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A SIMPLE CHIRAL SHIFT REAGENT FOR MEASUREMENT OF ENANTIOMERIC EXCESSES OF PHOSPHINE OXIDES

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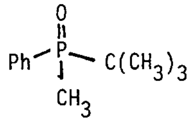
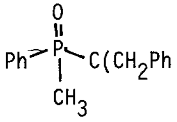
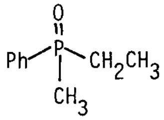
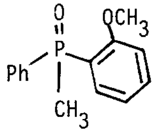
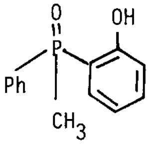
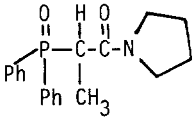
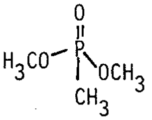
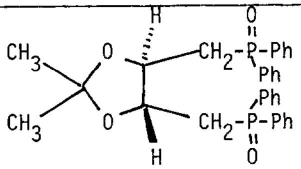
Abstract - (R)-(-)-N-(3,5-dinitrobenzoyl)-α-phenylethylamine is a chiral shift reagent which allows ee measurements of various phosphine oxides. Good results were obtained for monophosphine oxides with asymmetric phosphorus centers as well as with an asymmetric carbon in α position of phosphorus. The reagent is also able to differentiate the two enantiomers of racemic DIOP dioxide.

Chiral phosphines are of great importance in asymmetric catalysis as ligands for transition metals[1-3]. It is therefore expected that an increasing number of new chiral phosphines will be synthetized and it is helpful to have convenient and easy methods to measure their enantiomeric purities. Nmr spectroscopy was previously used to measure optical purities of phosphines after quaternization with a chiral organic halide[4] or after their combination with a chiral palladium complex[5]. It was also proposed to use an optically active phosphinothioic acid as a chiral reagent for phosphine oxides[6]. Small peak separations of chiral phosphine oxides were observed in ^1H nmr using chiral solvating agents[7]. We recently found that (R) or (S)-N-(3,5-dinitrobenzoyl)-α-phenylethylamine 1 is an excellent chiral shift reagent (^1H nmr) for sulfoxides[8]. We now wish to report our data which show that the same reagent can be used to measure enantiomeric excesses of chiral phosphine oxides. It applies also to the corresponding phosphines, after their *in situ* oxidation by *t*-BuOOH (optically active phosphines react with t-BuOOH with complete retention of optical activity[9]).

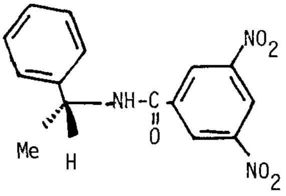
The standard conditions for enantiomer analysis are the following: The phosphine oxide is dissolved in $CDCl_3$ (0.1-0.3 M), one equivalent of the chiral reagent is added and the ^1H nmr is recorded.

The reagent 1 is easily prepared by acylation of α-phenylethylamine as previously described[8]. Pure (R)-1 is characterized by the following data : mp = 158-160°C, $(\alpha)_D$ = - 48.5° (c=0.9, acetone). IR (nujol) : 3320, 3060, 1620, 1532, 1334, 912 cm^{-1}. NMR (^1H, 90 MHz, $CDCl_3$) : 9.1 (1H, TABLE

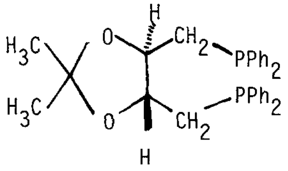
Resolution of some ^1H nmr signals (400 MHz) of racemic phosphine oxides in presence of one equivalent of (R)-1.

Entry	Phosphine oxide[a]	Solvent	Resolved signals	Separation (Hz)
1		$CDCl_3/CCl_4$ (9:1)	Me (d, $^2J_{P-H}$= 12 Hz) tBu (d, $^3J_{P-H}$= 15 Hz)	4.5 2.5
2		$CDCl_3$	Me (d, $^2J_{P-H}$= 12.5 Hz)	6
3		$CDCl_3/CCl_4$ (9:1)	Me (d, $^2J_{P-H}$= 12.5 Hz)	5.5
4		$CDCl_3/CCl_4$ (9:1)	Me (d, $^2J_{P-H}$= 14 Hz) OMe (s)	4 3
5		$CDCl_3$	Me (d, $^2J_{P-H}$= 13.4 Hz)	5
6		$CDCl_3$	Me (with spin decoupling on CH, d, $^2J_{P-H}$= 17 Hz)	3
7		$CDCl_3$ $CDCl_3$	O-Me (d, $^3J_{P-H}$= 11 Hz) O-Me	1 1.5[b]
8	 racemic	$CDCl_3$ $CDCl_3$	Me (s) CH (with spin decoupling on CH_2, d, $^3J_{P-H}$ = 8 Hz) CH_2 (with spin decoupling on CH) Me (s)	6 7 7 7[c]

