(1'*S*,4*S*)-2-ARYL-4-(1'-HYDROXYBENZYL)-4,5-DIHYDRO-OXAZOLE AS A USEFUL CHIRAL AUXILIARY FOR THE SYNTHESIS OF β-AMINO ACIDS AND β-LACTAMS IN A HIGHLY STEREOSELECTIVE MANNER

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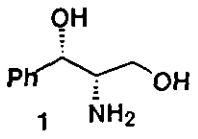
Abstract - (1'*S*,4*S*)-2-Aryl-4-(1'-hydroxybenzyl)-4,5-dihydrooxazole prepared from (1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol has been found to be a useful chiral auxiliary for the stereoselective synthesis of β-lactams and β-amino acids in the reaction of imine-ester enolate condensation or 1,4-addition of lithium amides to α,β-unsaturated esters.

β-Lactam antibiotics still constitute one of the most widely utilized classes of drugs due to their high therapeutic index in humans.[1] In connection with the structure-activity relationship study of drugs, stereoselective synthesis of β-lactams as well as β-amino acids, precursors of β-lactams, is highly desirable. In the course of studying stereoselective preparations of β-lactams by the imine-ester enolate condensation, a highly efficient imine possessing a chiral dioxolane derived from tartaric acid has been successfully used for the switchover of the diastereoselectivity.[2] From the standpoint of ready accessibility of the chiral auxiliary and its removal in the cyclization process, the esters having a chiral group at the alkoxy part of the ester have intrigued us. Among the chiral auxiliaries studied, amino alcohols derived from (+)-camphor have enabled the stereoselective synthesis of β-lactams.[3f] Considering



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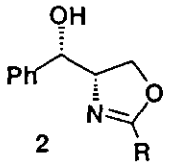

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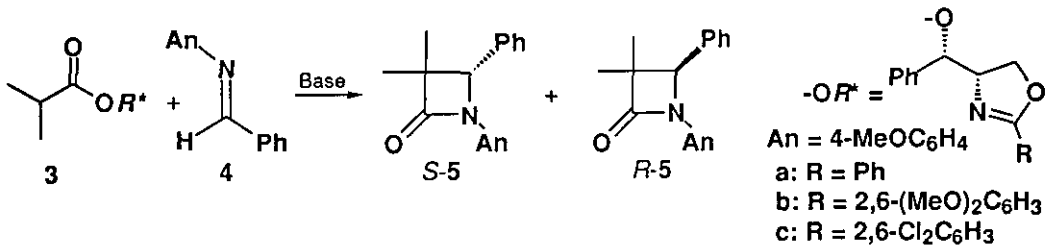
a: R = Ph
b: R = 2,6-$(MeO)_2C_6H_3$
c: R = 2,6-$Cl_2C_6H_3$
d: R = 2-Naphthyl
e: R = 2,6-$Me_2C_6H_3$

the accessibility of the chiral source, we have been interested in the use of easily available (1*S*,2*S*)-2-amino-1-phenyl-1,3-diol (**1**) as an auxiliary for useful C-C bond formations involving asymmetric addition of dialkylzinc to α,β-enones disclosed recently.[4] As one of the derivatives of this particular amino diol (**1**), 4,5-dihydrooxazole (**2**) has been attractive due in part to the relatively rigid ring structure and to the imino functionality capable of coordinating with metal species. Recent studies in the reaction of the ester enolate having the chiral auxiliary at the alkoxy part of the ester have shown that this approach effects the stereoselective synthesis of one of the enantiomers of β-lactam rings.[3] Moreover, the question of the switchover of the diastereoselectivity induced by the enolate metal species has been of great interest. On the other hand, 1,4-addition of metal amides to α,β-unsaturated esters also constitutes one of the most straightforward approaches to β-amino acids or β-lactams, and recently devices on stereocontrol have been reported.[5] We have now found that (1'*S*,4*S*)-2-aryl-4-(1'-hydroxybenzyl)-4,5-dihydrooxazole (**2**) works as a useful chiral auxiliary for the control of diastereoselectivity in ester enolate-imine condensation and 1,4-adition reaction of amide to α,β-unsaturated esters, leading to a stereoselective synthesis of β-lactams.

