Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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View Article Online
DOI: 10.1039/C8OB01988F

Journal Name

ARTICLE

Catalytic enantioselective one-pot approach to *cis*- and *trans*-2,3-diaryl substituted 1,5-benzothiazepines

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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The first enantioselective catalytic approach to *cis*- and *trans*-2,3-diaryl substituted 1,5-benzothiazepines has been conveniently developed in a one-pot fashion, starting from α,β-unsaturated acyl pyrazoles and *ortho*-amino-thiophenols. The organocatalytic two-step sulfa-Michael/lactamization sequence is promoted by a readily available bifunctional thiourea and *p*-toluensulfonic acid, respectively. The protocol enables the access to both *N*-unprotected *cis*- and *trans*-diastereoisomers in moderate to satisfactory overall yields (up to 84%) and good to excellent ee values (up to 99%). Mechanistic investigations helped to shed light on the regio- and stereoselective outcome of the process.

Introduction

1,5-Benzothiazepines are a class of privileged heterocyclic scaffolds in medicinal chemistry, showing important biological activities in the central nervous system, or used for the treatment of cardiovascular and gastrointestinal disorders.[1] The most renowned examples include the antidepressant agent Thiazesim, the blood-pressure regulator Diltiazem, also employed to treat angina and the potent antiulcer agent BTM-1086 (Fig. 1).

Over the last decades, 1,5-benzothiazepines have been the subject of intensive investigations focused on the development of efficient and environment friendly methodologies for their synthesis, in view of their potential applications in the pharmaceutical industry.[2] A good number of 1,5-benzothiazepines are chiral compounds. Consequently, the first methodologies reported to prepare both enantioenriched forms, useful for separate testing of their bioactivities, relied on optical resolution of the racemates.[3] Recent efforts in this field have resulted in the development of a few metal-catalysed[4] and organocatalytic protocols[5] to access either *N*-protected or N-H free 2-substituted 1,5-benzothiazepines with high level of enantioselectivity (Scheme 1a).

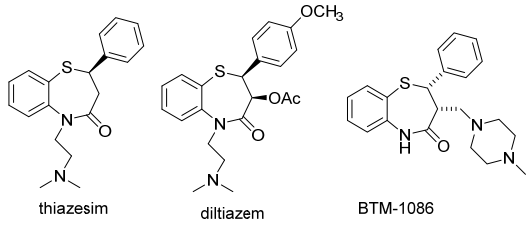
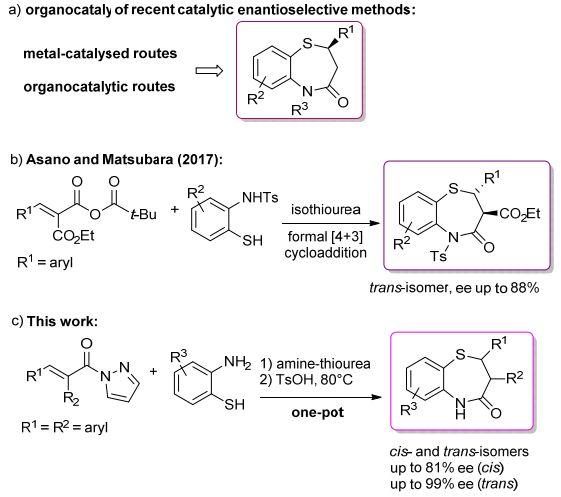


Fig. 1 Most renowned drugs and bioactive compounds showing the 1,5-benzothiazepine scaffold bearing one or two stereogenic centers.



Scheme 1 Catalytic stereoselective routes to 2,3-substituted 1,5-benzothiazepines.

The preparation of 2,3-disubstituted 1,5-benzothiazepines as both enantioenriched *cis*- and *trans*-diastereoisomers is a more ambitious goal. A classical solution to this challenge, has been the elaboration of starting enantiopure building blocks, as demonstrated for the synthesis of diltiazem from the enantiomerically enriched epoxide (Fig. 1).[6] No general methods exist to prepare this class of benzothiazepines in a truly catalytic manner. Within this context, only recently, the group of Asano and Matsubara succeeded in developing an effective organocatalytic method to *trans*-2,3-disubstituted 1,5-benzothiazepines (Scheme 1b).[7] A formal [4+3] cycloaddition reaction was devised from activated α,β-unsaturated anhydrides and *N*-protected 2-aminothiophenols

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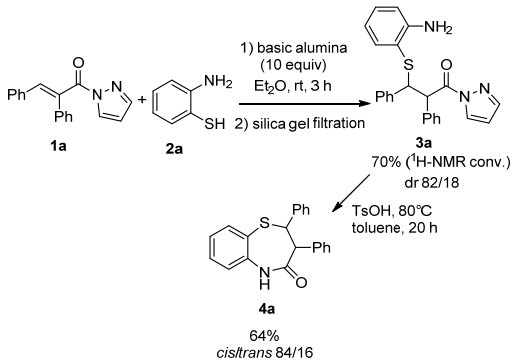
Electronic Supplementary Information (ESI) available: Preparations of substrates and new catalyst **XI**, optimization studies, characterization of adducts **3a** and **7**, mechanistic data. NMR spectra of new compounds, HPLC profiles, ECD spectra and computational data for compound **4e**. See DOI: 10.1039/x0xx00000x

under chiral isothiourea catalysis. The process turned out to be highly diastereoselective, leading to *trans*-isomers, bearing a 3-carboethoxy group, in good yield and good to high ee values.

In 2017, we disclosed a convenient and efficient method to prepare *N*-unprotected 2-substituted 1,5-benzothiazepines by conceiving an one-pot sulfa-Michael/lactamization sequence using *trans*-3-substituted α,β-unsaturated acylpyrazoles and 2-aminothiophenols.[8] The first step was catalysed by 1 mol% loading of a readily available *Cinchona* alkaloid derived squaramide, followed by silica gel mediated cyclization to give the products in good to excellent yield and enantioselectivity (up to 96% ee). The protocol was successfully applied in a concise preparation of (*R*)-thiazesim. Encouraged by these results and considering as highly desirable the development of catalytic methods for the synthesis of 2,3-disubstituted 1,5-benzothiazepines, we undertook an investigation exploiting the sulfa-Michael/lactamization route. Herein, we present our study on a first enantioselective approach to novel *cis*- and *trans*-*N*-unprotected 2,3-diaryl substituted-1,5-benzothiazepines based on the reaction of *trans*-2,3-disubstituted α,β-unsaturated acyl pyrazoles and 2-aminothiophenols promoted by common bifunctional organocatalysts followed by *p*-toluensulfonic acid (TsOH) catalysed lactamization (Scheme 1c). This one-pot catalytic method expands and complements the sole catalytic approach reported up to now to access this medicinally important heterocyclic scaffold.[7]

Results and Discussion

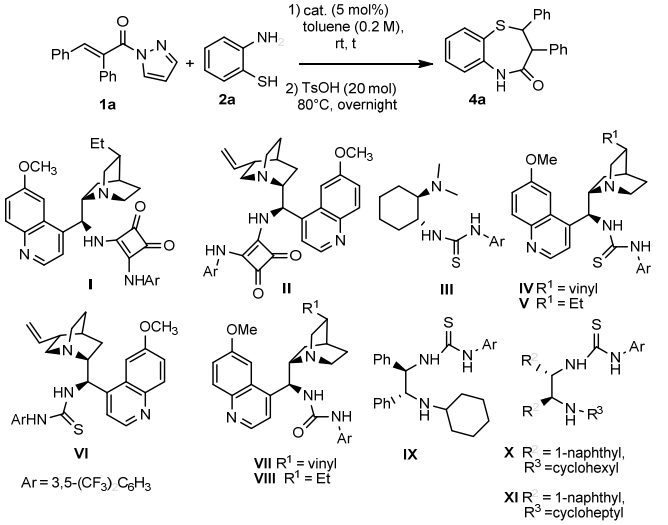
Model alkene **1a** and 2-amino thiophenol **2a** were initially treated with silica gel in toluene at room temperature, under our previously reported conditions, without success.[8] Further optimization of reaction conditions[9] enabled the identification of the most effective catalyst to provide both *cis*- and *trans*-diastereoisomers of compound **4a** (Scheme 2).[10] Readily available basic alumina promoted the formation of adduct **3a** in good yield and 82/18 diastereoisomeric ratio, when working at room temperature. After silica gel filtration, the crude reaction mixture was reacted in toluene at 80°C in the presence of TsOH to give product **4a** in 64% overall isolated yield and comparable diastereoselective ratio. We next turned our attention to develop an asymmetric procedure by using a variety of bifunctional organocatalysts.



Scheme 2 Optimized reaction sequence to racemic *cis*/*trans*-**4a**.

The screening was carried out in toluene at room temperature, starting from reagents **1a** and **2a** and using the organocatalysts at 5 mol% loading (Table 1). *Cinchona* derived amine-squaramide **I**, being selected as the optimal promoter in our previous study, was checked in the sulfa-Michael reaction followed by the one-pot acid catalysed lactamization sequence (entry 1).

Table 1 Screening of catalysts.[a]



Entry	Cat.	t [h]	Yield [%][b]	*cis*/*trans* [%][c]	*ee* **4a** [%][d]
1	**I**	5	56	83/17	75 (70)
2[e]	**I**	7	50	72/28	76 (65)
3	**II**	5	43	80/20	-73 (-59)
4	**III**	6	25	72/28	-53 (-42)
5	**IV**	4	35	73/27	66 (53)
6	**V**	4	24	83/17	74 (68)
7	**VI**	4	32	64/36	-57 (-50)
8	**VII**	7	33	70/30	73 (78)
9	**VIII**	8	68	82/18	81 (62)
10	**IX**	6	83	65/35	-79 (-94)
11	**X**	6	70	54/46	80 (93)
12	**XI**	7	55	56/44	74 (95)

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol, added in two portions), cat. (0.005 mmol) in toluene (500 μL) under N_2 atmosphere. After completion, *p*-toluenesulfonic acid monohydrate (0.02 mmol) was added. [b] Determined by ^{1}H NMR analysis with 1,3,5-$(MeO)_3C_6H_3$ as an internal standard. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture [d] Determined by chiral HPLC analysis on *cis*-**4a** and *trans*-**4a** (in parenthesis). [e] Reaction performed in Et_2O.

