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Diphenylethanediamine derivatives as chiral selectors VIII. Influence of the second amido function on the high-performance liquid chromatographic enantioseparation characteristics of (*N*-3,5-dinitrobenzoyl)-diphenylethanediamine based chiral stationary phases

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Abstract

The effect of the second amido group in (*R*,*R*)- and (*R*,*S*)-3,5-dinitrobenzoylated 1,2-diphenylethane-1,2-diamine (DPEDA) derived chiral selectors was investigated. Structurally related mono-amidic (''deaza'') model compounds were synthesized and immobilized. The HPLC performance of the resultant two new chiral stationary phases (CSPs) was compared with the broadly applicable diamidic analogues. On the ''deaza'' CSPs special enantioseparation capabilities for underivatized alcohols and carboxylic acids were significantly reduced whereas separation of amides, ureas and carbamates and also analytes containing ester functions were substantially improved. © 1998 Elsevier Science B.V.

Keywords: Enantiomer separation; Chiral stationary phases, LC; Chiral selectors; Diphenylethanediamine; Diphenylpentenamine

1. Introduction

Immobilized 3,5-dinitrobenzoylated diphenylethanediamine (DNB-DPEDA) derivatives yield chiral stationary phases (CSPs) of broad applicability in enantioselective normal-phase high-performance liquid chromatography (HPLC) [1,2]. The selector unit contains two centers of asymmetry and therefore two diastereomeric CSPs could be prepared and evaluated (Scheme 1).

The hitherto most useful versions are CSP II, which separates the largest number of differently structured analytes and its shorter tethered version CSP IIa, which separates underivatized arylsubstituted secondary alcohols [3,4] and a fair number of aryl substituted carboxylic acids [5] exceptionally well.

Mechanistic details of chiral recognition on brush type Pirkle CSPs have been investigated intensely. Although the results from all these studies led to considerable progress in the design of this type of CSPs, it is still difficult to predict reliably effects caused by even rather small structural changes of the selector. For example Pirkle and Welch [6][1] varied

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[1] See chromatographic data reported for CSPs VIII and IX.

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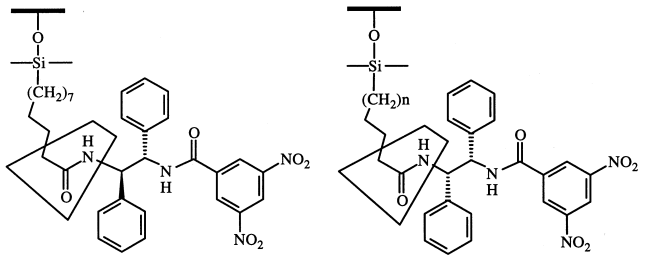
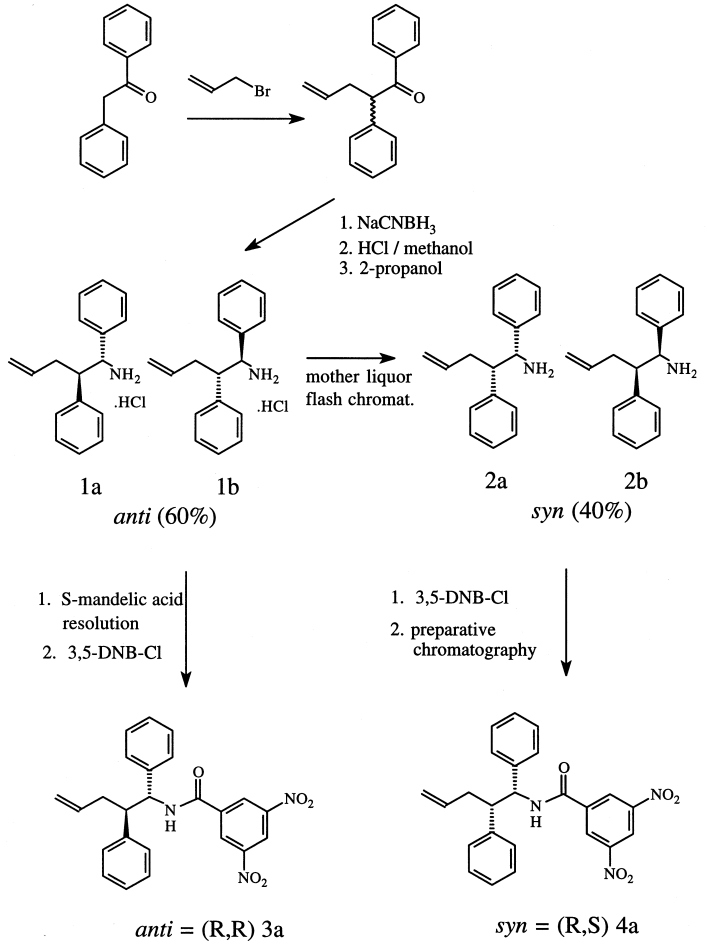


anti-type CSP I *syn-type* CSP II (n = 7)
CSP IIa (n =1)

Scheme 1.



Scheme 2.

only the mode of attachment in a CSP to find significant changes in the enantioseparation characteristics for analytes bearing functions of different polarity far remote from the chiral center. Non-stereoselective interactions by superfluous polar functionalities were shown to be responsible for surprisingly different enantioselectivities.

Consequently, in the design of efficient ''tailor made'' selectors [7] only a minimum set of appropriately arranged interaction sites should be considered to reduce the unfavorable non-stereoselective retention.

