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[al002]

Recent Developments in the Area of Asymmetric Transfer Hydrogenation.

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Abstract

The use of an enantiomerically pure amino alcohol, coupled to a transfer hydrogenation process, in the asymmetric catalysis of the reduction of ketones to alcohols, is described. The process works well for unfunctionalised ketones, affording e.e.s of up to 98%, and excellent conversions. We have recently extended, for the first time in this application, the scope of the methodology to the reductions of a-heteroatom substituted substrates, through the use of the appropriate protecting groups on each atom.

Introduction

The asymmetric reduction of ketones to enantiomerically enriched alcohols remains a pivotal transformation in organic synthesis [1],[2]. Of the methods available to achieve this reaction in a catalytic sense the most established are those based on either hydrogenation [3]-[7] or the use of oxazaborolidines for the catalysis of ketone reduction by borane [8],[9].

Catalytic hydrogenation using a homochiral phosphine in conjunction with an appropriate metal, usually rhodium or ruthenium, is a versatile method which requires only very low levels of catalyst. In general, however, the method is most suitable for ketones which bear a proximal co-ordinating group [3]-[7]. There are however a number of recent notable examples of reductions of simple ketones through the use of additives [10]-[13] and a remarkable system for the asymmetric hydrogenation of simple ketones using a combination of a Rh(I) complex of a chiral phosphine with lutidine and KBr as additives has been reported very recently [14].

The oxazaborolidine-catalysed borane reduction process is complementary to hydrogenation and is ideally suited to the reduction of unfunctionalised ketones and enones [8],[9]. The drawback of this method is the requirement for a relatively large quantity (usually at least 10 mol%) of catalyst and the non-compatibility of certain functional groups with borane.

In this paper the combination of a homochiral amino alcohol with ruthenium(II) is demonstrated to form an effective new system for the asymmetric catalysis of the transfer of hydrogen from isopropanol to acetophenone.

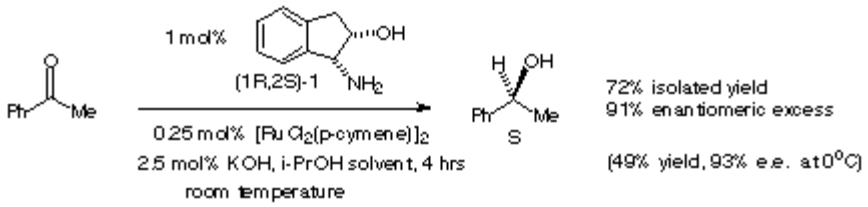
Transfer Hydrogenation of Ketones.

Asymmetric transfer hydrogenation with Ru(II) complexes, in which we have recently commenced a programme of research, has recently emerged as an effective approach to asymmetric carbonyl reduction [15].

A particular advantage of transfer hydrogenation methodology is the requirement for only very low quantities of catalysts; typically less than 1 mol%. Furthermore the ligands employed are often are indefinitely stable to the reaction conditions and may be recovered after use.

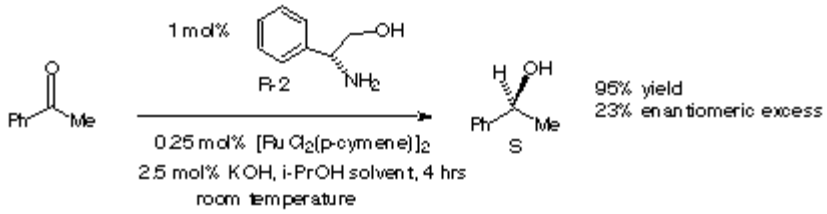
We have recently discovered that (1R,2S)-(+)-**1** is an excellent ligand for asymmetric transfer hydrogenation of ketones (Scheme 1) [16]. The use of 1 mol% of **1** in conjunction with 0.25 mol% of the ruthenium complex $[RuCl_2(p\text{-cymene})]_2$ and 2.5 mol% of KOH in propan-2-ol ([ketone]=0.1M) at room temperature resulted in reduction of acetophenone to S-(-)-1-phenethanol in 70% isolated yield and 91% e.e. after 90 minutes. Of a series of aromatic groups in the catalyst, p-cymene proved to be superior to benzene and 1,3,5-trimethylbenzene. The reaction does not require exclusion of water or air and may be worked up simply by filtration of the reaction mixture through a plug of silica followed by removal of solvent.

