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Novel catalysts for asymmetric reduction of carbonyl groups

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Abstract

The use of (i) enantiomerically pure phosphinamides coupled to borane and (ii) 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 former process is particularly suited to the reduction of alpha-chlorinated substrates, affording e.e.s of up to 94%, whilst the latter process is optimal for unfunctionalised ketones, affording e.e.s of up to 98%. © 1999 Elsevier Science B.V. All rights reserved.

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1. 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, two alternative systems for the highly enantioselective reduction of ketones by borane are described. In the first system, an enantiomerically pure phosphinamide, which acts as a Lewis base to activate ketone reduction by borane, is described. In the second system, the combination of a homochiral amino alcohol

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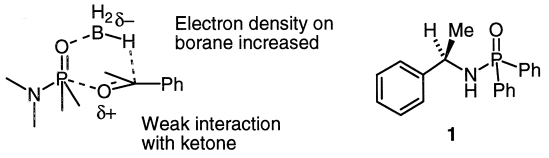


Fig. 1.

with ruthenium(II) is demonstrated to form an effective new system for the asymmetric catalysis of the transfer of hydrogen from isopropanol to acetophenone.

2. Phosphinamide catalysis of asymmetric ketone reduction

For some years, we have been engaged on a programme of research into catalysis of ketone reduction using phosphinamides and related materials containing an N–P=O structural unit. [1]

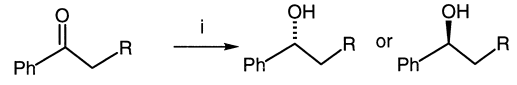
The basic premise for the use of phosphinamides in the reduction was based on the known electron-donor character of the oxygen atom. Such a property is dramatically demonstrated in numerous X-ray crystal structures of phosphoramides in complexes with salts such as lithium chloride, in which case the bonding between oxygen and metal cation is clearly apparent (Fig. 1) [15–18]. A Lewis-base interaction of this type with a molecule of borane would, we argued, increase the level of electron density on the latter and thus, modify its reactivity. There may also be a weaker, secondary interaction of the ketone with the phosphorus atom.

In this capacity, the proposed mechanism somewhat mirrors that of oxazaborolidines; however, the latter probably forms a rather stronger bond to the ketone, via the Lewis-acidic boron atom in the heterocyclic ring. We anticipated, however, that phosphinamides may be rather more robust reagents than oxazaborolidines, which are prone to hydrolysis by aqueous media [19].

We first sought a simple catalyst for initial screening. Reaction of α-methylbenzylamine with diphenylphosphinic chloride resulted in formation of phosphinamide **1** in high yield as a stable crystalline solid. Such a procedure is typical for the preparation of such compounds, which when isolated are frequently crystalline solids and stable to basic and nucleophilic conditions.

In the first experiment with this material, we simply followed the reduction of acetophenone in THF at room temperature using thin-layer chromatography (TLC), comparing a sample containing 10 mol% of **3** with a control lacking the catalyst (Scheme 1). After 1 h, the TLC of the control reaction showed only a tiny degree of reduction, although one has to bear in mind that the relative extinction coefficient of the ketone as compared to the alcohol means that one sees a 1:1 ratio of spot intensities at ca. 95% reduction. In contrast, we were astonished to see that after 1 h, the TLC of the reaction mixture containing 10 mol% of the catalyst contained essentially *no acetophenone* [20].

The enantiomeric induction of 27% e.e. obtained in the above reaction was rather low but a bonus in that the catalyst had not been designed with any particular structural element to induce high enantiomeric excesses [20]. Further tests showed that the catalyst did not decompose under the reaction conditions and could be recovered and reused after the reaction. The reaction was unaffected by addition of water (up to 10 mol% was deliberately added without detriment to the outcome) [21].



Reagents: (i) 2-10 mol% phosphinamide, rt, THF (catalyst **1**-**15**) or 110°C, toluene, (catalyst **18**). See Tables 1 and 2.

Scheme 1.

