Enantioselective Synthesis of β-Lactams Using a Chiral Auxiliary

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Abstract: An efficient and enantioselective synthesis of *trans*-β-lactams from carboximide **1** and imines **2** using a chiral auxiliary under the classical Reformatsky reaction conditions is described. An enolate–imine mechanism has been proposed for this reaction.

Key words: β-lactams, imines, Reformatsky reaction, enantioselectivity

Since Gilman[1] and Speeter reported the Reformatsky addition reaction to imines in 1943, it has been employed to synthesize β-lactams, β-amino acids and their derivatives.[2] The β-lactams are one of the best known and extensively investigated heterocyclic ring systems as a result of both their biological activity as antibiotics[3] and their utility as synthetic intermediates,[4] which spurred the stereocontrolled synthesis of this important building block. The Gilman–Speeter reaction gave almost always a mixture of *cis* and *trans* β-lactams with the *cis* isomer predominating.[5] The economic importance of enantiomerically pure compounds has stimulated considerable research efforts toward the enantioselective synthesis of β-lactams.[6] Previously, we developed an efficient method for the synthesis of *trans* β-lactams with high diastereoselectivity by the Refomatsky addition reaction of imines using an auxiliary.[7] To extend the applications of this methodology, we investigated the possibility for enantioselective formation of *trans* β-lactamic ring through a chiral auxiliary method (Scheme 1). We herein disclose the results of this effort.

Carboximides **1** were obtained by treating the corresponding carbonyl bromides with chiral auxiliary **4**, which can be prepared easily from inexpensive salicylamide according to the established procedure.[7,8] The Reformatsky reaction of **1** with imines **2** in the presence of zinc dust proceeded in THF under reflux conditions, and was completed within 10–20 minutes to give the corresponding β-lactam **3** with a recycle of chiral auxiliary **4**.[9] The products **3** were exclusively *trans* isomers. The *trans* configurations of **3** were assigned from the ^{1}H NMR spectra through the coupling constant J_{H-H} of the two protons on C_3 and C_4 (J_{trans} = 1.5–2.5 Hz, J_{cis} = 4.5–6.0 Hz).[10] The ee value turned out to be in the range of 75–86% determined by HPLC using a chiral column. Recrystallization from *n*-hexane–EtOAc gave optically pure **3b**. X-ray crystal structure analysis of **3b** confirmed the ^{1}H NMR assignment and showed that the absolute configuration of new chiral centers is 3*S* and 4*R* (Figure 1).[11]

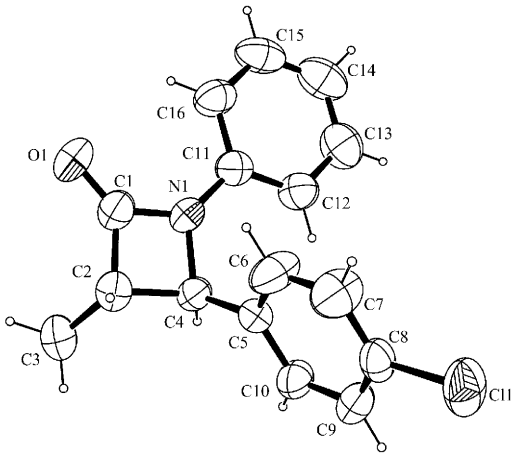
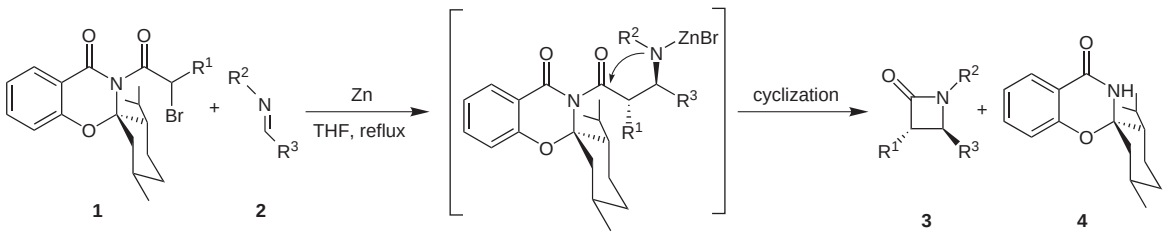


Figure 1 ORTEP view of **3b** (ellipsoids draw at 50% probability).

As shown in Table 1, imines derived from anilines and aromatic or α,β-unsaturated aldehydes gave good to satisfactory yields (63–81%). Unfortunately, *N*-benzylimine did not react. When there was no β-amino carbonyl, a



Scheme 1

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Table 1 Enantioselective Synthesis of β-Lactams

Entry	R^1	R^2	R^3	Product[a]	ee (%)[b]	Yield (%)[c]	$[\alpha]_D^{25}$
1	Me	Ph	Ph	**3a**	85	65	+67.2 (*c* 1.0, $CHCl_3$)
2	Me	Ph	4-ClC_6H_4	**3b**	80	73	+38.5 (*c* 0.7, $CHCl_3$)
3	Me	4-$MeOC_6H_4$	Ph	**3c**	77	81	+50.1 (*c* 1.0, $CHCl_3$)
4	Me	4-ClC_6H_4	3,4-$(OCH_2O)C_6H_3$	**3d**	83	75	+38.9 (*c* 0.8, $CHCl_3$)
5	Me	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**3e**	82	66	–31.3° (c 1.0, $CHCl_3$)
6	Et	4-ClC_6H_4	3,4-$(OCH_2O)C_6H_3$	**3f**	85	72	+43.6 (*c* 0.8, $CHCl_3$)
7	Et	4-ClC_6H_4	Ph	**3g**	86	63	+42.1 (*c* 0.7, $CHCl_3$)
8	Et	4-$MeOC_6H_4$	Ph	**3h**	83	69	+72.3 (*c* 0.9, $CHCl_3$)
9	Me	Ph	*trans*-Styryl	**3i**	75	79	+45.5 (*c* 1.0, $CHCl_3$)
10	Et	Ph	*trans*-Styryl	**3j**	78	70	+53.2 (*c* 1.0, $CHCl_3$)

