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Remarkable co-catalyst effects on the enantioselective hydrogenation of unfunctionalised enamines: both enantiomers of product from the same enantiomer of catalyst

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During studies on the enantioselective hydrogenation of unfunctionalised enamines, a very surprising switch in enantiopreference was observed; [((*R*,*R*)-Et-DUPHOS)-Rh(COD)]BF_4 hydrogenates an enamine to give (*R*)-amine with up to 73 % e.e., but when iodine is added as a co-catalyst, the (*S*)-amine is formed with up to 61% e.e. Mechanistic studies implicate a protonation-iminium ion reduction pathway.

The hydrogenation of a wide range of enamides containing activating and coordinating N-acyl substituents is a mature and core technology in industrial enantioselective catalysis. The applicability of this reaction at large scale stems not just from the high enantioselectivities observed, but the use of high substrate to catalyst (S/C) ratios that make the method economic.[1] The enantioselective hydrogenation of enamines that lack a coordinating substituent is a far more sluggish reaction and is problematic to implement commercially.[2-4] Some highly enantioselective catalysts have been reported for the especially challenging reduction of unfunctionalised enamines to tertiary alkyl amines, but S/C ratios are generally around 100 or lower.[5] In addition, a broad scope has not yet been demonstrated. We began addressing this challenge by assessing the catalyst structure requirements for high activity in these reactions using Rh catalysts.[6] We recently reported what seem to be the first examples of homogeneous hydrogenation of unactivated enamine at high S/C ratios (up to 5000) using an achiral catalyst.[6b] The key observation in this approach was that weakly-donating phosphines give the most active Rh catalysts. We have attempted to make use of some weakly electron-donating chiral ligands for this enamine hydrogenation, but getting meaningful enantioselectivity has been challenging thus far. We therefore considered if known hydrogenation catalysts might give good results if the reaction conditions could be optimised. Here we show a remarkable solvent effect *and* a remarkable co-catalyst effect that improves the activity and transforms the enantioselectivity of Rh / bidentate phospholane catalysts when used in the hydrogenation of unactivated unfunctionalised enamines.

Using the well known pre-catalysts, [Rh((*R*,*R*)-Et-BPE)(COD)]BF_4, (*R*,*R*)-**3**, and [Rh((*R*,*R*)-Et-DUPHOS)(COD)]BF_4, (*R*,*R*)-**4**, the hydrogenation of unfunctionalised enamine **1a** proceeds slowly and gives low enantioselectivity (Table 1, Entry 1-2 and 4-5). Testing of some other privileged ligands for hydrogenation catalysis also showed these substrates to give low e.e. when hydrogenated (see ESI). If the hydrogenations were carried out in chlorobenzene as solvent, we were delighted to find that the activity *and* the enantioselectivity increase markedly when using either catalyst, **3** and **4** (Table 1, entries 3 and 6).

In some hydrogenation processes, co-catalysts such as protic additives,[7] and halogens[8] are occasionally used to good effect. A combination of molecular iodine and acetic acid has been used as an additive for enamine hydrogenation; the iodine improved e.e. and the activity improved when acid was present.[5c] We studied the use of iodine as an co-catalyst in a bid to increase the enantioselectivity. The results were truly surprising (Chart 1a and 1b); while the use of [Rh((*R*,*R*)-Et-BPE)(COD)]BF_4 gives the (*R*)-enantiomer of product with either low (toluene, (*R*), 14-49% e.e.) or quite good enantioselectivity (chlorobenzene, (*R*), 58% e.e.), when the reactions are carried out in the presence of iodine as co-catalyst, the opposite enantiomer is formed with very significant enantioselectivity (chlorobenzene, (*S*), 58% e.e.). A similar dramatic switch occurs when using [Rh((*R*,*R*)-Et-DUPHOS)(COD)]BF_4 catalyst. In this case, we observe a selectivity of 86.5% for the (*R*)-enantiomer of product (i.e. 73% e.e.) switching to a selectivity of 80.5% for the (*S*)-enantiomer just by including a small amount of iodine in the reactor! Similarly large effects were also seen on the related enamine **1b** using both these catalysts (Chart 1b).

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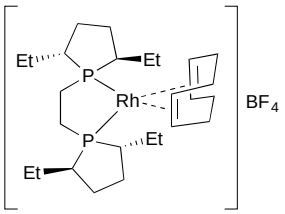
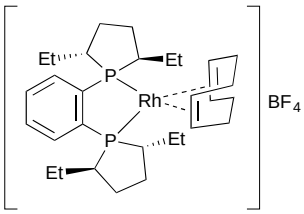
Electronic Supplementary Information (ESI) available: [NMR spectra, characterisation data and an experimental section are provided]. See DOI: 10.1039/x0xx00000x

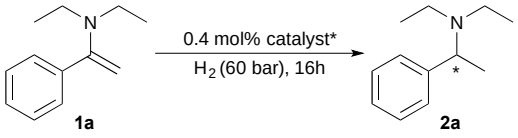
Table 1. Enantioselective hydrogenation of enamine 1a to amine 2a using chiral Rh catalysts 3 and 4.



