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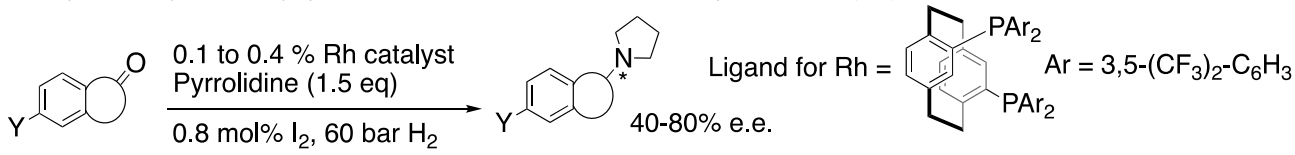

Rhodium catalysts derived from a fluorinated phanephos ligand are highly active catalysts for direct asymmetric reductive amination of secondary amines.

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An asymmetric hydrogenation of enamines is efficiently catalysed by rhodium complexed with a fluorinated version of the planar chiral paracyclophane-diphosphine ligand, Phanephos. This catalyst was shown to be very active, with examples operating at just 0.1 mol% of catalyst. This catalyst was then successfully adapted to Direct Asymmetric Reductive Amination, leading to the formation of several tertiary amines with moderate e.e., if activated ketone/amine partners are used.

Keyword 1: Enamine Hydrogenation.
Keyword 2: Electronic Effects.
Keyword 3: Enantioselective Hydrogenation.
Keyword 4: Planar Chirality
Keyword 5: Deuterium Labelling

Dedicated to the memory of Prof. Jon M. J. Williams: a very nice man, who was often ahead of his time in discovering new types of chemical reactivity.

1. Introduction.

Enantiomerically pure amines are extensively used in the synthesis of agrochemicals and pharmaceutical intermediates.[1] There are many methods to make chiral amines,[1,2] but those that make use of molecular hydrogen are of special interest in terms of being scalable, potentially economic technology for the manufacture of chiral amines at large scale.[3] Hydrogenations that produce tertiary amines as products urgently need further development; on one hand this is due to the importance of tertiary amines as synthesis building blocks, and as final drug products, but also since they appear to be the most challenging amine class to produce using hydrogenation. None of the results to date really compare with the best examples of hydrogenation used to make primary amines, secondary amines and amides.[4-6] There are several hydrogenation approaches to chiral tertiary amines. Not discussed in detail here are sequences in which hydrogenation is used to make chiral primary or secondary amines, which are then typically deprotected before being alkylated. In fact, consideration of this route reveals another reason why more direct hydrogenation approaches to tertiary amines are especially desired: the alternative routes starting from an enamide or imine hydrogenation possess neither atom or step economy. A more direct approach has been to hydrogenate isolated enamines or iminium ions. The hydrogenation of enamines lacking the coordinating activating group in

enamides is very challenging.[7] The very best studies in this area make use of catalyst loadings 100-or more times higher than what is typically used in commercial scale hydrogenations.[8] The most desirable approach would be Direct Asymmetric Reductive Amination (often given the acronym, DARA)[9] of a secondary amine with a carbonyl compound to produce a chiral tertiary amine directly. At the onset of this work, such reactions using molecular hydrogen were unknown, and the major breakthrough paper to initiate this topic has only recently been published.[10] This work establishes that high *ee* using mild conditions can be achieved in Direct Asymmetric Reductive Amination with a secondary amine using a chiral catalyst. Whilst this is a good step forward, it is worth noting the catalyst loadings of 1 mol% are again higher than might be required for a commercial hydrogenation. This approach made use of stoichiometric amounts of $Ti(O\textit{i}Pr)_4$ as a mediator: not ideal from the perspective of simplicity of operation or low cost. Our approach to this challenge has been to start with a search for the most active catalysts for achiral reductive aminations with secondary amines, since high catalyst loadings are a frequent barrier to commercialisation. This resulted in us finding that Rh catalysts derived from simple monodentate ligands like tris-(3,4,5-trifluorophenyl)phosphine enable achiral enamine hydrogenation to proceed using as little as 0.05 mol% catalyst loading.[11,12] More recently we have communicated one approach to DARA, which used electronically similar achiral Rh catalysts, this time derived from tris(-2-furyl)phosphine, to react readily available enantiomerically pure cyclic ketones with secondary amines in a highly effective diastereoselective DARA giving tertiary amine products with high *de.*[13] A more general advance would be if equally reactive *chiral* Rh catalysts with electron-withdrawing aromatic substituents on the phosphine ligand could be used in an effective DARA. The publication by Wu et al[10] prompted us to report our complementary approach to DARA; high catalytic activity has been observed without stoichiometric Lewis acids as activators, combined with moderate enantioselectivity. We believe DARA using secondary amine partners could be a truly effective catalytic methodology in the near future with further research.

