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Highly Efficient Chromatographic Resolution of α,α′-Dihydroxybiaryls

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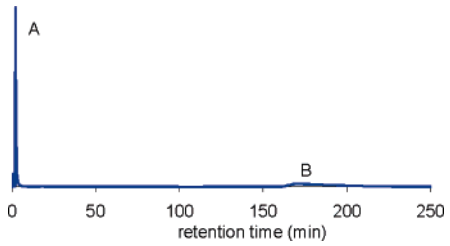
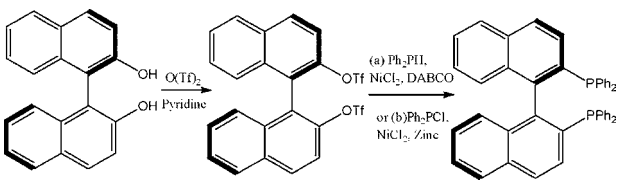
ABSTRACT



Separation factors as high as 115 were observed for the chromatographic resolution of many α,α′-dihydroxybiaryls with a single chiral stationary phase made from readily available amino acid derivatives. The stationary phase works well for biphenyl-type compounds. It works extremely well for larger bis-aromatic compounds, such as binaphthyl-type compounds.

Enantiomerically pure α,α′-dihydroxybiaryls (Figure 1), such as 1,1′-bi-2-naphthol (**8**), are widely used as chiral auxiliaries and ligands in asymmetric synthesis and have shown high stereocontrol properties in a wide range of asymmetric transformations.[1−3] They are also valuable precursors to enantiomerically pure phosphine-type chiral ligands, such as binap (Scheme 1), which are highly versatile and useful ligands for asymmetric transformations.[4] Despite their catalytic effectiveness, only a small number of enantiomerically pure α,α′-dihydroxybiaryls and the corresponding phosphine-type ligands are commercially available, possibly due to difficulty in their preparation. Ready access to these compounds is clearly important, as it will allow a greater number of such compounds to be examined in catalytic reactions.

Scheme 1. Merck (a) or Monsanto (b) Process of Preparing Enantiomerically Pure Binap



Although asymmetric synthesis of enantiomerically pure α,α′-dihydroxybiaryls has been reported, they are frequently obtained in enantiomerically pure forms by resolution of the racemic mixture.[1] The successful resolution methods often involves (1) chemical modification of the target compound to a derivative, (2) resolution of the derivative by fractional crystallization or enzymatic method, and (3) conversion of the derivative back to the target compound. For each compound, a different resolution procedure needs to be developed. Apparently, a resolution method that does not require the chemical modification and that is applicable to many different compounds is very desirable.

In this respect, chromatographic resolution, which usually does not require chemical derivatization, is an attractive alternative. However, for this method to be competitive, a column that can resolve many different compounds with high

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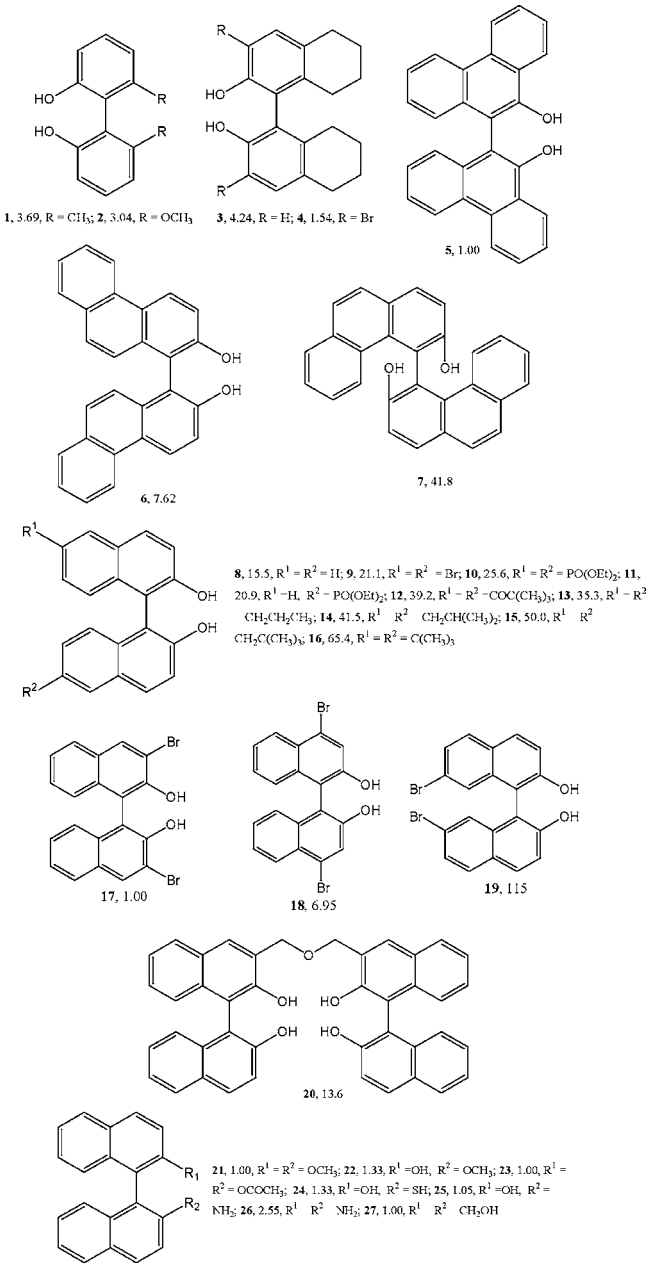

