

Stereoselective dihydroxylation reactions of γ -amino- α,β -unsaturated esters *via* their aryl ketimine derivatives

Joon Seok Oh, Jongho Jeon, Do Yeon Park and Young Gyu Kim*

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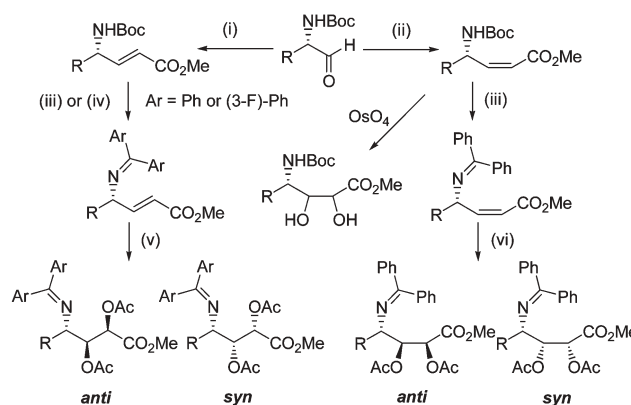
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OsO₄-catalysed dihydroxylation reactions of the aryl ketimine derivatives of (*E*)- γ -amino- α,β -unsaturated esters gave *anti* selectivity ranging from 6.7 : 1 to 19 : 1, whereas the opposite *syn* selectivity was consistently observed with those of (*Z*)- γ -amino- α,β -unsaturated esters (5.4 : 1 to >100 : 1).

The dihydroxylation reaction of allylic amines with OsO₄ is one of the most efficient methods to produce vicinal amino alcohols that are widely present in biologically active compounds and chiral auxiliaries.¹ In spite of its usefulness, the stereoselective dihydroxylation reaction of allylic amines has not been studied as much as that of allylic alcohols.^{2,3} Often, poor stereochemical results have been reported for the acyclic allylic amino derivatives with flexible conformation.^{2,4–6} In several cases, achieving good facial selectivity has been a problem even when the well-established Sharpless asymmetric dihydroxylation is applied.^{4,7–9} We have recently shown that the aryl ketimine derivatives of allylic amines with a terminal olefin resulted in consistent *anti* diastereofacial selectivity.¹⁰ Although the selectivities obtained were not high, it would be quite useful as the monosubstituted olefin has been a challenging substrate in the OsO₄-catalysed dihydroxylation reactions.^{9,11} The *syn* selectivity has also been observed with a few terminal olefins.¹² In an attempt to apply the dihydroxylation method of the aryl ketimine derivatives to the synthesis of various bioactive compounds such as α -hydroxy statine,⁵ 4-amino-7-guanidino-2,3-dihydroxyheptanoic acid (AGDHE),^{7,13} aza sugars,⁴ and dihydroxyglutamic acids,¹⁴ we found that the selectivity varied depending on the type of olefin substrates and wish to report the results as follows.

Both (*E*)- and (*Z*)- γ -amino- α,β -unsaturated methyl esters were prepared by the Wittig reactions of the readily available amino aldehydes (Scheme 1).¹⁵ The desired aryl ketimine derivatives were obtained in good to high yield after deprotection of the Boc group followed by transimination with benzophenone imine or a condensation reaction with 3,3'-difluorobenzophenone in the presence of TiCl₄. The aryl ketimine derivatives were then treated under the dihydroxylation reaction conditions as described in the previous study (Table 1).¹⁰ As expected, higher *anti* selectivities resulted from all the (*E*)-esters compared to those of the *N*-Boc derivatives reported in the literature (*anti* : *syn*: R = Me, 51 : 49; R = Bn, 59 : 41; R = *i*-Bu, 60 : 40; R = *i*-Pr, 81 : 19).¹⁶ The *anti* selectivity increases as the alkyl group gets larger. 3,3'-Difluorobenzophenone ketimine derivatives also give better *anti* selectivities than the unsubstituted ones as reported before.¹⁰ The stereochemistry at the newly generated chiral carbons was



Scheme 1 Reagents and conditions: (i) Ph₃P=CHCO₂Me, PhH, reflux, 78–81%; (ii) (CF₃CH₂O)₂POCH₂CO₂Me, KHMDS, 18-crown-6, –78 °C, 73–93%; (iii) 4 N HCl in dioxane, then benzophenone imine, DCM, 62–88%; (iv) 4 N HCl in dioxane, then TiCl₄, 3,3'-difluorobenzophenone, DME, TEA, –78 °C, 62–96%; (v) OsO₄, NMO, THF, then Ac₂O, TEA, DMAP; (vi) OsO₄, NMO, THF–H₂O, then Ac₂O, TEA, DMAP.

Table 1 Dihydroxylation reactions of the aryl ketimine derivatives of (*E*)- γ -amino- α,β -unsaturated methyl ester (Scheme 1)

R	Ar = phenyl		Ar = 3-fluorophenyl	
	Ratio ^a (<i>anti</i> : <i>syn</i>)	Yield (%)	Ratio ^a (<i>anti</i> : <i>syn</i>)	Yield (%)
Me	3.9 : 1	76	6.7 : 1	61
Bn	5.9 : 1	67	8.7 : 1	71
<i>i</i> -Bu	5.4 : 1	87	11.8 : 1	75
<i>i</i> -Pr	11.0 : 1	75	19.0 : 1	62

^a Determined by G/C.

determined by comparing the ¹H NMR data with those of known compounds in the literature.¹⁶ The stereochemical results obtained here with the aryl ketimine derivatives are complementary to those observed with the *N,N*-dibenzyl derivatives by Reetz and co-workers that showed the inherent *syn* selectivities.¹⁶

