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

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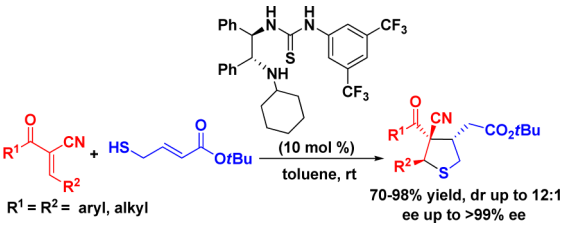
ABSTRACT



The stereoselective synthesis of highly functionalized tetrahydrothiophenes bearing three contiguous stereocenters, one of them quaternary, can be achieved by reacting *trans*-α-cyano-α,β-unsaturated ketones and *trans-tert*-butyl 4-mercapto-2-butenoate 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.[1] The most powerful asymmetric approaches are organocatalytic, relying on aminocatalysis and hydrogen bonding catalysis, although the former has been more extensively applied.[2] Organocatalyzed stereoselective cascade reactions have been developed to obtain valuable heterocyclic compounds such as thiochromenes,[3] chromenes,[4] 4-aminobenzopyrans,[5] and tetrahydrothiophenes,[6] via hetero-Michael/Michael, hetero-Michael/aldol, and hetero-Michael/Henry type reactions. Among the

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(4) For selected examples, see: (a) Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763. (b) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem.—Eur. J.* **2007**, *13*, 574. (c) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, 507. (d) Liu, C.; Zhang, X.; Wang, R.; Wang, W. *Org. Lett.* **2010**, *12*, 4948. (e) Alemán, J.; Núñez, A.; Marzo, L.; Marcos, V.; Alvarado, C.; Garcia Ruano, J. L. *Chem.—Eur. J.* **2010**, *16*, 9453. (f) Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 8379. (g) Hou, W.; Zheng, B.; Chen, J.; Peng, Y. *Org. Lett.* **2012**, *14*, 2378. (h) Yang, W.; Yang, Y.; Du, D.-M. *Org. Lett.* **2013**, *15*, 1190.

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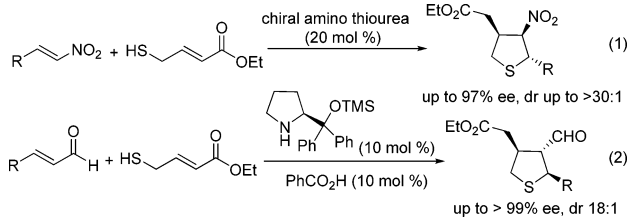
10.1021/ol4014975

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

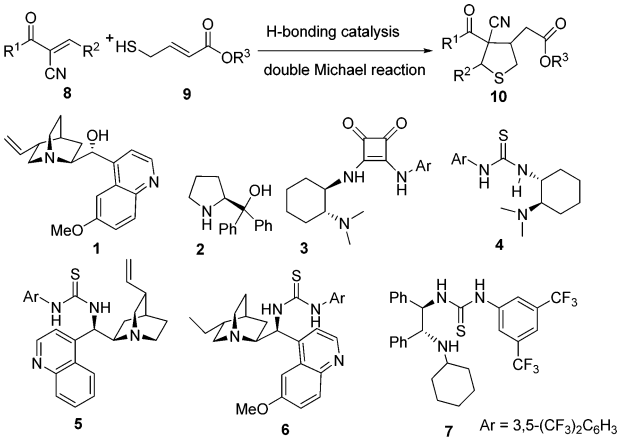
Scheme 1. Cascade Double Michael Approaches to Trisubstituted Tetrahydrothiophenes



Up to now, only nitroalkenes and α,β-unsaturated aldehydes have been successfully used as the Michael acceptors for this process under H-bonding catalysis (eq 1)[6e] or aminocatalysis (eq 2),[6b] 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[10] to cyclohexanones and Michael-initiated ring-closing (MIRC) reactions to three-membered heterocyclic compounds bearing a quaternary stereocenter.[11] 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*-α-cyano-α,β-unsaturated ketones **8** and *trans*-4-mercapto-2-butenoates **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*-α-cyano-α,β-unsaturated ketone **8a** and *trans*-ethyl 4-mercapto-2-butenoate **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**[12] 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-butenoate **9b** (entry 13) proceeded with similar stereocontrol. Pleasingly, more sterically demanding *trans-tert*-butyl 4-mercapto-2-butenoate **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).

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(7) (a) Tsygoanko, V. A.; Blume, Y. B. *Biopolim. Kletka* **1997**, *13*, 484. (b) De Clercq, P. J. *Chem. Rev.* **1997**, *97*, 1755. (c) Wirsching, J.; Voss, J.; Adiwidjaja, G.; Balzarini, J.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1049. (d) Begley, T. P. *Nat. Prod. Rep.* **2006**, *23*, 15.

(8) For selected examples, see: (a) Mukaiyama, T.; Asanuma, H.; Hachiya, I.; Harada, T.; Kobayashi, S. *Chem. Lett.* **1991**, *7*, 1209. (b) Julienne, K.; Metzner, P. *J. Org. Chem.* **1998**, *63*, 4532. (c) Zanardi, J.; Lamazure, D.; Miniere, S.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2002**, *67*, 9083.

(9) For a recent review, see: Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V. *Chem. Rev.* **2012**, *112*, 2129.

