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A new synthetic route to unsymmetric P-chirogenic bisphosphine ligands

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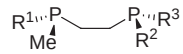
Abstract—A new type of P-chirogenic bisphosphine, unsymmetric BisP*, ligands with different alkyl groups on the two phosphorus atoms was designed and their new synthetic route was developed. A rhodium catalyst with one of the unsymmetric BisP* has demonstrated the ability of highly enantioselective (up to 98%) hydrogenation of the α-dehydroamino acid derivatives under mild conditions. © 2001 Elsevier Science Ltd. All rights reserved.

Optically active phosphine–transition metal complexes have played an important role in catalytic asymmetric synthesis.[1] Among many types of optically active phosphine ligands, the C_2 symmetric bisphosphine ligands have been considered to be endowed with superior properties in catalysis because of their attractiveness augmented by ease of synthesis.[2] It is well known that C_2 symmetric ligands such as BINAP[3] and DuPHOS[4] have exhibited superior enantioselectivity over a broad front. In a previous report,[5] (*S*,*S*)-1,2-bis(alkylmethylphosphino)ethane (alkyl = 1-adamantyl, *t*-butyl, cyclohexyl, cyclopentyl, 1,1-diethyl propyl; abbreviated as BisP*) gave high enantioselectivity in the hydrogenation of various α-dehydroamino acid derivatives when the BisP* was used as a BisP*–Rh catalyst. We had an idea that the enantioselectivity should be enhanced if [(*S*)-1-boranato(R^1)methylphosphino-(*S*)-2-boranato(R^2)methylphosphino]ethane (R^1, R^2 = 1-adamantyl, *t*-butyl, cyclohexyl, phenyl; abbreviated as unsymmetric BisP*) with different alkyl groups on the two phosphorus atoms could be used. This means the unsymmetric BisP* has no longer C_2 symmetry.

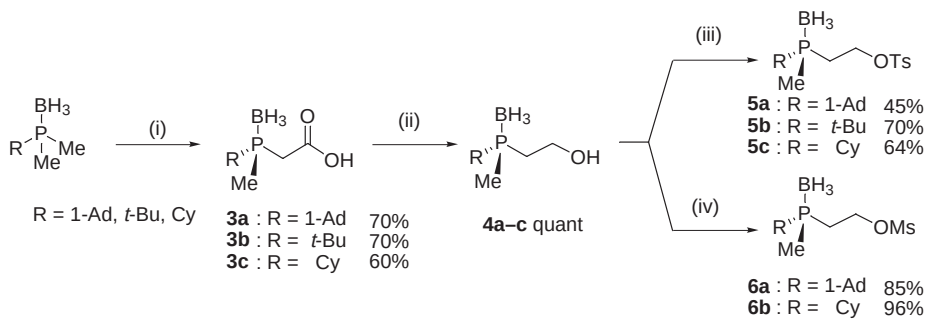


1a–e

Unsymmetric BisP*

1a : R^1 = 1-Ad; R^2 = *t*-Bu; R^3 = Me
1b : R^1 = 1-Ad; R^2 = Cy; R^3 = Me
1c : R^1 = *t*-Bu; R^2 = Cy; R^3 = Me
1d : R^1 = 1-Ad; R^2 = R^3 = Cy
1e : R^1 = 1-Ad; R^2 = R^3 = Ph

This paper reports a new synthetic route of the P-chirogenic bisphosphine, unsymmetric BisP*, (**1a**–**e**) and demonstrates the ability of high enantioselectivity



Scheme 1. (i) (a) *s*-BuLi/(−)-sparteine, ether, −78°C, 3 h; (b) CO_2. (ii) BH_3–THF, THF, 0°C, 1 h. (iii) *p*-TsCl, Py, rt, 5 h. (iv) MsCl, CH_2Cl_2, −15°C, 1 h.

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(more than 98%) in the hydrogenation of tetra-substituted α-dehydroamino acids when a BisP*–Rh (**2**) was used as a catalyst.