[1] Phosphinamides are strictly of the formula, $R_2NP(O)R_2$, although in this discussion, this term will be broadly used for closely related systems containing a N–P=O structural unit such as phosphonamides, $(R_2N)_2P(O)R$, and phosphoramides, $(R_2N)_3P(O)$.

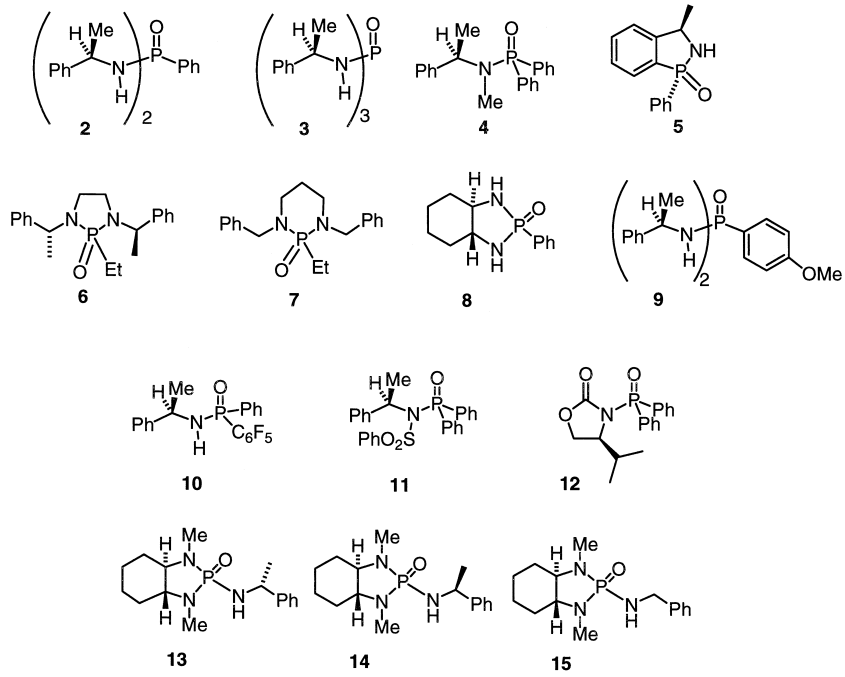


Fig. 2. Phosphinamide catalysts employed in asymmetric reduction of acetophenone by borane (see Table 1).

We have discovered a number of key features about the catalyst that are essential for high reactivity (Fig. 2; Table 1 illustrate some examples): (i) electron-rich catalysts are rather better that electron-poor ones, so replacement of a phenyl group with a *p*-methoxyphenyl group, as in **9**, gives an improved catalyst. In contrast, those containing electron-withdrawing groups,

Table 1
Asymmetric reductions of acetophenone (Scheme 1, R=H)

Catalyst	Percentage of catalyst	Reaction time [min] (> 98% reduction)	Yield alcohol [%]	Enantiomeric excess [%]
none	–	720	75	–
1	2	90	75	23(*S*)
1	10	< 60	82	26(*S*)
2	10	< 120	83	30(*S*)
3	10	< 60	70	20(*S*)
4	10	< 120	90	12(*S*)
5	10	240	85	35(*R*)
6	10	> 300	88	0
8	10	180	90	4(*S*)
9	5	15	90	24(*S*)
10	10	> 300	92	2(*S*)
13	10	60	82	8(*R*)
14	10	< 10	84	46(*R*)
15	10	30	88	19(*R*)

Reaction conditions: THF, r.t.

