Diastereospecific dihydroxylation and highly efficient asymmetric dihydroxylation kinetic resolution of *cis/trans*-2,6-dimethylbenzylidenecyclohexane

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, UK M60 1QD*

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

Achiral dihydroxylation and catalytic asymmetric dihydroxylation (AD) lead to reaction of only the *cis* (and not the *trans*) isomer of 2,6-dimethylbenzylidenecyclohexane, dihydroxylation is diastereoisomer specific and an efficient kinetic resolution is achieved using AD.

While the catalytic asymmetric epoxidation (AE) developed by Sharpless' group has proved widely effective for kinetic resolutions of allylic alcohol substrates,[1] kinetic resolutions with catalytic asymmetric dihydroxylation (AD) using cinchona alkaloid-derived catalysts[2] have been more limited.[2b,3–5] These catalysts are derived from the *pseudo*-enantiomeric alkaloids dihydroquinine (DHQ) and dihydroquinidine (DHQD), the most versatile being the phthalazine derivatives $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ (used in this study). Since these are not enantiomers, enantioselectivity for a given substrate can differ between these ligands, and, similarly, kinetic resolutions can give differing outcomes. We were interested in the potential use of AD kinetic resolution of hindered axially symmetric substrates. Sharpless and VanNieuwenzhe reported the AD kinetic resolution of (unhindered) axially symmetric 4-*tert*-butylcyclohexane exomethylene derivatives.[6] However, hindered axially symmetric exomethylene cyclohexanes possessing substitution α to the alkene functionality, such as *trans*- and *cis*-2,6-dimethylbenzylidenecyclohexanes, **1**/*ent*-**1** and **2**/*ent*-**2** respectively, differ significantly from these previous axially symmetric substrates. Several anomalous results have recently been described for unusual substrate classes using AD.[7] We therefore undertook the current study of **1**/*ent*-**1** and **2**/*ent*-**2** as substrates for AD which should contribute to debate on mechanistic alternatives for the AD process.[8,9] The surprising observation that with 4-*tert*-butylcyclohexane exomethylene derivatives, substrate and catalyst facial selectivities were mismatching,[6] led us also to evaluate substrate selectivity of achiral dihydroxylation of **1**/*ent*-**1** and **2**/*ent*-**2**.

Herein we report that achiral and asymmetric dihydroxylation are both highly selective between the two epimeric sterically hindered exocyclic alkenes **1**/*ent*-**1** and **2**/*ent*-**2** (present as a *ca.* 1:4 mixture†), with the minor *trans*-2,6-dimethyl alkene **1**/*ent*-**1** being unreacted. Furthermore, AD of the reactive *cis*-2,6-dimethyl alkene **2**/*ent*-**2** leads to highly efficient kinetic resolutions which are amongst the best yet reported, providing access to optically pure diols (−)-**3** and (+)-**3**. Achiral dihydroxylation (in the absence of chiral ligand‡) of the reactive alkene **2**/*ent*-**2** could give either or both of (−)-**3**/(+)-**3** and (±)-**4**. Gratifyingly, dihydroxylation proceeded with complete substrate diastereoisomeric control, affording (−)-**3**/(+)-**3** [not (±)-**4**] in good yield.§ AD of the **1**/*ent*-**1** and **2**/*ent*-**2** mixture proceeded at a reasonable rate using the commercial AD-mix β [containing $(DHQD)_2PHAL$] or AD-mix α [containing $(DHQ)_2PHAL$].¶ Efficient kinetic resolution was observed providing either enantiomer of a single diastereoisomeric diol product derived from **2**/*ent*-**2** (**1**/*ent*-**1** was again unreacted). Both these optically enriched diols from the AD kinetic resolutions were identical by NMR‖ to racemic diol (−)-**3**/(+)-**3** obtained by achiral dihydroxylation, establishing that both AD reactions gave the same diastereoisomer as that obtained by achiral dihydroxylation.

Using the $(DHQD)_2PHAL$ ligand, diol (+)-**3** was obtained in optimum ee of 86% (entry 1, Table 1), with a selectivity factor, k_{rel} = 26.7.[11] In previously reported applications of these catalytic AD systems, it is almost always the DHQD-based ligands which perform best.[2b,3–6] However, in sharp contrast, we were surprised to find that the $(DHQ)_2PHAL$ ligand

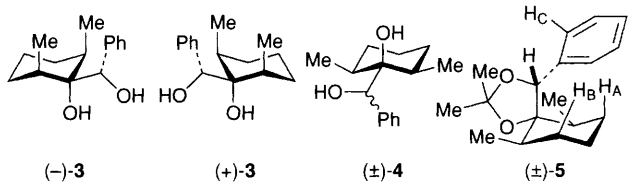
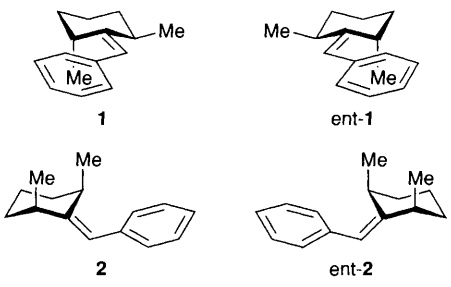


