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Structure Activity Relationship of the Tandem Asymmetric Dihydroxylation of a Biologically Relevant Diene and the Influence of Remote Stereocenters on Diastereofacial selectivity

Daniel M. Gill,^[a] Louise Male,^[b] and Alan M. Jones^{[a]*}

Abstract: The Sharpless asymmetric dihydroxylation (AD) finds widespread use in natural product and drug molecule syntheses, in part, due to its efficiency and predictability. However, the tandem AD of dienes is much less studied, but important in complex molecular synthesis. Herein, a biologically relevant tandem AD is reported, and several anomalies are discovered with the accepted model. These include the formation of unpredicted diastereoisomers, with matched and mismatched stereocenters contradicting the Sharpless mnemonic device. From a structure activity relationship analysis of the tandem AD, we present a strategy to improve asymmetric induction in sterically hindered alkenes using double diastereodifferentiation from a 10 bond distant stereocenter. A theoretical justification for the unpredicted stereoselectivity, accounting for the influence of steric hindrance and pre-installed chirality, is proposed.

Introduction

The Sharpless asymmetric dihydroxylation (AD) is a reliable enantioselective reaction that is used in industrial processes,^[1] natural product syntheses^[2] and drug molecule syntheses, such as, the opioid receptor antagonist (–)-Naltrexone.^[3]

The AD employs osmium tetroxide (OsO₄, typically 0.002 molar eq.) to install a vicinal *syn*-diol.^[4a-c] by reaction with a prochiral alkene. The Cinchona alkaloid derived ligand(s) command the diols resulting stereochemistry through asymmetric induction,^[5] with a predictable route to either accessible stereoisomer using the Sharpless mnemonic device.^[6]

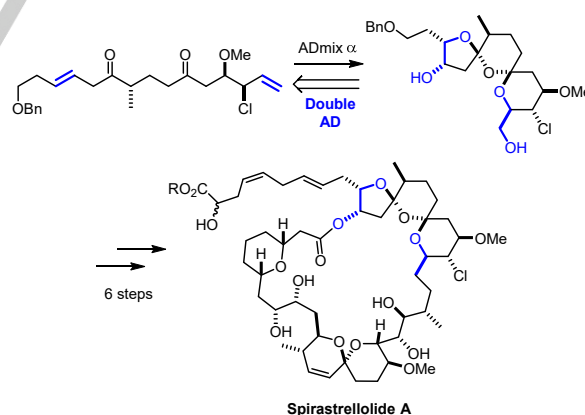
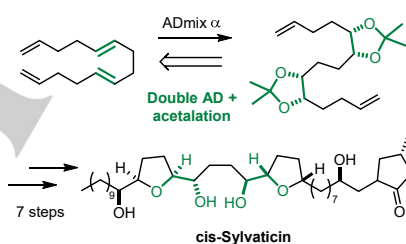
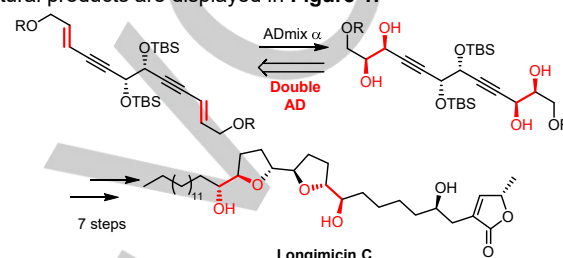
In spite of this predictability, AD of sterically hindered or linear aliphatic alkenes has shown to proceed with poor stereocontrol.^[4b,7] These observations motivated the development of different ligand classes^[6a] and the use of surrogate 'directing' groups to facilitate asymmetric induction.^[8] Overall, the stereochemical issues associated with linear aliphatic alkenes have been amended, however, the negative effect of steric hindrance remains comparably overlooked. Moreover, there are cases of product diols with inverted stereochemistry, in conflict with the Sharpless mnemonic.^[9,10]

Specifically, in systems where a tandem AD event is required (e.g. dienes), the Sharpless mnemonic is limited as there is evidence that stereocontrol is directed by pre-existing stereochemistry, irrespective of ligand choice.^[9b,e,11] Therefore, the predictability of the Sharpless

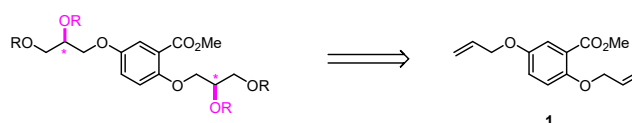
mnemonic for diene systems is open to interpretation.

The AD on single alkenes has been well explored, but to the best of our knowledge the scope of the tandem AD has not been purposefully investigated.

Limited examples that employ a tandem AD in the synthesis of natural products are displayed in **Figure 1**.^[12]



This work



R = SO₃H (bioactive glycomimetic)

* = stereochemistry derived from a tandem AD

Figure 1. Examples that use a tandem AD in the synthesis of natural products: Longimicin C (**red**),^[12a] cis-Sylvaticin (**green**)^[12b] and Spirastrellolide A

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(blue).^[12c] This work details our investigation to uncover the stereochemical outcome of a tandem AD reaction towards a bioactive molecule.

An Investigation into the Tandem AD

During a medicinal chemistry investigation towards highly sulfated heparin glycomimetics,^[13] we encountered a biologically relevant tandem AD.^[14] We found that the reported^[14] stereochemical outcome of the resulting tetraol contradicted the Sharpless mnemonic.

