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Chiral Amine Thiourea-Promoted Enantioselective Domino Michael-Aldol Reactions between 2-Mercaptobenzaldehydes and Maleimides

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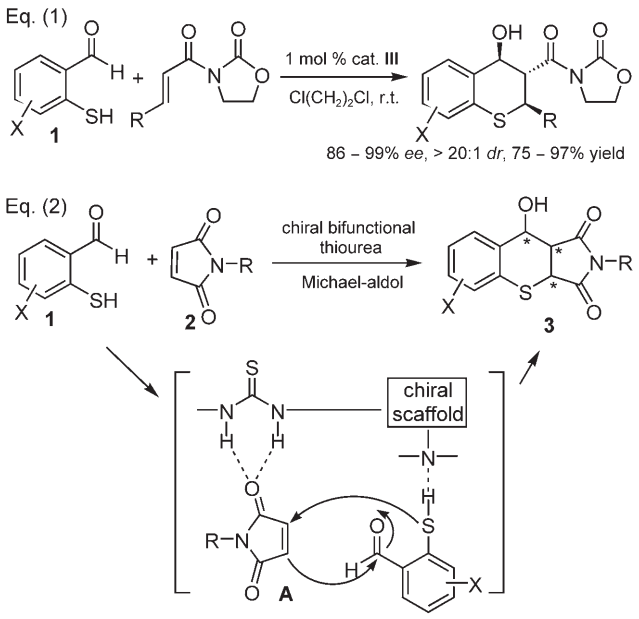
Abstract: An organocatalytic, enantioselective domino Michael-aldol reaction of 2-mercaptobenzaldehydes with maleimides has been developed. The process, catalyzed by a bifunctional chiral amine thiourea *via* a hydrogen-bonding mediated activation mechanism using as low as 1 mol% catalyst loading, affords versatile succinimide-containing benzothiopyrans with the generation of 3 stereogenic centers in one single operation.

Keywords: asymmetric catalysis; asymmetric synthesis; Michael addition; organic catalysis

The development of efficient synthetic methodologies, which allow for the incorporation of important pharmacophores into biologically interesting molecular architectures, is of considerable significance from the standpoint of the medicinal and organic chemistry. Succinimides are such moieties, found in numerous biologically interesting molecules and pharmaceuticals.[1,2] Therefore, they are often used as phramacophores in drug discovery. In this communication, we describe a novel cycloaddition reactions of 2-mercaptobenzaldehydes with maleimides for the facile assembly of succinimide motifs into complex biologically and medicinally significant benzothiopyrans.[3] The process is efficiently catalyzed by a robust, bifunctional amine-thiourea of low toxicity in high yields (83–96%) and good to high levels of diastereoselectivity (up to 20:1 *dr*) and enantioselectivity (74–94% *ee*). In addition, several features of the process are worthy of mention here: 1) pure hydrogen bonding as activation mode,[4] which is considered biomimetic; 2) utilization of as low as 1 mol% of catalyst; and 3) creation of 3 new stereogenic centers in one-pot transformation.

Recently, we have described highly enantioselective, *Cinchona* alkaloid thiourea-promoted domino Michael-aldol reactions of reactions of 2-mercaptobenzaldehydes (**1**) with α,β-unsaturated oxazolidinones [Scheme 1, Eq. (1)].[5–9] In this case, α, β-unsaturated oxazolidinones serve as Michael acceptor. We envisioned that the switch of the α,β-unsaturated oxazolidinones to maleimides (**2**) would generate a new efficient cascade process for the incorporation of succinimides into the complex benzothiopyrans [Scheme 1, Eq. (2)]. It should be pointed out that, to date, the electrophiles employed in organocatalyzed conjugate addition processes have been limited to enones,[10] nitroolefins,[11] unsaturated imides[12] and



Scheme 1. Organocatalytic, asymmetric domino Michael-aldol reactions.

