β-Sultones

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Catalytic Enantio- and Diastereoselective Formation of β-Sultones: Ring-Strained Precursors for Enantioenriched β-Hydroxysulfonyl Derivatives**

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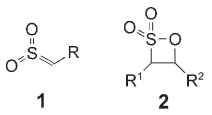
Ketenes are exceptionally versatile, widely used substrates in asymmetric catalysis that allow the stereoselective formation of various important compound classes.[1–2] Sulfenes **1**, the sulfonyl equivalents of ketenes,[3] have not been applied to date in asymmetric catalysis. This may be due in part to the fact that sulfenes are far less stable than ketenes: simple alkyl-substituted sulfenes have never been isolated, but their existence was spectroscopically demonstrated by IR spectroscopy at −196 °C.[4] The application of sulfenes in asymmetric catalysis would lead to more sustainable, resource- and time-saving approaches towards enantiomerically pure sulfonyl derivates.[5] As chiral sulfonyl analogues of carbonyl derivatives are of increasing importance in medicinal chemistry,[6] partly because they mimic the structural properties of the transition states leading to tetrahedral intermediates, the development of catalytic asymmetric methods using sulfene substrates is an important undertaking.

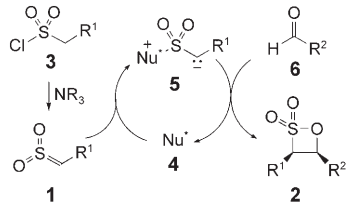


1 **2**

In this context, we became interested in β-sultones **2**, which are highly reactive sulfonyl analogues of β-lactones.[7] In contrast to the latter compounds, β-sultones are a less-investigated substance class despite their potentially high value as synthetic building blocks.[8] As a result of their inherent reactivity owing to ring strain, β-sultones are prone to regioselective nucleophilic ring-opening reactions under mild conditions to provide either β-substituted sulfonic acids or β-hydroxysulfonyl derivatives.[9] The evolution of such ring-opening strategies has so far been limited by the availability of functionalized β-sultones, and up to now the title compounds have never been prepared enantioselectively. The reason is that most β-sultones have been reported to be unstable at room temperature because of the occurrence of proton shift, elimination, and rearrangement reactions. Particularly thermally unstable are most β-sultones which contain an α-CH_2 moiety. They were often found to rearrange almost completely within several hours at room temperature to yield mixtures of isomeric unsaturated sulfonic acids as well as γ- and δ-sultones.[10] Exceptionally stable derivatives are those with the electron-withdrawing and bulky CCl_3 group at the β-position which significantly stabilizes the otherwise labile C–O bond.

Borrmann and Wegler reported in 1966 that β-sultones are accessible by a [2+2] cycloaddition route, which utilizes the parent sulfene as a reactive intermediate.[11] Ten years later, King and Harding discovered that the formation of β-sultones is improved by the use of a large excess of a sterically non-hindered tertiary amine such as NMe_3.[12] This behavior was attributed to the reversible formation of reactive zwitterionic intermediates from sulfenes and tertiary amines which subsequently undergo a cyclocondensation reaction with a strongly polarized aldehyde. Consequently, as the size of the base decreases, so the quantity of zwitterions at equilibrium should be increased.

On the basis of these results, we assumed that it should be possible to form β-sultones enantioselectively by the action of a catalytic amount of an enantiopure chiral nucleophile **4** (Scheme 1). The catalyst is regenerated during the internal esterification step for further turnover. The reactivity of a sulfene that normally acts as an electrophile would thus be reverted by the formation of a nucleophilic zwitterion **5**. The present work was inspired by the tertiary amine catalyzed enantioselective [2+2] cycloaddition of ketene and chloral, which furnished the corresponding β-lactone in high yield and with excellent enantioselectivity.[13]



Scheme 1. Proposed asymmetric formation of β-sultones catalyzed by enantiopure nucleophiles.

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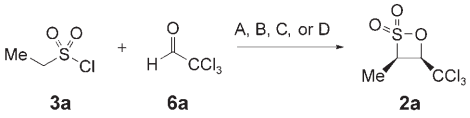
Supporting information, including the Experimental Section, for this article is available on the WWW under http://www.angewandte.org or from the author.

As a result of the stability problems, we focused on the formation of 3,4-disubstituted β-sultones that bear an electron-withdrawing group at the 4-position. Ethylsulfonylchloride (**3a**) and chloral (**6a**) were selected as model substrates. Using quinuclidine in stoichiometric amounts as a sterically undemanding nucleophile in dichloromethane at −15 °C, racemic β-sultone **2a** was isolated in almost 90 % yield as a single diastereomer [Eq. (1), A].