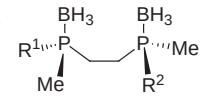
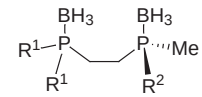
The synthetic route to the newly designed unsymmetric BisP* is shown in Schemes 1 and 2. Alkyl(dimethyl)-phosphine–boranes were enantioselectively deprotonated by treatment with *s*-BuLi in the presence of (−)-sparteine at −78°C,[6] and then bubbled with CO_2 to afford (*R*)-1-boranato[alkyl(methyl)phosphino]acetic acids (**3a**–**c**) (>90% ee) in 60–70% yields (Scheme 1).

Reduction of the carboxylic acids by borane–THF complex afforded in quantitative yields the (*R*)-1-boranato[alkyl(methyl)phosphino]ethanols (**4a**–**c**), which was treated with TsCl or MsCl to give corresponding (*R*)-1-boranato[alkyl(methyl)phosphino]ethanol 2-tosylates (**5a**–**c**) or (*R*)-1-boranato[alkyl(methyl)phosphino]-ethanol 2-mesylates (**6a**–**b**), respectively. These compounds were then coupled with (*S*)-alkylmethylphosphine–boranes[7] to provide (*S*,*S*)-unsymmetric BisP* (**7a**–**c**)[8] (>97% ee) together with small amounts of the corresponding diastereoisomers (Scheme 2).

On the other hand, the monochirogenic unsymmetric BisP* (**7d**–**e**)[8] was prepared using lithiated dicyclohexyl- or diphenylphosphine as the nucleophiles. The chemical yields of the coupling reactions are shown in Table 1. The combination of 1-adamantyl and *t*-butyl or 1-adamantyl and cyclohexyl groups provided quantitative yield of coupling products **7a** or **7b** (entries 1 and 2), while 1-Ad-BisP* ($R^1=R^2=$1-Ad) was obtained in moderate yield (entry 3). It is noteworthy that this coupling reaction was not effective for the preparation of compound **7c** (entry 4), probably due to the inhibition by undesired by-products. The alternative route to **7a**, in which the positions of R^1 and R^2 were changed, was also successful (entry 5). This procedure was not applicable to the preparation of unsymmetric BisP*, **7d**–**e** (entries 6 and 7).

An alternative route to **7d**–**e** was carried out from optically active secondary phosphine–borane with **5d** and **6c** prepared from dicyclohexyl- and diphenyl-(methyl)phosphine–borane, respectively (Scheme 3).

Table 1.

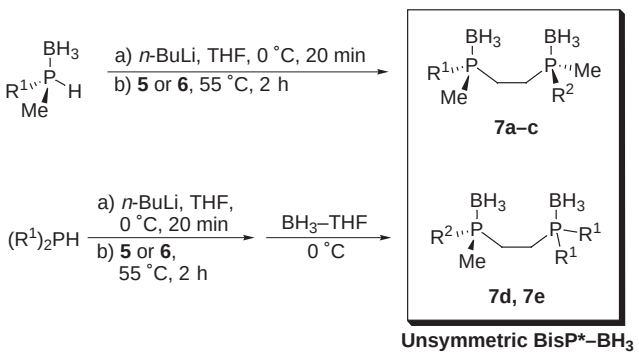
Entry[a]			R^1	R^2	Yield (%)
1[b,d]		**7a**	1-Ad	*t*-Bu	quant
2[d]		**7b**	1-Ad	Cy	quant
3[d,e]		**7a'**	1-Ad	1-Ad	40
4		**7c**	*t*-Bu	Cy	10
5[c]		**7a**	*t*-Bu	1-Ad	quant
6		**7d**	Cy	1-Ad	trace
7		**7e**	Ph	1-Ad	35

[a]The mixture of lithiated secodary phosphine–boranes and the mesylates **5** was stirred at 55 °C for 2 h unless otherwise noted. [b]The mixture was stirred at 55 °C for 10 min. [c]The mixture was stirred rt for 1 h. [d]The tosylates **6** was used. [e]Compound **7a'** is symmetric BisP*.

