Pergamon

Tetrahedron Letters, Vol. 35, No. 3, pp. 425-428, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0223-7

Anomalous Enantioselectivity in the Sharpless Catalytic Asymmetric Dihydroxylation Reaction of 1,1-Disubstituted Allyl Alcohol Derivatives

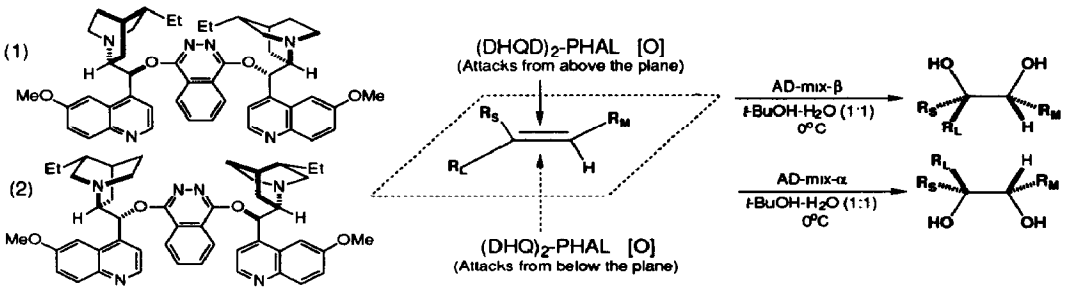
Karl J. Hale,* Soraya Manaviazar, and S. Andrew Peak

The Christopher Ingold Laboratories, Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, England.

Abstract: The Sharpless asymmetric dihydroxylation (AD) reaction has been examined on a number of 1,1-disubstituted allyl alcohol derivatives. In the majority of substrates studied, the product diols had ee's in the 11-91% range and had absolute stereochemistry **opposite** to that predicted using the Sharpless steric model.

Over the past year, the osmium-catalysed asymmetric dihydroxylation reaction of substituted alkenes with AD-mixes-α and -β has emerged as one of the most powerful and practical methods for controlling relative and absolute stereochemistry in secondary and tertiary alcohol derivatives.[1] Its applicability to a wide range of olefinic substrates has now been demonstrated on many occasions,[2] it delivering a variety of synthetically useful 1,2-diols in very high enantiomeric excess. AD-mix-β consists of a mixture of potassium ferricyanide, potassium carbonate and a catalytic quantity of potassium osmate blended with the chiral dihydroquinidine ligand $(DHQD)_2$-PHAL (**1**). It brings about dihydroxylation from the "top face" of an olefin when its largest substituent R_L is directed towards the observer, as shown in Scheme 1.[1] AD-mix-α, on the other hand, dihydroxylates the same olefin from its "bottom face" to generate the enantiomeric diol (Scheme 1).[1] AD-mix-α differs from AD-mix-β only in the nature of the chiral ligand present; thus, the former features the diastereomeric dihydroquinine-derived ligand $(DHQ)_2$-PHAL (**2**) instead of (**1**).

Scheme 1

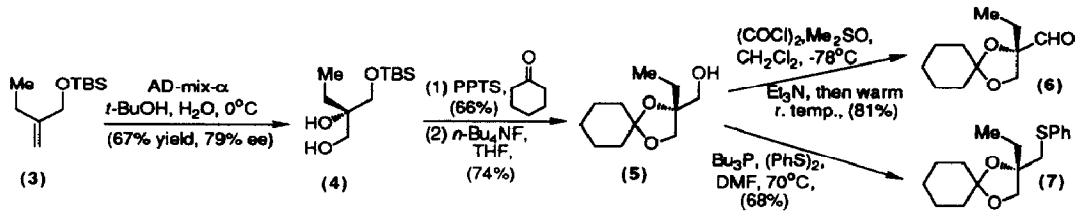


For all the alkenes studied to date, no deviations from the aforementioned pattern of facial selectivity have been observed. As a result, this face-selection rule of Sharpless *et al.*[1] has now become established as a reliable method for predicting absolute stereochemistry in the AD process. However, in recent months, we have had cause to question the reliability of this rule when it is applied to 1,1-disubstituted allyl alcohol derivatives. In our experience, such alkenes often react in their AD reactions with **opposite** enantioselectivity to the predictions of the Sharpless steric model, and the purpose of this letter is to discuss our findings.

