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Stereoselective amine-thiourea-catalysed sulfa-Michael/nitroaldol cascade approach to 3,4,5-substituted tetrahydrothiophenes bearing a quaternary stereocenter

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Letter

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Abstract

An investigation on the stereoselective cascade sulfa-Michael/aldol reaction of nitroalkenes and commercially available 1,4-dithiane-2,5-diol to 3,4,5-substituted tetrahydrothiophenes, bearing a quaternary stereocenter, is presented. A secondary amine thiourea derived from (*R*,*R*)-1,2-diphenylethylamine was found to be the most effective catalyst when using *trans*-β-methyl-β-nitrostyrenes affording the heterocyclic products in good yields and moderate stereoselectivities.

Introduction

The interest toward the development of stereoselective methodologies to prepare tetrahydrothiophenes bearing multiple chiral centers increased over the last years [1]. Indeed, chiral non-racemic functionalized tetrahydrothiophenes are endowed with different biological activities [2-5] and they are useful ligands in asymmetric catalysis [6]. However, few asymmetric approaches are available to obtain this class of compounds and only recently organocatalytic stereoselective cascade reactions have emerged as the most successful, and straightforward approach to access them [7,8]. Aminocatalytic [9-12] and non-covalent organocatalytic cascade sulfa-Michael/Michael [13-15] and sulfa-Michael/aldol reactions [16-20] enabled the synthesis of differently functionalized tetrahydrothiophenes bearing up to three contiguous chiral centers, including quaternary ones, with good to high control of the diastereo- and enantioselectivity.

Surprisingly, to date there has been one report on a dynamic system combining a 1,1,3,3-tetramethylguanidine (TMG)/ZnI_2-catalyzed diastereoselective cascade sulfa-Michael/nitroaldol reaction followed by lipases catalyzed kinetic resolution using

two representative *trans*-β-methyl-β-nitrostyrenes and 1,4-dithiane-2,5-diol as reagents [21]. One diastereoisomer of the racemic tetrahydrothiophenes, present at the equilibrium, was preferentially acylated by the enzyme to give the product in high ee.

Different amines such as Et_3N, DBU, TMG catalyze the sulfa-Michael/nitroaldol process of either *trans*-β-methyl-β-nitrostyrenes [21] and *trans*-β-nitrostyrenes [22] with 1,4-dithiane-2,5-diol. Based on all above considerations and prompted by our interest in asymmetric synthesis of functionalized tetrahydrothiophenes [14], we wondered whether we could use bifunctional organocatalysts to develop a diastereo- and enantioselective cascade sulfa-Michael/nitroaldol reaction and herein we report our preliminary results.

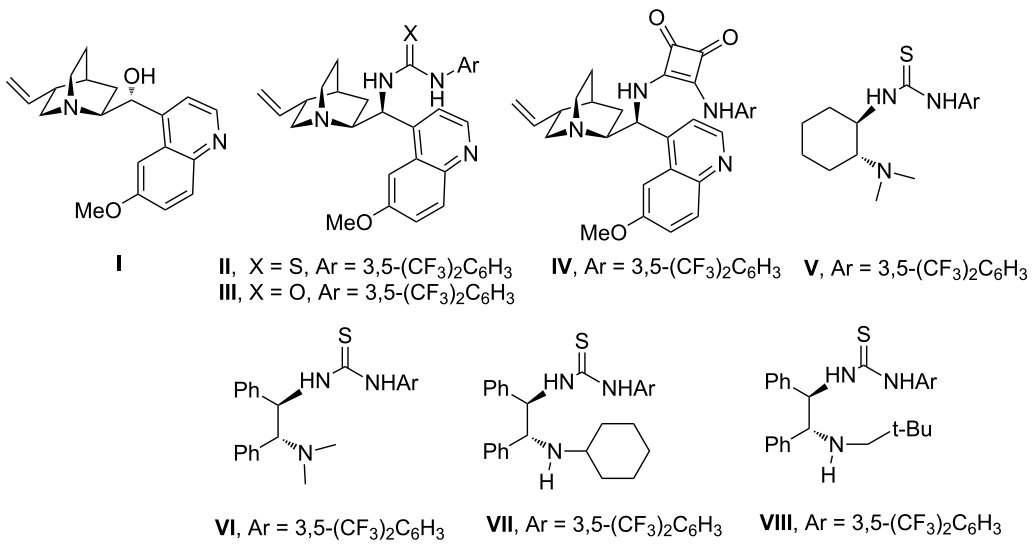
Results and Discussion

According to the literature data, low control of the diastereoselectivity was observed in the cascade reaction of 1,4-dithiane-2,5-diol with *trans*-β-nitrostyrenes, and in the case of (*E*)-1-aryl-2-nitropropene all four diastereoisomeric tetrahydrothiophenes were observed when using tertiary amines such Et_3N, DBU or TMG [21,22].

