Catalytic Asymmetric Wacker-Type Cyclization

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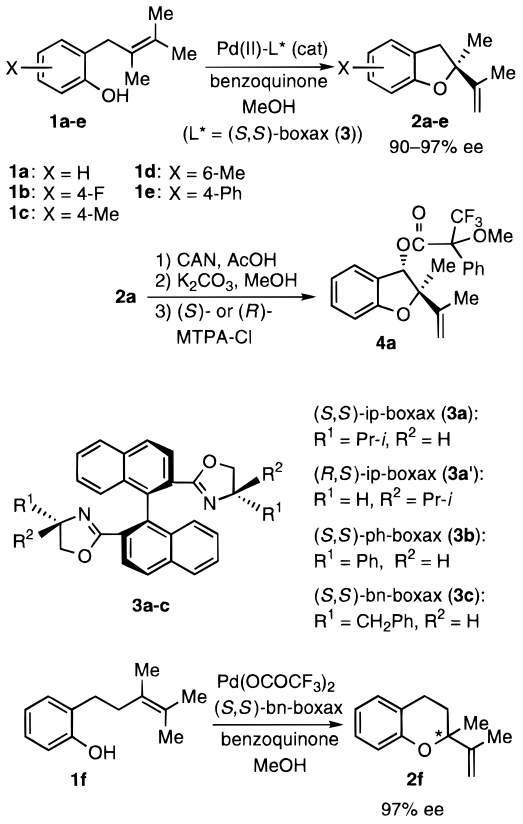
Wacker-type oxidation has proven to be one of the most versatile methods for functionalization of olefins.[1] Compared to the impressive development of asymmetric reactions with chiral palladium(0) catalyst,[2] asymmetric oxidative reactions with palladium(II) species have received only scant attention. To the best of our knowledge, previously reported works on catalytic asymmetric Wacker-type oxidation are limited to the pioneering works by Hosokawa and Murahashi, where the intramolecular cyclization of *o*-allylphenols was catalyzed by a chiral π-allylpalladium complex in the presence of cupric acetate under oxygen atmosphere to give optically active dihydrobenzofurans of 29% ee.[3] We report here that high enantioselectivity (up to 97% ee) is attained in the Wacker-type cyclization of *o*-allylphenols by use of palladium(II) catalysts coordinated with chiral bis(oxazoline) ligands based on 1,1′-binaphthyl backbone.

We have examined several palladium(II) salts, chiral ligands, and reoxidants for the cyclization of 2-(2,3-dimethyl-2-butenyl)-phenol (**1a**) (Scheme 1). It was found that the combination of palladium bis(trifluoroacetate), (*S*,*S*)-2,2′-bis[4-(alkyl)oxazolyl]-1,1′-binaphthyls[4] ((*S*,*S*)-boxax[5] (**3**)), and *p*-benzoquinone organizes a new efficient catalyst system with much higher enantioselectivity than other combinations. Some representative results are given in Table 1. A chiral bis(oxazoline) ligand, (*S*,*S*)-ip-boxax (**3a**) (47 μmol), and palladium bis(trifluoroacetate) (45 μmol) were dissolved in 0.3 mL of methanol at ambient temperature. To the solution, benzoquinone (1.8 mmol), *o*-allylphenol **1a** (0.45 mmol), and 0.6 mL of methanol were added, and the entire mixture was stirred at 60 °C for 24 h. The reaction mixture was chromatographed on silica gel to give 75% yield of (*S*)-(−)-2-methyl-2-isopropenyl-2,3-dihydrobenzofuran (**2a**) ($[\alpha]_D^{20}$ −83.1 (*c* 0.23, chloroform)). The enantiomeric excess (ee) was determined to be 96% ee by GLC analysis with a chiral stationary phase column (Cyclodex β236M19) (Table 1, entry 1). The absolute configuration of (*S*)-(−)-**2a** was assigned by NMR studies of the MTPA ester **4a**.[6,7] The cyclization carried out at 35 °C for 3 days raised the enantiomeric excess to 97% ee (entry 2). Allylphenols having 4-fluoro, 4-methyl, 6-methyl, and 4-phenyl substituents (**1b**, **1c**, **1d**, and **1e**) also underwent the asymmetric cyclization under similar reaction conditions to give the corresponding 2,3-dihydrobenzofurans, (−)-**2b**-**e**, in 92, 94, 94, and 90% ee, respectively (entries 4, 5, 6, and 7). The palladium(II)−boxax complex is also effective for the asymmetric cyclization forming a 6-membered ring. Thus, the oxidation of 2-[(3,4-dimethyl)-3-pentenyl]phenol (**1f**) in the presence of a palladium(II) complex of (*S*,*S*)-bn-boxax (**3c**) gave benzodihydropyran **2f** of 97% ee (entry 8).

