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Determination of Enantiomeric Purity of Hydroxy Biaryls Using ^{1}H and ^{31}P-NMR on Their Diazaphospholidine Derivatives

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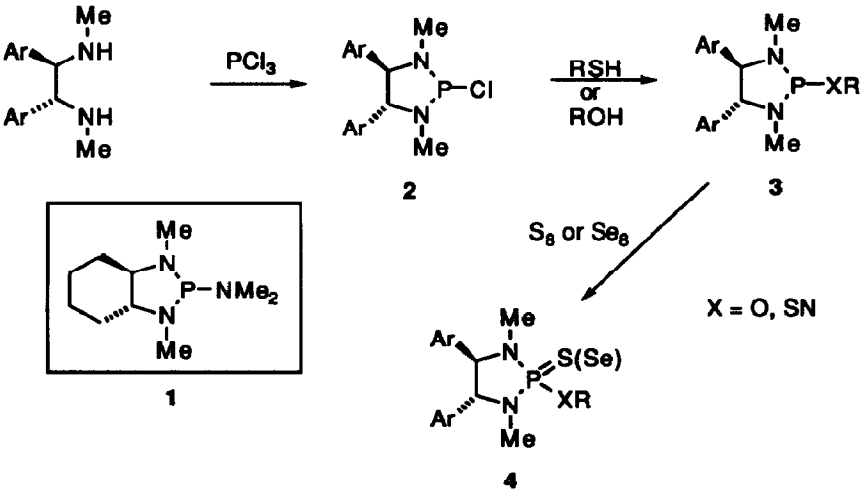
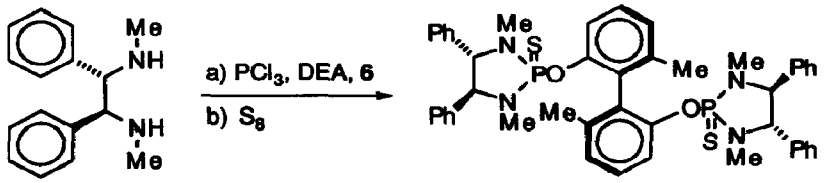
Summary: *Chiral biaryl alcohols were readily transformed in a single step, with chiral non-racemic 1,2-diamines, PCl_3, and sulfur in $CDCl_3$ - all in a NMR tube - to their diastereomeric diazaphospholidines and their diastereomeric ratios (also ee's) assessed directly.*

The determination of enantiomeric purity continues to be an endeavor of considerable importance as the need for pure enantiomers continues to grow, both in academic and industrial laboratories.[1] Recently, a novel derivatizing reagent, **1** was described which can form



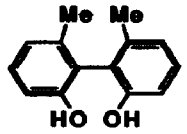
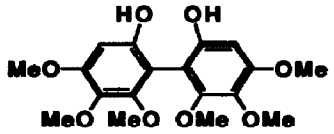
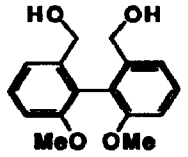
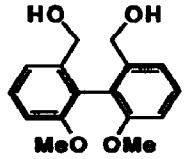
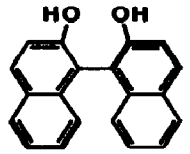
diastereomeric derivatives with a variety of alcohols and thiols.[2] In a more recent improvement, reagent **2** was prepared *in situ*, directly in a NMR tube. On reaction with alcohols or thiols, the diastereomeric ratios (for derivatives **3**) and therefore, the enantiomeric excesses (ee) were readily determined.[3] Furthermore, if sulfur is added (or more recently selenium[3]) to the solution in the NMR tube, the pentavalent chiral phosphorous heterocycle **4** is efficiently produced, which is capable of providing clean, separable ^{1}H, ^{31}P, or ^{13}C signals. Utilizing this same reagent, amines have also been recently analyzed for their enantiomeric ratios.[3] During our studies on chiral biaryl syntheses,[4] it was of interest to determine whether or not the extent of axial chirality would be sensitive to the diazaphospholidine moiety, since these had not been previously tested using **1** or **2**. By employing the biphenyl diamine **5**, various biaryl systems **6** (0.4 equiv, Table) were added to the solution containing **5**, PCl_3, and N,N-diethylaniline (DEA) in deuteriochloroform, all