However, our highly versatile selectors derived from DPEDA are characterized by a diamide backbone. Experimental data suggest that for some classes of analytes chiral discrimination occurs predominately on the DNB substituted chiral center, e.g., linker-modification of a DPEDA selector did not effect the elution order or did not change enantioselectivities for aryl alcohols significantly [3,4]. Thus, the nature of the influence of the substituents which are located at the second stereogenic center on the chiral discrimination process remains to be established. The polar amido function used for tethering might especially act as source of non-stereoselective interaction. This made it an attractive objective for us to prepare both stereoisomers of a selector derived from the DNB-DPEDA type by omittance of the second amido function (Schemes 2 and 3). In the present study we describe the synthesis and enantioseparation capabilities of these new ''deaza'' type CSPs for different classes of analytes relative to their corresponding diamide analogues.

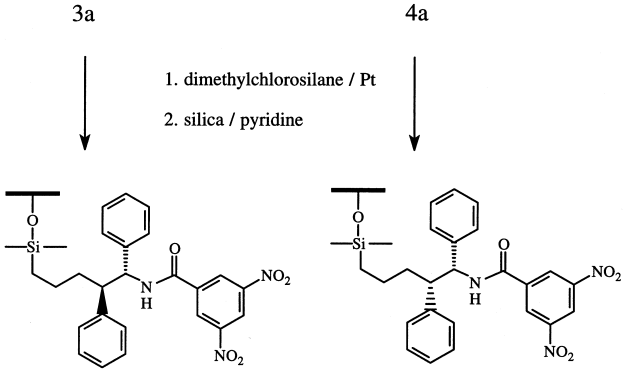
2. Experimental

2.1. Chemicals and reagents

Allylbromide, benzyltri-*n*-butylammonium chloride, sodium cyanoborohydride, ammonium acetate, 1,2-diphenylethanone, hydrogen hexachloro-(IV)-platinate hydrate, dimethylchlorosilane, hexamethyldisilazane and 3,5-dinitrobenzoyl chloride were all from Aldrich (Steinheim, Germany) and used as received. Lichrospher Si 100, 5 μm, (Merck, Darmstadt, Germany) was used as a support for grafting the chiral selectors after hydrosilylation. Analytes used for the evaluation of the new CSPs were available from previous studies.

2.2. Chromatography

HPLC evaluation of the new CSPs were executed on a Hewlett-Packard HP Series 1050 liquid chromatograph and HP Chemstation as the software. Mobile phases (Table 1) were mixed from isopropanol and *n*-heptane of gradient quality (Merck). 1,3,5-Tri-*tert*.-butylbenzene was used as void volume marker.



anti-type CSP III *syn-type* CSP IV

Scheme 3.

Table 1
Comparison of the separation capabilities of CSP I–CSP IV for underivatized aryl alcohols, carboxylic acids and other analytes without amido function[a]

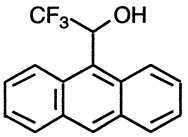
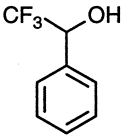
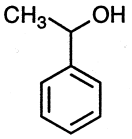
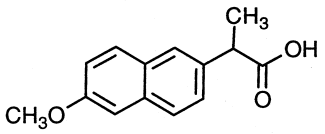
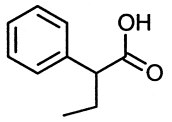
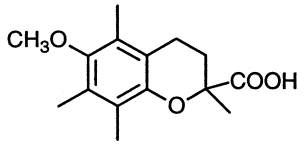
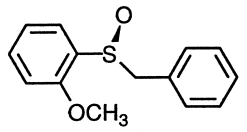
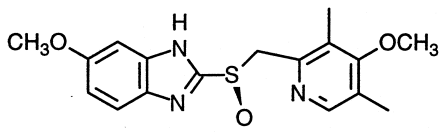
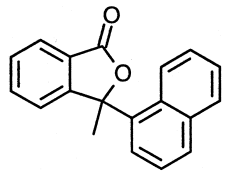
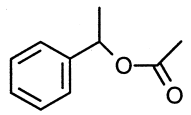
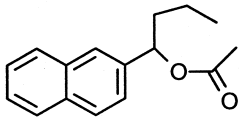
no	compound	mobile phase	CSP	k'_1	α	Res	mr[b]
underivatized alcohols[c]							
5		D	I	1.43	1.16	1.20	R
		D	II	1.50	1.82	5.32	R
		D/EtOH	III	3.95	1.10	1.02	S[d]
		D	IV	0.38	1.25	1.10	R
		C	IV	0.68	1.32	2.14	R
		A	IV	2.40	1.33	3.69	R
6		A	I, III,IV	not resolved			
		A	II	3.76	1.16	2.17	R
7		A	I, III,IV	not resolved			
		A	II	3.85	1.12	1.85	S[e]
underivatized acids[f]							
8		D/TFA	I	2.76	1.19	2.78	S
		D/TFA	II	3.30	1.46	6.65	S
		F/TFA	III	1.13	1.02	-	S
		B/TFA	IV	2.08	not resolved		
9			I, III, IV	not resolved			
		B/TFA	IIa	1.57	1.12	1.68	

Table 1. Continued

no	compound	mobile phase	CSP	k′1	α	Res mr[b]
10		D/TFA	I	3.06	1.73	8.52
		C/TFA	IIa	1.14	2.85	1.58
		G/TFA	III	0.84	1.16	0.91
		C/TFA	IV	1.28	1.16	1.58
sulfoxides						
11		E	I	1.11	not resolved	
		E	II	3.14	1.28	2.03
		D/EtOH	III	3.68	1.28	2.55
		D	IV	2.57	not resolved	
12		E	I	2.36	not resolved	
		E	II	7.29	1.65	0.96
		G	III	2.12	1.07	0.61
		E	IV	1.34	not resolved	
Ester and Lactones						
13		D	I	2.32	1.18	2.10
		D	II	3.71	1.29	1.73
		F/EtOH	III	7.02	1.14	1.54
		D	IV	3.06	1.84	9.23
14		A	I	0.47	not resolved	
		A	II	0.49	not resolved	
		A	IIa	0.74	1.10	1.11
		A	III	3.27	1.20	1.93
		A	IV	0.56	1.18	0.60

(Cont.)

