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Enantioselective cyanosilylation of aldehydes catalysed by a diastereomeric mixture of atropisomeric thioureas

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Abstract—New bifunctional atropisomeric thioureas **1** were synthesised and tested as both a mixture of diastereomers (a*R*/a*S*)-(*R*,*R*)-**1** and as single diastereomers (a*R*)-(*R*,*R*)-**1** and (a*R*)-(*S*,*S*)-**1**, in the organocatalysed, enantioselective, cyanosilylation of a range of aldehydes (aromatic and aliphatic). Moderate enantiomeric excesses (up to 69% ee) and quantitative yields were obtained. The best results were achieved using a mixture of thiourea diastereomers (a*R*/a*S*)-(*R*,*R*)-**1** instead of the single diastereomers alone.

1. Introduction

Interest in the field of asymmetric organocatalysis has increased greatly in recent years.[1] There are now many chiral organic molecules, which can act as effective catalysts for reactions that have normally relied upon metal-based catalysts. Bifunctional chiral thioureas, bearing additional acidic or basic functional groups, have emerged as a successful class of organocatalysts for a variety of asymmetric transformations, such as the cyanosilylation of ketones,[2] Strecker reactions,[3] Michael additions,[4] Baylis–Hillman reactions,[5] Mannich reactions,[6] Henry and aza-Henry reactions[7] and hydrophosphonylation of imines.[8] Their success as bifunctional organocatalysts is based upon their ability to function as hydrogen-bond donors,[9] and the incorporation of additional basic or acidic activating groups.

The asymmetric cyanation of aldehydes is an important and well-documented reaction, due to the fact that the product cyanohydrins are important intermediates for the synthesis of α-hydroxy acids and β-amino alcohols. The main methods employed for the synthesis of nonracemic cyanohydrins are either enzyme-catalysed, peptide-catalysed or metal-catalysed procedures.[10] There are very few examples of organocatalysed cyanide addition to aldehydes: these include cyclic peptides,[11] guanidines,[12] *N*,*N*′-dioxides,[13] and oxazaborolidinium ions.[14]

Herein, we report the use of a diastereomeric mixture of atropisomeric thioureas **1** (Fig. 1) as a bifunctional organocatalytic system for the enantioselective cyanosilylation of a range of aldehydes.

2. Results and discussion

Roussel et al. have worked on the synthesis and chiral separation of thiazoline-2-thione-based atropisomers **2** (Fig. 2).[15] The atropisomers of **2** can be separated by semi-preparative chiral HPLC on a Chiralcel OD column, using hexane/ethanol as the eluent, at 4.5 mL/min. The atropisomers have a barrier to rotation of $\Delta G^{\neq}_{rot} > 145$ kJ/mol, and do not racemise at room temperature.[15] We were interested in transforming thiazoline-2-thione **2**, via isothiocyanate **3** (the atropisomers of which also have a barrier to rotation $\Delta G^{\neq}_{rot} > 145$ kJ/mol), into a variety of chiral thioureas (Scheme 1).

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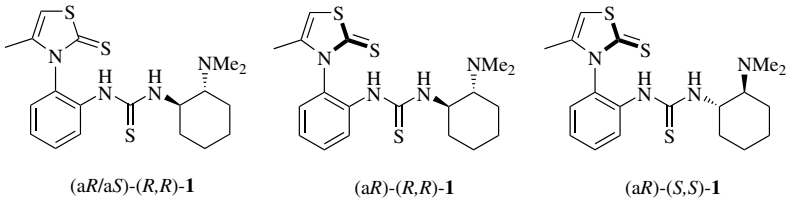


Figure 1. Bifunctional atropisomeric thioureas **1**: mixture of diastereomers (a*R*/a*S*)-(*R*,*R*)-**1** and single diastereomers (a*R*)-(*R*,*R*)-**1** and (a*R*)-(*S*,*S*)-**1**.

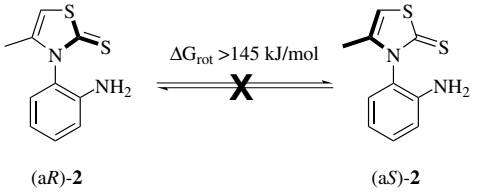
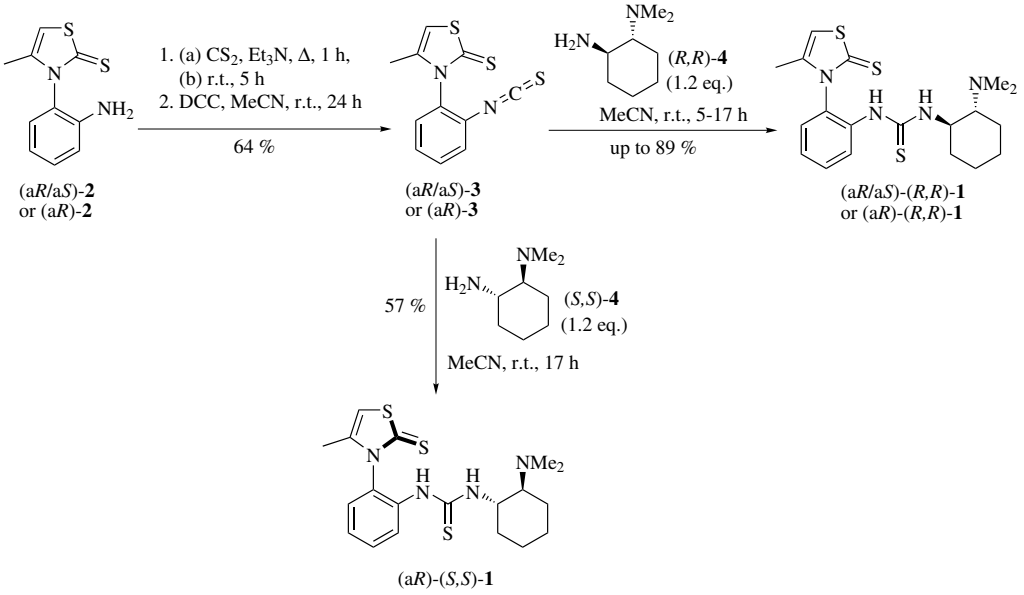


Figure 2. Atropisomers of thiazoline-2-thione **2**.

