

Preparation of New Binaphthol Derived Chiral Stationary Phases

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To develop more advanced binaphthol derived CSPs, two new 1,1-bi-2-naphthol derived chiral stationary phases (CSPs) (**CSP 1** and **CSP 2**) were prepared by connecting with silica gel at a hydroxy (OH) group of binaphthol. Previously reported two 1,1'-binaphthyl-2,2'-diamine derived CSPs (**CSP 3** and **CSP 4**) were also prepared to compare the role of their functional groups (-OH and -NH₂) with **CSP 1** and **CSP 2**. Enantioseparation of randomly selected, 11 chiral compounds on these four CSPs was performed and the results compared to each other. 3,5-Dinitrobenzoyl (3,5-DNB) derivatives of each CSP showed better results than the others and binaphthyldiamine derived CSP showed slightly better than binaphthol derived one.

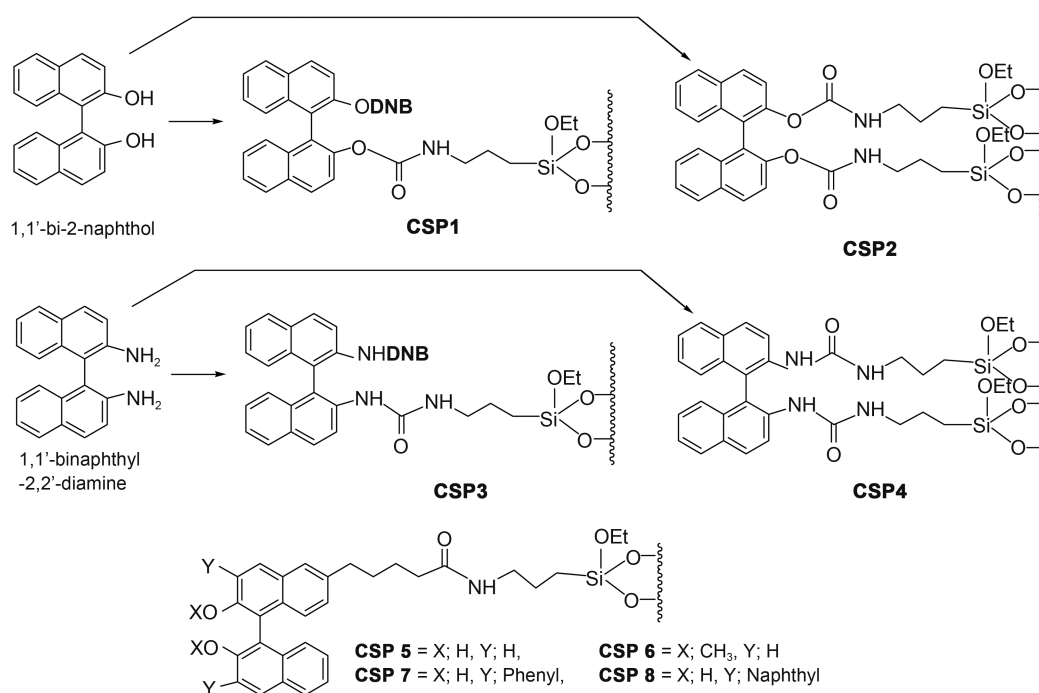
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Introduction

The increased demand for optically pure chiral compounds has led to the development of various asymmetric synthesis methods^{1,2} and a variety of chiral separation technologies.^{1,3} Among the methods of obtaining optically pure or active chiral compounds, direct chiral liquid chromatographic method by using various chiral stationary phases is the most important, because it can provide optically pure compounds directly and the information of optical purities of the optically active chiral compounds obtained from an asymmetric synthesis reaction.³ Various chiral stationary phases have been developed to separate as many chiral compounds

as possible with high selectivity.³ Many small chiral molecules were used as a candidate of a good chiral selector in the course of the development of a powerful chiral stationary phase.^{1,3}

