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Asymmetric Synthesis of Spiro β-Lactams *via* a Squaramide-Catalyzed Sulfa-Michael Addition/Desymmetrization Protocol

Pankaj Chauhan,[a] Suruchi Mahajan,[a] Uğur Kaya,[a] Arto Valkonen,[b] Kari Rissanen,[b] and Dieter Enders[a,*]

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
Fax: (+49)-241–809–2127; e-mail: enders@rwth-aachen.de
[b] Department of Chemistry, Nanoscience Center, University of Jyvaskyla, 40014 JYU, Finland

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Abstract: An efficient asymmetric synthesis of spirocyclohexenone β-lactams bearing three contiguous stereocenters has been achieved in moderate to good yields and high stereoselectivities. The protocol involves the combination of a squaramide-catalyzed sulfa-Michael addition under desymmetrization *via* a dynamic kinetic resolution of racemic 2,5-cyclohexadienones.

Keywords: asymmetric synthesis; desymmetrization; β-lactams; organocatalysis; spiro compounds; sulfa-Michael addition

The β-lactam (2-azetidinone) ring is one of the most attractive and highly studied heterocycles in chemistry, biology and medicine, especially due to the presence of this heterocyclic core in numerous antibiotics, representing an important class of modern pharmaceuticals.[1] The antibiotic properties and other interesting bioactivities of these heterocycles have led to the development of new β-lactam systems. Due to the frequent occurrence of spirocycles in natural products and biologically active molecules, the asymmetric synthesis of spiro compounds has always been a major area of research among synthetic organic chemists.[2] The spirocyclic β-lactams have also emerged as important candidates for biological evaluations.[3] The spiro β-lactams **I**[4] and **II**[5] have been identified as potent cholesterol absorption inhibitors, whereas β-lactam **III**[6] is an antiviral agent (Figure 1). The spiro β-lactams **IV** show β-lactamase inhibitor activity[7] and **V** serves as a precursor for the synthesis of glutamine synthetase inhibitors, i.e., tabtoxinine β-lactam.[8]

In recent years numerous methods have been established for the synthesis of enantiopure β-lactams.[9] However, there is only a limited number of examples for the organocatalytic asymmetric synthesis of β-lactams, mostly relying on the Staudinger reaction.[10] As an alternative, we herein realized the synthesis of spiro β-lactams *via* a desymmetrization of the racemic 2,5-cyclohexadienone β-lactams. The cyclohex-2-enones are well-established building blocks for the synthesis of a wide array of natural products and synthetic bioactive compounds.[11] The metal and organocatalyzed desymmetrization of 2,5-cyclohexadienones has emerged as an efficient strategy to obtain enantiopure cyclohex-2-enones.[12] The major emphasis during the asymmetric desymmetrization process was on the intramolecular addition reaction,[13] whereas the intermolecular desymmetrization of cyclohexadienones remained less explored, [14] especially for the synthesis of spiro compounds. Recently, Wang's group reported an organocatalytic asymmetric desymmetrization of prochiral spirooxindoles containing a cyclohexadienone to generate two vicinal stereogenic centers catalyzed by a multifunctional thiourea catalyst (Scheme 1).[14b] To the best of our knowledge, there is

