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FACTORS AFFECTING STEREOCHEMICAL CONTROL IN DIRECTED HOMOGENEOUS HYDROGENATION OF α-HYDROXYALKYLACRYLATES

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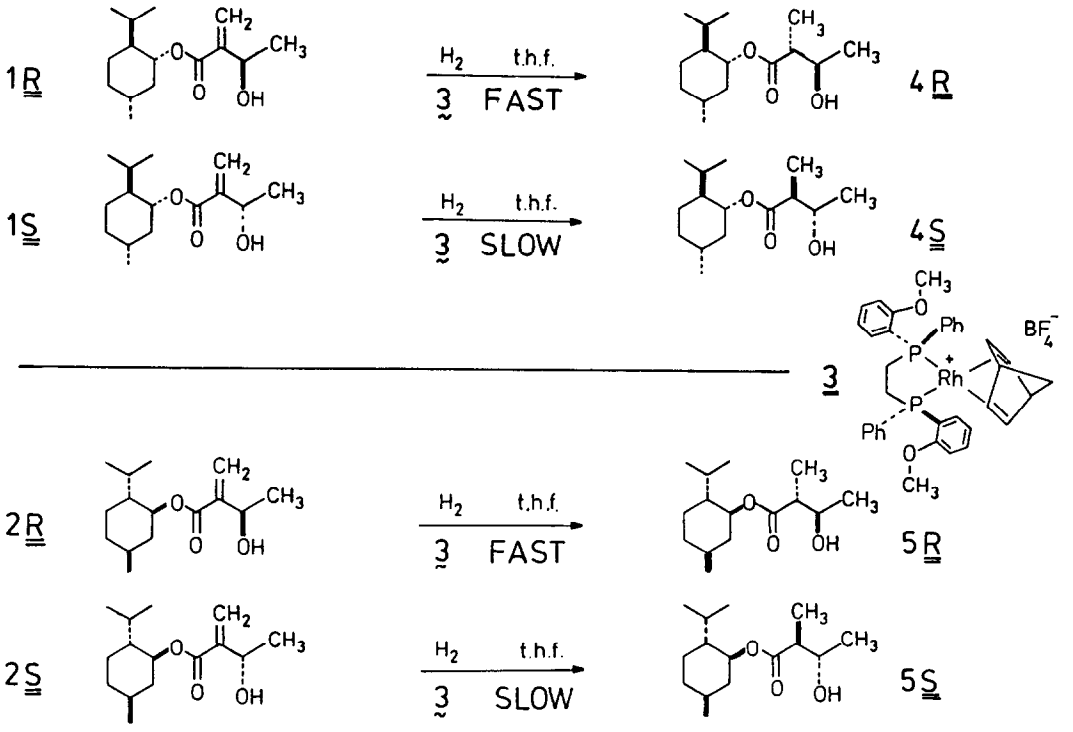
Summary The degree of asymmetric induction observed in hydrogenation of menthyl 3-hydroxy-2-methylenebutyrates catalysed by DIPAMP-Rh^+ complexes is strongly dependent on the configuration of the menthyl group. For a related methyl ester syn as well as anti-reduction product is formed with high enantioselection.

In a previous paper,[1] hydrogenation of α-(hydroxyalkyl) acrylates was shown to proceed with high anti-selectivity and kinetic resolution of the starting material was achieved with optically active catalysts. The maximum discrimination between enantiomers was 6.5: 1, and this requires reduction to >70% for recovery of starting material with better then 90% E.e.. We report further investigation of the factors controlling selectivity, including double asymmetric induction[2] employing the corresponding menthyl esters.

The readily synthesised l-menthyl acrylate[3] reacted with CH_3CHO (neat, 20°, 7d., 5 mol.% DABCO)[4] to give, after chromatographic purification on silica, the corresponding ester 1. This was apparently homogeneous by ^1H N.m.r. but a 58: 42 mixture of diastereomers differing in their configuration at C3' by ^{13}C N.m.r.,[5] $[\alpha]_D^{20}$=-75.3 (0.66, MeOH). In similar manner, d-menthyl acrylate reacted with CH_3CHO to give a 53:47 mixture of diastereomers 2.

Reduction of the l-menthyl ester mixture was carried out in t.h.f. solution at 0°, employing 1 mol.% of the DIPAMP derived rhodium catalyst 3.[6] Reaction was stopped after 8-60% hydrogenation is different experiments, and the catalyst removed by filtration through silica. The two diastereomers 1R and 1S were reduced to different extents, and this could conveniently be analysed by ^{13}C N.m.r., assuming on precedent[1] that the R-isomer was the more rapidly reduced and that the product has anti-configuration. Thus 1R gives rise to 4R, and 1S gives rise to 4S, and the former pathway is very strongly preferred. A similar series of experiments was carried out with the l-menthyl ester mixture 2, where the selectivity was observed to be very much lower (Figure 1). Accordingly it was shown that 1R is reduced about twice as rapidly as 1S with the achiral rhodium catalyst derived from $Ph_2P(CH_2)_4PPh_2$.