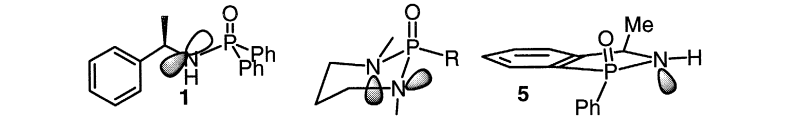


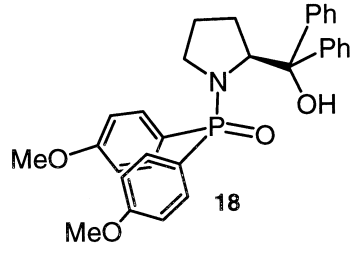
Fig. 3. The significance of orbital overlap.

i.e., **10**, **11** and **12** are very poor catalysts; (ii) virtually any compound containing a 'N–P=O' unit will work as a catalyst (but triphenylphosphine oxide does not) provided that *electron donation from the nitrogen lone pair to the P=O bond is permitted*. In the analysis of several X-ray structures, with some assistance from reported modelling studies by Cramer et al. [18], we found that the requirement is for the N–P=O unit and the two carbon atoms attached to the N atom (i.e., all five atoms) *to be able to lie in the same plane* (Fig. 3). Hence, compounds **5**–**8** are poor catalysts, but **13**–**15** are very effective ones, although they give products of low enantiomeric excess.

In spite of the sterling work carried out by Studley and Burns on the catalyst structure early on in the project (i.e., creating chirality at phosphorus [22], making rigid cyclic catalysts containing 'matched' chiral groups [23], using all sorts of other amines, etc.), we were for some time frustrated by a series of low asymmetric inductions.

We suspected that since the catalysis was essentially facilitated by a Lewis-base donation of electron density to the borane atom, the chiral environment of the catalyst was probably too far away from the reaction centre to be able to control it effectively. The secondary interaction of the ketone with the phosphorus atom was probably always going to be weak, mainly due to steric hindrance.

A radical redesign was required of the catalyst structure. In particular, there was a need for secure location for the ketone group within the transition state. This was actually achieved simply through the addition of a hydroxy group in a fixed position relative to the phosphinamide. Upon reaction with borane, a borate ester would be formed and would act as the Lewis acid site. After a series of investigations [24], the phosphinamide derived from diphenylprolinol proved to be the best of these, presumably because the five-membered ring maintains a rigid structure [25]. Of a series of derivatives, catalyst **18** has proved to be the best produced to date [26].



After some experimentation and the determined efforts of postdoctoral assistant, Gamble, we found to our surprise that the best conditions for reduction were ca. 100°C in toluene (Table 2). Using 10 mol% of the catalyst **18**, the reduction of a range of ketones could, thus, be achieved with high enantioselectivity, the best results being achieved with α-chloroacetophenone

Table 2
Reduction of α-chloroacetophenone by catalyst **18**; effect of temperature (Scheme 1, R=Cl)

Entry	Temperature [°C]	Yield [%]	Percentage of e.e.
1	110	91	94.4(*S*)
2	100	89	94.3(*S*)
3	80–85	88	93.3(*S*)
4	70–75	80	92.8(*S*)
5	60–65	69	80.1(*S*)
6	40–50	62	13.5(*S*)

