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Tetrahedron
Tetrahedron 63 (2007) 5490–5500

Efficient dual catalytic enantioselective diethylzinc addition to the exocyclic C=N double bond of some 1,2,4-*N*-triazinylarylimines using polymer-supported chiral β-amino alcohols derived from norephedrine

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Received 19 January 2007; revised 26 March 2007; accepted 12 April 2007
Available online 19 April 2007

Abstract—Chiral *N*,*N*-dialkylnorephedrines and their corresponding copolymers were evaluated as chiral ligands for the enantioselective diethylzinc addition to the exocyclic C=N double bond of some 4-arylideneamino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-ones **2a–f**. The use of a dual catalytic system (amino alcohol/halosilane) in the titled asymmetric reaction was examined. The enantioselective ethylation reaction has been successfully carried out in the heterogeneous system even at low temperature. The corresponding 4-(1-arylpropyl)amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-ones **4a–f** were obtained in high yields with high enantioselectivities using chiral polymers (up to 91% ee), which are almost the same as those obtained from homogeneous analogues (up to 92% ee). The diethylzinc reagent neither opened the 1,2,4-triazinyl heterocyclic ring nor attacked the carbonyl or the thione groups of the 1,2,4-triazinyl heterocyclic ring and the addition reaction took place exclusively at the exocyclic electrophilic carbon atom yielding the *C*-ethylated products **4a–f**. Reductive cleavage of the 1,2,4-triazinyl heterocyclic ring led smoothly to the corresponding primary aromatic amines **11a–f** without significant loss of enantiomeric purity. A suggestion about the possible transition state for the addition reaction is also presented.

1. Introduction

Since homogeneous reagents and catalysts have been found to be more efficient in asymmetric synthesis than their heterogeneous counterparts, the immobilization of homogeneous reagents and catalysts is of great interest.[1] The use of polymer-bound chiral ligands offers the advantages of solid phase organic synthesis; their easy separation from the reaction mixture and the easy reuse are major advantages of polymer-supported chiral reagents over homogenous chiral reagents.[2]

The synthetic usefulness of enantiomerically pure amines has stimulated great interest in developing methods for the asymmetric preparation of such molecules.[3] The asymmetric addition of organometallic reagents to the C=N double bonds is amongst the most important reactions for the synthesis of optically active amines. We have previously reported on the enantioselective allylation of various prochiral imines using various chiral ligands including chiral amino alcohols and their corresponding copolymers affording the corresponding optically active homoallylic amines in quantitative yields with enantioselectivities up to 96% ee.[4] Diastereoselective allylation of chiral imines derived from (*S*)-valine activated by Lewis acids, which afforded the corresponding optically active secondary homoallylic amines in excellent yields with perfect diastereoselectivities has been also developed by us.[5]

The enantioselective addition of diorganozinc reagents to imines, as a route to optically active amines, has recently received much attention, due to the good tolerance of various functionalities with respect to organolithiums and Grignard reagents.[6] As a result of the poor electrophilic character of imines, several quite effective methods based on the catalytic enantioselective dialkylzinc addition to imines have been recently developed.[7]

The addition of nucleophiles such as Grignard reagents and alkylithiums to the exocyclic C=N double bond of 4-arylideneamino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-ones **2**, prepared from the reaction of **1** with the corresponding aldehyde,[8] in the existence of C=O and C=N groups of the triazine heterocyclic ring had been difficult and the obtained

Keywords: Polymeric reagents and catalysts; Chiral polymers; 1,2,4-Triazines; Arylimines; Dual catalytic; Enantioselective ethylation; Lewis acids.
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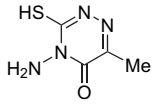
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.04.041

results proved that this heterocyclic ring was particularly sensitive towards such reagents.[9] However, we have recently reported on the successful chemoselective addition of various allylmetal reagents in homogeneous and heterogeneous systems to the exocyclic C=N double bond of some aldiminomercaptotriazinones **2**, in the presence of Lewis acids as activators, without any possibility for attacking the 1,2,4-triazine nucleus.[10] We have further recently reported on the first evaluation of 4-arylideneamino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-ones **2**, activated by halosilanes as Lewis acids, in the diethylzinc addition reaction, using chiral β-amino alcohols (1*S*,2*R*)-*N*-alkyl-*N*-benzylnorephedrines **3a–d** as homogeneous chiral ligands.[11] The enantioselective diethylzinc addition to the exocyclic C=N double bond of arylimines **2** proceeded smoothly affording the corresponding optically active secondary amines with high yields and with enantiomeric excesses up to 92% ee.

Thus, we wish here to extend this study to the enantioselective addition of diethylzinc to such arylimines using chiral β-amino alcohols derived from norephedrine supported on polystyrene in comparison with the results that are obtained from the corresponding low-molecular-weight counterparts. A suggestion about the possible transition state for the addition reaction is also presented.



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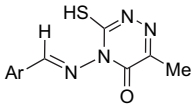

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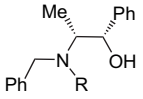
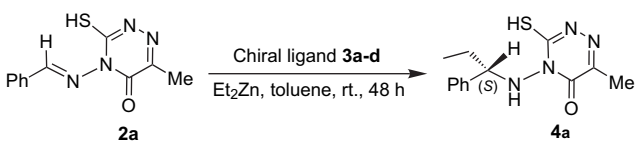


3

(1*S*, 2*R*)-**3a**: R = H
(1*S*, 2*R*)-**3b**: R = Me
(1*S*, 2*R*)-**3c**: R = Et
(1*S*, 2*R*)-**3d**: R = *n*-Bu

2. Results and discussion

In order to design a highly enantioselective polymeric chiral ligand, it is necessary to consider the related monomeric chiral ligands that would afford a highly enantioselective reaction. We have recently investigated the enantioselective diethylzinc addition to various *N*-triazinylarylimines using chiral β-amino alcohols derived from norephedrine as chiral ligands.[11] We first investigated the asymmetric ethylation reaction of 4-benzylideneamino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one **2a** as a standard substrate with diethylzinc (3 equiv) in the presence of an equimolar amount of chiral amino alcohols (1*S*,2*R*)-**3a–d** as chiral ligands in toluene at room temperature (Scheme 1). The obtained results are summarized in Table 1.



2a **4a**

Scheme 1.

The results in Table 1 showed that *N*,*N*-disubstituted chiral ligands (1*S*,2*R*)-**3b–d** showed relatively higher reactivity and stereoselectivity than *N*-monosubstituted chiral ligand **3a**. Among chiral ligands examined, (1*S*,2*R*)-*N*-benzylephedrine **3b** that possesses benzyl and methyl substituents on its nitrogen atom was found to be the most effective for the enantioselective diethylzinc addition to benzaldimine **2a** (55% yield, 79% ee, entry 2, Table 1). The chiral amino alcohol **3c** possessing ethyl group on its nitrogen resulted in a slightly diminished 76% ee (entry 3). Further increase in the bulkiness of the R group by replacement of the methyl of **3b** with *n*-butyl group of **3d** led to significant decreases in each of the chemical and optical yields (33% yield, 70% ee, entry 4), probably because the catalytic activity decreases due to steric hindrance on the nitrogen atom. It is worth mentioning that when the diethylzinc addition reaction to benzaldimine **2a** was performed for 5 days, in the presence of chiral ligand **3b** that showed the best result, the addition reaction did not go to completion and the product **4a** was obtained in only 69% yield, whilst slightly higher enantioselectivity was observed (82% ee, entry 5, Table 1).

