Enantiopure trans-1-amino-2-(arylsulfanyl)cyclohexanes: Novel chiral motifs for ligands and organocatalysts

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Enantiopure *trans*-1-amino-2-(arylsulfanyl)cyclohexanes: novel chiral motifs for ligands and organocatalysts

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ABSTRACT

In order to obtain the title compounds (1*R*,2*R*)-cyclohexane-1,2-diol was stereoselectively converted into *cis*-(1*R*,2*S*)-2-(arylsulfanyl)cyclohexanols and these products were submitted to the nucleophilic substitution via the Mitsunobu reaction (HN_3, DEAD). Reduction of the isolated azides gave the desired *trans*-(1*S*,2*S*)-1-amino-2-(arylsulfanyl)cyclohexanes. The (1*S*,2*S*)-1-amino-2-(2-aminophenylsulfanyl)cyclohexanes thus prepared were reacted with 3,5-bis(trifluoromethyl)phenyl isothiocyanate to furnish the respective bis-thiourea compounds. An application of a derivative of this type as an organocatalyst (20 mol %) in the Baylis–Hillman reaction gave the respective product in up to 93% ee.

1. Introduction

Over the last few decades, many studies have been devoted to the search of chiral ligands for metal-catalyzed enantioselective reactions. These studies have led to the identification of the most successful molecular motifs of various catalysts (*privileged catalysts*).[1] However, the often encountered ligand–substrate specificity poses serious limitations in their application to asymmetric transformations. Thus, there is still much interest in the development of new ligands. Recently, stereoselective organocatalytic procedures using chiral bifunctional thiourea catalysts have gained much attention.[2] In spite of being successfully applied in various enantioselective transformations, these catalysts also suffer from limitations, similarly to other ligands.

Most of the chiral ligands and organocatalysts used in asymmetric reactions are phosphorus-, nitrogen-, oxygen-, and sulfur-containing compounds.[1] In particular, C_2-symmetric derivatives with a relatively rigid cyclic structure, such as a *trans*-1,2-disubstituted cyclohexane framework, are regarded as catalysts belonging to the aforementioned *privileged* class.[1b] On the other hand, in a number of reactions chiral ligands and organocatalysts without C_2-symmetry perform better.[3] However, there is a limited number of readily available chiral C_1 derivatives of the *trans*-1,2-disubstituted cyclohexane type. Since the respective chiral *vic*-diols and *vic*-diamines[4] are easily accessible, we were interested in their transformation into the desired C_1 compounds. A direct approach via double nucleophilic substitution of a *vic*-diol is often hampered by neighboring group participation effects.[4e]

Recently, we have developed a stepwise enantiospecific substitution of chiral *vic*-diols into their respective *vic*-bis(sulfides).[5] Herein, we report the successful enantiospecific introduction of the corresponding sulfur- and nitrogen-containing *vic*-functionality to the cyclohexane backbone. We also report the preparation of novel chiral amino-compounds and their transformations into the respective thioureas. The results of our preliminary trials demonstrate their usefulness in catalytic asymmetric reactions.

2. Results and discussion

We reacted commercially available enantiopure (1*R*,2*R*)-cyclohexane-1,2-diol **1** with 3 equiv of $(PhS)_2/Bu_3P$ (the Hata reaction conditions),[5,6] and the nucleophilic substitution of one of the hydroxy groups stereoselectively gave *cis*-(1*R*,2*S*)-2-(phenylsulfanyl)cyclohexanol **3a** in 34% yield and with over 95% ee.[5] Extending this observation we undertook the synthesis of enantiomerically pure *cis*-(1*R*,2*S*)-2-(2-aminophenylsulfanyl)cyclohexanol **3b**, which has not been previously prepared. This compound was synthesized directly from (1*R*,2*R*)-**1** and the disulfide **2b** via the Hata reaction (Scheme 1). Similarly, we carried out the reaction of chiral diol **1** with disulfides **2c** and **2d**. Only 2-(2-quinolylsulfanyl)cyclohexanol **3c** was obtained in 35% yield and 84% de, while the reaction of **2d** led to the isolation of the C_2-symmetric bis-substituted product **4** only.

