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On the NH Effect in Ruthenium-Catalysed Hydrogenation of Ketones: Rational Design of Phosphine-Amino-Alcohol Ligands for Asymmetric Hydrogenation of Ketones

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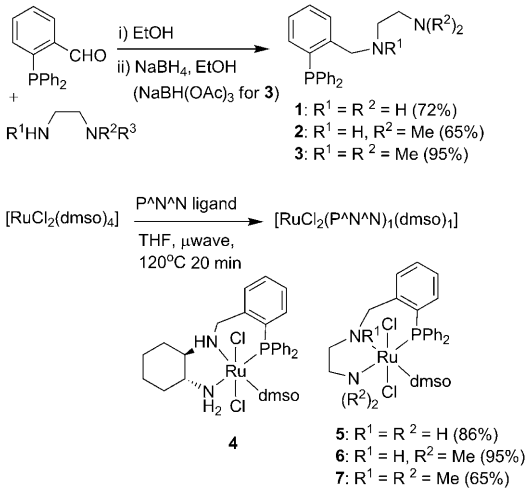
The asymmetric hydrogenation of simple ketones, such as acetophenones, has become an important synthetic method as a result of the development of [$RuCl_2$(diphosphine)-(diamine)] catalysts by Noyori and co-workers.[1] A large range of catalysts of this general type have now been prepared.[2] Their reactivity is quite in contrast to simple M-(diphos)X_n salts that are barely active as catalysts for ketones that cannot chelate to the metal centre. The enhanced reactivity for reduction of simple ketones is proposed to be due to the "bifunctional mechanism" in which the ketone–hydrogen bonds to the primary amine terminus of the ligand, activating it to attack by Ru–hydride and controlling stereoselectivity.[1c] There are reports that suggest these catalysts are not effective for certain ketones, such as bulky ketones (low reactivity), sterically similar aryl–aryl ketones (low selectivity), some ketones with strongly co-ordinating substituents (low reactivity), and alkyl–alkyl ketones (low selectivity) as well as a range of individual substrates that do not undergo asymmetric reduction readily. The discovery of structurally distinct, new classes of ketone hydrogenation catalyst[3] that deviate from the [$RuCl_2$(diphosphine)(di-primary-amine)] blueprint therefore might present one of the best opportunities to solve these problems; the importance of chiral secondary alcohols requires that methodology exists for every possible type of substrate in order to see this technology widely exploited in industry and more generally in synthesis. We have shown that Ru catalysts derived from P^N^NH_2 ligands can hydrogenate some poorly reactive ketones with good enantioselectivity. The initial design of the catalyst envisaged hydrogenation of polar bonds facilitated by the primary amine terminus of the ligand in a co-ordination environment that is more accessible for bulky substrates relative to the Noyori catalysts.[4]

Rather than synthesising a very large library of new P^N^NH_2 catalysts, we felt that an investigation of catalyst–structure activity relationships might throw up some leads for new catalysts, along with shedding light on some mechanistic issues, since it had not been possible to isolate the reaction intermediates in our previous studies. In this communication, we report some surprising findings from our kinetic experiments and the introduction of phosphino-amino-alcohol ligands for Ru-catalysed hydrogenation.

The new achiral ligands, **1–3** can be prepared in one step from commercial starting materials and then converted into complexes of type [$RuCl_2$(P^$NR^1N(R^2)_2$(dmso)] by microwave-assisted complexation with [$RuCl_2(dmso)_4$] in THF at 120 °C (Scheme 1). Complexes **4–7** can be obtained pure by chromatography or recrystallisation and are easily handled in air.

We carried out kinetic studies on the hydrogenation of α,α-dimethylpropiophenone, a substrate that was initially re-



Scheme 1. Synthesis of P^N^N ligands and their ruthenium complexes.

