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Unexpected Diastereoselectivity in AD of an L-Proline-Derived 1,1-Disubstituted Alkene

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Abstract: Asymmetric dihydroxylation of the L-proline-derived 1,1-disubstituted alkene **5** catalysed by either $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ unexpectedly leads to preference for the same diastereomer **7**, both reactions proceeding with apparently matching double diastereoselectivity. In contrast, AD using the analogous $(DHQ)_2PYR$ or $(DHQD)_2PYR$ ligands leads to preferences for diols **7** or **8** respectively.

Catalytic asymmetric dihydroxylation (AD) using cinchona alkaloid-derived catalysts developed by Sharpless and co-workers[1] has become a widely used methodology in recent years. The mnemonic proposed by Sharpless and co-workers is generally predictive for the sense of enantiofacial selectivity in dihydroxylations of a wide range of prochiral alkenes, and can be rationalized in most cases by consideration of (differing) mechanistic models proposed by the Sharpless group[2] and by Corey and co-workers.[3] Additionally, there are now a number of examples illustrating the subtleties of mechanism which can lead to unanticipated changes in selectivity. For example, while appropriately substituted 1,1-disubstituted alkenes can be dihydroxylated in good e.e., the nature of the substituents can drastically affect the degree and even the sense of selectivity. Such substrates with similar substituents or with an oxygen containing substituent tend to be poor substrates.[1a,b] Hale's group have reported that the nature of an oxygen substituent on 1,1-disubstituted alkenes can switch the facial selectivity,[4] while the enantiofacial preference of AD of α-substituted styrenes has recently been shown to switch with a change in the nature of the AD ligand series employed (between the PHAL series and PYR series).[5]

Using chiral enantiopure substrates offers the prospect of matching and mismatching diastereomeric outcomes for AD reactions, dependent on the substrate facial selectivity for dihydroxylation and the catalyst-mediated facial selectivity related to the substituents on the double bond (using either Corey or Sharpless rationales). Recently, Smith and co-workers reported the use of AD in a synthesis of calyculin where both ligand series catalysed AD reactions of a terminal, mono-substituted, alkene within a complex homochiral intermediate with the same sense of diastereoselectivity.[6] Similarly, unexpected diastereomeric outcomes have been observed by Carreira's group with a chiral *trans*-disubstituted alkene during synthesis of the zaragozic acids.[7]

Herein we report that AD of the chiral 1,1-disubstituted alkene **5** proceeds with the *same sense* of diastereoselectivity using *either pseudo*-enantiomeric AD ligands $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$, and, *in both cases, with enhanced* diastereoselectivity compared to the use of achiral dihydroxylation reaction conditions. This means that both ADs are behaving as if exhibiting matching double diastereoselectivity. In sharp contrast, analogous AD reactions with PYR series ligands gave the predicted differing diastereomeric preferences.

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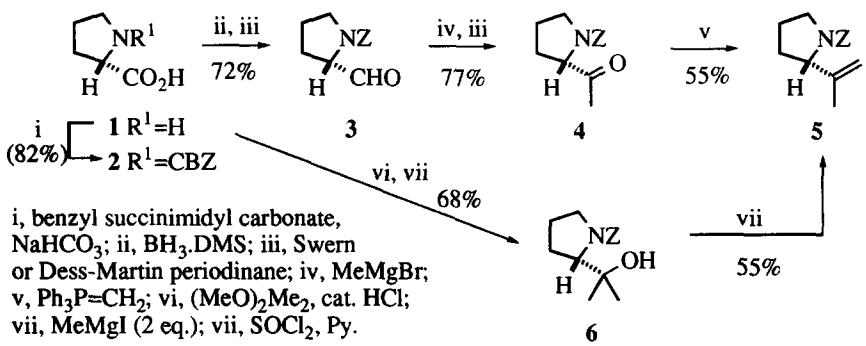
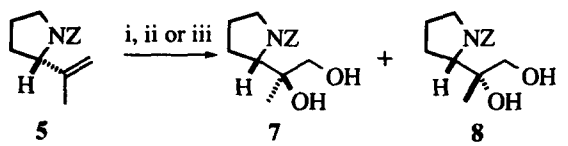
In several projects we have addressed the utility of AD for matching double diastereoselective reactions, and in one natural product synthesis we required diols **7** or **8**. Our synthesis of the requisite diol(s) envisaged using dihydroxylation of the 1,1-disubstituted alkene **5**.[11] We aimed to evaluate firstly the extent of substrate diastereoselectivity, and to then compare this with the use of either *pseudo*-enantiomeric AD ligands in both PHAL and PYR series, expecting one ligand in each series to lead to enhanced diastereoselectivity through matching double diastereoselection. Alkene **5** was prepared from L-proline **1** *via* the known CBZ-protected methyl ester derivative **2**. Reduction to the alcohol and oxidation using either Swern conditions or Dess-Martin periodinane provided aldehyde **3**. Reaction with MeMgBr followed by oxidation then provided ketone **4**, which underwent Wittig reaction to provide the substrate alkene **5**. Alternatively, using the method reported by Overman and Bell,[8] the intermediate ketone was converted directly to the tertiary alcohol **6** by reaction with 2 equivalents of MeMgI, which then underwent elimination using $SOCl_2$ to provide alkene **5**, however, in our hands this elimination proceeded only in modest yield (and was complicated by formation of the tetra-substituted internal alkene).