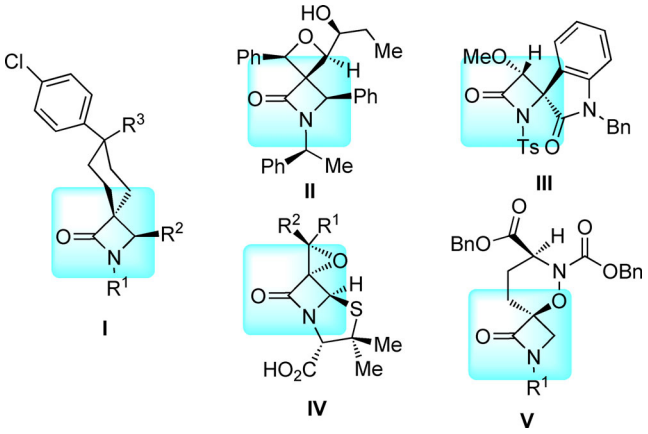
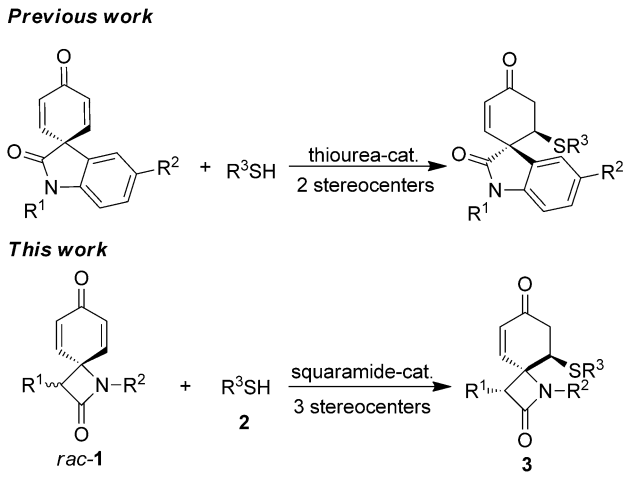


Figure 1. Biologically active spiro β-lactams.



Scheme 1. Organocatalytic intermolecular desymmetrization of 2,5-cyclohexadienones.

no report on the catalytic asymmetric synthesis of spiro cyclohexene β-lactams.

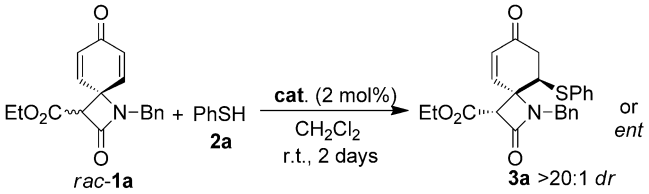
Due to the pharmaceutical significance of β-lactams and cyclohex-2-enones, we herein report a highly stereoselective sulfa-Michael addition/desymmetrization protocol, which leads to the formation of spirocyclohexene β-lactams.

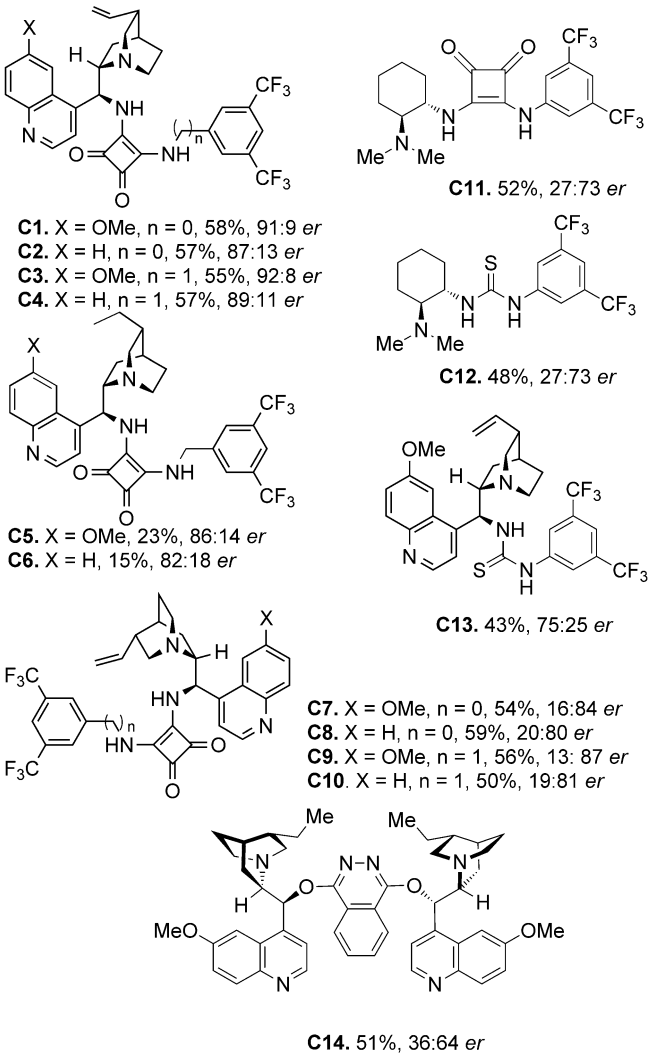
We envisaged that if a racemic 2,5-cyclohexadienone **1**[15] would be subjected to a sulfa-Michael addition (SMA)[16] in the presence of a bifunctional hydrogen-bonding catalyst[17] it could undergo a desymmetrization combined with a dynamic kinetic resolution (DKR) [18] to provide the spiro β-lactam **3** in high diastereo- and enantiomeric excess (Scheme 1).