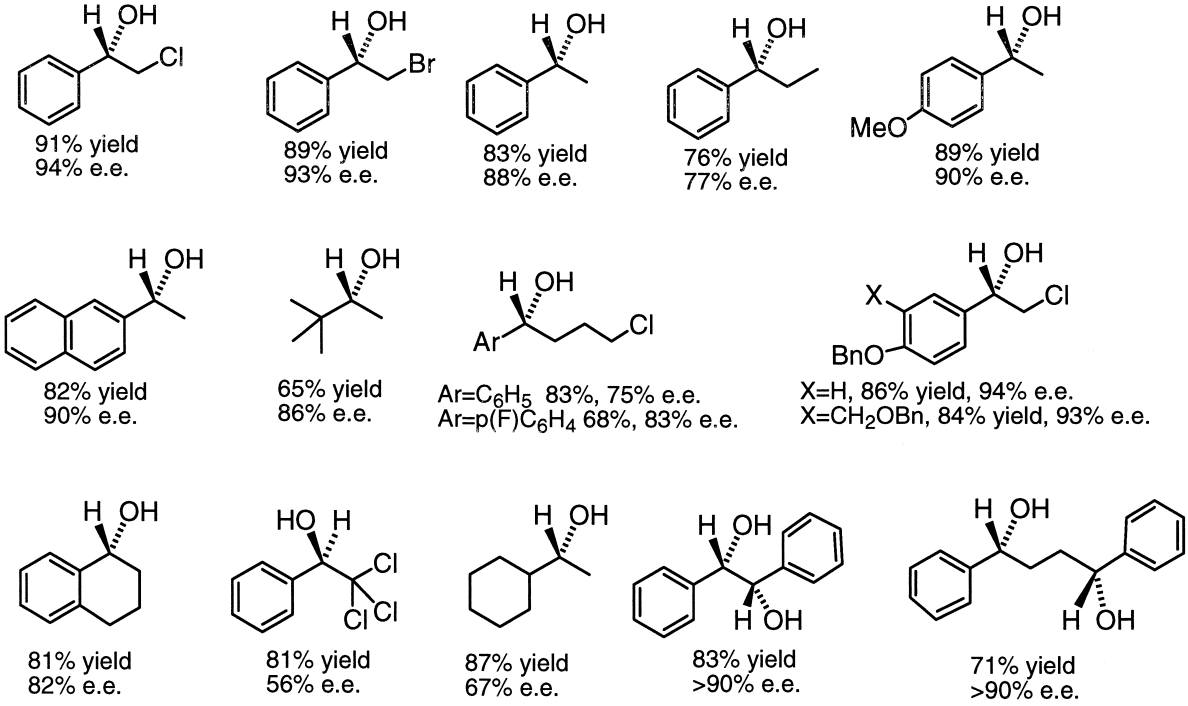


Fig. 4. Reduction products obtained using catalyst **18** (toluene, 110°C).

(Fig. 4). In all cases, the catalyst may be recovered from the reaction and reused. Boron and phosphorus nuclear magnetic resonance (NMR) studies show no appreciable decomposition of the catalyst during the reaction — a significant observation, since the possibility of decomposition to an oxazaboroline was always a matter of some concern to us.

Our model for the control of asymmetric induction (Fig. 5) involves the intermediacy of a complex in which borane and ketone are held in place by phosphinamide and borate ester, respectively. We speculate that the high temperature required for the reaction is probably required in order to assist the 'release' of the reduction product in order for the catalyst to reenter the catalytic cycle.

The importance of the practicality of the reagents should not be overlooked. The requirement is for minimal precautions regarding exclusion of moisture, in a system with a simple and recoverable catalyst.

At around the time this work was being completed, Professor Buono published a key paper on the use of oxazaphospholidine oxides **19** in asymmetric reductions [27].

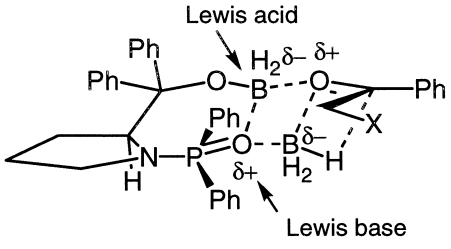
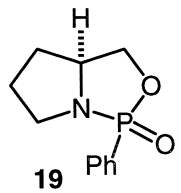


Fig. 5. Stereochemical control in the asymmetric reduction.



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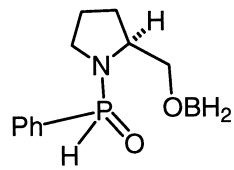

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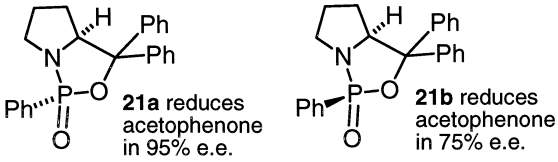


Fig. 6. Oxazaphospholidine oxide catalysts.

Buono's results mirrored ours closely — most significantly in the observation of optimal results for α-chloroacetophenone. Buono further noted that the catalysts underwent a cleavage of the endocyclic P–O bond early in the reduction reaction to give an 'active' catalyst of structure **20**, which was not recovered after the reaction.

