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Asymmetric transfer hydrogenation of C=O and C=N bonds

Matthew J. Palmer and Martin Wills *

Department of Chemistry, Warwick University, Coventry, CV4 7AL, UK

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Contents

1. Introduction

The synthesis of chiral non-racemic secondary alcohols by catalytic enantioselective reduction of the corresponding ketone remains a pivotal transformation in organic synthesis.[1] The three major catalytic procedures which have emerged in recent years are: (i) enantioselective hydride reduction; (ii) enantioselective hydrogenation; and (iii) enantioselective transfer hydrogenation.

* Corresponding author. E-mail: m.wills@warwick.ac.uk

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Some of the most successful and general catalysts for hydride reduction are based on the oxazaborolidine structure, developed by Corey,[2] following on from initial work by Itsuno.[3] Excellent results have been obtained with these materials, however the high level of catalyst often required (typically 10 mol%), and non-compatibility of borane with certain functional groups, limits its utility somewhat.

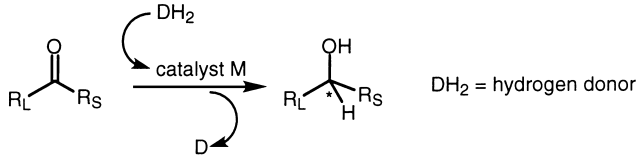
Enantioselective hydrogenation catalysts derived from various BINAP and DuPHOS ligands, amongst others, are capable of hydrogenating functionalised ketones in extremely high ees.[4,5] A major drawback of such catalytic systems is the need for an adjacent heteroatom in the substrate to coordinate to the metal centre. In response to this, Noyori has described a variant system which utilises a chiral diamine and KOH in propan-2-ol to activate a BINAP–Ru(II) complex to catalyse the hydrogenation of unfunctionalised aromatic ketones.[6]

Studies have shown that the reduction is the result of net hydrogenation and that an interesting synergistic relationship exists between the diphosphine and diamine. Later successful applications of this system[7,8] included the selective hydrogenation of the carbonyl group in conjugated and unconjugated enals and enones.[9] A remarkable system for the asymmetric hydrogenation of simple ketones, using a combination of a Rh(I) complex of a chiral phosphine with the essential additives lutidine and KBr, has been reported very recently.[10]

The third major method for asymmetric carbonyl reduction involves transfer hydrogenation. This has recently emerged as a powerful, practical and versatile system for the title transformation, and is described in detail below.

2. Enantioselective transfer hydrogenation: background and mechanism

Transfer hydrogenation is defined as "the reduction of multiple bonds with the aid of a hydrogen donor in the presence of a catalyst",[11] as depicted in Scheme 1.



Scheme 1.

Until quite recently, the catalytic enantioselective transfer hydrogenation of ketones lagged far behind both the oxazaborolidine– and BINAP–Ru(II) complex-catalysed reduction of ketones as a well-developed, viable method for the synthesis of chiral, non-racemic alcohols. This is in spite of some palpable benefits of transfer hydrogenation over other methods, as detailed by Noyori[12] and others.[11] These include procedural simplicity, avoidance of hazardous reagents such as molecular hydrogen and borane (thereby removing the need for specialised, expensive facilities for the handling of such reagents) and a distinct reactivity and chemo- and enantioselectivity, which may well complement other methods. Inevitably, there are drawbacks, the most serious being the unfavourable thermodynamics associated with the transfer hydrogenation of ketones using alcohols, especially propan-2-ol, as hydrogen source.[13] Judicious choice of hydrogen donor and reaction conditions are needed in such cases if good conversions are to be achieved.

Two discrete reaction mechanisms have been described for the transfer hydrogenation of ketones: (a) direct hydrogen transfer; and (b) hydridic route.[11]

2.1. Direct hydrogen transfer

This is a concerted process, involving a six-membered cyclic transition state in which both the hydrogen donor (^{i}PrOH) and hydrogen acceptor (ketone) are in close proximity to the metal centre (Fig. 1). This mechanism is similar to that proposed for the Meerwein–Ponndorf–Verley (MPV) reduction.[14–17]

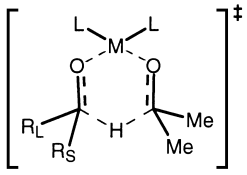
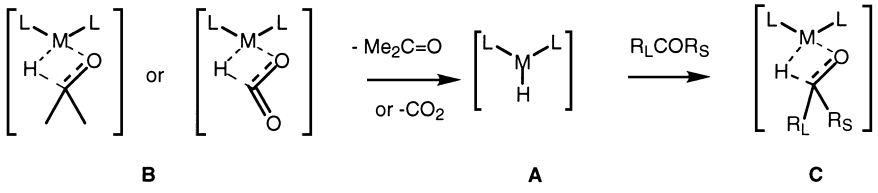


Figure 1.

2.2. Hydridic route

This proceeds in a stepwise manner by way of a putative metal hydride **A**, formed by elimination of acetone from **B**, which then undergoes hydride transfer with a coordinated ketone, depicted in **C** (Scheme 2).



Scheme 2.

The exact mechanism operating in a given system depends on the metal catalyst and hydrogen donor. Main group elements are reported to undergo the direct hydrogen transfer route preferentially, as in MPV reduction.[15,16] In contrast, transition metal complexes, as stated by Noyori, "prefer the hydride mechanism".[12] Such metal hydride species have been reported in various systems. [RhH(bipy)$_2$] is implicated in the mechanism of [Rh(bipy)$_2$Cl]-catalysed dehydrogenation of ethanol in the presence of a base.[18] Also, Bäckvall has suggested the involvement of a ruthenium dihydride species in a [RuCl$_2$(PPh$_3$)$_3$] and NaOH catalyst system for the transfer hydrogenation of ketones.[19]

