Di- and Tri-1-(1-naphthyl)ethylamino-Substituted 1,3,5-Triazine Derivatives: A New Class of Versatile Chiral Auxiliaries for NMR Spectroscopy

Gloria Uccello-Barretta, Anna Iuliano, Emanuela Franchi, Federica Balzano, and Piero Salvadori*

Centro di Studio del CNR per le Macromolecole Stereordinate ed Otticamente Attive, Dipartimento di Chimica e Chimica Industriale, via Risorgimento 35, 56126 Pisa-Italy

Received April 3, 1998

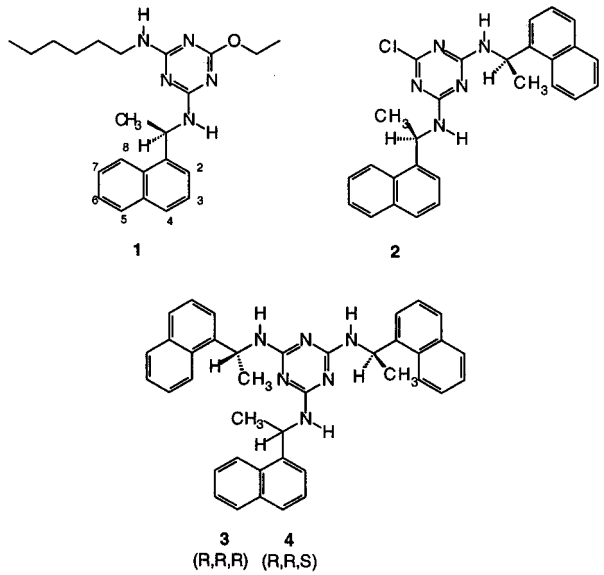
2-Chloro-4,6-bis[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine, 2,4,6-tris[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine, and 2,4-bis[(*R*)-1-(1-naphthyl)ethylamino]-6-[(*S*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine have been synthesized, and their efficiency and versatility as chiral solvating agents for the determination by NMR of the enantiomeric composition of derivatized or underivatized chiral compounds have been demonstrated.

Introduction

One of the most practical answers to the continuous demand for simple, accurate, and reliable methods of measuring enantiomeric purity comes from the use of chiral solvating agents (CSAs) for NMR spectroscopy, which impose a nonracemic influence on an enantiomeric mixture simply by virtue of the formation of short-lived diastereoisomeric species.[1] For this reason, a great deal of effort has been devoted to the development of new and efficient CSAs having applications as wide as possible.

Recently we have been concerned with an attractive class of chiral auxiliaries obtained by linking chiral selectors to *s*-trichlorotriazine.[2] Their use for the preparation of chiral stationary phases for HPLC[3] and GC[4] has been reported many years ago, and more recently, the possibility of obtaining more versatile systems by introducing two equal or different chiral auxiliaries into the triazine nucleus has been also suggested.[5] Attempts to use the soluble models[2] of the chiral stationary phases of Ôi and co-workers[3a] as new chiral auxiliaries for NMR spectroscopy revealed the potentiality of the triazine derivative **1**, containing the 1-(1-naphthyl)ethylamino moiety, in the direct NMR determination of enantiomeric composition of chiral compounds. These preliminary results prompted us to check the efficiency of the triazine derivatives, 2-chloro-4,6-bis[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (**2**) and diastereoisomeric 2,4,6-tris[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (**3**) and 2,4-bis[(*R*)-1-(1-naphthyl)ethylamino]-6-[(*S*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (**4**), respectively containing two and three 1-(1-naphthyl)ethylamino moieties, (Chart 1) as multiselector CSAs for enantiomeric mixtures of derivatized or underivatized compounds (**5**−**27**, Charts 2−4).

Chart 1



Results and Discussion

Synthesis of the Triazine Derivatives. The synthesis of triazine derivatives **1**−**4** was performed following a literature procedure, which exploits a nucleophilic substitution reaction under solid−liquid phase-transfer conditions.[6] The reaction, which is carried out in the presence of K_2CO_3 and a catalytic amount of 18-crown-6, allows one to substitute, employing the appropriate number of equivalents of the nucleophile and K_2CO_3, one, two, or all of the chlorine atoms of 2,4,6-trichloro-1,3,5-triazine, only by choice of reaction temperature.

Compound **1**[2] and the derivatives **2**−**4** were prepared (Scheme 1) with this method.

To obtain **2** as the only product, the displacement reaction of the two chlorine atoms of *s*-trichlorotriazine was carried out at room temperature in THF as solvent.

(1) (a) Pirkle, W. H.; Hoover, D. J. *Top Stereochem.* **1982**, *13*, 263. (b) Weisman, G. R. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 1, p 153. (c) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.

(2) Uccello-Barretta, G.; Iuliano, A.; Menicagli, R.; Peluso, P.; Pieroni, E.; Salvadori, P. *Chirality* **1997**, *9*, 113.

(3) (a) Ôi, N.; Nagase, M.; Sawada, Y. *J. Chromatogr., A* **1984**, *292*, 427. (b) Brukner, H.; Strecker, B. *J. Chromatogr., A* **1992**, *627*, 97. (c) Lin, J. Y.; Yang, M. H. *J. Chromatogr., A* **1993**, *644*, 277. (d) Lin, C. E.; Li, F. K. *J. Chromatogr., A* **1996**, *722*, 199.

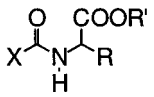
(4) Ôi, N.; Kitahara, N.; Matsushita, Y.; Kisu, N. *J. Chromatogr. A* **1996**, *722*, 229.

