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Structurally Well-Defined, Recoverable C_3-Symmetric Tris(β-hydroxy phosphoramide)-Catalyzed Enantioselective Borane Reduction of Ketones

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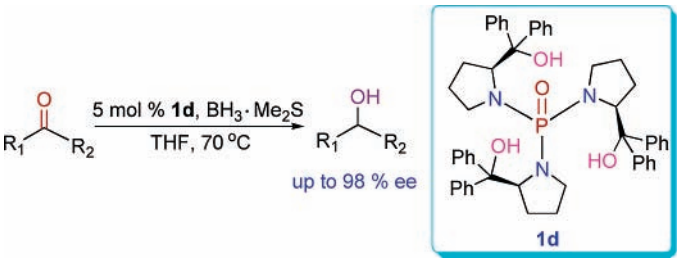
ABSTRACT



A series of new chiral C_3-symmetric tris(β-hydroxy phosphoramide) ligands have been synthesized via the reaction of trisphosphoramide ester and Grignard reagents. The catalytic asymmetric borane reduction of ketones with these new C_3-symmetric chiral tris(β-hydroxy phosphoramide)s was investigated. Structurally well-defined, recoverable ligand 1d is an efficient catalyst for the enantioselective borane reduction of both electron-deficient and electron-rich ketones, and high enantioselectivities were achieved (up to 98% ee).

C_3 symmetry is interesting, and recent reviews have illustrated the importance of C_3 symmetry and many C_3-symmetric compounds and their applications in asymmetric catalysis and chiral molecular recognition.[1] C_3-symmetric chiral ligands in octahedral complexes also permit a reduction in the number of possible diastereomorphous transition states just as C_2 symmetry in asymmetric catalysis. The development of new types of C_3-symmetic ligands for asymmetric catalysis has attracted attention in recent years. For example, the rhodium(I) complexes of enantiomerically pure tripodal phosphanes with C_3 symmetry have been reported in the hydrogenation of dimethyl itachonate giving high enantioselectivity (95% ee).[2] Katsuki and co-workers have developed tridentate trisoxazoline ligands as chiral auxiliaries in the asymmetric allylic oxidation of cycloalkenes with moderate to excellent enantioselectivities (up to 93% ee).[3] Ahn's group has reported interesting results of C_3-symmetric trisoxazolines in the asymmetric catalysis and the molecular recognition of aminonium ions and sugars.[4] Gade and co-

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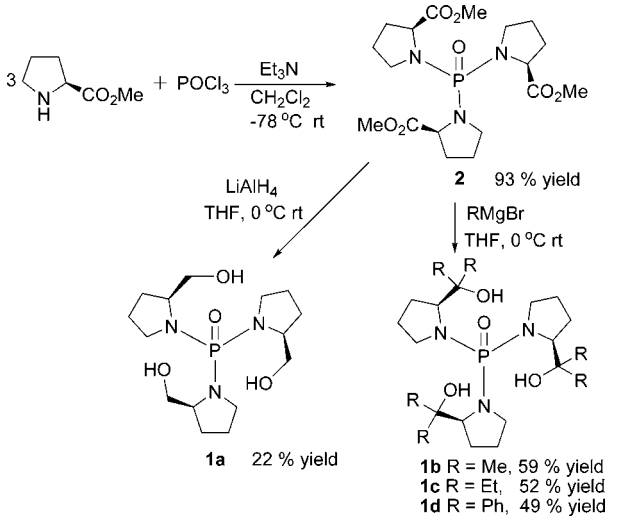
workers also reported that chiral C_3-symmetric trisoxazolines are highly efficient stereocontrolling ligands in the Cu(II)-catalyzed enantioselective α-amination (up to 99% ee) as well as the enantioselective Mannich reaction of prochiral β-ketoesters (up to 91% ee).[5]

