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anti Selective dihydroxylation by the ketimine derivatives of the allylic amine in monosubstituted olefins

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Abstract—Transformation of the allylic amine of monosubstituted olefins into the aryl ketimine derivatives resulted in consistent higher *anti* diastereofacial selectivity in the osmium-catalyzed dihydroxylation reactions, compared to the selectivities obtained from commonly used allylic amino derivatives such as *N*-acyl, *N*-Boc or *N*,*N*-dibenzyl. The *anti* selectivity ranged from 3:1 to 7:1 in dry THF and the best was observed with the 3,3′-difluorobenzophenone ketimine derivative. Application of the ketimine group is also reported with the substrates of biological importance. © 2002 Elsevier Science Ltd. All rights reserved.

There has been considerable interest in the synthesis of optically active amino alcohols and amino acids because of their wide occurrence in biologically active molecules.[1] They are also widely used as chiral intermediates, auxiliaries or ligands in asymmetric synthesis (Fig. 1).

Both efficient and stereoselective construction of the amino alcohol moiety could be achieved, in principle, by controlled osmium-catalyzed dihydroxylation reactions of chiral allylic amines. The amines can be readily prepared from one of the chirality pools, α-amino acids. Although the diastereoselective dihydroxylation of allylic alcohols has been well established,[2] there are only a few reports on diastereoselection in the dihydroxylation reactions of allylic amines. We and others reported that the *anti* selectivity was observed in the dihydroxylation of the cyclic allylic amino derivatives under the less favorable environment for the hydrogen bonding.[3] The similar results have been obtained with both cyclic and acyclic allylic alcohols.[2] However, the mixed results have been met with the acyclic allylic amides or carbamates that have flexible conformation.[2a,4] To the best of our knowledge, few systematic studies on asymmetric induction by allylic amino substituents in the dihydroxylation of acyclic olefins have been performed.[3b,5]

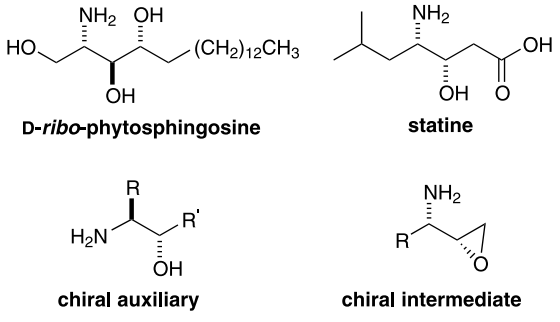

Figure 1.

We report herein a systematic study on the diastereofacial selectivity of monosubstituted olefins with allylic amino aryl ketimine derivatives.[6] For the monosubstituted olefins, the common protecting groups such as *N*-acyl, *N*-alkoxycarbonyl or *N*,*N*-dibenzyl have resulted in mostly the poor to reversed selectivities with several exceptions.[2a,4,5,7] They have also been challenging substrates in the stereoselective reactions of olefins such as the Sharpless asymmetric dihydroxylation or the Jacobsen asymmetric epoxidation owing to its lower selectivities.[8] We think it is the first time to employ the aryl ketimine group to improve the diastereofacial selectivity in the osmium-catalyzed dihydroxylation.[9a] Electronic effects by the allylic amino group can also be examined by simply changing the substituent on the phenyl ring of the aryl ketimines. The electronic factor of the allylic alcohol/alkoxy group is known to affect the facial selectivity in the dihydroxylation reactions.[2,10] They are also stable to the osmylation conditions, and relatively easy to introduce and to remove.[9b]

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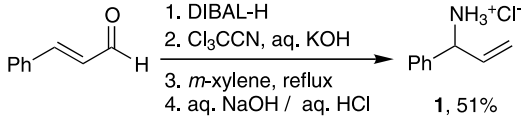
The required allylic amine, 1-phenyl-2-propenamine, was obtained as its hydrochloride salt **1** from cinnamaldehyde through the [3,3]-sigmatropic rearrangement of the imidate intermediate (Scheme 1).[11]

Preparation of the various ketimine derivatives with different substituents in electronic property could be achieved effectively by condensation of **1** with commercially available benzophenone derivatives in the presence of $TiCl_4$ and TEA (Table 1).[12] Excess use of **1** (2 equiv.) facilitated separation of the ketimine products **2**–**10** from the reaction mixture.

