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Diastereoselective addition of chlorotitanium enolates of *N*-acyl thiazolidinethione to activated imines — A novel synthesis of β-lactams[1]

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Abstract: We report a novel methodology for preparing enantiomerically pure β-lactams, starting from nitriles in diastereomeric ratios up to 10:1. The power of the methodology was demonstrated by the efficient synthesis of the cholesterol absorption inhibitor **SCH 48462**.

Key words: β-lactam, *N*-metalloaldimine, titanium Lewis acids, cholesterol absorption inhibitor.

Résumé : Nous rapportons une nouvelle méthode de préparation des β-lactames énantiomériquement pures à partir de nitriles avec des rapports diastereomériques allant jusqu'à 10 : 1. L'efficacité de la méthode a été démontrée par la synthèse de l'inhibiteur d'absorption du cholestérol **SCH 48462**.

Mots clés : β-lactame, *N*-metalloaldimine, acides de Lewis à base de titane, inhibiteur d'absorption du cholestérol.

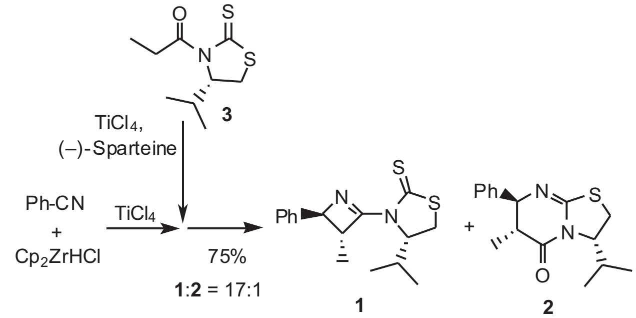
[Traduit par la Rédaction]

Introduction

The biological importance of β-lactams has been clearly demonstrated over the last five decades, particularly regarding the central role they play as antibiotics (1). The search continues for new β-lactams that exhibit a broader spectrum of antibacterial activity and a better resistance profile. Furthermore, the relevance of β-lactams in many important non-antibiotic uses, such as cholesterol absorption inhibitors (2) or a variety of enzyme inhibitors (3–6), continues to expand at a surprising rate.

Recently, our research group reported a diastereoselective, one-pot procedure for preparing novel azetine derivatives (**1**) from readily accessible nitriles (Scheme 1) (7). The diastereoselective additions of chlorotitanium enolates of *N*-propionylthiazolidine-2-thione (**3**) to various metalloaldimines, derived from the hydrometallation of the corresponding nitriles, resulted in the preferred formation of azetine **1** over tetrahydropyrimidinone derivatives (**2**) for both enolizable and non-enolizable substrates. Here, we describe an efficient, diastereoselective one-pot procedure for preparing β-lactams starting from nitriles.

Scheme 1. Diastereoselective synthesis of azetine derivatives, starting from nitriles.



Results and discussion

In the synthesis of azetine derivative **1**, a β-lactam side-product could be detected in a low percent. The formation of a β-lactam can mechanistically be explained as follows (Scheme 2).

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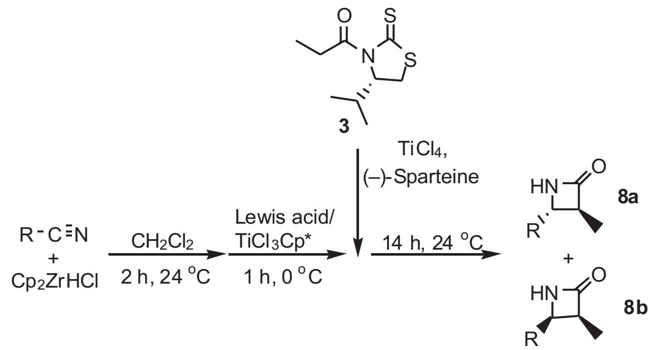
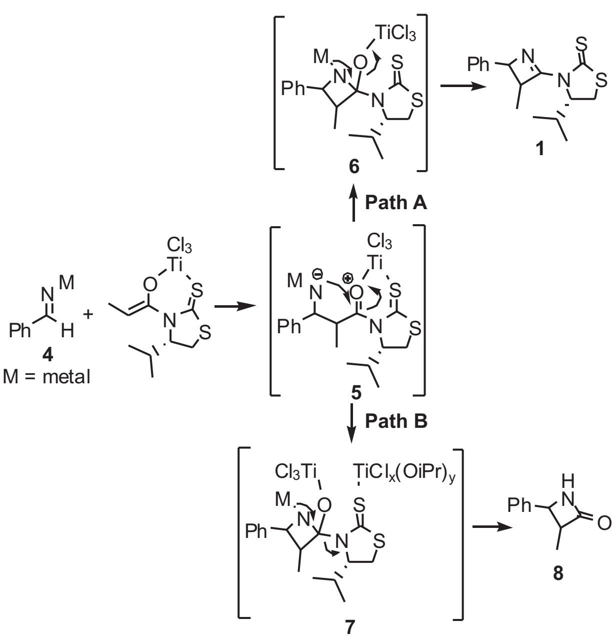
Table 1. Formation of β-lactam in the presence of titanium Lewis acids.