(5) (a) Lin, C. E.; Li, F. K.; Lin, C. H. *J. Chromatogr., A* **1996**, *722*, 211. (b) Lin, C. E.; Li, F. K.; Lin, C. H. *J. Chromatogr., A* **1996**, *722*, 189. (c) Brücner, H.; Wachsmann, H. *J. Chromatogr. A* **1996**, *728*, 447. (d) Iuliano, A.; Pieroni, E.; Salvadori, P. *J. Chromatogr. A* **1997**, *786*, 355.

(6) Menicagli, R.; Malanga, C.; Peluso, P. *Synth. Commun.* **1994**, *24*, 2153.

10.1021/jo9806153 CCC: $15.00
Published on Web 11/13/1998

Chart 2



R	R'	X	
Isopropyl	Methyl	DNP	**5**
Methyl	Methyl	DNP	**6**
Isobutyl	Methyl	DNP	**7**
sec-Butyl	Methyl	DNP	**8**
t-Butyl	Methyl	DNP	**9**
Phenyl	Methyl	DNP	**10**
Isopropyl	n-Butyl	DNP	**11**
Isopropyl	Isopropyl	DNP	**12**
Isopropyl	Methyl	Penta-F	**13**
Benzyl	H	DNP	**14**

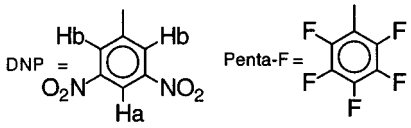
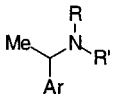
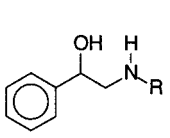


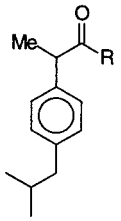
Chart 3



Ar	R	R'	
Phenyl	H	DNB	**15a**
Phenyl	Me	DNB	**15b**
2-Naphthyl	H	DNB	**16**



R	
DNB	**17a**
Me	**17b**
2-Naphthoyl	**17c**



R	
NH-DNP	**18**
OH	**19**

Although under these experimental conditions the reaction required 6 days to be completed, higher temperatures (i.e., over 50 °C) are not recommended, because they gave a significant amount of trisubstituted product.

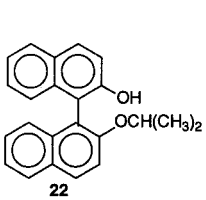
As far as the syntheses of **3** and **4** are concerned, in both the cases the reaction was carried out in acetonitrile as a solvent, under reflux, for 6 days. Compound **3** was prepared by reacting *s*-trichlorotriazine with 3 equiv of (*R*)-1-(1-naphthyl)ethylamine in the presence of three equivalents of K_2CO_3 and a catalytic amount of 18-crown-6, whereas **4** was obtained by reacting **2** with 1 equiv of (*S*)-1-(1-naphthyl)ethylamine in the presence of 1 equiv of K_2CO_3 and a catalytic amount of 18-crown-6. The yields of both the reactions were not quantitative, because the conversion from disubstituted to trisubstituted product is not complete even though the reaction is carried out for a longer time. However, this is not a serious drawback because pure **3** and **4** were easily obtained by flash chromatography of the crude product in 60 and 66% yields, respectively.

Use of Triazine Selectors as CSAs. A. Amino Acid Derivatives (Chart 2). The ^{1}H NMR spectrum of 3,5-dinitrobenzoyl derivative of racemic valine methyl ester (**5**) (Figure 1a), recorded in $CDCl_3$ at room temperature, shows a readily distinguishable singlet at 3.83 ppm due to the OMe protons and a double doublet at 4.82 ppm originated by the resonance of the methine proton on the chiral center. In the high-frequency spectral region, the 3,5-dinitrophenyl protons, named as H_b and H_a, produce a doublet centered at 8.97 ppm and a triplet at 9.19 ppm, respectively. The biselector triazine **2** (molar ratio **2**/**5** = 1:1) induces significant nonequivalences on the two enantiomers of **5**: as shown in Figure 1b, the 3,5-dinitrophenyl protons H_a and H_b produce two triplets at 9.13 and 9.11 ppm and two doublets at 8.91 and 8.93 ppm, both corresponding to a nonequivalence ($\Delta\Delta\delta$, difference between the chemical shifts of corresponding protons of the two enantiomers in the presence of the chiral auxiliary) of 7.3 Hz. Two partially superimposed multiplets ($\Delta\Delta\delta$ = 2.8 Hz) are obtained for the methine proton and two sharp well-separated singlets for the OMe protons ($\Delta\Delta\delta$ = 5.3 Hz). In the presence of equimolar amounts of the monoselector triazine **1**, only a small doubling of some resonances is observed, the measured nonequivalences being 1.1 Hz for the methine proton and 1.4 Hz for OMe; the other proton resonances remain practically unchanged (Table 1). The triselector triazine **3** (Figure 1c) induces a minor separation of the H_b absorptions, but remarkably higher nonequivalences are measured for the other aromatic proton H_a ($\Delta\Delta\delta$ = 22.6 Hz) and methine proton ($\Delta\Delta\delta$ = 5.0 Hz). Also the separation between the OMe signals (15.0 Hz) is remarkably greater than that measured in the presence of **2**.

