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Asymmetric Synthesis of Highly Functionalized Tetrahydrothiophenes by Organocatalytic Domino Reactions

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A simple approach for the formation of optically active highly functionalized tetrahydrothiophenes, which might have importance in biochemistry, pharmaceutical- and nanoscience is presented. The development of new organocatalytic Michael-aldol domino reactions is outlined and with the appropriate choice of additives it is possible to control the regioselectivity of these domino reactions yielding diastereomerically pure (tetrahydrothiophen-2-yl)phenyl methanones or tetrahydrothiophene carbaldehydes in good yields and with excellent enantioselectivities up to 96% ee. The stereochemical outcome of these reactions is investigated and the mechanism of these organocatalytic domino processes is presented.

Introduction

Substituted tetrahydrothiophenes and optically active tetrahydrothiophenes are endowed with a large spectrum of biological activities, ranging from the essential coenzyme biotin,¹ inhibitor of copper amine

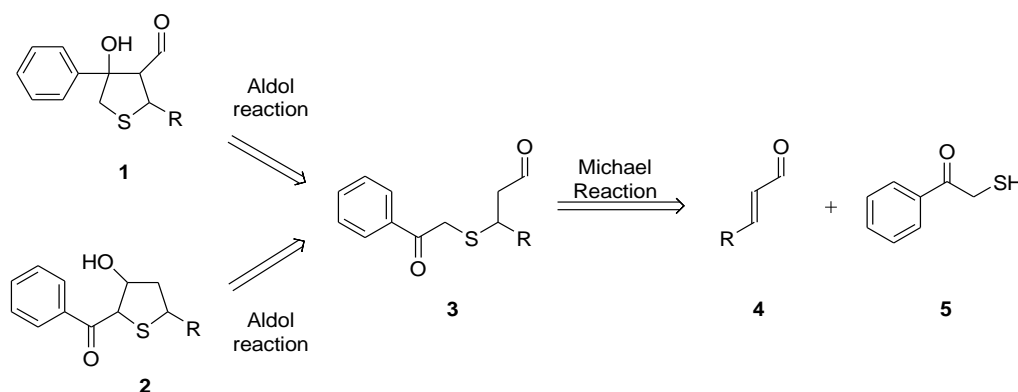
oxidases,² antioxidant activities,³ leukotriene antagonism⁴ or plant growth regulations.⁵ Tetrahydrothiophenes have been also used as building block for new chiral ligands in asymmetric catalysis⁶ and in natural product synthesis.⁷ In addition, the adsorption and the properties of the related achiral, aromatic thiophenes on gold surfaces are well known,⁸ as their benefit for the synthesis of gold nanoparticles.⁹ More recently chiral sulfur compounds have also shown new and interesting properties when adsorbed to Au(110) surfaces.¹⁰ The investigations of chiral tetrahydrothiophenes in these research areas are just in the beginning and the influence of functionalized chiral tetrahydrothiophenes will probably provide new advantages and possibilities in these fields. Despite their high benefits in numerous applications, very few examples for an asymmetric synthesis have been developed yet.¹¹

Asymmetric domino reactions have become a powerful tool for the synthetic chemist building up efficient complex cyclic and acyclic molecules in an easy way.¹² They can form multiple stereogenic centers and fulfill in an exemplary manner one demand of modern organic synthesis, namely minimizing the number of manual operations and purifications in a synthetic sequence.¹³ However, during the past few years the field of asymmetric domino reactions has been dominated by metal catalysis,¹⁴ and only few examples have been published using organocatalysis.¹⁵ Organocatalysis is usually a non-toxic, metal-free and selective powerful approach for the preparation of important optically active building blocks, therefore the field of organocatalysis is a rapidly progressing area with a large number of new asymmetric reactions.^{16,17}

Here we report the development of a new organocatalytic Michael-aldol domino reaction for the synthesis of diastereo- and enantiomerically pure tetrahydrothiophenes, building up highly functionalized tetrahydrothiophenes with three stereocenters in one step. We will present how the regioselectivity of the reaction can be controlled leading to the formation of different tetrahydrothiophenes, namely tetrahydrothiophene carbaldehydes **1**, or (tetrahydrothiophen-2-yl)phenyl methanones **2**, by the appropriate choice of simple additives to the organocatalytic system (Scheme 1). The common intermediate **3** for both tetrahydrothiophenes is synthesized by the first reaction in this

domino reaction, a Michael addition of a nucleophilic thiol **5** to different aliphatic α,β -unsaturated aldehydes **4**.