The monofunctionalized alcohols **3a**[5] and **3b** were used as starting materials for further transformations involving the alcohol fragment. Since an attempted hydroxyl substitution with DPPA and DBU did not lead to the desired product, we carried out this transformation using the Mitsunobu reaction with azidoic acid.[7] This reaction worked well and we obtained the expected azides **5** as single diastereomers (Scheme 2). The reduction to amines **6**

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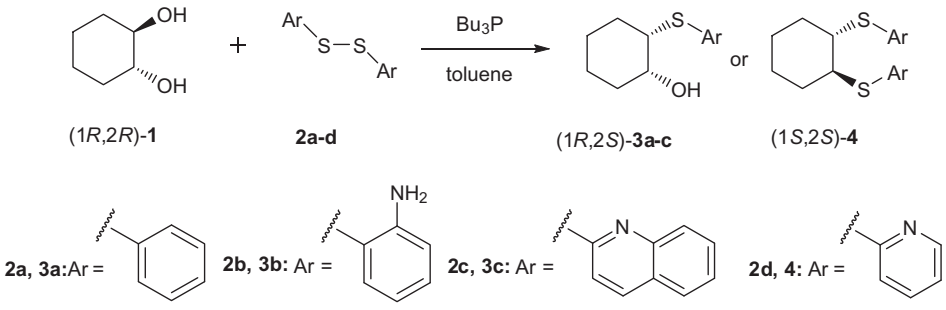
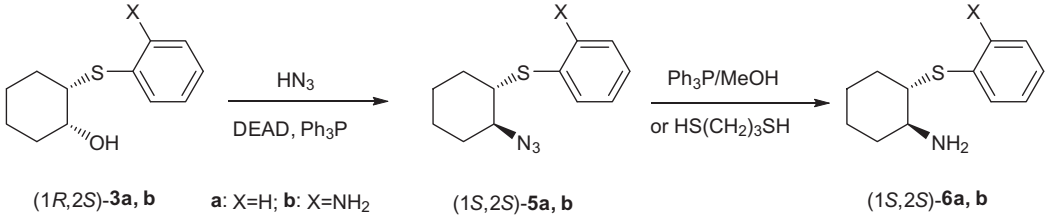


Scheme 1.

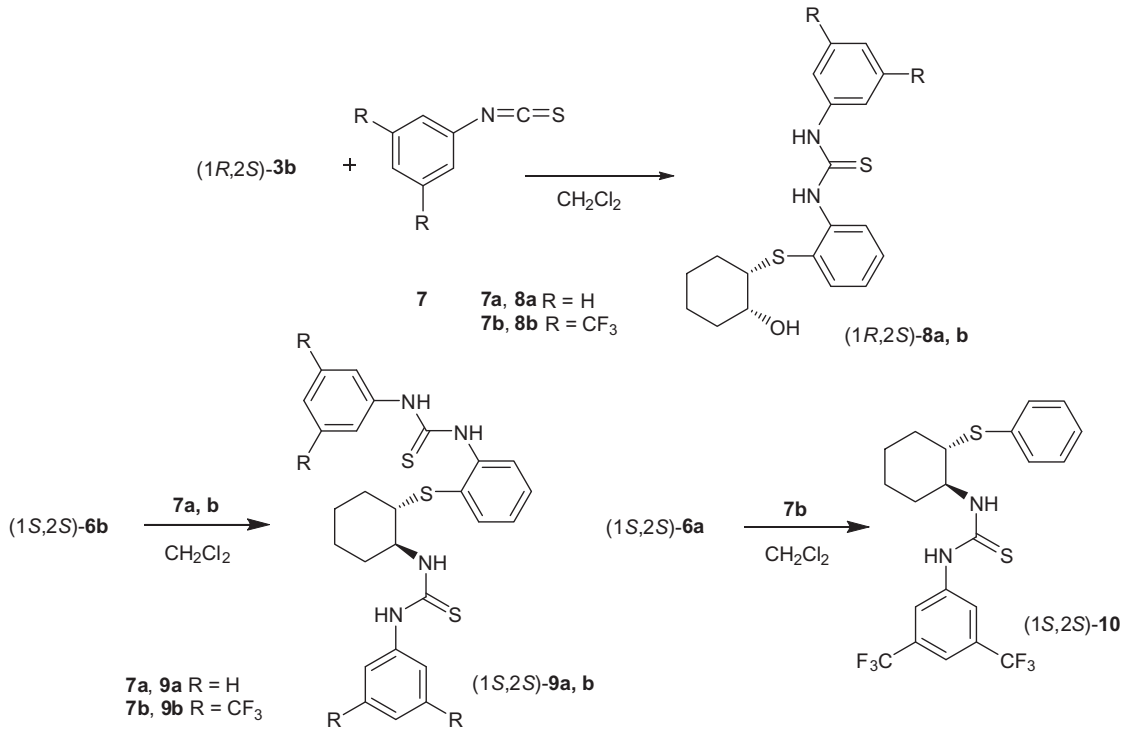


Scheme 2.

