(*S*)-Leucine and [(*S*)-1-(1-Naphthyl)ethyl]amine as Chiral Building Blocks for a Bifunctional System − Synthesis of a New Chiral Stationary Phase and Evaluation of Its Biselector Properties in the HPLC Resolution of Racemic Compounds

Anna Iuliano,[a] Emanuele Attolino,[a] and Piero Salvadori*[a]

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Two selectors derived from [(*S*)-1-(1-naphthyl)ethyl]amine and (*S*)-leucine have been chemically bonded to one another and the resulting chiral auxiliary linked covalently to silica gel, to produce a new chiral stationary phase (CSP) for the HPLC resolution of enantiomers. The CSP is able to separate the enantiomers of some selected racemic compounds: both those resolved by Oi's CSP {derived from [1-(1-naphthyl)ethyl]amine} and those enantiodiscriminated by Pirkle's CSP [derived from *N*-(3,5-dinitrobenzoyl)leucine]. The results obtained demonstrate that the CSP possesses the properties of an efficient biselector system.

Introduction

One of the most challenging goals relating to the use of enantioselective HPLC for the resolution of racemic mixtures is the development of chiral stationary phases (CSPs) capable of separating the enantiomers of a wide variety of structurally different racemates. Indeed, significant efforts have been devoted to searching for new and more effective chiral selectors that, when linked to silica gel, satisfactorily meet this need. These efforts have produced a great number of CSPs based on cellulose derivatives[1] and macrocyclic glycopeptide antibiotics[2−4] (two classes of very successful chiral selectors for HPLC, thanks to their wide applicability), cyclodextrins,[5] synthetic polymers,[6] proteins,[7] and optically active molecules of low molecular weight.[8−11] These last, also known as independent CSPs because each molecule linked to silica gel is considered to act independently,[12] have received a great deal of attention, owing to the relatively simple accessibility of knowledge of the factors governing the enantiodiscrimination process,[12] which allows more efficient CSPs to be designed.[13]

Some independent CSPs that function very well in terms of efficiency and versatility have indeed been developed,[13] but a CSP displaying a very wide applicability is still distant. This problem might be approachable through the construction of a biselector CSP that possesses the structural characteristics of two dissimilar chiral auxiliaries known to act as selectors for HPLC toward different classes of racemic compounds.[14] Two problems need to be addressed in designing a biselector system: that of how the two different chiral selectors are to be connected to each other, and that of how the final system is to be linked to silica gel.

s-Trichlorotriazine looks suitable for this goal because the chlorine atoms can be displaced one by one by amino or hydroxy groups, simply by varying the experimental conditions of the reactions.[15] The *s*-triazine can therefore act as the connecting moiety for the two chiral selectors and the bifunctional system can be linked to silica gel by exploiting the third chlorine atom present on the heteroaromatic ring. This idea was first introduced some years ago, by Ching-Erh and co-workers[16,17] and by ourselves,[18] in preparations of mixed CSPs by linking the *s*-triazine moiety to optically active 1-(1-naphthyl)ethylamine and an amino acid[16,17] or to a tripeptide[18] component. The aim of these works was the development of a CSP capable of separating the enantiomers of the racemates resolved by the *s*-triazine-based CSP containing only the 1-(1-naphthyl)ethylamine, developed by Oi and co-workers,[19] as well as those enantiodiscriminated by the *s*-triazine-based CSP possessing tripeptide or amino acid moieties, developed by Oi[19] and by Lin,[20] respectively. These mixed CSPs, however, did not exhibit any wider applicability than did the two CSPs containing only one chiral moiety, but were able to resolve only those racemates enantiodiscriminated by the amino acid-*s*-triazine or peptide-*s*-triazine CSPs.[16−18]

We felt that this drawback might be present because the *s*-triazine ring is not simply a connecting arm but also plays a role in the enantiodiscrimination process; as a consequence the true chiral selector in the *s*-triazine-based CSPs is not the [1-(1-naphthyl)ethyl]amine or the amino acid or peptide moiety, but the overall *s*-triazine/chiral moiety. Thus, when two different molecules that function as chiral selectors solely by virtue of the presence of the *s*-triazine ring are both linked to this aromatic system, the moiety (the amino acid/triazine or peptide/triazine) that establishes the stronger interactions with the racemic substrates will prevail, and consequently only the racemates enantiodiscriminated by that will be resolved on the corresponding CSP.[18] On the basis of these considerations, *s*-tria-

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[a] Centro di Studio del CNR per le Macromolecole Stereordinate ed Otticamente Attive, Dipartimento di Chimica e Chimica Industriale,
Via Risorgimento 35, 56126 Pisa, Italy
Fax: (internat.) + 39-050/918409
E-mail: psalva@dcci.unipi.it

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zine should be usable for obtaining a biselector system only by linking to the aromatic ring one optically active molecule that acts as a chiral selector by virtue of its linkage to the aromatic moiety, and connecting another optically active molecule − that itself acts independently as a chiral selector − to the same ring, by means of a spacer (Figure 1).