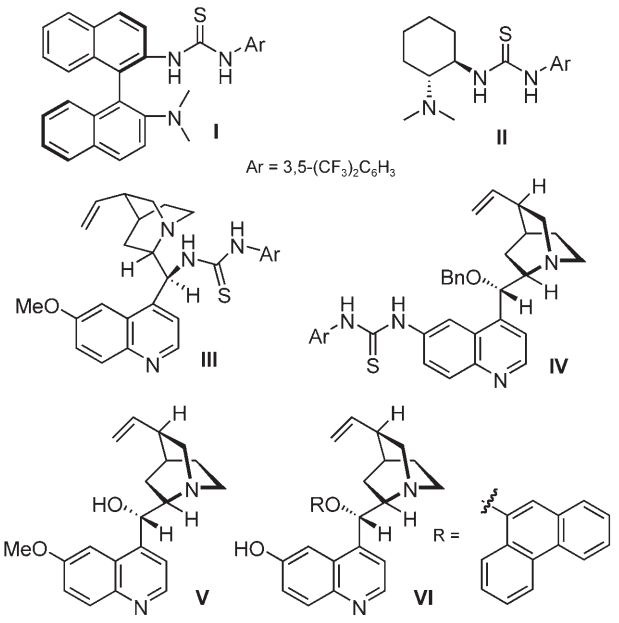


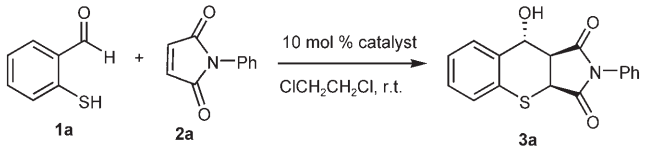
Figure 1. Structures of chiral organocatalysts.

sulfones.[13] In contrast, maleimides as electrophiles[14] have been much less explored.

To probe the feasibility of the proposed organocatalytic domino Michael-aldol process, a model reaction between 2-mercaptobenzaldehyde (**1a**) and *N*-phenylmaleimide (**2a**) in 1,2-dichloroethane at room temperature in the presence of a chiral bifunctional organocatalyst including amine thioureas **I–IV** and the *Cinchona* alkaloids **V** and **VI** was evaluated (Figure 1).[4] The results of the investigation, summarized in Table 1, revealed that the reaction proceeded smoothly to yield the desired benzothiopyran **3a** in high yields (75–94%) with moderate *dr* (5:3 to 4:1, Table 1). However, the enantioselectivities varied greatly depending on the organocatalyst used. Takemoto's catalyst **II** exhibited the most promising results in terms of *ee* (70%), *dr* (4:1) and yield (94%) (Table 1, entry 2). This prompted us to select this catalyst for further optimization of the reaction conditions. It is noted that in our cascade Michael-aldol reactions of 2-mercaptobenzaldehydes (**1**) with α, β-unsaturated oxazolidinones [Scheme 1, Eq. (1)], *Cinchona* alkaloid thiourea **III** is the best promoter.[5a]

In an effort to seek the optimal conditions for the **II**-catalyzed domino Michael-aldol reaction, we first investigated the effect of the reaction medium on the process. The studies showed that the reaction proceeded smoothly in non-polar, aprotic solvents (Table 2, entries 1–7) and poor results were obtained for polar solvents (entry 9). This is expected since non-polar, aprotic solvents can minimize the disruption of the hydrogen-bonding interactions between catalyst and substrates; and thus high catalytic activity and stereoselectivity toward the reaction are generally observed. Among the non-polar, aprotic solvents probed, the process carried out in xylenes afforded the most encouraging results (entry 4). When the catalyst loading was reduced from 10% to 1 mol%, a comparable result was obtained (entry 5). Lowering the reaction temperature to 0°C led to improvement of both enantioselectivity and diastereoselectivity (entry 6).

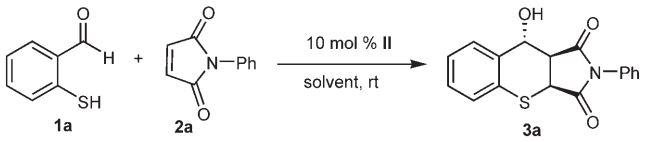
Table 1. Organocatalytic enantioselective domino Michael-aldol reaction of 2-mercaptobenzaldehyde (**1a**) with *N*-phenylmaleimide (**2a**).[a]



Entry	Catalyst	*t* [h]	Yield [%][b]	% *ee*[c]	*dr*[d]
1	**I**	8	75	rac.[e]	3:1
2	**II**	5	94	70	4:1
3	**III**	5	82	−42	5:2]
4	**IV**	5	85	−33	5:2
5	**V**	5	90	−47	3:1
6	**VI**	5	90	−23	5:3

[a] *Reaction conditions:* see Experimental Section.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H).
[d] Determined by 1H NMR.
[e] Racemic.