Scheme 1 Asymmetric transfer hydrogenation of acetophenone using (1R,2S)-1



The presence of a primary amine function on the ligand appears to be crucial; use of the methylated amine gave a product of only 20% e.e. In order to determine the importance of the rigid structure of the ligand we repeated the reaction under identical conditions using R-phenylglycinol **2**. In this reaction S-(-)-phenethanol was obtained in 95% yield but only 23% enantiomeric excess (Scheme 2). Although we have not yet investigated a systematic series of ligand modifications, it appears that a primary amine function in the ligand is essential. We have also established that the relationship between the enantiomeric purity of the ligand and the e.e. of the product is *linear*, suggesting that the active catalyst contains a 1:1 ligand:Ru ratio [17].

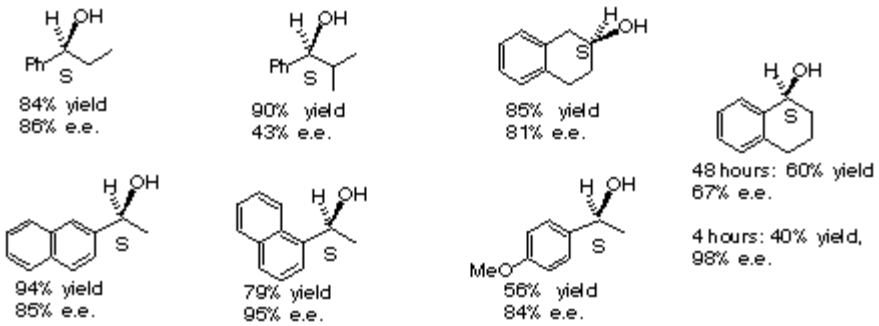
Scheme 2 Asymmetric transfer hydrogenation of acetophenone using (R)-2



Reduction of a series of aromatic ketones under identical conditions using ligand **1** resulted in formation of the corresponding alcohols in good to excellent yields and enantiomeric excesses (Figure 1). The reduction of 1-tetralone gave the most remarkable result; up to 98% enantiomeric excess under the room temperature reduction conditions. Extended reaction times resulted in loss of selectivity due to he reversibility of the reaction. Isolated yields of only 39 to 63% were obtained however when account was taken of the quantity of recovered starting material the mass balance is generally excellent. In all instances where e.e.s are observed to reduce over extended times it is likely that this is a result of the slow reversibility of the reaction.

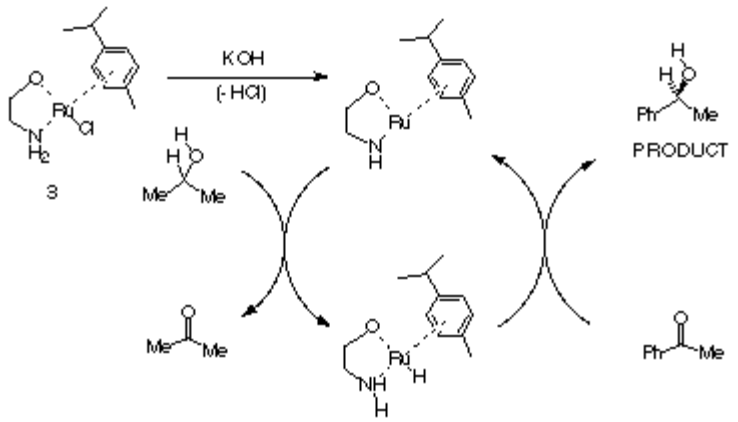
Although aromatic/alkyl ketones were generally good substrates, alkyl/alkyl ketones gave products of lower enantiomeric excess. An exception to this trend was observed for 2-tetralone, which gave a product of 81% e.e., which represents a result competitive with any of the best alternative methods.