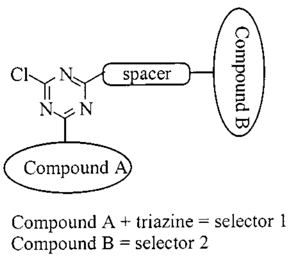


Figure 1. General structure of the biselector system

In this way, the two selectors should work independently, provided that the spacer is short enough to prevent folding of selector 2 onto selector 1. (*S*)-*N*-(3,5-Dinitrobenzoyl)leucine, which when linked to silica gel represents one of the most popular Pirkle CSPs [21] (Figure 2), was chosen as selector 2, and [(*S*)-1-(1-naphthyl)ethyl]amine as the molecule that, when bonded to the *s*-triazine, gives rise to selector 1, the same selector as in one of Oi's *s*-triazine-based CSPs (Figure 2).

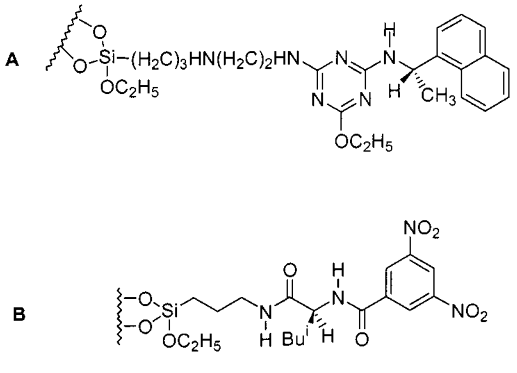


Figure 2. Structure of Oi's (**A**) and Pirkle's (**B**) CSPs

These chiral auxiliaries were also chosen because the two phases obtained after linking them to silica resolve different classes of racemic compounds: Pirkle's CSP separates the enantiomers of binaphthyl derivatives, (alkylaryl)carbinols, and amides endowed with electron-rich aromatic groups,[21−25] while Oi's CSP resolves 3,5-dinitrobenzamides of (alkylaryl)amines and 3,5-dinitroanilides of 2-arylpropionic acids.[19]

Results and Discussion

Synthesis of the Biselector CSP A

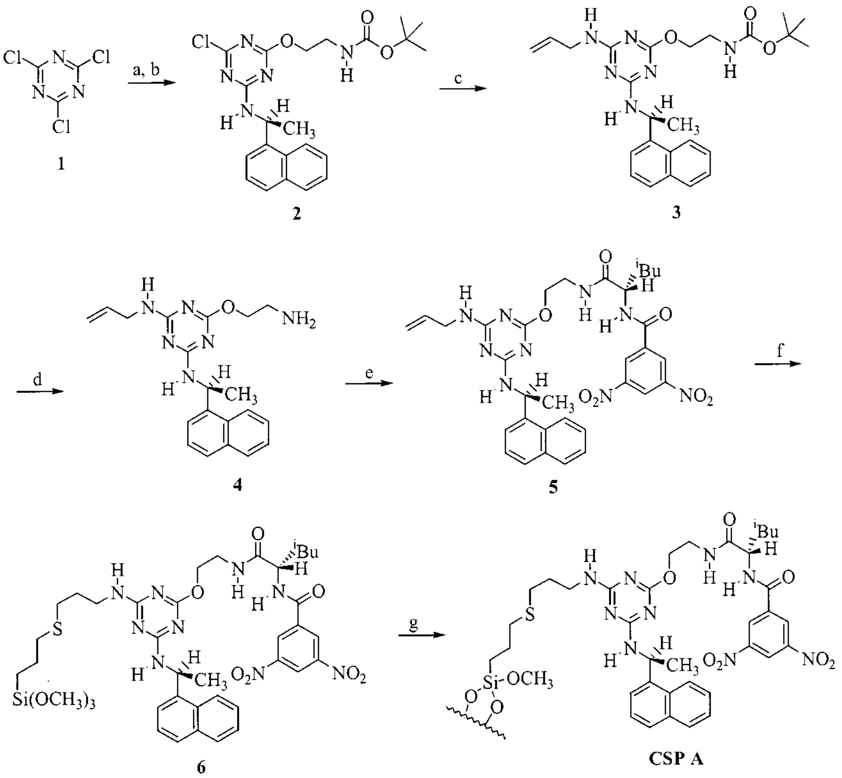
The synthetic route to **CSP A** is illustrated in Scheme 1. The trisubstituted *s*-triazine scaffold, containing the [1-(1-naphthyl)ethyl]amino moiety, the spacer group, and the connecting arm to silica gel, was prepared by selective displacement of the three chlorine atoms of *s*-trichlorotriazine. The order of introduction of the nucleophiles was chosen taking account of the fact that the *s*-triazine nucleus becomes less reactive toward nucleophilic substitutions when the electron-withdrawing chlorine atoms are substituted by electron-donating nitrogen or oxygen atoms. *s*-Trichlorotriazine was therefore treated first with *N*-BOC-ethanolamine, the weakest nucleophile. [(*S*)-1-(1-Naphthyl)ethyl]amine was introduced as the second substituent, since, because of its steric hindrance, it is less reactive than allylamine. The high nucleophilicity of allylamine allows it to be introduced easily as the last substituent, even if the *s*-triazine derivative is now poorly reactive thanks to the presence of two electron-donating groups.

