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(*R*)-2-Phenylglycine as a Chiral Auxiliary in the Asymmetric Synthesis of 2-Azetidinones

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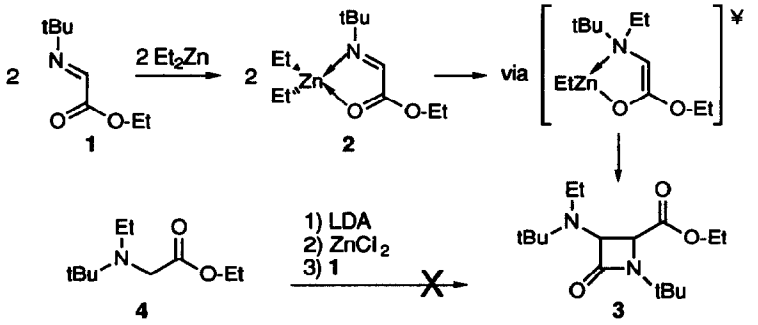
Abstract: *The chlorozinc enolate of ethyl-[(2,2,5,5-tetramethyl-1-aza-2,5-disila)cyclopentyl]-acetate was reacted with the $ZnCl_2$ complex of N-benzylidene-2-phenylglycine methyl ester in THF at -70 °C. After removal of the protecting silyl moiety (3S, 4S, αR)-1-(methoxycarbonyl)(phenyl)methyl-3-amino-4-phenyl-2-azetidinone was obtained in 73% yield with >97% d.e.. By treatment with aqueous ammonia complete epimerization at the α-position was accomplished. The (3S, 4S, αS) enantiomer was crystallized from THF and the absolute configuration was determined by X-Ray crystallography.*

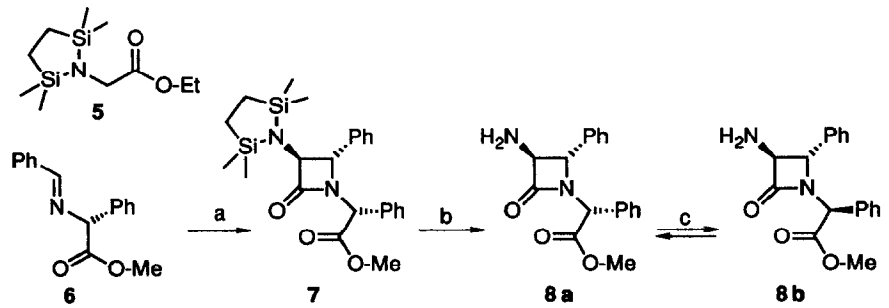
One of the principal routes to β-lactams (2-azetidinones) is the condensation of ester enolates and imines[1]. Diastereocontrol occurs via the metal: lithium[1] enolates generally result in the formation of *cis*-2-azetidinones, whereas zinc enolates produce *trans*-2-azetidinones almost exclusively, as we have shown recently[2a,b]. The diastereocontrol via aluminum enolates is dependent on the ester precursor used. An intramolecular coordinating enolate affords *trans*-2-azetidinones[2c], whereas the *cis*-diastereoisomer is formed when non-coordinating aluminum enolates are employed[3]. In general, the zinc-mediated reactions are superior to the lithium- or aluminum-mediated ones, since they combine high yields with excellent stereoselectivity. The use of tin[4], boron[5] or zirconium[6] enolates results in the formation of β-amino esters, usually with good diastereoselectivity. In a separate step the β-amino esters are cyclized to afford the desired 2-azetidinones.

Most β-lactam antibiotics contain a carboxylic acid or ester substituted side chain on the nitrogen atom. Usually, the introduction of these functionalities is achieved via formation of the N-unsubstituted 2-azetidinone[2d,7]. Direct introduction of an ester substituent[8] would result in a short synthesis of valuable intermediates. We have previously shown[2d] that the enantioselectivity of the C-C bond formation could best be controlled by the use of stereogenic imine-nitrogen substituents. Imines derived from chiral amino acids could be employed to combine excellent stereocontrol with *atom economy*. In this report, we demonstrate the use of (*R*)-2-phenylglycine as the chiral auxiliary in the ester enolate-imine condensation reaction. Recent reports on the use of imine derivatives of (*R*)-2-phenylglycine[9] prompted us to disclose our preliminary results.