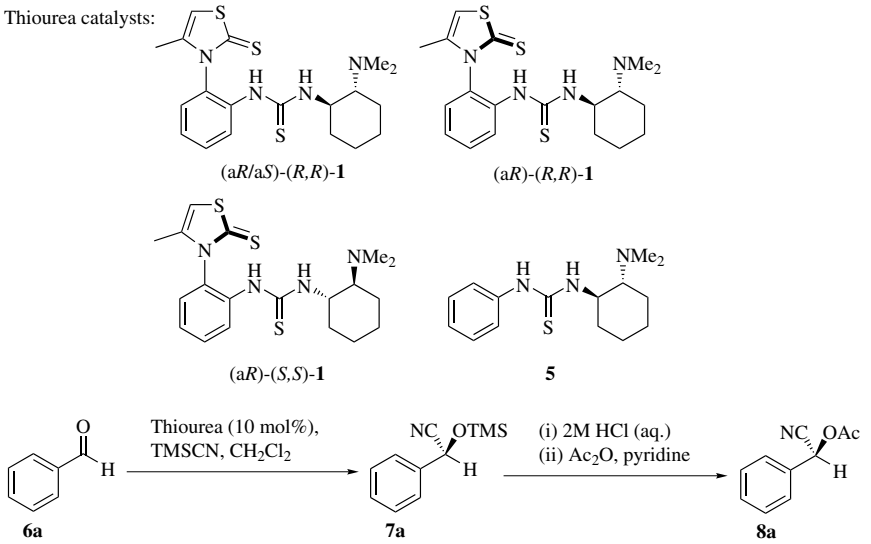
Initially, we synthesised catalyst (a*R*/a*S*)-(*R*,*R*)-**1** (see Scheme 1), which is a 1:1 inseparable mixture of the two diastereomers (a*R*)-(*R*,*R*)-**1** and (a*S*)-(*R*,*R*)-**1**, to test for catalytic activity in the addition of trimethylsilylcyanide (TMSCN) to aldehydes: it seemed inappropriate to first test the single diastereomers, which were only available in small amounts (due to the semi-preparative HPLC separation of the atropisomers of **2**). Treatment of racemic thiazoline-2-thione (a*R*/a*S*)-**2** with carbon disulfide, triethylamine and then dicyclohexylcarbodiimide in acetonitrile furnished isothiocyanate (a*R*/a*S*)-**3**, which was subsequently treated with (*R*,*R*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane **4** in acetonitrile to yield the inseparable diastereomeric mixture of thioureas (a*R*/a*S*)-(*R*,*R*)-**1**. The synthesis of the single diastereomers (a*R*)-(*R*,*R*)-**1** and (a*R*)-(*S*,*S*)-**1** was achieved via the same route shown in Scheme 1. The (a*R*)-atropisomer of the racemic thiazoline-2-thione (a*R*/a*S*)-**2** was separated by semi-preparative HPLC and converted to the isothiocyanate (a*R*)-**3**. Isothiocyanate (a*R*)-**3** was then treated with either (*R*,*R*)- or (*S*,*S*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane **4** to afford the two single diastereomers (a*R*)-(*R*,*R*)-**1** and (a*R*)-(*S*,*S*)-**1**, respectively [the diastereomer (a*R*)-(*S*,*S*)-**1** is the enantiomer of (a*S*)-(*R*,*R*)-**1**, which is present in the diastereomeric mixture (a*R*/a*S*)-(*R*,*R*)-**1**].

Our initial test of (a*R*/a*S*)-(*R*,*R*)-**1** in the trimethylsilylcyanation of benzaldehyde (see Scheme 2 and Table 1) was run using 10 mol % loading of thiourea (a*R*/a*S*)-(*R*,*R*)-**1** and 1.5 equiv of TMSCN, in dichloromethane at −20 °C (Table 1, entry 1). After 24 h, the reaction seemed slow and so a further 1.5 equiv of TMSCN was added. After 42 h, the cyanohydrin trimethylsilylether **7a** was obtained in 84% yield and a moderate enantioselectivity was noted (60.8% enantiomeric excess measured on the acetate derivative **8a**). At this point, the reaction was repeated, using a full 3 equiv of TMSCN, and in 27 h the cyanohydrin trimethylsilylether was furnished in a quantitative yield and, after conversion to the acetate derivative **8a**, 66.3% enantiomeric excess (Table 1, entry 2).

Importantly, we were able to show that the axial chirality in our atropisomeric mixture (a*R*/a*S*)-(*R*,*R*)-**1** was essential for achieving the 66.3% enantiomeric excess, and that this was not all due to the stereogenic centres from the diamine



Scheme 1. Synthesis of bifunctional atropisomeric thioureas **1**.



Scheme 2. Thiourea catalysed trimethylsilylcyanation of benzaldehyde.