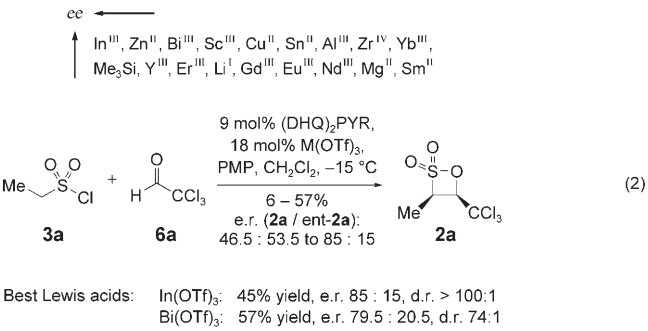
3a **6a** **2a** (1)

A: 1.05 equiv quinuclidine, CH_2Cl_2, −15 °C (89%, **2a** + *ent*-**2a**)
B: 10 mol% quinuclidine, 1.45 equiv *i*Pr_2NEt, CH_2Cl_2, −15 °C (76%, **2a** + *ent*-**2a**)
C: 10 mol% MeQ / BnQ / TMSQ / $(DHQ)_2$PYR, 1.45 equiv *i*Pr_2NEt, CH_2Cl_2, −15 °C (yield; e.r. (**2a** / *ent*-**2a**): 8%; 55.5:44.5 / 3%; nd / 2%; nd / 23%, 47:53)
D: 9 mol% MeQ / BnQ / TMSQ / $(DHQ)_2$PYR, 18 mol% $Sc(OTf)_3$, 1.45 equiv *i*Pr_2NEt, CH_2Cl_2, −15 °C (yield; e.r. (**2a** / *ent*-**2a**); d.r.: 18%; 59:41; 27:1 / 13%; 63:37; 16:1 / 26%; 70:30; 23:1 / 41%; 75.5:24.5; 30:1)

The reaction still proceeded well with a catalytic amount of the nucleophile in combination with a stoichiometric, bulky non-nucleophilic auxiliary base for the formation of the sulfene by dehydrochlorination of sulfonyl chloride **3** [Eq. (1), B]. With 10 mol % of quinuclidine in the presence of 1.45 equivalents of *i*Pr_2NEt, the diastereomerically pure target molecule **2a** was obtained in 76 % yield. However, the transfer to chiral quinuclidine catalysts, namely cinchona alkaloid derivatives, turned out to be a nontrivial task. With 10 mol % of various quinine derivatives in combination with 1,2,2,6,6-pentamethylpiperidine (PMP) as stoichiometric base in CH_2Cl_2 at −15 °C, the product was formed in very low yield (2–23 %) and with almost no enantioselectivity (e.r. ≤ 55.5:44.5) [Eq. (1), C; MeQ: methylquinine; BnQ: benzylquinine; TMSQ: trimethylsilylquinine ether; $(DHQ)_2$PYR: dihydroquinine-2,5-diphenyl-4,6-pyrimidinediyl diether].

The low enantioselectivities observed might be surprising at first sight given the high e.r. values obtained in the formation of β-lactones through ketene-derived zwitterionic enolates. However, fundamental structural differences between the anticipated reactive intermediates **5** and the ketene-derived zwitterionic enolates **7** must be expected (Scheme 2). Whereas in the case of **7** both enolate carbon atoms are sp^2-hybridized, the sulfur atom in **5** and presumably also the α-carbon atom are pyramidalized in analogy to the majority of lithiated sulfone carbanions that bear one alkyl group at the α-position as the only substituent.[14] This implies that the diastereomeric zwitterionic species **5a** and **5a′** are formed, whereas in the case of the ketene the cinchona alkaloid is supposed to bind selectively *trans* to the enolate residue R.[1b] The absolute configuration of the β-sultone products **2** primarily depends on the reactive configuration of the zwitterion. The sulfene-amine adducts **5a** and **5a′** would be expected to be diastereomeric species even if their α-carbon atoms are planar (as expected, for example, for aromatic residues R) owing to the existence of favored C_α–S conformations whereby both sulfonyl oxygen atoms should be arranged *gauche* to the lone pair in the α-carbon atom as a result of a stabilizing negative hyperconjugation (n_C-σ^*_{SN}) leading to hindered C_α–S rotation. This would be in analogy to (n_C-$\sigma^*_{S-C'}$) interactions, which are known to stabilize sulfone carbanions.[15]