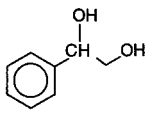
Analogous results have been obtained in the case of the other 3,5-dinitrobenzoyl amino acids methyl esters **6**−**10** (Table 2), i.e., triazines **2** and **3** are both able to induce relevant nonequivalences in the two enantiomers, although it is not possible to make a generalization about the nature of the amino acids sites which are more sensitive to the presence of one or the other chiral

Chart 4

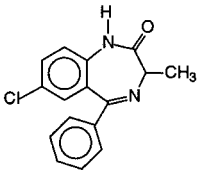
R	R'	R"	
Methyl	t-Butyl	4-(OMe)Ph	**20a**
Phenyl	H	Butyl	**20b**
Isopropyl	H	2-Naphthyl	**20c**
Methyl	H	C≡CH	**21a**
t-Butyl	H	C≡CH	**21b**
H	Phenyl	C≡CH	**21c**
t-Butyl	Methyl	C≡CH	**21d**
Methyl	Phenyl	C≡CH	**21e**



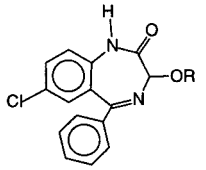
22



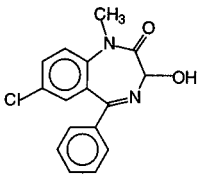
23



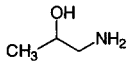
24



25
R=$CO(CH_2)_2COOH$

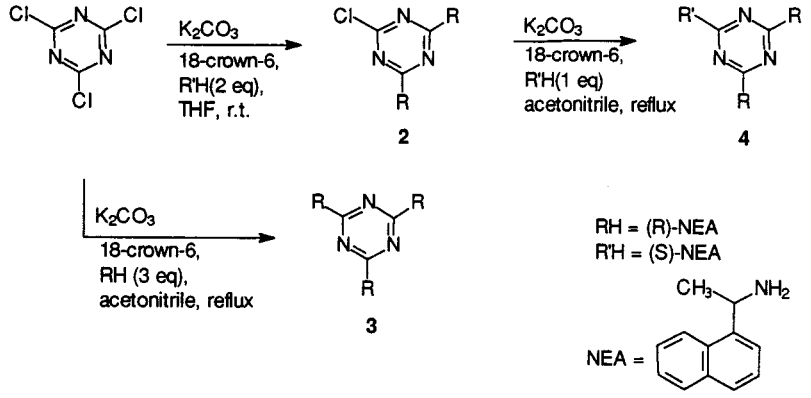


26



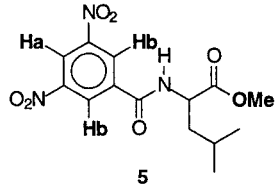
27

Scheme 1



auxiliary. The important result is that in each case an accurate integration of the diastereotopic signals of the two enantiomers can be performed, and, overall for the sharp OMe singlets, the enantiomeric composition can be accurately determined also by comparing their heights (the bandwidth of these absorptions are equal).

The expected increase of the nonequivalence is observed on increasing the molar ratio CSA/substrate (Table 1); in the presence of 2 equiv of the chiral auxiliary **3**, the separations between the diastereotopic methine and OMe signals of the two enantiomers increase to 8.2 and 25.3 Hz, respectively. Surprisingly, when less than



