Organocatalysis

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Catalytic Enantioselective Addition of Sodium Bisulfite to Chalcones**

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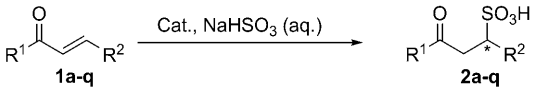
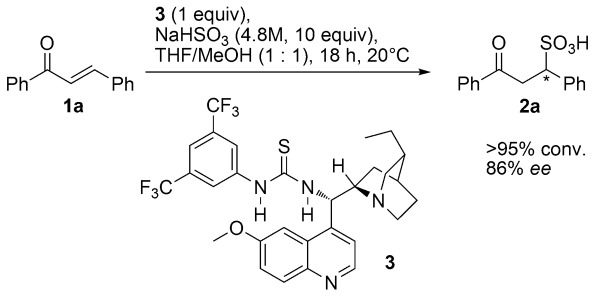
Dedicated to Professor Alfredo Ricci on the occasion of his retirement

Herein we report the first example of the catalytic enantioselective addition of sodium bisulfite to α,β-unsaturated alkenes **1a–q** which was achieved by the selection of an appropriate aminothiourea bifunctional catalyst (Scheme 1).[1–3]

Following the pioneering work carried out by the groups of Soo's, Connon, Deng, and Wang,[2] bifunctional catalysis has matured to become a prominent area of organic synthesis[3] and a key enabling technology for the planning of cascade reactions.[4]



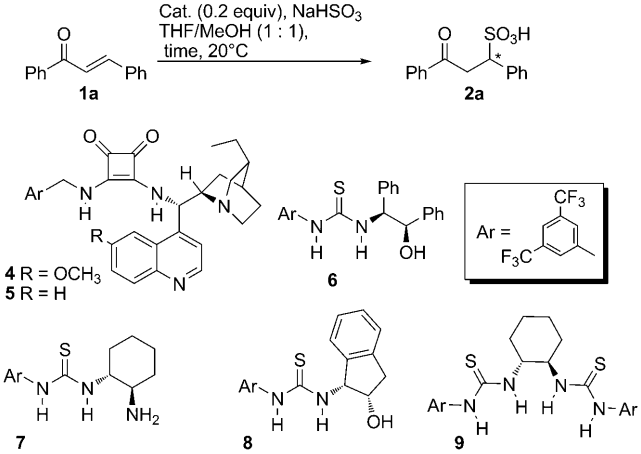
Scheme 1. Enantioselective addition of bisulfite to chalcones.



Scheme 2. Enantioselective addition of bisulfite to chalcone **1a** mediated by aminothiourea **3**.

Sulfonic acids are among the strongest acids in organic chemistry and are extensively employed as resolving agents. Kellogg et al. reported a few enantiopure sulfonic acids **2**, obtained from chalcones, as resolving agents[5] by a "Dutch Resolution" approach.[6] Several multistep syntheses of chiral sulfonic acids have been reported.[7–11] However, the simple addition of bisulfite to olefins, discovered over a century ago,[12] remains the most straightforward access to aliphatic sulfonic acids. This reaction employs reactants in large excess and requires high temperature, which limits its synthetic utility.[5,13] We have recently shown that 1) decreasing the concentration of bisulfite and 2) employing organic base catalysis can increase the rate of addition of bisulfite to electrophilic alkenes.[14] Careful adjustment of these conditions resulted in a mild protocol for the addition of bisulfite to electrophilic alkenes.[14]

Table 1: Sulfonylation of **1a** using bifunctional catalysts **3–9**.



Entry	Cat.	$NaHSO_3$	*t* [h]	Conv. [%][a]	*ee* [%] of **2a**[b]
1	**3**	4.8 M (1.2 equiv)	72	>99	40
2	**3**	0.48 M (1.2 equiv)	18	>99	70
3	**4**	0.48 M (1.2 equiv)	21	>99	60
4	**5**	0.48 M (1.2 equiv)	96	>99	38
5	**6**	0.48 M (1.2 equiv)	120	>90	0
6	**7**	0.48 M (1.2 equiv)	120	<20	0
7	**8**	0.48 M (1.2 equiv)	120	>90	0
8	**9**	0.48 M (1.2 equiv)	120	>90	0

[a] Conversion >99% evaluated by disappearance of **1a** by thin-layer chromatography (silica gel 60 F_{254}) and then verified by ^{1}H NMR analysis. Incomplete conversions evaluated by ^{1}H NMR analysis with an internal standard. [b] Enantiomeric excess determined with the sulfonic acid methyl ester generated by reaction of **2a** with Me_3SiCHN_2 and analysis by HPLC on a chiral stationary phase.

