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Biselector enantioselective stationary phases for HPLC: dependence of the chiral discrimination properties on stereochemistry and chemical nature of each unit of the chiral auxiliary

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Abstract—Optically active 1-(1-naphthyl)ethylamine, *N*-3,5-dinitrobenzoylphenylglycine and *N*-3,5-dinitrobenzoylleucine were used as chiral building blocks to prepare three new enantiomerically pure bifunctional chiral auxiliaries for enantioselective HPLC, belonging to a family of biselector systems, the first example of which (**CSP1**) has been described previously. These compounds were covalently linked to silica gel to produce three chiral stationary phases (**CSPs 2–4**), whose enantiodiscriminating capability towards the HPLC resolution of selected racemic compounds was assessed. The obtained results allowed us to establish the influence of the stereochemistry and/or the chemical structure of each chiral moiety of the biselector system on their enantiorecognition properties.

1. Introduction

Selective molecular interactions are the essence of vital biochemical processes, such as molecular transport, genetic information processing and protein assembly. An elucidation of the phenomena which govern these interactions is important not only for the understanding of these processes but also for their manipulation. Studies in molecular recognition have given chemists the tools needed to design, build and evaluate enantioselective molecular systems to be used for synthetic, separative and analytical purposes. In this field, a great deal of attention has been devoted to chiral stationary phases (CSPs), which allow the direct liquid chromatographic separation of enantiomers. Since this has been recognized as one of the most powerful means for the determination of the enantiomeric composition of chiral compounds, the preparation of a CSP having high efficiency and versatility has became more and more important.[1] This problem has been approached in a rational fashion in the case of independent CSPs,[2] whose chiral recognition mechanism is fairly well understood,[2] mainly due to the work of Pirkle and co-workers,[3] who prepared some independent CSPs, showing good effectiveness in the resolution of a wide range of racemic compounds.[4] Recently, we faced this problem directing our attention towards the preparation of a novel chiral auxiliary, obtained by linking two different selectors [(*S*)-NEA and (*S*)-Leu] to one another, that, once attached to silica gel through the *s*-triazine moiety, afforded a so-called biselector CSP.[5] Because of the complementarity of the two selectors in the enantiodiscrimination of different chiral compounds, **CSP1** (Fig. 1) had wider applicability than the two monoselector CSPs. Indeed, **CSP1** did work as a biselector CSP[5] since it was able to separate the enantiomers of racemic compounds resolved by Pirkle's (*S*)-Leu CSP[6]—reproduced in the derivatized amino acid moiety of **CSP1**—(Fig. 1) as well as those enantiodiscriminated by Oi's CSP[7]—reproduced in the *s*-triazine-(*S*)-1-(1-naphthyl)ethylamine moiety—(Fig. 1). In addition, it was able to resolve racemic compounds which are not enantiodiscriminated by either of the CSPs presented by Pirkle and Oi.[5]

Prompted by these results, we decided to evaluate whether the two portions of the biselector system are independent, or if changing of the stereochemistry and/or chemical structure of one chiral moiety influences the enantiodiscriminating capability of the other. This

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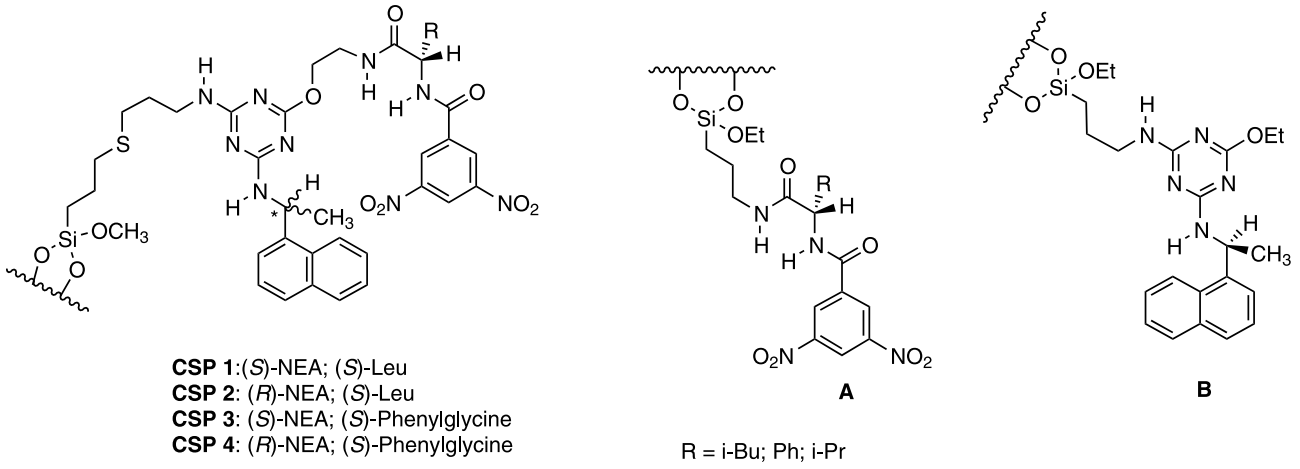


Figure 1. Structure of CSPs **1**–**4**, Pirkle CSPs (A) and Oi's CSP (B).

could afford some useful insights for the design of 'broad spectrum' selectors capable of discriminating the enantiomers of several structurally different compounds, and could also give further information about the mechanisms governing enantiorecognition. To this end, we synthesized the three CSPs reported in Fig. 1: **CSP2** was obtained starting from (*R*)-NEA and (*S*)-Leu, i.e. its selector is in a diastereoisomeric relationship to that of **CSP1**, whereas **CSP3** and **CSP4** derive from (*S*)-NEA and (*S*)-phenylglycine and (*R*)-NEA and (*S*)-phenylglycine, respectively, i.e. they constitute pairs of diastereoisomeric CSPs.

The aim of the present work is to compare the enantiodiscriminating capability of the four CSPs in the HPLC resolution of selected racemic compounds, in order to determine the influence of both the chemical structure and the stereochemistry of the two chiral components of the biselector system on the enantiorecognition properties of the phase.