5

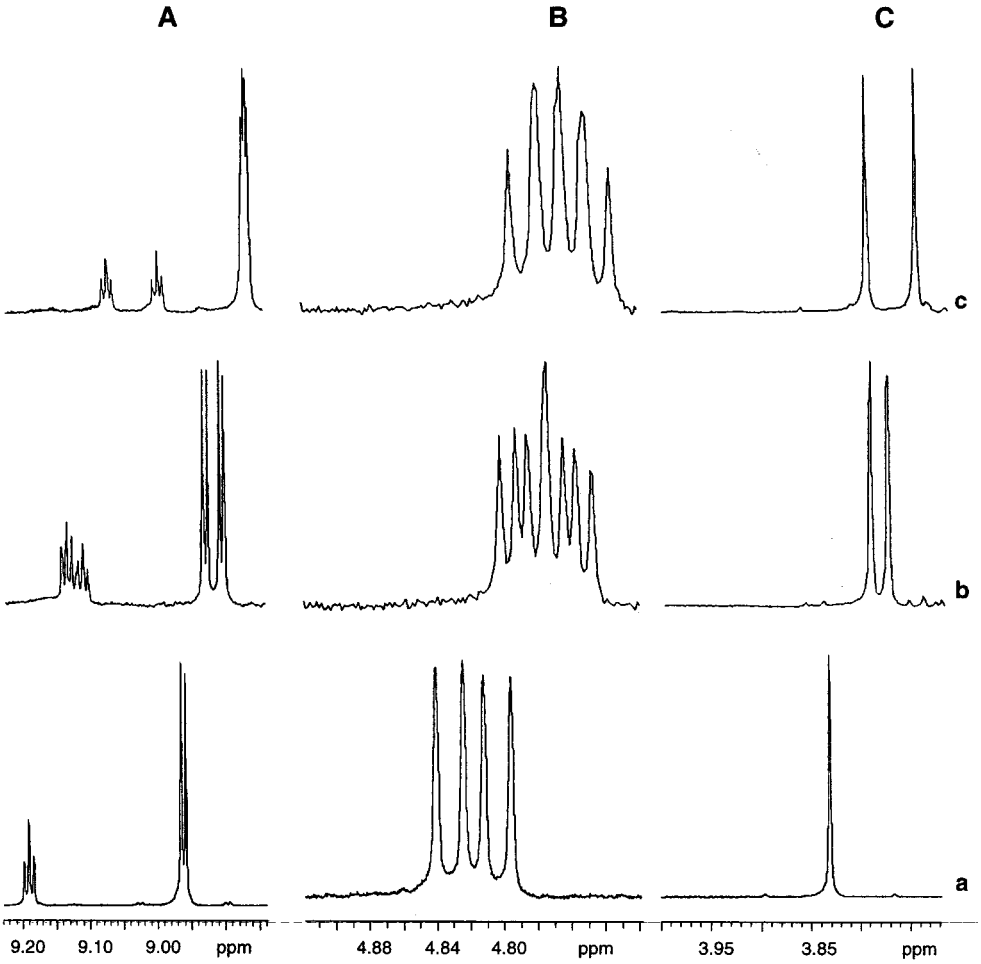


Figure 1. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, ppm referred to TMS as internal standard) spectral regions corresponding to the 3,5-dinitrobenzoyl (A), CH (B), and COOMe (C) proton absorptions of racemic **5** (20 mM): (a) free compound; (b) equimolar mixture of **2**/(*R*,*S*)-**5**; (c) equimolar mixture of **3**/(*R*,*S*)-**5**.

Table 1. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) Nonequivalences ($\Delta\Delta\delta$, Hz, Difference between the Chemical Shifts of Corresponding Protons of the Two Enantiomers) for Protons of 5 in the Presence of the CSAs 1, 2, or 3 at Different Molar Ratios of Substrate:CSA

	$\Delta\Delta\delta$						
	1	**2**		**3**			
	1:1	1:1	2:1	1:1	2:1	3:1	1:2
H_a	0	7.3	6.6	22.6	19.9	16.6	17.2
H_b	0	7.3	7.0	0.8	0	0	0
CH[a]	1.1	2.8	2.4	5.0	3.6	3.0	8.2
OMe	1.4	5.3	4.9	15.0	13.4	11.8	25.3

[a] Proton at the chiral center.

Table 2. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) Nonequivalences ($\Delta\Delta\delta$, Hz, Difference between the Chemical Shifts of Corresponding Protons of the Two Enantiomers) Measured in the Presence of Equimolar Amounts of Triazines 2 or 3 for Protons of the Aminoacid Derivatives 5−14

		$\Delta\Delta\delta$			
		H_a	H_b	CH[a]	OMe
5	**2**	7.3	7.3	2.8	5.3
5	**3**	22.6	0.8	5.0	15.0
6	**2**	24.3	15.8	0	6.5
6	**3**	2.1	6.5	5.3	11.0
7	**2**	29.9	20.3	6.0	9.9
7[b]	**2**	27.0	18.2	6.0	8.9
7	**3**	15.2	2.0	8.6	18.9
8	**2**	8.7	9.2	2.4	6.5
8	**3**	25.5	2.5	0	14.1
9	**3**	15.7	0	2.9	7.2
10	**2**	11.4	10.8	7.1	5.0
11	**2**	8.7	9.3	4.7	
11	**3**	22.7	0.8	4.8	
12	**2**	8.7	9.8	4.4	
12[b]	**2**	8.1	8.8	4.3	
13[c] (NH)	**3**	9.0			
13[c] (CH_3)	**3**	3.2			
14	**3**	13.6	14.9		

[a] Proton at the chiral center. [b] Molar ratio of substrate:CSA = 2:1. [c] The reported nonequivalence data are referrred to the protons specified in the parentheses.

1 equiv of CSA is present, the nonequivalence remains nearly unchanged as shown in Table 1. Therefore the two triazines **2** and **3** behave rather differently relative to the commonly used CSAs: in fact, equimolar or high ratios CSA/substrate mixtures must be usually employed to obtain satisfactory nonequivalences by diamagnetic chiral auxiliaries for NMR spectroscopy and the magnitudes of the doublings drop when minor amounts of the CSA are employed.[1] This fact can be considered an advantageous property of this kind of solvating agent, as minor amounts of the CSA are required.

The effect of structural changes in the amino acid derivatives on the nonequivalences has been investigated: as far as the ester group is concerned, very similar nonequivalences of the 3,5-dinitrobenzoyl and methine protons of **5**, **11**, and **12**, respectively having a methyl, *n*-butyl, and isopropyl group (Table 2), are measured in the presence of **2**, and the same has been verified for **5** and **11** in the presence of equimolar amounts of **3**. Furthermore, the above-discussed dependence of the nonequivalence from the molar ratio CSA/substrate has been confirmed, as practically identical values are measured in the mixtures of **12**/**2** at the molar ratios of 1:1 and 2:1.

Table 3. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) Nonequivalences ($\Delta\Delta\delta$, Hz, Difference between the Chemical Shifts of Corresponding Protons of the Two Enantiomers) Measured in the Presence of Equimolar Amounts of Triazines 2 or 3 for Derivatized Amines (15 and 16), Amino Alcohols (17a and 17c), and Acids (18)

	$\Delta\Delta\delta$		
	H_a	H_b	CH[a]
15a/3	5.7	7.3	10.0
15b/3	0	0	0
16/3	10.2	10.0	37.3
17a/2	1.3	1.2	1.6
17a/3	12.3	7.0	8.8
17c/3			2.2
18/2	2.1	4.0	0
18/3	6.6	1.9	14.8
18/3[b]	14.9	26.9	57.2

[a] Proton at the chiral center. [b] Nonequivalences measured at −10 °C.

Therefore, the efficiency of the two triazines **2** and **3** is comparable when the amino acids contain a 3,5-dinitrobenzoyl and an ester group. This changes dramatically for different kinds of derivatives: the pentafluorobenzoyl valine methyl ester (compound **13**) or the phenyl alanine derivative bearing a 3,5-dinitrobenzoyl moiety but having an unprotected acid function (compound **14**) still shows significant doubling in the presence of **3**, but they are not discriminated by **2** (Table 2).

