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An Efficient Chiral Phosphorus Derivatizing Agent for the Determination of the Enantiomeric Excess of Chiral Alcohols and Amines by ^{31}P NMR Spectroscopy

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ABSTRACT: *The chiral phosphorus derivatizing agent (CDA) 1 was prepared from optically pure (S)-*1,1-bis-2-naphthol*. It was first used in the determination of the enantiomeric excess of chiral alcohols and amines by means of ^{31}P NMR spectroscopy. It showed that, for the chiral aromatic alcohols, no apparent kinetic resolution was noted and good base-line separation was observed. Furthermore, the chemical shift difference ($\Delta\delta$) of ^{31}P NMR spectroscopy was much larger than those determined by the use of other chiral phosphorus derivatizing agents reported previously. However, for aliphatic alcohols, it showed not only obvious kinetic resolutions but incomplete base-line separation. Moreover, we also found that the use of CDA* **1** *was suitable for the determination of enantiomeric excess of chiral primary amines.* © 2002 John Wiley & Sons, Inc. Heteroatom Chem 13:93–95, 2002; DOI 10.1002/hc.10018

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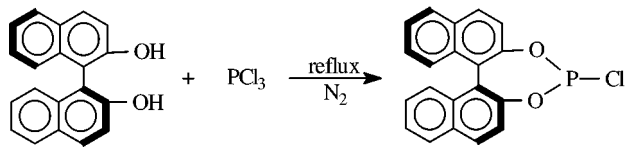
INTRODUCTION

The great progress in asymmetric synthesis and the rapidly increasing use of enantiomerically pure compounds require the development of an accurate and fast method for the determination of the optical purity of the enantiomeric compounds. Among the numerous analytical procedures, polarimetry is often used for comparative purposes in the literature, but it is not very accurate or reliable [1]. In recent years, despite the rapid progress made in the use of the GC and HPLC analytical methods [2], NMR spectroscopy is still a most attractive technique, for it is usually fast and convenient to perform [3].

The enantiomeric excess determination by means of NMR spectroscopy can be carried out using the chiral lanthanide shift reagent [4], chiral complexing reagents [5], and chiral derivatizing agents (CDA)[6]. However, at present, determination of ee using CDA is the most widely used NMR spectroscopy technique, as discrete diastereomers show chemical shift nonequivalences, $\Delta\delta$, that are typically five times higher than for the use of other chiral reagents [6]. The most widely used CDA is α-methoxy-α-(trifluoromethyl)benzeneacetic acid (MTPA) introduced by Mosher in 1969 [7]. Chiral derivatization agents often contain more than one NMR active nucleus, e.g. ^{19}F, ^{1}H, ^{31}P, and ^{77}Se,



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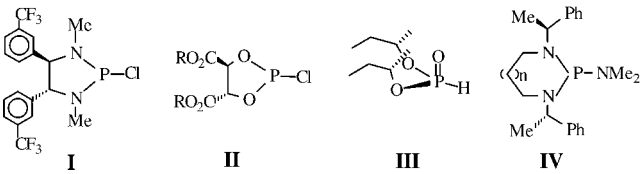
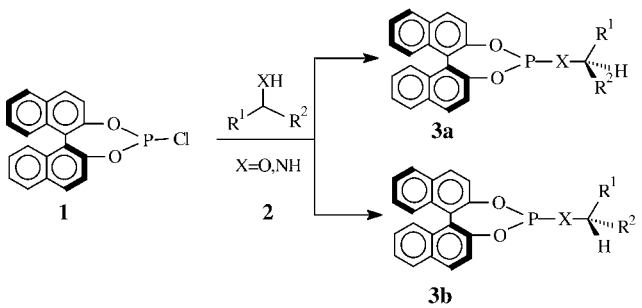
SCHEME 1

which is useful for the ee determination of the chiral substrate [8]. However the H—H or H—X coupling pattern often makes the analysis difficult because of the overlapping of signals. With respect to the use of ^{31}P nuclei, the chemical shift dispersions are larger and the nuclei are very sensitive to small structural changes in diastereomeric adducts. Especially when broad band-proton decoupling is used, most of the spectra are very simple. Thus, ^{31}P NMR methods have become very popular because of these attractive features. Several phosphorus derivatizing agents (e.g. **I–IV**) have been developed in recent years [9].



I **II** **III** **IV**

In this paper, we reported a simple and highly efficient ^{31}P NMR method for the ee determination of chiral alcohols and amines (Scheme 1) based on the use of the chiral phosphorus derivatizing agent **1,** which is easily prepared from (*S*)-1,1-bis-2-naphthol (BINOL) and PCl_3. Derivatizing agent **1** reacted with chiral alcohols or chiral amines **2** in the presence of triethylamine to form the diastereomeric adducts **3a** and **3b**. The adducts **3a** and **3b** were not further purified and were directly recorded by ^{31}P NMR spectroscopy (Scheme 2).