These results clearly demonstrate that the configuration of the ester moiety plays a significant part in controlling the stereoselectivity of reduction. The effect is present to some extent even when the catalyst is achiral, and may originate in different interactions between the ester side-chain and P-aryl groups in the ligand. The model illustrated in Figure 2 is based on X-ray crystallographic data available for menthyl esters.[7] Although speculative at present, it does help to visualise the origin of double asymmetric induction.

All rhodium-catalysed hydrogenations of α-(hydroxyalkyl)acrylates are highly anti-selective; under the "worst" experimental conditions (H_2, CH_3OH, $[Ph_2P(CH_2)_4PPh_2/Rh^+]$), only 2.5% of syn-isomer is formed from racemic compound 6. Reduction of the same compound in CH_3OH was carried out with DIPAMP Rh^+ and chromatographic separation of starting material and product effected at 65% reaction. The product 7 was 99.7% anti with the 2R 3S enantiomer predominating, and the starting material better than 90% optically pure S-enantiomer. The latter was again hydrogenated to 65% reaction with RR-DIPAMP Rh^+ in a much slower reaction and product reisolated. In this case the selectivity is 97.4%-anti, (2S 3R) demonstrating a much stronger tendency for formation of the syn-product (2R 3R)from the S-enantiomer of starting material. This means that enantioselective reduction always involves the preferential addition of H_2 to the Si-face of the double-bond giving R-configuration at the new chiral centre in both syn and anti-products, which in turn implies that factors governing enantioselectivity are distinct from those controlling diastereoselectivity, the latter being governed by internal non-bonded interactions of the coordinated substrate.[1] The observation encourages further efforts to discover a syn-selective directed hydrogenation.

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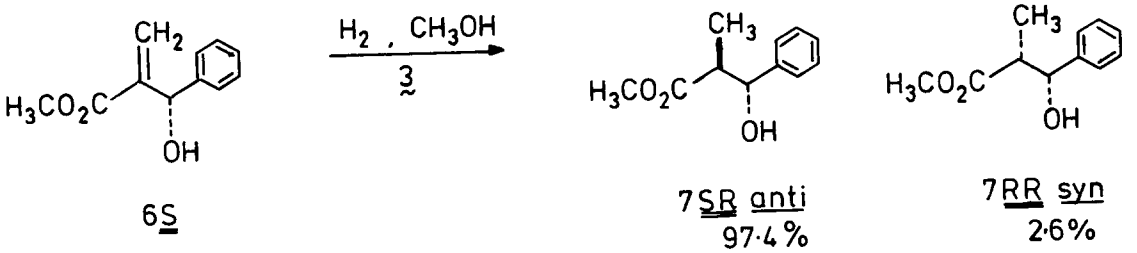

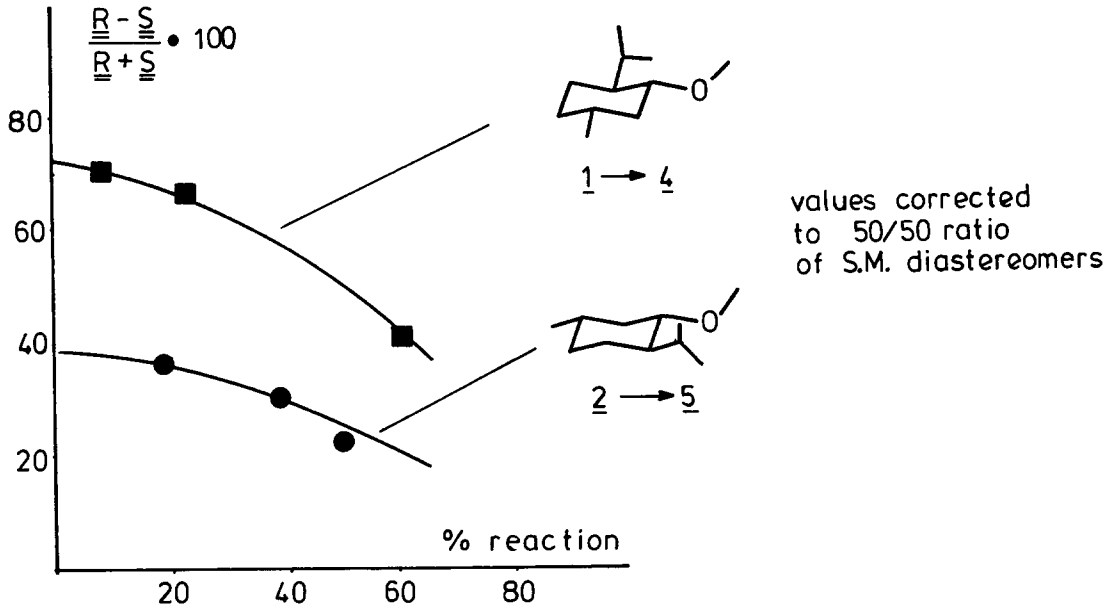

Figure 1 Diastereomer excess in recovered 4 or 5 for reductions of menthyl esters 1 and 2 to varying extents with RR-DIPAMP in t.h.f.

