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Organic Synthesis

Asymmetric Synthesis of Allylic Sulfonic Acids: Enantio- and Regioselective Iridium-Catalyzed Allylations of Na_2SO_3

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Abstract: An enantioselective allylation reaction of allylic carbonates with sodium sulfite (Na_2SO_3) catalyzed by Ir complex was accomplished, providing allylic sulfonic acids in good to excellent yields with a high level of enantio- and regioselectivities. (*R*)-2-Phenyl-2-sulfoacetic acid, a key intermediate for the synthesis of Cefsulodin and Sulbenicillin, was synthesized as well.

Sulfonic acid (RSO_3H) is one of the important acids in the area of biochemistry and is exceptionally involved in physiological processes.[1] 2-Aminoethanesulfonic acid (Taurine) is widely distributed in animal tissues, which is essential for cardiovascular function, and development and function of skeletal muscle.[2] 6-Ginger sulfonic acid isolated from *Zingiberis Rhizoma* also displays antiulcer activity.[3] A number of sulfonic acids, such as Prempro, Sulfotanshinone,[4] Metamizole,[5] Cefsulodin,[6] and Sulbenicillin,[7] have been popular in the drug market (Figure 1). Among these drugs, either Cefsulodin or Sulbenicillin, a semisynthetic cephalosporin antibiotic and a penicillin antibiotic respectively, contain a chiral sulfonic acid. Notably, the absolute configuration of the chiral sulfonic acids or their derivatives has an influence on the pharmacological efficacy.

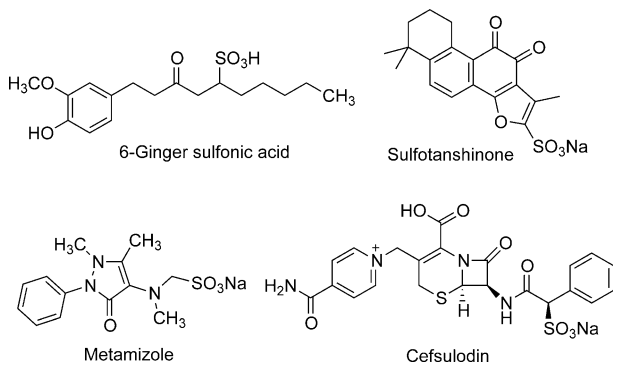

Figure 1. Four representative sulfonic acid containing drugs.

For example, (*S*)-α-phosphono sulfonate is more potent than the (*R*)-enantiomer as an inhibitor of squalene synthase.[8] Moreover, camphorsulfonic acid and its derivatives are often employed as resolving agents in the pharmaceutical industry.[9]

Sulfonic acids in enantiomerically pure form are usually attained from the corresponding racemates by a resolution technique with chiral amines.[10] Several enantiomeric α-substituted sulfonic acids were achieved by "Dutch resolution".[11] Also, enantiomeric β-substituted sulfonic acids[12] and sulfonates[13] were obtained by asymmetric synthesis. In 1992, Corey for the first time reported an (*R*)-1-phenylethanesulfonic acid derived from an enantiopure alcohol in multistep reactions.[14] Biller[8] and Enders[15] synthesized chiral sulfonic acids by using a chiral auxiliary, which induced an asymmetric sulfonation at the adjacent carbon atom. Adamo[16] and Peters[17] reported cinchona alkaloid-catalyzed asymmetric reactions for the formation of sulfonic acids. By this token, the practical methods for the construction of chiral sulfonic acids are less reported, of which an efficient approach is highly desirable. The most direct synthesis of allylic sulfonic acids, which can be easily converted into sulfonic acids, is by direct transition-metal-catalyzed allylation of a sulfite anion. Advances in enantioselective iridium-catalyzed allylation reactions[18] inspired us to explore this strategy. Carbon–sulfur bond formation by enantioselective transition-metal-catalyzed allylations has been less reported[19] since sulfur reagents may poison the catalyst.[20] To the best of our knowledge, iridium-catalyzed sulfonation has not yet been reported at present. We herein report an enantioselective iridium-catalyzed allylation reaction of allylic carbonates with sodium sulfite (Na_2SO_3), which directly produces the allylic sulfonic acids. The synthesis of (*R*)-2-phenyl-2-sulfoacetic acid was also discussed.