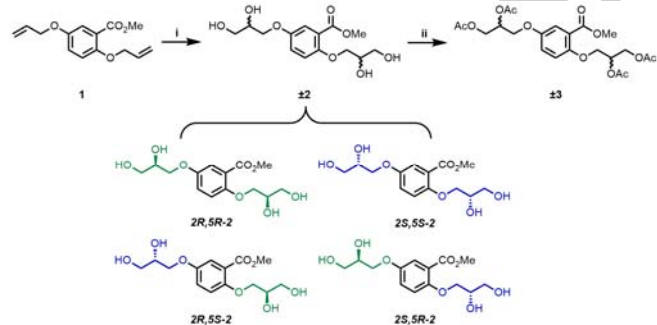
Inspired by the importance of chirality in drug-receptor binding,^[15] we sought to conclusively elucidate the stereochemical outcome of the AD. Herein we describe an investigation into the tandem AD, exploring chemoselectivity, the roles of steric hindrance, and pre-installed point chirality on stereofacial selectivity (and the overall stereochemical outcome), using the biologically relevant precursor, diene **1**.

Results and Discussion

The Chiral Stationary Phase-Based High Performance Liquid Chromatography Method for Stereochemical Analysis

In order to quantify, for the first time, the stereochemical outcome of the tandem AD on diene **1**, we developed a chiral stationary phase-based high performance liquid chromatography (cHPLC) method to resolve the four possible diastereoisomers that can be generated (**2R,5R-2**, **2S,5S-2**, **2R,5S-2** and **2S,5R-2**, **Scheme 1**).^[16] The racemic standard used for this analysis was synthesised by Upjohn dihydroxylation of **1** to afford tetraol **±2** (**Scheme 1**).

Early in the investigation it was found that tetraol (**2**) gave poor separation with a variety of chiral stationary phases, under normal and reverse phase conditions.^[17] Therefore, derivatisation was required for cHPLC analysis. A survey of protecting groups revealed the tetrakis acetate (**±3**) enabled full resolution under reverse phase cHPLC conditions.^[18]



Scheme 1. Synthesis of **±3** for reverse phase cHPLC optimisation and the four potential stereoisomers of tetraol **±2**. Conditions: i) $K_2OsO_2(OH)_4$, NMO, acetone/ H_2O , 9:1, 40 °C, 12 h, 95%; ii) AcCl, pyridine, CH_2Cl_2 , 0 °C, 0.5 h, 97%.

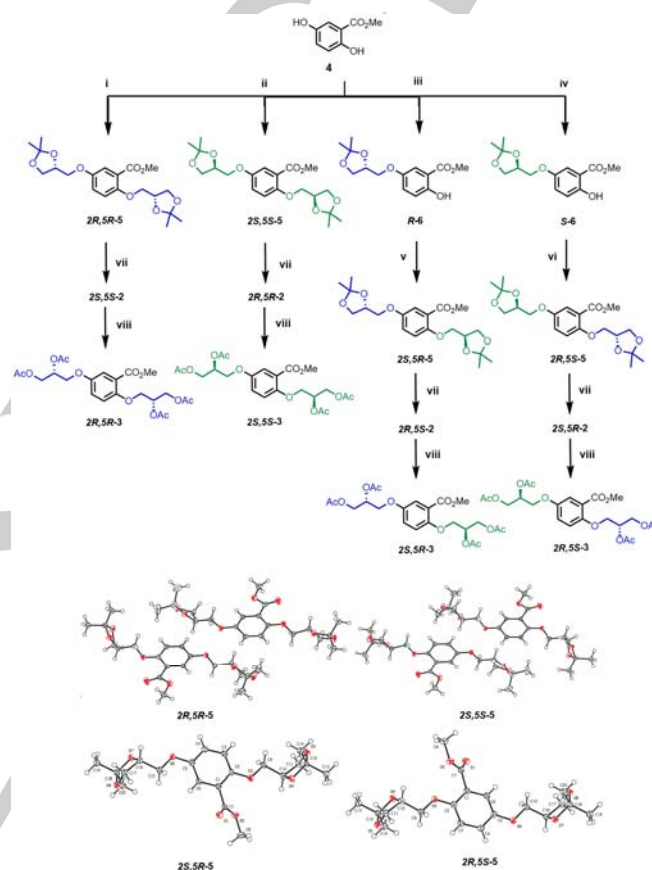
Synthesis of Enantiopure Acetals as cHPLC standards

Each individual stereoisomer of **2** was elucidated by comparison to an authentic chiral standard. This was achieved through chiral pool synthesis of four enantiopure diacetals (**5**, **Scheme 2**) using solketal triflates (98% e.e.). This provided a step-wise route to each stereochemical combination in moderate yield (33–40%, after sequential recrystallization steps),^[19] with the absolute

stereochemical assignments obtained from small molecule X-ray crystallography (**Scheme 2**, inset).^[22]

Hydrolysis of acetals **5** in trifluoroacetic acid gave each corresponding tetraols (**2**) in high yield,^[20] followed by acylation to their tetrakis acetates (**3**) for cHPLC analysis.^[21]

Overall, the specific retention times of each stereoisomer were revealed in the elution order of: **2R,5R-3**, **2S,5S-3**, **2R,5S-3**, **2S,5S-3**.^[23] Furthermore, the acidic hydrolysis and subsequent acylation steps did not degrade the stereochemical integrity.^[24]