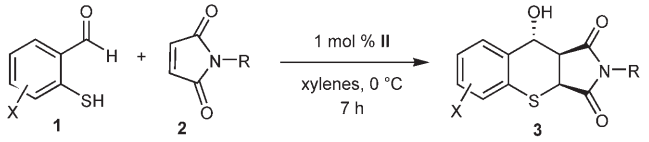
Table 2. Optimization of reaction conditions of **II**-catalyzed domino Michael-aldol reaction of 2-mercaptobenzaldehyde (**1a**) with *N*-phenylmaleimide (**2a**).[a]

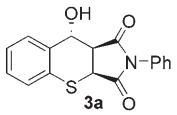
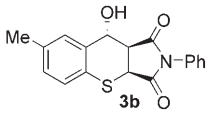
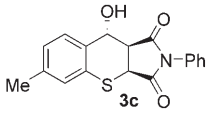
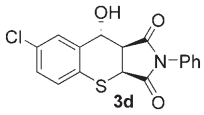
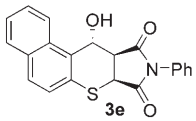
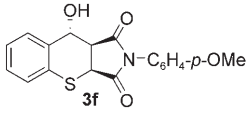
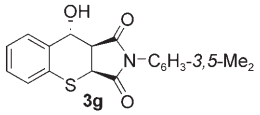
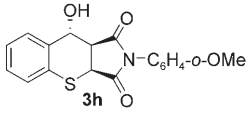
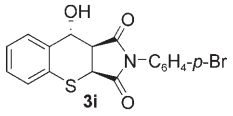
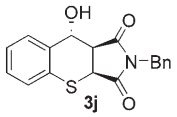


Entry	Solvent	*t* [h]	Yield [%][b]	% *ee*[c]	*dr*[d]
1	$Cl(CH_2)_2Cl$	5	94	70	4:1
2	CH_2Cl_2	5	93	72	3:1
3	toluene	5	90	80	5:1
4	xylenes	5	95	81	6:1
5[e]	xylenes	5	92	81	6:1
6[f]	**xylenes**	**7**	**90**	**84**	**10:1**
7	*p*-cymene	5	85	79	5:1
8	THF	5	85	20	5:2
9	*i*-PrOH	5	70	56	1:1

[a] Unless specified, see Experimental Section.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H).
[d] Determined by ^{1}H NMR.
[e] 1 mol% catalyst used.
[f] 1 mol% catalyst used and reaction performed at 0°C.

Table 3. Catalyst **II** promoted domino Michael-aldol reactions of 2-mercaptobenzaldehydes (**2**) with maleimides (**3**).[a]



Entry	Product **3**	Yield [%][b]	% *ee*[c]	*dr*[d]
1	 **3a**	90	84	10:1
2	 **3b**	95	83	8:1
3	 **3c**	92	83	7:1
4	 **3d**	95	78	8:1
5	 **3e**	83	94	20:1
6	 **3f**	96	86	5.5:1
7	 **3g**	90	75	10:1
8	 **3h**	88	74	3:1
9	 **3i**	84	83	11.5:1
10	 **3j**	92	80	3:1

[a] Unless specified, see Experimental Section for reaction conditions.
[b] Isolated yields after flash chromatography.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H and Chiralpak AD, AS-H or OJ-H).
[d] Determined by ^{1}H NMR.

The new methodology proves to be a general approach to the preparation of a range of substituted thiochromanes **3** containing 3 chiral centers in good to high enantiomeric excesses (74–94% *ee*) and respected levels of diastereoselectivities (3:1 to 20:1) (Table 3). The **II**-promoted domino Michael-aldol process took place with a variety of 2-mercaptobenzaldehydes, which possess neutral (entries 1 and 6–10), electron-donating (entries 2 and 3), electron-withdrawing (entry 4), and aromatic (entry 5) substituents. Moreover, experimentation revealed that the electronic nature of the maleimides (**2**) has limited impact on efficiency, enantioselectivity and diastereoselectivity of the domino reaction (entries 6–9). In each case, the process proceeded rapidly (7 h) in high yields (84–96%) and with good *ee*s (74–86%). *N*-Alkylmaleimides also efficiently participated in the reaction albeit with a slight drop in diastereoselectivity (entry 10).

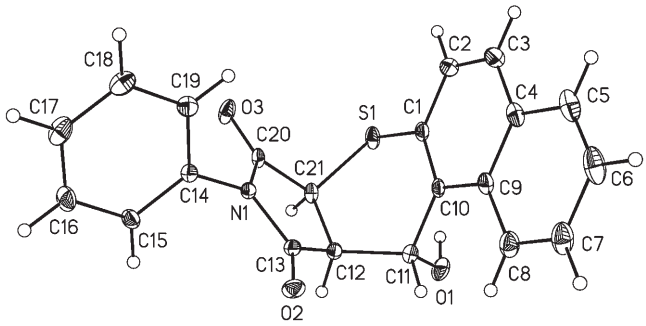


Figure 2. X-ray crystal structure of **3e**.