Table 1. Thiourea catalysed trimethylsilylcyanation of benzaldehyde

Entry	Thiourea	TMSCN (equiv)	Temperature (°C)	Time (h)	Yield of **7a**[b] (%)	% ee of **8a** (Config.)[c,d]
1	(a*R*/a*S*)-(*R*,*R*)-**1**	1.5 + 1.5[a]	−20	42	84	60.8 (*S*)
2	(a*R*/a*S*)-(*R*,*R*)-**1**	3	−20	27	Quant.	66.3 (*S*)
3	**5**	3	−20	27	15	32.4 (*S*)
4	(a*R*/a*S*)-(*R*,*R*)-**1**	3	−40	24	47	55.5 (*S*)
5	(a*R*/a*S*)-(*R*,*R*)-**1**	3	−78	64	31	37.6 (*S*)
6	(a*R*/a*S*)-(*R*,*R*)-**1**	3	0	24	81	58.0 (*S*)
7	(a*R*)-(*R*,*R*)-**1**	3	−20	24	30	46.7 (*S*)
8	(a*R*)-(*S*,*S*)-**1**	3	−20	26	Quant.	55.0 (*R*)

[a] 1.5 equiv of TMSCN was added initially, then a further 1.5 equiv was added after 24 h.
[b] GC yield relative to decane standard.
[c] % ee determined by GC analysis on a DMePentilBETACDX (OV1701).
[d] Absolute configuration determined by comparison to the reported specific rotation.

moiety. We performed the addition of TMS cyanide to benzaldehyde using 10 mol % of thiourea **5**, which possessed the same (*R*,*R*)-stereogenic centres from the diamine moiety, but crucially did not possess the axial chirality of our atropisomeric thioureas. Using thiourea **5**, we obtained a 15% yield of the cyanohydrin trimethylsilylether with only 32.4% enantiomeric excess (Table 1, entry 3).

It was decided to first optimise the reaction using a mixture of diastereomers (a*R*/a*S*)-(*R*,*R*)-**1**, then to test the two single diastereomers (a*R*)-(*R*,*R*)-**1** and (a*R*)-(*S*,*S*)-**1**.

Our choice of dichloromethane as solvent was based on the rationalisation that the use of more polar or protic solvents could disguise the catalytic activity of the bifunctional thiourea, by competing with both the nucleophile (cyanide) and the electrophile (aldehyde) activation. It has been demonstrated that solvents such as dichloromethane or toluene are generally good solvents for these kinds of organocatalysed reactions as they should not interfere with the hydrogen bonding.[2] However, we found that toluene was not adapted to our system, as the thiourea was only partially soluble in toluene at low temperatures which were required for this reaction.

In an attempt to improve the enantiomeric excess, the addition of TMSCN to benzaldehyde was carried out at −40 °C (Table 1, entry 4), −78 °C (Table 1, entry 5) and at 0 °C (Table 1, entry 6). We found that running the reaction at −40 °C gave us only 47% yield of the cyanohydrin trimethylsilylether **7a** and a poorer enantiomeric excess (55.5% ee) than at −20 °C. To confirm this effect, we attempted to run the reaction at −78 °C, which gave us, after 64 h, only 31% yield and 37.6% enantiomeric excess. Given that a lower temperature gave us worse results, we then tried running the reaction at 0 °C, which gave us 89% yield and, again, a poorer enantiomeric excess of 59.7%.

Having found the optimal temperature for the reaction (−20 °C), we decided that it was time to test the single diastereomers (a*R*)-(*R*,*R*)-**1** and (a*R*)-(*S*,*S*)-**1**. We expected to find that one of the two diastereomers would be better than the other as well as the mixture (a*R*/a*S*)-(*R*,*R*)-**1**. However, we discovered that diastereomer (a*R*)-(*R*,*R*)-**1** gave us only 30% yield of the cyanohydrin trimethylsilylether and a 46.7% enantiomeric excess (Table 1, entry 7), while diastereomer (a*R*)-(*S*,*S*)-**1** afforded the cyanohydrin trimethylsilylether in a quantitative yield and again with a moderate enantiomeric excess [55.0%, in favour of the (*R*)-enantiomer,

Table 1, entry 8].[16] So, both diastereomers gave worse results than the mixture![16]

We wanted to confirm this effect in the addition of TMSCN to another aldehyde, that is, cyclohexanecarboxaldehyde (Table 2, entries 4–6). The use of (a*R*)-(*R*,*R*)-**1** afforded the cyanohydrin trimethylsilylether in quantitative yield, with a 60.2% enantiomeric excess, while the other diastereomer (a*R*)-(*S*,*S*)-**1** gave a 95% yield and 62.8% enantiomeric excess. Use of the mixture of diastereomers (a*R*/a*S*)-(*R*,*R*)-**1** gave a quantitative yield and 68.1% enantiomeric excess.

This result confirmed that the mixture of the two diastereomers performs better, in terms of enantioselectivity, than either of the single diastereomers alone. It can tentatively be suggested that this surprising effect is due to more than one molecule of thiourea being present in the transition state of the catalysed reaction (with a co-operation of the two diastereomeric thioureas).[17] For example, self-association in the mixture of the two diastereomers (e.g., dimer formation in CH_2Cl_2 at −20 °C) might stabilise a suitable thiourea conformation ('preorganisation') for catalytic activity better than in the single diastereomers.[18]

This result is also very important from a practical point of view, in that there is no need to separate the atropisomers of thiazoline-2-thione **2**, and the isothiocyanate **3** can be used as a racemate. In this way, the thiourea catalyst (a*R*/a*S*)-(*R*,*R*)-**1** can be prepared on a large scale, in a simple three-step procedure.

We then investigated the scope of the cyanosilylation reaction with a range of aldehydes, using the mixture (a*R*/a*S*)-(*R*,*R*)-**1** as catalyst (see Scheme 3 and Table 2). Of the aromatic aldehydes tested, benzaldehyde gave a slightly better result than 4-chlorobenzaldehyde (Table 2, cf. entry 1 and entry 7), 2-naphthaldehyde (Table 2, entry 8) or the heterocyclic aromatic 2-furaldehyde (Table 2, entry 9). The linear alkenyl (*E*)-cinnamaldehyde (Table 2, entry 10) and aliphatic hydrocinnamaldehyde (Table 2, entry 11) gave the poorest results, both in terms of yield and enantioselectivity. We found that the branched aliphatic aldehydes, cyclohexanecarboxaldehyde and isobutyraldehyde, gave the best overall results: quantitative yield with 68.1% enantiomeric excess and 82% yield with 69.0% enantiomeric excess, respectively (Table 2, entries 4 and 12).

We are actively investigating the use of the diastereomeric mixture of thioureas (a*R*/a*S*)-(*R*,*R*)-**1** as an organocatalyst for the cyanosilylation of ketones, and for other asymmetric transformations.

