A Diphenylprolinol TMS Ether/Bile Acid Organocatalytic System for the Asymmetric Domino Sulfa-Michael/Aldol Condensation Reactions of 1,4-Dithiane-2,5-diol and Cinnamaldehydes

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Abstract: Organocatalytic asymmetric domino sulfa-Michael/aldol condensation reactions between 1,4-dithiane-2,5-diol (the dimer of mercaptoacetaldehyde) and cinnamaldehydes were efficiently promoted by (S)-diphenylprolinol TMS ether in the presence of bile acid derivatives, leading to hitherto unknown 4,5-dihydrothiophene-2-carbaldehydes in moderate to good yields and good enantioselectivities.

Keywords: Sulfa-Michael reactions, domino reactions, asymmetric organocatalysis, dihydrothiophenes, bile acids.

The development of organocatalytic enantio- and diastereoselective sulfa-Michael addition (SMA) reactions of sulfur-centered nucleophiles to electron-deficient olefins, has provoked much interest in the last years [1], since the preparation of sulfur-containing molecules continues to be a mainstay of organic synthesis as a result of their broad application to organic and medicinal chemistry [2].

A well established strategy to obtain chiral sulfur-containing building blocks entailed on the use of stoichiometric chiral auxiliaries and reagents, while there are still only a limited number of catalytic enantioselective corresponding variants [3].

Asymmetric organocatalysis, especially with *L*-proline and its derivatives [4], has witnessed important progress in a variety of sulfa-Michael initiated domino reactions, furtherly assessing the synthetic value of asymmetric organocatalytic cascade reactions for the efficient and stereoselective construction of complex molecules from simple precursors in a single process [5].

Notably, efficiency of these approaches has been markedly improved by the addition of acid co-catalysts (e.g. $PhCO_2H$) to the chiral organocatalysts [6-10].

In 2005, 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine has been successfully used to accomplish the first organocatalytic conjugated addition of thiols to α,β-unsaturated aldehydes with excellent yields and enantioselectivities [6]. Notably, this organocatalytic sulfa-Michael reaction served as the first step in a 'one-pot' domino conjugated nucleophilic addition-electrophilic amination reaction allowing for the synthesis of enantiopure 1,2-aminothiols.

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Later, it has been demonstrated that (*S*)-diarylprolinol TMS ether-catalyzed domino processes between 2-mercapto-1-phenylethanone and α,β-unsaturated aldehydes can furnish different tetrahydrothiophenes, depending whether the reaction was carried out under basic conditions or in the presence of benzoic acid [7].

Recently, an organocatalytic tandem sulfa-Michael/aldol reaction has emerged as an efficient method for the preparation of synthetically useful chiral thiochromenes with good to high enantioselectivities [8]. *L*-proline and pyrrolidine diamines were used as the catalysts, and higher enantioselectivities in the model reaction between cinnamaldehyde and 2-thiosalicylaldehyde were observed using (*S*)-diphenylprolinol TMS ether. After 'extensive optimization' of the reaction conditions, the best results were obtained performing the reaction in toluene in the presence of benzoic acid. Interestingly, molecular sieves were also added to the reaction mixture, although the authors did not comment on their role.

Comparable results have been obtained in tandem sulfa-Michael/aldol reactions of α,β-unsaturated cyclic ketones [9].

More recently, an organocatalytic thiol-initiated domino double Michael addition reaction between a variety of α,β-unsaturated aldehydes and *trans*-ethyl-4-mercapto-2-butenoate efficiently catalyzed by (*S*)-diphenylprolinol TMS ether has been developed [10].

Besides these approaches, the asymmetric counterion-directed catalysis (ACDC) [11] entailing on the use of the salt derived from 9-amino-(9-deoxy)-*epi*-hydroquinine and D-*N*-Boc-phenylglycine, in which both the cation and anion are chiral, has recently emerged as a valuable tool for an enantioselective organocatalytic sulfa-Michael addition to α,β-unsaturated ketones [3].