Table 1. Enantioselective diethylzinc addition to benzaldimine **2a** in the presence of chiral ligands (1*S*,2*R*)-**3a–d**[a]

Entry	Chiral ligand	R	Yield[b] (%)	ee[c,d] (%)
1	**3a**	H	14	57
2	**3b**	Me	55	79
3	**3c**	Et	41	76
4	**3d**	*n*-Bu	33	70
5[a]	**3b**	Me	69	82

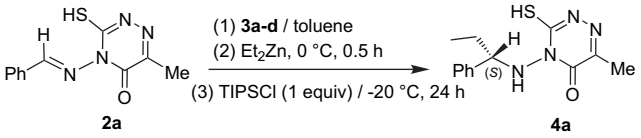
[a] All reactions were performed in the presence of a stoichiometric amount of chiral ligand **3** at room temperature for 48 h except for run 5, which was performed for 5 days.
[b] Isolated yields after flash chromatography (pentane/ethyl acetate: 3:7).
[c] Determined by HPLC analysis using a Chiralcel OD-H column.
[d] The absolute configuration was assigned as the *S*-isomer based on the absolute configuration of the primary amine obtained after reductive cleavage of the 1,2,4-triazinyl heterocyclic ring and comparing its HPLC retention time with the literature value.[11,12]

The addition of silylating agents acting as Lewis acids in the dialkylzinc addition reaction to imines has been reported to enhance the reaction rate through activation of the arylimine substrates, while leaving asymmetric induction untouched.[13] Pericàs and co-workers have successfully applied an interesting approach for the use of a dual catalytic system consisting of a chiral amino alcohol, to control the enantioselectivity of the addition process, and a bulky silylating agent, to further activate the imine substrate.[13b,c] We have recently investigated analogous dual amino alcohol/halosilane mediation for the diethylzinc addition reaction to benzaldimine **2a** using chiral ligand **3b** in conjunction with a stoichiometric amount of different silylating reagents.[11] Among various silylating reagents as well as various reaction conditions examined, the highest level of catalytic activity was observed by adding a stoichiometric amount of silylating agent *i*-Pr_3SiCl (TIPSCl; 95% yield, 84% ee, entry 2, Table 2, Scheme 2).[11]

Table 2. Enantioselective diethylzinc addition to imine **2a** activated by **3a–d**/TIPSCl[a]

Entry	Chiral ligand	R	Yield[b] (%)	ee[c,d] (%)
1	**3a**	H	48	59
2	**3b**	Me	95	84
3	**3c**	Et	91	77
4	**3d**	*n*-Bu	93	73
5[e]	—	—	92	—

[a] Unless otherwise specified, all reactions were carried out in the presence of a stoichiometric amount of chiral ligand **3** and TIPSCl at −20 °C for 24 h.
[b] Isolated yields after flash chromatography (pentane/ethyl acetate: 3:7).
[c] Determined by HPLC analysis using a Chiralcel OD-H column.
[d] The absolute configuration was assigned as the *S*-isomer based on the absolute configuration of the primary amine obtained after reductive cleavage of the 1,2,4-triazinyl heterocyclic ring and comparing its HPLC retention time with the literature value.[11,12]
[e] The reaction was performed in the absence of any chiral ligands.



Scheme 2.

In an extension to the above-mentioned study and under the same reaction conditions that are displayed in Scheme 2, the chiral ligands **3a**, **c**, **d** were tested further in the enantioselective ethylation of benzaldimine **2a** in the presence of a stoichiometric amount of TIPSCl as Lewis acid catalyst (Table 2). As expected, in all cases, the reaction rate was also greatly enhanced and the addition product (*S*)-**4a** was obtained in excellent yields within 24 h of reaction time. Interestingly, the order of catalytic activity of chiral ligands **3a–d** was in complete accordance with that observed for the same reaction in the absence of TIPSCl (see Tables 1 and 2). More interestingly, on performing the above-mentioned reaction with diethylzinc but without using any chiral ligands, the addition product **4a** was obtained in 92% chemical yield as a racemic mixture (entry 5, Table 2). The above-mentioned set of experiments seem to strongly confirm that in the dual catalytic system under investigation, turnover is primarily controlled by the silylating agent, while, as expected, enantioselectivity mainly depends on the presence of the chiral amino alcohol ligand.

The above-mentioned interesting results encouraged us to explore further the use of chiral polymers possessing similar chiral β-amino alcohols as pendant groups in the above-mentioned enantioselective ethylation reaction. There are two main methods to obtain the polymer-supported chiral amino alcohol ligands, namely a chemical modification method and a copolymerization method. However, our previous research on asymmetric reactions using polymer-supported chiral amino alcohols showed that the chemical modification method always resulted in decreased enantioselectivities.[4b,d,14] We have thus decided to employ the copolymerization method, which is the polymerization of a chiral monomer with styrene and a crosslinking agent, to obtain the polymer-supported chiral ligand. For this purpose, the chiral monomers *N*-alkyl-*N*-vinylbenzylnorephedrines **5a–e** were prepared and subjected to polymerization with styrene and divinylbenzene (DVB) as a crosslinker under the conditions of suspension polymerization in aqueous media[4d,15] to afford the corresponding polymer-supported chiral amino β-alcohols **6–10** in good yields (Scheme 3).

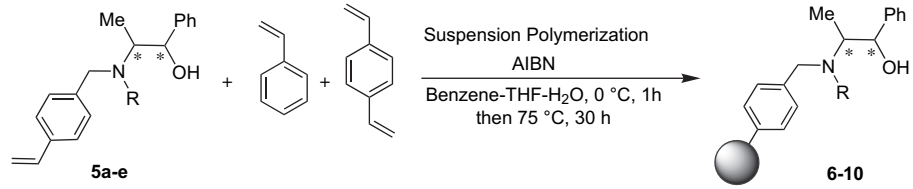
Loading of the chiral amino alcohol residues and the degree of crosslinking were easily controlled by the polymerization method. From chiral amino alcohol (1*S*,2*R*)-**5b**, several polymers **7a–h**, having various crosslinking and loading degrees, were prepared (Table 3). The loading degree of the chiral amino alcohol residues was easily estimated from the elemental analysis of the nitrogen atom.

The synthesized chiral polymers **6–10** were examined as chiral ligands in the enantioselective diethylzinc addition

Table 3. Synthesis of polymer-supported chiral β-amino alcohols **6–10**

Entry	Chiral monomer	Chiral polymer	Molar ratios[a]	Yield (%)	Loading of chiral amino alcohol residues (mmol/g)[b] (DF)[c]
1	(1*S*,2*R*)-**5a**	(1*S*,2*R*)-**6**	1:7:2	91	0.764 (0.10)
2	(1*S*,2*R*)-**5b**	(1*S*,2*R*)-**7a**	1:7:2	89	0.771 (0.10)
3	(1*S*,2*R*)-**5b**	(1*S*,2*R*)-**7b**	1:8:1	93	0.750 (0.10)
4	(1*S*,2*R*)-**5b**	(1*S*,2*R*)-**7c**	1:6:3	90	0.821 (0.10)
5	(1*S*,2*R*)-**5b**	(1*S*,2*R*)-**7d**	1:5:4	94	0.735 (0.10)
6	(1*S*,2*R*)-**5b**	(1*S*,2*R*)-**7e**	2:6:2	91	1.292 (0.20)
7	(1*S*,2*R*)-**5b**	(1*S*,2*R*)-**7f**	3:5:2	90	1.863 (0.30)
8	(1*S*,2*R*)-**5b**	(1*S*,2*R*)-**7g**	4:4:2	95	2.127 (0.40)
9	(1*S*,2*R*)-**5b**	(1*S*,2*R*)-**7h**	5:3:2	87	2.449 (0.50)
10	(1*S*,2*R*)-**5c**	(1*S*,2*R*)-**8**	1:7:2	90	0.792 (0.10)
11	(1*S*,2*R*)-**5d**	(1*S*,2*R*)-**9**	1:7:2	89	0.721 (0.10)
12	(1*R*,2*S*)-**5e**	(1*R*,2*S*)-**10**	1:7:2	93	0.807 (0.10)

[a] Molar ratio of copolymerization: chiral monomer:styrene:DVB.
[b] Determined by elemental analysis.
[c] Degree of functionalization.