The stereoconfiguration of the products from the domino Michael-aldol process was determined by X-ray crystallography based on compound **3e** (Figure 2, Table 2, entry 5).[15] It was found that *cis* stereochemistry with (*2S, 3S*) configuration was formed (Figure 3). Two possible reaction pathways were proposed for the observation. In the cascade Michael-aldol reaction (Pathway 1), a transition state **A** was proposed based on the recent theoretical studies of the bifunctional amine thiourea catalyst catalyzed Michael addition reactions.[16] The orientation of the maleimide by the thiourea moiety of the catalyst allows the thiol group in 2-mercaptobenzaldehyde, which is activated and directed by the amine functionality of the catalyst, for *si* face attack to form the *2S* configuration. The observed *cis* (2*S*,3*S*) stereochemistry could result from *cis*-cyclic maleimide **2a**. This is in contrast to the observation from the H-bonding-mediated domino Michael-aldol reactions or cascade Michael-aldol reaction of *trans*-α,β-unsaturated aldehydes with 2-mercaptobenzaldehyde **1a** that give rise to *trans* products.[5a] The second possible reaction mechanism, responsible for the formation of *cis*-products of the process, could be a Diels–Alder process (Pathway 2). The tautomer **1a′** from 2-mercapto-ben-

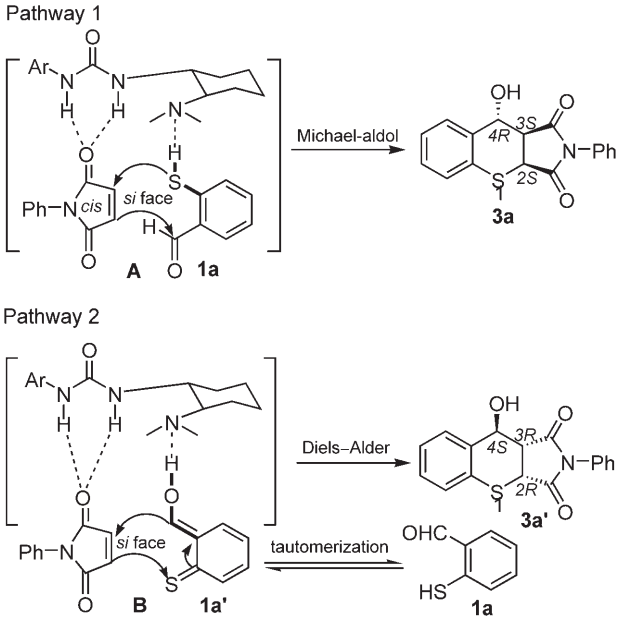


Figure 3. Proposed transition states.

zaldehyde **1a** could serve as a diene for the Diels-aldol reaction with *cis*-cyclic maleimide **2a**. Such reaction also could afford product **3a′** with *cis* stereoconfiguration, but with an opposite absolute (2*R*,3*R*,4*S*) stereochemistry. As shown in proposed transition state **B**, in contrast to the transition state **A**, the amine moiety in the catalyst directs the enol moiety of **1a′** rather than thiolphenol of **1a** *via* an H-bond for the Diels–Alder reaction. The transition state would lead to a (2*R*,3*R*,4*S*) outcome. Based on the experimental results, the Diels–Alder pathway could be ruled out. The detailed mechanistic study is underway in our laboratory.

In summary, we have developed an efficient, enantioselective and diastereoselective organocatalytic domino Michael-aldol process for the preparation of synthetically useful and medicinally important chiral succinimide-containing thiochromanes. The new one-pot process, starting with simple substances, is promoted by using as low as 1 mol% of a robust amine thiourea **II**. The activity of the catalyst derives from non-covalent hydrogen-bonding interactions between the bifunctional amine-thiourea unit in **II** which synergistically activate both the nucleophiles and electrophiles. This strategy closely mimics that is often used by many enzyme catalysts. It is found that the process might undergo a Michael-aldol reaction. Future studies of the reaction are aimed at investigating its full scope, mechanism, and application to the synthesis of biologically important targets.

Experimental Section

Typical Procedure (Table 3, entry 1)

A mixture of 2-mercaptobenaldehyde **1** (21 mg, 0.15 mmol), 1-phenylpyrrole-2,5-dione **2a** (17 mg, 0.1 mmol) and the catalyst **II** (0.414 mg, 0.001 mmol) in xylenes (0.5 mL) was stirred at 0 °C for 7 h. The crude product was purified directly by column chromatography on silica gel, eluted by hexane/EtOAc = 2:1 to give the desired product **3a**; yield: 28 mg (90%) with 84% *ee*, determined by HPLC (Chiralcel OD-H, *i*-PrOH/hexane = 30/70, flow rate = 0.5 mL min^{-1}, λ = 254 nm): t_{minor} = 32.80 min, t_{major} = 43.32 min, *ee* = 84%, *dr* = 10:1; $[\alpha]_D^{23}$: +183.3 (*c* 1.0, $CHCl_3$).

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