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PALLADIUM CATALYZED DIASTEREOSELECTIVE ADDITION OF SECONDARY ALCOHOLS TO ACYLOXYAZETIDINONES

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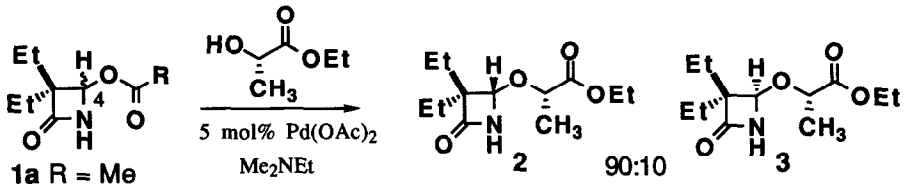
Abstract : Palladium catalyzed addition of lactate esters or phenethyl alcohols to acyloxyazetidinones gives 4-oxy-substituted β-lactams with 6-9:1 diastereoselectivity. The stereochemistry of the major products was established as S*S* by X-ray crystallography.

The addition of secondary alcohols to 4-acyloxyazetidinones represents a straightforward method for the preparation of 4-oxy-β-lactam derivatives such as those found in elastase inhibitors[1] and modified clavams.[2] The most widely used method to achieve this transformation utilizes a zinc acetate catalyzed condensation of the alcohol and acetoxy azetidinone.[3] Higher yields for the condensation have been achieved using palladium acetate catalysis, a method introduced by Muller and Weigele.[4] The third method commonly used to synthesize 4-oxy-β-lactam derivatives employs the displacement of a C-4 sulfinyl substituent by an alcohol.[5] Since we had ready access to 4-acyloxyazetidinones in high yield[6], our attention focused on utilizing the palladium acetate catalyzed method of Muller and Weigele. During the course of these investigations it was noted that the addition of ethyl lactate to the acyloxyazetidinone **1b** in the presence of palladium acetate gave the adduct **2** with high diastereoselectivity. This represented an unusual example in which the observed stereocontrol at C-4 of the β-lactam ring could not have resulted from substituents at C-3. Since this type of transformation was virtually unexplored in the literature[4,7] we initiated a study to define the scope and limitations of this reaction. In this communication, we describe the reaction parameters which afford the highest stereocontrol, and provide an X-ray structure which conclusively defines the structure of the major diastereomer **2**.



1a R = Me
1b R = 2-ethylbutyl

2 **3**

The reaction of (S)-ethyl lactate with azetidinones **1a/b** was highly sensitive to choice of solvent. Using toluene, hexane or ethyl acetate provided good diastereoseletivity (>6:1) and 100% conversion, while solvents such as CH_2Cl_2, THF, CH_3CN, and DMF resulted in low conversion (5-30%) and decreased selectivity (2-3:1). Substitution at C-3 was essential for the observed stereoselection. Using the parent acetoxy azetidinone with hydrogens at C-3 the stereoselection was 1.9:1 in the same reaction. Reaction temperature and nature of the

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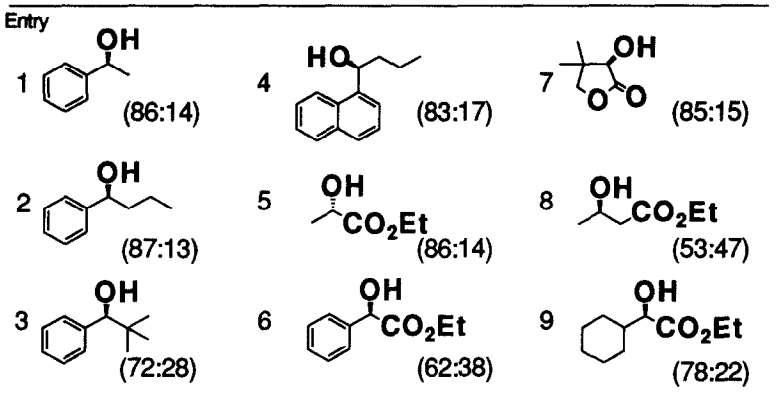
azetidinone leaving group (e.g. acetoxy vs 2-ethylbutyryloxy) were not factors in controlling the diastereoselectivity although, both increasing the temperature and decreasing the size of the leaving group increased the reaction rate.

