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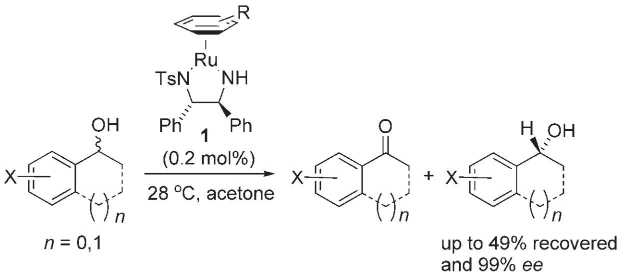
Asymmetric Catalysis Using Air: Clean Kinetic Resolution of Secondary Alcohols

*Martin Wills**

aerobic oxidation · alcohols · kinetic resolution

Enantiomerically pure secondary alcohols are pivotal compounds in organic synthesis, being represented in many important target molecules, intermediates, and reagents. An attractive approach to their synthesis is through kinetic resolution by selective oxidation of one enantiomer of a racemic mixture by using a catalyst. Although this method (even when the selectivity is perfect) generates "unwanted" ketone, this can be reduced and recycled. Alternatively, selective oxidation of one of two alcohols in a *meso* substrate can, in principle, give a product in 100% conversion and enantiomeric excess (*ee*).

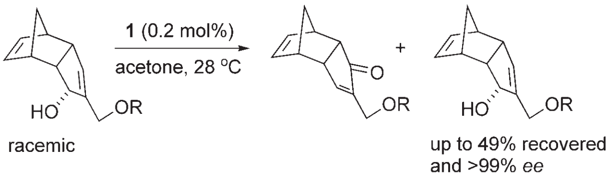
Oxidative kinetic resolution (KR) of alcohols requires an acceptor for the hydrogen atoms generated in the reaction. Several groups have reported the use of a "sacrificial" ketone, which must be used in excess, for this role. Acetone is often used, since its reduction product is readily removed. One of the most significant recent contributions to this area was in 1997, when Noyori, Ikariya et al. reported the use of complex **1** for the kinetic resolution of aryl alcohols (Scheme 1).[1]



Scheme 1. Kinetic resolution of alcohols with a ruthenium complex.

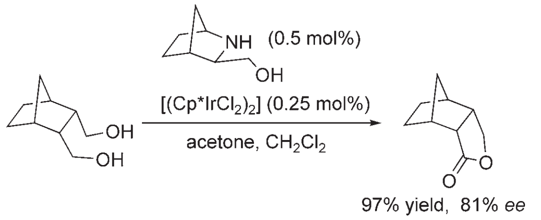
With this catalyst, in solution in acetone, alcohols of up to 99% *ee* were formed, and *meso* diols could also be converted into enantiomerically enriched ones.

Catalyst **1** works by removing two hydrogen atoms at a time from a substrate, via a six-membered cyclic transition state (see also Figure 1), to give a metal hydride complex. These two hydrogen atoms are then transferred to a molecule of acetone, thus regenerating the catalyst for a further cycle. Other catalysts have been used in a similar manner.[2–8] This process has been employed to good effect in some quite complex synthetic challenges; Masaguer et al.,[4] for example, employed the original Noyori system for the kinetic resolution of benzocycloalkanols. Ogasawara et al.[5] performed kinetic resolutions of 2-cyclopentenols derived from cyclic precursors (Scheme 2) and were able to isolate products of >99% *ee*, in 49% conversion in the best cases.



Scheme 2. Kinetic resolution of 2-cyclopentenols. R = H, *tert*-butyldimethylsilyl, Piv = pivaloyl.

