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# The classical Kagan's amides are still practical NMR chiral shift reagents: determination of enantiomeric purity of *P*-chirogenic phospholene oxides

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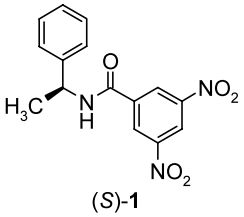
**Abstract**—Application of the (*S*)-(+)-*N*-(3,5-dinitrobenzoyl)-1-phenylethylamine **1** and (*S*)-(+)-*N*-(3,5-dinitrobenzoyl)-1-(1-naphthyl)ethylamine **2** as chiral NMR shift agents for a variety of phospholene derivatives is described. $^{1}H$ and $^{31}P$ NMR spectra recorded in the presence of Kagan's amides **1** or **2** show well resolved signals of vinylic protons as well as $^{31}P$ signals and allow effective measurement of the enantiomeric excesses. The experimental rule for determination of the absolute configuration at P is also proposed. 

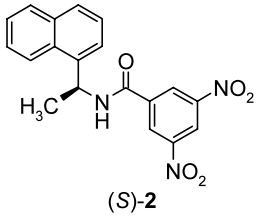
Chiral phosphines play an important role in organic synthesis as chiral catalysts and as ligands for transition metals.[1] Operationally simple methods for determination of the enantiomeric purity of nonracemic phosphines and derivatives thereof are in high demand. NMR spectroscopy employing chiral solvating agents is one of the most straightforward and commonly available techniques for direct discrimination of enantiomers. In the case of organophosphorus compounds it also offers an added possibility for observing $^{31}P$ nuclei characterized by a wide range of chemical shifts and simplicity of the spectra.

In this paper application of (*S*)-(+)-*N*-(3,5-dinitrobenzoyl)-1-phenylethylamine **1** and (*S*)-(+)-*N*-(3,5-dinitrobenzoyl)-1-(1-naphthyl)ethylamine **2** as chiral NMR discriminating agents for a wide range of *P*-chiral phospholene derivatives is described. The corresponding sulfides were also tested.[2]

Amides **1** and **2** were first used by Kagan et al. for the determination of the enantiomeric purity of nonracemic sulfoxides.[3] Amide **1** was also demonstrated by Dunach and Kagan[4] to be useful for the measurement of the enantiomeric excess of simple phosphine oxides for which typical $\Delta\delta$ values[5] observed in the $^{1}H$ NMR spectra (400 MHz) were found in the range of 1–7 Hz.



(*S*)-**1**



(*S*)-**2**

We have studied the effect of chiral amides (*S*)-**1** and (*S*)-**2** on the separation of the NMR signals of *P*-chirogenic unsaturated phosphorus-containing heterocycles, mainly derivatives of the 2- and 3-phospholene oxides.[6] First, we tested a series of 4-hydroxy-1-phenyl-2-phospholene 1-oxide derivatives.[7] Observed splittings for H-2 (vinyl) protons in the presence of amide (*S*)-**1** as chiral shift agent were generally high ($\Delta\delta = 12.5$–$23.1$ Hz),[6] whereas for the H-3 protons they were less significant ($\Delta\delta = 1.8$–$2.9$ Hz) or even no effect was recorded. Resolution of the phosphorus signals was also observed in most of the cases and $\Delta\delta$ values in the range of 3.6–10.6 Hz were recorded. In all cases studied the results obtained allowed us to measure the ee's by $^{1}H$ NMR. $^{31}P$ NMR signals of the studied phospholenes bearing free hydroxyl group were not sufficiently well resolved due to broadening effects. In turn, $^{31}P$ NMR signals of the propargylic derivatives were sharp and allowed measurement of the enantiomeric ratios also from the phosphorus spectra (Fig. 1). Addition of the chiral amide (*S*)-**2** instead of (*S*)-**1** usually increased the shift effects and the separation of signals of individual enan-

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tiomers was frequently very high (up to $\Delta\delta = 25.3$ Hz for H-2 proton). Also the $^{1}H$ NMR signals of more distant substituents (methyl groups at C-3 or C-4 positions) as well as $^{31}P$ NMR signals were well separated in this case (Fig. 1).