To confirm our hypothesis, we started our investigation with the sulfa-Michael addition of thiophenol **2a** to the racemic 2,5-cyclohexadienone **1a** catalyzed by 2 mol% of various bifunctional hydrogen bonding organocatalysts. Initially, the reaction was catalyzed by the squaramide **C1**, which led to the formation of a single diastereomer of the desired product **3a** in 58% yield with 91:9 *er*. After further screening of different squaramide catalysts **C2–C11**, the squaramide **C3** was identified as the best catalyst, as it provided 55% yield with an *er* of 92:8. The thioureas **C12**, **C13** and a dimeric *Cinchona* alkaloid **C14** gave lower yields and enantioselectivities than the squaramide catalysts (Table 1).

Further optimization of the reaction conditions were carried out through solvent screening (Table 2, entries 1–8), which revealed that the reaction in 1,4-dioxane provides the best *er* of 93:7 (entry 8). The screening of various additives (entries 9–12) showed that using molecular sieves resulted in an improvement of the enantiomeric ratio. The lowering of the reaction temperature and a longer reaction time provided a better yield of up to 76% and an *enantiomeric ratio* of up to 95:5 (entries 13 and 14).

Table 1. Catalyst screening.[a]

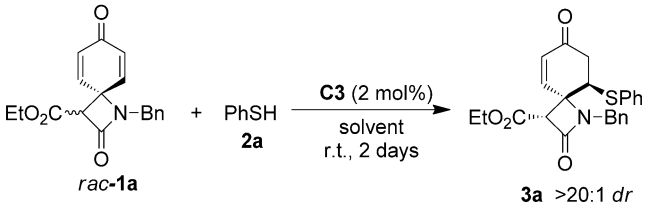




[a] *Reaction conditions:* 0.22 mmol of **1a**, 0.20 mmol of **2a**, 2 mol% of catalyst and 1 mL of CH_2Cl_2 at room temperature.

With the optimized reaction conditions in our hand, we evaluated the substrate scope and the limitations of this transformation by screening various 2,5-cyclohexadienones and thiols (Table 3). The reaction works very well with electron-neutral aryl thiols, however, with 2-naphthyl thiol a lower yield and *er* of **3b** compared to **3a** was observed. The thiophenol derivatives bearing electron-releasing groups provided good yields and enantiomeric ratios of **3c–e** with the excep-

Table 2. Optimization studies.[a]