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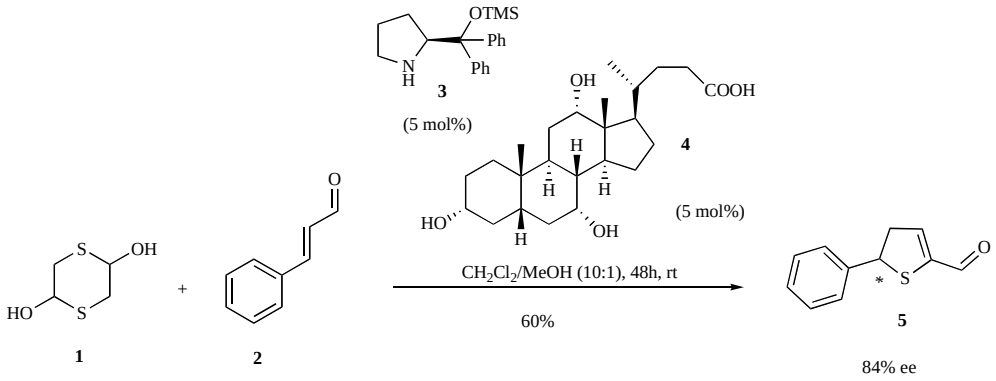


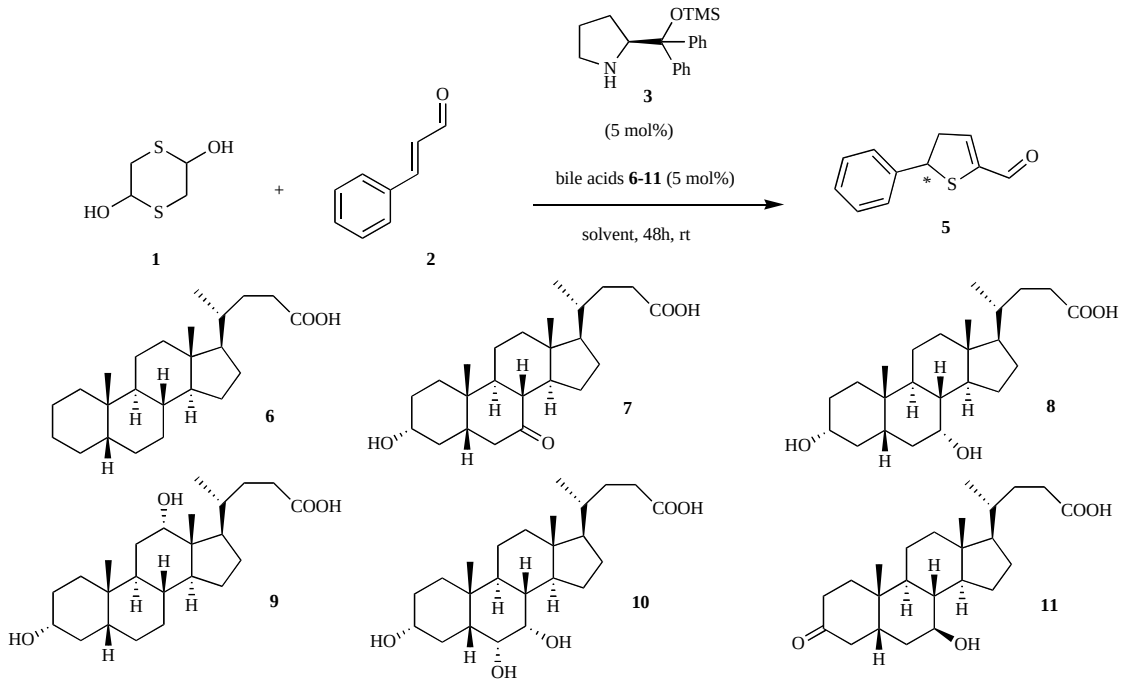
Scheme 1.

