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An Air-Stable P-Chiral Phosphine Ligand for Highly Enantioselective Transition-Metal-Catalyzed Reactions

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Optically active phosphine ligands have played a significant role in transition-metal-catalyzed asymmetric reactions.[1] Although numerous chiral phosphine ligands have been reported so far, the design and synthesis of novel and highly efficient ligands are still an important research subject in the field of asymmetric catalysis.[2] We have previously synthesized a new class of P-chiral phosphine ligands, 1,2-bis(alkylmethylphosphino)ethanes (abbreviated as BisP*) and bis(alkylmethylphosphino)methanes (MiniPHOS), and demonstrated their excellent enantioinduction ability in Rh-catalyzed asymmetric hydrogenations,[3−5] as well as their utility in the mechanistic study of the hydrogenations.[6] However, these ligands are extremely sensitive to air owing to the high electron density at the phosphorus atoms, and this drawback has prevented their widespread application in asymmetric catalyses. Herein, we report a new air-stable P-chiral phosphine ligand that exhibits excellent to almost perfect enantioselectivity in not only Rh-catalyzed hydrogenation but also Rh- or Pd-catalyzed carbon−carbon bond-forming reactions.

The newly designed ligand **1** (abbreviated as QuinoxP*) contains a quinoxaline backbone whose strong electron-withdrawing ability decreases the electron density at the phosphorus atoms, rendering the phosphine moieties less susceptible to air oxidation. Although this ligand is similar to *t*-Bu-BisP* in the structural motif, it forms more rigid chelate rings owing to the quinoxaline backbone.

Ligand **1** was readily prepared from enantiomerically enriched (*R*)-*tert*-butyl(hydroxymethyl)methylphosphine−borane (**2**)[7] (Scheme 1). Compound **2** was converted into benzoyl derivative **3**, which was recrystallized from ethyl acetate two times to give the enantiomerically pure form. This substrate, after hydrolysis, underwent ruthenium-catalyzed oxidative one-carbon degradation in the presence of potassium persulfate and potassium hydroxide to form secondary phosphine−borane **4** with >99% ee. Deprotonation with *n*-butyllithium and subsequent nucleophilic substitution reaction with 2,3-dichloroquinoxaline, followed by treatment with TMEDA, provided the desired ligand **1** as an orange powder in 80% yield. Notable is that the ligand was neither oxidized nor epimerized at the P-stereogenic phosphorus atoms on standing in air at room temperature for more than 8 months.

The utility of the ligand in asymmetric catalysis was examined in the Rh-catalyzed asymmetric hydrogenation of several representative prochiral amino acid and amine derivatives. All reactions were carried out in methanol at room temperature at an initial hydrogen pressure of 3 atm, and the results are summarized in Table 1. In all cases, excellent to almost perfect enantioselectivities were observed. One notable feature is that both (*E*)- and (*Z*)-*β*-(acetylamino)acrylates could be reduced in >99.0% enantioselectivity (entries 3 and 4).[8] It is also worthy to mention that the reduction of 1-acetylamino-1-phenylethene afforded the *R* configuration product with 99.9% ee (entry 5), and in sharp contrast, 1-acetylamino-1-adamantylethene was converted into the *S* configuration product with 96.3% ee (entry 6). This dramatic stereochemical reversal is consistent with the results obtained by the use of (*S*,*S*)-*t*-Bu-BisP*,[9,10] (*R*,*R*)-*t*-Bu-MiniPhos,[10] and (*S*,*S*)-Me-DuPhos.[11,12]

Scheme 1. Preparation of Ligand **1**

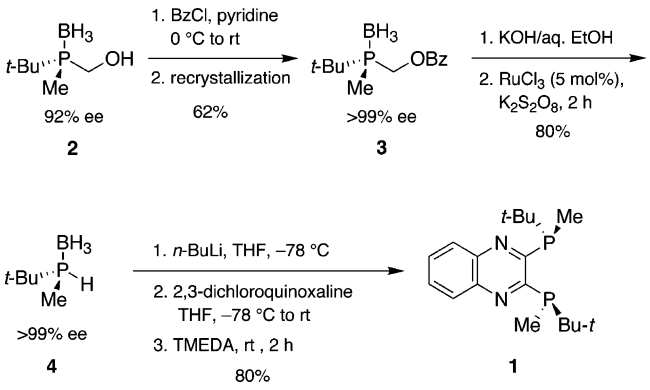
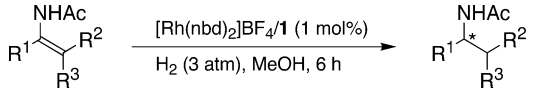