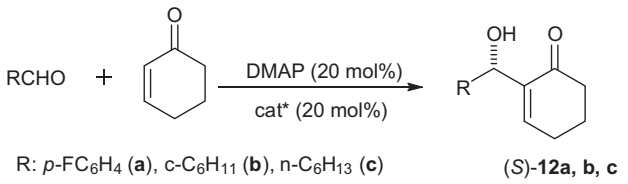
was carried out using 1,3-propanedithiol as a reductant[8] for **5a** and the Staudinger reaction conditions[9] for **5b**.

Since many successful organocatalysts are thiourea derivatives forming specific hydrogen bonds,[2] we decided to prepare compounds **8** and **9** (Scheme 3). Both **8b** and **9b**, which contain the strongly electron withdrawing 3,5-bis(trifluoromethyl)phenyl group[10] were regarded as particularly promising structures. This type of organocatalyst has already been applied in the Baylis–Hillman reaction.[11,12] However, there are relatively few examples of the successful asymmetric version of this reaction. For a comparison with **8**, we obtained compound **11** (*p*-toluenesulfonamide of **3b**), which was also tested in the organocatalytic Baylis–Hillman reaction.

Thus for the preliminary screening, we tested the catalytic properties of **8a**,**b**, **9a**,**b**, and **10** in the model Baylis–Hillman reaction[11h] (Scheme 4). The reaction of *p*-fluorbenzaldehyde with 2-cyclohexenone in the presence of 20 mol % of DMAP and the chiral catalyst was examined first (Table 1, entries 1–5). In most cases, the obtained product **12a** was nearly racemic, but for **9b** the chemical yield was considerable. For **8a** the yield was poor, but moderate



Scheme 3.



Scheme 4.

Table 1
Results of the catalyzed Baylis–Hillman reaction[a]

Entry	Catalyst	Yield (%)	ee (%)
1	**8a**	25 (19)[b]	44 (41)[b]
2	**8b**	40	5
3	**9a**	31	8
4	**9b**	77	5
5	**11**	32	4
6	**9b**	88[c]	75[c]
7	**9b**	30[d]	93[d]
8	**8a**	10[c]	24[c]
9	**8a**	25[d]	>5[d]

[a] The catalytic reaction was run using 2-cyclohexenone (2 equiv), 4-fluorobenzaldehyde (1 equiv), DMAP (0.2 equiv) and the catalyst (0.2 equiv), in the absence of solvent, for 7 days at room temperature; for further details, see Section 4.
[b] DABCO was used instead DMAP.
[c] Cyclohexanecarboxaldehyde was used instead of 4-fluorobenzaldehyde.
[d] Heptanal was used instead of 4-fluorobenzaldehyde.

enantioselectivity was observed, namely 44% and 41% ee of (*S*)-**11a** with DMAP and DABCO, respectively. These two catalysts **8a** and **9b** were tested in a reaction with cyclohexanecarboxaldehyde (entries 6 and 8) and *n*-heptanal (entries 7 and 9). Catalyst **9b** performed well in these two reactions giving 75% and 93% ee of (*S*)-**12b** and (*S*)-**12c**, respectively. As it was already noted,[11,12] the enantioselectivity in the Baylis–Hillman reaction is strongly substrate-dependent. In spite of the limited results, bis-thiourea **9b** seems to outperform the corresponding C_2 symmetric bis-thiourea derived from 1,2-cyclohexanediamine.[11h]

Compound **3b** and bis-pyridyl derivative **4** were also examined as ligands in the palladium-catalyzed Tsuji–Trost allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate,[13] but the results obtained were disappointing (for **3b**: 92% yield, 8% ee, for **4**: 29% yield, 4% ee).

3. Conclusions

In conclusion, the sequential displacement of the hydroxy groups in *trans*-1,2-cyclohexanediol can be carried out enantioselectively. Reactions leading to the corresponding *cis*-2-(phenylsulfanyl)cyclohexanol followed by the Mitsunobu reaction with azidoic acid and the reduction of the resulting azides allowed for the easy preparation of the respective thioureas, which are promising organocatalysts for the Baylis–Hillman reaction.

4. Experimental

4.1. General

Melting points were measured using the open capillary tube method. IR spectra were recorded on a Perkin Elmer System 2000 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DRX 300 Avance spectrometer (^{1}H, 300 MHz; ^{13}C, 75.5 MHz) using a residual $CHCl_3$ signal as a lock and the internal standard. Optical rotations were measured using an Optical Activity Ltd, Model AA-5 automatic polarimeter. High resolution mass spectra were recorded using a LCT Premier (Waters) instrument utilizing electrospray ionization mode. Chromatographic separations were performed on Silica Gel 60 (70–230 mesh) purchased from Merck. Thin layer chromatography analyses were performed using Silica Gel 60 precoated plates (Fluka). Enantiomeric excess was determined by ^{1}H NMR using a chiral shift reagent Eu(hfc)$_3$ and chiral HPLC using Chiracel OB-H, Chralpak AS-H, and Chiracel OD-H columns.