Figure 1. Structures and separation factors for the α,α′-dihydroxybiaryls and other compounds studied. Separation factors are listed after compound number (bold). See Supporting Information for complete chromatographic data.

separation factors [ratio of the retention times (T_R, T_S) of the two enantiomers, after subtracting dead time (T_0), $(T_R - T_0)/(T_S - T_0)$] is required. Herein we would like to report a chiral column that resolves many racemic α,α′-dihydroxybiaryls with unusually high enantioselectivity.

By screening a small peptide library, we discovered a chiral stationary phase, Fmoc-Asn(Trt)-Asn(Trt)-NH$(CH_2)_6$-CO-APS (Figure 2), that resolved racemic 1,1′-bi-2-naphthol (**8**) with a separation factor of 7.2 when CH_2Cl_2 was used as the mobile phase.[5] This separation factor is significantly higher than other separation factors reported for this well-

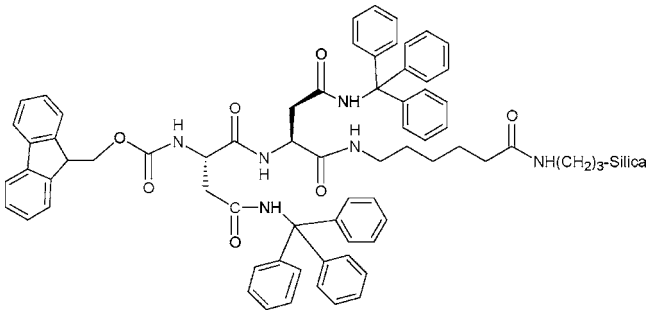

Figure 2. Structure of the Fmoc-Asn(Trt)-Asn(Trt)-NH$(CH_2)_6$CO-APS chiral stationary phase. APS, 3-aminopropylsilica gel.

known analyte.[6−12] Encouraged by this finding, we decided to study the chiral resolution of other α,α′-dihydroxybiaryls with this stationary phase.

Before studying other α,α′-dihydroxybiaryls, the impact of the mobile phase on the resolution of 1,1′-bi-2-naphthol (**8**) was studied. With 2-propanol/hexanes (86.1% *n*-hexane, 9.7% methylcyclopentane, 4.2% various methylpentanes) as the mobile phase, the separation factor dropped to 2.11. However, the separation factor increased to 15.5 when the mobile phase was switched to $CHCl_3$ (containing 50 ppm pentene, no ethanol). The large increase in separation factor with $CHCl_3$ as the mobile phase is unexpected, considering the similarity between $CHCl_3$ and CH_2Cl_2. The separation factor, however, is not sensitive to the presence of hexanes. For 1,1′-bi-2-naphthol (**8**), the separation factor changed slightly to 13.5 when 50% chloroform in hexanes was used as the mobile phase. Similar results were observed for compound **16**. With 100% chloroform as the mobile phase, the separation factor is 65.4. With 50% chloroform in hexanes as the mobile phase, the separation factor becomes 65.7.