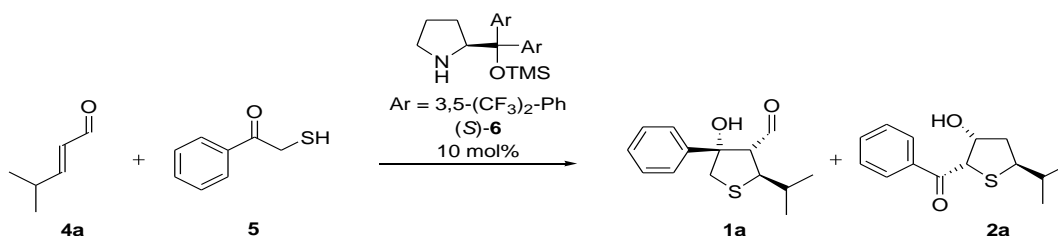
Scheme 1. Domino Reactions to Chiral Tetrahydrothiophenes.



Results and Discussion

Acid-Catalyzed Domino Reactions. The organocatalytic Michael-aldol domino reaction of thiol **5** with different aliphatic α,β -unsaturated aldehydes **4** was first investigated under acidic conditions. The enantioselective formation of tetrahydrothiophene carbaldehydes **1** was initially developed by reaction of (*E*)-4-methylpent-2-enal **4a** and 2-mercapto-1-phenylethanone **5** in different solvents in the presence of the L-proline derivative (*S*)-2-[bis(3,5-bis(trifluoromethyl)phenyl)trimethylsilanyloxymethyl]-pyrrolidine (*S*)-**6**¹⁶ as the catalyst (Table 1).

Table 1. Solvent Screening for the Domino Reaction between (*E*)-4-Methylpent-2-enal **4a** and 2-Mercapto-1-phenylethanone **5**.^a



entry	additive	solvent	yield 1a (%) ^b	ee (%) ^c	yield 2a (%) ^b	ee (%) ^d
1 ^e	-	toluene	40	92	-	-
2 ^f	PhCO ₂ H	toluene	56	94	-	-
3	PhCO ₂ H	<i>o</i> -xylene	54	93	-	-
4	PhCO ₂ H	benzene	57	95	-	-
5	PhCO ₂ H	<i>n</i> -pentane	63	92	-	-
6	PhCO ₂ H	CH ₂ Cl ₂	9	76	-	-
7	PhCO ₂ H	THF	30	10	-	-
8	PhCO ₂ H	DCE	17	80	-	-
9	PhCO ₂ H	Et ₂ O	24	60	-	-
10	PhCO ₂ H	DME	20	37	-	-
11	PhCO ₂ H	H ₂ O	26	96	16	80

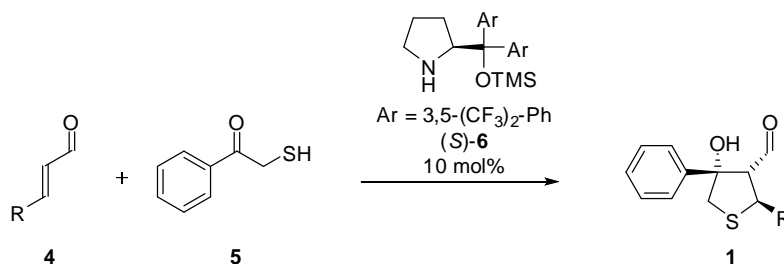
^a All reactions were performed on a 0.25 mmol scale at room temperature for 2 days. ^b Yield of isolated product. ^c Determined by chiral HPLC after reduction to the corresponding alcohol (see below). ^d Determined by chiral HPLC. ^e 5 days reaction time. ^f At 0 °C we obtained under these reaction conditions **1a** in 54% yield with 95% ee, at 50 °C we observe partial decomposition.