Table 1. Continued

no	compound	mobile phase	CSP	k′1	α	Res mr[b]
15		A	I	0.84	1.09	0.89
		A	II	1.33	not resolved	
		A	IIa	1.41	1.53	3.00
		E	III	3.53	1.11	1.10
		A	IV	0.96	2.88	6.79

[a] For comparison some data for CSPs I and II were taken from Refs. [2–5].
[b] Most retained enantiomer.
[c] About 100 examples of aryl alcohols resolved on CSP II can be found in Refs. [3,4].
[d] In this special case of anthryltrifluoroethanol we found an obvious deviation of the otherwise strictly conform elution order.
[e] Same elution order as trifluoromethyl derivatives, change is due only to the CIP nomenclature rules.
[f] Twenty-seven examples of aryl-substituted carboxylic acids resolved on CSP II can be found in Ref. [5].
Mobile phases: (TFA: 0.1% trifluoroacetic acid; EtOH: replaces 2-propanol). A=*n*-heptane–2-propanol (99.5:0.5); B=*n*-heptane–2-propanol (99:1); C=*n*-heptane–2-propanol (98:2); D=*n*-heptane–2-propanol (95:5); E=*n*-heptane–2-propanol (90:10); F=*n*-heptane–2-propanol (70:30); G=*n*-heptane–dioxane (50:50); H=dioxane–2-propanol (50:50). UV detection at 230 nm, 20°C.

Analysis of the enantiomeric purity of the 3,5-dinitrobenzoyl derivatives **3** and **4** was performed on an analytical 250×4 mm I.D. column packed with D-*N*-2-naphthylalanine supported on 5 μm silica (Regis, IL, USA).

Preparative separation of the enantiomers of **4** was achieved using a Waters HPLC pump 600E coupled with variable-wavelength detector (Knauer) and a 10-ml sample loop on a 250×20 mm I.D. column, containing L-*N*-2-naphthylalanine as selector immobilized on 5 μm silica (Regis).

2.3. Preparations

2.3.1. 2-Diphenyl-4-penten-1-one

1,2-Diphenyl-4-penten-1-one was prepared from 1,2-diphenyl-ethanone and allylbromide similar to a literature procedure [8]. However, in this case the alkylation was carried out in presence of a phase transfer catalyst. In short, a mixture of 49.10 g (250 mmol) 1,2-diphenylethanone, 250 ml toluene, 26.0 ml (36.10 g, 300 mmol) allylbromide, 740 mg (2.37 mmol) benzyltri-*n*-butylammonium chloride and 200 ml aqueous NaOH (40%) was intensely stirred for 3 h at ambient temperature. After addition of 200 ml ether and 200 ml water, the organic phase was separated and washed with 2 *M* HCl (2×200 ml), water (2×200 ml) and dried ($MgSO_4$). Removal of the solvents under reduced pressure gave 59 g (≈100%) yellowish oil, that solidified on standing at ambient temperature.

*2.3.2. Syn- and anti-1,2-diphenyl-4-penten-1-amine **1** and **2** (diastereomeric mixture)*

A 2-l round-bottomed flask was charged with 21.00 g (0.30 mol) sodium cyanoborohydride and a solution of 39.40 g (0.167 mol) 1,2-diphenyl-4-penten-1-one and 128.00 g (1.66 mol) ammonium acetate in 1 l methanol. The mixture was refluxed for five days (do not use boiling chips but rather a magnetic stirrer to prevent bumping!). Subsequently about 600 ml methanol were distilled off. The reaction mixture was allowed to cool to 60°C and treated with 400 ml 4 *M* KOH to adjust to pH 9. From the heterogenous mixture more liquid (about 420 ml) was distilled at ambient pressure to establish an inner temperature of 99°C. After cooling to ambient temperature the mixture was adjusted to pH 2 with 500 ml 4 *M* HCl. Hydrogen cyanide formed during the acidification step was swept out of the mixture by a strong stream of nitrogen and absorbed in 2 *M* NaOH. Subsequently the precipitated hydrochlorides were collected by filtration and washed with ether (3×100 ml) to yield 36.10 g (79%) of a

white solid. In order to obtain the free bases 6.60 g (24 mmol) of the hydrochlorides were stirred with 100 ml concentrated aqueous ammonia followed by extraction with dichloromethane (3×60 ml). Drying of the organic extracts ($MgSO_4$) and removal of the solvent under reduced pressure gave 5.74 g (quantitative) of a slightly yellow liquid. ^{1}H NMR analysis revealed the presence of a diastereomeric mixture **1**:**2**=60:40.

*2.3.3. Racemic anti-1,2-diphenyl-4-penten-1-amine **1***

Fractional crystallization of 18.50 g of the crude hydrochlorides from 1-propanol yielded 6.83 g (37% calculated from the mixture of diastereomers, 29% from the ketone) pure *anti*-diastereomer **1·HCl** as a white solid; m.p. 280°C; $C_{17}H_{19}N$·HCl; calc. C, 74.57; H, 7.36; N, 5.12; found: C, 74.80; H, 7.30; N, 5.07. The free base was isolated as described above in quantitative yield as a colorless oil. ^{1}H NMR ($CDCl_3$) 360 MHz δ 1.40 (s, 2H, NH_2) 2.20 (m, 2H, allyl-CH_2), 2.85 (m, 1H, Ph–CH) 4.10 (d, J=9 Hz, 1H, CH–NH_2), 4.80 (m, 2H), 5.45 (m, 1H) and 7.20–7.45 ppm (m, 10 H).