Figure 1 Asymmetric transfer hydrogenation of ketones using 1 mol% (1R,2S)-1, 0.25 mol% $[RuCl_2(p\text{-cymene})]_2$, 2.5 mol% KOH, i-PrOH solvent, 1.5 hrs, room temperature.



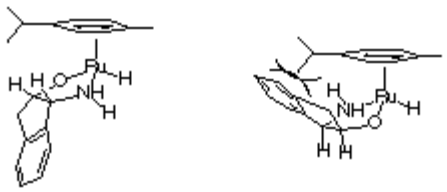
Our speculation on the mechanism of the reaction follows on from the suggestion by Noyori that hydrogen bonding may play a key role in the catalytic process [18]. This speculation has been supported by a series of enlightening X-ray crystallographic studies [19]. We have obtained results which suggest a 1:1 relationship between the ligand and the metal and have observed that the nature of the aryl group has an effect on the enantiomeric excess [16]. This leads us to suggest that the **?**pro-catalyst**?** is probably an 18 electron compound such as **3**, which forms upon treatment of the ligand **1** and the ruthenium complex precursor with base. Further elimination of HCl allows the active catalyst to form and enter the catalytic cycle of hydrogen transfer (Scheme 3) in a process analogous to that proposed by Noyori.

Scheme 3 Proposed catalytic cyclic for transfer hydrogenation using (1R,2S)-1 as catalyst.



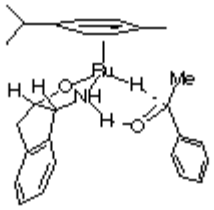
The origin of the asymmetric induction is less clear, however the highly rigid nature of the amino indanol ligand ensures that any complex will be well defined. In this the hydrogenated ligand will have a choice of two geometries for complexation (Figure 2), one of which is likely to be rather more congested than the other and thus disfavoured.

Figure 2 Possible diastereomeric complexes of 1 and ruthenium (arene) Cl.



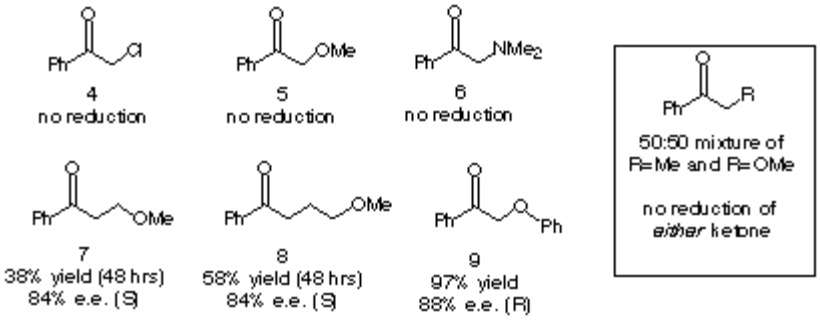
Having thus generated a rigid and well defined chiral environment in the complex, the hydrogen transfer, which may involve a hydrogen bond from the amine nitrogen atom to the carbonyl oxygen, will take place in a stereochemically predictable manner (Figure 3). We have no direct evidence, however, for the structure shown in Figure 3, which is our present speculation and the subject of ongoing investigations [17].

Figure 3 Proposed transition state for asymmetric reduction



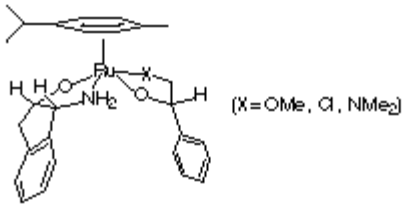
With a view to extending the transfer hydrogenation methodology to a variety of substrates we have studied the reductions of a series of a-heteroatom substituted ketones (the results are summarised in Figure 4). The reaction of a-chloro acetophenone **4** failed to give any product, a result which we initially explained by assuming in-situ cyclisation to the epoxide and thus deactivation of catalyst by neutralisation of the base. However we were most surprised by the same lack of reactivity of both a-methoxy and a-amino substituted ketones **5** and **6**. It was clearly the case *either* these ketones were poor substrates *or* that some form of product inhibition was terminating the catalytic process.

