Synthetic Methods

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Catalytic Asymmetric Conjugate Addition of Thiols to α,β-Unsaturated Thioamides: Expeditious Access to Enantioenriched 1,5-Benzothiazepines**

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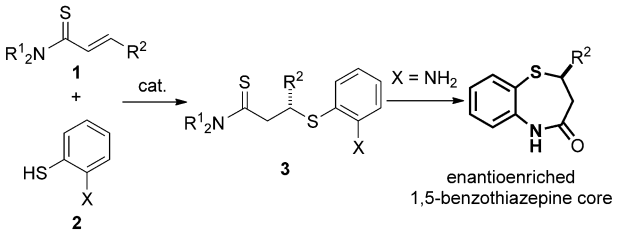
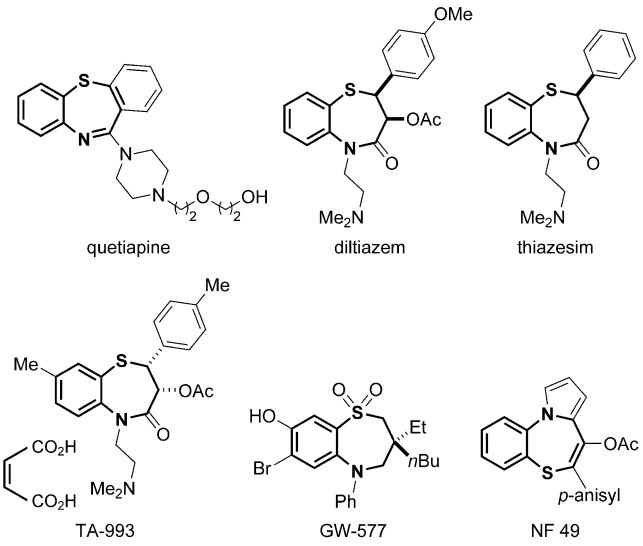
Conjugate addition offers a general strategy for site-specific reactions at carbon–carbon double bonds and is frequently used in organic synthesis. Recent advances in this field have rendered the transformation viable in both a catalytic and asymmetric manner. Although a wide variety of carbon and heteroatom nucleophiles are used in this process,[1–5] the range of electrophiles used has been mostly limited to highly electrophilic conjugate addition acceptors, such as enones, enals, and nitroolefins. α,β-Unsaturated carboxylic acid derivatives exhibit inherently lower electrophilicity at the β-carbon atom and are thus less-common substrates in catalytic asymmetric conjugate addition reactions. We recently found that soft Lewis acids enhance the electrophilicity of α,β-unsaturated thioamides **1**, thus making them amenable to conjugate addition with in situ generated carbon nucleophiles.[6] To expand the scope of conjugate additions using a thioamide electrophiles, we envisioned that the use of a soft Lewis basic heteroatom nucleophile would preferentially produce an electrophile and nucleophile assembly in an asymmetric environment at the transition state, thereby affording the enantioenriched conjugate-addition product. Herein, we report a catalytic asymmetric conjugate addition (sulfa-Michael reaction) of thiols **2**, as a soft nucleophile, to α,β-unsaturated thioamides **1** (Scheme 1).[5,7,8] Optically active sulfides have a wide range of applications in chemistry and biology as chiral auxiliaries, ligands for asymmetric catalysis, and biologically active compounds.[9] In particular, the 1,5-benzothiazepine skeleton is an important structure that is found in various pharmaceuticals and its efficient construction is of considerable interest (Scheme 2).[10,11] We envisioned that a conjugate addition reaction that involves the use of thioamides, and is compatible with an amino moiety, could be applied in the efficient synthesis of a 1,5-benzothiazepine core bearing a stereogenic center.



Scheme 1. Catalytic asymmetric conjugate addition of thiols **2** to α,β-unsaturated thioamides **1** and expeditious access to 1,5-benzothiazepines.



