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Hydrogen-Bond-Mediated Cascade Reaction Involving Chalcones: Facile Synthesis of Enantioenriched Trisubstituted Tetrahydrothiophenes

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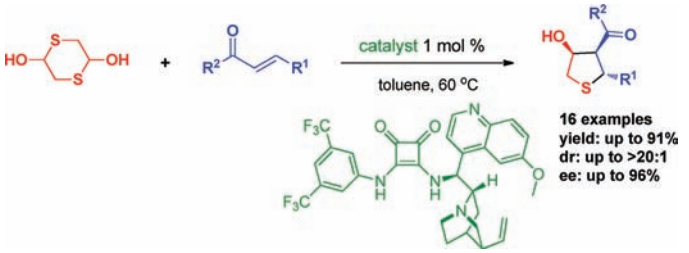
ABSTRACT



A bifunctional squaramide catalyzed sulfa-Michael/aldol cascade reaction between 1,4-dithiane-2,5-diol and chalcones with a low catalyst loading has been developed. Trisubstituted tetrahydrothiophenes with three contiguous stereogenic centers are obtained in a highly stereocontrolled manner. Additionally, a remarkable temperature effect on reaction efficiency was observed and a synthetically potential gram-synthesis was also conducted.

The development of organocatalyzed cascade reactions[1] attracted continuing efforts owing to their ability toward facile and stereoselective assembly of complex and diverse molecules as well as their operational simplicity and environmental friendliness. Based on the covalent enamine or iminium ion intermediate[2] generated *in situ* from carbonyl compounds and chiral amines, substantial progress has been made in the realm of amine-catalyzed cascade transformations. Meanwhile, by means of the H-bonding interaction between the chiral catalyst and H-bond acceptors such as activated alkenes and imines, H-bond-mediated cascade reactions are also extensively explored.[3] Nevertheless, to our knowledge, there is no precedent for noncovalent interaction mediated cascade reactions of chalcones[4] despite the fact that chalcones have been widely used as Michael acceptors in H-bond-mediated single-step transformations.[5] Therefore, the design and development of H-bond-mediated cascade reactions involving chalcones will largely extend the scope of current organocascade reactions and holds great potential in the synthesis of structurally diverse molecules (Scheme 1).

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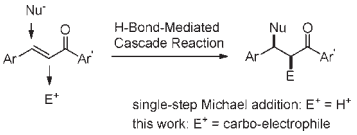
Scheme 1. Development of Hydrogen-Bond-Mediated Asymmetric Cascade Reaction of Chalcones



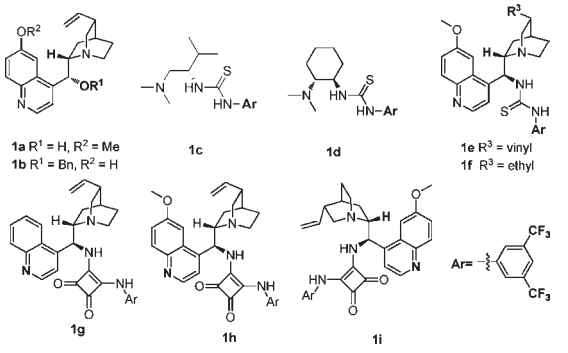


Figure 1. Bifunctional catalysts screened in this study.

Tetrahydrothiophenes are unique sulfur-containing heterocycles and have gained much attention due to their biological activities and diverse applications.[6] Polysubstituted tetrahydrothiophenes are of particular value regarding their potential toward further synthetically and biologically useful elaboration. Surprisingly, practical and efficient approaches, especially catalytic asymmetric variants to assemble this useful architecture, are rare.[7] In view of the importance of this class of molecules as well as the lack of generality and efficiency to access these important synthetic targets, the development of a new catalytic asymmetric synthesis of polysubstituted tetrahydrothiophenes is still in demand. As our group is working on the development of novel and practical asymmetric cascade reactions[8] and inspired by the previous achievements in H-bonding activation of chalcones toward nucleophilic addition, herein we propose that the trisubstituted tetrahydrothiophenes **4** could be directly constructed from commercially available 1,4-dithiane-2,5-diol **2** and chalcones **3** via a sulfa-Michael[9]/aldol cascade reaction with suitable H-bond donor catalyst **1**.

