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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-one derivatives

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Abstract—4-Arylideneamino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-ones **2a–f** have been evaluated as substrates in the enantioselective diethylzinc addition reaction in the presence of (1*S*,2*R*)-*N*-alkyl-*N*-benzylnorephedrines **3a–d** as chiral ligands. The utility of using a dual catalytic system (amino alcohol/halosilane) for the diethylzinc addition reaction has been also examined. The addition products 4-(1-arylpropyl)amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-ones **4a–f** were obtained in high yields and with enantiomeric excesses of up to 92%. The treatment of arylimines **2a–f** with a diethylzinc reagent did not affect the hetero-ring opening although the C=N double bond of the lateral chain did undergo an addition reaction to yield the C-ethylated products **4a–f**. The reductive cleavage of the 1,2,4-triazinyl heterocyclic ring from addition products **4a–f** led smoothly to the corresponding free primary amines **5a–f** without a significant loss of enantiomeric purity.

1. Introduction

The important synthetic uses of chiral amines has stimulated a great interest in developing methods for the asymmetric preparation of such molecules.[1] The development of efficient methods for preparing chiral amines has received much attention. We have recently reported on an efficient method for the enantioselective addition of chirally modified allylboron reagents to various prochiral imines with the resulting homoallylic amines being obtained in high yields with enantioselectivities up to 96%.[2] We have also reported on the diastereoselective allylation of chiral imines derived from (*S*)-valine, which afforded enantiomerically pure secondary amines in excellent yields with perfect diastereoselectivities.[3]

Enantioselective dialkylzinc addition to imines is an efficient approach to chiral amines and has recently received much attention.[4] Dialkylzinc addition to imines has been extensively studied. As a result of the poor electrophilic character of imines, several quite effective methods based on the catalytic enantioselective addition of dialkylzinc reagents to activated imines have been developed.[5]

The addition of 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** in the presence of C=O and C=N groups of the triazine heterocyclic ring had been reported to be difficult. The results obtained particularly proved that this heterocyclic ring was very sensitive towards such reagents.[6] It is worth mentioning that we have recently reported on the successful addition of various allylmetal reagents to the exocyclic C=N double bond of some aldiminomercaptotriazinones, in the presence of Lewis acids as activators, without any possibility for attacking the 1,2,4-triazine nucleus.[7] These promising results prompted us to further explore the dialkylzinc addition to such arylimines **2**. To the best of our knowledge, the evaluation of such arylimines as substrates in the dialkylzinc addition reaction has not been reported so far. Herein we report the first evaluation of 4-arylideneamino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-ones **2** as substrates in the diethylzinc addition reaction, using chiral β-amino alcohols **3a–d** as chiral ligands and halosilanes as activators (Fig. 1). The reductive cleavage of the 1,2,4-triazinyl group from the addition products was also investigated, which afforded the corresponding free amines, without the loss of enantiomeric purity. A suggestion about the possible transition state for the addition reaction is also presented.

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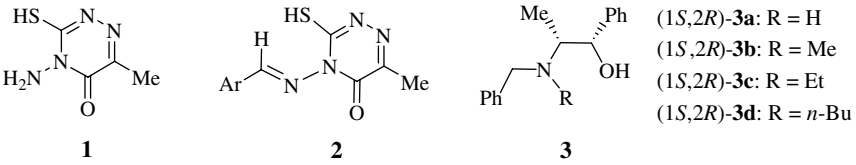


1 2 3

Figure 1.

2. Results and discussion

Chiral ligands (1*S*,2*R*)-*N*-alkyl-*N*-benzylorephedrines **3a–d** (Fig. 1) selected for the present study were readily synthesized using the reported method by the reaction of *N*-(alkyl)norephedrine or ephedrine hydrochloride (2 mmol) with benzyl chloride (2 mmol) in the presence of potassium carbonate (4 mmol) in refluxing ethanol for 7 h.[8] 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.[9]

Our initial efforts focused on examining the efficiency of the chiral ligands (1*S*,2*R*)-**3a–d** bearing different alkyl groups on their nitrogen atoms in terms of chemical yields and enantioselectivities, in the diethylzinc addition reaction to benzaldimine **2a** as a standard substrate. The non-polar solvent toluene, which was found to maximize the rate difference between the catalyzed and noncatalyzed reaction,[10] was chosen as a reaction medium. The asymmetric ethylation of benzaldimine **2a** with diethylzinc (3 equiv), in the presence of (1*S*,2*R*)-**3a–d** (1 equiv) as chiral ligands, in toluene at room temperature was first examined (Scheme 1). The summarized results are shown in Table 1.