B. 3,5-Dinitrophenyl and 2-Naphthoyl Derivatives of Amines, Amino Alcohols, and Acids (Chart 3). The usefulness of **2** and **3** as CSAs for determining the enantiomeric purities of different kinds of compounds containing a 3,5-dinitrophenyl moiety has been also evaluated, and to this aim, the *N*-3,5-dinitrobenzoyl derivatives of α-phenylethylamine (**15a**,**b**), 2-amino-1-phenyl-1-ethanol (**17a**), 1-(2-naphthyl)ethylamine (**16**), and the *N*-3,5-dinitrophenyl-2-(*p*-isobutylphenyl)propionamide (**18**) have been considered. One equivalent of **3** induces relevant doubling of the H_a, H_b, and CH protons (12.3, 7.0, and 8.8 Hz) of the amino alcohol derivative **17a** (Table 3). Remarkably minor nonequivalences are induced by **2** of less than 2.0 Hz. The introduction of a different derivatizing group as in **17c**, bearing an *N*-2-naphthoyl group does not prevent splitting of the enantiomeric absorption in the presence of **3**, but no doubling is detected in the presence of **2**. Analogously, in the mixture **18**/**2**, only doubling of the 3,5-dinitrophenyl protons is observed; in the presence of **3**, under the same experimental conditions, remarkably higher nonequivalences are measured and its protons are all split.

When the temperature is lowered only to −10 °C, the nonequivalences undergo a significant increase. As an example, for the H_b protons, a separation of about 27 Hz is measured, and the separation between the methine proton absorption undergoes a 4-fold increase.

The behavior of the amine derivatives **15a** and **16**, respectively bearing a phenyl and 2-naphthyl moieties, has been checked only in the presence of the trisubstituted triazine, which produced satisfactory nonequivalences of the 3,5-dinitrobenzoyl and methine protons in both cases (Table 3). However, the triazine **3** fails to induce nonequivalence when a *N*-methyl group is introduced into **15** (compound **15b**).

Therefore, a very large range of compounds, amines, amino alcohols, or acids, bearing a 3,5-dinitrophenyl moiety can be analyzed with both **3** and **2** as CSAs; however, **2** is less efficient than **3**.

Table 4. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) Nonequivalences ($\Delta\Delta\delta$, Hz, Difference between the Chemical Shifts of Corresponding Protons of the Two Enantiomers) Measured in the Presence of Equimolar Amounts of Triazines 2 or 3 for Underivatized Chiral Compounds

		$\Delta\Delta\delta$		
		CH[a]	**R**	R
24/3	**CH_3**, NH	3.2	2.1	4.1
26/3	**N-CH_3**	2.0	5.3	
25/2	**COOH**	0	0	
25/2[b]	**COOH**	1.2	3.9	
25/3	**COOH**	4.7	61.8	
20a/3	**CH**, $(CH_3)_2$	4.9	2.9	4.1
20b/3	**tBu**, CH_3		1.2	1.7
20c/3		2.2		
22/3	**CH**, $(CH_3)_2$		1.5	1.7
23/3	C**H**H	2.5	5.7	4.3
23/3[b]	C**H**H	5.0	11.3	8.9
21a/3	**C≡CH**, CH_3		1.5	1.2
21b/3	**C≡CH**, C(CH_3)		3.7	1.6
21c/3	**C≡CH**, H		9.3	2.2
21d/3	**C≡CH**, C(CH_3)		1.1	1.1
21e/3	**C≡CH**, CH_3		7.7	2.0
17b/3	**CH_3**	0	2.3	
17b/3[b]	**CH_3**	4.8	1.6	
19/3		8.9		
27/3	**CH_3**	0	0	

[a] Proton at the chiral center. [b] Molar ratio of 1:2.

Table 5. ^{1}H NMR (300 MHz, $CDCl_3$,25°C) Nonequivalences ($\Delta\Delta\delta$, Hz, Difference between the Chemical Shifts of Corresponding Protons of the Two Enantiomers) Measured in the Presence of Equimolar Amounts of the Two Diastereoisomeric Triazines 3 and 4

	$\Delta\Delta\delta$	
	4	**3**
7 (H_a)	6.9	15.2
7 (H_b)	0	2.0
7 (CH)	0	8.6
7 (OCH_3)	7.3	18.9
15a (H_a)	2.1	5.7
15a (H_b)	2.8	7.3
21e (C≡CH)	3.4	7.7
21e (CH_3)	0.8	2.0
18 (H_a)	4.4	6.6
18 (H_b)	2.0	1.9
18 (CH)	7.0	14.8
19 (CH)	2.9	8.9
19 (CH_3)		1.6

C. Underivatized Compounds (Charts 3 and 4).

The encouraging results described above prompted us to extend the use of triazine derivatives to underivatized substrates. In all cases examined, the disubstituted triazine **2** did not show satisfactory enantiodiscriminating ability, whereas **3** was efficient and also versatile.

In the case of hydroxy compounds (carbinols **20**, binaphthol **22**, and diol **23**), doubling of some proton absorptions is always observed in the presence of 1 equiv of **3** (Table 4), and the nonequivalences can be increased sufficiently to perform an accurate enantiomeric purity determination by increasing the molar ratio of CSA/substrate or lowering the temperature. However, the most interesting application of **3** to the hydroxy compounds regards the analysis of propargyl alcohols **21**, important intermediates for synthesis: independent of the nature of the groups bound to the chiral center, nonequivalences are always measured for the acetylene proton and also suitable alkyl protons can be considered for the evaluation of the enantiomeric ratios (Table 4).

