



Direct Chromatographic Resolution of P-Chiral Phosphinoylethenes on a Chiral Stationary Phase Containing *N,N'*-(3,5-Dinitrobenzoyl)-*trans*-1,2-diaminocyclohexane as Selector

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Abstract: *A π -acidic, totally synthetic HPLC chiral stationary phase is used to separate the enantiomers of a wide range of unsaturated P-chiral phosphine oxides. It allows for fast, sensitive and accurate e.e. determinations and secures easy access to optically pure enantiomers by chromatography on preparative columns.*

Introduction

One of the most important problems in the field of enantioselective synthesis is to determine the enantiomeric excess (e.e.) of starting materials and products in an accurate and possibly straightforward manner. High-performance liquid chromatography (HPLC) utilizing chiral stationary phases (CSPs) offers many advantages in this respect: precision, reliability, speed of analysis, little amounts of the samples required, are the typical features of this technique.¹ Recently, P-chiral phosphine oxides bearing carbon unsaturation as the added functionality emerged as useful substrates for effecting chirality transfer from phosphorus to carbon^{2,3} and for synthesis of other P-chiral phosphine oxides of known configuration.^{4,5} However, such compounds usually lack the enantiopure models for comparison and they typically do not lend themselves to reliable quantitative NMR analysis with chiral shift reagents.^{2,6} The development of a convenient and possibly general method for determination of enantiomeric purity of such compounds as well as for their resolution has become therefore important.

Recent success in HPLC resolution of a large diversity of organic as well as heteroorganic compounds on a synthetic chiral stationary phase based on *trans*-1,2-diaminocyclohexane as selector (CSP1)⁷ prompted us to evaluate its utility also for resolution of P-chiral phosphinoylethenes. Previously reported direct

chromatographic resolutions of tertiary phosphine oxides on brush-type chiral phases were limited practically only to alkyldiarylphosphine oxides and most frequently required the presence of *P*-naphthyl substituent in the phosphine oxide structure to secure satisfactory resolution.⁸ In this report we wish to demonstrate that a wide range of *P*-chiral phosphinoylethenes including both unsubstituted and terminally substituted ones of either *E* or *Z* configuration, cyclic and acyclic, can be readily resolved into enantiomers by means of HPLC utilizing a brush-type π -acidic CSP containing the *N,N'*-3,5-dinitrobenzoyl derivative of either (*R,R*)- or (*S,S*)-1,2-diaminocyclohexane covalently bound to silica microparticles (Chart I).

