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Enantioselective Synthesis of N-H Free 1,5−Benzothiazepines

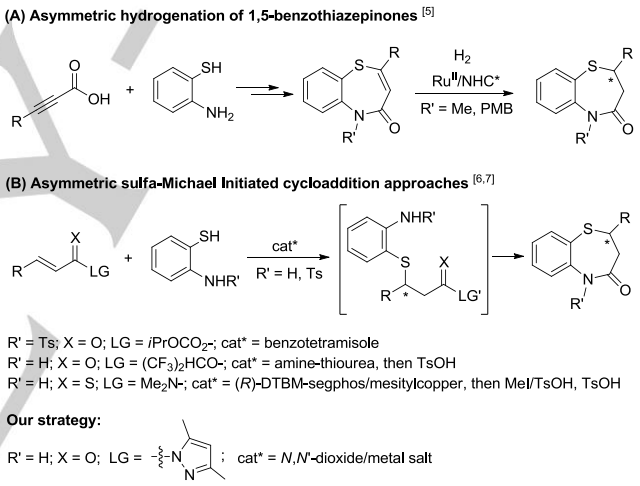
Guojin Wang, Yu Tang, Yu Zhang, Xiaohua Liu*[a], Lili Lin, and Xiaoming Feng*[a]

Dedication ((optional))

Abstract: An enantioselective sulfa-Michael-cyclization reaction was developed for the synthesis of 1,5-benzothiazepines with versatile pharmacological activities. The reaction between 2-aminothiophenol and α,β-unsaturated pyrazoleamides gave a direct access to N-H free 1,5-benzothiazepines in the presence of a chiral *N*,*N*′-dioxide/Yb(OTf)$_3$ complex. Excellent enantioselectivities (up to 96% ee) and high yields (up to 99%) were obtained for a broad range of substrates under mild reaction conditions. This method provided a facile approach to antidepressant drug *R*-(-)-thiazesim.

1,5-Benzothiazepine derivatives containing a seven-membered heterocyclic ring were highlighted as important biologically active scaffolds.[1] For example, diltiazem and clentiazem are in therapeutic use as calcium antagonists, and thiazesim as antidepressant.[2] It is important to establish direct and readily available methods for the enantioselective synthesis of such skeletons to support assay evaluation. Optically active 1,5-benzothiazepines were initially synthesized from resolution of racemic nitrocarboxylic acids with brucine in 1988.[3] Beckmann rearrangement of optically active thiochromanone oximes provided an alternative.[4] Nevertheless, catalytic asymmetric reactions for the enantioselective synthesis of 1,5-benzothiazepine derivatives were realized only recently. A chiral ruthenium(II) NHC complex catalyzed hydrogenation of vinylthioethers, which was synthesized from 2-amino-thiophenol and β-substituted propiolic acid, was reported by the Glorius group to give optically active 1,5-benzothiazepinones (Scheme 1A).[5] Asano and Matsubara utilized a chiral isothiourea accelerated enantioselective net [4+3] cycloaddition through α,β-unsaturated acylammonium intermediates to afford the desired targets (Scheme 1B).[6] These strategies give direct access to 2-substituted 1,5-benzothiazepines, but *N*-protection and deprotection processes are inevitable in order to obtain (*R*)-thiazesim. Although sequential sulfa-Michael addition and cyclization reactions between thiols and α,β-unsaturated carboxylic acid derivatives could give N-H free 1,5-benzothiazepines, but the present methods are substrate-dependent and unusual leaving groups are required (Scheme 1B).[7] We expected to develop a direct and easily available protocol for the asymmetric synthesis of N-H free 1,5-benzothiazepinone derivatives.

