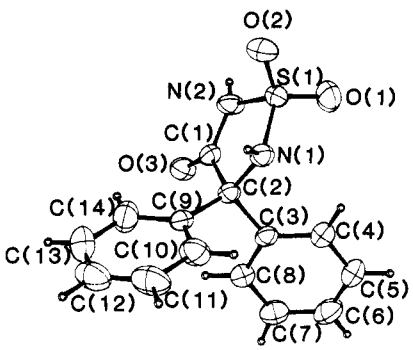
mmol) of *tert*-butyl alcohol and 50 mL of hexane. Chlorosulfonyl isocyanate (3.00 g, 21.0 mmol) in 25 mL of hexane was added dropwise at such a rate that the mixture gently refluxed. Following the addition the mixture was heated at reflux for 45 min and then cooled to room temperature. To the reaction mixture containing *tert*-butylsulfamoyl chloride was added dropwise a solution containing 5.00 g (21.0 mmol) diphenylglycine methyl ester and 3.00 g (30.0 mmol) of triethylamine in 75 mL of THF. The mixture was stirred for 2 days at room temperature. Workup as described above for **10a** gave 2.64 g (39%) of **10b**: mp 179–180 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.1 (s, 9 H), 3.75 (s, 3 H), 6.1 (s, 1 H), 7.4 (m, 10 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 29.33, 53.59, 53.78, 71.15, 127.98, 128.31, 129.42, 138.45, 172.50. Anal. Calcd for $C_{19}H_{24}N_2O_4S$: C, 60.61; H, 6.44; N, 7.54. Found: C, 60.58; H, 6.29; N, 7.43.

**4,4-Diphenyl-2-*tert*-butyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide (11b).** Via the general procedure for the preparation of **11a**, a solution of 0.70 g (1.8 mmol) of **10b** in 50 mL of THF was added dropwise to a stirred mixture of 0.13 g (56 mmol) of NaH and 10 mL of THF. The mixture was heated at reflux for 75 min. Workup afforded 0.47 g (76%, from hexane–chloroform) of **11b**: mp 136–138 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.65 (s, 9 H), 7.4 (s, 10 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 26.99, 61.52, 72.84, 127.53, 128.76, 128.89, 138.52, 169.67. Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13. Found: C, 62.73; H, 5.65; N, 8.02.

**X-ray Determination of 4,4-Diphenyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide.** Compound $C_{14}H_{12}O_3N_2S$ (288 g/mol) crystallizes in the monoclinic space group $C2/c$ with $a$ = 16.467 (5) Å, $b$ = 13.451 (4) Å, $c$ = 13.386 (5) Å, $\beta$ = 115.47 (3)°, and $z$ = 8. The calculated crystal density is 1.43 g/cm$^3$. Data were




collected at room temperature on an Enraf-Nonius CAD-4 diffractometer with Mo K$\alpha$ ($\lambda$ = 0.7173 Å) radiation with an incident beam graphite monochromator. The structure was solved by direct methods and refined by full-matrix least-squares methods. Refinement of non-hydrogen atoms anisotropically and hydrogen atoms with isotropic temperature factors by using 1974 observed reflections ($I > 3\sigma(I)$) from a set of 2274 unique reflections gave a final $R$ = 0.043. There are no significant features in the final difference Fourier map. All computer programs used were from the SDP package.[16]

**Note Added in Proof.** Recent work by H. Kohn further illustrates the utility of cyclization reactions like those shown for our conversion of **10a,b** to **11a,b**. Furthermore, their X-ray structure parameters of the first-determined 3-oxo-1,2,5-thiadiazolidine 1,1-dioxide agree with ours.[17]

**Acknowledgment**. Portions of this research were sponsored by The Research Corporation (J.W.T.) and The National Institutes of Health (E.D.S.), and their support is gratefully acknowledged.

**Supplementary Material Available**: Tables of atomic coordinates and bond lengths and angles are available from the Cambridge Crystallographic Data Base: Crystallographic Data Centre, Cambridge University, University Chemical Lab, Cambridge, CB2 1EW, England.