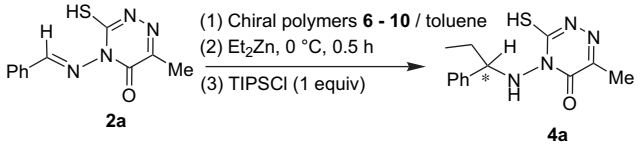


(1*S*, 2*R*)-**5a**: R = H
(1*S*, 2R)-**5b**: R = Me
(1*S*, 2*R*)-**5c**: R = Et
(1*S*, 2*R*)-**5d**: R = *n*-Bu
(1*R*, 2*S*)-**5e**: R = Me

(1*S*, 2*R*)-**6**: R = H
(1*S*, 2R)-**7**: R = Me
(1*S*, 2*R*)-**8**: R = Et
(1*S*, 2*R*)-**9**: R = *n*-Bu
(1*R*, 2*S*)-**10**: R = Me

Scheme 3. Preparation of polymer-supported chiral β-alcohols **6–10**.

reaction to benzaldimine **2a** (Scheme 4). From our survey on the effect of solvent in the enantioselective addition of dialkylzinc reagents to imines using the same family of polymer-supported *N*,*N*-disubstituted norephedrines as chiral ligands, we have found that hexane as well as toluene affords the addition products with higher ee values.[15b,16] Moreover, the nonpolar solvent toluene was found to maximize the rate difference between the catalyzed and noncatalyzed reaction.[12d,17] Based on the above-mentioned findings, toluene was used as a reaction medium.



Scheme 4. Enantioselective diethylzinc addition to benzaldimine **2a** using chiral polymers **6**–**10**.

In the first series of experiments, the copolymers **6**, **7a**, **8** and **9** (molar ratio of copolymerization; chiral monomer:styrene: DVB=1:7:2) were examined as chiral ligands in the enantioselective ethylation of benzaldimine **2a**. In the presence of chiral ligands **6**–**9** and a stoichiometric amount of TIPSCl, benzaldimine **2a** reacted with diethylzinc (3 molar equiv), in toluene at −10 °C to afford the corresponding optically active secondary amine **4a** (Scheme 4, Table 4).

In spite of the heterogeneous reaction, the diethylzinc addition reaction to benzaldimine **2a** using chiral polymers **6**–**9** smoothly occurred even at low temperature to afford the desired secondary amine (*S*)-**4a** in moderate to high yields (Table 4). The diethylzinc addition reaction to benzaldimine **2a** using chiral polymers possessed methyl (**7a**) and ethyl (**8**) substituents on the nitrogen atom of their pendant groups afforded the addition product **4a** with much higher enantioselectivities than did the chiral polymers possessing the hydrogen atom (**6**) and *n*-butyl (**9**) substituents. Thus, polymer-supported chiral ligand **7a** afforded the addition product (*S*)-**4a** with the highest chemical yield and enantioselectivity (92%, 82% ee, respectively; entry 2, Table 4). It is noteworthy that chiral polymer **9** having *n*-butyl group on the nitrogen atom of its pendant group afforded the addition product (*S*)-**4a** in a much decreased ee value (48% ee, entry 4, Table 4) when compared to the result that was obtained from the corresponding monomeric chiral ligand **3d** (73% ee, entry 4, Table 2). This result suggests that the bulky butyl group on the nitrogen atom decreases the catalytic activity when the chiral moiety is directly connected to the polymer support. Surprisingly, the obtained results clearly showed that the order of catalytic activity of chiral polymers **6**, **7a**, **8** and **9** in the diethylzinc addition reaction to benzaldimine **2a** (Table 4) is similar to that of the same family of the corresponding monomeric chiral ligands **3a**–**d** (see Tables 1 and 2).

Table 4. Enantioselective diethylzinc addition to benzaldimine **2a** activated by chiral polymers **6**–**10**/TIPSCl[a]

Entry	Chiral polymer	Temp (°C)	Addition product **4a**		
			Yield[b] (%)	ee[c] (%)	Config.[d]
1	(1*S*,2*R*)-**6**	−10	44 (48)[e]	55 (59)[e]	*S*
2	(1*S*,2*R*)-**7a**	−10	92 (95)[e]	82 (84)[e]	*S*
3	(1*S*,2*R*)-**8**	−10	82 (91)[e]	73 (77)[e]	*S*
4	(1*S*,2*R*)-**9**	−10	64 (93)[e]	48 (73)[e]	*S*
5	(1*S*,2*R*)-**7a**	rt	41	61	*S*
6	(1*S*,2*R*)-**7a**	0	55	73	*S*
7[a]	(1*S*,2*R*)-**7a**	−20	71	84	*S*
8	(1*S*,2*R*)-**7b**	−10	82	78	*S*
9	(1*S*,2*R*)-**7c**	−10	75	75	*S*
10	(1*S*,2*R*)-**7d**	−10	65	63	*S*
11	(1*S*,2*R*)-**7e**	−10	93	81	*S*
12	(1*S*,2*R*)-**7f**	−10	85	77	*S*
13	(1*S*,2*R*)-**7g**	−10	81	72	*S*
14	(1*S*,2*R*)-**7h**	−10	74	61	*S*
15	(1*R*,2*S*)-**10**	−10	93	82	*R*

[a] All reactions were carried out in toluene in the presence of a stoichiometric amount of TIPSCl for 48 h except for run 5, which was performed for 3 days.
[b] Isolated yields after flash chromatography (pentane/ethyl acetate: 3:7).
[c] Determined by HPLC analysis using a Chiralcel OD-H column.
[d] The absolute configuration was assigned based on the absolute configuration of the primary amine obtained after reductive cleavage of the 1,2,4-triazinyl heterocyclic ring and comparing its HPLC retention time with the literature value.[11,12]
[e] Yields and % enantioselectivities in parentheses were obtained from the corresponding low-molecular-weight reagents in solution system.[11]

In order to improve the chemical yield and enantioselectivity, we have thus tried to optimize the reaction conditions of the enantioselective ethylation of benzaldimine **2a** using chiral polymer (1*S*,2*R*)-**7a**, which had been shown to give the best results (entry 2, Table 4).

To clarify the effect of reaction temperature, the enantioselective ethylation reaction of benzaldimine **2a** was examined, in the presence of a stoichiometric amount of TIPSCl as a catalyst, at different temperatures using chiral polymer (1*S*,2*R*)-**7a** (Table 4). The enantioselective ethylation reaction of benzaldimine **2a** using chiral polymer **7a** was found to be temperature-dependant as expected and in the best case, the ethylated product (*S*)-**4a** was obtained with the highest enantiomeric excess (82% ee) and with chemical yield of 92% at −10 °C (entry 2, Table 4). At −20 °C, only a slight increase in the enantiomeric excess was observed but there was a considerable decrease in the chemical yield even on performing the reaction for 3 days (entry 7, Table 4). At both room temperature and 0 °C, the enantioselectivities and the chemical yields of the addition product (*S*)-**4a** were markedly decreased (entries 5 and 6, Table 4). However, considering the accepted mechanism of the amino alcohol mediated addition of diethylzinc to aldehydes[18] and imines,[13a–c] which involves as a first step the formation of a very stable ethylzinc alkoxide chelate from diethylzinc and the amino alcohol, the free amino alcohol ligand should never coexist with the trialkylsilyl halide. In this way, both activation modes could be, in principle, compatible. As it has been mentioned previously,[13a–c] success in this dual (amino alcohol/Lewis acid) activation would critically depend on the absence of temporary coexistence of free amino alcohol and silylating agent, which would lead to deactivation of the chiral ligand as well as on the stability towards Lewis acids of the initially formed ethylzinc alkoxide chelate. To ensure maximum adherence to these conditions, the experimental protocol mentioned here (Scheme 4) should be followed and the reaction temperature should be low as much as possible.

