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Title: Organocatalytic Asymmetric Sulfa-Michael Addition of 2-Aminothiophenols to Chalcones. First Enantioselective Access to 2,3,4,5-Tetrahydro-1,5-benzothiazepines

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Organocatalytic Asymmetric Sulfa-Michael Addition of 2-Aminothiophenols to Chalcones. First Enantioselective Access to 2,3,4,5-Tetrahydro-1,5-benzothiazepines

Vasco Corti,[a] Patricia Camarero Gonzalez,[a] Julie Febvay,[a] Lorenzo Caruana,[a] Andrea Mazzanti,[a] Mariafrancesca Fochi,*[a] and Luca Bernardi*[a]

Abstract: 1,5-Benzothiazepine frameworks are highly relevant in medicinal chemistry. Reported catalytic asymmetric approaches to these scaffolds have targeted 2,3-dihydro-1,5-benzothiazepin-4-ones, leaving the corresponding amines (2,3,4,5-tetrahydro-1,5-benzo-thiazepines) out of reach. Herein, we present the first entry to these important compounds in enantioenriched form. Our approach is based on the catalytic asymmetric sulfa-Michael addition of 2-aminothiophenols to *trans*-chalcones, followed by intramolecular reductive amination. Both reactions have required a careful study to solve several challenging issues. The resulting optimized two-step protocol afforded a range of 2,3,4,5-tetrahydro-1,5-benzothiazepines as single *trans*-diastereoisomers in moderate to good yields and enantioselectivities.

Introduction

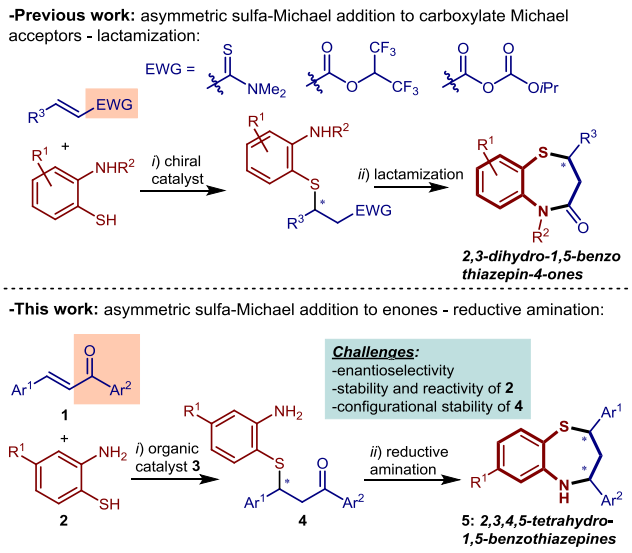
The 1,5-benzothiazepine is a heterocyclic scaffold (highlighted in Scheme 1) commonly found in drugs featuring a variety of pharmacological properties.[1] For example, thiazesim is an antidepressant, while diltiazem is used in the treatment of hypertension and angina. Even if 1,5-benzothiazepines have attracted much attention in the pharmaceutical field since many decades,[1] prompting a variety of synthetic approaches, there is still a high demand for new efficient routes to these compounds in enantioenriched form.[2] The sulfa-Michael addition of 2-aminothiophenols to α,β-unsaturated compounds, followed by cyclization, is one of the most straightforward approaches to this motif. Accordingly, such type of sequential reaction has been recently developed in catalytic asymmetric settings.[3] Carboxylate-based Michael acceptors were used, giving access to optically active 2,3-dihydro-1,5-benzothiazepin-4-ones (Scheme 1, top). In contrast, an enantioselective methodology to access 2,3,4,5-tetrahydro-1,5-benzothiazepines **5**, bearing an amine instead of an amide functionality (Scheme 1, bottom), has not been developed so far.

To fill this gap, we set out to study the catalytic enantioselective sulfa-Michael addition of 2-aminothiophenols **2** to *trans*-chalcones **1** catalyzed by organic catalysts **3**.[4,5] A subsequent reductive amination on adducts **4** gives 2,4-disubstituted 2,3,4,5-tetrahydro-1,5-benzo-thiazepines **5**, hitherto unreported in enantioenriched form (Scheme 1, bottom). As herein presented, the realization of this sequential reaction required solving different challenging issues:

i) the peculiar features of thiophenols **2**, wherein the aniline functionality can give additional H-bond interactions with the bifunctional catalysts typically employed in sulfa-Michael reactions, made in our hands conditions useful for enantioselective additions of simple thiophenols to *trans*-chalcones[5] unsuitable;

ii) the dimerization of **2** to the disulphide, decreasing substantially the yield of the reaction, appeared to be a facile process which had to be avoided;

iii) the susceptibility of adducts **4** to racemization during the reductive amination processes to **5** demanded a careful tuning of reaction conditions in this cyclization step.