4.2. Preparation of sulfides

Tributylphosphine (0.99 mL, 4 mmol, 4 equiv) was added via syringe to a solution of diol **1** (116 mg, 1 mmol) and diaryldisulfide **2a**–**2d** (3 equiv) in 8 mL of dry toluene in an ampoule, which was filled with argon and sealed. This reaction mixture was kept at 80 °C for 3–4 days. The solvent was evaporated and products **3a**, **3b**, **3c** and **4** were purified by column chromatography (hexane → hexane/ethyl acetate 5:1).

4.2.1. (−)-(1*R*,2*S*)-2-(2-Aminophenylsulfanyl)cyclohexanol 3b

Yield 82%; $[\alpha]_D^{20} = -52.1$ (*c* 0.86, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34–1.41 (m, 3H, cyclohexane ring), 1.53–1.84 (m, 5H, cyclohexane ring), 2.9 (br s, 1H, OH), 3.01–3.07 (m, 1H, CH), 3.58–3.61 (m, 1H, CH), 4.34 (br s, 2H, NH_2), 6.61–6.70 (m, 2H, ArH), 7.05–7.11 (m, 1H, ArH), 7.20–7.35 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$), δ = 19.2, 24.2, 26.7, 30.8, 52.7 (CH), 66.3 (CH), 114.4, 116.0, 118.0, 129.3, 136.2, 147.5; IR (film): 3447, 3345, 1607, 1254, 751 cm^{-1}; HRMS (ESI, $[M+H]^+$): calcd for $[C_{12}H_{17}NOS+H]^+$ 224.1104, found 224.1111. R_f = 0.78 (hexane/ethyl acetate 1:1).

4.2.2. (−)-(1*R*,2*S*)-2-(2-Quinolylsulfanyl)cyclohexanol 3c

Yield 35%; $[\alpha]_D^{20} = -52.1$ (*c* 0.92, CH_2Cl_2, 84% de); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05–1.98 (m, 8H, cyclohexane ring), 3.43–3.48 (m, 1H, CH), 3.62–3.66 (m, 1H, CH), 4.80 (br s, 1H, OH), 7.37–7.45 (m, 2H, ArH), 7.67–7.71 (m, 1H, ArH), 7.86–7.89 (m, 1H, ArH), 8.11–8.16 (m, 1H, ArH), 8.91–8.95 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ = 21.7, 23.8, 28.6, 30.8, 47.7 (CH), 47.8 (CH); 120.3, 125.2, 125.5, 128.3, 128.7, 129.5, 129.7, 136.6, 149.5; IR (film): 3375, 3060, 2932, 2856, 1593, 1493, 1456, 1069, 789, 757 cm^{-1}; HRMS (ESI, $[M+H]^+$): calcd for $[C_{15}H_{17}NOS+H]^+$ 260.1104, found 260.1109. R_f = 0.72 (hexane/ethyl acetate 1:1).

4.2.3. (−)-(1*S*,2*S*)-1,2-Bis(2-pirydylsulfanyl)cyclohexane 4

Yield 62%; $[\alpha]_D^{20} = -40.0$ (*c* 1.046, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47–1.58 (m, 2H, cyclohexane ring), 1.71–1.80 (m, 4H, cyclohexane ring), 2.28–2.37 (m, 2H, cyclohexane ring), 4.22–4.23 (m, 2H, CH), 6.83–6.95 (m, 2H, ArH), 7.09–7.21 (m, 2H, ArH), 7.42–7.45 (m, 2H, ArH), 8.37–8.38 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$): δ = 24.6, 31.9, 47.1 (CH), 119.8, 123.4, 136.3, 149.8, 159.4; IR (film): 3043, 2931, 2854, 1578, 1452, 1413, 757, 724 cm^{-1}; HRMS (ESI, $[M+H]^+$): calcd for $[C_{16}H_{18}N_2S_2+H]^+$ 303.0984, found 303.0958. R_f = 0.56 (hexane/ethyl acetate 3:1).

4.3. Synthesis of azide 5 and its reduction to amine 6

Compound **3b** (0.16 g, 0.72 mmol) and Ph_3P (0.246 g, 0.94 mmol, 1.3 equiv) were dissolved in dry toluene (8 mL). Next, HN_3 (0.94 mL, 0.937 mmol, 1.3 equiv in benzene) was added dropwise under an argon atmosphere followed by a solution of DEAD (0.17 mL, 1.082 mmol, 1.5 equiv, 40% solution in toluene). After stirring for 24 h, the solvent was evaporated and the crude product **5a** was purified by column chromatography using hexane/ethyl acetate (6:1 v/v) as an eluent. The analogous procedure was applied for the synthesis of compounds **5b**, using alcohol **3a**.

