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Asymmetric Synthesis of α-Chiral Hydroxyalkylphosphines by a Catalytic Enantioselective Reduction of Acylphosphines

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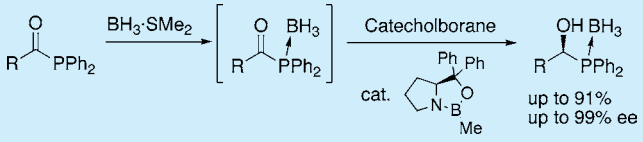
Supporting Information

ABSTRACT: Enantioselective reduction of acylphosphines, after precomplexation with borane, proceeded smoothly in the presence of a chiral oxazaborolidine catalyst and catecholborane. α-Hydroxyalkylphosphine products were obtained as phosphine−borane complexes in good yield and enantioselectivity. One of the products of the enantioselective reduction was successfully applied as an optically active phosphine ligand for asymmetric catalysis after suitable derivatization.



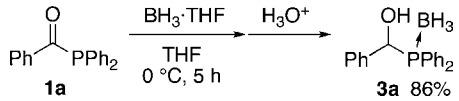
The development of new chiral phosphine ligands is a fascinating research topic since asymmetric reactions catalyzed by a chiral phosphine−transition-metal complex provide a number of advantages in the organic synthesis of chiral molecules.[1] Most chiral phosphines have a chirality derived from optically active natural compounds, whether it is embedded into the skeleton or indirectly transferred during resolution processes. On the other hand, catalytic asymmetric synthesis of a chiral phosphine itself is a promising and challenging subject that can lead to the efficient preparation of various chiral phosphines.[2] Chiral phosphines having a chiral carbon atom at the α position to the phosphorus atom generally show good performance in selectivity when they are used as a chiral ligand.[3] Hydroxyalkylphosphines are one of the promising precursors of chiral phosphines.[4] However, only a few preparations of α-chiral hydroxyalkylphosphines through asymmetric addition of a phosphorus nucleophile to carbonyl compounds have been reported.[5] α-Chiral hydroxyalkylphosphines could also be accessed if the carbonyl group of acylphosphines were reduced with enantioselectivity. Actually, there are a few examples of the asymmetric reduction of acylphosphines and α-ketophosphonates.[6]

Herein, we report a successful asymmetric reduction of acylphosphines for the preparation of chiral α-hydroxyalkylphosphine derivatives. A successful application of one of these products as a chiral ligand in a Pd-catalyzed asymmetric allylation of an amine is also described.

Acylphosphines having a P(III) atom are conveniently and quantitatively synthesized by the reaction of acyl halides with silylphosphines.[7] Acylphosphines are key intermediates for the synthesis of low coordinate phosphorus compounds.[8] However, they have rarely been used in the synthesis of trivalent phosphines, while their oxides have been successfully and widely used as photochemical radical initiators and functional additives for UV curing materials and inkjet ink.[9]

Initial attempts were made to search for a suitable reducing agent for acylphosphines. Among tested reducing agents in the reduction of benzoyldiphenylphosphine **1a**, only BH_3 reagent cleanly afforded the expected alcohol **3a** as a phosphine−borane complex without cleavage of the P−C/P−O bond (Scheme 1).[10] At least 2 equiv of borane was required due to consumption of borane by complexation with the phosphine. Use of other reagents, such as $LiAlH_4$ and DIBAL, caused partial cleavage of the P−C bond.

Scheme 1. Reduction of 1a with BH_3



It is advantageous to obtain the product as a phosphine−borane complex since the BH_3 group serves as a useful protective group for a trivalent phosphine preventing it from undergoing oxidation during organophosphine synthesis.[10a,11] Since complexation of the phosphorus atom with borane confers high electrophilicity on the adjacent carbonyl carbon, the real species to be reduced is considered as the acylphosphine−borane complex. However, an NMR examination of the reduction of acetylphosphine **1b** with BH_3·THF (1.0 equiv) revealed that a two-step sequence of complexation and reduction proceeded at the same time to give a mixture of the products including hydroxyethylphosphine−borane **3b**, acetylphosphine−borane **2b**, together with noncomplexed **1b** (Figure 1d). Since reaction of a single species is preferable for asymmetric versions of the reduction, selective complexation of the phosphorus with BH_3 prior to the reduction was investigated using several borane reagents. In contrast to the above result with BH_3·THF, BH_3·SMe_2 was found to be suitable for the stepwise reaction; an equimolar amount of BH_3·SMe_2 selectively afforded the complex **2b** without reduction (Figure 1b), and the reduction slowly proceeded to give **3b**