Entry	Nitrile (R)	Lewis acid	Yield (%)[a]	*anti:syn* Ratio[b]
1	Ph	$TiCl_3(OiPr)$	70	4:1
2	Ph	$TiCl_2(OiPr)_2$	89	2:1
3	Ph	$TiCl(OiPr)_3$	80	1:2
4	Ph	$TiCl_3Cp^*$	<50[b]	7:1
5	Ph	$TiCl_3Cp^*/TiCl_3(OiPr)$	81	7:1
6	*p*-MeO–Ph	$TiCl_3Cp^*/TiCl_2(OiPr)_2$	76	7:1
7	*p*-Me–Ph	$TiCl_3Cp^*/TiCl_2(OiPr)_2$	70	6:1
8	*p*-CF_3–Ph	$TiCl_3Cp^*/TiCl_2(OiPr)_2$	74	1:3
9	2-Thienyl	$TiCl_3Cp^*/TiCl_3(OiPr)$	65	8:1

[a]Isolated material after silica gel chromatography.
[b]Determined by ^{1}H NMR analysis of the crude reaction mixture; ~5% error of the stated values.

Scheme 2. Proposed mechanism for the formation of lactam **8** and azetine **1**.

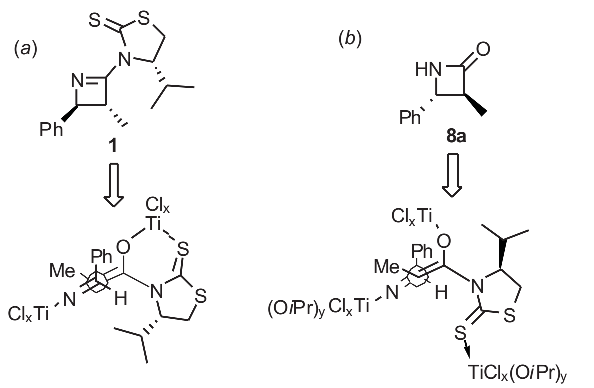


The nitrile is converted in situ to the *N*-metalloaldimine species (**4**), thereby activating it for attack by the titanium enolate. After the C–C bond formation, the resulting zwitterion (**5**) undergoes ring closure by nitrogen attack at the carbonyl group (8).[3] When the oxygen in intermediate (**6**) coordinates with a second titanium Lewis acid, it becomes the preferred leaving group, leading to the formation of the azetine **1** (path A). Alternatively, Lewis acid coordination with the chiral auxiliary converts it to a reasonable leaving group, resulting in the production of the β-lactam (**8**) (path B). In principle, redirecting the reaction to favor the lactam over the azetine could be achieved by employing a Lewis acid that is more thiaphilic than oxaphilic (i.e., one that would preferably coordinate to the thiocarbonyl group of the chiral auxiliary). In this way, the thiazolidine-2-thione could be activated as a leaving group, thereby leading to lactam formation.

In our initial investigation, we chose the thiaphilic Lewis acid, titanium trichloroisopropoxide, and were gratified to find that a mixture of *syn* and *anti* β-lactams was formed in a 70% yield (Table 1, entry 1). Each of these isomers was produced in an enantiomerically pure form as confirmed by chiral HPLC studies. The absolute stereochemistry of the β-lactams was elucidated using X-ray crystallography. The yields (but not the diastereomeric ratios) could be improved by increasing the isopropoxide content of the Lewis acid (Table 1, entries 2 and 3). To increase the diastereoselectivity of the lactam formation, a screening of other titanium Lewis acids was conducted. Although the use of pentamethylcyclopentadienyl titanium trichloride increased the ratio of the lactam diastereoselectivity (Table 1, entry 4),

[3] Consistent with literature results from both Crimmins laboratory (see ref. 8) and our own, we have never observed any stereoinduction resulting from the use of sparteine in titanium addition reactions. We use it primarily because we obtain better chemical yields relative to other tertiaty amines, e.g. triethylamine and Huenig's base.

Scheme 3. Proposed transition-states for the formation of (*a*) azetine and (*b*) lactam.