2. Results and discussion

2.1. Synthesis of the CSPs

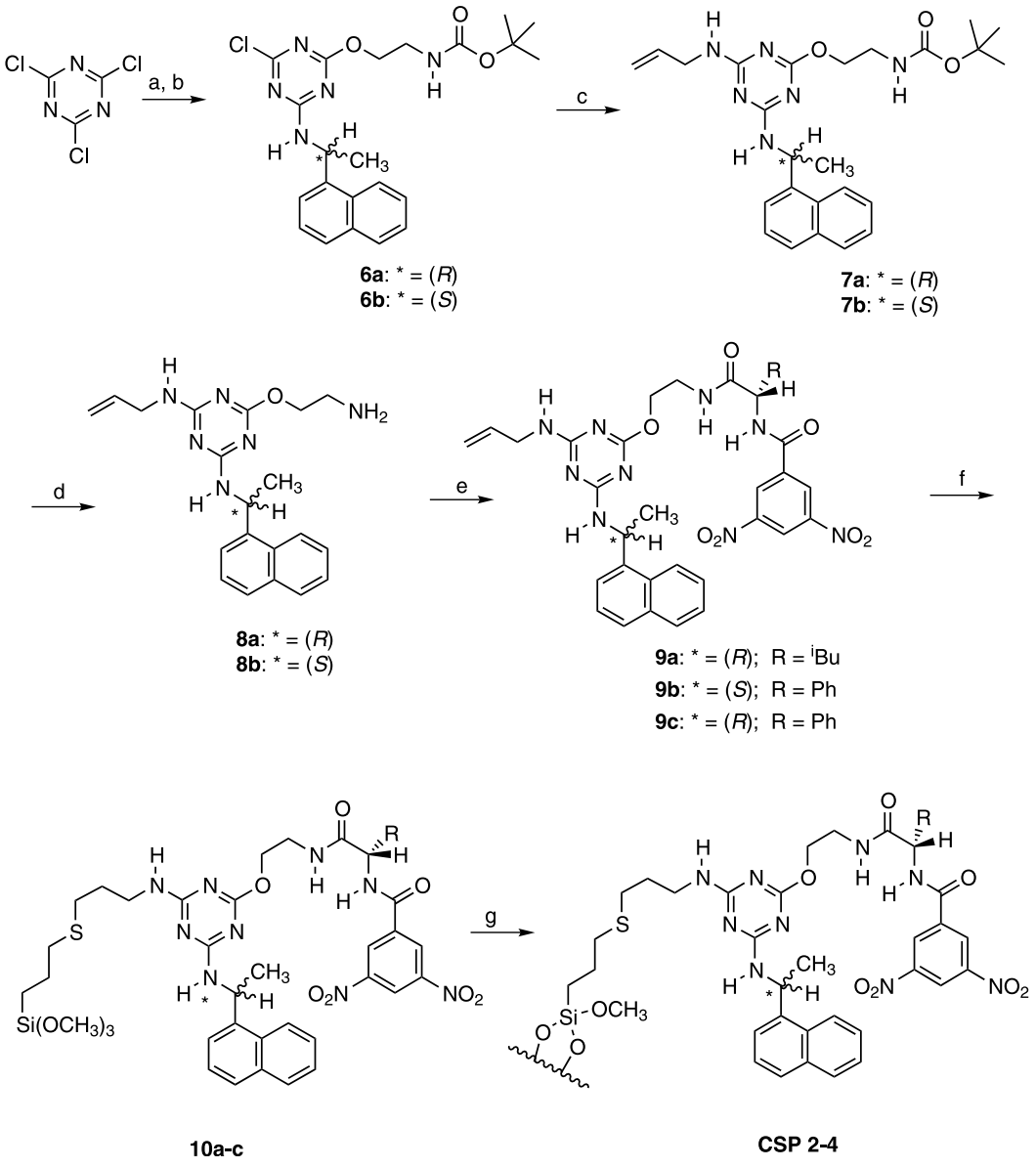
CSPs **2**–**4** were synthesized according to the method used for preparing **CSP1**:[5] Scheme 1 shows the general synthetic route to the three CSPs. The three chlorine atoms of *s*-trichlorotriazine were displaced in succession by *N*-*tert*-butoxycarbonyl ethanolamine, optically active 1-(1-naphthyl)ethylamine and allylamine, affording the trisubstituted *s*-triazine scaffold **7**. The first two nucleophilic displacements were carried out in the same reaction vessel,[8] adding the second nucleophile, 1-(1-naphthyl)ethylamine, when complete conversion of *s*-triclorotriazine had occurred. The disubstituted derivative **6**, isolated and purified by column chromatography, was then treated with an excess of allylamine, affording chemically pure **7** in nearly quantitative yield. After removal of the BOC protecting group, the free amine was reacted with the 3,5-dinitrobenzoyl amino acid in the presence of EEDQ:[9] the chiral auxiliaries **9a**–**c** were obtained in 35–38% yield after chromatographic purification.

The three selectors were covalently linked to silica gel by means of the terminal double bond.[10] They were treated with a five-fold excess of 3-mercaptopropyltrimethoxysilane, in the presence of a catalytic amount of AIBN in refluxing $CHCl_3$, affording the corresponding chemically pure silanes in quantitative yield. The derivatized silica materials were obtained by reacting the silanes **10a**–**c** with silica gel in refluxing of toluene and were slurry packed in stainless steel columns using conventional techniques. The loading of the organic material on silica gel, determined by elemental analysis, ranges from 0.23 to 0.29 mmol/g for the three different CSPs and is comparable to that found for **CSP1**.

2.2. Comparison of the enantiodiscriminating capability of CSPs 1–4 in the separation of enantiomers

The racemic compounds resolved by **CSP1** (Chart 1) were used to compare the enantiodiscrimination properties of **CSPs 1**–**4**. Table 1 reports on the chromatographic resolution of π-acceptor racemates **11**–**14**. Their enantiodiscrimination on **CSP1** has been attributed to the presence, in the structure of the biselector system, of the π-donor 1-(1-naphthyl)ethylamino-*s*-triazine moiety,[5] which reproduces the structure of Oi's CSP.[7] The same moiety is present on CSPs **2**–**4**, therefore the comparison of the data concerning the resolution of this class of racemates, allows us to obtain some information about the influence of the chemical structure and the stereochemistry of the amino acid moiety on the chiral recognition exhibited by the 1-(1-naphthyl)ethylamine-*s*-triazine fragment.

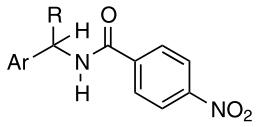
As previously reported,[5] **CSP1** is able to resolve all the π-acceptor racemic compounds **11**–**14** (Table 1): it was found to be more versatile towards this class of racemates than Oi's CSP, which showed enantiodiscrimination for only the 3,5-dinitrophenyl derivatives of



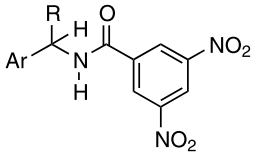
Scheme 1. *Reagents and conditions*: (a) *N*-BOCethanolamine, DIPEA, CH_3CN, 60°C; (b) 1-(1-naphthyl)ethylamine, DIPEA, 25°C; (c) allylamine (4 equiv.), CH_3CN, 50°C; (d) TFA, CH_2Cl_2, 25°C; (e) (*S*)-3,5-dinitrobenzoyl amino acid, EEDQ, THF, 25°C; (f) 3-mercaptopropyltrimethoxysilane (5 equiv.), AIBN, $CHCl_3$, reflux; (g) silica gel, toluene, reflux.

1-arylpropionic acids and (alkylaryl)methylamines.[7] **CSP2**, which differs from **CSP1** in the absolute configuration at the stereogenic center of 1-(1-naphthyl)ethylamine, behaves in a rather different way. In fact, **CSP2** is able to resolve only the 3,5-DNB derivatives of (alkylaryl)methylamines **12** and the 3,5-dinitroanilide of ibuprofen **13** (entries 3–5). In contrast, no separation is observed for the enantiomers of the 3,5-dinitrobenzoyl derivatives of amino acid alkyl esters **14** (entries 6–16) and 4-nitrobenzamides **11** (entries 1 and 2); only a very poor resolution is obtained for the phenylalanine derivative **14i** (entry 14). These results demonstrate that the stereochemical relationship between the two chiral moieties of the biselector system deeply influences the enantiodiscrimination properties of the 1-(1-naphthyl)ethylamino-*s*-triazine fragment towards π-acceptor racemic compounds: the (*S*)-amine/(*S*)-amino acid, which is the chiral selector in **CSP1**, behaves as a matched pair[11] of this chiral auxiliary, whereas the diastereoisomeric (*R*)-amine/(*S*)-amino acid system, from which **CSP2** has been obtained, ehave as a mismatched pair.[11]

