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.

Limited examples that employ a tandem AD in the synthesis of natural products are displayed in Figure 1.

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

Supporting information for this article is given via a link at...
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[15] stereochemical outcome of the resulting tetrool contradicted the Sharpless mnemonic.

Inspired by the importance of chirality in drug-receptor binding,[16] 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 preinstalled 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 tetrool ±2 (Scheme 1).

Early in the investigation it was found that tetrool (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 tetrool 2. Conditions: i) K2OsO2(OH)4, NMO, acetone/H2O, 9:1, 40 °C, 12 h, 95%; ii) AcCl, pyridine, CH2Cl2, 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 stereocchemical 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).[20]

Hydrolysis of acetals 5 in trifluoroacetic acid gave each corresponding tetrool (2) in high yield,[21] followed by acylation to their tetrakis acetates (3) for chPLC analysis.[22]

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

A Contradicting Stereochemistry from the Tandem AD

The tandem AD of 1 using ADmix α (ligand (DHQ)2PHAL) or β (ligand (DHQD)2PHAL) should afford tetrools (2) with opposite stereochemistry.[25] Using the Sharpless mnemonic device, ADmix α was predicted to give tetrool 2R,5S-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.[12]
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.r.) 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. Additionally, ADmix α conditions gave a contradicting stereochemical inversion for α-2, affording 2S,5R-2 as the major diastereoisomer, which is in agreement with the Sharpless mnemonic and the original assignment.14

**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 regiosomer to serve as a stereoelectronic comparison (7-9, Scheme 4).

The 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 reactions27 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: (DHQ)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 confliction 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.20 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 products (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. 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.e. at the vicinal (2-position) alkene.[24]

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.[8,11 & 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.e (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 stereoselective 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.[9h] 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 stereoselective 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).

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 diastereochromic 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.[9g]

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.

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

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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-ADs 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 (DHQ)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 (DHQ)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 hypothesize 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.
hindrance, gaining higher enantioselectivity on sterically blocked strategy to counteract blocking of asymmetric induction from steric a reacting alkene. Moreover, we have demonstrated a potential effective when a chiral centre is installed up to 10 bonds distant from present a case for diastereofacial selectivity, which can be otherwise blocked from chiral transmission. Therefore, we have AD, we were able to improve the We have shown that by using double diastereodifferentiation in an molecules.

Finally, we have uncovered a potential cause to the conflicting alkene, for future applications in AD.

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 OsO₄-ligand complex, but, inhibits chiral transmission to the product diols/tetrads. 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 tetrads 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 enantioslectivity 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, (DHQD)₂PHAL or (DHQD)₂PHAL) are intertwined. This can be capitalised on to synthesise target diols, with enhanced diastereomeric ratios or an unpredicted stereoselective 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 K₂Fe(CN)₆ (3.0 eq.), K₂CO₃ (3.0 eq.), K₂OsO₂(OH)₄ (0.002 eq.), BuOH/H₂O (1:1, 10 mL) and either (DHQD)₂PHAL or (DHQD)₂PHAL (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 Na₂SO₄ (12.0 eq) and warmed to room temperature over 1 h. The flask was charged with H₂O (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 (MgSO₄). Filtration of the solids and removal of solvent under reduced pressure afforded the desired compound.

Methyl 5-((R)-2,3-dihydroxypropoxy)-2-((±)-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, Rₓ = 0.20). The solvent was removed under reduced pressure and the crude mixture was directly purified by chromatography (SiO₂, EtOAc/EtOH 1:4) yielding the title as a clear oil (156 mg, 99%); [α]₂^25 –13.15 (c. 1.0, MeOH, 36:6:4:54 e.r/d.r (2R₅R,2S₅S,2R₅S,2S₅R)); IR ν max cm⁻¹ 3268 w, 2939 w, 2899 w, 1699 s (C=O), 1611 w, 1577 w, 1499 s, 1435 w, νOH cm⁻¹ 3260 br s (O-H), 2951 w, 2874 w, 1725 (C=O), 1611 w, 1577 w.