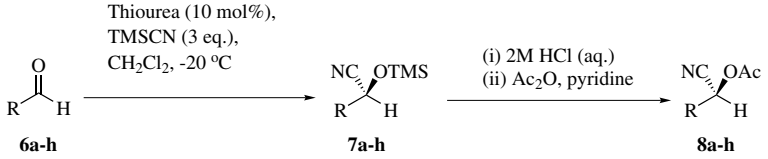
3. Conclusion

We synthesised a new atropisomeric thiourea organocatalyst **1** and tested it as both a mixture of diastereomers (a*R*/a*S*)-(*R*,*R*)-**1** and as the single diastereomers (a*R*)-(*R*,*R*)-**1** and (a*R*)-(*S*,*S*)-**1**, in the cyanosilylation of a range of aldehydes. We showed that the axial chirality in the thiourea was necessary for good enantioselectivity in this reaction. We demonstrated that by using the mixture of diastereomers (a*R*/a*S*)-(*R*,*R*)-**1**, it gave better results for the cyanosilylation of aldehydes than the use of a single diastereomer alone. This means that there is no need for semi-preparative HPLC separation of the atropisomers of the thiazoline-2-thione **2**; therefore, the catalyst can be synthesised on a much larger scale. We speculated that the better results obtained using the diastereomeric mixture

Table 2. Thiourea catalysed trimethylsilylcyanation of a range of aldehydes

Entry	Aldehyde	Thiourea	Time (h)	Yield of **7**[a,b] (%)	% ee of **8** (Config.)[c,d]
1	Benzaldehyde **6a**	(a*S*/a*R*)-(*R*,*R*)-**1**	27	Quant.[a]	66.3 (*S*)
2	Benzaldehyde **6a**	(a*R*)-(*R*,*R*)-**1**	24	30[a]	46.7 (*S*)
3	Benzaldehyde **6a**	(a*R*)-(*S*,*S*)-**1**	25	Quant.[a]	55.0 (*R*)
4	Cyclohexanecarboxaldehyde **6b**	(a*S*/a*R*)-(*R*,*R*)-**1**	27	Quant.[b]	68.1 (*S*)
5	Cyclohexanecarboxaldehyde **6b**	(a*R*)-(*R*,*R*)-**1**	25	Quant.[b]	60.2 (*S*)
6	Cyclohexanecarboxaldehyde **6b**	(a*R*)-(*S*,*S*)-**1**	26	95[b]	62.8 (*R*)
7	4-Chlorobenzaldehyde **6c**	(a*S*/a*R*)-(*R*,*R*)-**1**	47	75[b]	65.5 (*S*)
8	2-Naphthaldehyde **6d**	(a*S*/a*R*)-(*R*,*R*)-**1**	46	84[b]	64.6 (*S*)
9	2-Furaldehyde **6e**	(a*S*/a*R*)-(*R*,*R*)-**1**	48	Quant.[b]	61.7 (*S*)
10	(*E*)-Cinnamaldehyde **6f**	(a*S*/a*R*)-(*R*,*R*)-**1**	25	43[b]	45.2 (*S*)
11	Hydrocinnamaldehyde **6g**	(a*S*/a*R*)-(*R*,*R*)-**1**	26	45[b]	51.4 (*S*)
12	Isobutyraldehyde **6h**	(a*S*/a*R*)-(*R*,*R*)-**1**	43	82[b]	69.0 (*S*)

[a] GC yield relative to decane standard.
[b] Isolated yield.
[c] % ee determined by GC analysis on a DMePentilBETACDX (OV1701).
[d] Absolute configuration determined by comparison to the reported specific rotation.



Scheme 3. Thiourea catalysed trimethylsilylcyanation of a range of aldehydes.

of thioureas (a*R*/a*S*)-(*R*,*R*)-**1** could be due to more than one molecule of thiourea being present in the transition state of the catalysed reaction.

4. Experimental

4.1. General experimental

All reactions were carried out in flame-dried glassware with magnetic stirring under an argon atmosphere. All aldehydes with the exception of 4-chlorobenzaldehyde and 2-naphthaldehyde were distilled before use. All other commercially available reagents were used as received. The following solvents were dried by distillation over CaH_2: CH_2Cl_2, MeCN, Et_3N, pyridine. The reactions were monitored by analytical thin-layer chromatography (TLC) by using silica gel $60F_{254}$ precoated glass plates (0.25 mm thickness). Visualisation was accomplished by irradiation with a UV lamp and/or staining with a permanganate solution. Flash column chromatography was performed using silica gel 60 Å, particle size 40–64 μm, following the procedure by Still et al.[19] Proton NMR spectra were recorded on a spectrometer operating at 400.13 MHz. Proton chemical shifts are reported in ppm (δ) with the solvent relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ 7.26 ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad signal, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets. Carbon NMR spectra were recorded on a 400 spectrometer operating at 100.56 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$ δ 77.0 ppm). Infra-red spectra were recorded on a standard FT/IR; peaks are reported in cm^{-1}. Optical rotation values were measured on an automatic polarimeter with a 1 dm cell at the sodium D line. Gas chromatography was performed on a GC instrument equipped with a flame ionisation detector, by using a chiral capillary column [DMePentilBETACDX (OV1701) by MEGA-Capillary Columns Laboratory (Legnano, Milano, Italy)]. High resolution mass spectra (HRMS) were performed on a hybrid quadrupole time of flight mass spectrometer equipped with an ESI ion source. A Reserpine solution 100 pg mL^{-1} (about 100 $counts^{-1}$), 0.1% HCOOH/CH_3CN 1:1, was used as reference compound (Lock Mass).

4.2. (1*R*,2*R*)-1-Amino-2-(dimethylamino)cyclohexane 4

This compound was prepared according to the procedure reported in the literature[20] and the spectroscopic data are in accordance with those described. $[\alpha]_D^{22} = -32.0$ (*c* 1.0, $CHCl_3$) {lit.[21] $[\alpha]_D^{20} = -32.5$ (*c* 1.0, $CHCl_3$)}.