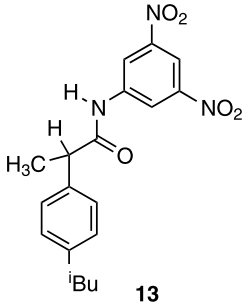
The influence of the chemical structure of the derivatized amino acid moiety on the enantiodiscriminating capability of the 1-(1-naphthyl)ethylamine-*s*-triazine fragment can be assessed by comparing the chromatographic data obtained with **CSP3**, derived from (*S*)-NEA and (*S*)-phenylglycine, with the results from the separations on **CSP1**, derived from (*S*)-NEA and (*S*)-Leu. The retention times of the analytes are higher on **CSP3** than on **CSP1** in all the examined cases: this is not surprising if one takes into account that the amino acid portion of **CSP3** possesses a phenyl group that can



11a: R = CH_3, Ar = Ph
11b: R = ^{i}Pr, Ar = 1-naphthyl



12a: R = CH_3, Ar = Ph
12b: R = CH_3, Ar = 1-naphthyl



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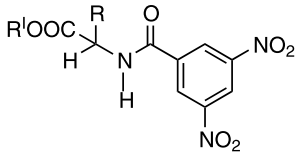
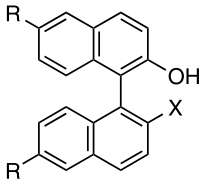
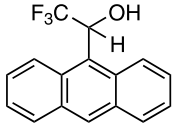


14a: R = CH_3, R^{I} = CH_3
14b: R = ^{i}Bu, R^{I} = CH_3
14c: R = ^{t}Bu, R^{I} = CH_3
14d: R = ^{s}Bu, R^{I} = CH_3
14e: R = ^{i}Pr, R^{I} = CH_3
14f: R = ^{i}Pr, R^{I} = ^{i}Pr
14g: R = ^{i}Pr, R^{I} = ^{s}Bu
14h: R = ^{i}Pr, R^{i} = n-$C_{12}H_{25}$
14i: R = Bz, R^{I} = CH_3
14l: R = Bz, R^{I} = ^{i}Bu
14m: R = Bz, R^{I} = n-Bu



15a: R = H, X = OH
15b: R = Br, X = OH
15c: R = H, X = O-allyl
15d: R = H, X = NH_2



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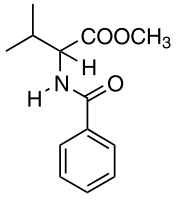

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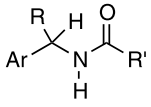

17a: R = CH_3, R^{I} = Ph, Ar = 1-naph
17b: R = CH_3, R^{I} = 2-naph, Ar =1-naph
17c: R = CH_3, R^{I} = Ph, Ar = Ph
17d: R = cyclohex, R^{I} = CH_3, Ar = 1-naph
17e: R = cyclohex, R^{I} = ^{i}Bu, Ar = 1-naph
17f: R = cyclohex, R^{I} = ^{t}Bu, Ar = 1-naph

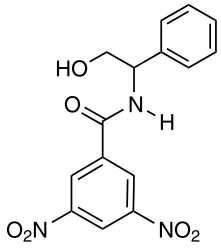

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Chart 1.

engender attractive interactions with the π-acceptor racemic compounds.[2] As far as the enantioseparations are concerned, **CSP3** resolves the *N*-3,5-dinitrobenzoyl derivatives of (alkylaryl)methylamines **12** and the 3,5-dinitroanilide of ibuprofen **13** (entries 3–5), although to a reduced extent with respect to **CSP1**; in addition, few amino acid derivatives and only one of the two 4-nitrobenzamides are resolved on **CSP3** with lower enantioselectivity factors than those found for the same compounds on **CSP1**. It also noteworthy that the amino acid derivatives **14f–h** and **14m** are enantiodiscriminated only if the alkyl ester group is more complex than methyl (entries 11–13 and 16). Comparison of these chromatographic data suggests that the enantiodiscriminating behavior of the 1-(1-naphthyl)ethylamino-*s*-triazine fragment depends on the chemical structure of the amino acid moiety, as well as its stereochemistry: in fact the resolving power of the biselector system towards π-acid racemates, which is good when the amino acid moiety is leucine (**CSP1**), decreases when the amino acid partner is phenylglycine.

Changing the configuration at the stereogenic center of the amino acid affects the enantiodiscriminating properties of the 1-(1-naphthyl)ethylamine-*s*-triazine also in the case of the chiral auxiliaries containing the derivatized phenylglycine. **CSP4**, prepared starting from the diastereoisomer (*R*)-NEA/(*S*)-phenylglycine, shows slightly better performances in the chromatographic resolution of amino acid derivatives than **CSP3**. The

Table 1. Chromatographic resolution[a] of π-acidic racemic compounds on **CSPs 1–4**

		CSP 1		CSP 2		CSP 3		CSP 4	
Entry	Compound	$k^{I,b}$	α^c (e.o.)[d]	$k^{I,b}$	α^c(e.o.)[d]	$k^{I,b}$	α^c (e.o.)[d]	$k^{I,b}$	α^c (e.o.)[d]
1	**11a**	2.02	1.10 (−)	4.03	1.00	3.73	1.00 (+)	3.06	1.00
2	**11b**	3.01	1.38 (−)	4.27	1.00	3.89	1.09 (+)	4.35	1.00
3	**12a**	4.42	1.28 (−)	5.60	1.14 (+)	5.39	1.13 (−)	5.85	1.09 (+)
4	**12b**	3.40	1.51 (−)	3.31	1.50 (+)	4.97	1.11 (−)	3.80	1.30 (+)
5	**13**	2.00	1.49 (+)	2.63	1.35 (−)	2.68	1.34 (+)	2.66	1.35 (−)
6	**14a**	10.07	1.10	13.45	1.00	10.13	1.00	12.50	1.00
7	**14b**	3.64	1.30	3.70	1.00	4.73	1.00	4.68	1.10
8	**14c**	1.93	1.19	1.86	1.00	2.12	1.00	2.52	1.00
9	**14d**	2.57	1.30	2.56	1.00	2.96	1.00	3.64	1.00
10	**14e**	3.06	1.27	3.32	1.00	3.50	1.00	4.30	1.00
11	**14f**	1.77	1.44	1.67	1.00	1.88	1.19	2.33	1.15
12	**14g**	1.44	1.39 (−)	1.59	1.00	1.94	1.13 (−)	2.36	1.12 (+)
13	**14h**	2.13	1.64	1.10	1.00	1.39	1.13	1.70	1.13
14	**14i**	4.22	1.27	4.12	1.05	5.29	1.00	6.11	1.18
15	**14l**	10.78	1.26	4.34	1.00	5.25	1.00	6.23	1.10
16	**14m**	5.05	1.50	1.88	1.01	2.79	1.14	3.45	1.18

[a] Chromatographic conditions: UV detection ($\lambda = 254$ nm), $T = 25$°C, flow 1 ml/min, eluent: hexane–dichloromethane–propan-2-ol, 70:30:1.
[b] Retention factor of the first eluted enantiomer.
[c] Enantioselectivity factor.
[d] Sign of the circular dichroism at 254 nm of the first eluted enantiomer.

3,5-dinitrobenzoyl derivative of phenylalanine is resolved even as methyl ester, **14i**, and *iso*-butyl ester, **14l**, (entries 14 and 15) and separation of the enantiomers of the leucine derivative **14b** is also observed (entry 7).