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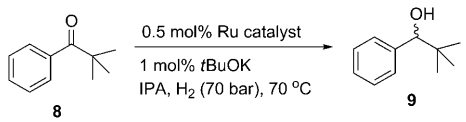
ported to be nearly unreactive with [$RuCl_2$(binap)(diamine)] (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) catalysts (6% yield),[1c] but can be reduced readily with catalyst **4** at room temperature, or more conveniently for kinetic studies at 70°C. A catalyst that can reduce this ketone in high yield therefore has significant competence in ketone hydrogenation. We were intrigued to find in batch experiments that all the catalysts reduced α,α-dimethylpropiophenone in high yield after 16 h reaction time. Reactions carried out with real-time gas-uptake and subsequent processing of the data in graphical form[5] enable a number of insights to be gained. For brevity, the kinetics graphs are placed in the Supporting Information. Plotting a graph of rate against time clearly shows a significant induction time; maximum turnover frequencies and average initial turnover frequencies during the first 35 min for all four catalysts are shown in Table 1, along with notes on the rate profile.

There is a drop in activity and an increase in induction time in going from catalyst **4** to the achiral P^NH^NH_2 catalyst, **5**. This indicates that the shape of the catalyst, and perhaps the geometry at the Ru centre has a very significant influence on the catalyst productivity. Surprisingly, exchanging the NH_2 groups for an NMe_2 group as in **6** gives a catalyst with quite similar activity, casting significant doubt on the primary amine-assisted transition state that would have seemed likely with these catalysts. There is a significant drop in activity in switching to the P^NMe^NMe_2 catalyst, **7**, although this catalyst does slowly reduce α,α-dimethylpropiophenone through to completion in about 12 h. The fact that even trimethylated, **7** does function as a catalyst for this low reactivity substrate suggests that an inner-sphere mechanism can operate, albeit rather slowly. Both the P^NH^NH_2 catalysts **4** and **5** catalyse reduction with pseudo first-order dependence in ketone concentration. The P^NH^NMe_2 catalyst, **6** clearly undergoes a relatively sudden drop in activity during reaction, although is of broadly similar rate as the catalyst **5**. Most interestingly, the P^NMe^NMe_2 catalyst reduces this low reactivity ketone with no dependence on ketone concentration. This was also checked in individual batch experiments at different concentrations. The lack of an induction period and contrasting rate profile with the trimethylated catalyst is good evidence that the catalyst is not converted into another species (i.e., demethylation), although this remains a very unlikely possibility until a catalytic intermediate is isolated. The fastest reactions are limited, most likely by several factors including an event involving the ketone substrate (most likely either ketone binding or nucleophilic attack of hydride), whereas the slower catalyst is slow due to other steps in the catalytic cycle, most likely hydrogen activation, being retarded to a greater degree when the NH is not present.

With these results in hand, we were intrigued if similar reactivity patterns would be present in Noyori catalysts; the details of these hydrogenations has generated intense interest,[6,7] because of their significant importance. However, despite the quality and depth of the studies reported, the relative importance of the NH effect to each step in the catalytic cycle has been rather problematic to study experimentally since the hydrogenation is fast, and the NH substituents undergo exchange in the protic solvents which are required for effective catalysis. Noyori reported early on that at least one primary NH_2 group is necessary for effective reaction.[1d] However, some ketone reduction catalysts that do not have NH ligands have been reported. We carried out hydrogenations with the "non-NH" catalyst [$RuCl_2$(binap)Py_2][8] at different concentrations of acetophenone. These results reveal that the reactions are also pseudo-zero order in ketone, in contrast to the pseudo first order kinetics that have been described for [$RuCl_2$(binap)(dpen)] (dpen = 1,2-diphenylethylenediamine) under similar conditions (Scheme 2).[6] Thus ketone binding or reduction is not rate-determining in the slower hydrogenations catalysed by the non-NH containing catalyst [$RuCl_2$(binap)Py_2] either.