2. Results/discussion.

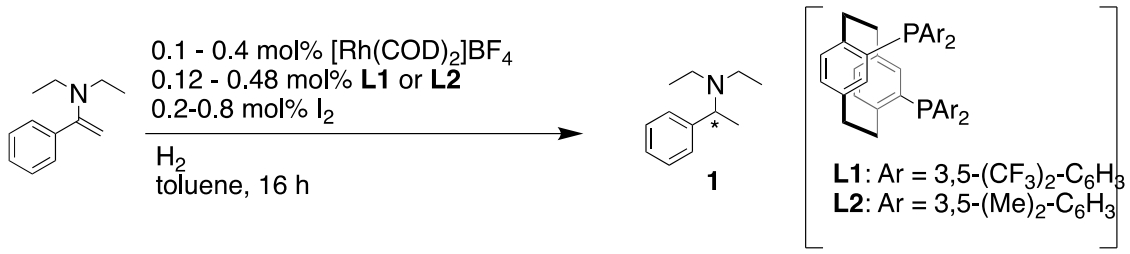
Our working hypothesis was that a chiral diphosphine with fluorinated aryl rings might have the unusually high activity we observed with simple monodentate phosphines. F_{24}-Phanephos[14] was selected as a good candidate. Phanephos derivatives have been reported to be highly active and enantioselective as ligands in a range of organometallic reactions, including enantioselective hydrogenations.[15] F_{24}-Phanephos, **L1** and Xylyl-Phanephos **L2** were chosen for testing as both have broadly similar steric bulk, but **L1** is an electron-deficient Phanephos analogue and **L2** is an electron-rich one.

Enantioselective enamine hydrogenation.

We studied the enamine hydrogenation by combining either of these Phanephos analogues with the rhodium source $Rh[(COD)_2]BF_4$. Following a period of premixing ligand and rhodium source, the enamine substrate was added and placed under hydrogenation conditions. Table 1 describes the results for the formation of amine **1**, and compares the effects of these different ligands, alongside other conditions. Iodine was tested as a co-catalyst, as there are several analogous enamine hydrogenation conditions which benefit from such an additive.[7d,16] The

presence of iodine assisted both the **L1** and **L2** catalytic systems, increasing both conversion and enantioselectivity. In our previous work,[7d] we obtained evidence for the typical Rh(I) hydrogenation catalysts undergoing oxidative addition with iodine which could make for more acidic Rh(III)-dihydrogen intermediates, which could be active catalysts for iminium ion hydrogenation. The mechanism will be discussed further later. The electron-deficient **L1** ligand produces significantly more productive catalysts than those derived from **L2** (most clearly shown by comparing Table 1 entries 8 and 9). This shows for the first time that the rate enhancements offered by the use of phosphine ligands with electron-withdrawing substituents using achiral mono-phosphines[11,13] are therefore also seen with a catalyst derived from a diphosphine ligand.

Table 1. Enantioselective enamine hydrogenation of *N,N*-diethyl-1-phenylethenamine using Rh/Phanephos catalysts.



Entry[a]	Ligand	Rh mol%	I_2 mol%	T (°C)	P (bar)	Conv.[b] [yield][c]	*ee* [d] (%)
1	(*S*)-**L2**	0.4	-	40	20	12	9 (*R*)
2	(*S*)-**L2**	0.4	0.8	40	20	98	11(*R*)
3	(*R*)-**L1**	0.4	-	40	20	90	7 (*S*)
4	(*R*)-**L1**	0.4	0.8	40	20	99	50 (*S*)
5	(*R*)-**L1**	0.4	0.8	65	60	99	45 (*S*)
6	(*R*)-**L1**	0.4	0.8	25	60	>99 [77]	50 (*S*)
7	(*R*)-**L1**	0.4	0.8	25	20	93	50 (*S*)
8	(S)-**L2**	0.1	0.2	40	20	25	*rac*
9	(*R*)-**L1**	0.1	0.2	40	20	>99	50 (*S*)
10[e]	(*R*)-**L1**	0.1	0.2	40	20	>99	46 (*S*)

[a] General conditions: See equation. The rhodium:ligand ratio is 1:1.2. 1-methylnapthalene is used as the internal standard.

[b] Determined by ^{1}H NMR relative to 1-methylnaphthalene.

[c] Isolated by acid-base work up.