α,β-Unsaturated pyrazolamides have been attractive electrophilic conjugate addition acceptors,[8] which indeed have been used for the preparation of five- and six-membered heterocycles.[9] We sought to extend the utility of α,β-unsaturated pyrazolamide to the direct synthesis of seven-membered heterocyclic rings. We hypothesized that N-H free 1,5-benzothiazepines should be accessible via asymmetric sulfa-Michael reaction[7a,10,11] of 2-amino-thiophenol and the release of the pyrazole unit. Herein, we describe the successful execution of chiral *N*,*N*′-dioxide-Yb(III) complex[12] in the enantioselective sulfa-Michael-cyclization, and present the first direct synthesis of optically active N-H free 1,5-benzothiazepine derivatives. This methodology provides the most straightforward process with a broad substrate scope for the asymmetric synthesis of 1,5-benzothiazepines as well as *R*-(-)-thiazesim.



Scheme 1. Catalytic asymmetric reactions accessing to 1,5-benzothiazepines

Critical to the asymmetric sulfa-Michael addition/cyclization of α,β-unsaturated pyrazolamide was the identification of an appropriate chiral Lewis acid catalysts. Initially, different metal salts coordinated with chiral *N*,*N*′-dioxide **L-PiPr$_2$** were evaluated for the reaction between α,β-unsaturated pyrazolamide **1a** and 2-aminobenzenethiol **2** in CH_2Cl_2 at 35 °C (Table 1, entries 1–2). It was established that chiral **L-PiPr$_2$**/Yb(OTf)$_3$ gave better yield and enantioselectivity than **L-PiPr$_2$**/Gd(OTf)$_3$ complex, resulting in the desired product 1,5-benzothiazepines **3a** in 99% yield with 77% ee. Furthermore, investigation of the subunits of chiral *N*,*N*′-dioxide revealed that *L*-ramipril derived **L-RaPr$_2$** provided sharply enhanced enantioselectivity (95% ee), albeit the yield dropped a little (entry 4). The use of **L-PrPr$_2$**/Yb(OTf)$_3$ catalyst afforded the product **3a** in a moderte and reversed enantioselectivity (entry 3). The reaction at air atmosphere slightly deteriorated the outcomes (entry 5). It was noteworthy that the sulfa-Michael addition intermediate **4a** was detected in low less than 10% isolated yield, and none of the byproduct **5a**

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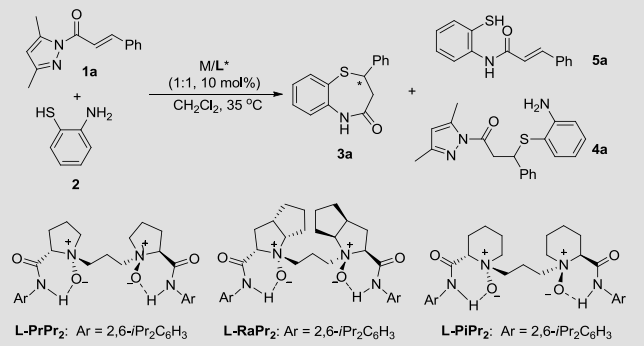
Table 1. Optimization of the reaction conditions[a]



Entry	Metal salt	L	Yield of **3a** (%)[b]	Ee of **3a** (%)[c]
1	$Gd(OTf)_3$	**L-PiPr$_2$**	55	61 (*R*)
2	$Yb(OTf)_3$	**L-PiPr$_2$**	99	77 (*R*)
3	$Yb(OTf)_3$	**L-PrPr$_2$**	78	50 (*S*)
4	$Yb(OTf)_3$	**L-RaPr$_2$**	86	95 (*R*)
5[d]	$Yb(OTf)_3$	**L-RaPr$_2$**	78	91 (*R*)

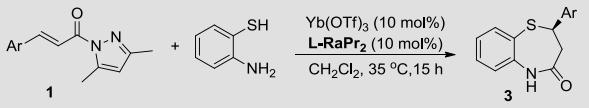
[a] Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol), **2** (1.1 equiv), and **L**-metal salt (1:1, 10 mol%) in CH_2Cl_2 (1.0 mL) under nitrogen at 35 °C for 15 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] At air atmosphere.

was observed in these cases. Therefore, the optimized conditions entailed the use of **L-RaPr$_2$**–$Yb(OTf)_3$ as the catalyst in CH_2Cl_2 at 35 °C (entry 4).