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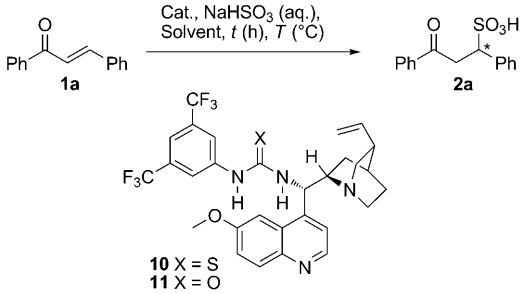
The catalysis displayed by organic bases[14] prompted us to explore the effect of enantiopure amines on the addition of bisulfite to alkenes. Preliminary studies indicated that 1.0 equivalent of (−)-sparteine, (−)-ephedrine, (−)-diphenylprolinol, or quinine promoted the addition of bisulfite to **1a**, giving sulfonic acid **2a** in low enantioselectivity (9–30% *ee*). Conversely, 1.0 equivalent of the bifunctional compound **3**[2b] gave **2a** in 86% *ee* (Scheme 2).

Encouraged by this result, we undertook an in-depth screening of the catalyst structure (Table 1) and the reaction conditions (Table 2). It was confirmed that the concentration of bisulfite strongly affects the reaction rate and catalyst turnover, as was observed previously for triethylamine.[14] Surprisingly, the concentration of bisulfite also has an effect on the enantioselectivity of the reaction. Alkene **1a** reacted with 38% solution of bisulfite in water (4.8 M) in the presence of 0.2 equivalents of **3** to provide **2a** in 40% *ee*. The same reaction carried out using a more dilute solution of bisulfite (0.48 M) gave **2a** in 70% *ee* (Table 1, entries 1 and 2). Squaramide-based bifunctional catalysts **4** provided **2a** in lower but still significant enantioselectivity (Table 1, entry 3). Bifunctional catalysts **5**–**9** gave compound **2a** in low *ee* or as a racemate (Table 1, entries 4–8). This study identified chinchona-based thiourea **3** as the best catalyst, and we retained it in the next round of optimization involving variation of solvent and temperature (Table 2). The reaction of **1a** and bisulfite was conducted in different solvents and at different temperatures. This study identified methanol/toluene (3:1) as the best solvent mixture and −2 °C as the optimal reaction temperature (Table 2, entry 9) giving **2a** in 95% *ee* with only 0.1 equivalent of catalyst **3**.

The scope of the reaction was demonstrated by reacting chalcones **1b**–**q** under the optimized conditions. The results collected (Table 3) point out the following facts: 1) Both electron-withdrawing and electron-donating groups at R^1 and aryl groups at R^2 are tolerated. 2) It was verified that at least compound **2a** could be obtained in a multigram (5–6 g) preparative scale (Table 3, entry 1) without loss of yield or enantioselectivity. 3) The use of the quasi-enantiomeric catalyst **3′** allowed the preparation of compounds *ent*-**2a**,

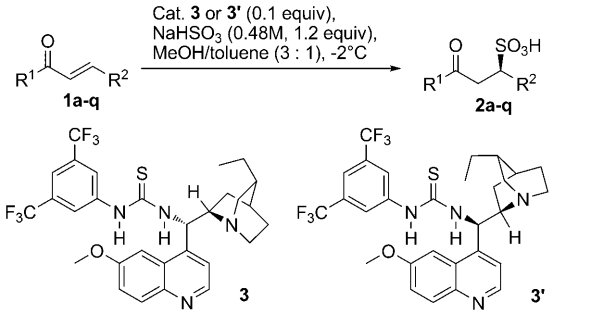
Table 2: Optimization of sulfonylation of **1a** using bifunctional catalysts **3**, **10**, and **11**.[a]



Entry	Cat. (equiv)	Solvent mixture	*T* [°C]	*t* [h][b]	Conv. [%][c]	*ee* [%] of **2a**[d]
1	**3** (0.2)	CH_3OH/CH_3CN 1:1	20	18	>99	70
2	**3** (0.2)	CH_3OH/CH_2Cl_2 1:1	20	18	>99	82
3	**3** (0.2)	CH_3OH/Tol 1:1	20	18	>99	95
4	**3** (0.2)	CH_3OH/Tol 3:1	20	2	>99	93
5	**3** (0.2)	CH_3OH/Tol 1:3	20	72	<10	n.d.
6	**10** (0.2)	CH_3OH/Tol 3:1	20	21	>99	91
7	**11** (0.2)	CH_3OH/Tol 3:1	20	21	>99	83
8	**3** (0.2)	CH_3OH/Tol 3:1	−2	18	>99	96
9	**3** (0.1)	CH_3OH/Tol 3:1	−2	40	>99	95
10	**3** (0.05)	CH_3OH/Tol 3:1	−2	40	>99	89