Dihydroxylation of **5** was carried out using OsO_4 under *achiral* catalytic conditions, and under standard AD conditions using either AD-mix α (containing $(DHQ)_2PHAL$ as chiral ligand) or AD-mix β (containing $(DHQD)_2PHAL$). The diastereomeric ratios were determined by g.c. analysis[9] (**Figure 1**) and corroborated by ^1H NMR[10] integrations of the methyl signals (**Figure 2**). The achiral dihydroxylation reaction afforded an approximately 1:1 mixture of diastereomeric products **7** and **8** in good yield, with a slight excess of **7** (about 2% d.e.). This indicates little significant substrate directing ability for any mismatching catalyst-substrate combination to overcome. Catalytic AD reactions using AD-mix β or AD-mix α in both cases gave clean diol products. Applying the Sharpless mnemonic would predict that AD-mix α would favour formation of **7**, and using AD-mix β would favour **8**. When the AD reaction using AD-mix α was carried out on **5**, the diastereomeric ratio of products **7**:**8** was 1.9:1,[11] an enhancement on the diastereoselectivity observed in the absence of chiral additives, and in the direction anticipated from the simplest application of the mnemonic for this (i.e. DHQ) ligand type. This could indicate matching double diastereoselection, in which case, it would be anticipated that reaction using AD-mix β would lead to selectivity, if any, in the opposite sense, and thus lead to an excess of **8**. However, AD reaction using AD-mix β lead instead to the diols **7** and **8** in a ratio of 3.5:1, even more in favour of the diastereomer favoured using AD-mix α. Thus, both AD reactions lead to the *same sense of diastereofacial selectivity*, though differing enhancement relative to substrate control.

We thus undertook an evaluation of AD using the PYR-based ligands for which reversal of mnemonic-predicted facial selectivities of prochiral 1,1-disubstituted alkenes, and a plausible explanation, have recently been described.[5] In this case, AD using $(DHQ)_2PYR$ as ligand led to same direction of selectivity as for both PHAL ligand catalysed reactions, with a **7**:**8** ratio of 1.8:1. However, AD using $(DHQD)_2PYR$ provided the only example of selectivity in favour of **8**, affording diols **7** and **8** in a 1:2.5 ratio respectively. This is thus the only example of AD of **5** consistent with location of the prolinyl group in the AD ligand's 'attractive binding pocket'.

A partial explanation of the results with PHAL ligands may be that a change between DHQD and DHQ ligand leads to a change in the type of orientation (relative to the mnemonic) adopted by the substrate, so that the ligand switch does not lead to a switch of facial selectivity but instead to a matching enhancement in each case. Prolinyl is not ideally related to the types of groups preferred for binding in the PHAL series catalysts 'pocket', and the outcome reported herein suggests perhaps that steric effects can perhaps significantly alter the anticipated substrate orientation in the AD transition state. The results with the PYR ligands, in contrast, provide an example of opposite selectivity preferences, each apparently consistent with the mnemonic.



5 **7** **8**

i. $OsO4$, H_2O, Me_2CO, Pyr
ii. AD-mix α or β, $MeSONH_2$, 0.6% $K_2OsO_2(OH)_2$.
iii. $(DHQD)_2PYR$ or $(DHQ)_2PYR$, $MeSONH_2$ 0.6% $K_2OsO_2(OH)_2$, K_2CO_3, $K_3Fe(CN)_6$.