With the optimized conditions established, a series of β-aryl-substituted α,β-unsaturated pyrazolamides were explored. As shown in Table 2, this protocol is useful with a range of Michael acceptors (**3a**–**3m**, 60–98% yields, and 90–95% ee; entries 1–13). The yield of the reaction is relatively affected by the electronic nature of the substituent on aryl group, with substrates possessing electron donating functionalities demonstrating reduced reactivity. In respect of the enantioselectivities, neither the steric hindrance nor the electronic nature of the substituents had an obvious influence. In addition, 2-naphthyl and heteroaryl containing α,β-unsaturated pyrazolamides were also suitable substrates, giving the desired products **3n**–**3p** in 70–84% yields with 81–94% ee (entries 14–16).

We sequently sought to investigate the scope of the β-alkyl substituted α,β-unsaturated pyrazolamides. The results were listed in Table 3. Gratifyingly, not only the linear but also the branched alkyl substituents could be compatible, thus forming the 1,5-benzothiazepines **3q**−**3v** in good to excellent yields (76−94%) with 82−96% ee (entries 1–6). Even *n*-decanyl substitued pyrazolamide was found to be suitable (entry 6). β-Alkyl pyrazolamides bearing three-, four-, five-, and six-menmbered rings, could be successfully utilized, providing the perfect results (99% yields and 89–96% ee; entries 11–14). Meanwhile, ethoxyl- and ester-substituted ones could also afford the corresponding products **3y** and **3z** in 92% and 65% yields with 80% and 91% ee, respectively (entries 9 and 10). Interestingly, 2,4-dien-1-amides were also suitable in this catalytic system, generating the sole 1,4-addition product **3w** and **3x** in moderate yields (55% and 60%, respectively) and

Table 2. Scope for β-aryl substituted α,β-unsaturated pyrazolamides [a]



Entry	Ar	**3**	Yield (%)[b]	ee (%)[c]
1[d]	Ph	**3a**	86	95 (*R*)
2	4-ClC_6H_4	**3b**	98	93
3	4-BrC_6H_4	**3c**	80	93
4	4-FC_6H_4	**3d**	92	92
5	3-BrC_6H_4	**3e**	71	91
6	2-BrC_6H_4	**3f**	95	94
7	4-MeC_6H_4	**3g**	82	93
8	3-MeC_6H_4	**3h**	90	92
9	4-$MeOC_6H_4$	**3i**	78	90
10	2-$MeOC_6H_4$	**3j**	78	93
11	4-$CF_3C_6H_4$	**3k**	62	92
12	3,4-$Cl_2C_6H_3$	**3l**	62	90
13	3,4-$(MeO)_2C_6H_3$	**3m**	75	90
14	2-naphthyl	**3n**	84	94
15	2-thienyl	**3o**	81	88
16	2-furyl	**3p**	70	81

[a] Unless otherwise noted, all reactions were carried out with **1** (0.1 mmol), **2** (1.1 equiv), and **L-RaPr$_2$**-$Yb(OTf)_3$ (1:1, 10 mol%) in CH_2Cl_2 (1.0 mL) under nitrogen at 35 °C for 15 h. [b] Yield of the isolated product. [c] Determined by chiral HPLC analysis. [d] The absolute configuration of **3a** was determined to be *R* by comparing the optical rotation with the literature value.[7b]

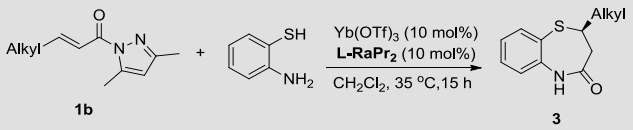
good enantioselectivities (86% ee; Table 2, entries 7 and 8).

With the scope of the asymmetric reaction shown to be broa across a range of 1,5-benzothiazepines, we next turned to th synthetic application of this methodology. As shown in Schem 2, when the reaction was scaled-up to 5 mmol of α,β unsaturated pyrazolamide **1a** in the presence of 7.5 mol% of th **L-RaPr$_2$**-$Yb(OTf)_3$ complex, the 1,5-benzothiazepine **3a** wa given in 72% yield and 90% ee. Then after recrystallization, th optical purity of **3a** could be improved to 95% ee. Subsequer alkylation reaction resulted in the formation of *R*-(-)-thiazesim i 93% yield with maintained ee.