As can be seen in Table 1, the size of the substituents bonded to the nitrogen atom of chiral ligands (1*S*,2*R*)-**3a–d** led to an obvious effect on each of the chemical yields and enantiomeric excesses. In general, *N*,*N*-disubstituted chiral ligands **3b–d** showed relatively higher reactivities and stereoselectivities than does the *N*-monosubstituted chiral ligand **3a**. In the diethylzinc reaction using (1*S*,2*R*)-2-benzylamino-1-phenylpropan-1-ol **3a**, as the chiral ligand, which is a secondary amine, the addition product **4a** was obtained in a poor chemical yield (14%) with a moderate ee value of 57% (Table 1, run 1). Among the chiral ligands examined, (1*S*,2*R*)-*N*-benzylephedrine **3b** was found to be the most effective for the diethylzinc addition reaction to benzaldimine **2a** under the above-mentioned reaction conditions affording addition product **4a** with an ee of 79% in moderate chemical yield (55%, run 2).

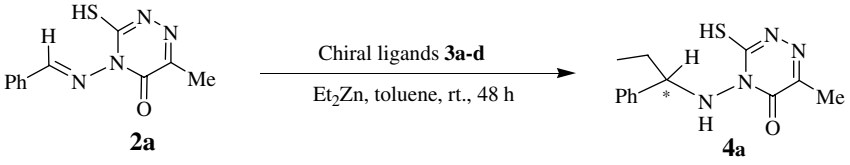
Chiral amino alcohol **3c** possessing an ethyl group on its nitrogen resulted in a slightly reduced stereochemical outcome of 76% ee (run 3). A further increase in the bulkiness of the R group by the replacement of the methyl **3b** with *n*-butyl group **3d** led to a significant decrease in each of the chemical yield and enantiomeric excess (run 4) probably because the catalytic activity decreases by steric hindrance on the nitrogen atom. It is noteworthy to mention that when the diethylzinc addition reaction to benzaldimine **2a** using chiral ligand **3b** was performed for 5 days, the reaction was not complete and addition product **4a** was obtained only in a 69% chemical yield after work-up, together with some unreacted starting imine **2a**. However, a slightly higher enantioselectivity was obtained (82% ee, run 5). Interestingly, the above-mentioned chiral ligands **3a–d** exhibited similar behaviour for both applications in terms of catalytic activity and enantioselectivity when they were employed in the enantioselective addition of diethylzinc to *N*,*N*-diphenylphosphinoyl imines.[8b,c,11] This might represent a solid evidence in favour of a close similarity of the transition states for these processes.

In an attempt to enhance the reaction rate, while leaving the asymmetric induction untouched, silylating agents acting as Lewis acids in the dialkylzinc addition reaction to imines have been successfully used to activate the arylimine substrates.[12] Pericàs et al. have recently successfully applied an interesting approach for the use of a dual cata-

Table 1. Enantioselective addition of diethylzinc to benzaldimine **2a** in the presence of chiral ligands **3a–d**[a]

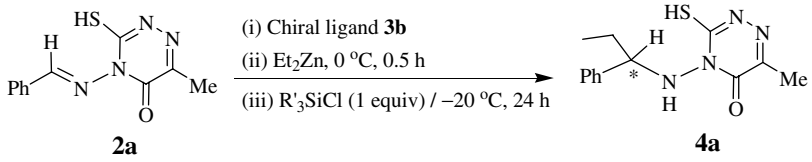
Run	Ligand	Yield[b] (%)	ee[c] (%)
1	**3a**	14	57
2	**3b**	55	79
3	**3c**	41	76
4	**3d**	33	70
5[a]	**3b**	69	82

[a] All reactions were carried out in the presence of a stoichiometric amount of chiral ligand **3** at room temperature for 48 h except run 5 which was performed for 5 days.
[b] Isolated yields after flash chromatography (pentane/ethyl acetate: 3/7).
[c] Determined by HPLC analysis on a Chiralcel OD-H column.



2a 4a

Scheme 1. Diethylzinc addition to benzaldimine **2a** in the presence of chiral ligands **3a–d**.