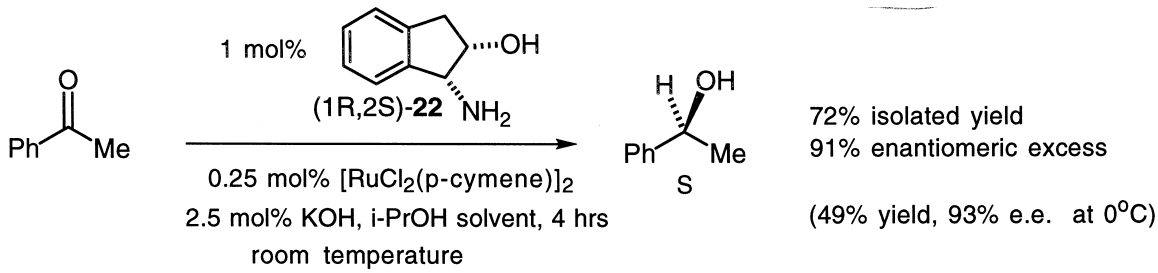
Professor Martens also reported at this time the use of the related compound **21** which gave yet better results than **19** [28]. Again, it is likely that this undergoes a reductive ring opening to a compound analogous to **20**. We have since found that the two diastereoisomers of **21** give quite different results (Fig. 6), suggesting that information about the configuration is retained upon ring-opening and is an important factor in the control of the asymmetric induction [26]. Kellogg has also reported studies on related reduction catalysts [29].

3. Transfer hydrogenation of ketones

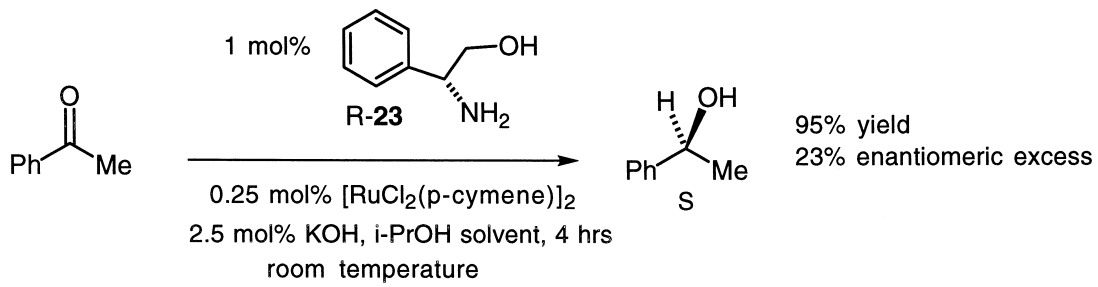
Asymmetric transfer hydrogenation with Ru(II) complexes, in which we have recently commenced a programme of research, has recently emerged as an effective alternative approach to asymmetric carbonyl reduction [30–45].

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 indefinitely stable to the reaction conditions and may be recovered after use.

A paper on this preliminary work has been published [36]. We have recently discovered that (1*R*,2*S*)-(+)-**22** is an excellent ligand for



Scheme 2. Asymmetric transfer hydrogenation of acetophenone using (1*R*,2*S*)-**22**.



Scheme 3. Asymmetric transfer hydrogenation of acetophenone using (*R*)-**23**.