4.3. (1*S*,2*S*)-1-Amino-2-(dimethylamino)cyclohexane 4

This compound was prepared according to the procedure reported in the literature[20] and the spectroscopic data are in accordance with those described. $[\alpha]_D^{22} = +32.0$ (*c* 1.0, $CHCl_3$) {lit.[21] $[\alpha]_D^{20} = -32.5$ (*c* 1.0, $CHCl_3$) for (*R*,*R*)}.

4.4. Racemic 3-(2-aminophenyl)-4-methyl-thiazoline-2-thione (a*R*/a*S*)-2

This compound was prepared according to the procedure reported in the literature[22] and the spectroscopic data are in accordance with those described. Mp 180 °C (lit.[22] 184 °C).

Separation of atropisomers:[15] Chiral HPLC: analytical separation on Chiralcel OD-H (250 × 4.6 mm) in hexane/ethanol (1:1) at 1 mL/min and 25 °C with UV detection 254 nm and polarimeter, $t_{R1}(+, aS) = 4.72$ min, $t_{R2}(-, aR) = 5.82$ min, $k_1(+) = 0.52$, $k_2(-) = 0.88$, $\alpha = 1.68$, Rs = 3.05. Semi-preparative separation on Chiralcel OD (250 × 10 mm) in hexane/ethanol (1:1) at 4.5 mL/min with UV detection 254 nm, 0.5 mL of a 7.5 mg/mL racemic solution was injected every 3 min. The (−)-enantiomer was derivatised by (*S*)-1-(1-naphthyl)ethyl isocyanate and its absolute configuration determined after X-ray analysis. Compound (a*S*)-**2**: mp 166 °C; $[\alpha]_D^{25} = +414.3$ (*c* 0.5, $CHCl_3$). Compound (a*R*)-**2**: mp 166 °C; $[\alpha]_D^{25} = -397.0$ (*c* 0.5, $CHCl_3$).

4.5. (a*R*)-3-(2-Isothiocyanato-phenyl)-4-methyl-thiazoline-2-thione (a*R*)-3

A mixture of the (a*R*)-*N*-(2-aminophenyl)-4-methyl-thiazoline-2-thione (50 mg, 0.225 mmol) and triethylamine (315 μL, 2.25 mmol) in carbon disulfide (2.00 mL) was heated at reflux for 1 h, then allowed to cool to room temperature and stirred for 5 h. The precipitate was filtered off and washed with diisopropyl ether. To a solution of the resulting triethylammonium dithiocarbonate (79 mg, 0.197 mmol) in acetonitrile (1.50 mL), dicyclohexylcarbodiimide (43 mg, 0.207 mmol, 1.05 equiv) was added and the mixture stirred at room temperature for 24 h. The dicyclohexylurea was filtered off and the solvent removed under reduced pressure. The crude was purified by column chromatography, eluting with 100% CH_2Cl_2, to give the (a*R*)-**3** as a colourless solid (46 mg, 77%), mp 151 °C [lit.[15] 151 °C]. $[\alpha]_D^{23} = -20.1$ (*c* 0.5, $CHCl_3$) {lit.[15] $[\alpha]_D^{25} = -21.4$ (*c* 0.5, $CHCl_3$)}. IR (Nujol): $\upsilon = 2037$, 1588, 1342, 1287, 1247, 1225, 1138, 1114, 1058, 960, 934 cm^{-1}. ^1H NMR($CDCl_3$): $\delta = 1.98$ (3H, d, $J = 1.2$ Hz), 6.43 (1H, q, $J = 1.2$ Hz), 7.34 (1H, dd, $J = 1.7$, 7.8 Hz), 7.40 (1H, dd, $J = 1.7$, 7.8 Hz), 7.45–7.57 (2H, m). ^{13}C NMR ($CDCl_3$): $\delta = 16.1$, 107.6, 126.9, 128.8, 130.5, 131.7, 134.9, 140.3, 142.2, 191.4. MS (EI): *m*/*z* (%) = 264 (30, M^+), 206 (100).

4.6. (a*R*)-1-((1*R*,2*R*)-2-Dimethylamino-cyclohexyl)-3-[2-(4-methyl-2-thioxo-thiazol-3-yl)-phenyl]-thiourea (a*R*)-(*R*,*R*)-1

To a solution of the (a*R*)-3-(2-isothiocyanato-phenyl)-4-methyl-thiazoline-2-thione **3** (44 mg, 0.166 mmol) in dry acetonitrile (1.0 mL), under argon, a solution of (*R*,*R*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane **4** (28 mg, 0.199 mmol) was added in acetonitrile (0.2 mL). The reaction mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure and the crude purified by column chromatography, eluting with 5–10% triethylamine/toluene, giving (a*R*)-(*R*,*R*)-**1** as a pale yellow amorphous solid (60 mg, 89%), mp (decomp.)

180–181.5 °C; $[\alpha]_D^{22} = -485.0$ (*c* 1.0, $CHCl_3$). R_f (Et_3N/toluene 1/9) = 0.21. IR (Nujol): $\upsilon = 2361$, 1521, 1289, 1174, 1062, 959 cm^{-1}. ^1H NMR($CDCl_3$): $\delta = 1.02$–1.43 (5H, m), 1.67–1.76 (1H, m), 1.78–1.95 (2H, m), 2.08 (3H, d, $J = 0.8$ Hz), 2.28 (6H, s), 2.30–2.45 (1H, m), 3.66 (1H, br s), 6.37 (1H, q, $J = 0.8$ Hz), 6.69 (1H, br s), 7.20 (1H, d, $J = 7.8$ Hz), 7.45 (1H, dd, $J = 7.2$, 7.8 Hz), 7.57 (1H, dd, $J = 7.2$, 7.8 Hz), 7.78 (1H, d, $J = 7.8$ Hz), 8.30 (1H, br s). ^{13}C NMR ($CDCl_3$): $\delta = 17.0$, 22.9, 25.1, 25.7, 33.4, 40.9, 56.9, 67.7, 107.7, 128.6, 128.9, 130.9, 131.1, 133.8, 137.0, 141.6, 182.0, 189.8. HRMS (ESI) $[M+H]^+$, found 407.13857. $C_{19}H_{26}N_4S_3$ requires $[M+H]^+$, 407.13924.