Scheme 2. Diethylzinc addition to benzaldimine **2a** in the presence of ligand **3b** and halosilanes.

lytic 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.[12b,c] Stimulated by these reports, an analogous dual amino alcohol/halosilane mediation was investigated for the diethylzinc addition to benzaldimine **2a** using chiral ligand **3b** that showed the highest level of enantioselectivity. In the primary stage of this study, chiral ligand **3b** was tested in conjunction with a stoichiometric amount of different silylating agents in the diethylzinc addition to benzaldimine **2a** (Scheme 2, Table 2), to determine optimal reaction conditions.

As clearly seen in Table 2, the use of silylating agents greatly enhanced the diethylzinc addition reaction rate and excellent yields of the addition product **4a** were obtained only after 24 h of reaction time. Among the various Lewis acids tested, the silylating agent $^{i}Pr_3SiCl$ (TIPSCl) was found to give the best results (95% yield, 84% ee; run 4). Interestingly, silylating agents containing the bulkiest silyl groups still provoked a substantial rate increase, while the observed enantioselectivity remained high.

Prompted by the previously mentioned results obtained from the use of TIPSCl in the diethylzinc addition reaction to benzaldimine **2a** (Table 2, run 4), we explored further the effect of decreasing the amount of chiral ligand **3b** in the same transformation. In the presence of TIPSCl (1 equiv) which provided the most promising result, several addition reactions of diethylzinc (3 equiv) to benzaldimine **2a** were set up with different amounts of ligand **3b** (0.75, 0.50 and 0.25 equiv; Table 2, runs 5–7, respectively), under identical reaction conditions as for the stoichiometric process. On decreasing the amount of chiral ligand **3b** (runs 5–7), chemical conversions were found to be very similar to those observed in the stoichiometric reaction (run 4) within the same reaction time. However, the enantioselectivities obtained when decreasing the amounts of ligand **3b** are very promising. Only a small loss in enantioselectivity was observed when going from a full equivalent of chiral ligand **3b** (84% ee, run 4) to 0.75 equiv (81% ee, run 5) and to 0.5 equiv (77% ee, run 6). A moderate value of 65% ee resulted from decreasing the amount of ligand **3b** from a stoichiometric amount to 0.25 equiv (run 7) is also very promising. Interestingly, in the presence of TIPSCl (1 equiv) and in the absence of any chiral ligand, the diethylzinc addition reaction to benzaldimine **2a** afforded the addition product **4a** in a 92% chemical yield as an almost racemic mixture (run 8).

Table 2. Enantioselective diethylzinc addition to benzaldimine **2a** activated by **3b**/R'_3SiCl[a]

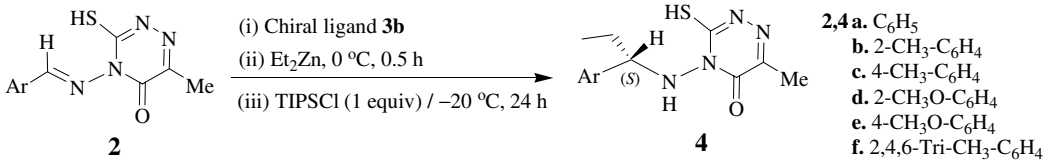
Run	**3b** (equiv)	Additives	Yield[b] (%)	ee[c] (%)
1	1.00	Me_3SiCl	89	54
2	1.00	Ph_3SiCl	93	78
3	1.00	$^{t}BuPh_2SiCl$	97	73
4	1.00	$^{i}Pr_3SiCl$	95	84
5	0.75	$^{i}Pr_3SiCl$	93	81
6	0.50	$^{i}Pr_3SiCl$	95	77
7	0.25	$^{i}Pr_3SiCl$	94	65
8	—	$^{i}Pr_3SiCl$	92	—

[a] All reactions were performed for 24 h at −20 °C.
[b] Refers to the isolated yield after flash chromatography (pentane/ethyl acetate: 3/7).
[c] Determined by HPLC analysis on a Chiralcel OD-H column.

The previously mentioned set of experiments seemed to strongly confirm that in the dual catalytic system under investigation, the yield is primarily controlled by the silylating agent, while, as expected, enantioselectivity mainly depends on the amount of the chiral amino alcohol ligand.