Scheme 1. Sequential asymmetric sulfa-Michael – cyclization processes to access 1,5-benzothiazepine derivatives.

Results and Discussion

We began our investigations on the reaction between 2-aminothiophenol **2a** and *trans*-chalcone **1a** (Table 1) using the reaction conditions reported in literature for the enantioselective addition of thiophenols to this substrate, entailing the use of catalyst **3a** (Figure 1), in toluene at room temperature.[5a] Unfortunately, these parameters were not suitable for

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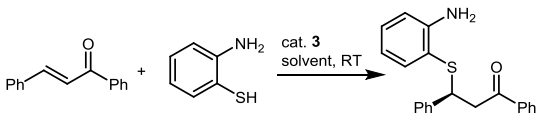
nucleophile **2a** (Table 1, entry 1); therefore we started a thorough optimization of the reaction conditions.[6] A screening (entries 2-7) of other bifunctional organocatalysts **3b-g** featuring H-bond donors flanked by a basic tertiary amine[7] (Figure 1) pointed our attention to catalyst **3d**, a sulphonamide derived from 9-amino(9-deoxy)*epi* cinchonidine,[8] which gave the best enantioselectivity. Then, we tested different solvents in order to evaluate their influence on the reaction (entries 8-12). 1,4-Dioxane was found to be the best candidate. In addition, reducing the catalyst loading from 10 mol% to 5 mol% slightly improved the enantioselectivity (entry 13); further lowering to 1 mol% was instead not practical (entry 14). Despite the good values observed in the first experiment with 5 mol% loading (entry 13), the enantiomeric excess and the conversion of this reaction displayed poor reproducibility. After a thorough investigation, we found that dimerization of nucleophile **2a** to

Table 1. Screening of catalysts **3** and conditions in the test reaction between 2-aminothiophenol **2a** and *trans*-chalcone **1a**. Representative results.[a]



1a **2a** **4a**

Entry	Catalyst **3** [mol %]	Solvent [M]	Conv.[b] [%]	*ee*[c] [%]
1	**3a** [10]	toluene [0.18]	65	32[d]
2	**3b** [10]	toluene [0.18]	62	20[d]
3	**3c** [10]	toluene [0.18]	84	18
4	**3d** [10]	toluene [0.18]	66	70
5	**3e** [10]	toluene [0.18]	50	rac
6	**3f** [10]	toluene [0.18]	64	50
7	**3g** [10]	toluene [0.18]	92	21
8	**3d** [10]	CH_2Cl_2 [0.18]	>99	40
9	**3d** [10]	CH_3CN [0.18]	80	62
10	**3d** [10]	acetone [0.18]	>99	66
11	**3d** [10]	THF [0.18]	50	74
12	**3d** [10]	1,4-dioxane [0.18]	68	80
13	**3d** [5]	1,4-dioxane [0.18]	60	82
14	**3d** [1]	1,4-dioxane [0.18]	46	46
15[e]	**3d** [5]	1,4-dioxane [0.12]	>99	86

[a] Conditions: *trans*-chalcone **1a** (0.10 mmol), catalyst **3** (x mol%), solvent (x M), 2-aminothiophenol **2a** (0.15 mmol), RT, 1-5 h. [b] Determined by ^{1}H NMR after filtration on a plug of silica gel and solvent evaporation. [c] Determined by CSP-HPLC. [d] *ent*-**4a** was obtained as major enantiomer. [e] Reaction performed with degassed 1,4-dioxane, adding nucleophile **2a** as a 1,4-dioxane solution.