Enantioselective borane reduction of ketones is a standard method for the synthesis of chiral secondary alcohol. Among the catalysts which have been disclosed in the literature,[6] the system devised by Corey, Bakshi, and Shibata, known as CBS catalyst,[7] affords excellent enantioselectivities and chemical yields. In this catalyst system, the formation of five-membered oxazaborolidine ring by the reaction of NH and OH groups with borane was important for achieving high enantioselectivities. Various heterogeneous polymer-supported and fluorous analogues were synthesized in order to facilitate the recovery of this useful catalyst and simplify reaction conditions.[8] Chiral phosphinamides as robust catalysts for the reduction of ketones have also been reported.[9] One C_3-symmetric phosphoramide synthesized from (*R*)-(+)-α-methylbenzylamine has been used in enantioselective borane reduction of ketones, and 20% ee was obtained.[9b] Our interest is to explore and to expand the application of C_3-symmetric compounds in asymmetric catalysis.[10] Herein, we report a new series of structurally well-defined, recoverable C_3-symmetric trisphosphoramides catalyzed enantioselective borane reduction of prochiral ketones.

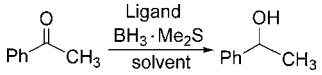
The C_3-symmetric ligands were obtained in two steps. The reaction of phosphorus oxychloride and L-proline methyl ester to give the corresponding trisphosphoramide ester **2** with high yield (93%) under simple experimental conditions (Scheme 1). Reduction of trisphosphoramide ester **2** with $LiAlH_4$ in THF afforded tris(β-hydroxy phosphoramide) **1a**. The reactions of the trisphosphoramide ester **2** with Grignard reagents gave the corresponding tripodal ligands **1b**−**d** with moderate yields after recrystallization from a mixture of petroleum ether and ethyl acetate.

Scheme 1. Synthesis of New C_3-Symmetric Ligands



First, the C_3-symmetric ligands **1** were evaluated in the asymmetric reduction of acetophenone using in situ generated borane complex at room temperature for 1 h. The results are summarized in Table 1. Ligands **1a** and **1b** gave only low enantioselectivity, less than 25% ee (Table 1, entries 1 and 2). A promising result (76% ee) was obtained with ligand **1c** (Table 1, entry 3). When it comes to ligand **1d**, the best result (90% ee) was obtained (Table 1, entry 4). All of the reduction products have an *R* configuration. It is well-known

Table 1. Enantioselective Borane Reduction of Acetophenone[a]



entry	ligand (mol %)	solvent	*T* (°C)	time (h)	yield[b] (%)	ee[c] (%)	config[e]
1	**1a** (10%)	THF	rt	1	92	0	
2	**1b** (10%)	THF	rt	1	98	23	*R*
3	**1c** (10%)	THF	rt	1	93	76	*R*
4	**1d** (10%)	THF	rt	1	95	90	*R*
5	**1d** (10%)	THF	90	1	94	93	*R*
6	**1d** (5%)	THF	70	1	94	95	*R*
7	**1d** (5%)	CH_2Cl_2	70	1	92	88	*R*
8	**1d** (5%)	toluene	70	1	95	89	*R*
9	**1d** (5%)	THF	45	1	94	90	*R*
10	**1d** (5%)	THF	rt	1	88	72	*R*
11	**1d** (5%)	THF	20	2	94	62	*R*
12	**1d** (5%)	THF	0	2	81[d]	5	*R*
13	**1d** (5%)	THF	−20	2	31[d]	4	*R*
14	**1d** (10%)[f]	THF	rt	1	94	90	*R*
15	**1d** (10%)[g]	THF	rt	1	93	92	*R*

[a] Reaction carried out with 0.5 mmol scale in 2 mL of solvent, molar ratio of $PhCOCH_3/BH_3$= 1:1.2. [b] Isolated yield by column chromatography. [c] ee determined by HPLC analysis using a Daicel Chiralcel OB column. [d] Yield determined by HPLC. [e] The absolute configuration assigned by comparison with the literature; see the Supporting Information. [f] Catalyst was recycled once. [g] Catalyst was recycled twice.