[a] Determined by ^1H NMR to be 100% *trans*.
[b] Determined by HPLC with a chiral column (Chiralpak AD-H 0.46 × 15 cm, Daicel Chemical Ind. Ltd).
[c] Isolated yield based on carboximide.

non-cyclized product formed as the by-product in these reactions, which is usually a big problem in the reported Reformatsky-type reactions.[5] This may be due to the good leaving ability of the chiral auxiliary **4**, which facilitates the cyclization of the intermediate.

The first step of the Reformatsky reaction should involve the reduction of the α-bromocarbonyl group of **1** to give the *Z*-imide enolate, which nucleophilically attacks the imine as shown in Scheme 2. The formation of the *Z*-enolate involved in the transition state may be due to the steric repulsion of the menthyl moiety. The stereochemistry of the reaction could be explained by the chair-like transition state involving the imine and the *Z*-enolate. In the chelated transition state, zinc enolate disfavors a *si*-face attack on imine because the isopropyl group is oriented in a sterically hindered environment. The zinc enolate then favors the less hindered *re*-face attack on the imine, preferably leading to major isomer.

In summary, we successfully synthesized β-lactams with good enantioselectivity via a chiral auxiliary induced Reformatsky reaction. The chiral auxiliary **4** could be recycled in the reaction. An enolate–imine mechanism was proposed for this reaction.

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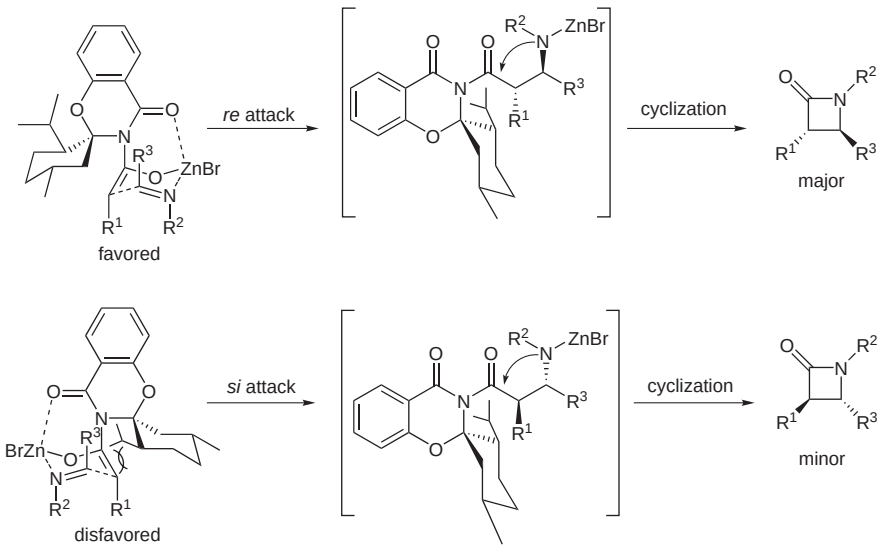

Scheme 2

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(9) **Typical Procedure for the Synthesis of β-Lactams 3.** A mixture of carboximide **1** (1.0 mmol), imine **2** (1.2 mmol) and zinc dust (3 mmol) in THF (5 mL) was refluxed for 10–20 min, cooled to r.t., poured into H_2O (5 mL), and then extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine, dried over anhyd Na_2SO_4, and evaporated in vacuo. The residue was chromatographed through a silica gel column with hexane–EtOAc to give pure β-lactams **3** and chiral auxiliary **4**.
(3*S*,4*R*)-4-(4-Chlorophenyl)-3-methyl-1-phenylazetidin-2-one (3a): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 7.4 Hz, 3 H), 3.16 (dq, *J* = 2.4, 7.4 Hz, 1 H, H-3), 4.61 (d, *J* = 2.4 Hz, 1 H, H-4), 7.06 (m, 1 H) 7.26–7.43 (m, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.35, 55.56, 62.97, 117.21, 123.99, 126.07, 128.69, 129.28, 129.38, 138.08, 138.20, 168.63. ESI-MS: *m/z* = 238 $[M + H]^+$.
(3*S*,4*S*,*E*)-3-Ethyl-1-phenyl-4-styrylazetidin-2-one (3j): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.4 Hz, 3 H), 1.83 (m, 1 H), 1.94 (m, 1 H), 3.06 (m, 1 H, H-3), 4.33 (dd, *J* = 1.9, 8.4 Hz, 1 H, H-4), 6.30 (dd, *J* = 8.4, 15.9 Hz, 1 H), 6.78 (d, *J* = 15.9 Hz, 1 H), 7.03–7.50 (m, 10 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.63, 21.85, 59.21, 60.04, 117.03, 123.93, 126.83, 127.67, 128.53, 128.95, 129.28, 133.84, 136.02, 138.56, 167.61. ESI-MS: *m/z* = 278 $[M + H]^+$, 300 $[M + Na]^+$, 577 $[2 M + Na]^+$.

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(11) CCDC 273640 contains the supplementary crystallographic data (excluding structure factors) for compound **3b**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; or deposit@ccdc.cam.ac.uk].