4.7. (a*R*)-1-((1*S*,2*S*)-2-Dimethylamino-cyclohexyl)-3-[2-(4-methyl-2-thioxo-thiazol-3-yl)-phenyl]-thiourea (a*R*)-(*S*,*S*)-1

To a solution of the (a*R*)-3-(2-isothiocyanato-phenyl)-4-methyl-thiazoline-2-thione **3** (85 mg, 0.321 mmol) in dry acetonitrile (2.0 mL), under argon, a solution of (*S*,*S*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane **4** (54 mg, 0.385 mmol) was added in acetonitrile (0.3 mL). The reaction mixture was stirred at room temperature for 17 h. The solvent was removed under reduced pressure and the crude purified by column chromatography, eluting with 5–10% triethylamine/toluene, giving (a*R*)-(*S*,*S*)-**1** as an off-white amorphous solid (74 mg, 57%), mp (decomp.) 80–83 °C; $[\alpha]_D^{22} = -358.2$ (*c* 1.0, $CHCl_3$); R_f (Et_3N/toluene 1/9) = 0.21. IR (Nujol): $\upsilon = 2361$, 1521, 1289, 1174, 1062, 959 cm^{-1}. ^1H NMR($CDCl_3$): $\delta = 1.00$–1.45 (5H, m), 1.63–1.78 (1H, m), 1.79–1.91 (2H, m), 2.07 (3H, d, $J = 0.8$ Hz), 2.16 (6H, s), 2.45–2.57 (1H, m), 3.47–3.68 (1H, m), 6.37 (1H, q, $J = 0.8$ Hz), 6.80 (1H, br s), 7.21 (1H, dd, $J = 1.4$, 7.6 Hz), 7.45 (1H, td, $J = 1.4$, 7.6 Hz), 7.57 (1H, td, $J = 1.4$, 7.6 Hz), 7.72 (1H, dd, $J = 1.4$, 7.6 Hz), 7.90 (1H, br s). ^{13}C NMR ($CDCl_3$): $\delta = 16.2$, 21.5, 24.5, 24.6, 25.0, 39.8, 55.7, 66.2, 107.1, 128.1, 128.3, 130.5, 130.8, 133.3, 136.2, 141.3, 181.2, 189.1. HRMS (ESI) $[M+H]^+$, found 407.13945. $C_{19}H_{26}N_4S_3$ requires $[M+H]^+$, 407.13924.

4.8. (a*R*/a*S*)-1-((1*R*,2*R*)-2-Dimethylamino-cyclohexyl)-3-[2-(4-methyl-2-thioxo-thiazol-3-yl)-phenyl]-thiourea (a*R*/a*S*)-(*R*,*R*)-1

To a solution of the (a*R*/a*S*)-3-(2-isothiocyanato-phenyl)-4-methyl-thiazoline-2-thione **3** (200 mg, 0.756 mmol) in dry acetonitrile (4.0 mL), under argon, a solution of (*R*,*R*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane **4** (128 mg, 0.906 mmol) was added in acetonitrile (0.6 mL). The reaction mixture was stirred at room temperature for 18 h. A colourless solid was precipitated out from the reaction mixture and collected by filtration and dried, giving (a*R*/a*S*)-(*R*,*R*)-**1** as a colourless solid (205 mg, 67%), mp 177.5–179.5 °C; $[\alpha]_D^{22} = -18.5$ (*c* 1.0, $CHCl_3$); R_f (Et_3N/toluene 1/9) = 0.21. IR (Nujol): $\upsilon = 2361$, 1521, 1289, 1174, 1062, 959 cm^{-1}. ^1H NMR($CDCl_3$): $\delta = 1.02$–1.43 (10H, m), 1.67–1.76 (2H, m), 1.78–1.92 (4H, m), 2.08 (3H, d, $J = 1.2$ Hz), 2.09 (3H, d, $J = 1.2$ Hz), 2.23 (6H, s), 2.27 (6H, s), 2.30–2.42 (1H, m), 2.43–2.55 (1H, m), 3.66 (2H, br s), 6.37 (1H, q, $J = 1.2$ Hz), 6.38 (1H, q, $J = 1.2$ Hz), 6.70 (1H, br s), 7.00 (2H, br s), 7.18–7.23 (2H, m), 7.42–7.48 (2H, m), 7.54–7.61 (2H, m), 7.75–7.79 (2H, m), 7.79 (1H, br s). ^{13}C NMR ($CDCl_3$): $\delta = 16.2$, 16.3, 21.6, 22.1, 24.4, 24.9, 32.1, 32.6, 39.8, 40.2, 55.5, 56.2, 66.3, 67.0, 107.0, 107.2, 127.9, 128.2, 130.4, 130.8, 133.1, 136.3, 141.1, 141.2, 181.2, 181.3, 189.0, 189.1. HRMS (ESI) $[M+H]^+$, found 407.13915. $C_{19}H_{26}N_4S_3$ requires $[M+H]^+$, 407.13924.

