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Invited Review

비고리 알릴아민 화합물의 입체선택적 이중알코올화 반응

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Stereocontrolled Dihydroxylation Reactions of Acyclic Allylic Amines

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초 록

비고리 알릴아민 화합물의 이중알코올화 반응은 아미노 다이올 구조를 도입할 수 있는 효율적인 합성법으로 아미노 다이올 구조를 포함하는 다양한 생리활성 천연물의 효율적인 합성에 적용될 수 있다. 본 리뷰에서는 기질 그 자체, 혹은 카이랄 리간드를 이용한 다양한 입체선택적 이중알코올화 반응들을 소개하고 이를 실제 천연물의 합성에 적용한 최근의 반응 결과들을 살펴보고자 한다.

Abstract

The dihydroxylation reaction of allylic amines is a facile and useful synthetic method to obtain amino diol structures that are widely found in lots of biologically important natural products. This review will focus on the recent methods of both substrate-controlled and ligand-controlled dihydroxylation reactions of acyclic allylic amines. In addition, several applications of the diastereoselective dihydroxylation methods to asymmetric syntheses of natural products are presented.

Keywords: *Dihydroxylation, Acyclic conformation, Asymmetric synthesis, Natural product, Osmium tetroxide*

1. Introduction

A vicinal amino diol moiety is commonly found in a large number of natural products and pharmaceutical intermediates such as amino sugars, sphingolipids, γ-amino acids, and amino alcohols[1]. The dihydroxylation reaction of chiral allylic amines using osmium catalyst is one of the most convenient and straightforward methods for preparing an amino diol group (Figure 1). Until now, a lot of diastereoselective dihydroxylation methods have been developed for asymmetric synthesis of chiral products. In the case of conformationally rigid cyclic allylic amines, stereoselectivity of the dihydroxylation reaction can be easily controlled because the facial selectivity of osmium catalyst is mostly determined by either the configuration of the adjacent chirality or favored conformation of cyclic substrates[2]. On the other hand, acyclic allylic amines normally give low stereoselectivity

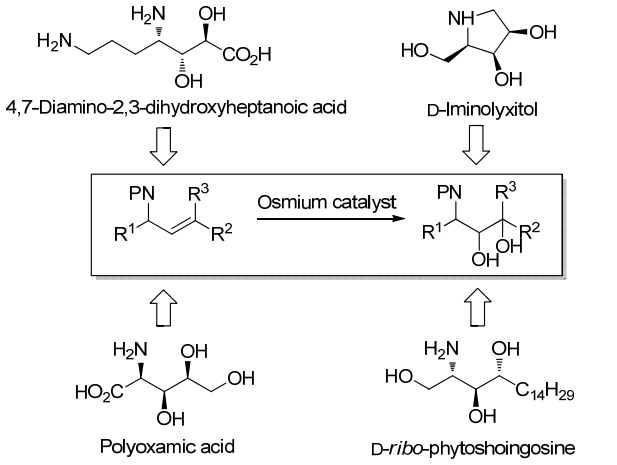

Figure 1. Dihydroxylation reactions of chiral allylic amines for natural product synthesis.

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due to the flexible conformation of the substrate. Even the well-known asymmetric dihydroxylation methods employing chiral agents (i.e., AD-mix-α, AD-mix-β) often showed poor to moderate results in several kinds of acyclic allylic amines. In 1995, an excellent review on acyclic stereocontrol of the dihydroxylation reactions induced by allylic alkoxy groups was published by Cha and Kim[2]. It showed the dihydroxylation results of various acyclic allylic alcohols and some allylic amines and their mechanistic considerations. For the last two decades, a lot of new or modified dihydroxylation results of acyclic allylic amines have been developed to overcome low stereochemical control by either substrate-controlled or chiral ligand-controlled dihydroxylations. In this report, we would like to review on recent advances of the dihydroxylation reaction methods of acyclic allylic amines and their applications to asymmetric syntheses of chiral intermediates and natural products with the amino diol functionality.

2. Mechanistic Models of Dihydroxylation Reactions in Acyclic Allylic Systems

2.1. Substrate-controlled dihydroxylation

The mechanistic basis of the dihydroxylation reactions of allylic amines has not been studied as much as those of allylic alkoxy groups including allylic alcohols. Therefore, a review on the conformation models of allylic alkoxy group will be useful to predict the facial selectivity and understand the observed diastereoselectivity of allylic amines in the dihydroxylation reactions. The proposed mechanism of stereochemical results in this report will be explained by the following models (Figures 2-4).

2.1.1. Kishi empirical model

Kishi and co-workers reported the dihydroxylation results of various allylic alcohol systems[3]. According to their papers, the relative stereochemistry between the pre-existing alkoxy (or hydroxy) group and the adjacent newly introduced hydroxy groups of the major product showed *anti* selectivity except for few cases. Moreover, the stereoselectivities observed for the (*Z*)-olefins were normally higher than those of the corresponding (*E*)-olefin isomers. An eclipsed conformation is known to be more stable than other conformations and thus, it is considered as reactive conformations. Among three eclipsed conformations, *H*-eclipsed conformation A is more preferred to the others, because it is sterically less compressed (Figure 2). The dihydroxylation takes place preferentially in the opposite side to the allylic oxygen in conformation A, which resulted in the *anti* major product.