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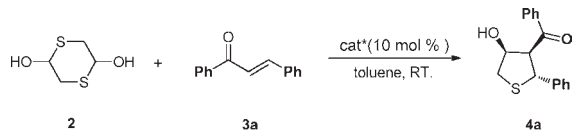
Table 1. Optimization of the Reaction Conditions



2 3a 4a

entry[a]	cat.	solvent	t (h)	yield(%)[b]	dr[c]	ee (%)[d]
1	**1a**	toluene	48	70	>20:1	33
2	**1b**	toluene	48	75	>20:1	5
3	**1c**	toluene	120	85	>20:1	20
4	**1d**	toluene	24	86	7:1	-19
5	**1e**	toluene	12	90	>20:1	57
6	**1f**	toluene	12	86	>20:1	46
7	**1g**	toluene	48	79	>20:1	80
8	**1h**	toluene	48	85	>20:1	86
9	**1i**	toluene	48	81	>20:1	-82
10	**1h**	*m*-xylene	48	81	>20:1	84
11	**1h**	DCM	12	90	>20:1	81
12	**1h**	CH_3CN	12	86	>20:1	74
13	**1h**	PhCN	12	85	>20:1	75
14	**1h**	DCE	12	91	>20:1	79
15	**1h**	PhCl	36	86	>20:1	83
16[e]	**1h**	toluene	36	79	>20:1	83
17[f]	**1h**	toluene	96	86	>20:1	80
18[g]	**1h**	toluene	12	80	>20:1	84
19[g,h]	**1h**	toluene	12	87	>20:1	88
20[g,i]	**1h**	toluene	12	49	>20:1	89
21[i,j]	**1h**	toluene	6	81	>20:1	89

[a] Unless otherwise noted, the reaction was carried out with **2** (0.3 mmol), **3a** (0.2 mmol), and **1** (0.02 mmol) in dry toluene (1 mL) at rt. [b] Isolated yield. [c] Determined by ^{1}H NMR or HPLC analysis. [d] Determined by HPLC analysis. [e] 20 mol % catalyst was used. [f] The reaction was conducted at 15 °C. [g] The reaction was conducted at 40 °C. [h] 5 mol % catalyst was used. [i] 1 mol % catalyst was used. [j] The reaction was conducted at 60 °C.

We were pleased to find that the model reaction of 1,4-dithiane-2,5-diol **2** with chalcone **3a** with 10 mol % quinine **1a** (Figure 1) in toluene at 25 °C for 48 h proceeded as anticipated furnishing the cyclic product **4a** in satisfying yield and diastereoselectivity, albeit low enantioselectivity was observed (Table 1, entry 1). Then the effects of various bifunctional H-bond donor catalysts were probed under the same conditions in hopes of enhancing the enantioinduction, and the results are outlined in Table 1. To our surprise, Deng's catalyst **1b**[10] gave a nearly racemic product (Table 1, entry 2) . Switching from **1b** to bifunctional thiourea **1c**,[11] **1d**,[12] and **1e**−**1f**[13] also led to poor stereochemical induction (Table 1, entries 3−6). Inspired by a recent success in squaramide catalysis,[14] squaramide tertiary−amine bifunctional catalysts **1g**−**1h** were tested (Table 1, entries 7−9). Gratifyingly, improved results in terms of reactivity and selectivity were obtained and quinine-derived catalyst **1h** was identified as the best catalyst among those screened. Subsequently, a brief survey of solvents revealed that toluene was better than other solvents tested (Table 1, entries 10−15). Improving the catalyst loading to 20 mol % did not influence the selectivity evidently (Table 1, entry 16). Lowering the reaction temperature to 15 °C led to a slight decrease of enantioselectivity, yet a longer reaction time was required (Table 1, entry 17). To enhance the reaction efficiency, we conducted the reaction at elevated temperature (40 °C) (Table 1, entries 18−20). An improvement of selectivity of 88% ee was obtained at this temperature when 5 mol % catalyst was used. Further reducing the catalyst loading to 1 mol % gave 89% ee while in this case the reaction cannot be completed in a 12 h period. The best result was obtained with the reaction was performed at 60 °C and the catalyst loading was maintained at 1 mol % (81% yield, > 20:1 dr, 89% ee) (Table 1, entry 21).

The scope of a current sulfa-Michael/aldol cascade reaction between 1,4-dithiane-2,5-diol **2** and vaious chalcones **3** was next explored under the established conditions. As summarized in Table 2, in all the cases, the reaction proceeded smoothly affording the corresponding trisubstituted tetrahydrothiophenes in generally good yield and high levels of diastereo- and enantioselectivity. The nature and the position of the substituents of the phenyl ring of chalcones have no obvious influence on the enantioinduction, yet a little effect on the yield (Table 2, entries 1−13). However, when the halogented chalcones were used, the products were obtained with decreased diastereoselectivity, possibly owing to a retro-aldol process (Table 2, entries 4, 7−8, 11−12). Notably, satisfying results are also achieved with the chalcones bearing heteroaromatic rings (Table 2, entries 14−15).

In addition, cinnamaldehyde-derived dienone **5** can also be utilized as a suitable reaction partner in the cascade sulfa-Michale/aldol reaction to furnish the desired product **6** with high diastereo- and enantioselectivity while a 1,6 adduct was not observed. To demonstrate the potential utility of this methodology, a gram-synthesis of **4c** was performed (Scheme 2). The reaction proceeded smoothly affording the corresponding product in comparable yield and slightly decreased stereoselectivity.