In order to evaluate the generality of the titled asymmetric reaction, the optimal procedure for the diethylzinc addition reaction to the benzaldehyde derived imine **2a** (Table 2, run 4) was thereafter examined for *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 3 are summarized in Table 3.

In the presence of stoichiometric amounts of chiral ligand **3b** and TIPSCl, the diethylzinc addition reaction to various *N*-arylimines containing *ortho*- and *para*-substituents on the phenyl group proceeded smoothly to afford the corresponding chiral amines **4a**–**f** with chemical yields up to



Scheme 3. Diethylzinc addition reaction to arylimines **2a**–**f** in the presence of TIPSCl.

Table 3. Enantioselective ethylation to arylimines **2a–f** mediated by **3b**/TIPSCl[a]

Run	Ar	Imine	Adduct	Yield[b] (%)	ee[c,d] (%)
1	Ph	**2a**	**4a**	90	84
2	2-CH_3–C_6H_4	**2b**	**4b**	88	79
3	4-CH_3–C_6H_4	**2c**	**4c**	93	87
4	2-CH_3O–C_6H_4	**2d**	**4d**	92	82
5	4-CH_3O–C_6H_4	**2e**	**4e**	95	88 (92)[e]
6	2,4,6-Tri-CH_3–C_6H_4	**2f**	**4f**	78	72

[a] All reactions were carried out at −20 °C (Molar ratio: Imine/**3b**/TMSiCl/Et_2Zn = 1:1:1:3).
[b] Refers to the 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 to be *S* based on the specific rotation of the amine resulted after reductive cleavage and comparison with the literature (see Section 4).
[e] Crystallized from hexane/ethanol (1/9).

95% and good to high enantioselectivities (72–88%). It should be noted in Table 3, which 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 addition product **4c** with a relatively higher enantioselectivity of 87% ee (run 3) than that of 79% ee (run 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 (Table 3, runs 4 and 5), respectively. Arylimine **2f**, bearing a 2,4,6-tri-methylphenyl group, provided the addition product **4f** with a lower yield of 78% and enantioselectivity of 72%, which may be due to the steric hindrance imposed by the di-*ortho*-substituted benzene ring (run 6).

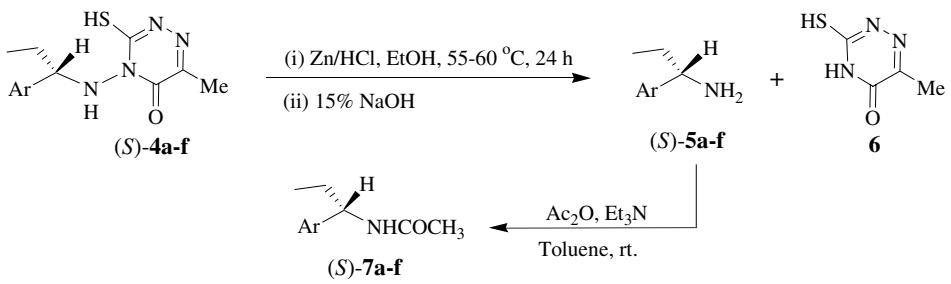
It should be noted that all addition products **4a–f** obtained are solids and thus their enantiomeric excess could be enhanced by crystallization. For example, the enantiomeric purity of **4e** (88%, run 4) could be upgraded to 92% by a simple crystallization from hexane/ethanol (Table 3, run 5).

It is worth noting that, although a stoichiometric amount of amino alcohol as chiral ligand was used, more than 90% of it could be easily recovered during the work-up in a typical experiment. The recovered ligand could be used in further experiments without a significant loss of chiral induction.

It is worthwhile to note 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 ligand **3b** and TIPSCl, the starting material was recovered almost unchanged. This result indicates that the diethylzinc reagent neither opened the hetero-ring in the 1,2,4-triazine derivative **2a** nor attacked the carbonyl or the thione group of the 1,2,4-triazine 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 the microanalytical and spectral data.