Recently, optically pure 1,1'-binaphthyl-2,2'-diamine was used as a chiral selector, and four binaphthyldiamine derived chiral stationary phases (CSPs) were prepared and used for chiral separation of some chiral compounds.^{4,5} 1,1'-Bi-2-naphthol also used a powerful chiral catalyst^{6,7} or a chiral derivatizing agent⁸ for asymmetric synthesis. Sudo *et al.* reported four binaphthol derived CSPs (**CSP 5-8**) by connecting with silica gel at 6-position of binaphthol and showed very poor enantioselectivities for 23 chiral samples.⁹



In this study, two 1,1'-bi-2-naphthol derived CSPs (**CSP 1** and **CSP 2**) were newly prepared by connecting with silica gel at a hydroxy (OH) group of binaphthol to compare the chiral separation results from **CSP 5-8** and application of the **CSP 1** and **CSP 2** for the separation of some randomly selected eleven chiral compounds will be shown. For an exact comparison between these CSPs and the previously reported two 1,1'-binaphthyl-2,2'-diamine derived CSPs (**CSP 3** and **CSP 4**), we prepared the **CSP 3** and **CSP 4** again under similar synthetic procedure of **CSP 1** and **CSP 2** and compared the chiral separation results of the eleven chiral compounds on these columns.

Experimental

¹H-NMR spectra were recorded on a Bruker AVANCE digital 400 Spectrometer (400 MHz). IR spectra were measured with a Thermo Nicolet IR 200 FT-IR Spectrometer. Elemental analysis data were obtained using a ThermoFisher Flash 2000 Elemental Analyzer. All reactions were performed under a nitrogen atmosphere.

The HPLC system consisted of a JASCO (Tokyo, Japan) PU-2080 Plus Intelligent HPLC pump, a Rheodyne (Cotati, CA, USA) Model 7725i injector with a 20 μ L sample loop, a UV-2075 Plus Intelligent UV-Vis Detector. All chromatographic data were obtained using 2.5-10% 2-propanol (IPA) in hexane, as a mobile phase at a flow rate of 0.3-1.0 mL/min. Dead time (t_0) was checked by injecting 1,3,5-tri-*tert*-butylbenzene, a presumed unretained solute obtained from Aldrich Chemical Co. Chiral Columns: **CSP 1** was packed into 2.1 mm I.D. \times 150 mm stainless steel column, while **CSP 2**, **CSP 3** and **CSP 4** were packed into 4.6 mm I.D. \times 150 mm stainless steel column. (*S*)-1,1'-Binaphthyl-2,2'-diamine, (*R*)-1,1'-bi-2-naphthol, 3-(triethoxysilyl)propyl isocyanate, 3,5-dinitrobenzoyl chloride and an underivatized

racemic sample (**S1**) were purchased from Sigma-Aldrich Korea (Seoul, Korea). Spherical silica gel (5 μ m) was purchased from Merck Korea (Seoul, Korea). Other racemic samples (**S2-S11**) were obtained from Prof. DW Armstrong's lab. (U. Texas, Arlington, USA) or Prof. MH Hyun's lab. (Pusan Nat'l Univ., Korea) The structures of chiral samples used in this study are shown in Figure 1.

Preparation of CSP 1.

Preparation of 2'-hydroxy-[1,1'-binaphthalen]-2-yl 3,5-dinitrobenzoate (1): (*R*)-1,1'-Bi(2-naphthol) (0.60 g, 2.07 mmol) and triethylamine (0.28 mL, 2.07 mmol) were dissolved in 100 mL of dry methylene chloride in a 250 mL two-necked round bottom flask. To the stirred solution, a solution of 3,5-dinitrobenzoyl chloride (DNB-Cl) (0.49 g, 1.73 mmol) in 50 mL dry methylene chloride was dropped as slowly as possible under nitrogen at 0 $^{\circ}$ C. The reaction mixture was stirred at room temperature under nitrogen for 6 h and then washed with 1.0 M HCl, saturated aqueous NaHCO₃, and brine. The organic solution was dried over anhydrous MgSO₄, filtered and evaporated. The residue was purified by flush column chromatography over silica gel with EtOAc/*n*-hexane (1:6) to afford **1** (0.90 g, yield 90%) as a yellow powder. ¹H-NMR (CDCl₃) δ 7.0-7.7(m, 12H), 8.41-8.43 (d, 1H), 8.6 (d, 2H), 9.1 (t, 1H). IR (KBr) cm⁻¹: 3484, 3079, 2925, 2855, 1748, 1543, 1344.