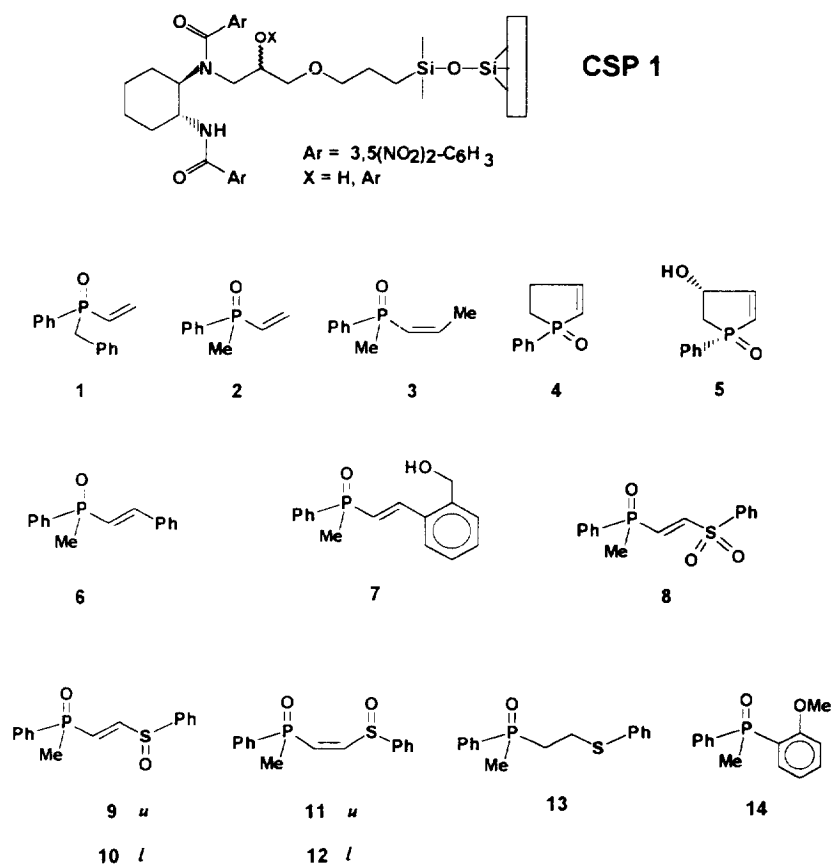


Chart I

Results and discussion

Chromatographic data obtained on the (*R,R*)-CSP1 for a number of phosphine oxides are listed in Table I; although we used, for comparison purposes, a single eluent throughout the whole series of compounds, baseline resolutions were observed in most of the cases,⁹ thanks to the good selectivity and high chromatographic efficiency of our column (Fig. 1).

Table I. Chromatographic data for the resolution of P chiral compounds on (*R,R*)-CSP1

compd	k'_1 ^a	α ^b	compd	k'_1 ^a	α ^b
1	2.41 (<i>R</i>)	1.18	8	6.17	1.17
2	5.41 (<i>R</i>)	1.03	9	5.43	1.17
3	3.40	1.09	10	5.85	1.42
4	7.14 (<i>R</i>)	1.13	11	8.38	1.13
5	7.84 (<i>R</i>)	1.11	12	12.21	1.07
6	5.41 (<i>R</i>)	1.11	13	3.23	1.24
7	6.33 (<i>R</i>)	1.31	14	7.70 (<i>S</i>)	1.04

Eluent: *n*-hexane/dioxane/methanol 60/40/5. Flow rate: 1.5 mL/min. Temperature: 25 °C. UV detection at 260 nm.

a) Retention factor of the first eluted enantiomer. b) Enantioselectivity factor.

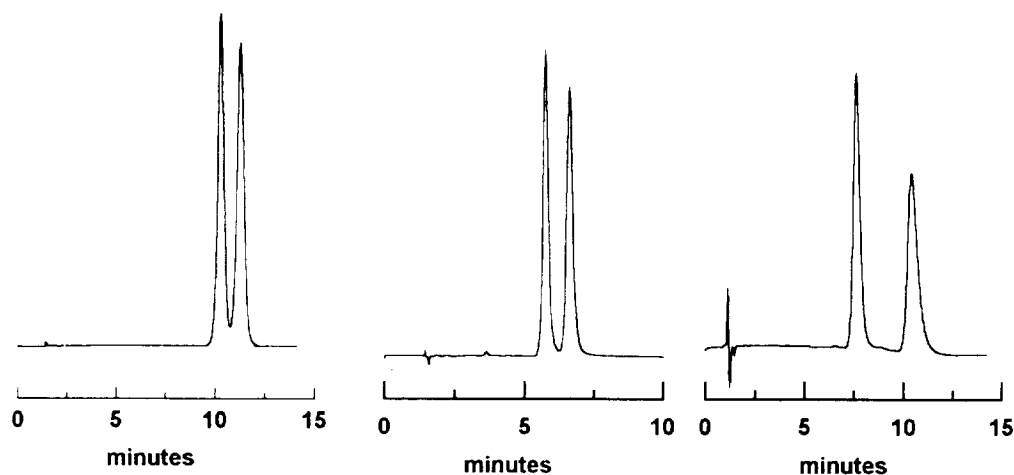


Figure 1. Chromatographic separations of racemic **6**, **13** and **10** (from left to right) on (*R,R*)-CSP1. For compound **6**, flow rate 1.0 mL/min. Other conditions as in Table I.

