

# Asymmetric Synthesis of Trisubstituted Tetrahydrothiophenes Bearing a Quaternary Stereocenter via Double Michael Reaction Involving Dynamic Kinetic Resolution

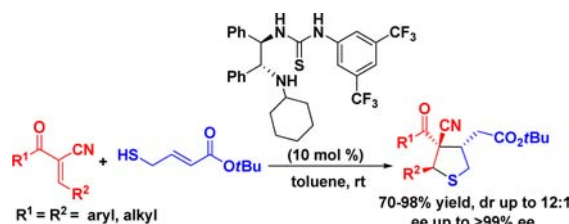
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Received May 28, 2013

## ABSTRACT



The stereoselective synthesis of highly functionalized tetrahydrothiophenes bearing three contiguous stereocenters, one of them quaternary, can be achieved by reacting *trans*- $\alpha$ -cyano- $\alpha,\beta$ -unsaturated ketones and *trans*-*tert*-butyl 4-mercapto-2-butenolate in the presence of a readily available amine thiourea. The products are obtained in high yield, good diastereoselectivity, and excellent enantioselectivity. The overall formation of tetrahydrothiophenes occurs via a cascade double Michael reaction involving a highly efficient process of dynamic kinetic resolution.

The development of cascade reactions to synthesize carbo- and heterocyclic compounds of different ring sizes, in a single operation, is a topic of intense investigation, in view of the evident advantages over traditional single-step

less economic procedures.<sup>1</sup> The most powerful asymmetric approaches are organocatalytic, relying on aminocatalysis and hydrogen bonding catalysis, although the former has been more extensively applied.<sup>2</sup> Organocatalyzed stereoselective cascade reactions have been developed to obtain valuable heterocyclic compounds such as thiochromenes,<sup>3</sup> chromenes,<sup>4</sup> 4-aminobenzopyrans,<sup>5</sup> and tetrahydrothiophenes,<sup>6</sup> via hetero-Michael/Michael, hetero-Michael/aldol, and hetero-Michael/Henry type reactions. Among the

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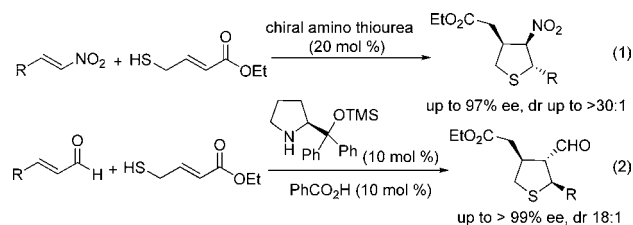
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sulfur containing heterocycles, tetrahydrothiophenes are particularly interesting due to their important biological activities, as naturally occurring products, in medicinal chemistry,<sup>7</sup> and as ligands in asymmetric catalysis.<sup>8</sup> However, few methods have been reported for the stereoselective synthesis of these compounds.<sup>9</sup> Among the organocatalytic cascade reactions, the one-pot double Michael addition to enantioenriched trisubstituted tetrahydrothiophenes is a straightforward and convenient process.

**Scheme 1.** Cascade Double Michael Approaches to Trisubstituted Tetrahydrothiophenes

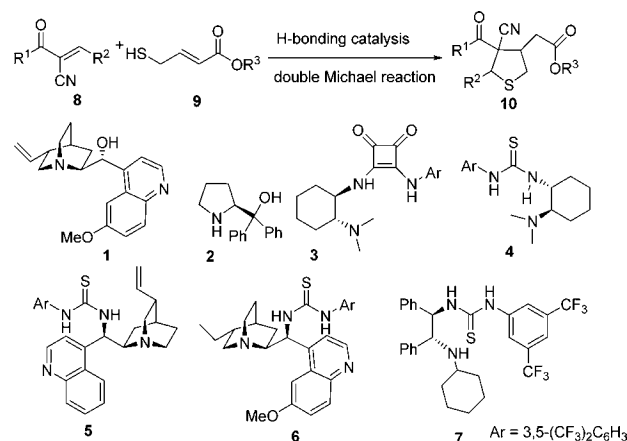


Up to now, only nitroalkenes and  $\alpha,\beta$ -unsaturated aldehydes have been successfully used as the Michael acceptors for this process under H-bonding catalysis (eq 1)<sup>6c</sup> or aminocatalysis (eq 2),<sup>6b</sup> respectively (Scheme 1). Trisubstituted tetrahydrothiophenes, bearing tertiary stereocenters, have been synthesized with excellent stereocontrol.