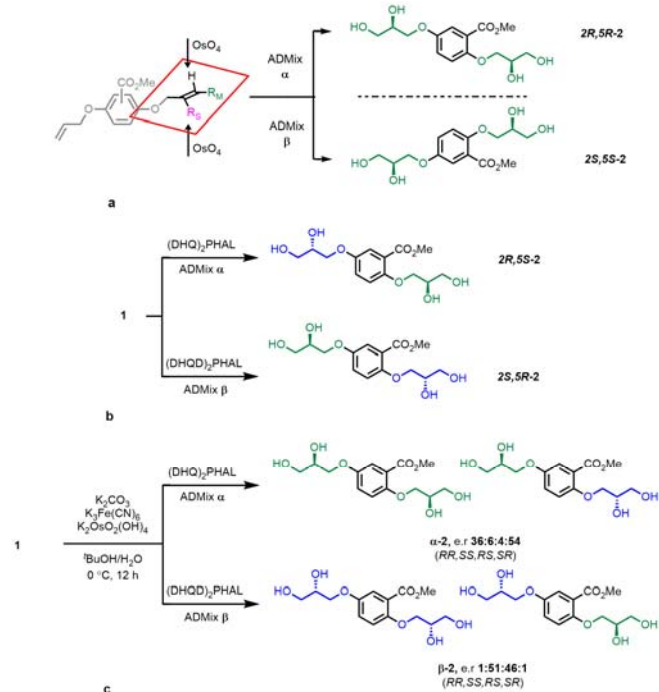
Scheme 2. Chiral pool synthesis of enantiopure diacetals **2S,5S-5**, **2R,5R-5**, **2R,5S-5** and **2S,5R-5** with representative single crystal X-ray ORTEP visualisation inset (ellipsoids drawn at the 50% probability level). Conditions: i) (S)-Solketal triflate (3.0 eq.), K_2CO_3 (2.0 eq.), MeCN, 82 °C, 12 h, 33%; ii) (R)-Solketal triflate (1.5 eq.), K_2CO_3 (2.0 eq.), MeCN, 82 °C, 12 h, 82%; iii) (S)-Solketal triflate (1.5 eq.), K_2CO_3 (2.0 eq.), MeCN, 82 °C, 12 h, 40%; iv) (R)-Solketal triflate (1.5 eq.), K_2CO_3 (2.0 eq.), MeCN, 82 °C, 12 h, 43%; v) (S)-Solketal triflate (1.5 eq.), K_2CO_3 (2.0 eq.), MeCN, 82 °C, 12 h, 43%; vi) (R)-Solketal triflate (1.5 eq.), K_2CO_3 (2.0 eq.), MeCN, 82 °C, 12 h, 43%; vii) TFA, MeOH, 40 °C, 90–96%; viii) AcCl, Py, CH_2Cl_2 , 0 °C 95–99%

A Contradicting Stereochemistry from the Tandem AD

The tandem AD of **1** using ADmix α (ligand (DHQD)₂PHAL) or β (ligand (DHQD)₂PHAL) should afford tetraols (**2**) with opposite stereochemistry.^[25] Using the Sharpless mnemonic device, ADmix α was predicted to give tetraol **2R,5R-2**, whilst ADmix β was predicted to give **2S,5S-2** (**Scheme 3a**).^[26] Conversely, this prediction contradicts the original assignment of a single **RS-2** diastereoisomer with ADmix α (and **2S,5R-2** from ADmix β , **Scheme 3b**) from the identical substrate (**1**) and its hydrolysed analogue, respectively.^[13]

The chPLC analysis of α -2 and β -2 (Scheme 3c) demonstrated that a diastereoisomeric mixture was obtained in both products. Furthermore, the installation of the diol at the 2-position, *ortho* to the methyl ester, caused the reversed diastereoselectivity. The diol at the 5-position (*meta*) was installed with good stereocontrol (>90% e.e) in accordance with the Sharpless mnemonic.

We speculated that the methyl ester inhibited chiral transmission at the 2-position alkene, as this effect has been previously observed in the AD of substituted aryl allyl ethers.^[7] Additionally, ADMix α conditions gave a contradicting stereochemical inversion for α -2, affording 2S,5R-2 as the major diastereoisomer, which, is not in agreement with the Sharpless mnemonic and the original assignment.^[14]



Scheme 3. a) The predicted stereochemical outcome, from the Sharpless mnemonic of a tandem AD of diene 1 using ADMix α and β ; b) The originally reported stereochemistry of a tandem AD of diene 1 using ADMix α and β ; ^[13,14] c) The confirmed diastereoisomeric outcomes, measured by chPLC, for the tandem AD on diene 1 using ADMix α and β .

Stereochemical Analysis of a Single AD on Related Alkenes

As a model study to confirm that the *ortho* ester inhibits chiral transmission, we deconstructed diene 1 into its component alkenes, with the addition of a *para* regioisomer to serve as a stereoelectronic comparison (7-9, Scheme 4).