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that the enantioselectivity of borane reduction is affected profoundly by solvent, temperature, and the amount of catalyst. To examine these effects, the reduction of acetophenone was further investigated at various reaction conditions. At high temperature, only a slight increase in enantioselectivity was obtained (Table 1, entry 5). It was observed that a decrease in the catalyst loading from 10 to 5 mol % at room temperature resulted in a dramatic decrease in the enantioselectivity with a slight loss of yield (Table 1, entries 4 and 10). Catalyst loading of 10 mol % provided the optimum level of enantioselectivity. This is presumably because at this loading the rate of the catalyzed reaction is sufficiently faster than the noncatalytic reduction with $BH_3 \cdot Me_2S$.[11]

When the temperature exceeded 45 °C, high enantioselectivities were obtained with only small variety (Table 1, entries 5, 6, and 9). Furthermore, solvent affected the enantioselectivity slightly (Table 1, entries 7 and 8). However, when the temperature was decreased from 20 to 0 or −20 °C, distinct results were obtained with obvious decreases of both conversion and enantiomeric excess even at longer reaction times (Table 1, entries 11−13). The recycling of **1d** was investigated in borane reduction of acetophenone. The catalyst can be simply recovered by crystallization from reaction mixture (>70% yield) and reused with no loss of catalytic efficiency (Table 1, entries 14 and 15).

Meanwhile, it is important to note that this catalyst system can tolerate continuous addition of $BH_3 \cdot Me_2S$ and acetophenone in situ at a proper interval. We tested eight continuous additions of borane and acetophenone to the system. There was no any distinct decrease in enantioselectivities (Table 2). These results indicate that the catalyst still has catalytic efficiency even after the reaction was complete, and no loss of activity nor selectivity even after eight iterative additions of acetophenone and borane. Thus, this catalyst system can endure in situ recycling.[11b] This in situ recycling of the catalyst is very important for large-scale preparation of chiral secondary alcohols.

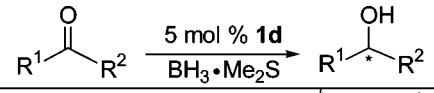
Table 2. Tolerance of Continous Addition of Borane and Acetophenone in Asymmetric Reduction[a]

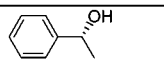
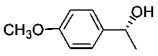
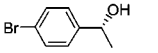
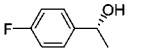
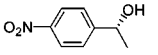
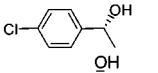
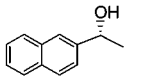
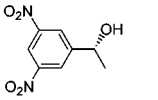
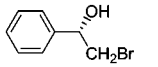
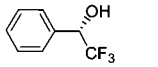
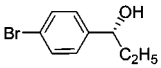
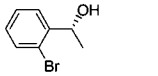
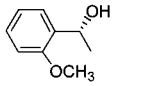
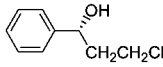
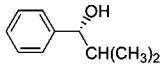
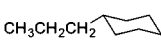
entry	$BH_3 \cdot Me_2S$ (mL) (2 M in THF)	PhCOMe (mmol)	yield[b] (%)	ee[c] (%)
1	0.3	0.5	99	87
2	0.3	0.5	99	95
3	0.3	0.5	99	91
4	0.3	0.5	99	93
5	0.3	0.5	99	91
6	0.3	0.5	99	93
7	0.3	0.5	99	90
8	0.3	0.5	99	89

[a] Reaction carried out using 5 mol % of ligand **1d** in 2 mL of THF. [b] Yield determined by HPLC. [c] ee determined by HPLC analysis using a Daicel Chiralcel OB column.

Under the optimized, simple reaction conditions, ligand **1d** was applied to the asymmetric borane reduction of a variety of aromatic and aliphatic ketones. As the results summarized in Table 3 show, high yields and enantioselectivities were obtained for prochiral ketones containing electron-withdrawing or electron-donating groups (Table 3, entries 1−11) unlike the CBS system, of which the enantioselectivity is dependent to the electronic effect of ketones.[12] A slightly decreased ee was obtained with the substitution at the *ortho* position, probably due to steric effects (Table 3, entries 12 and 13). It is interesting to note that ketones

