reaction. 1,2-Dihydro-2-methyl-1-naphthol **10** was obtained with 80% yield and 80% ee with 5 mol % of (*S*)-Pr^i-PHOX **6**, and in the presence of 5 mol % of (*R*)-BINAP **4**, 1,2-dihydro-2-ethyl-1-naphthol **11** was obtained with 81% yield and 92% ee (Scheme 3).

Scheme 3



Although the detailed pathway is not clear, on the basis of the *syn*-stereochemistry of products and the known chemistry of ring opening of oxabicylic alkene with dialkylzinc in the presence of Pd catalyst,[12, 6] the mechanism for the reaction is expected to involve transmetalation of the palladium catalyst with benzylzinc bromide to generate palladium alkyl species.[13] Coordination of the carbon−carbon double bond of the alkene substrate and subsequent β-oxygen elimination and then protonation of the latter species afford the ring-opening product and a Pd(II) species.

In conclusion, we have developed a Pd-catalyzed nucleophilic ring-opening reaction of oxabicylic alkenes with readily available organozinc halides, and high ee is provided. It is complementary to metal-catalyzed ring opening with dialkylzinc developed by Lautens[3,4] and thus widens the scope of the reaction. Further applications of organozinc halides in asymmetric synthesis are in progress.

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Supporting Information Available: Experimental details describing the synthesis, spectral data, and HPLC analysis for all new compounds and CIF file for compound **3ab**. This material is available free of charge via the Internet at http://pubs.acs.org.

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