Pergamon

Tetrahedron Letters, Vol. 35, No. 7, pp. 1087-1090, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0380-3

Oxazaborolidine Catalyzed Enantioselective Reductions of Cyclic *meso*-Imides

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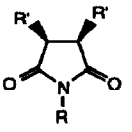
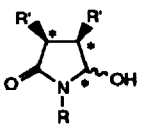
Abstract: A new asymmetric reduction method for *meso*-imides is reported. Treatment of various imides with a mixture of a chiral oxazaborolidine and BH_3 leads to a mixture of *cis*- and *trans*-hydroxylactams and, after subsequent ethanolysis, to the corresponding diastereomerically pure *trans*-ethoxylactams. The enantiomeric excesses were shown to be 75-89% by both chiral HPLC-determinations and conversion of the reduction products into the corresponding, known lactones.

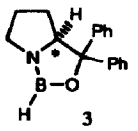
Cyclic *meso*-imides such as the cyclic *cis*-3,4-disubstituted succinimides **1** form an interesting and useful class of starting materials in the field of asymmetric synthesis. A single, enantioselective transformation, namely a reduction of one of the carbonyls, leads to a product with three contiguous stereocenters. Furthermore, the 5-hydroxy-2-pyrrolidinones (**2**), being the products of such reductions, have been shown to be versatile building blocks for the synthesis of various natural products.[2] In recent years several research groups, including ours, have been interested in obtaining these hydroxylactams in optically pure form. Different methods have been studied for the asymmetric reduction of *meso*-imides in order to obtain the desired compounds, including yeast reductions and reductions of *meso*-imides bearing a chiral *N*-substituent.[3] Very recently, an enantioselective reduction method by using optically active BINAL-H complexes has been reported.[4]



1



2



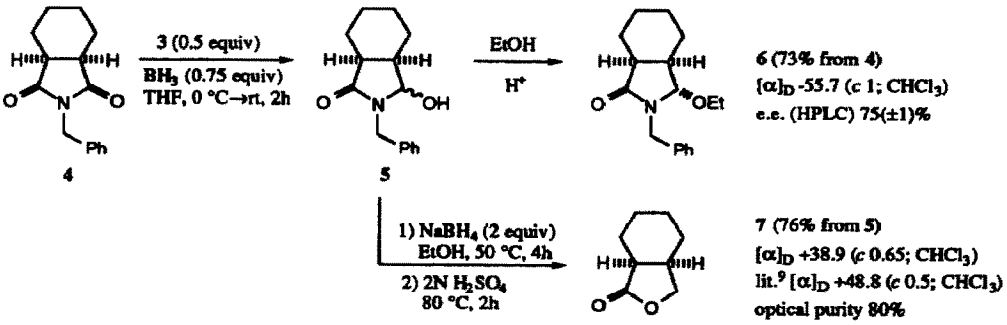
3

Our attention was drawn by the use of chiral oxazaborolidines such as the α,α-diphenyl-*L*-prolinol derived borane complex **3** in catalytic asymmetric reductions. Since the discovery of the high potential of these complexes as catalysts,[5] a rapidly growing number of papers has appeared on the use of these oxazaborolidines.[6,7] So far, however, they have mainly been used in the enantioselective reductions of ketones.[8] In this paper, we describe the first enantioselective reductions of *meso*-imides using an oxazaborolidine/BH_3 mixture.