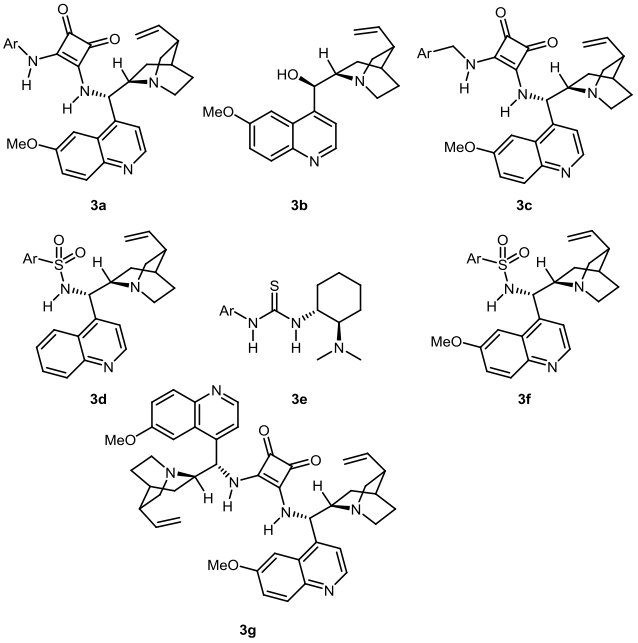
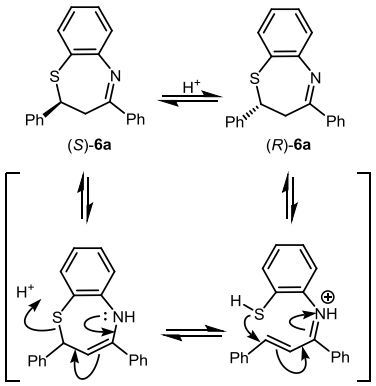


Figure 1. Representative bifunctional catalysts **3a-3g** screened in the reaction. Ar = 3,5-$(CF_3)_2C_6H_3$.

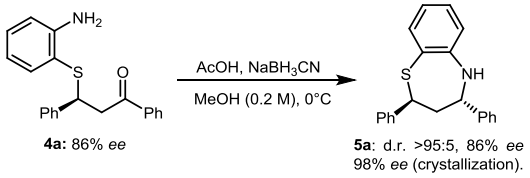
disulphide, occurring to variable extents during the reactions, could strongly affect the conversion values. Besides, we were using a protocol involving addition of neat thiophenol **2a** to the reaction mixture containing catalyst **3d** and *trans*-chalcone **1a**. Probably, depending on the addition rate, thiophenol **2a** did not have time to dilute into the mixture before reaction, compromising in some cases the enantiomeric excess.[9] These issues were overcome by degassing the reaction solvent to exclude oxygen, and by adding thiophenol **2a** in solution. This new protocol (entry 15) not only provided satisfactory results, but proved to be fully reproducible.

We then moved to study the second synthetic step towards 1,5-benzothiazepines **5**: the reductive amination. This apparently simple transformation required instead an in-depth investigation, since the first attempts of cyclizing and reducing **4a** were accompanied by substantial racemization. Indeed, the racemization of imine intermediate **6a** through a retro-sulfa-Michael pathway (Scheme 2) may easily occur in the presence of acids.[10] Acid promoters are normally required to effect reductive aminations.



Scheme 2. Plausible racemization pathway occurring during reductive amination.

After a thorough investigation[11] we found that rather classic reductive amination conditions ($NaBH_3CN$ as reducing agent in combination with AcOH as acidic promoter, in methanol as solvent), could be used successfully in the reaction. At room temperature, they delivered product **5a** as a single diastereoisomer and with only a small deterioration of the enantiomeric excess. Moreover, lowering the temperature to 0 °C avoided any loss of enantioenrichment (Scheme 3).



Scheme 3. Optimized reaction conditions for the reductive amination step.

Product **5a** is a crystalline compound, and could be obtained in nearly enantiopure form after a single crystallization from methanol (Scheme 3). Single crystal X-Ray analysis allowed to determine its absolute configuration, as S,S (Figure 2).[12]

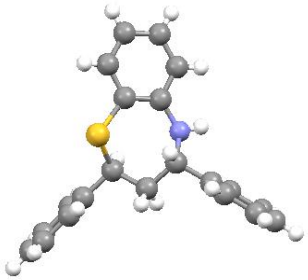
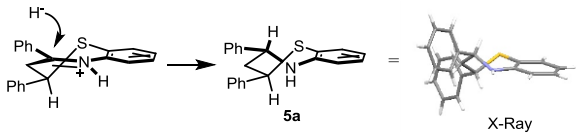


Figure 2. X-Ray structure of compound **5a**.