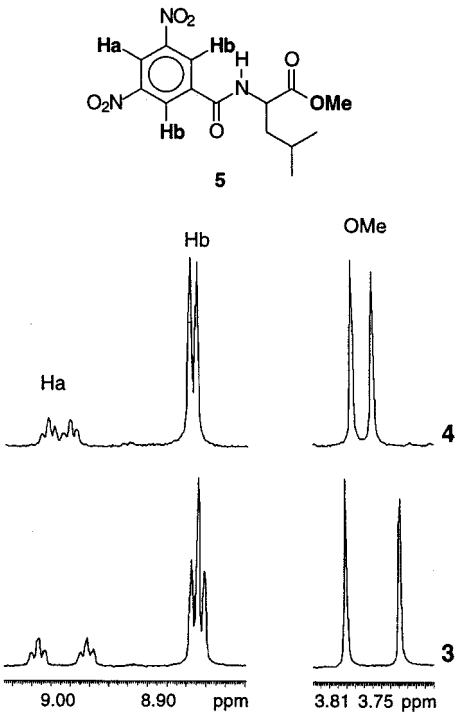


Figure 2. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, ppm referred to TMS as internal standard) spectral regions corresponding to the 3,5-dinitrobenzoyl and COOMe proton absorptions of racemic **5** (20 mM) in the presence of equimolar amounts of **3** and **4**.

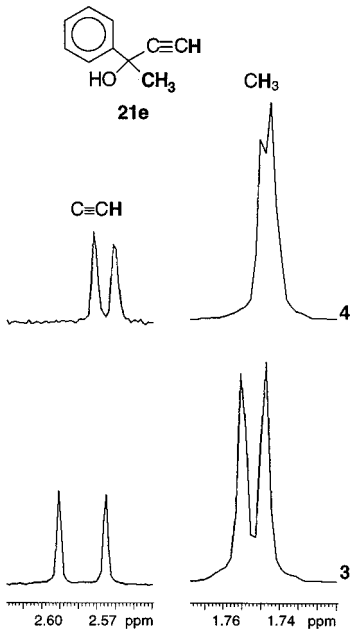


Figure 3. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, ppm referred to TMS as internal standard) spectral regions corresponding to the acetylene and methyl proton absorptions of racemic **21e** (20 mM) in the presence of equimolar amounts of **3** and **4**.

In addition to testing the analysis of chiral alcohols by use of **3**, we attempted to analyze free acids (**19**) and amino alcohols (**17b** and **27**). Satisfactory nonequivalence has been measured for the methine (8.9 Hz) proton of ibuprofen (**19**) and a small but detectable doubling (2.3 Hz) of the *N*-methyl protons of **17b** was obtained; in this last case, in the presence of 2 equiv of **3**, the methine

resonance at the chiral center also feels the presence of the chiral auxiliary, undergoing a doubling of about 5.0 Hz.

Additionally, the benzodiazepines **24** and **26** and the hemisuccinate derivative of oxazepam (**25**) were discriminated by **3**, and the corresponding nonequivalence data are summarized in Table 4.

The presence of an OH or COOH group seems to be mandatory, as no nonequivalence is measured in the case of free amines; furthermore, in the case of amino alcohols, the presence of an aromatic group is required, as the compound **27** is not discriminated by **3**.

D. Diastereoisomeric Triazines 3 and 4. Finally, the efficiency as CSAs of the two diastereoisomeric trisubstituted triazines **3** and **4** has been compared at the same experimental conditions (total concentration 20 mM, molar ratio 1:1, 25 °C).

As a general trend, although triazine **4** discriminates between the enantiomers of all of the above-described substrates, its efficiency is minor relative to the diastereoisomer **3**, and Table 5 collects some comparison results. It can be observed that also in the most favorable case of the 3,5-dinitrobenzoyl derivatives of amino acids, remarkably lower nonequivalences are induced by **4** and no doubling at all is observed for some protons. Also in the case of propargyl alcohols, free acids, or their derivatives, **4** is a less efficient CSA than **3** is. Figures 2 and 3 report the comparison between the NMR spectra of some mixtures of **3**/substrate or **4**/substrate.

Conclusions

In the development of multiselector chiral auxiliaries, triazine derivatives open interesting new perspectives. Compounds **2** and **3**, respectively having two and three chiral 1-(1-naphthyl)ethylamino groups bonded to the triazine nucleus, are very attractive chiral solvating agents for NMR spectroscopy. The experimental procedures involved in their preparation are quite simple, their proton signals are found in limited spectral regions, and they are also readily soluble in $CDCl_3$, the solvent most commonly employed. These chiral auxiliaries allowed us to cover a wide range of analysis: both of them induced significant nonequivalences in the proton nuclei of enantiomers of 3,5-dinitrophenyl derivatives of amines, amino acids alkyl esters, amino alcohols, and acids, but **3** also produced enantiodiscrimination in underivatized chiral compounds, showing a remarkable versatility toward hydroxy compounds. It is noteworthy that the corresponding chiral auxiliary **1**, containing only one 1-(1-naphthyl)ethylamino moiety, only discriminated the 3,5-dinitrobenzoyl derivatives of amines and amino acids and that in these cases quite poor nonequivalences were obtained, remarkably lower than with **2** and **3**, thus confirming the higher efficiency of multiselector chiral auxiliaries in enantiodiscrimination processes.

Experimental Section

General. Melting points were taken using a Reichart Termovar apparatus and are uncorrected. Optical rotations were measured in a 1 dm tube. TLC analysis were performed using silica gel plates (Si 60). Flash chromatography was performed using silica gel (230−400 mesh). Elemental analyses were performed by the Microanalytical Laboratory of the University of Pisa.