The use of allylamine as a connecting arm to silica gel was preferred over the most common approach used for linking *s*-triazine-based chiral auxiliaries − nucleophilic displacement of the third chlorine atom of a disubstituted system by the amino group of aminopropylsilica gel[19,26,27] − in order to distance the chiral selector from the silica gel. In fact, it is well known that the best results in terms of enantioselectivity of a CSP are obtained when the chiral auxiliary is remote from the silica gel.[12] Indeed, reaction between the terminal double bond of the allylamino moiety and (3-mercaptopropyl)trimethoxysilane, followed by treatment of the silane derivative with silica gel,[28,29] allows the biselector system to be connected to silica through an eight-unit tether.

The disubstituted *s*-triazine derivative **2** was obtained according to a literature method used for preparing amino-substituted *s*-triazine derivatives,[30] treating *s*-trichlorotriazine with an equimolar amount of *N*-BOC-ethanolamine in acetonitrile in the presence of DIPEA as a base. In view of the poor nucleophilicity of the hydroxy group, the reaction was carried out at 60 °C in order to increase the degree of conversion of the substrate. The monosubstituted derivative was not isolated; equimolar amounts of [(*S*)-1-(1-naphthyl)-ethyl]amine and DIPEA were added to the same reaction mixture when the conversion of **1** was completed. Compound **2** was isolated and purified by column chromatography, and then treated with a fourfold excess of allylamine at 50 °C in acetonitrile, affording the trisubstituted *s*-triazine derivative **3** in nearly quantitative yield.

In order to link (*S*)-*N*-(3,5-dinitrobenzoyl)leucine to the trisubstituted *s*-triazine scaffold, the BOC protecting group was removed using trifluoroacetic acid; hydrolysis of the reaction mixture with $NaHCO_3$ afforded the free amine. Compound **4** was then treated with an equimolar amount of (*S*)-*N*-(3,5-dinitrobenzoyl)leucine in the presence of EEDQ,[31] affording the bis(amide) **5** in 38% yield after chromatographic purification.

The biselector system was linked to silica gel by treatment of **5** with a fivefold excess of (3-mercaptopropyl)trimethoxysilane in refluxing $CHCl_3$ [29] and in the presence of a catalytic amount of AIBN for 48 h. Evaporation of the solvent and washing of the crude product with pentane, in order to remove excess (3-mercaptopropyl)trimethoxysilane, afforded the chemically pure silane **6** in quantitative yield.



Scheme 1. Reagents and conditions: a) *N*-BOC-ethanolamine, DIPEA, CH_3CN, 60 °C; b) [(*S*)-1-(1-naphthyl)ethyl]amine, DIPEA, 25 °C; c) allylamine (4 equiv.), CH_3CN, 50 °C; d) TFA, CH_2Cl_2, 25 °C; e) (*S*)-*N*-(3,5-dinitrobenzoyl)leucine, EEDQ, THF, 25 °C; f) (3-mercaptopropyl)trimethoxysilane (5 equiv.), AIBN, $CHCl_3$, reflux; g) silica gel, toluene, reflux

This was then treated with silica gel in refluxing toluene. The derivatized material, washed and dried, was slurry-packed in a stainless steel column using conventional techniques.

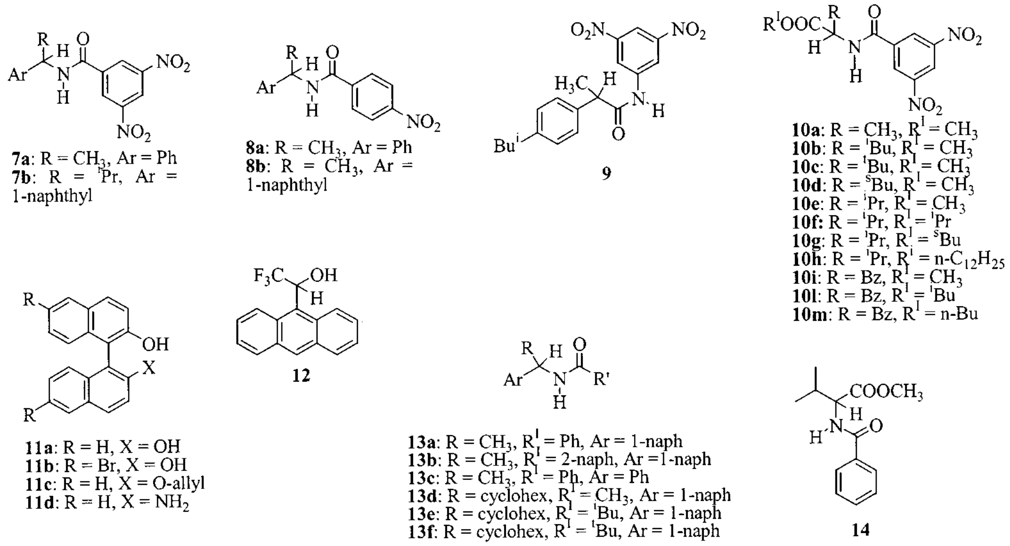
Use of CSP A in the HPLC Resolution of Racemic Compounds

Compounds **7−14** (Scheme 2) were used to assess the enantiodiscriminating capability of **CSP A**. π-Acidic racemates such as 3,5-dinitrobenzamides of amines **7** and the 3,5-dinitroanilide of ibuprofen (**9**) were used to verify whether or not the [1-(1-naphthyl)ethyl]amino/*s*-triazine moiety still functioned as in the Oi CSP. In addition, the enantioseparation of other classes of π-acidic racemic compounds, such as the 4-nitrobenzamides **8** and the 3,5-dinitrobenzoyl derivatives of amino acid alkyl esters **10**, not resolved by Oi's CSP, was also examined. The results relating to the chromatographic resolution of these racemic compounds are summarized in Table 1.