When the hexahydrophthalimide derivative **4** was reacted with varying amounts of **3** and BH_3, a mixture of optically active *cis*- and *trans*-5-hydroxy-2-pyrrolidinones **5** was obtained (Scheme 1). The ratio of these two separable isomers was variable and dependent on the reaction conditions. When the crude mixture was, however, immediately treated with $EtOH/H_2SO_4$, the *trans*-ethoxylactam **6** was isolated as a single product in good overall yield and with high specific rotation. The optimum conditions turned out to involve 0.75 equiv of BH_3 and 0.5 equiv of **3**. A smaller amount of **3** led to a lower specific rotation of **6** (e.g. with 0.2 equiv of **3**,

the $[\alpha]_D$ of product **6** decreased from -55.7 to -39.5 (*c* 1.2; $CHCl_3$)). The enantiomeric excess (e.e.) was at first assessed by converting the mixture **5** into the known lactone **7** using the two-step procedure of Mukaiyama *et al.*[3a] Comparison of the specific rotation with the literature value for (+)-(1*R*,6*S*)-*cis*-8-oxabicyclo[4.3.0]-nonan-7-one[9] implied an optical purity of 80%. This value was confirmed by measuring the e.e. of **6** by HPLC using a Chiralpak AS column, and it was established to be 75(±1)%.

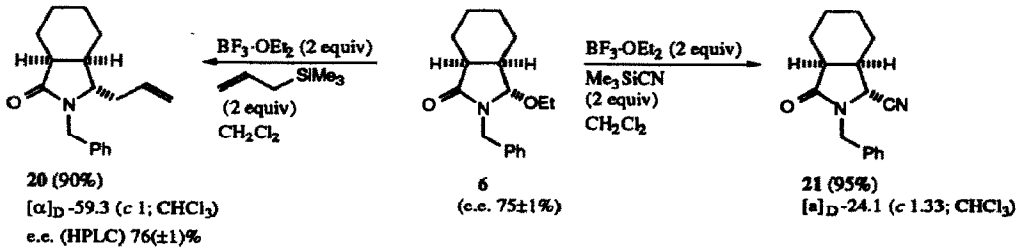
Scheme 1



After this encouraging result, the reduction method was applied to several other substrates. The results of this study are collected in Table 1. In every case, the same experimental procedure was used for the reductions and ethanolysis reactions.[10] In entries 2 and 3, the optical purities were determined indirectly by converting the hydroxylactams into the corresponding, known lactones, while in entries 4 and 5 chiral HPLC techniques were applied to determine the e.e.'s. Furthermore, in entries 1-3 the absolute configurations of the products are known and as indicated, while in entries 4 and 5 the absolute configurations are yet unknown.

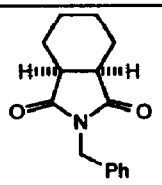
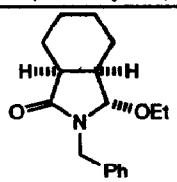
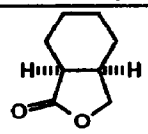
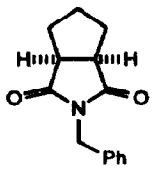
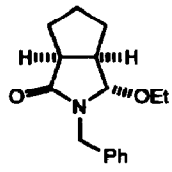
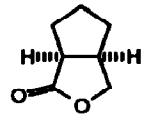
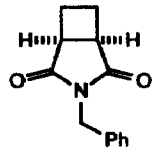
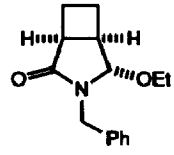
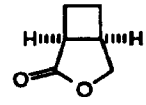
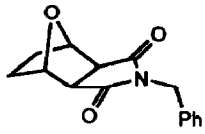
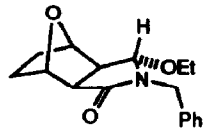
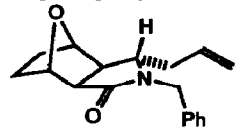
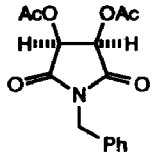
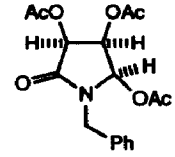
It can be seen from the Table that all reactions described proceeded in good overall yields. The ethoxylactams were obtained with complete *trans*-stereoselectivity and high enantioselectivity by a simple two-step procedure. This first series of reactions show that it is possible to obtain a range of optically active 5-hydroxy-2-pyrrolidinones, although the e.e.'s still need to be optimized. One factor that might influence the stereoselectivity of the reduction is the nature of the *N*-substituent. However, when the *N*-benzyl group in **4** was replaced by a methyl group, the reaction sequence as indicated in Scheme 1 afforded lactone **7** with a similar yield and optical rotation. We are currently investigating the effect of other *N*-substituents on the reaction as well as several other variables, such as the structure of the hydride donor[11] and the oxazaborolidine.