NMR measurements were performed on a spectrometer, operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C or a spectrometer, operating at 200 MHz for ^{1}H, equipped with a temperature control unity (±0.1 °C).

Materials. Tetrahydrofuran (THF) and diethyl ether were distilled from Na/K alloy, and acetonitrile and triethylamine were distilled from CaH_2. 2,4,6-Trichloro-1,3,5-triazine was purchased from Aldrich Chemical Co. and was recrystallized from CCl_4. (*R*)-1-(1-Naphthyl)ethylamine and (*S*)-1-(1-naphthyl)ethylamine were purchased from Fluka Chemical Co. and were distilled under reduced pressure. Unless noted, all other reagents were used without purification.

2-Hexylamino-4-ethoxy-6-[(*S*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine was prepared as described elsewhere and matched the reported characteristics.[2]

Temazepam was purchased from Sigma Chemical Co. 1,2-Dihydroxyphenylethane was purchased from Fluka.

Literature methods were used to prepare the aroyl amides of amino acid alkyl esters[7] and of 2-amino-1-hydroxy-1-phenylethane,[8] the alkylarylcarbinols,[9] the propargyl alcohols,[10] and the hemisuccinate of oxazepam.[11]

The binaphthyl derivative **22** was prepared according to the procedure of Pirkle.[12] The preparation of 3,5-dinitrophenylanilide of ibuprofen was described elsewhere.[13]

The benzodiazepine **24** was kindly provided by Prof. W. H. Pirkle (School of Chemical Science, University of Illinois at Urbana−Champaign).

2-Chloro-4,6-bis[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (2). To a solution of 2,4,6-trichloro-1,3,5-triazine (0.51 g, 2.77 mmol) in dry THF (25 mL) were added K_2CO_3 (0.76 g, 5.54 mmol) and a catalytic amount of 18-crown-6. The mixture was cooled to 0 °C, and a solution of (*R*)-1-(1-naphthyl)ethylamine (0.95 g, 5.54 mmol) in dry THF (15 mL) was added dropwise. The mixture was stirred at room temperature, monitoring the reaction by TLC (hexane/EtOAc 1:1). After 6 days, the mixture was centrifuged and the solvent was evaporated under reduced pressure. Flash chromatography (SiO_2, hexane/AcOEt 1:1) of the crude product afforded 2-chloro-4,6-bis[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (**2**) (1.2 g, 95%) as a foaming solid: mp 68−71 °C, $[\alpha]_D^{19}$ +62.08 (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C, δ/ppm) 8.14 (d, 2H, H_8), 7.89 (d, 2H, H_5), 7.77 (d, 2H, H_4), 8.60 (m, 4H, H_7 and H_6), 7.45 (m, 4H, H_3 and H_2), 5.78 (br s, 2H, C*H*), 1.37 (br s, 6H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, 120 °C, δ/ppm) 164.4, 167.7 (3C, triazinics), 139.5, 133.1, 130.0 (6C, C_1, C_9, C_{10}) 128.1 (2C, C_5), 126.6 (2C, C_4), 125.4 (2C, C_6), 124.8 (4C, C_2, C_3), 122.4 (4C, C_8, C_7), 45.7 (2C, *C*H), 20.7 (2C, *C*H_3). Anal. Calcd for $C_{27}H_{24}ClN_5$: C, 71.44; H, 5.33; Cl, 7.81; N, 15.43. Found: C, 71.37; H, 5.32; Cl, 7.81; N, 15.42.

2,4,6-Tris[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (3). To a solution of 2,4,6-trichloro-1,3,5-triazine (0.35 g, 1.94 mmol) in dry CH_3CN (30 mL) were added K_2CO_3 (0.80 g, 5.83 mmol), a catalytic amount of 18-crown-6, and (*R*)-1-(1-naphthyl)ethylamine (1.00 g, 5.83 mmol). The mixture was stirred at reflux, monitoring the reaction by TLC (AcOEt/hexane 4:6). After 7 days, the mixture, cooled to room temperature, was centrifuged and the solvent was evaporated under vacuum. Flash chromatography (SiO_2, AcOEt/hexane 4:6) of the crude product gave 2,4,6-tris[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (**3**) (0.70 g, 60%) as a foaming solid: mp 104−106 °C, $[\alpha]_D^{25}$ −62.00 (*c* 1.09, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6,

(7) Salvadori, P.; Pini, D.; Rosini, C.; Uccello-Barretta, G.; Bertucci, C. *J. Chromatogr.* **1988**, *450*, 163.

(8) Salvadori, P.; Rosini, C.; Pini, D.; Bertucci, C.; Uccello-Barretta, G. *Chirality* **1989**, *1*, 161.

(9) Pini, D.; Rosini, C.; Bertucci, C.; Altemura, P.; Salvadori, P. *Gazz. Chim. Ital.* **1986**, *116*, 603.

(10) (a) Campbell, K. N.; Campbell, B. K.; Eby, L. K. *J. Am. Chem. Soc.* **1938**, *60*, 2882. (b) Papa, D.; Villani, F. J.; Ginsberg, H. F. *J. Am. Chem. Soc.* **1954**, *76*, 4446.

(11) Bertucci, C.; Domenici, E.; Uccello-Barretta, G.; Salvadori, P. *J. Chromatogr.* **1990**, *506*, 617.

(12) Pirkle, W. H.; Schreiner, J. L. *J. Org. Chem.* **1981**, *46*, 4988.