As far as enantiodiscrimination of the amide derivatives is concerned, it is difficult to establish a general trend. In fact, the enantiomers of the 4-nitrobenzamide **11b** resolved by **CSP3** (entry 2) are not separated by **CSP4**, whereas only one of the two 3,5-dinitrobenzamides (**12b**, entry 4) shows a higher enantioselectivity factor on **CSP4**.

The data reported in Table 1 demonstrate that both the nature and stereochemistry of the amino acid derivative influence the enantiorecognition properties of the 1-(1-naphthyl)ethylamino-*s*-triazine moiety in the biselector systems of CSPs **1–4**. Furthermore, the enantiodiscriminating capability of the 1-(1-naphthyl)ethylamino-*s*-triazine moiety is affected by the stereochemistry of the amino acid fragment to a greater extent when it is leucine, than in the case of phenylglycine.

In order to establish whether the enantioseparation properties of the derivatized amino acid moiety are influenced by the stereochemistry of the 1-(1-naphthyl)ethylamine-*s*-triazine unit, some π-basic compounds, such as the binaphthyl derivatives **15**, 2,2,2-trifluoro-1-(9-anthryl)ethanol **16** and the amides **17** (Chart 1), i.e. compounds belonging to classes of racemates resolved by Pirkle's CSPs **A**,[6] were analyzed on CSPs **1–4**.

The data from the chromatographic resolutions of binaphthyl derivatives and 2,2,2-trifluoro-1-(9-anthryl)ethanol are listed in Table 2. **CSP1**, as previously reported,[5] shows good enantiodiscriminating capability towards these racemates[5] and the α values show the same trend observed with the leucine-based

Table 2. Chromatographic resolution[a] of binaphthylic derivatives and alcohol **16** on **CSPs 1–4**

		CSP 1		CSP 2		CSP 3		CSP 4	
Entry	Compound	$k^{I,b}$	α^c (e.o.)[d]	$k^{I,b}$	α^c (e.o.)[d]	$k^{I,b}$	α^c (e.o.)[d]	$k^{I,b}$	α^c
1	**15a**	2.91	1.22 (−)/*R*	5.76	1.09 (+)/*S*	3.23	1.20 (−)/*R*	3.55	1.00
2	**15b**	7.87	1.36 (−)/*R*	6.43	1.12 (+)/*S*	8.10	1.28 (−)/*R*	10.45	1.00
3	**15c**	2.87	1.20 (−)/*R*	2.19	1.03 (+)/*S*	3.11	1.18 (−)/*R*	3.45	1.00
4	**15d**	1.64	1.16 (−)/*R*	4.84	1.03 (+)/*S*	2.08	1.13 (−)/*R*	2.31	1.00
5	**16**[e]	4.78	1.19	4.52	1.00	6.15	1.35	6.92	1.16

[a] Chromatographic conditions: UV detection ($\lambda = 254$ nm), $T = 25$°C, flow 1 ml/min, eluent: hexane–dichloromethane–propan-2-ol, 70:30:1.
[b] Retention factor of the first eluted enantiomer.
[c] Enantioselectivity factor.
[d] Sign of the circular dichroism at 240 nm/absolute configuration of the first eluted enantiomer.
[e] Eluent: hexane–dichloromethane–propan-2-ol, 75:20:5.

Pirkle CSP.[6d] When the same compounds were analyzed on **CSP2**, the enantioseparations were poorer in all cases examined. In fact, although the enantiomers of the binaphthyl derivatives are still separated on **CSP2**, their α values are lower, whereas the carbinol **16** is not resolved at all (entry 5).

The chromatographic separations on **CSP3** (Table 2) show that this phase retains compounds more than **CSP1**, with binaphthyl derivatives or the alkylarylcarbinol. This behavior can be attributed to the change in the amino acid structure: in this case the presence of a phenyl instead of an *iso*-butyl group can engender attractive π–π interactions[4] with this class of racemates, which result in higher k' values. The enantioselectivities are good and comparable to those obtained with **CSP1**. Only **16** exhibits a higher α value: this is not surprising if we take into account that the leucine-based Pirkle CSP shows lower enantioselectivity towards alkylaryl carbinols than the analogous CSP containing phenylglycine. The different behavior of **CSP1** and **CSP3** towards this compound, therefore, is in keeping with that observed for the two different Pirkle's CSPs.[6e] By comparing the data obtained using **CSP3** with those found upon the diastereoisomeric **CSP4** (Table 2) one can observe that not only compounds **15a–d** and **16** are more retained than upon **CSP3**, but also more significant differences are present as far as the enantioselectivities are concerned: in fact, **CSP4** does not resolve any binaphthyl derivative, whereas the enantiomers of **16** are separated with a lower α value. The results obtained with these racemates demonstrate that the stereochemistry of the 1-(1-naphthyl)ethylamino-*s*-triazine moiety influences the enantioresolution capability of the derivatized amino acid fragment in the biselector system. The matched pair[11] towards the resolution of binaphthyl derivatives and carbinol **16** is (*S*)-amine/(*S*)-amino acid, whereas (*R*)-amine/(*S*)-amino acid represents the mismatched couple,[11] independently of the chemical nature of the amino acid. Furthermore, the change in stereochemistry of the 1-(1-naphthyl)ethylamino-*s*-triazine moiety has a greater influence on the enantioselectivity of the biselector system when the amino acid is phenylglycine: in fact **CSP2** is still able to resolve binaphthyl derivatives whereas **CSP4** does not.

Data concerning the resolution of the last class of racemates, i.e. π-basic amides **17** and **18**, are listed in Table 3. **CSP1** is able to resolve all the compounds, showing α values that depend on the nature of the amide. On the contrary, its diastereoisomeric phase, **CSP2**, is unable to resolve any of the π-basic amides of Table 3, although the k' values, higher than those found upon **CSP1**, suggest that the racemates-selector interaction is not negligible on **CSP2**. Even **CSP3** is able to separate the enantiomers of π-basic amides (Table 3), although to a lesser extent than **CSP1** (the sole exception is compound **17d** that shows a higher α value); furthermore, two amides are not resolved. The trend observed going from **CSP1** to **CSP2** is confirmed also with the diastereoisomeric couple **CSP3**/**CSP4**. In fact, **CSP4** resolves only three compounds, **17a–b** and **17d** (entries 1, 2 and 4) with lower enantioselectivity factors than those observed on **CSP3**. Therefore, even towards this class of racemates the change in stereochemistry of the 1-(1-naphthyl)ethylamine-*s*-triazine moiety influences the enantiodiscriminating capability of the 3,5-dinitrobenzoyl amino acid fragment in the same sense either when the amino acid is leucine or phenylglycine. In fact, the matched pair[11] towards the resolution of π-basic amides for both the biselector systems is the (*S*)-amine/(*S*)-amino acid, whereas the (*R*)-amine/(*S*)-amino acid represents the mismatched pair.[11]

The analysis of compound **19** (Table 3) on CSPs **1–4** is rather interesting. This compound shows the features of a carbinol, resolved by the *N*-3,5-dinitrobenzoyl amino acid based CSPs,[6e] and those of a 3,5-dinitrobenzamide, a compound related to a class of racemates discriminated by the Oi's CSP.[7] This substrate is well resolved on CSPs **1** and **3** whereas poor or no separation is observed on CSPs **2** and **4**. This result confirms that (*S*)-amine/(*S*)-amino acid is the matched pair: in fact, the synergistic action of the two moieties helps the