Figure 4 Results of asymmetric transfer hydrogenation substrates bearing α-heteroatom functions (1 mol% (1R,2S)-1, 0.25 mol% $[RuCl_2(p\text{-cymene})]_2$, 2.5 mol% KOH, i-PrOH solvent, 1.5 hrs, room temperature).



In order to test this we examined the transfer hydrogenation of a 1:1 mixture of propiophenone (which is known to be a good substrate) and a-methoxyacetophenone. In the event *neither* ketone was reduced, thus confirming that the catalyst is clearly inhibited by certain substrates or their reduction products. Our present speculation is that the formation of a chelating product results in inhibitory complexation and ultimately decomposition of the catalytic species (Figure 5) [20]. The proposed complex is a 20-electron complex and is likely to undergo rapid decomposition through loss of the aromatic ring.

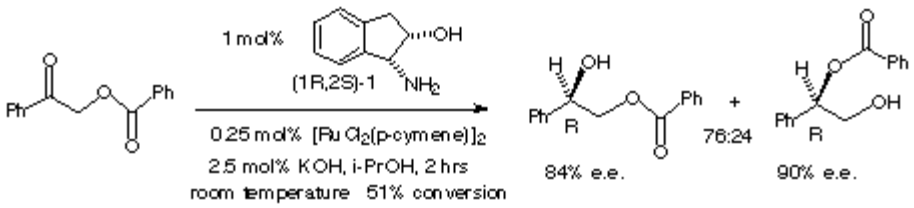
Figure 5 Proposed intermediate leading to catalyst inactivation by a chelating product



Further investigations have added support to the product inhibition theory. Reduction of b-methoxy substituted ketone **7** proceeds rather more slowly than the acetophenone reaction whilst reduction of g-methoxy substituted ketone **8** is once again a rapid process. These results suggest that, as one would predict, an increase in the distance between the potential chelating groups in the product causes the inhibitory effect to decrease sharply. Furthermore the reduction of a-phenoxy substituted acetophenone **9** proceeds rapidly and with high selectivity; a valuable and noteworthy result [20]. In the latter case the lone pair of the oxygen atom adjacent to phenyl is delocalised with the aromatic group and is thus unavailable to contribute to a strongly chelating product.

Armed with a realistic hypothesis for the mechanism of inhibition we have been able to design functionalised systems which are compatible with transfer hydrogenation reactions under our conditions. Mindful of the need to deactivate the electron-donating ability of the alkoxy substituted substrates we have discovered that the acylation of the adjacent hydroxy group gives a substrate which is both rapidly and selectivity reduced to the acylated diol (Scheme 4). Although some product of acyl transfer is isolated, both products are of essentially identical e.e. and we have therefore assumed that the isomerisation process follows the reduction reaction. To our knowledge this is the first example of the reduction of an a-alkoxy functionised substrate containing a removable protecting group under these conditions of transfer hydrogenation [20].

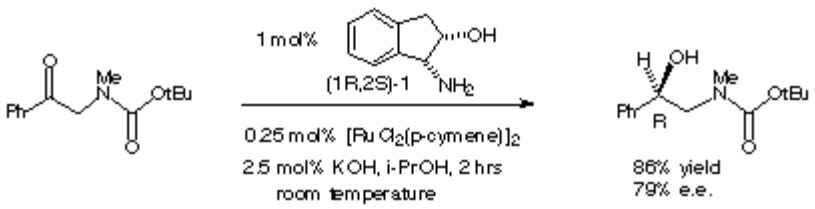
Scheme 4 Asymmetric transfer hydrogenation of α-acyloxy substrates using (1R,2S)-1



In a similar manner we have demonstrated that a-amino substituted substrates bearing an electron-withdrawing group

on the nitrogen atom are valuable reagents for our process (Scheme 5) [20]. In our example the use of an acylated primary amine function gave no reduction, however Noyori has reported one example of the reduction of a substrate containing such a functional group. [15s].