At the outset, the sulfa-Michael/nitroaldol reaction was studied by reacting *trans*-β-nitrostyrene, (*E*)-1-phenyl-2-nitropropene and (*E*)-1-phenyl-2-nitrobutene in toluene at room temperature with 1,4-dithiane-2,5-diol as precursor of mercaptoacetaldehyde, using 10 mol % loading of different bifunctional organocatalysts (Scheme 1, Table 1).

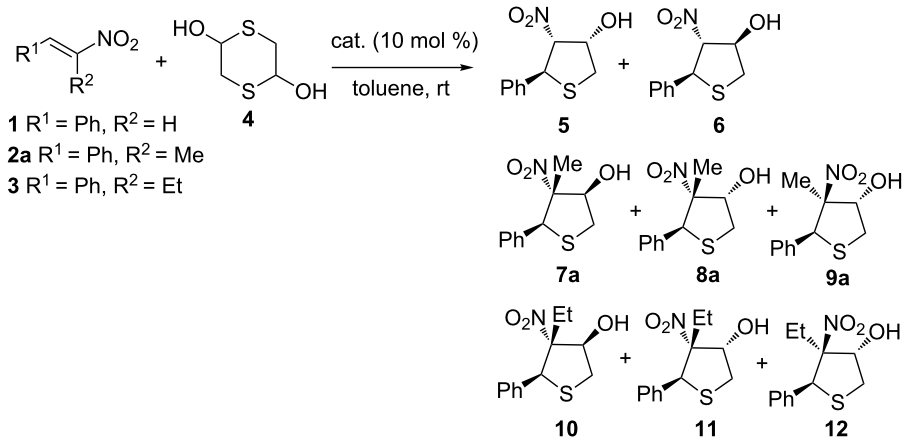
In the case of *trans*-β-nitrostyrene (**1**), a mixture of diastereoisomers **5** and **6** were rapidly formed, irrespective of the catalyst used, with a poor level of diastereo- and enantioselectivity (Table 1, entries 1–5). Thiourea catalyst **VII** afforded the best result, leading to products **5**/**6** in a ratio of 72/28 although with low ee values (Table 1, entry 6). Reacting trisubstituted olefin **2a** with compound **4**, led to three isomers with modest diastereocontrol when using catalysts (**I–VII**). Among the catalysts tested, compound **VII** proved to be the most active and enantioselective, giving the major diastereoisomer **7a** with 44% ee (Table 1, entry 13). Taking into account that amine thiourea **VII**, bearing a sterically hindered secondary amine moiety, was significantly more effective than tertiary amine-based thioureas [14,23], catalyst **VIII**, bearing a sterically demanding neopentyl group, was synthesized in order to check its impact on the stereoselectivity (Scheme 2).

Catalyst **VIII** was easily obtained in a two-step procedure in fair overall yield. Compound **VIII** proved to be less active, affording a comparable level of diastereoselectivity than compound **VII**, but a lower ee value for major diastereoisomer **7a** was measured (Table 1, entry 14). Moreover, the opposite enantiomer of product **7a** was preferentially obtained, thus suggesting that the nature of the alkyl group on the secondary amine moiety greatly affects the stereochemical outcome of the process. The relative configuration of diastereoisomers **7a**/**8a**/**9a** was established by NOESY and NOE analysis on diastereoisomerically pure **7a** and on a diastereoisomeric mixture of compounds **8a** and **9a** (see the Supporting Information File 1) [24].