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Synthesis of 2:

General AD procedure: A 25 mL round bottom flask was charged with K₂Fe(CN)₆ (3.0 eq.), K₂CO₃ (3.0 eq.), K₂OsO₂(OH)₄ (0.002 eq.), BuOH/H₂O (1:1, 10 mL) and either (DHQD)₂PHAL or (DHQD)₂PHAL (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 Na₂SO₄ (12.0 eq) and warmed to room temperature over 1 h. The flask was charged with H₂O (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 (MgSO₄). Filtration of the solids and removal of solvent under reduced pressure afforded the desired compound.
Asymmetric induction in sterically bulky alkenes is diminished or inhibited. A possible explanation involves the relative destabilisation of the transition state, which is alkene dependent. However, the complexity of this hypothesis makes it difficult to account for steric effects. Alternative hypotheses propose different alkene OsO$_4$-ligand binding, as the “U-shape” like ‘binding pocket’ of the Sharpless ligands can potentially tolerate the presence of sterically bulky substituents. The functional theory, transition state calculations and computational tools to help predict the stereochemical outcome exist. However, this is limited to simple mono-alkenes. (a) H. C. Kolb, P. G. Andersson, K. B. Sharpless, J. Am. Chem. Soc. 1994, 116, 1279-1291; (b) H. Becker, P. T. Ho, H. C. Kolb, S. Loren, P. O. Nortby, K. B. Sharpless, Tetrahedron Lett. 1994, 35, 7315; (c) E. J. Corey, M. C. Noe, S. Sarshar, J. Am. Chem. Soc., 1993, 115, 3828-3829; (d) E. J. Corey, M. C. Noe, J. Am. Chem. Soc. 1996, 118, 319-329; (e) P. O. Nortby, H. C. Kolb, K. B. Sharpless, Organometallics 1994, 13, 344-347; (f) Y. D. Wu, Y. Wang, K. N. Houk, J. Am. Chem. Soc., 1999, 121, 10186-10192; (g) N. Moftassier, C. Henry, C. Len, Y. Chapleur, J. Org. Chem. 2002, 67, 7275-7282


Mosher’s acid derivatives for $^1$H NMR spectroscopic analysis was considered. However, analysis of complex mixtures of diastereoisomers would be less a direct read out of the reaction than chPLC.

The racemic diol $\pm 2$ was screened on proprietary chiral stationary phases (Phenomenex$^a$) under reverse phase (H$_2$O and acetoni trole) and normal phase (hexane and isopropyl alcohol/ethanol) conditions.

$^a$ gave the best preliminary results and the conditions were optimised using 28% acetoni trole/72% H$_2$O, 1.0 mL min$^{-1}$ at 30°C, see supplementary data for further details.


CCDC-1956970 (2R,5R-3), 1956969 (2S,5S-3), 1956968 (2S,5R-3), 1956967 (2R,5S-3) 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.

Upon esterification to the tetrakis acetyl esters the CIP assignments invert due to group priority changes. Therefore, the order the compounds elute are as follows: 2R,5R-3, 2S,5R-3, 2R,5S-3, 2S,5S-3.

Further evidence for this was obtained by hydrolysing and re-acetyllating an enantiopure standard of acetylated diol S12 and S12'. See supplementary information: hydrolysis analysis.

Ligands from the ADmix are pseudo enantiomers and are opposing diastereoisomers.

Based on the Sharpless mnemonic device and reference [4b].

See supplementary information.


See supplementary information: regioselectivity analysis.

Double diastereo-differentiation: the stereochemical outcome of a given reaction, involving two chiral reactants, is influenced by the already present stereocenters. They can represent a ‘matched’ pair in which there is complimentary diastereofacial selectivity, and a new stereocentre(s) is formed with high diastereoselection. They can represent a ‘mismatched’ pair, in which the uncomplimentary diastereofacial selectivity creates a stereocentre with little to no diastereoselection. For a comprehensive review, see: S. Masamune, W. Choy, J. S. Petersen, L. R. Sita, Angew. Chem. Int. Ed. 1985, 24, 1-30.


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.