CSP A separates the enantiomers of π-acidic compounds with α values ranging from 1.10 (Entries 4 and 6) to 1.64 (Entry 13). It is noteworthy that not only are the 3,5-dinitrobenzamides **7** and the anilide **9** (Entries 1, 2, 5) resolved, but that the 4-nitrobenzamides **8** and the derivatives of amino acid **10** are as well (Entries 4, 6−16). These results are very interesting, since either poor or no resolution was observed with Oi's CSP for the 3,5-dinitrobenzoyl derivatives of amino acid alkyl esters; 3,5-dinitrobenzoylphenylalanine methyl ester, for example, was not resolved by Oi's CSP[19] and the analogous valine derivative[19] showed an α value of 1.15. On the contrary, **CSP A** separates the enantiomers of the former of these (Entry 14) and provides better resolution (α = 1.27) for the latter (Entry 10). The degree of enantiodiscrimination of the amino acid derivatives depends both on the nature of the ester group and on the structure of the group present at the stereogenic center. With the amino acid remaining the same, the best separations are obtained when the ester group is a long or a branched alkyl chain (Entries 11−13 and 16). As far as the type of amino acid is concerned, with the ester group remaining the same, the α values are very similar both for alkyl and for benzyl amino acids (Entries 7, 9, 10, 14), they decrease only in the cases of alanine and *tert*-leucine (Entries 6 and 8).

On the basis of the results obtained in the resolutions of π-acid racemic compounds, we are able to say that the [1-(1-naphthyl)ethyl]amino-*s*-triazine moiety, when a component of the biselector system **5**, not only preserves its enantiodiscriminating capability, but also displays greater versatility with respect to the cases in which it is an isolated chromatographic selector. In fact, **CSP A** is able to resolve a greater number of racemic compounds than Oi's CSP.

It having been established that the presence of the derivatized amino acid moiety linked to the *s*-triazine nucleus does not represent a drawback to the enantiodiscriminating capability exhibited by the [1-(1-naphthyl)ethyl]amino-*s*-tri-



Scheme 2

Table 1. Chromatographic resolution of π-acidic racemic compounds on **CSP A**

Run[a]	Compound	k^{I}[b]	α[c]	E.O.[d]
1	**7a**	2.02	1.10	(−)
2	**7b**	3.01	1.38	(−)
3	**8a**	4.42	1.28	(−)
4	**8b**	3.40	1.51	(−)
5	**9**	2.00	1.49	(+)
6	**10a**	10.07	1.10	(−)
7	**10b**	3.64	1.30	
8	**10c**	1.93	1.19	(−)
9	**10d**	2.57	1.30	(−)
10	**10e**	3.06	1.27	
11	**10f**	1.77	1.44	
12	**10g**	1.44	1.39	(−)
13	**10h**	2.13	1.64	
14	**10i**	4.22	1.27	(−)
15	**10l**	10.78	1.26	
16	**10m**	5.05	1.50	

[a] Chromatographic conditions: UV detection (λ = 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.

Table 2. Chromatographic resolution of binaphthyl derivatives and alcohol **12** on **CSP A**

Run[a]	Compound	k^{I}[b]	α[c]	E.O.[d]
1	**11a**	2.91	1.22	(−) (*R*)
2	**11b**	7.87	1.36	(−) (*R*)
3	**11c**	2.87	1.20	(−) (*R*)
4	**11d**	1.64	1.16	(−) (*R*)
5	**12**[e]	4.87	1.19	(+)

[a] Chromatographic conditions: UV detection (λ = 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 and absolute configuration of the first eluted enantiomer. − [e] Eluent hexane/dichloromethane/propan-2-ol, 75:20:5.

azine moiety, the second step of our work was to check the influence of this on the enantiorecognition properties of *N*-(3,5-dinitrobenzoyl)leucine, the other chiral component of the biselector system **5**, reproducing the Pirkle phase. To this end, the separation of the enantiomers of the racemates **11−14**, which can be successfully resolved on the *N*-(3,5-dinitrobenzoyl)leucine-based Pirkle CSP,[21−25] was studied. The chromatographic data relating to the resolutions of binaphthol derivatives **11** and (9-anthryl)(trifluoromethyl)carbinol (**12**) are reported in Table 2.

