Catalytic Enantioselective Synthesis of Protecting-Group-Free 1,5-Benzothiazepines

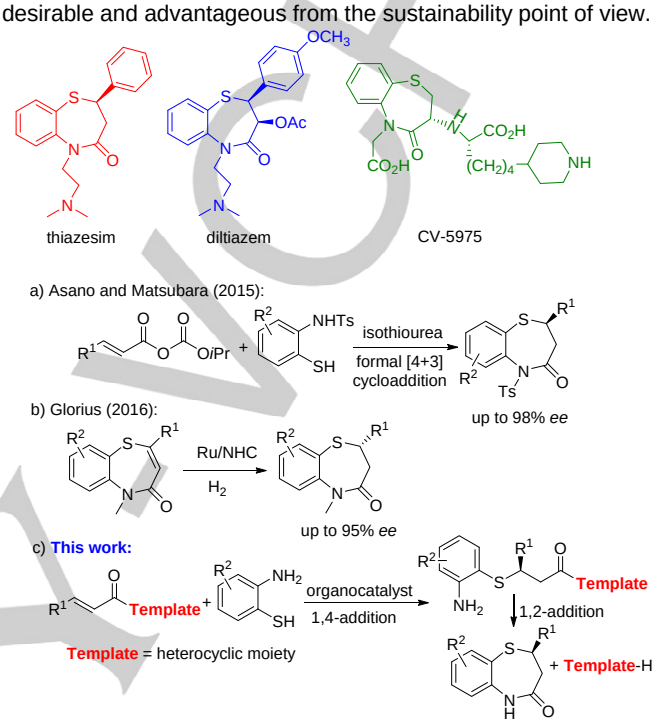
Sara Meninno, Chiara Volpe, and Alessandra Lattanzi*

Abstract: A one-pot enantioselective route to N-unprotected 2,3-dihydro-1,5-benzotiazepinones, via an organocatalysed sulfa-Michael reaction of readily available α,β-unsaturated N-acyl pyrazoles with 2-aminothiophenols followed by silica gel catalysed lactamization, has been developed. The method proceeds under mild conditions at room temperature and it requires only 1 mol% catalyst loading, to give 2-aryl/alkyl-substituted 1,5-benzotiazepines in generally good to excellent yields and enantioselectivities. The process, used for a short synthesis of antidepressant drug (*R*)-(-)-thiazesim, represents a first access to enantioenriched unprotected 1,5-benzotiazepines, useful for rapid derivatization in drug discovery.

Optically active 1,5-benzothiazepines are amongst the most famous drugs in medicinal chemistry,[1] been known and used since the sixties. They are representatively illustrated by the antidepressant agent (*R*)-(-)-thiazesim marketed as its hydrochloride salt Altinil,[2] diltiazem employed for the treatment of antihypertension and angina,[3] and the ACE inhibitor CV-5975 (Scheme 1).[4] Unsurprisingly, a variety of protocols have been developed for the racemic synthesis of these compounds,[5] which are also endowed with antimicrobial, antifungal, anti-HIV, anticancer and antiulcer activities.[1] Concerning their asymmetric synthesis, a limited number of procedures relies on racemate resolution[2a,6] and occasional examples were reported in methodological studies.[7] To date only two catalytic enantioselective approaches to 2,3-dihydro-1,5-benzotiazepinones have been developed. In 2015, Matsubara, Asano and coworkers illustrated a formal [4+3] cycloaddition reaction using a chiral isothiourea catalyst (Scheme 1a).[8] In 2016, Glorius and co-authors devised a different approach based on the enantioselective ruthenium-N-heterocyclic carbene catalysed hydrogenation of heterocyclic vinyl thioethers (Scheme 1b).[9]

One-pot multistep asymmetric procedures are highly attractive tools for the asymmetric synthesis of heterocyclic compounds, including pharmaceuticals.[10] Given the paucity of methods to access optically active 2,3-dihydro-1,5-benzotiazepinones and our interest in developing stereoselective methodologies to prepare heterocyclic compounds,[11] we embarked in a study aimed at the development of a simple asymmetric synthesis of this versatile and relevant class of pharmacophores.

The elegant methods illustrated in Scheme 1, afforded N-substituted-1,5-benzothiazepinones, whose deprotection was necessary to prepare analogs and drugs.[1] Thereby circumventing this additional step, by developing a direct asymmetric methodology to the core scaffold, would be highly desirable and advantageous from the sustainability point of view.



Scheme 1. Asymmetric catalytic routes to 1,5-benzotiazepines.