Table 3. Catalytic Asymmetric Reduction of Ketones[a]



entry	product	yield (%)[b]	ee (%)[c]	config[d]
1		94	95	*R*
2		92	93	*R*
3		96	95	*R*
4		95	95	*R*
5		95	98	*R*
6		95	94	*R*
7		94	94	*R*
8		94	95	*R*
9		95	97	*S*
10		99	95	*S*
11		96	91	*R*
12		91	84	*R*
13		94	87	*R*
14		91	83	*R*
15		92	43	*R*
16		88	63	*R*

[a] Reaction carried out with 0.5 mmol scale in 2 mL of THF, molar ratio of $PhCOCH_3/BH_3 = 1:1.2$. [b] Isolated yield by column chromatography.[c] ee determined by HPLC analysis using a Daicel Chiralcel OB column. [e] The absolute configurations assigned by comparison with the literature; see the Supporting Information.

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containing an electron-withdrawing group give excellent enantioselectivities (Table 3, entries 3, 4, 5, 8, and 10). Changing linear 1-phenylbutan-1-one to branched 2-methyl-1-phenylpropan-1-one, the selectivity decreased greatly due to its steric effect (Table 3, entries 14 and 15). Aliphatic ketone 1-(*trans*-4-propylcyclohexyl) ethanone also gave moderate enantioselectivity determined by HPLC analysis after transformation to the phenyl isocyanate ester (Table 3, entry 16).

To further understand the structural effect of new C_3-symmetric ligands on their catalytic activity, a crystal structure of borane complex should be useful. But all attempts to get borane complex for XRD analysis failed. The crystal structure of ligand **1d** was determined by X-ray crystal diffraction analysis. **1d** was obtained as an air-stable, colorless crystal upon slow evaporation in ethyl acetate−petroleum ether. A perspective view of ligand **1d** was shown in Figure 1. From the crystal structure of **1d**, we can see

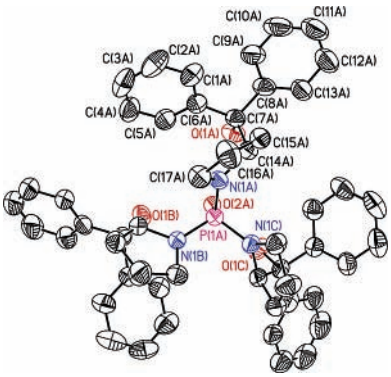

Figure 1. ORTEP diagram of ligand **1d**.

that P═O and three OH group are arranged to the same side owing to hydrogen-bonding interaction (O(1)−HO1···O(2)), this conformationally restricted system was important to form a well-defined chiral environment around the phosphorus atom. Thus, this chiral environment in the corresponding borane complex will result in high enantioselectivity in borane reduction of the ketone.

Although we do not know the exact modality of this complex, we can assume that it differs from the well-studied CBS system due to absence of an active N−H group. We assumed that the plausible transition state is one borane atom associated with three oxygens of hydroxy groups, and Lewis base interaction of the phosphoramide oxygen atom with another borane will facilitate the attack of borane to carbonyl group from the *Re*-face of prochiral ketone and afford the secondary alcohol in the *R* configuration (Figure 2).

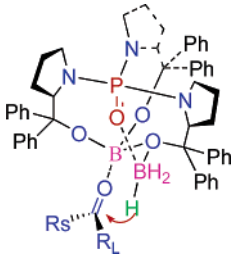

Figure 2. Presumed transition state for borane reduction.

In summary, a series of new chiral C_3-symmetric tris(β-hydroxy phosphoramide) ligands have been conveniently synthesized from commercially available L-proline methyl ester in two steps. Structurally well-defined, recoverable C_3-symmetric ligand **1d** was used as an efficient catalyst in the enantioselective borane reduction of prochiral ketones containing electron-withdrawing or electron-donating groups, and high enantioselectivities were obtained (up to 98% ee). Meanwhile, this robust catalyst can be recovered and reused or in situ recycled. This simple catalyst system is practical for the large-scale asymmetric synthesis of chiral secondary alcohols. The development of other asymmetric reactions using these C_3-symmetric ligands is ongoing in our group.

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Supporting Information Available: Experimental procedures, the crystal data of **1d** (CIF), copies of ^{1}H NMR and ^{13}C NMR spectra of **1** and **2**, and HPLC spectra of secondary alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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