Triphenylphosphine (0.161 g, 0.615 mmol, 1.5 equiv) was added to a solution of azide **5** (0.102 g, 0.41 mmol) in methanol (5 mL). After refluxing for 2 h, the solvent was evaporated and

the product **6** was purified on a silica column. Elution with $CHCl_3$ containing CH_3OH (5–10%) yielded a fraction containing amine **6**.

4.3.1. (+)-(1*S*,2*S*)-*trans*-2-(Phenylsulfanyl)cyclohexylazide 5a

Yield = 76%; $[\alpha]_D^{20} = +46.4$ (*c* 0.47, CH_2Cl_2), (ee >95%), ^{1}HNMR (300 MHz, $CDCl_3$): δ = 1.21–1.30 (m, 2H, cyklohexyl), 1.39–1.45 (m, 2H, cyklohexyl), 1.66–2.72 (m, 2H, cyklohexyl), 2.05–2.33 (m, 2H, cyklohexyl), 2.93 (td, 1H, J_1 = 9.8, Hz J_2 = 4 Hz, CH), 3.20–3.25 (td, 1H, J_1 = 9.7, Hz J_2 = 4 Hz), 7.24–7.31 (m, 3H, ArH), 7.46–7.47 (m, 2H, ArH); ^{13}CNMR ($CDCl_3$): δ = 24.2, 25.3, 31.8, 32.7, 52.1, 64.4, 127.9, 129.3, 130.5, 133.7; IR (film): 2936, 2858, 2096, 1474, 1448, 1439, 1259, 753, 739, 692 cm^{-1}.

4.3.2. (+)-(1*S*,2*S*)-*trans*-2-(2-Aminophenylsulfanyl) cyclohexylazide 5b

Yield 64%, de >95%; $[\alpha]_D^{20} = +118$ (*c* 0.39, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10–1.51 (m, 4H, cyclohexane ring), 1.65–1.78 (m, 2H, cyclohexane ring), 1.99–2.06 (m, 1H, cyclohexane ring), 2.14–2.21 (m, 1H, CH), 2.74 (td, J_1 = 11.1 Hz, J_2 = 4.2 Hz, 1H, CH), 3.22 (td, J_1 = 10.2 Hz, J_2 = 3.9 Hz, 1H, CH), 4.51 (s, 2H, NH_2), 6.65–6.75 (m, 2H, ArH), 7.13–7.19 (m, 1H, ArH), 7.40 (dd, J_1 = 7.2 Hz, J_2 = 1.5 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ = 24.1, 25.2, 31.6, 32.7, 51.2, 64.0, 115.0, 118.2, 130.6 (two signals overlapped), 138.1, 149.6; IR (film): 3463, 3357, 2935, 2858, 2095, 1607, 1478, 1308, 1256, 752 cm^{-1}; HRMS (ESI, $[M+H]^+$): calcd for $[C_{12}H_{16}N_4S+H]^+$ 249.1168, found 249.1146. R_f = 0.6 (hexane/ethyl acetate 6:1).

4.3.3. (+)-(1*S*,2*S*)-*trans*-2-(Phenylsulfanyl)cyclohexylamine 6a

Yield = 91%; $[\alpha]_D^{20} = +84.2$ (*c* 0.38, CH_2Cl_2), (ee >95%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.30 (m, 4H, cyclohexsyl), 1.68–1.80 (m, 4H, cyclohexyl), 2.00–2.13 (m, 2H, CH), 2.57–2.74 (m, 2H, NH_2), 7.22–7.35 (m, 3H, ArH), 7.46–7.49 (m, 2H, ArH); IR (film): 3401, 3063, 2927, 2855, 2098, 1621, 1578, 1474, 1445, 1376, 1336, 1089, 839, 746, 695 cm^{-1} This compound has already been obtained and described as a racemate[4c] and its ^{1}H NMR spectrum is in agreement with the given above.

