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Organocatalytic Asymmetric Sulfa-Michael Additions to α,β-Unsaturated Sulfonates

Dieter Enders*[a] and Krzysztof Hoffman[a]

Dedicated to Professor Alain Krief

Keywords: Michael addition / Asymmetric catalysis / Organocatalysis / Bifunctional thioureas

The reactivity of α,β-unsaturated sulfonates and aromatic thiols in an organocatalyzed sulfa-Michael addition was explored. Bifunctional chiral thiourea catalysts were found to promote the reaction, and the corresponding Michael adducts were afforded in moderate to good yields (24–92 %) and with moderate levels of asymmetric induction (33–64 % *ee*). This study represents the first use of α,β-unsaturated sulfonates in a catalytic asymmetric Michael addition.

Introduction

Asymmetric organocatalysis provides a powerful approach to prepare a great variety of structurally diverse and useful organic compounds in a highly enantiomerically enriched form.[1] In recent years, much effort has been focused on the design and synthesis of efficient organocatalysts for use in enantioselective Michael additions.[2] A large number of carbon- and heteroatom-based nucleophiles and Michael acceptors have been utilized and impressive levels of asymmetric induction have been achieved. Despite this, the search for new nucleophiles and Michael acceptors is requisite for broadening the chemical space accessible through organocatalyzed Michael additions. α,β-Unsaturated sulfonates **1** serve as interesting candidates for exploration in asymmetric synthesis, as their Michael adducts **2** can be easily elaborated into valuable chiral sulfonic acid derivatives (Figure 1).

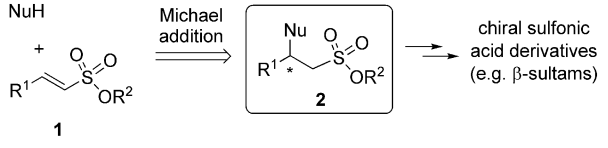


Figure 1. α,β-Unsaturated sulfonates **1** as Michael acceptors in asymmetric synthesis.

Indeed previous work in our research group focused on the use of α,β-unsaturated sulfonates **1** and enantiopure nitrogen nucleophiles in stoichiometric asymmetric aza-Michael additions as a means to prepare enantiomerically enriched β-aminosulfonates, β-sultams, and γ-sultones.[3] To the best of our knowledge, the use of α,β-unsaturated sulfonates in metal- or organocatalyzed asymmetric Michael additions has not been reported.

Bifunctional organocatalysts possess a combination of hydrogen-bond donors (e.g. alcohol, thiourea) and basic functions (e.g. amine, phosphane) and have received increased attention in recent years (Figure 2).[4] Synergistic effects between these two resident functional groups can lead to a marked increase in substrate reactivity in conjunction with a highly ordered transition state and excellent levels of asymmetric induction. As such, Michael additions have been conducted by using this catalytic platform with a range of Michael acceptors (e.g. α,β-unsaturated esters, nitroalkenes), activated by hydrogen bonding, and nucleophiles (e.g. malonates, thiols), activated by deprotonation/general-base catalysis.[5]

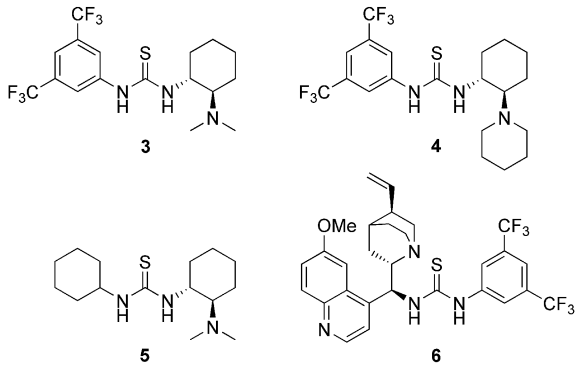


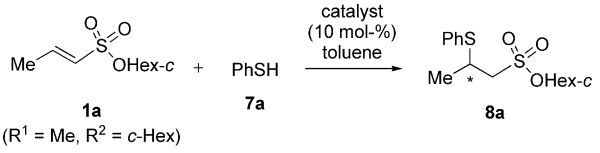
Figure 2. Typical bifunctional thiourea/tertiary amine organocatalysts.

