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A New ^{31}P NMR Method for the Enantiomeric Excess Determination of Alcohols, Amines and Amino Acid Esters.

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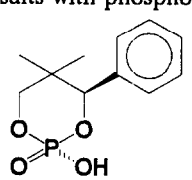
Abstract: Diastereoisomeric ester and amide derivatives of phosphoric acid chloride **2** show well separated signals in the ^{31}P NMR spectra allowing accurate e.e. determination of chiral alcohols, esters of amino acids and amines.

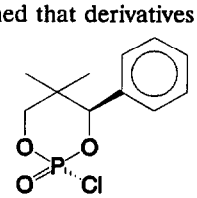
The steadily growing use of optically pure materials as chiral building blocks, auxiliaries or chiral ligands in numerous asymmetric syntheses[1] demand fast and accurate methodology for enantiomeric excess (e.e.) determination.
The enantiomeric purity of various classes of compounds can be routinely analyzed by means of chromatographic methods using chiral phases[2] or alternatively, after derivatization with an optically pure reagent by analysis of the diastereoisomers on achiral phases[3].
Although rapid progress has been made in the development of GC and HPLC methods, NMR is probably the most popular technique[4] for rapid assesment of the enantiomeric composition. E.e. determination by means of NMR can be performed using chiral lanthanide shift reagents[5], chiral complexing agents[6] or after derivatization with chiral non-racemic[7] or, using Horeau's principle[8], achiral reagents[9], mainly employing ^{1}H, ^{13}C, ^{31}P and ^{19}F nuclei. Methods based on ^{31}P NMR are rapidly emerging due to the attractiveness of the ^{31}P nucleus for NMR analysis of chiral compounds. Several methods have been developed based upon the use of pentavalent phosphoric acid chlorides[10,11], phosphites[12] or achiral reagents like PCl_3 or $MePOCl_2$[13]. Trivalent phosphorus derivatizing agents are also known to give excellent diastereomeric shift differences in the decoupled ^{31}P NMR[14].

We now wish to report a simple and efficient new ^{31}P NMR method for the e.e. determination of alcohols, amines and esters of amino acids based on chiral derivatizing agent **2**.

In 1985 ten Hoeve and Wynberg[15] reported the applicability of phosphoric acid **1** as an excellent resolving agent for amines, aminoalcohols and amino acids by means of diastereomeric salt formation. Although the e.e.'s of these compounds could not be determined via NMR analysis of their diastereomeric salts with phosphoric acid **1**, we established that derivatives of types **3** or **4**



1.



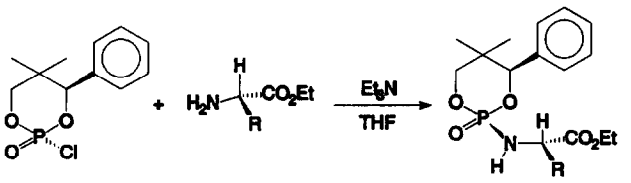
2.

afford excellent diastereomeric peak separation in the ^{31}P NMR. ^{1}H NMR analysis might also be

used but the spectra are much more complex to interpret due to excessive (P-H and H-H) coupling.

Reagent **2** is readily obtained from enantiomerically pure phosphoric acid **1** which on its turn is easily prepared from benzaldehyde and isobutyraldehyde followed by a simple resolution via a single step crystallization[15].

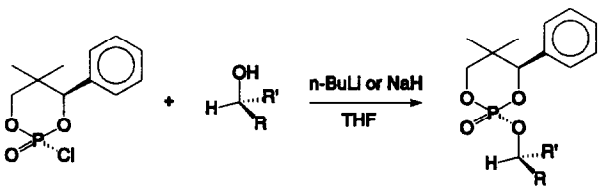
Diastereoisomers of phosphonic amides **3** and phosphonates **4** are easily prepared from the air and moisture stable phosphoric acid chloride **2**. Primary amines and esters of amino acids react with **2** in THF using Et_3N as a base at reflux temperature affording **3** in the case of amino acid esters (eq 1).