Our recent work focused on the development of a noncovalent organocatalyzed cascade double Michael reaction<sup>10</sup> to cyclohexanones and Michael-initiated ring-closing (MIRC) reactions to three-membered heterocyclic compounds bearing a quaternary stereocenter.<sup>11</sup> Being interested in expanding the organocatalytic approach as a tool to access targets of increased complexity, we now report a study aimed at constructing synthetically more challenging trisubstituted tetrahydrothiophenes **10**, bearing a quaternary stereocenter (Scheme 2). We envisaged a cascade double Michael reaction to compounds **10** catalyzed by a bifunctional organocatalyst, reacting easily available *trans*- $\alpha$ -cyano- $\alpha,\beta$ -unsaturated ketones **8** and

*trans*-4-mercapto-2-butenates **9** in a one-pot operation. The process was found to be efficiently catalyzed by a simple amino thiourea, leading to tetrahydrothiophenes with good diastereoselectivity and excellent enantioselectivity.

**Scheme 2.** Noncovalent Organocatalyzed Synthesis of Trisubstituted Tetrahydrothiophenes Bearing a Quaternary Stereocenter via Cascade Double Michael Reaction



At the outset of our study, *trans*- $\alpha$ -cyano- $\alpha,\beta$ -unsaturated ketone **8a** and *trans*-ethyl 4-mercapto-2-butenate **9a** were reacted in the presence of a variety of bifunctional organocatalysts at 20 mol % loading (Scheme 2) in toluene at room temperature (Table 1). Quinine afforded racemic product **10a** in moderate yield and diastereoselectivity (entry 1), whereas L-diphenyl prolinol **2** gave compound **10a** in a better yield, diastereoselectivity, and 19% enantiomeric excess (ee) (entry 2). The use of catalysts with more effective H-bond donor groups, such as squaramide **3** (entry 3) and the Takemoto thiourea **4** (entry 4), significantly improved the enantiocontrol (ee up to 75%). These results prompted us to investigate other amino thioureas as catalysts.

Cinchona derived thioureas **5** and **6** behaved similarly to catalyst **4** in terms of activity and stereoselectivity (entries 5 and 6). Interestingly, catalyst **7**<sup>12</sup> gave the product in good yield with an inverted diastereoisomeric ratio and 98% ee for the major diastereoisomer (entry 7). A solvent screen showed that good results are generally obtained when working in nonpolar aromatic solvents (entries 8–12), with toluene being the most effective. The reaction using *trans*-methyl 4-mercapto-2-butenate **9b** (entry 13) proceeded with similar stereocontrol. Pleasingly, more sterically demanding *trans*-*tert*-butyl 4-mercapto-2-butenate **9c** enabled the isolation of the corresponding product **10c** in good yield, improved diastereoisomeric ratio (dr = 9:1), and 99% ee (entry 14). A comparable result was achieved when the catalyst loading was reduced to 10 mol % (entry 15).

Under optimized conditions, the scope of the double cascade Michael reaction was investigated (Table 2).

(12) Catalyst **7** is easily obtained in 60% overall yield over two steps from (1*R*,2*R*)-1,2-diphenylethylenediamine. See the Supporting Information for details.