The first "non-conformist" alkene that we encountered in the Sharpless AD reaction was molecule **3**.[3] Computer-assisted molecular modelling with the programme SYBYL, and space-filling molecular models of **3**,

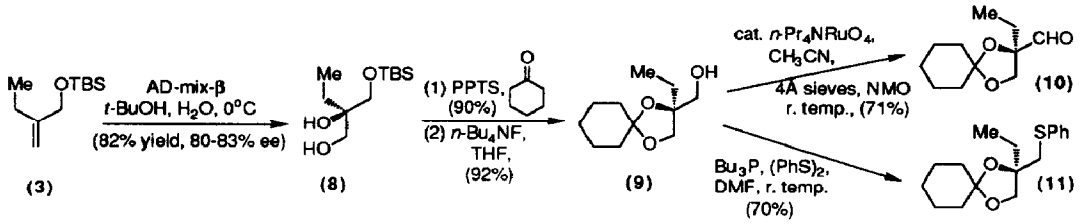
conclusively indicated that the *tert*-butyldimethylsilyloxymethyl substituent had significantly greater steric bulk than the ethyl group. As a result, when we applied the Sharpless facial-selectivity rule to **3**, we predicted that the (*R*)-diol would be the major enantiomer formed in the reaction with AD-mix-α. However, when we carried out this reaction we found, to our surprise, that the opposite (*S*)-enantiomer **4** was produced in 67% yield and 79%

Scheme 2



ee (Scheme 2).[4] The absolute configuration of **4** was unambiguously assigned after it was transformed into aldehyde **6**, and its optical rotation {$[\alpha]_D$ -6.9° (*c* 1.45, $CHCl_3$)} compared with that previously recorded in the literature for its enantiomer **10** {$[\alpha]_D$ +8.1° (*c* 1.43, $CHCl_3$) ca. 85% ee}.[5] Further proof of the stereochemistry in **4** came after it was converted into sulphide **7**; our material had $[\alpha]_D$ -3.0° (*c* 1.35, $CHCl_3$), which was opposite in sign to that previously reported for its enantiomer **11** {$[\alpha]_D$ +3.3° (*c* 1.35, $CHCl_3$)}.[5,6]

Scheme 3



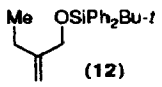
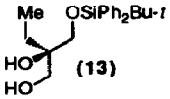
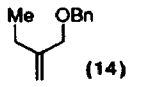
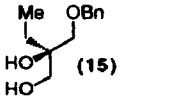
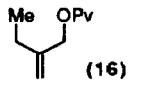
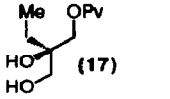
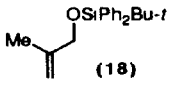
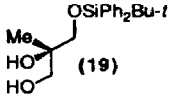
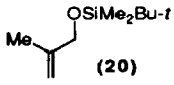
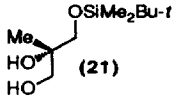
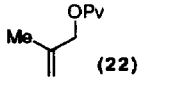
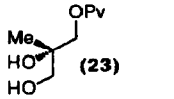
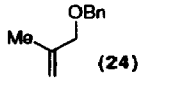
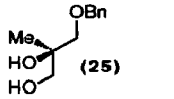
In view of these findings, we decided to investigate the reaction of olefin **3** with AD-mix-β, and observed that the (*R*)-diol **8** was formed in 80-83% ee (Scheme 3).[7] The absolute configuration of **8** was deduced after it was converted to aldehyde **10** {$[\alpha]_D$ +6.9° (*c* 1.45, $CHCl_3$) }and phenylthio ether **11** {$[\alpha]_D$ +4.4° (*c* 1.35, $CHCl_3$)}.[5,6]

Intrigued by this unexpected reversal of enantioselectivity, we explored the AD reactions of other 1,1-disubstituted allylic alcohol derivatives. One of the systems that we studied was alkene **12** (Table 1); here, the *tert*-butyldiphenylsilyloxymethyl group has even greater steric bulk than the ethyl substituent, and so the Sharpless model predicts that the (*S*)-diol will be the major enantiomer formed in the reaction with AD-mix-β. However, when the experiment was performed, the opposite (*R*)-enantiomer **13**[7] was isolated in 70% yield and 91% ee (Table 1). It was converted to (**10**) {$[\alpha]_D$ +6.4° (*c* 2, $CHCl_3$)} as in Scheme 3.

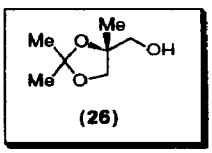
In light of these results, we next examined the asymmetric osmylation of alkenes **14** and **16** with AD-mix-β (Table 1). In both these substrates, the $-CH_2OBn$ and $-CH_2OPv$ groups are sterically more demanding than the ethyl group, and so the Sharpless face-selection rule predicts that the (*S*)-diols will be the respective products formed after treatment with AD-mix-β. However, both alkenes reacted with AD-mix-β to give predominantly the (*R*)-optical antipodes **15**[7] and **17**[7] (Table 1).