Preparation of 2'-(((3-(triethoxysilyl)propyl)carbamoyloxy)-[1,1'-binaphthalen]-2-yl 3,5-dinitrobenzoate (2): 3-(Triethoxysilyl)-propyl isocyanate (0.46 mL, 1.78 mmol) and triethylamine (0.25 mL, 1.78 mmol) were added to a stirred solution of **1** (0.85 g, 1.78 mmol) in 100 mL dry methylene chloride. The whole reaction mixture was stirred for 72 h under reflux, and then the solvent was evaporated. The residue was purified by column chromatography over silica gel with EtOAc/*n*-hexane/CH₂Cl₂ (1:4:10) to afford **2** (0.65 g, yield 50.3%) as a yellow powder. ¹H-NMR (CDCl₃)

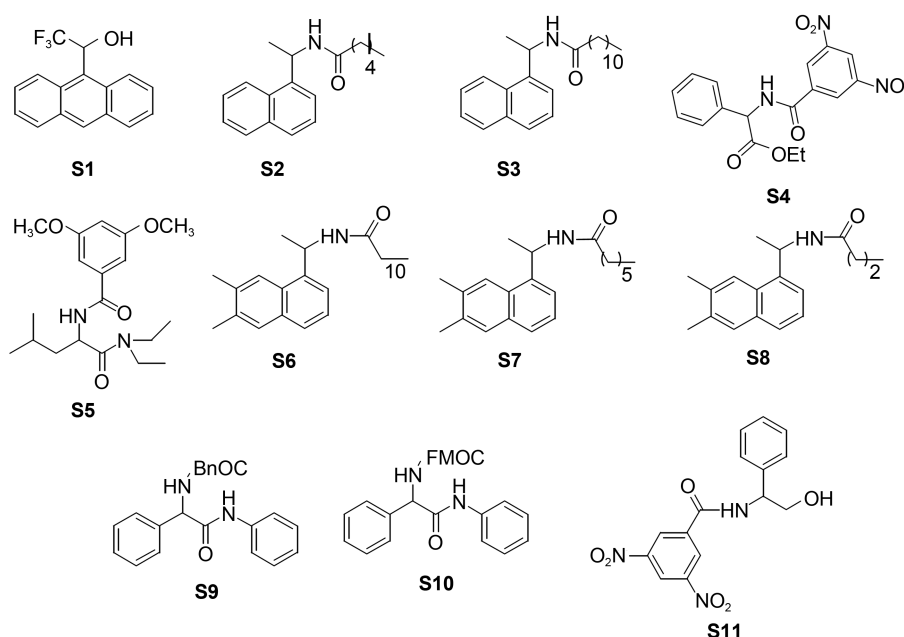


Figure 1. Structures of racemic samples.

δ 0.5 (t, 2H), 1.2 (m, 9H), 1.5 (m, 2H), 2.9 (q, 2H), 3.9 (q, 6H), 7.0-7.7 (m, 12H), 8.41-8.43 (d, 1H), 8.6 (d, 2H), 9.1 (t, 1H). IR (KBr) cm^{-1} : 3551, 3413, 3130, 1742, 1638, 1618, 1401.

Preparation of CSP 1 and Column Packing: A flask equipped with a Dean-Stark trap and a condenser was charged with Spherical silica gel (2.72 g, particle size: 5 μm) and toluene (40 mL). After heating the heterogeneous mixture under reflux until azeotropic removal of water was complete, compound **2** (0.60 g, 1.79 mmol), dissolved in 10 mL toluene, was added and then the whole mixture heated to reflux for 72 h under nitrogen. The silica gel was filtered and washed extensively with toluene, ethyl acetate, methanol, acetone, diethyl ether and hexane successively. Then the modified silica gel was slurried in methanol and packed into a 4.6 mm ID, 250 mm length stainless steel HPLC column using a conventional method^{8,9} with an Alltech HPLC Slurry Packer.