4.9. 1-(2-Dimethylamino-cyclohexyl)-3-phenyl-thiourea 5

A mixture of phenyl isothiocyanate (88 μL, 0.74 mmol) and (*R*,*R*)-*N*,*N*-dimethyl-1,2-diaminocyclohexane **4** (105 mg, 0.74 mmol) in dry benzene was stirred at room temperature, under argon, for 4 h. The solvent was removed under reduced pressure. Purification by column chromatography, eluting with $CHCl_3$/MeOH/Et_3N 100:5:1, gave **5** as a pale yellow gum (190 mg, 92%); $[\alpha]_D^{25} = -115.2$ (*c* 1.0, $CHCl_3$) {lit.[4c] $[\alpha]_D^{21} = -112$ (*c* 0.98, $CHCl_3$)}. ^1H NMR ($CDCl_3$): $\delta = 0.96$–1.10 (1H, m), 1.11–1.28 (2H, m), 1.28–1.40 (1H, m), 1.67 (1H, br d, $J = 14.4$ Hz), 1.75–1.90 (2H, m), 2.21 (6H, s), 2.38 (1H, td, $J = 3.2$, 10.8 Hz), 2.66 (1H, m), 3.95 (1H, br s), 7.08 (1H, br s), 7.14–7.22 (1H, m), 7.28–7.37 (4H, m), 8.80 (1H, br s). ^{13}C NMR ($CDCl_3$): $\delta = 22.1$, 25.1, 25.7, 33.4, 40.4, 56.7, 67.3, 125.1, 126.6, 130.0, 138.1, 180.3.

4.10. General procedure for the organocatalysed cyanosilylation of aldehydes 6

A mixture of freshly distilled aldehyde (0.20 mmol) and the thiourea catalyst (8 mg, 0.02 mmol) in dry CH_2Cl_2 (500 μL), under argon, was cooled to −20 °C. Trimethylsilylcyanide (80 μL, 0.60 mmol) was added and the mixture stirred at −20 °C for 24 h. The reaction was quenched by addition of water (400 μL), then the organic layer separated and purified by column chromatography, eluting with 5% EtOAc/hexane to give the isolated yield of the corresponding cyanohydrin trimethylsilylether **7**.

4.11. Derivatisation of cyanohydrin trimethylsilylethers 7

The cyanohydrin trimethylsilylether **7** in CH_2Cl_2 was treated with 2 M aqueous HCl, at room temperature, for 2 h. The organic layer was separated and dried (Na_2SO_4), then treated with acetic anhydride (160 μL) and pyridine (40 μL) for 5 h at room temperature. The reaction mixture was concentrated under reduced pressure and the residue purified by column chromatography, eluting with 5% EtOAc/hexane, giving the corresponding acetate **8**. The enantiomeric purity of the acetate was determined by GC analysis. Conditions: DMePentilBETACDX (OV1701) column (25 m length × 0.25 mm ID × 0.25 μm film thickness); carrier H_2 (100 kPa); inject temperature = 225 °C; detector temperature = 225 °C.

4.12. (*S*)-(−)-2-Acetyloxy-2-phenylacetonitrile 8a

$[\alpha]_D^{25} = -7.0$ (*c* 0.60, $CHCl_3$) for 66.3% ee {lit.[23] $[\alpha]_D^{24} = -7.24$ (*c* 2.3, $CHCl_3$) for >99.0% ee (*S*)}. ^1H NMR ($CDCl_3$): $\delta = 2.19$ (3H, s), 6.44, (1H, s), 7.48 (3H, m), 7.55 (2H, m). ^{13}C NMR ($CDCl_3$): $\delta = 21.1$, 63.5, 116.7, 128.5, 129.9, 131.0, 132.4, 169.5. Enantiomeric excess determined by chiral GC: 66.3% ee; $t_{R1} = 5.690$ min

(minor), $t_{R2} = 6.739$ min (major). Column isothermal at 140 °C.

4.13. (*S*)-(−)-2-Acetyloxy-2-cyclohexylacetonitrile 8b

$[\alpha]_D^{25} = -14.0$ (*c* 0.40, $CHCl_3$) for 68.1% ee {lit.[23] $[\alpha]_D^{20} = -65.0$ (*c* 1.05, $CHCl_3$) for 99.0% ee (*S*)}. ^{1}H NMR($CDCl_3$): $\delta = 1.23$ (5H, m), 1.73 (1H, m), 1.87 (5H, m), 2.16 (3H, s), 5.19 (1H, d, $J = 6.0$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = 20.4$, 25.2, 25.3, 25.7, 27.8, 28.1, 39.9, 65.4, 116.2, 169.3. Enantiomeric excess determined by chiral GC: 68.1% ee; $t_{R1} = 3.637$ min (minor), $t_{R2} = 4.081$ min (major). Column isothermal at 150 °C.

4.14. (*S*)-(+)-2-Acetyloxy-2-(4′-chlorophenyl)-acetonitrile 8c

$[\alpha]_D^{25} = +6.9$ (*c* 0.80, $CHCl_3$) for 65.5% ee {lit.[24] $[\alpha]_D^{25} = -10.5$ (*c*, 1.00, $CHCl_3$) for >99% ee (*R*)}. ^{1}H NMR ($CDCl_3$): $\delta = 2.19$ (3H, s), 6.40 (1H, s), 7.47 (4H, m). ^{13}C NMR ($CDCl_3$): $\delta = 20.4$, 62.2, 115.8, 129.3, 129.5, 130.3, 136.7, 168.8. Enantiomeric excess determined by chiral GC: 65.5% ee; $t_{R1} = 6.789$ min (minor), $t_{R2} = 7.892$ min (major). Column isothermal at 160 °C.

4.15. (*S*)-(+)-2-Acetyloxy-2-(2′-naphthyl)-acetonitrile 8d

$[\alpha]_D^{25} = +10.2$ (*c* 0.90, $CHCl_3$) for 64.6% ee {lit.[25] $[\alpha]_D^{25} = +20.9$ (*c* 1.13, $CHCl_3$) for 85% ee (*S*)}. ^{1}H NMR($CDCl_3$): $\delta = 2.22$ (3H, s), 6.61 (1H, s), 7.59 (3H, m), 7.79 (3H, m), 8.05 (1H, s). ^{13}C NMR ($CDCl_3$): $\delta = 20.6$, 63.1, 116.2, 124.3, 127.1, 127.6, 127.8, 128.0, 128.4, 128.9, 129.5, 132.9, 133.9. Enantiomeric excess determined by chiral GC: 64.6% ee; $t_{R1} = 14.793$ min (minor), $t_{R2} = 15.576$ min (major). Column isothermal at 180 °C.