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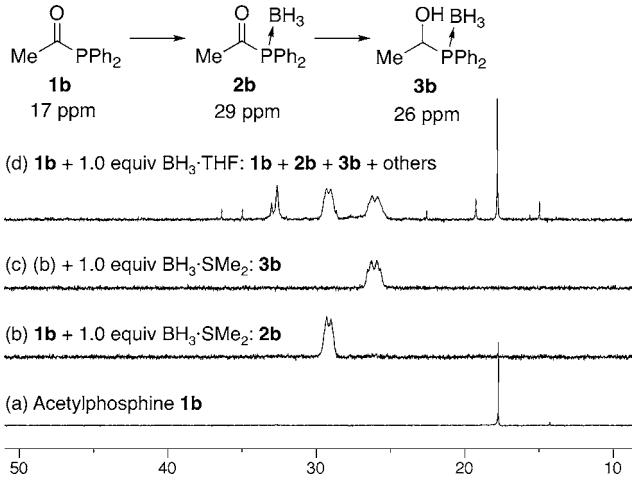


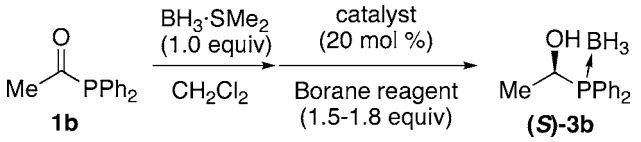
Figure 1. 162 MHz ^{31}P NMR experiments of the stepwise complexation and reduction of acetylphosphine **1b** in CH_2Cl_2.[12]

after the addition of another BH_3·SMe_2 (Figure 1c). These results clearly indicate that in situ precomplexation using BH_3·SMe_2 can make the reduction process simple as a reduction of the complex **2b**.

The CBS reduction is one of the most effective enantioselective reductions of a carbonyl group with borane reagents using a chiral oxazaborolidine catalyst.[13] Therefore, we investigated the CBS reduction of acylphosphine−borane complexes prepared in situ using excess BH_3·SMe_2 reagent for both complexation and reduction. Initial investigation of the enantioselective reduction of **1b** was performed by using 20 mol % (*S*)-(−)-*B*-methyl-CBS-oxazaborolidine (***S***)**-4** with 2.5 equiv BH_3·SMe_2. Reaction at 23 °C for 6 h gave the 1-hydroxyethylphosphine−borane complex (***S***)**-3b** in high yield and selectivity (Table 1, entry 1). Then, several catalysts, reagents, and conditions were surveyed for optimizing the enantioselective reduction of **1b** (Table 1). Poor enantioselectivity was observed when lower amounts of the catalyst were used (entry 3). Other oxazaborolidines and related catalysts were not effective for the present reduction; all catalysts gave the alcohol in good yield but with low-to-moderate enantioselectivity (entries 5−7).

During this optimization, we found anomalous behavior for the present reaction in regard to enantioselectivity. It is unusual, but quite important, that the enantioselectivity of the present reduction depends on the reaction period; enantioselectivity gradually improves as the reaction period increases (entries 1 and 2), despite the same chemical yield being observed in each reaction. In addition, the reaction at low temperature gave racemic alcohol **3b** (entry 4), probably because the catalytic reaction was slower than the noncatalytic reduction at this temperature (noncatalytic reduction was confirmed to occur slowly, even at −42 °C, to give the racemic alcohol).[14] Moreover, enantioselectivity was induced by catalyst (***S***)**-4** from racemic 1-hydroxyethylphosphine−borane once prepared in situ.[15] Both the time dependency of selectivity and the induction of chirality from a racemic product cannot be simply interpreted by the mechanistic investigations reported for ketone reduction, such as dimerization of oxazaborolidine catalyst at low temperature.[14] These results show that the present reduction does not involve a simple kinetic control of the facial selection, but other mechanisms of chirality induction.[16]

Table 1. Enantioselective Reduction of 1b under Various Conditions[a]



entry	cat.[b]	borane[c]	conditions	yield[d] (%)	% ee[e]
1	A	BMS[f]	23 °C, 6 h	91	85
2	A	BMS[f]	23 °C, 1 h	91	54
3[g]	A	BMS[f]	23 °C, 6 h	84	27
4	A	BMS[f]	−42 °C, 3 h	51	0
5	B	BMS[f]	23 °C, 6 h	88	26
6	C	BMS[f]	23 °C, 6 h	86	11
7	D	BMS[f]	23 °C, 6 h	85	32
8	A	PB	23 °C, 18 h	84	74
9	A	PB	−78 °C, 6 h	77	3
10	A	CB[h]	23 °C, 6 h	80	87
11	A	CB[h]	−42 °C, 6 h	81	96
12	A	CB[h]	−78 °C, 6 h	70	99