However, opposite *syn* selectivities were found for all the aryl ketimine derivatives of (*Z*)- γ -amino- α,β -unsaturated esters (Table 2). The selectivities are moderate to excellent even with the unsubstituted benzophenone ketimine derivatives. Therefore, fluorine-substituted benzophenone was not used to improve the selectivity. For comparison, the Boc derivatives of the same (*Z*)-esters were made and subjected to the same dihydroxylation conditions (Table 2). No or poor selectivities were shown regardless of the size of the alkyl group. The relative stereochemistry between the stereogenic carbons bearing the amino and the hydroxyl group was determined by measuring the coupling

*ygykim@snu.ac.kr

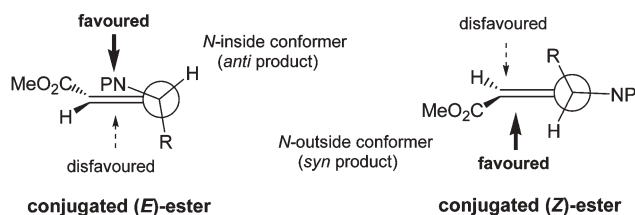


Fig. 1 Probable transition state models (PN = aryl ketimine).

Table 2 Dihydroxylation reactions of the derivatives of (Z)- γ -amino- α,β -unsaturated methyl ester (Scheme 1)

R	N-Boc derivative		Benzophenone ketimine	
	Ratio ^a (<i>anti</i> : <i>syn</i>)	Yield (%)	Ratio ^c (<i>anti</i> : <i>syn</i>)	Yield (%)
Me	1 : 1.6	58 (24) ^b	1 : 5.4	90
Bn	1 : 1.5	82	1 : 15	71
i-Bu	1 : 1	65 (13) ^b	1 : >50	80
i-Pr	1 : 1.5	72 (25) ^b	1 : >100	66

^a Determined by ¹H NMR. ^b Recovered starting material.

^c Determined by G/C.

constants and the NOE enhancement data, after conversion of each amino diol product into the corresponding lactam.¹⁷ The consistent high *syn* selectivity shown in the present study would be useful in the synthesis of the related compounds since mixed results were reported for a few (Z)-esters in the literature.^{8,18}

The selectivities observed in this study could be explained with the Houk transition state models shown in Fig. 1.¹⁹ In the absence of severe A^{1,3} allylic strain, the aryl ketimine group that is a deactivating substituent would take preferentially an 'N-inside' conformation of the (E)-conjugated esters.²⁰ Preferential osmylation from the less hindered top side would give the *anti* diols. For the (Z)-conjugated esters, severe allylic steric hindrance from the methoxy carbonyl group would exist and the aryl ketimine group is directed toward the outside to minimize the A^{1,3} interaction, favouring an 'N-outside' conformation. Addition of OsO₄ from the bottom side of the 'N-outside' conformer would result in the *syn* diol isomers as a major product. However, the Kishi empirical models can be advanced to rationalize our results, too.^{2,21}

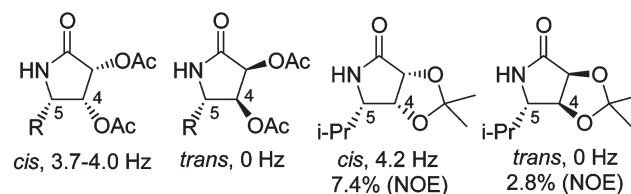
In summary, a systematic study on the dihydroxylation reactions of both (E)- and (Z)- γ -amino- α,β -unsaturated esters was performed and introduction of the aryl ketimine group into allylic amine resulted in much improved stereoselectivity for their osmium-catalysed dihydroxylation reactions. With the (E)-esters, *anti* selectivity from 6.7 : 1 to 19 : 1 is obtained and the opposite *syn* selectivity is observed with the (Z)-esters (5.4 : 1 to >100 : 1) even without using expensive chiral auxiliaries. The stereoselective results with the aryl ketimine derivatives are quite high compared to those of the N-Boc derivatives. They are also complementary to those of the N,N-dibenzyl derivatives for the (E)-esters. The consistent *syn* selectivity with the (Z)-esters would be useful in predicting the stereochemical outcome of dihydroxylation products. The potential of the present method is an efficient and highly selective synthesis of natural or unnatural γ -amino- α,β -dihydroxy carboxylic acids and their derivatives. Application of this strategy for the synthesis of two of the target compounds, AGDHE and dihydroxyglutamic acid, is currently underway in our laboratory.

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Joon Seok Oh, Jongho Jeon, Do Yeon Park and Young Gyu Kim*
School of Chemical Engineering, Seoul National University, Seoul,
151-744, Republic of Korea. E-mail: ygkim@snu.ac.kr

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- Both *trans* and *cis* lactams were prepared as follows from the N-Boc amino diol derivatives that were separable by column chromatography. Each N-Boc amino diol derivative was transformed into the N-Cbz derivative that was treated with Pd/C and ammonium formate under reflux to give the lactam diol. The following acetylation gave the corresponding lactam diacetates shown below. The coupling constant of 3.7–4.0 Hz between H-4 and H-5 was assigned to the *cis* lactam and that of 0 Hz to the *trans* lactam.⁸ Then, a mixture of ketimine diols was independently transformed into the same lactams by following a similar procedure described for the N-Cbz derivative above. The major lactam derived from a mixture of ketimine diols matched the *cis* lactam obtained from the N-Boc amino diol. The minor lactam was not seen on the ¹H NMR spectrum except when R is Me. The assignment of relative configuration was confirmed by observation of the larger NOE enhancement for the *cis* bicyclic lactam as shown below (*cis* lactam: 7.4% between H-4 and H-5; *trans* lactam: 2.8% between H-4 and H-5).



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