4.3.4. (+)-(1*S*,2*S*)-2-(2-Aminophenylsulfanyl)cyclohexylamine 6b

Yield 90%; $[\alpha]_D^{20} = +54.2$ (*c* 0.24, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14–1.42 (m, 4H, cyclohexane ring), 1.64–1.68 (m, 2H, cyclohexane ring), 1.94–2.03 (m, 2H, cyclohexane ring), 2.50–2.61 (m, 2H, CH), 3.20 (s, 4H, NH_2), 6.63–6.73 (m, 2H, ArH), 7.09–7.15 (m, 1H, ArH), 7.60–7.80 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$): δ = 24.6, 26.4, 33.3, 35.8, 54.2, 57.0, 115.0, 118.2, 128.6, 132.1, 137.8, 149.4; IR (film): 3441, 3348, 3177, 2930, 1607, 1479, 1446, 1309, 1158, 750 cm^{-1}; HRMS (ESI, $[M+H]^+$): calcd for $[C_{12}H_{18}N_2S+H]^+$ 223.1263, found 223.1260. R_f = 0.3 ($CHCl_3$/MeOH, 10:1).

4.4. Preparation of thiourea derivatives

A solution of compound **3b** (0.144 g, 0.64 mmol) and phenyl isothiocyanate **7a** (0.08 mL, 0.64 mmol, 1 equiv) in CH_2Cl_2 (4–5 mL) was stirred for 5 days at room temperature. The solvent was then evaporated, and the product **8a** was purified by column chromatography. For the synthesis of compound **8b**, 3,5-bis(trifluoromethyl)phenyl isothiocyanate **7b** (1.2 equiv) was used in place of **7a**, and the reaction was carried out under an argon atmosphere. An analogous procedure was applied for the synthesis of compounds **9** and **10**, using amines **6** and 2 equiv of isothiocyanate **7a** or **7b**.

4.4.1. (+)-3-(2-{[(1*S*,2*R*)-2-Hydroxycyclohexyl]sulfanyl}phenyl)-1-phenylthiourea 8a

Yield 82%; $[\alpha]_D^{20} = +18.4$ (*c* 3.16, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16–1.67 (m, 8H, cyclohexane ring), 2.07 (s, 1H, OH), 2.95–2.98 (m, 1H, CH), 3.57 (s, 1H, CH), 7.10–7.13 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.24–7.49 (m, 7H, ArH), 8.20 (d, J = 8.0 Hz, 1H, ArH), 8.45 (s, 1H, NH), 8.74 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 20.4, 24.6, 27.9, 31.9, 54.5 (CH), 67.8 (CH), 125.3, 126.0, 126.2, 127.6, 127.7, 128.9, 130.0, 135.4, 136.6, 140.1, 179.5 (C=S); IR (film): 3243, 1581, 1539, 1520, 1442, 1293, 1254, 758, 695 cm^{-1}. HRMS (ESI): calcd for $[C_{19}H_{22}N_2OS_2+Na]^+$ 381.1066, found 381.1068. R_f = 0.4 (hexane/ethyl acetate 5:1).

4.4.2. (+)-1-[3,5-Bis(trifluoromethyl)phenyl]-3-(2-{[(1*S*,2*R*)-2-hydroxycyclohexyl]sulfanyl}phenyl)thiourea 8b

Yield 73%; $[\alpha]_D^{20} = +90.9$ (*c* 0.66, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36–1.79 (m, 8H, cyclohexane ring), 2.75 (s, 1H, OH), 3.21–3.23 (m, 1H, CH), 3.78–3.80 (m, 1H, CH), 7.21 (td, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H, ArH), 7.37 (td, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1H, ArH), 7.60 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H, ArH), 7.67 (s, 1H, ArH), 7.94 (dd, J_1 = 7.8 Hz, J_2 = 1.0 Hz, 1H, ArH), 8.00 (s, 2H, ArH), 8.41 (s, 1H, NH), 9.23 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 21.2, 23.6, 28.7, 31.9, 54.8 (CH), 69.3 (CH), 119. 2 (br r), 123.0 (J_{CF} = 277.5 Hz), 124.4 (br r), 125.1, 127.0, 129.3, 132.2 (J_{CF} = 30 Hz), 135.8, 137.2, 139, 139.8, 179.6 (C=S); IR (film): 3252, 1574, 1538, 1471, 1276, 744, 701, 682 cm^{-1}. HRMS (ESI, $[M+H]^+$) calcd for $[C_{21}H_{20}F_6N_2OS_2+H]^+$ 495.0994, found 495.1000. R_f = 0.38 (hexane/ethyl acetate 3:1). Column chromatography, eluent: hexane/ethyl acetate 5:1.