In 1991, Bäckvall had discovered that the use of catalytic amounts of NaOH in the [RuCl$_2$(PPh$_3$)$_3$]-catalysed transfer hydrogenation of ketones by propan-2-ol dramatically increased the activity of the catalyst.[19] Without added NaOH, or other bases such as potassium carbonate, no transfer hydrogenation occurred. This observation was important, as previously ruthenium-catalysed transfer hydrogenation of ketones had frequently been performed at high temperatures.[20]

The hydrogen donors most commonly used for the transfer hydrogenation of ketones are propan-2-ol (generally used with sodium or potassium hydroxide as a base) and formic acid (generally used as an azeotrope with triethylamine), the latter of which allows reduction of ketones to be achieved under essentially irreversible conditions. If propan-2-ol is employed as the hydrogen donor, it is often present in large excess in order to achieve useful conversions in the face of the unfavourable equilibrium.[13]

3. Ligands for the enantioselective transfer hydrogenation of ketones

Many ligands have been reported for the enantioselective transfer hydrogenation of ketones, most commonly with either rhodium, iridium or ruthenium metals. A brief summary of the most notable, together with a comparison of the relative effectiveness of the prototype acetophenone reduction, is presented below (Table 1, Fig. 2).

3.1. Phosphines

Some of the earliest catalytic systems disclosed used phosphine-containing Ru, Rh and Ir complexes.[21–23] In general, the conversions and enantioselectivities were modest, with a requirement in some cases for the use of harsh conditions. Speculation on the mechanism of these reactions has centred upon the intermediacy of a ruthenium dihydride,[11] following the precedents of Cole-Hamilton[18] and Bäckvall.[19]

Genêt reported a series of dibromodiphosphinoruthenium catalysts ([RuP*$_2$Br$_2$], where P*=diphosphine such as **2**) for transfer hydrogenation of ketones, achieving good conversion in short reaction times and moderate enantioselectivities (7–52% ee).[24] Some quite impressive results (up to 72% ee) have been obtained in recent work using a ruthenium(II) complex of the diferrocene-derived phosphine ligand (*S*)–(*R*)-Pigiphos **4**.[25]

An interesting paper has described the use of BINAP, which is not one of the better ligands for this application,[24] for the stereo- and chemoselective hydrogenation of unsaturated ketones.[26] Although ees were low, the combination proved to be a good one for selective reduction of the C=O bond in enones when a phosphate salt was used as a hydride source. Good diastereoselectivities were also obtained for the reduction of α-substituted and cyclic β-keto esters, which were opposite to those obtained using the well-established Ru(II)/BINAP hydrogenation system.

3.2. Pyridine derived chiral ligands containing nitrogen donors

Rh(I) complexes with chiral bipyridines **5**[27] and Ir(I) complexes with chiral phenanthrolines **6**[28] and chiral imines **7**[29] have shown poor to moderate enantioselectivity in the transfer hydrogenation of acetophenone.

The reaction of the Rh(I) complex containing phenanthroline **6** has been proposed, from UV and other data, to proceed via the pentacoordinated rhodium hydride **33** (Fig. 3).[28] This species, derived from deprotonation of **34** by KOH followed by hydride abstraction from the alkoxide **35**, then adds selectively to the *Re* face of acetophenone. Displacement of (*S*)-1-phenylethanol by propan-2-ol then completes the catalytic cycle.

In contrast, transfer hydrogenation using the Ir(I) complexes containing chiral imine ligands, such as **7**, were speculated to proceed via the direct hydrogen transfer mechanism, within a six-membered transition state.[29]

3.3. Tetrahydrobi(oxazole) ligands

Although significant advances were made by several researchers[11,21–23,27–29] as detailed above, the enantioselective transfer hydrogenation of ketones has only emerged as a viable synthetic tool in recent years. This is in part the result of a report by Pfaltz in 1991, detailing the use of tetrahydrobi(oxazole) ligands **8**, which described the attainment of >90% ee for the transfer hydrogenation of certain ketones.[30]

Table 1
Asymmetric transfer hydrogenation of acetophenone (hydride source/solvent is isopropanol unless otherwise indicated)

Entry	Ligand	Metal	Time/h	Temp/ ˚C	Yield/%[1]	e.e./%	Ref
1	**1**	Ru(II)	111	120	35	4 (S)	21
2	**2**	Rh(I)	3,5	82	60	9 (R)	22
3	**2**	Ir(I)	23	82	71	58 (S)	22
4	**2**	Ru(II)	0.03	100	80	52 (S)	24
5	**3**	Ir(I)	8	82	87	42 (R)	23
6	**4**	Ru(II)	120	68	99	72 (R)	25
7	**5**	Rh(I)	-	82	-	7 (R)	27
8	**6**	Rh(I)	4	82	89	63 (S)	28
9	**7**	Ir(I)	-	82	89	37 (S)	29
10	**8**	Ir(I)	3	80	89	58 (R)	30
11	**9**	Ru(II)	0.17	82	91	97 (S)	31
12	**10**	Sm(III)	2	rt	74	96 (R)	32
13	**11**	Rh(I)	168	rt	100	67 (R)	36
14	**12**	Rh(I)	24	70	100	60 (S)	40
15	**13**	Rh(I)	168	60	97	43 (R)	41
16	**14**	Ru(II)	9	82	98	87 (S)	42/43
17	**16**	Ru(II)	120	-30	95	80 (R)	44
18	**17**	Ir(I)	12	rt	74	78 (R)	45
19	**19**	Ru(II)	2-8	82	89	28 (S)	47
20	**20**	Ru(II)	15	rt	95	97 (S)	49
21	**20**[2]	Ru(II)	20	rt	99	98 (S)	50
22	**20**	Rh(III)	48	rt	80	90 (S)	54
23	ent-**20**	Rh(III)	12	30	14	90 (R)	55
24	**20**	Ir(III)	48	rt	58	90 (S)	54
25	**21**	Ru(II)	24	rt	97	56 (R)	56
26	**21**[2]	Ru(II)	120	rt	42	83 (R)	56
27	**22**	Ru(II)	24	22	97	89 (R)	56
28	**22**[2]	Ru(II)	24	30	99	94 (R)	56
29	**22**	Rh(III)	12	30	85	97 (R)	55
30	**22**	Ir(III)	12	30	36	96 (R)	55
31	**23**	Ru(II)	1	rt	94	92 (S)	58
32	**24**	Ru(II)	1.5	rt	70	91 (S)	59
33	**25**	Ru(II)	5	83	95	95 (S)	60
34	**26**	Ru(II)	0.5	82	74	86 (R)	61
35	**27**	Ru(II)	7	28	80	94 (R)	62
36	**28**	Ru(II)	24	rt	91	35 (R)	63
37	**29**	Ru(II)	24	rt	96	20 (R)	64
38	**30**	Ru(II)	0.2	80	72	79 (R)	65
39	**31**	Ru(II)	1	45	60	60 (R)	66
40	**32**	Ru(II)	7	45	93	97 (R)	67