An investigation of the effect of structural changes in the alcohol was conducted (Table 1). One important feature required of the alcohol was an adjacent carbonyl or phenyl group (entries 1 through 5). Displacement of the carbonyl group from the hydroxyl by a single methylene moiety resulted in almost no selectivity (entry 5 *vs* entry 8). In cases where a carbonyl group competes with a phenyl, decreased selectivity was seen (entry 6) while removing the aromatic ring through saturation restores some of the stereocontrol (entry 6 *vs* 9). Steric effects were less pronounced, for example, entries 2 and 4 resulted in diastereomer ratios which were similar to entry 1. However, the t-butyl group present in entry 3 reduced the selectivity. When ethyl thiolactate was employed (entry not shown), low levels of diastereocontrol were obtained (68:32). Lastly, when racemic alcohols were used the diastereomer ratios were unchanged, however, the products were racemic.[8]

Table 1* Reaction of β-lactam 1b with secondary alcohols. Influence of alcohol structure on diastereocontrol



*Numbers in parentheses denote diastereomer ratio in the unpurified product. The ratios were determined by integration of the C-4 proton and by HPLC. Structural proof was unambiguously obtained for the adducts derived from entries 1 and 5. All reactions were run in toluene at 40°C, using 5 mol% $Pd(OAc)_2$, and triethylamine as the base.

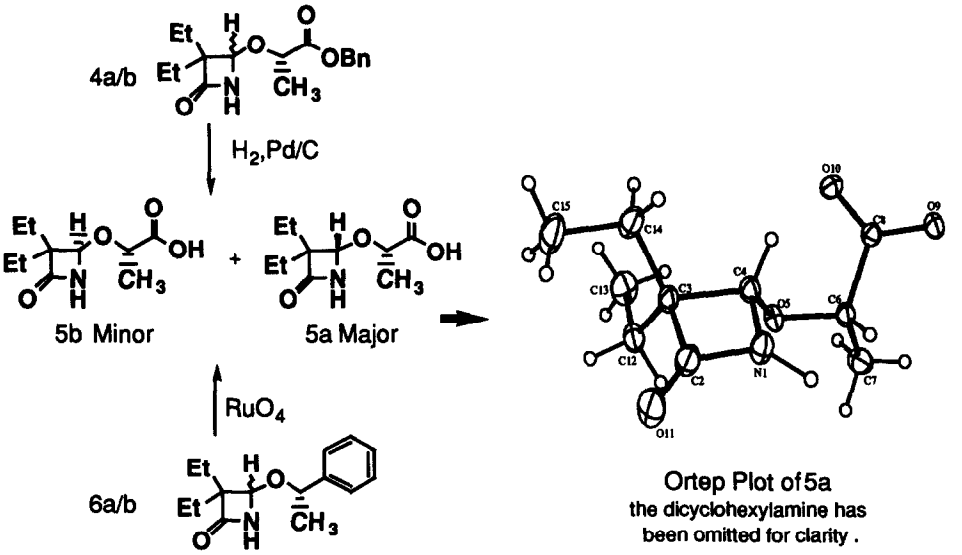
A clear trend was observed with variations in the alkyl amine base (Table 2). Less sterically hindered tertiary alkyl amines gave increased diastereoselectivity. Use of dimethylethylamine provided the highest selectivity in the reaction of azetidinone **1b** with the representative alcohols ethyl lactate, sec-phenethylalcohol and pantolactone.[9] In the absence of added base almost no selectivity was observed.

Table 2 Influence of base on the reaction of 1b with ethyl lactate

Base	Diastereoselectivity
pyridine	no reaction
none	1.5:1
$[i\text{-}Pr]_2NEt$	3.0:1
Et_3N	6.1:1
Me_2NEt	9.0:1

The stereocenters present in azetidinones **2** and **3** are separated by a heteroatom, which led to ambiguous interpretations when using NMR techniques for structural proof[10]. Thus a suitable derivative for X-ray crystal analysis was required. Benzyl esters **4a/b**[11] were hydrogenated to the acids **5a/b**, and the diastereomers separated by silica gel chromatography (Scheme 1). Crystals suitable for X-ray crystallography were prepared from the major isomer **5a** after forming the dicyclohexylamine salt.[12] The relative stereochemistry of the major isomer is S*S* as shown in the ortep plot. Correspondingly the adducts **6a/b** (7:1 mixture of diastereomers) were prepared from the reaction of (S)-sec-phenethylalcohol with azetidinone **1b**. Oxidative cleavage[13] afforded the diastereomeric acids **5a/b** with acid **5a** being the major product. Thus the products derived from the benzylic alcohol series were correlated to the lactate series and both series were shown to provide the S*S* diastereomer as the major product.