[a] Reactions were carried out in a test tube on a 0.1 mmol scale without any precautions to exclude moisture and air. [b] Free sulfonic acids were obtained by passing the crude reaction mixture through freshly activated acidic ion-exchange resin. [c] Conversion evaluated by disappearance of **1a** by thin-layer chromatography (silica gel 60 F_{254}) and then verified by ^{1}H NMR analysis. [d] Enantiomeric excess determined with the sulfonic acid methyl ester generated by reaction of **2a** with Me_3SiCHN_2 and analysis by HPLC on a chiral stationary phase. n.d. = not determined.

Table 3: Catalytic enantioselective sulfonylation of chalcones **2a**–**n**.[a]



Entry	Prod. **2**	R^1	R^2	Yield [%] of **2**[b]	*ee* [%] of **2**[c]
1	**2a**	C_6H_5	C_6H_5	97[d] (99)	96[d] (92)
2	**2b**	C_6H_5	4-$CH_3OC_6H_4$	97	93
3	**2c**	C_6H_5	4-$NO_2C_6H_4$	87	92
4	**2d**	4-ClC_64_4	C_6H_5	97 (95)	93 (97)
5	**2e**	C_6H_5	4-FC_6H_4	91	90
6	**2f**	C_6H_5	4-ClC_6H_4	95 (94)	92 (94)
7	**2g**	4-$CH_3OC_6H_4$	C_6H_5	95	91
8	**2h**	4-FC_6H_4	C_6H_5	96	92
9	**2i**	C_6H_5	3-ClC_6H_4	96	98
11	**2l**	C_6H_5	2,4-$Cl_2C_6H_3$	97	99
12	**2m**	C_6H_5	3-$CH_3C_6H_4$	96	93
13	**2n**	C_6H_5	CH_3	97	83
14	**2o**	CH_3	C_6H_5	96	82
15	**2p**	$(CH_3)_2CHCH_2$	C_6H_5	94	85
16	**2q**	C_6H_5	$(CH_3)_3C$	92	84

[a] Reactions carried out in a test tube on 0.1 mmol scale without any precautions to exclude moisture and air. [b] Free sulfonic acids were obtained passing the reaction crude through freshly activated acidic ion exchange resin. [c] Enantiomeric excess determined after methylation of sulfonic acid **2a**–**q** with $TMSCHN_2$ and chiral stationary phase HPLC carried out on sulfonic acid methyl ester. Results in brackets refer to the opposite enantiomer, obtained using **3′** as the catalyst. [d] Reaction performed on 20 mmol scale.

ent-**2d**, and *ent*-**2f** with enantioselectivities comparable to those obtained with catalyst **3** (Table 3, entries 1, 4, 6, values in brackets). 4) Substrates **1n–q** bearing an aliphatic group on either R^1 or R^2 (Table 3, entries 13–16) reacted equally well, providing the corresponding acids **2n–q** in high 82–85% *ee*. The present method significantly expands the range of sulfonic acids that can be prepared. Only a few enantiopure aromatic sulfonic acids, such as **2a**, **2d**, and **2g**, can be prepared by resolution;[5] the other aromatic sulfonic acids in Table 3 and those bearing aliphatic groups, that is, **2n–q**, can be prepared only by the present methodology.

In conclusion, we have reported the first protocol for the enantioselective addition of bisulfite to α,β-unsaturated ketones.[15] The reaction was catalyzed by the bifunctional catalysts **3** and **3′** and afforded desired sulfonic acids **2a–q** in high yields and excellent enantioselectivity. The methodology described afforded multigram quantities of sulfonic acids and allowed the preparation of both enantiomers in high enantioselectivity. The sulfonic acids described herein could be recrystallized to provide a single enantiomer.[16] These materials will therefore be of interest to the synthetic community as resolving agents, Brønsted acids, or chiral building blocks.

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[15] The asymmetric addition of bisulfite to α,β-unsaturated alkenes is unprecedented. The group of Wang reported the addition of thioacetic acid, a different thio nucleophile, to alkenes to proceed under the catalysis of bifunctional aminothioureas with low enantioselectivity. See H. Li, L. Zu, J. Wang, W. Wang, *Tetrahedron Lett.* **2006**, *47*, 3145.

[16] An HPLC trace of enantiopure (+)-**2a** is included in the Supporting Information.

