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Diastereospecific Epoxidation/AE Kinetic Resolution of *cis/trans*-2,6-Dimethylbenzylidene Cyclohexane and Solution Conformation of 4,8-Dimethyl-2-phenyl-1-oxaspiro[2.5]octane.

John M. Gardiner*[a], Marck Nørret[a] and Ian H. Sadler[b]

[a]*Department of Chemistry, University of Manchester Institute of Science and Technology (UMIST), PO Box 88, Manchester M60 1QD, United Kingdom.*

[b]*Ultra-High Field NMR Centre, Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, United Kingdom.*

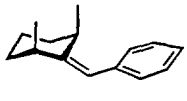
Abstract: Epoxidation using a (salen)Mn catalyst shows complete selectivity between 2,6-*trans* and 2,6-*cis* dimethylbenzylidene cyclohexanes, is diastereospecific, and exhibits a kinetic resolution with k_{rel}=5. Stereochemistry and conformation of the product 4,8-dimethyl-2-phenyl-1-oxaspiro[2.5]octane were determined by DQF-COSY and nOe difference measurements at 600MHz.

The catalytic asymmetric epoxidation (AE) developed by Sharpless' group has proved widely effective for kinetic resolutions of allylic alcohol substrates,[1] and recently a first example of a kinetic resolution of racemic chromenes (containing an *endocyclic* double bond) using (salen)Mn catalysed epoxidation was reported by Jacobsen's group.[2] We have been interested in the stereochemical outcomes of oxidations of hindered α,α'-disubstituted *exocyclic* alkenes, and kinetic resolution of such substrates. Dihydroxylation of a mixture of **1**/ent-**1** and **2**/ent-**2** leads *exclusively* to *diastereospecific* dihydroxylation of **2**/ent-**2** to give **3**/ent-**3** (with the 2,6-*trans* isomers **1**/ent-**1** being completely unaltered, even after one week).[3] From DQF-COSY assignments and nOe difference experiments, the conformation of the *cis* dimethyl alkene substrate **2**/ent-**2** was evidently the *diaxial* conformation shown.[3] Thus, the diastereospecificity of the dihydroxylation reactions of this substrate was rationalized from steric considerations, though the reasons for the relative inertness of **1**/ent-**1** are unclear. Using catalytic *asymmetric dihydroxylation* with $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ ligands[4] lead to very efficient kinetic resolution between **2** and ent-**2**, affording **3** *or* ent-**3** respectively,[3] proceeding in one sense with a $k_{rel} \sim 50$, which appears the highest yet reported for AD kinetic resolutions.[5-9]

The remarkable diastereospecificity of, and kinetic resolution through, dihydroxylation led to consideration of epoxidation of these 2,6-dimethylbenzylidene cyclohexanes, and herein we report (1) proof of the diastereospecificity of epoxidation and (2) that kinetic resolution does occur, though this is less effective than kinetic resolution using AD with this substrate.

1

ent-**1**



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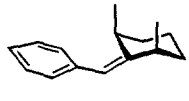
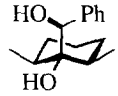


ent-**2**



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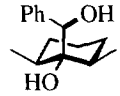

ent-**3**

Epoxidation was evaluated using a (salen)Mn asymmetric epoxidation system.[2] Epoxidation of the enantiomeric pairs of 2,6-*trans* and 2,6-*cis* dimethylbenzylidene cyclohexane, **1**/ent-**1** and **2**/ent-**2**, could lead to four *diastereomeric* spiro epoxides, within any one or more of which kinetic resolution may be exhibited. The alkene mixture **1**/ent-**1** and **2**/ent-**2** was thus epoxidized at -78°C using (*R*,*R*)-(-)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride[10] as catalyst and *m*-CPBA as oxidant.[2] The epoxidation was notably faster than catalytic asymmetric dihydroxylation of this substrate, with 20%, 41% and 61% conversion after 40 minutes, 2 hrs and 5 hrs, respectively.[11] The conversion and enantioenrichment of alkene were followed by chiral g.c.[12] The product epoxide, 4,8-dimethyl-2-phenyl-1-oxaspiro[2.5]octane, was a *single* diastereomer, and from g.c. it was conclusive that this arose from epoxidation of **2**/ent-**2**. Alkene **1**/ent-**1** was unaltered. Thus, epoxidation, *like dihydroxylation*,[3] leads to *selective reaction of the cis substrates with complete diastereocontrol.*[13] This (salen)Mn catalysed epoxidation also exhibited modest kinetic resolution. The residual alkene enantiomeric excess of 38% at 41% conversion illustrated in Figure **1** compares with residual alkene ees for AD kinetic resolution of ~ 61-70% at similar percentage conversion using either ligand series.[3] The *sense* of resolution is such that alkene ent-**2** is epoxidized preferentially (established by reference to alkene resolution by AD and the absolute stereochemical assignment made in that process[3]). The k_{rel} is 5.2[14] which compares favourably with the relative rates for AE kinetic resolution of endocyclic alkenes (chromenes).[2]