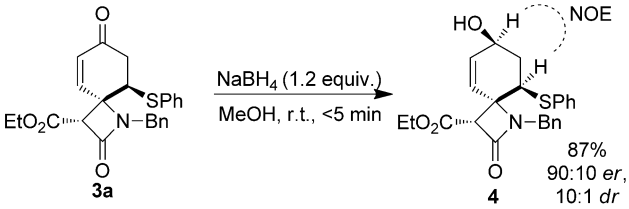


Entry	Solvent	Additive	Yield [%][b]	*er* [c]
1	CH_2Cl_2	–	55	92:8
2	$CHCl_3$	–	37	91:9
3	$ClCH_2CH_2Cl$	–	51	89:11
4	toluene	–	42	89:11
5	*p*-xylene	–	52	88:12
6	THF	–	59	88:12
7	MTBE	–	63	90:10
8	1,4-dioxane	–	56	93:7
9	1,4-dioxane	4 Å MS	64	94:6
10	1,4-dioxane	3 Å MS	58	94:6
11	1,4-dioxane	Na_2SO_4	51	93:7
12	1,4-dioxane	$MgSO_4$	49	91:9
13[d]	1,4-dioxane	4 Å MS	71	95:5
14[e]	1,4-dioxane	4 Å MS	76	95:5

[a] *Reaction conditions:* 0.22 mmol of **1a**, 0.20 mmol of **2a**, 2 mol% of catalyst **C3** and 1 mL of solvent at room temperature.
[b] Yield **3a** isolated after column chromatography.
[c] *Enantiomeric ratio* determined by HPLC on a chiral stationary phase.
[d] The reaction was carried out at 13 °C for 3 days.
[e] The reaction was carried out at 13 °C for 4 days.

tion of 2-methoxythiophenol, which gave **3f** only in 38% yield but with a high *er* of 95:5. The thiophenol derivatives bearing electron-withdrawing groups led to the formation of the desired products **3g–k** in 41–51% yield with 88:12–92:8 *er*. In these cases, only a slight improvement in the product yields was observed when using a higher catalyst loading of 5 mol%. We further tested a heteroaryl thiol, which provided **3l** in 46% yields and acceptable *er* of 89:11. After the screening of thiols, different 2,5-cyclohexadienones were tested. Using a methyl ester instead of ethyl ester led to the formation of the desired products **3m–q** in good yields (except 2-methoxythiophenol) and high enantioselectivities (90:10–96:4 *er*). The 2,5-cyclohexadienone derivatives bearing different *N*-protecting groups such as an electron-withdrawing and an electron-releasing substituent at the aryl ring as well as a heteroaryl group were also tolerated and provided the respective products **3r–t** in 72–80% yield and 93:7 *er* The gram-scale reaction of thiophenol with **1a** worked very well to provide **3a** with somewhat lower yield and a similar level of stereoselectivity. The 2,5-cyclohexadienone bearing a cyano group instead of the ester function also reacts well under the optimized conditions to afford the β-lactam **3u** in 49% yield, 5:1 *dr* and 92:8 *er*.

The synthetic utility of this transformation was demonstrated by the chemo- and diastereoselective reduction of the ketone group of **3a** to the alcohol **4** bearing four stereogenic centers with a high *dr* value (Scheme 2).



Scheme 2. Chemoselective reduction of **3a**.

The absolute configuration of the spiro β-lactam products **3a–u** was assigned as 3*R*,4*S*,9*R* by X-ray crystallographic analysis of **3j** with an *er* of >99:1 (Figure 2).[19]

On the basis of the observed absolute configuration of the products, a mechanism of this transformation may be proposed (Scheme 3). The plausible transition state involves the hydrogen bonding activation of the (*R*)-enantiomer of the dienone with the squaramide moiety of the catalyst for the attack of the sulfur nucleophile, which in turn is activated by the tertiary amine of the catalyst *via* deprotonation to provide product **3a** (**TS 1**). The possibility of the (*S*)-enantiomer of the substrate to form the product is less due to the steric repulsion between the ester group and the incoming S-nucleophile and hence (*S*)-**1** undergoes a rapid transformation to (*R*)-**1** in the presence of the catalyst *via* deprotonation of the acidic proton.