4.16. (*S*)-(−)-2-Acetyloxy-2-(2′-furyl)-acetonitrile 8e

$[\alpha]_D^{25} = -2.6$ (*c* 2.1, $CHCl_3$) for 61.7% ee {lit.[23] $[\alpha]_D^{20} = +24.3$ (*c* 1.6, $CHCl_3$) for 98% ee (*R*)}. ^{1}H NMR($CDCl_3$): $\delta = 2.18$ (3H, s), 6.47 (1H, dd, $J = 1.8$, 3.4 Hz), 6.50 (1H, s), 6.70 (1H, d, $J = 3.4$ Hz), 7.53 (1H, d, $J = 1.8$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = 20.3$, 55.7, 111.1, 112.6, 114.1, 144.1, 145.0, 168.8. Enantiomeric excess determined by chiral GC: 61.7% ee; $t_{R1} = 2.638$ min (minor), $t_{R2} = 2.871$ min (major). Column isothermal at 140 °C.

4.17. (*S*)-(+)-2-Acetyloxy-4-phenyl-3-(*E*)-butenenitrile 8f

$[\alpha]_D^{25} = +14.4$ (*c* 1.1, $CHCl_3$) for 45.2% ee {lit.[26] $[\alpha]_D = -99.1$ (*c* 0.8, $CHCl_3$) for 94% ee (*R*)}. ^{1}H NMR ($CDCl_3$): $\delta =$ 2.20 (3H, s), 6.05 (1H, dd, $J = 1.0$, 6.8 Hz), 6.22 (1H, dd, $J = 6.8$, 15.6 Hz), 6.70 (1H, dd, $J = 1.0$, 15.6 Hz), 7.39 (3H, m), 7.46 (2H, m). ^{13}C NMR ($CDCl_3$): $\delta = 21.1$, 62.2, 116.2, 119.1, 127.9, 129.5, 130.1, 135.1, 138.6, 169.6. Enantiomeric excess determined by chiral GC: 45.2% ee; $t_{R1} = 16.760$ min (minor), $t_{R2} = 19.432$ min (major). Column isothermal at 150 °C.

4.18. (*S*)-(−)-2-Acetyloxy-4-phenylbutanenitrile 8g

$[\alpha]_D^{25} = -10.2$ (*c* 1.0, $CHCl_3$) for 51.4% ee {lit.[23] $[\alpha]_D^{20} = -43.4$ (*c* 1.95, $CHCl_3$) for 93% ee (*S*)}. ^{1}H NMR ($CDCl_3$): $\delta = 2.15$ (3H, s), 2.26 (2H, m), 2.86 (2H, m), 5.29 (1H, t, $J = 6.8$ Hz), 7.20–7.35 (5H, m). ^{13}C NMR ($CDCl_3$): $\delta = 20.4$, 30.7, 33.8, 60.5, 116.7, 126.7, 128.3, 128.8, 139.0, 169.1. Enantiomeric excess determined by chiral GC: 51.4% ee; $t_{R1} = 8.865$ min (minor), $t_{R2} = 9.731$ min (major). Column isothermal at 155 °C.

4.19. (*S*)-(−)-2-Acetyloxy-3-methylbutanenitrile 8h

$[\alpha]_D^{25} = -54.5$ (*c*, 0.60, $CHCl_3$) for 69.0% ee {lit.[25] $[\alpha]_D^{25} = -42.9$ (*c* 1.02, C_6H_6) for 51% ee (*S*)}. ^{1}H NMR($CDCl_3$): $\delta = 1.10$ (3H, d, $J = 6.8$ Hz), 1.14 (3H, d, $J = 6.8$ Hz), 2.17 (3H, s), 2.18 (1H, m), 5.20 (1H, d, $J = 5.8$ Hz). ^{13}C NMR ($CDCl_3$): $\delta = 18.0$, 18.4, 21.0, 31.7, 67.0, 116.6, 169.0. Enantiomeric excess determined by chiral GC: 69.0% ee; $t_{R1} = 2.103$ min (minor), $t_{R2} = 2.719$ min (major). Column isothermal at 110 °C.

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16. It is clear that the results obtained using the single diastereomer (a*R*)-(*S*,*S*)-**1** are the same as would be obtained using the single diastereomer (a*S*)-(*R*,*R*)-**1**: as in fact the two catalysts are enantiomers, the opposite absolute configuration of the reaction product is obtained, but with the same yield and ee. For this reason, we can conclude that the mixture (a*R*/a*S*)-(*R*,*R*)-**1** (which gives (*S*)-2-hydroxy-2-phenylacetonitrile in quantitative yield and 66.3% ee) performs better than the two separated diastereomers, (a*R*)-(*R*,*R*)-**1** [which gives (*S*)-2-hydroxy-2-phenylacetonitrile in 30% yield and 46.7% ee] and (a*S*)-(*R*,*R*)-**1** (which gives (*S*)-2-hydroxy-2-phenylacetonitrile in quantitative yield and 55.0% ee, as inferred from the experiment with its enantiomer (a*R*)-(*S*,*S*)-**1**, which gives (*R*)-2-hydroxy-2-phenylacetonitrile in quantitative yield and 55.0% ee).
17. Both the single diastereomers (a*R*)-(*R*,*R*)-**1**, (a*R*)-(*S*,*S*)-**1** and the mixture (a*R*/a*S*)-(*R*,*R*)-**1** are completely soluble in the reaction mixture (0.04 M in dichloromethane at −20 °C). Therefore, the enhanced performance of the mixture of the diastereomers compared to the single diastereomers alone cannot be explained in terms of their different solubility in the reaction medium.
18. The involvement of a dimeric organocatalyst was proposed for explaining the kinetics of cyanohydrin formation catalysed by the cyclic dipeptide *cyclo*[(*R*)-His-(*R*)-Phe], see Ref. 11a and references therein.
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