4.4.3. (+)-1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(1*S*,2*S*)-2-(phenylsulfanyl)cyclohexyl]thiourea 10

Yield 98%; $[\alpha]_D^{20} = +110.5$ (*c* 0.19, CH_2Cl_2). Mp = 156–157 °C. ^{1}H NMR (300 MHz, $CDCl)_3$: δ = 1.21–1.45 (m, 4H, cyclohexyl), 1.66–1.75 (m, 2H, cyclohexyl), 1.66–1.76 (m, 1H, cyclohexyl), 2.42–2.53 (m, 1H, cyclohexyl), 3.00 (td, 1H, J_1 = 12 Hz, J_2 = 6 Hz, CH), 4.18–4.31 (m, 1H, CH), 6.46 (d, J = 6 Hz, NH), 7.24–7.29 (m, 3H, ArH), 7.41–7.44 (m, 2H, ArH), 7.67 (s, 1H, ArH), 7.83 (s, 1H, ArH), 8.50 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 24.3, 25.7, 33.1 (two signals overlapped), 52.1 (CH), 58.3 (CH), 119.3 (br r), 122.8 (J_{CF} = 271.3 Hz), 123.7 (br r), 128.0, 129.2, 132.2, 133.0 (J_{CF} = 33.8 Hz), 133.6, 138.9, 179.5 (C=S); IR (KBr): 3236, 3139, 3063, 2946, 2863, 1587, 1557, 1473, 1459, 1387, 1343, 1315, 1279, 1176, 1130, 1107, 982, 884, 705, 681 cm^{-1}; HRMS (ESI, $[M+H]^+$): calcd for $[C_{21}H_{20}F_6N_2S_2+H]^+$ 479.1045, found 479.1050. R_f = 0.5 (hexane/ethyl acetate 5:1). Column chromatography, eluent: hexane/ethyl acetate 6:1.

4.4.4. (+)-1-Phenyl-3-[(1*S*,2*S*)-2-({2-[(phenylcarbamothioyl) amino]phenyl}sulfanyl)cyclohexyl]thiourea 9a

Yield 50%, Mp = 113–114 °C. $[\alpha]_D^{20} = +46.3$ (*c* 0.8, CH_2Cl_2) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.03–1.22 (m, 2H, cyclohexane ring), 1.23–1.43 (m, 2H, cyclohexane ring), 1.56–1.71 (m, 2H, cyclohexane ring), 1.72–1.89 (m, 1H, cyclohexane ring), 2.19–2.30 (m, 1H, cyclohexane ring), 2.82–2.94 (m, 1H, CH), 4.34–4.49 (m, 1H, CH), 6.25 (d, J = 9 Hz, 1H, NH), 7.10–7.14 (m, 3H, ArH), 7.15–7.23 (m, 1H, ArH), 7.29–7.34 (m, 4H, ArH), 7.38–7.43 (m, 4H, ArH), 7.53 (d, J = 9 Hz, 1H, ArH) 8.07–8.11 (m, 2H, NH+ArH), 8.52 (s, 1H, NH), 8.63 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 24.3, 25.6, 32.7, 33.2, 53.1, 58.7, 124.6, 125.3, 125.7, 126.5, 126.6, 127.5, 127.7, 129.1, 129.8, 135.8, 136.5, 136.8, 140.0, (one aromatic signal overlapped), 179.4, 179.5; HRMS (ESI, $[M+H]^+$): calcd for $[C_{26}H_{28}N_4S_3+H]^+$ 493.1543, found 493.1562. R_f = 0.79 (chloroform/acetone 98:2).

4.4.5. 1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(1*S*,2*S*)-2-{[2-({[3,5-bis(trifluoromethyl)phenyl]carbamothioyl}amino)phenyl]sulfanyl}cyclohexyl]thiourea 9b

Yield 95%; $[\alpha]_D^2 = +3.6$ (*c* 0.41, CH_2Cl_2). Mp = 107–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (m, 1H, cyclohexane ring), 1.23–1.25 (m, 2H, cyclohexane ring), 1.61–1.90 (m, 4H, cyclohexane ring), 2.05 (m, 1H, cyclohexane ring), 2.37 (m, 1H, CH), 2.75 (m, 1H, CH), 4.50 (br s, 1H, NH), 6.77–6.80 (d, 1H, ArH), 7.30 (td, 1H, ArH), 7.45 (m, 1H, ArH), 7.58 (s, 1H, ArH), 7.69–7.70 (m, 2H, ArH), 7.88 (s, 2H, ArH), 7.95 (s, 2H, ArH), 8.40 (br s, 2H, NH), 8.51 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 14.0, 24.4, 25.8, 33.5, 54.6, 57.7, 118.4 (br r), 120.5 (br r), 122.8 (J_{CF} = 272.7 Hz), 123.0 (J_{CF} = 272.3 Hz), 123.1 (br r), 125.2 (br r), 126.4, 128.4, 130.0, 130.2, 131.5 (J_{CF} = 28.1 Hz), 132.5 (J_{CF} = 29.2 Hz), 137.6, 138.1, 139.0, 139.7, 179.5 (C=S), 179.9 (C=S); IR (KBr): 3421, 2940, 1536, 1471, 1383, 1279, 1179, 1134, 982, 888, 681 cm^{-1}; HRMS (ESI, $[M+H]^+$) calcd for $[C_{30}H_{24}S_3N_4F_{12}+H]^+$ 765.1038 found 765.1005. R_f = 0.24 (hexane/ethyl acetate 4:1).