SCHEME 1 Assignment of Stereochemistry via Chemical Correlation with an X-Ray Structure



In conclusion we have shown that useful levels of diastereoselection may be obtained in the reaction of secondary alcohols with 3,3-diethyl acyloxyazetidinones under palladium catalysis by employment of the appropriate base. Further investigation into the role of palladium in this reaction is continuing.

Typical Procedure: A solution of azetidinone **1b** (0.58 g, 2.41 mmol) in toluene (1 ml) was added to a solution of (S)-ethyl lactate (0.19 g, 1.61mmol), dimethylethylamine (0.20 ml, 1.86 mmol) and $Pd(OAc)_2$ (0.018 g, 0.08 mmol) in toluene (3 ml). The resulting yellow solution was stirred at 40°C for 3h under N_2. The mixture was washed successively with 2N HCl, saturated $NaHCO_3$, saturated $NaHSO_3$, and brine. After drying (Na_2SO_4) and evaporation of solvent the residual yellow oil was purified by chromatography on silica gel to give 0.30 g (76%) of **2** and **3** as a colorless oil in a 9:1 ratio. **2**: ^1H NMR (300 MHZ, $CDCl_3$) d 7.32 (br s, 1H, NH), 4.73 (s, 1H, C-4 H), 4.18-4.08 (m, 2H), 4.07 (q, J=6.7 Hz,

1H), 1.78-1.58 (m, 4H), 1.37 (d, J=6.7 Hz, 3H), 1.21 (t, J=7.4 Hz, 3H), 0.94 (t, J=7.4 Hz, 3H), 0.87 (t, J=7.4 Hz, 3H). **3**· 4.59 (s, 1H, C-4 H).

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6. Clauss, K.; Grimm, D.; Prossel, G. *Liebigs Ann. Chem.* **1974**, 539. Use of hindered vinyl esters in this reaction results in greatly improved yields of isolated acyloxyazetidinone, the results of these studies will be reported in due course.
7. The authors in references 4a and 4b noted diastereocontrol of 4:1 and 2:1 respectively. Optimization of stereocontrol was not the main issue of these reports. For an example of the addition of ethyl lactate to a β-lactam, see: Okonogi, T.; Shibahara, S.; Murai, Y.; Inouye, S.; Kondo, S. Christensen, B. G. *Heterocycles*, **1990**, *31*, 791. The observed stereocontrol in this example is derived from the α-substituent at C-3.
8. Racemic and optically active azetidinones **2** and **3** could be analyzed by chiral HPLC using a Chiralcel AS (25 cm x 4.6 mm column).
9. For a similar selectivity dependence on tertiary amine size in the reaction of secondary alcohols with ketenes see: Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1989**, *111*, 7650.
10. In all cases the chemical shift of the proton at C-4 was resolved in each pair of diastereomers. However, both peaks were singlets and the relative chemical shifts for the major and minor isomers would vary. Chemical shift data for selected examples from Table 1 are as follows; entry (major:minor): 1 (4.62:4.66), 2 (4.57:4.62), 5 (4.73:4.59), 6 (5.02:4.98), 7 (5.3:4.8), 9 (4.7:4.5).
11. We employed benzyl lactate for the structure proof so that ester removal would not have the potential for epimerization. The resulting acids derived from ethyl ester hydrolysis (1-2 equivalents of LiOH in THF:water at 20°C) were identical to that obtained from benzyl lactate. Furthermore, re-esterfication of pure **5a** afforded **2** without any detectable epimerization. For the esterification conditions, see: Ono, N.; Takashi, Y.; Saito, T.; Tanaka, K.; Kaji, A. *Bull. Chem.Soc.Jpn.* **1978**, 2401.
12. Crystals of the dicyclohexylamine salt were grown from ethyl acetate/methanol, m.p.166-168°C. The crystal structure details are:$C_{22}H_{40}N_2O_4$, MW=396.58, monoclinic space group $P2_1/c$, a = 9.9794 (9), b = 10.213 (1), c = 22.904 (2) Å, β = 91.996 (6)°, V = 2333 Å^3, Z = 4, D_{calc} = 1.129g/cm^3, monochromatized radiation λ(Cu Kα) = 1.54184 Å, μ = 0.58/mm, $F(000)$ = 872, T = 296 K. Final agreement statistics are: R = 0.066, wR = 0.078, S = 4.84, $(\Delta/\sigma)_{max}$ = 0.6. Weighting scheme is $1/\sigma^2(F)$.
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