In conclusion, we have developed an efficient method to procure diastereomerically pure and highly enantio-enriched spirocyclohexenone β-lactams bearing three contiguous stereocenters *via* desymmetrization of 2,5-cyclohexadiones through a sulfa-Michael addition/dynamic kinetic resolution process catalyzed by a low loading of a squaramide. The reaction can

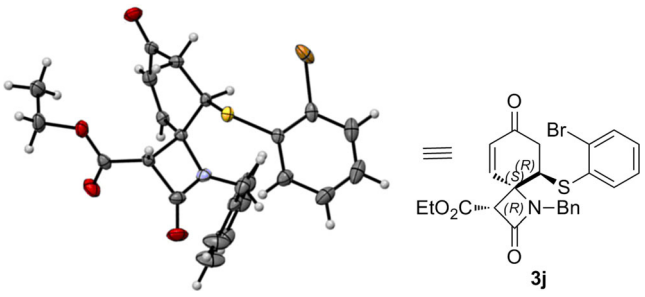
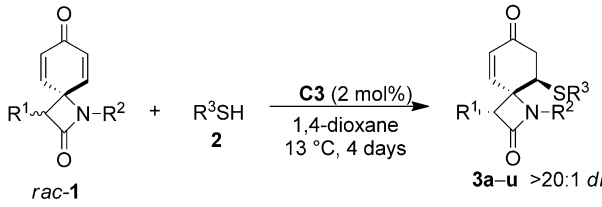
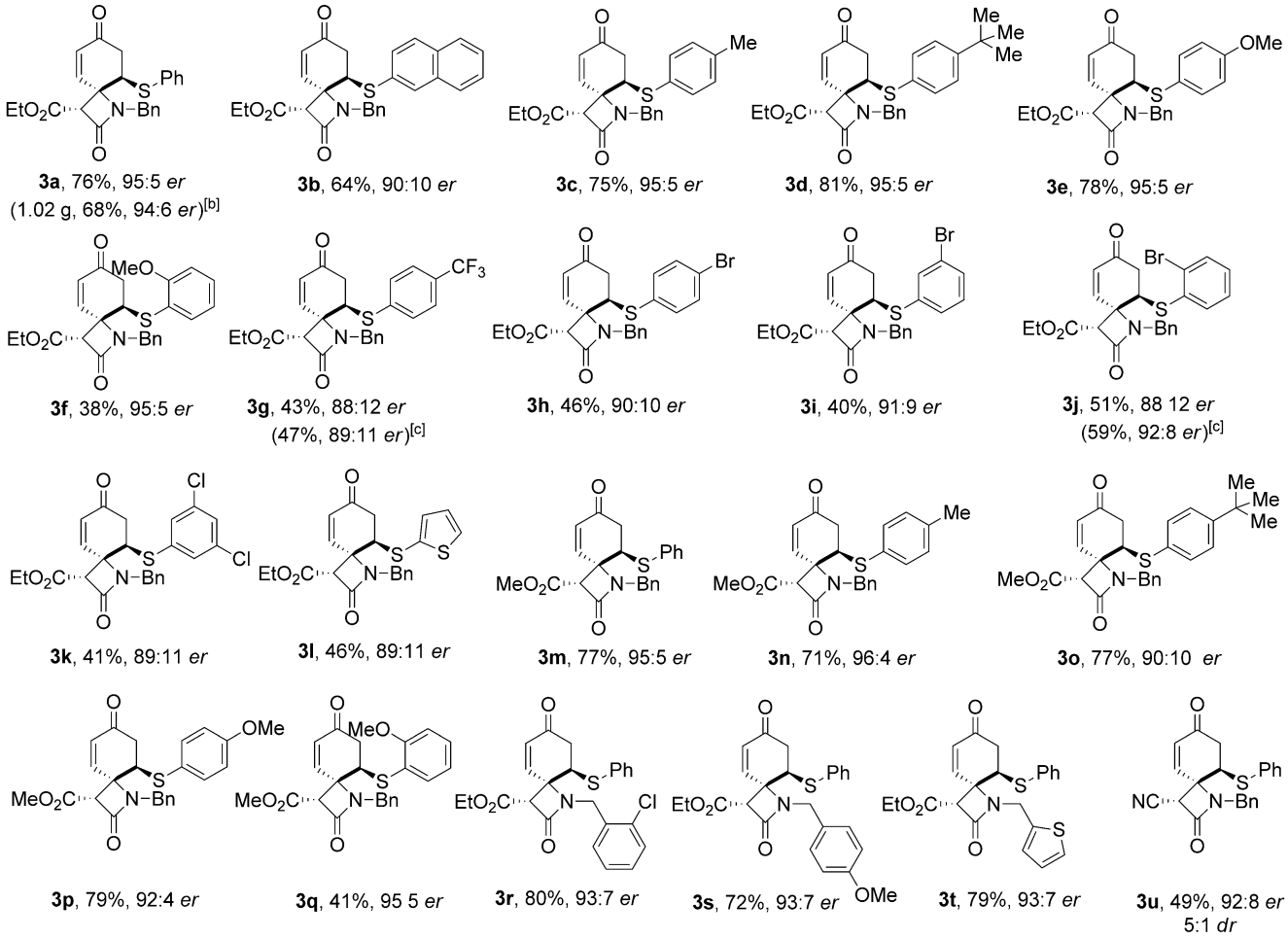