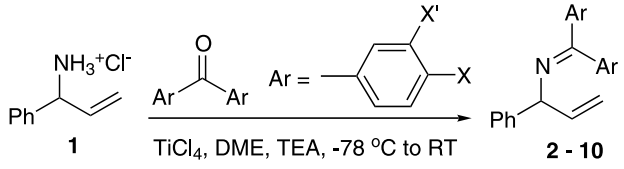
Osmium-catalyzed dihydroxylation reactions of the ketimine derivatives were then explored under the following standard conditions; 1 equiv. of the ketimine derivative, 0.1 equiv. of OsO_4, 2 equiv. of NMO in dry THF. The results are shown in Table 2. Use of the dry solvent[13] was necessary for in-situ conversion of the diols produced into the corresponding diacetates. Otherwise, an undesired cyclization reaction by one of the hydroxyl groups with the ketimine carbon into an oxazolidine ring complicated the analysis of the diastereomeric ratio of the diol products.[14]

In Table 2, the *anti* selectivity is evident with all of the ketimine derivatives used, regardless of the electronic property of the substituents. It is also apparent that the electron-withdrawing substituents bring about a little higher selectivity than the electron-donating substituents. However, the degree of increase does not match the electron-withdrawing capabilities of the substituents. The best selectivity (5.2:1) obtained with **7** is much higher than those with the *N*-trichloroacetyl, *N*-benzoyl, *N*-Boc, or *N*,*N*-dibenzyl substituted allylic amines, for which the poor to reversed selectivities were



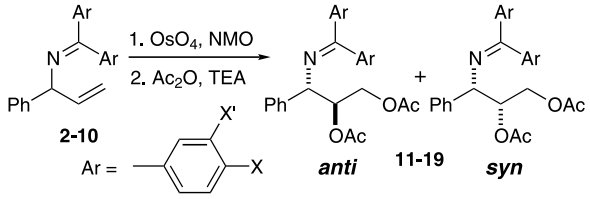
Scheme 1. Preparation of the model substrate **1**.

Table 1. Preparation of the aryl ketimine derivatives **2**–**10**



Olefin	X	X′	Yield (%)
2	Me	H	Quant.
3	OMe	H	70
4	H	H	98
5	F	H	Quant.
6	Cl	H	Quant.
7	H	F	73
8	H	CF_3	53
9	H	NO_2	96
10	Cl	NO_2	Quant.

Table 2. Dihydroxylation reactions of the aryl ketimines **2**–**10**

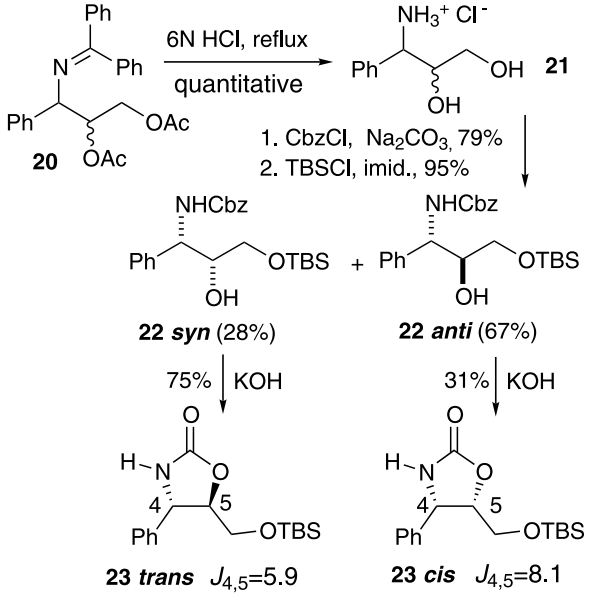


Olefin	Diacetate	Ratio *anti*:*syn*	Yield (%)
2	**11**	3.0:1[a]	82
3	**12**	3.1:1[b]	70
4	**13**	3.3:1[a]	83
5	**14**	3.8:1[a]	70
6	**15**	3.5:1[b]	90
7	**16**	5.2:1[a]	69
8	**17**	4.8:1[a]	94
9	**18**	4.4:1[b]	89
10	**19**	4.0:1[b]	75