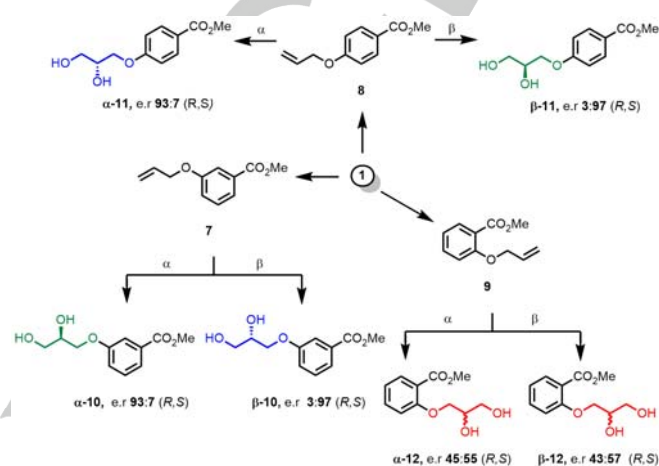
chPLC analysis of the resulting diols α -10 and β -10, from the *meta* substituted alkene 7, displayed high enantiomeric ratios (α = 93:7 & β = 3:97 R:S, Scheme 4) in accordance with previous results of 1. The stereochemical outcome was comparable to diols α -11 and β -11, from the *para* substituted alkene 8, with a similar e.r (α = 93:7 & β = 3:97 R:S, Scheme 4).

For the AD of alkene 9, we observed diols of low e.r from both ADMix's (α = 43:57 & β = 45:55 R:S, Scheme 4), demonstrating the consequence of the steric effects attributed to the *ortho*-methyl ester, which blocks asymmetric induction to the vicinal alkene.

All reactions^[27] were high yielding (93-99%), within 6 h at 0 °C, thus ligand accelerated catalysis was operational.^[28] Therefore, for alkene

9 (and consequently diene 1), the lack of stereocontrol was expected to be caused by poor transition state stability of the alkene in the OsO₄-ligand binding pocket, due to the steric hindrance of the *ortho* methyl ester.^[10a] The results of alkenes 7 and 8 further highlight that this inhibitory effect is a steric phenomenon, as there is no evidence to suggest electronic interactions, associated with the aromatic system, have an effect.

The overall results demonstrate the considerable effects of steric hindrance on stereo-control, in the AD of mono and dienes.



Scheme 4. The AD of methyl allyloxy benzoate regioisomers as the deconstructed alkenes present in 1. Conditions: K₂OsO₂(OH)₄, K₃Fe(CN)₆, K₂CO₃, ^tBuOH/H₂O 1:1, 0 °C, 6h, Ligand for ADMix α : (DHQD)₂PHAL and for ADMix β : (DHQD)₂PHAL. 96-99%

Examining Chemoselectivity in the Tandem AD of Diene 1

The influence of the methyl ester on asymmetric induction, and the conflicting chPLC result of α -2 (Scheme 3c), prompted us to consider how the reaction could be manipulated with the intent of improving the e.r. of the vicinal (2-position) alkene. Therefore, we sought to find the cause of the stereochemical conflict and we first examined chemoselectivity in the double AD of 1.

By conducting a standard AD experiment on 1 using a sub-stoichiometric equivalent of reagents, we were able to determine the relative ratios of intermediate diols.^[29] The same reaction was also carried out under Upjohn conditions, providing the control experiment. The reactions were stopped when no diene (1) was observed by thin layer chromatography, and ¹H NMR spectra were recorded on the crude samples (in DMSO-d₆).

From analysis of the crude products, each reaction was found to contain diols 13 and 14 (Figure 2). However, from the relative integration of peaks X and Y, it was observed that under AD conditions diol 14 had formed in a 2:1 ratio with 11 (Figure 2, red). This demonstrated that installation of a diol at the more sterically encumbered 2-alkene was preferred. Expectedly, the opposite result was found in the control experiment, which favoured installation of the diol at the 5-position alkene (Figure 2, blue).

Structural elucidation of the diols (13 and 14) was established by ¹H-¹H NOESY NMR spectroscopy on a purified sample of 14, and, independently by synthesising enantiomers R-13, S-13 and R-14 (Table 1).

We have attributed this chemoselectivity to the Sharpless ligand ((DHQD)₂PHAL in ADMix β). However, previous results from alkene 9 verified that AD on the 2-position alkene produces diols of low e.r., using either ADMix. Therefore, we hypothesised that the *vicinal*

methyl ester has a favourable interaction with the OsO₄-ligand complex. However, regardless of this enhanced regioselectivity, chiral transmission from the ligand to the reacting alkene is blocked. Unfavourable stacking interactions within the binding pocket of the OsO₄-ligand complex has been hypothesised to reduce stereoselectivity in other complex systems.^[7,10] This hypothesis is not in agreement with our results. Furthermore, it does not explain the mnemonic opposing stereochemistry of α -2.