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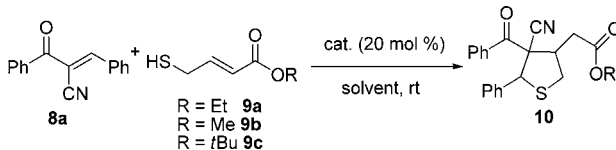
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**Table 1.** Optimization of the Reaction Conditions<sup>a</sup>


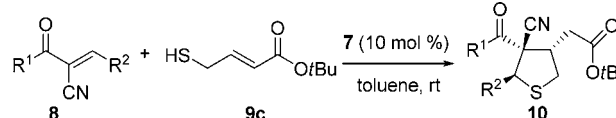
entry	cat.	9	solvent	time (h)	yield <sup>b</sup> (%)	dr <sup>c</sup> (%)	ee <sup>d</sup> (%)
1	1	9a	toluene	69	56	2:1	rac
2	2	9a	toluene	70	76	3:1	19
3	3	9a	toluene	70	65	3:1	-39
4	4	9a	toluene	89	85	3:1	-75
5	5	9a	toluene	70	80	3:1	-83
6	6	9a	toluene	68	78	2:1	74
7	7	9a	toluene	48	80	1:4	98
8	7	9a	CHCl <sub>3</sub>	74	69	1:4	98
9	7	9a	Et <sub>2</sub> O	74	76	1:4	94
10	7	9a	<i>m</i> -xylene	71	67	1:3	97
11	7	9a	ClC <sub>6</sub> H <sub>5</sub>	72	74	1:3	97
12	7	9a	CF <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	70	74	1:3	94
13	7	9b	toluene	60	90	1:4	98
14	7	9c	toluene	36	84	1:9	99
15 <sup>e</sup>	7	9c	toluene	50	94	1:9	99

<sup>a</sup> Reaction conditions: **8a** (0.1 mmol), **9** (0.12 mmol), catalyst (0.02 mmol) in 1 mL of solvent. <sup>b</sup> Yield of isolated product. <sup>c</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>d</sup> Determined by chiral HPLC analysis of major diastereoisomer. <sup>e</sup> 10 mol % of catalyst **7** and 0.13 mmol of **9c** were used.

As expected, compounds **8** bearing electron-donating substituents on the aryl moiety at the  $\beta$ -position were less reactive, although the level of stereoselectivity was maintained (entries 2 and 3).  $\alpha$ -Cyano enones bearing electron-poor substituents gave the product in excellent yield and enantioselectivity as well as good diastereocontrol (entries 4–7). Other aromatic or heteroaromatic residues were also well-tolerated (entries 8 and 9).

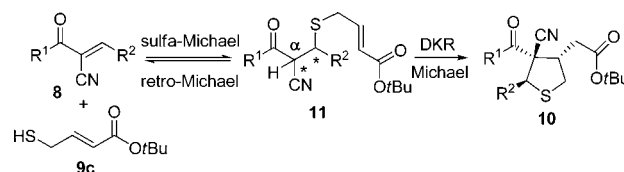
Substitution on the aryl moiety at the keto position of compounds **8** had almost no effect on yield and stereoselectivity (entries 10 and 11). Although the presence of an alkyl group at the  $\beta$ -position of enone **8** led to the product **10n** as a 1:1 ratio of diastereoisomers, excellent yield and enantioselectivities were observed (entry 12). Alkyl substituted enone on the keto moiety afforded the product **10o** in a 3:1 diastereoisomeric ratio, and the major diastereoisomer was recovered with 89% ee (entry 13). The absolute configuration of the major diastereoisomer of compound **10i** was determined to be 3*S*,4*R*,5*S*, whereas the relative configuration of the minor racemic diastereoisomer **10e** was determined to be (3*S*\*,4*S*\*,5*R*\*) by single crystal X-ray analysis.<sup>13</sup>

In a double asymmetric organocatalytic Michael cascade reaction to thiochromenes starting from nitroalkenes,