2.1.2. Houk model

Houk and co-workers suggested the inside alkoxy model based on the theoretical studies and computational predictions (Figure 3)[4]. They proposed two lowest energy conformations in electrophilic addition reactions (conformations **D** and **E**). OsO_4 species was envisioned to approach *anti* periplanar to the σ-donating and sterically bulky group (R^1). Electronic deactivation of the olefin was minimized in conformations **D** and **E** because efficient overlap between the electron

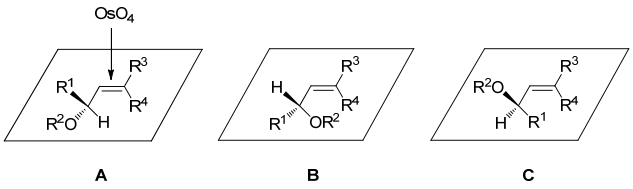


Figure 2. Eclipsed conformations of allylic alcohol substrates (Kishi model).

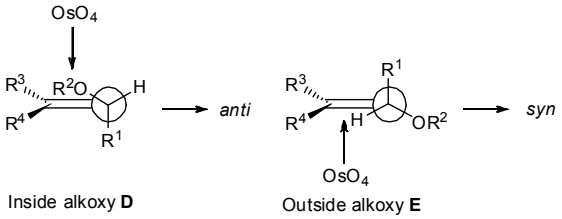


Figure 3. Houk model.

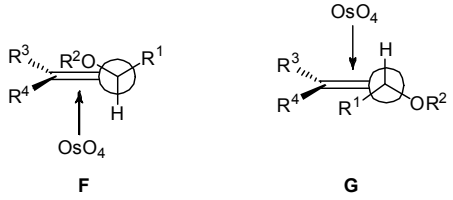


Figure 4. Vedejs model.

withdrawing σ^* orbital of C-O bond and π-electron of the olefin was avoided. Additionally, electron donating effect by the alkyl group (R^1) was maximized. In the absence of strong steric effect, inside conformation **D** was more stable than **E** since the deactivating C-O bond was nearly coplanar to the olefin and thus the *anti*-selective product was observed. On the other hand, as the steric hindrance of R^1 group was increased, outside conformation **E** was expected to be a reactive conformation due to reduced 1,3-allylic ($A^{1,3}$) strain with the olefin substituent.

2.1.3. Vedejs model

Vedejs emphasized the importance of steric effects between the OsO_4 reagent and the substrate[5]. In an (*E*)-olefin system, the lowest energy transition state was *H*-perpendicular conformations **F** and **G** (Figure 4). The choice between **F** and **G** was governed by the relative size of an allylic substituent (R^1 and OR^2). For a (*Z*)-olefin, on the other hand, the sterically dominant interactions were proposed to lie between the R^1 substituent and the allylic substituent (R^4). As a result, *H*-eclipsed conformation was clearly favored on steric grounds.

2.2. Hydrogen bonding-directed dihydroxylation

In OsO_4-catalyzed dihydroxylation reactions, amine bases like pyridine or quinuclidine are able to coordinate to osmium and accelerate the reaction rate of the dihydroxylation process. Donohoe have reported that the dihydroxylation of allylic alcohols and protected allylic amines with OsO_4 and tetramethylethylenediamine (TMEDA) gave the *syn* selectivity[6]. A hydrogen bonding between OsO_4-TMEDA com-

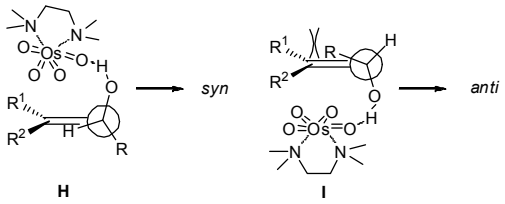


Figure 5. Hydrogen bonding-directed dihydroxylation.

plex and allylic alcohol or allylic amine resulted in *syn* major product (Figure 5). This result is opposite to Kishi's reports which utilized catalytic or substoichiometric amount of osmium reagent and co-oxidant (typically *N*-methylmorpholine *N*-oxide). The configuration of the olefin also plays an important role in the hydrogen bonding-directed dihydroxylation of allylic substrates. The diastereoselectivity of reactions of (*Z*)-olefins was significantly higher than that of analogous (*E*)-olefins. This observation has been attributed to the severe $A^{1,3}$ strain between R and R^2 group in the (*Z*)-olefin system. Conformation **H** for *syn* dihydroxylation avoids this strain.

3. Dihydroxylation Results of Acyclic Allylic Amines

Because of increasing importance of chiral amino alcohols as synthetic targets or intermediates in complex molecules such as natural products and chiral auxiliaries[1], development of stereoselective dihydroxylation methods has undoubtedly stimulated considerable interests in the field of organic synthesis. Since the Cha's review report[2], a large number of dihydroxylation results of acyclic allylic amines have been reported. Recent literature results are compiled in Tables 1-9, according to substitution patterns of the olefin. Several excellent or interesting stereochemical results will be discussed with their proposed transition states which are shown in Figures 2-5. Unless noted otherwise, the dihydroxylation reactions were carried out using catalytic amount of osmium reagent and co-oxidant such as *N*-methylmorpholine *N*-oxide (NMO) at ambient temperature.

3.1. Monosubstituted allylic amines

In most cases, monosubstituted allylic amines with the common *N*-protecting group such as *N*-carbamate, *N*-acyl or *N,N*-dibenzyl have resulted in poor or mixed selectivities with some exceptions. Table 1 showed the dihydroxylation results of *N*-carboxybenzyl (Cbz) protected vinyl glycine methyl ester **1** under different conditions[7].