To this end, the combination of a sulfa-Michael reaction/lactamization sequence, based on readily available reagents, was considered the most expeditious route to achieve this goal (Scheme 1c).[12] We envisioned bifunctional hydrogen-bonding aminocatalysts could promote the sulfa-Michael reaction of heteroatom linked α,β-unsaturated ester equivalents. Indeed, these compounds are good Michael acceptors, amenable to replacement of the heterocyclic moiety by different nucleophiles.[13] To establish this approach, two challenging issues had to be addressed: i) the identification of a suitable α,β-unsaturated ester equivalent able to undergo a regioselective sulfa-Michael reaction by dinucleophilic 2-aminothiophenols; ii) setting up controlled conditions to foster lactamization, while avoiding potential racemization of the adduct.

A preliminary investigation was performed using 5 mol% of Takemoto's catalyst **I** in toluene at room temperature with different α,β-unsaturated surrogate esters and 2-amino thiophenol (see the Supporting Information for optimization table). We were pleased to find that *trans*-α,β-unsaturated N-acylpyrazole **1a** regioselectively afforded product **3a** in good yield and encouraging 52% *ee*, after a prolonged reaction time (Table 1, entry 1). The lactamization step was then studied under different conditions using catalyst **I**. After the disappearance of **1a**, warming the reaction mixture to 40°C helped to speed up the conversion and increase the enantioselectivity (entry 2).

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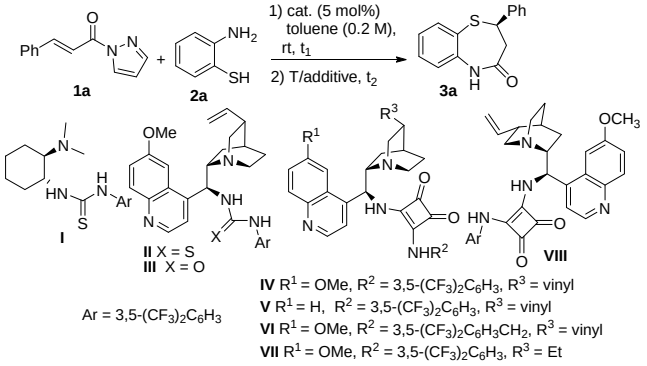
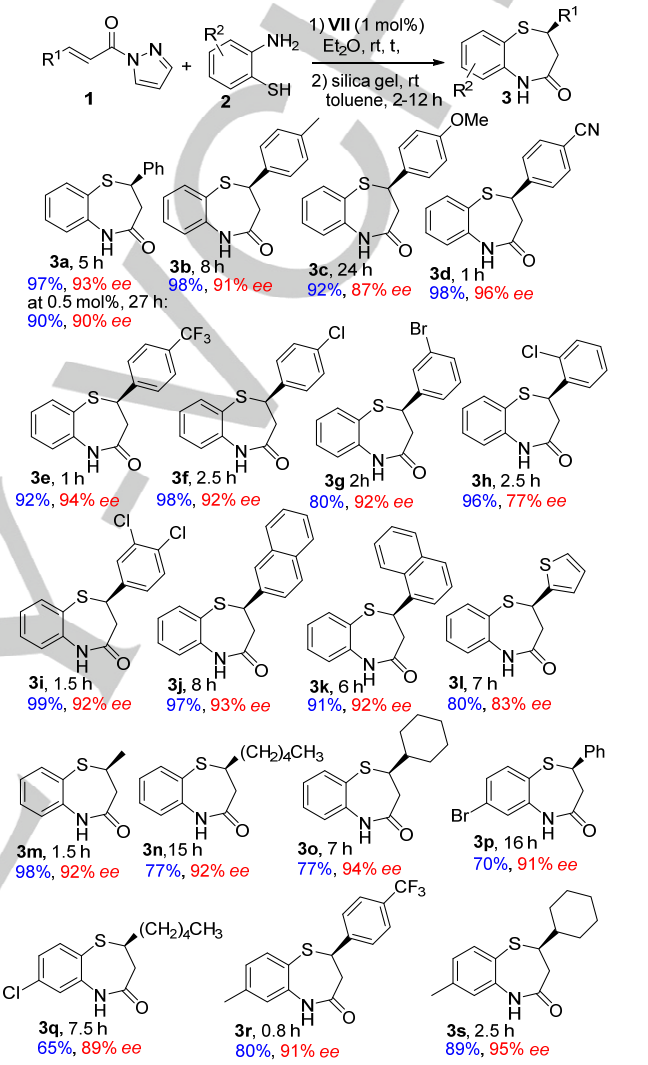
Table 1. Catalyst screening.[a]