The chiral 4,5-dihydrooxazoles (**2**) were prepared readily from (1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol (**1**) in the following manner:[6] acylation of the amino group was followed by tosylation and cyclization to give 4,5-dihydrooxazole in good overall yield. Esterification was carried out in a usual manner with acyl chloride and triethylamine in the presence of 4-dimethylaminopyridine. First, the ester enolate-imine condensation was carried out, and the results are shown in Table 1.[7]

Initial examination into the reaction of the chiral ester (**3a**) possessing a phenyloxazole derivative (**2a**) met with good discrimination. The reaction afforded a good ratio of the 4*S*-β-lactam (*S*-**5**) ($S : R = 91 : 9$) upon treatment of the potassium enolate with the imine (**4**) in the presence of tetramethylstannane, and the bromozinc enolate prepared *via* transmetallation of the corresponding potassium enolate with zinc bromide also gave *S*-**5** in a better ratio of $S : R = 94 : 6$ (Entries 1 & 2). Although the product yield was not high, the changeover of the diastereoselectivity was observed, in which the lithium enolate prepared by deprotonation with LDA in the presence of triethylborane gave *R*-**5** in a ratio of $S : R = 30 : 70$ (Entry 4). 2,6-Dimethoxyphenyl derivative (**3b**) led to the formation of 4*S*-β-lactam (*S*-**3**) regardless of switching the enolate metal species. However, almost no diastereofacial discrimination was observed with the 2,6-



3 4 *S*-5 *R*-5

Table 1 Reaction of Ester (3) with Imine (4).[a]

Entry	Ester	Base[b]	Additive	Solvent	Yield/%[c]	*S*-5: *R*-5[d]
1	**3a**	KHMDS	Me_4Sn	THF	88	91 : 9
2	**3a**	KHMDS	$ZnBr_2$	THF	62	94 : 6
3	**3a**	KHMDS	$ZnCl_2$	THF	83	77 : 23
4	**3a**	LDA	Et_3B	Et_2O	16	30 : 70
5	**3b**	LDA	Et_3B	THF	71	92 : 8
6	**3b**	KHMDS	$ZnBr_2$	THF	90	78 : 22
7	**3b**	KHMDS	Me_4Sn	THF	86	76 : 24
8	**3c**	LDA	None	THF	50	66 : 34
9	**3c**	KHMDS	$ZnBr_2$	THF	32	58 : 42

a) The reaction was carried out according to the typical experimental procedure. b) The following abbreviations are used; LDA: lithium diisopropylamide; KHMDS: potassium hexamethyldisilazide. c) Isolated yields. d) Determined by HPLC analysis using a chiral stationary phase column (Daicel OJ), and for determination of stereochemistry, see ref 8.

dichlorophenyl derivative (**3c**). The absolute configurations of the β-lactams obtained in the present study were determined by comparison with the authentic samples.[8] These results indicate that a chelation-type transition state and a non-chelation counterpart as reported recently[9] may be responsible for the reversal of the diastereoselectivity.

For the preparation of 3-unsubstituted β-lactams 1,4-addition reaction of metal amide to α,β-unsaturrated esters offers another straightforward access to this useful class of compound. The chiral 4,5-dihydrooxazole derivative (**2**) described above also offered good environment for the induction of chirality, where the chiral unsaturated esters possessing oxazole (**6a**, **d**, **e**) were used as substrates. The addition reaction of the lithium amide (**7**) derived from benzyltrimethylsilylamine[5c-e] was examined, and the results are summarized in Table 2.[10]

As shown, the addition of the lithium amide (**7**) in THF gave 3*S*-adduct (*S*-**8**) predominantly in the cases

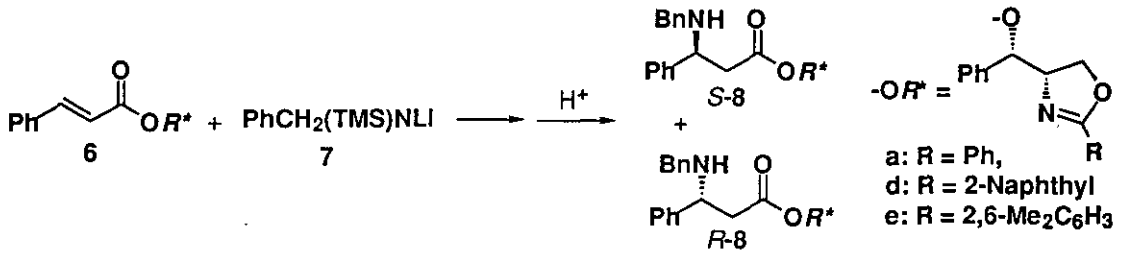


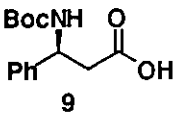
Table 2 Addition of the Metal Benzyltrimethylsilylamide (7) to α,β-Unsaturated Ester (6).[a]