*2.3.4. Racemic syn-1,2-diphenyl-4-penten-1-amine **2***

In order to isolate the minor *syn*-diastereomer the combined mother liquors were concentrated and the free base was isolated. Purification via flash chromatography (150 g silica, mobile phase petroleum ether–ethyl acetate–triethylamine, 600:400:2) of 7.54 g recovered material yielded 3.91 g **2** as yellowish oil (24% yield calculated from the mixture of diastereomers, 19% from the ketone). ^{1}H NMR ($CDCl_3$) 360 MHz δ 1.60 (s, 2H, NH_2) 2.55 (m, 2H, allyl-CH_2), 3.00 (m, 1H, Ph–CH) 4.15 (d, J=6.3 Hz, 1H, CH–NH_2), 4.90 (m, 2H), 5.60 (m, 1H) and 6.95–7.40 ppm (m, 10 H).

*2.3.5. (R,R)-(−)-1,2-Diphenyl-4-penten-1-amine **1a***

6.76 g (28.5 mmol) Racemic 1,2-diphenyl-4-penten-1-amine **1** and 4.33 g (28.5 mmol) *S*-(−)-mandelic acid were dissolved in 40 ml hot ethanol. The resulting precipitate (3.10 g) was recrystallized from 10 ml ethanol to give 2.17 g of a white solid. A final crystallization from 7 ml ethanol gave 1.85 g white crystals (27%). m.p. 160°C; $[\alpha]_{546}=-63.0$ (c=1.10, MeOH). After treatment with ammonia as described for the racemic hydrochloride, the free base **1a** was isolated as a colorless oil, $[\alpha]_{546}=-2.45$ (c=1.00, MeOH).

*2.3.6. (R,R)-N1-(1,2-Diphenyl-4-pentenyl)-3,5-dinitrobenzamide **(R,R)-3a***

1.39 g (5.87 mmol) of **1a** dissolved in 5 ml dichloromethane and 1 ml dry pyridine were cooled with an ice-bath and 1.35 g (5.87 mmol) 3,5-dinitrobenzoyl chloride was added. After 2 h the mixture was allowed to warm to room temperature, diluted with 70 ml dichloromethane and washed with 2 *M* HCl (30 ml), water (30 ml), saturated sodium bicarbonate (30 ml) and water (30 ml).

After evaporation of the solvent 1.74 g (70%) off-white crystals **(*R,R*)-3a** were isolated. m.p. 210°C (racemic: m.p. 184°C); $C_{24}H_{21}N_3O_5$; calc.: C, 66.81; H, 4.91; N, 9.74; found: C, 66.81; H, 4.87; N, 9.71; $[\alpha]_{546}=-29.7$ (c=1.60, dichloromethane). ^{1}H NMR ($CDCl_3$) 360 MHz δ 2.40 (t, 2H) 3.25 (q, 1H), 4.90 (m, 2H,CH_2=) 5.35 (t, 9Hz, CHN), 5.60 (m, 1H), 6.45 (d, 9 Hz, NH), 7.20–7.45 (m, 10 H), 8.50 (d, J=2.2 Hz, 2H) and 9.05 ppm (t, J=2.2 Hz, 1H). HPLC analysis on a D-*N*-2-naphthylalanine CSP [2-propanol–*n*-heptane, (70:30, v/v); flow: 2 ml/min; detection: 254 nm] confirmed ee>98% ee [k_1'=4.22, α=1.15; **(*R,R*)-3a** being the more retained enantiomer].

*2.3.7. Enantiomers of syn-1N-(1,2-diphenyl-4-pentenyl)-3,5-dinitrobenzamide **(R,S)-4a** and **(S,R)-4b***

In spite of considerable experimental efforts resolution of diastereomer **2** could not be achieved by crystallization. Diastereomeric salts of **2** with mandelic acid, tartaric acid, diacetyl- dibenzoyl- and ditoluoyltartaric acid and camphorsulfonic acid crystallized from a broad range of solvents (methanol, ethanol, isopropanol, acetone, ethyl acetate) gave no enantiomeric enrichment.

Therefore the racemic dinitrobenzoylated product **4** was prepared starting from 2.11 g crude **2** (yield 2.70 g; 70%) and resolution was achieved using a preparative version of the Pirkle's L-*N*-2-naphthylalanine CSP (250×20 mm I.D.). Best separation but rather poor sample-solubility was found with 1-propanol–petroleum ether (20:80) as mobile phase.

However, solubility was significantly improved by addition of acetonitrile. Thus, 2.31 g (5.35 mmol) of crude **4** were dissolved in 20 ml CH_3CN and 5 ml 1-propanol. The solution was filtered and diluted with 125 ml of the mobile phase. Four ml of this solution was injected for a single run using a flow of 20 ml/min and peak-detection at 274 nm. Retention time of the first eluting enantiomer was 8 min, of the second eluting enantiomer 9 min. To avoid contamination due to peak-overlap the ''middle'' fractions (about 25% of the total amount) were not collected. After evaporation of the solvent from the pooled product fractions the resultant solids were crystallized from 1-propanol. Yield: 0.70 g of the first eluting enantiomer **(*R,S*)-4a** and 0.59 g of the second eluting enantiomer **(*S,R*)-4b** (74%, 56% overall). **(*R,S*)-4a**: m.p. 189°C; $[\alpha]_{546}=-36.2$ ($c=0.50$, CH_3CN); **(*S,R*)-4b**: m.p.189°C; $[\alpha]_{546}=+39.5$ ($c=1.00$, CH_3CN), ^{1}H NMR ($CDCl_3$) 360 MHz δ 2.60 (m, 2H) 3.35 (m, 1H), 5.05 (m, 2H,$CH_2=$) 5.50 (t, $J=9$ Hz, CHN), 5.75 (m, 1H), 6.75 (d, 9 Hz, NH), 7.00 and 7.25 (m, 10 H), 8.90 (d, $J=2$ Hz, 2H) and 9.17 ppm (t, $J=2$ Hz, 1H); $C_{24}H_{21}N_3O_5$; calc.: C, 66.81; H, 4.91; N, 9.74; found: C, 66.82; H, 4.86; N, 9.66;