[a] Analysis by GC: HP 5, 30 m×0.25 mm, I.D. 0.25 μm.
[b] Analysis by LC: Allsphere Silica 5μ, 150×4.6 mm.

observed.[5,7] Specifically, the opposite *syn* selectivity (*anti*:*syn* = 1:1.3) was found with the *N*-Boc derivative of **1**. Krysan and co-workers reported also the similar *syn* selectivity (*anti*:*syn* = 1:1.5) with the *N*-Boc monosubstituted olefin in *i*-PrOH.[5] Therefore, the consistent *anti* selectivity obtained with the ketimine derivatives in the present study should be important for the reliable prediction of the stereochemical outcome in the dihydroxylation products of monosubstituted olefins.

Use of conventional aqueous THF (1:1) instead of dry THF as a reaction solvent resulted in slightly lower selectivity (4.4:1) but higher yield (82%) of the same product, compared to those of diacetate **16**. The effect of solvents on the facial selectivity has been known[5,15]



Scheme 2. Determination of the relative stereochemistry of the diastereomers in **20**.

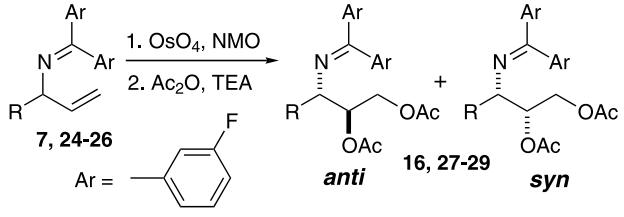
and was tested in several dry solvents. The similar selectivities of about 5.2:1, 5.0:1, and 5.4:1 for the *anti* isomer were achieved in toluene, CH_2Cl_2, and acetone, respectively. The ratio was lower in benzene (4.1:1) and *i*-PrOH (3.7:1). The solvent polarity does not seem to have a bearing on the selectivity.

Possibility of the kinetic resolution in the in situ acetylation of the diol products seems very low. The crude amino diol HCl salt, obtained after direct hydrolysis of the dihydroxylation product of **7**, showed similar selectivity (ca. 5:1) on the ^{1}H NMR spectrum. Use of stoichiometric amount of OsO_4 to prevent the secondary catalytic osmylation cycle did not improve the selectivity.[5,16]

For determination of the relative stereochemistry of the product, a diastereomeric mixture was transformed into the corresponding oxazolidinone derivatives (Scheme 2). It is well known that the coupling constant ($J_{4,5}$) on the ^{1}H NMR spectrum of a *cis* isomer of oxazolidinone rings is larger than that of a *trans* isomer.[17] The starting diastereomeric mixture **20** with a ratio of about 2.5:1 was produced from the dihydroxylation reaction of **4** in *i*-PrOH without additional water.[6]

The mixture was separable with column chromatography after conversion of **20** to the *N*-Cbz-*O*-TBS protected amino diol derivative **22** via amino diol HCl salt **21**. The major and the minor isomers, **22** *anti* and **22** *syn*, were isolated in 67 and 28% yield, respectively. Each isomer was then independently cyclized to give the corresponding 1,3-oxazolidin-2-one, **23** *cis* and **23** *trans*, respectively. The low yield for **23** *cis* seems to reflect the unfavorable cyclization of **22** *anti* giving the *cis* isomer. Measurement of the coupling constants ($J_{4,5}$) reveals that the relative stereochemistry of the major isomer of **22** is *anti* ($J_{4,5}$ of **23** *cis* = 8.1 Hz) and that of the minor isomer is *syn* ($J_{4,5}$ of **23** *trans* = 5.9 Hz). The larger chemical shift of both protons at C-4 and C-5 of **23** *cis* ($\delta_{H\text{-}4}$ 4.98 and $\delta_{H\text{-}5}$ 4.86) than that of **23** *trans* ($\delta_{H\text{-}4}$ 4.86 and $\delta_{H\text{-}5}$ 4.36) is another indication of their relative stereochemistry.[17] The major isomer of other products **11**–**19** was confirmed by comparison of the same HCl salts of the crude amino diols as **21** on the ^{1}H NMR spectra.