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
Fax: +49-241-80-92-127
E-mail: enders@rwth-aachen.de

We envisioned the possibility of activating α,β-unsaturated sulfonates **1** using a chiral bifunctional catalyst for reaction in a sulfa-Michael addition (SMA). Hydrogen bonding by the catalyst to the sulfonyl function could activate the conjugated double bond to nucleophilic attack. The resultant Michael adducts **2** would contain a β-sulfur-substituted sulfonic acid moiety, which resides in many biologically active molecules.[6,7] Herein, we report our initial investigations towards realizing this goal.

Results and Discussion

During initial experimentation, several cinchona alkaloids were screened as catalysts in the sulfa-Michael reaction of thiophenol (**7a**) and (*E*)-cyclohexyl prop-1-ene-1-sulfonate (**1a**) (Scheme 1).



1a (R¹ = Me, R² = *c*-Hex) **7a** **8a**

Scheme 1. Catalyst screening in sulfa-Michael additions.

Most of the cinchona alkaloids did not catalyze the reaction to an appreciable extent and/or gave low enantioselectivities. Quinine was the best catalyst and afforded the product in moderate yield and enantioselectivity (Table 1, Entry 1). Chiral bifunctional thioureas have been used in the enantioselective Michael addition of cyanoacetates[5k] and α,β-unsaturated sulfones. This class of Michael acceptor is somewhat analogous to α,β-unsaturated sulfonates, therefore we decided to screen several of these catalysts.

Table 1. Catalyst screening in sulfa-Michael additions.

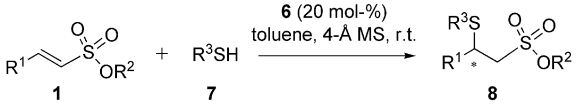
Entry[a]	Catalyst	Time [h]	Yield [%]	*ee*[b] [%]
1	quinine	44	61	25
2[c]	**3**	20	49	35
3	**4**	16	97	31
4	**5**	24	75	40
5[c]	**6**	16	72	37
6[c,d]	**6**	16	85	44

[a] All reactions were performed in toluene at room temperature with 10 mol-% of the catalyst unless otherwise stated. [b] The enantiomeric excess was determined by HPLC with a chiral stationery phase (Whelk 01). [c] 20 mol-% catalyst used. [d] Performed in the presence of 4-Å molecular sieves.

We observed that catalysts **3** and **4**, developed by Takemoto et al.,[5a] efficiently promoted the reaction to afford the corresponding sulfa-Michael adduct in high yields (Entries 2 and 3). However, the product was formed in only moderate enantioselectivity. Catalyst **5**, used for enantioselective dynamic kinetic resolution of azlactones,[8] furnished the desired product in good yield (75%) and moderate enantioselectivity (40% *ee*) (Entry 4).

A quinine-derived catalyst[5h] was then screened and found to be comparable to catalyst **5** and afforded the sulfa-Michael addition product in good yield and moderate enantioselectivity but in a shorter reaction time (Entry 5). With the use of catalyst **6** in the presence of molecular sieves, the reaction rate remained equally good but allowed both the yield and enantioselectivity to be increased, thus giving the best overall results for all conditions screened (Entry 6). Thus, all further experiments were performed under these conditions.

A variety of α,β-unsaturated sulfonates and aromatic thiols were then evaluated in the sulfa-Michael reaction with the use of catalyst **6** (Scheme 2). The more sterically hindered α,β-unsaturated sulfonate **1b** (R^1 = *i*Pr, R^2 = *c*-Hex) was found to react with thiophenol (**7a**, R^3 = Ph). However, it led to a lower yield and enantioselectivity than the parent compound **1a** (Table 2, Entry 2).



1 **7** **8**

Scheme 2. Catalyst **6**-promoted sulfa-Michael additions.

Table 2. Catalyst **6**-promoted sulfa-Michael additions.

Entry[a]	**8**	R^1	R^2	R^3	Time [h]	Yield [%]	*ee*[b] [%]
1	**a**	Me	*c*-Hex	Ph	16	85	44
2	**b**	*i*Pr	*c*-Hex	Ph	20	75	37
3	**c**	Ph	*c*-Hex	Ph	72	<5%	–[c]
4	**d**	CH_2OTBS	*c*-Hex	Ph	20	94	33
5	**e**	Me	*c*-Hex	4-*t*Bu-C_6H_4	20	63	36
6	**f**	*i*Pr	*c*-Hex	4-*t*Bu-C_6H_4	22	24	36
7	**g**	CH_2OTBS	*c*-Hex	4-*t*Bu-C_6H_4	22	63	32
8	**h**	Me	*c*-Hex	2-naphthyl	142	56	31
9	**i**	Me	*c*-Hex	2-TMS-C_6H_4	32	37	64
10	**j**	Me	Et	Ph	16	66	35
11	**k**	Me	*i*Pr	Ph	16	63	36

[a] All reactions were performed at room temperature in toluene with 20 mol-% of catalyst **6**. [b] The enantiomeric excess was determined by HPLC with a chiral stationery phase (Whelk 01). [c] Not determined.