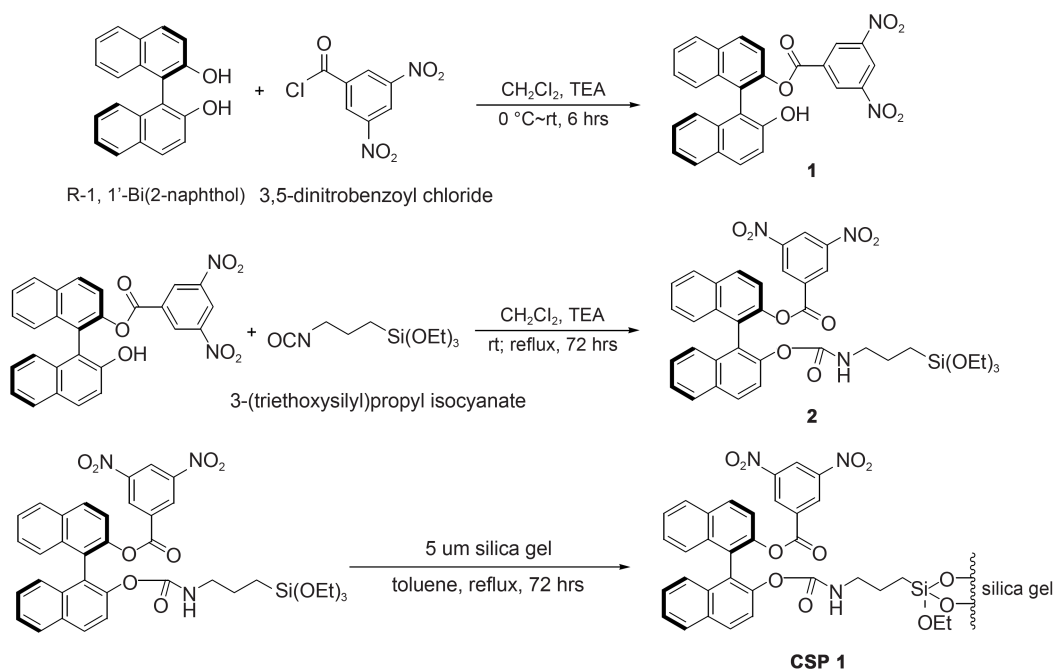
Preparation of CSP 2.

Preparation of [1,1'-binaphthalene]-2,2'-diyl bis((3-(triethoxysilyl)propyl)carbamate) (3**):** (*R*)-1,1'-Bi(2-naphthol) (1.00 g, 3.46 mmol) and triethylamine (0.97 mL, 6.92 mmol) were dissolved in 100 mL of dry methylene chloride in a 250 mL two-necked round bottom flask. To the stirred solution, 3-(triethoxysilyl)propyl isocyanate (1.81 mL, 6.92 mmol) were added. The whole reaction mixture was stirred for 12 h at room temperature, and then the solvent in the flask was evaporated. The residue was purified by column chromatography over silica gel with EtOAc/*n*-hexane/ CH_2Cl_2 (1:4:10) to afford **3** (1.50 g, yield 55.5%) as a colorless high viscosity liquid. $^1\text{H-NMR}$ (CDCl_3) δ 0.5 (t, 4H), 1.2 (m, 18H), 1.7 (m, 4H), 2.9 (m, 4H), 3.8 (q, 12H), 7.2-8.0 (m, 12H). IR (KBr) cm^{-1} : 3552, 3412, 3130, 1749, 1637, 1533, 1401, 1222, 1104.