All four binaphthyl derivatives **11a−d** and also the alcohol **12** are resolved on **CSP A**, with α values comparable to those obtained by Pirkle using the *N*-(3,5-dinitrobenzoyl)leucine-based CSP. Similarly, the dependence of the enantioselectivity of the CSP on the nature of the binaphthol derivatives reflects the trend observed in the *N*-(3,5-dinitrobenzoyl)leucine-based CSP.[24] Indeed, **CSP A** resolves a binaphthol derivative in which the OH group has been replaced by an amino function (Entry 4) that establishes a weaker hydrogen bond with the selector, with lower enantioselectivity, thus behaving like Pirkle's CSP.[20] These data suggest that the enantiorecognition mechanism exhibited by the derivatized amino acid moiety of the biselector system **5** must be similar to that operating in the case of the *N*-(3,5-dinitrobenzoyl)leucine CSP. This is borne out by the elution orders of this class of racemates on **CSP A** (Table 2), determined by measurement of the circular dichroism of the eluted fractions at 240 nm, the wavelength corresponding to the maximum of the first component of the exciton couplet of the binaphthyl moiety.[32] On the basis of the sign of the circular dichroism at this wavelength, it is possible to determine the absolute configuration of the eluted enantiomers by using the ECCD method.[33] The elution orders on **CSP A** were found to be the same as observed on the Pirkle phase,[24] thus confirming that the presence of the [1-(1-naphthyl)ethyl]amino-*s*-triazine moiety does not exert any appreciable influence on the enantiorecognition exhibited by the derivatized amino acid moiety towards binaphthol derivatives.

The last classes of racemic compounds examined were amides of aliphatic and aromatic acids, the enantiomers of which are separated on the *N*-(3,5-dinitrobenzoyl)leucine CSP.[22,23] The data collected in Table 3 show that these classes of racemates are also well resolved upon **CSP A**, with α values that allow accurate determinations of the enantiomeric compositions of enriched samples to be performed in most of the cases examined.

Table 3. Chromatographic resolution of π-basic amides on **CSP A**

Run[a]	Compound	k^{I}[b]	α[c]	E.O.[d]
1	**13a**	6.14	1.27	(−)
2	**13b**	7.54	1.26	(−)
3	**13c**	4.86	1.07	(+)
4	**13d**[e]	2.06	1.15	(−)
5	**13e**	1.86	1.40	
6	**13f**	1.95	1.37	
7	**14**	2.50	1.21	(−)

[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 230 nm (for naphthalene-containing compounds) or 254 nm of the first eluted enantiomer. − [e] Eluent hexane/dichloromethane/propan-2-ol, 75:20:5.

The enantioselectivities depend on the π-basic nature of the aromatic moieties present in the racemic substrates; the benzamide of [1-(1-naphthyl)ethyl]amine is better resolved than that of (1-phenylethyl)amine (Entries 1 and 3). Given that one of the interactions involved in the enantiodiscrimination process on the *N*-(3,5-dinitrobenzoyl)leucine-based CSP is the π−π interaction, taking place between electronically complementary aromatic rings,[12] the dependence of the **CSP A** enantioselectivity on the π-basic character of the substrates suggests that the π-acid aromatic ring of the amino acid moiety is able to interact with the racemates both in **CSP A** and in Pirkle's CSP. Even the amides of aliphatic acids show good enantioseparations on **CSP A**, these being dependent on the nature of the acyl group, with the best separation being obtained when the acyl group of an alkylamide is β-branched (Entries 5 and 6). The data concerning chromatographic separations of compounds **11−14** indicate that the presence of the [1-(1-naphthyl)ethyl]amino-*s*-triazine moiety does not prevent the enantioselective interaction between the *N*-(3,5-dinitrobenzoyl)leucine and the racemic substrates resolved by Pirkle's CSP.

In conclusion, the results obtained in the separation of the enantiomers of the racemates **7−14** demonstrate that **CSP A** possesses the requirements of a biselector CSP. In fact, it is able to resolve both the π-acidic racemic compounds enantiodiscriminated by Oi's CSP, reproduced in the [1-(1-naphthyl)ethyl]amino-*s*-triazine moiety, and the analytes resolved by Pirkle's CSP, reproduced in the *N*-(3,5-dinitrobenzoyl)leucine moiety (Figure 3).

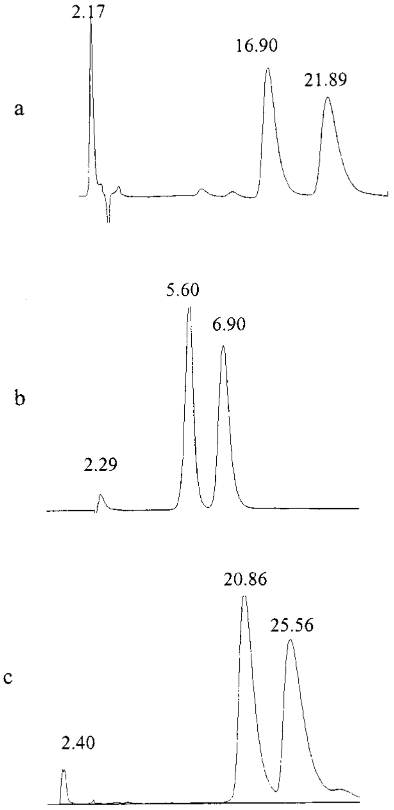


Figure 3. Chromatographic resolutions of: a) 6,6′-dibromo-2,2′-dihydroxy-1,1′-binaphthyl; b) *N*-(3,5-dinitrobenzoyl)valine methyl ester; c) *N*-(2-naphthoyl)-[1-(1-naphthyl)ethyl]amine; for chromatographic conditions see Tables 1, 2, and 3