[1] Isolated yield or conversion reported
[2] Formic acid/triethylamine 5/2 used as solvent and hydride source

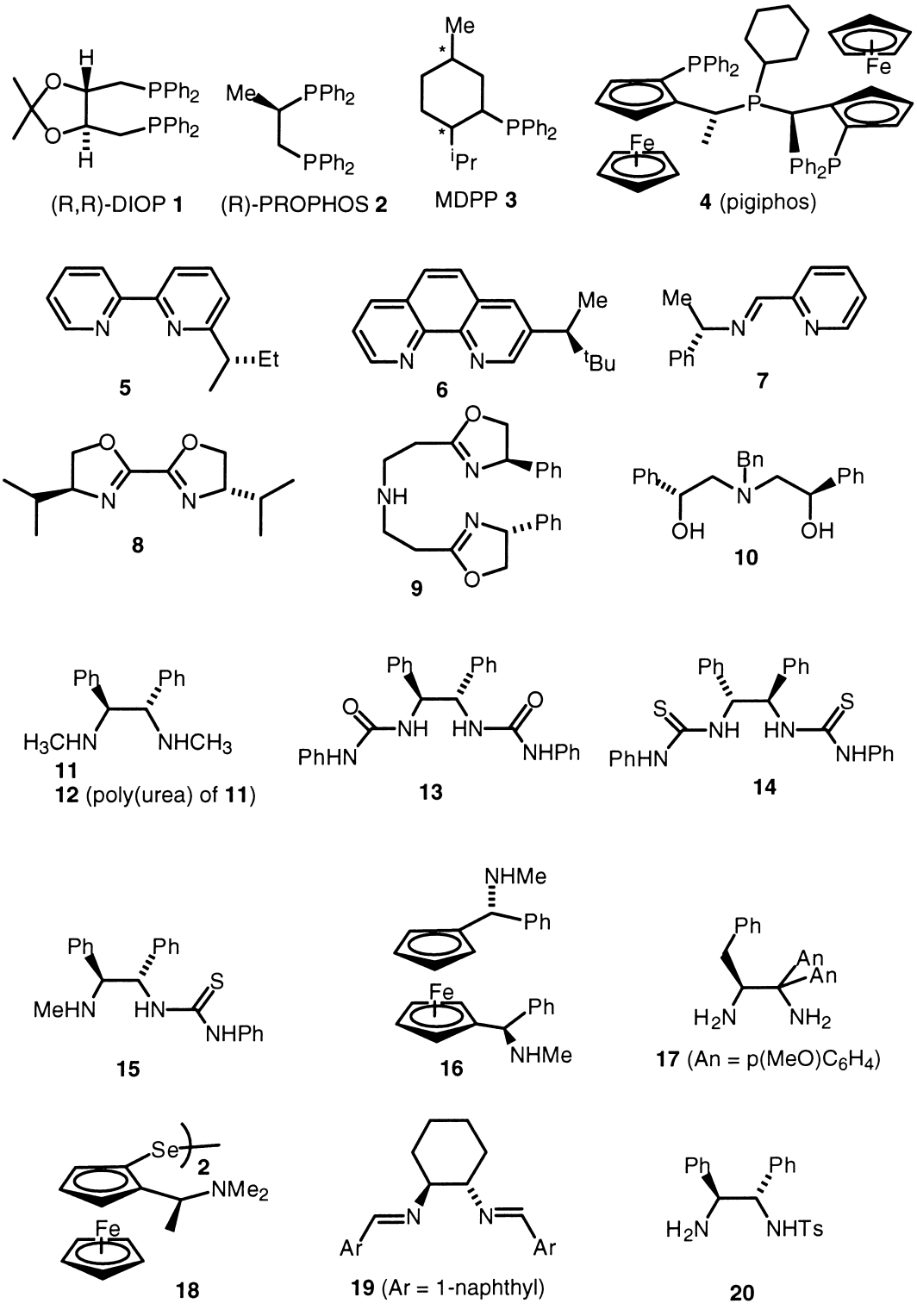


Figure 2. Ligands used in asymmetric transfer hydrogenation of acetophenone

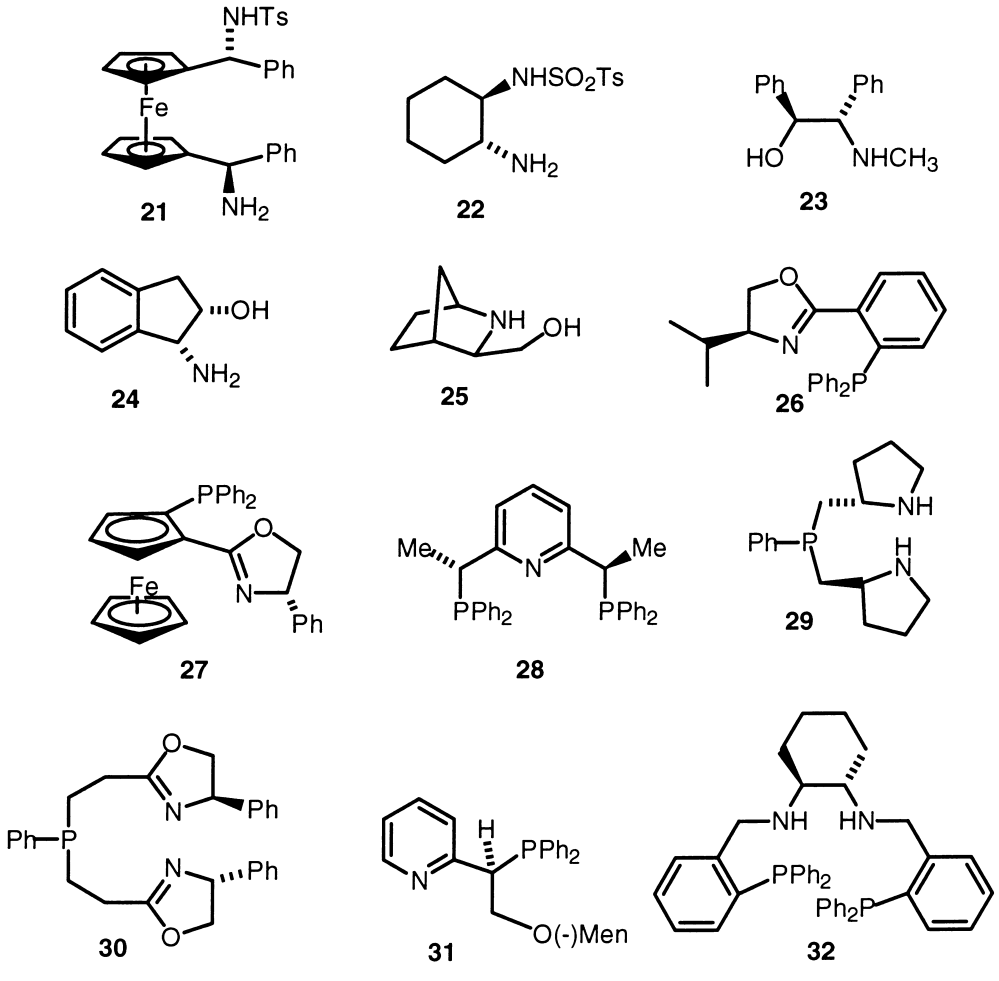


Figure 2—continued

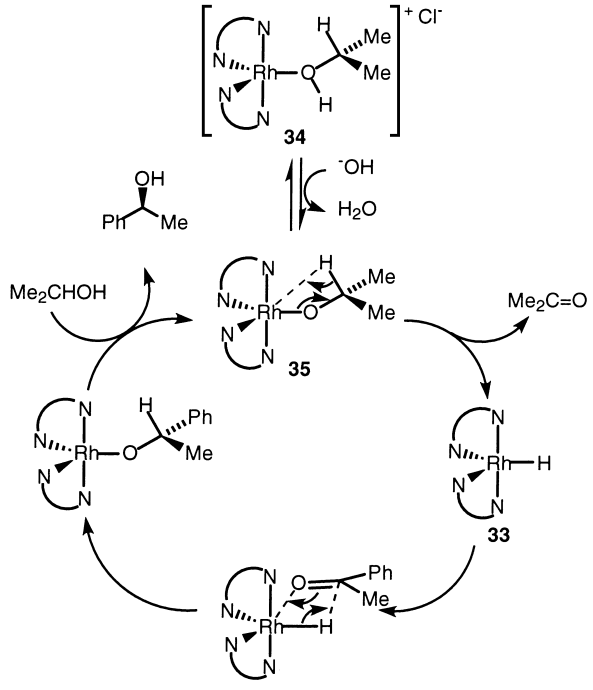
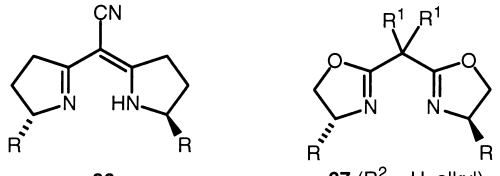


Figure 3.

Ir(I) complexes of tetrahydrobi(oxazoles), such as **8**, catalyse the transfer hydrogenation of various aromatic ketones with enantioselectivities ranging from 47 to 91% ee.[30] The exact structure of the ligand is important; isopropyl substituents on the oxazole rings appears optimal, with benzyl-substituted ligands giving products of lower ee and *tert*-butyl-substituted ligands giving essentially no conversion at all. The best substrate for reduction, out of a short series studied, was phenyl/isopropyl substituted ketone, which is surprising since this substrate generally affords products of lower ee than acetophenone in transfer hydrogenations. The latter observation is probably the result of steric hindrance in the active catalyst complex. In sharp contrast to the results obtained using **8**, semicorrins **36** and bis(oxazolines) **37** produced no significant catalytic activity when used in this application.

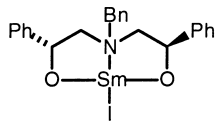


The amine-bridged bis(oxazoline) **9** acts as a tridentate ligand in combination with Ru(II) and successfully furnishes reduction products in excellent ee (generally >95% for a series of aryl/alkyl ketones).[31] The presence of the central amine is considered essential for high reactivity and enantioselectivity.

3.4. Tridentate ligands in Sm(III) complexes

Evans has utilised a chiral Sm(III) complex **38**, based on ligand **10**, in enantioselective MPV reduction of various aromatic ketones in propan-2-ol, obtaining generally excellent enantioselectivities.[32] Two-

point binding of *o*-methoxyacetophenone **39** to the metal centre was suggested to account for the increase in reaction rate for this substrate relative to acetophenone.