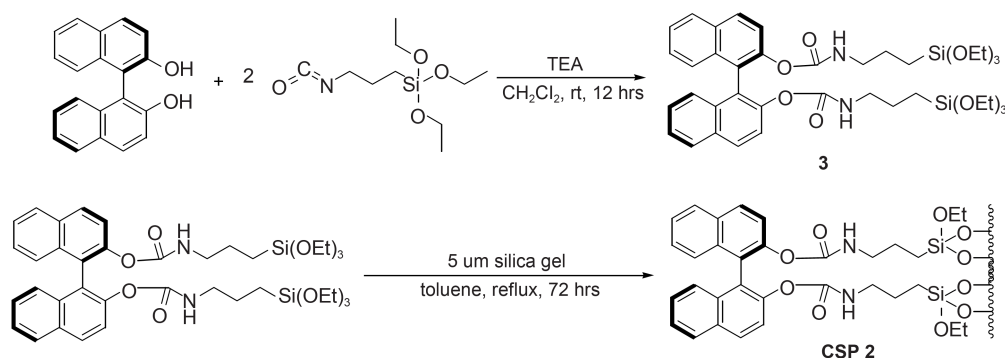
Preparation of CSP 2 and Column Packing. A flask equipped with a Dean-Stark trap and a condenser was charged with Spherical silica gel (3.20 g, particle size: 5 μm) and toluene (50 mL). After heating the heterogeneous mixture under reflux until the azeotropic removal of water was complete, compound **3** (0.80 g, 1.79 mmol), dissolved in 10 mL toluene, was added and then the whole mixture was heated to reflux for 72 h under nitrogen. The silica gel was filtered and washed extensively with toluene, ethyl acetate, methanol, acetone, diethyl ether, and hexane successively. Then the modified silica gel was slurried in methanol and packed into a 4.6 mm ID, 250 mm length stainless steel HPLC column using a conventional method with an Alltech HPLC Slurry Packer.

Results and Discussion

The preparation of **CSP 1** is summarized in Scheme 1. The synthetic procedures outlined in Scheme 1 involved only three major steps: Esterification, silylation and bonding to silica gel. These simple reactions have been reported in literature previously.^{4,5,8-12} First, the mono-substituted compound **1** was a major product at low temperatures, but a di-substituted product also appeared. Because the yield of the esterification was bigger than the amidation (the first step of synthesis of **CSP 3**), the di-substituted one could be cleanly and easily removed by classical extraction with high pH (~ 13) of the aqueous solution. The preparation of **CSP 2** is summarized in Scheme 2. The synthetic procedures outlined in Scheme 2 involved only two steps: Silylation and bonding to silica gel. The **CSP 2** has a binaphthol group but no additional π -acidic group. **CSP 3** and **CSP 4** were easily prepared by following the previously reported method⁴ under the similar synthetic conditions with different starting



Scheme 1



Scheme 2

Table 1. Elemental analysis of **CSP 1**, **CSP 2**, **CSP 3**, and **CSP 4**

	C	N	based on N	based on C
CSP 1	7.718%	1.043%	0.248 mmol/g	0.207 mmol/g
CSP 2	6.078%	0.599%	0.214 mmol/g	0.181 mmol/g
CSP 3	6.238%	1.155%	0.165 mmol/g	0.167 mmol/g
CSP 4	7.233%	1.141%	0.204 mmol/g	0.215 mmol/g

material of **CSP 1** or **CSP 2**. The covalently modified silica gels were packed into 150 mm length \times 4.6 mm I.D. (2.1 mm for **CSP 1**) stainless steel columns using conventional methods.^{10,11}

All CSPs possess two π -basic naphthyl moieties; furthermore, **CSP 1** and **CSP 3** have an additional π -acidic 3,5-dinitrobenzoyl group. The results of elemental analysis of **CSP 1**-**CSP 4** are shown in Table 1. The amount of covalent bonding of each selector to silica was about 0.2 mmol per one gram of silica gel. This is similar result of previous work.^{1,9}

Some examples of the enantiomeric separation of 2,2,2-trifluoro-1-(9-anthryl)ethanol (**S1**) on **CSP 1** and **CSP 3**, and **S11** on **CSP 2** and **CSP 4** is shown in Figure 2.

As shown in Figure 2, both **CSP 1** and **CSP 3** showed good resolution, and **CSP 1** showed better resolution than **CSP 3**. Racemic phenylglycinol-*N*-3,5-dinitrobenzamide (**S11**) was slightly separated on **CSP 2** and **CSP 4**. The chromatographic separation data of the 11 racemic samples on **CSP 1**-**CSP 4** are summarized in Table 2.