The presence of the [1-(1-naphthyl)ethyl]amino-*s*-triazine component does not seem to have any influence on the enantiodiscrimination properties of the *N*-(3,5-dinitrobenzoyl)leucine; in fact, the elution order for the binaphthyl derivatives on **CSP A** are equal to those found on Pirkle's CSP. This presumably indicates that the *N*-(3,5-dinitrobenzoyl)leucine moiety operates with the same enantiorecognition mechanism in both the CSPs. Furthermore, the presence of the amino acid component seems to have a positive influence on the enantioselectivity of the [1-(1-naphthyl)ethyl]amino-*s*-triazine unity; indeed, **CSP A** is able to resolve a greater number of racemic compounds than Oi's CSP.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Varian Gemini-200 NMR spectrometer, using TMS as external standard. The following abbreviations are used: s = singlet, d = doublet, dd = double doublet, t = triplet, q = quadruplet, m = multiplet, br. = broad. − TLC analyses were performed on Merck 60 F_{254} silica gel sheets; chromatographic separations were carried out on columns of suitable dimensions using Merck 60 silica gel (70−230 mesh). − HPLC analyses were performed with a Jasco

PU-980 intelligent HPLC pump equipped with a Jasco UV-975 detector and a Jasco J-710 spectropolarimeter. − Optical rotations were measured with a Jasco DIP-360 digital polarimeter. − Melting points were taken using a Kofler Reichert-Jung apparatus and are uncorrected. − The IR spectra were recorded with a Perkin−Elmer 1710 spectrophotometer. − Elemental analysis were carried out at ICMAT-CNR, Area della Ricerca di Roma. − Toluene and THF were refluxed in the presence of sodium benzophenone and distilled before use. Allylamine, diisopropyl(ethyl)amine (DIPEA), and CH_3CN were distilled from CaH_2, and [(*S*)-1-(1-naphtyl)ethyl]amine was 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.[34]

***tert*-Butyl 2-(4-Chloro-6-{[(1*S*)-1-(1-naphthyl)ethyl]amino}-1,3,5-triazin-2-yloxy)ethylcarbamate (2):** *N*-(*tert*-Butoxycarbonyl)ethanolamine (1.61 g, 0.010 mol) was added to a solution of *s*-trichlorotriazine (1.84 g, 0.010 mol) and dry DIPEA (1.74 mL, 0.010 mol) in dry acetonitrile (30 mL). The reaction mixture was stirred at 60 °C for 21 h and then allowed to cool to room temperature. Dry DIPEA (1.74 mL, 0.010 mol) and [(*S*)-1-(1-naphthyl)ethyl]amine (1.61 mL, 0.010 mol) were added. The reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure and the crude product dissolved in dichloromethane. The organic phase was washed sequentially with 10% hydrochloric acid, water, a saturated solution of $NaHCO_3$ and water, and then dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (SiO_2; hexane/ethyl acetate, 6:4) to afford 2 g of **2** (0.0045 mol, 45% yield). M.p. 68−70 °C. − $[\alpha]_D^{22}$ = +34 (*c* = 0.865, CH_2Cl_2). − ^{1}H NMR (200 MHz, [D$_6$]DMSO, 130 °C): δ = 1.40 (s, 9 H, O*t*Bu), 1.65 (d, 3 H, CH_3), 3.20 (dd, 2 H, C*H$_2$*NH), 4.22 (t, 2 H, C*H$_2$*OH), 5.92 (q, 1 H, *CH), 6.31 (br. s, 1 H, N*H*CO), 7.42−8.22 (m, 7 H, aromatics), 8.78 (br. s, 1 H, NHAr). − ^{13}C NMR (50 MHz, [D$_6$]DMSO, 100 °C): δ = 21.5 (CH_3), 28.2 [C(*C*H$_3$)$_3$], 39.1 (*CH), 47.1 (CH_2NH), 67.2 (CH_2OAr), 79.3 [*C*(CH$_3$)$_3$], 122.3, 122.5, 125.4, 125.8, 126.4, 128.2, 129.0, 130.5, 133.8, 138.4, 155.7, 165.9, 170.5. − IR (KBr): ṽ = 3418, 3287, 2973, 2925, 1701, 1571, 1518, 1260, 1167, 1028, 861, 802, 776 cm^{-1}. − $C_{22}H_{26}ClN_5O_3$ (443.9309): calcd. C 59.72, H 5.93, Cl, 8.02, N 15.68; found C 59.52, H 5.90, Cl, 7.99, N 15.78.