The reaction performed well in toluene at room temperature (Table 1, entry 1), yielding the tetrahydrothiophene carbaldehyde **1a** in 40% overall yield in 92% ee as a single regio- and diastereomer. Spectroscopic experiments revealed that the domino reaction of (*E*)-4-methylpent-2-enal **4a** and 2-mercapto-1-phenylethanone **5** needs 5 days for completion. It turned out that in the presence of benzoic acid, the reaction time is shorten from 5 to 2 days without any loss of selectivity in **1a**, which is obtained now in 56% yield and 94% ee as a single isomer (entry 2). The screening of different solvents in Table 1 showed that the reaction gave the highest yield and enantioselectivity of the desired product **1** in aromatic solvents (entry 2-4). Using *n*-pentane, **1a** was formed in a good yield of 63% over two-steps, but in slightly lower enantioselectivity (entry 5). Decomposition products were detected in polar, aprotic

solvents, therefore the desired tetrahydrothiophene **1a** was obtained in lower yields (entry 6-10). The enantioselectivity of **1a** in these solvents was between 10-80% ee, showing that the conjugate addition of the thiol to the α,β -unsaturated aldehyde accomplish in a more non-stereoselective way than in non-polar solvents. Performing the reaction in H₂O (entry 11) we observe the formation of two regioisomers, the tetrahydrothiophene carbaldehyde **1a** in 26% yield and 96% ee, and the (tetrahydrothiophen-2-yl)phenyl methanone **2a** in 16% yield and 80% ee. Each regioisomer is formed as a single diastereomer. The formation of the second regioisomer will be explained in detail in the mechanistic section. However, avoiding the toxicity of benzene and the harsh conditions to remove *o*-xylene in the crude products we decided to use toluene as solvent for further investigations.

The reaction is very general for different aliphatic α,β -unsaturated aldehyde bearing different groups (Table 2). Excellent enantioselectivities were obtained for all tetrahydrothiophenes **1a-h** ranging from 90-96% ee. No other regioisomer was detected under these reaction conditions, leading to a stereoselective domino reaction of diastereomerically pure highly functionalized tetrahydrophenes **1**.

Table 2. Reaction of Thiol **5a** with Different α,β -Unsaturated Aldehydes under Acidic Conditions.^a



entry	R	catalyst	yield (%) ^b	ee (%) ^c
1	Me – 4b	(<i>S</i>)- 6	1b – 59	90
2	Et – 4c	(<i>S</i>)- 6	1c – 73	95
3	<i>n</i> -Pr – 4d	(<i>S</i>)- 6	1d – 74	95

4	<i>i</i> -Pr – 4a	(<i>S</i>)- 6	1a – 56	94
5 ^d	<i>i</i> -Pr – 4a	(<i>R</i>)- 6	<i>ent</i> - 1a – 51	–89
6	<i>i</i> -Pr – 4a	L-proline	<i>ent</i> - 1a – 52	–2
7	<i>n</i> -Bu – 4e	(<i>S</i>)- 6	1e – 62	90
8	<i>n</i> -Hept – 4f	(<i>S</i>)- 6	1f – 44	90
9	(<i>Z</i>)- <i>n</i> -Hex-3-en – 4g	(<i>S</i>)- 6	1g – 61	93
10	CH ₂ CH ₂ OTBDMS – 4h	(<i>S</i>)- 6	1h – 44	96

^a All reactions were performed on a 0.25 mmol scale in toluene, catalyst 10 mol% and PhCO₂H as additive. ^b Yields of isolated product. ^c Determined by chiral HPLC after reduction to the corresponding alcohol (see below). ^d Contains small amounts of impurities (~5%) .