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## Chiral Purity Determination by $^1$H NMR Spectroscopy. Novel Use of 1,1′-Binaphthyl-2,2′-diylphosphoric Acid

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*Received May 25, 1989*

The ability to determine the chiral purity of a substrate is a highly investigated area of research in NMR, partly due to the increasing availability and utility of enantioselective organic reagents. In order to use NMR as a tool for such determinations the substrates must be made diastereomeric. This is accomplished by converting the enantiomers to diastereomers by the use of a chiral auxiliary. These auxiliaries come in three varieties: chiral lanthanide shift reagents[1] (CLSR), chiral "solvents" or complexing agents,[2] and chemical derivatizing reagents like Mosher's[3] or Anderson–Shapiro[4] reagent.

During the course of analyzing potential therapeutic agents, we became involved with the determination of the chiral purity of secondary and tertiary amines. We tried to use chiral lanthanide shift reagents and chiral complexing agents but often found them unacceptable for various reasons. These unsatisfactory results led us to explore the possibility of finding a "new" reagent. Of particular interest was to obtain a reagent that was easy to use and would have an NMR spectrum devoid of signals in the important 1–6 ppm region of the proton NMR spectrum. In this respect, we have examined the utility of (*R* or *S*)-1,1′-binaphthyl-2,2′-diylphosphoric acid (BNPPA) as a NMR chiral complexing agent. BNPPA is well known as a reagent for the resolution of amines.[6]

Further support for using BNPPA as a chiral reagent stems from a report showing the utility of $\alpha$-methoxy-$\alpha$-(trifluoromethyl)phenylacetic acid (MTPA) in the determination of amine chiral purity by proton NMR.[5] Because of its greater acidity it was felt that BNPPA would be a better complexing agent than MTPA and also would give rise to larger shift nonequivalence due to its more extensive ring current.

### Results

Given in Table I are the data obtained for amine substrates using BNPPA as well as comparisons with MTPA data from the literature. For each compound there were several resonances that showed chemical shift nonequivalences between enantiomers, but not all were suitable for accurate integration and thus quantitation of composition. It can be seen that the $\Delta\delta$ values[7] for BNPPA are generally larger than those observed for MTPA, and in at least one instance this difference is substantial, e.g. **7**. The spectral data for **7** is shown in Figure 1. When there is good interaction between BNPPA and the substrate, as shown

(1) Sullivan, G. R. *Topics in Stereochemistry*; Eliel, E. L.; Allinger, N. L., Eds; Wiley-Interscience: New York, 1978; p 287.
(2) (a) Pirkle, W. H.; Sikkenge, D. L. *J. Org. Chem.* **1977**, *42*, 1370. (b) Abraham, R. J; Plant, J.; Bedford, G. R.; Wright, B. *Org. Magn. Reson.* **1984**, *22*, 57. (c) Toda, F.; Mori, K.; Okada, J.; Node, M.; Itoh, A.; Oomine, K.; Fuji, K. *Chem. Lett.* **1988**, 131. (d) Rosini, C.; Uccello-Barretta, G.; Pini, D.; Abete, C.; Salvadori, P. *J. Org. Chem.* **1988**, *53*, 4579. (e) Benson, S. C.; Cai, P.; Colon, M.; Haiza, A.; Tokles, M.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 5335.
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(4) Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, *49*, 1304.
(5) Villani, F. J., Jr.; Costanzo, M. J.; Inners, R. R.; Mutter, M. S.; McClure, D. E. *J. Org. Chem.* **1986**, *51*, 3715.
(6) Arnold, W.; Daly, J. J.; Imhof, R.; Kyburz, E. *Tetrahedron Lett.* **1983**, *24*, 343.
(7) The $\Delta\delta$ value is the chemical shift difference between the signals from a proton experiencing nonequivalence by the BNPPA.