Despite all these excellent advances, the development of new asymmetric sulfa-Michael addition reactions remains an important challenge for the synthesis of chiral sulfur-containing compounds.

As an extension of our continuous interest in the use of tandem annulation chemistry for the preparation of new *S*-heterocycles [12], we wish to report in this paper the first synthesis of chiral 4,5-dihydrothiophene-2-carbaldehydes through 'one-pot' organocatalytic asymmetric domino sulfa-Michael/aldol condensation reaction between 1,4-dithiane-2,5-diol **1** (the dimer of mercaptoacetaldehyde) and cinnamaldehydes.

To the best of our knowledge, 4,5-dihydrothiophene-2-carbaldehydes has never been prepared from **1** by use of

Table 1. Bile Acid and Solvent Screen for the Model Reaction Between 1 and 2



Entry	Bile Acid	Solvent	Yield[a] (%)	ee[b] (%)
1	**6**	CH_2Cl_2	75	70
2	**7**	CH_2Cl_2	67	86
3	**8**	CH_2Cl_2	42	72
4	**9**	CH_2Cl_2/MeOH[c]	57	79
5	**10**	CH_2Cl_2/MeOH[d]	74	80
6	**11**	CH_2Cl_2	58	78

[a]Isolated yield.
[b]Determined by GC analysis on chiral column.
[c]Ratio 10:1 (v/v).
[d]Ratio 10:0.5 (v/v).

such a domino reaction. Reaction of **1** with acrolein [13] and 3-methyl-crotonaldehyde [14] gave exclusively 2,5-dihydrothiophene-3-carbaldehyde derivatives.

Our investigations led us discover that (*S*)-diphenyl-prolinol TMS ether **3** and cholic acid **4** were efficient promoters for the model reaction between 1,4-dithiane-2,5-diol **1** and cinnamic aldehyde **2** [15], giving 4,5-dihydrothiophene-2-carbaldehyde **5** in 60% yield and 84% ee (Scheme **1**) [16].

Remarkably, compound **5** was also formed in similar reaction conditions using $PhCO_2H$ as the acid additive, but lower levels of chemical yield and enantioselectivity (40% yield, 62% ee) were observed.

These results prompted us to further explore the model reaction by using different bile acids (**6-11**) and solvents. A selection of results is presented in Table **1**.

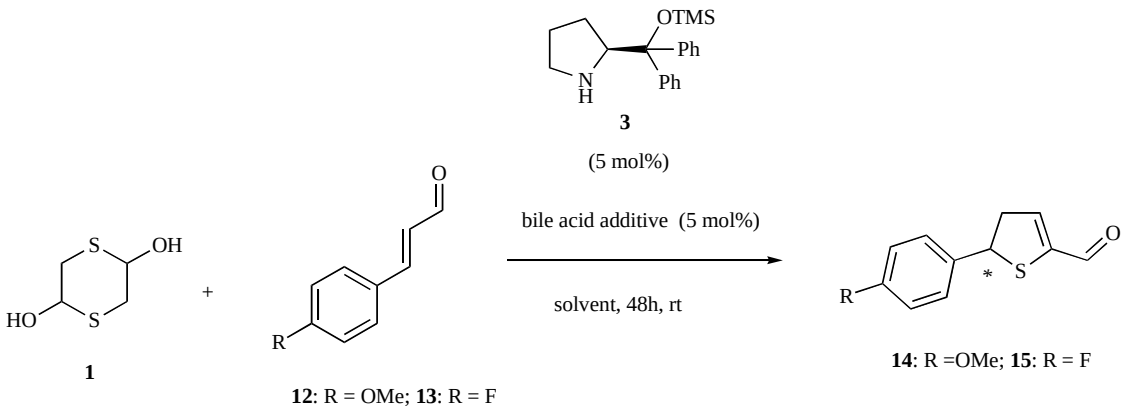
Similarly, the reaction of α,β-unsaturated aldehydes **12** and **13** with thiol **1** promoted by the new catalytic system proceeded smoothly to give enantiomerically enriched compounds **14** and **15** (Table **2**) [17], while less satisfactory results in term of enantioselectivity have been obtained in the presence of (*S*)-diphenylprolinol TMS ether in combination with $PhCO_2H$ (compound **14**: 55% ee; compound **15**: 58% ee).