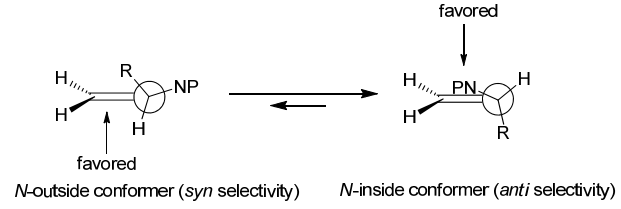
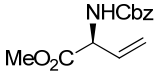
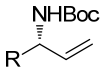


Figure 6. A proposed transition state model for monosubstituted allylic amines (P = 3,3'-(bisfluoro)diphenylmthylene).

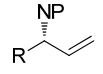
Table 1. Dihydroxylation of Monosubstituted Allylic Amines

Substrate	Conditions	*Anti : syn*	Yield (%)	Ref.
 **1**	OsO_4, NMO	5.4 : 1	32	7
	OsO_4, barium chlorate	1 : 12.2	66	
	$K_2OsO_2(OH)_4$, NMO	1 : 1.3	97	
	OsO_4, NMO			
2 R = Me		1 : 2	73	8
3 R = Bn		1.5 : 1	97	
4 R = Ph		1 : 1.3	93	
5 R = i-P		1 : 1	71	

Under the condition employing catalytic amount of OsO_4 or stoichiometric amount of NMO, modest *anti* selectivity was observed, while reversed *syn* selectivity was provided with different co-oxidant, barium chlorate.

We have introduced the *N*-diarylmethylene groups in monosubstituted allylic amines to improve the diastereoselectivity in the OsO_4 catalyzed dihydroxylation[8]. Among several kinds of the *N*-protection groups, the *N*-3,3'-(bisfluoro)diphenylmethylene group showed the higher *anti* selectivity than those of other *N*-substituted (*N*-carbamate, *N*-acyl or *N,N*-dibenzyl) allylic amines. Table 2 shows the dihydroxylation reactions of the *N*-3,3'-(bisfluoro)diphenylmethylene protected allylic amines with different side alkyl chains. Under the same reaction conditions, all substrates **6-9** gave better *anti* selectivities than those of **2-5** in Table 1. Moreover, the higher selectivity was observed with the bulkier alkyl side group (substrates **7-9**, Table 1). The observed stereochemical results from *N*-3,3'-(bisfluoro)diphenylmethylene protected substrates were explained by a combination of transition state models which were introduced in Figures 3 and 4 (Figure 6). According to the Houk model, a deactivating group would take preferentially inside conformation with the olefin in the absence of strong steric interactions. As a result, the *N*-inside conformer was predominant with electron-deficient diaryl methylene group in the monosubstituted allylic amines. The selectivities affected by the size of the alkyl substituents could be explained by the Vedejs model. The severe allylic strain ($A^{1,2}$ or $A^{1,3}$) between the large side group and the substituent on the olefin would strongly disfavor the *N*-outside conformation of the substrates.

Table 2. Dihydroxylation of *N*-3,3'-(bisfluoro)diphenylmethylene Protected Monosubstituted Allylic Amines

Substrate	Conditions	*Anti : syn*	Yield (%)	Ref.
	OsO_4, NMO			
6 R = Me		3.7 : 1	68	8
7 R = Bn		4.6 : 1	80	
8 R = Ph		5.2 : 1	69	
9 R = i-Pr		7.0 : 1	77	

P = 3,3'-(Bisfluoro)diphenylmethylene

3.2. 1,2-Dialkyl substituted (*E*)-allylic amines

Table 3 shows the dihydroxylation results from 1,2-dialkylsubstituted (*E*)-allylic amines. In most cases, they gave low to modest or reversed selectivities under either substrate-controlled or chiral agent-used reaction conditions. However, substrate **10** provided excellent *anti* or *syn* selective diols with AD-mix-α or AD-mix-β, respectively[9]. Dehydrohomotyrosine derivative **14** was studied with several kinds of chiral ligands to obtain *syn* selective diol for total synthesis of Echinocandins, a cyclic peptide isolated from marine natural product[13]. Interestingly, only $(DHQ)_2$-PHAL ligand gave the desired *syn* stereochemical result whereas others yielded reversed *anti* selectivity. Recently, S. G. Davies *et al*. have reported dihydroxylation studies of β-amino ester derivatives (**17**-**19**, Table 3). They used two different reaction conditions which were catalytic conditions (0.1 equiv. of OsO_4 and 4 equiv. of NMO) or stoichiometric conditions (1.1 equiv. of OsO_4 and 1.4 equiv. of TMEDA at -78 ℃). Without an aid of hydrogen bonding effect, the catalytic conditions of substrate **17** provided an excellent *syn* selectivity (> 99 : 1), while the stoichiometric conditions afforded the poor result[16]. Next, α-hydroxy β-amino ester substrates were investigated using the same reaction conditions. Dihydroxylation of **18** under the stoichiometric conditions also gave the amino diol with high *syn* selectivity and thus the α-hydroxy group did not affect the trend of facial selectivity of the reaction previously noted from **17**[16]. However, the reversed configuration of α-hydroxy group in substrate **19** had a great effect on the facial selectivity and provided high *anti* selectivity under the stoichiometric conditions[17]. The obtained amino diol products from **18** and **19** were applied to the asymmetric synthesis of 3,6-dideoxy-3-amino-L-talose and a constituent of Microsclerodermins, respectively.