Taking into consideration the previously reported hypotheses on the AD and the results so far: the regioselectivity of the 2-position alkene and the unpredictable stereochemical outcome we have observed with α -2, we proposed that double diastereodifferentiation could be used to gain an improved *e.r* at the vicinal (2-position) alkene.^[30]

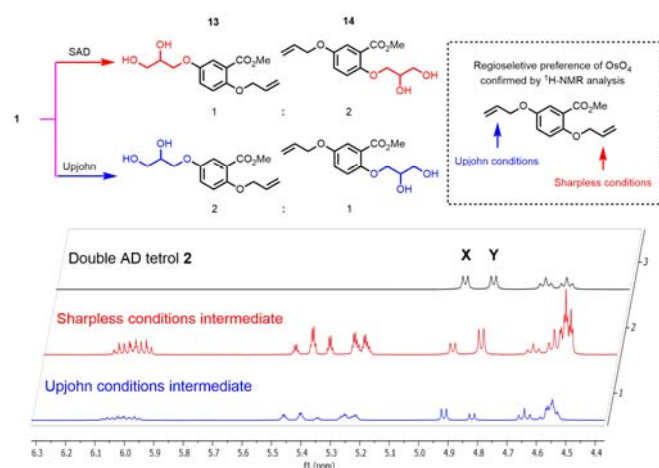


Figure 2. Regioselectivity of a dihydroxylation under AD and Upjohn conditions with the stacked ¹H-NMR spectra of the crude samples from each reaction, displaying diols **13** and **14** in opposing 2:1 concentrations.

Investigating Diastereodifferentiation in the Tandem AD

Previous reports of diastereofacial selectivity in the AD use substrates with a stereogenic centre 1-2 bonds distant from the reacting alkene. This has provided stereo-selective syntheses of various polyols.^[8,9a,11 & 31] Importantly, there are examples where a reversal of facial selectivity is observed which capitalise on double diastereodifferentiation.^[9]

We used acetal **S-6** to install a stereogenic centre of known *e.r* (99:1) at the 5-position. Then, by installing an alkene at the 2-position it provided chiral alkene **S-13** (Scheme 5). The aim was to perform an AD on **S-13**, to determine if double diastereodifferentiation was achievable from a distal chiral centre, installed 10 bonds from a reacting alkene which is otherwise blocked from chiral transmission by the vicinal methyl ester.

In order to verify our hypothesis, we ran control experiments under AD and Upjohn conditions. Additionally, the use of a regioisomer **14**, unprotected diols (**S-11** and **R-11**) and opposite enantiomers **R-13** and **S-11** (Scheme 5) provided a data set of 15 different stereochemical outcomes based on point changes to the substrate. The results are summarised in Table 1.

A Structure Activity Relationship for the AD of Diene 1

The stereochemical results for alkene **S-15** (Table 1, entries 4-5) are representative of a matched and mismatched pair.^[30] Conditions with

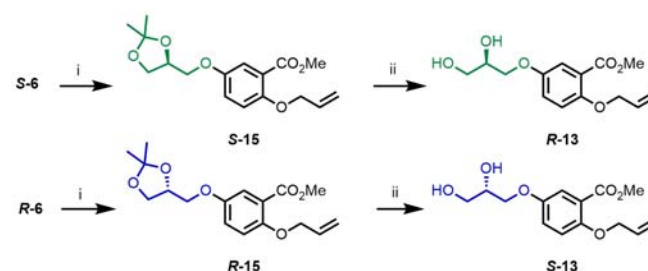
ADmix α gave an increase in *e.e* of +24% to the **2S,5R-2** diastereoisomer over **2R,5R-2** (entry 4). ADmix β gave no diastereofacial selectivity (entry 5), and a comparable result was obtained under Upjohn conditions (entry 6). Interestingly, under ADmix α conditions (entry 4), the stereochemical outcome contradicts the Sharpless mnemonic and from the previous results on mono-alkenes (**7** & **8**), therefore, it represents a matched pair but a mismatched stereochemical outcome.

Using the regioisomer **S-16** (entries 7–9) we probed the effects of swapping the alkene and chiral centre. No significant diastereofacial selectivity was observed, giving the predicted stereochemical outcomes for both α and β conditions (entries 7 and 8). Furthermore, with alkenes **R-13** & **R-14** (entries 10-15) we considered the effects of free diols under AD conditions. These species are formed during the tandem AD of **1**, mimicking the intermediates found in the ¹H NMR spectroscopy study (Figure 2). Therefore, a pre-fixed chiral centre could influence the installation of the subsequent diol. However, the results from **R-13** demonstrated no significant diastereofacial selectivity under both conditions (entries 10-11). However, for **R-12**, when the diol is installed in the 2-position we observed excellent diastereoselection under AD conditions (entries 13-14). These results, and the results of alkene **S-16** (entries 7 & 8), can be attributed to chiral transmission from the Sharpless ligand(s) outweighing diastereofacial effects, as the AD of alkene **5** proceeded with good stereo-control regardless of pre-installed chiral centres (Scheme 3).

Anomalously, for **R-13**, under Upjohn conditions (entry 12) a preference for the **2S,5R-2** stereoisomer was observed. This outcome was considered to be an effect of diol chelation to OsO₄ *in situ*.^[32] Therefore, it was anticipated that the opposite enantiomer **S-13** would give the opposite diastereochemical result (**2R,5S-2**) but did not occur (entry 18).

We anticipated the results for alkene **R-15** (entries 16-17) to be similar to **S-15**, with a similar increase in the stereoisomer **2R,5S-2** gained from opposite AD conditions, using ADmix β . However, chPLC analysis provided a further unexpected result, defining **2S,5S-2** as the major product with +28% *e.e* (entry 17). Therefore, this case represents a matched pair with a matching stereochemistry to the Sharpless mnemonic.