Entry	Cat.	T [°C]/Additive	$t_1(t_2)$ [h]	Yield [%][b]	*ee* [%][c]
1	**I**	rt	92	85	52
2	**I**	40°C	14(11)	81	66
3	**I**	rt/silica gel[d]	1.5(4)	82	76
4	**-**	rt	72	30	-
5	**-**	rt/silica gel[d]	5	85	-
6	**II**	rt/silica gel[d]	1.5(4)	85	-61
7	**III**	rt/silica gel[d]	1.5(4)	81	-61
8	**IV**	rt/silica gel[d]	2(4)	80	-81
9	**V**	rt/silica gel[d]	2.5(4)	75	-76
10	**VI**	rt/silica gel[d]	14(4)	95	-64
11	**VII**	rt/silica gel[d]	0.5(4)	97	-80
12	**VIII**	rt/silica gel[d]	4.5(4)	71	66

[a] Unless otherwise noted reactions were conducted with **1a** (0.1 mmol), **2a** (0.15 mmol), cat. (0.005 mmol) in toluene (0.5 mL) under nitrogen. [b] Determined by ^{1}HNMR spectroscopy using 1,3,5-$(MeO)_3C_6H_3$ as an internal standard. [c] Determined by HPLC on a chiral stationary phase. Negative sign indicates the enantiomeric excess for the opposite enantiomer. [d] Silica gel (111 mg) was added.

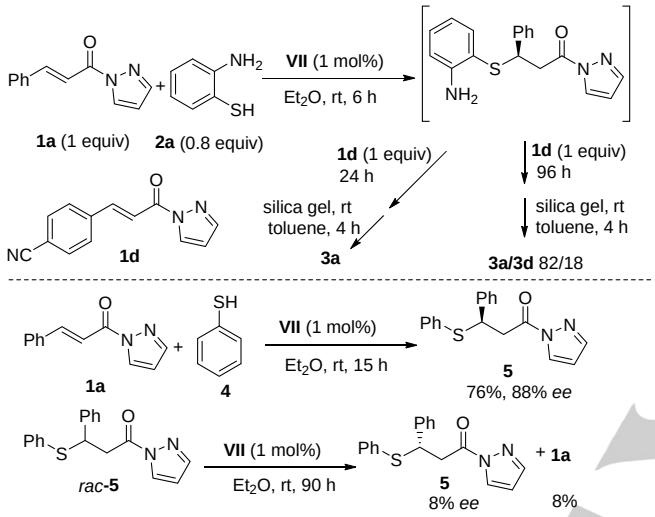
Interestingly, the addition of silica gel at room temperature rapidly yielded **3a** with up to 76% *ee* (entry 3).[14] Background catalysis was next investigated by performing the reaction in absence of catalyst **I** (entries 4 and 5). A modest formation of **3a** was detected after prolonged reaction time (entry 4), justifying a lower *ee* value observed in entry 1, presumably affected by contribution of the racemic pathway. Interestingly, the process was silica gel catalysed, as a convenient way to obtain racemic products **3** (entry 5). However, this finding indicated a controlled timing was necessary for the silica gel addition in the asymmetric version. Cinchona alkaloids-derived thiourea **II** and urea **III**, tested under conditions reported in entry 3 (entries 6 and 7), proved of comparable effficiency, whereas squaramides gave better results (entries 8-12). Pleasingly, hydroquinine-derived squaramide **VII** furnished **3a** in excellent yield and 80% ee after a short overall reaction time (entry 11). Upon solvent and reaction parameters screening (see the Supporting Information for optimization tables), Et_2O was found the best medium where to conduct the first step, using 1 mol% of catalyst **VII** at room temperature. Since the lactamization proceeded faster in toluene, after evaporation of Et_2O at the end of the first step, the crude mixture was charged in toluene with silica gel to complete the process. To our delight, product **3a** was isolated in 97% yield and 93% ee (Scheme 2).



Scheme 2. Substrates scope of the one-pot reaction to 1,5 benzothiazepines. Reaction conditions: **1** (0.3 mmol), **2** (0.39 mmol) and **VII** (0.003 mmol) in Et_2O were stirred at room temperature under nitrogen for the indicated times. After removing Et_2O, toluene (3 mL) and silica gel (335 mg) were added and stirring was maintained for 2-12 h. Yields of isolated products; ee determined by HPLC on a chiral stationary phase. Absolute configuration of (*R*)-**3a** was determined by comparison of the optical rotation with the literature.[7a]

Remarkably, working with 0.5 mol% of the catalyst, guaranteed product formation in high yield and 90% *ee*, at the expense of a longer reaction time (Scheme 2). With the optimized conditions in hand, we explored the scope of the process by using 1 mol% of catalyst **VII** (Scheme 2). Either electron-withdrawing and donating substituents at the *para* and *meta*–positions in Michael acceptors **1** were tolerated, with compounds **3b-g**,**i** being recovered in high to excellent yield and enantioselectivity (88-96% *ee*). As expected, β-aryl α,β-unsaturated N-acyl pyrazoles,