A plausible catalytic cycle of the current cascade reaction is outlined in Scheme 3. The reaction could be initiated via synergistic activation of both mercaptoacetaldehyde and enone **3d** by bifunctional squaramide to form

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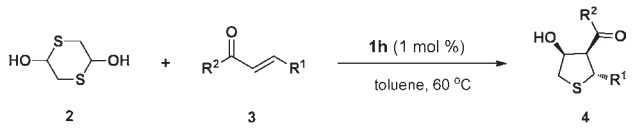
Table 2. Scope of Sulfa-Michael/Aldol Cascade Reaction

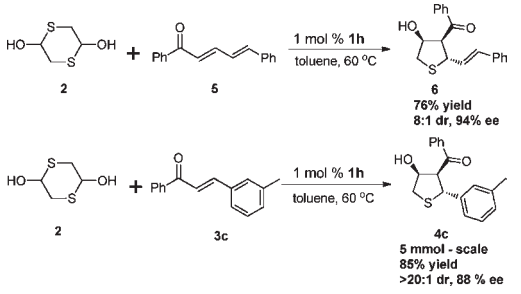


2 3 4

entry[a]	R^1, R^2	4	t (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	Ph, Ph	**4a**	6	81	>20:1	89
2	2-MeC_6H_4, Ph	**4b**	12	80	>20:1	90
3	3-MeC_6H_4, Ph	**4c**	8	91	>20:1	96
4	3-ClC_6H_4, Ph	**4d**	6	79	15:1	87
5	4-MeC_6H_4, Ph	**4e**	6	75	>20:1	89
6	4-FC_6H_4, Ph	**4f**	6	89	>20:1	88
7	4-ClC_6H_4, Ph	**4g**	6	86	11:1	90
8	4-BrC_6H_4, Ph	**4h**	6	76	15:1	84
9	4-MeOC_6H_4, Ph	**4i**	6	91	>20:1	90
10	Ph, 3-BrC_6H_4	**4j**	2	88	>20:1	91
11	Ph, 4-ClC_6H_4	**4k**	6	86	9:1	88
12	Ph, 4-BrC_6H_4	**4l**	2	71	11:1	88
13	Ph, 4-MeOC_6H_4	**4m**	6	80	>20:1	93
14	Ph, 2-thienyl	**4n**	6	90	>20:1	89
15	Ph, 2-furyl	**4o**	12	82	>20:1	92

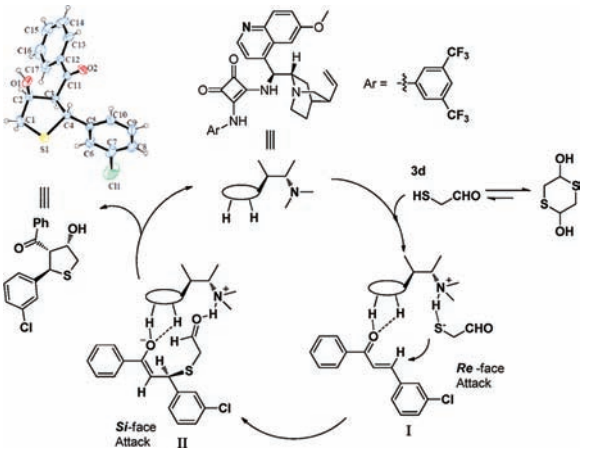
[a] Unless otherwise noted, the reaction was carried out with **2** (0.3 mmol), **3** (0.2 mmol), and **1h** (0.002 mmol) in dry toluene (1 mL) at 60 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR or HPLC analysis. [d] Determined by HPLC analysis.

Scheme 2. Further Investigation of the Potential of the Reaction



intermediate **I**, which undergoes the intramolecular sulfa-Michael addition to provide the intermediate **II**. Subsequent intramolecular aldol reaction closed the catalytic cycle delivering the product **4d** and regenerating the bifunctional catalyst **1h**. The absolute configuration of the product was determined as (2*R*, 3*S*, 4*S*) by using X-ray crystallographic analysis of **4d** (Scheme 3).[15]

Scheme 3. Proposed Catalytic Cycle for the Sulfa-Michael/Aldol Cascade Reaction toward **4d**



In summary, we have disclosed a chalcone-involved sulfa-Michael/aldol cascade reaction furnishing tetrahydrothiophenes with three contiguous chiral centers in generally good yield and high diastereo- and enantioselectivity. Salient features of the present protocol include the utilization of chalcones in the cascade reaction, effective stereocontrol in multistereogenic formation, a relatively low catalyst loading, and a remarkable temperature effect upon reaction efficiency. The synthetic potential of this chemistry was demonstrated by the functional diversity of the products and a gram-scale synthesis. From a synthetic standpoint, this study extends the scope of current H-bond-mediated cascade reactions.

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Supporting Information Available. Complete experimental procedures and characterization of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) CCDC 859341 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The authors declare no competing financial interest.