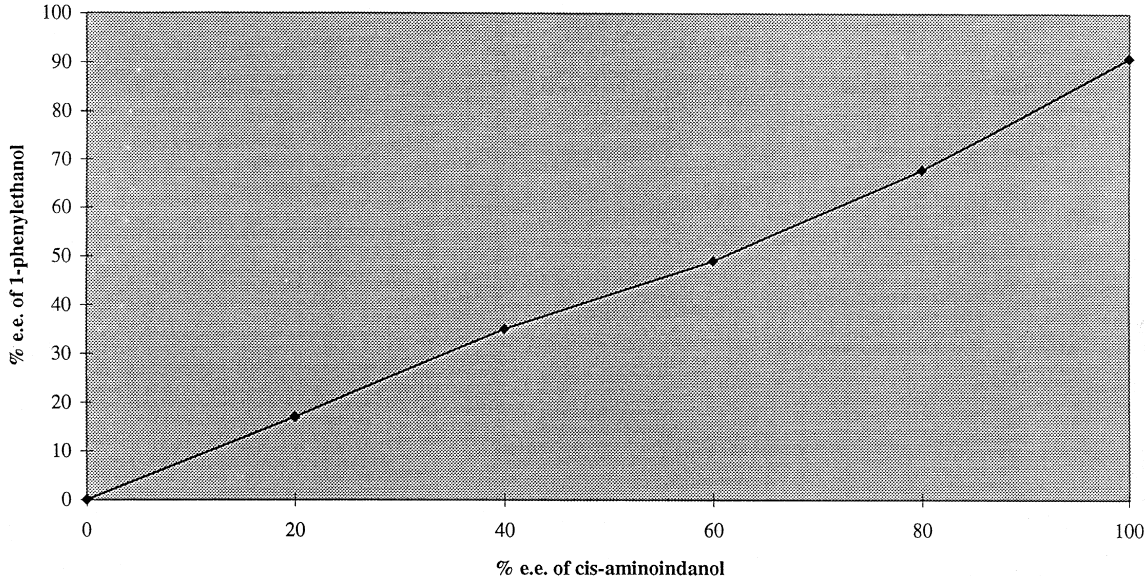


Fig. 7. Relationship of enantiomeric excess of ligand to reduction product.

asymmetric transfer hydrogenation of ketones (Scheme 2). The use of 1 mol% of **22** 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] = 0.1 M) at room temperature resulted in reduction of acetophenone to *S*-(−)-1-phenethanol in 70% isolated yield and 91% e.e. after 90 min. 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. In order to determine the importance of the rigid structure of the ligand, we repeated the reaction under identical conditions using *R*-phenylglycinol **23**. In this reaction, *S*-(−)-phenethanol was obtained in 95% yield but only 23% enantiomeric excess (Scheme 3). 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 a 1:1 ligand:Ru ratio in the active catalyst (Fig. 7).

Reduction of a series of aromatic ketones under identical conditions using ligand **22** resulted in the formation of the corresponding alcohols in good to excellent yields and enantiomeric excesses (Fig. 8a). The reduction of

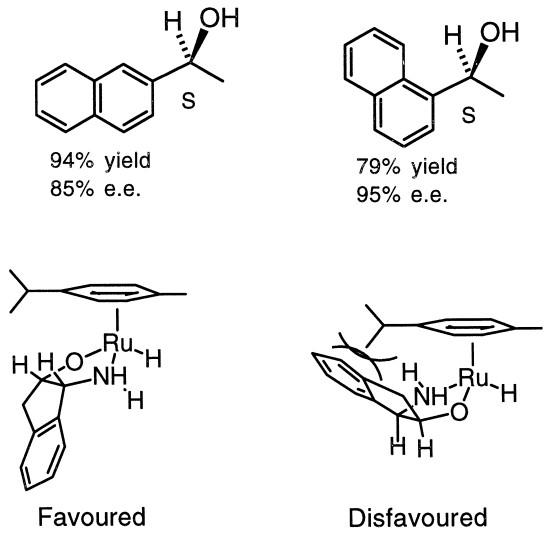
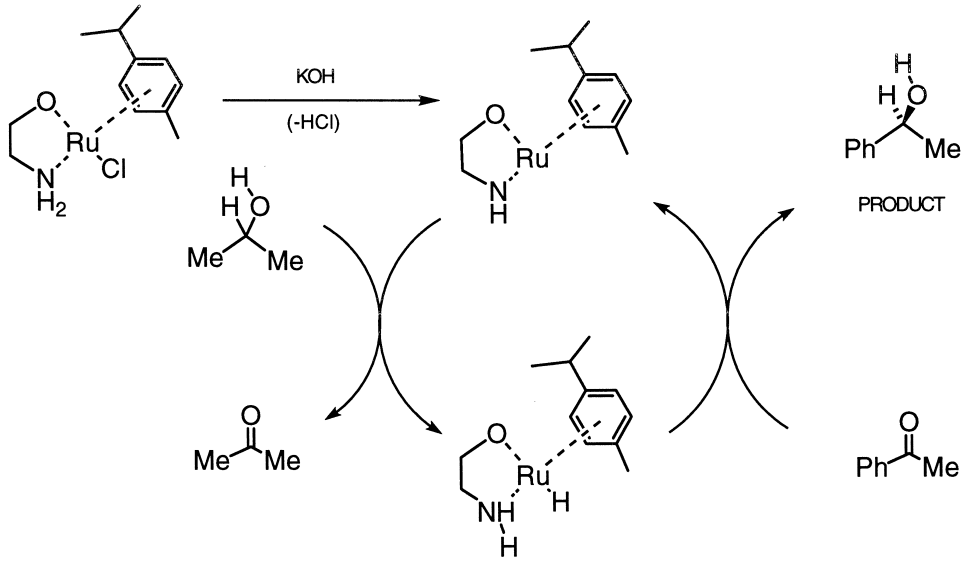