Operando IR experiments were performed to probe into the reaction process between α,β-unsaturated pyrazolamide **1a** and 2-aminobenzenethiol **2**. As shown in Figure 1, the peaks at 1682, and 1726 cm^{-1} are related to the final product **3a** and the intermediate **4a** of the sulfa-Michael addition. Surprisingly, sulfa-Michael adduct **4a** gets to the maximum within 20 mins, then gradually decreased in intensity. Afterwards, the peak related to the cyclic product **3a** increased gradually (for details, see the

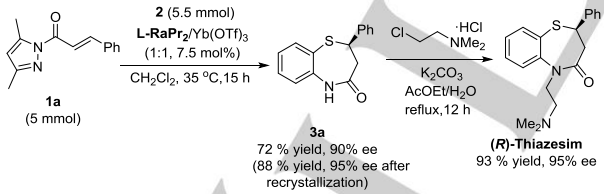
Supporting Information). These phenomena indicate that the catalyst is extremely efficient for the asymmetric sulfa-Michael reaction, and the cyclization process is the rate-determining step. The reaction did not occur via an intramolecular sulfa-Michael reaction of **5a**.

Table 3. Scope for β-alkyl substituted α,β-unsaturated pyrazolamides [a]



Entry	Alkyl	3	Yield (%)[b]	ee (%)[c]
1[d]	CH_3	**3q**	76	87
2	*n*-C_3H_7	**3r**	88	94
3	*n*-C_4H_9	**3s**	91	96
4	*n*-C_7H_{15}	**3t**	87	86
5	*n*-$C_{10}H_{21}$	**3u**	94	82
6	*i*-butyl	**3v**	83	94
7		**3w**	55	86
8		**3x**	60	86
9	EtOOC	**3y**	65	91
10	EtO	**3z**	92	80
11	cyclohexyl	**3aa**	99	96
12	cyclopentyl	**3ab**	99	96
13	cyclobutyl	**3ac**	99	93
14	cyclopropyl	**3ad**	99	89

[a–c] Reaction conditions were the same as these in Table 2.



Scheme 2. Scaled-up version for the synthesis of (*R*)-thiazesim

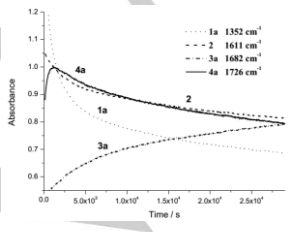
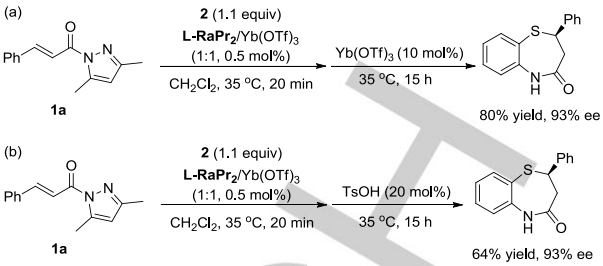


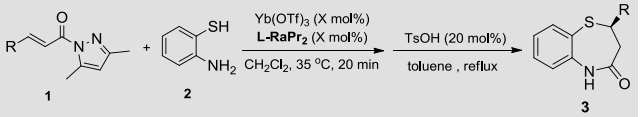
Figure 1. Operando IR experiments.



Scheme 3. Control experiments.

We next carried out control experiments to confirm the enantiocontrol of the catalyst at lower loading (Scheme 3). The asymmetric sulfa-Michael reaction performed well at 0.5 mol% of **L-RaPr$_2$**-Yb(OTf)$_3$ within 20 min (**4a**: 64% yield and 93% ee). If 10 mol% Yb(OTf)$_3$ was added afterwards, the 1,5-benzothiazepines **3a** was isolated in 80% yield and 93% ee (Scheme 3, eq a). Using inexpensive *p*-toluenesulfonic acid to promote the cyclization in one pot, a yield of 64% with 93% ee was found (Scheme 3b). It provides an alternative one-pot and sequential process for the efficient synthesis of the target product.