Considering the stereochemical outcomes from the AD of enantiomers **S-15** and **R-15**, it was non-trivial to explain the divergent results. Previous reports have revealed that selectivity can be dependent on chiral substituents, and in limited cases the use of either ADmix gave identical stereoisomers.^[9b]



Scheme 5. Chiral pool synthesis of chiral alkenes **S-13** and **R-13** from **S-15** and **R-15**. Conditions: i) Allyl bromide, K₂CO₃, TBAI, acetone, 56 °C, 4 h, 95-99%; ii) TFA, H₂O, 40 °C, 4 h, 99%.

Table 1: The stereochemical outcomes of the AD (and Upjohn dihydroxylation) of chiral alkenes for the sturcutre acitivt relationship of diene 1. **Green** = major diastereoisomer; **Red** = minor diastereoisomer; **Blue** = low/insignificant diastereoisomeric ratios (*d.r.*).

Entry	Alkene	Conditions	Stereochemical Outcome (e.r./d.r)				Product
			2 <i>S</i> ,5 <i>S</i>	2 <i>R</i> ,5 <i>S</i>	2 <i>S</i> ,5 <i>R</i>	2 <i>R</i> ,5 <i>R</i> *	
1		ADMix α	6	4	54	36	
2		ADMix β	51	46	1	1	
3		OsO ₄ /NMO	25	25	25	25	
4		ADMix α	1	1	61	37	
5		ADMix β	1	1	49	48	
6		OsO ₄ /NMO	1	2	48	49	
7		ADMix α	—	6	3	91	
8		ADMix β	3	95	—	2	
9		OsO ₄ /NMO	2	47	3	48	
10		ADMix α	—	—	56	44	
11		ADMix β	2	3	51	45	
12		OsO ₄ /NMO	—	—	67	33	
13		ADMix α	—	8	3	89	
14		ADMix β	2	94	—	4	
15		OsO ₄ /NMO	—	48	—	52	
16		ADMix α	51	49	—	—	
17		ADMix β	64	36	—	—	
18		OsO ₄ /NMO	50	50	—	—	

Improving Diastereoselectivity in the AD

To assist the explanation for the observed diastereoselectivity, we have made deductions based on the evidence presented so far: (i) The alkene of **S-15** and **R-15** approaches the OsO₄-ligand 'binding pocket' with identical orientation to the neighbouring ester, as preferential binding of position 2 was observed by ¹H-NMR spectroscopy (Figure 3). Furthermore, complete inhibition of chiral transmission was observed in alkene **7** (Scheme 3), therefore, both ligands have the same attraction to the alkene at position 2. (ii) The protected diol, as its corresponding acetal derivative, is important for diastereodifferentiation, as the free diol has no significant effect on the resulting stereochemical outcomes (Table 1, entries 10-11). (iii) Stereofacial interactions outweigh steric hindrance and directly contribute to the stereochemical outcome (results obtained with **S-15** and **R-15**). (iv) Ligand accelerated catalysis is operational in all AD reactions, regardless of the stereochemical outcome. Therefore, non-asymmetric dihydroxylations have minimal effect on the resulting diols stereochemistry and stereochemical rules applied to non-ADs³³ are not applicable.^[33]

We therefore propose that alkenes **S-15** and **R-15** approach the OsO₄-ligand 'binding pocket' with the same orientation, due to the *vicinal* methyl ester. However, the transition state of **S-15** inside (DHQD)₂PHAL is opposite to **R-15** in (DHQD)₂PHAL, and, is directly related to the stereochemistry of the acetal functionality and its interactions with the Sharpless ligands.

The presence of the acetal in (**R/S**)**13** diminishes the steric hindrance of the ester and in both cases facilitates asymmetric induction. However, the steric bulk of the (*S*)-acetal flips the geometry of **S-15**'s interaction with (DHQD)₂PHAL, leading to a lower energy transition state and the observed stereochemical inversion relative to the Sharpless mnemonic. This hypothesis is in similar accordance to a previous report on the AD of symmetrical divinylcarbinols.^[34] For enantiomer **R-15**, we hypothesise that interactions with (DHQD)₂PHAL already leads to a lower energy transition state, with no geometric inversion due to the pre-organised stereochemistry of the (*R*)-acetal, thus, giving the predicted diastereoisomer from the Sharpless mnemonic. These hypotheses are illustrated in Figure 3.