The synthesis of lactones from diols avoids the problem of reversibility by combining a second oxidation reaction (i.e. of the in situ formed lactol) to a thermodynamically more stable carboxy group. Hiroi et al. employed an iridium(III) complex of an amino alcohol in this process,[6] and extended the application to an asymmetric variant through the use of a chiral ligand.[7] Enantiomeric excesses of up to 81% were realized in this process, in 97% yield (Scheme 3). Ikariya et al. employed a versatile and highly active Cp*Ru^{II} complex (TOF > 100 h^{-1}; Cp* = pentamethylcyclopentadienyl) con-



Scheme 3. Desymmetrization of *meso* diols with an iridium(III) amino alcohol catalyst.

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[*] Prof. M. Wills
Department of Chemistry
The University of Warwick
Coventry, CV4 7AL (UK)
Fax: (+44) 24-7652-3260
E-mail: m.wills@warwick.ac.uk
Homepage: http://www2.warwick.ac.uk/fac/sci/chemistry/research/willsgroup/

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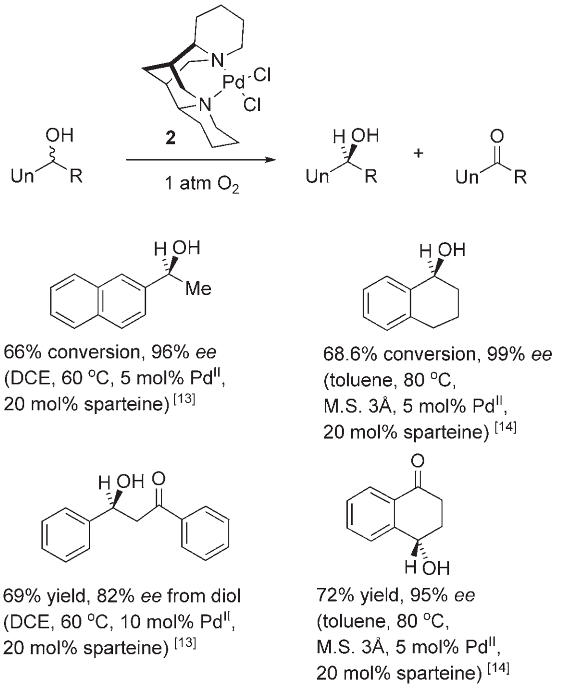
taining a P,N donor ligand, for lactone synthesis from diols.[8] In a clever variation on this theme, Williams et al.[9] have employed 1,4-butanediol as a hydrogen source for asymmetric transfer hydrogenation of ketones.

In certain cases, where hydrogen is transferred from one part of a substrate to another in an isomerization, a hydrogen acceptor is not required, since the catalyst itself is capable of the hydrogen transfer process.[10] Ikariya et al. have employed this process, using a Ru^{II}/P,N donor ligand system, in a very concise asymmetric synthesis of muscone.[11]

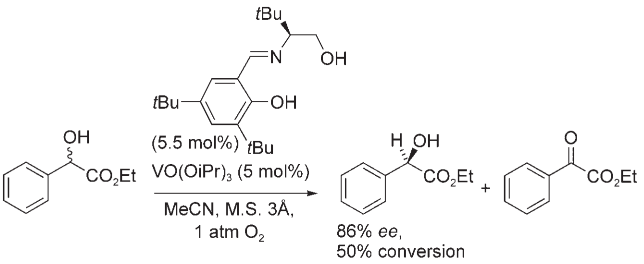
But what makes the kinetic resolution of alcohols especially attractive from a "green" point of view, is the prospect of using oxygen (i.e. from air) as the direct and primary oxidant for the reaction. There are many reports on the use of aerobic oxidation for the conversion of alcohols into aldehydes and ketones,[12] however very few of these are enantioselective. One of the most significant discoveries in this area was the finding in 2001 that a palladium(II) complex of sparteine (**2**) was capable of catalyzing the aerobic oxidative kinetic resolution of alcohols, and particularly aryl alcohols, to give products of remarkably high *ee* under optimized conditions.[13–15] Some examples are given in Scheme 4, which serve to highlight the versatility of this method.