2.3.8. CSP III and CSP IV

Hydrosilylation of **(*R,R*)-3a** and **(*R,S*)-4a** with dimethylchlorosilane – Speier's catalyst and grafting were achieved following a protocol described in a previous report [2]. 1.43 g (3.30 mmol) of **(*R,R*)-3a** and 3.20 g silica were used in preparation of CSP III and 0.66 g (1.53 mmol) of selector **(*R,S*)-4a** and 2.00 g silica for CSP IV. Loading: CSP III: 400 μmol/g; CSP IV: 153 μmol/g. The new CSPs were slurry-packed into 150×4 mm I.D. stainless steel columns with methanol and ''dynamically'' endcapped using hexamethyldisilazane [2].

3. Results and discussion

3.1. Synthetic approach to the new ''deaza'' selectors

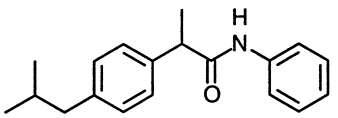
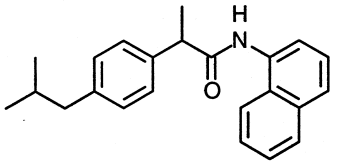
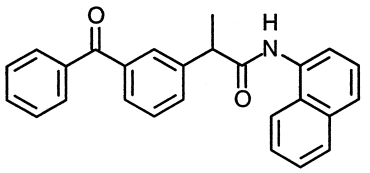
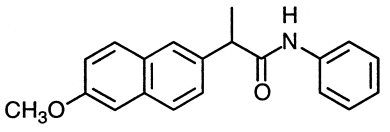
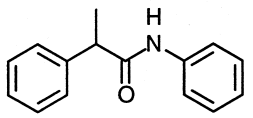
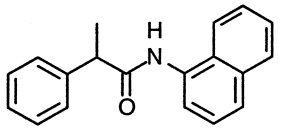
Synthesis of a diastereomeric mixture of amines **1** and **2** (Scheme 2) started from racemic 1,2-diphenyl-4-pentenone, which was easily prepared according to the literature from allylbromide and 1,2-diphenylethanone [8]. However using a newly developed phase transfer procedure we obtained the product in quantitative yield. Reductive amination was also achieved in good yield using sodium cyanoborohydride–ammonium acetate. Noteworthy, even simple 1,2-diphenylalkylamines are almost unknown in the literature. Only one similar primary amino analogue was found, namely 1,2-diphenylpentylamine, prepared in 1942 from the corresponding saturated ketone with ammonium formate at 230°C [9]. A tetramethoxy ringsubstituted *N*-benzyl analogue was recently reported by Sotomayor et al. [10]. ^{1}H NMR analysis of our crude amine revealed a diastereomeric mixture in a ratio of **1**:**2**=60:40. The relative configuration of the major diastereomer **1** was assigned to be ''anti'', due to its smaller coupling constant (6.3 Hz) of the two hydrogens in 1,2-position analogous to the tetramethoxy derivative. The correct assignment of the relative configuration of the latter has been confirmed by data from NOE experiments after a ring closure procedure in Sotomayors study.

Purification of the major diastereomer **1** was easily accomplished by crystallization of the hydrochlorides from 2-propanol. Isolation of the minor diastereomer **2** required chromatographical work-up of the free bases recovered from the mother liquors.

Resolution of **1** was achieved easily by fractional crystallization of the mandelic acid salt to give enantiomerically pure amine **1a** which was subsequently converted to the target *anti*-selector **3** by treatment with 3,5-dinitrobenzoyl chloride in pyridine. Resolution of **2** via fractional crystallization of diastereomeric salts failed despite considerable experimentation. Therefore *syn*-selector **4** was prepared as racemic mixture from **2** by acylation and the enantiomers **4a** and **4b** were resolved via preparative liquid chromatography on a π-basic Pirkle CSP.

Hydrosilylation, grafting to silica followed by endcapping gave new CSPs III and IV. Surprisingly, selector loadings of the silicas turned out to be significantly different: Whereas *anti*-type CSP III had a unusually high loading of 400 μmol/g, the much more elaborate *syn*-type CSP IV had only a value of 153 μmol/g. This and the diastereomeric

Table 2
Comparison of the separation capabilities of CSPs I–IV for amides, ureas and carbamates

no	compound	mobile phase[a]	CSP	k'_1	α	Res	mr[b]
carboxylic acids as amides							
16		D	I	1.15	not resolved		
		D	II	1.28	1.22	1.24	S
		E/EtOH	III	5.13	1.12	1.19	S
		D	IV	1.44	1.39	3.82	S
17		E	I	2.66	1.39	2.25	S
		E	II	2.10	1.38	2.57	S
		F/EtOH	III	5.67	1.45	3.31	S
		D	IV	4.12	2.05	9.83	S
18		E	I	9.13	1.04	0.53	
		E	II	9.17	1.17	0.98	
		F/EtOH	III	17.3	1.41	3.50	
		E	IV	5.25	1.75	6.22	
20		E	I	2.96	1.08	0.66	S
		E	II	4.42	1.23	1.19	S
		F/EtOH	III	6.61	not resolved		
		E	IV	3.49	1.31	3.84	S
21		D	I	1.78	not resolved		
		E	II	2.47	1.20	1.38	
		E	III	8.38	1.04	0.47	
		E	IV	1.16	1.18	1.46	
22		E	I	3.35	1.50	3.18	S
		E	II	2.89	1.38	2.68	S
		F/EtOH	III	8.25	1.55	4.61	S
		E	IV	3.15	1.80	6.28	S

(Cont.)