Scheme 2. Therapeutics, therapeutic candidates, and biological tools bearing a 1,5-benzothiazepine core.[11]

Our previous investigations revealed that a mesitylcopper/chiral bisphosphine catalyst forms an active copper nucleophile with the liberation of mesitylene.[6b,d] An analogous catalytic cycle can be delineated for the conjugate addition of thiols **2** (Scheme 3). As the initial entry to the catalytic cycle, proton exchange with mesitylcopper and **2** would produce copper thiolate **4**, which activates the thioamide functionality as a soft Lewis acid to enable an enantioselective C–S bond formation to afford **5**. The intermediary copper thioamide enolate **5** serves as a soft Lewis acid/hard Brønsted base cooperative catalyst to promote proton exchange with thiol **2** to regenerate copper thiolate **4**.[12] Mesitylcopper/(*R*)-DTBM-segphos (DTBM = 3,5-di-*tert*-butyl-4-methoxy) was quickly found to be a suitable precatalyst for the conjugate addition reaction of α,β-

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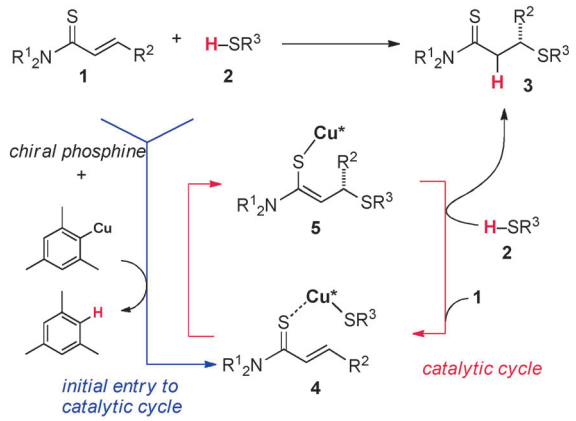
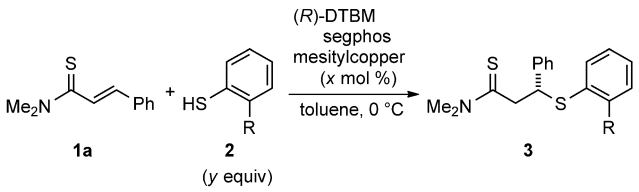


Cu*: Cu/chiral bisphosphine complex

Scheme 3. Designed catalytic cycle using mesitylcopper/bisphosphine precatalyst.

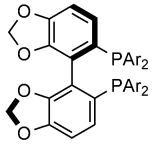
unsaturated thioamides **1a** and thiophenol (**2a**); the corresponding product **3aa** was obtained in high yield and enantioselectivity (Table 1, entry 1). However, the use of 2-aminothiophenol (**2b**) as a nucleophile presented a challenge, as both the amine and thiol functionalities are potentially nucleophilic and the presence of the acidic N–H protons could compromise the proton transfer catalysis. Moreover, we hypothesized that an amine functionality would decrease the reactivity of the copper thiolate as a result of the formation of a stable complex **6** (Scheme 3). Fortunately, **2b** served as suitable sulfur nucleophile and there was no detrimental

Table 1: Initial screening.[a]



Entry	x	y	R		t [h]	Product	Yield[b] [%]	ee [%]
1	3	2	H	**2a**	24	**3aa**	quant.	98
2	3	2	NH_2	**2b**	6	**3ab**	quant.	98
3	3	1.2	NH_2	**2b**	24	**3ab**	quant.	98
4	1	1.2	NH_2	**2b**	48	**3ab**	quant.	98
5[c]	0.25	1.2	NH_2	**2b**	40	**3ab**	82[d]	>99

[a] Reactions were run at a 0.5 M concentration. [b] Determined by ^{1}H NMR analysis. [c] 1.0 g of **1a** was used. [d] Yield of the isolated product recovered by filtration after adding *n*-hexane to the reaction mixture.