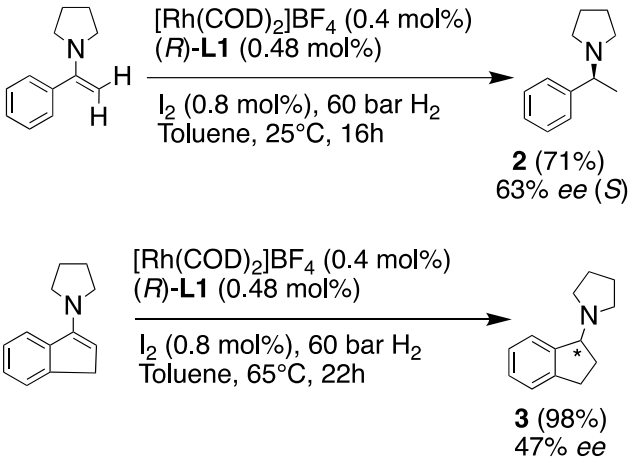
[d] *ee* determined by ^{1}H NMR after addition of excess of (*R*)-(-)- α-methoxyphenylacetic acid.

[e] Solvent = chlorobenzene.

Chlorobenzene has been used to beneficial effect in enamine hydrogenations before,[7d] but did not improve the e.e. (Table 1, Entry 10). Altering temperature and pressure had a marginal effect on yield and enantioselectivity, within the range explored. Catalyst loadings as low as

0.1 mol% were used without significant changes in enantioselectivity, these loadings are some of the lowest achieved for reported unfunctionalised enamine hydrogenation.
While this Rh/**L1** catalyst is not the most selective enamine hydrogenation catalyst, it is one of the most productive: the use of 0.1 mol% of catalyst is a lower catalyst loading than is used in the literature, combined with mild conditions. For the production of both amines **1** (Table 1) and **2** (Scheme 1), (*R*)-configured catalysts give the (*S*)-products. Other products here were not assigned due to a lack of literature precedent and inability to easily derivatise to stereo-defined products. Scheme 1 shows that changing the amine group from diethylamino- group to a pyrrolidino- group increases enantioselectivity (Scheme 1, top reaction), and that a cyclic enamine also reduced efficiently.

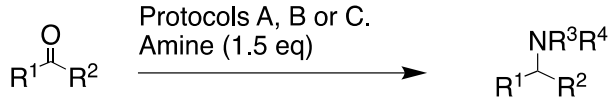
Scheme 1. Enantioselective enamine hydrogenation of pyrrolidino-enamines. General conditions: See equation. Yield given is isolated yield after acid-base work up. *ee* determined by chiral HPLC or by ^{1}H NMR after addition of excess of (*R*)-(-)-α-methoxyphenylacetic acid.

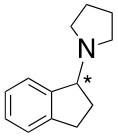
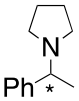
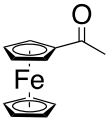
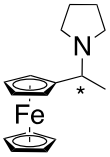
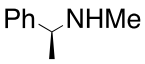
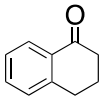
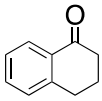
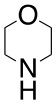
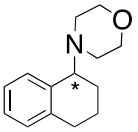
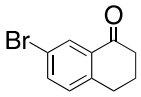
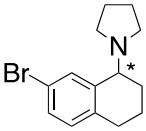
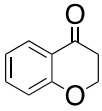
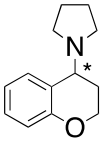
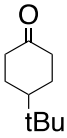
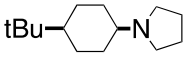


The amine **3** is readily formed by enamine hydrogenation as shown in Scheme 1, giving quantitative yields and moderate enantioselectivity with the iodine co-catalyst. To translate this to a reductive amination procedure requires that the catalyst is tolerant of the conditions used, including the water produced in the condensation reaction. Our objective in this study was also to use conditions that either avoided the use of noxious additives altogether or merely used relatively cheap and benign trifluoroacetic acid (TFA) as a promoter. However, it is known that direct reductive aminations of many ketones do not proceed well in the absence of strong Lewis acids, since the condensation reactions are too sluggish. Cyclic ketones (such as 1-indanone) readily undergo enamine formation – they can undergo condensation without the need of forcing additives such as $TiCl_4$ (see ESI).[17-19] Similar cyclohexanone substrates were recently reported to undergo additive-free catalytic diastereoselective reductive amination to form tertiary amines.[13] Moreover, it is reasonable to expect that pyrrolidine will be the best possible secondary amine partner since it is an unusually nucleophilic secondary amine, while other secondary amines may be problematic without potent additives. While the previous reactivity predictions are logical, there did not appear to be any information in the literature describing what ketone and amine partners might be used in catalytic direct reductive amination using hydrogen as reductant, without a Lewis acid promoter. This aspect was

therefore studied with the results reported in Table 2. Table 2 shows a range of substrates tested using a protocol related to the **L1**/Rh catalysed enamine hydrogenation described in Table 1 (Protocol A), or using conditions similar to our first papers using Rh/monophosphine catalysts for enamine hydrogenations[11,13] (Protocol B). Reductive amination protocols using $NaBH(OAc)_3$ are also reported as a control (Protocol C). An attempt to carry the reactions out as a transfer hydrogenation using formic acid-triethyl amine azeotropic mixture was entirely unsuccessful.