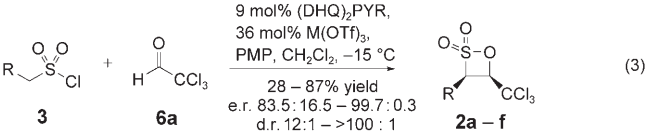
To enhance the reactivity of the catalytic system, the effect of activation by Lewis acids was investigated. Initial experiments in the presence of 18 mol % $Sc(OTf)_3$ (Tf: trifluoromethanesulfonyl) revealed that both the yield and e.r. values were significantly improved, with the best values being obtained with $(DHQ)_2$PYR (9 mol %) as enantiopure nucleophile (41 % yield, e.r. = 75.5:24.5; [Eq. (1), D]).[16] This nucleophile was initially developed by Sharpless and coworkers as a ligand for asymmetric dihydroxylations.[17] By screening various metal triflate salts [Eq. (2)], $In(OTf)_3$ (best e.r. values) and $Bi(OTf)_3$ (best yields) emerged as the most promising co-catalysts.



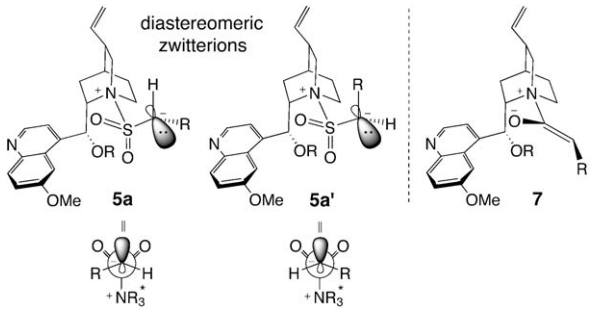
3a **6a** **2a** (2)

Best Lewis acids: $In(OTf)_3$: 45% yield, e.r. 85 : 15, d.r. > 100:1
$Bi(OTf)_3$: 57% yield, e.r. 79.5 : 20.5, d.r. 74:1

A final optimization of the reaction conditions (temperature, amount of catalyst and co-catalyst, stoichiometry, achiral auxiliary base) finally gave **2a** in a yield of 61–78 % with excellent diastereomeric ratios and e.r. values of 83.5:16.5 to 89:11 ([Eq. (3)]; Table 1, entries 1 and 2). With increasing bulk of the sulfonyl chloride residue R, the e.r. values were enhanced to 90.5:9.5–99.7:0.3 ([Eq. (3)]; Table 1,



3 **6a** **2a – f** (3)



Scheme 2. Comparison of the structure of the proposed sulfene zwitterions **5a**/**5a′** with the ketene-derived enolate **7**.

Table 1: Investigation of the formation of β-sultones **2** employing different sulfonyl chlorides **3**.

Entry	R	Product	M	Yield [%][a]	d.r.[b]	e.r.[c]
1[d,e]	Me	**2a**	Bi	78	96:1	83.5:16.5
2[d,e]	Me	**2a**	In	61	>100:1	89:11
3	Et	**2b**	Bi	65	>100:1	96:4
4[d]	Et	**2b**	In	28	>100:1	97:3
5	Pr	**2c**	Bi	47	>50:1	91.5:8.5
6	Pr	**2c**	In	36	>50:1	94.5:5.5
7	$(CH_2)_2Cl$	**2d**	Bi	87	>50:1	97.5:2.5
8	$(CH_2)_2Cl$	**2d**	In	58	15:1	90.5:9.5
9	CH_2Ph	**2e**	Bi	60	22:1	95.5:4.5
10	CH_2Ph	**2e**	In	57	12:1	92:8
11	$MeOC_6H_4O(CH_2)_2$	**2f**	Bi	83	>100:1	99.7:0.3
12	$MeOC_6H_4O(CH_2)_2$	**2f**	In	69	>100:1	99.6:0.4

[a] Yield of isolated product. [b] d.r. values were determined by ^{1}H NMR spectroscopy. [c] The e.r. values were determined by chiral column HPLC (Daicel OD-H). [d] 18 mol% of $M(OTf)_3$ was used. [e] iPr_2NEt was used instead of PMP.

entries 3–12). To obtain preparatively useful yields, 0.36 equivalents of the metal triflate salt were necessary. In general, $Bi(OTf)_3$ provided better yields than $In(OTf)_3$, while in terms of the stereoselectivity a clear-cut trend is not obvious. Surprisingly, even the chloroethyl substituent was well tolerated in the presence of the nucleophilic catalyst (Table 1, entries 7–8).