Compound **4a** was obtained in acceptable conversion, satisfactory level of enantioselectivity and 83/17 *cis*/*trans* ratio. Performing the first step in diethyl ether did not improve the outcome (entry 2). Quinidine-derived squaramide **II** proved to be only slightly less efficient than *pseudo*-enantiomeric catalyst **I** (entry 3). Common amine-thioureas such as Takemoto's catalyst **III** and *Cinchona* derived promoters **IV-VI** were significantly less active and similar level of stereoselectivities were observed (entries 4-7). Between quinine and hydroquinine-derived ureas **VII** and **VIII** (entries 8 and 9) a good conversion, diastereo- and enantioselectivity were achieved when using catalyst **VIII**. In particular, *cis*-**4a** was recovered preferentially with up to 81% ee (entry 9).

DOI: 10.1039/C8OB01988F

Finally, amine-thioureas derived from 1,2-diaryl substituted diamines, successfully employed by our group in domino reactions,[11] were evaluated in the process (entries 10-12). Interestingly, they proved to be more effective than other thioureas and both *cis*- and *trans*-diastereoisomers of **4a** were obtained in similar ratio, satisfactory combined yield and significantly improved enantioselectivity (up to 95% ee for the *trans*-isomer). Given the practical absence of any protocols to access enantiomerically enriched *trans*- and *cis*-2,3-substituted-1,5-benzothiazepines, we considered of high interest the development of a straightforward method that would enable their preparation under mild conditions.

Further optimization of the model reaction was then carried out using catalyst **X** able to furnish both diastereoisomers with a view to improve the enantioselectivity (Table 2). The reaction performed in toluene at 0°C led to a lower level of enantioselectivity for *cis*-**4a** (entry 1). Dilution or concentration of the reaction mixture, when working at room temperature, negatively affected either the conversion to the product and level of enantioselectivity (entries 2 and 3). Solvent screening showed that neither ethereal or halogenated solvents outperformed the result achieved in toluene (entries 4 and 5).

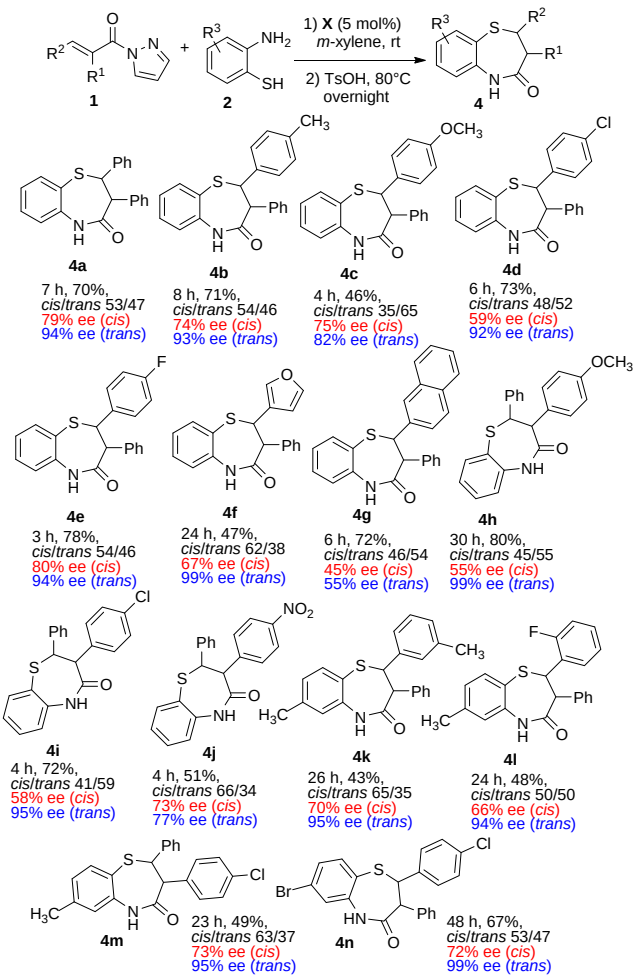
Table 2 Optimization of the reaction conditions.[a]

Entry	Solvent	t [h]	Yield [%][b]	*cis*/*trans* [%][c]	*ee* **4a** [%][d]
1[e]	toluene	7	72	55/45	70 (94)
2[f]	toluene	70	37	55/45	76 (92)
3[g]	toluene	5	52	65/35	54 (86)
4	Et_2O	5	54	48/52	60 (95)
5	CH_2Cl_2	26	25	64/36	54 (88)
6	C_6H_5Cl	7	58	57/43	66 (90)
7	mesitylene	7	61	51/49	80 (95)
8	xylenes	5	47	51/49	75 (94)
9	*m*-xylene	7	75	51/49	79 (95)
10	benzene	7	60	65/35	75 (90)

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol, added in two portions), **X** (0.005 mmol) in solvent (500 µL) under inert atmosphere. After completion, *p*-toluenesulfonic acid monohydrate (0.02 mmol) was added. [b] Determined by ^{1}H NMR analysis with 1,3,5-$(MeO)_3C_6H_3$ as an internal standard. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis on analysis on *cis*-**4a** and *trans*-**4a** (in parenthesis). [e] Reaction performed at 0°C. [f] Reaction performed at C = 0.05 M. [g] Reaction performed at C = 0.5 M.

Among the aromatic solvents furtherly checked (entries 6-10) *m*-xylene afforded both *cis*- and *trans*-**4a** with the highest yield and ee values. The scope and limitation of the methodology was then investigated working under conditions in Table 2, entry 9 (Table 3). 2-Amino thiophenol was first used as the nucleophile. 1,5-Benzothiazepines bearing electron-donating groups in the aryl ring at 2-position (**4b** and **4c**) were isolated with similar diastereoselectivity, although lower enantioselectivity was observed with the less reactive alkene **1c**. Both diastereoisomers of benzothiazepines bearing electron-withdrawing group in the aromatic ring at 2-position or heteroaromatic residues (**4d**-**f**) were isolated in good to acceptable yield and good to high ee values. A more sterically demanding 2-naphthyl moiety at the β-position of the corresponding alkene was found to significantly reduce the level of enantioselectivity for both diastereoisomers (**4g**).

Table 3 Substrate scope and limitations.[a]



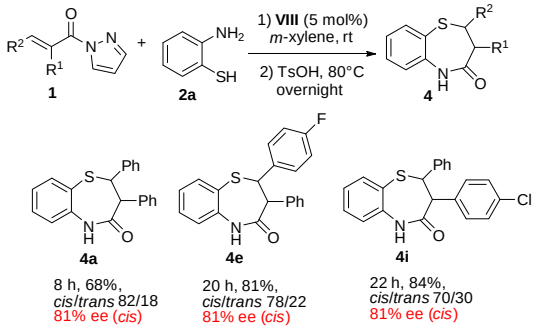
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol, added in two portions), **X** (0.010 mmol) in toluene (1 mL) under inert atmosphere. Yield of isolated products are given.

Starting alkenes bearing α-aryl substituted moieties were also converted to the desired products in high ee values for the *trans*-isomer and moderate for the *cis*-isomer (**4h,i**), with the exception of product **4j**, whose diastereoisomers were obtained with 73% and 77% ee (**4j**). Unfortunately, the process was incompatible with α,β-unsaturated acyl pyrazoles bearing alkyl substitutents, which provided low conversion to the final product after prolonged reaction time.[12] Substituted 2-aminothiophenols were then reacted with different alkenes to give both *cis*- and *trans*-2,3-disubstituted 1,5-benzothiazepines **4k**-**n** in comparable ratio, moderate to satisfactory yield,[13] consistently high to excellent ee values for the *trans*-isomer, also when using an *ortho*-substitution on the β-aromatic ring in the starting alkene (**4l**).

According to previously optimized conditions (Table 1, entry 9), the feasibility of obtaining *cis*-2,3-substituted 1,5-benzothiazepines with improved level of enantioselectivity has

been shortly investigated using catalyst **VIII** in *m*-xylene at room temperature (Table 4).

Table 4 Reaction sequence mediated by catalyst **VIII**.[a]



[a] Reaction conditions as reported in Table 3. Yields of isolated products are given.

Pleasingly, the prevalent *cis*-**4** diastereoisomer was always recovered in good yield and ee value, attesting that it is possible to obtain good to high enantiocontrol for both diastereoisomers of 1,5-benzothiazepines, by proper choice of two organocatalysts. Unfortunately, it was not possible to obtain good crystals for any compound. For this reason a hybrid approach based on NMR spectroscopy and Electronic Circular Dichroism (ECD), supported by DFT conformational analysis and TD-DFT calculation of ECD spectra was employed to assign the relative and absolute configuration of compounds *trans*-**4e** and *cis*-**4e**. The relative configuration was determined by the analysis of the coupling constants between the two CH in position 2 and 3 of 1,5-benzothiazepine, and the ECD spectra were successfully simulated considering the 2*R*,3*R* absolute configuration for *trans*-**4e**, and the 2*S*,3*R* configuration of *cis*-**4e** (Fig. 2).[9]

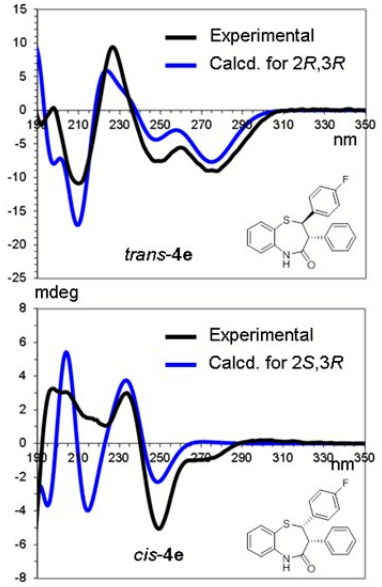


Fig. 2 TD-DFT simulations of the ECD spectra of *trans*-**4e** and *cis*-**4e**. Simulations were run at the TDDFT-CAM-B3LYP/6-311++G(2d,p) level. Geometry optimization was obtained at the PCM-B3LYP/6-311 +G(d,p) level.

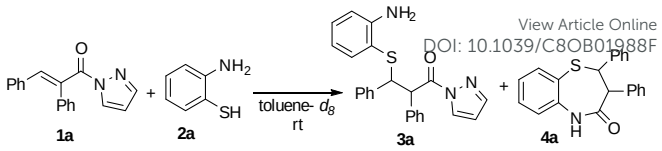
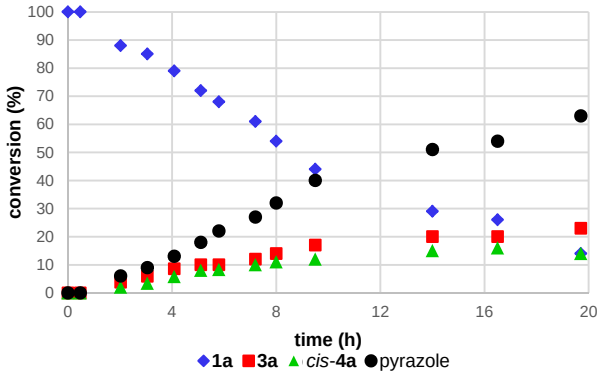


Fig. 3 Reaction progress profile over time in the presence of 1,2-dichloroethane as



internal standard without catalyst in toluene-d_8 at rt.