[a]Unless otherwise noted, 1 equiv of BH_3·SMe_2 was added prior to the catalytic reduction. [b]Unless otherwise noted, 20 mol % of catalyst was used. Catalyst: A, Me-CBS-oxazaborolidine ((***S***)**-4**) = (*S*)-(−)-*B*-methyl-4,4-diphenyl-1,3,2-oxazaborolidine; B, (−)-diphenylprolinol + additional BH_3·SMe_2 (1 equiv); C, Ph-CBS-oxazaborolidine = (*S*)-(−)-*B*-phenyl-4,4-diphenyl-1,3,2-oxazaborolidine; D, acyloxyborane = (−)-proline + additional BH_3·SMe_2 (1 equiv). [c]Borane reagent (1.5 equiv): BMS = BH_3·SMe_2; PB = pinacolborane; CB = catecolborane. [d]Isolated yield. [e]Determined by HPLC analysis using Daicel Chiralpak IA column. [f]BH_3·SMe_2 (2.5 equiv) was added in one portion. [g]5 mol % of catalyst was used. [h]Catecholborane (1.8 equiv) was used.

Other borane sources were investigated as reductants for enantioselective reduction of acetylphosphine−borane **2b**, prepared in situ by the reaction of **1b** with 1 equiv of BH_3·SMe_2 in CH_2Cl_2 (entries 8−12). These results clearly showed that catecholborane was found to be the best for the enantioselective reduction of acylphosphine−borane **2b**. Temperature dependencies were also observed in these investigations, though they depended on the reductant used. Reduction of acetylphosphine by catecholborane showed different dependencies from other cases; this seemed to involve simple kinetic control, since the reaction proceeded at lower temperature in better yield and selectivity.

By applying the two-step reactions with BH_3·SMe_2 (complexation) and catecholborane (reduction) with Me-CBS catalyst, several acylphosphines were successfully reduced to the corresponding α-hydroxyalkylphosphine−borane complexes in good yield and enentioselectivity (Table 2).

The results shown in Table 2 indicate that the induction of selectivity is related to electronic effects in the substituent R. Acylphosphines with an electron-withdrawing substituent on the carbonyl group (**1b−d** and **1j**) tend to show better selectivity at low temperature, probably because of a rapid reaction, due to high reactivity of the electronically activated carbonyl group resulting in kinetic control of the catalytic reaction predominantly. The stereoselectivity of the present reaction is in accordance with that expected in the CBS reduction of prochiral ketones.[13] Oxalyldiphosphine **1m** gave the corresponding diphosphine derivative, though the ee and chemical yield were poor. On the other hand, several alkanoylphosphines (**1e**, **1f**) and aroylphosphines (**1a**, **1h**, **1i**) gave opposite results; they gave better selectivity at higher

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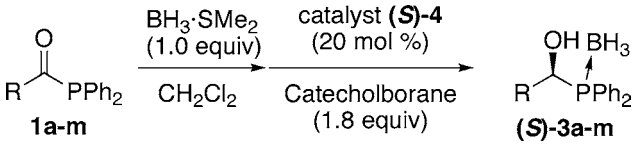
Table 2. Enantioselective Reduction of Acylphosphines Using (*S*)-4 and Catecholborane.[a]



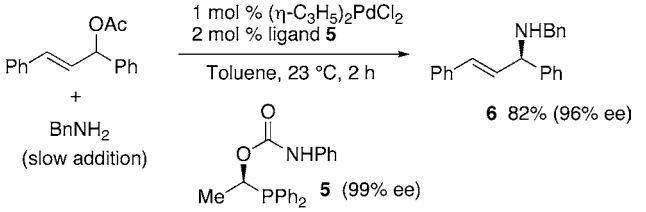
1	−78 °C time (h)	−78 °C % yield[b] (% ee[c])	23 °C time (h)	23 °C % yield[b] (% ee[c])
$PhCOPPh_2$ (**1a**)	4	28 (8)	24	81 (85)
$MeCOPPh_2$ (**1b**)	6	91 (95)[d]	24	89 (90)
$ClCH_2COPPh_2$ (**1c**)	6	91 (98)	7[e]	91 (90)
$MeOCH_2COPPh_2$ (**1d**)	6	90 (87)	7[e]	78 (71)
$EtCOPPh_2$ (**1e**)	7	59 (33)	6	91 (97)
i$PrCOPPh_2$ (**1f**)	7	17 (5)	4	68 (91)
t$BuCOPPh_2$ (**1g**)	*f*	*f*	23	0 (−)[g]
p-$MeC_6H_4COPPh_2$ (**1h**)	8	9 (25)	24	84 (84)
p-$MeOC_6H_4COPPh_2$ (**1i**)	*f*	*f*	24	36 (73)
p-$NO_2C_6H_4COPPh_2$ (**1j**)	20	85 (97)	10	67 (53)
$MeCOPCy_2$ (**1k**)	*f*	*f*	10	33 (68)[h,i]
$MeCOP(tBu)_2$ (**1l**)	*f*	*f*	24	6 (35)[h,j]
$Ph_2PCOCOPPh_2$ (**1m**)	*f*	*f*	5	25 (21)[k]

