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Palladium-Catalyzed Asymmetric Hydrophosphorylation of Norbornenes

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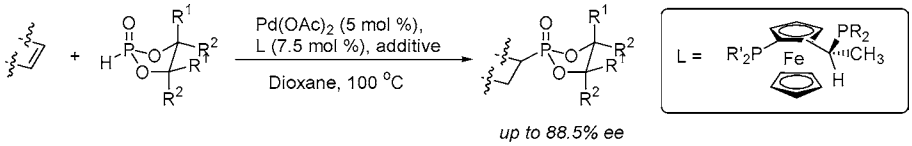
ABSTRACT



By using Josiphos ligands, palladium-catalyzed hydrophosphorylation of norbornenes with hydrogen phosphonates proceeded efficiently to give the corresponding phosphonates in high enantioselectivities.

Metal-catalyzed enantioselective addition of hydrogen−heteroatom bonds to alkenes is a powerful tool for the preparation of optically active heteroatom compounds.[1] Chiral organophosphorus compounds are highly useful in biochemistry, organic synthesis, and asymmetric catalysis.[2] However, successful enantioselective preparation of these compounds via metal-catalyzed asymmetric addition of H−P bonds to alkenes is limited.[3,4] While further pursuing our transition-metal-mediated selective additions of P(O)−H bonds to carbon−carbon unsaturated bonds,[5] we found that by using Josiphos ligands **2**[6] the palladium-catalyzed asymmetric hydrophosphorylation of norbornenes with a five-membered cyclic dioxaphospholane 2-oxide **1** proceeded efficiently to give the corresponding phosphonates in high enantioselectivity (Figure 1).

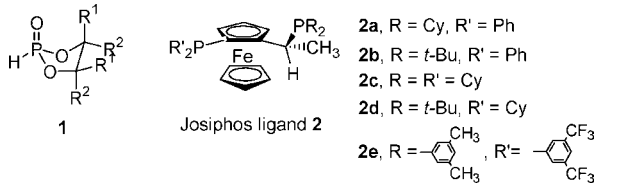


Figure 1. Cyclic hydrogen phosphonates **1** and Josiphos ligands **2** (Cy = cyclohexyl).

The asymmetric addition of **1a** to norbornene **3a** was investigated first using $Pd(OAc)_2$ in the presence of a chiral ligand (Table 1). Although most chiral phosphines (Figure

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(6) For recent applications of Josiphos ligands, see: (a) Lopez, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 2752. (b) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371. (c) Spindler, F.; Blaser, H.-U. *Adv. Synth. Catal.* **2001**, *343*, 68.

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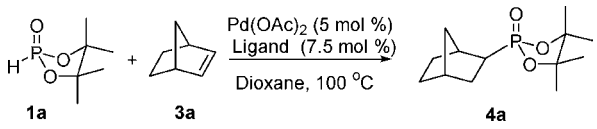
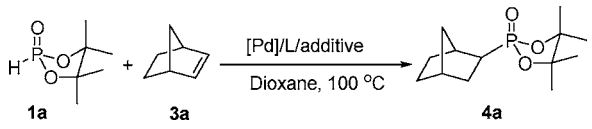
Table 1. Ligand Evaluation[a]



entry	ligand[b]	time (h)	% yield	% ee
1	(*S*,*S*)-BCPM	16	99	2
2	(*R*)-BINAP	16	99	0
3	(*S*,*S*)-BPPM	16	99	10.1(+)
4	(*S*,*S*)-CHIRAPHOS	20	81	13.1(+)
5	(*S*,*S*)-DIOP	16	99	9.9(+)
6	(*R*)-MOP	16	99	4
7	(*S*)-NMDPP	15	99	9.3(+)
8	(*R*,*R*)-NORPHOS	19	80	2
9	(*R*)-PROPHOS	24	24	6
10	(*R*)-QUINAP	15	99	8
11	(*R*)-Tol-BINAP	16	99	23.6(+)
12	trost ligand	16	99	8(+)
13	**2a**	15	99	30.8(−)
14	**2b**	15	99	48.8(−)
15	**2c**	15	99	55.5(−)
16	***2d***	***17***	***99***	***81.5(−)***

[a] A mixture of **1a** (0.2 mmol) and **3a** (0.4 mmol), $Pd(OAc)_2$ (0.01 mmol), and the ligand (0.015 mmol) in dioxane (0.6 mL). Yield was determined by ^{31}P NMR, and ee % was determined by HPLC (Chiralpak AS column). [b] See Figure 2 for the abbreviations of the chiral ligands.