Scheme 2



The synthetic utility of 5-ethoxy-2-pyrrolidinones is based on the possibility to effect C-C bond formation at the 5-position *via* *N*-acyliminium chemistry. As examples of this, ethoxylactam **6** was reacted under Lewis acidic conditions with two types of carbon nucleophiles, namely allyltrimethylsilane and trimethylsilyl cyanide, furnishing optically active derivatives **20** and **21** as single diastereomers, respectively (Scheme 2). The e.e. of **20** was also measured by using chiral HPLC and established at 76(±1)%. In a similar way, ethoxylactam **14**

Table 1. Reductions of *meso*-imides using chiral oxazaborolidine 3

entry	imide[a]	ethoxylactam (isolated yield[b])	derivative (isolated yield)
1	 **4**	 **6** (73%) $[\alpha]_D$ -55.7 (*c* 1; $CHCl_3$)[c] e.e. (HPLC)[e] 75(±1)%	 **7** (76%)[d] $[\alpha]_D$ +38.9 (*c* 0.65; $CHCl_3$) lit.$[\alpha]_D$ +48.8 (*c* 0.5; $CHCl_3$)[9] optical purity 80%
2	 **8**	 **12** (85%) $[\alpha]_D$ -37.9 (*c* 1.55; $CHCl_3$)	 **16** (60%)[d] $[\alpha]_D$ +74.7 (*c* 2.21; $CHCl_3$) lit.$[\alpha]_D$ +96.9 (*c* 1; $CHCl_3$)[9] optical purity 77%
3	 **9**	 **13** (68%) $[\alpha]_D$ -18.9 (*c* 1.5; $CHCl_3$)	 **17** (72%)[d] $[\alpha]_D$ +106 (*c* 5.3; $CHCl_3$) lit.$[\alpha]_D$ +118.7 (*c* 10; $CHCl_3$)[9] optical purity 89%
4	 **10**	 **14** (68%) $[\alpha]_D$ +23.8 (*c* 0.58; $CHCl_3$)	 **18** (92%)[f] $[\alpha]_D$ +33.8 (*c* 1.34; $CHCl_3$) e.e. (HPLC)[e] 76%
5	 **11**		 **19** (51%)[g] $[\alpha]_D$ +43.7 (*c* 0.60; $CHCl_3$) e.e. (HPLC)[e] 87%

[a] Starting imides were generally prepared either from the corresponding dicarboxylic acids, *via* reaction with acetyl chloride (to give the anhydride), benzylamine, and again acetyl chloride, or by benzylation of the corresponding NH-compound using NaH/BnBr. [b] After reduction and ethanolysis; conditions: see Scheme 1. [c] All specific rotations were determined at 25 °C. [d] Overall yield from the corresponding hydroxylactam, after bulb-to-bulb distillation; conditions: see Scheme 1. [e] Using a Chiralpak AS column, and *n*-hexane/*i*-propanol 95:5 as the eluent for **8**, and *n*-hexane/EtOH 90:10 in all other cases. [f] After treatment of **14** with allyltrimethylsilane and BF_3-OEt_2 in CH_2Cl_2, analogous to **20** (Scheme 2). [g] After treatment of the hydroxylactam with Ac_2O (5 equiv) and DMAP (cat) in pyridine.

was reacted with allyltrimethylsilane to give the corresponding allyl-derivative **18** (see Table 1). The functionalities, introduced in this way, can be used as tools in further synthetic operations.