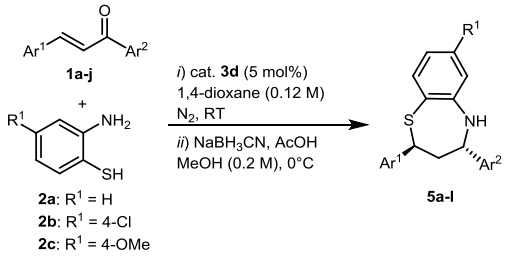
The relative 1,3-*trans* configuration of **5a**, resulting from the reduction of the imine **6a**, is in line with previous literature data describing the synthesis of compounds **5** in racemic form.[13] In the most stable conformation of compound **5a**, a twist-boat,[14] the 1,3-*trans* stereochemistry arranges the two bulky phenyl groups in more favourable pseudo-equatorial positions, as inferred from X-Ray and related literature data.[13c,15] Thus, the full diastereoselectivity of the reduction can be rationalized considering a transition state resembling the twist-boat conformation[14] of product **5a**, and implicating a selective attack of the hydride to the *Re*-face of the iminium ion to place the 4-phenyl ring in a pseudo-equatorial position (Scheme 4).



Scheme 4. Rationalization of the *trans*-selectivity of the reduction.

With optimized conditions for both synthetic steps in hand, we evaluated the reaction scope (Table 2). All *trans*-chalcones

Table 2. Scope of the reaction.[a]



Entry	**1**: Ar^1,Ar^2	**2**	**5**-Yield[b] [%]	*ee*[c] [%]
1	**1a**: Ph, Ph	**2a**	**5a**-80	86
2	**1b**: 4-BrC_6H_4, Ph	**2a**	**5b**-83	80
3	**1c**: 4-MeC_6H_4, Ph	**2a**	**5c**-77	82
4	**1d**: 3-MeC_6H_4, Ph	**2a**	**5d**-85	79
5	**1e**: 2-MeC_6H_4, Ph	**2a**	**5e**-65	55
6	**1f**: 4-MeOC_6H_4, Ph	**2a**	**5f**-79	80
7	**1g**: Ph, 4-MeOC_6H_4	**2a**	**5g**-82	80
8	**1h**: Ph, 4-MeC_6H_4	**2a**	**5h**-75	80
9	**1i**: 4-MeC_6H_4, 4-ClC_6H_4	**2a**	**5i**-71	78
10	**1j**: 1-naphthyl, Ph	**2a**	**5j**-90	71
11	**1a**: Ph, Ph	**2b**	**5k**-70	87
12	**1b**: Ph, Ph	**2c**	**5l**-73	81

[a] Conditions: *i*) *trans*-chalcones **1a-j** (0.20 mmol), 1,4-dioxane (870 µL), catalyst **3d** (5 mol%), 2-aminothiophenols **2a-c** in 1,4-dioxane (0.30 mmol in 800 µL), RT, 5 h, filtration on silica gel, evaporation; *ii*) MeOH (1.0 mL), $NaBH_3CN$ (0.80 mmol), AcOH (0.40 mmol), 0 °C. [b] Yield of isolated product after chromatography on silica gel. A single *trans*-diastereoisomer was obtained in all cases. [c] Determined by CSP-HPLC on the purified products **5**.

1a-j tested, bearing differently substituted aromatic rings, reacted smoothly and afforded the corresponding 2,3,4,5-tetrahydro-1,5-benzothiazepines **5a-j** in moderate to good yields (entries 1-9). Enantiomeric excesses for these compounds were around 80%, with the exception of the 2-methylphenyl and the 1-naphthyl derivatives **1e** and **1j**, (entries 5,10) which gave lower values. These latter results suggest that the steric hindrance in the chalcone substrate **1** has a negative influence on the stereoselectivity of the sulfa-Michael reaction.[16] A very good tolerance to substrate variation was instead found when we tested 2-aminothiophenols **2b** and **2c** with a 4-chloro and a 4-methoxy substituent, which gave the corresponding products **5k** and **5l** with good results (entries 11-12). All reactions gave 1,5-benzothiazepines **5a-l** as single diastereoisomers; their relative and absolute configuration was assigned by analogy with compound **5a**.

Conclusions

To summarize, we have developed a catalytic asymmetric sulfa-Michael addition of 2-aminothiophenols **2** to *trans*-chalcones **1**, which after a highly diastereoselective reductive amination afforded the corresponding 2,3,4,5-tetrahydro-1,5-benzothiazepines **5** in moderate to good yields and enantioselectivities. A careful optimization of both reaction steps was essential to face challenges such as the unsuitability of previously reported protocols for asymmetric additions of simpler thiophenols to *trans*-chalcones **1**, the poor stability of 2-aminothiophenol substrates **2**, and the stereochemical lability of the Michael adducts under the acidic conditions required in the reductive amination step. Being the catalytic asymmetric addition of 2-aminothiophenols **2** to *trans*-chalcones **1** unreported so far, the present protocol represents the first enantioselective access to 2,3,4,5-tetrahydro-1,5-benzothiazepine structures **5**.