Table 4. Sequential one-pot synthesis of 1,5-benzothiazepines[a]



entry	R	x (mol %)	3	Yield (%)[b]	Ee (%)[c]
1	Ph	0.5	**3a**	64	93
2	4-ClC_6H_4	0.5	**3b**	70	90
3	2-BrC_6H_4	0.5	**3f**	65	91
4	4-MeC_6H_4	1.0	**3g**	52	86
5	2-MeOC_6H_4	1.0	**3j**	50	85
6	*n*-C_3H_7	0.2	**3r**	75	93

[a] Unless otherwise noted, all reactions were carried out with **L-RaPr$_2$**/Yb(OTf)$_3$ (1:1), **1a** (0.2 mmol), **2** (1.1 equiv) in CH_2Cl_2 (2.0 mL) at 35 °C for 20 min, then solvent was removed, toluene (2.0 mL) and *p*-toluenesulfonic acid was added in one-pot. [b] Isolated yield. [c] Determined by chiral HPLC.

The sequential one-pot procedure is also suitable for the synthesis of other enantiomerically enriched 1,5-benzothiazepines at low loading of the chiral catalyst (0.2–1 mol%) (Table 4). It is not a surprise that the two transformations worked well for substrates **1** bearing electron-donating and electron-withdrawing functionalized aryl substituents and alkyl substituent, and the corresponding 1,5-benzothiazepines were formed in moderate yields (50–75%) with good enantioselectivities (85–93% ee). This process can significantly reduce the cost for the synthesis of thiazesim.

In summary, we introduced an facial approach for efficient catalytic enantioselective synthesis of optically active N-H free 2,3-dihydro-1,5-benzothiazepinones. The direct and sequential sulfa-Michael addition/cyclization procedures resulted in excellent enantioselectivities for a broad range of substrates.

Furthermore, the reactions were applied to enable the concise synthesis of chiral drug (*R*)-thiazesim. Easily available chiral catalyst and substrates, mild reaction conditions, and simple procedure made this new strategy attractive. Further studies on the asymmetric synthesis of other functionalized 1,5-benzothiazepinone derivatives and others with biological activities are underway.

Experimental Section

General procedure for the direct catalytic asymmetric sulfa-Michael addition/cyclization reaction: A mixture of $Yb(OTf)_3$ (10 mol%), **L-RaPr$_2$** (10 mol%) and α,β-unsaturated pyrazolamide **1** (0.1 mmol) was stirred in CH_2Cl_2 (1.0 mL) at room temperature in N_2 for 30 min. Then, 2-aminobenzenethiol **2** (1.1 equiv) was added, and the mixture continued stirring for 15 h at 35 °C. Next, directly purification by flash chromatography on silica gel (petroleum ether/ethyl acetate = 2/1) afforded the desired product **3a** (86% yield, 95% ee).

Acknowledgements ((optional))

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Keywords: asymmetric catalysis • 1,5-benzothiazepine • Lewis acid catalysis • sulfa-Michael reaction • α,β-unsaturated pyrazolamide

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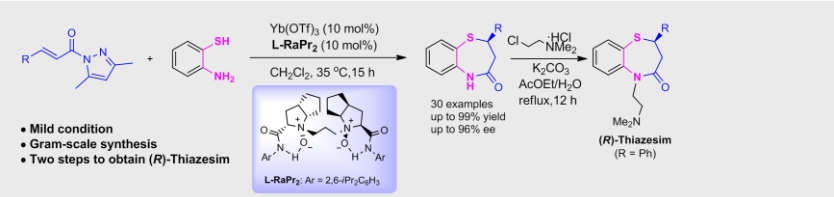

An enantioselective sulfa-Michael-cyclization reaction was developed for the synthesis of 1,5-benzothiazepines with versatile pharmacological activities. Excellent enantioselectivities (up to 96% ee) and high yields (up to 99%) were obtained for a broad range of substrates under mild reaction conditions. Furthermore, the reactions were applied to enable the concise synthesis of chiral drug (*R*)-thiazesim.

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