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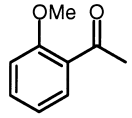
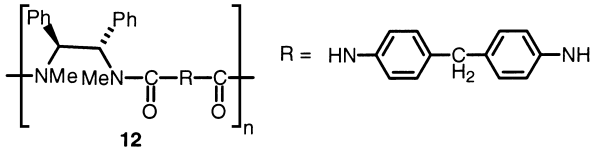


39

In a closely related process the use of *R*-(−)-1-phenyl-2,2-dimethylpropane-1,3-diol gave a reduction product from acetophenone of 46% ee in combination with Er metal.[33] Enantiomerically pure 1,1,2-triphenylethane-1,2-diol, in combination with zirconium, acts as a catalyst and generates products of up to 62% ee. However it is necessary to use 20 mol% of the reagent for optimal results.[34,35]

3.5. Diamine and poly(urea) ligands

Rh complexes of various C_2-symmetric chiral diamines have been investigated by Lemaire as viable catalysts for transfer hydrogenation.[36,37] In general, the enantioselectivities obtained were modest, the best being the secondary diamine **11** derived from (*S*,*S*)-diphenylethylenediamine. The Rh(I) complex of **11** has recently been isolated and characterised by mass spectrometry.[38] The cobalt complex of **11** catalyses reductions in up to 58% ee (*R*).[39] Lemaire subsequently incorporated **11** into a polymer backbone, by preparing its poly(urea) **12**.[40]



12

Polymer **12** proved to be a better ligand than **11** in terms of both reaction rate and enantioselectivity. The pseudo-C_2 symmetry of **12** was the reason suggested for the observed enantioselectivity. The diurea **13** gave a slightly better enantioselectivity (up to 80% for propiophenone)[41] whilst the thiourea **14** gave even better results still with enantiomeric inductions of up to 91% ee (propiophenone) and 96% yield when employed in conjunction with ruthenium(II).[42] As for **13**, propiophenone gives a slightly better result than acetophenone, and the 2-methylpropiophenone is yet more optimal for this catalyst (94% ee).[42] The monothiourea derivative **15** performed poorly as a catalyst, thus confirming the importance of the C_2-symmetric nature of these reagents.[43]

A series of notable C_2-symmetric diamines, typified by **16**, have been reported by Knichel to be valuable transfer hydrogenation catalysts.[44] Using this diamine, reduction can be carried out at temperatures as low as −30°C to give products of up to 90% ee (for 1-acetonaphthone). The combination of iridium(I) with the diamine **17** is an excellent one for reduction of a range of ketones,[45] whilst the Rh(I) complex of the diselenide-bridged **18** gives reduction products in generally modest ee but notably 95% for the 2,2-dimethylpropiophenone reduction.[46] It should be noted that in the latter case the transfer hydrogenation was achieved using a combination of a silane and methanol as the source of hydrogen.

3.6. Diimine ligands

Moderate enantioselectivities (up to 40% ee) have been obtained by the use of several aromatic substituted diimine ligands, such as **19**, in the Ru(II)-catalysed transfer hydrogenation of aromatic ketones.[47] A heterogenised version of these diimine ligands in conjunction with Ir(I) gave products of up to 70% ee but exhibited poor recyclability.[48]

3.7. Monotosylated diamine ligands

Of all the developments in this area in recent years perhaps the most important and significant is the rise in status of monotosylated 1,2-diamines. This work has been led by Noyori who has reported the use of monoarylsulfonylated diamines, in particular **20**, as ligands in Ru(II)-catalysed transfer hydrogenation.[12,49–52] The conversions and enantioselectivities achieved for a variety of aromatic ketones have been outstanding (Fig. 4). Indeed, **20** can be considered the most effective and best understood ligand yet reported. Both propan-2-ol[49] and 5:2 formic acid:triethylamine azeotrope[50,53] have been utilised as hydrogen donor. The latter system has afforded generally excellent enantioselectivities (83–99% ee) for a wide array of substrates, due, in part, to the irreversible nature of the transfer hydrogenation. The choice of aromatic ligand is important; complexes of either *p*-cymene or mesitylene give rather better selectivities than those of benzene alone, although the latter are more reactive. Complexes of hexamethylbenzene appear to be relatively sluggish in this application.

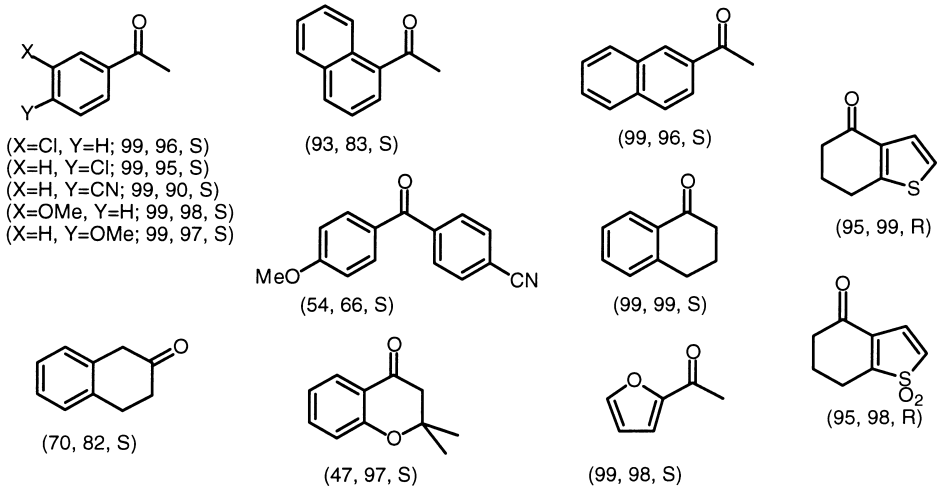
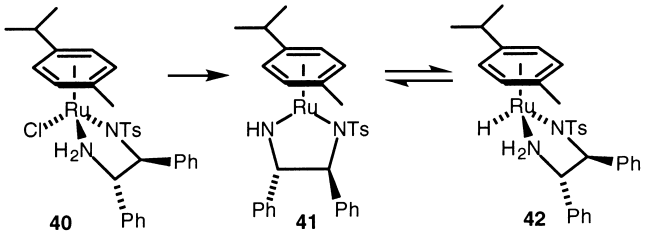


Figure 4. Ketones which may be reduced using (*S*,*S*)-**40**/HCO_2H/Et_3N (0.5 mol% catalyst, parentheses contain % yield, ee and configuration of product)