Ar = 3,5-(*t*Bu)$_2$-4-MeOC$_6$H$_2$
(*R*)-DTBM-segphos

effect to the reactivity in the presence of the amine group (Table 1, entry 2).[13] The amount of **2b** and the catalyst loading could be reduced to 1.2 equivalents and 0.25 mol%, respectively, without any loss of enantioselectivity (Table 1, entries 3–5). The reaction could be carried out on a 1 g scale and an aqueous work-up was avoided by the addition of *n*-hexane to the reaction mixture to form a suspension that was then filtered; the recovered solid product had an enriched *ee* value of up to >99% *ee* (Table 1, entry 5).[14]

We then focused on the scope of this conjugate addition protocol (Table 2). Irrespective of the electronic nature of the *ortho* substituent of the thiophenols, the corresponding conjugate addition products were obtained with high enantioselectivity (Table 2, entries 1–6). An *ortho*-hydroxy group had no negative effects on reactivity and enantioselectivity

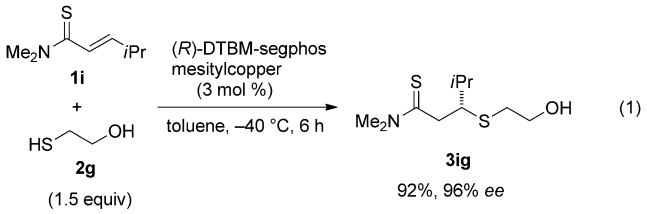
Table 2: Substrate generality.[a]

Entry	Thioamide (**1**) R^1		Thiophenol (**2**) X		Product (**3**)	T [°C]	t [h]	Yield[b] [%]	ee [%]
1	Ph	**1a**	H	**2a**	**3aa**	0	24	93	94
2	Ph	**1a**	NH_2	**2b**	**3ab**	0	6	88	98
3	Ph	**1a**	OH	**2c**	**3ac**	0	20	92	93
4	Ph	**1a**	Me	**2d**	**3ad**	0	72	83	93
5	Ph	**1a**	OMe	**2e**	**3ae**	0	96	64	97
6	Ph	**1a**	Cl	**2f**	**3af**	0	96	47	95
7	4-MeC_6H_4	**1b**	NH_2	**2b**	**3bb**	0	24	85	98
8	4-ClC_6H_4	**1c**	NH_2	**2b**	**3cb**	0	6	86	98
9	4-MeOC_6H_4	**1d**	NH_2	**2b**	**3db**	0	20	90	98
10[c]	2-furyl	**1e**	NH_2	**2b**	**3eb**	0	24	81	97
11	2-thienyl	**1f**	NH_2	**2b**	**3fb**	0	24	78	97
12	(*E*)-CH=CHCH$_3$	**1g**	NH_2	**2b**	**3gb**	0	24	71	95
13	Me	**1h**	NH_2	**2b**	**3hb**	0	1	85	88
14	Me	**1h**	NH_2	**2b**	**3hb**	−40	2	90	97
15	*i*Pr	**1i**	NH_2	**2b**	**3ib**	−40	6	93	99

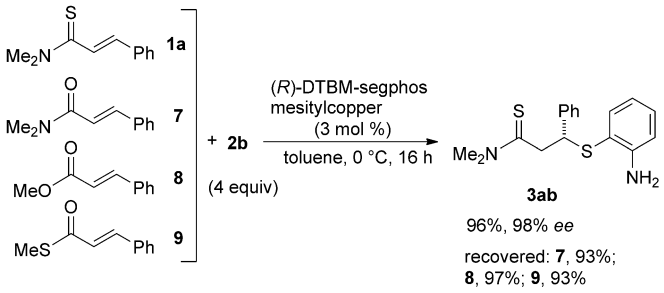
[a] **1**: 0.4 mmol; **2**: 0.6 mmol. [b] Yield of the isolated product. [c] **1e**: 1.0 mmol; **2b**: 1.5 mmol.

(Table 2, entry 2). The reactions of α,β-unsaturated thioamides **1b–f**, which bear β-aryl or β-heteroaryl substituents, produced the products with high enantioselectivity and were accelerated by the presence of an electron-withdrawing substituent on the aryl ring (Table 2, entries 7–11). The reaction of diene-conjugated thioamide **1g** led to the exclusive formation of the 1,4-conjugate addition product (Table 2, entry 12). β-Alkyl (Me) substituted thioamide exhibited much higher reactivity, with the reaction reaching full conversion after 1 h at 0°C, albeit with lower enantioselectivity (Table 2, entry 13). Even at −40°C the reaction proceeded rapidly, and the enantioselectivity was improved to 97% *ee* (Table 2, entry 14). These modified reaction conditions were applied to thioamides having a β-isopropyl substituent to give the desired product with high enantiose-

lectivity (Table 2, entry 15). The catalytic system was also applicable to a functionalized alkylthiol; the reaction of α,β-unsaturated thioamide **1i** and 2-mercaptoethanol (**2g**) proceeded smoothly at −40 °C without protection of the hydroxy group, to afford the corresponding product **3ig** with high enantioselectivity [Eq. (1)].