3.3. 1,2-Dialkyl substituted (*Z*)-allylic amines

Several dihydroxylation results of 1,2-disubstituted (*Z*)-allylic amines are presented in Table 4. Especially the (*Z*)-olefins of L-serine derivatives were useful intermediates for synthesis of biologically important sphingolipids and glucoceramides such as sphingosines, pachastissamine, and KRN7000. Dihydroxylation of the (*Z*)-1,2-disubstituted olefins under the catalytic dihydroxylation conditions (cat. OsO_4, and NMO) generally gave low *syn* diastereoselectivities. In the presence of chiral agents, the observed selectivities were slightly enhanced but they still showed modest results. In the case of *N*-Boc-*N,O*-isopropylidene protected substrate **22**, the dihydroxylation reaction with AD-mix-β provided even lower stereochemical result (1.0 : 1)[10] than that of the substrate-controlled reaction (3.0 : 1)[18]. Interestingly, substrate **25** afforded an excellent *anti* selectivity (>99 : 1) under both catalytic and stoichiometric dihydroxylation conditions. In the absence of the hydrogen bonding donors, substrate **25** would take an *H*-eclipsed conformation and then OsO_4 approached to the less hindered face of the olefin and thus the reaction provided the *anti* selective product. The major product of substrate **25** was utilized in the synthesis of methyl *N,O*-diacetyl-D-ristosaminide.

We have also investigated stereoselective dihydroxylation of 1,2-dialkyl substituted (*Z*)-allylic amines by introducing several protection

Table 3. Dihydroxylation of 1,2-Dialkyl Substituted (*E*)-Allylic Amines

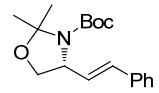
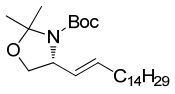
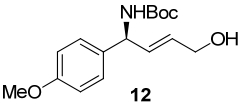
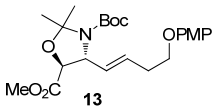
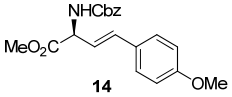
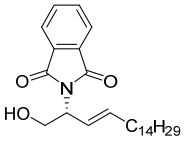
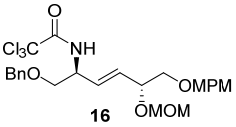
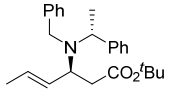
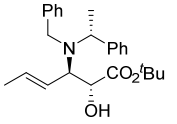
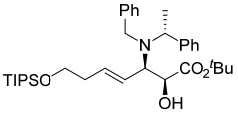
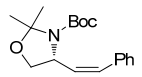
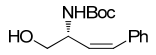
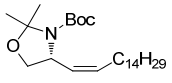
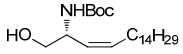
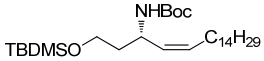
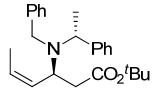
Substrate	Conditions	*Anti : syn*	Yield (%)	Ref.
 **10**	OsO_4, NMO	1.3 : 1	71	9
	AD-mix-α	99 : 1	70	
	AD-mix-β	1 : 99	60	
 **11**	AD-mix-β	1.5 : 1	85	10
 **12**	OsO_4, NMO	1.1 : 1	85	11
	OsO_4, DHQ-CLB	1 : 1.6		
 **13**	OsO_4, NMO	2 : 1	48	12
	$K_2OsO_2(OH)_4$, DHQD-IND	1 : 5.1	19	
	$K_2OsO_2(OH)_4$, DHQ-IND	7.4 : 1	85	
	$K_2OsO_2(OH)_4$, $(DHQD)_2$-PHAL	15 : 1	97	
	$K_2OsO_2(OH)_4$, $(DHQ)_2$-PHAL	1 : 5	74	
 **14**	$K_2OsO_2(OH)_4$, $(DHQD)_2$-AQN	9 : 1	84	13
	$K_2OsO_2(OH)_4$, $(DHQ)_2$-AQN	8 : 1	81	
	$K_2OsO_2(OH)_4$, $(DHQD)_2$-PYR	1.2 : 1	99	
	$K_2OsO_2(OH)_4$, $(DHQ)_2$-PYR	1.2 : 1	67	
 **15**	OsO_4, NMO	3.3 : 1	99	14
	$K_2OsO_2(OH)_4$, $(DHQ)_2$-PYR	5.1 : 1	99	
 **16**	AD-mix-β	3 : 1	85	15
 **17**	OsO_4, NMO	3 : 1	75	16
	OsO_4, TMEDA, -78 ℃	> 99 : 1	90	
 **18**	OsO_4, NMO	19 : 1	81	16
	OsO_4, TMEDA, -78 ℃	1 : 19	56	
 **19**	OsO_4, TMEDA, -78 ℃	> 99 : 1	53	17

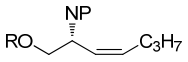
Table 4. Dihydroxylation of 1,2-Dialkyl Substituted (*Z*)-Allylic Amines

Substrate	Conditions	*Anti* : *syn*	Yield (%)	Ref.
 **20**	OsO_4, NMO	1 : 1.1	54	9
	AD-mix-α	5.7 : 1	13	
	AD-mix-β	1 : 1	4	
 **21**	OsO_4, NMO	1 : 2.4	92	9
	AD-mix-α	1 : 6	55	
	AD-mix-β	6 : 1	55	
 **22**	OsO_4, NMO	3.3 : 1	74	18
	AD-mix-β	1.0 : 1	55	10
 **23**	OsO_4, NMO	1 : 2.4	84	9
	AD-mix-α	1 : 4.9	86	
	AD-mix-β	4.9 : 1	89	
 **24**	AD-mix-β	3.5 : 1	84	19
 **25**	OsO_4, NMO	> 99 : 1	76	20
	OsO_4, TMEDA, -78 ℃	> 99 : 1	40	

groups of amine and/or alcohol (Table 5)[21]. Both *N*-Boc derivative **26** and *N*-dipheylmethylene derivative **27** yielded low to modest *syn* selectivity. However, *N,N*-dibenzyl (**28**, **29**) and *N,N*-diBoc (**30**, **31**) protected olefins showed good to excellent *anti* selectivity. It is noteworthy that substrate **31** with a small *O*-protection group provided higher facial selectivity than that of *O*-Boc protected olefin **30** and the better *anti* selectivity of the amino diol was obtained for compound **30** in less polar solvent (10 : 1 in DCM vs 3.3 : 1 in aqueous THF).