***tert*-Butyl 2-[4-(Allylamino)-6-{[(1*S*)-1-(1-naphthyl)ethyl]amino}-1,3,5-triazin-2-yloxy]ethylcarbamate (3):** Allylamine (1.3 mL, 0.0175 mol) was added to a solution of **2** (1.94 g, 0.00437 mol) in dry CH_3CN (25 mL). The reaction mixture was stirred at 50 °C for 20 h. The solvent was evaporated under reduced pressure and the crude product dissolved in dichloromethane. The organic phase was washed sequentially with 10% hydrochloric acid, water, a saturated solution of $NaHCO_3$ and water, and then dried with Na_2SO_4. The solvent was evaporated under reduced pressure to afford 1.82 g of **3** (0.00393 mol, 91% yield). M.p. 72−75 °C. − $[\alpha]_D^{23}$ = +52 (*c* = 1, CH_2Cl_2). − ^{1}H NMR (200 MHz, [D$_6$]DMSO, 100 °C): δ = 1.40 (s, 9 H, O*t*Bu), 1.59 (d, 3 H, CH_3), 3.18 (dd, 2 H, C*H$_2$*NH), 3.80 (t, 2 H, CH_2OAr), 4.15 (t, 2 H, CH_2allylic), 5.00 (m, 2 H, =CH_2), 5.78 (m, 1 H, CH=), 5.95 (m, 1 H, *CH), 6.38 (br. s, 1 H, NHCO), 6.80 (t, 1 H, CH_2N*H*), 7.35 (d,1 H, N*H**CH), 7.40−7.65 (m, 4 H, aromatics), 7.77 (d, 1 H, aromatic), 7.90 (d, 1 H, aromatic), 8.23 (d,1 H, aromatic). − ^{13}C NMR (50 MHz, [D$_6$]DMSO, 100 °C): δ = 21.5 (CH_3), 28.2 [C(*CH$_3$*)$_3$], 39.6 (*CH), 42.9 (*CH$_2$*CH=), 46.1 (CH_2NH), 65.5 (CH_2OAr), 79.1 [*C*(CH$_3$)$_3$], 122.1, 122.9, 125.2, 125.5, 125.9, 127.5, 128.7, 130.6, 134.6, 133.7, 139.6, 155.7, 156.6, 165.9, 166.8, 166.9. − IR (KBr): ṽ = 3413, 3263, 3155, 3068, 2976, 2930, 1702, 1580, 1510, 1457, 1426, 1365, 1162, 992, 917, 865, 814, 800, 778 cm^{-1}. − $C_{25}H_{32}N_6O_3$ (464.3): calcd. C 64.64, H 6.94, N 18.09; found C 64.37, H 6.91, N 18.15.

2-[4-(Allylamino)-6-{[(1*S*)-1-(1-naphthyl)ethyl]amino}-1,3,5-triazin-2-yloxy]ethylamine (4): Trifluoroacetic acid (15 mL) was added to a solution of **3** (1.77 g, 0.00381 mol) in dry CH_2Cl_2 (30 mL), and the reaction mixture was stirred at room temperature for 15 min. The mixture was poured into a saturated solution of $NaHCO_3$ and the product was extracted with ethyl acetate (4 × 50 mL). The collected organic extracts were washed with water, then dried with Na_2SO_4. The solvent was evaporated under reduced pressure to afford 1.38 g of **4** (0.00378 mol, quantitative yield). M.p. 60−63 °C. − $[\alpha]_D^{23}$ = +64 (*c* = 0.98, CH_2Cl_2). − ^{1}H NMR (200 MHz, [D$_6$]DMSO, 100 °C): δ = 1.59 (d, 3 H, CH_3), 2.95 (dd, 2 H, C*H$_2$*NH$_2$), 3.45 (t, 2 H, CH_2OAr), 4.25 (t, 2 H, CH_2 allylic), 5.00 (m, 2 H, =CH_2), 5.79 (m, 1 H, CH=), 5.95 (m, 1 H, *CH), 6.90 (t, 1 H, NH allylic), 7.38−7.65 (m, 5 H, 4 aromatic superimposed upon 1, N*H**CH), 7.77 (d, 1 H, aromatic), 7.90 (d, 1 H, aromatic), 8.23 (d, 1 H, aromatic). − ^{13}C NMR (50 MHz, [D$_6$]DMSO, 100 °C): δ = 21.5 (CH_3), 28.2 [C(*CH$_3$*)$_3$], 39.6 (*CH), 42.9 (*CH$_2$*CH=), 46.1 (CH_2NH), 65.5 (CH_2OAr), 79.1 [*C*(CH$_3$)$_3$], 122.1, 122.9, 125.2, 125.5, 125.9, 127.5, 128.7, 130.6, 134.6, 133.7, 139.6, 155.7, 156.6, 165.9, 166.8, 166.9. − IR (KBr): ṽ = 3408, 3277, 3063, 2966, 2931, 1685, 1584, 1508, 1426, 1332, 1260, 1202, 1131, 917, 813, 780, 778 cm^{-1}. − $C_{20}H_{24}N_6O$ (364.2): calcd. C 65.91, H 6.64, N 23.06; found C 65.82, H 6.65, N 23.13.