The absolute configuration of **2b** (*R*,*R*) was established by the first X-ray crystal structure analysis of a monocyclic β-sultone (Figure 1).[18] The ring system of the *cis*-configured

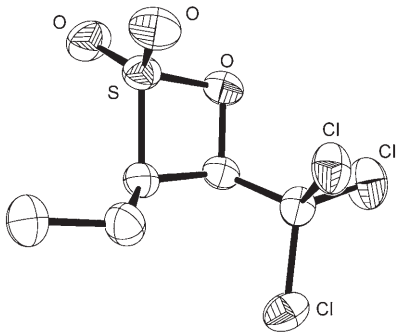
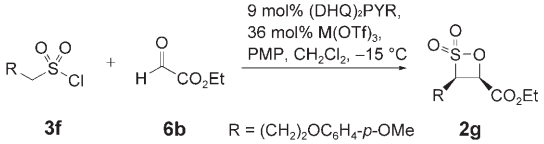


Figure 1. ORTEP representation of β-sultone **2b** in the crystal structure (50% probability ellipsoids, hydrogen atoms are omitted for clarity, non-carbon atoms are labeled).

species is almost completely flat and has a C-S-O angle of 82.7°.[19]

The optimized reaction conditions can also be adapted to alternative electron-poor aldehydes as demonstrated for ethyl glyoxylate **6b** ([Eq. (4)], Table 2). The five most useful metal



(4)

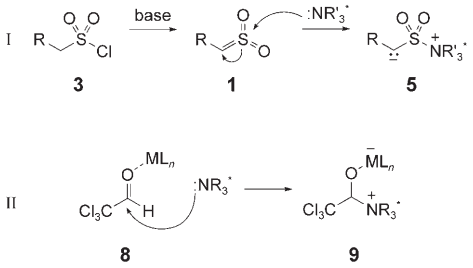
Table 2: Optimization of β-sultone formation with ethyl glyoxylate (**6b**).

Entry	M	Yield [%][a]	d.r.[b]	e.r.[c]
1	$In(OTf)_3$	62	2.5:1	95:5
2	$Bi(OTf)_3$	52	2:1	95:5
3	$Cu(OTf)_2$	32	3.5:1	93.5:6.5
4	$Zn(OTf)_2$	23	>100:1	88.5:11.5
5	$Sc(OTf)_3$	14	>100:1	nd
6[d]	$In(OTf)_3$	7	3:1	97:3

[a] Yield of isolated product. [b] d.r. values were determined by ^{1}H NMR spectroscopy. [c] The e.r. values were determined by chiral column HPLC (Daicel OD-H); nd: not determined. [d] Reaction was performed at −40 °C.

triflate salts from the previous Lewis acid screening with chloral (**6a**) were investigated with **6b**, and the best results were obtained again with $In(OTf)_3$ and $Bi(OTf)_3$ (Table 2, entries 1 and 2). Both the yield and stereoselectivity were lower than with chloral but still in a preparatively useful range.[20]

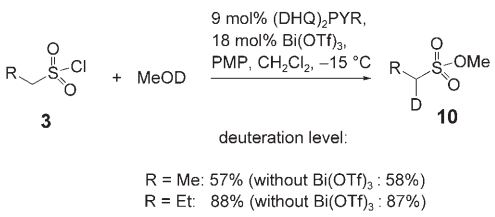
From a mechanistic point of view, two scenarios might in principal account for the product formation (Scheme 3): I the proposed formation of a sulfene-derived zwitterionic inter-



Scheme 3. Potential reactive intermediates for the formation of β-sultones catalyzed by nucleophiles.

mediate **5** or II the formation of a zwitterionic chloral-amine adduct **9**, which undergoes a cyclocondensation reaction with sulfonyl chloride **3** or the corresponding sulfene.