**Table 2.** Double Michael Reaction of Alkenes **8** and *trans*-*tert*-Butyl 4-Mercapto-2-Butenoate **9c** Catalyzed by Thiourea **7**<sup>a</sup>


entry	R <sup>1</sup> , R <sup>2</sup>	time (h)	10	yield <sup>b</sup> (%)	dr <sup>c</sup> (%)	ee <sup>d</sup> (%)
1	Ph, Ph	50	<b>10c</b>	94	9:1	99
2	Ph, 4-MeOC <sub>6</sub> H <sub>4</sub>	120	<b>10d</b>	70	12:1	99
3 <sup>e</sup>	Ph, 4- <i>t</i> BuC <sub>6</sub> H <sub>4</sub>	150	<b>10e</b>	70	7:1	99
4	Ph, 4-BrC <sub>6</sub> H <sub>4</sub>	88	<b>10f</b>	97	12:1	99
5	Ph, 3-BrC <sub>6</sub> H <sub>4</sub>	85	<b>10g</b>	98	10:1	99
6	Ph, 4-CNC <sub>6</sub> H <sub>4</sub>	65	<b>10h</b>	98	9:1	99
7	Ph, 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	40	<b>10i</b>	98	9:1	>99
8	Ph, 2-naphthyl	180	<b>10j</b>	85	9:1	>99
9	Ph, 3-furyl	160	<b>10k</b>	72	9:1	99
10	4-MeOC <sub>6</sub> H <sub>4</sub> , Ph	78	<b>10l</b>	98	9:1	99
11	3-ClC <sub>6</sub> H <sub>4</sub> , Ph	70	<b>10m</b>	96	5:1	98
12	Ph, cyclohexyl	69	<b>10n</b>	98	1:1	>99(87)
13	(CH <sub>2</sub> ) <sub>2</sub> Ph, Ph	96	<b>10o</b>	79	3:1	89

<sup>a</sup> Reaction conditions: **8** (0.1 mmol), **9c** (0.13 mmol), catalyst (0.01 mmol) in 1 mL of solvent. <sup>b</sup> Yield of isolated product. <sup>c</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>d</sup> Determined by chiral HPLC analysis of major diastereoisomer. In parentheses the enantiomeric excess of the other diastereoisomer. <sup>e</sup> 20 mol % of catalyst **7** was used.

**Scheme 3.** Suggested Cascade Pathway Involving Dynamic Kinetic Resolution

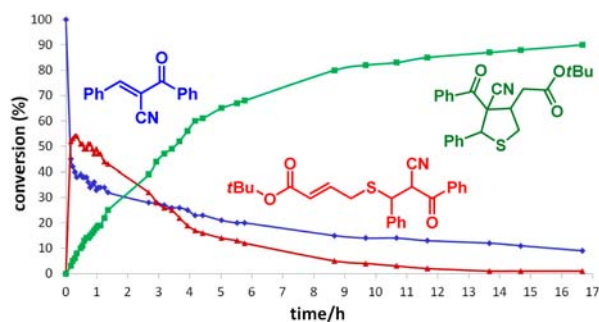
a dynamic kinetic resolution (DKR)<sup>14</sup> was found to govern the stereochemical outcome via a retro-sulfa Michael/sulfa-Michael/Michael process.<sup>3g</sup> We speculated that given the relative acidity of the intermediate adduct **11**  $\alpha$ -proton, a retro-sulfa Michael reaction followed by a selective sulfa-Michael/Michael process catalyzed by **7** might occur (Scheme 3). The reaction of **8a** and **9c**, catalyzed by **7**, was preliminarily monitored by <sup>1</sup>H NMR spectroscopy to check the evolution of adduct **11c** over time (Figure 1).

According to the reaction progress profile, adduct **11c** is rapidly formed and consumed. The racemic mixture of diastereoisomers **11c** could be isolated working under more controlled conditions.<sup>13</sup> To verify the hypothesis illustrated in Scheme 3, adduct **11c** was treated under the same reaction conditions reported in Table 2 (Scheme 4).