The effect of the molar ratio of DVB as a crosslinking reagent on the enantioselective ethylation reaction of

benzaldimine **2a** was next examined using the copolymerized chiral ligands (1*S*,2*R*)-**7a–d** possessing different ratios of DVB under the above optimal reaction conditions mentioned in Table 4 (entry 2) and the obtained results are also shown in Table 4 (entries 2, 8–10). The ee of the resulting secondary amine (*S*)-**4a** was as high as 82% when (1*S*,2*R*)-**7a** having 2 molar equiv. of DVB was utilized as a chiral ligand (entry 2, Table 4). Interestingly, the enantioselectivity of the addition product **4a** obtained from the use of **7b** having 1 molar equiv. of DVB was very close to that observed with the use of **7c** having 3 molar equiv. of DVB (78 and 75% ee, entries 8 and 9, respectively, Table 4). Significant decreases in each of the chemical yields and enantioselectivities of the addition product **4a** were observed with chiral polymer **7d** (65% yield and 63% ee), which had a higher ratio of crosslinking (4 molar equiv.; entry 10, Table 4).

The effect of the loading degree of the chiral amino alcohol residue in chiral polymer **7** was also examined. The use of chiral polymers (1*S*,2*R*)-**7e–h** (DF=0.2–0.5, entries 11–14, Table 4) having higher loading ratios of the chiral amino alcohol residues than chiral polymer **7a** (DF=0.1, entry 2, Table 4) for the enantioselective diethylzinc addition to benzaldimine **2a** was found to have a significant effect on the enantioselective ethylation reaction. With the use of chiral polymer **7e** (DF=0.2), no significant change in each of the chemical yield and enantioselectivity of the addition product **4a** was observed (entry 11, Table 4), whilst significant decreases in the chemical yields and enantioselectivities were observed with increasing the loading ratio of chiral amino alcohol residue (entries 12–14, Table 4). The use of chiral polymer **7h** (DF=0.5) afforded the addition product in a much decreased enantioselectivity (61%; entry 14, Table 4), a result probably explained in terms of a higher degree of polymer loading of ephedrine in (1*S*,2*R*)-**7h** than in other chiral polymers. A high degree of polymer loading may give rise to active site interactions, which interfere with the formation of an appropriate transition state.

In asymmetric synthesis it is important that both enantiomers of a given compound can be prepared. Thus, polymer-supported chiral ligand (1*R*,2*S*)-**10** was prepared from its corresponding chiral monomer (1*R*,2*S*)-**5e**. The enantioselective ethylation of benzaldimine **2a** using the polymeric chiral ligand (1*R*,2*S*)-**10** worked as well as chiral polymer (1*R*,2*S*)-**7a** that was prepared from chiral monomer (1*S*,2*R*)-**5b** and led smoothly to the desired secondary chiral amine **4a** with almost the same chemical yield and enantioselectivity, but with reversed stereoselectivity (entry 15, Table 4).

The amount of the chiral polymeric ligand **7a** used in the reaction was then further examined (Table 5). With the other reaction conditions fixed (reaction time=48 h, reaction temperature=−10 °C, solvent=toluene, and an equivalent amount of TIPSCl), the amount of chiral polymer **7a** was varied in the range of 0.4–2.0 equiv compared with the benzaldimine **2a**. As can be seen from the results shown in Table 5, the enantiomeric excess increased with increasing the amount of chiral polymer **7a**.

The chemical yield and enantioselectivity of the addition product (*S*)-**4a** was maximized with equivalent amounts of polymer **7a** as the chiral ligand and substrate **2a** (entry 4).

Table 5. Effect of the amount of polymeric ligand (1*S*,2*R*)-**7a**[a]

Entry	**7a** (equiv)	Yield[b] (%)	ee[c,d] (%)
1	0.4	63	62
2	0.6	71	69
3	0.8	81	77
4	1.0	92	82
5	2.0	75	83

[a] All reactions were performed for 48 h at −10 °C in the presence of equimolar amount of TIPSCl.
[b] Isolated yields after flash chromatography (pentane/ethyl acetate: 3:7).
[c] Determined by HPLC analysis using a Chiralcel OD-H column.
[d] The absolute configuration was assigned as the *S*-isomer based on the absolute configuration of the primary amine obtained after reductive cleavage of the 1,2,4-triazinyl heterocyclic ring and comparing its HPLC retention time with the literature value.[11,12]

The use of a lesser amount of chiral polymer **7a** (0.4–0.8 mol %; entries 1–3, Table 5) resulted in the decreased yields and enantioselectivities of the addition product (*S*)-**4a**. No considerable change in the enantioselectivity of the addition product (*S*)-**4a** could be observed on using more than 1 equiv of chiral polymer **7a** but a considerable decrease in the chemical yield was observed (entry 5, Table 5). It is noticeable that these characteristics were identical to those observed on examining the same effect using the corresponding chiral ligand *N*-benzyl-*N*-methylnorephedrine **3b** (at −20 °C) in the same reaction under similar reaction conditions.[11] As expected, the above-mentioned set of results strongly confirms that the enantioselectivity of the addition product **4a** mainly depends on the amount of the chiral amino alcohol ligand.

In order to evaluate the generality of the above-mentioned asymmetric reaction, the optimal procedure for the diethylzinc addition reaction to the benzaldehyde derived imine **2a** using polymeric chiral ligand **7a** was thereafter examined for other *N*-arylimines having various substituents bonded to the phenyl group at different positions. The results of the diethylzinc addition reactions that are displayed in Scheme 5 are summarized in Table 6.

In the presence of stoichiometric amounts of polymeric chiral ligand **7a** and TIPSCl, the diethylzinc addition reaction to various *N*-arylimines containing *ortho*- and *para*-substituents on the phenyl group proceeded smoothly to afford the desired chiral amines (*S*)-**4a–f** with chemical yields up to 93% and good to high enantioselectivities (62–87%). Table 6 shows that varying the substituents on the phenyl group of arylimine **2** exhibited a dramatic influence on the reaction. Generally, imines bearing an *ortho*-substituted phenyl group would provide lower enantioselectivities than their analogues containing a phenyl group with *para*-substituents. For example, the diethylzinc addition reaction to imine **2c**, having a *p*-methylphenyl group, afforded the addition product **4c** with a relatively higher enantioselectivity of 84% ee (entry 3) than that of 75% ee (entry 2) given by its analogue **2b**, which possessed an *ortho*-methylphenyl group. Similar results were also observed with imines **2d** and **2e** having *ortho*-methoxyphenyl and *para*-methoxyphenyl groups (entries 4 and 5, Table 6), respectively. Arylimine **2f** bearing a 2,4,6-trimethylphenyl group provided the addition product **4f** with a lower chemical yield of 71% and enantioselectivity of 62%. This result might be explained on the basis of the

Scheme 5. Diethylzinc addition to arylimines **2a–f** using **7a** as chiral ligand.