Experimental Section

General procedure for the preparation of enantioenriched products 5a-l In a Schlenk tube equipped with a magnetic stirring bar, under N_2 atmosphere, *trans*-chalcones **1a-j** (0.20 mmol) and catalyst **3d** (5.6 mg, 0.010 mmol, 5.0 mol%) were dissolved in degassed 1,4-dioxane (870 µL). A solution of 2-aminothiophenols **2a-c** in degassed 1,4-dioxane (0.30 mmol in 800 µL) was then added. The reaction mixture was stirred until ^{1}H-NMR analysis showed complete conversion (less than 5 h). The mixture was then filtered through a short plug of silica gel, the Schlenk flask washed two times with CH_2Cl_2, these washings filtered through the same plug, the plug flushed with CH_2Cl_2, and all the solvents evaporated under vacuum. The thus obtained sulfa-Michael crude products **4** were re-dissolved in CH_2Cl_2, transferred to a test tube equipped with a magnetic stirring bar and the solvent evaporated by flushing the tube with N_2. 1.0 mL of MeOH was then added to the residue, and the resulting solution cooled to 0 °C with stirring. $NaBH_3CN$ (50 mg, 0.80 mmol) and acetic acid (22.8 µL, 0.40 mmol) were added portion-wise every 2 h until TLC analysis (eluent *n*-hexane/EtOAc 5:1) showed complete consumption of the corresponding sulfa-Michael adducts **4**. Afterwards, the reaction was quenched with 1.0 mL of a saturated Na_2CO_3 aqueous solution, and the mixture extracted three times with CH_2Cl_2. The organic layers were filtered through a short plug of silica gel, the plug flushed with CH_2Cl_2, and the solvents removed under vacuum. Purification by column chromatography on silica gel (*n*-hexane/CH_2Cl_2 1:1) afforded the corresponding 2,3,4,5-tetrahydro-1,5-benzothiazepines **5a-l**. ^{1}H-NMR analysis of the products **5a-l** showed the presence of a single *trans*-diastereoisomer.

Acknowledgements

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Keywords: Amines • Asymmetric Synthesis • Michael Addition • Organocatalysis • Sulfur Heterocycles

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[6] It must be noted that many of the reactions performed during the optimization gave mixtures of the simple addition product **4a** (usually highly predominant) and the corresponding cyclized imine **6a** (see Scheme 2). However, the presence of this latter product did not compromise the determination of the conversion by ^{1}H NMR (calculated on both compounds **4a** and **6a** vs chalcone **1a**), nor of the enantiomeric excess of **4a** by CSP-HPLC.

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[9] This reaction is rather rapid, and we found a decrease of the enantioselectivity with lower dilutions.

[10] For 1,5-benzodiazepine racemization through a retro-aza-Michael pathway, see: K. Horiguchi, E. Yamamoto, K. Saito, M. Yamanaka, T. Akiyama, *Chem. Eur. J.* **2016**, *22*, 8078.

[11] Different "organocatalytic" conditions and catalysts/reagents were investigated, but proved unsuccessful; for details, see the Supporting Information.

[12] CCDC 1497615 contains the supplementary crystallographic data of compound **5a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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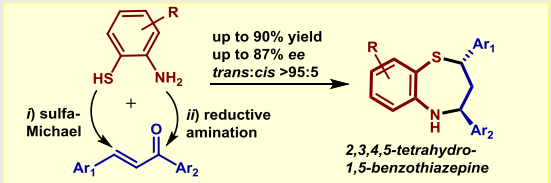
[16] Unfortunately, α,β-unsaturated ketone substrates bearing aliphatic substituents either at the ketone or at the double bond gave worse results in terms of enantioselectivities (0-40% *ee*).

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION



Organocatalysis

Vasco Corti, Patricia Camarero Gonzalez, Julie Febvay, Lorenzo Caruana, Andrea Mazzanti, Mariafrancesca Fochi, Luca Bernardi**

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Organocatalytic Asymmetric Sulfa-Michael Addition of 2-Aminothiophenols to Chalcones. First Enantioselective Access to 2,3,4,5-Tetrahydro-1,5-benzothiazepines

A two-step synthetic methodology delivering 2,3,4,5-tetrahydro-1,5-benzothiazepines in enantioenriched form is presented. The two-step sequence involves an organocatalytic asymmetric sulfa-Michael reaction, followed by a highly diastereoselective reductive amination.