Effective Kinetic Resolution in the Asymmetric Hydrogenation of α-(Hydroxyalkyl)acrylate Esters

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The title compounds are reduced by H_2 and biphosphine–rhodium catalysts with high *anti*-selectivity; asymmetric catalysts give up to 7 : 1 discrimination between the enantiomers of starting material.

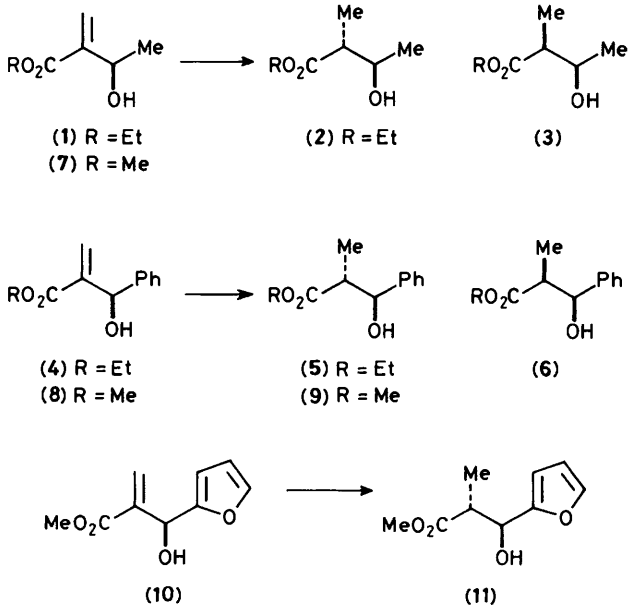
The stereoselective formation of α-substituted β-hydroxy-esters has generated much recent effort, because of their widespread applicability in natural product synthesis. Aldol-related methods are frequently unselective[1] but preference for the *anti*-isomer pertains with some modified enolate nucleophiles.[2] Chemical[3] or enzymological[4] reduction of α-alkyl-β-ketoesters is *syn*-selective, whereas the *anti*-isomer may be obtained by direct alkylation of the dianion of α-hydroxyesters.[4,5] We report an alternative and highly *anti*-selective preparation *via* hydrogenation.

Ethyl 3-hydroxy-2-methylenebutanoate (**1**) is readily prepared from MeCHO and ethyl propenoate.[6] It is rapidly and quantitatively reduced by the rhodium catalysts previously used in directed hydrogenation[7] with exclusive formation of the *anti*-isomer (**2**). Even in MeOH solution, where competitive solvent binding had vitiated hydroxyl-induced selectivity[7] in earlier examples, the *syn*-isomer (**3**) is undetected (Table 1). The related arylpropanoate (**4**) is hydrogenated with comparable selectivity to (**5**) in CH_2Cl_2, but the *syn*-isomer (**6**) is observed when reaction is conducted in MeOH.

Cationic rhodium complexes are uniquely effective for selective reduction of α-(hydroxyalkyl)acrylates. With 5% Pd–C, hydrogenation is unselective and homogeneous catalysis by $ClRh(PPh_3)_3$ is very slow and ineffective. Surprisingly the iridium complex $py(PCx_3)(C_8H_{12})IrPF_6$ (py = pyridine, Cx = cyclohexyl), which is useful for cyclic allylic and homoallylic alcohols,[8] is a poor catalyst for reduction of either (**1**) or (**4**).

The optically active ligand dipamp† has proved efficient in asymmetric hydrogenation of a range of α-disubstituted alkenes, particularly when an electron withdrawing group is attached,[9] giving superior results with unsaturated esters.[10] When its rhodium complex was used for reduction of compound (**1**) in MeOH the enantiomers were reduced at different rates [60% enantiomeric excess (e.e.) in recovered (**1**) at 75% reaction] with (−)-(*R,R*)-(**2**)[11] formed preferentially. Much higher discrimination is obtained in tetrahydrofuran, thf, employing the Me ester (**7**) for ease of analysis. At ambient temperature the rate ratio k_R/k_S is 4.5 : 1, rising to 6.5 : 1 when hydrogenation is carried out at 0 °C. Superior results were obtained with aryl esters[6] (**8**) and (**10**) which were respectively reduced to compounds (**9**)[13] and (**11**)[14] exclusively. Other asymmetric catalysts give inferior results, but the high *anti*-selectivity was sustained in all cases (Figure 1).

Since the enantiomeric rate ratio is constant (within experimental error) up to 95% e.e., a single mechanistic pathway is indicated. Preferential formation of the (*R,R*)-diastereoisomer of (**2**) in dipamp reductions suggests a



The enantiomer which reacts faster with dipamp–Rh is shown.

† *Abbreviations:* dipamp = (*R,R*)-1,2-bis[(2-methoxyphenyl)phenylphosphino]ethane; chiraphos = (*S,S*)-2,3-bis(diphenylphosphino)-butane; diop = (*R,R*)-4,5-bis(diphenylphosphino)-2,2-dimethyldioxolane.

