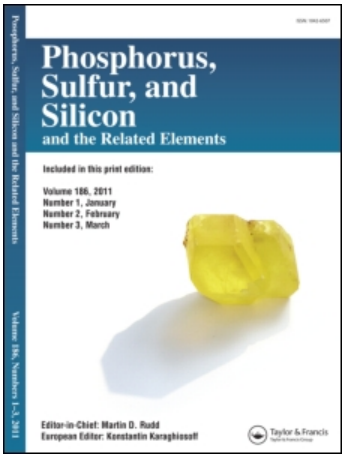

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Enantioselective Borane Reduction of Ketones Catalyzed by a Chiral Oxazaphospholidine Borane Complex

Gerard Buono[a]; Jean-Michel Brunel[a]; Bruno Faure[a]; Olivier Pardigon[a]
[a] Ecole Nationale Supérieure de Synthèses, de Procédés et d'Ingénierie Chimiques d'Aix-Marseille (E.N.s.S.P.I.C.A.M.); URA 1410 Réactivité catalyse; Faculté des Sciences et Techniques de St Jérôme, Université Aix-Marseille III, Marseille, Cedex 13, France

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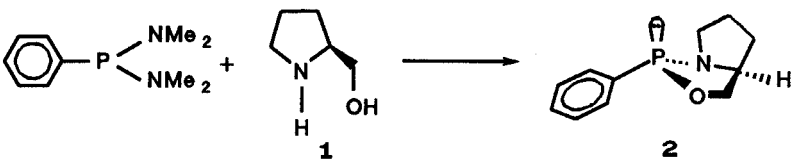
ENANTIOSELECTIVE BORANE REDUCTION OF KETONES CATALYZED BY A CHIRAL OXAZAPHOSPHOLIDINE BORANE COMPLEX

GERARD BUONO*, JEAN-MICHEL BRUNEL, BRUNO FAURE and OLIVIER PARDIGON
Ecole Nationale Supérieure de Synthèses, de Procédés et d'Ingénierie Chimiques d'Aix-Marseille (E.N.S.S.P.I.C.A.M.); URA 1410 Réactivité catalyse; Faculté des Sciences et Techniques de St Jérôme; Université Aix-Marseille III; Avenue Escadrille Normandie Niemen; 13397 Marseille Cedex 13; France.

ABSTRACT : The borane complex of (2*R*,4*S*)-2-phenyl-1,3,2-oxazaphospholidine **2** was readily synthetized. This complex can be used as catalyst in enantioselective reduction of ketones in toluene, with BH_3:THF (or BH_3:SMe_2) as reducing agent. The catalytic reduction of *iso*-propyl methyl ketone yields (*R*)-3-methyl-2-butanol in 92% e.e. and 100% conversion. Reduction of different ketones under stoichiometric conditions gives the corresponding alcohols in e.e. = 99%.

Chiral oxazaphospholidines have recently found several applications in asymmetric synthesis either as chiral ligands[1-3] or precursors for the preparation of optically pure tricoordinated organophosphorus compounds[4]. In this paper we report the first application of chiral oxazaphospholidine borane complexes in enantioselective borane reduction of ketones.

It was reported[1,5,6] the diastereoselective synthesis of (2*R*,4*S*)-2-phenyl-1,3,2-oxazaphospholidine **2** from (*S*)-(+)-prolinol **1**.



EQUATION 1

Under these catalytic conditions, the different ketones were reduced in 36-92 % e.e. These results demonstrate for the first time the effectiveness of complex **3** 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 amounts of oxazaphospholidine borane complex **3**. As shown in Table 1, complete enantioselectivity was achieved with 1 equiv. of **3**.

TABLE 1 : Influence of the equiv. of **3** on the enantiomeric excess at 110°C.

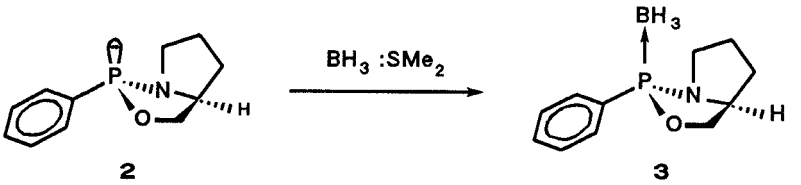
entry	ketone	equiv. (**2**)	e.e. (%)
1	**5**	0.02	33
2	**5**	0.04	48
3	**5**	0.08	55
4	**5**	0.16	63
5	**5**	1.00	>99
6	**6**	1.00	>99
7	**7**	1.00	>99
8	**8**	1.00	>99
9	**9**	1.00	>99