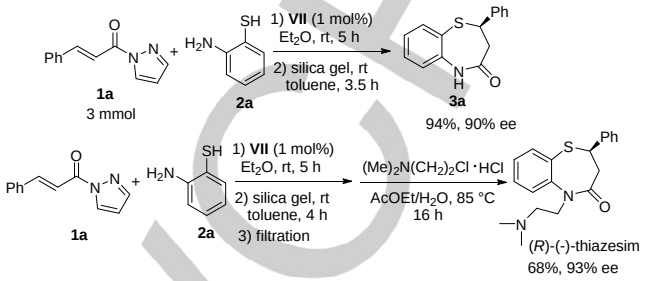
bearing electron-withdrawing groups, underwent faster conversion (**3d-g,i**). The *ortho*-chlorine substituted product **3h** was obtained in 96% yield and with somewhat lower *ee* value. Alkenes **1j-l**, bearing naphthyl and heteroaromatic substituents, were smoothly converted into the products in fairly good to high *ee* values (83-94% *ee*). Pleasingly, the protocol was successfully applied for the synthesis of linear or branched 2-alkyl substituted benzotiazepines **3m-o**, obtained in good to high yield and high enantioselectivity (92-94% *ee*). Other 2-aminothiophenols served as suitable reagents to produce 2-aryl/alkyl derivatives **3p-s** in good yield and high level of enantiocontrol (89-95% *ee*).



Scheme 3. Mechanistic investigations on the reversibility of the sulfa-Michael reaction.

To have a better insight into the reversibility of the first step,[11b,12d] and given the instability displayed by the Michael adduct, **1a** was treated with substoichiometric amount of **2a** under the optimized conditions (Scheme 3). After the disappearance of **2a**, highly reactive alkene **1d** was added and left under stirring for 96 hours, followed by lactamization. ^{1}H-NMR analysis of the crude mixture showed the presence of **3a/3d** in 82/18 ratio. When the same experiment was carried out for 24 hours only compound **3a** was detected. Hence, the catalyst promoted the retro-sulfa Michael reaction at a low rate; however, according to reaction times in Scheme 2, these observations did not affect the results. Additionally, we studied the sulfa-Michael reaction of **1a** using thiophenol **4**. The (*R*)-adduct **5**, was regioselectively obtained in 76% yield and 88% *ee*.[15] To check the reversibility of the sulfa-Michael reaction, racemic **5** was stirred with catalyst **VII** for 90 hours. A small amount of **1a** was detected, whereas (*S*)-**5** was recovered with 8% ee. The retro-sulfa Michael reaction confirmed to be a negligible, but undesirable process, as the catalyst preferentially selected the (*R*)-adduct, eroding the enantioselectivity.

The robustness of the process was probed by carrying out the model reaction at 3 mmol scale, maintaining high yield and enantioselectivity (Scheme 4). The synthetic utility of the methodology was demonstrated in a concise preparation of the antidepressant drug (*R*)-(-)-thiazesim (Scheme 4). The model process was followed by filtration and the crude mixture was directly treated with the alkylating reagent to give the product in 68% overall yield and 93% *ee*. The absolute configuration of thiazesim was assessed by comparison of optical rotation with the literature.[7a,9]



Scheme 4. Scale up of model reaction and concise asymmetric synthesis of antidepressant drug (*R*)-(-)-thiazesim.

In conclusion, we developed the first methodology to prepare a variety of unprotected 1,5-benzothiazepinones in good to excellent yields and enantioselectivities. Notable features of the methodology include: i) low catalyst loading, ii) general applicability, iii) mild reaction conditions, ready availability of the reagents and the organocatalyst. The protocol expedites the entry to optically active 1,5-benzothiazepines useful for bioassay testing. Further applications on the synthesis of related heterocycles will be reported in due course.

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Keywords: asymmetric synthesis• •1,5-benzothiazepine • enoate equivalent • Michael addition • organocatalysis

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[15] Absolute configuration of **5** was determined by chemical derivatization (see the Supporting Information for details).

Layout 2:

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Catalytic Enantioselective Synthesis of Protecting-Group-Free 1,5-Benzothiazepines

Set them free: The first method to access optically active N-unprotected 1,5-benzothiazepinones has been developed under operational mild conditions by using only 1 mol% loading of an organocatalyst and readily available reagents. These important pharmacophores, isolated in good to excellent yields and enantioselectivities (up to 96% ee), are useful for rapid derivatization, as demonstrated in the synthesis of antidepressant drug (*R*)-(-)-thiazesim.