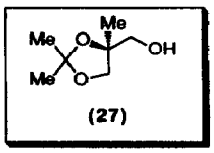
At this point, we investigated the AD reactions of the corresponding methallyl alcohol derivatives with AD-mix-α (Table 1). Molecular modelling with SYBYL again left us with no doubts that the methyl group would

Table 1. Asymmetric Dihydroxylation of 1,1-Disubstituted Allyl Alcohol Derivatives

Substrate	*AD-Mix*	*% Yield*	*%ee*	*Product*
 (12)	β	70	91	 (13)
 (14)	β	63	31	 (15)
 (16)	β	63	11	 (17)
 (18)	α	94	47	 (19)
 (20)	α	92	43	 (21)
 (22)	α	63	15	 (23)
 (24)	α	93	45	 (25)

be the smaller substituent in each of these systems. Accordingly, when we reacted **18**, **20**, **22** and **24** with AD-mix-α we expected the (*R*)-diols to be formed if the Sharpless predictive rule was to hold. However, for alkenes **18**, **20** and **22**, the opposite optical antipodes **19**, **21** and **23** predominated (Table 1). The absolute configuration of each product was unambiguously proven by transformation into known *(R)*-(+)-2,2,4-trimethyl-4-(hydroxymethyl)-1,3-dioxolane **26**.[8] The ee's of these three AD reactions were determined by 400 MHz ^{1}H NMR analysis of the *(R)*-MTPA esters derived from each of the samples of alcohol **26**. The only alkene in Table 1 that conformed to the Sharpless predictive model was compound **24**. It reacted with AD-mix-α to give the (*R*)-diol **25** in 45% ee and 93% yield; the product stereochemistry was assigned after it was converted into *(S)*-(-)-2,2,4-trimethyl-4-(hydroxymethyl)-1,3-dioxolane **27**[8] {$[\alpha]_D$ -2.5° (*c* 2, CH_2Cl_2); Lit.[8] $[\alpha]_D$ -5.33° (*c* 0.3, CH_2Cl_2)}.


(26)


(27)

Clearly, all these results emphasise the need for exercising great caution when applying the Sharpless face-selection rule to 1,1-disubstituted allylic alcohol derivatives. In closing, we hope that our findings will stimulate further work aimed at establishing the AD mechanism in these systems.[9]

Acknowledgement: We are very grateful to the SERC for supporting this investigation through project grant GR/G/43102. We thank Dr. Alex Drake and Mrs Beaulah Banfield (Birkbeck College, SERC National Chiroptical Service) for assistance with optical rotation and ORD measurements, and the London School of Pharmacy (ULIRS)-MS service for HRMS accurate mass determinations.

