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Catalytic Racemisation of Alcohols: Applications to Enzymatic Resolution Reactions

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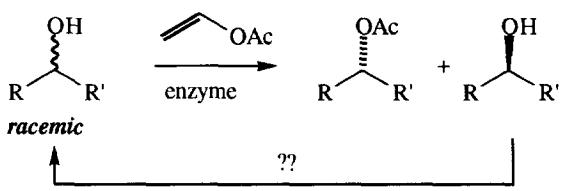
Abstract: The racemisation of enantiomerically enriched alcohols has been achieved using a catalyst in the presence of a suitable ketone. Aluminium, rhodium or iridium catalysts have been successfully employed. This methodology allows recycling of substrate for enzymatic resolution reactions.

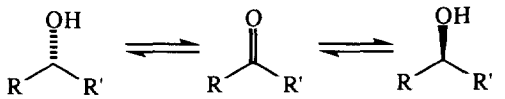
The enzymatic kinetic resolution of alcohols is a well studied reaction.[1] In the presence of a suitable acyl donor, one enantiomer of alcohol is selectively converted into the corresponding ester. For an efficient synthetic process, the less reactive enantiomer of alcohol should be recycled to racemic starting material.



Scheme 1. Enzymatic kinetic resolution

Ideally, the racemisation procedure should be feasible in the presence of the enzyme.[2] If this is to be possible, not only must the enzyme and racemisation reagents be able to co-exist, but the stereochemical integrity of the acetate must be unaffected, and the conditions must not cause a non-enzymatic esterification pathway to take place.[3] Specific categories of alcohol such as lactols[4] and cyanohydrins[5] have been elegantly applied to dynamic resolution reactions.[6] However, our objective is to find a method which could become more generalised.

With these attributes in mind we have examined the catalytic racemisation of alcohols by temporary oxidation, followed by reduction using hydrogen transfer catalysts.



Scheme 2. Racemisation by temporary oxidation

We have investigated the racemisation of S-(–)-phenethyl alcohol **1** in the presence of the corresponding ketone **2** and a suitable catalyst. There are many literature reports of metals capable of catalysing the transfer hydrogenation between ketones and alcohols,[7] including the use of rhodium,[8] iridium,[9] ruthenium[10] and aluminium[11] catalysts. Table 1 demonstrates that the racemisation of alcohols can be achieved using these catalysts (*a low ee is a good result!!*)

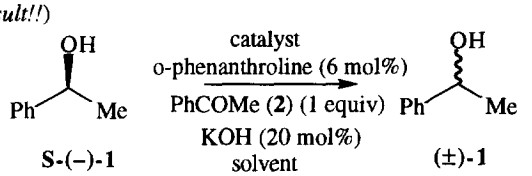


Table 1. Racemisation of S-(–)-**1** with metal catalysts

catalyst	time	solvent[a]	yield (%)	ee (%)[b]
3 mol% $[Ir(coe)Cl]_2$	24 h	CH_2Cl_2	70	8
20 mol% $Al(OiPr)_3$[c]	72 h	C_6H_{12}	80	0
3 mol% $Ru(PPh_3)_3Cl_2$	48 h	CH_2Cl_2	71	51
3 mol% $[Rh(cod)Cl]_2$	72 h	CH_2Cl_2	69	39
3 mol% $Rh_2(OAc)_4$[d]	72 h	CH_2Cl_2	73	0

[a] The reactions were conducted under reflux. [b] Enantiomeric excess was determined by chiral hplc using a Chiralcel OD column (hexane:isopropanol 99:1). [c] In this case no potassium hydroxide or o-phenanthroline were added. [d] Using 0.35 equiv of **2**, see Table 2

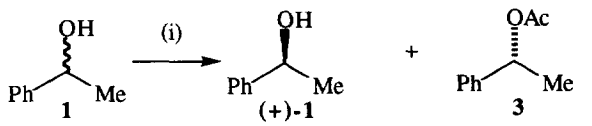
At the end of the reaction, the 1:1 ratio of phenethyl alcohol **1** to acetophenone remained unchanged, and we therefore examined the use of catalytic amounts of ketone to effect the racemisation process. Whilst the rate of reaction was slower, the use of sub-stoichiometric amounts of ketone still provides a useful method for the racemisation of phenethyl alcohol, as demonstrated in Table 2.