Table 3. Dihydroxylation reactions of the aryl ketimines with different alkyl side chains



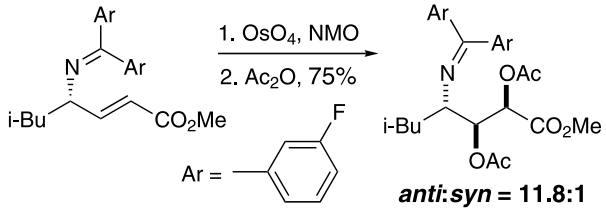
R	Olefin	Diacetate	Ratio[a] *anti*:*syn*	Yield (%)
Me	**24**	**27**	3.7:1	68
$PhCH_2$	**25**	**28**	4.6:1	80
Ph	**7**	**16**	5.2:1	69
i-Pr	**26**	**29**	7.0:1	77

[a] Analysis by GC: HP 5, 30 m×0.25 mm, I.D. 0.25 μm.

Stereodirecting results by the ketimine derivative on some monosubstituted olefins **24**–**26**, prepared from the corresponding amino acids,[18] are shown in Table 3. The higher *anti* selectivity is clearly maintained, compared to the corresponding *N*-Boc derivatives. The inherent selectivity of the *N*-Boc derivative of **25** for the *anti* diol isomer was 1.5:1 regardless of the osmium reagents used; i.e. cat. OsO_4/NMO, AD-mix-α, or AD-mix-β.[4b] The amino diol with the same stereochemistry as that of **28** *anti* was required for the preparation of the nitrogen analogue of Saquinavir, an HIV protease inhibitor. The *N*-Boc derivatives of **24** and **26** showed the reversed (*anti*:*syn* = 1:2) and no (1:1) selectivities (^{1}H NMR), respectively. The relative stereochemistry of the diastereomers in each product was also confirmed as described above for **20**. It is interesting to note the selectivity increases as the alkyl group gets bigger. The similar results by the alkyl groups have been known, too.[4a,19]

In Scheme 3, a selective synthesis for a derivative of α-hydroxystatine,[20] a stable transition-state isostere for pseudopeptide templates, is shown using the ketimine group. Lower selectivities for the *anti* diol product (1.5:1 and 2.4:1) have been reported with the *N*-Boc derivative of **30** in the literature.[4a,20a]

The sense and trend of the selectivity in the present study could be explained by employing the transition state models that are advanced for the diastereoselective dihydroxylation reactions of allylic alcohols and ethers; i.e. Kishi, Houk, and Vedejs models.[21] The transition state model in Fig. 2 is a combination of the Houk and Vedejs models. It represents a subtle interplay between the steric and electronic aspects. Accord-



Scheme 3. An application of the ketimine group to a conjugated disubstituted *E*-olefin.

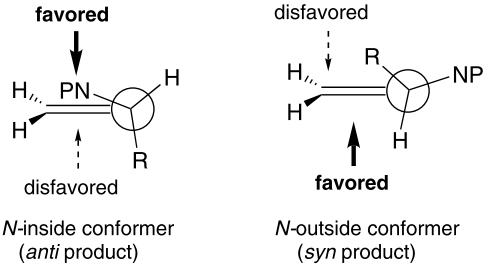


Figure 2. A proposed transition state model (P = aryl ketimine).

ing to the Houk model, a deactivating substituent would take preferentially the 'inside' conformer in the absence of strong steric interaction with a double bond. As a result, the *N*-inside conformer will be predominant here with the electron-deficient aryl ketimines in the monosubstituted olefins. However, the selectivity depends on the size of the alkyl substituents as shown in Table 3, which cannot be explained by the Houk model only. The Vedejs model would be suitable for the steric effect by the alkyl groups. The severe allylic strain, $A^{1,2}$ or $A^{1,3}$, between the large alkyl side chain and the substituents on the double bond[22] would strongly disfavor the *N*-outside conformer.

Acknowledgements

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