At the outset, we carried out a sulfonation reaction between (*E*)-cinnamyl methyl carbonate **1a** and sulfite salt **2** in the presence of an Ir complex[21] made from 2 mol% of $[IrCl(cod)]_2$ (cod = 1,4-cyclooctadiene) and 4 mol% of **L1**[22] at room temperature (Table 1). Interestingly, the formation of the allylic sulfonic acids[23] (**3a** and **4a**) was observed when Na_2SO_3 (**2a**) was used (Table 1, entry 1). Other alkali–metal sulfites including K_2SO_3 (**2b**) and $NaHSO_3$ (**2c**) were also examined. These alkali–metal sulfites are cheap, abundant, and green. Compound **2b** gave rise to similar results; however, **2c** led to a trace amount of **3a** along with **4a**. Taking into consideration the economic reason, Na_2SO_3 (**2a**) was chosen in our further investigation on the sulfonation reaction. The nature of solvents has a great impact on the reaction outcomes. Significantly, when a component solvent, such as MeOH/H_2O (4:1) was employed, 60%

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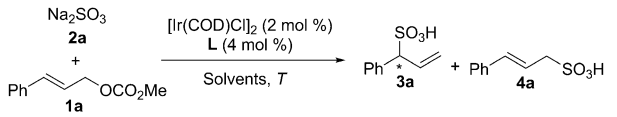
Table 1. Optimizing conditions for the allylic sulfonation of (*E*)-cinnamyl methyl carbonate **1a** with sulfite **2a**.[a]



Entry	Solvent	*T* [°C]	L	Yield **3a**+**4a** [%][b]	**3a**/**4a**[c]	*ee* [%][d]
1	MeOH	25	**L1**	7	98:2	–
2	MeOH/H_2O	25	**L1**	28	98:2	60
3	CH_2Cl_2/H_2O	25	**L1**	trace	–	–
4	toluene/H_2O	25	**L1**	trace	–	–
5	THF/H_2O	25	**L1**	97	98:2	95
6	MeCN/H_2O	25	**L1**	8	–	–
7	THF/H_2O	25	**L1**	97	98:2	95
8	THF/H_2O	10	**L1**	50	98:2	95
9	THF/H_2O	40	**L1**	85	95:5	90
10[e]	THF/H_2O	25	**L1**	93	97:3	95
11[f]	THF/H_2O	25	**L1**	95	98:2	95
12[g]	THF/H_2O	25	**L1**	11	98:2	–
13	THF/H_2O	25	**L2**	80	93:7	96
14	THF/H_2O	25	**L3**	75	98:2	95
15	THF/H_2O	25	**L4**	65	91:9	91
16	THF/H_2O	25	**L5**	–	–	–
17	THF/H_2O	25	**L6**	trace	–	–

[a] Reaction conditions: **1a** (0.40 mmol, 1 equiv), **2a** (0.80 mmol, 2 equiv), $[Ir(cod)Cl]_2$ (2 mol%), **L1**–**L6** (4 mol%), and mixed solvents (5.0 mL, organic solvent/H_2O = 4:1 for entries 2–11 and 13–17) at room temperature under argon. The reaction mixture was purified through a plug of freshly activated acidic ion exchange resin. [b] Calculated yield, for which the weight of H_2O is reduced from the hydrated sulfonic acids based on the integration of the hydrogen of H_2O in the ^{1}H NMR spectra. For the details, see the Supporting Information. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase (Diacel CHIRALPAK IC) with the sulfonic acid methyl ester made by esterification of **3a** with $TMSCHN_2$. [e] **1a**/**2a** = 1:2. [f] **1a**/**2a** = 2:1. [g] THF/H_2O (9:1) was used.