We were interested to investigate if the presence of NH groups had any effect on the hydrogenation of alkenes. We carried out hydrogenation of styrene, a substrate that can be assumed to be reduced exclusively by inner-sphere processes. In our original studies, we found that catalyst **4** does show significant chemoselectivity for reduction of C=O over C=C bonds, but it is less chemoselective than Noyori catalysts unless conditions are carefully controlled. Thus at 70°C, styrene is hydrogenated within 12 h with all the catalysts with similar rates for each catalyst and no significant induction period. These results argue for the NH effect (and the sensitivity to ligand shape) being specific for ketone hydrogenation; our view is that the most likely possibility is that alkene hydrogenations share very little of the ketone hydrogenation catalytic cycle, with the cycle operating being relatively insensitive to ligand structure.

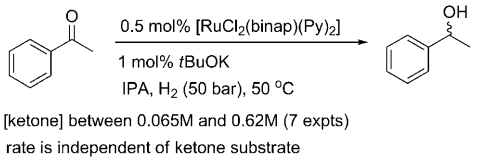
Table 1. Summary of kinetic data for the hydrogenation of α,α-dimethylpropiophenone using Ru catalysts **4**–**7**.



8 **9**

Catalyst[a]	Maximum TOF[b]	Average initial TOF[b]	Notes on kinetics[c]
4	655	350	induction period followed by pseudo-first-order kinetics
5	653	106	longer induction period followed by pseudo-first-order kinetics
6	403	115	Induction period, then fast reaction with sudden decrease in rate
7	188	35	constant rate throughout; zero order in ketone substrate

[a] Reaction carried out as described in the Scheme and in the Supporting Information, at constant pressure of 70 bar with hydrogen feed monitored. [b] Average initial TOF in mol product per mol catalyst per h measured from first 35 min of the reaction. Maximum TOF in mol product per mol catalyst per h is the rate reached after the induction period take from a plot of rate against time.

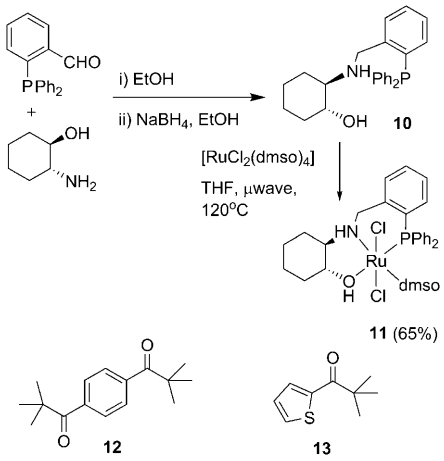


Scheme 2. Hydrogenation of acetophenone using the non-N–H Noyori catalyst, $[RuCl_2(binap)(pyridine)_2]$; productivity is independent of ketone concentration. IPA = isopropyl alcohol.

The NH–ketone hydrogen bond in the Noyori mechanism almost certainly defines a well-defined transition state that enables a high level of enantioselectivity, but in terms of productivity, it's more significant role is in enhancing hydrogen activation. It is likely there are many highly reactive ketone-hydrogenation catalysts that do not use NH ligands waiting to be discovered, with an efficient mechanism for hydrogen activation being the more important feature that needs to be addressed in designing a new catalyst. Some recent studies have suggested that the original proposal that heterolytic splitting of hydrogen takes place between an amido NH(−) ligand and Ru needs to be modified, since the amido complex seems to be protonated readily.[6] However, when a final detailed picture of the mechanism is decided, it should reconcile the importance of the NH ligand in hydrogen activation as well as ketone binding. Our working hypothesis for catalyst **4** is that the secondary amine part of the ligand provides a weak interaction that places (but does not strongly activate) one face of the ketone in the correct orientation for the hydride attack. This could be followed by either deprotonation of the NH ligand to deliver product or proceed by the "re-entry mechanism" postulated by Bergens and co-workers[7u] (early part of transition state is outer-sphere with concerted C–H and Ru–O bond formation). All of the NH-containing catalysts presumably benefit from the ability of the NH ligand to promote some part of the hydrogen activation process. This could utilise the interplay between amino/amido bonding or the reduced steric demand of NH substituents. In any case, we felt these observations gave us a lead to investigate catalysts that do not contain a primary amine terminus, and herein we also report a new type of catalyst based on P^NH^OH ligands.