The absolute configuration of the other compounds **4** was assigned by analogy.

At this point, mechanistic investigations were carried out to shed light on the regio- and stereochemical outcome of the model process. The uncatalysed model reaction was monitored by ^{1}H NMR in toluene-d_8 over time (Fig. 3). It is interesting to note that in absence of any catalyst, low amounts (< 10%) of the adduct **3a** and compound **4a** were formed after 5 h.

Moreover, the amount of free pyrazole is always higher than the amount of *cis*-**4a**, which was the only detected diastereoisomer besides Michael adduct **3a**. In particular, after 7 h 12% of adduct **3a** in 87/13 dr ratio, 10 % of *cis*-**4a**, 62% of **1a** and 27% of pyrazole were detected. Hence, the uncatalysed parallel reaction might contribute to lower the final ee value for the *cis*-diastereoisomer. This experiment points out that a competitive 1,2-addition/elimination reaction would occur on the starting alkene **1a** to give the corresponding α,β-unsaturated thioester.[14] The same study was then carried out in C_6D_6[15] in the presence of 5 mol% of catalyst **X** (Fig. 4).

The adduct **3a** was gradually formed with a constant level of the diastereoselectivity over time (65/35 dr). Compound **4a** was not observed in the reaction mixture, thus attesting that the uncatalysed reaction is likely to be a negligible process, when compared to a faster conversion of alkene **1a** to **3a**, promoted by the organocatalyst. The estimated conversion to the adduct is in agreement with the final isolated yield of compound **4a** reported in Tables 2 and 3. Moreover, the organocatalyst promoted the competitive 1,2-addition/elimination reaction as attested by detection of 30% of free pyrazole at the end of reaction.[16] The presence of either the adduct **3a** and the α,β-unsaturated thioester **5a** was also confirmed by high resolution mass spectrometry analysis (HRMS) of the crude reaction mixture.[17]

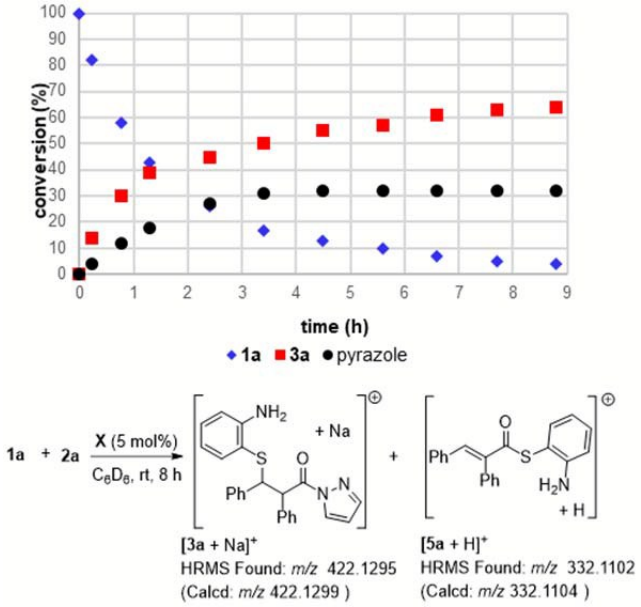
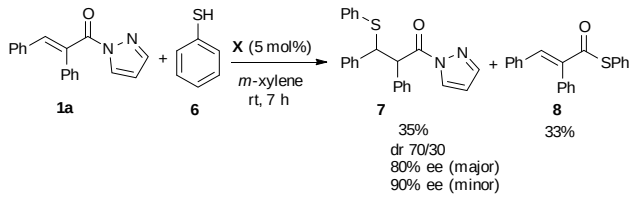


Fig. 4 Reaction progress profile over time in the presence of 1,2-dichloroethane as internal standard with 5 mol% **X** in C_6D_6 at room temperature and HRMS analysis of the crude reaction mixture.

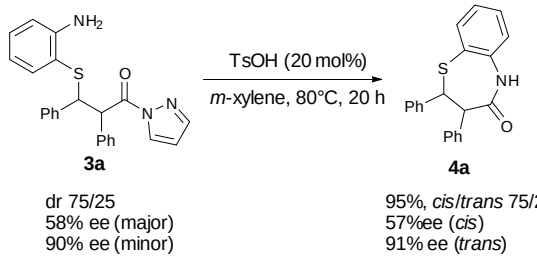
Since we could not isolate compound **5a** by silica gel chromatography, the reaction of model compound **1a** with thiophenol **6** was also investigated in the presence of catalyst **X** under standard conditions (Scheme 3).

The adduct **7** was isolated in 35% yield and 70/30 diastereoisomeric ratio, with both diastereoisomers showing good ee values. Moreover, the α,β-unsaturated thioester **8** was isolated in 33% yield.[18]



Scheme 3 Asymmetric sulfa-Michael reaction of **1a** with thiophenol.

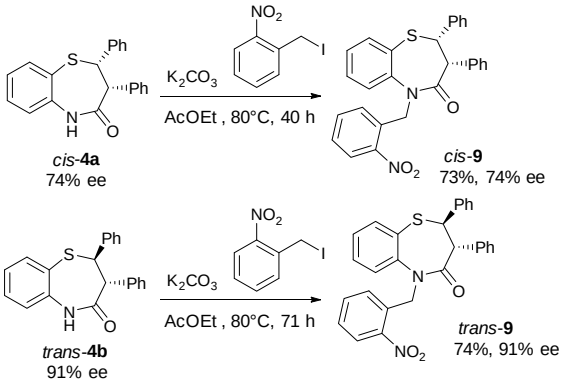
This experiment confirmed that competitive 1,2-addition/elimination process is partially promoted by the organocatalyst, thus affecting the overall yield of compounds **4**. The lactamization step was next studied by reacting diastereo- and enantiomerically enriched **3a** in *m*-xylene at 80°C with 20 mol% of TsOH, to control the stereochemical integrity over the cyclization step (Scheme 4). The mixture of *cis*/*trans*-**4a** was recovered with the same level of diastereo- and enantioselectivity of the starting adduct **3a**, running out the possibility of a retro-sulfa Michael/sulfa-Michael process that would lead to epimerization/racemization. In this regard, a racemic mixture of the adduct **3a** (dr 71/29) treated under usual conditions at room temperature with catalyst **X** for two days showed a poor amount of *trans*-**4a** (<10%), attesting that the organocatalysed lactamization is a negligible process within the reaction times reported in Table 3.[9] Overall, mechanistic investigations enabled to observe that the first step is regioselective with the sulfa-Michael reaction being the prevalent process with respect to 1,2-addition/elimination route, when using the amine thiourea catalyst.[19]



Scheme 4 Lactamization of the diastereo- and enantioenriched mixture of adduct **3a**.

The uncatalysed Michael reaction and lactamization, as well as catalyst promoted lactamization might affect the overall outcome in terms of diastereo- and enantioselectivity. However, they are predicted to be poorly effective processes during the reaction times generally exploited in Table 3.[20]

In view of synthetic applications of the methodology toward preparation of benzothiazepine libraries, *N*-alkylation of both enantioenriched *cis*-**4a** and *trans*-**4a** was carried out under basic conditions in ethyl acetate at 80°C with *o*-nitro-benzyl iodide (Scheme 5). Pleasingly, the corresponding *N*-alkylated derivatives were isolated in good yield as pure *cis*-**9** or *trans*-**9** diastereoisomers, maintaining the level of enantioselectivity.



Scheme 5 *N*-Alkylation of enantioenriched *cis*-**4a** and *trans*-**4a**.

Conclusion

In conclusion, we developed a one-pot organocatalytic sulfa-Michael/lactamization route from *trans*-2,3-disubstituted α,β-unsaturated acyl pyrazoles and 2-aminothiophenols. The methodology, which proceeds at room temperature with readily available chiral amine-thiourea or urea and low cost TsOH, represents a first catalytic route where both *cis*- and *trans*-2,3-disubstituted 1,5-benzothiazepines are obtainable in optically enriched form. The N-H free 2,3-substituted 1,5-benzothiazepines are recovered in moderate to good yield and good to excellent enantioselectivity. Mechanistic studies usefully highlighted that the stereoselectivity is established in the sulfa-Michael reaction and it is maintained during the

DOI: 10.1039/C8OB01988F

lactamization step. The process is of interest not only because both diastereoisomers can be produced with useful level of enantioselectivity, but it is also advantageous in view of the crucial elaboration of the seven-membered ring scaffold. The *N*-deprotection step is not required and the enantioenriched 1,5-benzothiazepines are immediately suited for *N*-alkylation or acylation, which are typical derivatizations to create libraries of compounds for bioassay testing.