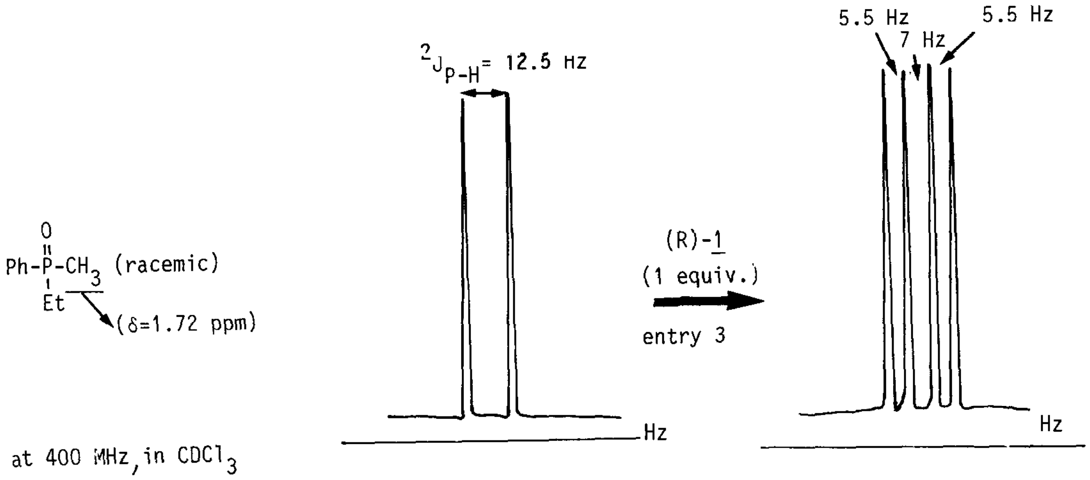
a) The concentration is 0.1-0.3 M
b) Proportion:substrate : (R)-1 = 1:4
c) Proportion:substrate : (R)-I = 1:2

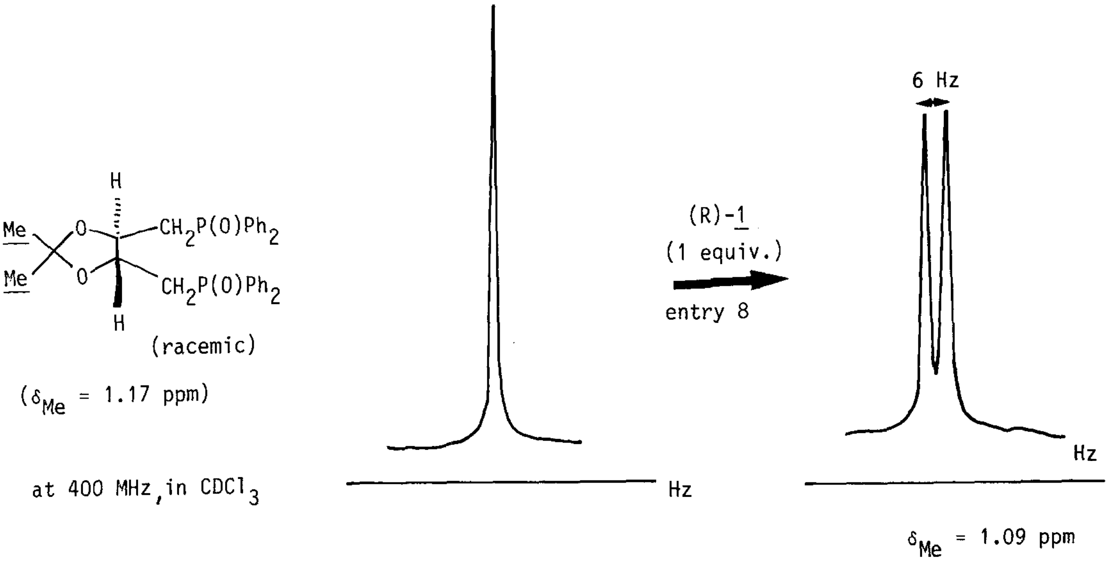

NO2
NH-C
O
Me
H
NO2

(-)-(R)-1

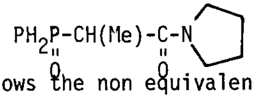

H
H3C
O
CH2
PPh2
H3C
O
PPh2
CH2
H

(-)-(S,S)-DIOP 2


O
Ph-P-CH3 (racemic)
Et
(δ=1.72 ppm)
at 400 MHz, in CDCl3
²J P-H = 12.5 Hz
Hz
(R)-1
(1 equiv.)
entry 3
5.5 Hz
7 Hz
5.5 Hz
Hz


H
Me
O
CH2P(O)Ph2
Me
O
CH2P(O)Ph2
H
(racemic)
(δMe = 1.17 ppm)
at 400 MHz, in CDCl3
Hz
(R)-1
(1 equiv.)
entry 8
6 Hz
Hz
δMe = 1.09 ppm

d, J=2Hz) ; 8.9 (2H, d, J=2Hz) ; 7.45-7.2 (5H, m) ; 6.8 (1H, broad,s, NH) ; 5.35 (1H, q,J=7Hz) 1,65 (3H, d, J=7Hz). MS (70ev)M^+(%) : 315 (60.2), 300 (95), 195 (100), 147 (23), 104 (64), 75 (66).

^1H nmr spectra of mixtures of 1 and phosphine oxides were registered at 400 MHz in $CDCl_3$ (or better, when possible, in $CDCl_3$-CCl_4 mixtures). The main results using various racemic phosphine oxides (1:1 mixture with 1) are summarized in the Table. The splittings are not very large (a few Hz) but the absence of broadening effect often allows to measure the ee. Several phosphine oxides RR'R"P=O as well as  were resolved by the reagent. The prochiral compound Me-P(O)$(OMe)_2$ shows the non equivalence of the methoxy groups which should allow, for example, to measure the ee of the chiral analog Me-P(O)(OMe)(OCD_3). An interesting case is that of chiral diphosphines, widely used in asymmetric catalysis. DIOP 2 was studied as a typical example. As shown in the Table, dioxide of racemic DIOP 2 (prepared *in situ* from racemic DIOP by 10 min. contact at room temperature with an excess of *t*-BuOOH solution in CH_2Cl_2 or toluene, followed by vacuum evaporation) was resolved for its CH_3, CH_2 and CH groups. Because of the couplings between CH and CH_2 it is necessary to use spin decoupling. This successful result gives good hope that the method can be applied to many chiral diphosphines (of C_2 or C_1 symmetry) in which the phsophorus is not an asymmetric center.

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