Scheme 5 Asymmetric transfer hydrogenation of α-acylamino substrates using (1R,2S)-1



It is also noteworthy that, since our own studies, the highly enantioselective asymmetric reduction of a-chloroacetophenone using a combination of formic acid/triethylamine in conjunction with a ruthenium(II)/monotosylated diamine system has recently been reported [21].

In conclusion it has been demonstrated that transfer hydrogenation using stereochemically rigid amino alcohols is a versatile and practical method for the synthesis of enantiomerically enriched secondary alcohols. Recent developments have extended the scope of the reaction system to substrates containing heteroatoms adjacent to the ketone, thus greatly increasing the applicability of the system. Our current research portfolio in this area is focused at the extension of the methodology to related systems, the reduction of C=N bonds [22], the solid phase support of our reagents [23], [15l] and the reverse process, which allows kinetic resolution of alcohols through an enantioselective oxidation [24].

Acknowledgements

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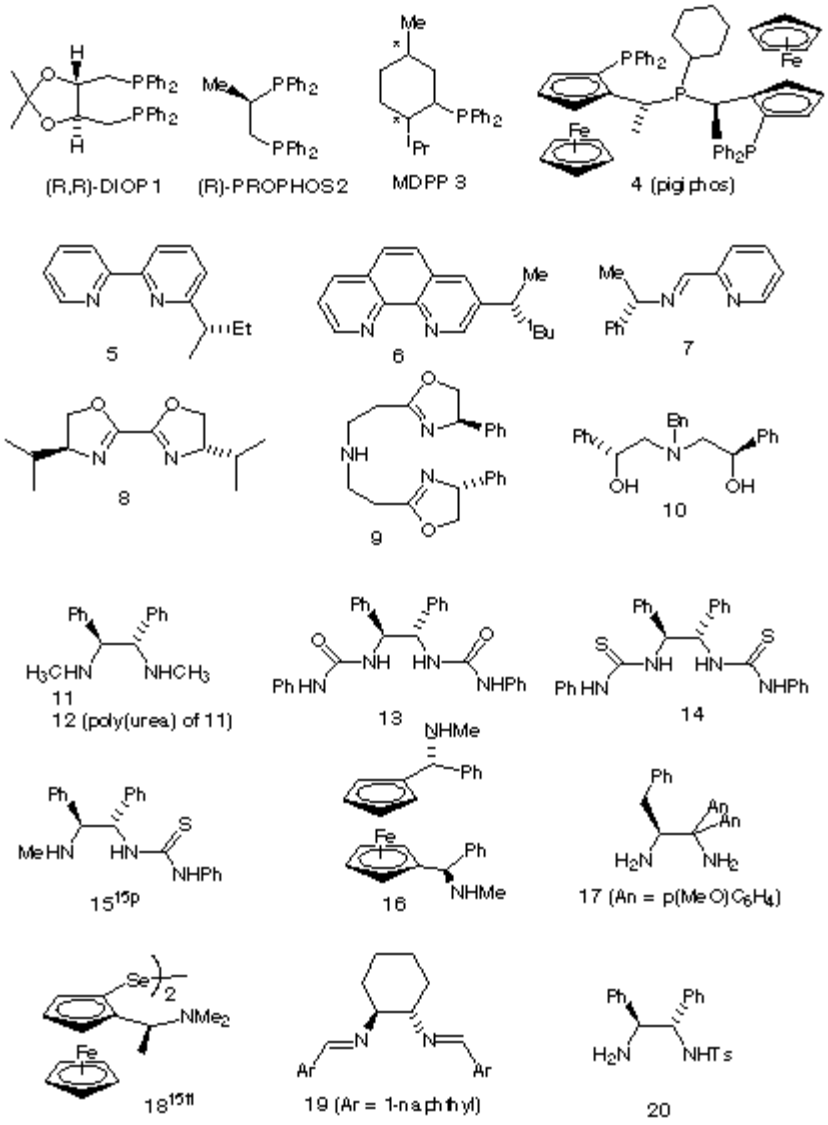
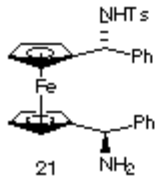
[15] A summary of ligands (including our own) which have recently been reported for the asymmetric transfer hydrogenation of ketones are given below. For reasons of space the comparison is limited to the reduction of acetophenone.