Additional studies demonstrated that the process can be extended to asymmetric primary amine synthesis through deprotection of the *N*-triazinyl group. The removal of the 1,2,4-triazinyl heterocyclic ring via reductive cleavage was uneventful and furnished the corresponding free (*S*)-1-aryl-1-propylamines **5a–f** without racemization and in nearly quantitative yields in addition to the expected 4-amino-3-mercapto-6-methyl-4*H*-1,2,4-triazine-5-one **6**[9] (Scheme 4). The absolute configurations of the major isomer of the addition products **4a–f** were assigned to be (*S*)-isomer based on the absolute configuration of products **5a–f** obtained after the reductive cleavage of the 1,2,4-triazinyl heterocyclic ring from the addition products **4a–f** and a comparison of the retention times on HPLC with the literature values.[10b,13] The ee values of the (*S*)-1-aryl-1-propylamines **5a–f** were determined by HPLC analysis after derivation of the amine to the corresponding acetamide derivatives **7a–f** by a reported method[10b] by the treatment of **5a–f** with acetic anhydride and triethylamine and comparison with the literature value.[13] The ee values were found to be in very good agreement with the enantiomeric excesses of the starting secondary amines **4a–f**.

Although the mechanistic details for the asymmetric process are currently unclear, the observed results might be rationalized by assuming that the addition takes place through the transition states depicted in Figure 2. However, sulfur is more nucleophilic than oxygen and proved particularly to be stronger than oxygen in complexation with a Zn atom.[14] Therefore, the mercapto group (SH)



Scheme 4. Preparation of chiral amines **5a–f** via reductive cleavage of the triazinyl group.

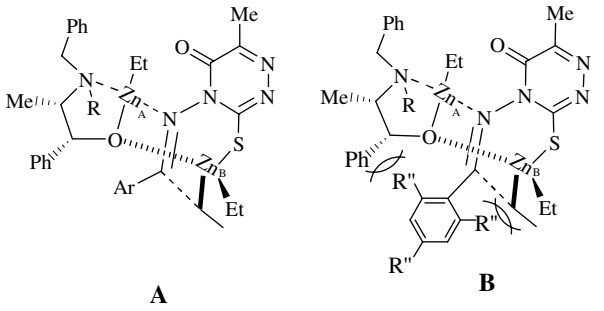


Figure 2. Proposed transition state for the diethylzinc addition reaction to arylimines **2a**–**f**.

would be more nucleophilic than the carbonyl group (C=O) and consequently the S–Zn interaction may be stronger than that of O–Zn. The steric hindrance brought about by each of the substituents on the nitrogen atom of ligand **3**, as well as by the triazine heterocyclic ring forces Zn_B to be in the position shown, thus determining 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 a bicyclic transition state such as the one shown in Figure 2. The transfer of one of the ethyl groups of Zn_B to the imine carbon would give the addition products with the observed stereochemistry.

As shown in structure **A**, products with an (*S*)-absolute configuration should be given by ligands **3a**–**d**, which was consistent with our experimental results. The transition state **B** 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 (Table 3, compare entry 1 with entries 2, 4 and 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 **A**, for steric reasons, it appears advantageous to have a small alkyl (R) group on the nitrogen atom of the ligand **3** in order to get high selectivities, and this assumption was also borne out experimentally (Table 1, runs 1–4).

3. Conclusion

In conclusion, we have demonstrated the first application of diethylzinc addition reaction to the exocyclic C=N double bond of 4-arylideneamino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-ones **2a**–**f** as substrates in the presence of β-amino alcohols **3a**–**d** as chiral ligands and chloro trialkylsilanes as activators. The activation of arylimines with silylating reagent renders the alkylation to be an easy, efficient, and high yielding reaction. In the presence of **3b**/TIPSCl, the addition reaction took place smoothly affording the addition products in high yields with enantioselectivities up to 92%. The removal of the 1,2,4-triazinyl heterocyclic ring via reductive cleavage was uneventful and furnished the corresponding free (*S*)-1-aryl-1-propylamines **5a**–**f** without racemization and in nearly quantitative yields. Due to the simplicity of the process and the ready availability of imine precursor **2**, we believe that a broad applicability of the reported catalytic reaction can be anticipated. Further work in this area is still needed. Efforts along this line including the use of other organozinc reagents to achieve higher stereoselectivities are currently under way and the results will be reported in due course.