The dihydroxylation results shown in Table 5 were applied to the stereoselective synthesis of D-*ribo* and L-*arabino* phytoshingosine (**34** and **37**, respectively, Scheme 1). The observed *anti* selectivity (20 : 1) of **32** was better than those of similar (*Z*)-olefins **22-24** (Scheme 1).

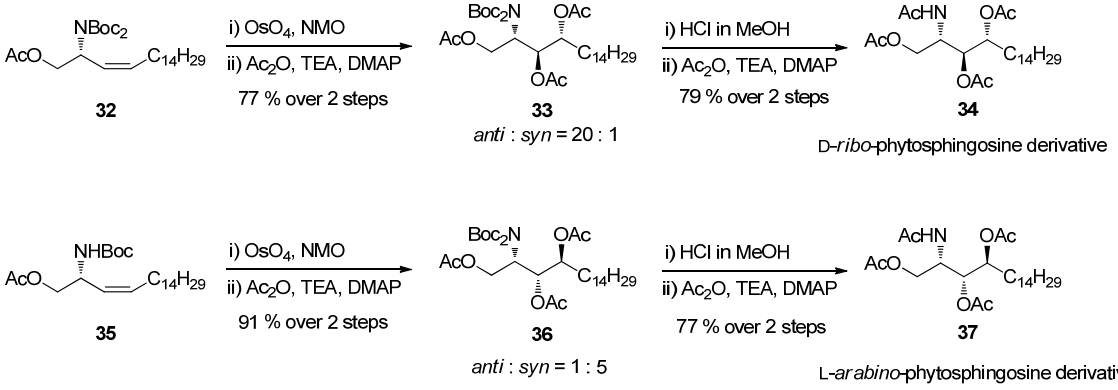
Table 5. Dihydroxylation of *N*-Boc, *N*-diphenylmethylene, *N,N*-dibenzyl, and *N,N*-diBoc Derivatives of (*Z*)-olefin Substrates[21]

Substrate	Conditions	*Anti* : *syn*	Yield (%)
			
26 P = HBoc, R = Boc	OsO_4, NMO (THF/H_2O)	1.1 : 1	84
	OsO_4, NMO (iPrOH)	1 : 1.8	62
	OsO_4, NMO (Toluene)	1 : 3.0	78
	OsO_4, NMO (DCM)	1 : 3.8	84
27 P = CPh_2, R = Ac	OsO_4, NMO (DCM)	1 : 2.2	88
28 P = Bn_2, R = Ac	OsO_4, NMO (THF/H_2O)	7.7 : 1	50
29 P = Bn_2, R = TBDMS	OsO_4, NMO (THF/H_2O)	> 10 : 1	21
	OsO_4, NMO (Toluene)	> 10 : 1	19
	OsO_4, NMO (DCM)	> 10 : 1	19
30 P = Boc_2, R = Boc	OsO_4, NMO (THF/H_2O)	3.3 : 1	52
	OsO_4, NMO (iPrOH)	4.0 : 1	82
	OsO_4, NMO (Toluene)	6.3 : 1	84
	OsO_4, NMO (DCM)	10 : 1	83
31 P = Boc_2, R = Ac	OsO_4, NMO (DCM)	20 : 1	78

The selectivity in this study was explained by a transition state of an *H*-eclipsed conformation in Figure 2 as suggested by Kishi and co-workers (Figure 7). It has been reported that the *N*-outside conformation is favored with 1,2-dialkyl substituted *N*-Boc-(*Z*)-allylic amine to give the *syn* diol as a major product. The *N*-outside conformation of **35** would reduce the 1,3-allylic ($A^{1,3}$) strain between the *N*-Boc group (P = H) and the alkyl group ($C_{14}H_{29}$) although there is some increase in the 1,2-allylic ($A^{1,2}$) strain between the *N*-Boc group and the vinylic hydrogen atom. With *N,N*-diBoc protected (*Z*)-allylic amine **32**, however, the $A^{1,2}$ strain between the bulky *N,N*-diBoc group and the vinylic hydrogen atom would be so severe that the *H*-eclipsed conformation was preferred to give *anti* diol as a major product.

3.4. Carbonyl group-conjugated allylic amines

Table 6 shows the dihydroxylation results of carbonyl conjugated allyl-



Scheme 1. Stereoselective synthesis of D-*ribo* and L-*arabino* phytoshingosine derivatives, 34 and 37.

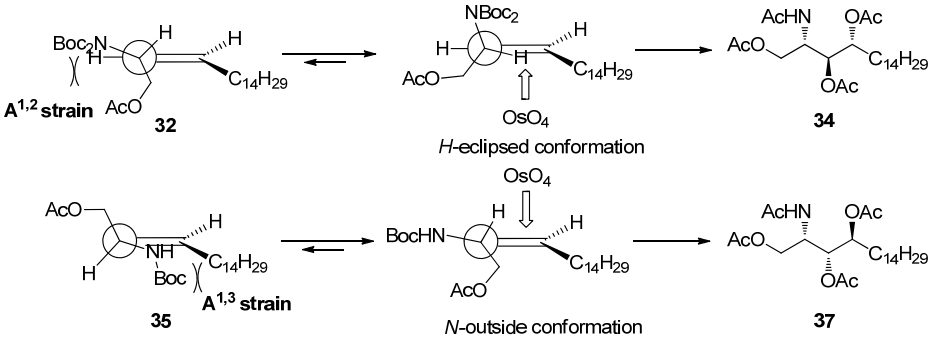


Figure 7. Proposed transition states of (*Z*)-allylic amines, 32 and 35.