Table 2. Optimization of the Reaction Condition



entry	Pd[a]/**2d**/additive (mol %)	time (h)	% yield	% ee
1	10/5/−	17	>99	34.2(−)
2	5/5/−	17	>99	60.5(−)
3	5/10/−	17	>99	81.4(−)
4[b]	5/7.5/−	17	>99	81.6(−)
5[c]	5/7.5/−	5	>99	80.5(−)
6	−[d]	112	90	81.2(−)
7[e]	5/5/−	169	91	80.8(−)
8[f]	5/7.5/−	17	>99	79.0(−)
9[g]	5/7.5/10	17	>99	80.7(−)
10[g]	5/7.5/20	17	>99	79.5(−)
11[h]	5/7.5/5	35	>99	84.2(−)
12[h]	5/7.5/10	35	87	86.2(−)
13[h]	***5/7.5/20***	***81***	***>99***	***88.5(−)***
14[h]	5/7.5/50	145	88	84.0(−)

[a] $Pd(OAc)_2$ was used unless otherwise noted. [b] $Pd(OAc)_2$ and **2d** were heated at 100 °C in dioxane for 30 min prior to the addition of **3a** and **1a**. [c] Under microwave irradiation. [d] Me_2Pd[**2d**] was used as the catalyst. [e] 2.5 mol % $Pd_2(dba)_3$ was used instead of $Pd(OAc)_2$. [f] Air (0.5 mL) was introduced to the reaction flask (25 mL). [g] AcOH was added. [h] Et_3N was added.

2) investigated gave high yields of the adduct, the enantioselectivities were low (entries 1−12). However, as Josiphos

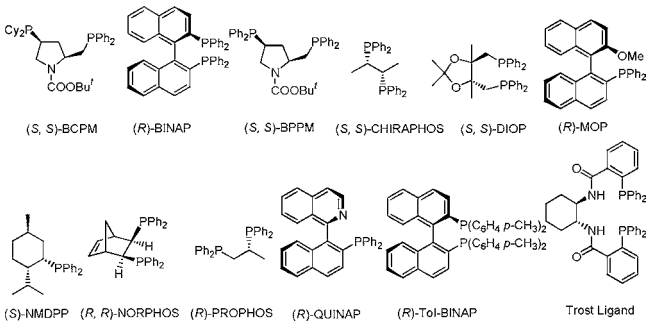


Figure 2. Abbreviations for chiral ligands.

ligands were employed, good ee's were obtained. Thus, when (*R*)−(*S*)-Josiphos **2a** (R = Cy, R′ = Ph) was used, 30.8% ee of the adduct was obtained (Table 1, entry 13). The steric bulkiness of the bidentate ligand played an important role in controlling the enantioselectivity of the reaction. Thus, it was shown that as the Josiphos ligands became bulkier (*t*-Bu > Cy > Ph, entries 13−16), a better ee was obtained. Ligand **2d** was the best ligand investigated, which gave an 81.5% ee of the adduct.

The reaction using ligand **2d** (entry 16, Table 1) was optimized (Table 2). The Pd/ligand ratio was crucial (entries 1−4). Although lower loading of **2d** resulted in a great drop in the adduct ee (entries 1 and 2), a large excess of **2d** did not improve the adduct's ee either (entry 3). Thus, the proper Pd/ligand ratio was fixed at 1:1.5 (entry 16, Table 1). The addition sequence of the chemicals did not affect the ee of the adduct as no difference was observed when a mixture of $Pd(OAc)_2$ and **2d** was preheated for 30 min before the addition of **1a** and **3a** (entry 4). Meanwhile, the reaction was also conducted using microwave irradiation. Although the reaction proceeded faster, unfortunately no improvement of the ee could be observed (entry 5).