Table 6. Diethylzinc addition to arylimines **2a–f** mediated by (1*S*,2*R*)-**7a**/TIPSCl[a]

Entry	Imine	Ar	Adduct product	Yield[b] (%)	ee[c,d] (%)
1	**2a**	Ph	**4a**	92 (90)[e]	82 (84)[e]
2	**2b**	2-CH_3–C_6H_4	**4b**	89 (88)[e]	75 (79)[e]
3	**2c**	4-CH_3–C_6H_4	**4c**	91 (93)[e]	84 (87)[e]
4	**2d**	2-CH_3O–C_6H_4	**4d**	93 (92)[e]	77 (82)[e]
5	**2e**	4-CH_3O–C_6H_4	**4e**	93 (95)[e]	87 (88)[e] (91)[f]
6	**2f**	2,4,6-Tri-CH_3–C_6H_4	**4f**	71 (78)[e]	62 (72)[e]
7[g]	**2e**	4-CH_3O–C_6H_4	**4e**	91	86

[a] All reactions were carried out at −10 °C (molar ratio: imine **7a**/TIPSCl/Et_2Zn: 1:1:3).
[b] Isolated yields after flash chromatography (pentane/ethyl acetate: 3:7).
[c] Determined by HPLC analysis using a Chiralcel OD-H column.
[d] The absolute configuration was assigned as the *S*-isomer based on the absolute configuration of the primary amine obtained after reductive cleavage of the 1,2,4-triazinyl heterocyclic ring and comparing its HPLC retention time with the literature value.[11,12]
[e] Values in parentheses are for the results obtained from the corresponding low-molecular-weight counterparts.[11]
[f] Value in parenthesis obtained after crystallization from petroleum ether/ethanol (1:9).
[g] Recovered polymer was used.

steric hindrance imposed by the di-*ortho*-substituted benzene ring (entry 6, Table 6).

It should be noted that all the addition products **4a–h** obtained are solids and thus their optical purity could be enhanced by crystallization. For example, the enantiomeric purity of **4e** (87%, entry 5, Table 6) could be upgraded to 91% by a simple crystallization from petroleum ether/ethanol (entry 5, Table 6).

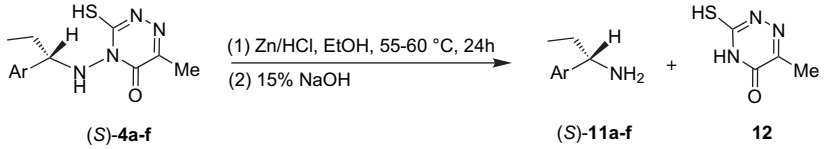
Interestingly, the order of catalytic activity obtained using the polymeric chiral ligand **7a** was found to be also in complete accordance with that of the corresponding monomeric chiral ligand **3b**, under similar reaction conditions, as shown from the values in parentheses in Table 6. More interestingly, the enantioselectivity of the addition product **4a** obtained from the diethylzinc addition reaction to benzaldimine **2a** using monomeric chiral ligand (1*S*,2*R*)-**3b** and its corresponding polymer-supported analogue (1*S*,2*R*)-**7a** is seen to be high.

One of the advantages of a polymeric chiral ligand is its easier separation from the reaction mixture. The chiral polymers were easily separated from the reaction mixture by simple filtration and were easily recovered quantitatively during the workup in a typical experiment. The recovered polymeric chiral ligand could be reused in further experiments and showed unchanged reactivity and enantioselectivity in the same reaction. In entry 7 (Table 6), recycled chiral polymeric ligand, which had been used in entry 5, recovered by filtration and washed with acid and base, was examined. As a result, (*S*)-**4a** was obtained with almost the same ee (86% ee) and chemical yield (91%) as that in entry 5 (87% ee and 93% yield, Table 6).

It is noteworthy that under the above-mentioned reaction conditions, when 4-amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one **1** was allowed to react with diethylzinc, in the presence of equimolar amounts of chiral ligand **3b** or its polymeric analogue **7a** and in the presence of TIPSCl, the starting material was recovered almost unchanged. This result indicates that the diethylzinc reagent neither opened the hetero-ring in the arylimine derivatives **2** nor attacked the carbonyl or the thione group of the 1,2,4-triazinyl heterocyclic ring. Therefore, under all the aforementioned reaction conditions, the addition of diethylzinc to arylimines **2a–f** took place exclusively at the exocyclic electrophilic carbon atom yielding the *C*-ethylated products **4a–f** as evidenced by their microanalytical and spectral data.[11]

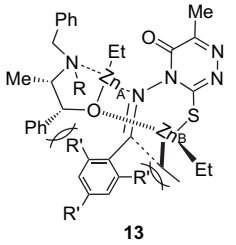
The removal of the 1,2,4-triazinyl heterocyclic ring via reductive cleavage was uneventful and furnished the corresponding free optically active 1-arylpropylamines **11a–f** without significant racemization and in nearly quantitative yields in addition to the expected known 3-mercapto-6-methyl-4*H*-1,2,4-triazine-5-one **12**[8] (Scheme 6). The absolute configurations of the major isomer of the addition products **4a–f** were assigned based on the absolute configurations of products **11a–f** and comparison of the HPLC retention times with the literature values.[12] The ee values of the 1-arylpropylamines **11a–f** were determined by HPLC analysis after derivation of the amine to the corresponding acetamide derivatives by a reported method[12d] and comparison with the literature values.[12] The obtained ee values were found to be in very good agreement with the enantiomeric excess of the starting secondary amine **4a–f**.

Although the mechanistic details for the asymmetric process are currently unclear, the observed results might be rationalized assuming that the addition takes place through the depicted transition state **13**. However, sulfur is more



Scheme 6. Preparation of chiral amines **11a–f** via reductive cleavage of the 1,2,4-triazinyl heterocyclic ring.

nucleophilic than oxygen and proved particularly to be stronger than oxygen in complexation with Zn atom.[19] Therefore, the mercapto group (SH) should be more nucleophilic than the carbonyl group (C=O) and consequently S–Zn interaction may be stronger than that of the O–Zn. The steric hindrance brought about by each of the substituents on the nitrogen atom of chiral ligands **3** as well as by the triazine heterocyclic ring forces Zn_B to be in the position shown, determining in this way the stereochemistry at Zn_A. Coordination of the ligand to Zn atoms (N–Zn_A and O–Zn_B), coordination of the imine nitrogen to Zn_A as well as the extra coordination between the mercapto group (SH) with zinc (S–Zn_B) would lead to the formation of bicyclic transition state like that as shown in structure **13**. The transfer of one of the ethyl groups of Zn_B to the imine carbon would give the addition products with the observed stereochemistry.



13

Proposed transition state for the diethylzinc addition reaction to arylimines **2a-f**

As shown in structure **13**, the product with the *S* absolute configuration should be given by ligands (1*S*,2*R*)-**3a–d** or their corresponding polymeric analogues (1*S*,2*R*)-**6–9**, which was consistent with our experimental results. The transition state **13** also clearly explained that the presence of *ortho*-substituents on the phenyl group bonded to the imine carbon would disfavour the formation of the well-ordered bicyclic transition state than that formed by imine bearing *para*-substituted phenyl groups, leading to a decrease in the enantioselectivity, which has been observed experimentally (compare entry 1 with entries 2, 4 and 6, Table 6). Therefore, arylimines with a *para*-substituent afforded higher enantioselectivities than their structural analogues bearing an *ortho*-substituted phenyl group. Moreover, as shown in structure **13**, for steric reasons, it appears advantageous to have a small alkyl (R) group on the nitrogen atom of the monomeric chiral ligands **3** or their corresponding copolymers **6–9** in order to get high selectivities, and this assumption was also borne out experimentally (entries 1–4 in each of Tables 1, 2 and 4).

3. Conclusion

Enantioselective diethylzinc addition to the exocyclic C=N double bond of easily accessible arylimines derived from 3-aminotriazine using chiral β-amino alcohols derived from norephedrine and their corresponding copolymers as chiral ligands in the presence of TIPSCl as activator have been demonstrated. The enantioselectivities of the addition products obtained from the use of copolymerized chiral ligands (up to 91% ee) were comparable and have similar tendency with those obtained from the use of the corresponding monomeric chiral ligands (up to 92% ee). The activation of arylimines with silylating reagents renders (or leads to) the diethylzinc addition reaction to arylimines to be easy, efficient, and high yield reaction. Reductive cleavage of the 1,2,4-triazinyl heterocyclic ring from the addition products **4a–f** afforded the corresponding optically active primary amines **11** without significant loss of optical purity. Due to the simplicity of the process and the good availability of the imine precursors, we believe that a broad applicability of the reported catalytic reaction can be anticipated. The extension of this methodology to other organozinc reagents and other kinds of branched polymers to achieve higher stereoselectivity is in progress and will be reported in due course.