enantiomeric excesses (*ee*) of **3a** were obtained; and the yield of **3a** was also increased from 7 to 28% (entry 2). We assumed that a combination of MeOH with water is beneficial to this sulfonation reaction. Subsequent investigation on the solvents revealed that THF/H_2O (4:1) is the optimal component solvent with the gratified results, 97% yield, b/l 98:2 (branched/linear), and 95% *ee* (entry 5). CH_3CN/H_2O resulted in an 8% yield of **3a**, whereas other mixed solvents, such as CH_2Cl_2/H_2O and toluene/H_2O were ineffective (entries 3–4, and 6). Variation of both reaction temperature and the ratio of the reactants (**1a**/**2a**) has a considerable effect on the sulfonation reaction (entries 5, 8–9 and 10–11). The reduction of water in a component solvent (THF/H_2O) greatly decreased the yields of **3a**+**4a** due to the decreased amount of solubilized Na_2SO_3 (**2a**) (Table 1, entry 12). The effect of phosphoramidite ligands including Feringa's, **L2**–**L6**,[24–28] on the sulfonation was investigated (Figure 2). The direct sulfonation of Na_2SO_3 (**2a**) occurred with the best enantioselectivity and regioselectivity with the assistance of the catalyst made from Feringa's **L1** ligand (entry 5). However, reactions catalyzed by the complex generated from **L2**–**L4** occurred in moderate to good yields with a high level of enantio- and regioselectivities (entries 13–15). Reactions conducted with the catalysts made from **L5** and **L6** took place with poor results (entries 16–17).

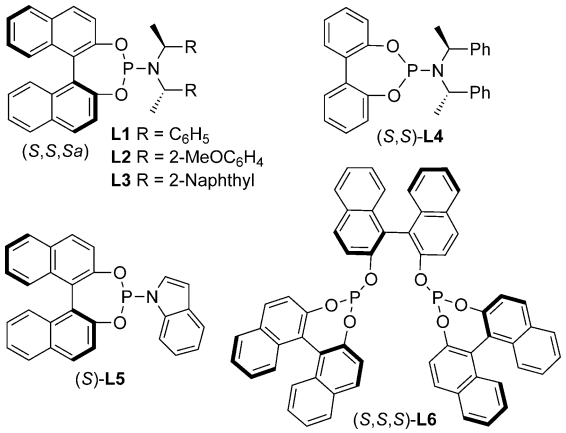


Figure 2. Chiral ligands **L1**–**L6** used in this sulfonation.

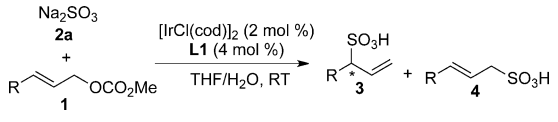
With the optimized conditions in hand, the scope of the sulfonation of various allylic carbonates **1** with Na_2SO_3 (**2a**) was further explored (Table 2). (*E*)-Cinnamyl methyl carbonate (**1a**) and allylic carbonates (**1b**–**j**) with a variety of substitution patterns at the aromatic moiety, such as either electron-donating groups (e.g., 3-Me, 3-MeO, 4-Me, and 4-MeO) or electron-withdrawing groups (e.g., 3-F, 3-Cl, 4-F, 4-Cl, and 4-Br) afforded the corresponding branched allylic sulfonic acids (**3a**–**j**) in moderate to high yields (60–97%) with a high level of regioselectivities (95:5–99:1) and enantioselectivities (93–96% *ee*). Noticeably, both **3d** and **3h** bearing a fluorine atom on the phenyl ring are promising for the synthesis of monofluorinated Cefsulodin due to the importance of fluorine in drugs.[29] 2-Naphthalenyl or hetero-aryl-substituted allylic carbonates (**1k**–**m**) gave rise to the sulfonation products (**3k**–**m**) in 76–99% yields with excellent regioselectivities (97:3–99:1) and 89–98% *ee* (Table 2). Because of the significance of heterocyclic compounds in the pharmaceutical industry, the construction of chiral heterocyclic sulfonic acids is meaningful. Furthermore, aliphatic allylic carbonate (**1n**) led to the aliphatic sulfonic acid (**3n**) in good yield (80%) with a high regioselectivity (91:9) and 89% *ee* (Table 2).