4. Experimental

All reactions were performed under a nitrogen atmosphere. Melting points were measured on an electrothermal digital melting point apparatus and are uncorrected. All commercially available reagents and solvents were employed as supplied, except for toluene, which was freshly distilled under nitrogen prior to use. Diethylzinc reagent was purchased from Aldrich Co. Flash chromatography was performed on deactivated silica gel (Matrix 60A, 37–70 μm) and the spots were detected with UV model UVGL-58. Optical rotations were measured with a Perkin–Elmer 341 Polarimeter in a 10 cm cell with the solvent indicated. HPLC analyses were carried out on a chiral column (Chiralcel OD-H column, 25 cm, 30 °C), with a 254 nm UV detector and a flow rate of 1.0 mL/min. ^{1}H 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. Mass spectra were recorded on a JEOL JMS-SX120A. IR spectra were recorded on Perkin–Elmer 1760 FTIR spectrophotometer instrument.

4.1. Enantioselective addition of diethylzinc to arylimines 2 in the presence of chiral ligands 3

4.1.1. In the absence of Lewis acids. Typical experimental procedure. Benzaldimine **2a** (73.9 mg, 0.3 mmol) and amino alcohol **3b** (76.6 mg, 0.3 mmol) were dissolved in dry toluene (2.0 mL) under nitrogen and the mixture was stirred for 10 min at room temperature. The solution was cooled to 0 °C and diethylzinc (0.9 mL, 1.0 M solution in hexane, 0.9 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for a further 30 min. The reaction mixture was allowed to rise slowly to room temperature and stirred for a further 48 h at that temperature and then quenched with saturated aqueous NH_4Cl (15 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were dried over $MgSO_4$. The solvents were evaporated and the residue purified by flash chromatography on silica gel (deactivated silica gel, pentane/ethyl acetate: 95:5–30:70) to afford 45.6 mg (55% yield) of **4a**. The resultant solid was analyzed by HPLC on a Chiralcel OD-H column. The obtained yields and ee's with the use of other ligands are given in Table 1.

4.1.2. In the presence of Lewis acids. Typical experimental procedure. Arylimine **2e** (82.8 mg, 0.3 mmol) and ligand **3b** (76.6 mg, 0.3 mmol) were dissolved in dry toluene

(2.0 mL) under nitrogen, at room temperature, and the reaction mixture was cooled to 0 °C. To this mixture, 0.9 mL (0.9 mmol) of 1 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 then quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers 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: 95:5–30:70) to afford 4-[1-(4′-methoxyphenyl)propyl]amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one **4e** in 95% yield (87.3 mg) as a white solid and in 88% ee. The enantiomeric purity of **4e** could be upgraded to 92% by simple crystallization from hexane/ethanol (1:9). The product was analyzed by HPLC on a Chiralcel OD-H column. The yields and enantiomeric compositions of the secondary amines obtained with arylimines **2a**–**f** are shown in Tables 2 and 3.

4.1.3. 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); IR (cm^{-1}) 3277 (NH), 1707 (C=O), 1205 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.89 (t, 3H, $J = 7.5$ Hz, CH_3CH_2), 1.75–1.88 (m, 1H, CH_2CH_3), 1.96–2.08 (m, 1H, CH_2CH_3), 2.38 (s, 3H, CH_3–C_6), 3.42 (m, 1H, NHN), 4.04–4.16 (m, 1H, CHNH), 7.33–7.68 (m, 5H, H_{Ar}), 12.17 (br s, 1H, SH); ^{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 (Ar), 129.33 (Ar), 130.26 (Ar), 137.30 (Ar), 149.31 (C_6), 165.40 (C_5), 170.11 (C_3); MS (EI) *m*/*z* (rel. intensity) 276 (M^+, 6%), 249 (44), 248 (14), 232 (8), 157 (14), 146 (71), 142 (6), 134 (33), 130 (17) and 119 (23). 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.

4.1.4. 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); IR (cm^{-1}) 3270 (NH), 1701 (C=O), 1207 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.79 (t, 3H, $J = 7.4$ Hz, CH_3CH_2), 1.78–1.90 (m, 1H, CH_2CH_3), 1.96–2.09 (m, 1H, CH_2CH_3), 2.32 (s, 3H, Ar–CH_3), 2.56 (s, 3H, CH_3–C_6), 3.28 (br s, 1H, NHC), 3.99–4.08 (m, 1H, CHNH), 6.78–6.98 (m, 2H, H_{Ar}), 7.09–7.44 (m, 2H, H_{Ar}), 12.29 (br s, 1H, SH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 10.66 (CH_3CH_2), 16.69 (CH_3–C_6), 21.49 (Ar–CH_3), 31.93 (CH_2CH_3), 57.36 (*C*HNH), 120.93 (Ar), 126.71 (Ar), 127.85 (Ar), 133.29 (Ar), 152.31 (C_6), 165.92 (C_5), 169.67 (C_3); MS (EI) *m*/*z* (rel. 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) and 91 (6). 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.

