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Cascade Michael−Aldol Reactions Promoted by Hydrogen Bonding Mediated Catalysis

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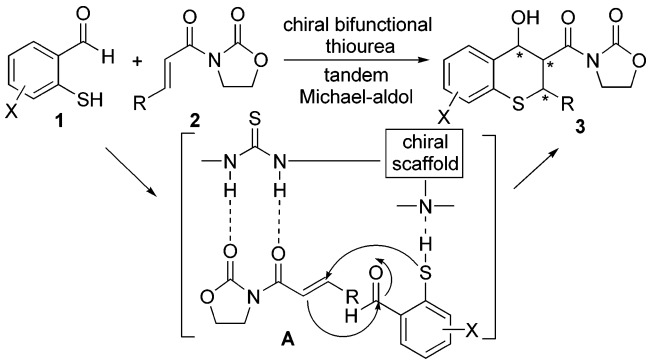
The development of new synthetic strategies for the efficient construction of complex molecules containing multiple stereogenic centers is an important goal of research carried out in both academic and industrial laboratories.[1] Tandem reactions serve as a powerful tool for the rapid and efficient assembly of complex structures from simple starting materials and with minimized production of wastes.[2] Organocatalytic enantioselective tandem processes are even more appealing because of their operational simplicity and environmental friendliness.[3−5] In this communication, we disclose a new organocatalyzed enantioselective cascade Michael−aldol reaction that generates diverse, structurally and stereochemically complex benzothiopyrans[6] in a highly concise fashion. The notable features of the process include (1) the tandem reactions efficiently catalyzed by a chiral cinchona alkaloid thiourea via hydrogen bonding mediated catalysis using as low as 1 mol % of catalyst loading in high yields (75−97%); (2) the generation of three new stereogenic centers with high enantio- (91−99% ee) and diastereoselectivities (>20:1 dr) in a one-pot transformation.

Recently, we uncovered a diarylprolinol silyl ether organocatalyzed tandem Michael−aldol reaction of α,β-unsaturated aldehydes with 2-mercaptobenzaldehydes that affords chiral thiochromenes.[7] It is noted that the initially formed Michael−aldol products undergo spontaneous dehydration, giving products that contain only one new chiral center. The process is driven by formation of a reactive iminium intermediate through reaction of the diarylprolinol silyl ether with the α,β-unsaturated substrate, a strategy that has been intensively explored.[5] We envisioned that change of the aldehyde group in the α,β-unsaturated system to a carboxylic acid derivative might enable the process to be activated by hydrogen bonding rather than covalent interactions. This could prevent the undesirable dehydration process. α,β-Unsaturated oxazolidinones **2** (Scheme 1) were selected as Michael receptors. Typically, Lewis acid catalysts are used to conjugate addition reactions of these substrates.[8] We hypothesized that a thiourea would be capable of forming two hydrogen bonds with the oxazolidinone **2** (**A** in Figure 1) and, as such, should enhance conjugate additions of nucleophiles.[9,10] In addition, an ideal catalyst for the tandem Michael−aldol reaction should also possess an amine group as a general base to enhance the nucleophilicity of the 2-mercaptobenzaldehyde substrate.[10c] Thus, we felt that a chiral bifunctional amine thiourea, capable of participating in multiple hydrogen bonding interactions with both substrates, would be an ideal promoter for a newly designed asymmetric Michael−aldol reaction.