Tetrahydrothiophene **10c** was obtained in 75% yield, a 9:1 diastereoisomeric ratio, and 98% ee for the major diastereoisomer. This result is the same achieved when reacting enone **8a** and thiol **9c** directly, thus showing that

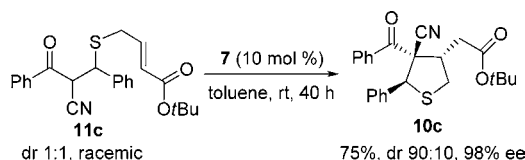
(13) See the Supporting Information for details.

(14) For reviews on dynamic kinetic resolution, see: (a) Caddick, S.; Jenkins, K. *Chem. Soc. Rev.* **1996**, 447. (b) Bäckvall, J.-E. *Trends Biotechnol.* **2004**, 22, 130. (c) Pellissier, H. *Adv. Synth. Catal.* **2011**, 353, 659.



**Figure 1.** Reaction progress profile (entry 1 of Table 2) monitored by  $^1\text{H}$  NMR in deuterated toluene.

**Scheme 4.** Michael Addition of Adduct **11c** Catalyzed by Compound **7**



an efficient process of dynamic kinetic resolution is involved. This represents the first example where dynamic kinetic resolution completely controls the stereochemical outcome of an asymmetric reaction to access tetrahydrothiophenes.<sup>15</sup>

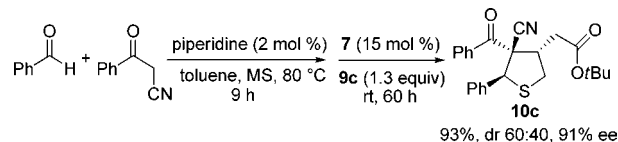
Given the ever-increasing importance of multicomponent reactions in asymmetric synthesis and medicinal chemistry to obtain complex scaffolds, starting from simple reagents,<sup>16</sup> we investigated the feasibility of a one-pot sequential access to tetrahydrothiophenes (Scheme 5). After treatment of benzaldehyde and benzoyl acetonitrile under typical Knoevenagel conditions to generate **8a**, catalyst **7** and thiol **9c** were added at room temperature.

(15) For an example of interplay between DKR and catalyst control in the stereoselective synthesis of trisubstituted tetrahydrothiophenes, see ref 6e.

(16) For reviews, see: (a) Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J. *Tetrahedron: Asymmetry* **2010**, 21, 1085. (b) De Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, 41, 3969. (c) Slobbe, P.; Ruijter, E.; Orru, R. V. A. *Med. Chem. Commun.* **2012**, 3, 1189.

Although the process has not been optimized, a promising result has been achieved, since product **10c** was isolated in 93% yield, with a 60:40 diastereoisomeric ratio and 91% ee being observed for the major diastereoisomer.

**Scheme 5.** Stereoselective One-Pot Sequential Knoevenagel/Double Michael Reaction to Tetrahydrothiophene **10c**



In conclusion, an effective cascade double Michael reaction has been developed for the stereoselective construction of trisubstituted tetrahydrothiophenes in a single operation by using a readily available amino thiourea as an organocatalyst. These densely functionalized products are isolated in high yield, good diastereoselectivity, and excellent enantiocontrol. Notably, one all-carbon quaternary stereocenter was installed, which is a well-known challenge in asymmetric synthesis.<sup>17</sup> A highly efficient process of DKR is involved in the cascade reaction. The organocatalyst is able to catalyze a reversible sulfa-Michael reaction, followed by a highly stereoselective cascade sulfa-Michael/Michael reaction. Interestingly, it has been demonstrated that tetrahydrothiophenes can be stereoselectively obtained via a sequential one-pot Knoevenagel/double Michael cascade process.

**Acknowledgment.** We thank the Italian Ministry of University and Research (MIUR) for financial support. A.L. thanks the COST Action CM0905 Organocatalysis (ORCA). We thank Prof. R. Zanasi (University of Salerno) for useful discussions.

**Supporting Information Available.** Experimental procedures, characterization data,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for new compounds, X-rays crystal structures, and HPLC traces. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.