4.1.5. 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_2Cl_2); HPLC conditions: 15% ^{i}PrOH in hexane, retention times, 21.55 min (minor, *R*-isomer) and 27.82 min (major, *S*-isomer); IR (cm^{-1}) 3280 (NH), 1703 (C=O), 1208 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.86 (t, 3H, $J = 7.6$ Hz, CH_3CH_2), 1.74–1.87 (m, 1H, CH_2CH_3), 1.97–2.13 (m, 1H, CH_2CH_3), 2.35 (s, 3H, Ar–CH_3), 2.44 (s, 3H, CH_3–C_6), 3.42 (br s, 1H, NHC), 4.06–4.16 (m, 1H, CHNH), 7.07 (d, $J = 8.3$ Hz, 2H, H_{Ar}), 7.18 (d, $J = 8.3$, 2H, H_{Ar}), 11.57 (br s, 1H, SH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 10.95 (CH_3CH_2), 16.92 (CH_3–C_6), 21.64 (Ar–CH_3), 32.2 (CH_2CH_3), 54.65 (*C*HNH), 125.88 (Ar), 128.84 (Ar), 136.38 (Ar), 140.69 (Ar), 150.43 (C_6), 166.76 (C_5), 170.18 (C_3); MS (EI) *m*/*z* (rel. intensity) 290 (M^+, 11%), 263 (27), 246 (9.5), 218 (4), 158 (9), 146 (52), 134 (18), 130 (25), 119 (21), 105 (9) and 91 (19). Anal. Calcd for $C_{14}H_{18}N_4OS$: 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.

4.1.6. 4-[1-(2′-Methoxyphenyl)propyl]amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one 4d. White solid, 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); IR (cm^{-1}) 3285 (NH), 1795 (C=O), 1209 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.76 (t, 3H, $J = 7.4$ Hz, CH_3CH_2), 1.74–1.89 (m, 1H, CH_2CH_3), 1.96–2.05 (m, 1H, CH_2CH_3), 2.37 (s, 3H, CH_3–C_6), 3.28 (br s, 1H, NHC), 3.83 (s, 3H, OCH_3), 4.38–4.52 (m, 1H, CHNH), 6.98 (d, 1H, $J = 8.0$ Hz, H_{Ar}), 7.09 (t, 1H, $J = 7.6$ Hz, H_{Ar}), 7.35 (t, 1H, $J = 7.6$ Hz, H_{Ar}), 7.59 (d, 1H, $J = 7.6$ Hz, H_{Ar}), 8.08 (dd, $J = 1.94$, 1.77 Hz, 1H, H_{Ar}), 12.44 (br s, 1H, SH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 10.93 (CH_3CH_2), 17.49 (CH_3–C_6), 32.29 (CH_2CH_3), 53.49 (OCH_3), 57.62 (*C*HNH), 121.73 (Ar), 127.52 (Ar), 128.21 (Ar), 131.89 (Ar), 151.09 (C_6), 165.87 (C_5), 170.19 (C_3); MS (EI) *m*/*z* (rel. intensity) 306 (M^+, 14%), 278 (19), 262 (11), 234 (5), 157 (13), 146 (76), 150 (26), 131 (28), 118 (17), 105 (13), 91 (37) and 91 (11). Anal. Calcd for $C_{14}H_{18}N_4O_2S$: 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.