Scheme 1



For the present oxidation, chiral phosphine−palladium complexes generated from palladium salts and BINAP (**6**)[8] or MOP (**7**)[9] cannot be used. The phosphines were readily oxidized into the phosphine oxides under the reaction conditions[10] resulting in the formation of racemic cyclization products. The Hosokawa system, [(3,2,10-η^3-pinene)PdOAc]$_2$ (**5**)[3] and cupric acetate−O_2, gave 18% ee of **2a** in 88% yield. In the reaction with boxax, the relative configuration of central chirality on the oxazoline to axial chirality on binaphthyl has a great influence on the enantioselectivity and catalytic activity. While the ligand (*S*,*S*)-ip-boxax (**3a**) gave high yield of **2a** with highest enantioselectivity (96% ee) (entry 1), the palladium catalyst of its diastereoisomer (*R*,*S*)-ip-boxax (**3a′**) was much less active and less enantioselective (entry 11). Other boxax ligands, (*S*,*S*)-ph-boxax (**3b**) and (*S*,*S*)-bn-boxax (**3c**) which have 4-phenyl and 4-benzyl groups, respectively, on the oxazoline, showed almost the same high stereoselectivity as (*S*,*S*)-ip-boxax (**3a**) (entries 9 and 10). The 1,1′-binaphthyl backbone in boxax is important for the high

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(5) The abbreviation "boxax" comes from bis(oxazoline) (box) with axial (ax) chirality. The first *S* refers to the carbon central chirality on the oxazoline moieties and the second *S* to the axial chirality of 1,1′-binaphthyl.

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(7) Selected $\Delta\delta$ values (ppm) on ^{1}H NMR (500 MHz, $CDCl_3$) experiment of MTPA ester **4a** are as follows: $\Delta\delta$ +0.163 (2-CH_3), +0.039 (2-C(=CH$_2$)CH_3), +0.026 (2-C(=CH_EH)CH$_3$), +0.023 (2-C(=CHH_Z)CH$_3$), −0.033 (5-*H*), −0.031 (7-*H*). Proton resonances of substituents at C2 position and aromatic ring in the (*S*)-MTPA ester of (−)-**2a** appeared at higher field and at lower field, respectively, than those of the (*R*)-MTPA ester, indicating that the absolute configuration of (−)-**2a** is *S*.

(8) (*R*)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl: Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

(9) 2-(Diphenylphosphino)-2′-methoxy-1,1′-binaphthyl (MOP): Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945.

(10) (a) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177. (b) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818.

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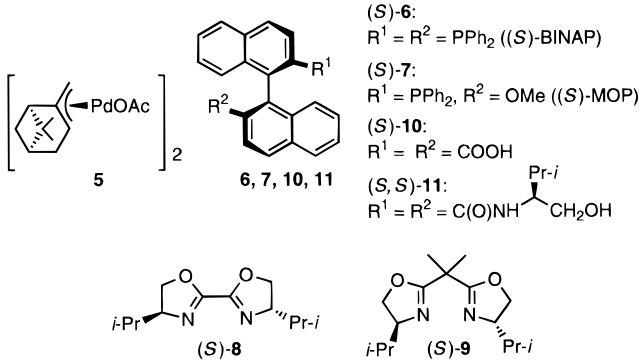
Table 1. Palladium(II)-Catalyzed Asymmetric Cyclization of **1**[a]

entry	substrate	catalyst (ligand/palladium salt)	solvent	yield (%) of **2**[c]	recovered **1** (%)[c]	% ee of **2**[b] (config)	specific rotation ($[\alpha]_D^{20}$ in chloroform)
1	**1a**	(*S*,*S*)-ip-boxax (**3a**)/Pd(OCOCF$_3$)$_2$	MeOH	75	12	96 (*S*)	−83.1 (*c* 0.23)
2[d]	**1a**	(*S*,*S*)-ip-boxax (**3a**)/Pd(OCOCF$_3$)$_2$	MeOH	72	13	97 (*S*)	−84.9 (*c* 0.16)
3[e]	**1a**	(*S*,*S*)-ip-boxax (**3a**)/Pd(OCOCF$_3$)$_2$	MeOH	43	46	96 (*S*)	
4[f]	**1b**	(*S*,*S*)-ip-boxax (**3a**)/Pd(OCOCF$_3$)$_2$	MeOH	82	8	92 (*S*)[g]	−51.3 (*c* 0.33)
5	**1c**	(*S*,*S*)-ip-boxax (**3a**)/Pd(OCOCF$_3$)$_2$	MeOH	86	8	94 (*S*)[g]	−46.9 (*c* 0.44)
6	**1d**	(*S*,*S*)-ip-boxax (**3a**)/Pd(OCOCF$_3$)$_2$	MeOH	71	7	94 (*S*)[g]	−73.9 (*c* 0.48)
7	**1e**	(*S*,*S*)-ip-boxax (**3a**)/Pd(OCOCF$_3$)$_2$	MeOH	62	19	90 (*S*)[g]	+5.9 (*c* 0.16)
8[h]	**1f**	(*S*,*S*)-bn-boxax (**3c**)/Pd(OCOCF$_3$)$_2$	MeOH	61	25	97 (*S*)[g]	−34.2 (*c* 0.24)
9	**1a**	(*S*,*S*)-ph-boxax (**3b**)/Pd(OCOCF$_3$)$_2$	MeOH	71	10	93 (*S*)	
10	**1a**	(*S*,*S*)-bn-boxax (**3c**)/Pd(OCOCF$_3$)$_2$	MeOH	59	22	94 (*S*)	
11	**1a**	(*R*,*S*)-ip-boxax (**3a′**)/Pd(OCOCF$_3$)$_2$	MeOH	3	78	18 (*R*)	
12	**1a**	(*S*,*S*)-ip-boxax (**3a**)/PdCl$_2$(CH$_3$CN)$_2$	MeOH	0	98		
13	**1a**	(*S*,*S*)-ip-boxax (**3a**)/Pd(OCOCH$_3$)$_2$	MeOH	44	33	54 (*S*)	
14	**1a**	(*S*,*S*)-ip-boxax (**3a**)/Pd(OCOCF$_3$)$_2$	THF	8	71	6 (*R*)	
15	**1a**	(*S*,*S*)-ip-boxax (**3a**)/Pd(OCOCF$_3$)$_2$	benzene	11	72	17 (*R*)	