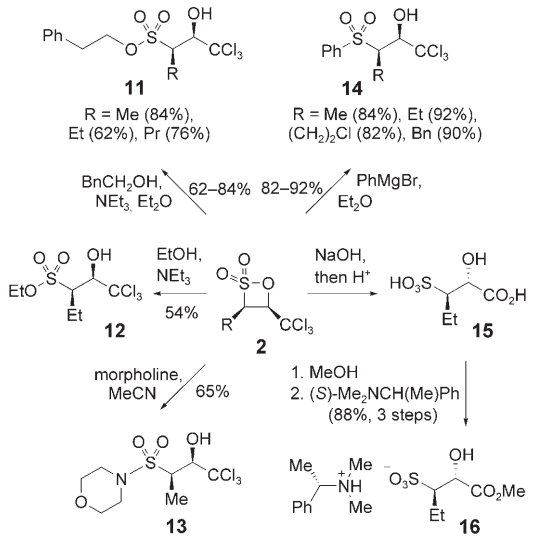
The formation of sulfenes under the described reaction conditions was verified by deuteration experiments.[21] When sulfonyl chlorides **3** were treated with base, catalyst, and Lewis acid in the presence of MeOD, the monodeuterated esters **10** were selectively formed [Eq. (5)]. Double deuteration was not detected, thus excluding a random deprotonation process. The deuteration level was not influenced by the Lewis acid co-catalyst.



(5)

Unusual temperature characteristics were found for the model reaction with ethylsulfonyl chloride (**3a**) and chloral (**6a**). The e.r. values reached a maximum at −25 °C using $In(OTf)_3$ and at −40 °C using $Bi(OTf)_3$ as co-catalyst, and they decreased significantly at both higher or lower temperatures.[22] These results might be attributed to a simultaneous action of two competing reaction pathways I and II (Scheme 3). The following finding points to the mechanistic scenario I as the major reaction pathway: the results listed in Table 1 were obtained by addition of a solution of the sulfonyl chloride **3** to the reaction mixture over a period of 2.5 h using a syringe pump to maintain a low concentration of sulfene so as to avoid sulfene dimerization and oligomerization. Stirring was then continued for an additional 15 min before the reaction mixture was quenched. However, if the addition time of the sulfonyl chloride was reduced to just 5 min, the e.r. values were significantly increased, for example, from 97:3 to 99.75:0.25 (entry 4 , Table 1), although at the expense of diminished yields (< 15 %). Under these conditions, the concentration of the reactive sulfene intermediates was increased thus favoring pathway I.[23]

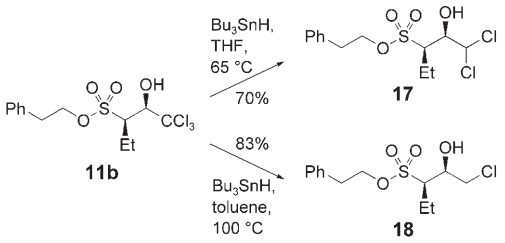
Ring-opening reactions with alcohols, amines, or Grignard reagents gave regioselective access to enantioenriched β-hydroxysulfonates **11** and **12**, β-hydroxysulfonamide **13**, and β-hydroxysulfones **14**, thus exemplifying the synthetic value of enantioenriched β-sultones (Scheme 4). No epimerization



Scheme 4. Regioselective nucleophilic ring opening of enantioenriched β-sultones. Bn: benzyl.

or racemization occurred during these transformations. In addition, the trichloromethyl group was readily hydrolyzed by aqueous NaOH to furnish α-hydroxy acid **15**, which was transformed to ammonium salt **16**.[24] Enantiopure β-hydroxysulfonyl derivatives are attractive synthetic targets as they exhibit a variety of biological activity and are investigated for the treatment of diseases such as diabetes, peripheral vascular disease, cardiac failure, Alzheimer's disease, atherosclerosis, thrombosis, neurodegenerative disorders, or pain.[25–27]

The trichloromethyl group can be partially reduced by Bu_3SnH (Scheme 5). Depending upon the reaction conditions, either the di- or the monochloro derivatives **17** or **18** were selectively obtained, thus significantly enhancing the synthetic usefulness of the chloral-derived β-sultones.[28]



Scheme 5. Reduction of the CCl_3 group in **11b**.

In conclusion, a methodology has been developed which enables a rapid enantio- and diastereoselective access to highly enantioenriched β-hydroxysulfonyl derivatives comprising two vicinal stereocenters—compounds hardly accessible in a stereoselective way by alternative means. The starting materials are inexpensive, and the catalysts are easily recycled by acid–base workup. After this first application of sulfenes in asymmetric catalysis, this work is expected to pave the way to further applications on synthesizing enantiopure sulfonyl compounds by nucleophilic catalysis, as is currently being investigated in our laboratory.

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[8] The most common way so far to synthesize β-sultones is by sulfonylation of olefins. However, this method which provides racemic products is mainly restricted to terminally or symmetrically disubstituted olefins (see Ref. [9]).

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