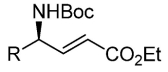
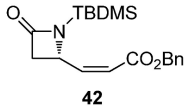
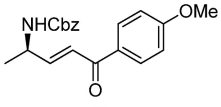
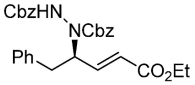
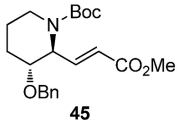
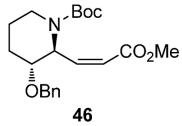
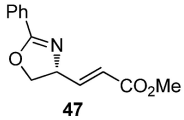
ic amines. The observed diastereoselectivities were mainly determined by the structure of substrates. Most of the carbonyl conjugated allylic amines showed low or mixed diastereoselectivities under the catalytic dihydroxylation conditions except for some cases. The *N*-Boc derivatives of α,β-unsaturated (*E*)-ester (**38**-**41**) gave low *anti* selective products under the catalytic dihydroxylation conditions[22]. Upon reacting the *N*-Boc protected substrates with AD-mix-α were observed the *anti* selective results, while the opposite *syn* selective results were provided by using AD-mix-β.

Piperidine-substituted (*E*)- and (*Z*)-allylic amines **45** and **46** yielded single *syn* selectivity due to its fixed conformation in the lowest energy transition state of the dihydroxylation reactions[26]. Substrate **51** with a quaternary chiral center gave low *anti* selectivity and its (*Z*)-olefin analog **52** also showed the same stereochemical result regardless of the stereochemistry of the olefins[29].

Some of the substrates provided enhanced diastereoselectivity with prior coordination to an incoming chiral catalyst. The observed *anti* selectivity of oxazoline α,β-unsaturated (*E*)-ester **47** was greatly enhanced by using AD-mix-α. Dihydroxylation with AD-mix-β of oxazoline α,β-unsaturated (*Z*)-ester **48** provided the single *syn* diol product while low *syn* selectivity was observed without using a chiral ligand[27]. Both products from **47** and **48** were used in the synthesis of the pyrrolidine azasugars. Carbonyl conjugated (*E*)-allylic amine **53** gave excellent diastereoselectivity by using the HQN-CLB chiral ligand[30]. On the other hand no stereoselectivity was obtained with the same substrate in the presence of an achiral ligand, DABCO. The *syn* selective diol from **53** was applied to the synthesis of (+)-polyoxamic acid. Imizazolidin-2-imine derivative of α,β-unsaturated (*E*)-ester **54** gave a single isomer with AD-mix-α and the observed result was used in the asymmetric synthesis of mannopeptimycins[31].

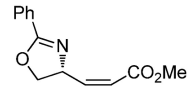
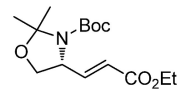
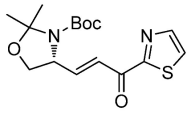
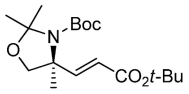
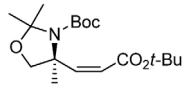
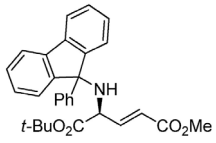
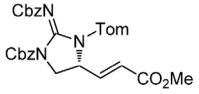
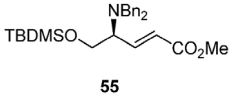
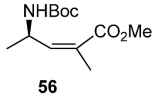
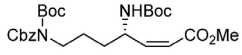
Although several successful results of highly enhanced stereoselectivity with chiral ligands, asymmetric dihydroxylation methods still showed limited stereochemical results. *N*,*N*-dibenzyl protected substrate **55** was tried with AD-mix-α and AD-mix-β, but better selectivity was not obtained compared to that with the catalytic dihydroxylation conditions[32]. In addition, trisubstituted carbonyl conjugated (*Z*)-allylic amine **56** also showed low facial selectivities even with AD-mix-α or AD-mix-β[33]. Several kinds of chiral ligands and conditions were applied with L-ornithine derivative **57** to obtain the *syn*

Table 6. Dihydroxylation of Carbonyl Group-conjugated Allylic Amines

Substrate	Conditions	*Anti* : *syn*	Yield (%)	Ref.
				
38 R = Me **39** R = Bn **40** R = i-Bu **41** R = I-Pr	OsO_4, NMO	1.0 : 1 1.4 : 1 1.5 : 1 4.3 : 1	> 96 > 96 > 96 > 96	22
 **42**	OsO_4, NMO	4 : 1	75	23
 **43**	OsO_4, NMO AD-mix-β	1.2 : 1 10 : 1	92 99	24
 **44**	OsO_4, NMO	1 : 5	92	25
 **45**	OsO_4, NMO	0 : 1	72	26
 **46**	OsO_4, NMO	0 : 1	70	26
 **47**	OsO_4, NMO AD-mix-α	1.6 : 1 13 : 1	71 71	27

(Continued)

Table 6. Dihydroxylation of Carbonyl Group-conjugated Allylic Amines (continued)