The chiral complex **3** could be easily recovered and recycled without any loss of reactivity nor selectivity. Thus, despite unusually high temperature conditions, moderate e.e. found with less than 1 equiv. of **3** for the reduction of **5** cannot be attributed to thermal instability of the catalyst. However, the limitation of selectivity may rather be a consequence of competing noncatalyzed reduction by BH_3:THF. Although the rate of the catalytic process is obviously higher than the uncatalyzed one, it appears that the former decreases more rapidly at lower temperature than the latter.

Nevertheless, use of 1 equiv. of complex **3** leads to an e.e. up to 99% at 110°C in a few minutes. To the best of our knowledge, it is the first use of chiral tricoordinated phosphorus borane complex as an enantioselective reducing agent.

Informations concerning mechanism are given by the reaction between the BD_3-oxazaphospholidine **2** complex, acetophenone and BH_3:SMe_2 in a molar ratio ratio 1:1:1. Direct and quantitative transfer of deuterium atom was observed, and 2-^{2}H phenylethanol was obtained in e.e. > 99 % (Equation 4). Furthermore, in the

We have prepared a new chiral oxazaphospholidine borane complex[7] by mixing **2** with 1.3 equiv. of BH_3:THF (or BH_3:SMe_2) in THF, and allow it to react during 12 hours at room temperature (Equation 2). After flash chromatography on silicagel (acetone/pentane 60:40) compound **3** was isolated in 97% chemical yield as an oil, stable to air and moisture.



2 **3**

δP = 147.0 ppm

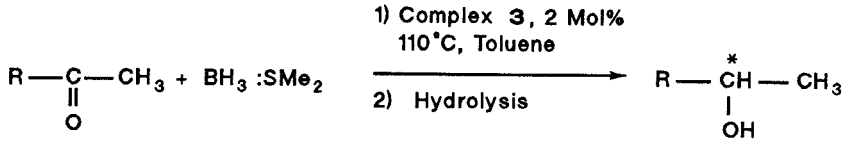
δB= -20.6 ppm

δP = 139.9 ppm
δB = -20.6 ppm
$^1J_{P-B}$ = 73 Hz

EQUATION 2

Following this method, we have prepared several oxazaphospholidine complexes from (*S*)-(+)-prolinol with different extracyclic substituents such as dimethylamino, aryl and phenoxy. The structure of the borane complex **4** with o-methoxyphenyl as substituent has been analyzed by single-cristal X-ray diffraction. The phosphorus atom configuration was retained during borane complexation. The sum of bond angles around nitrogen atom is 341.6°, showing its non-planar configuration, but the short P-N bond (1.66 Å) does not exclude a $p\pi$-$d\pi$ contribution.

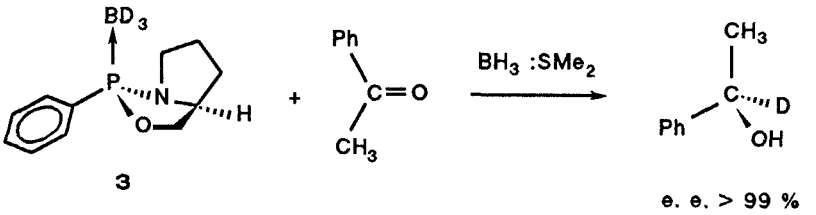
Complex **3** was used as catalyst (2 mol %) in enantioselective reduction of ketones (Equation 3) by 1 equiv. of BH_3:THF (or BH_3:SMe_2) in toluene solution. Pure isolated alcohols were obtained in 75-80% chemical yield. In the case of acetophenone we have studied the influence of temperature on the enantioselectivity with 0.02 equiv. of catalyst **3**. The higher temperature has a benificial 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 in 33% e.e.



R = Ph e.e. = 33% EtOOCCH$_2$ 76%
t-Bu 36% i-Pr 92%
PhCH$_2$ 45%

EQUATION 3

absence of BH_3:SMe_2, action of one equiv. of borane complex **3** at high temperature on ketones provided alcohols in low enantiomeric excess, revealing a participation of the "free" borane in the reduction process.



3

e. e. > 99 %

EQUATION 4

Complementary experiments are in progress to elucidate this mechanism and to design new efficient chiral P^{III}-BH_3 complexes as catalysts.

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