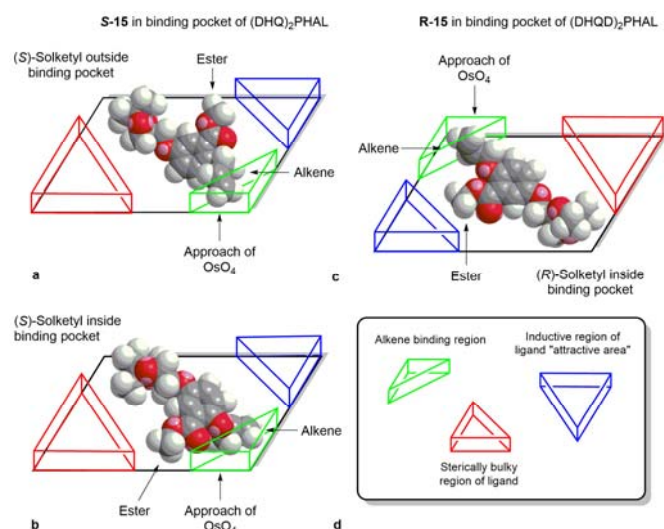


Figure 3. Demonstrating the different modes of transition state binding for **S-15** and **R-15** in the ligands $(\text{DHQ})_2\text{PHAL}$ and $(\text{DHQD})_2\text{PHAL}$, as reasoning behind the differences in diastereofacial selectivity. For **S-15** and **R-15**, all energies were minimized using molecular force field-MM2 calculations. **a)** (S)-acetal functionality in **S-15** resides outside the 'binding pocket' due to the orientation of approach; **b)** the proposed binding mode of **S-15** in $(\text{DHQ})_2\text{PHAL}$ due to interactions with the ligand, providing a lower energy transition state and preferential attack of OsO_4 to the opposite face of the alkene, generating the unpredicted diastereoisomer **c)** The binding mode for **R-15** in $(\text{DHQD})_2\text{PHAL}$, demonstrating an exact orientation of approach and a matched interaction of the (R)-acetal leads to a lower energy transition state with no geometric inversion, giving the predicted diastereoisomer; **d)** regions of the ' OsO_4 -ligand 'binding pocket' adapted from the Sharpless mnemonic.^[6]

Conclusions

From the chPLC analysis of the tandem AD on diene **1** and related alkenes **5-7**: we have demonstrated that a vicinal (methyl ester) functionality facilitates preferential binding of a reacting alkene inside the OsO_4 -ligand complex, but, inhibits chiral transmission to the product diols/tetraols. Therefore, we have confirmed that asymmetric induction in the mono and tandem AD is strongly influenced by steric interactions. Furthermore, we have amended previous results, providing the stereochemical assignments of biologically relevant tetraols **α -2** and **β -2** *en route* to the glycomimetic class of bioactive molecules.

We have shown that by using double diastereodifferentiation in an AD, we were able to improve the *e.e.* of a diol by +28%, which was otherwise blocked from chiral transmission. Therefore, we have presented a case for diastereofacial selectivity, which can be effective when a chiral centre is installed up to 10 bonds distant from a reacting alkene. Moreover, we have demonstrated a potential strategy to counteract blocking of asymmetric induction from steric hindrance, gaining higher enantioselectivity on sterically blocked alkenes, for future applications in AD.

Finally, we have uncovered a potential cause to the conflicting stereochemistry gained from AD reactions in the literature, by demonstrating that a substrate's pre-installed point chirality and choice of chiral conditions (α or β , $(\text{DHQD})_2\text{PHAL}$ or $(\text{DHQ})_2\text{PHAL}$) are intertwined. This can be capitalised on to synthesise target diols, with enhanced diastereomeric ratios or an unpredicted stereochemical result. These findings have implications in the design

of total syntheses that use AD and provides a roadmap to the use of tandem AD in complex molecular synthesis.

Experimental Section

For a general description of the chemicals and analytical methods that were used within this study see the Supporting Information.

Synthesis of 2:

General AD procedure: A 25 mL round bottom flask was charged with $\text{K}_3\text{Fe}(\text{CN})_6$ (3.0 eq.), K_2CO_3 (3.0 eq.), $\text{K}_2\text{OsO}_2(\text{OH})_4$ (0.002 eq.), $^t\text{BuOH}/\text{H}_2\text{O}$ (1:1, 10 mL) and either $(\text{DHQ})_2\text{PHAL}$ or $(\text{DHQD})_2\text{PHAL}$ (0.02 eq.), forming a biphasic homogeneous mixture. The flask was cooled to 0 °C (ice bath) and stirred vigorously for 20 min, creating a heterogeneous orange slurry to which the alkene (1.0 eq.) was added. The reaction mixture was stirred at 0 °C until complete consumption of starting material was observed (TLC, EtOAc/hexane 1:1, or EtOH/EtOAc 1:4). The reaction was quenched with neat Na_2SO_3 (12.0 eq) and warmed to room temperature over 1 h. The flask was charged with H_2O (5 mL) and extracted with EtOAc (3×20 mL). The combined organic extracts were washed with 1.0 M HCl (aq.) (2×30 mL), brine (30 mL) and dried (MgSO_4). Filtration of the solids and removal of solvent under reduced pressure afforded the desired compound.

Methyl 5-((R)-2,3-dihydroxypropoxy)-2-((S)-2,3-dihydroxypropoxy)benzoate (α -2)

Adapted from general procedure 1: Methyl 2,5-bis(allyloxy)benzoate (**1**) (158 mg, 0.50 mmol) was added and the reaction mixture was stirred at 0 °C for 6 h with monitoring (EtOH/EtOAc 1:4, $R_f = 0.20$). The solvent was removed under reduced pressure and the crude mixture was directly purified by chromatography (SiO_2 , EtOH/EtOAc 1:4) yielding the title as a clear oil (156 mg, 99%). $[\alpha]_D^{25} -13.15$ (c. 1.0, MeOH, 36:6:4:54 e.r./d.r (2R5R,2S5S,2R5S,2S5R)); IR $\nu_{\text{max}} \text{ cm}^{-1}$ 3268 w, 2939 w, 2890 w, 1699 s (C=O), 1601 w, 1499 s, 1435 w; $^1\text{H-NMR}$ (400 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{H} 7.18 (d, $J = 2.7$ Hz, 1H, C6-H), 7.15 – 7.04 (m, 2H, C3-H & C4-H), 4.94 (d, $J = 5.0$ Hz, 1H, CH-OH), 4.84 (d, $J = 5.0$ Hz, 1H, CH-OH), 4.66 (t, $J = 5.7$ Hz, 1H, CH_2 -OH), 4.59 (t, $J = 5.7$ Hz, 1H, CH_2 -OH), 4.01 – 3.85 (m, 3H), 3.86 – 3.69 (m, 6H, Me), 3.55 – 3.35 (m, 4H); $^{13}\text{C-NMR}$ (101 MHz, $(\text{CD}_3)_2\text{SO}$) δ_{C} 166.0 ($\text{C}=\text{O}$), 152.2 (C5), 152.0 (C2), 121.0 (C1), 119.8 (C3/C4), 115.94 (C3/C4), 115.89 (C6), 71.3 (O-CH₂), 70.3 (O-CH₂), 69.9 (2C, CH-OH), 62.72 (CH₂-OH), 62.66 (CH₂-OH), 52.0 (Me); LRMS m/z (ESI+) 339.12 (100%, $[\text{M}+\text{Na}]^+$); HRMS m/z (ESI+) $\text{C}_{14}\text{H}_{20}\text{O}_8\text{Na}$ requires 339.1056, found 339.1057 ($[\text{M}+\text{Na}]^+$)