Experimental section

All reactions requiring dry or inert conditions were conducted in flame-dried glassware under a positive pressure of nitrogen. Anhydrous THF, toluene, *m*-xylene, methanol were purchased from Aldrich and used as received, all other solvents were dried over molecular sieves. Molecular sieves (Aldrich Molecular Sieves, 4 Å, 1.6 mm pellets) were activated under vacuum at 200 °C overnight. Reactions were monitored by thin layer chromatography (TLC) on Macherey-Nagel pre-coated silica gel plates (0.25 mm) and visualized by UV light, potassium permanganate and cerium sulfate staining solutions. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance III HD 600, Bruker Avance-400, Bruker Avance-300 or Bruker Avance-250 spectrometer in $CDCl_3$ or CD_3OD as solvents at room temperature. Chemical shifts for protons are reported using residual solvent protons (^{1}H NMR: δ = 7.26 ppm for $CDCl_3$, δ = 3.31 ppm for CD_3OD) as internal standard. Carbon spectra were referenced to the shift of the ^{13}C signal of $CDCl_3$ (δ = 77.0 ppm) or CD_3OD (δ = 49.0 ppm). The following abbreviations are used to indicate the multiplicity in NMR spectra: s - singlet; d -doublet; t - triplet; q - quartet; dd - double doublet; m - multiplet; bs - broad signal. Optical rotation of compounds was performed on a Jasco P-2000 digital polarimeter using WI (Tungsten-Halogen) lamp (λ = 589 nm). High resolution mass spectra (HRMS) were acquired using a Bruker solariX XR Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 7 T refrigerated actively-shielded superconducting magnet. The samples were ionized in positive ion mode using a MALDI ionization source. Melting points were measured with a Stuart Model SMP 30 melting point apparatus and are uncorrected. Petrol ether (PE) refers to light petroleum ether (boiling point 40-60 °C). All starting materials (unless otherwise noted) were purchased from Aldrich and used as received. Enantiomeric excess of 1,5-benzothiazepines **4**, **9**, adduct **3a** and **7** was determined by HPLC (Waters-Breeze 2487, UV dual λ absorbance detector and 1525 Binary HPLC Pump) using Daicel chiral columns. The absolute configuration of 1,5-benzothiazepines was determined by a hybrid NMR/ECD approach supported by DFT conformational analysis and TD-DFT calculation of ECD spectra of compound **4e**. Other configurations were assigned in analogy. Catalyst **III** was purchased from Strem Chemicals and used as received. Catalysts **I-II**,[21] **IV-VI**,[22] **VII-VIII**,[23] **IX**,[11a] **X**, [11b] were prepared according to the literature. Alkenes **1** were prepared following general procedures reported in the literature.[24]

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1S,2S)-2 (cycloheptylamino)-1,2-di(naphthalen-1yl)ethyl) thiourea (XI)

(1*S*,2*S*)-N^{1}-cycloheptyl-1,2-di(naphthalen-1-yl)ethane-1,2-diamine (86 mg, 0.21 mmol), synthesized according to literature,[11b] was dissolved in anhydrous CH_2Cl_2 (1 mL) in a flamed-dried two-necked round-bottom flask under a positive pressure of nitrogen. The solution was cooled to 0 °C and 3,5-bis(trifluoromethyl)phenylisothiocyanate (38 µL, 0.21 mmol) was added via syringe dropwise in 10 min. After ca. 1 h at 0 °C, the crude mixture was allowed to warm up gradually to room temperature. After reaction completion, as monitored by TLC ($CHCl_3$/MeOH 98/2), the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (PE/EtOAc 98/2 – 90/10) to give the catalyst **XI** in 95% yield. Light yellow solid, 97.2 mg, 65% yield. mp 95.1-98.2 °C. $[\alpha]^{D}_{19}$ = +39.81 (c 0.52, $CHCl_3$). ^{1}H NMR (CD_3OD, 400 MHz): δ 8.29 (d, 2H, J = 7.9 Hz), 8.23 (s, 2H), 7.80-7.73 (m, 3H), 7.67-7.62 (m, 3H), 7.60 (d, 1H, J = 7.1 Hz), 7.48-7.34 (m, 6H), 6.82 (bs, 1H), 5.23 (d, 1H, J = 4.4 Hz), 2.50-2.43 (m, 1H), 1.72-1.63 (m, 1H), 1.62-1.52 (m, 1H), 1.50-1.41 (m, 1H), 1.40-1.14 (m, 8H), 1.05-0.95 (m, 1H). ^{13}C NMR (CD_3OD, 100 MHz): δ 182.6, 143.1, 138.2, 137.6, 135.3, 133.0, 132.6 (q, $^{2}J_{CF}$ = 33.1 Hz), 132.2, 130.1, 129.8, 129.2, 129.0, 127.0, 126.9, 126.7, 126.3, 126.2, 126.0, 125.5, 124.7 (q, $^{1}J_{CF}$ = 271.0 Hz), 124.6, 123.8, 123.4, 117.8, 59.6, 57.0, 36.9, 34.0, 29.2, 29.0, 25.3, 24.7. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{38}H_{36}F_6N_3S$: 680.2529, found: 680.2524.

General procedure for the synthesis of racemic 2,3-substituted-1,5-benzothiazepines (4)

To a suspension of (*E*)-α,β-unsaturated *N*-acylpyrazole **1** (0.1 mmol) and aluminum oxide (aluminium oxide Fluka for chromatography 17994 pH = 10 ± 0.5, 101.96 mg) in dry diethyl ether (500 µL) 2-aminothiophenol **2** (0.11 mmol) was added under N_2 atmosphere. The reaction mixture was stirred at room temperature for 5-24 h. After completion, the reaction mixture was filtered through a short pad of flash silica-gel and the organic solvent was evaporated. Then, the crude mixture was dissolved in dry toluene (500 µL), *p*-toluenesulfonic acid monohydrate (0.02 mmol) was added and the suspension was stirred at 80 °C for 20 h. The crude product was purified by flash chromatography (hexane/ EtOAc100/1 - 70/30) to afford racemic 1,5-benzothiazepines **4**.

General procedure for the enantioselective synthesis of *cis*- and *trans*-2,3-substituted-1,5-benzothiazepine (4)

(*E*)-α,β-unsaturated *N*-acylpyrazole **1** (0.2 mmol) and catalyst **X** or **VIII** (0.01 mmol) were dissolved in dry *m*-xylene (1 mL) and 2-aminothiophenol **2** (0.11 + 0.10 mmol) was added in two portions (the second portion added after 2 hours) under nitrogen atmosphere at room temperature. After completion, *p*-toluenesulfonic acid monohydrate (0.04 mmol) was added. The suspension was stirred at 80°C until completion. The crude mixture was analysed by ^{1}H-NMR to determine the diastereoisomeric ratio. The crude product was purified by

DOI: 10.1039/C8OB01988F

flash chromatography (hexane/EtOAc 100/1 - 70/30) to afford product **4**.

(2*S*,3*R*)-2,3-Diphenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4a)

White solid, 41.1 mg, 62% yield. mp 187.6-189.7 °C. $[\alpha]_D^{17}$ = +17.4 (c 0.66, $CHCl_3$), 81% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (bs, 1H), 7.73 (d, 1H, J = 7.6 Hz), 7.43 (t, 1H, J = 7.6 Hz), 7.32-7.20 (m, 6H), 7.13-7.11 (d, 2H, J = 7.6 Hz), 7.07-7.03 (m, 2H), 6.92 (d, 2H, J = 7.5 Hz), 4.98 (d, 1H, J = 6.3 Hz), 4.22 (d, 1H, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.1, 142.3, 136.2, 135.0, 134.6, 130.8, 130.2, 130.1, 128.9, 128.6, 128.0, 127.4, 127.3, 126.6, 123.2, 61.3, 51.1. HRMS (MALDI-FTICR) exact mass calculated $[M+H]^+$ calculated for $C_{21}H_{18}NOS$: 332.1104, found: 332.1110. HPLC analysis with Chiralpak IC column, 95:5 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 17.4 min, major enantiomer t_R = 21.4 min.

(2*R*,3*R*)-2,3-Diphenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4a)[10b]

White solid, 21.9 mg, 33% yield. mp 190.2-193.7 °C. $[\alpha]_D^{17}$ = -318.54 (c 0.68, $CHCl_3$), 94% ee. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (d, 1H, J = 7.9 Hz), 7.53-7.48 (m, 2H), 7.30 (t, 1H, J = 7.7 Hz), 7.26-7.07 (m, 9H), 6.96-6.93 (m, 2H), 4.89 (d, 1H, J = 12.2 Hz), 4.17 (d, 1H, J = 12.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.6, 142.7, 141.5, 136.3, 135.4, 130.5, 129.9, 128.4, 128.0, 127.4, 127.0, 126.6, 126.4, 123.4, 58.3, 54.4. HRMS (MALDI-FTICR) exact mass calculated $[M+H]^+$ calculated for $C_{21}H_{18}NOS$: 332.1104, found: 332.1110. HPLC analysis with Chiralpak IC column, 80:20 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 9.6 min, major enantiomer t_R = 14.2 min.

(2*S*,3*R*)-3-Phenyl-2-(*p*-tolyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4b)

White solid, 26.2 mg, 38% yield. mp 189 °C (Decomp.). $[\alpha]_D^{18}$ = +36.4 (c 0.54, $CHCl_3$), 74% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.99 (bs, 1H), 7.72 (d, 1H, *J* = 7.2 Hz), 7.42 (t, 1H, *J* = 7.5 Hz), 7.29-7.26 (m, 1H), 7.21-7.19 (m, 2H), 7.16-7.03 (m, 6H), 6.93-6.91 (m, 2H), 4.94 (d, 1H, *J* = 6.2 Hz), 4.20 (d, 1H, *J* = 6.2 Hz), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 172.0, 142.2, 138.4, 134.9, 134.7, 133.1, 130.8, 130.1, 130.0, 129.0, 128.7, 127.4, 127.3, 126.5, 123.1, 60.9, 51.0, 21.2. HRMS (MALDI-FTICR) exact mass calculated $[M+H]^+$ calculated for $C_{22}H_{20}NOS$: 346.1260, found: 346.1265. HPLC analysis with Chiralpak IC column, 95:5 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 31.0 min, major enantiomer t_R = 25.1 min.

(2*R*,3*R*)-3-Phenyl-2-(*p*-tolyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4b)

White solid, 22.8 mg, 33% yield. mp 146.0-150.0 °C. $[\alpha]_D^{18}$= -233.72 (c 0.60, $CHCl_3$), 93% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.63 (d, 1H, *J* = 7.7 Hz), 7.49 (t, 1H, *J* = 7.6 Hz), 7.29 (t, 1H, *J* = 7.6 Hz), 7.24-7.08 (m, 7H), 6.90 (d, 2H, *J* = 8.0 Hz), 6.84 (d, 2H, *J* = 8.1 Hz), 4.88 (d, 1H, *J* = 12.2 Hz), 4.17 (d, 1H, *J* = 12.2 Hz), 2.19 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 173.0, 141.6, 139.8, 137.0, 136.2, 135.6, 130.4, 129.9, 129.1, 127.9, 127.3, 126.8, 126.5, 126.1, 123.3, 58.0, 54.3, 21.0. HRMS (MALDI-FTICR) exact mass calculated $[M+H]^+$calculated for $C_{22}H_{20}NOS$: 346.1260, found: 346.1265. HPLC analysis with Chiralpak IC column, 80:20 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 10.6 min, major enantiomer t_R = 15.8 min.