Table 3. Chromatographic resolution[a] of π-basic amides and **19** on **CSPs 1–4**

		CSP 1		**CSP 2**		**CSP 3**		**CSP 4**	
Entry	Compound	$k^{I,b}$	α^c (e.o.)[d]	$k^{I,b}$	α^c (e.o.)[d]	$k^{I,b}$	α^c (e.o.)[d]	$k^{I,b}$	α^c (e.o.)[d]
1	**17a**	6.14	1.27 (−)	7.89	1.00	6.64	1.17 (+)	7.59	1.07 (+)
2	**17b**	7.54	1.26 (−)	9.64	1.00	9.73	1.19 (+)	10.46	1.07 (+)
3	**17c**	4.86	1.07 (+)	6.05	1.00	2.03	1.04 (−)	4.95	1.00
4	**17d**[e]	2.06	1.15 (−)	3.65	1.00	2.23	1.31 (−)	2.51	1.09 (−)
5	**17e**	1.86	1.40	2.63	1.00	1.93	1.00	2.19	1.00
6	**17f**	1.95	1.37	2.67	1.00	1.91	1.00	2.17	1.00
7	**18**	2.50	1.21 (−)	3.26	1.00	2.49	1.11 (−)	2.86	1.00
9	**19**[e]	7.96	1.41 (−)	7.11	1.10 (+)	7.75	1.44 (−)	7.04	1.00

[a] Chromatographic conditions: UV detection (λ = 254 nm), T = 25°C, flow 1 ml/min, eluent: hexane–dichloromethane–propan-2-ol, 90:10:1.
[b] Retention factor of the first eluted enantiomer.
[c] Enantioselectivity factor.
[d] Sign of the circular dichroism at 254 nm (230 nm for the naphthalene containing compounds) of the first eluted enantiomer.
[e] Eluent: hexane–dichloromethane–propan-2-ol, 75:20:5.

resolution of **19** affording a higher α value than that obtained when the two moieties of the biselector system are mismatched.

2.3. Analysis of the elution orders on CSPs 1–4

The comparison of the chromatographic data obtained on CSPs **1**–**4** has shown that the behavior of these CSPs depends on the relative stereochemistry of the two chiral moieties of the biselector system as well as on the chemical structure of the amino acidic fragment. This should be attributable to some differences in the enantiorecognition mechanism exhibited by these CSPs. In order to gain some insights about this point we have determined the elution order of the racemic compounds resolved upon the four biselector CSPs. In fact, if a class of racemates exhibits the same elution order on different CSPs whose chiral moiety responsible of its enantiodiscrimination has the same stereochemistry (for example compounds listed in Table 1 upon CSPs **1** and **3**), we can reasonably conclude that these CSPs exhibit a similar enantiorecognition mechanism towards the racemic compounds. In other words, this means that the two chiral moieties of the biselector system are not influenced by each other so much that the enantiorecognition mechanism changes.

The elution orders were determined by means of a CD detector:[12] in order to make a comparison, only the data concerning compounds which are resolved upon all (or the majority) of the CSPs have been reported. The measurements were performed at 254 nm in the case of π-acidic compounds and the results are listed in Table 1. **CSP1** and **CSP2**, which have opposite absolute configuration at the stereogenic center of the 1-(1-naphthyl)ethylamino-*s*-triazine moiety, show opposite elution orders for the racemic compounds resolved by both phases (entries 3, 4 and 6). Since the chromatographic resolution of these compounds is attributable to this moiety, the change in the elution order is only due to the different stereochemistry of this fragment in **CSP1** and **CSP2** and, therefore, the stereochemistry of the derivatized amino acid group does not influence the enantiodiscrimination mechanism exhibited by the 1-(1-naphthyl)ethylamino-*s*-triazine moiety. The same consideration can be made for CSPs **3** and **4** that are still epimeric at the stereogenic center of the 1-(1-naphthyl)ethylamino-*s*-triazine fragment: the racemates that are resolved by both the phases show opposite elution orders (entries 3–5 and 12). However, the elution order of the two 4-nitrobenzamides upon **CSP1** and **CSP3**, (which differ in the nature of the amino acid moiety; leucine for **CSP1** and phenylglycine for **CSP3** but have the same absolute configuration at the two stereogenic centers) is opposite (entries 1–2): this suggests that the two phases show a different enantiodiscrimination mechanism for the two compounds. Therefore, we should say that the nature of the amino acid group influences the enantiorecognition mechanism exhibited by the 1-(1-naphthyl)ethylamino-*s*-triazine moiety at least as far as the resolution of the 4-nitrobenzamides is concerned.

The elution order of the binaphthyl derivatives is shown in Table 2: the measurements were performed at 240 nm, a wavelength corresponding to the low-energy component of the exciton couplet present in the CD spectra of these derivatives. On the basis of the CD sign,[13] by using the ECCD method,[14] it is possible to determine the absolute configuration of the eluted enantiomers. Since the elution order of these derivatives on the Pirkle's phases is known[6d] it is possible to compare it with those obtained upon CSPs **1**–**4**, which allows us to verify if the enantiorecognition mechanism of the derivatized amino acid moiety inserted in the biselector system of the CSPs **1**–**4** is the same as in the Pirkle's CSPs or not. All the CSPs possess a (*S*)-configured amino acid moiety. The elution order observed on CSPs **1** and **3** (Table 2), constituted by the (*S*,*S*)-couple, is the same as the (*S*)-configured Pirkle CSPs,[6d] whereas it is opposite on **CSP2** (Table 2), whose absolute configuration at the stereogenic center of the 1-(1-naphthyl)ethylamino-*s*-triazine moiety is (*R*). This result suggests that changing the stereochemistry of the 1-(1-naphthyl)ethylamino-*s*-triazine moiety dramatically affects the enantiorecognition properties of the derivatized amino acidic fragment: when the amino acid is phenylglycine the couple (*S*)-amino acid/(*R*)-amine is unable to separate the enantiomers of the binaphthyl derivatives (Table 2), in the case of leucine a change in the elution order (Fig. 2) together with lower enantioselectivity with respect to the (*S*)-amino acid/(*S*)-amine couple (Table 2) is observed. This indicates that the (*S*)-3,5-dinitrobenzoylleucine moiety coupled to (*R*)-1-(1-naphthyl)ethylamine in the biselector system resolves the binaphthyl derivatives by means of a different enantiorecognition mechanism with respect to that operating in the case of the Pirkle's CSP, whose chiral selector has the same absolute configuration.