Extensive research has resulted in the characterisation and X-ray analysis of all rate limiting complexes involved in the Ru-catalysed transfer hydrogenation employing **20** (Scheme 3).[51] Formation of the 18-electron complex **40** from $[RuCl_2(p\text{-cymene})]_2$ and **20**, and subsequent treatment of **40** with KOH, afforded a 16-electron complex **41**. Noyori describes **40** and **41** as the catalyst precursor and 'true' catalyst, respectively. Complex **41** was then shown to form a stable ruthenium hydride **42** as a single diastereomer on treatment with propan-2-ol. Both **41** and **42** were able to catalyse the transfer hydrogenation of acetophenone in the absence of KOH, affording enantioselectivities comparable to those obtained with the in situ formed catalyst. >From these and other data, Noyori concluded that "KOH is necessary only for the generation of catalyst **41** via the precursor **40**".[51] Also, the isolation of **42** confirms that the Ru-catalysed transfer hydrogenation takes place by way of a metal hydride rather than the metal alkoxides presumed for the MPV-type reaction.[51]

In a later review of this work, Noyori postulated that hydrogen transfer occurs via a six-membered cyclic transition state (Fig. 5), which is stabilised by hydrogen bonding from the NH to the carbonyl oxygen.[12]

Knochel has also reported some monoarylsulfonylated ligands (**21** and **22**) derived from diaminoferrocene and diaminocyclohexane, respectively.[44,56] Significantly, ligand **21** gave better enantioselectivity



Scheme 3.

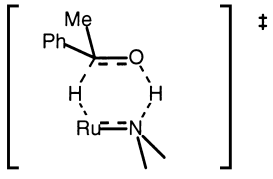


Figure 5.

with formic acid as the hydrogen source than propan-2-ol. Ligand **22** and similar derivatives afforded good levels of enantioselectivity, some of which were close to those obtained using **20** (67–96% ee).

Although Noyori and Knochel initially focused their studies on ruthenium(II) complexes, two very recent papers have described the extension of monotosylated diamines **20** and **22** to applications in iridium(III) and rhodium(III) complexes.[54,55] The complexes used in this work (Fig. 6) notably contain pentamethylcyclopentadienyl counterions which makes them isoelectronic with **40** and distinct to most other complexes of these metals which rely on rhodium(I) and iridium(I) metal derivatives. Although the specific applications of the new complexes shown in Fig. 6 have been limited to date, there is obviously great promise here. In a very detailed paper by Noyori, the complex of Rh(III) with **22** emerges as a marginally superior catalyst to that of Rh(III) with **20**, which is in contrast to the pattern described by the Ru(II) complexes.[55]

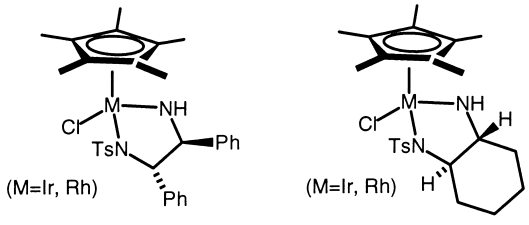


Figure 6. Rh(III) and Ir(III) complexes of **20** and **22**

A polymer-supported version of Noyori's ligand **20** has been prepared by the copolymerisation of a vinylic derivative with styrene and a crosslinking agent. The reagent thus formed worked well in reductions in conjuction with Ru(II) and, whilst recyclable, was much less effective than the homogeneous system.[57a] In contrast, the Ir(I) complexes of the supported catalysts performed rather better than the homogeneous systems. In an alternative approach to a supported reagent, it has been shown that a functionalised version of **20** may be attached to a commercial amine-loaded solid support such as TentaGel or Merrifield resin.[57b] This material appears to be capable of repeated usage in the ketone reduction process, using either formic acid or isopropanol as hydrogen source. The material may be recycled but, although the enantioselectivities remain high, the reaction time for good conversion becomes impractically long after three cycles.

3.8. β-Amino alcohol ligands

The ligand-acceleration effect of simple racemic β-amino alcohols in Ru-catalysed transfer hydrogenation was observed by Noyori.[58] It is noteworthy that of all the ligands which Noyori has tested, β-amino alcohols have proved to afford the highest levels of acceleration to the reduction reactions (some 70-fold over the background rate).[12] Monotosylated diamines gave the second-highest level of rate increase (ca. 30-fold over background) whilst all others gave little more than a seven- to eightfold acceleration. Various chiral β-amino alcohols, of differing relative configuration and nitrogen substitution, were then examined as ligands, of which the best was **23**. Notable features of this system were the need for a primary or secondary amine in the ligands and the reaction reversibility.

The stereochemically rigid amino alcohols **24**[59] and **25**[60] also work well in transfer hydrogenation in combination with Ru(II). In the case of **24** deletion of the methylene bridge (i.e. the use of phenylglycinol) results in a dramatic decrease of ee to 23% thus emphasising the importance of the rigid stucture.[59] The introduction of a two-methyl group adjacent to the hydroxy group in **25** resulted in a completely unselective reagent. Notably, the use of the ever-popular prolinol gave only an 8% ee for the transfer hydrogenation of acetophenone.[60]

Although β-amino alcohols give excellent results in terms of rate and enantioselectivity, they appear, in common with most other ligands, to be incompatible with the formic acid/triethylamine reduction system.

3.9. Phosphinooxazoline ligands

Helmchen has applied Ru(II) complexes of chiral phosphinooxazolines, such as **26**, to the transfer hydrogenation of aromatic and aliphatic ketones in propan-2-ol.[61] Notable amongst the results were the enantioselectivities obtained for aliphatic ketones (up to 60% ee).

The closely related ferrocene derivative **27** is also an excellent ligand (ees of 84–96% in a complex with Ru for a series of aryl–alkyl ketones).[62] Careful experimentation revealed that the presence of triphenyl phosphine (from the catalyst precursor $RuCl_2(PPh_3)_3$) was essential for optimum results — its removal resulted in reduction in catalytic activity and enantioselectivity.