Although several amine bases served to catalyze this reaction, (−)-sparteine was found to be the single most effective ligand for the application. Whilst this is an excellent method, sparteine does suffer from the limitation that only the (−)-enantiomer is available in large quantities, and until an effective method is found for the preparation of quantities of its enantiomer or a surrogate thereof,[16] this will remain a limitation.



Scheme 4. Examples for the kinetic resolution of ketones with the palladium(II) (−)-sparteine complex **2** as catalyst and oxygen as the oxidant. Un = unsaturated group, R = alkyl. DCE = 1,2-dichloroethane.

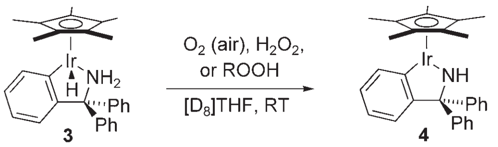
In recent years, several other methods have been reported for the catalysis of the aerobic oxidative kinetic resolution of alcohols, which include the use of a vanadium complex by Toste et al. (Scheme 5),[17] which has been highly effective for the generation of enantiomerically enriched α-hydroxy esters.



Scheme 5. Kinetic resolution in air with a vanadium complex.

This catalyst also works efficiently in the kinetic resolution of α-hydroxy esters bearing multiple stereocenters, for example at the β-position. Katsuki et al. reported on a Ru–salen complex for the catalysis of the asymmetric formation of lactones from *meso* diols in up to 81 % *ee*.[18,19] These Ru^{II}–salen complexes, which contain a combination of a C_2-symmetric diamine linked to two homochiral binaphthyl groups, have also proven to be very effective at the asymmetric deracemization of *meso* diols, giving products in up to 93 % *ee*.[18]

The recent paper by Ikariya et al.[20] on this subject represents a significant contribution because it contains an account of the use of a relatively simple and well established class of alcohol kinetic resolution catalyst; an iridium complex with a structure closely related to that of the TsDPEN catalyst **1** first reported by Noyori and Ikariya (Scheme 1).[1] The starting point for their studies was the finding that catalyst **3**, containing an Ir–arene bond,[21] could be converted into the corresponding 16-electron complex **4** rapidly upon exposure to air at room temperature (Scheme 6). This transformation could also be achieved by using peroxide oxidants. The mechanism of this process is assumed to involve insertion of dioxygen into the Ru–H bond, followed by the release of **4** and hydrogen peroxide, which then reacts with another molecule of **3** to generate **4** and water. A detailed mechanistic study on this reaction, using the optimized Ir complex **5**, has provided further evidence related to the mechanism.[22]



Scheme 6. Oxidation of an Ir–H complex by oxygen in air.

With this result in hand, Ikariya et al. extended their studies to aerobic alcohol oxidation, reasoning that the unsaturated complex **4** would remove two hydrogen atoms

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from one enantiomer of the alcohol (following the mechanism established for **1**) to give a hydride, which would then be oxidized by air. This worked well, and complex **4** was competent in the oxidation of 1-phenylethanol. An analogous compound containing a dimethylamino group was not effective, thus underlining the importance of the N–H interaction to the established mechanism of concerted dehydrogenation of alcohols via a six-membered cyclic transition state (Figure 1).