Use of the enantiomeric catalyst (*R*)-**6** for the domino reaction of thiol **5a** and the α , β -unsaturated aldehyde **4a** afforded the enantiomeric product *ent*-**1a** in 51% yield and with an enantiomeric excess of 89% ee (Table 2, entry 5). For the Michael-addition step of this domino reaction, the organocatalyst 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine **6** could highlight the fact that this catalyst is very effective in iminium-ion activation of α , β -unsaturated aldehydes and through a steric shielding of one side of the α , β -unsaturated aldehyde a high asymmetric induction is obtained. The use of proline as catalyst in this domino reaction gave the product **1a** in 52% yield as single isomer, but only in 2% ee (entry 6).

The absolute configuration of the tetrahydrothiophene carbaldehydes **1** was confirmed by a single-crystal X-ray analysis of **1d** (Figure 1).¹⁹

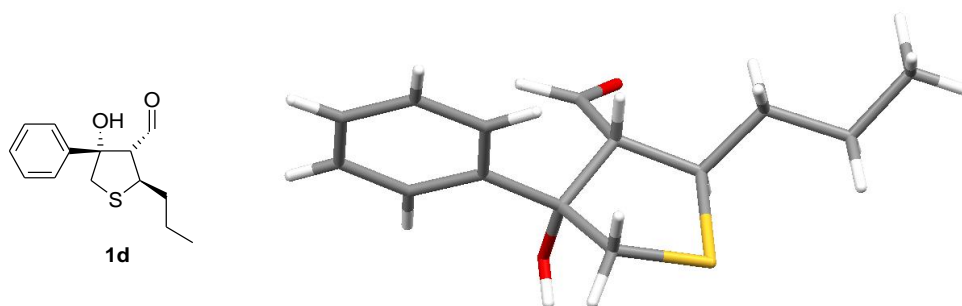


Figure 1. X-ray crystal structure of (2*R*,3*R*,4*S*)-4-hydroxy-4-phenyl-2-propyltetrahydrothiophene-3-carbaldehyde **1d**.

Tetrahydrothiophenols are sensitive compounds in regard to oxidation and elimination processes, catalyzed by for *e. g.* acids, leading to aromatic thiophenes.²⁰ During our studies we observed no transformation of the tetrahydrothiophenols **1** to the aromatic thiophenes. One reason for the stability of the compounds **1** could be strong intra- or intermolecular hydrogen bondings. The crystal structure of **1d** revealed intermolecular hydrogen bonds with a distance of 2.07(0) Å, which might prevent aromatization (Figure 2).

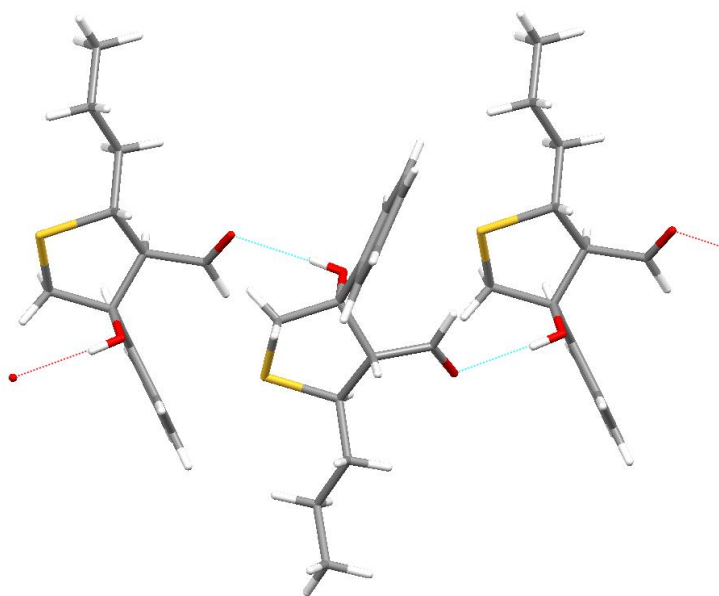
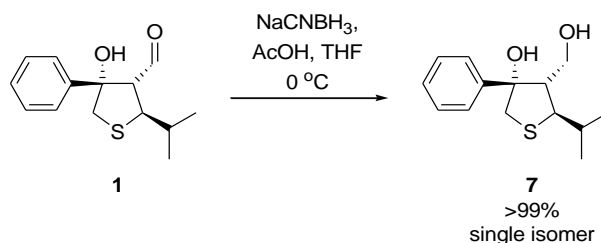


Figure 2. Hydrogen bonds in (2*R*,3*R*,4*S*)-4-hydroxy-4-phenyl-2-propyltetrahydrothiophene-3-carbaldehyde **1d**.