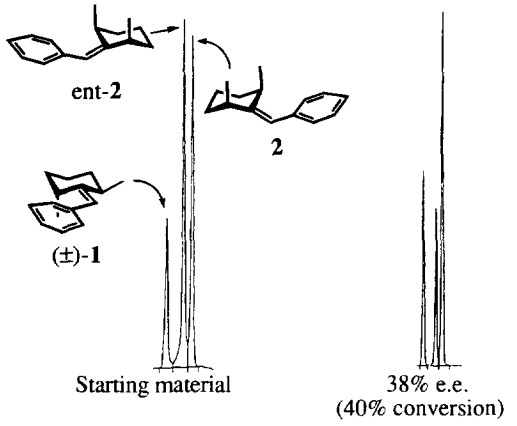

Figure 1: Chiral g.c.

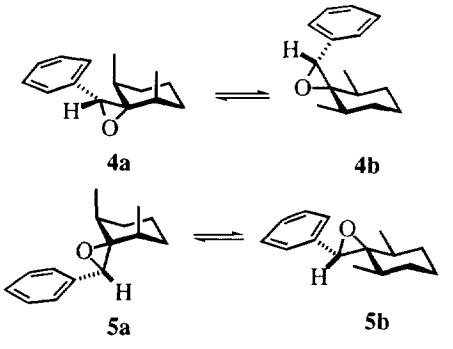

Figure 2

The two diastereomeric epoxides **4** and **5** potentially available from epoxidation of **2**/ent-**2** can each exist in two alternative chair conformations (the equilibria in Figure **1**). The 1D ^{1}H NMR spectrum of the product shows that one of the ring methyls is shifted to substantially lower frequency (0.6ppm compared to 1.18ppm for the other ring methyl) than any other signal, suggesting that this methyl is within the shielding cone of the phenyl ring. This is not plausible for structure **5a**, in which a specific *ring methine proton* would be shifted to low frequency instead, however, such a methyl shift is consistent with structure **4a** and also perhaps with **4b** or **5b**. As with the product of dihydroxylation,[3] the quaternary (in this case spiro) ring junction precludes using direct coupling connectivities alone to establish relative stereochemistry and ring conformation. A combination of nOe and DQF-COSY experiments at 600MHz were thus necessarily employed to distinguish between these structural possibilities.

The DQF-COSY spectrum shows couplings between protons[15] Me_A and H_G and between H_F and Me_B, identifying H_F and H_G as the ring methines. Characteristic cross peak patterns establish the three geminal

methylene pairs as H_C-H_J, H_H-H_D and H_E-H_K, while the large couplings[13] between H_J and H_H, and between H_K and H_H indicate *trans*-diaxial relationships between these. That there is no evidence of *trans*-diaxial coupling between H_G and either of the H_C-H_J geminal pair, militates against the methyls being equatorial (which would necessitate that H_G be axial and would thus possess a *trans*-diaxial coupling) and thus excludes both structures **4b** and **5b**. Since **5a** is inconsistent with the shift of Me_A [above] these data suggest diastereomer and conformer **4a** to be the sole product from the AE reaction of **1**/ent-**1** and **2**/ent-**2**.

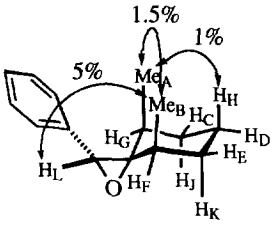

Figure 3: Assignments from DQF-COSY and key nOe data for **4a**.