The same trends were observed in a series of non-hydroxyl 1-phenyl-2-phospholene 1-oxide derivatives. Shifts of their H-2 proton signals were much higher than those shown in Figure 1 for hydroxy phospholene derivatives and even reached 31.3 Hz in the best case. Especially remarkable were also $\Delta\delta$'s in the range of 17.3–32.8 Hz found in the corresponding $^{31}P$ NMR spectra (Fig. 2).

Enantiomers of fused bicyclic derivatives of 1-phenyl-2-phospholene oxide showed only moderate or very low differences for their $^{1}H$ and $^{31}P$ NMR signals in the presence of (*S*)-**1**. In some cases, amide (*S*)-**2** slightly improved the efficiency of the signals resolution. Although the splittings were not very large, the absence of broadening effect allowed a reliable measurement of

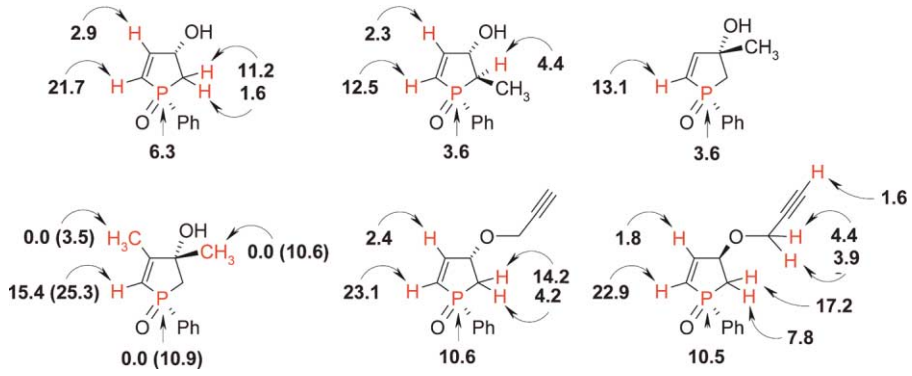



**Figure 1.** Enantiomeric discrimination ($\Delta\delta$ in Hz) in the $^{1}H$ NMR (500 MHz) and $^{31}P$ NMR (202.5 MHz) spectra of racemic allylic alcohols in the presence of (*S*)-**1** and (*S*)-**2** (numbers in parentheses).

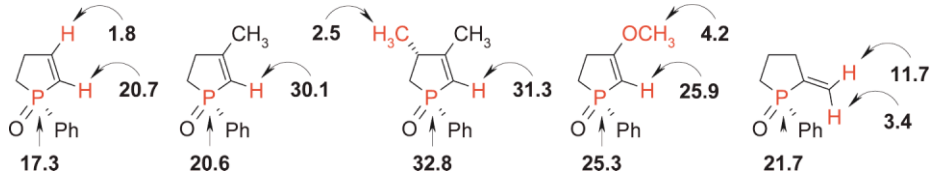



**Figure 2.** Enantiomeric discrimination ($\Delta\delta$ in Hz) in the $^{1}H$ NMR (500 MHz) and $^{31}P$ NMR (202.5 MHz) spectra of racemic 2-phospholene oxide and exomethylene derivatives in the presence of (*S*)-**1**.

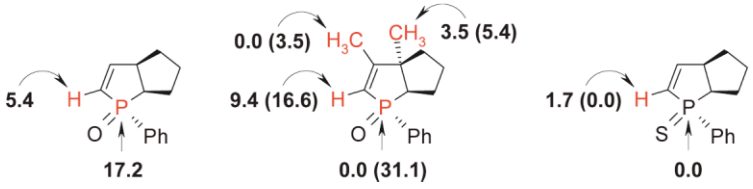



**Figure 3.** Enantiomeric discrimination ($\Delta\delta$ in Hz) in the $^{1}H$ NMR (500 MHz) and $^{31}P$ NMR (202.5 MHz) spectra of racemic bicyclic 2-phospholene oxide and sulfide derivatives in the presence of (*S*)-**1** and (*S*)-**2** (numbers in parentheses).