5 **7**

in a NMR tube. The initially formed trivalent phosphorous species (e.g. **3**) was treated with elemental sulfur to give the bis-diazaphosphorous sulfide, **7**. This was then subjected directly to ^{31}P-NMR analysis (Table). In most cases, the separation ($\Delta\delta$) was good to excellent for the observed diastereotopic signals. For the bis-biarylcarbinol (entry 3), there was no signal separation in the ^{31}P spectrum using $CDCl_3$. However, in benzene-d_6-dichloromethane the ^{31}P spectrum exhibited clean signal separation (entry 4). In some cases, the ^{1}H-NMR spectrum also showed peak separation of the diastereomers for N-CH_3 and ArCH-N (benzylic) protons (entries 1 and 5). Thus, integration of the appropriate signals showed good correlation to the enantiomeric ratios already determined by either Mosher esters[5] or chiral hplc (Chiracel OD, Diacel).

Table 1.

Entry	Biaryl 6	Solvent	6		
			^{31}PNMR δ (ppm) (Δδ) (ppm)	^{1}H NMR δ (ppm)	%de found (known)
1[a]		$CDCl_3$	80.9598 79.5298 (1.4300)	3.33 (dd) 3.80 (dd)	88 (90)
2[a]		$CDCl_3$	81.6990 81.5817 (0.1173)	---	93 (94)
3[a]		$CDCl_3$	NO SEPARATION		
4[a]		C_6D_6 CH_2Cl_2	84.0467 83.9043 (0.1424)	---	58 (54)
5		$CDCl_3$	80.0933 78.7472 (1.3462)	3.90 (dd) 3.68 (dd)	32 (33)

a) For preparation, see ref. 4.

In summary, chiral vicinal diamines continue to show outstanding properties in spectral discrimination of enantiomeric determinations,[6] and an example of the current experimental technique is provided below.

Typical Experimental. The following was done entirely in a NMR tube:[7]

(S,S)-N,N-dimethyl-1,3-bisphenylethyl-1,2-diamine **5** (Aldrich or Janssen, 38.45 mg, 0.16 mmol) was dissolved in the solvent of choice ($CDCl_3$ or CH_2Cl_2 + C_6D_6). To this was added N,N-diethylaniline (127.3 µL, 0.8 mmol), followed by PCl_3 (13.95 µL, 0.16 mmol). The reaction was exothermic. To the formed chloro diazaphospholidine was added the bis-biarylcarbinol **6** (0.065 mmol) shown in the table. After 10 minutes, elemental sulfur (6.4 mg, 0.20 mmol) was added and the ^{31}P NMR spectrum of the pentavalent phosphorous compound, **7** was analyzed. The data are presented in the table.

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References and Notes:

1. Morrison, J. D. *Asymmetric Synthesis*; Academic: New York, 1983; Vol. 1. b) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.
2. a) Alexakis, A.; Mutti, S.; Mangeney, P.; Normant, J. F. *Tetrahedron: Asymmetry* **1990**, *1*, 437. b) Alexakis, A.; Mutti, S.; Mangeney, P.; *J. Org. Chem.* **1992**, *57*, 1224.
3. For an improvement in the procedure and the use of trifluoromethyl substituted systems to allow ^{19}F-NMR to also be employed, see Alexakis, A.; Frutos, J. C.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1994**, *59*, in press.
4. a) Meyers, A. I.; Meier, A.; Rawson, D. *Tetrahedron Lett.* **1992**, *33*, 853. b) Nelson T. D.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 3061. c) Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6989, 6993. d) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *54*, in press.
5. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543; *J. Am. Chem. Soc.* **1973**, *95*, 512.
6. For a recent example of chiral vicinal diamines used as a chiral solvating agent to discriminate (NMR) between enantiomeric carboxylic acids and cyclic ketones, respectively, see: a) Fulwood, R.; Parker, D. *J. Chem. Soc. Perkin Trans. 2* **1994**, 57. b) Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2431.
7. The quantities of sample employed do not reflect a limitation on this method. The sensitivity of the NMR instrument will dictate the scale of the analysis.

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