To explore the proposed catalytic tandem Michael−aldol process, reactions of 2-mercaptobenzaldehyde **1a** with α,β-unsaturated oxazolidinone **2a** were performed in toluene at room temperature in the presence of an organocatalyst. Four chiral bifunctional thioureas **I**−**IV** and the cinchona alkaloid **V** were screened (Figure 1).[9,10] The results of these reactions, summarized in Table 1, demonstrate that the tandem thio-Michael−aldol reaction proceeds smoothly to yield the desired benzothiopyran **3a** in high yields

Scheme 1. Organocatalyzed Tandem Enantioselective Thio-Michael−Aldol Reactions



(85−93%, entries 1−3, 7, and 8) and with excellent diastereoselectivities (>20:1 for all cases). However, the enantioselectivities varied greatly depending on the organocatalyst used. For example, a 0% ee was observed when thiourea **I** (entry 1) was used, and moderate enantiomeric excesses were seen in the cases of **IV** (82%) and **V** (60%). In contrast, **II** and **III** promote reactions that take place with excellent levels of enantioselectivity (94 and 97%, entries 2 and 3). The results emphasize the importance of double hydrogen bonding interactions and a correct relative orientation of acidic and basic functional groups in the catalyst's chiral scaffold. Notably, catalyst **III** displays the highest catalytic activity; reaction is completed within 0.5 h.[11] The analogues of catalyst **III** with AcNH, $CH_3NH(C{=}S)NH$, and $3,5\text{-}(CF_3)_2C_6H_3NH(C{=}O)NH$ were screened (see Supporting Information). The lower enantiomeric excesses are observed, indicating that the $3,5\text{-}(CF_3)_2C_6H_3NH(C{=}S)NH$ is critical for stereoselectivity.[12] An investigation of the effects of the reaction medium led to the selection of $Cl(CH_2)_2Cl$ as the ideal solvent system for reactions to further evaluate the **III**-catalyzed tandem process (entry 4). Also, studies show that as low as 1 mol % of **III** brings about complete reaction of **1a** with **2a** within 1 h in 90% yield, 99% ee, and >20:1 dr (entry 6).

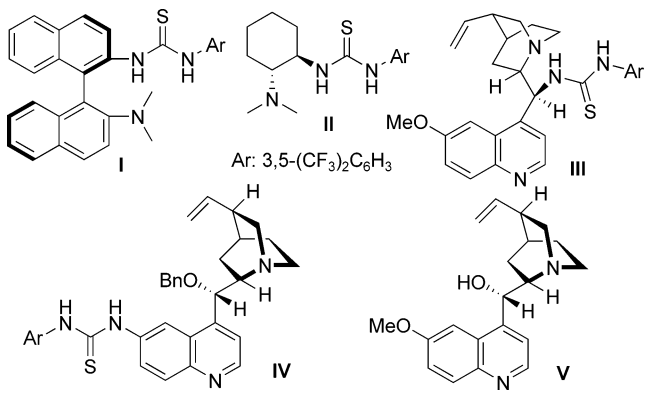


Figure 1. Structures of bifunctional organocatalysts.

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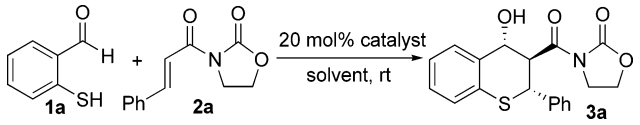
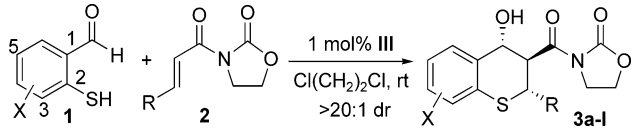
Table 1. Organocatalyzed Michael−Aldol Reaction of 2-Mercaptobenzaldehyde (**1a**) with α,β-Unsaturated Oxazolidinone (**2a**)[a]



entry	cat	solvent	*t* (h)	% yield[b]	% ee[c]	dr[d]
1	**I**	toluene	20	90	0	>20:1
2	**II**	toluene	2	93	−94	>20:1
3	**III**	toluene	0.5	90	97	>20:1
4	**III**	$Cl(CH_2)_2Cl$	0.5	95	99	>20:1
5[e]	**III**	$Cl(CH_2)_2Cl$	0.5	92	99	>20:1
6[f]	**III**	**$Cl(CH_2)_2Cl$**	**1**	**90**	**99**	**>20:1**
7	**IV**	toluene	2	85	−82	>20:1
8	**V**	toluene	2	92	−60	>20:1

[a] Reaction conditions: unless specified, a mixture of **1a** (0.15 mmol), **2a** (0.1 mmol), and a catalyst (0.02 mmol) in a solvent (0.2 mL) was stirred at rt. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H). [d] Determined by ^{1}H NMR. [e] 5 mol % of catalyst used. [f] 1 mol % of catalyst used.