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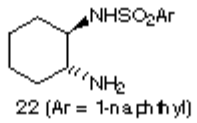
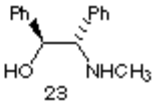


22 (Ar = 1-naphthyl)



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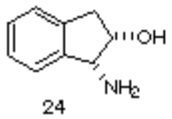

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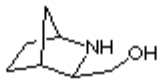

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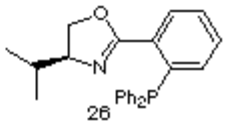

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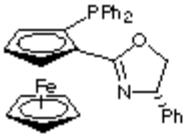

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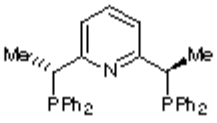

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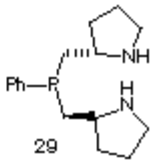

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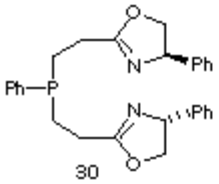

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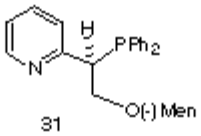

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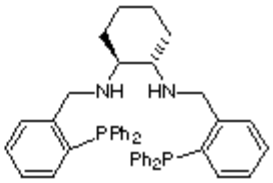

32

Table Asymmetric Transfer Hydrogenation of Acetophenone (hydride source/solvent is isopropanol unless otherwise indicated)

Entry	Ligand	Metal	Time/h	Temp/oC	Yield/%	e.e./%	Ref
1	1	Ru (II)	111	120	35	4 (S)	a
2	2	Rh (I)	3.5	82	60	9 (R)	b
3	2	Ir(I)	23	82	71	58 (S)	b
4	2	Ru (II)	0.03	100	80	52 (S)	b
5	3	Ir(I)	8	82	87	42 (S)	c
6	4	Ru (II)	120	68	99	72 (R)	d
7	5	Rh (I)	-	82	-	7 (R)	e
8	6	Rh (I)	4	82	89	63 (S)	f
9	7	Ir(I)	-	82	89	37 (S)	g
10	8	Ir(I)	3	80	89	58 (R)	h
11	9	Ru (II)	0.17	82	91	97 (S)	i
12	10	Sm(III)	2	rt	74	96 (R)	j
13	11	Rh (I)	168	rt	100	67 (R)	k
14	12	Rh (I)	24	70	100	60 (S)	l
15	13	Rh (I)	168	60	97	43 (R)	m
16	14	Ru (II)	9	82	98	87 (S)	n,b
17	16	Ru (II)	120	-30	98	80 (R)	p
18	17	Ir(I)	12	rt	74	78 (R)	q
19	19	Ru (II)	2-8	82	89	28 (S)	r
20	20	Ru (II)	15	rt	95	97 (S)	s
21	20*	Ru (II)	20	rt	99	98 (S)	t
22	21	Ru (II)	24	rt	97	56 (R)	u
23	21*	Ru (II)	120	rt	42	83 (R)	u
24	22*	Ru (II)	24	30	99	96 (R)	u
25	23	Ru (II)	1	rt	94	92 (S)	v
26	24	Ru (II)	1.5	rt	70	91 (S)	w
27	25	Ru (II)	5	83	95	95 (S)	x
28	26	Ru (II)	0.5	82	74	86 (R)	y
29	27	Ru (II)	7	28	80	94 (R)	z
30	28	Ru (II)	24	rt	91	35 (R)	aa
31	29	Ru (II)	24	rt	96	20 (R)	bb
32	30	Ru (II)	0.2	80	72	79 (R)	cc
33	31	Ru (II)	1	45	60	60 (R)	dd
34	32	Ru (II)	7	45	93	97 (R)	ee

* Formic acid/triethylamine 5/2 used as solvent and hydride source

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