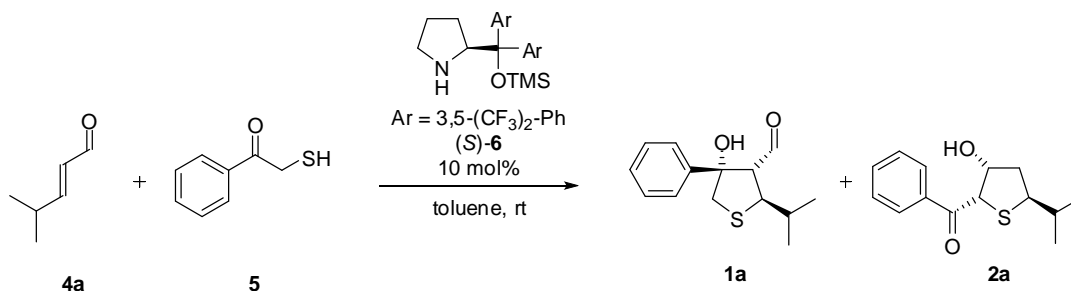
We were pleased to find that the tetrahydrothiophene carbaldehydes **1** undergo a smooth quantitative reduction to the corresponding alcohols **7** without any racemization (Scheme 2). Even in the presence of AcOH we observed no elimination reaction leading to the aromatic thiophenes.

Scheme 2. Reduction of Tetrahydrothiophene Carbaldehydes **1** to Tetrahydrothiophen-3-ols **7**.



Base-Catalyzed Domino Reactions. The course of the organocatalytic domino mechanism is dependent on small variations in the cyclization reaction step. Temperature and solvent have an influence of yield and enantioselectivity and the additive benzoic acid increase the rate of the domino reaction path to the tetrahydrothiophene carbaldehydes **1**. Changing the additive benzoic acid to a base, we observed in several cases competing reaction path and the formation of the tetrahydrothiophene **2** (Table 3). Therefore we tested different additives on the conversion and regioselectivity of the domino reaction of (*E*)-4-methylpent-2-enal **4a** with 2-mercapto-1-phenylethanone **5**. The results are presented in Table 3.

Table 3. Reaction of (*E*)-4-Methylpent-2-enal **4a** and 2-Mercapto-1-phenylethanone **5** under Basic Conditions.^a



entry	additive	conversion (%) ^b	1a:2a	ee (%) ^c
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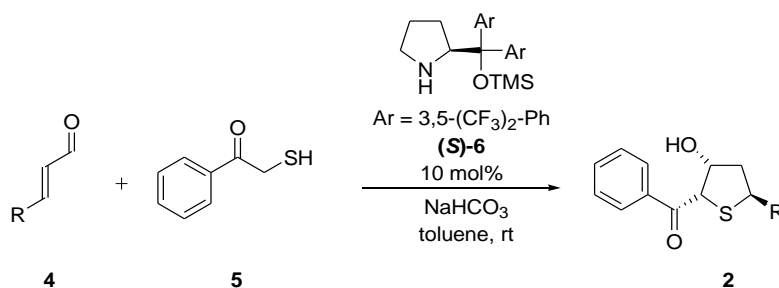
1	NaOH	No reaction	-	-
2	LiOH	22	0:100	nd
3	Na ₂ HPO ₄	22	100:0	nd
4	NaHCO ₃	97	2:98	80
5	Na ₂ CO ₃	48	83:17	nd
6	Cs ₂ CO ₃	17	0:100	nd
7	Et ₃ N	54	50:50	nd

^a All reactions were performed on a 0.25 mmol scale in toluene with 10 mol% catalyst (*S*)-**6a**; ^b Determined by ¹H NMR after 48 h; ^c Determined by chiral HPLC.