Table 1

Entry	Chiral ligand	7 : 8[¥]
1	None	1.1 : 1 (1.2 : 1)
2	$(DHQ)_2PHAL$	1.9 : 1 (2.3 : 1)
3	$(DHQD)_2PHAL$	3.5 : 1 (3.8 : 1)
4	$(DHQ)_2PYR$	1.8 : 1 (1.7 : 1)
5	$(DHQD)_2PYR$	1 : 2.5 (1 : 2.2)

[¥]G.c. ratios given (NMR ratios in parenthesis)

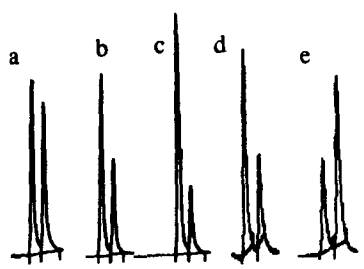


Figure 1: g.c. peaks for diastereomeric diols **7** and **8**.

Key: [a]Achiral Dihydroxylation, [b]AD-mix α, [c]AD-mix β, [d]$(DHQ)_2PYR$, [e]$(DHQD)_2PYR$.

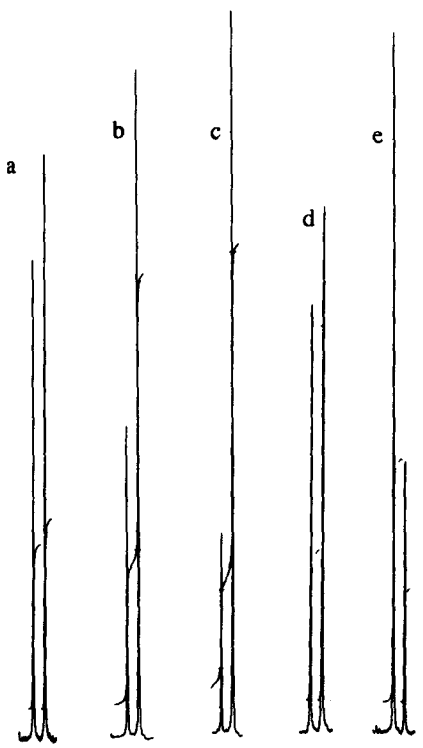


Figure 2: ^1H NMR methyl group signals for diastereomeric diols **7** and **8**.

In conclusion, an unexpected outcome of diastereoselective ADs of a chiral 1,1-disubstituted alkene has been observed. While substrate selectivity for dihydroxyaltion of **5** is very low, both *pseudo*-enantiomeric PHAL series AD ligands catalyse AD reactions giving the *same sense* of enhanced diastereoselectivity, one thus consistent and one inconsistent with the mnemonic for predicting selectivity preferences. However, the analogous PYR0-series ligand catalyzed AD reactions do lead to the anticipated opposing diastereomeric outcomes. This a rare example of this type of phenomenon using AD and the first example we are aware of using 1,1-disubstituted substrates. These results provide useful further information which will hopefully be additionally helpful in delineating some of the limitations of AD predictions, and of assistance to further mechanistic considerations in the current debate on AD.

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8. Overman, L. E.; Bell, K. L. *J. Am. Chem. Soc.* **1981**, *103*, 1851. Stereostructures of epoxides were in this case established through conversion to stereochemcially unambiguous known targets.

9. Perkin Elmer 8500 gas chromatograph. SE30 dimethyl silicone capillary column 12m x 0.25mm. Conditions: ramped over 80-280 °C at 10 °C per min.

10. Spectra were recorded at 300 MHz on a Bruker AC-300.

11. Semi-prep hplc was used to isolate the two diastereomers, and data for the isolated compounds confirmed these to be two diastereomeric diols. Stereochemical assignment of the diols[12] was provided by conversion of the diol product mixtures to the corresponding epoxides and separation of these by hplc. These epoxides are known[8] and comparison of the NMR spectra of the AD-derived epoxides with the NMR data reported allows a clear assignment of epoxide structure and a retrospective assignment of diol configurations.

12. All new compounds provided satisfactory analytical data.