3.10. Tridentate P,N-containing ligands

Zhang has prepared and evaluated a series of nitrogen-containing phosphine ligands in Ru(II)-catalysed transfer hydrogenation.[63–65] The first reported was the pyridine-based diphosphine **28**, which afforded enantioselectivities of 30–74% ee.[63] More recently, N,P,N-tridentate ligands **29** and **30** have been utilised.[62,63] Notable enantioselectivities of up to 92% ee were achieved in the transfer hydrogenation of certain aliphatic ketones using ligand **30**.[65]

The tridentate O,N,P donor ligand **31** has also proved effective as a ligand although the enantioselectivities achieved do not compare favourably with most other reagents.[66]

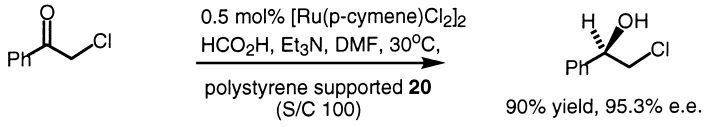
3.11. Tetradentate diamine/diphosphine ligands

Ru(II) complexes containing a tetradentate diamine/diphosphine ligand **32** (Fig. 2) have been applied in the transfer hydrogenation of aromatic ketones, furnishing products in up to 97% ee.[67] The corresponding diimino/diphosphine ligand was far less effective, presumably due to its lack of the crucial NH function.[12]

4. Specific applications of asymmetric transfer hydrogenation

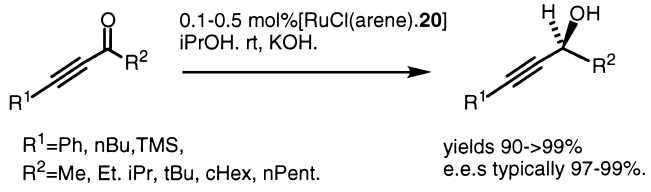
Whilst the majority of catalyst development has focused on the reduction of aryl/alkyl ketones of simple structure, there are a number of examples of alkyl/alkyl ketone reduction, although these generally proceed with somewhat lower selectivity. For example, the reduction of cyclohexyl methyl ketone with a combination of ruthenium(II) and either ligand **30** or **26** gives products of ca. 60% ee.[61,65] In a rather more useful experiment, reduction of *tert*-butyl methyl ketone gave a product of 92% ee when **30** was employed as ligand.[65]

Substituted substrates such as 2-chloroacetophenone are valuable substrates for asymmetric reduction, since their products may be converted to epoxides and other valuable synthetic intermediates. Using a polymer-supported version of **20** with the formic acid/triethylamine system, this process has been used to give (*R*)-2-chloro-1-phenethanol of 95.3% ee (Scheme 4).[57b]



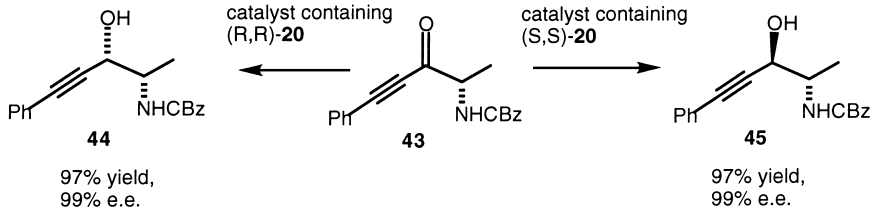
Scheme 4.

Although the transfer hydrogenation of the carbonyl group of enones appears underdeveloped,[26] the asymmetric reduction of acetylenic ketones provides a valuable method for the synthesis of functionalised target molecules.[52] In general, the reductions are highly selective, efficient and versatile (Scheme 5). In this reaction a substrate/catalyst ratio of as high as 1000 was all that was required for ees in the range of 98–99% to be obtained in virtually quantitative yield. Of the arenes in the complex, *p*-cymene and mesitylene were the optimal derivatives.



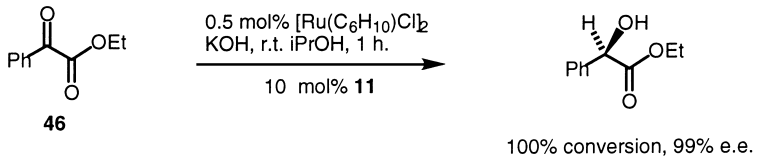
Scheme 5.

Enantiomerically pure substrates such as **43** may be employed as substrates in this process. Using either enantiomer of the ligand, i.e. (*R*,*R*)- or (*S*,*S*)-**20** in the complex leads, respectively, to the products **44** (97% yield, >99% ee) and **45** (97% yield, >99% ee) thus confirming that the catalyst selectivity greatly overrides that of the inherent diastereoselectivity in this process (Scheme 6).[52]



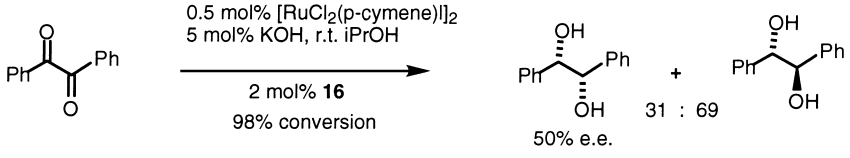
Scheme 6.

Diamine **11** has been applied to the reduction of a series of ketones including, notably, the α-keto ester **46**.[36] An almost unique result in this area was the generation of a product of 99% ee (Scheme 7), although Noyori has obtained a product of 75% ee from the reduction of the isopropyl ester derivative of **46**.[12]



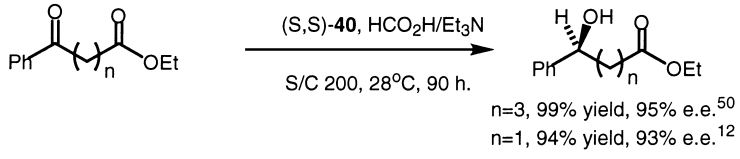
Scheme 7.