Methyl 5-((S)-2,3-dihydroxypropoxy)-2-((±)-2,3-dihydroxypropoxy)benzoate (β -2)

Adapted from general procedure 1: Methyl 2,5-bis(allyloxy)benzoate (**1**) (158 mg, 0.50 mmol) was added and the reaction mixture was stirred at 0 °C for 6 h with monitoring (EtOH/EtOAc 1:4, $R_f = 0.20$). The solvent was removed under reduced pressure and the crude mixture was directly purified by chromatography (SiO_2 , EtOH/EtOAc 1:4) yielding the title as a clear oil (156 mg, 99%). $[\alpha]_D^{25} -7.62$ (c. 1.0, MeOH, 1:51:46:2 e.r./d.r (2R5R,2S5S,2R5S,2S5R)); IR $\nu_{\text{max}} \text{ cm}^{-1}$ 3260 br s (O-H), 2951 w, 2874 w, 1725 (C=O), 1611 w, 1577 w,

1498 s, 1432 w; ¹H-NMR (400 MHz, (CD₃)₂SO) δ_H 7.18 (d, *J* = 2.7 Hz, 1H, C6-H), 7.13 – 7.07 (m, 2H, C3-H & C4-H), 4.94 (d, *J* = 5.0 Hz, 1H, CH-OH), 4.84 (d, *J* = 5.0 Hz, 1H, CH-OH), 4.66 (t, *J* = 5.7 Hz, 1H, CH₂-OH), 4.59 (t, *J* = 5.7 Hz, 1H, CH₂-OH), 4.01 – 3.85 (m, 3H), 3.86 – 3.69 (m, 6H, Me), 3.55 – 3.35 (m, 4H); ¹³C-NMR (101 MHz, (CD₃)₂SO) δ_C 166.1 (C=O₂Me), 152.2 (C5), 152.0 (C2), 121.0 (C1), 119.8 (C3/C4), 115.95 (C3/C4), 115.91 (C6), 71.3 (O-CH₂), 70.4 (O-CH₂), 69.9 (2C, CH-OH), 62.73 (CH₂-OH), 62.67 (CH₂-OH), 52.0 (Me); LRMS *m/z* (ESI+) 339.12 (100%, [M+Na]⁺); HRMS *m/z* (ESI+) C₁₄H₂₀O₃Na requires 339.1056, found 339.1057 ([M+Na]⁺)

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Keywords: Asymmetric Dihydroxylation • Sharpless • Tandem • Diastereodifferentiation • Stereofacial selectivity

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- [18] **±3** gave the best preliminary results and the conditions were optimised using 28% acetonitrile/72% H₂O, 1.0 mL min⁻¹ at 30 °C, see supplementary data for further details.
- [19] See supplementary data **2R,5R-5**, **2S,5S-5**, **2R,5S-5** and **2S,5S-5**

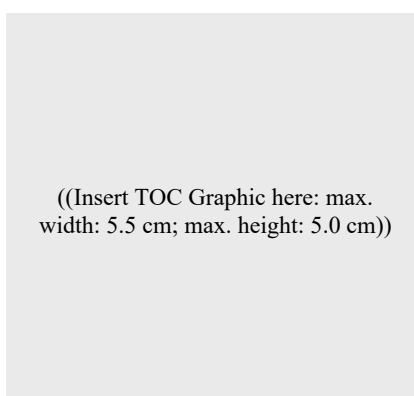
- [20] See supplementary data **2R,5R-2**, **2S,5S-2**, **2R,5S-2** and **2S,5S-2**
- [21] See supplementary data, HPLC section: **2R,5R-3**, **2S,5S-3**, **2R,5S-3** and **2S,5S-3**
- [22] CCDC-1956970 (**2R,5R-5**), 1956969 (**2S,5S-5**), 1956968 (**2S,5R-5**), 1956967 (**2R,5S-5**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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Structure Activity Relationship of the Tandem Asymmetric Dihydroxylation of a Biologically Relevant Diene and the Influence of Remote Stereocenters on Diastereofacial selectivity

Double Diastereodifferentiation at a Distance: A biologically relevant tandem asymmetric dihydroxylation reaction contradicts the accepted mnemonic prediction. Asymmetry can be restored with a remote stereocentre, at an unprecedented 10 bonds away from the reacting centre.