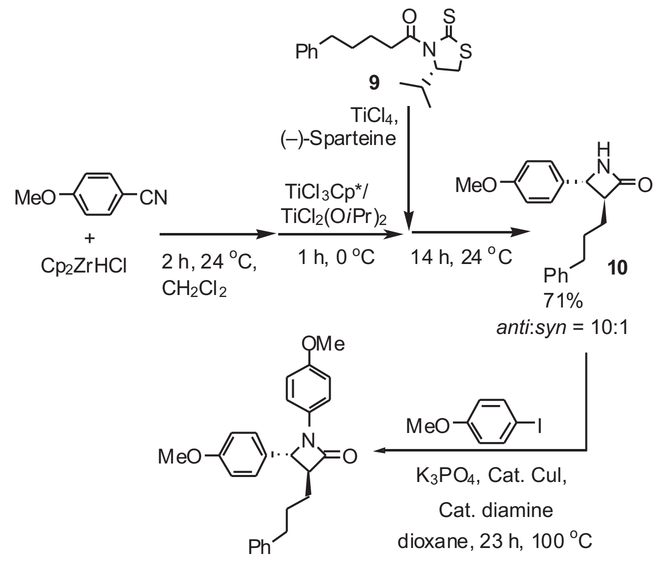


dihydropyrimidinone **2** was also produced in significant quantities (**8**:**2** ratio was 2:1). Because we observed high lactam yields and only traces of dihydropyrimidinone (Table 1, entries 1–3), we speculated that the 6-membered ring formation might be suppressed by adding titanium trichlorodiisopropoxide to the reaction mixture. Indeed, a combination of the Lewis acids, pentamethylcyclopentadienyl titanium trichloride and titanium trichloride isopropoxide, resulted in an efficient formation of the mixture of lactams in a good diastereomeric ratio with nearly complete suppression of dihydropyrimidinone (Table 1, entry 5). The process works well with other non-enolizable nitriles (Table 1, entries 6–9) but resulted in poor yields (0–20%) when attempted with several enolizable nitriles. The diastereoselectivity is highly dependent on the electronic properties of the nitriles, favoring *syn*-lactam fromation for nitriles with electron withdrawing substituents (Table 1, entry 8).

Interestingly, the absolute stereochemistries observed in the formation of *anti*-azetine derivatives are opposite to those observed in the *anti*-lactams (Scheme 3). To explain the difference in the stereochemical outcome, we propose the competing transition-states shown in Scheme 3 as our models. In the azetine formation, we postulate an open transition-state that minimizes dipole interactions (9) between the (*Z*)-titanium enolate (10–12) and the titanium imine.[4] As a consequence, the thiazolidinethione blocks the *re* side of the enolate, and the imine must approach from the *si* side. Diastereomeric transition-states presumably create larger dipole and steric interactions. In case of the lactam formation; however, the coordination of an additional thiaphilic Lewis acid to the thiocarbonyl group of the chiral auxiliary eliminates chelation, thereby allowing it to rotate 180° to minimize dipole effects of the thiocarbonyl group and the carbonyl group of the enolate. As a consequence, the thiazolidinethione blocks the *si* side of the enolate and the imine has to attack from the *re* side. The *syn*-lactam is presumably formed by attack on the other face of the imine.

To probe the scope of this newly developed methodology, we applied it to the synthesis of the cholesterol absorption inhibitor **SCH 48462** (Scheme 4) (2, 13–15). Using the combination of titanium dichlorodiisopropoxide and pentamethyl cyclopentadienyl titanium trichloride, the reaction proceeded in 71% yield and gave improved diastereoselectivity (an *anti* to *syn* ratio of 10:1). In the second step of the synthesis, the β-lactam **10** was readily *N*-arylated (89% yield) by using copper catalysis as described by Klapars et al. (16) (63% overall yield for the two-pot process).

Scheme 4. Synthesis of the cholesterol inhibitor **SCH 48462**.



Conclusions

In summary, we have developed a novel methodology for the preparation of enantiomerically pure β-lactams, starting from nitriles in diastereomeric ratios up to 10:1. The power of the methodology was demonstrated by the efficient synthesis of the cholesterol absorption inhibitor **SCH 48462**.

Experimental section

General procedure for β-lactam formation

The nitrile (1.72 mmol) and Cp_2ZrHCl (445.00 mg, 1.72 mmol) were dissolved in dry dichloromethane (2 mL) in a 50-mL flask and stirred for 2 h under argon at room temperature. The respective titanium Lewis acid (3.45 mmol) was added, and the reaction mixture was stirred for 1 h at 0 °C. During this time, titanium enolate of compound **3** or **9** was generated by dissolving **3** or **9** (1.15 mmol) in dry dichloromethane (5 mL) at 0 °C under argon, then dropwise addition of titanium tetrachloride (0.13 mL, 1.15 mmol), stirring for 5 min, and the addition of (–)-sparteine (0.66 mL, 2.87 mmol). The brown solution was stirred 40 min at 0 °C and then added to the first reaction mixture via a cannula. The reaction mixture was stirred for 14 h at room temperature. It was then quenched with 20 mL saturated aq. ammonium chloride solution with continuous stirring, and dichloromethane (30 mL) and distilled water

[4] We considered and rejected Zimmerman–Traxler-like transition-states primarily because the absolute stereochemistries of the newly formed stereogenic centers would have been derived from an unfavorable *trans* diaxial substituent pattern.

(30 mL) were added. The organic phase was separated, and the aq. phase extracted with dichloromethane (2 × 30 mL). The combined organic phases were washed with saturated aq. sodium bicarbonate solution, then with brine, dried with anhyd. magnesium sulfate, and finally concentrated under vacuum. The product mixture was purified by silica gel flash chromatography (EtOAc:hexanes was 1:10 – 1:3).

For spectroscopic and physical data of **8a**, **8b**, **9**, **10**, and **SCH 48462**, refer to the supplementary data.[5]

Acknowledgments

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[5] Supplementary data for this article are available on the journal Web site or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada. DUD 5116. For more information on obtaining material, refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 628790 and 628791 contain the crystallographic data for this manuscript. 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).