Table 1. Asymmetric Hydrogenations of Dehydroamino Acid Esters and α-Enamides[a]



entry[b]	R^1	R^2	R^3	ee (%) (config)
1[c]	CO_2Me	Ph	H	99.9 (*R*)
2	CO_2Me	4-AcO-3-$MeOC_6H_3$	H	99.6 (*R*)
3	Me	H	CO_2Me	99.7 (*R*)
4	Me	CO_2Me	H	99.2 (*R*)
5	Ph	H	H	99.9 (*R*)
6	1-adamantyl	H	H	96.3 (*S*)

[a] All hydrogenation reactions were performed with 0.5 mmol of substrate and 0.005 mmol in situ-prepared $[Rh(nbd)_2]BF_4$/**1** in methanol at room temperature. [b] All reactions were completed under the conditions. [c] The reaction was completed within 1 h.

The enantioinduction ability of the new ligand was examined also in transition-metal-catalyzed carbon−carbon bond-forming reactions. We first applied **1** to the Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to α,*β*-unsaturated carbonyl compounds.[13] As shown in Table 2, the reactions proceeded at 40−50 °C to give the corresponding addition products in high yields with excellent enantiomeric excesses. These results compare favorably with those obtained by the use of BINAP as the chiral ligand.[13a,b]

The high utility of this ligand was demonstrated also in the Pd-catalyzed asymmetric ring-opening reaction.[14] Our cursory experiments that used a premixing catalyst with $PdCl_2$(cod) and **1** provided high yields of the products with excellent enantiomeric excesses of up to 97.6% (Table 3). These enantioselectivities bear comparison with the highest reported hitherto for this transformation.

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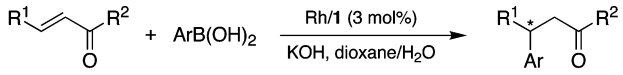
Table 2. Asymmetric 1,4-Addition of Arylboronic Acids to α,β-Unsaturated Carbonyl Compounds Catalyzed by Rh(I)/**1**[a]

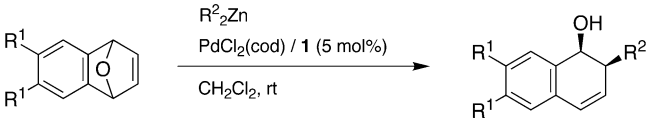


enone: 2-cyclohexenone (**5**), 2-cycloheptenone (**6**), (*E*)-5-methyl-3-hexen-2-one (**7**)

entry	enone	Ar	temp (°C)	time (h)	yield (%)[b]	ee (%) (config)
1	**5**	Ph	40	1	93	98.2 (*R*)
2	**5**	4-$MeOC_6H_4$	40	1	97	93.9 (*R*)
3	**5**	4-$CF_3C_6H_4$	50	12	92	99.4 (*R*)
4	**6**	Ph	50	12	90	96.2 (*R*)
5	**7**	Ph	40	1	97	99.1 (*S*)

[a] All reactions were performed with 0.3 mmol α,β-unsaturated carbonyl compound, 0.6 mmol arylboronic acid, and 0.009 mmol rhodium catalyst generated in situ from $[RhCl(C_2H_4)_2]_2$ (0.0045 mmol) and **1** (0.099 mmol). [b] Isolated yield.

Table 3. Asymmetric Alkylative Ring Opening Catalyzed by $PdCl_2$(cod)/**1**[a]



entry	R^1	R^2	time (h)	yield (%)[b]	ee (%) (config)
1	H	Me	2	90	95.6 (1*S*,2*S*)
2	H	Et	15	88	97.6 (1*S*,2*S*)
3	F	Me	2	90	93.8 (1*S*,2*S*)

[a] All reactions were performed with 0.5 mmol of substrate and 0.025 mmol of in situ-prepared $PdCl_2$(cod)/**1**. [b] Isolated yield.

In conclusion, we have prepared a new P-chiral phosphine ligand **1** by reacting enantiomerically pure *tert*-butylmethylphosphine−borane with commercially available 2,3-dichloroquinoxaline. This ligand, in contrast to most of the previously reported P-chiral ligands, is an air-stable solid and exhibits excellent enantioselectivities in both Rh-catalyzed asymmetric hydrogenations and Rh- or Pd-catalyzed carbon−carbon bond-forming reactions. These findings indicate its versatile utility in a wide variety of transition-metal-catalyzed asymmetric reactions.

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Supporting Information Available: Synthesis and characterization of phosphine ligand **1** and detailed experimental procedures of catalytic asymmetric reactions using ligand **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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