0022-3263/89/1954-5826$01.50/0 

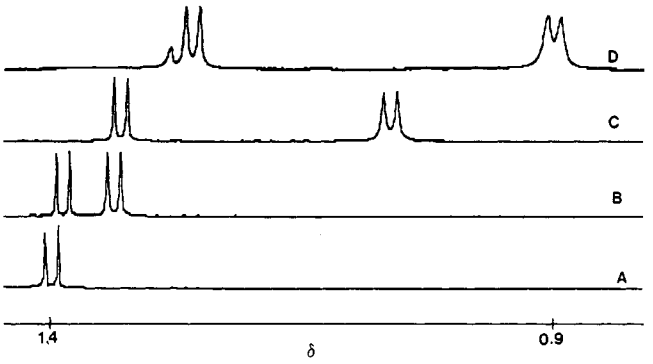



**Figure 1.** 500-MHz proton NMR spectrum of a 60:40 D:L mixture of 7 in n $CDCl_3$. A–D are 0, 0.1, 0.5, and 1.0 equiv of (*S*)-(+)-BNPPA.

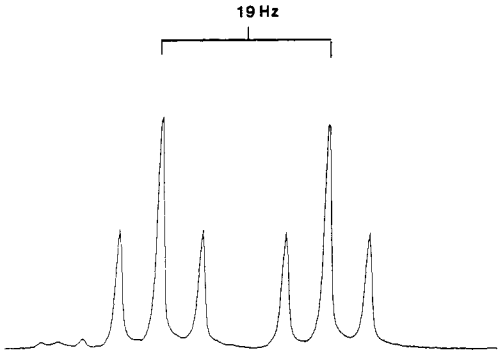



**Figure 2.** 500-MHz proton NMR spectrum of 8 in $CDCl_3$ with 0.5 equiv of BNPPA.

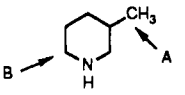
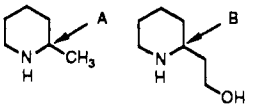
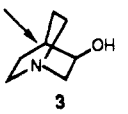
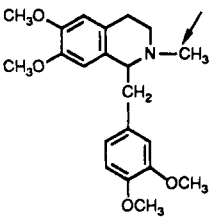
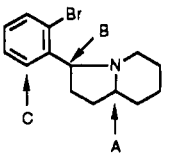
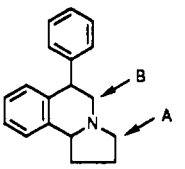
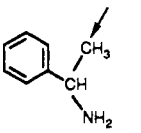
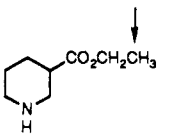
in the figure, chiral purity can be determined with relatively low concentrations of BNPPA. It should also be noted from the data in Table I, that the reference proton is not necessarily the same for BNPPA and MTPA, thus providing a choice if one of the reagents does not work effectively. Diastereotopic shifts can also be seen in the $^{13}C$ NMR spectrum of the substrates, but owing to the increased time necessary to collect the data, this proved to be not as useful as the proton data. The NMR spectra, $^{1}H$, $^{13}C$, and $^{31}P$, show only one set of resonances of BNPPA in the complex.

The utility of BNPPA was further shown for the chiral purity analysis of the bifunctional compound 8. Here, useful data could not be obtained using chiral shift reagent or Pirkle's solvent. The CLSR studies were unsuccessful in a large part due to severe broadening of the NMR spectrum even at low concentrations of the shift reagent. Based on a recent report describing the use of polar solvents in such cases,[8] we tried the determination in acetonitrile-$d_3$. The broadening was reduced, but the shift differentials were not large enough to obtain useful information. Shown in Figure 2 are the data obtained using 0.5 equiv of BNPPA. As is readily observed, base-line resolutin is obtained.