4. Experimental

4.1. General

All reactions were performed under dry nitrogen atmosphere. Toluene was freshly distilled from CaH_2 under nitrogen prior to use. Diethylzinc in hexane was purchased from Aldrich Co. Chiral ligands *N*-alkyl-*N*-benzylnorephedrines **3a–d**[15b,16b,20] and **5a–d**,[15a,b,16a,21] were readily prepared according to the respective literature procedures. The required 4-arylideneamino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-ones **2a–f** were prepared by the reaction of 4-amino-3-mercapto-6-methyl-4*H*-1,2,4-triazine-5-one **1** with the corresponding aldehyde in refluxing methanol according to the literature.[8] Deactivated silica gel plates (Merck 5554, $60F_{254}$) were obtained by eluting TLC plates with 5% Et_3N in pentane and drying before applying the sample and the spots were detected with UV model UVGL-58. It turned out to be crucial to deactivate the silica gel with Et_3N before purifying the products by flash chromatography in order to get good yields, presumably due to decomposition on the otherwise slightly acidic silica. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL GSX-400 (400/100.4 MHz) spectrophotometer in $CDCl_3$; chemical shifts are relative to TMS as internal reference. High resolution mass spectra were recorded on a JEOL JMS-SX120A. IR spectra were recorded on Perkin Elmer 1760 FTIR spectrophotometer instrument. Optical rotations were measured using a Perkin-Elmer 341 Polarimeter in a 10 cm cell with the solvent indicated. High performance liquid chromatography (HPLC) analyses were carried out on a chiral column (Chiralcel OD-H column, Daicel, 25 cm, 30 °C), with a 254 nm UV detector and a flow rate of 1.0 mL/min. Loading of the polymers is expressed in millimoles of functional groups per gram of the dry resin (mmol/g) or as degree of functionalization (DF). For example, DF=0.10 if 10% of the styrene units are functionalized.

4.2. General procedure for the enantioselective diethylzinc addition to benzaldimine 2a using chiral ligands 3a–d in the presence of TIPSCl

Benzaldimine **2a** (73.9 mg, 0.3 mmol) and chiral ligand **3** (0.3 mmol) were dissolved in dry toluene (2.0 mL), at room temperature, and the reaction mixture was cooled to 0 °C. To this mixture, 0.9 mL (0.9 mmol) of 1.0 M Et_2Zn in hexane was added dropwise. After stirring at 0 °C for 30 min, the reaction mixture was cooled to −20 °C and TIPSCl (64 μL, 0.3 mmol) was added. Stirring was continued for 24 h at that temperature and the reaction mixture was then quenched

with saturated aqueous NH_4Cl (2 mL). The aqueous phase was extracted with CH_2Cl_2 (3×15 mL), and the combined organic layers were dried over $MgSO_4$. After removal of the solvents, the residue was purified by flash chromatography on silica gel (deactivated silica gel, pentane/ethyl acetate: 95:5 to 30:70) to afford 4-(1-phenylpropyl)amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one (**4a**) as a white solid. The product was analyzed by HPLC on a Chiralcel OD-H column. The yields and enantiomeric compositions of the secondary amine **4a** obtained with arylimine **2a** are shown in Table 2. The absolute configuration of the addition product **4a** was determined to be *S*-isomer based on the absolute configuration of the corresponding (*S*)-1-phenylpropylamine obtained after reductive cleavage of the 1,2,4-triazinyl heterocyclic ring and correlated to that described in the literature [11,12] (see the hydrolysis part).

4.3. Preparation of polymer-supported chiral ligands (1*S*,2*R*)-6, 7a, 8 and 9

4.3.1. Typical procedure for the synthesis of chiral polymer 7a. To a water solution (25 mL) of poly(vinyl alcohol) (0.1 g) were added (1*S*,2*R*)-**5b** (R=Me) (0.56 g, 2 mmol), styrene (1.64 g, 1.6 mL, 14 mmol), divinylbenzene (DVB, 0.52 g, 0.57 mL, 4 mmol), α′,α′-azobisisobutyronitrile (AIBN, 0.065 g, 4 mmol), benzene (6 mL) and tetrahydrofuran (6 mL). After 1 h of stirring at 0 °C to homogenize the particle size, the temperature was raised to 75 °C and the reaction mixture was stirred vigorously for 30 h at the same temperature. The resulting polymer beads were filtered off and washed successively with water, MeOH, THF/MeOH, THF and MeOH (50 mL each), followed by drying in vacuo at 40 °C for 5 h to afford the corresponding chiral polymer (1*S*,2*R*)-**7a**. Elemental analysis of (1*S*,2*R*)-**7a** [Found (%) C, 89.85; H, 7.80; N, 1.08] indicated that the content of chiral amino alcohol in (1*S*,2*R*)-**7a** corresponding to 0.771 mmol/1.0 g of polymer.

In a similar manner, copolymerization using (1*S*,2*R*)-**5a**, (1*S*,2*R*)-**5c** and (1*S*,2*R*)-**5d** afforded the corresponding chiral polymers (1*S*,2*R*)-**6**, (1*S*,2*R*)-**8** and (1*S*,2*R*)-**9**, respectively. Elemental analysis of **6**: Found (%) C, 89.88; H, 7.79; N, 1.07. Content of chiral amino alcohol: 0.764 mmol/1.0 g of polymer; **8**: Found (%) C, 89.61; H, 7.95; N, 1.11. Content of chiral amino alcohol: 0.792 mmol/1.0 g of chiral polymer: **9**: Found (%) C, 89.63; H, 8.13; N, 1.01. Content of chiral amino alcohol: 0.721 mmol/1.0 g of chiral polymer.

4.3.2. Synthesis of chiral polymers (1*S*,2*R*)-7b–h. Chiral polymers (1*S*,2*R*)-**7b–h** were synthesized in a similar manner for the preparation of (1*S*,2*R*)-**7a** except for the use of various ratios of the chiral monomer **5b**, styrene and DVB that are indicated in Table 3. Elemental analysis of the nitrogen atom in the resulting polymers indicated the loading ratios of chiral amino alcohols corresponding to the values that are shown in Table 3.

4.3.3. Synthesis of chiral polymer (1*R*,2*S*)-10. Chiral polymer (1*R*,2*S*)-**10** was synthesized in a similar manner for the preparation of (1*S*,2*R*)-**7a** except for the use of chiral monomer (1*R*,2*S*)-**5e**. Elemental analysis of (1*R*,2*S*)-**10**: Found (%) C, 89.82; H, 7.85; N, 1.10. Content of nitrogen atom: 0.807 mmol/1.0 g of polymer.