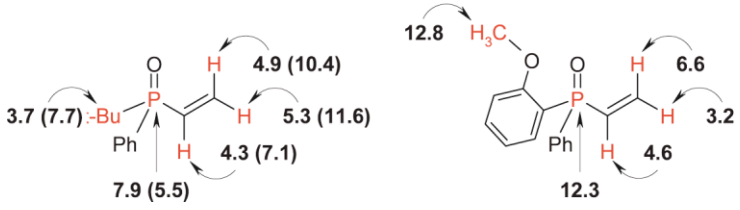



**Figure 4.** Enantiomeric discrimination ($\Delta\delta$ in Hz) in the $^{1}H$ NMR (500 MHz) and $^{31}P$ NMR (202.5 MHz) spectra of racemic vinyl phosphine oxides in the presence of (*S*)-**1** and (*S*)-**2** (numbers in parentheses).

the ee's. Determination of enantiomeric excess of the corresponding phosphine sulfide was not possible due to very poor shift effects (Fig. 3).

Some acyclic vinylphosphine oxide derivatives were also studied for comparison. As exemplified in Figure 4, they showed moderate enantiomer discrimination in the $^{1}H$ and $^{31}P$ NMR spectra in the presence of (*S*)-**1** but the signals were sufficiently well resolved and sharp enough for direct measurement of the enantiomeric excess. Surprisingly, however, neither $^{1}H$ nor $^{31}P$ NMR signals of methylphenylvinylphosphine oxide showed any sign of enantiomeric discrimination in the presence of (*S*)-**1** and (*S*)-**2**.

The NMR spectra of 1-phenyl-3-phospholene 1-oxide derivatives in the presence of amides **1** and **2** gave only moderate resolution of signals which usually was not sufficient for determination of enantiomeric excess of the sample (Fig. 5). As also exemplified in Figure 4, some 3-phospholene oxides and sulfides did not exhibit any measurable effects.

The use of tetrachloromethane as co-solvent to improve of the signals splitting in such measurements has been known.[4] In our hands, however, the influence of admixed tetrachloromethane was not significant and only very little differences between the spectra recorded in $CDCl_3$ and $CDCl_3/CCl_4$ (1:1 mixture) were observed. The most important changes were found for 1-phenyl-2-phospholene-1-oxide. Addition of tetrachloromethane to the chloroform solution of the phosphine oxide and (*S*)-**1** caused an increase of $\Delta\delta$ value for $^{1}H$ NMR signals of the vinyl protons, whereas a decrease of $\Delta\delta$ value for the same signals recorded in the spectra in the presence of the amide (*S*)-**2** was observed. In both cases addition of tetrachloromethane caused an increase of the signals splitting in the $^{31}P$ NMR spectra (Fig. 6).

The use of the enantiomerically enriched 2-phospholene derivatives of known absolute configurations[8] in the above measurements revealed also a practical regularity in the observed $\Delta\delta$ signs. In the whole series studied the signals of the H-2 protons of the $R_P$ enantiomers were always found at lower field as compared to the same signals of their $S_P$ counterparts (Table 1). This regularity was also paralleled in the $^{31}P$ NMR spectra of these compounds in which the signals of the $R_P$ enantiomers always appeared at higher field than the corresponding signals of the $S_P$ enantiomers (Table 1). The observed 'double-check' regularity may thus be of value for preliminary assignments of the absolute configuration at phosphorus in nonracemic 2-phospholene oxide derivatives.

In summary, we have demonstrated that the Kagan's amides **1** and **2** are convenient and efficient chiral resolving agents which may be recommended for the determination of the enantiomeric excess of a wide range of nonracemic unsaturated phosphine oxides. They are especially effective for 2-phospholene oxide derivatives for which they offer also the possibility of a tentative assignment of the absolute configuration at P.