Scheme 1

The zinc mediated C-C coupling of N,N-disubstituted glycine ester enolates and imines constitutes a very versatile one-pot synthesis of *trans*-β-lactams, as we have shown previously[2]. When imines based upon α-amino esters were subjected to chlorozinc ester enolates using standard reaction conditions, the starting materials were recovered; no C-C coupling products were formed. This lack of reactivity is not unprecedented. In a related study concerning the coordination chemistry[10] of α-imino esters it was found, that upon addition of diethylzinc to **1** at -70 °C first a 1:1 coordination complex **2** was formed, which reacted upon warming to give β-lactam **3** (scheme 1). Alkyl transfer from the metal to the nitrogen atom generates an ethylzinc enolate, which reacts rapidly with the α-imino ester. When 0.5 equivalent of Et_2Zn was employed in this reaction, the yield of **3** dropped to <50%, indicating that the *in situ* formed zinc enolate does not react with α-imino ester **1**, but exclusively with the complexed imine **2**. Furthermore, the chlorozinc enolate of N-*tert*-butyl-N-ethyl-glycine ethyl ester **4** showed no reactivity towards **1**[11]. Apparently, activation of the α-imino ester by coordination to diethylzinc is necessary for this reaction.



a: 1) $ZnCl_2$, THF, -30 °C; 2) chlorozinc enolate of **5**, THF, -70 °C to r.t., 79%;
b: 1) 1 N HCl, THF; 2) NH_3, H_2O / CH_2Cl_2, pH < 11, 92%; **c**: NH_3, H_2O / CH_2Cl_2.

Scheme 2

Following this interpretation, we have now developed a double activation procedure for the reaction of ethyl-[(2,2,5,5-tetramethyl-1-aza-2,5-disila)cyclopentyl]acetate[12] **5** with (*R*)-N-benzylidene-2-phenylglycine methyl ester **6**[13] (scheme 2), employing $ZnCl_2$ instead of Et_2Zn. Deprotonation of **5** in diethyl ether or THF

with LDA at -70 °C , followed by transmetallation with dry $ZnCl_2$, yielded the corresponding chlorozinc enolate[2b]. At the same time, the $ZnCl_2$ complex of **6** was prepared *in situ* in THF at -30 °C. The solution of the complexed imine was added to the zinc enolate solution at -70 °C. After standard work-up[2b], **7** was obtained as the main product[14], together with a small amount of the deprotected product **8a**[14]. Complete deprotection[2b] of the crude product yielded (3*S*, 4*S*, α*R*)-1-(methoxycarbonyl)(phenyl)methyl-3-amino-4-phenyl-2-azetidinone **8a** with 97% d.e. However, during basic work-up at pH > 11, partial epimerization at the α-carbon was observed, affording a mixture of **8a** and **8b**[14]. Therefore, 97% is the minimum value for the enantioselectivity of the C-C coupling reaction.

Determination of the absolute stereochemistry of **8a** was not possible, since it is an oil. However, its α-epimer **8b** is a white solid. Epimerization to a 1:1 mixture of **8a** and **8b** was achieved by treating a CH_2Cl_2 solution of **8a** with concentrated aqueous ammonia. Precipitation of **8b** from diethyl ether, in which **8a** is very soluble, was found to be a convenient method of separation of the two diastereoisomers. A 13:1 mixture of **8b** and **8a** was isolated in 39% yield; the remaining 61% was recovered and again epimerized by treatment with aqueous NH_3. Crystallization from THF yielded crystals of **8b** suitable for X-Ray structure determination[15] (figure 1). By repeating the epimerization / separation / crystallization sequence, **8a** can be completely converted to **8b**. This preferential crystallization is an example of an asymmetric transformation of the second order[16] because ultimately the whole sample can be crystallized as **8b**.

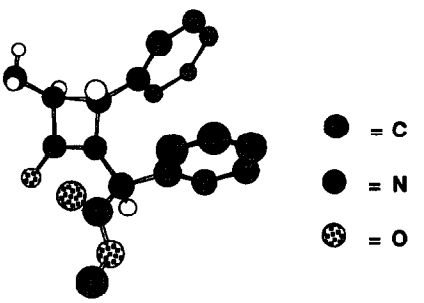


Figure 1: Molecular structure of **8b**

Complexation of the imino ester to $ZnCl_2$ before the addition of the enolate is essential to the success of this reaction. By using two equivalents of $ZnCl_2$ in the formation of the zinc enolate of **5**, followed by the addition of **6**, only a very low conversion (~10%, 24 hrs.) to **7** was observed. Significant amounts of unidentified decomposition products had formed[2e].

We have shown, that the (*R*)-configuration of the stereogenic center of the chiral auxiliary completely controls the absolute stereochemistry of the two newly formed stereogenic centers. The use of amino acid derivatives as chiral auxiliaries in the ester enolate-imine condensation reaction requires the complexation of the imine to a suitable Lewis acid prior to the reaction, resulting in a selective reaction without racemization. Current research is aimed at extending the scope of this reaction to the synthesis of other functionally substituted 2-azetidinones.

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15 X-Ray data were collected on an Enraf-Nonius CAD4T / Rotating anode system [MoKα, λ = 0.71073 Å] at 100 K for a colorless crystal glued on a capillary: $C_{18}H_{18}N_2O_3$, Mw = 310.35, monoclinic, space group $P2_1$, unit cell parameters: a = 7.9063(3), b = 9.8227(4), c = 10.0298(6) Å, β = 97.60(1)°. The structure was solved by direct methods (SHELXS-86) and refined with SHELX76 to a final R = 0.059 (R_w = 0.048) for 1361 observed reflections with $I > 2.5\ \sigma(I)$. Final parameters have been deposited with the Cambridge Structural Database Centre.

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