No cyclization reaction was observed in the case of NaOH as additive (Table 3, entry 1). The domino cyclization reaction proceeds to the tetrahydrothiophenes with low conversion using LiOH, Na₂HPO₄, Na₂CO₃, Cs₂CO₃ or Et₃N (Table 3, entries 2,3,5-7), while applying NaHCO₃ as the additive leads in the reaction of (*E*)-4-methylpent-2-enal **4a** and 2-mercapto-1-phenylethanone **5** to 97% conversion (entry 4). The regioselectivity for the latter reaction was determined by ¹H NMR spectroscopy to be 98:2 in favor to the tetrahydrothiophene **2a**. Isolation provided the single diastereoisomere **2a** in 61% yield and with 80% ee.

Experiments that probe the scope of the α,β -unsaturated aldehyde component are summarized in Table 4.

Table 4. Reaction of Thiol **5a** with Different α,β -Unsaturated Aldehydes **4** under Basic Conditions.^a



entry	R	yield 2 (%) ^b	ee (%) ^c
1	Me – 4b	2b – 59	74
2	Et – 4c	2c – 44	72
3	<i>n</i> -Pr – 4d	2d – 43	82
4	<i>i</i> -Pr – 4a	2a – 61	80
5	<i>n</i> -Bu – 4e	2e – 66	64
6	(<i>Z</i>)- <i>n</i> -Hex-3-en – 4g	2f – 57	76
7	(CH ₂) ₂ OTBDMS – 4h	2g – 61	70

^a All reactions were performed on a 0.25 mmol scale in toluene, catalyst 10 mol% and NaHCO₃ as additive. ^b Yields of isolated product. ^c Determined by chiral HPLC.

The tetrahydrothiophen-3-ols **2** are formed as a single diastereomer in good yields of 43-66% yield over two-steps and with 64-82% ee. The domino process, providing tetrahydrothiophen-3-ols **2**, starts with a Michael-addition of the thiol **5** to the α,β -unsaturated aldehyde **4**, as in the asymmetric domino reaction for the formation of **1**. But the ee of the final product **2** (64-82% ee) is lower than the tetrahydrophene carbaldehydes **1** (90-95% ee), derived from the acid-catalyzed domino reaction. Including the result running the reaction in water and with benzoic acid as additive (Table 1, entry 11), it demonstrates the existence of two totally different pathways in the second step, the aldol reaction. One catalytic cycle is probably an asymmetric aldol reaction, catalyzed by (*S*)-**6**, which leads to an enantioenrichment for the product **1** after the Michael addition, whereby the second catalytic cycle to the formation of **2** is a simple enolization of the Michael adduct by NaHCO₃ without further asymmetric induction. Therefore the enantiomeric excess of **2** reflects the asymmetric induction of the Michael-addition of **5** to the α,β -unsaturated aldehyde **4**.

An X-ray crystal structure with anomalous diffraction revealed the absolute configuration of (*2S,3R,5R*)-(5-ethyl-3-hydroxytetrahydrothiophen-2-yl)phenyl methanone **2c** (Figure 3).²¹