[a] All reactions were carried out at 60 °C for 24 h in the presence of 4 equiv of benzoquinone and 10 mol % of palladium catalyst prepared in situ by mixing a palladium salt and a ligand (Pd/ligand 1:1) unless otherwise noted. [b] Determined by GLC analysis with a chiral stationary phase column (Cyclodex β236M19). [c] Isolated yield by column chromatography. [d] Reaction at 35 °C for 3 days. [e] One equivalent of benzoquinone was used. [f] In the presence of 8 equiv of benzoquinone. [g] The absolute configuration of (−)-**2b**−**e** was assigned to be *S* by simiality to **2a** in the order of retention time in the GC analysis. [h] In the presence of 25 mol % of the catalyst.



enantioselectivity. The bis(oxazoline) ligands 2,2′-bioxazolyl (*S*)-**8**[11] and 2,2-bis(oxazolyl)propane (*S*)-**9**,[12] which lack the binaphthyl moiety, gave **2a** with much lower selectivity (18% ee (*S*) in 64% yield and 35% ee (*S*) in 6% yield, respectively), although these chiral oxazolines have been successfully used for some other catalytic asymmetric reactions.[13]

It is noteworthy that, after the reaction with (*S*,*S*)-ip-boxax (**3a**) (entry 1), the chiral oxazoline ligand was recovered quantitatively by treatment of the crude reaction mixture with excess potassium cyanide in methanol. The recovery indicates that the ligand coordinates to palladium without change of its bis(oxazoline) structure during the asymmetric oxidation. The chelate coordination of the boxax ligand is expected to construct highly enantioselective surroundings on the catalytically active species. No enantioselectivity was observed with binaphthyl dicarboxylic acid (*S*)-**10** or dicarboxamide (*S*)-**11**, supporting that the oxazoline in (*S*,*S*)-ip-boxax (**3a**) does not undergo solvolysis under the reaction conditions.

It was found that an excess of benzoquinone is required for the high yield of **2a** (entries 1 and 3). Thus, with 1 equiv of benzoquinone, the reaction gave 43% yield of (*S*)-**2a** (96% ee) after 24 h, during which complete consumption of benzoquinone forming hydroquinone was observed (entry 3). It has been well documented that palladium(II) suffers from reduction via palladium alkoxide intermediates by alcohols,[14] accounting for the consumption of benzoquinone in methanol.

Chemical yield and enantiomeric purity of the product **2a** are strongly affected by the anionic part of the catalyst. A catalyst generated from dichlorobis(acetonitrile)palladium and (*S*,*S*)-ip-boxax (**3a**) did not catalyze the cyclization of **1a**, and that from palladium diacetate gave 54% ee of (*S*)-**2a** in 44% yield (entries 12 and 13). The trifluoroacetate is considered to play a key role on activation of the coordinated olefin on palladium. Use of methanol as solvent is essential to perform the cyclization successfully. The reaction in benzene or THF was very slow to give low yield of (*R*)-**2a** with much lower enantioselectivity (entries 14 and 15).

Taking into account of the versatility of the Wacker-type reaction, the present results pave the way for a variety of asymmetric transformations of prochiral olefins.

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Supporting Information Available: Experimental details for preparation of **4a** and spectroscopic data for **2a**−**f** (3 pages). See any current masthead page for ordering and Internet access instructions.

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(14) For example, see: Lloyd, W. G. *J. Org. Chem.* **1967**, *32*, 2816.