Table 2. Continued

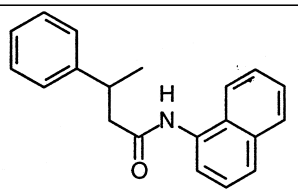
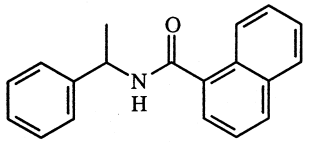
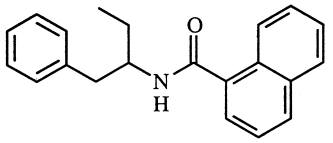
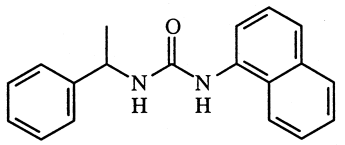
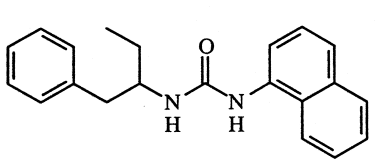
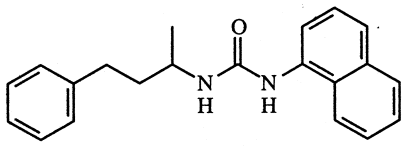
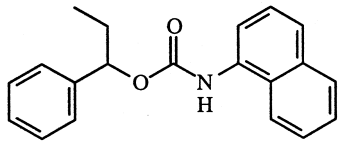
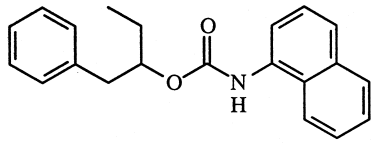
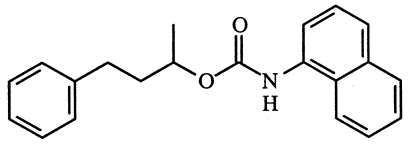
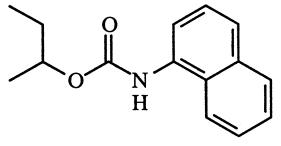
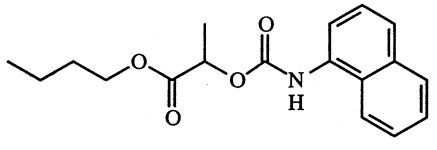
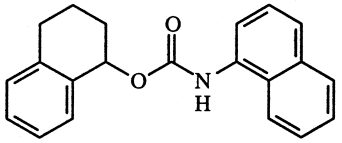
no	compound	mobile phase[a]	CSP	k'_1	α	Res	mr[b]
23		E	I	3.62	1.11	1.24	
		E	II	4.07	1.09	0.50	
		FEtOH	III	4.43	1.15	1.40	
		E	IV	3.13	1.18	1.32	
amines as amides							
24		F	I	1.37	not resolved		
		F	II	1.91	1.14	1.47	R
		F/EtOH	III	12.8	1.29	2.46	R
		E	IV	3.58	1.53	2.54	R
25		E	I	3.74	1.14	1.29	
		E	II	5.21	not resolved		
		F/EtOH	III	8.81	1.15	1.23	
		E	IV	3.50	1.05	0.53	
amines as ureas							
26		F	I	1.89	1.11	1.24	R
		F	II	1.42	1.32	1.49	R
		F/EtOH	III	10.2	1.39	3.37	R
		F	IV	1.08	1.75	4.40	R
27		E	I	3.28	1.31	2.42	
		E	II	3.76	1.22	1.10	
		F/EtOH	III	6.89	1.33	2.80	
		E	IV	3.74	1.26	1.70	

Table 2. Continued

no	compound	mobile phase[a]	CSP	k´1	α	Res	mr[b]
28		F	I	1.34	1.16	1.08	
		F	II	1.65	1.08	0.50	
		F/EtOH	III	7.85	1.26	2.33	
		F	IV	1.07	1.45	3.23	
alcohols as carbamates:							
29		E	I	1.18	1.28	1.87	
		E	II	1.68	1.39	2.86	
		H/EtOH	III	3.89	1.65	4.63	
		D	IV	0.90	2.16	8.01	
30		D	I	1.04	1.16	1.15	
		D	II	1.68	1.09	0.55	
		F/EtOH	III	3.34	1.34	2.44	
		D	IV	1.05	1.22	2.10	
31		E	I	1.11	1.08	0.83	
		E	II	1.87	not resolved		
		F/EtOH	III	3.22	1.19	1.60	
		E	IV	0.88	1.29	2.43	
32		E	I	1.31	not resolved		
		E	II	1.09	not resolved		
		F/EtOH	III	2.48	not resolved		
		B	IV	2.29	1.09	1.12	
33		D	I	1.04	1.18	1.41	
		D	II	1.60	not resolved		
		F/EtOH	III	2.09	1.35	2.71	
		D	IV	0.94	1.59	4.08	

(Cont.)