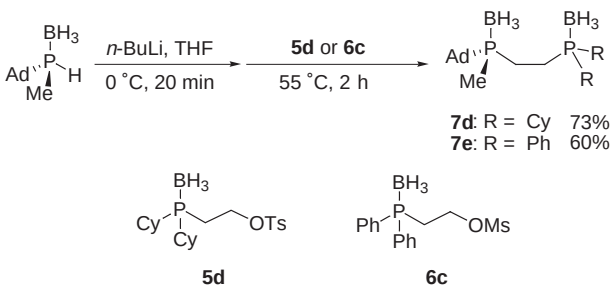
The chemical yields of **7d**–**e** were improved to 73% and 60%, respectively, probably due to reduced steric hindrance of the nucleophile. One of the unsymmetric BisP*–boranes, **7b,** was converted into the corresponding cationic rhodium complex, **2**, as a quantitative yield according to the reported procedure (Scheme 4).[8,9]

Preliminary asymmetric catalytic hydrogenation of dehydro-*N*-acetyl-α-cyclohexylglycine methyl ester **8** in the presence of rhodium complex **2** provided the quantitative yield of *N*-acetyl-α-cyclohexylglycine methyl ester **9** with 98.2% ee (*R*). Compared with 1-Ad-BisP* (82.4% ee (*R*)), Cy-BisP* (89.3% ee (*R*)), as a symmetric BisP*,[5] and (*S*,*S*)-Me-DuPHOS (96.2% ee (*S*)),[10] this result was drastically improved (Scheme 5).

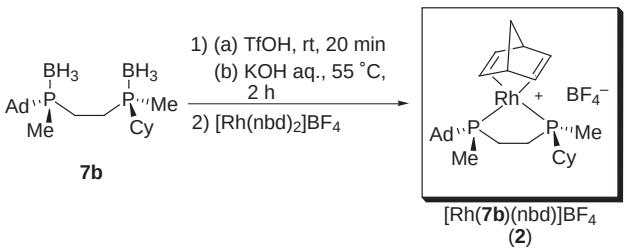
In summary, new P-chirogenic bisphosphine ligands with different alkyl groups on two phosphorus atoms (unsymmetric BisP*) were designed and prepared. In catalytic asymmetric hydrogenation of dehydro-*N*-acetyl-α-cyclohexylglycine methyl ester, the unsymmetric BisP*–Rh gave high reactivity and enantioselectivity. A new class of P-chirogenic bisphosphine, unsymmetric BisP*, will produce a highly asymmetric environment around the rhodium center and will give highly effective enantioselectivity.



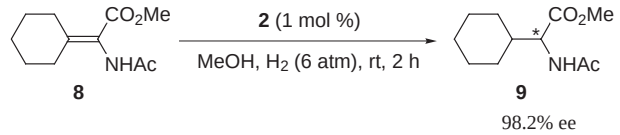
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

Acknowledgements

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8. Compounds data: **7a**; mp 198–200°C; $[\alpha]_D$ 5.7 (*c* 0.93, $CHCl_3$); ^{31}P NMR (202 MHz, $CDCl_3$): δ 24.2 ($J_{PB}=33$ Hz), 28.6–28.9 ($J_{PB}=105$ Hz). **7b**; mp 197–199°C; $[\alpha]_D$ 2.9 (*c* 1.1, $CHCl_3$). ^{31}P NMR (161 MHz, $CDCl_3$): δ 19.2 ($J_{PB}=49$ Hz), 25.2 ($J_{PB}=52$ Hz). **7c**; mp 136–138°C; $[\alpha]_D$ −12 (*c* 0.29, $CHCl_3$). ^{31}P NMR (202 MHz, $CDCl_3$): δ 18.2 ($J_{PB}=100$ Hz), 28.9 ($J_{PB}=104$ Hz). **7d**; mp 141–143°C; $[\alpha]_D$ −4.0 (*c* 0.71, $CHCl_3$). ^{31}P NMR (202 MHz, $CDCl_3$): δ 24.2 ($J_{PB}=70$ Hz), 27.8 ($J_{PB}=56$ Hz). **7e**; mp 167–169°C; $[\alpha]_D$ 6.4 (*c* 0.67, $CHCl_3$). ^{31}P NMR (202 MHz, $CDCl_3$): δ 18.2 ($J_{PB}=100$ Hz), 28.9 ($J_{PB}=104$ Hz). Complex **2**; ^{31}P NMR (161 MHz, $CDCl_3$): δ 53.3 ($J_{PRh}=178$ Hz), 57.9 ($J_{PRh}=175$ Hz).
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