As to the catalytic precursors, $Pd(OAc)_2$/**2d** seems to be the best combination. Catalyst precursors such as Me_2Pd[**2d**] or $Pd_2(dba)_3$/**2d** were less reactive (entries 6 and 7). The reaction using $Pd(OAc)_2$/**2d** (run 16, Table 1) was also investigated under different concentrations of the reactants (1.0 and 0.1 M). Though a higher concentration (1.0 M) resulted in a slight drop of the adduct's ee (78.2%), a lower concentration (0.1 M) gave no improvement of the selectivity (79.9% ee). Furthermore, solvent (toluene, benzene, THF, and acetonitrile) and temperature (60, 80, 100, and 120 °C) effects were also investigated. However, no condition better than that of using dioxane at 100 °C could be found. On the other hand, an additive significantly affects the reaction. First, it was found that water lowered the ee of the adduct. Thus, the ee of the reaction using Me_2Pd[**2c**] could be improved from 39.3% (commercial anhydrous dioxane without further drying) to 65.9% (dioxane sodium/benzophenone dried). Other possible contaminants such as air and acetic acid were also found to have a negative effect on the adduct's ee (entries 8−10). On the contrary, a base

such as triethylamine could improve the ee up to 88.5%, though it also slowed the reaction rate (entries 11−14).

This asymmetric addition of hydrogen phosphinates to norbornenes is strongly affected by the steric hindrance on the substrates (Figure 3 and Table 3). Thus, it was found

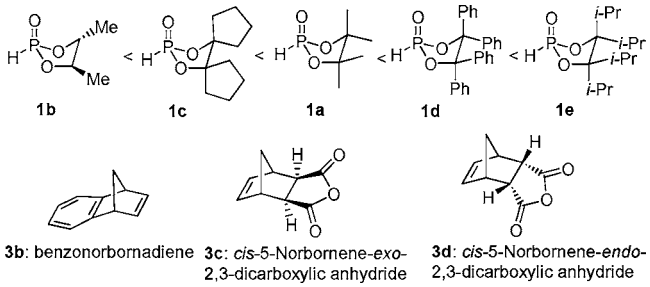
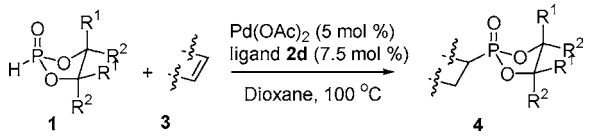


Figure 3. Steric order of **1** and substituted norbornenes **3**.

that the increasing steric hindrance order of **1b** < **1c** < **1a** was consistent with the increasing order of the corresponding product ee, **4b** < **4c** < **4a** (entries 1 and 2), i.e., the bulkier the substituents, the higher the ee of the adduct. In this regard, we expected that a higher enantioselectivity might be achieved by employing a bulkier hydrogen phosphonate **1d** or **1e.** Unfortunately, when **1d** or **1e** was heated with **3a** in the presence of $Pd(OAc)_2$/**2d**, the addition did not proceed at all.

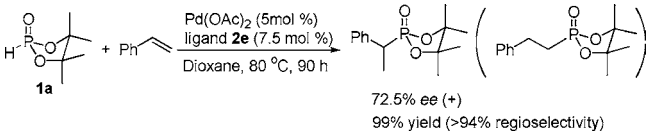
Table 3. Asymmetric Hydrophosphorylation of Norbornenes



entry	**1**, alkene, product	time (h)	% yield	% ee
1	**1b**, **3a**, **4b**	10	99	72.5(−)
2	**1c**, **3a**, **4c**	15	99	77.6(−)
3	**1a**, **3b**, **4d**	86	84	73.2(−)
4	**1a**, **3c**, **4e**	108	99	87.1(+)
5	**1a**, **3d**, **4f**	53	nd	−

As to other norbornenes, benzonorbornadiene **3b**[7] and **3c** also reacted with **1a** to give 73.2% ee and 87.1% ee selectivity (entries 3 and 4). In sharp contrast, **3d** (the endo isomer of **3c**) did not react under similar conditions, probably because of the steric hindrance of the *endo*-dicarboxylic anhydride moiety (entry 5).

The Josiphos ligand was also a better ligand for the asymmetric addition of **1a** to styrene. Thus, although a series of chiral phosphine ligands investigated failed to induce an asymmetric addition of **1a** to styrene, ligand **2e** gave the branched adduct regioselectively (>94%) in 72.5% ee, which exceeds the recently reported highest ee (54%) by Beletskaya et al. using (*R*,*S*)-binaphos.[4]



In summary, we have found that by employing sterically bulky Josiphos ligands palladium-catalyzed asymmetric addition of hydrogen phosphonates to norbornenes proceeded efficiently to produce the corresponding phosphonates in high enantioselectivity. We are currently modifying these phosphine ligands, and the results will be reported in due course.

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Supporting Information Available: Experimental details and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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