Table 2. Continued

no	compound	mobile phase[a]	CSP	k′1	α	Res	mr[b]
34		D	I	1.60	not resolved		
		D	II	3.13	1.06	0.50	
		F/EtOH	III	4.61	1.07	0.69	
		D	IV	1.51	not resolved		

[a] Mobile phases: H=*n*-heptane–ethanol, others as in Table 1.
[b] Most retained enantiomer.
Some data for CSPs I and II were taken from Ref. [4].
UV detection at 230 nm, 2 ml/min, 20°C.

nature of the new selectors may explain the extremely different retention behavior observed on the new phases. While CSP III displayed extreme retention for polar analytes, the opposite effect was found with CSP IV. An evaluation of new CSPs III and IV also revealed large differences in the separation capabilities. Unexpectedly, the deaza CSPs exhibited poor enantioselectivities for arylalcohols compared to DPEDA derived CSP II (vide infra, Table 1). On the other hand, enantiomers of acylated aromatic amines could be discriminated much better than with DPEDA based CSPs.

Subsequently a broader set of analytes was used to evaluate the stereodiscrimination potential of deaza versus DPEDA type selectors. The results, obtained on *anti*- and *syn*-type CSPs of both series are depicted in Tables 1–3.

Absolute configuration of the 3,5-dinitrobenzoylamido substituted carbon in CSP III and IV was established by comparison of the elution order of a representative range of analytes with the data obtained on Pirkle type CSPs containing DNB-phenylglycine [2] and DNB-DPEDA as selectors of well established stereochemistry.

3.2. Evalution of CSP III and CSP IV

3.2.1. Underivatized alcohols, carboxylic acids and other analytes without amido function (Table 1)

The separation factors for pronounced π-basic anthryltrifluoroethanol **5** reveal significant differences in the chiral recognition of underivatized arylcarbinols. Clearly the *syn*-DPEDA-derived selector present in CSP II exhibits the best enantioseparation.

Using less polar mobile phases, this value can be as high as 2.04 (2% 2-propanol, $k_1'=4.35$). All three other CSPs show α-values between 1.10 and 1.33 which are typical in the range of other π-acidic donor-acceptor type CSPs.

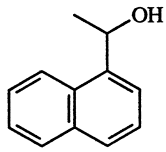
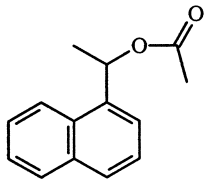
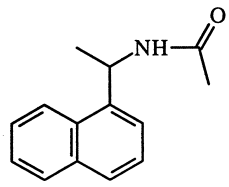
Further, diamidic CSP II is the only one which separates less π-basic phenyltrifluoroethanol **6** and the parent compound **7**. A large set of enantioseparation data for simple phenylcarbinols and diarylcarbinols on CSP II and even more efficient CSP IIa, which is linked by a shorter tether, has been published recently by us [3,4].

Note that deaza *anti*-type CSP III exhibits by far the strongest retention and therefore in most cases 2-propanol had to be replaced by ethanol. In sharp contrast, deaza *syn*-type CSP IV had to be operated with highly non-polar mobile phases.

A similar tendency is observed comparing the separation coefficients of underivatized naproxen **8**, Table 1. The two new deaza CSPs III and IV exhibit almost no chiral recognition power for simple carboxylic acids. Phenylbutyric acid **9** containing a moderately π-basic aryl substituent can be resolved on CSP II only [5]. Sterically demanding acid **10** (trolox) can also be separated most efficiently on CSP II.

Somewhat different results are found in the chiral recognition behaviour towards aryl sulfoxides **11** and **12**. In these cases deaza *anti*-type CSP III shows

Table 3
Comparison of the separation capabilities of CSPs I–IV for 1-naphthylethanol, its acetate and the corresponding acetamide

no	compound	mobile phase[a]	CSP	k'_1	α	Res
35		C	I	2.43	not resolved	
		C	II	3.06	1.14	2.67
		F	III	1.40	not resolved	
		A	IV	1.89	not resolved	
36		C	I	1.47	1.07	0.87
		C	IIa	0.84	1.24	2.61
		E	III	3.10	1.06	0.57
		A	IV	0.81	2.48	7.83
37		E	I	3.90	1.39	3.91
		F	II	0.83	1.44	2.49
		F/EtOH	III	4.50	1.08	0.66
		E	IV	2.99	2.74	9.19

[a] Mobile phases: see Table 1.
UV detection at 230 nm, 2 ml/min, 20°C.

enantioselectivities similar to CSP II. The other two CSPs have no chiral recognition capabilities for chiral sulfoxides.

A totally different picture can be seen with esters of aryl alcohols.

Deaza *syn*-type CSP IV has especially remarkable resolution capabilities for these racemates (**13**–**15**). The excellent resolution of the acetates of 1-(1-naphthyl) and 1-(2-naphthyl)ethanol is depicted in chromatogram C in Fig. 1. Interestingly, on *anti*-type CSP III clean baseline-separation for acetate **14** could be achieved while the enantioseparation was significantly reduced for more pronounced π-basic esters **13** and **15** compared to CSP IV. In the series of DPEDA derived selectors only the shortly tethered CSP IIa separates acetates of aryl alcohols (**14**, **15** and **36**, Table 3) as illustrated in chromatograms A and B in Fig. 1. In contrast, with cyclic ester **13** and many other aryl alcohols [3] we had found no fundamental difference between CSPs II and IIa in terms of enantioselectivity. This observation suggests that in chiral discrimination of aryl alcohol acetates the short tethers (CSP IIa, CSP III and CSP IV) lead to a favourable contribution of the surface of the silica in stereodiscrimination.

3.2.2. Amides, ureas and carbamates (Table 2)

CSP IV displays an outstanding stereodiscrimination potential for π-basic analytes capable of forming strong hydrogen bonding interactions. The enantioselectivities observed for naphthyl substituted amides, ureas and carbamates are denoted in Table 2.

All of the amides sterically ''uncrowded'' at the chiral center (**16**–**24**) are separated best on this deaza type CSP. The enantiomers of amide **25** with a more remote phenyl substituent are separated significantly better on *anti*-type selectors present in CSPs I and III.