The interaction sites involved in the recognition processes operated by **CSP1** are its amide and π -acidic 3,5-dinitrobenzoyl groups. Thus, phosphine oxides with an aromatic ring close to the stereogenic phosphorus center possess the complementary functionalities (the strong H-bond acceptor P=O moiety and the π -basic aromatic) required for successful separation. For six phosphinoylethenes (**1**, **2**, **4**, **5**, **6**, **7**) the elution order

was established by chromatographing the samples enriched in one enantiomer of known configuration. The enantiomer on the (*R,R*)-CSP1 more strongly retained was found to have the *S* configuration. Although structurally related P-oxides are expected to have the same elution order on CSP1 we noted that the (*R*) enantiomer of PAMPO (**14**) eluted last from (*R,R*)-CSP1. The observed inversion of elution order and the low α value suggest the occurrence of two competing recognition processes working in opposite senses. This is not totally unexpected, since in fact in this case the CSP-analyte π - π interaction can be established by either of the two aromatic rings flanking the stereogenic center.

Additional polar groups, like hydroxyl, sulfinyl or sulfonyl, in the analyte backbone have little and unpredictable effects on enantioselectivity. This small sensitivity of the α values to the presence of polar functions other than P=O ensures the potential applicability of CSP1 to resolution of structurally diverse P-chiral compounds.

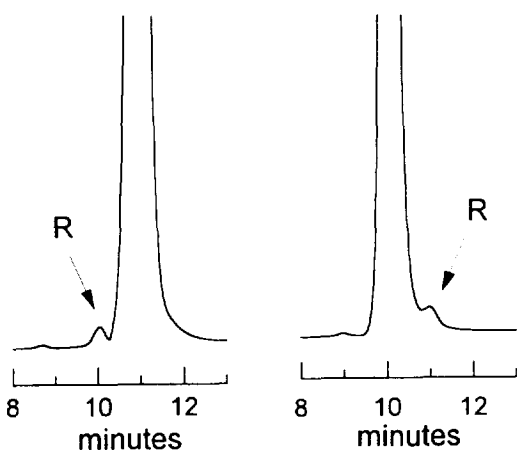


Figure 2. Column switching in enantiomeric trace analysis. Sample: (*S*)-**6**, 98.7% e.e. on (*R,R*)-CSP1 (left) and (*S,S*)-CSP1 (right). Flow rate 1.0 ml/min; other conditions as in Table I

In addition to enantio-selectivity, CSP1 shows considerable degrees of diastereo-selectivity. It has been demonstrated that all the stereoisomers of either *E* (**9**, **10**) or *Z* (**11**, **12**) ethenes having both P and S stereogenic centers can be effectively separated on the same CSP. Inspection of chromatographic data revealed that *Z* isomers (having larger dipole moments) are more strongly retained than *E* isomers; the latter, on the other hand, exhibit higher degrees of enantioselectivity. Examples of e.e. measurements of optically enriched samples are shown in Fig. 2. Since CSP1 is available in both enantiomeric forms, one can choose the proper CSP configuration in order to elute the trace enantiomer before the major component thus avoiding overlap between the tail of the principal peak and the minor peak, a desirable condition for obtaining accurate e.e. determinations.

Analytical separations can be easily scaled-up to a preparative column (250×10 mm I.D.) which usually accommodates racemic samples in the 20-100 mg scale. As an example, the enantiomeric fractionation of 30 mg of racemic **7** was obtained by the peak-shaving recycle technique (Fig. 3). Although the selectivity and peak symmetry were largely reduced as compared to the analytical run, the collected fractions gave 14 mg of (*R*)-**7** (99.9% e.e.) and 13 mg of (*S*)-**7** (99.1% e.e.).

To summarize, most of the examined phosphinoylethenes were readily separated on CSP1 permitting thus its prompt use for the reliable determinations of e.e.'s of the corresponding enantiomerically enriched samples. As demonstrated further with two examples (compounds **13** and **14**), structurally related alkyldiaryl- and arylalkylphosphine oxides can be similarly resolved on this CSP. Studies involving other classes of P-chiral phosphine derivatives are in progress in our Laboratories and will be reported in due course.¹⁴