During the course of the work on amines, we were faced with determination of the enantiomeric ratios of the non-amine multifunctional compounds **9** and **10**. Both compounds showed resistance to evaluation by traditional methods. In this case BNPPA was also unsuccessful due to insolubility of BNPPA in chloroform or benzene. Since it was necessary to have BNPPA in solution for it to work, it was decided to prepare a 1:1 BNPPA–pyridine-$d_5$ salt. This BNPPA salt proved to be soluble in both solvents and furthermore was found to be useful in the chiral purity determination of **9** and **10**, as shown in Table II. While these $\Delta\delta$ values are relatively small, the resolution at 500 MHz was sufficient to make an analysis of the chiral purity. In the case of **9**, we were able to detect and quantitate an enantiomeric purity as low as 0.5%.

(8) Sweeting, L. M.; Crans, D. C.; Whitesides, G. M. *J. Org. Chem.* **1987**, *52*, 2273.

**Table I. Chemical Shift Differences for Chiral Amines as Their BNPPA Salts**

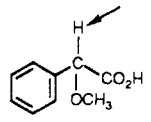
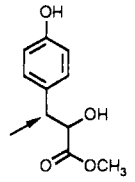
| substrate | CSA[a] | $\Delta\delta$[b] | solvent |
|---|---|---|---|
|  **1** | BNPPA | 0.161,[c] A<br>0.246, B | $C_6D_6$ |
|  **2a** **2b** | BNPPA<br>MPTA | 0.376, A<br>0.089, B | $C_6D_6$<br>$CDCl_3$ |
|  **3** | BNPPA | 0.108 | $C_6D_6$ |
|  **4** | BNPPA | 0.100 | $C_6D_6$ |
|  **5** | BNPPA | 0.087, A<br>0.016, B<br>0.067, C | $CDCl_3$ |
|  **6** | BNPPA<br>MTPA | 0.147, A<br>0.160,[5] A<br>0.120, B | $CDCl_3$ |
|  **7** | BNPPA<br>MTPA<br>CoTPPBr<br>2,2′-dihydro-naphthalene | 0.350<br>0.007[5]<br>0.010[2b] (estimate)<br>0.042[2c] | $CDCl_3$<br>pyridine<br>$CDCl_3$<br>$CDCl_3$ |
|  **8** | BNPPA (0.5 equiv) | 0.038 | $CDCl_3$ |

[a] Chiral solvating agent. [b] Difference in chemical shift between enantiotopic protons in the substrate as indicated by the arrows. [c] A typical experiment involves 5–10 mg of substrate in 0.6 mL of the appropriate solvent. One equivalent of BNPPA is added to the NMR tube, and the resultant solution's NMR spectrum is measured.

## Conclusion

The above data clearly indicate that BNPPA can be used as a chiral "solvating" agent for the determination of enantiomeric ratio of amines and other substrates via

**Table II. Chemical Shift Difference for Chiral Substrates with BNPPA•Py-$d_5$**

| substrate | $\Delta\delta$ | solvent |
|---|---|---|
|  9 | 0.005 | $CDCl_3$ |
|  10 | 0.006 | $CDCl_3$ |

NMR. Measurement of the chiral purity is fast and convenient; simply add BNPPA to the NMR solution and record a proton spectrum. In all cases studied there is at least one proton with high enough chemical shift dispersion to be integrated accurately. The only drawback to using BNPPA was line broadening induced by complexation, presumably due to exchange processes.

**Acknowledgment**. We would like to acknowledge K. Gunderson for preliminary studies, R. C. Anderson for helpful discussions, V. Parrino for compound **7**, J. Linder for compound **9**, R. Strohschein for compound **10**, and McNeil Laboratories for compounds **5** and **6**. We would also like to thank R. Lomelo for typing the manuscript.