Figure 2. X-Ray crystal structure of **3j**.

Table 3. Substrate scope.[a]





[a] *Reaction conditions:* 0.44 mmol of **1**, 0.4 mmol of **2**, 2 mol% of catalyst **C3** in 3 mL of 1,4-dioxane and 200 mg of 4 Å molecular sieves.
[b] The results obtained for a gram scale reaction at 3.5 mmol.
[c] The results obtained with 5 mol% of catalyst.

be scaled up to a gram level and the enantioselectivity can be improved through a single crystallization.

Experimental Section

General Procedure

In a 10-mL reaction tube equipped with a magnetic stirring bar, the 2,5-cyclohexadienone **1** (1.1 equiv., 0.44 mmol), catalyst **C3** (2 mol%) and 4 Å molecular sieves (200 mg) were stirred in 1,4-dioxane (3.0 mL) at 13 °C. After 5 minutes, thiol **2** (1.0 equiv., 0.4 mmol) was added and the stirring was continued for 4 days at the same temperature. The crude product was directly purified by flash column chromatography (*n*-hexane/EtOAc = 7:3) to afford the spiro β-lactams **3a–3u**.

Acknowledgements

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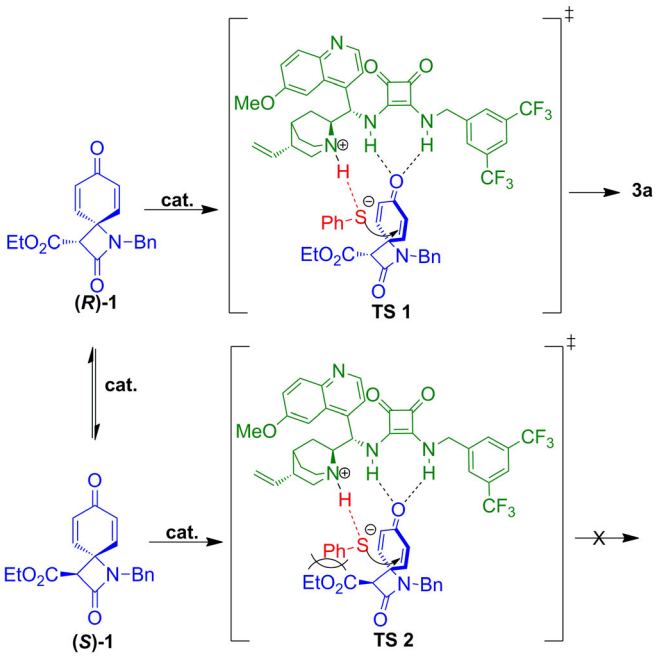

Scheme 3. Plausible mechanism.

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[19] The crystals of enantiopure **3j** were obtained from ethyl acetate:*n*-hexane (1:1) upon slow evaporation/solvent diffusion. CCDC 1476009 (**3j**) 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. For more data, see the Supporting Information.