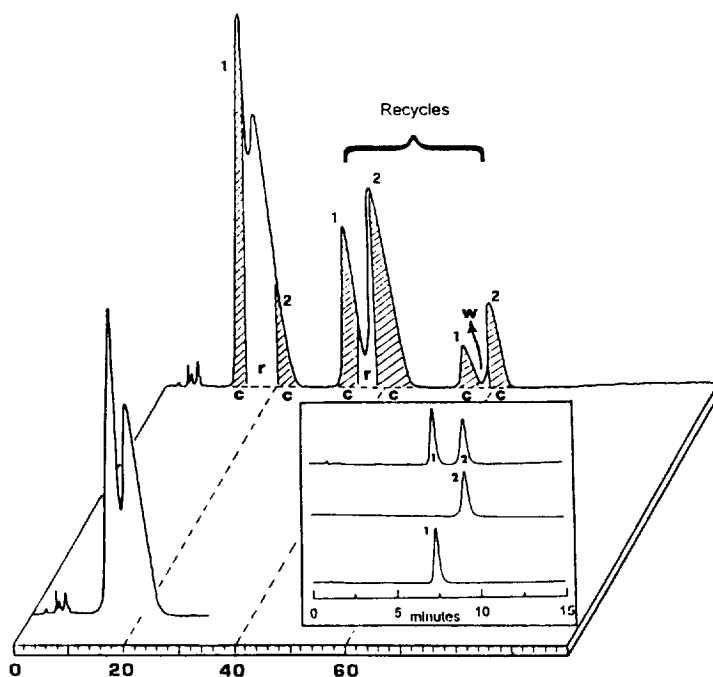


Figure 3. Semipreparative resolutions of racemic **7** on (*R,R*)-CSP1. Column: 250×10 mm ID. Eluent: *n*-hexane/dioxane/methanol 60/40/5. Flow rate: 5 mL/min. UV detection at 310 nm. Sample size: 30 and 20 mg (upper and lower trace). c: collect, r: recycle, w: waste. Inset shows the analytical runs for the racemate and the collected fractions.

Experimental

Compounds. Phosphinoylethenes **1**,^{4c} **2**,^{3a} **3**,^{6c} **4**,¹⁰ **6**,^{3e} **7**,^{3c} **3**,¹¹ **13**¹² employed in this study were either available from other studies or were prepared by literature procedures as indicated by the pertinent citation. Phosphinoylethenes **8-12** were obtained in the course of another ongoing project and full details of their preparation will be reported elsewhere.¹³ **8**: mp > 230 °C. ¹H NMR (CDCl₃ + CF₃COOH) δ: 2.05 (d, ²J_{PH} = 13.7 Hz, 3H), 7.27-7.92 (m, 12 H). ³¹P NMR (CDCl₃ + CF₃COOH) δ: 36.26 ppm. **9**: mp = 174-176 °C. ¹H NMR (CDCl₃) δ: 1.88 (d, ²J_{PH} = 13.4 Hz, 3H), 7.14 (dd, ³J_{HH} = 15.9 Hz, ³J_{PH} = 23.8 Hz, 1H), 7.42-7.74 (m, 11H). ³¹P NMR (CDCl₃) δ: 26.61 ppm. **10**: mp = 224-227 °C. ¹H NMR (CDCl₃) δ: 1.81 (d, ²J_{PH} = 13.4 Hz, 3H), 7.11 (dd, ³J_{HH} = 15.9 Hz, ³J_{PH} = 23.8 Hz, 1H), 7.36-7.78 (m, 11H). ³¹P NMR (CDCl₃) δ: 26.04 ppm. **11**: mp = 177-181 °C. ¹H NMR (CDCl₃) δ: 1.85 (d, ²J_{PH} = 13.4 Hz, 3H), 6.53 (dd, ³J_{HH} = 11.9 Hz, ²J_{PH} = 20.9 Hz, 1H), 6.95 (dd, ³J_{HH} = 11.9 Hz, ³J_{PH} = 34.4 Hz, 1H), 7.43-8.05 (m, 10H). ³¹P NMR (CDCl₃) δ: 25.37 ppm. **12**: this compound was obtained only in very small quantities and was not isolated in the pure state. It was analyzed as the admixture in one of the crude samples of **11**.

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