eq. 1

2. **3.**

Secondary amines and alcohols react in THF at room temperature using nBuLi or NaH as base affording for instance **4** (eq. 2).



eq. 2

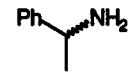
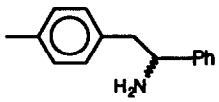
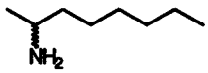
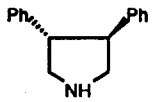
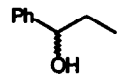
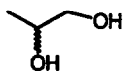
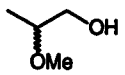
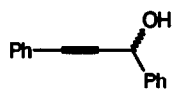
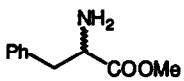
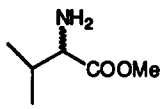
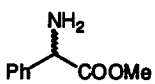
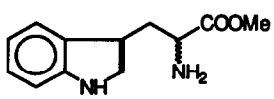
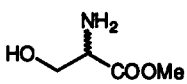
2. **4.**

After the mixture is taken to dryness a decoupled ^{31}P NMR spectrum is recorded directly in the required solvent ($CDCl_3$ or C_6D_6) without the need of further purification. ^{31}P NMR data for various chiral amines and alcohols are summarized in table 1. When Et_3N is used as a base the reaction can alternatively be run in an NMR tube using C_6D_6 as solvent allowing easy monitoring of the reaction. From these NMR studies it can be concluded that no side products are formed, except for the formation of some pyrophosphate in the formation of phosphonic amides **3**, when traces of water are present. The formation of pyrophosphate however, has no influence upon the actual e.e. determination and its ^{31}P NMR signal appears at δ -20.6 ppm, well separated from the signals (see table 1 for actual positions) of **3**.

Several e.e. determinations were performed on partially enriched compounds. Comparison with the e.e.'s as determined by the α-chloropropionylchloride method[16] and the ratio of enantiomers as determined by rotation showed that the enantiomeric ratios are in excellent agreement. These results demonstrate that no racemization occurs during the formation of adducts **3** and **4**. Furthermore, monitoring the formation of **3** and **4** by means of ^{31}P NMR showed that no kinetic resolution occurred during the reactions. The method presented here compares favourably with other known ^{31}P NMR e.e. determining methods because of the easy handling and good accessibility of the reagent and the rather large shift differences of the derivatives[17].

In conclusion, the chiral derivatizing agent **2** gives excellent results in e.e. determinations allowing broad structural variation.

table 1 ^{31}P NMR data using 2 and racemic amines, alcohols and esters of amino acids recorded in $CDCl_3$ at 121.42 MHz.

Entry		δ (ppm)	Δδ (ppm)	measured ratio
1		5.05	0.63	49.5:50.5
2		1.86	0.54	49.5:50.5
3		2.25	0.11	50:50
4		3.35	0.48	49.5:50.5
5	d,l menthol	-1.25	0.05	49.5:50.5
6		-7.91	0.26	50:50
7		-7.41	0.91	49.5:50.5
8		-5.23	0.07	49.5:50.5
9		-11.65	0.17	49:51
10		4.73	0.51	49.5:50.5
11		2.28	0.21	49.5:50.5
12		0.82	0.24	49:51
13		11.51	0.44	49.5:50.5
14		-7.45	0.20	49.5:50.5

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17 A typical e.e. determining experiment follows: A mixture of **2** (1.1 mmol), chiral amine or alcohol (1.0 mmol), base (Et_3N, nBuLi or NaH, 1.1 mmol) and 5 ml solvent (ether or THF) is stirred for 8 h at RT for primary amines and reflux temperatures for secondary amines and alcohols. After this period the mixture is taken to dryness, filtered and the residue dissolved in $CDCl_3$ or C_6D_6 and a decoupled ^{31}P NMR spectrum is recorded. The adducts **3** and **4** can be further purified if necessary by crystallization from ethylacetate/petroleum-ether mixtures affording white solid materials.

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