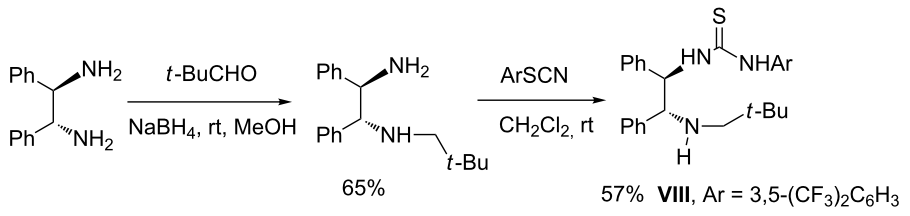
Scheme 1: Organocatalysts screened in the cascade reaction.

Table 1: Asymmetric sulfa-Michael/nitroaldol reaction of nitroalkenes **1**–**3** with 1,4-dithiane-2,5-diol (**4**) catalyzed by catalysts **I**–**VIII**.



entry	cat.	1–3	time (h)	yield [%][a]	dr[b]	ee [%][c]
1	**I**	**1**	5.5	75	58/42 (**5**/**6**)	9 (**5**)/15 (**6**)
2	**II**	**1**	2.5	79	60/40 (**5**/**6**)	rac (**5**)/24 (**6**)
3	**III**	**1**	1.5	53	44/56 (**5**/**6**)	rac (**5**)/12 (**6**)
4	**IV**	**1**	25	52	50/50 (**5**/**6**)	−14 (**5**)/20 (**6**)
5	**V**	**1**	2	89	38/62 (**5**/**6**)	−3 (**5**)/−10 (**6**)
6	**VII**	**1**	2	73	72/28 (**5**/**6**)	−12 (**5**)/−24 (**6**)
7	**I**	**2a**	21	77	66/28/6 (**7a**/**8a**/**9a**)	19 (**7a**)
8	**II**	**2a**	17	77	66/27/7 (**7a**/**8a**/**9a**)	13 (**7a**)
9	**III**	**2a**	17	69	68/24/8 (**7a**/**8a**/**9a**)	4 (**7a**)
10	**IV**	**2a**	27	59	70/23/7 (**7a**/**8a**/**9a**)	2 (**7a**)
11	**V**	**2a**	18	72	68/24/8 (**7a**/**8a**/**9a**)	−19 (**7a**)
12	**VI**	**2a**	44	16	69/25/6 (**7a**/**8a**/**9a**)	1 (**7a**)
13	**VII**	**2a**	28	90	58/30/12 (**7a**/**8a**/**9a**)	−44 (**7a**)
14	**VIII**	**2a**	40	70	65/29/6 (**7a**/**8a**/**9a**)	19 (**7a**)
15	**VII**	**3**	52	80	50/27/23 (**11**/**10**/**12**)	42 (**11**)

[a]Isolated yield of all diastereoisomers after silica gel chromatography. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Determined by chiral HPLC analysis. Negative values indicate the prevalent formation of the opposite enantiomer.



Scheme 2: Synthesis of catalyst **VIII**.

Finally, catalyst **VII** was checked in the reaction of alkene **3** under the same conditions (Table 1, entry 15). After a longer reaction time, diastereoisomers **10**–**12** were isolated with poor diastereomeric ratio and major isomer **11** was recoverd with 42% ee [25].

The diastereoselective ratios, determined for tetrahydrothiophenes deriving from alkenes **2a** and **3**, are in line with their computed thermodynamic stability in toluene (see the Supporting Information File 1). Indeed, products **8a** and **9a** were found to be 0.7 kcal/mol less stable compared to compound **7a**. In the

case of products **10–12**, the predicted relative free energies for **10**, **11** and **12** fall within a range of 0.1 kcal/mol.

Pleasingly, a solvent screening for the cascade reaction carried out on compound **2a** with catalyst **VII** enabled to improve the diastereoselectivity as only **7a**/**8a** were detected in 75:25 ratio and the enantiocontrol increased to 50% ee for diastereoisomer **7a** when using chlorobenzene as the solvent at room temperature (Table 2, entry 5).

It is worth noting that bifunctional organocatalyst **VII** appears to be more effective in terms of diastereocontrol than previously employed Brønsted base/Lewis acid system TMG/ZnI_2 giving four diastereoisomers instead [21].