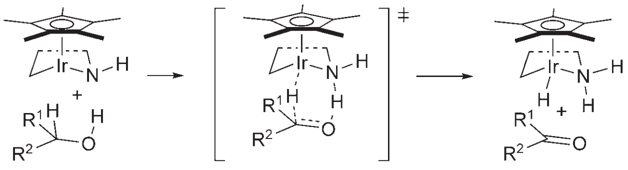
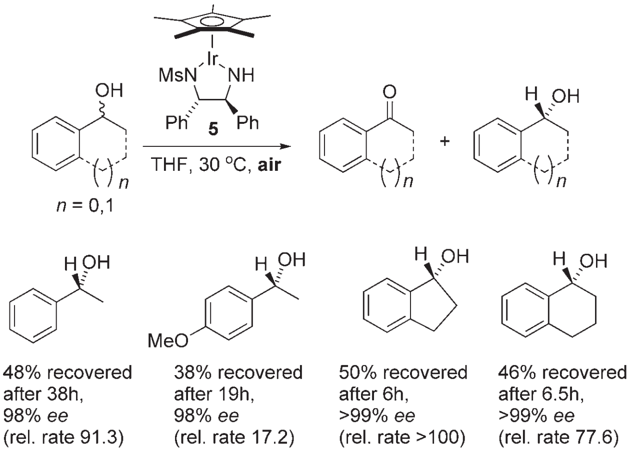


Figure 1. Mechanism of hydrogen elimination from a secondary alcohol by unsaturated Cp*Ir complexes. The iridium complex is drawn in a simplified manner.

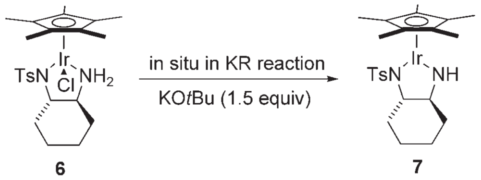
Although a homochiral 1-naphthylethylamine derivative of catalyst **4** was capable of kinetic resolution, the recovered product (48 %) was of only 14 % *ee*. Following further investigation, however,[20] it was found that the TsDPEN-derived Ir complex **5** acted as an excellent catalyst for the oxidative kinetic resolution of alcohols in air; a number of applications are summarized in Scheme 7.



Scheme 7. Aerobic kinetic resolution of alcohols with an iridium complex. Ms = methanesulfonyl (mesyl).

Complex **5** contains a combination of an iridium(III) metal complexed to a pentamethylcyclopentadiene (rather than an arene as is the case with the Ru^{II} complexes) and a mesylated diphenylethylenediamine ligand to provide the chiral control of the reaction. In all the examples reported, near-optimal recoveries of high *ee* alcohol were achieved, and in one case the relative rates of oxidation of each enantiomer was > 100. The tosylated analogue also worked, but was less selective.

A further useful observation, from a practical point of view, was that the chloride precursors of the catalyst, that is, **6**, (for this experiment, the investigators used the cyclohexane-derived ligand system) could also be employed through the use of an alkoxide base to drive HCl elimination and form the active unsaturated catalyst **7** in situ (Scheme 8). This is important because the chloride catalyst precursors are readily prepared in high yields. The authors also tested some other catalysts; an analogous rhodium(III) complex gave good results (although not as good as Ir) and ruthenium(II)–arene complexes proved to be less active and selective.



Scheme 8. A chloride precursor can be converted into an active unsaturated catalyst by using an alkoxide base. Ts = *para*-toluenesulfonyl (tosyl).

Whilst there are still some limitations to the method; for example 10 % of catalyst is required, it provides a method for the direct kinetic resolution of secondary alcohols in air under mild conditions and with a readily accessible catalyst that is available in either enantiomeric form. No doubt further exciting examples of improved applications of this and related catalyst systems to aerobic kinetic resolutions will be reported in the near future.

To be successful, this requires insertion of oxygen into a metal–hydride bond at some stage in the catalytic cycle; several examples of this type of process have been reported, and these are referenced in Ikariya's publication.[20]

Just prior to the appearance of the paper by Ikariya et al., Rauchfuss and Heiden published a very detailed full paper describing the use of essentially the same catalysts as used by Ikariya (i.e. **3**, although they examined the N-tosylated catalysts).[22] The focus of this group's work was on the reduction of the dioxygen, however, rather than the potential uses of the catalyst as an asymmetric oxidation catalyst. Rauchfuss and Heiden obtained a large amount of kinetic and mechanistic data which provide very valuable insights to the mechanism of the catalyst.

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