Substrate	Conditions	*Anti : syn*	Yield (%)	Ref.
 **48**	OsO_4, NMO	1 : 3.2	73	27
	AD-mix-α	1 : 3.8	81	
	AD-mix-β	0 : 1	85	
 **49**	OsO_4, NMO	3 : 1	82	28
 **50**	OsO_4, NMO	6 : 1	70	28
 **51**	OsO_4, NMO	3 : 1	92	29
 **52**	OsO_4, NMO	3 : 1	80	29
 **53**	$K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$	1 : 1	< 2	30
	$K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, DABCO	> 1 : 32	84	
	$K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, HQN-CLB		99	
 **54**	AD-mix-α	1 : 0	78	31
 **55**	OsO_4, NMO	1 : 1.19	59	32
	AD-mix-α	1 : 1.9	65	
	AD-mix-β	2.1 : 1	68	
 **56**	AD-mix-α	1.6 : 1	30	33
	AD-mix-β	3.5 : 1	70	
 **57**	OsO_4, $K_3Fe(CN)_6$ $(DHQD)_2PHAL$	1 : 5		34
	OsO_4, $K_3Fe(CN)_6$ $(DHQD)_2PYR$	< 1 : 2		
	OsO_4, $K_3Fe(CN)_6$ $(DHQD)_2AQN$	1 : 5		
	OsO_4, $K_3Fe(CN)_6$ $(DHQD)_2IND$	1 : 1.5		
	OsO_4, $K_3Fe(CN)_6$ $(DHQ)_2PHAL$	1 : 1		
	OsO_4, $K_3Fe(CN)_6$ $(DHQ)_2PYR$	1 : 2		
	OsO_4, $K_3Fe(CN)_6$ $(DHQ)_2IND$	1 : 5		
	OsO_4, NMO	1 : 1	98	

selective diol but most of the reactions showed low *anti* selectivity[34].

We have reported a systematical dihydroxylation study of γ-amino-α,β-unsaturated esters by introducing *N*-diarylmethylene as an amine protection group[35]. Table 7 shows the dihydroxylation results of γ-amino-α,β-unsaturated (*E*)-esters with *N*-diarylmethylene as an amine protection group. Compared with the *N*-Boc protected substrates

Table 7. Dihydroxylation Study of *N*-diarylmethylene Protected γ-amino-α,β-unsaturated (*E*)-esters[35]

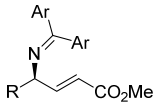
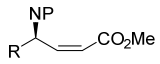
R	Ar = phenyl *Anti* : *syn*	Yield (%)	R	Ar = 3-fluorophenyl *Anti* : *syn*	Yield (%)
 **58-65**					
Me (**58**)	3.9 : 1	76	Me (**62**)	6.7 : 1	61
Bn (**59**)	5.9 : 1	67	Bn (**63**)	8.7 : 1	71
i-Bu (**60**)	5.4 : 1	87	i-Bu (**64**)	11.8 : 1	75
i-Pr (**61**)	11.0 : 1	75	i-Pr (**65**)	19.0 : 1	62

Table 8. Dihydroxylation Study of *N*-diarylmethylene Protected γ-amino-α,β-unsaturated (*Z*)-esters[35]

R	P = HBoc *Anti* : *syn*	Yield (%)	R	P = Diphenylmethylene *Anti* : *syn*	Yield (%)
 **66-73**					
Me (**66**)	1 : 1.6	58	Me (**70**)	1 : 5.4	90
Bn (**67**)	1 : 1.5	82	Bn (**71**)	1 : 15	71
i-Bu (**68**)	1 : 1	65	i-Bu (**72**)	1 : >50	80
i-Pr (**69**)	1 : 1.5	72	i-Pr (**73**)	1 : >100	66

(**38-41**, Table 6), the diphenylmethylene derivatives (**58-61**) showed higher *anti* selectivities and the better selectivity was obtained with a larger side chain (R). Moreover the *N*-3,3'-(bisfluoro)diphenylmethylene derivatives (**62-65**) showed enhanced *anti* selectivities than those of the *N*-diphenylmethylene derivatives (**58-61**). The observed results were complementary to the *syn* selective results (1 : 3-1 : 11.5) of the *N,N*-dibenzyl derivatives of γ-amino-α,β-unsaturated (*E*)-esters[22]. We have also synthesized the *N*-diphenylmethylene derivatives of γ-amino-α,β-unsaturated (*Z*)-esters (Table 8)[35]. Interestingly, opposite *syn*-selectivities were observed with the (*Z*)-olefinic substrates (Table 8) and α,β-unsaturated unsaturated (*Z*)-esters with a larger R group showed better *syn* selectivity (**70** vs **73**). For comparison, the *N*-Boc derivatives of the same (*Z*)-esters were prepared and subjected to the same dihydroxylation conditions. No or poor selectivities were shown regardless of the size of the alkyl group (**66-69**, Table 8).

For the *N*-diarylmethylene derivatives of γ-amino-α,β-unsaturated (*E*)-esters, the transition state of the reactions was similar to that of monosubstituted allylic amines (Figure 8). When the electron-withdrawing carbonyl functionality is present, stereoelectronic effect might become important in the dihydroxylation reactions. Therefore, the selectivities observed in this study could be explained with the Houk transition state model shown in Figure 2. In the absence of severe $A^{1,3}$ allylic strain, the diarylmethylene group that is a deactivating substituent would take preferentially an *N*-inside conformation of the γ-amino-α,β-unsaturated unsaturated (*E*)-esters (Figure 8). Preferential dihydroxylation from the less hindered top side would give the *anti* diols. However, severe allylic steric hindrance from the methoxy carbonyl group would exist in the (*Z*)-ester substrate and thus the diphe