4.1.7. 4-[1-(4′-Methoxyphenyl)propyl]amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one 4e. White solid, 144–145 °C; $[\alpha]_D^{25} = -34.6$ (*c* 2.39, CH_2Cl_2); HPLC conditions: 15% ^{i}PrOH in hexane, retention times, 9.32 min (minor, *R*-isomer) and 15.52 min (major, *S*-isomer); IR (cm^{-1}) 3285 (NH), 1695 (C=O), 1210 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.87 (t, 3H, $J = 7.5$ Hz, CH_3CH_2), 1.75–1.92 (m, 1H, CH_2CH_3), 1.98–2.11 (m, 1H, CH_2CH_3), 2.42 (s, 3H, CH_3–C_6), 3.34 (br s, 1H, NHC), 3.82 (s, 3H, OCH_3), 4.09–4.17 (m, 1H, CHNH), 6.93 (d, $J = 8.7$ Hz, 2H, H_{Ar}), 7.26 (d, $J = 8.7$ Hz, 2H, H_{Ar}), 11.87 (br s, 1H, SH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 11.7 (CH_3CH_2), 17.87 (CH_3–C_6), 31.3 (CH_2CH_3), 55.59 (OCH_3), 56.44 (*C*HNH), 115.87 (Ar), 126.67 (Ar), 134.72 (Ar), 146.43 (Ar), 152.52 (C_6), 164.55 (C_5), 171.09 (C_3); MS (EI) *m*/*z* (rel. intensity) 306 (M^+, 18%), 279 (22), 262 (6), 234 (4), 157 (24), 150 (21), 146 (64), 130 (16), 119 (9) and 105 (7). Anal. Calcd for $C_{14}H_{18}N_4O_2S$:

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.

4.1.8. 4-[1-(2′,4′,6′-Tri-methylphenyl)propyl]amino-3-mercapto-6-methyl-4*H*-1,2,4-triazin-5-one 4f. White solid, 198–199 °C; $[\alpha]_D^{25} = -46.6$ (*c* 0.98, CH_2Cl_2); HPLC conditions: 15% ^{i}PrOH in hexane, retention times, 12.82 min (minor, *R*-isomer) and 19.42 min (major, *S*-isomer); IR (cm^{-1}) 3283 (NH), 1704 (C=O), 1205 (C=S); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.91 (t, 3H, $J = 7.7$ Hz, CH_3CH_2), 1.72 (s, 3H, Ar–CH_3), 1.84–1.96 (m, 1H, CH_2CH_3), 2.01–2.11 (m, 1H, CH_2CH_3), 2.21 (s, 6H, Ar–CH_3), 2.31 (s, 3H, Ar–CH_3), 2.40 (s, 3H, CH_3–C_6), 3.39 (br s, 1H, NHC), 4.16–4.31 (m, 1H, CHNH), 6.72 (s, 1H, Ar–H), 6.89 (s, 1H, H_{Ar}), 7.31 (s, 1H, H_{Ar}), 11.57 (br s, 1H, SH); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 11.18 (CH_3CH_2), 17.12 (CH_3–C_6), 19.98 (Ar–CH_3), 20.55 (Ar–CH_3), 21.95 (Ar–CH_3), 31.8 (CH_2CH_3), 53.44 (*C*HNH), 128.31 (Ar), 131.67 (Ar), 136.19 (Ar), 139.52 (Ar), 152.18 (C_6), 165.49 (C_5), 169.78 (C_3); MS (EI) *m*/*z* (rel. intensity) 318 (M^+, 13%), 290 (21), 274 (4), 246 (7), 175 (32), 162 (29), 158 (23), 146 (61), 131 (33), 118 (17), 105 (8) and 91 (12). Anal. Calcd for $C_{16}H_{22}N_4OS$: 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.

4.2. Removal of the 1,2,4-triazinyl heterocyclic ring via reductive cleavage of addition products 4a–f. General procedure

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) was added and the reaction mixture heated at 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. 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 removed in vacuo. Purification by flash chromatography (deactivated silica gel, pentane/ether: 95:5–80:20) afforded the pure 1-arylpropylamine. All the physical and spectroscopic data for compounds **5a**–**f** were in complete agreement with the reported data.[10b,13] The absolute configurations of the major isomer of addition products **4a**–**f** were assigned to be the (*S*)-isomer based on the absolute configuration of **5a**–**f** and comparison of the retention times on HPLC with the literature values.[10b,13] The ee values of the (*S*)-1-aryl-1-propylamines **5a**–**f** were determined by HPLC analysis after their derivation to the corresponding acetamide derivatives **7a**–**f** by reported method[10b] by treatment with acetic anhydride and triethylamine and comparison with the literature value.[13] The ee values that were determined by HPLC were found to be in very good agreement with the enantiomeric excesses 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 give **6**. In all cases, the product was identified as the expected 4-amino-3-hydroxy-6-methyl-4*H*-1,2,4-triazin-5-one. Melting and mixed melting point determinations gave no depression.[9]

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