In conclusion, we have shown that several cyclic *meso*-imides can be reduced with high enantioselectivity by using the oxazaborolidine 3 as chiral catalyst. The optically active lactams and lactones obtained in this way may serve as starting materials for various synthetic purposes.[12]

Acknowledgement: We thank A.L.L. Duchateau (DSM Research) for the e.e.-determinations by HPLC. These investigations were supported (in part) by the Netherlands' Foundation for Chemical Research with financial aid from the Netherlands' Technology Foundation.

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8. A few papers on the reduction of the C=N double bond in imines and ketoxime *O*-alkyl ethers have appeared; see ref 7b.
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10. All compounds described in this paper were appropriately characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS. A typical experimental procedure: preparation of **6**. The chiral catalyst (3) was prepared by heating a mixture of α,α-diphenyl-*L*-prolinol and BH_3 (3 equiv) in THF at reflux for 17 h under an Argon atmosphere, followed by removal of the volatiles using a vacuum pump. A solution of 3 (0.50 mmol) in THF (1.5 mL) was added at 0 °C to a solution of imide **4** (167 mg, 1.00 mmol) in THF (5.0 mL). After the addition of BH_3 (0.75 mL of a 1 M solution in THF, 0.75 mmol), the mixture was allowed to warm up to rt and stirring was continued for 2 h. After cooling to 0 °C, the reaction mixture was quenched with 5% aq HCl, and extracted with ether (3 ×). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a *cis/trans* mixture of hydroxylactams, which was dissolved in EtOH (10 mL), acidified to pH = 2 with 2 M H_2SO_4 in EtOH, and stirred for 3 h. After careful neutralization using 5% KOH in EtOH, the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL), poured out into aq saturated $NaHCO_3$ and extracted with $CHCl_3$ (3 ×). Drying of the combined organic layers (Na_2SO_4), removal of the solvent *in vacuo* and purification by flash chromatography afforded **6** (210 mg, 0.77 mmol, 77% yield based on **4**) as a yellow oil, R_f 0.64 (CH_2Cl_2/acetone 95:5). ^{1}H NMR (400 MHz, $CDCl_3$): 7.35-7.25 (m, 5 H, *Ph* CH_2), 4.99 (AB d, 1 H, J = 14.7 Hz, Ph-C*H*H), 4.10 (s, 1 H, NC*H*-OEt), 4.01 (AB d, 1 H, J = 14.7 Hz, Ph-CH*H*), 3.48-3.38 (m, 2 H, OCH_2CH_3), 2.88-2.79 (m, 1 H, C*H* C(O)), 2.24-2.18 (m, 2 H, C*H*H-CHC(O) and C*H* CHOEt), 1.64-1.50, 1.19 and 0.74 (m, 7 H, C(O)CHCH*H* (CH_2)$_3$), 1.18 (t, 3 H, J = 7 Hz, OCH_2CH_3). ^{13}C-NMR (50 MHz, $CDCl_3$): 176 (*C*(O)N), 136.8, 128.4, 128.3, 127.3 (Ph), 92.1 (*C*HOEt), 63.2 (OCH_2CH_3), 44.3 (CH_2Ph), 38.6 (CHC(O)), 37.6 (*C*HCHOEt), 26.7, 23.4, 22.8, 22.78 ((CH_2)$_4$), 15.2 (OCH_2CH_3). HRMS calcd for $C_{17}H_{23}NO_2$ 273.1729, found 273.1736.
11. Upon using catecholborane as the hydride donor no reduction was observed.
12. These compounds could, for example, be used as intermediates in the synthesis of certain indolizidine alkaloids. See, e.g.: Maggini, M.; Prato, M.; Rancelli, M.; Scorrano, G. *Tetrahedron Lett.* **1992**, *33*, 6537.

(*Received in UK* 29 *October* 1993; *revised* 7 *December* 1993; *accepted* 10 *December* 1993)