1 **2** **3a** **3b**

SCHEME 2

EXPERIMENTAL

Preparation of Derivatizing Agent **1**

According to the method in reference [10], the chiral derivatizing agent **1** was obtained as a light yellow solid when PCl_3 and BINOL were refluxed under dry N_2 for several hours (monitored by TLC). Yield 98.7%, ^{31}P $\delta = 178.55$. The crude product was used directly in the following reaction without further purification because of its high sensitivity towards moisture.

Synthesis of Diastereomeric Adducts **3a** *and* **3b**

In a 5 ml reaction flask, 0.2 mmol of CDA **1**, 3 ml of dry toluene, and 0.18 mmol of alcohol or amine **2** were mixed under N_2. Then a mixture of 1 ml of toluene and 0.2 mmol of Et_3N was added drop wise with vigorous stirring of the mixture. After 30 min, the reaction mixture was filtered. Removal of the solvent under reduced pressure gave the crude product, which was directly examined by ^{31}P spectroscopy without further purification.

RESULTS AND DISCUSSION

Associated with the use of CDAs, two of the major problems are the observation and resolution of appropriate signals in complex NMR spectra and the potential for asymmetric induction during the formation of diastereomers. In order to test the potential of asymmetric induction we chose several racemic (entries 1–11, Table 1) and enantiomerically enriched (entries 12–14, Table 1) alcohols or amines as the reaction substrates. The findings are summarized in Table 1.

As detailed in Table 1, we found that no apparent kinetic discrimination was observed for the aromatic alcohols (entries 1–7). Moreover, the value of $\Delta\delta$ (5.10–8.38 ppm) is larger than the ones obtained from the other chiral phosphorus derivatizing agents reported previously. For example when rac-α-methylphenylmethanol was used as the substrate, the $\Delta\delta$ (6.88 ppm) was much larger than the results determined by use of other chiral phosphorus derivatizing agents [11–14], which ranged from 0.10 ppm to 1.40 ppm.

However, for the chiral aliphatic alcohols, great asymmetric induction was observed (entries 8–10). Furthermore, we found that a group substitued on the chiral center had a significant effect on the $\Delta\delta$. For instance, the values of $\Delta\delta$ decreased from 0.44 ppm to 0.10 ppm with an increase of steric hindrance (entries 8–10). On the other hand, there was also no good base-line separation (entry 10).

TABLE 1 ^{31}P NMR Shift Difference of Diastereomers **3a** and **3b**[a]

	Compound ***2***					
Entry	R^1	R^2	*X*	^{31}P *(ppm)*[b]	$\Delta\delta$ *(ppm)*	*Ratio*[c]
1	Ph	Me	O	148.66, 141.78	6.88	50:50
2	Ph	Et	O	151.11, 142.85	8.26	49:51
3	Ph	CH_2Cl	O	150.60, 142.22	8.38	49:51
4	2-Cl-Ph	Me	O	147.62, 139.70	7.92	50:50
5	*p*-NO_2-Ph	Me	O	144.15, 139.05	5.10	48:52
6	*m*-Cl-Ph	Me	O	147.73, 139.51	8.22	48.5:51.5
7	*o*-Br-Ph	Me	O	139.46, 146.04	6.58	48.5:51.5
8	Et	Me	O	148.54, 148.10	0.44	46:54
9	*n*-C_7H_{15}	Me	O	148.41, 148.00	0.41	40:60
10	*t*-Bu	Me	O	152.63, 152.73	0.10	–[d]
11	Ph	Me	NH	151.37, 152.43	1.06	47:53
12[e]	Ph	Me	NH	151.36	–	100:0
13[f]	Ph	CN	O	138.39, 132.82	5.57	86.5:13.5
14[g]	Ph	Me	O	142.00, 148.80	6.80	45.5:54.5

[a]Recorded in $CDCl_3$ (200 MHz), using 85% H_3PO_4 as an external standard.
[b]^{31}P NMR of diastereomeric **3a** and **3b**.
[c]^{31}P NMR integral ratio of **3a** and **3b**.
[d]No good base-line separation.
[e]*l*-1-phenylethylamine was used.
[f]70% Enantiomeric excess (ee) determined by polarimetry; 68% ee determined by HPLC.
[g]8.8% ee determined by polarimetry.

As far as chiral amines were concerned, primary amines can react well with the chiral derivatizing agent (entry 11), but the process is not useful for the secondary amines. For example, when *N*-phenyl-1-phenylethylamine was used as the substrate, the ^{31}P NMR spectra was very complicated.

Moreover, we also compared the outcomes obtained by the use of CDA **1** with the results determined by polarimetry (entries 12–14). We found that they agreed well with each other. The possibility for the determination of enantiomeric excess of other amines, amino acid esters, and chiral thiols by use of CDA **1** is being subjected to investigation.

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