We have found that an analogous phosphine-amino-alcohol ligand **10** (Scheme 3) on treatment with $[RuCl_2(dmso)_4]$, gave a similar type of complex of type $[RuCl_2(dmso)$-(P^NH^OH)] (**11**). There were no problems connected to OH deprotonation or lability despite the weaker binding and more reactive OH function.

Our structure–activity studies suggested that swapping the primary amine terminus for an alcohol should still deliver active catalysts for the reduction of a deactivated ketone, and a validation of our model would be complex **11** giving the same sense of enantioselection with similar *ee*. Pleasingly, complex **11** does reduce ketones readily and seems to give either very similar or slightly higher enantioselectivity when compared to the original P^NH^NH_2 catalyst (Table 2) (although the differences are only just outside experimental variability, they do seem to be reproducible; we have probably run the reduction of **8** with catalyst **4** over 100 times and never got over 77% *ee*). There are, however, some differences between catalysts **4** and **11**. Whereas, the original catalyst is somewhat unusual in operating well using a Ru/base co-catalyst ratio of just 2, catalyst **11** requires a Ru/base ratio of 5 to work well. Another difference is that the P^NH^OH catalyst is exclusively a pressure-hydrogenation catalyst and does not promote transfer hydrogenation with reasonable rates. In general, catalyst **11** is slightly less reactive catalyst than **4**, but in some cases shows significantly increased reactivity; thus reduction of ketone **13**, deactivated by bulk and the heterocycle completely inhibits hydrogenation with **4**, but can be reduced albeit with quite moderate results with catalyst **11**.



Scheme 3. Synthesis of a phosphine-amino-alcohol catalyst, and new ketones reduced in Table 2.

Table 2. Comparison of some hydrogenations of deactivated ketone substrates using complexes **4** and **11** as catalyst.

Entry	Catalyst	T [°C]	t [h]	Ketone	Conversion [%][a]	*ee*
1	**4**	50	3	**8**	>99	77 (*S*)
2	**11**	35	16	**8**	>99	79 (*S*)
3[b]	**11**	50	3	**8**	>99	80 (*S*)
4[c]	**4**	50	16	**12**	>99	94
5[d]	**11**	50	16	**12**	>99 {93}	97
6	**4**	50	16	**13**	0	n.d
7	**11**	50	16	**13**	15	n.d
8	**11**	50	65	**13**	65 {46}	64 (*S*)

[a] Reactions carried out using 0.5 mol% of the (*R*,*R*) catalyst with base/catalyst ratio of 2:1 for catalyst **4**, and 5:1 for catalyst **11** in isopropyl alcohol as solvent and using initial pressure of 50 bar hydrogen unless stated otherwise. Conversion determines against methyl naphthalene internal standard, with products isolated in selected experiments; {yields after chromatography}. [b] 1 mol% catalyst used. [c] (*R*,*R*)+(*S*,*S*)/*meso* = 6:1. [d] (*R*,*R*)+(*S*,*S*)/*meso* = 7:1.

In conclusion, the NH rather than the NH_2 substituent within tridentate P^NH^NH_2 ligands is of significant importance to the catalytic cycle. Kinetic studies suggest that a step in the catalytic cycle that does not involve the substrate, most likely hydrogen activation, is most significantly enhanced by an NH group in both our catalysts and the

Noyori system. Following on from these observations, we have reported the first results which suggest phosphine-amino-alcohol ligands might be useful in Ru-catalysed ketone hydrogenation. The significance of these results is primarily in opening up this class of complex as a potential candidate for effective hydrogenation catalysis. Our search for a toolbox of catalysts that can deal with every ketone substrate with high enantioselectivity and reactivity will now also incorporate phosphine-amino-alcohol ligands derived from the plethora of enantiopure amino alcohols.

Experimental Section

Full Experimental details, characterisation data and graphical rate equations can be found in the Supporting Information.

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Keywords: chirality · hydrogenation · kinetics · phosphines · tridentate ligands

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