The formation of 4,5-dihydrothiophene-2-carbaldehyde compounds instead of the expected 2,5-dihydrothiophene-3-carbaldehyde derivatives deserves some comments.

During our studies, we were unable to detect 2,5-dihydrothiophene-3-carbaldehyde derivatives in the organo-catalyzed reactions, the isomeric 4,5-dihydrothiophene-2-carbaldehydes being isolated in any case.

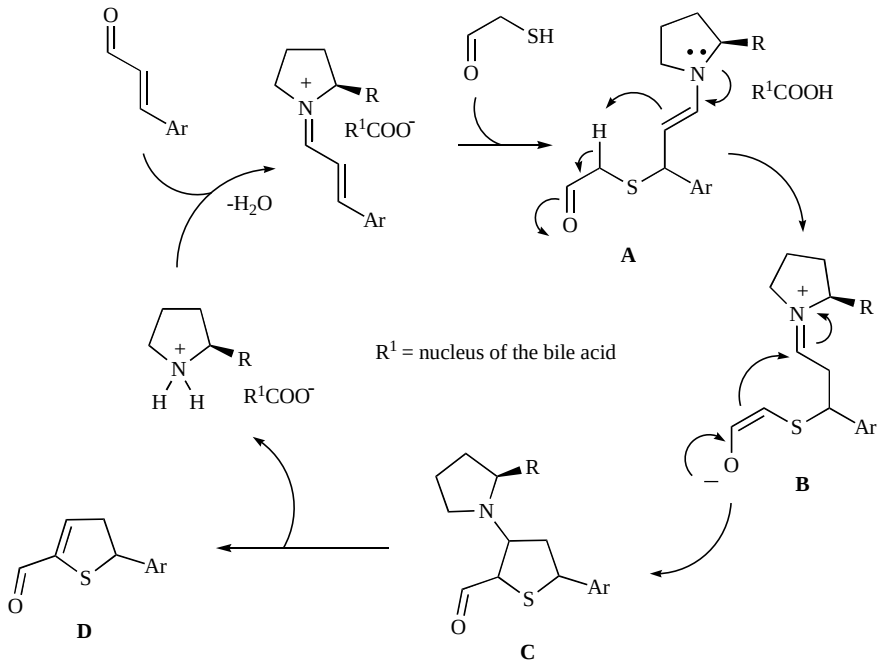
As outlined in Scheme **2**, a plausible explanation for their formation is likely to involve the initial formation of chiral iminium intermediates, promoted by the secondary amine salts generated *in situ* from (*S*)-diphenylprolinol TMS ether and bile acid derivatives. Subsequent Michael addition of

Table 2. Synthesis of compounds 14 and 15



Aldehyde	Bile Acid	Solvent	Yield[a] (%)	ee[b](%)
12	**4**	CH_2Cl_2/MeOH[c]	40	65
12	**6**	CH_2Cl_2	70	77
12	**7**	CH_2Cl_2	70	75
12	**8**	CH_2Cl_2	80	79
12	**9**	CH_2Cl_2/MeOH[c]	15	62
12	**10**	CH_2Cl_2/MeOH[d]	43	70
12	**11**	CH_2Cl_2	60	70
13	**4**	CH_2Cl_2/MeOH[c]	76	82
13	**6**	CH_2Cl_2	17	61
13	**7**	CH_2Cl_2	68	67
13	**8**	CH_2Cl_2	45	64
13	**9**	CH_2Cl_2/MeOH[c]	56	80
13	**10**	CH_2Cl_2/MeOH[d]	35	66
13	**11**	CH_2Cl_2	49	64

[a]Isolated yield.
[b]Determined by GC analysis on chiral column.
[c]Ratio 10:1 (v/v).
[d]Ratio 10:0.5 (v/v).