The influence of the stereochemistry of the 1-(1-naphthyl)ethylamino moiety on the enantiorecognition mechanism involved in the resolution of π-basic amides can be analyzed only in the case of the phenylglycine-containing systems **CSP3** and **CSP4**, which are both able to separate the enantiomers of three compounds (Table 3, entries 1, 2 and 4). The elution order of **17a**, **17b** and **17d** remains unchanged from **CSP3** to **CSP4**, suggesting that the enantiorecognition mechanism of the derivatized amino acid moiety is not affected to a great extent by the change in the stereochemistry of 1-(1-naphthyl)ethylamine residue. However, it is interesting to note that, although the absolute configuration of the two chiral moieties of the biselector system is the same, the elution order of **17a** and **17b** (Table 3) on **CSP1** is opposite to that observed on **CSP3**. This suggests that some change in the enantiodiscrimination mechanism, passing from **CSP1** to **CSP3**, must take place. Furthermore, the elution order for these compounds on a commercial covalent (*S*)-DNBPG phase is the same as that observed on **CSP1** and it depends only on the stereochemistry of the amino acid[2] in the case of this kind of CSPs (it is the same for leucine, phenylglycine and valine based CSPs). Therefore, we can conclude that the enantiorecognition mechanism exhib-

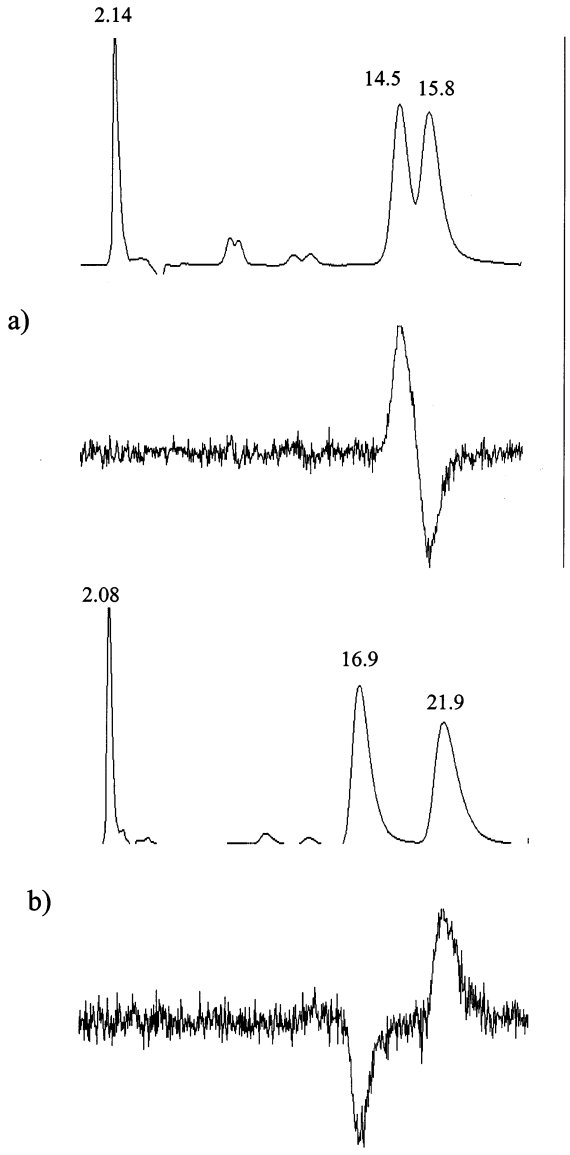

Figure 2. UV (upper traces) and CD (lower traces) chromatographic detection concerning the separation of 6,6′-dibromo-2,2′-dihydroxy-1,1′-binaphthyl **15b** on **CSP2** (a) and **CSP1** (b).

ited by the derivatized amino acid moiety of the biselector system towards these compounds is influenced by the presence of the other chiral fragment when the amino acid is phenylglycine so much that their elution order is opposite to that found on the Pirkle's CSP. Also when the amino acid residue is leucine, we observe different behavior depending on the stereochemistry of the other moiety. In fact **CSP2** is unable to resolve these compounds at all.

The elution order of **19** changes depending on the absolute configuration at the stereogenic center of the 1-(naphthyl)ethylamine-*s*-triazine moiety (Table 3): this suggests that although both moieties are involved in the enantiodiscrimination of this compound, as previously discussed, the 1-(1-naphthyl)ethylamine-*s*-triazine fragment dominates in the enantiorecognition process.

3. Conclusions

A comparison of the chromatographic data obtained using CSPs **1–4** in the HPLC resolution of selected racemic compounds has allowed us to gain some insights about the enantiorecognition properties of this family of biselector systems.

In fact, both the stereochemistry and the chemical structure of the derivatized amino acid fragment influence the enantiodiscrimination properties of the 1-(1-naphthyl)ethylamino-*s*-triazine moiety: the best results in terms of efficiency and versatility towards π-acidic racemic compounds are obtained with **CSP1**.

The enantioresolution capability of the derivatized amino acid moiety is dramatically influenced by the stereochemistry of the 1-(1-naphthyl)ethylamino-*s*-triazine fragment: either in the case of the leucine-containing systems (**CSP1** and **CSP2**) or with the phenylglycine-bearing selectors (**CSP3** and **CSP4**), the matched couple is the (*S*,*S*)-system. The most interesting result is the change in the elution order of binaphthyl derivatives going from one CSP to another bearing diastereoisomeric selectors (Fig. 2). Since the two selectors are diastereoisomeric by virtue of the opposite absolute configuration at the stereogenic center of the 1-(1-naphthyl)ethylamino moiety, the elution order of the above mentioned class of racemates, whose resolution is attributable to the derivatized amino acid fragment, must remain the same. The change in the elution orders observed with this family of CSPs for the binaphthyl derivatives suggests that a difference in the enantiorecognition mechanism should be present passing from a biselector system to its diastereoisomer. Taking into account that the enantiodiscrimination model proposed by Pirkle for the 3,5-dinitrobenzoyl amino acid based CSPs depends on the preferred conformation assumed by the selector,[6] the different enantiorecognition mechanism operating in the case of the diastereoisomeric CSPs, should be attributed to a change of conformation that the amino acid moiety undergoes in the biselector system, depending on the absolute configuration at the stereogenic center of the 1-(1-naphthyl)ethylamine-*s*-triazine fragment. This last point, although requiring further examination, is quite interesting because it suggests that the conformation and, consequently, the enantiorecognition properties of chiral moieties that are components of structurally complex molecules such as these biselector systems, can be markedly affected by the 'remote chirality' present on the same molecule. This can give helpful insights for the development of 'broad spectrum' chiral auxiliaries. In fact, systems having wider applicability can be built up by linking two different and complementary selectors to one another, provided the two chiral units are 'well coupled' as far as both chemical nature and stereochemistry are concerned.[15]

4. Experimental

4.1. General

^{1}H and ^{13}C spectra were recorded in $CDCl_3$ on a 200 MHz NMR spectrometer, using TMS as an external standard. The following abbreviations are used: s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet, br s = broad signal. TLC analyses were performed on silica gel sheets; chromatographic separations were carried out on adequate dimension columns using silica gel 60 (70–230 mesh). HPLC analyses were performed using an intelligent HPLC pump equipped with an UV detector and a spectropolarimeter. Optical rotations were measured with a digital polarimeter. Melting points are uncorrected. The IR spectra were recorded on a Perkin–Elmer 1710 spectrophotometer. Elemental analyses were carried out at ICMAT-CNR, AREA della RICERCA di ROMA. Toluene and THF were refluxed over sodium benzophenone and distilled before use. Allylamine, diisopropylethylamine (DIPEA) and CH_3CN were distilled over CaH_2; (*S*)- and (*R*)-1-(1-naphthyl)ethylamine were distilled under reduced pressure. Unless otherwise specified the reagents were used without any purification.

Standard procedures were used for preparing racemic amides, the 3,5-dinitrobenzoyl derivatives of amino acids and the 3,5-dinitroanilide of ibuprofen.[5]

The preparation of **CSP1** has been previously described. 2-{[4-Allylamino-6-(*S*)-(1-(1-naphthyl)-ethylamino)-1,3,5-triazin-2-yl]oxy}ethylamine **8b** was prepared as described elsewhere[5] and matched the reported characteristics. Its enantiomer **8a** was obtained according to the same procedure.[5]

4.1.1. *tert*-Butyl-2-{[4-chloro-6-(*R*)-(1-(1-naphthyl)ethylamino)-1,3,5-triazin-2-yl]oxy}ethylcarbamate, 6a. Mp = 67–70°C; $[\alpha]_D^{22} = -34.2$ (*c* 0.9, CH_2Cl_2).