Table 1 AD kinetic resolution of **1**/*ent*-**1** and **2**/*ent*-**2**[a]

Entry	AD-mix[b]	*t*/h	Ee_{diol} (%)[c]	Diol[d] yield	Ee_{alkene} (%)[e]
1	β	3	86	23	27
2	β	8	79	35	47
3	β	16	71	46	74
4	β	24	65	50	83
5	β	48	60	58	98
6	α	3	≥95	24	30
7	α	8	≥95	40	61
8	α	16	92	45	75
9	α	24	88	49	88
10	α	36	82	53	100

[a] All experiments at ambient temperature (17 °C). Total mass recovery of isolated diol and residual alkenes was ≥90%. [b] Ligands: AD-mix β = $(DHQD)_2PHAL$; AD-mix α = $(DHQ)_2PHAL$. [c] Determined by integration of appropriate ^1H NMR resonances of menthyl carbonate derivatives.‖ [d] AD-mix β gave diol (+)-**3**; AD-mix α gave diol (−)-**3**. [e] Determined by chiral GC analysis.



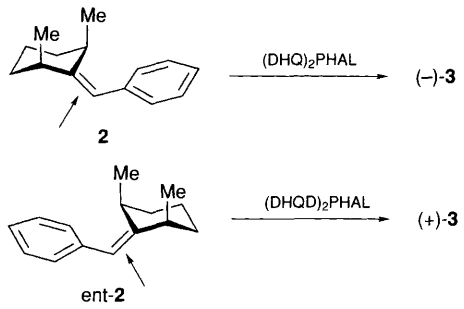


Fig. 1 Facial selectivities of kinetic resolutions of **2**/*ent*-**2** leading to chiral diols (−)-**3** and (+)-**3**

performed significantly better here, kinetic resolution affording diol (−)-**3** in very high enantiopurity, even at 40% conversion (entry 7, Table 1), with a significantly higher k_{rel} of 51.1.[11] These k_{rel} values are notable in comparison with previously reported AD kinetic resolutions,[6] being amongst the highest selectivities to date. Enantiomerically pure diol (+)-**3** was obtained by AD using $(DHQD)_2PHAL$ ligand of alkene enriched in enantiomer *ent*-**2** [residual from resolution using $(DHQ)_2PHAL$].

The diastereoisomeric outcome of these dihydroxylations may be rationalized on the basis that (axial) dihydroxylation of **2**/*ent*-**2** proceeds on the diaxial conformer it adopts** *anti* to the two axial methyls.[12,13] However, the inertness of the *trans*-2,6-dimethyl substrate (±)-**1** (after 10 days essentially no dihydroxylation is observed) remains anomalous.†† The results for AD resolutions are consistent with substrate control of dihydroxylation *anti* to the (diaxial) *cis*-2,6-dimethyl groups (as in the achiral case), but matched with catalyst facial selectivities based on the Sharpless mnemonic.[14] How these selective reactions of **2**/*ent*-**2** lead to the two enantiomeric diols (−)-**3** and (+)-**3**, respectively, is represented by the arrows in Fig. 1.

In summary, AD leads to efficient kinetic resolution of alkene substrates **2** and ent-**2**, providing the homochiral diols (−)-**3** and (+)-**3** in high enantiopurity (≥95% ee), with selectivity for (−)-**3** being the highest yet reported in an AD kinetic resolution. These results should prove significant to ongoing debate regarding the mechanism of AD.[8,9]

NMR spectra (600 MHz) were obtained on the EPSRC supported centre at Edinburgh University, and the authors also thank the Danish Government and the Mønsted Foundation for an MSc studentship (M. N.), and Professor K. B. Sharpless and Dr M. S. VanNieuwenzhe for helpful discussion and comments.

Footnotes

† The alkene substrate mixture was obtained in good yield (*ca.* 70–80%) by Wittig reaction of 2,6-dimethylcyclohexanone (a *ca.* 1 : 4 C_2 : *meso* mixture) providing an inseparable mixture of **1**/*ent*-**1** and **2**/*ent*-**2** in a 1 : 4 ratio. This appeared to be the thermodynamic ratio from equilibration experiments.

‡ Typical AD reaction conditions were used but replacing the chiral ligand by quinuclidine. A similar procedure has now been published (ref. 10), though in our case this proved substantially slower than the asymmetric variant.