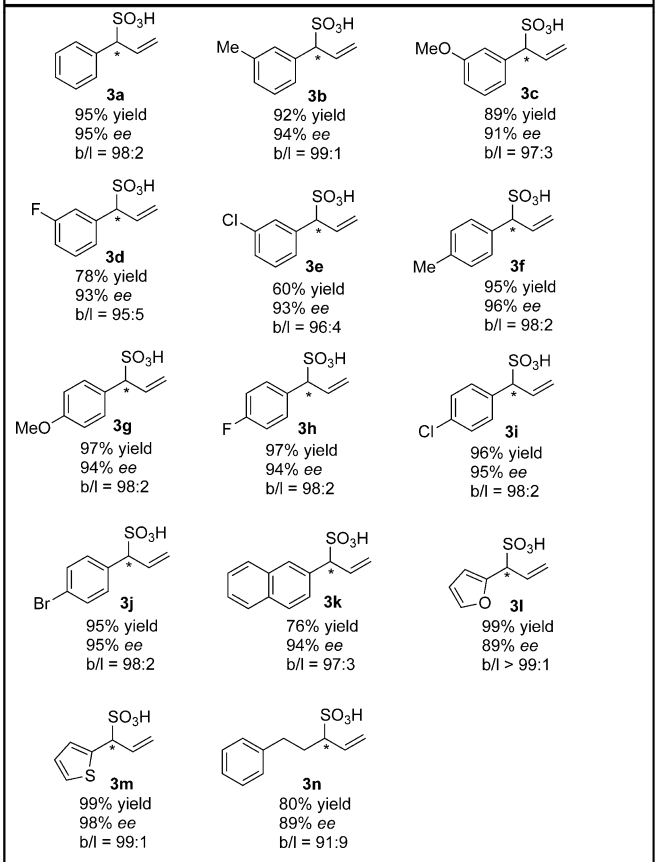
A single-crystal X-ray diffraction analysis of Ca[**3j**]$_2$[30] (Figure 3), which was generated from **3j** in the enantiopure form and $CaSO_3$, reveals the absolute configuration of **3j** as *S* (see the Supporting Information for details).

The synthetic utility of the sulfonation product **3** generated in this way for the synthesis of Cefsulodin was demonstrated in Scheme 1. Cefsulodin shows specific potent in vivo anti-pseudomonal activity against *Pseudomonas aeruginosa*.[31]

A known procedure for the synthesis of enantiopure (*R*)-2-phenyl-2-sulfoacetic acid **3ab** is by using a resolution technique with L-lysine.[6a] Until now, asymmetric catalysis with transition-metal complexes for the construction of sulfonic acid has not been reported yet. We performed a sulfonation reaction of (*E*)-cinnamyl methyl carbonate (**1a**) with Na_2SO_3 (**2a**) under the optimal conditions on a large scale. Consequently, (*S*)-1-phenylprop-2-ene-1-sulfonic acid ((*S*)-**3a**) (550 mg, 71% yield) was obtained with both excellent regio- and enantioselectivity (b/l 93:7 and 94% *ee*). Allylic sulfonic

Table 2. The scope of the sulfonations between allylic carbonates **1** and sodium sulfite **2a**.[a]





[a] Reaction conditions: **1** (0.40 mmol, 1 equiv), Na_2SO_3 **2a** (0.80 mmol, 2 equiv), $[IrCl(cod)]_2$ (2 mol%), **L1** (4 mol%), THF/H_2O (4:1, 5.0 mL), argon and room temperature. The reaction mixture was purified through a plug of freshly activated acidic ion-exchange resin. Yield = calculated yield, for which the weight of H_2O is reduced from the hydrated sulfonic acid based on the integration of the hydrogen of H_2O in the ^1H NMR spectra; for the details, see the Supporting Information. b/l ratio was determined by ^1H NMR spectroscopy. Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase with the sulfonic acid methyl ester made by esterification of **3** with $TMSCHN_2$.

acid **3a** was oxidized with ozone in $MeOH/CH_2Cl_2$ at −78 °C to give **3ab** in 61% yield,[32] the latter can be readily applied to the formation of Cefsulodin according to the known procedure.[6]

In conclusion, we have developed a practical protocol for the construction of chiral sulfonic acids through Ir-catalyzed sulfonation, which afforded the allylic sulfonic acids in moderate to excellent yields with high enantio- and regioselectivities. The method allows the use of Na_2SO_3 under mild conditions, demonstrates excellent tolerance of various substrates, and provides a direct, economic, and green way for the synthesis of chiral sulfonic acids. This is the first iridium-catalyzed sulfonation reaction to directly synthesize the chiral sulfonic acids.