As shown in Table 2, nine racemic compounds were separated on **CSP 1** and all chiral samples used in this study were separated on **CSP 3**, while only four chiral compounds were separated on **CSP 2** and **CSP 4**. The dinitrobenzoyl (DNB) group containing CSPs (**CSP 1** and **CSP 3**) showed much broader and higher selectivity than the previously reported binaphthol, binaphthalene, or diphenylethanedi-amine derived CSPs.^{9,12,13} In the resolution of various 23 chiral samples on the first reported four binaphthol derived CSPs (**CSP 5**-**8**), **CSP 5** resolved 11 racemates from 23 samples with a maximum selectivity factor (α) of 1.12, 9/23 (maximum α value is 1.062) on **CSP 6**, 13/23 (maximum α value is 1.11) on **CSP 7**, and 14/23 (maximum α value is 1.18) on **CSP 8**.⁹ In the case of newly developed a 1,1'-bi-2-

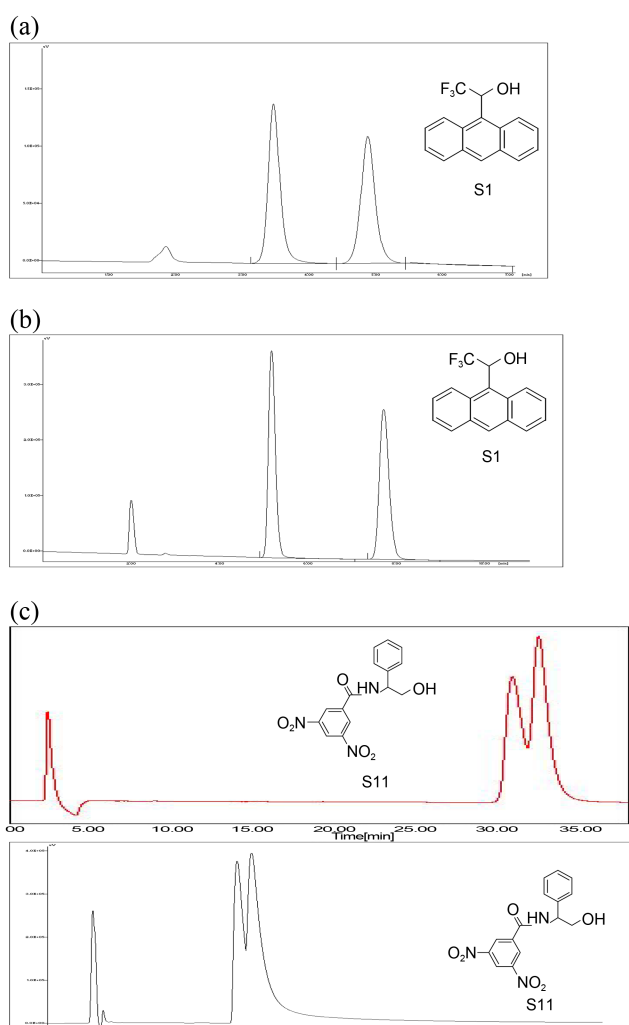


Figure 2. (a) Resolution of **S1** on **CSP 1**. Column size; 2.1 mm \times 15 cm, Eluent; 10% IPA in hexane, Flow rate; 0.3 mL/min, Detection at 254 nm. (b) Resolution of **S1** on **CSP 3**. Column size; 4.6 mm \times 15 cm, Eluent; 10% IPA in hexane, Flow rate; 1 mL/min, Detection at 254 nm. (c) Resolution of **S11** on **CSP 2** and **CSP 4**. Column size; 4.6 mm \times 15 cm, Eluent; 10% IPA in hexane, Flow rate; 1 mL/min, Detection at 254 nm.

naphthol derived **CSP 1** by connecting with silica gel at a hydroxy (OH) group of binaphthol showed much better resolution than the previous four binaphthol derived CSPs.