§ The diastereoisomeric outcome of dihydroxylation was established by converting racemic diol (−)-**3**/(+)-**3** to its conformationally-constrained isopropylidene acetal derivative, which was identified as (±)-**5** by DQF-^{1}H–^{1}H-COSY and NOE experiments. At 600 MHz, H_B shows NOE enhancement from the phenyl *ortho* proton H_C (3.5%), while H_A is shifted to lower frequency at δ 0.61 (0.6 ppm lower than any other ring proton), accounted for by its location in the phenyl ring shielding cone (the adjacent methyl is also shifted to lower frequency relative to the other ring methyl substituent due to shielding). Five protons on different ring carbons possess *trans* diaxial couplings of 10.3–10.4 Hz. An X-ray structure confirms the structure of (−)-**3** (AD-mix α derived).

¶ Kinetic resolutions were carried out using commercial AD-mixes (1 mol% ligand and 0.02 mol% K_2OsO_4) in Bu^tOH–H_2O solvent. Optical rotations for pure diols: (−)-**3** $[\alpha]_D^{23}$ −13.7 (*c* 1.13, $CHCl_3$ and (+)-**3** $[\alpha]_D^{23}$ + 13.7 (*c* 3.35, $CHCl_3$).

‖ ^{1}H NMR of the menthyl carbonate derivatives of the two enantiomeric diols (−)-**3** and (+)-**3** corresponded to the two diastereoisomeric signals (dt at δ 4.39 and 4.49, respectively) in the ^{1}H NMR spectrum of the derivative of diol (−)-**3**/(+)-**3** from achiral dihydroxylation.

** ^{1}H NMR at 600 MHz indicates the diaxial conformation shown for **2**/*ent*-**2**, specifically through NOE between the two ring methyls and between these methyls and a C4 ring proton, along with a set of five protons on different ring carbons all showing diaxial coupling.

†† Notably, we found that 2-methylbenzylidenecyclohexane, lacking one ring methyl, yielded a mixture of diastereoisomeric products with modest selectivity. Thus, while the higher reactivity of **2** with respect to **1**, is determined by the relative configuration of the methyl substituents (*cis*-2,6-dimethyl over *trans*-2,6-dimethyl), the diastereoselectivity of reaction of 2,6-*cis*-dimethyl substrate **2**/*ent*-**2** requires two ring substituents.

References

1 V. S. Martin, S. S. Woodward, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237; R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 1993, ch. 4.4.

2 (*a*) R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*; ed. I. Ojima, VCH, New York, 1993, ch. 4.1; (*b*) H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.

3 J. M. Hawkins and A. Meyer, *Science*, 1993, **260**, 1918; B. B. Lohray and V. Bhusan, *Tetrahedron Lett.*, 1993, **34**, 3911; F. J. A. D. Bakkeren, A. J. H. Klunder and B. Zwanberg, *Tetrahedron*, 1996, **52**, 7901.

4 While this study was ongoing, a kinetic resolution–recycling protocol appeared, employing high ligand (5–10%) and osmium (1–35%) loadings: C. W. Jefford and G. Timári, *J. Chem. Soc., Chem. Commun.*, 1995, 1501.

5 E. J. Corey, M. C. Noe and A. Guzman-Perez, *J. Am. Chem. Soc.*, 1995, **117**, 10817.

6 M. S. VanNieuwenhze and K. B. Sharpless, *J. Am. Chem. Soc.*, 1993, **115**, 7864.

7 D. J. Krysan, *Tetrahedron Lett.*, 1996, **37**, 1375; M. Iwashima, T. Kinsho and A. B. Smith, *Tetrahedron Lett.*, 1995, **36**, 2199.

8 E. J. Corey, A. Guzman-Perez and M. C. Noe, *J. Am. Chem. Soc.*, 1995, **117**, 10805; P.-O. Norrby, H. Becker and K. B. Sharpless, *J. Am. Chem. Soc.*, 1996, **118**, 35, and references cited therein.

9 P.-O Norrby, H. C. Kolb and K. B. Sharpless, *J. Am. Chem. Soc.*, 1994, **116**, 8470; P.-O. Norrby and K. P. Gable, *J. Chem. Soc., Perkin Trans. 2*, 1996, 161.

10 J. Eames, H. J. Mitchell, A. Nelson, P. O'Brien, S. Warren and P. Wyatt, *Tetrahedron Lett.*, 1995, **36**, 1719.

11 k_{rel} Values calculated using the Kagan equation: H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 1988, **18**, 249.

12 Steric effects blocking dihydroxylation *syn* to these diaxial methyls. This dihydroxylation is also consistent with the Cieplak model involving σ,σ* interactions: C. R. Johnson, B. D. Tait and A. S. Cieplak, *J. Am. Chem. Soc.*, 1987, **109**, 5875.

13 (Salen)–Mn catalysed epoxidation of the **1**/*ent*-**1** and **2**/*ent*-**2** mixture also leads to a single diastereoisomer derived from **2**/*ent*-**2**, and kinetic resolution is observed: J. M. Gardiner, M. Nørret and I. H. Sadler, *Tetrahedron Lett.*, 1996, in the press.

14 K. B. Sharpless, W. Amberg, Y. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu and X.-L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768.

Received, 21st August 1996; Com. 6/05820E