4.4. General procedure for the enantioselective ethylation of arylimines using copolymerized chiral ligands in the presence of TIPSCl as a Lewis acid

To an ice cold suspension of chiral polymer (0.2 mmol, based on the content of the nitrogen atom by elemental analysis of chiral polymer) in dry toluene (3 mL) were added the appropriate imine (0.2 mmol) and Et_2Zn (0.6 mmol, 1 M hexane solution, 6.0 mL). The reaction mixture was cooled to −10 °C and TIPSCl (42 μL, 0.2 mmol) was added. Stirring was continued for 24 h at that temperature and the reaction mixture was then quenched by adding hydrochloric acid (1 M, 5 mL). The polymer was removed by filtration and washed thoroughly with dichloromethane. The filtrate was extracted with CH_2Cl_2 (3×10 mL) and the combined extracts were dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (deactivated silica gel, pentane/ethyl acetate: 95:5 to 30:70) to afford the corresponding optically active secondary amine 4-(1-arylpropyl)amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one (**4**). The yields and enantiomeric excesses of the secondary amines obtained with arylimines **2a–f** are shown in Tables 4–6. The enantiomeric excesses for the addition products **4a–f** were determined by HPLC analysis using a chiral stationary-phase column (Daicel Chiralcel OD-H, 254 nm UV detector, 30 °C). The absolute configuration of the major isomer of the secondary amine **4** was assigned based on the absolute configuration of the secondary amine 1-arylpropylamine obtained after the reductive cleavage of the 1,2,4-triazinyl heterocyclic ring and correlated with that described in literature.[11,12] The structure of the addition products **4a–f** was confirmed by microanalytical and spectral data.[11]

4.4.1. 4-(1-Phenylpropyl)amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one 4a. White solid, mp 117–118 °C; $[\alpha]_D^{25}$ −57.4 (*c* 1.03, CH_2Cl_2); HPLC conditions: 9% *i*-PrOH in hexane, retention times, 20.18 min (minor, *R*-isomer) and 27.26 min (major, *S*-isomer); Anal. Calcd for $C_{13}H_{16}N_4OS$: C, 56.50; H, 5.84; N, 20.27; S, 11.60. Found: C, 56.51; H, 5.79; N, 20.30; S, 11.58; IR (cm^{-1}) 3277 (NH), 1707 (C=O), 1205 (C=S); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.89 (3H, t, J=7.5 Hz, CH_3CH_2), 1.75–1.88 (1H, m, CH_2CH_3), 1.96–2.08 (1H, m, CH_2CH_3), 2.38 (3H, s, CH_3–C_6), 3.42 (1H, m, N*H*N), 4.04–4.16 (1H, m, C*H*NH), 7.33–7.68 (5H, m, H_{Ar}), 12.17 (1H, br s, S*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 11.63 (CH_3CH_2), 17.92 (CH_3–C_6), 31.25 (CH_2CH_3), 56.36 (*C*HNH), 128.39 (C_{Ar}), 129.33 (C_{Ar}), 130.26 (C_{Ar}), 137.30 (C_{Ar}), 149.31 (C_6), 165.40 (C_5), 170.11 (C_3); MS (EI) (*m*/*z*, relative intensity) 276 (M^+, 6), 249 (44), 248 (14), 232 (8), 157 (14), 146 (71), 142 (6), 134 (33), 130 (17), 119 (23).

4.4.2. 4-[1-(2′-Methylphenyl)propyl]amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one 4b. White solid, mp 152–153 °C; $[\alpha]_D^{25}$ −96.8 (*c* 0.98, $CHCl_3$); HPLC conditions: 12% *i*-PrOH in hexane, retention times, 14.62 min (minor, *R*-isomer) and 22.97 min (major, *S*-isomer); Anal. Calcd for $C_{14}H_{18}N_4OS$: C, 57.91; H, 6.25; N, 19.29; S, 11.04. Found: C, 60.02; H, 6.24; N, 19.31; S, 11.09; IR (cm^{-1}) 3270 (NH), 1701 (C=O), 1207 (C=S); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.79 (3H, t, J=7.4 Hz,

C*H*$_3$CH$_2$), 1.78–1.90 (1H, m, C*H*$_2$CH$_3$), 1.96–2.09 (1H, m, C*H*$_2$CH$_3$), 2.32 (3H, s, Ar–C*H*$_3$), 2.56 (3H, s, C*H*$_3$–C$_6$), 3.28 (1H, br s, N*H*C), 3.99–4.08 (1H, m, C*H*NH), 6.78–6.98 (2H, m, H$_{Ar}$), 7.09–7.44 (2H, m, H$_{Ar}$), 12.29 (1H, br s, S*H*); ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 10.66 (*C*H$_3$CH$_2$), 16.69 (*C*H$_3$–C$_6$), 21.49 (Ar–*C*H$_3$), 31.93 (*C*H$_2$CH$_3$), 57.36 (*C*HNH), 120.93 (C$_{Ar}$), 126.71 (C$_{Ar}$), 127.85 (C$_{Ar}$), 133.29 (C$_{Ar}$), 152.31 (C$_6$), 165.92 (C$_5$), 169.67 (C$_3$); MS (EI) (*m*/*z*, relative intensity) 290 (M$^+$, 9), 262 (33), 246 (6.5), 218 (8), 158 (11), 146 (56), 134 (14), 131 (38), 119 (13), 109 (29), 105 (14), 91 (6).

4.4.3. 4-[1-(4′-Methylphenyl)propyl]amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one 4c. White solid, mp 182–183 °C; $[\alpha]_D^{25}$ −78.1 (*c* 1.28, CH$_2$Cl$_2$); HPLC conditions: 15% *i*-PrOH in hexane, retention times, 21.55 min (minor, *R*-isomer) and 27.82 min (major, *S*-isomer); Anal. Calcd for C$_{14}$H$_{18}$N$_4$OS: C, 57.91; H, 6.25; N, 19.29; S, 11.04. Found: C, 57.87; H, 6.30; N, 19.23; S, 11.12; IR (cm^{-1}) 3280 (NH), 1703 (C=O), 1208 (C=S); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 0.86 (3H, t, *J*=7.6 Hz, C*H*$_3$CH$_2$), 1.74–1.87 (1H, m, C*H*$_2$CH$_3$), 1.97–2.13 (1H, m, C*H*$_2$CH$_3$), 2.35 (3H, s, Ar–C*H*$_3$), 2.44 (3H, s, C*H*$_3$–C$_6$), 3.42 (1H, br s, N*H*C), 4.06–4.16 (1H, m, C*H*NH), 7.07 (2H, d, *J*=8.3, H$_{Ar}$), 7.18 (2H, d, *J*=8.3, H$_{Ar}$), 11.57 (1H, br s, S*H*); ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 10.95 (*C*H$_3$CH$_2$), 16.92 (*C*H$_3$–C$_6$), 21.64 (Ar–*C*H$_3$), 32.2 (*C*H$_2$CH$_3$), 54.65 (*C*HNH), 125.88 (C$_{Ar}$), 128.84 (C$_{Ar}$), 136.38 (C$_{Ar}$), 140.69 (C$_{Ar}$), 150.43 (C$_6$), 166.76 (C$_5$), 170.18 (C$_3$); MS (EI) (*m*/*z*, relative intensity) 290 (M$^+$, 11), 263 (27), 246 (9.5), 218 (4), 158 (9), 146 (52), 134 (18), 130 (25), 119 (21), 105 (9), 91 (19).

4.4.4. 4-[1-(2′-Methoxyphenyl)propyl]amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one 4d. White solid, mp 129–131 °C; $[\alpha]_D^{25}$ −94.5 (*c* 0.77, CHCl$_3$); HPLC conditions: 15% *i*-PrOH in hexane, retention times, 10.41 min (minor, *R*-isomer) and 18.16 min (major, *S*-isomer); Anal. Calcd for C$_{14}$H$_{18}$N$_4$O$_2$S: C, 54.88; H, 5.92; N, 18.29; S, 10.47. Found: C, 54.79; H, 5.97; N, 18.36; S, 10.38; IR (cm^{-1}) 3285 (NH), 1795 (C=O), 1209 (C=S); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 0.76 (3H, t, *J*=7.4 Hz, C*H*$_3$CH$_2$), 1.74–1.89 (1H, m, C*H*$_2$CH$_3$), 1.96–2.05 (1H, m, C*H*$_2$CH$_3$), 2.37 (3H, s, C*H*$_3$–C$_6$), 3.28 (1H, br s, N*H*C), 3.83 (3H, s, OC*H*$_3$), 4.38–4.52 (1H, m, C*H*NH), 6.98 (1H, d, *J*=8.0 Hz, H$_{Ar}$), 7.09 (1H, t, *J*=7.6 Hz, H$_{Ar}$), 7.35 (1H, t, *J*=7.6 Hz, H$_{Ar}$), 7.59 (1H, d, *J*=7.6, H$_{Ar}$), 8.08 (1H, dd, *J*=1.94, 1.77, H$_{Ar}$), 12.44 (1H, br s, S*H*); ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 10.93 (*C*H$_3$CH$_2$), 17.49 (*C*H$_3$–C$_6$), 32.29 (*C*H$_2$CH$_3$), 53.49 (OCH$_3$), 57.62 (*C*HNH), 121.73 (C$_{Ar}$), 127.52 (C$_{Ar}$), 128.21 (C$_{Ar}$), 131.89 (C$_{Ar}$), 151.09 (C$_6$), 165.87 (C$_5$), 170.19 (C$_3$); MS (EI) (*m*/*z*, relative intensity) 306 (M$^+$, 14), 278 (19), 262 (11), 234 (5), 157 (13), 146 (76), 150 (26), 131 (28), 118 (17), 105 (13), 91 (37), 91 (11).