4.5. Preparation of (+)-*N*-(2-{[(1*S*,2*R*)-2-hydroxycyclohexyl]sulfanyl}phenyl)-4-methylbenzene-1-sulfonamide 11

Method A: Compound **3b** (0.1 g, 0.45 mmol) and *p*-toluenesulfonyl chloride (0.147 g, 0.77 mmol, 1.7 equiv) were dissolved in 3 mL of CH_2Cl_2. To the stirred mixture, aqueous KOH (3%, 0.046 g, 0.82 mmol, 1.8 equiv) and DMAP (15 mg, 0.12 mmol) were added. After stirring for 96 h at room temperature, the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated. The crude product **11** was purified by column chromatography with hexane/ethyl acetate 5:1.

Method B: Alternatively, **11** could be prepared by the reaction of compound **3b** with *p*-toluenesulfonyl chloride in pyridine with DMAP as a catalyst. A mixture of compound **3b** (0.1 g, 0.45 mmol), *p*-toluenesulfonyl chloride (0.09 g, 0.47 mmol, 1.05 equiv), pyridine (6 mL) and DMAP (10 mg, 0.08 mmol) was stirred for 4 h at 90 °C. Then, the hot mixture was poured into 20 mL of ice-cold water and 15 mL of CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with 2 M aqueous HCl (5 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the crude product **11** was purified by column chromatography using hexane/ethyl acetate 5:1. Yield 68% (method A)/60% (method B). $[\alpha]_D^{20} = +10.6$ (*c* 1.64, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18–1.63 (m, 8H, cyclohexane ring), 2.28 (s, 3H, CH_3), 2.42 (s, 1H, OH), 2.65–2.71 (m, 1H, CH), 3.63 (d, *J* = 3.05 Hz, 1H, CH), 6.90–6.91 (m, 1H, ArH), 7.13–7.20 (m, 1H, ArH), 7.35–7.39 (m, 1H, ArH), 7.55–7.58 (m, 1H, ArH), 7.64–7.67 (m, 2H, ArH), 8.55 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 20.7, 21.6, 24.1, 28.4, 32.0 (CH_3), 55.4 (CH), 68.0 (CH), 119.7, 124.4, 127.3, 129.7, 130.3, 137.2, 139.8, 143.9, (two aromatic signals hidden); IR (film): 3508, 3243, 1334, 1598, 1587, 1393, 1334, 1185, 1156, 914, 814, 666 cm^{-1}; HRMS (ESI, $[M+H]^+$): calcd for $[C_{19}H_{23}NO_3S_2+H]^+$ 378.1192, found 378.1201. R_f = 0.81 (hexane/ethyl acetate 1:1).

4.6. Procedure for the catalytic Baylis–Hillman reaction

To a preweighed sample of 0.1 mmol of catalysts **8a**, **8b**, **9a**, **9b** or **11** and DMAP (12.2 mg, 0.1 mmol) was added 0.5 mmol of suitable aldehyde: *p*-fluorobenzaldehyde (53.7 μL), cyclohexanecarboxaldehyde (60.6 μL) or heptanal (72.5 μl) and 2-cyclohexenone (96.5 μL, 1.0 mmol). The resulting mixture was magnetically stirred at room temperature for 7 days. The crude products **12a–c** were purified by column chromatography (hexane/ethyl acetate 8:1 → 2:1) and analyzed by chiral HPLC.

(*S*)-**12a**: Chiralcel OB-H, hexane/2-propanol 95:5, 1.0 mL/min, λ = 254 nm, (*S*)-major: 30.9 min, (*R*)-minor: 44.4 min. Spectroscopic data are in agreement with the literature.[14]

(*S*)-**12b**: Chiralpak AS-H, hexane/2-propanol 90:10, 1.0 mL/min, λ = 254 nm, (*S*)-major: 10.24 min, (*R*)-minor: 13.92. Spectroscopic data are in agreement with the literature.[15]

(*S*)-**12c**: Chiralpak AS-H, hexane/2-propanol 90:10, 1.0 mL/min, λ = 254 nm, (*S*)-major: 7.78 min, (*R*)-minor: 10.35 min. Spectroscopic data are in agreement with the literature.[15]

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