**Registry No.** (*R*)-**1**, 16078-25-4; (*S*)-**1**, 17305-22-5; (±)-**1**, 53152-98-0; (*R*)-**2a**, 1722-95-8; (*S*)-**2a**, 3197-42-0; (U)-**2a**, 3000-79-1; (*R*)-**3**, 25333-42-0; (*S*)-**3**, 34583-34-1; (±)-**3**, 3684-26-2; (*R*)-**4**, 85-63-2; (*S*)-**4**, 2688-77-9; (±)-**4**, 1699-51-0; **5**, 123409-80-3; **6**, 123409-81-4; (*R*)-**7**, 3886-69-9; (*S*)-**7**, 2627-86-3; (±)-**7**, 618-36-0; (*R*)-**8**, 25137-01-3; (*S*)-**8**, 37675-18-6; (±)-**8**, 71962-74-8; (*R*)-**9**, 3966-32-3; (*S*)-**9**, 26164-26-1; (±)-**9**, 7021-09-2; (*R*)-**10**, 123359-32-0; (*S*)-**10**, 123359-33-1; (±)-**10**, 123409-82-5; (*R*)-BNPPA, 39648-67-4; (*S*)-BNPPA, 35193-64-7.

## Palladium-Catalyzed Chemistry of β-Lactam Vinyl Triflates: Coupling with Organostannanes and Alkoxycarbonylation†

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*Received July 18, 1989*

Modification of β-lactam nuclei has been limited only by the stability of the nucleus and the imagination of the medicinal chemist. In our exploration of the enhanced stability provided by the 1-carbacephalosporin over the cephalosporin nucleus,[1] we focused on 3-substituents which exploited this stability difference. Access to 1-carbacepham-3-enol triflate (**1a**)[2,3] prompted methods of development for conversion to the 3-vinyl (**2**), 3-(substituted)-alkyl (**2**), and 3-ester (**4**) analogues. Numerous reports, especially from Stille's group, have demonstrated the utility of the palladium-catalyzed coupling of vinyl halides and triflates with organostannanes.[4] Unfortunately, there have been few attempts to apply this chemistry in areas that demand its selectivity and scope.[5] The mechanistically related palladium-catalyzed conversion of steroidal vinyl triflates to unsaturated esters has been reported by Cacchi et al.,[6] and other reports[7] have utilized this methodology on structurally diverse yet, in general, chemically unreactive substrates. We report[8] here that palladium-catalyzed chemistry upon the complex enol triflates **1** has successfully attained both structural goals, **2** and **4**. Alkenyl groups, as well as a variety of other ligands, can be transferred from tin to C-3 of **1** (3-bromocephalosporin[9] is also a viable substrate). In the presence of carbon monoxide and alcohols, alkoxycarbonylation of **1** (Z = $CH_2$) provides entry into C-3 esters.

### Results and Discussion

The *p*-nitrobenzyl (6*R*,7*S*)-7-(phenoxyacetamido)-1-carba-1-dethia-3-[[(trifluoromethyl)sulfonyl]oxy]-3-cepham-4-carboxylate (**1a**) could be converted to **1b**[10] by reduction (zinc, HCl(aq)/DMF, 0 °C) of the *p*-nitrobenzyl group and esterification ($Ph_2CN_2$, $CH_3CN$, 23 °C) in 78% overall yield. Further transformation of **1b** by C-7 sidechain cleavage [(i) $PCl_5$, $CH_2Cl_2$, pyridine; (ii) i-BuOH, $CH_2Cl_2$, −10 °C; (iii) $H_2O$] and acylation with the 4,6-dimethoxy-1,3,5-triazine active ester of D-(t-Boc)phenylglycine[11] produced **1c** (28% yield).

Attempted vinylation of **1a** under standard conditions[4] (tri-*n*-butylvinylstannane, LiCl) with $(Ph_3P)_4Pd$ as catalyst in a variety of solvents produced only traces of product. Forcing conditions in an attempted carbonylation of **1b** utilizing a stoichiometric amount of $(Ph_3P)_4Pd$ with 1 atm of CO, *n*-$Bu_3SnH$ and LiCl afforded a crystalline material in 16% yield which contained palladium. This same material could be produced in 78% yield from **1a**, omitting the carbon monoxide and tin hydride. The spectral data[12]

† This paper is dedicated to the memory of the late Professor J. K. Stille.

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