Entry	Ester	Additive	Temp/°C	Solvent	Yield/%[b]	*S*-8: *R*-8[c]
10	**6a**	None	-78-rt	THF	27	77 : 23
11	**6a**	CuI	-100	THF	77	81 : 19
12	**6a**	$ZnCl_2$	-100	THF	75	82 : 18
13	**6a**	Bu_4Sn	-100	THF	52	84 : 16
14	**6a**	None	-80	DME	18	43 : 57
15	**6a**	Me_4Sn	-80	DME	80	42 : 58
16	**6d**	Bu_4Sn	-100	THF	66	83 : 17
17	**6d**	Me_4Sn	-80	DME	64	37 : 63
18	**6e**	Bu_4Sn	-115	THF	39	92 : 8
19	**6e**	Me_4Sn	-80	DME	59	45 : 55

a) The reaction was carried out according to the typical experimental procedure. b) Isolated yields. c) Determined by HPLC analysis using Merck Hibar column, and for determination of stereochemistry, see text.

with phenyloxazole derivative (**6a**). Better diastereofacial discrimination was observed when the reactionwas carried out in the presence of Bu_4Sn (Entry 13), whereas the lithium amide in the presence of Me_4Sn in DME induced the reversal of the diastereroselectivity, although the ratio was not high (Entry 15). This trend was also true for the derivatives possessing 1-naphthyl or 2,6-dimethylphenyl substituent (**6d, e**). In particular, 2,6-dimethylphenyl derivative (**6e**) recorded the highest diastereomer ratio when the reaction was conducted at -115 °C (Entry 18). The determination of the absolute stereochemistry was carried out by transforming the adduct (**8**) into amino alcohol (**10**) by reduction with DIBAL, and comparison of its specific rotation with the authentic sample prepared from the known amino acid (**9**) *via* benzylation followed by reduction and deprotection.[11] The separation of *S*-**8** from *R*-**8** was readily carried out by simple silica gel chromatography, and the diastereomerically pure adduct (**8a**) was transformed into β-lactam (**11**) *via* hydrolysis with LiOH-H_2O_2 followed by cyclization with Ph_3P-$(PyS)_2$ in 61% overall yield without affecting its stereochemical integrity. The present good diastereofacial discrimination is most

reasonably understood in terms of the addition of a well-dissociated metal amide to α,β-enone in an analogy to the Michael type reaction disclosed recently.[9]



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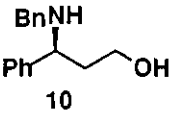

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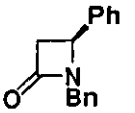
from **8a** (66 %ee): 88%, $[\alpha]^{23}_D$ -24.7° (c 0.93, MeOH)
from **9** (75%ee): 78%, $[\alpha]^{23}_D$ -28.1°(c 0.06, MeOH)



11 $[\alpha]^{23}_D$ -54.4° (c 0.59, MeOH)
overall 61% , >99%ee

In conclusion, the present two types of diastereofacial discrimination reactions by the use of heterocyclic chiral auxiliaries derived readily from (1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol realize simple approaches to β-lactams in a stereo-controlled fashion. Since a variety of imino compounds are readily available and the esterification of the chiral 4,5-dihydrooxazole derivative is readily carried out, this kind of approaches will be applied to the synthesis of a series of aldol and Michael type reactions.

ACKNOWLEDGEMENT

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7. A typical procedure is as follows: To a solution of KHMDS (1.68 mL, 0.5M in toluene, 0.84 mmol) in THF (2 mL) was added a solution of the ester **3a** (262 mg, 0.84 mmol) in THF (3 mL) at -40 °C. After stirring for 15 min, zinc bromide (189 mg, 0.84 mmol) was added, and the mixture was allowed to stand at 0 °C for 1 h. A solution of the imine (**4**) (30 mg, 0.14 mmol) in THF (3 mL) was added dropwise at -78 °C, and the mixture was allowed to stand at -40 °C - rt for 17 h. After usual work-up the crude product was purified on preparative TLC to give **5** (24 mg, 62 %) as a colorless oil. The ratio of the isomers was determined by HPLC using a chiral stationary phase column (Daicel OJ) to be *S*-**5** : *R*-**5** = 94 : 6.
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10. The following example represents a typical procedure: To a solution of benzyltrimethylsilylamine[5d] (70 mg, 0.39 mmol) in THF (1.5 mL) was added n-BuLi (0.22 mL, 1.75N in hexane, 0.39 mmol) at -78 °C, and the mixture was stirred for 30 min. A solution of Me_4Sn (135 mg, 0.39 mmol) in THF (1.5 mL) was added to the resulting orange solution at 0 °C. After the mixture was stirred for 30 min, a solution of the ester (**6**) (80 mg, 0.19 mmol) in THF (1.5 mL) was added at -100 °C, and the whole mixture was allowed to stand for 2 h. After usual work-up, the crude oil was purified on silica

gel TLC to give the adduct (**8e**) (68 mg, 68%) as a colorless oil. The diastereomeric ratio was determined to be 3*S* : 3*R* = 88 : 12 by HPLC using a Merck Hibar column.

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