[((*R*,*R*)-Et-BPE)Rh(COD)]BF_4 (**3**)



[((*R*,*R*)-Et-DUPHOS)Rh(COD)]BF_4 (**4**)



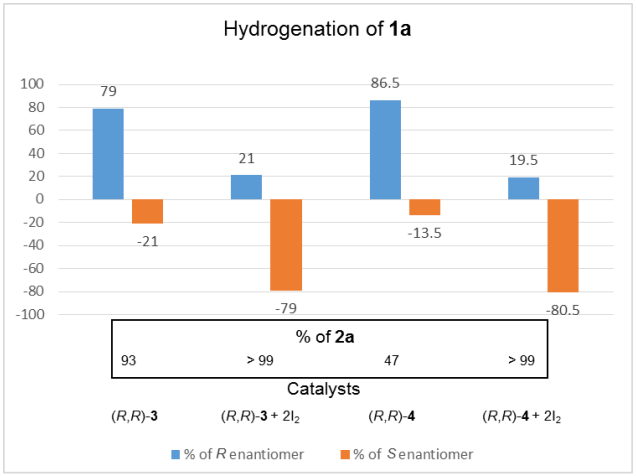
Entry[a]	Solvent	Catalyst	T, °C	**2a**, %[b]	ee, %[c]
1	PhMe	(*R*,*R*)-**3**	65	>99	14 (*R*)
2	PhMe	(*R*,*R*)-**3**	25	36	49 (*R*)
3	PhCl	(*R*,*R*)-**3**	25	93	58 (*R*)
4	PhMe	(*R*,*R*)-**4**	65	>99	28 (*R*)
5	PhMe	(*R*,*R*)-**4**	25	16	27 (*R*)
6	PhCl	(*R*,*R*)-**4**	25	47	73 (*R*)

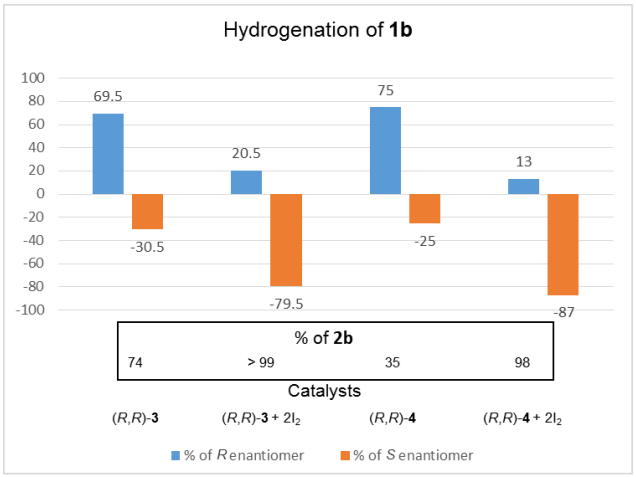
[a] General conditions: 1 mmol of enamine, 0.4 mol% of Rh catalyst, 0.1 mL of 1-methylnaphthalene as an internal standard, H_2 gas (60 bar), solvent (2 mL), 16 hours. [b] Determined by ^{1}H NMR relative to 1-methylnaphthalene. The only side product observed is a ketone which is formed due to partial hydrolysis of enamine. This did not exceed 5% in the reactions above. [c]Enantiomeric excess determined by ^{1}H NMR after addition an excess of (*R*)-(–)-α-methoxyphenylacetic acid. Stereochemistry of amines was assigned after comparison to authentic sample of enantiomerically pure (*S*)-**2a**.

Iodine has been used before as an additive, but we are not aware of any examples of the co-catalyst promoting such a dramatic switch in enantioselectivity in any alkene hydrogenation. The additive also has a strong co-catalytic effect. This can be seen for both the reactions in chlorobenzene (compare the right hand side of Chart 1) and in toluene where iodine also exerts this switch in selectivity with dramatic differences in productivity (compare Table 1, entry 2 with Table 2, entry 3). The ESI also shows an example where over a thousand turnovers are accomplished in 16 hours reaction time at 40 °C in chlorobenzene. In contrast, THF was a far less effective solvent (Table 2, entries 7 and 8) and reactions carried out in methanol as solvent gave racemic products (Table 2, entries 5 and 6). A sample of amine **2a** of 61% e.e. was subjected to the reaction conditions of hydrogenation in methanol overnight both with and without iodine co-catalyst. No racemisation occurs and hence this is not the origin of the lack of selectivity.