***N*^{1}-{2-[4-(Allylamino)-6-{[(1*S*)-1-(1-naphthyl)ethyl]amino}-1,3,5-triazin-2-yloxy]ethyl}-*N*^{2}-(3,5-dinitrobenzoyl)leucinamide (5):** 2-Ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ) (0.678 g, 2.74 mmol) was added to a solution of (*S*)-*N*-(3,5-dinitrobenzoyl)-leucine (0.946 g, 2.74 mmol) in dry THF (60 mL), and the reaction mixture was stirred at room temperature. After 3 h, compound **4** (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 was dissolved in dichloromethane. The organic solution was washed sequentially with 10% hydrochloric acid, water, a saturated solution of $NaHCO_3$ and water, and then dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (SiO_2; hexane/ethyl acetate, 2:8) to afford 0.75 g of **5** (1.05 mmol, 38% yield). M.p. 112−116 °C. − $[\alpha]_D^{23}$ = +55 (*c* = 0.5, CH_2Cl_2). − ^{1}H NMR (200 MHz, [D$_6$]DMSO, 100 °C): δ = 0.90 [t, 6 H, CH(*CH$_3$*)$_2$], 1.58 (d, 3 H, C*CH$_3$), 1.68 (m, 3 H, CHCH$_2$), 3.40 (dd, 2 H, C*H$_2$*NH), 3.79 (s sl, 2 H, CH_2OAr), 4.20 (t, 2 H, CH_2 allylic), 4.58 (m, 1 H, *CH*i*Bu), 5.00 (m, 2 H, =CH_2), 5.76 (m, 1 H, CH=), 5.92 (m, 1 H, *CH-naphth), 6.74 (t, 1 H, NH allylic), 7.30 (d, 1 H, N*H**CH-naphth), 7.40−7.92 (m, 6 H, aromatics superimposed upon 1 H, CH_2N*H*), 8.22 (d, 1 H, aromatic), 8.95 (t, 1 H, aromatic superimposed upon d, 1 H, *CHN*H*CO), 9.05 (d, 2 H, aromatic). − ^{13}C NMR (50 MHz, [D$_6$]DMSO, 100 °C): δ = 21.2−21.3 [CH(*CH$_3$*)$_2$], 22.2 (CH_3), 24.1 (CH*CH$_2$*), 38.1 (*CH-naphth), 40.3 [*CH*(CH$_3$)$_2$], 42.1 (*CH$_2$*CH=), 45.3 (CH_2NH), 52.3 (CO**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): ṽ = 3408, 3292, 3090, 2976, 2931, 2875, 1729, 1660, 1628, 1583, 1543, 1427, 1343, 1258, 1237, 1187, 1152, 1105, 1076, 993, 918, 813, 780, 730 cm^{-1}. − $C_{33}H_{37}N_9O_7$ (671.3): calcd. C 59.01, H 5.55, N 18.77; found C 58.92, H 5.53, N 18.84.

Compound 6: Freshly distilled (3-mercaptopropyl)trimethoxysilane (0.85 mL 4.5 mmol) and AIBN (0.033 g, 0.2 mmol) were added to a solution of **5** (0.60 g, 0.9 mmol) in dry $CHCl_3$ (10 mL) and the mixture was stirred under reflux for 48 h. The solvent was removed by evaporation under reduced pressure and the residual oil was dispersed in pentane to afford a solid, which was filtered and washed with pentane (5 × 20 mL). The pure product **6** was obtained in quantitative yield (0.78 g). $[\alpha]_D^{23} = +58$ (c = 0.92, CH_2Cl_2). − ^1H NMR (200 MHz, $[D_6]$DMSO, 100 °C): δ = 0.65 (m, 2 H, $SiCH_2$), 0.90 (t, 6 H, $CH(\mathit{CH_3})_2$], 1.50−1.80 (m, 10 H, C* CH_3, $CHCH_2$, $SiCH_2\mathit{CH_2}$, $\mathit{CH_2}CH_2NHAr$), 2.50 (m, 4 H, CH_2SCH_2), 3.20−3.80 (m, 13 H, $C\mathit{H_2}NH$, CH_3OSi, CH_2OAr), 4.20 (m, 2 H, $\mathit{CH_2}NHAr$), 4.58 (m, 1 H,*C$\mathit{H}$$i$Bu), 5.93 (m, 1 H,* CH-naphth), 6.70 (s, 1 H, $CH_2N\mathit{H}Ar$), 7.30−8.30 (m, 9 H, 7 aromatic superimposed upon NH*CH-naphth and CH_2NHCO), 8.93−9.10 (m, 4 H, 3 aromatic superimposed upon *CHNHCO). − $C_{39}H_{53}N_9O_{10}SSi$ (867.3): calcd. C 53.96, H 6.15, N 14.52, S 3.69, Si, 3.24; found C 54.02, H 6.14, N 14.48, S 3.68, Si, 3.25.

Preparation of CSP A: A solution of the silane **6** (0.76 g, 0.88 mmol) in 15 mL of dry toluene was added dropwise to LiChrospher Si 100 silica gel (2.5 g, 100 Å, 5 μm particle size, 300 m^2/g), previously dried at 180 °C/0.05 Torr for 15 h and slurried in 15 mL of dry toluene. The mixture was gently stirred at reflux for 24 h. The mixture, once allowed to cool to 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), and then dried at 50 °C at 0.05 Torr. − The amount of chiral selector linked to silica gel was determined by elemental analysis: C 10.44, H 1.32, N 2.80, S 1.05, corresponding to 0.245 mmol/g (0.7 μmol/m^2). − The derivatized silica gel was slurry-packed into a 15-cm stainless steel column, using conventional techniques.

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