(2*S*,3*R*)-2-(4-Methoxyphenyl)-3-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4c)

Yellow solid, 11.6 mg, 16% yield. mp 68.7-73.7 °C. $[\alpha]_D^{19}$ = +47.1 (c 0.44, $CHCl_3$), 75% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (bs, 1H), 7.72 (d, 1H, J = 7.2 Hz), 7.43 (t, 1H, J = 7.5 Hz), 7.29-7.26 (m, 1H), 7.23 (d, 2H, J = 8.4 Hz), 7.15-7.12 (m, 2H), 7.09-7.05 (m, 2H), 6.93 (d, 2H, J = 7.5 Hz), 6.77 (d, 2H, J = 8.1 Hz), 4.94 (d, 1H, J = 6.0 Hz), 4.19 (d, 1H, J = 6.0 Hz), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.0, 159.8, 142.2, 134.9, 134.7, 131.2, 130.8, 130.1, 129.2, 128.1, 127.4, 127.3, 126.6, 123.1, 113.4, 60.6, 55.2, 51.1. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{22}H_{20}NO_2S$: 362.1209, found: 362.1206. HPLC analysis with Chiralpak IC column, 70:30 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 17.8 min, major enantiomer t_R = 7.4 min.

(2*R*,3*R*)-2-(4-Methoxyphenyl)-3-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4c)

White solid, 21.7 mg, 30% yield. mp 142.2-144.1 °C. $[\alpha]_D^{20}$ = -165.0 (c 0.58, $CHCl_3$), 82% ee. ^{1}H NMR ($CDCl_3$, 600 MHz): *δ* 7.64 (dd, 1H, *J* = 7.6, 1.1 Hz), 7.62 (bs, 1H), 7.49 (td, 1H, *J* = 7.6, 1.4 Hz), 7.29 (td, 1H, *J* = 7.6, 1.1 Hz), 7.22 (d, 1H, *J* = 7.7 Hz), 7.19-7.17 (m, 2H), 7.16-7.14 (m, 2H), 7.12-7.11 (m, 1H), 6.87 (d, 2H, *J* = 8.7 Hz), 6.62 (d, 2H, *J* = 8.7 Hz), 4.87 (d, 1H, *J* = 12.2 Hz), 4.13 (d, 1H, *J* = 12.2 Hz), 3.68 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 172.7, 158.6, 141.5, 136.3, 135.6, 135.1, 130.5, 129.9, 128.0, 127.4, 127.3, 126.9, 126.5, 123.3, 113.7, 57.9, 55.1, 54.6. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{22}H_{20}NO_2S$: 362.1209, found: 362.1206. HPLC analysis with Chiralpak IC column, 70:30 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 10.1 min, major enantiomer t_R = 14.7 min.

(2*S*,3*R*)-2-(4-Chlorophenyl)-3-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4d)

Brown solid, 25.6 mg, 35% yield. mp 193 °C (Decomp.). $[\alpha]_D^{17}$ = +34.00 (c 0.50, $CHCl_3$), 59% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.72 (d, 1H, *J* = 7.8 Hz), 7.52-7.44 (m, 2H), 7.31-7.27 (m, 1H), 7.26-7.23 (m, 4H), 7.17-7.13 (m, 2H), 7.10-7.07 (m, 2H), 6.94 (d, 2H, *J* = 7.7 Hz), 4.93 (d, 1H, *J* = 6.3 Hz), 4.19 (d, 1H, *J* = 6.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 171.7, 142.1, 135.1, 134.8, 134.4, 134.3, 131.4, 130.7, 130.4, 128.6, 128.2, 127.6, 127.5, 126.8, 123.2, 60.5, 50.8. HRMS (MALDI-FTICR) exact mass calculated $[M+H]^+$ calculated for $C_{21}H_{17}ClNOS$: 366.0714, found: 366.0718. HPLC analysis with Chiralpak IC column, 95:5 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 22.8 min, major enantiomer t_R = 11.7 min.

(2*R*,3*R*)-2-(4-Chlorophenyl)-3-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4d)

Light brown solid, 27.8 mg, 38% yield. mp 76.1-78.6 °C. $[\alpha]_D^{17}$ = -247.83 (c 0.46, $CHCl_3$), 92% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.63 (d, 1H, *J* = 7.4 Hz), 7.52 (td, 1H, *J* = 7.6, 1.3 Hz), 7.31 (t, 1H, *J* = 7.8 Hz), 7.26-7.23 (m, 2H), 7.18-7.12 (m, 5H), 7.06 (d, 2H, *J* = 8.0 Hz), 6.88 (d, 2H, *J* = 8.0 Hz), 4.86 (d, 1H, *J* = 12.2 Hz), 4.09 (d, 1H, 12.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 172.7, 141.6, 141.3, 136.1, 135.1, 133.0, 130.7, 129.9, 128.6, 128.2, 128.1, 127.7, 127.5, 127.0, 123.5, 57.6, 54.3. HRMS (MALDI-FTICR) exact mass calculated $[M+H]^+$ calculated for $C_{21}H_{17}ClNOS$: 366.0714, found: 366.0717. HPLC analysis with Chiralpak IC

column, 80:20 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 9.8 min, major enantiomer t_R = 13.9 min.

(2*S*,3*R*)-2-(4-Fluorophenyl)-3-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4e)

Brown solid, 28.0 mg, 40% yield. mp 174 °C (Decomp.). $[\alpha]_D^{22}$ = +37.9 (c 0.87, $CHCl_3$), 81% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (bs, 1H), 7.73 (d, 1H, J = 7.6 Hz), 7.46 (t, 1H, J = 7.7 Hz), 7.31-7.25 (m, 3H), 7.17-7.13 (m, 2H), 7.09-7.06 (m, 2H), 6.94-6.90 (m, 4H), 4.96 (d, 1H, J = 6.3 Hz), 4.20 (d, 1H, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4, 162.8 (d, $^1J_{CF}$ = 245.9 Hz), 142.3, 134.9, 134.5, 132.0 (d, $^4J_{CF}$ = 3.0 Hz), 131.8 (d, $^3J_{CF}$ = 8.2 Hz), 130.7, 130.3, 128.6, 127.5, 127.4, 126.6, 123.3, 114.8 (d, $^2J_{CF}$ = 21.3 Hz), 60.6, 50.9. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{21}H_{17}FNOS$: 350.1009, found: 350.1006. HPLC analysis with Chiralpak IC column, 95:5 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 13.6 min, major enantiomer t_R = 12.6 min.

(2*R*,3*R*)-2-(4-Fluorophenyl)-3-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4e)

White solid, 26.6 mg, 38% yield. mp 182.0-184.1 °C. $[\alpha]_D^{22}$ = -322.3 (c 0.99, $CHCl_3$), 94% ee. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.90 (bs, 1H), 7.65-7.60 (m, 1H), 7.50 (td, 1H, J = 7.6, 1.3 Hz), 7.33-7.11 (m, 7H), 6.94-6.89 (m, 2H), 6.80-6.74 (m, 2H), 4.88 (d, 1H, J = 12.2 Hz), 4.09 (d, 1H, J = 12.2 Hz). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 172.7, 161.7 (d, $^1J_{CF}$ = 245.0 Hz), 141.6, 138.7 (d, $^4J_{CF}$ = 3.1 Hz), 136.1, 135.3, 130.6, 129.9, 128.0, 127.9, 127.5, 126.9, 126.0, 123.4, 115.3 (d, $^2J_{CF}$ = 21.4 Hz), 57.6, 54.7. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{21}H_{17}FNOS$: 350.1009, found: 350.1006. HPLC analysis with Chiralpak IC column, 80:20 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 9.7 min, major enantiomer t_R = 13.8 min.

(2*S*,3*R*)-2-(Furan-3-yl)-3-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4f)

Ochre yellow solid, 19.3 mg, 30% yield. mp 76.4-79.6 °C. $[\alpha]_D^{21}$ = +1.1 (c 0.60, $CHCl_3$), 67% ee. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.72-7.69 (dd, 1H, J = 7.5, 1.2 Hz), 7.54 (bs, 2H), 7.45-7.41 (dd, 1H, J = 7.4, 1.7), 7.20-7.13 (m, 8H), 6.62 (s, 1H), 4.95 (d, 1H, J = 6.3 Hz), 4.17 (d, 1H, J = 6.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.9, 143.1, 142.2, 142.0, 135.0, 134.7, 130.6, 130.3, 128.6, 127.6, 127.5, 126.7, 123.1, 121.0, 111.0, 51.7, 50.3. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{19}H_{16}NO_2S$: 322.0896, found: 322.0892. HPLC analysis with Chiralpak IC column, 90:10 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 15.0 min, major enantiomer t_R = 11.8 min.

(2*R*,3*R*)-2-(Furan-3-yl)-3-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4f)

Brown solid, 10.9 mg, 17% yield. mp 151.8 °C (Decomp.). $[\alpha]_D^{19}$ = -175.9 (c 0.51, $CHCl_3$), 99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.92 (s, 1H), 7.67 (d, 1H, *J* = 7.6 Hz), 7.48 (t, 1H, *J* = 7.2 Hz), 7.30-7.28 (m, 1H), 7.23-7.19 (m, 6H), 7.15 (s, 1H), 6.97 (s, 1H), 6.00 (s, 1H), 4.84 (d, 1H, *J* = 11.9 Hz), 3.88 (d, 1H, *J* = 11.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 172.7, 143.1, 141.6, 138.8, 136.3, 135.8, 130.6, 129.8, 128.1, 127.7, 126.89, 126.80, 126.0, 123.3, 108.5, 54.5, 50.0. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{19}H_{16}NO_2S$: 322.0896, found: 322.0892. HPLC analysis with Chiralpak IC column, 80:20 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 10.7 min, major enantiomer t_R = 17.4 min.

(2*S*,3*R*)-2-(Naphthalen-2-yl)-3-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4g)

Yellow solid, 25.9 mg, 34% yield. mp 205 °C (Decomp.). $[\alpha]_D^{17}$ = +36.1 (c 0.69, $CHCl_3$), 45% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.84 (d, 1H, *J* = 7.5 Hz), 7.79 (d, 1H, *J* = 8.4 Hz), 7.75 (t, 2H, *J* = 6.5 Hz), 7.69 (s, 1H), 7.60-7.57 (m, 2H), 7.50-7.44 (m, 3H), 7.30 (t, 1H, *J* = 7.6 Hz), 7.19 (d, 1H, *J* = 7.4 Hz), 7.11-7.07 (m, 1H), 7.01-6.97 (m, 2H), 6.94-6.92 (m, 2H), 5.15 (d, 1H, *J* = 6.4 Hz), 4.29 (d, 1H, *J* = 6.4 Hz). ^{13}C NMR ($CDCl_3$, 62.5 MHz): *δ* 171.9, 142.2, 135.0, 134.6, 133.8, 133.4, 132.8, 130.8, 130.3, 129.7, 128.9, 128.2, 127.7, 127.6, 127.5, 127.42, 127.39, 126.7, 126.3, 126.0, 123.1, 61.4, 51.1. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{25}H_{20}NOS$: 382.1260, found: 382.1283. HPLC analysis with Chiralpak IC column, 80:20 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 13.6 min, major enantiomer t_R = 7.9 min.