(13) Uccello-Barretta, G.; Cuzzola, A.; Menicagli, R.; Balzano, F.; Iuliano, A.; Salvadori, P. *J. Org. Chem.* **1997**, *62*, 827.

120 °C, δ/ppm) 8.20 (d, 3H, H_8), 7.87 (d, 3H, H_5), 7.74 (d, 3H, H_4), 7.50 (m, 6H, H_7 and H_6), 7.42 (m, 6H, H_3 and H_2), 6.46 (br s, 3H, N*H*), 5.86 (br s, 3H, C*H*), 1.36 (s, 9H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, 120 °C, δ/ppm) 164.8 (3C, triazinics), 140.7, 133.1, 130.1 (9C, C_1, C_9, C_{10}), 127.9 (3C, C_5), 126.3 (3C, C_4), 125.2 (3C, C_6), 124.8 (3C, C_2), 124.6 (3C, C_3), 122.8 (3C, C_8), 122.1 (3C, C_7), 44.8 (3C, *C*H), 21.2 (3C, *C*H_3). Anal. Calcd for $C_{39}H_{36}N_6$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.58; H, 6.16; N, 14.28.

2,4-Bis[(*R*)-1-(1-naphthyl)ethylamino]-6-[(*S*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (4). To a solution of 2-chloro-4,6-bis[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (0.50 g, 1.10 mmol) in dry CH_3CN (30 mL) were added K_2CO_3 (0.15 g, 1.10 mmol), a catalytic amount of 18-crown-6 and (*S*)-1-(1-naphthyl)ethylamine (0.19 g, 1.10 mmol). The mixture was stirred at reflux, monitoring the reaction by TLC (AcOEt/hexane 4:6). After 7 days, the mixture, cooled at room temperature, was centrifuged and the solvent was evaporated under vacuum. Flash chromatography (SiO_2, AcOEt/hexane 4:6) of the crude product gave 2,4-bis[(*R*)-1-(1-naphthyl)-ethylamino]-6-[(*S*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine (**4**) (0.40 g, 66%) as a foaming solid: mp 103−105 °C, $[\alpha]_D^{25}$ −20.6 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C, δ/ppm) 8.20−6.80 (m, 21H, aromatics), 6.38 (br s, 3H, *N*H), 5.87 (m, 3H, C*H*), 1.54 (d, 6H, CH_3), 1.45 (d, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, 120 °C, δ/ppm) 164.9 (3C, triazinics), 140.6 133.1, 130.1 (9C, C_1, C_9, C_{10}), 127.9 (3C, C_5), 126.3 (3C, C_4), 125.2 (3C, C_6), 124.8 (3C, C_2), 124.6 (3C, C_3), 122.8 (3C, C_7), 122.2 (3C, C_8), 44.9 (3C, *C*H), 21.4 21.3 (3C, *C*H_3). Anal. Calcd for $C_{39}H_{36}N_6$: C, 79.56; H, 6.16; N, 14.27. Found: C, 79.58; H, 6.16; N, 14.26.

***N*-(3,5-Dinitrobenzoyl)alkylarylamines: General Procedure.** To a solution of the amine (16 mmol) and triethylamine (18 mmol) in dry diethyl ether was added dropwise a solution of 3,5-dinitrobenzoyl chloride (16 mmol) in dry diethyl ether. After 24 h of stirring at room temperature, the triethylamonium hydrochloride was filtered off, and the ethereal phase was washed with a 10% solution of HCl, a 10% solution of $NaHCO_3$, and H_2O (in that order) and then dried (Na_2SO_4). The solvent was evaporated under vacuum, and the crude product was recrystallized from $CHCl_3$−hexane.

***N*-(3,5-Dinitrobenzoyl)-1-phenylethylamine:** yield 86%; ^{1}H NMR (200 MHz, $CDCl_3$, δ/ppm) 9.2 (t, 1H, aromatic), 8.9 (d, 2H, aromatics), 8.4−7.3 (m, 5H, aromatics), 6.1 (d, 1H, amidic), 5.5 (m, 1H, C*H*), 1.7 (d, 3H,CH_3). Anal. Calcd for $C_{15}H_{13}N_3O_5$: C, 57.14; H, 4.16; N, 13.33. Found: C, 57.03; H, 4.16; N, 13.32.

***N*-(3,5-Dinitrobenzoyl)-1-(2-naphthyl)ethylamine:** yield 80%; ^{1}H NMR (200 MHz, $CDCl_3$, δ/ppm) 9.1−8.9 (m, 3H, aromatics), 8.0−7.4 (m, 7H, aromatics), 6.9 (d, 1H, amidic), 6.0 (m, 1H, C*H*), 1.7 (d, 3H,CH_3). Anal. Calcd for $C_{19}H_{15}N_3O_5$: C, 62.46; H, 4.14; N, 11.50. Found: C, 62.49; H, 4.14; N, 11.51.

***N*-(3,5-dinitrobenzoyl)-*N*′-methyl-1-phenylethylamine:** yield 54%; ^{1}H NMR (200 MHz, $CDCl_3$, δ/ppm) 9.2 (t, 1H, aromatic), 8.6 (d, 2H, aromatics), 7.6−7.3 (m, 5H, aromatics), 6.1 (m, 1H, C*H*), 2.8 (d, 3H, NCH_3), 1.6 (d, 3H, CH_3). Anal. Calcd for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.76. Found: C, 58.39; H, 4.59; N, 12.77.

Acknowledgment. This work was supported by the Ministero della Ricerca Scientifica e Tecnologica (MURST) and CNR, Italy.

JO9806153