Table 2. Separation data for eleven racemic compounds on **CSP 1-4** as a function of different mobile phase compositions^a

Sample	CSP 1				CSP 2				CSP 3				CSP 4			
	Eluent (percent of IPA in Hexane)															
	2.5		10		2.5		10		2.5		10		2.5		10	
	<i>k</i>	α	<i>k</i>	α	<i>k</i>	α	<i>k</i>	α	<i>k</i>	α	<i>k</i>	α	<i>k</i>	α	<i>k</i>	α
S1	2.87	2.16	0.93	1.84	2.66	1.05	0.82	1.00	4.74	1.68	1.88	1.75	2.83	1.00	0.79	1.00
S2	5.16	1.04	1.28	1.00	5.53	1.00	1.05	1.00	13.96	1.48	4.67	1.65	5.51	1.00	1.40	1.00
S3	3.75	1.05	0.96	1.00	4.01	1.00	0.75	1.00	10.37	1.63	3.48	1.86	3.93	1.00	0.98	1.00
S4	5.79	1.00	1.83	1.00	5.30	1.00	1.23	1.00	11.69	1.08	4.2	1.05	6.94	1.00	1.86	1.00
S5	2.16	1.00	2.28	1.09	2.80	1.00	0.61	1.00	2.87	1.06	2.28	1.09	2.61	1.00	0.72	1.00
S6	3.49	1.07	1.13	1.09	2.43	1.00	0.10	1.00	13.49	1.17	4.42	1.20	2.92	1.00	0.76	1.00
S7	4.05	1.10	1.22	1.08	3.62	1.00	1.00	1.00	14.43	1.12	4.89	1.15	3.52	1.00	0.94	1.00
S8	7.86	1.08	6.17	1.07	5.57	1.00	1.58	1.00	23.78	1.02	7.26	1.05	6.14	1.06	1.53	1.00
S9	2.35	1.10	0.88	1.00	2.20	1.12	0.54	1.00	6.89	1.19	1.45	1.12	2.96	2.08	0.66	1.71
S10	3.77	1.07	1.32	1.00	2.22	1.11	0.53	1.00	8.41	1.25	1.77	1.19	3.16	2.63	0.66	2.13
S11	12.9	1.00	1.65	1.00	13.6	1.07	1.41	1.00	3.57	1.13	3.62	1.14	22.2	1.07	3.65	1.10

^aFlow rate for **CSP 1** = 0.3 mL/min.; **CSP 2-4** = 1.0 mL/min. ^bThe data of **CSP 1-4** not obtained under optimum conditions. Detection wavelength is 254 nm.

(9/11, maximum α value is 1.84) The reason for these broader and higher selectivities on the dinitrobenzoyl (DNB) group containing CSPs is related to the additional face-to-face π - π interaction between the π -acidic DNB group on the CSP and the π -basic group on the chiral samples.^{4,11}

In comparison of the two 3,5-DNB-derived CSPs, **CSP 3** showed better resolution than **CSP 1**. The reason for these results cannot be explained clearly at this moment, but it can be assumed that the amide hydrogen in the **CSP 3** plays an important role (for example, additional hydrogen bonding with chiral samples) under these resolutions. There are some interesting points in this resolution. Samples 9 and 10 (**S9**, **S10**) were separated on all four CSPs used in this study, but showed much better resolution on **CSP 4**.

In conclusion, two new 1,1'-bi-2-naphthol-derived CSPs (**CSP 1** and **CSP 2**) were very easily prepared by following a simple two- or three-step synthetic procedure. These binaphthol-derived CSPs were prepared much easier than previous binaphthol CSPs and demonstrated improved selectivity over the previously reported CSP. In general, the ease and simplicity of the preparation process of the CSP is important from a practical standpoint. For an exact comparison of the two CSPs and the previously reported two 1,1'-binaphthyl-2,2'-diamine derived CSPs (**CSP 3** and **CSP 4**), the **CSP 3** and **CSP 4** were prepared again; the chiral separation result of 11 chiral compounds were then compared on these four columns. The two dinitrobenzoyl (DNB) groups containing CSPs (**CSP 1** and **CSP 3**) showed much better results than **CSP 2** and **CSP 4**. The **CSP 3**

showed better results than **CSP 1** in the chiral separation of the tested samples.

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