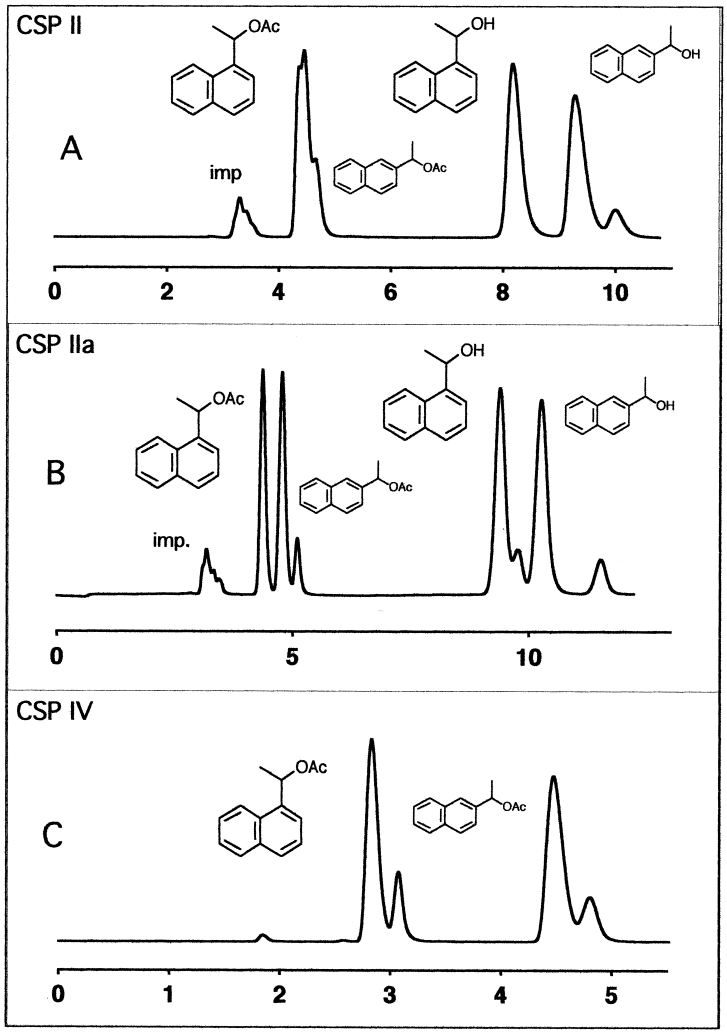


Fig. 1. Comparison of the enantioseparation for naphthylalcohols and its acetates on the two *syn*-type CSPs II and short chained version IIa with deaza type CSP IV. [2-naphthyl derivatives, which are present as minor components were separated with similar separation coefficients (values not in Table 3); in some cases the second enantiomer is hidden under the major component.]

A very similar picture can be found comparing data for the separation of ureas (**26**–**28**) and carbamates (**29**–**34**). Most analytes of this type are separated best on CSP IV, the carbamate of 2-butanol can be separated only on CSP IV. An interesting exemption is the cyclic analyte **34**.

3.2.3. Comparison of the chiral recognition of alcohols, esters and amides (Table 3*)*

More information can be gained with π-basic analytes which are structurally based on an identical skeleton but containing different functional groups. Data in Table 3 for alcohol **35**, acetate **36** and amide **37** clearly show the different abilities of all four CSPs. Alcohol **35** is separated by CSP II only, whereas ester **36** is only well separated on *syn*-type selectors, and especially well on deaza CSP IV. As we have already shown in two previous publications [1,2], *syn*-type selectors derived from DPEDA were in most cases more useful than the *anti*-type versions. For amide **37** all CSPs exhibit stereodiscrimination. Interestingly, diamidic DPEDA derived

phases *anti*-type CSP I and *syn*-type CSP IIa show similar levels of enantioselectivity. In sharp contrast, amide **37** was barely separated on deaza *anti*-type CSP III, whereas on the corresponding *syn*-type the best separation could be observed.

4. Conclusions

In summary, the second amido functions in DPEDA derived CSPs have a strong influence on the overall enantioseparation characteristics. Especially in *syn*-type selectors this structure element displays a favourable influence on the chiral recognition of unsubstituted aryl alcohols and aryl substituted carboxylic acids. However, for analytes containing functionalities having a high potential for hydrogen bonding interactions, e.g., amides, ureas and carbamates, the second amido group seems to display a source of non-stereoselective interaction, leading to reduced enantioselectivities. Remarkably, the special ability of shortly tethered selectors to recognize the enantiomers of aryl alcohol acetates suggests a favourable contribution of the silica surface in chiral discrimination. However, the specific role of the second amido function in DPEDA derived selectors using the available data is still difficult to estimate. There is little evidence that this group is – at least in the classes of analytes investigated in this report – actively involved as a stereoselective interaction site in chiral recognition. More probably it might serve as an effective tool to control and/or restrict the number of possible low-energy conformations of the selector backbone.

References

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[4] N.M. Maier, G. Uray, Chirality 8 (1996) 490.
[5] G. Uray, N.M. Maier, Enantiomer 1 (1996) 211.
[6] W.H. Pirkle, Ch.J. Welch, J. Chromatogr. 589 (1992) 45.
[7] Ch.J. Welch, J. Chromatogr. A 666 (1994) 3.
[8] Y. Kimura, P. Kirszensztejn, St.L. Regen, J. Org. Chem. 48 (1983) 385.
[9] N. Ogata, Yakugaku Zasshi 62 (1942) 152.
[10] N. Sotomayor, T. Vicente, E. Dominguez, E. Lete, M.-J. Villa, Tetrahedron 50 (1994) 2207.