Table 2. Racemisation of S-(–)-**1** using sub-stoichiometric quantities of acetophenone

catalyst	solvent	time	PhCOMe	yield (%)	ee (%)
3 mol% $[Ir(coe)Cl]_2$	CH_2Cl_2	24 h	1 equiv	70	8
3 mol% $[Ir(coe)Cl]_2$	CH_2Cl_2	72 h	0.45 equiv	63	11
3 mol% $[Ir(coe)Cl]_2$	CH_2Cl_2	72 h	0.3 equiv	63	39
3 mol% $[Ir(coe)Cl]_2$	CH_2Cl_2	24 h	0.6 equiv	59	43
20 mol% $Al(OiPr)_3$[a]	C_6H_{12}	66 h	0.5 equiv	73	1
3 mol% $Ru(PPh_3)_3Cl_2$	CH_2Cl_2	96 h	0.55 equiv	70	58
3 mol% $Rh_2(OAc)_4$	CH_2Cl_2	120 h	0.35 equiv	73	0
3 mol% $Rh_2(OAc)_4$	CH_2Cl_2	120 h	0.5 equiv	59	3

[a] No KOH or o-phenanthroline were added

The racemisation methodology is of use in conjunction with enzymatic kinetic resolutions. Thus, the alcohol **1** undergoes a kinetic resolution with PFL to give the alcohol enriched in one enantiomer, as well as the ester **3** also enriched in one enantiomer. It is now possible to racemise the remaining alcohol using the hydride transfer methodology, and recycle.



91% ee, 45 % yield >98% ee, 47 % yield

conditions: (i) *Pseudomonas fluorescens* Lipase, vinyl acetate, 40 °C, 24 h

However, simple kinetic resolutions are limited by maximum conversions of 50% or recycling. We therefore turned our attention towards the possibility of a dynamic resolution employing the enzyme and catalyst in the same reaction vessel, thereby generating enantiomerically enriched products with greater than 50% conversion in a single pot. In Table 3, our preliminary results are summarised. Whilst the enantioselectivity of the reaction is somewhat compromised (sometimes severely),[12] the principle of the dynamic resolution has been demonstrated. Thus, when the product is formed with 76% conversion and with 80% ee, the enantioselectivity is higher than it should be theoretically if a simple kinetic resolution was in operation (at this conversion, the highest possible enantioselectivity of the ester should be 32% ee). In principle, provided the starting alcohol remains racemic throughout, it should be possible to obtain 100% conversion to the acetate with an enantioselectivity comparable to the enzyme only system. Either the transition metal is compromising the selectivity of the enzyme, or perhaps the transition metal is catalysing an achiral transesterification. We intend to investigate this matter further.

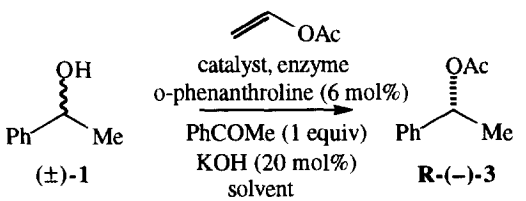


Table 3. Enzyme and catalyst combinations

catalyst	enzyme	time	temp.	conv. (%)	ee (%)	max. th. ee (%)[g]
3 mol% $[Ir(coe)Cl]_2$[a]	PSL[b]	96 h	60 °C[c]	91	**2**	10
20 mol% $Al(OiPr)_3$[e]	PFL	72 h	80 ° C[c]	86	**20**	16
3 mol% $[Rh(cod)Cl]_2$	PFL	144 h	50 °C[d]	76	**80**	32
2 mol% $Rh_2(OAc)_4$[f]	PFL	72 h	20 °C[c]	60	**98**	67

[a]Base activated Amberlite was used in place of KOH [b] *Pseudomonas species* Lipase. [c]Conducted in vinyl acetate/cyclohexane (2:1). [d]Conducted in vinyl acetate/dichloromethane (3:1). [e] No added KOH or o-phenanthroline. [f]No added KOH [g] This column refers to the maximum ee expected at this conversion for a simple kinetic resolution

In summary, we have shown that it is possible to racemise alcohols using a number of catalytic systems, and that there are exciting prospects for the possibility of a system where a dynamic resolution reaction can be effected. We are currently examining other enzyme/catalyst combinations to improve the selectivity of the dynamic resolution reaction, as well as investigating immobilisation strategies in an attempt prevent the enzyme and catalyst from interfering with one another. Additionally, we are looking at the applicability of the racemisation reaction to other substrates.

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12. The use of the higher temperature (up to 80 °C) was not responsible for the lower selectivities. Thus, the PFL catalysed acylation of phenethyl alcohol **1** at 80 °C in the absence of any co-catalyst afforded the product in 95% ee at 43% conversion after 24 hours.

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