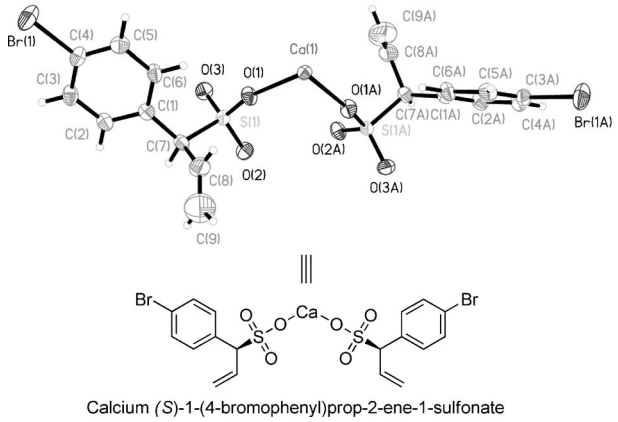
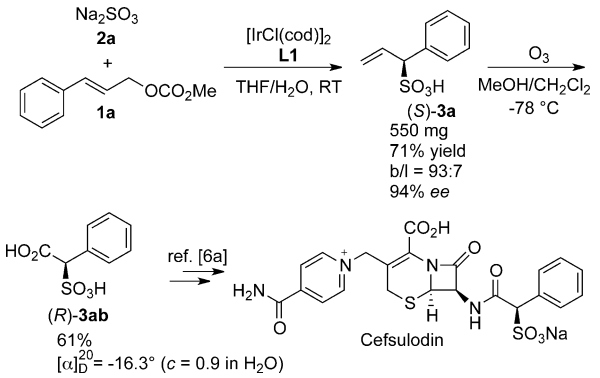


Figure 3. X-ray structure of calcium (S)-1-(4-bromophenyl)prop-2-ene-1-sulfonate ($Ca[(S)\text{-}\mathbf{3j}]_2$).



Scheme 1. Application of chiral sulfonic acid **3a** in the synthesis of Cefsulodin.

Experimental Section

General procedure for the Ir-catalyzed allylic sulfonation reaction of Na_2SO_3 (2a)

Allylic carbonate **1** (0.40 mmol, 1 equiv) and a mixture of THF (4.0 mL) and H_2O (1.0 mL) in a reaction tube equipped with a magnetic stirring bar were added in sequence at room temperature under argon. To this solution were sequentially added the catalyst made from both $[IrCl(cod)]_2$ (0.008 mmol, 2 mol%) and phosphoramidite ligand **L1** (0.016 mmol, 4 mol%) and sodium sulfite Na_2SO_3 (**2a**) (0.80 mmol, 2 equiv). The reaction was vigorously stirred at room temperature for the stated time. The reaction mixture was stirred until the allylic carbonate **1** was completely consumed. Workup was performed through a plug of freshly activated acidic ion-exchange resin.[33] The crude residue was purified by flash column chromatography (methanol/ethyl acetate) to give the desired products **3**.

The allylic sulfonic acid **3** (0.2 mmol) was added into the mixture of CH_2Cl_2 (2.0 mL) and HBF_4 (50% aq, 20 μL) at room temperature, and then trimethylsilyl diazomethane (Me_3SiCHN_2, 1.0 mmol, 1.0 mL) was added dropwise into above-mentioned solution. The reaction mixture was stirred for 1 h and then the volatile solvent was removed under reduced pressure. The methylated sulfonic acids **3aa**–**na** were obtained by purifying the crude residue by column chromatography (petroleum ether/ethyl acetate).

Acknowledgements

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Keywords: enantioselectivity · regioselectivity · sodium sulfite · sulfonation · sulfonic acids

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[30] CCDC-976963 ($Ca[(S)$-**6j**$]_2$) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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