(2*R*,3*R*)-2-(Naphthalen-2-yl)-3-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4g)

Yellow solid, 28.2 mg, 37% yield. mp 210 °C (Decomp.). $[\alpha]_D^{18}$ = -82.0 (c 0.42, $CHCl_3$), 55% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.73-7.61 (m, 5H), 7.53 (td, 1H, *J* = 7.6, 1.3 Hz), 7.39-7.27 (m, 5H), 7.26-7.22 (m, 2H), 7.16-7.05 (m, 4H), 5.09 (d, 1H, *J* = 12.2 Hz), 4.33 (d, 1H, *J* = 12.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): *δ* 172.7, 141.5, 139.9, 136.4, 135.3, 133.0, 132.5, 130.6, 129.8, 128.7, 128.5, 128.0, 127.8, 127.5, 127.0, 126.5, 126.1, 125.9, 125.4, 123.9, 123.4, 58.3, 53.9. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{25}H_{20}NOS$: 382.1260, found: 382.1263. HPLC analysis with Chiralpak IC column, 70:20 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 8.1 min, major enantiomer t_R = 10.7 min.

(2*S*,3*R*)-3-(4-Methoxyphenyl)-2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4h)

Ochre yellow solid, 28.9 mg, 40% yield. mp 167.4-172.0 °C. $[\alpha]_D^{19}$ = +57.4 (c 0.51, $CHCl_3$), 55% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 8.18 (bs, 1H), 7.72 (d, 1H, *J* = 7.7 Hz), 7.44-7.40 (m, 1H), 7.33-7.22 (m, 6H), 7.12 (d, 1H, *J* = 7.8 Hz), 6.80 (d, 2H, *J* = 8.7 Hz), 6.60 (d, 2H, *J* = 8.8 Hz), 4.94 (d, 1H, *J* = 6.3 Hz), 4.17 (d, 1H, *J* = 6.3 Hz), 3.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 172.3, 158.8, 142.3, 136.3, 135.0, 131.9, 130.2, 130.1, 128.9, 128.6, 128.0, 126.6, 126.5, 123.1, 112.8, 61.3, 55.1, 50.3. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{22}H_{20}NO_2S$: 362.1209, found: 362.1206. HPLC analysis with Chiralpak IC column, 80:20 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 13.8 min, major enantiomer t_R = 10.0 min.

(2*R*,3*R*)-3-(4-Methoxyphenyl)-2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4h)

Ochre yellow solid, 28.9 mg, 40% yield. mp 157.8 °C (Decomp.). $[\alpha]_D^{19}$ = -245.3 (c 0.54, $CHCl_3$), 99% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.65-7.62 (dd, 1H, *J* = 7.7, 1.1 Hz), 7.55 (bs, 1H), 7.52-7.48 (td, 1H, *J* = 7.7, 1.3 Hz), 7.32-7.28 (td, 1H, *J* = 7.5, 1.1 Hz), 7.23 (d, 1H, *J* = 7.8 Hz), 7.11-7.09 (m, 5H), 6.95-6.93 (m, 2H), 6.67 (d, 2H, *J* = 8.7 Hz), 4.83 (d, 1H, *J* = 12.2 Hz), 4.12 (d, 1H, *J* = 12.2 Hz), 3.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ*

173.3, 158.6, 142.9, 141.7, 136.2, 130.9, 130.4, 128.4, 127.5, 127.3, 126.8, 126.42, 126.35, 123.3, 113.4, 58.4, 55.0, 53.5. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{22}H_{20}NO_2S$: 362.1209, found: 362.1206. HPLC analysis with Chiralpak IC column, 70:30 *n*-hexane:2-propanol, 1 mL/min, 220 nm; minor enantiomer t_R = 14.1 min, major enantiomer t_R = 25.1 min.

(2*S*,3*R*)-3-(4-Chlorophenyl)-2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4i)

Yellow solid, 22.0 mg, 30% yield. mp 158 °C (Decomp.). $[\alpha]_D^{20}$ = +63.07 (c 0.56, $CHCl_3$), 81% ee. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.75-7.72 (dd, 1H, *J* = 7.2, 0.7 Hz), 7.51 (bs, 1H), 7.47-7.43 (dd, 1H, *J* = 7.7, 1.3 Hz), 7.32-7.30 (m, 6H), 7.18-7.15 (m, 1H), 7.02 (d, 2H, *J* = 8.5 Hz), 6.85 (d, 2H, *J* = 8.7 Hz), 4.92 (d, 1H, *J* = 6.4 Hz), 4.17 (d, 1H, *J* = 6.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 141.9, 135.8, 135.1, 133.4, 133.0, 132.1, 130.3, 130.1, 128.8, 128.7, 128.1, 127.6, 126.8, 123.2, 61.0, 50.4. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{21}H_{17}ClNOS$: 366.0714, found: 366.0711. HPLC analysis with Chiralpak IC column, 95:5 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 17.4 min, major enantiomer t_R = 15.7 min.

(2*R*,3*R*)-3-(4-Chlorophenyl)-2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4i)

White solid, 30.7 mg, 42% yield. mp 182.8-185.2 °C. $[\alpha]_D^{19}$ = -282.2 (c 0.60, $CHCl_3$), 95% ee. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.86 (s, 1H), 7.64 (d, 1H, *J* = 7.3 Hz), 7.50 (t, 1H, *J* = 7.3 Hz), 7.31 (t, 1H, *J* = 7.5 Hz), 7.21 (d, 1H, *J* = 7.8 Hz), 7.14-7.10 (m, 7H), 6.93-6.92 (m, 2H), 4.81 (d, 1H, *J* = 12.2 Hz), 4.14 (d, 1H, *J* = 12.2 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.3, 142.5, 141.4, 136.3, 134.1, 133.3, 131.3, 130.6, 128.6, 128.2, 127.6, 127.1, 126.4, 126.3, 123.4, 58.3, 53.8. HRMS (MADI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{21}H_{17}ClNOS$: 366.0714, found: 366.0711. HPLC analysis with Chiralpak IC column, 80:20 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 7.6 min, major enantiomer t_R = 10.7 min.

(2*S*,3*R*)-3-(4-Nitrophenyl)-2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4j)

Pale yellow solid, 23.3 mg, 31% yield. mp 207.4-211.8 °C. $[\alpha]_D^{19}$ = +71.3 (c 0.58, $CHCl_3$), 73% ee. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.02 (bs, 1H), 7.90 (d, 2H, *J* = 8.0 Hz), 7.75 (d, 1H, *J* = 7.5 Hz), 7.49 (t, 1H, *J* = 7.7 Hz), 7.35-7.24 (m, 6H), 7.16 (d, 1H, *J* = 7.7 Hz), 7.13 (d, 2H, *J* = 8.7 Hz), 4.96 (d, 1H, *J* = 6.5 Hz), 4.31 (d, 1H, *J* = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 147.0, 142.0, 141.8, 135.2, 131.7, 130.6, 129.9, 129.1, 128.5, 128.3, 127.0, 123.4, 122.4, 60.9, 50.7. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{21}H_{17}N_2O_3S$: 377.0954, found: 377.0951. HPLC analysis with Chiralpak IC column, 90:10 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 31.0 min, major enantiomer t_R = 24.7 min.

(2*R*,3*R*)-3-(4-Nitrophenyl)-2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4j)

Ochre yellow solid, 15.1 mg, 20% yield. mp 175.5-177.5 °C. $[\alpha]_D^{19}$ = -132.7 (c 0.42, $CHCl_3$), 77% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01-7.99 (m, 3H), 7.68 (d, 1H, *J* = 8.0 Hz), 7.54 (t, 1H, *J* = 7.4 Hz), 7.40-7.33 (m, 3H), 7.11-7.10 (m, 3H), 6.92-6.91 (m, 2H), 4.86 (d, 1H, *J* = 12.2 Hz), 4.28 (d, 1H, *J* = 12.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.4, 147.0, 142.9, 142.0, 141.1, 136.3, 131.0, 130.8, 128.7, 127.9, 127.4, 126.2, 126.1, 123.6, 123.0, 58.2, 54.1. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{21}H_{17}N_2O_3S$: 377.0954, found: 377.0951. HPLC analysis with Chiralpak IC column, 90:10 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 31.0 min, major enantiomer t_R = 25.1 min.

(2*S*,3*R*)-7-Methyl-3-phenyl-2-(*m*-tolyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4k)

White solid, 18.7 mg, 26% yield. mp 181.5-183.8 °C. $[\alpha]_D^{19}$ = +17.3 (c 0.54, $CHCl_3$), 70% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (s, 1H), 7.58 (d, 1H, *J* = 7.7 Hz), 7.11-7.04 (m, 8H), 6.93-6.90 (m, 3H), 4.89 (d, 1H, *J* = 6.2 Hz), 4.81 (d, 1H, *J* = 6.2 Hz), 2.39 (s, 3H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.0, 142.0, 140.7, 137.5, 136.2, 134.7, 130.8, 130.7, 129.3, 127.8, 127.34, 127.28, 127.2, 125.4, 123.7, 61.1, 51.1, 21.4, 21.2. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{23}H_{22}NOS$: 360.1417, found: 360.1413. HPLC analysis with Chiralpak IE-3 column, 70:30 *n*-hexane:2-propanol, 0.6 mL/min, 254 nm; minor enantiomer t_R = 30.6 min, major enantiomer t_R = 15.2 min.

(2*R*,3*R*)-7-Methyl-3-phenyl-2-(*m*-tolyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4k)

White solid, 12.2 mg, 17% yield. mp 199.6-201.9 °C. $[\alpha]_D^{20}$ = -333.2 (c 0.60, $CHCl_3$), 95% ee. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.50 (d, 1H, *J* = 7.8 Hz), 7.20-7.18 (m, 2H), 7.14 (t, 2H, *J* = 7.4 Hz), 7.11-7.10 (m, 2H), 7.04 (s, 1H), 6.97 (t, 1H, *J* = 7.9 Hz), 6.87 (d, 1H, *J* = 7.3 Hz), 6.75-6.74 (m, 2H), 4.82 (d, 1H, *J* = 12.2 Hz), 4.17 (d, 1H, *J* = 12.2 Hz), 2.45 (s, 3H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.8, 142.7, 141.4, 141.1, 138.0, 136.1, 135.6, 129.9, 128.2, 128.1, 127.9, 127.8, 127.30, 127.27, 124.0, 123.2, 123.1, 58.1, 54.3, 21.32, 21.28. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{23}H_{22}NOS$: 360.1417, found: 360.1413. HPLC analysis with Chiralpak IE-3 column, 70:30 *n*-hexane:2-propanol, 0.6 mL/min, 254 nm; minor enantiomer t_R = 24.3 min, major enantiomer t_R = 22.9 min.