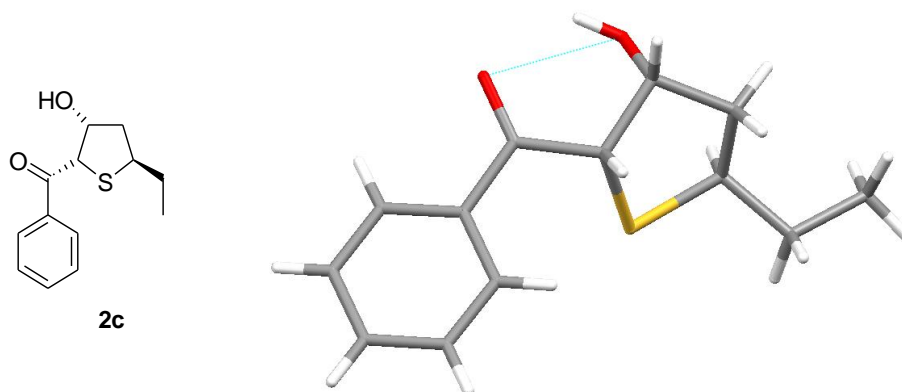
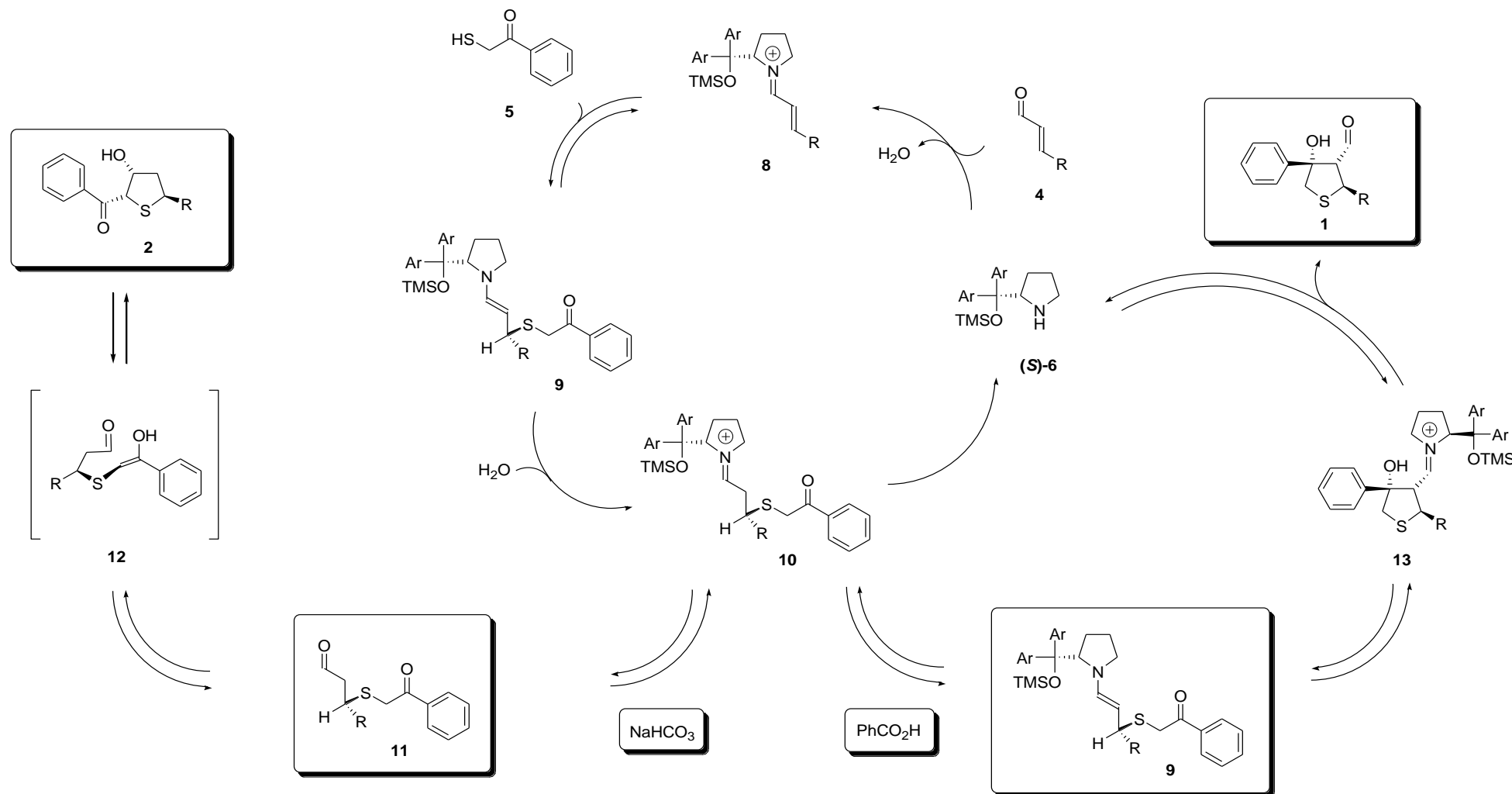


Figure 3. X-ray crystal structure of (2*S*,3*R*,5*R*)-(5-ethyl-3-hydroxytetrahydrothiophen-2-yl)phenyl methanone **2c**.