In a similar application, the reduction of 1,2-diketones has been achieved through the use of a ruthenium complex of monotosylated diamine **16** (Scheme 8).[44] Although the conversion was excellent, the ee of the product was rather low.



Scheme 8.

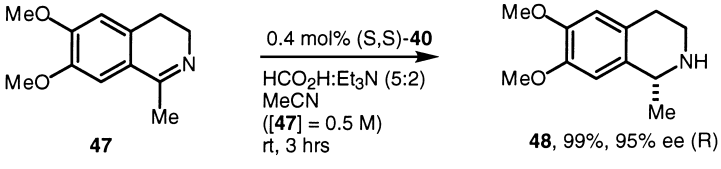
The asymmetric transfer hydrogenation of β-keto esters and higher homologues has also been reported (Scheme 9). As in previous examples, the combination of **40** with the formic acid/triethylamine system appears to be ideal for these applications. In the example shown, the aromatic group in the ligand was mesitylene rather than *p*-cymene, although the author notes that complexes derived from either ligand work well in the application.



Scheme 9.

5. Transfer hydrogenation of imines

In contrast to ketones, imines have seldom been reported as viable substrates for enantioselective transfer hydrogenation. A notable recent exception has been reported by Noyori (one representative example is shown in Scheme 10), who finds that the rate of imine reduction under the stated conditions outpaces that of ketone reduction by some 1000 times.[68]

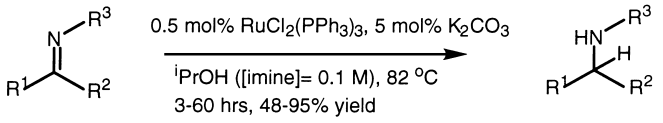


Scheme 10.

Unlike the ketone reduction, the use of an additional solvent such as acetonitrile or dimethylformamide appears to be critical for optimum results.

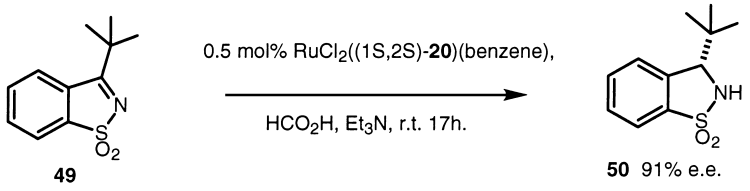
A preformed chiral Ru(II) complex, such as **40**, catalysed the transfer hydrogenation of various cyclic and acylic imines with a formic acid:triethylamine mixture. Particularly effective substrates were dihydroisoquinoline derivatives **47** which yielded tetrahydroisoquinolines **48** with high ee. Labelling studies with deuterated propan-2-ol indicated that propan-2-ol could not be used as a hydrogen source for this particular catalytic system. However, Bäckvall had earlier reported the ruthenium-catalysed

(racemic) transfer hydrogenation of imines by propan-2-ol in the presence of an appropriate base such as potassium carbonate (Scheme 11).[69] Unlike the Noyori reaction (Scheme 10) the reduction of imines using the Bäckvall method was reported to be somewhat slower than the corresponding ketone reductions.



Scheme 11.

Transfer hydrogenation provides an excellent method for the asymmetric synthesis of enantiomerically pure sultams.[70] Reduction of the cyclic precursor **49** with Noyori's monotosylated diamine **20** in a complex with ruthenium(II) under the formic acid/triethylamine conditions results in clean reduction to **50** in 91% ee (Scheme 12). The material could be recrystallised to an enantiomerically pure product in 75% overall yield.



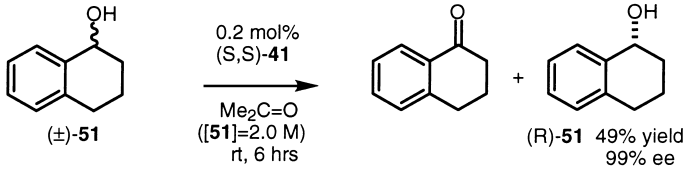
Scheme 12.

6. Kinetic resolution of racemic secondary alcohols

Although the reversibility of the asymmetric transfer hydrogenation of ketones catalysed by chiral Ru(II) complexes is its greatest drawback, the situation can be turned to the chemist's advantage by utilising this inherent reversibility to effect kinetic resolution of racemic alcohols. Noyori has elegantly demonstrated the potential of this approach using the 16-electron Ru(II) complex **41** (Scheme 13).[71]

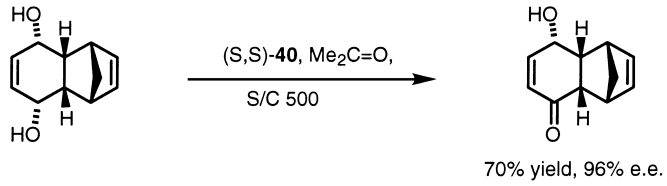
Scheme 13.

An outstanding example of this work is the kinetic resolution of racemic α-tetralol ((±)-**51**); when a 2.0 M solution of (±)-**51** in acetone was exposed to the preformed catalyst **41** at room temperature for 6 h, (*R*)-**51** of 99% ee was recovered in 49% yield (Scheme 14).[71]



Scheme 14.

Although by its nature, the process can only provide a theoretical yield of chiral alcohol of 50%, Noyori notes that some alcohols obtained in high ee via this method are difficult to obtain by enantioselective reduction of the corresponding ketone. In addition, kinetic resolution of *meso* diols was also described, potentially more appealing because the theoretical yield of chiral product is 100% (Scheme 15).



Scheme 15.

7. Conclusions

The use of transfer hydrogenation is a valuable and versatile reaction which is now emerging as one of the very best methods for achieving asymmetric transformations. The combination of practical simplicity, mild reaction conditions, relatively non-hazardous reagents and high selectivities from which this method benefits is unparalleled by most other processes in synthetic organic chemistry. No doubt even further impressive developments will soon be forthcoming in this rapidly moving area.

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