These findings show alternative reaction conditions can have a profound effect on the hydrogenation of unfunctionalised enamines. These co-catalyst effects imply that the pre-catalysts have been changed very significantly by the addition of iodine. If both catalysts operated by a traditional mechanism, it is surprising that both can give similarly high selectivity for different enantiomers. It seems quite possible that the mechanism of enamine hydrogenation, at least using the iodine-modified catalysts, could differ significantly from that of an enamide hydrogenation.

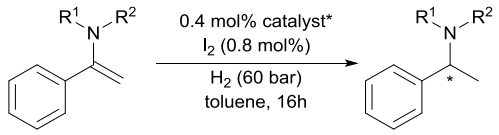
Chart 1a and 1b: Enantioselective hydrogenation of enamines **1a** (Chart 1a) and **1b** (Chart 1b): remarkable effects of iodine co-catalyst in chlorobenzene as the solvent.





While fully elucidating all pathways in enamine hydrogenation catalysis is a project in its own right, we have carried out some informative mechanistic experiments and report these here. The reaction of pre-catalyst and iodine was monitored by $^{31}P\{^1H\}$ NMR. [Rh((*R*,*R*)-Et-BPE)(COD)]BF_4 was dissolved in CD_2Cl_2, reacted with 1 equivalent of iodine (See ESI for spectra). This gives a mixture of starting material and a new species ($^{31}P\{^1H\}$ NMR: δ = 114.5, d, $J_{P\text{-}Rh}$ = 113 Hz; δ = 108.9, d, $J_{P\text{-}Rh}$ = 115 Hz). The reaction with two equivalents of Iodine forms the new species more or less exclusively. Exact mass spectroscopy of the solid forms after removal of solvent suggests the presence of the $[C_{36}H_{72}I_5P_4Rh_2]^+$ ion.

Table 2. Enantioselective hydrogenation of enamines **1a** and **1b** using Rh-bis-phospholane catalysts in the presence of iodine co-catalysts in toluene.



1a: $R^1 = R^2 = Et$
1b: R^1 = Me, R^2 = Bn

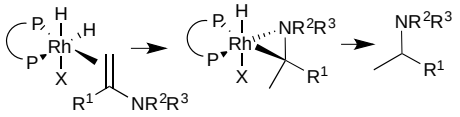
2a, 2b

Entry[a]	Enamine	Catalyst*	T, °C	Conversion of enamine, %[b,c]	Amine, %[b]	ee, %[d]
1	**1a**	(*R*,*R*)-**3**	65	>99	>99	48 (*S*)
2	**1a**	(*R*,*R*)-**4**	65	>99	>99	58 (*S*)
3	**1a**	(*S*,*S*)-**3**	25	>99	>99 [76]	65 (*R*)
4	**1a**	(*R*,*R*)-**4**	25	48	44	69 (*S*)
5[e]	**1a**	(*S*,*S*)-**3**	65	>99	83	racemic
6[e]	**1a**	(*R*,*R*)-**4**	65	>99	83	racemic
7[f]	**1a**	(*S*,*S*)-**3**	65	>99	>99	51 (*R*)
8[f]	**1a**	(*R*,*R*)-**4**	65	>99	96	10 (*S*)
9	**1b**	(*R*,*R*)-**3**	65	>99	>99	46 (*S*)
10	**1b**	(*R*,*R*)-**3**	25	>99	>99 [85]	60 (*S*)
11	**1b**	(*R*,*R*)-**4**	25	59	56	77 (*S*)

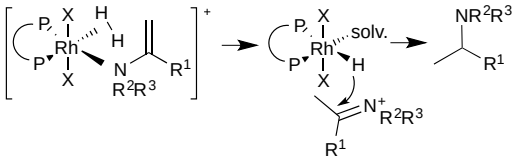
[a]General conditions: 1 mmol of enamine, 0.4 mol% of Rh, 0.48 mol% ligand, 0.1 mL of 1-methylnaphthalene as an internal standard, H_2 gas (60 bar), toluene as a solvent (2 mL), 16 hours. [b]Determined by ^{1}H NMR relative to 1-methylnaphthalene. Isolated yield in square brackets. [c]The only side product observed is a ketone which is formed due to partial hydrolysis of enamine. [d]Enantiomeric excess determined by ^{1}H NMR after addition an excess of (*R*)-(–)-α-methoxyphenylacetic acid. Stereochemistry of amines was assigned after comparison to authentic samples of chiral amines. [e]Solvent = MeOH. [f]Solvent = THF.