References and Notes

1. Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K-S.; Kwong, H-L; Morikawa, K.; Wang, Z-M.; Xu, D.; Zhang, X-L., *J. Org. Chem.*, **1992**, *57*, 2768.
2. See for example: Crispino, G.A.; Ho, P.T.; Sharpless, K.B., *Science*, **1993**, *259*, 64; Turpin, J.A.; Weigel, L.O., *Tetrahedron Lett.*, **1992**, *33*, 6563; Soderquist, J.A.; Rane, A.M., *Tetrahedron Lett.*, **1993**, 34, 5031; Tani, K.; Sato, Y.; Okamoto, S; Sato, F., *Tetrahedron Lett.*, **1993**, *34*, 4975; Jeong, K.-S; Sjö, P.; Sharpless, K.B., *Tetrahedron Lett.*, **1992**, *33*, 3833; Crispino, G.A.; Jeong, K.-S.; Kolb, H.C.; Wang, Z.-M.; Xu, D.; Sharpless, K.B., *J. Org. Chem.*, **1993**, *58*, 3785; Wang, Z-W.; Sharpless, K.B., *Synlett*, **1993**, 603.
3. Hale, K.J.; Bhatia, G.S.; Peak, S.A.; Manaviazar, S., *Tetrahedron Lett.*, **1993**, *34*, 5343.
4. Diol (**4**) was converted into alcohol (**5**) {$[\alpha]_D$ +1.25° (*c* 2, CH_2Cl_2)} and the ee determined by 400 MHz ^1H NMR analysis of the derived (*R*)-MTPA ester.
5. Magnus, P.; Mendoza, J., *Tetrahedron Lett.*, **1992**, *33*, 899; Magnus, P.; Mendoza, J.S.; Stamford, A.; Ladlow, M.; Willis, P., *J Am. Chem. Soc.*, **1992**, *114*, 10232.
6. We have repeated the route described by Magnus *et al.* (Ref. 5) for obtaining phenylthio ether **11**; the material that we obtained had $[\alpha]_D$ +3.0° (*c* 2, $CHCl_3$). {Lit.[5] $[\alpha]_D$ +3.3° (*c* 1.35, $CHCl_3$)}. We also converted this product into aldehyde **10** using the Magnus procedure; the compound **10** that we obtained (88% ee) had $[\alpha]_D$ +7.5° (*c* 2, $CHCl_3$) {Lit.[5] $[\alpha]_D$ +8.1° (*c* 1.43, $CHCl_3$) 85% ee}. In addition, compounds **10** and **11** that we prepared via the Magnus route, were indistinguishable in their 400 MHz ^1H and 100 MHz ^{13}C NMR, IR, and mass spectra from the same compounds prepared via the AD route (Schemes 2 and 3).
7. Enantiomeric excess for this diol was determined by 400 MHz ^1H NMR analysis, after it had been converted to alcohol **9** and its (*R*)-MTPA ester had been prepared.
8. Dung, J.-S.; Armstrong, R.W.; Anderson, O.P.; Williams, R.M., *J. Org. Chem.*, **1983**, *48*, 3592.
9. For current views of the AD mechanism, see: Corey, E.J.; Noe, M.C.; Sarshar, S., *J. Am. Chem. Soc.*, **1993**, *115*, 3828; Gobel, T.; Sharpless, K.B., *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 1329.
10. Selected analytical data:(**4**) $[\alpha]_D$ +4.0° (*c* 1, CH_2Cl_2); 100 MHz ^{13}C NMR ($CDCl_3$): δ 73.5, 67.3, 66.4, 26.9, 25.8, 18.2, 7.4, -5.56, -5.59; (**13**) $[\alpha]_D$ -1.3° (*c* 1, CH_2Cl_2); 100 MHz ^{13}C NMR ($CDCl_3$): δ 135.6, 135.5, 132.7, 129.9, 127.8, 74.1, 67.1, 66.0, 26.9, 26.8, 19.2, 7.3; HRMS: 359.2049; (**9**) {obtained from (**13**)} $[\alpha]_D$ -1.3° (*c* 2, CH_2Cl_2); 400 MHz ^1H NMR ($CDCl_3$): δ 3.81 (1/2 AB q, 1H, *J* = 8.6 Hz), 3.72 (1/2 AB q, 1H, *J* = 8.6 Hz), 3.52 (1/2 AB q, 1H, *J* = 11.2 Hz), 3.43 (1/2 AB q, 1H, *J* = 11.2 Hz), 2.06 (br s, 1H), 1.66-1.49 (complex m, 10H), 1.45-1.25 (complex m, 2H), 0.86 (t, 3H, *J* = 7.6 Hz); 100 MHz ^{13}C NMR ($CDCl_3$): δ 110.0, 83.3, 69.0, 64.9, 36.7, 36.3, 27.9, 25.0, 23.9, 23.8, 8.3; HRMS: 201.1496; (**15**) 100 MHz ^{13}C NMR ($CDCl_3$): δ 137.7, 128.4, 127.8, 127.6, 74.1, 73.6, 66.5, 27.2, 7.4; $[\alpha]_D$ -2.43° (*c* 1.52, CH_2Cl_2); (**19**) m.p. 59-61°C; $[\alpha]_D$ +0.7° (*c* 2, CH_2Cl_2); 100 MHz ^{13}C NMR ($CDCl_3$): δ 135.6, 135.5, 132.8, 132.6, 130.0, 127.9, 72.5, 69.1, 67.9, 26.9, 21.0, 19.3; Anal. Calcd. for $C_{20}H_{28}O_3Si$: C, 69.72; H, 8.19. Found: C, 69.46; H, 8.20; (**26**) {obtained from (**19**)} $[\alpha]_D$ +3.6° (*c* 2, CH_2Cl_2) {Lit.[6] $[\alpha]_D$ +5.2° (*c* 0.5, CH_2Cl_2) (for material with 100% ee)}; 100 MHz ^{13}C NMR ($CDCl_3$): δ 109.6, 81.3, 71.0, 66.8, 27.1, 26.9, 22.3; HRMS: 147.1031; all new compounds reported in this paper gave satisfactory 400 MHz ^1H and 100 MHz ^{13}C NMR and IR spectra, as well as HRMS and/or microanalyses within 0.4%.

(Received in UK 22 September 1993; revised 12 November 1993; accepted 5 November 1993)