Fig. 8. (a) Asymmetric transfer hydrogenation of ketones using (1*R*,2*S*)-**22** (1 mol% **22**), 0.25 mol% $[RuCl_2(p\text{-cymene})]_2$, 2.5 mol% KOH, i-PrOH solvent, 1.5 h, room temperature. (b) Possible diastereomeric complexes of **22** and ruthenium (arene) Cl.



Scheme 4. Proposed catalytic cyclic for transfer hydrogenation using **22** as catalyst.

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 the 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.

Our speculation on the mechanism of the reaction follows on from the suggestion by Noyori [34] and Haack et al. [35] that hydrogen bonding may play a key role in the catalytic process. We have obtained results which suggest a 1:1 relationship between the ligand and the metal (Fig. 7) and have observed that the nature of the aryl group has an effect on the enantiomeric excess [36]. This leads us to suggest that the 'pro-catalyst' is probably an 18-electron compound such as **24**, which forms upon treatment of the ligand **22** and the ruthenium complex precursor with base. Further elimination of HCl allows the true catalyst to form and enter the catalytic cycle of hydrogen transfer (Scheme 4) in a process analogous to the Noyori system.

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 (Fig. 8b), one of which is likely to be rather more congested than the other and thus, disfavoured. In this process, the ruthenium is rendered asymmetric, and the hydrogen transfer, which may involve a hydrogen bond from the amine nitrogen atom to the carbonyl

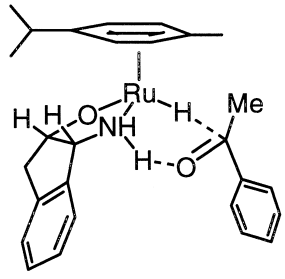


Fig. 9. Proposed transition state for asymmetric reduction.

oxygen, will take place in a chiral environment, from which information will be transferred to the product (Fig. 9). We have no direct evidence, however, for the transition state shown in Fig. 9, which is our present speculation and the subject of ongoing investigations.

Acknowledgements

I am indebted to a number of excellent researchers who have contributed to the projects described above. The phosphinamide chemistry was initiated by John Studley and Barry Burns and taken on by Mark Gamble and Athene Smith. The transfer hydrogenation and the remarkable activity of *cis*-aminoindanol was discovered by Matthew Palmer in the last year of his PhD project and was extended by Jennifer Kenny and Athene Smith. The project was funded largely by the EPSRC (Postdoctoral award to Mark Gamble and CASE awards) and SmithKline Beecham (Tonbridge) which have provided generous support through CASE awards to Matthew and Jennifer. Oxford Asymmetry International has provided some very generous recent fundings to extend the transfer hydrogenation work further.

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