An intramolecular hydrogen bond with a distance of 2.20(0) Å stabilizes the tetrahydrothiophenes and prevents the elimination of water which would lead to the aromatic compounds.

Mechanistic Insights. The proposed mechanisms for the two domino reactions are summarized in Scheme 3. The Michael addition of the thiol **5** and the α,β -unsaturated aldehyde **4** follows the known pathway of related organocatalytic transformations.^{15m,n,18c,d,22} The TMS-protected proline derivative (*S*)-**6** generates with the α,β -unsaturated aldehyde **4** the iminium-ion **8** shielding the *Si*-side of the reactive intermediate. The nucleophilic attack of the thiol **5** approaches from the *Re*-side leading to the formation of a (*R*)-configured stereocenter in the enamine **9**. The diastereotopic differentiation of the nucleophile is directed from the catalyst yielding a diastereomeric ratio of ~6:1. Hydrolysis of the product in aqueous media or in the presence of NaHCO₃ releases the catalyst (*S*)-**6** and the thioether **11** which can, after a fast enolization to **12**, react in a diastereospecific aldol reaction to the tetrahydrothiophene **1**.

Scheme 3. Mechanism of the Domino Michael-Aldol Reaction for the Formation of Optically Active Tetrahydrothiophenes.



Ar = 3,5-(CF₃)₂-Ph

Assuming a thermodynamic controlled (*E*)-enol in the intermediate **12** with a pseudo-equatorial group R, a hydrogen bonding between the enol and the aldehyde supports the formation of the *syn*-relationship of the substituents in the product **2**. The role of NaHCO₃ as additive is therefore to promote the hydrolysis and the enolization. No asymmetric induction through the catalyst (*S*)-**6** is observed for the second catalytic step in the formation of (tetrahydrothiophen-2-yl)phenyl methanones **2**.

In the presence of benzoic acid as additive in toluene no hydrolysis to the thioether **11** takes place. The catalyst remains in the catalytic cycles forming the enamine **8** as reactive intermediate. Due to steric hindrance of the chiral substituent in the pyrrolidine ring the enamine **8** reacts from an (*E*)-enamine state attacking selectively the carbonyl moiety from the *Re*-side leading to the observed (2*R*,3*R*,4*S*)-configuration of the tetrahydrothiophenes **1**. Hydrolysis of the iminiumion-ion intermediate **13** gives the diastereomerically pure product **1** and sets the catalyst (*S*)-**6** free. The increase of the reaction rate using benzoic acid as an additive can be explained by a possible protonation of the carbonyl group of the intermediate **8** forming a more reactive intermediate. Within this mechanistic cascade the catalyst has a multiple asymmetric induction yielding the products **1** with higher enantioenrichment (>90% ee) than the tetrahydrothiophenes **2** (70-80% ee).^{15k}

Conclusion

In summary, we have developed new and simple organocatalytic domino reactions for the formation of highly functionalized optically active tetrahydrothiophenes. The catalytic domino reaction can be controlled by the addition of benzoic acid yielding tetrahydrothiophene carbaldehydes **1** in good yields and with excellent enantio- and diastereoselectivity or NaHCO₃ giving (tetrahydrothiophen-2-yl)phenyl methanones **2** in moderate yields with very good selectivity. Furthermore we were able to explain the stability of these class of compounds by hydrogen bonding and could show easy, highly efficient transformations of these compounds as a synthetic application.

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Supporting Information Available. Complete experimental procedures and characterization. This material is free of charge via the internet at <http://pubs.acs.org>.

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Graphical Abstract