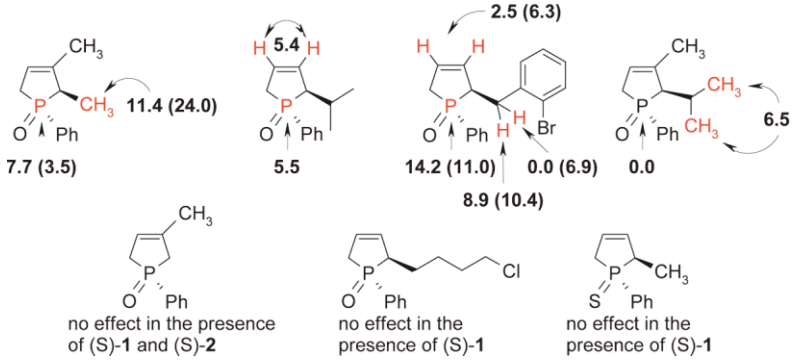



**Figure 5.** Enantiomeric discrimination ($\Delta\delta$ in Hz) in the $^{1}H$ NMR (500 MHz) and $^{31}P$ NMR (202.5 MHz) spectra of racemic 3-phospholene oxide derivatives in the presence of (*S*)-**1** and (*S*)-**2** (numbers in parentheses).

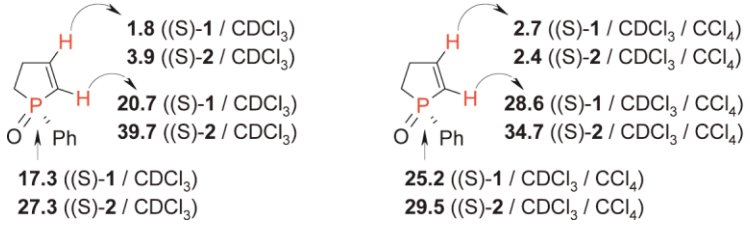
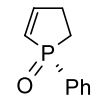
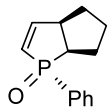
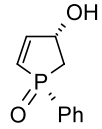
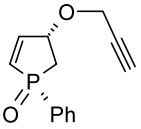
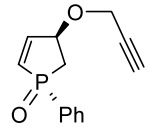
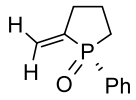



**Figure 6.** Influence of tetrachloromethane used as co-solvent for splitting of $^{1}H$ and $^{31}P$ NMR signals of 1-phenyl-2-phospholene-1-oxide ($\Delta\delta$).

**Table 1.** Absolute $\Delta\delta$ [Hz] value in the presence of (*S*)-**1** versus absolute configuration

| | Abs. config. | $\Delta\delta^{1}$H (H-2) | $\Delta\delta^{31}$P | | Abs. config. | $\Delta\delta^{1}$H (H-2) | $\Delta\delta^{31}$P |
|---|---|---|---|---|---|---|---|
|  | $R_P$ | -20.7 | +17.3 |  | $S_P,4R,5R$[#] | -5.4 | +17.2 |
|  | $R_P,S$ | -21.7 | -[*] |  | $R_P,S$ | -23.1 | +10.6 |
|  | $R_P,R$ | -22.9 | +10.5 |  | $R_P$ | -11.7<br>-3.4<br>(=$CH_2$) | +21.7 |

[#]Absolute configuration at phosphorus has been changed due to reversed priority of the substituents.
[*]Not sufficiently resolved.


## Acknowledgements

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5. $\Delta\delta$ (Hz) is the separation of the signals of the two enantiomers. A $-\Delta\delta$ value corresponds to a lower field shift (deshielding), whereas a $+\Delta\delta$ value corresponds to a higher field shift (shielding) of the particular signal.
6. In a standard measurement a sample of phosphine oxide was dissolved in $CDCl_3$, chiral reagent (*S*)-**1** or (*S*)-**2** was added (1.1 equiv.) and the $^1$H (500 MHz) and $^{31}$P NMR (202.5 MHz) spectra were recorded with a Bruker AM-500 spectrometer using $Me_4Si$ (internal) and $H_3PO_4$ (external) standards, respectively.
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