[a]The reaction was conducted by using 20 mol % of (*S*)-**4** with catecholborane (1.8 equiv) after precomplexation with BH_3·SMe_2 (1 equiv) in CH_2Cl_2. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis and shown in parentheses. [d]By using (*R*)-**4**, (*R*)-**3b** was obtained in 85%, 98% ee. [e]The reaction was conducted at 0 °C. [f]Not examined. [g]No alcohol was formed. Pivaloyldiphenylphosphine−borane was observed instead in the mixture. [h]Enantiomeric excess was determined after conversion to phenoxyacetate. [i]By using BH_3·SMe_2 as a reductant, **3k** was obtained in 64%, 83% ee (23 °C, 20 h). [j]By using BH_3 SMe_2 as a reductant, **3l** was obtained in 14%, 48% ee (23 °C, 24 h). [k]Diastereomer mixture (*dl*/*meso* = 88/12).

temperature. These results clearly indicated that there are at least two possible courses of selectivity-determining steps based on the electronic situation in the carbonyl carbon. Dialkylphosphino derivatives (**1k**, **1l**) also gave the corresponding hydroxyalkylphosphines, though low yield and selectivity were observed under the standard conditions. Since the dialkylphosphino group in **1k** and **1l** has a more electron-donating nature than diphenyl derivatives, they are less reactive than diphenyl derivatives. Use of a more reactive reductant such as BMS is sometimes effective in these cases. With appropriate choice of the reaction conditions, the present borane reduction provides a versatile route toward chiral α-hydroxyalkylphosphine derivatives.

Application of the resulting hydroxyalkylphosphines was investigated as a source of a chiral phosphine ligand for a transition-metal-catalyzed asymmetric reaction. Several modifications[17] of the hydroxy group in 1-hydroxyethylphosphine-borane complex (*S*)-**3b** revealed that the carbamate (*S*)-**5**, prepared by a treatment of (*S*)-**3b** with phenyl isocyanate, was as an effective chiral ligand for Pd-catalyzed asymmetric allylation. After deprotection of the borane complex (*S*)-**5**·BH_3 by treatment with morpholine,[18] phosphine carbamate (*S*)-**5**-Pd complex successfully catalyzed the allylation of benzylamine in excellent enantioselectivity (Scheme 2).[19]

Scheme 2. Application of Phosphine Carbamate (*S*)-5 as a Chiral Ligand for Pd-Catalyzed Enantioselective Allylation of Benzylamine



In conclusion, we have found that acylphosphines are successfully reduced by borane reagents to produce α-chiral hydroxyalkylphosphines as a borane complex. Me-CBS oxazaborolidine was found to be effective for the enantioselective reduction of the precomplexed acylphosphine−borane prepared in situ. High enantioselectivities can be achieved under suitable conditions, although the course of enantioselection strongly depends on the electronic properties of the substituent in the acylphosphines. The resulting chiral phosphine can be modified and successfully applied to asymmetric catalysis as a chiral ligand. Further applications of the products and mechanistic elucidation of the unusual chirality induction of the present reduction process are now under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Determinaton of the absolute configuration of the product and plausible mechanisms of chirality induction. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) Aliquot of the reaction mixture in CH_2Cl_2 was dissolved in C_6D_6 and the NMR spectrum was measured. Phosphine−borane compounds usually show a couple of broad doublet signals in $^{31}P\{^1H\}$ spectra due to B−P coupling.

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(15) Acylphosphine **1b** was reacted with $BH_3{\cdot}SMe_2$ (2.7 equiv) in CH_2Cl_2 in the presence of (*N*,*N*-dimethylamino)ethanol (0.2 equiv) at rt for 11 h. After the formation of alcohol was confirmed by TLC analysis, (***S***)**-4** (0.2 equiv) was added to the mixture, and then the mixture was stirred for 6 h at rt. Enantiopurity of the product **3b** was determined by HPLC analysis (53% ee).

(16) Proposal of some plausible mechanisms for enantioselection with some experimental evidence is described in the Supporting Information.

(17) Several conversions of (***S***)**-3** are described in the Supporting Information.

(18) Conversion of the hydroxy group is necessary before deprotection of phosphine−borane **3** with amine due to spontaneous degradation; see: Moiseev, D. V.; Patrick, B. O.; James, B. R. *Inorg. Chem.* **2007**, *46*, 11467−11474.

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