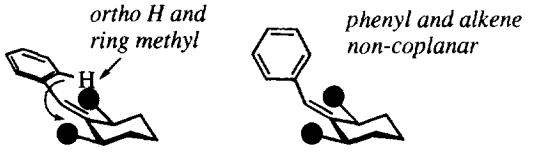

Figure 4

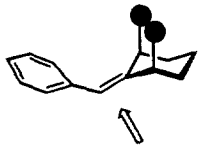

Figure 5

NOes were observed between H_H and Me_A (consistent with both being axial), and between Me_A and Me_B (only possible if these are both diaxial), supporting the ring conformational assignment from DQF-COSY. Critically, as regards diastereomeric assignment, only the higher frequency methyl (Me_B at 1.19ppm) shows an nOe to the benzylic proton H_L. This is consistent with Me_A being proximate to the phenyl ring but remote from H_L. Overall, these coupling connectivities and the observed nOes can *only* be consistent with one unambiguous diastereomer and *only* the ring conformation in which both methyl groups are axial, namely **4a**. From chiral g.c. indicating preferential consumption of ent-**2**, the enantioselectivity of this AE kinetic resolution with (*R*,*R*)-ligand favours formation of (2*S*)-4,8-dimethyl-2-phenyl-1-oxaspiro[2.5]octane, the indicated structure of **4a**.

Several considerations may contribute to the diastereospecific outcome of this epoxidation. Considering the reacting alkene substrate **2**/ent-**2**, for the conformer with two *equatorial* methyl groups, if alkene and phenyl were coplanar then the *ortho* hydrogen and ring methyl would be directly abutting, and thus the phenyl and alkene would have to be forced out of coplanarity (Figure **4**). ^{1}H NMR (600MHz) experiments indicate that this alkene exists in a conformation with the two methyls *diaxial*,[3,16] and thus the requirement for alkene/phenyl non-coplanarity in the diequatorial conformer presumably contributes to the energetics favouring ring flipping to the preferred conformation with the methyl groups axial. This conformational bias in solution has implications for control of diastereoselectivity in epoxidation (and also in the previously reported dihydroxylation reactions), in that addition occurs to the alkene face *anti* to the two diaxial methyls (Figure **5**). Furthermore, these electrophilic oxidations of this alkene are consistent with models proposed for stereoelectronic factors influencing the axial/equatorial selectivity of additions to exocyclic alkenes. Specifically, the Cieplak model[17] proposes the role of σ,σ^* interactions, where the bond to the incoming electrophile (in this case oxygen) forms *anti* to the most effective potential σ-bond donor at C2 (in this case both *axial* methyl groups at C2 *and* at C6). [There have been other studies of electrophilic additions to 2-methylexomethylene cyclohexane bearing substitution at only one α-carbon.[18]]

In summary, (*R*,*R*)-(-)-*N*,*N*'-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride catalyzed epoxidation of a mixture of **1**/ent-**1** and **2**/ent-**2** shows complete 'isomer' selectivity for **2**/ent-**2** (as does dihydroxylation), and this epoxidation is diastereospecific with addition *anti* to the ring methyls (as is dihydroxylation). The epoxidation shows kinetic resolution with k_{rel}=5.2 in favour of (2*S*)-4,8-dimethyl-2-phenyl-1-oxaspiro[2.5]octane **4**. The solution conformation of this spiro epoxide product has been unambiguously established by NMR as **4a** in which both methyl groups are axial.

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References and notes

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11. 40% conversion using catalytic AD conditions took ≥8 hrs. Furthermore, using an achiral version of the same dihydroxylation conditions was much slower than AD.
12. Chiralpak cyclodextrin-β chiral g.c. column. Retention times: (±)-**1** 13.1min; ent-**2** 13.4 min; **2** 13.6 min.
13. NMR and all other analytical data for **4a** were consistent. Selected data: ^{1}H NMR (600MHz, $CDCl_3$) δ 7.4-7.3 (m, 5H), 3.85 (s, 1H), 1.90 (dddd, 1H, *J*=13.2, 11.8, 5.0, 3.7Hz), 1.78 (m, 1H), 1.69 (m, 1H), overlapping signals centred at 1.62 (m, 1H) and 1.60 (m, 1H), 1.53 (m, 1H), overlapping signals centred at 1.44 (m, 1H) and 1.43 (m, 1H), 1.18 (d, 3H, *J*=7.5Hz), 0.60 (d, 3H, *J*=7.6Hz). Anal. calcd. for $C_{15}H_{20}O$ C, 83.3; H, 9.3. Found C, 83.0; H, 9.2% MS (FAB) MH^+ 217.
14. Stereoslectivity factor, k_{rel} calculated using the Kagan equation: $k_{rel} = \ln[1-C)(1-e.e.)]/[\ln[(1-C)(1+e.e.)]$, where *C*=conversion. Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.
15. Alphabetic labels refer to observed signals from lowest frequency (A) to highest frequency (L).
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