Scheme 1. Possible structure of the ion detected by HRMS (top), and key aspects of two possible mechanisms for enamine hydrogenation.

(1) Conventional alkene hydrogenation pathway H_2 ox. addition could precede enamine coordination or occur afterwards.



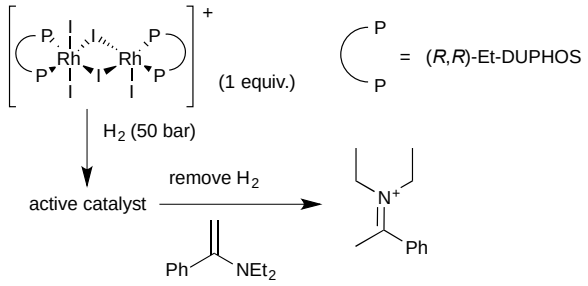
(2) Protonation-hydride reduction pathway (iminium ion intermediate)



A possible structure is shown in Scheme 1, which is likely to show the observed two separate resonances in the $^{31}P\{^1H\}$ NMR spectrum with equivalent phosphorus environments within each ligand. This bimetallic rhodium iodide complex was generated first, isolated as a solid and tested as a catalyst; it was found to be catalytically competent and to give the characteristic enantiopreference of the iodine-modified catalysts. The Et-BPE derived complex gave nearly identical results to the *in situ* catalyst (62% e.e. and full conversion under conditions similar to Table 2, entry 3). The DUPHOS based system under similar conditions of Table 2, entry 4 returned slightly lower e.e. and conversion (53% e.e. 28% conversion). None-the-less, these results are consistent with this iodide complex being the pre-catalyst for hydrogenation. It is possible that this species can be reduced to form a Rh-hydride or dihydride of some form allowing a conventional mechanism for alkene hydrogenation (Scheme 1, eq. 1).[9] However, an alternative mechanism could involve protonation of the enamine, most likely from a Rh-dihydrogen complex (e.g. $[Rh(I)_2(diphosphine)(H_2]+$, followed by addition of Rh hydride to the iminium ion formed (Scheme 1, eq. 2). The viability of iminium ion hydrogenation has been proven using Ru(II) and Rh(III) hydride piano-stool complexes.[10] Despite these complexes favouring the reverse acid-base reaction where iminium ions are protonated by Rh-H to form enamines, a single example of an enamine hydrogenation using 10 mol% of an achiral Ru catalyst was demonstrated. It can be envisaged that the Rh-iodide complex generated here could form an unusually acidic dihydrogen complex, certainly relative to the $[Rh(diphosphine)(H)_2]BF_4$ intermediates formed from iodine-free catalysts. To shed further light on this, we carried out a stoichiometric experiment where 100 mol% of the Rh iodide catalyst was generated from [Rh((*R*,*R*)-Et-DUPHOS)(COD)]BF_4 and iodine and then treated with 50 bar of hydrogen. ‡ The gas pressure was reduced to 1 atmosphere and then treated with enamine **1a**. The proton NMR shows essentially quantitative conversion of the enamine to a species

that can be assigned as the iminium ion (the ^{1}H and ^{13}C resonances resemble the known iminium ion formed when we add HBF_4 is added to enamine **1a**). The hydride region of the NMR is too weak to fully characterise, implying that some catalyst decomposition may occur when the hydrogen pressure is removed. This strongly implicates a protonation-hydride reduction mechanism as being operative when using the iodine modified catalysts.

Scheme 2. Stoichiometric reaction between catalyst and enamine **1a** gives an iminium ion when hydrogen is removed.



In summary, we believe these findings may be enabling towards solving the unresolved challenge of making catalysts that are active enough to be industrially useful for the hydrogenation of unfunctionalised enamines. The use of iodine co-catalyst, especially in chlorobenzene as solvent, transforms the otherwise poor pre-catalyst [Rh((*R*,*R*)-Et-DUPHOS)(COD)]BF_4 so that it gives the opposite enantiomer and gives much higher rates of hydrogenation. Preliminary investigations show that a Rh-iodide complex is involved as a pre-catalyst and that this may utilise a protonation-hydride reduction pathway with an iminium ion intermediate for enantioselective hydrogenation. The imimium ion pathway may help accelerate, or change the nature of, the slow steps in the catalytic cycle for the hydrogenation of unfunctionalised enamines. Further studies on the mechanism and using these insights to identify new catalysts and substrate scope for enamine hydrogenation, along with some new applications in catalysis are underway.

Notes and references

‡ The stoichiometric reaction was carried out in CD_2Cl_2 to avoid any solubility issues, but catalytic enamine hydrogenation does occur with a rate enhancement and enantiomer switch in this solvent). This reaction was carried out with the enamine added both before the hydrogen and after and gave the same result.

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