(2*S*,3*R*)-2-(2-Fluorophenyl)-3-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4l)

White solid, 16.7 mg, 23% yield. mp 214.6-218.4 °C. $[\alpha]_D^{18}$ = +5.4 (0.59, $CHCl_3$), 66% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (s, 1H), 8.08-8.04 (td, 1H, *J* = 7.5, 1.3 Hz), 7.61 (d, 1H, *J* = 7.8 Hz), 7.26-7.25 (m, 1H), 7.17-7.13 (m, 2H), 7.10-7.06 (m, 3H), 6.99 (d, 2H, *J* = 7.5 Hz), 6.91 (s, 1H), 6.80 (t, 1H, *J* = 8.9), 5.48 (d, 1H, *J* = 6.6 Hz), 4.21 (d, 1H, *J* = 6.6 Hz), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3, 160.8 (d, $^1J_{CF}$ = 245.8 Hz), 142.0, 141.0, 135.0, 134.4, 131.1, 130.4, 129.9 (d, $^2J_{CF}$ = 8.4 Hz), 127.5, 127.4, 124.9, 124.1 (d, $^4J_{CF}$ = 2.9 Hz), 123.9, 123.7, 123.6, 114.6 (d, $^3J_{CF}$ = 22.8 Hz), 51.0, 50.6, 21.2. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{22}H_{19}FNOS$: 364.1166, found: 364.1163. HPLC analysis with Chiralpak IC column, 95:5 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 16.4 min, major enantiomer t_R = 12.1 min.

(2*R*,3*R*)-2-(2-Fluorophenyl)-3-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4l)

Cream coloured solid, 18.2 mg, 25% yield. mp 201.0-205.9 °C. $[\alpha]_D^{18}$ = -369.0 (c 0.62, $CHCl_3$), 94% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (bs, 1H), 7.46 (d, 1H, *J* = 7.8 Hz), 7.24-7.22 (m,

2H), 7.17-7.13 (m, 3H), 7.11-7.05 (m, 2H), 7.03-6.98 (m, 2H), 6.89 (t, 1H, *J* = 7.5 Hz), 6.82 (t, 1H, *J* = 9.3 Hz), 5.30 (d, 1H, *J* = 12.5 Hz), 4.24 (d, 1H, *J* = 12.4 Hz), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.8, 158.9 (d, $^1J_{CF}$ = 245.4 Hz), 141.23, 141.20, 135.9, 135.2, 129.7, 128.7 (d, $^3J_{CF}$ = 8.3 Hz), 128.0, 127.6 (d, $^2J_{CF}$ = 23.9 Hz), 127.18, 127.15, 124.1 (d, $^4J_{CF}$ = 3.4 Hz), 124.0, 122.6, 115.5 (d, $^2J_{CF}$ = 22.4 Hz), 52.9, 50.0, 21.3. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{22}H_{19}FNOS$: 364.1166, found: 364.1163. HPLC analysis with Chiralpak IC column, 90:10 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 17.8 min, major enantiomer t_R = 18.9 min.

(2*S*,3*R*)-3-(4-Chlorophenyl)-7-methyl-2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4m)

White solid, 20.5 mg, 27% yield. mp 192.8-194.0 °C. $[\alpha]_D^{17}$ = +47.0 (c 0.52, $CHCl_3$), 73% ee. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.78 (s, 1H), 7.59 (d, 1H, *J* = 7.8 Hz), 7.32-7.25 (m, 5H), 7.09 (d, 1H, *J* = 7.1 Hz), 7.02 (d, 2H, *J* = 8.5 Hz), 6.94 (s, 1H), 6.85 (d, 2H, *J* = 8.5 Hz), 4.89 (d, 1H, *J* = 6.5 Hz), 4.16 (d, 1H, *J* = 6.4 Hz), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 171.6, 141.8, 140.9, 136.0, 134.8, 133.4, 133.2, 132.1, 130.1, 128.7, 128.1, 127.59, 127.57, 125.3, 123.8, 61.0, 50.5, 21.2. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{22}H_{19}ClNOS$: 380.0870, found: 380.0866. HPLC analysis with Chiralpak IC column, 95:5 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 21.6 min, major enantiomer t_R = 13.8 min.

(2*R*,3*R*)-3-(4-Chlorophenyl)-7-methyl-2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4m)

White solid, 16.7 mg, 22% yield. mp 180.6 °C (Decomp.). $[\alpha]_D^{20}$ = -518.8 (c 0.98, $CHCl_3$), 95% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (s, 1H), 7.51 (d, 1H, *J* = 7.8 Hz), 7.12-7.09 (m, 8H), 7.03 (s, 1H), 6.94-6.91 (m, 2H), 4.77 (d, 1H, *J* = 12.2 Hz), 4.13 (d, 1H, *J* = 12.2 Hz), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4, 142.6, 141.3, 141.1, 136.0, 134.1, 133.2, 131.2, 128.5, 128.1, 128.0, 127.5, 126.3, 124.1, 122.8, 58.2, 53.8, 21.3. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{22}H_{19}ClNOS$: 380.0870, found: 380.0866. HPLC analysis with Chiralpak IC column, 80:20 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 8.4 min, major enantiomer t_R = 10.9 min.

(2*S*,3*R*)-7-Bromo-3-(4-chlorophenyl)-2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4n)

White solid, 32.9 mg, 37% yield. mp 60.4-65.4 °C. $[\alpha]_D^{25}$ = +23.38 (c 0.61, $CHCl_3$), 72% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (bs, 1H), 7.57 (d, 1H, J = 8.2 Hz), 7.42-7.39 (dd, 1H, J = 8.3, 1.9), 7.314-7.309 (m, 1H), 7.22-7.21 (m, 4H), 7.15 (d, 1H, J = 7.4 Hz), 7.10 (m, 2H), 6.93 (d, 2H, J = 7.5 Hz), 4.92 (d, 1H, J = 6.3 Hz), 4.16 (d, 1H, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, 136.0, 134.6, 134.4, 134.0, 131.4, 130.6, 129.6, 129.4, 128.9, 128.3, 127.7, 127.4, 126.2, 123.9, 60.6, 50.9. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{21}H_{16}BrClNOS$: 442.9640, found: 442.9637. HPLC analysis with Chiralpak IE3 column, 70:30 *n*-hexane:2-propanol, 0.6 mL/min, 220 nm; minor enantiomer t_R = 17.1 min, major enantiomer t_R = 10.7 min.

(2*R*,3*R*)-7-Bromo-3-(4-chlorophenyl)-2-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (4n)

White solid, 26.7 mg, 30% yield. mp 206.2-210.7 °C. $[\alpha]_D^{18}$ = -405.1 (c 0.77, $CHCl_3$), 99 % ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.26 (bs, 1H), 7.47-7.41 (m, 2H), 7.385-7.381 (m, 1H), 7.18-7.13 (m, 5H), 7.07 (d, 2H, *J* = 8.4 Hz), 6.86 (d, 2H, *J* = 8.4 Hz), 4.86 (d, 1H, *J* = 12.2 Hz), 4.07 (d, 1H, *J* = 12.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.6, 142.9, 140.9, 137.1, 134.7, 133.2, 130.0, 129.8, 128.7, 128.2, 127.7, 127.6, 126.4, 124.9, 124.3, 57.6, 54.3. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{21}H_{16}BrClNOS$: 442.9640, found: 442.9637. HPLC analysis with Chiralpak IC column, 70:30 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 10.5 min, major enantiomer t_R = 7.9 min.

Synthesis of *N*-*o*-nitrobenzyl-1,5-benzothiazepines (9)

trans- or *cis*- 1,5-Benzothiazepine **4a** (33.1 mg, 0.1 mmol) was dissolved in ethyl acetate (770 µL), then 1-(iodomethyl)-2-nitrobenzene (52.6 mg, 0.2 mmol) and potassium carbonate (27.6 mg, 0.2 mmol) were added and the mixture was stirred at 85°C for 48 hours. After completion, the mixture was cooled to room temperature and diluted with ethyl acetate. The aqueous phase was extracted with ethyl acetate (50 mL x 3), then the combined organic phases were washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the crude mixture was purified by flash chromatography (hexane/ethyl acetate 100/0 - 90/10) to give pure *trans*-**9** or *cis*-**9**.

(2*R*,3*R*)-5-(2-Nitrobenzyl)-2,3-diphenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (*trans*-9)

White solid, 34.5 mg, 74% yield. mp 188.8-191.5 °C. $[\alpha]_D^{22}$ = -466.5 (c 0.78, $CHCl_3$), 91% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, 1H, *J* = 8.2 Hz), 7.90 (d, 1H, *J* = 7.8 Hz), 7.62-7.51 (m, 3H), 7.42 (d, 1H, *J* = 8.0 Hz), 7.37 (t, 1H, *J* = 7.8 Hz), 7.31 (t, 1H, *J* = 7.5 Hz), 7.23-7.21 (m, 2H), 7.16-7.08 (m, 6H), 6.91-6.88 (m, 2H), 5.54 and 5.50 (ABq, 2H, *J* = 17.2 Hz), 4.95 (d, 1H, *J* = 12.2 Hz), 4.28 (d, 1H, *J* = 12.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3, 148.0, 145.9, 142.2, 137.0, 135.5, 133.6, 132.6, 131.0, 129.9, 129.7, 128.4, 127.99, 127.95, 127.5, 127.4, 127.0, 126.3, 124.8, 123.5, 57.9, 54.8, 49.9. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{28}H_{22}N_2KO_3S$: 505.0983, found: 505.0978. HPLC analysis with Chiralpak AD column, 70:30 *n*-hexane:2-propanol, 1 mL/min, 254 nm; minor enantiomer t_R = 22.6 min, major enantiomer t_R = 27.7 min.

