Catalytic Enantioselective Synthesis of 3-Substituted Benzosultams via Corey–Bakshi–Shibata Reduction of Cyclic *N*-Sulfonylimines

Dieter Enders,* Matthias Seppelt

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
Fax +49(241)8092127; E-mail: enders@rwth-aachen.de

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Abstract: The catalytic asymmetric synthesis of 3-substituted benzo-fused sultams employing the Corey–Bakshi–Shibata reduction with catecholborane of the corresponding cyclic *N*-sulfonylimines is reported. Good to excellent yields (74–95%) and enantiomeric excesses (69–94%) are obtained.

Key words: asymmetric synthesis, imine, reduction, catalysis, sulfonamide

Sultams can be seen as sulfur analogues of lactams and represent an important class of heterocyclic compounds, which can be found in many biologically active compounds[1] such as the anti-inflammatory agent **A**, the carbonic anhydrase inhibitor **B**, and the herbicide **C** (Figure 1).[2] In addition, the sultam **D** developed by Oppolzer et al. has been used as a chiral auxiliary in many asymmetric syntheses.[3] This is also true for the 3-substituted benzosultam title compounds, which as N–F reagents can be used for electrophilic fluorinations.[3d] Benzo-fused sultams have also received much attention as potent HIV reverse-transcriptase inhibitors.[4]

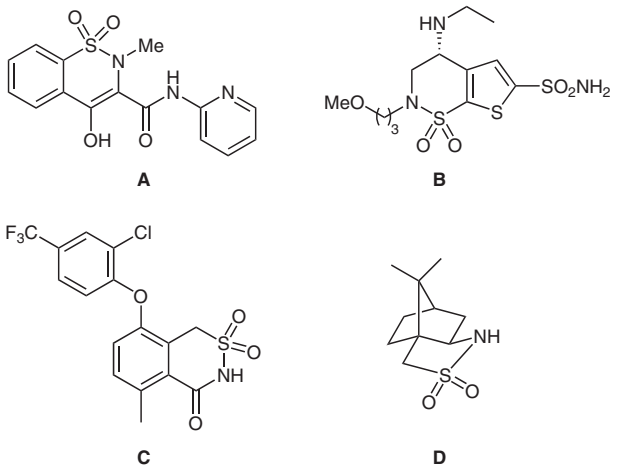
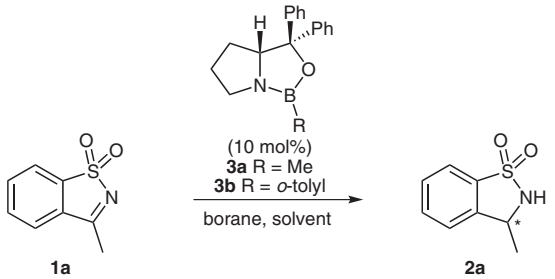


Figure 1 Selected compounds with biological activity **A**–**C** and the Oppolzer sultam **D**

Many protocols for the synthesis of sultams have been described offering a broad substrate diversity. The formation of the sultam structure can be realized by cycloadditions,[5] Friedel–Crafts reactions,[6] Heck couplings,[7] ring-closing metathesis[8] along with a number of cyclization reactions.[9,10] Beyond these methods a very convenient synthesis of chiral sultams is the hydrogenation of cyclic *N*-sulfonylimines. Whilst various enantioselective metal-catalyzed hydrogenations of such imines have been developed,[11] to the best of our knowledge an enantioselective organocatalytic reduction of cyclic *N*-sulfonylimines has not been published so far. A transition-metal-free approach can be envisaged by utilizing the well-established Corey–Bakshi–Shibata (CBS) reduction.[12] While this is known to provide easy access to a wide range of highly enantioenriched alcohols by the reduction of ketones, relatively few examples for the enantioselective reduction of imines are described in the literature.[13] Difficulties in the enantioselective borane reduction of ketimines stem from the equilibrium between the *E*- and *Z*-isomers and their differentiation by the catalyst.[14] Furthermore, oxazaborolidines as Lewis acids may be trapped by the basic nitrogen of the imine moiety. However, there exist several examples for the enantioselective reduction of imines with catalytic amounts of chiral boron reagents. This method has been applied to various aromatic and aliphatic imines[15] and oximes[16] as well as to stable N–H imines.[17] A successful attempt to reduce a cyclic *N*-sulfonylimine by applying a CBS catalyst, however, has not been described so far.[18]



Scheme 1 Catalytic asymmetric synthesis of sultam **2a** by CBS reduction of the cyclic *N*-sulfonylimine **1a**

In continuation of our efforts in the asymmetric synthesis of various sultams,[10] we herein report the enantioselective Corey–Bakshi–Shibata reduction of prochiral cyclic *N*-sulfonylimines **1** to highly enantioenriched benzo-fused sultams **2**. Scheme 1 shows the model system for our investigation of the CBS reduction of cyclic *N*-sulfonylimines.