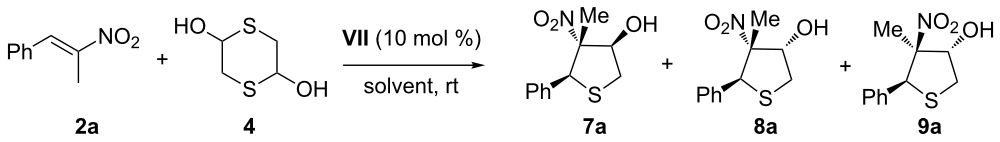
Finally, the sulfa-Michael/nitroaldol cascade reaction was applied to other *trans*-β-methyl-β-nitrostyrenes under the optimized conditions (Table 3).

Tetrahydrothiophenes, bearing three contiguous stereocenters, were isolated in good to high yield, moderate diastereoselectivity and up to 59% ee.

Conclusion

In conclusion, we reported a diastereo- and enantioselective cascade sulfa-Michael/nitroaldol reaction of (*E*)-1-aryl-2-nitropropenes with 1,4-dithiane-2,5-diol. The process was catalyzed by an easily available amine thiourea to give 3,4,5-substituted tetrahydrothiophenes, bearing a quaternary stereocenter, in good yield and moderate enantiocontrol. It has been demonstrated that a simple bifunctional amine thiourea secures a more effective control of the diastereoselectivity than Brønsted base/Lewis acid systems. Data herein illustrated suggest that fine tuning of the bifunctional organocatalyst structure and reaction conditions will be required for further improvements of the challenging cascade process.

Table 2: Solvent screening in the asymmetric Michael/nitroaldol reaction of **2a** with 1,4-dithiane-2,5-diol (**4**) catalysed by amine thiourea **VII**.

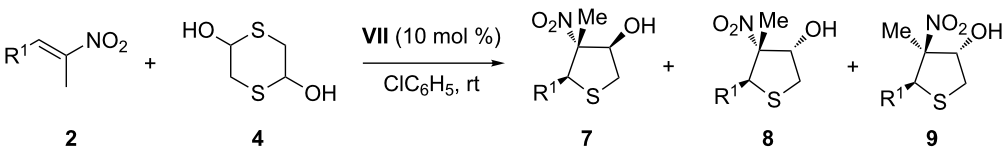


2a **4** **7a** **8a** **9a**

entry	solvent	time (h)	yield [%][a]	dr[b]	ee **7a** [%][c]
1	CH_3CN	21	83	69/31 (**7a**/**8a**)	5
2	CH_3Ot-Bu	47	93	72/24/4 (**7a**/**8a**/**9a**)	30
3	$CHCl_3$	63	56	68/28/4 (**7a**/**8a**/**9a**)	51
4	$ClCH_2CH_2Cl$	63	55	70/30 (**7a**/**8a**)	51
5	C_6H_5Cl	16	69	75/25 (**7a**/**8a**)	50

[a]Isolated yield of all diastereoisomers after silica gel chromatography. [b]Determined by ^1H NMR analysis of the crude mixture. [c]Determined by chiral HPLC analysis.

Table 3: Asymmetric sulfa-Michael/nitroaldol reaction of nitroalkenes **2** with 1,4-dithiane-2,5-diol (**4**) catalysed by amine thiourea **VII**.



2 **4** **7** **8** **9**

entry	R^1	time (h)	yield [%][a]	dr[b]	ee **7** [%][c]
1	Ph	16	69	75/25 (**7a**/**8a**)	50
2	4-ClC_6H_4	16	66	69/31 (**7b**/**8b**)	51
3	4-MeC_6H_4	40	76	74/26 (**7c**/**8c**)	42
4	2-naphthyl	45	90	66/26/8 (**7d**/**8d**/**9d**)	59

[a]Isolated yield of all diastereoisomers after silica gel chromatography. [b]Determined by ^1H NMR analysis of the crude mixture. [c]Determined by chiral HPLC analysis.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, NMR spectra of new compounds and HPLC traces of synthesized compounds, computational details.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-63-S1.pdf]

Acknowledgements

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24. Diastereoisomers **8a** and **9a** and have the same mobility on TLC.
25. Diastereoisomers **10**, **11** and **12** have very similar mobility on TLC. The relative configurations of diastereoisomers **10**/**11**/**12** were assigned by analogy of chemical shifts observed in the ^{1}H NMR spectra with those of diastereoisomers **7a**/**8a**/**9a**.

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