4.4.5. 4-[1-(4′-Methoxyphenyl)propyl]amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one 4e. White solid, mp 144–145 °C; $[\alpha]_D^{25}$ −34.6 (*c* 2.39, CH$_2$Cl$_2$); HPLC conditions: 15% *i*-PrOH in hexane, retention times, 9.32 min (minor, *R*-isomer) and 15.52 min (major, *S*-isomer); Anal. Calcd for C$_{14}$H$_{18}$N$_4$O$_2$S: C, 54.88; H, 5.92; N, 18.29; S, 10.47. Found: C, 55.01; H, 5.89; N, 18.33; S, 10.45; IR (cm^{-1}) 3285 (NH), 1695 (C=O), 1210 (C=S); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 0.87 (3H, t, *J*=7.5 Hz, C*H*$_3$CH$_2$), 1.75–1.92 (1H, m, C*H*$_2$CH$_3$), 1.98–2.11 (1H, m, C*H*$_2$CH$_3$), 2.42 (3H, s, C*H*$_3$–C$_6$), 3.34 (1H, br s, N*H*C), 3.82 (3H, s, OC*H*$_3$), 4.09–4.17 (1H, m, C*H*NH), 6.93 (2H, d, *J*=8.7, H$_{Ar}$), 7.26 (2H, d, *J*=8.7, H$_{Ar}$), 11.87 (1H, br s, S*H*); ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 11.7 (*C*H$_3$CH$_2$), 17.87 (*C*H$_3$–C$_6$), 31.3 (*C*H$_2$CH$_3$), 55.59 (OCH$_3$), 56.44 (*C*HNH), 115.87 (C$_{Ar}$), 126.67 (C$_{Ar}$), 134.72 (C$_{Ar}$), 146.43 (C$_{Ar}$), 152.52 (C$_6$), 164.55 (C$_5$), 171.09 (C$_3$); MS (EI) (*m*/*z*, relative intensity) 306 (M$^+$, 18), 279 (22), 262 (6), 234 (4), 157 (24), 150 (21), 146 (64), 130 (16), 119 (9), 105 (7).

4.4.6. 4-[1-(2′,4′,6′-Tri-methylphenyl)propyl]amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one 4f. White solid, mp 198–199 °C; $[\alpha]_D^{25}$ −46.6 (*c* 0.98, CH$_2$Cl$_2$); HPLC conditions: 15% *i*-PrOH in hexane, retention times, 12.82 min (minor, *R*-isomer) and 19.42 min (major, *S*-isomer); Anal. Calcd for C$_{16}$H$_{22}$N$_4$OS: C, 60.35; H, 6.96; N, 17.59; S, 10.07. Found: C, 60.31; H, 6.99; N, 17.58; S, 10.11; IR (cm^{-1}) 3283 (NH), 1704 (C=O), 1205 (C=S); ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm) 0.91 (3H, t, *J*=7.7 Hz, C*H*$_3$CH$_2$), 1.72 (3H, s, Ar–C*H*$_3$), 1.84–1.96 (1H, m, C*H*$_2$CH$_3$), 2.01–2.11 (1H, m, C*H*$_2$CH$_3$), 2.21 (6H, s, Ar–C*H*$_3$), 2.31 (3H, s, Ar–C*H*$_3$), 2.40 (3H, s, C*H*$_3$–C$_6$), 3.39 (1H, br s, N*H*C), 4.16–4.31 (1H, m, C*H*NH), 6.72 (1H, s, H$_{Ar}$), 6.89 (1H, s, H$_{Ar}$), 7.31 (1H, s, H$_{Ar}$), 11.57 (1H, br s, S*H*); ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm) 11.18 (*C*H$_3$CH$_2$), 17.12 (*C*H$_3$–C$_6$), 19.98 (Ar–*C*H$_3$), 20.55 (Ar–*C*H$_3$), 21.95 (Ar–*C*H$_3$), 31.8 (*C*H$_2$CH$_3$), 53.44 (*C*HNH), 128.31 (C$_{Ar}$), 131.67 (C$_{Ar}$), 136.19 (C$_{Ar}$), 139.52 (C$_{Ar}$), 152.18 (C$_6$), 165.49 (C$_5$), 169.78 (C$_3$); MS (EI) (*m*/*z*, relative intensity) 318 (M$^+$, 13), 290 (21), 274 (4), 246 (7), 175 (32), 162 (29), 158 (23), 146 (61), 131 (33), 118 (17), 105 (8), 91 (12).

4.5. General procedure for the reductive cleavage of the 1,2,4-triazinyl heterocyclic ring

To a stirred solution of 4-(1-arylpropyl)amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one **4** (3 mmol) in ethanol (15 mL), concd HCl (5 mL) and Zn (0.2 g) were added and the reaction mixture was heated under reflux at 55–60 °C for 24 h (TLC-control). The solvent was evaporated and 1.5 M aqueous HCl (15 mL) was added. The reaction mixture was then extracted with diethyl ether (3×10 mL). The aqueous layer was basified with 15% aqueous NaOH and extracted with ethyl acetate (3×15 mL). The combined organic layers were dried over MgSO$_4$ and the solvent was removed in vacuo. Purification by flash chromatography (deactivated silica gel, pentane/ether: 95:5 to 80:20) afforded the pure 1-arylpropylamine. All the physical and spectroscopic data for compounds **11a–f** were in complete agreement with the reported data.[12] The absolute configurations of the major isomer of addition products **4a–f** were assigned based on the absolute configuration of **11a–f** and comparison of the HPLC retention times with the literature values.[11,12] The ee values of the (*S*)-1-arylpropylamines **11a–f** were determined by HPLC analysis after their derivation to the corresponding acetamide derivatives by reported method[12d] by treatment with acetic anhydride and triethylamine and comparison with the literature value.[12] The ee values determined by HPLC were found to be in very good agreement with the enantioselectivities of the starting secondary amines **4a–f**.

The aqueous layer was acidified again with dilute HCl and the solid obtained was filtered off and crystallized from ethanol to afford **12**. In all cases, the product was identified as the expected known 3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one **12**.[8] All physical and analytical data of compound **12** were found to be identical with those reported.[8]

4.6. Typical procedure for the recovery of chiral polymer 7a

The used polymer **7a** (2.0 g) recovered from the quenched mixture by filtration, was stirred in a mixture of THF (15 mL), 6 M aqueous HCl (2 mL) and water (5 mL) and then after being filtered off it was stirred again for 4 h in a mixture of THF (15 mL) and 2 M aqueous sodium hydroxide (5 mL). The polymer **7a** was then filtered off and washed successively with 50 mL portions of water, methanol, THF, aqueous THF, THF and methanol. After being dried at 40 °C in vacuo for 5 h, it was recycled and used for the enantioselective ethylation reaction (recovery: 1.84 g).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.04.041.

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