(2*S*,3*R*)-5-(2-Nitrobenzyl)-2,3-diphenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (*cis*-9)

White solid, 34.1 mg, 73% yield. mp 142.8-146.4 °C. $[\alpha]_D^{24}$ = -118.1 (c 0.74, $CHCl_3$), 74% ee. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04-8.00 (m, 2H), 7.78-7.75 (dd, 1H, *J* = 7.6, 1.5 Hz), 7.63-7.59 (td, 1H, *J* = 7.6, 1.2 Hz), 7.50-7.46 (m, 1H), 7.44-7.39 (m, 1H), 7.37-7.29 (m, 3H), 7.25-7.22 (m, 2H), 7.17-7.15 (m, 2H), 7.13-7.10 (m, 1H), 7.05-7.01 (m, 2H), 6.92-6.90 (m, 2H), 5.61 and 5.57 (ABq, 2H, *J* = 17.3 Hz), 4.87 (d, 1H, *J* = 6.8 Hz) 4.29 (d, 1H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.1, 148.1, 146.8, 135.8, 134.6, 133.6, 133.0, 130.8, 130.7, 130.1, 129.83, 129.79, 128.6, 128.0, 127.5, 127.41, 127.39, 125.0, 123.6, 61.1, 51.6, 50.5. HRMS (MALDI-FT ICR) exact mass calculated $[M+H]^+$ calculated for $C_{28}H_{22}N_2KO_3S$: 505.0983, found: 505.0978. HPLC

DOI: 10.1039/C8OB01988F

analysis with Chiralpak IC column, 95:5 *n*-hexane:2-propanol, 1 mL/min, 220 nm; minor enantiomer t_R = 39.8 min, major enantiomer t_R = 25.5 min.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank MIUR, the Regione Campania (POR CAMPANIA FESR 2007/2013 O.O. 2 .1, CUP B46D14002660009) for the FT-ICR mass spectrometer facilities and Farma-BioNet (CUP B25C13000230007) and the "Centro di Tecnologie Integrate per la Salute" (CITIS, Project PONa3-00138), Università di Salerno, for the 600 MHz NMR facilities, for financial support. We thank Dr. P. Iannece and Dr. P. Oliva for assistance with mass spectra and NMR analyses.

Notes and references

1 For a review on biological activities of 1,5-benzothiazepines, see: J. B. Bariwal, K. D. Upadhyay, A. T. Manvar, J. C. Trivedi, J. S. Singh, K. S. Jain and A. K. Shah, *Eur. J. Med. Chem.,* 2008, **43**, 2279.

2 For reviews, see: (a) K. Asano and S. Matsubara, *ACS Catal.* 2018, **8**, 6273; (b) D. Saha, G. Jain and A. Sharma, *RCS Adv.,* 2015, **5**, 70619; (c) B. C. Sekhar, *Acta Chim. Slov.,* 2014, **61**, 651; (d) A. Lévai and A. Kiss-Szikszai, *ARKIVOC,* 2008, **1**, 65.

3 S. Ohno, K. Itzumi, K. Mizukoshi, K. Kato and M. Hori, *Chem. Pharm. Bull.,* 1983, **31**, 1780.

4 (a) T. Ogawa, N. Kumagai and M. Shibasaki, *Angew. Chem. Int. Ed.,* 2012, **51**, 8551; (b) W. Li, C. Schlepphorst, C. Daniliuc and F. Glorius, *Angew. Chem. Int. Ed.,* 2016, **55**, 3300; (c) G. Wang, Y. Tang, Y. Zhang, X. Liu and X. Feng, *Chem. Eur. J.,* 2017, **23**, 554.

5 For sulfa-Michael reactions applied to the asymmetric synthesis of (*R*)-Thiazesim, see: (a) Q.-L. Pei, H.-W. Sun, Z.-J. Wu, X.-L. Du, X.-M. Zhang and W.-C. Yuan, *J. Org. Chem.,* 2011, **76**, 7849; (b) X. Fang, J. Li and C.-J. Wang, *Org. Lett.,* 2013, **15**, 3448. For general enantioselective approaches to 1,5-benzothiazepines, see: (c) N. K. Rana and V. K. Singh, *Org. Lett.,* 2011, **13**, 6520; (d) Y. Fukata, K. Asano and S. Matsubara, *J. Am. Chem. Soc.*, 2015, **137**, 5320; (e) C. Fang, T. Lu, J. Zhu, K. Sun and D. Du, *Org. Lett.,* 2017, **19**, 3470. For enantioselective access to 2,3,4,5-tetrahydro-1,5-benzothiazepines, see: (f) V. Corti, P. C. Gonzalez, J. Febvay, L. Caruana, A. Mazzanti, M. Fochi and L. Bernardi, *Eur. J. Org. Chem.,* 2017, 49.

6 (a) T. Hashiyama, H. Inoue, M. Konda and M. Takeda, *J. Chem. Soc. PT 1,* 1984, 1725; (b) A. Schwartz, P. B. Madan, E. Mohacsi, J. P. O'Brien, L. J. Todaro and D. L. Coffen, *J. Org. Chem.,* 1992, **57**, 851; (c) E. N. Jacobsen, L. Deng, Y. Furukawa and L. E. Martínez, *Tetrahedron,* 1994, **50**, 4323; (d) B. M. Adger, J. V. Barkley, S. Bergeron, M. W. Cappi, B. E. Flowerdew, M. P. Jackson, R. McCague, T. C. Nugent and S. M. Roberts, *J. Chem. Soc. PT 1,* 1997, 3501; (e) M. Seki, T. Furutani, R. Imashiro, T. Kuroda, T. Yamanaka, N. Harada, H. Arakawa, M. Kusama and T. Hashiyama, *Tetrahedron Lett.,* 2001, **42**, 8201.

7 Y. Fukata, K. Yao, R. Miyaji, K. Asano and S. Matsubara, *J. Org. Chem.,* 2017, **82**, 12655.

8 S. Meninno, C. Volpe and A. Lattanzi, *Chem. Eur. J.*, 2017, **23**, 4547.

9 See the Electronic Supporting Information for details.

10 (a) H. Duddeck, M. Kaiser and A. Lévai, *Liebigs Ann. Chem.,* 1985, 869; b) G. Kaupp and E. Ringer, *Chem. Ber.,* 1986, **119**, 1525.

11 For selected examples, see: (a) S. Meninno, G. Croce and A. Lattanzi, *Org. Lett.,* 2013, **15**, 3436; (b) S. Meninno, J. Overgaard and A. Lattanzi, *Synthesis,* 2017, **49**, 1509; (c) S. Meninno, A. Roselli, A. Capobianco, J. Overgaard and A. Lattanzi, *Org. Lett,* 2017, ***19***, 5030.

12 The reaction carried out on aliphatic substituted α,β-unsaturated acyl pyrazole (R^1 = Me, R^2 = *n*-propyl), followed by treatment with TsOH, gave the expected product in less than 30% yield after 7 days.

13 2-Aminothiophenols undergo easy oxidation by molecular oxygen to the corresponding disulfides. The degree of oxidation is expected to be higher for electron-rich aryl thiols, which in turn affects the yield of compounds **4**. See: A. Lattanzi In *Comprehensive Organic Synthesis II*; P. Knochel, G. A. Molander, Eds.; Elsevier: Oxford, 2014; Vol. 7, pp 837. See also ref. 5f.

14 B.-L. Zhao and D.-M. Du, *Org. Biomol. Chem.,* 2014, **12**, 1585.

15 The choice of C_6D_6 as the solvent instead of toluene-d_8 was dictated by the necessity to have an aromatic solvent showing the 6÷9 ppm region as free as possible of solvent signals to facilitate the analysis.

16 It has to be noted that the diastereoisomeric mixture of adduct **3a** was found to be unstable on silica gel, which fosters the cyclization of *syn*-**3a** to *trans*-**4a**, thus affecting the original diastereoisomeric ratio of adduct **3a** determined on the crude mixture by ^{1}H-NMR analysis.

17 For examples on mechanistic studies in organocatalytic reactions aided by the HRMS tool, see: (a) F. Bächle, J. Duschmalé, C. Ebner, A. Pfaltz, and H. Wennemers, *Angew. Chem. Int. Ed.,* 2013, **52**, 12619; (b) P. G. Isenegger, F. Bächle, and A. Pfaltz, *Chem. Eur. J.*, 2016, **22**, 17595; (c) N. Kaplaneris, C. Spyropoulos, M. G. Kokotou, and C. G. Kokotos, *Org. Lett.,* 2016, **18**, 5880; (d) E. Voutyritsa, A. Theodorou, M. G. Kokotou, and C. G. Kokotos*, Green Chem.*, 2017, **19**, 1291.

18 H. Yoshida, and T. Ogata, *Nippon Kagaku Kaishi,* 1982, 534.

19 Amino urea **VIII** (Table 4) and cinchona derived squaramides (see ref. 8) appear to be more regioselective than thiourea catalysts, as the 1,4-conjugate addition was exclusively observed.

20 It is likely these processes would have a significant impact on less reactive alkenes and substituted 2-amino thiophenols.

21 (a) W. Yang and D.-M. Du, *Org. Lett.,* 2010, **12**, 5450; (b) H. Y. Bae, S. Some, J. H. Lee, J.-Y. Kim, M. J. Song, S. Lee, Y. J. Zhang and C. E. Song, *Adv. Synth. Catal.,* 2011, **353**, 3196.

22 B. Vakulya, S. Varga, A. Csámpai and T. Soós, *Org. Lett.,* 2005, **7**, 1967.

23 (a) E. Sorrentino and S. J. Connon, *Org. Lett.,* 2016, **18**, 5204; (b) R. Miyaji, K. Asano and S. Matsubara, *J. Am. Chem. Soc.,* 2015, **137**, 6766; (c) W. Wu, L. Min, L. Zhu and C.-S. Lee*, Adv. Synth. Catal.,* 2011, **353**, 1135; (d) R. Miyaji, K. Asano and S. Matsubara, *Org. Lett.,* 2013, **15**, 3658; (e) M. Amere, M.-C. Lasne and J. Rouden, *Org. Lett.,* 2007, **9**, 2621; (f) M S. Manna and S. Mukherjee, *J. Am. Chem. Soc.*, 2015, **137**, 130.

24 (a) M. Pieroni, G. Annunziato, E. Azzali, P. Dessanti, C. Mercurio, G. Meroni, P. Trifiro, P. Vianello, M. Villa, C. Beato, M. Varasi and G. Costantino, *Eur. J. Med. Chem.*, 2015, **92**, 377; (b) J. Zhang, X. Liu and R. Wang, *Chem. Eur. J.*, 2014, **20**, 4911.