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For initial tests the cyclic *N*-sulfonylimine **1a** was added slowly to a solution of the borane–THF complex and 10 mol% of oxazaborolidine **3a**. When performed at room temperature only a very low enantioselectivity was achieved. The enantiomeric excess could be increased to 53% ee by lowering the temperature to –78 °C (Table 1, entry 1 and 2). Encouraged by these results we decided to test catecholborane as a bulkier hydride source which led to a significant improvement of the enantioselectivity (73–79%). Varying the order of addition of the reagents or changing the catalyst to oxazaborolidine **3b** did not improve the reaction further (entry 5 and 6).

Table 1 Evaluation of the Reaction Conditions for the Asymmetric Synthesis of Sultam **2a** (Scheme 2).

Entry[a]	Catalyst	Borane	Temp	Yield (%)[b]	ee (%)[c]
1	**3a**	BH_3·THF	r.t.	63	21
2	**3a**	BH_3·THF	–78 °C to r.t.	72	53
3	**3a**	catecholborane	r.t.	59	73
4	**3a**	catecholborane	0 °C	60	79
5[d]	**3a**	catecholborane	r.t.	67	76
6	**3b**	catecholborane	0 °C	55	56

[a] A solution of imine **1a** (0.5 mmol) in THF (5 mL) was added by syringe pump addition over 1 h to a solution of catalyst **3** (0.1 equiv) and BH_3·THF (0.6 equiv) or catecholborane (1.0 equiv) in THF (1 mL). The reaction mixture was stirred overnight.
[b] Yield of isolated product **2a**.
[c] Determined by chiral stationary phase HPLC analysis.
[d] Instead of a slow addition of the imine **1a**, a solution of catecholborane in THF (1.0 mL) was added over 30 min to the THF solution of **1a** and **3a**.

We assumed that a higher enantioselectivity could be achieved by using a less polar solvent than THF. Since the solubility of imine **1a** was very low in nonpolar solvents a 1:1 mixture of THF and toluene was chosen, which led to a very high selectivity of 90% ee. Unfortunately, the yield did not increase (Table 2, entry 2). An increased amount of catecholborane (1.6 equiv) delivered both a high enantiomeric excess and yield (entry 4). The highest enantioselectivity was obtained using toluene as the solvent in combination with a direct addition of imine **1a** in its solid form (entry 5). This method provided sultam **2a** in high yield with an excellent enantiomeric excess of 94%. The stereocenter of the sultam **2a** possesses the *S*-configuration, which was determined by comparison of its optical rotation with the value reported in the literature.[19]

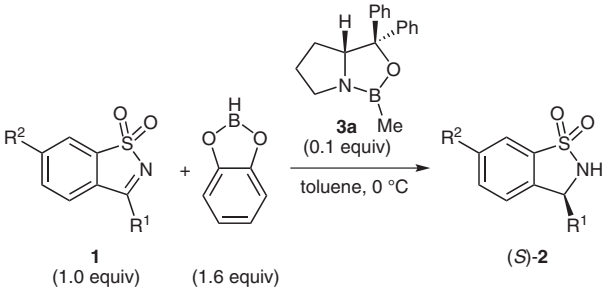
Having identified the optimal reaction conditions a short survey of the substrate scope for the CBS reduction of cyclic *N*-sulfonylimines **1** was examined (Scheme 2, Table 3).[20] Variation of the R^1 group to ethyl and *n*-butyl delivered the corresponding sultams in high yield and enantioselectivity. Introducing a phenyl ring in this position led to a considerable decrease of stereoselectivity.

Table 2 Optimization of the Reaction Conditions

Entry	Solvent[a]	Catecholborane (equiv)	Yield (%)	ee (%)
1	THF	1.0	60	79
2	THF–toluene 1:1	1.0	58	90
3	THF–toluene 1:1	1.2	73	89
4	THF–toluene 1:1	1.6	90	91
5[b]	toluene	1.6	74	94

[a] Imine **1a** was dissolved in the listed solvent and then added at 0 °C via syringe pump as previously described.
[b] Solid imine **1a** was added in one portion.

However, a brominated sultam **2e** is available in good enantioselectivity and high yield with our protocol with the option of further transformation at this position of the aromatic ring.



Scheme 2 Optimized reaction conditions for the enantioselective synthesis of chiral sultams **2**

Table 3 Substrate Scope for the Enantioselective Catalytic Synthesis of Sultams **2** via CBS Reduction

Entry	2[a]	R^1	R^2	Time (d)	Yield (%)	ee (%)
1	**2a**	Me	H	1	74	94
2	**2b**	Et	H	2	86	81
3	**2c**	*n*-Bu	H	1	91	84
4	**2d**	Ph	H	5	95	69
5	**2e**	Me	Br	4	92	74

[a] Solid imine **1a** (0.5 mmol) was added in one portion to a stirred solution of catalyst **3a** (0.1 equiv) and catecholborane (1.0 equiv) in toluene (10 mL) at 0 °C.

In conclusion we have developed an efficient catalytic asymmetric synthesis of 3-substituted benzo-fused sultams in high yields (74–95%) and very good enantiomeric excesses (69–94% ee). Thus, the substrate scope of the Corey–Bakshi–Shibata reduction could be extended to cyclic *N*-sulfonylimines opening a simple entry to the title compounds.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(20) For experimental details, see Supporting Information.