4.1.2. *tert*-Butyl-2-{[4-allylamino-6-(*R*)-(1-(1-naphthyl)-ethylamino)-1,3,5-triazin-2-yl]oxy}ethylcarbamate, 7a. Mp = 71–74°C; $[\alpha]_D^{22} = -51.9$ (*c* 0.865, CH_2Cl_2).

4.1.3. 2-{[4-Allylamino-6-(*R*)-(1-(1-naphthyl)ethylamino)-1,3,5-triazin-2-yl]oxy}ethylamine, 8a. Mp = 60–63°C; $[\alpha]_D^{25} = -64$ (*c* 1, CH_2Cl_2).

4.2. General procedure for the preparation of compounds 9

To a solution of the 3,5-dinitrobenzoyl amino acid (2.74 mmol) in dry THF (60 ml), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) (0.678 g, 2.74 mmol) was added and the reaction mixture was stirred at room temperature. After 3 h, **8a** or **8b** (1 g, 2.74 mmol) was added and the reaction mixture was stirred for 15 h at room temperature. The solvent was evaporated under reduced pressure and the crude product dissolved in dichloromethane. The organic solution was washed sequentially with 10% hydrochloric acid, water, saturated $NaHCO_3$ solution and water, then dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (SiO_2, hexane:ethylacetate = 2:8).

4.2.1. 2[(*S*)-*N*-(3,5-Dinitrobenzoyl)amino-*iso*-butylacetyl] - 2 - {[4 - allylamino - 6 - (*R*) - (1 - (1 - naphthyl)ethylamino)-1,3,5-triazin-2-yl]oxy}ethylamine, 9a. Yield: 38%; mp = 120–124°C; $[\alpha]_D^{24} = -26$ (*c* 1, CH_2Cl_2); ^{1}H NMR (200 MHz, DMSO-d_6 100°C, δ/ppm): 0.92 (t, 6H, CH($\underline{CH_3}$)$_2$); 1.58 (d, 3H, C*CH_3); 1.69 (m, 3H, $CHCH_2$); 3.39 (dd, 2H, -C$\underline{H_2}$NH); 3.80 (br s, 2H, -CH_2OAr); 4.20 (t, 2H, allylic -CH_2); 4.60 (m, 1H, *CH-^{i}Bu); 5.00 (m, 2H, =CH_2); 5.78 (m, 1H, CH=); 5.92 (m, 1H, *CH-Naft); 7.00 (br s, 1H, NH allylic); 7.40–7.82 (m, 5H, aromatic protons superimposed to 1H, -N$\underline{H}$*CH-naph); 7.88–8.00 (d, 1H, aromatic superimposed to t, 1H, -CH_2N$\underline{H}$CO); 8.22 (d, 1H, aromatic); 8.96 (t, 1H, aromatic); 9.02 (d, 1H, *CHN$\underline{H}$CO); 9.09 (d, 2H, aromatics); ^{13}C NMR (50 MHz, DMSO-d_6, 100°C, δ/ppm): 21.2–21.3 (CH($\underline{CH_3}$)$_2$); 22.2 (-CH_3); 24.1 (CH$\underline{CH_2}$); 38.1 (*CH-naph); 40.2 ($\underline{CH}$(CH_3)$_2$); 42.1 ($\underline{CH_2}$CH=); 45.3 (CH_2NH); 52.3 (CO*$\underline{C}$HNH); 69.8 (CH_2OAr); 114.9, 116.0, 120.1, 122.2, 122.7, 124.8, 124.9, 125.3, 126.5, 127.2, 128.1, 135.2, 171.2; IR (KBr): 3408, 3292, 3090, 2976, 2931, 2875, 1729, 1660, 1628, 1583, 1543, 1427, 1343, 1258, 1237, 1187, 1152, 1105, 1076, 993, 918, 813, 780, 730. Anal. calcd for $C_{33}H_{37}N_9O_7$: C, 59.01; H, 5.55; N, 18.77. Found: C, 58.92; H, 5.53; N, 18.84%.

4.2.2. 2[(*S*)-*N*-(3,5-Dinitrobenzoyl)amino-phenylacetyl]-2-{[4-allylamino-6-(*S*)-(1-(1-naphthyl)ethylamino)-1,3,5-triazin-2-yl]oxy}ethylamine, 9b. Yield: 38%; mp = 92–97°C; $[\alpha]_D^{22} = +60$ (*c* 0.92, CH_2Cl_2); ^{1}H NMR (200 MHz, DMSO-d_6 100°C, δ/ppm): 1.59 (d, 3H, -CH_3); 3.40 (dd, 2H,-C$\underline{H_2}$NH); 3.80 (t, 2H, -CH_2OAr); 4.22 (t, 2H,-CH_2 allylic); 5.00 (m, 2H, =CH_2); 5.78 (m, 1H, CH= superimposed to 1H, *CH-Ph); 5.95 (m, 1H, *CH-naph); 6.80 (t, 1H, NH allylic); 7.20–7.90 (m, 11H, aromatics superimposed to 1H, N$\underline{H}$*CH-naph); 8.22 (d, 1H, aromatic superimposed to t, 1H, -CH_2N$\underline{H}$); 8.95 (t, 1H, aromatic); 9.10 (d, 2H, aromatics); 9.42 (d, 1H, *CHN$\underline{H}$CO); ^{13}C NMR (50 MHz, DMSO-d_6, 100°C, δ/ppm): 20.3 (-CH_3); 37.2 (*CH-naph); 41.0 ($\underline{CH_2}$CH=); 44.3 (CH_2NH); 56.3 (CO*$\underline{C}$HNH); 62.6 (CH_2OAr); 113.9,119.1, 121.2, 121.6, 123.7, 123.9, 124.3, 125.4, 126.1, 126.2, 126.4, 126.7, 127.0, 132.0, 134.2, 135.7, 136.4, 139.5, 146.7, 161.0, 164.7, 165.5, 168.0, 168.7. IR (KBr): 3408, 3292, 3090, 2976, 2931, 2875, 1729, 1660, 1628, 1583, 1543, 1427, 1343, 1258, 1237, 1187, 1152, 1105, 1076, 993, 918, 813, 780, 730. Anal. calcd for $C_{35}H_{33}N_9O_7$: C, 60.77; H, 4.81; N, 18.22. Found: C, 60.92; H, 4.83; N, 18.35%.