The resolution of other α,α′-dihydroxybiaryls in Figure 1 was subsequently studied with $CHCl_3$ or $CHCl_3$/hexanes as the mobile phase, and the separation factors obtained are listed in Figure 1 besides compound numbers. These α,α′-dihydroxybiaryls were chosen based on their availability and structural representation regarding size and substitution of the aromatic ring. Some of the compounds (**3**, **4**, **8**, **9**, **17**, **20**, **21**, **23**, **26**, **27**) are commercially available, and many were made by following literature procedures.

The stationary phase works very well for biphenyl-type compounds (**1**−**4**). It works extremely well for larger bis-

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aromatic compounds, such as binaphthyl-type compounds. Separation factors as high as 115 were observed (Figure 3)!

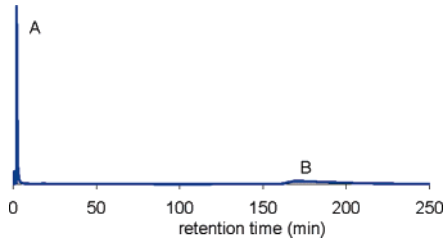

Figure 3. Resolution of compound **19**. Column size, 5 cm × 4.6 mm. Flow rate, 1 mL/min. Mobile phase, 100% $CHCl_3$. Peaks A and B are the enantiomers.

These separation factors are among the highest ever reported for chiral separation, where the typical separation factors are often less than 1.5. Compound **20**, which contains two binaphthyl units, was also resolved with high separation factor.

Steric properties of the substituents seem to influence the separation factors more than the electronic properties of the substituents. In compounds **13**−**16**, which contain electron-donating alkyl groups, excellent separation factors were observed and they increased with the steric bulkiness of the alkyl substituents. Excellent separation factors were also observed for compounds **10**−**12**, in which strong electron-withdrawing groups exist. The separation factors for compounds **12** and **15**, one containing an electron-withdrawing and another one containing an electron-donating group of similar size, are not very different. Position of the substitution can have a significant impact on the separation factor. For the four dibromo-substituted binaphthols (**9**, **17**, **18**, **19**), the separation factors range from 1 to 115. No separation was observed for compound **17**, in which the two bromo substituents are α to the OH groups. However, a separation factor of 115 was observed when the bromo substituents are at 7,7′ positions.

Modification of two hydroxyl groups drastically reduces the separation factors. In compound **22**, in which one of the OH is converted to an OCH_3 group, the separation factor dropped to 1.33. In compound **21**, in which both OH groups are converted to OCH_3 groups, no separation was observed. No separation was observed for compound **23**, in which both OH groups are converted to $OCOCH_3$ groups. As both conversions remove the acidic hydrogen atom, these results suggest that the hydrogen bonding donor ability of the HO groups is important in the chiral recognition, although steric effects cannot be ruled out. Studies of compound **24** or **25**, in which one OH group is replaced with a SH or a NH_2, support such a hydrogen bond donor argument, as separation factors in both cases dropped significantly. When compared with OH groups, SH and NH_2 are generally considered as weaker hydrogen bond donors. Interestingly, a modest separation factor of 2.55 was observed when both HO groups are replaced with NH_2 groups as in compound **26**. Location of the two OH groups is also important, as no separation was observed for compound **27**.

Severe peak tailing was observed for the latter eluting enantiomer for the compound shown in Figure 3. Such peak tailing is common for resolution with high separation factors and can be readily eliminated by switching to a more polar mobile phase after the first enantiomer is eluted.

The chiral stationary phase is made readily from commercially available amino acid derivatives by stepwise solid-phase synthesis. The ready availability of the stationary phase and the large separation factors bode well for large-scale preparative separations. Preliminary examination with an analytical column (25 cm × 4.6 mm) looks promising; 10 mg of compound **9** was base-line resolved in one injection using a simple isocratic elution with quantitative recovery. Other elution conditions and techniques more suitable for large-scale separation will be investigated.

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Supporting Information Available: Chromatograms and chromatographic data (dead time, retention times, retention factors, separation factors, mobile phase), literature references for the preparation of analytes. This material is available free of charge via the Internet at http://pubs.acs.org.

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