Scheme 2.

mercaptoacetaldehyde to the initially formed chiral iminium intermediates gives rise to enamines **A**, which, *via* tautomer **B**, produce tetrahydrothiophenes **C**. These are eventually converted to dihydrothiophenes **D** by elimination of the catalyst, thus accounting for a formal aldol condensation.

In summary, we have developed a very simple approach for the asymmetric synthesis of unprecedented 4,5-dihydrothiophene-2-carbaldehydes, useful building blocks for future synthetic applications.

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[16] Typical procedure for the synthesis of 5: 1,4-Dithiane-2,5-diol 1 (200 mg, 1.30 mmol) and cinnamaldehyde (344 mg, 2.60 mmol) were added to a solution of 3 (42 mg, 0.13 mmol) and 4 (53 mg, 0.13 mmol) in a CH_2Cl_2/MeOH mixture (8 mL, 10:1 v/v), at room temperature. The reaction mixture was stirred at the same temperature for 48h, then the solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography on silica gel (ethyl acetate-cyclohexane, 1:4 v/v) to afford pure adduct 5 as an oil. IR (neat): ν 3050, 2950, 2820, 1670, 1595, 1500, 1220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.05 (ddd, *J* = 17.8, 2.8, 2.0 Hz, 1H), 4.22 (ddd, *J* = 17.8, 5.5, 2.5 Hz, 1H), 5.55 (app. dt, *J* = 5.5, 2.0 Hz, 1H), 7.10 (m, 1H), 7.20-7.40

(m, 5H), 9.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ38.80 (CH_2), 54.86 (CH), 125.2 (CH), 127.52 (2CH), 128.59 (2CH), 142.22 (C), 145.13 (C), 148.91 (CH), 187.12 (CHO); Anal. Calcd for $C_{11}H_{10}OS$: C, 69.44; H, 5.30. Found C, 69.31; H, 5.43.

[17] Selected analytical data for compounds 14 and 15. Compound 14: oil. IR (neat): ν 3045, 2960, 2830, 1670, 1600, 1500, 1240 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H), 4.03 (ddd, *J* = 18.3, 2.9, 2.1 Hz, 1H), 4.22 (ddd, *J* = 18.3, 5.6, 2.6 Hz, 1H), 5.49 (app. dt, *J* = 5.6, 2.1 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 2H), 7.00 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 9.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.5 (CH_2), 54.31 (CH_3), 55.31 (CH), 113.86 (2CH), 128.47 (2CH), 134.28 (C), 148.55 (CH),148.71 (C), 158.79 (C), 187.12 (CHO); Anal. Calcd for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49. Found C, 65.50; H, 5.42. Compound 15: oil. IR (neat): ν 3050, 2955, 2825, 1675, 1600, 1495, 1220 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ4.20 (ddd, *J* = 17.9, 2.8, 2.1 Hz, 1H), 4.28 (ddd, *J* =17.9, 5.5, 2.4 Hz, 1H), 5.55 (app. dt, *J* = 5.5, 2.1 Hz, 1H), 6.92-7.05 (m, 2H), 7.08 (m, 1H), 7.22-7.35 (m, 2H) 9,78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.76 (CH_2), 54.21 (CH), 115.44 (d, *J* = 4.0 Hz, 2CH), 129.20 (2CH), 138.04 (C), 148.60 (C), 149.02 (CH), 163.15 (d, *J* = 50.0 Hz, C), 187.02 (CHO); Anal. Calcd for $C_{11}H_9FOS$: C, 63.44; H, 4.36. Found C, 63.41; H, 4.39.