4.2.3. 2[(*S*)-*N*-(3,5-Dinitrobenzoyl)amino-phenylacetyl]-2-{[4-allylamino-6-(*R*)-(1-(1-naphthyl)ethylamino)-1,3,5-triazin-2-yl]oxy}ethylamine, 9c. Yield: 36%; mp = 123–127°C; $[\alpha]_D^{22} = -5.4$ (*c* 0.8, CH_2Cl_2) ^{1}H NMR (200 MHz, DMSO-d_6 100°C, δ/ppm): 1.59 (d, 3H, -CH_3); 3.40 (dd, 2H, -C$\underline{H_2}$NH); 3.80 (t, 2H, -CH_2OAr); 4.22 (t, 2H,-CH_2 allylic); 5.00 (m, 2H, =CH_2); 5.78 (m, 1H,

CH= superimposed to 1H, *CH-Ph); 5.95 (m, 1H, *CH-naph); 6.80 (t, 1H, NH allylic); 7.20–7.90 (m, 11H, aromatics superimposed to 1H, NH*CH-naph); 8.22 (d, 1H, aromatic superimposed to t, 1H, -CH_2NH); 8.95 (t, 1H, aromatic); 9.10 (d, 2H, aromatics); 9.42 (d, 1H, *CHNHCO); ^{13}C NMR (50 MHz, DMSO-d_6, 100°C, δ/ppm): 20.3 (-CH_3); 37.2 (*CH-naph); 41.0 (CH_2CH=); 44.3 (CH_2NH); 56.3 (CO*CNH); 62.6 (CH_2OAr); 113.9, 119.1, 121.2, 121.6, 123.7, 123.9, 124.3, 125.4, 126.1, 126.2, 126.4, 126.7, 127.0, 132.0, 134.2, 135.7, 136.4, 139.5, 146.7, 161.0, 164.7, 165.5, 168.0, 168.7; IR (KBr): 3408, 3292, 3090, 2976, 2931, 2875, 1729, 1660, 1628, 1583, 1543, 1427, 1343, 1258, 1237, 1187, 1152, 1105, 1076, 993, 918, 813, 780, 730. Anal. calcd for $C_{35}H_{33}N_9O_7$: C, 60.77; H, 4.81; N, 18.22. Found: C, 60,68; H, 4.82; N, 18.28%.

4.3. General procedure for preparation of compounds 10a–c

To a solution of **9** (0.9 mmol) in dry $CHCl_3$ (10 ml) freshly distilled 3-mercaptopropyl trimethoxysilane (0.85 ml, 4.5 mmol) and AIBN (0.033 g, 0.2 mmol) were added and the mixture was stirred under reflux for 48 h. The solvent was eliminated by evaporation under reduced pressure and the residual oil was dispersed in pentane affording a solid, which was filtered and washed with pentane (5×20 ml). The pure product **10** was obtained in quantitative yield.

4.3.1. Compound 10a. $[\alpha]_D^{22} = -27$ (c 1.08, CH_2Cl_2); ^{1}H NMR (200 MHz, DMSO-d_6 100°C, δ/ppm): 0.65 (m, 2H, $SiCH_2$); 0.92 (t, 6H, CH(CH_3)$_2$); 1.55–1.75 (m, 10H, C*CH_3, $CHCH_2$, $SiCH_2CH_2$, CH_2CH_2NHAr); 2.50 (m, 4H, CH_2SCH_2); 3.20–3.50 (m, 11H, -CH_2NH, CH_3OSi); 3.80 (m, 2H, -CH_2OAr); 4.20 (m, 2H,-CH_2NHAr); 4.60 (m, 1H, *CH-^{t}Bu); 5.95 (m, 1H, *CH-Naft); 6.80 (s sl, 1H, CH_2NHAr); 7.40–8.20 (m, 7H, aromatics superimposed to 1H, -NH*CH-naph and to 1H, CH_2NHCO); 8.96 (t, 1H, aromatic); 9.03 (d, 1H, *CHNHCO); 9.11 (d, 2H, aromatics). Anal. calcd for $C_{39}H_{53}N_9O_{10}SSi$: C, 53.96; H, 6.15; N, 14.52; S 3.69. Found: C, 54.01; H, 6.14; N, 14.49; S, 3.68%.

4.3.2. Compound 10b. $[\alpha]_D^{22} = +62$ (c 0.9, CH_2Cl_2); ^{1}H NMR (200 MHz, DMSO-d_6 100°C, δ/ppm): 0.68 (m, 2H, $SiCH_2$); 1.55–1.75 (m, 7H, C*CH_3, $SiCH_2CH_2$, CH_2CH_2NHAr); 2.50 (m, 4H, CH_2SCH_2); 3.20 (m, 2H, -CH_2NH); 3.35–3.80 (m, 11H, -CH_2OAr, CH_3OSi); 4.20 (t, 2H, -CH_2NHAr); 5.72 (d, 1H, *CH-Ph); 5.92 (m, 1H, *CH-Naft); 6.70 (t, 1H, CH_2NHAr); 7.22–8.26 (m, 12H, aromatics superimposed to 1H-NH*CH-naph and to 1H, CH_2NHCO); 8.93 (t, 1H, aromatic); 9.05 (d, 2H, aromatics); 9.38 (d, 1H, *CHNHCO). Anal. calcd for $C_{41}H_{49}N_9O_{10}SSi$: C, 55.45; H, 5.56; N, 14.20; S, 3.61. Found: C, 55.42; H, 5.57; N, 14.19; S, 3.62%.

4.3.3. Compound 10c. $[\alpha]_D^{24} = -16$ (c 0.9, CH_2Cl_2); ^{1}H NMR (200 MHz, DMSO-d_6 100°C, δ/ppm): 0.68 (m, 2H, $SiCH_2$); 1.55–1.75 (m, 7H, C*CH_3, $SiCH_2CH_2$, CH_2CH_2NHAr); 2.50 (m, 4H, CH_2SCH_2); 3.20 (m, 2H, -CH_2NH); 3.35–3.80 (m, 11H, -CH_2OAr, CH_3OSi); 4.20 (t, 2H, -CH_2NHAr); 5.75 (d, 1H, *CH-Ph); 5.93 (m, 1H, *CH-naph); 6.80 (t, 1H, CH_2NHAr); 7.20–8.30 (m, 12H, aromatics superimposed to 1H, -NH*CH-naph and to 1H, CH_2NHCO); 8.96 (t, 1H, aromatic); 9.08 (d, 2H, aromatics); 9.40 (d, 1H, *CHNHCO). Anal. calcd for $C_{41}H_{49}N_9O_{10}SSi$: C, 55.45; H, 5.56; N, 14.20; S, 3.6. Found: C, 55.47; H, 5.55; N, 14.21; S, 3.60%.

4.4. Preparation of CSPs 2–4

A solution of the silane **10**, 0.88 mmol) in dry toluene (15 ml) was added dropwise to LiChrospher Si 100 silica gel (100 Å, 5 μm particle size, 300 m^2/g, 2.5 g), previously dried at 180°C at 0.05 mm Hg for 15 h and slurried in dry toluene (15 ml) and the mixture was gently stirred under reflux for 24 h. The mixture, cooled at room temperature, was filtered and washed with toluene (3×30 ml), dichloromethane (3×30 ml), methanol (3×30 ml), THF (3×30 ml) and pentane (3×30 ml), then dried at 50°C at 0.05 mmHg.

The amount of chiral selector linked to silica gel was determined by elemental analysis.
CSP 2: C, 9.80; H, 1.24; N, 2.62; S, 0.98% corresponding to 0.230 mmol/g (0.66 μmol/m^2).
CSP 3: C, 14.48; H, 1.86; N, 2.87; S, 0.91 corresponding to 0.292 mol/g (0.89 μmol/m^2).
CSP 4: C, 11.59; H, 1.33; N, 2.53; S, 1.09 corresponding to 0.260 mol/g (0.74 μmol/m^2).

The derivatized silica gels were slurry-packed into 15 cm stainless steel columns, using conventional techniques.

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15. It has been shown for other kinds of CSPs that the further introduction of suitable moieties on a CSP can affect its enantiodiscrimination properties (see Ref. 1c).