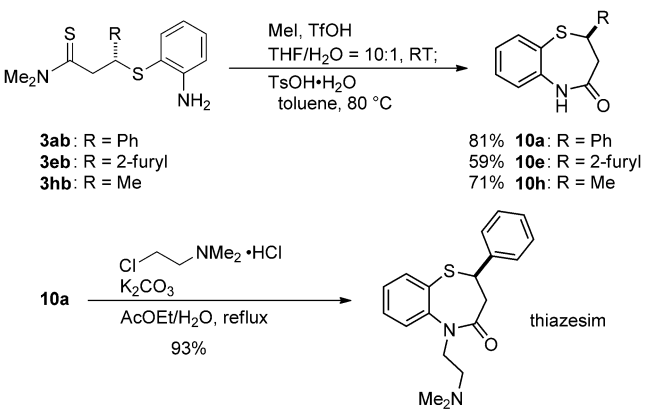
The present conjugate addition reaction is highly chemoselective. A competition reaction of α,β-unsaturated carboxylic acid derivatives, thioamide **1a**, amide **7**, ester **8**, and thioester **9**, with 2-aminothiophenol resulted in the exclusive formation of conjugate addition product **3ab** with recovery of unreacted **7**–**9** (Scheme 4). This result is presumably due to the specific activation of the thioamide functionality in soft Lewis acidic copper thiolate **4** to form the favorable six-membered transition state (Scheme 3).



Scheme 4. Competitive reaction with α,β-unsaturated carboxylic acid derivatives.

Notably, the product obtained from 2-aminothiophenol (**2b**) can be transformed into the corresponding 1,5-benzothiazepin-4(5*H*)-ones (Scheme 5).[10,15] Chemoselective methylation of the thioamide functionality by MeI in THF/H_2O (10:1) under acidic conditions gave a transient thioester, and subsequent heating with a catalytic amount of TsOH·H_2O in toluene at 80 °C furnished the corresponding 1,5-benzothiazepin-4(5*H*)-ones.[16] This procedure was effective for β-aryl, β-heteroaryl, and β-alkyl substituted substrates **3ab**, **3eb**, and **3hb**. Product **10a** was further transformed into thiazesim, an antidepressant agent.[17–20]

In conclusion, we have developed a catalytic asymmetric conjugate addition of thiols to α,β-unsaturated thioamides. The reaction was performed by mixing a commercially available mesitylcopper and (*R*)-DTBM-segphos precatalyst with the substrates, and work-up by filtration offers operational simplicity. The compatibility of the reaction with a free amino group and a suitable thioamide allowed for expeditious access to the 1,5-benzothiazepine skeleton.



Scheme 5. Transformation of the product into 1,5-benzothiazepin-4-ones and the enantioselective synthesis of thiazesim. Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

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[14] The absolute configuration of the product was determined after converting into the reported compounds. See the Supporting Information for details.

[15] For the construction of enantioenriched 1,5-benzothiazepin-4(5*H*)-one from catalytic asymmetric protonation coupled with the conjugate addition of 2-aminothiophenol, see Ref. [8e].

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Communications

Synthetic Methods

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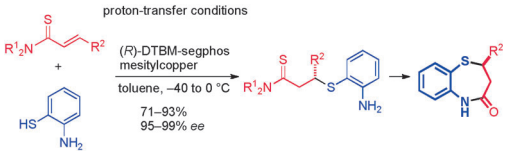
Catalytic Asymmetric Conjugate Addition of Thiols to α,β-Unsaturated Thioamides: Expeditious Access to Enantioenriched 1,5-Benzothiazepines



Softly does it: The title reaction proceeded under proton transfer conditions with a catalyst prepared from commercially available reagents to afford the desired product in high enantioselectivity. The reaction was compatible with a free amino group, thus allowing for expeditious access to enantiomerically enriched 1,5-benzothiazepines, which are important chemical entities in medicinal chemistry.