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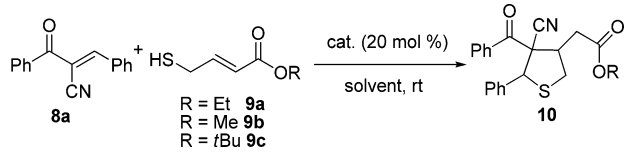
(12) Catalyst **7** is easily obtained in 60% overall yield over two steps from (1*R*,2*R*)-1,2-diphenylethylenediamine. See the Supporting Information for details.

Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	9	solvent	time (h)	yield[b] (%)	dr[c] (%)	ee[d] (%)
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**	$CHCl_3$	74	69	1:4	98
9	**7**	**9a**	Et_2O	74	76	1:4	94
10	**7**	**9a**	*m*-xylene	71	67	1:3	97
11	**7**	**9a**	ClC_6H_5	72	74	1:3	97
12	**7**	**9a**	$CF_3C_6H_5$	70	74	1:3	94
13	**7**	**9b**	toluene	60	90	1:4	98
14	**7**	**9c**	toluene	36	84	1:9	99
15[e]	**7**	**9c**	toluene	50	94	1:9	99

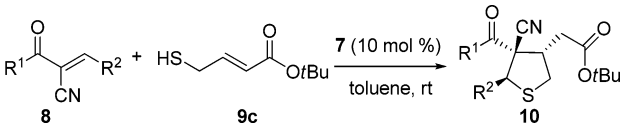
[a] Reaction conditions: **8a** (0.1 mmol), **9** (0.12 mmol), catalyst (0.02 mmol) in 1 mL of solvent. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis of major diastereoisomer. [e] 10 mol % of catalyst **7** and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

As expected, compounds **8** bearing electron-donating substituents on the aryl moiety at the β-position were less reactive, although the level of stereoselectivity was maintained (entries 2 and 3). α-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 β-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.[13]

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

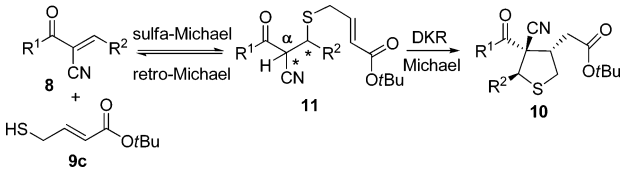
Table 2. Double Michael Reaction of Alkenes **8** and *trans-tert*-Butyl 4-Mercapto-2-Butenoate **9c** Catalyzed by Thiourea **7**[a]



entry	R^1, R^2	time (h)	10	yield[b] (%)	dr[c] (%)	ee[d] (%)
1	Ph,Ph	50	**10c**	94	9:1	99
2	Ph, 4-$MeOC_6H_4$	120	**10d**	70	12:1	99
3[e]	Ph, 4-*t*BuC_6H_4	150	**10e**	70	7:1	99
4	Ph, 4-BrC_6H_4	88	**10f**	97	12:1	99
5	Ph, 3-BrC_6H_4	85	**10g**	98	10:1	99
6	Ph, 4-CNC_6H_4	65	**10h**	98	9:1	99
7	Ph, 4-$NO_2C_6H_4$	40	**10i**	98	9:1	>99
8	Ph, 2-naphthyl	180	**10j**	85	9:1	>99
9	Ph, 3-furyl	160	**10k**	72	9:1	99
10	4-$MeOC_6H_4$, Ph	78	**10l**	98	9:1	99
11	3-ClC_6H_4, Ph	70	**10m**	96	5:1	98
12	Ph, cyclohexyl	69	**10n**	98	1:1	>99(87)
13	$(CH_2)_2$Ph, Ph	96	**10o**	79	3:1	89

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

Scheme 3. Suggested Cascade Pathway Involving Dynamic Kinetic Resolution



a dynamic kinetic resolution (DKR)[14] was found to govern the stereochemical outcome via a retro-sulfa Michael/sulfa-Michael/Michael process.[3g] We speculated that given the relative acidity of the intermediate adduct **11** α-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 ^{1}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.[13] 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.

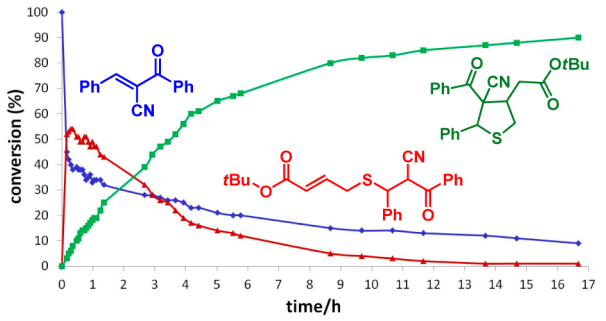
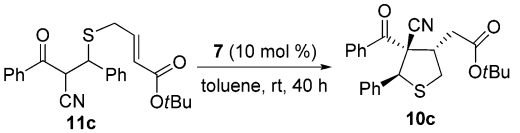


Figure 1. Reaction progress profile (entry 1 of Table 2) monitored by ^{1}H NMR in deuterated toluene.

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



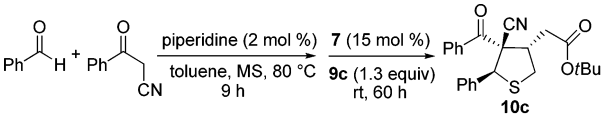
dr 1:1, racemic

75%, dr 90:10, 98% ee

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.[15]

Given the ever-increasing importance of multicomponent reactions in asymmetric synthesis and medicinal chemistry to obtain complex scaffolds, starting from simple reagents,[16] 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. 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**



93%, dr 60:40, 91% ee

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.[17] 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.

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Supporting Information Available. Experimental procedures, characterization data, ^{1}H and ^{13}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.

(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.

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