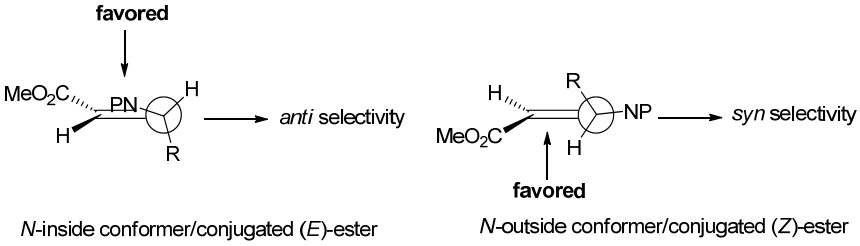
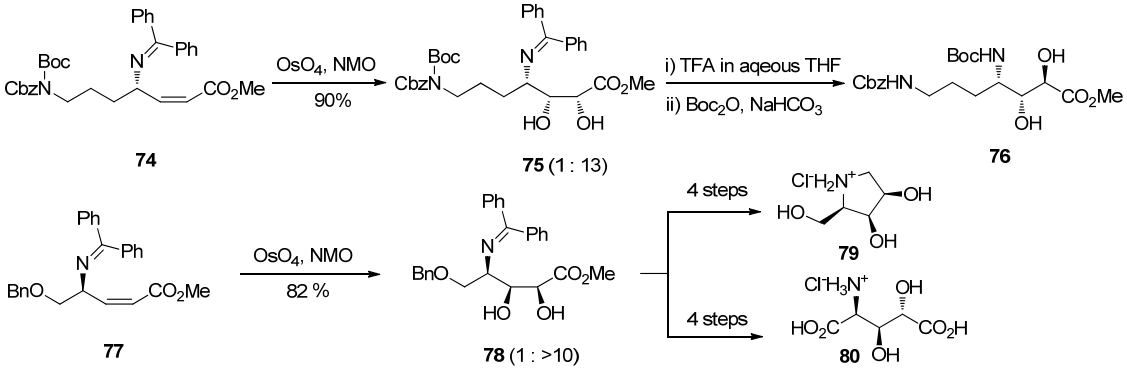
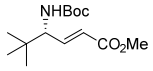
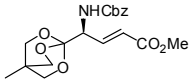


Figure 8. Probable transition states of α,β-unsaturated esters (P = *N*-diarylmethylene).



Scheme 2. Asymmetric synthesis of natural products using the *syn* selective dihydroxylation of *N*-diphenylmethylene derivatives of α,β-unsaturated (*Z*)-ester.

Table 9. Dihydroxylation Study of Allylic Amines with a Bulky Side Group[39]

Substrate	Conditions	*Anti : syn*	Yield (%)
 **81**	OsO_4, NMO	20 : 1	63
 **82**	OsO_4, NMO	20 : 1	83
 **83**	OsO_4, NMO	> 13 : 1	94

nylmethylene group was directed toward the outside to minimize the $A^{1,3}$ interaction, favoring an *N*-outside conformation. Addition of OsO_4 from the bottom side of the *N*-outside conformer would result in the *syn* diol isomer as a major product.

The selective results from γ-amino-α,β-unsaturated (*Z*)-esters were applied to asymmetric synthesis of natural products. Substrate **74** from L-ornithine in Scheme 2 provided a good *syn* selectivity (> 13 : 1) which was a better result than those of the asymmetric dihydroxylations employing various chiral agents (**57**, Table 6). The obtained amino diol was used for the synthesis of protected (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyheptanoic acid **76** found in marine natural products, callipeltin A and D[36]. Stereoselective syntheses of D-iminolyxitol **79**[37] and (2*S*,3*S*,4*S*)-3,4-dihydroxyglutamic acid **80**[38] were also successfully achieved by the *syn* selective dihydroxylation of α,β-unsaturated (*Z*)-ester from L-serine (Scheme 2).

We also have studied the stereoselective dihydroxylation of monosubstituted and (*E*)-ester conjugated allylic amines controlled by bulky side groups. As shown in Table 9, the dihydroxylations of both *N*-Boc protected monosubstituted allylic amine (**81**) and γ-amino-α,β-unsaturated (*E*)-ester (**82**) with a bulky *tert*-butyl group gave excellent *anti* selectivities[39]. Due to the severe $A^{1,3}$ strain of the *tert*-butyl group in *N*-outside conformer, *N*-inside conformer would be strongly favored in the transition state model. Therefore, both allylic amines **81** and **82** with the *tert*-butyl group gave highly selective products. With the observed result in hand, we have synthesized (*E*)-3,4-dehydroglutamate OBO ester **83** (Table 9) to obtain stereoselective amino diol product which would be a useful synthetic intermediate[39]. Under the catalytic dihydroxylation conditions, substrate **83** provided a good *anti* selective product (>13 : 1). A chiral 2-pyrrolidinone azasugar, an effective α-glucosidase inhibitor, was synthesized by employing the major dihydroxylation product from **83**.

4. Conclusions

In conclusion, a variety of recent examples in the dihydroxylation reactions of acyclic allylic amines and derivatives have been investigated to show synthetically useful levels of the stereochemical results. The observed selectivity of the dihydroxylation reactions was determined by some factors in which the nature of the protection group on the allylic nitrogen atom plays an important role along with the reaction conditions. We have introduced the *N*-diarylmethylene, the *N,N*-diBoc, and the OBO ester group to some allylic amine substrates for efficient control of acyclic conformations. These strategies gave improved stereochemical outcomes compared with those of previously published reports of substrate-controlled and even chiral agent-controlled dihydroxylation reactions. Further studies are necessary to improve *anti* and *syn* selective dihydroxylation reactions for all types of allylic amines which will result in efficient syntheses of a great number of bioactive natural products.

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