Michael acceptor **1c** (R^1 = Ph) was found to be unreactive under the reaction conditions (Entry 3). The reaction with silyl-ether-containing Michael acceptors and **1d** (R^1 = CH_2OTBS) afforded the Michael product in excellent yield (94%) and moderate enantioselectivity (33%) (Entry 4). In general, 4-*tert*-butylthiophenol (**7b**, R^3 = 4-*t*Bu-C_6H_4) could be used as a nucleophile; however, only moderate enantioselectivities were observed (Entries 5–7). 2-Thionaphthalene **7c** (R^3 = 2-naphthyl) also reacted, but required an extended reaction time and led to the product in moderate yield (56%) and enantioselectivity (31% *ee*) (Entry 8). 2-(Trimethylsilyl)thiophenol (**7d**, R^3 = 2-TMS-C_6H_4) is a useful sulfur nucleophile as its steric bulk can lead to increased levels of stereoselection, yet it can readily be desilylated following addition to an electrophile.[9] Therefore, thiophenol

7d was evaluated and found to react, but the product was obtained in low yield (37%) (Entry 9). Nevertheless, the enantioselectivity of the process was good (64% *ee*). Finally, the sulfonate *O*-alkyl substituent (R^2) was varied to determine its effect on the reaction. Replacement of the cyclohexyl group in Michael acceptor **1a** (R^2 = *c*-Hex) with ethyl or isopropyl did not lead to any significant change in yield or enantioselectivity (Entries 10 and 11).

Conclusions

The activity of α,β-unsaturated sulfonates in organocatalyzed Michael additions has been investigated for the first time, and a general procedure for their bifunctional-thiourea-catalyzed sulfa-Michael addition with aromatic thiols has been developed. The sulfa-Michael adducts were obtained in generally good yields (24–92%) and with moderate enantiomeric excesses (31–64%). Current work is focused on converting the Michael adducts into β-sulfur-substituted sulfonic acids and exploring the use of α,β-unsaturated sulfonates in other organocatalytic reactions.

Experimental Section

General Procedure for the Sulfa-Michael Additions: An oven-dried flask was charged with catalyst **6** (0.12 mmol, 20 mol-%), 4-Å molecular sieves (20 mg) and toluene (2.5 mL). α,β-Unsaturated sulfonate **1**[10] (0.6 mmol) and aromatic thiol **7** (0.5 mmol) were then added sequentially to the flask. The flask was flushed with argon and stoppered, and the mixture stirred at room temperature for 16–142 h. Direct purification of the crude reaction mixture by chromatography (silica gel, ether/pentane 1:6) afforded the desired Michael adducts **8a**–**8k** as colorless or pale-yellow oils. Data for cyclohexyl 2-(phenylthio)propane-1-sulfonate (**8a**): Yield (0.134 g, 85%). IR (film): $\tilde{\nu}$ = 2938, 1449, 1354, 1163, 930, 871, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.44 (m, 5 H, Ph), 4.64 (quintet, $^3J_{H,H}$ = 5.0 Hz, 1 H, *c*-Hex), 3.70 (m, 1 H, C*H*SPh), 3.38 (dd, $^3J_{H,H}$ = 14.3, 3.0 Hz, 1 H, C*H*HSO$_3$), 3.12 (dd, $^3J_{H,H}$ = 14.3, 10.6 Hz, 1 H, CH*H*SO$_3$), 1.55 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, CH_3), 1.20–1.96 (m, 10 H, *c*-Hex) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 132.4, 131.6, 129.0, 128.1, 81.6, 57.5, 38.0, 32.6, 24.8, 23.5, 19.8 ppm. MS (EI): *m*/*z* (%) = 314 (39), 232 (100), 151 (29), 150 (54), 110 (17), 109 (15), 83 (6), 65 (5), 55 (9). $C_{15}H_{22}O_3S_2$ (314.47): calcd. C 57.29, H 7.05; found C 57.48, H 7.04.

Acknowledgments

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