Enantioselective Borane Reduction of Ketones Catalysed by a Chiral Oxazaphospholidine–Borane Complex

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The chiral oxazaphospholidine–borane complex **2** was used as catalyst (2 mol %) in asymmetric reduction of ketones by borane with an enantioselectivity ranging from 33 to 92% at 110 °C and 100% conversion; under stoichiometric conditions the reduction proceeded with 99% enantiomeric excess.

Enantioselective reductions of ketones by a wide variety of reagents made from boron hydrides and various chiral diols or amino alcohols have been reported.[1–3] Recently, Corey has prepared a chiral oxazaborolidine which was successfully used as catalyst in asymmetric reduction of ketones with 84–100% enantiomeric excess (e.e.).[4,5]

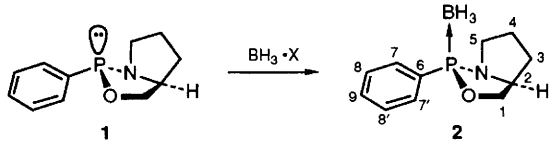
Synthesis of diastereoisomerically pure (2*R*,4*S*)-2-phenyl-1,3,2-oxazaphospholidine **1** from bis(dimethylamino)phenylphosphine and (*S*)-(+)-prolinol has been described.[6,7] We have prepared a new chiral oxazaphospholidine–borane complex by mixing **1** with 1.3 equiv. of BH_3·tetrahydrofuran (THF) (or BH_3·SMe_2) in THF, and allow it to react during 12 h at room temperature† (Scheme 1). After flash chromatography on silica gel (acetone–pentane, 60:40 as eluent) compound **2** was isolated in 97% chemical yield as an oil, stable to air and moisture.‡

Complex **2** was used as a catalyst (2 mol%) in the enantioselective reduction of ketones (Scheme 2) by 1 equiv. of BH_3·THF (or BH_3·SMe_2) in toluene solution. Pure alcohols **6**, **7** and **8** were isolated in 75–80% chemical yield with the *R* configuration in excess§ for **6** and **7**, and *S* for **8**

† Recently, a borane complex was obtained from the reaction between an oxazaphospholidine derived from (−)-ephedrine and BH_3·SMe_2.[8]

‡ Compound **2**: oil; ^{1}H NMR ($CDCl_3$) δ 1.2–2.1 (m, 4H), 2.3–2.6 (m, 1H), 3.7–4.6 (m, 4H), 7.1–7.9 (m, 5H); ^{13}C NMR. ($CDCl_3$) δ 26.4 (d, $^3J_{CP}$ 2.4 Hz, C-4), 31.0 (d, $^3J_{CP}$ 1.7 Hz, C-3), 48.3 (d, $^2J_{CP}$ 6.9 Hz, C-5), 62.4 (d, $^2J_{CP}$ 1.3 Hz, C-2), 72.1 (d, $^2J_{CP}$ 6.2 Hz, C-1), 128.4 (d, $^2J_{CP}$ 10.7 Hz, C-7,7′), 130.1 (d, $^3J_{CP}$ 10.7 Hz, C-8,8′), 131.7 (d, $^4J_{CP}$ 2.7 Hz, C-9), 130.5 (m, $^1J_{CP}$ 83.9, $^2J_{CB}$ 33.6 Hz, C-6); ^{31}P NMR ($CDCl_3$) δ 139.9 (q, $^1J_{PB}$ 72.6 Hz); ^{11}B NMR (C_6D_6) δ −40.7 (d, $^1J_{PB}$ 77.6 Hz); $[\alpha]_D^{25}$ +103.5 (*c* = 1, CH_2Cl_2); IR (neat) ν/cm^{-1} 3050, 2940, 2860, 2350 (B–H), 1430 (P–Ph), 1090 (C–O), 950 (P–O–C), 700, 666.

§ Based upon measurement of optical rotation.



Scheme 1 X = THF or Me_2S

Table 1 Influence of temperature on the enantiomeric excess with 2 mol% of complex **2**

Ketone	Temp./°C	E.e. (%)	*t*/min
3	−60	0	150
3	−20	5	70
3	0	7	30
3	30	12	15
3	110	33	5
4	110	76	5
5	110	92	5

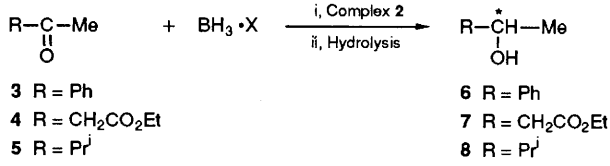
In the case of acetophenone we have studied the influence of temperature on the enantioselectivity with 0.02 equiv. of catalyst **2**. As shown in Table 1, higher temperatures have a beneficial effect on the e.e. and the reaction rate. At 110 °C the reaction is complete in 5 min and the (*R*)-phenylethanol was obtained with 33% e.e.¶ Under these catalytic conditions, ethyl acetoacetate **4** and isopropyl methyl ketone **5** gave the corresponding alcohols **7** and **8** with 76 and 92% e.e., respectively. These results demonstrate for the first time the effectiveness of complex **2** which provided the highest enantioselectivity to date for the reduction of isopropyl methyl ketone.

In order to improve the enantiomeric excess under optimum thermal conditions, we have used higher proportions of the oxazaphospholidine–borane complex **2**. As shown in Table 2, complete enantioselectivity was achieved with 1 equiv. of **2**.

The chiral complex **2** could be recovered easily and recycled without any loss of reactivity or selectivity. Thus, despite the unusually high temperature conditions, the moderate e.e. found with less than 1 equiv. of **2** with respect to **3** cannot be attributed to thermal instability of the catalyst. However, the limitation of the selectivity may be a consequence of the competing noncatalysed reduction by BH_3·THF. Although the rate of the catalytic process is obviously higher than that of the uncatalysed one, it appears that the rate of the former decreases more rapidly at lower temperature than that of the latter.

Nevertheless, use of 1 equiv. of complex **2** leads to an e.e. up to 99% at 110 °C in a few minutes. To the best of our knowledge, this is the first example of the use of a chiral tricoordinated phosphorus–borane complex as an enantioselective reducing agent. The easy accessibility of both enantiomers of **2** from the chiral oxazaphospholidine prepared from the commercially available (*S*)-proline and from the cheaper (*R*)-glutamic acid *via* (*R*)-pyroglutamic acid[9] makes these new reagents very attractive.

¶ Enantiomeric excess was determined by CPG analysis of the isopropyl urethane derivatives on a chiral capillary column XE-S-60-(*S*)-valine-(*S*)-α-phenylethylamide.



Scheme 2 X = THF or Me_2S

Table 2 Influence of the proportion of **2** on the enantiomeric excess at 110 °C

Ketone	Equiv. of **2**	E.e. (%)
3	0.02	33
3	0.04	48
3	0.08	55
3	0.16	63
3	1.00	>99
4	1.00	>99
5	1.00	>99

The generalisation of such asymmetric reductions by modifying the chiral auxiliary on phosphorus and by use of the complexes with a wide variety of ketones as well as mechanistic features are currently being investigated.

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