Table 2. **III**-Promoted Michael−Aldol Reactions of 2-Mercaptobenzaldehydes (**1**) with α,β-Unsaturated Oxazolidinones (**2**)[a]



entry	X	R	*t* (h)	% yield[b]	% ee[c]
1	H	Ph	1	90	99
2	5-Me	Ph	1	95	98
3	5-Cl	Ph	1	97	97
4	4,6-Me_2	Ph	2	86	99
5	5,6-$(CH)_4$	Ph	2	86	99
6	H	4-ClC_6H_4	1	92	99
7	H	3-ClC_6H_4	1	95	97
8	H	2-ClC_6H_4	2	90	99
9	H	4-$MeOC_6H_4$	1	90	97
10	H	3-MeC_6H_4	1	92	99
11	H	1-naphthyl	10	75	93
12	H	3-thienyl	5	85	91

[a] Reaction conditions: unless specified, see footnote *a* in Table 1. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H and Chiralcel OD−H) and dr by ^{1}H NMR.

The new methodology, uncovered in the exploratory effort, serves as a facile approach for the preparation of a range of substituted thiochromanes **3** containing three chiral centers in high enantiomeric excesses (91−99% ee) and excellent diastereoselectivities (>20:1 dr in all cases) (Table 2).[13] The **III**-promoted tandem Michael−aldol process takes place with a variety of 2-mercaptobenzaldehyde Michael donors, which possess neutral (entries 1 and 6−12), electron-donating (entries 2 and 4), electron-withdrawing (entry 3), and aromatic (entry 5) groups. It appears that steric crowding, imposed by *ortho*-bismethyl substitution in **1** (entry 4), has little effect on this reaction. Experimentation reveals that the electronic and steric nature of the α,β-unsaturated oxazolidinones (**2**) has minimal impact on efficiency, enantioselectivity, and diastereoselectivity of the Michael−aldol reaction (entries 1−12). In each case, the process proceeds rapidly (1−10 h), in high yields (75−97%), and with high to excellent enantiomeric excesses (91−99%) and diastereomeric ratios (>20:1 for all cases).

The program described above has led to the development of an efficient, highly enantioselective and diastereoselective organocatalytic tandem Michael−aldol process for the preparation of synthetically useful and medicinally important chiral thiochromanes. The new one-pot process, starting with simple substances, is promoted by using as low as 1 mol % of the cinchona alkaloid-derived thiourea **III**. The activity of the catalyst is derived from noncovalent hydrogen bonding interactions between the bifunctional amine thiourea unit in **III**, which synergistically activates both the Michael donor and acceptor. This strategy, closely mimicking the action mode of enzyme catalysis, differs from that used in diarylprolinol TMS ether promoted thio-Michael−aldol dehydration process by employing the formation of a covalent-bonded iminium ion intermediate to foster the reaction.

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Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR and HRMS data for products **3**, and X-ray data (CIF file) of **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) We have conducted a reaction of benzaldehyde with **2a** in the presence of catalyst **III** under the same reaction conditions; no reaction occurred. This eliminates a possible Baylis−Hillman-involved cascade process.

(12) Studies (see refs 9 and 10) have been shown that thiourea 3,5-$(CF_3)_2$-$C_6H_3NH(C{=}S)NH$ provides the optimal results in many cases.

(13) The absolute stereoconfiguration of compound **3b** is determined by X-ray crystal structure (see Supporting Information for details).

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