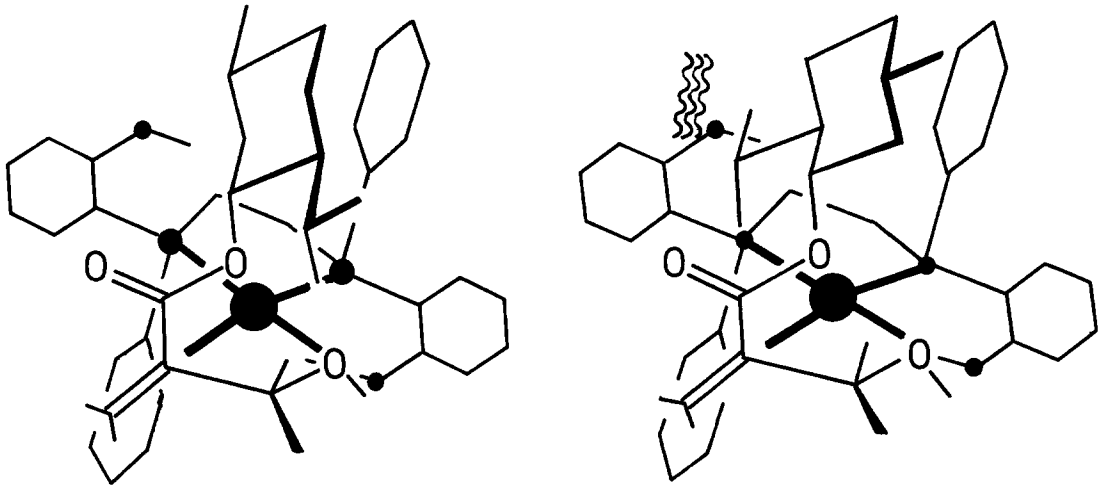

Figure 2 Coordination of menthyl esters 1R and 2R to DIPAMPRh$^+$. Unfavourable steric interactions between arene and iso-propyl are apparent in the latter case when the CH_2=C-C=O moiety is cis-related.

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3. By the general method of W. Oppolzer, M. Kurth, D. Reichlin, C. Chapuis, M. Mohnhaupt and F. Moffatt, Helv. Chim. Acta, 1981, 64, 2802.
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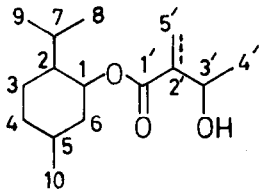
5. Based on literature assignments for menthyl acetate[4]; Compound 1R (≡ 2S): C1' 166.1, C2' 144.2, C5'(123.17), C1 74.76, C3' 67.00, C2 47.11, C6 40.77, C4 34.18, C5 31.36, C7 26.37, C3 23.51, C4' 22.04, C10 21.91 C8, 9 20.65, 16.33 p.p.m.; Compound 1S (≡ 2R), separated resonances only: C5' (123.25), C3' 67.05, C7 26.92, C3 23.56, C4' 22.14, C9 16.38. Compound 4R (≡ 5S): C1' 176.0, C1 74.38, C3' 69.26, C2 47.11, C2' (46.96), C6 40.74, C4 34.21, C5 31.36, C7 26.21, C3 23.35, C10 21.93, C8,9 20.70, 16.13, C4' 14.11; compound 4S (≡ 5R), separated resonances only: C1 74.50, C3' 69.47, C2 47.07, C2' (46.92), C6 40.91, C9 16.05 p.p.m. Spectra were recorded in $CDCl_3$ solution at 125.7 MHz.



Chirality of 3' specified

6. This catalyst, which always had to be prepared in situ previously is now available in analytically pure form by a new procedure, as follows:

   To a yellow solution of bicyclo [2,2,1] heptadiene-2,4-pentanedionatorhodium (0.118 g, 0.4 mMol)[9] in thf (5 ml) was added trimethylsilyl trifluoromethanesulphonate (0.089 g, 1 equiv). The resulting yellow-orange solution was cooled to -78° before adding a solution of RR-DIPAMP (0.185 g)., 1.0 equiv) in thf (10 ml., precooled to -78°) with stirring under Ar. The solution was then stirred for a further 30 m. at -78°, brought to 20° and evacuated to half its volume. This solution was then added to vigorously stirred ether (100 mls, maintained at 0°). The bulk of supernatant liquid was removed from the bright orange precipitate before adding further Et_2O (50 ml.) filtering and drying in vacuo. There was thus obtained the complex (3) (0.248 g, 77% as an orange powder, m.p. >190° (dec). N.m.r. (^1H, CD_2Cl_2, 300 MHz): δ 7.67 - 6.95 (18H, m, Ar) 5.21 5.06 (brs, 2H,. 2H, vinyl) 4.15 (brs, 2H, C-H) 3.65 (s, 6H, OCH_3) 2.33 (brm, 4H, P-CH_2) 1.77 (s, 2H, CH_2); (^{31}P, CH_2Cl_2; 101 MHz) δ 45.9 (d, J_{PRh} = 159 Hz).
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