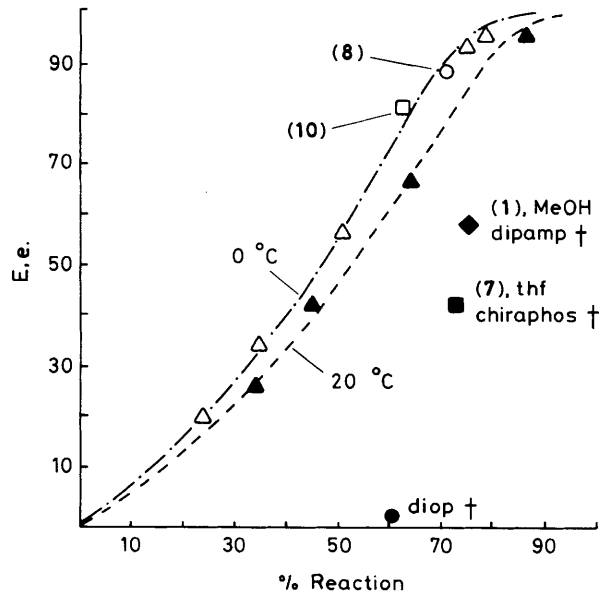


Figure 1. E.e. in recovered substrate *vs.* % reaction, *cf.* ref. 12. Samples were analysed by g.c. (ov 225, 6') and separated by preparative g.c. or flash column chromatography, then reanalysed by n.m.r. spectroscopy (tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III); $CDCl_3$). Dipamp-derived catalysts were prepared *in situ* (9 mg biphosphine, 14 mg $Rh(C_7H_8)_2BF_4$, 1 ml thf, H_2; then filter solution into reaction vessel containing 250 μl substrate, 4 ml thf), others by standard procedures. For substrate (**7**) dashed lines represent 4.5 : 1 (20 °C) and 6.5 : 1 (0 °C) enantiomeric rate ratio. Others (*R*-configuration at new chiral centre first) ● 1 : 1.05; ■ 1 : 2.1; ◆ 2.5 : 1; ○ 6.2 : 1; □ 7.1 : 1.

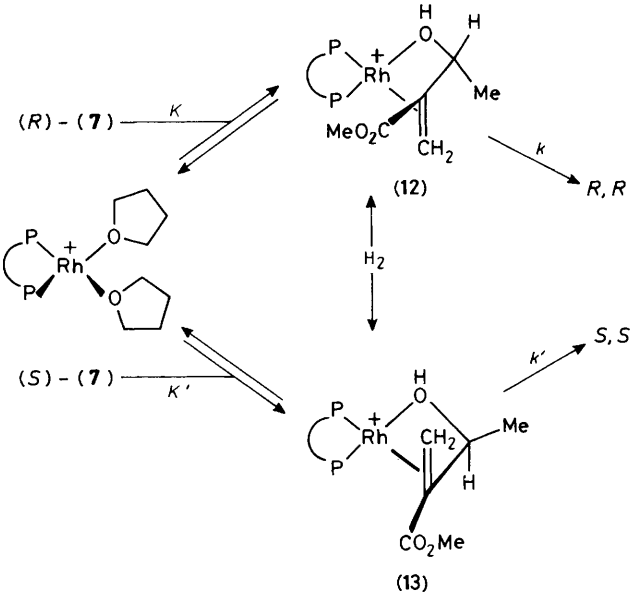


Figure 2. Kinetic resolution *via* chelate binding of the hydroxy alkene moiety.

similarity to asymmetric hydrogenation of enamides, with the MeCHOH functionality playing the same role as NHCOR.[15] *anti*-Selectivity over-rides enantioselectivity and hence only two intermediate complexes (**12**) and (**13**) need to be considered. In the absence of further evidence, we think it probable that the enantiomeric rate ratio is approximated by $kK/k'K'$ (Figure 2).

Table 1. Reduction of α-(hydroxyalkyl)acrylates.[a]

Compound	Catalyst	Solvent	*syn* : *anti*
(**1**)	$Ph_2P(CH_2)_4PPh_2$–Rh^+	MeOH	1 : 100[c]
(**1**)		CH_2Cl_2[b] or thf	1 : 100[c]
(**1**)	5% Pd–C	thf	1 : 2.5
(**4**)	$Ph_2P(CH_2)_4PPh_2$–Rh^+	MeOH	1 : 40
(**4**)	$Ph_2P(CH_2)_4PPh_2$–Rh^+	CH_2Cl_2	1 : 100[c]
(**4**)	5% Pd–C	thf	1 : 1.2

[a] *Conditions:* 20 °C, 1 atm H_2, 100 : 1 catalyst : substrate, reaction time 1—2 h. [b] Carried out on 5 g scale (100 mg catalyst) without loss of yield. [c] Minimum value.

These results provide a viable route to optically active α-(hydroxyalkyl)acrylates with >90% e.e. at 70% conversion in all three cases studied. Apart from weak diastereoselectivity in asymmetric hydrogenation of dehydrodipeptides,[16] the prospect of kinetic resolution in homogeneous hydrogenation has not been realised previously. The simplicity of the present examples makes extension probable.

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