Table 2. Investigating ketone and secondary partners for their ability to undergo reductive amination without Lewis acid catalysis.



Entry	Ketone	Amine (1.5 eq.)	Product	Protocol[a]	Yield (%) [b]	Comments
1				A	>99	For *ee* see scheme 2.
				B	49	
				C	47	
2				A	n.d	20% yield of very impure material isolated.
3				A	39	24% *ee*
				A	66	CF_3CO_2H (0.5 eq), 21% *ee*
				B	11	
				C	21	
4			Not formed	A	Trace	
				A	Trace	CF_3CO_2H (0.5 eq)
5		Bn_2NH	Not formed	A	0	
				B	0	
6				A	<5%	
				B	Trace	
7				A	40	TFA (0.5 eq), 29% product,
				C	8	11% debrominated product.
8				A	23	For *ee* see scheme 2.
				A	34	CF_3CO_2H (0.5 eq) added
				B	Trace	
				C	7	
9				A	71	*dr* = >99:1[c]
				B[d]	98	*dr* = 98:2
				C[e]	98[e]	*dr* = 71:29[e]

[a] **Protocol A**: 0.4 mol% $[Rh(COD)_2]BF_4$, 0.48 mol% L1, 0.8 mol% Iodine, toluene, 65°C, 60 bar H_2, 22h.
Protocol B: 0.2 mol% $[Rh(COD)Cl]_2$, 0.8 mol% tri(2-furyl)phosphine, toluene, 65°C, 60 bar H_2, 22h.
Protocol C: 1.4 equivalents $NaBH(OAc)_3$ DCE, r.t, 18h.

[b] Isolated yield after acid-base extraction.
[c] Diastereomeric ratio favouring *cis* product: see ESI for structural assignment. [d] Protocol B, but tris-(3,4,5-trifluorophenyl)phosphine used as ligand in place of tri(2-furyl)phosphine. [e] Results from literature using THF as solvent and 1 equiv AcOH promoter, see ref. 20.

The results show that without Lewis acidic promoters, only activated combinations of ketone and secondary amine undergo reductive amination using these mild conditions. A truly practical and green protocol is likely to also need the combination of a recyclable non-noxious Lewis or Brønsted acid in sub-stoichiometric amounts (low catalyst loadings) to promote enamine formation, as well as a reactive and enantioselective hydrogenation catalyst. This would be a desirable goal for the future. Nevertheless, some of the findings deserve further comment; the reductive amination of acetyl-ferrocene proceeded significantly better than acetophenone, despite being a more bulky ketone (Table 2, Entry 3). A ferrocene substituent is more electron-donating, and might provide a higher equilibrium concentration of a more stable iminium ion, which may be the step that limits productivity more than hydrogenation activity. Poor enantioselectivity was observed, and no further studies were undertaken. We were surprised to find debromination occurring for the bromo-tetralone substrate (Table 2, Entry 7). The reaction mixtures remained homogeneous, although reductive cleavage of aryl bromides is more commonly associated with heterogeneous catalysts. Slow decomposition of the catalysts to soluble (invisible to naked eye) nanoparticles is not out of the question based on this result, although given the extensive use of Rh/diphosphine catalysts for a range of hydrogenations that are known to be exclusively homogeneous, this would be surprising. The reductive amination of the bulky achiral 4-*tert*-butylcyclohexanone was essentially perfectly diastereoselective, as was the case using a simpler triarylphosphine/Rh catalyst (Table 2, entry 9). This level of diastereoselectivity is not observed using stoichiometric reagents for reductive amination such as $NaBH(OAc)_3$.[20] We suggest Rh catalysed hydrogenation approaches to similar tertiary amines are likely to be the preferred method of making such molecules.

To complete this investigation into the reactivity of F24-Phanephos/Rh derived catalysts, we studied DARA between pyrrolidine and cyclic ketones in the presence of the F24-Phanephos/Rh catalysts in more detail. First, the reductive amination of indanone with pyrrolidine was studied in more detail; 1-indanone, followed by pyrrolidine were added to the premixed solution of **L1**, the rhodium precursor and I_2, before placing under hydrogenation conditions.

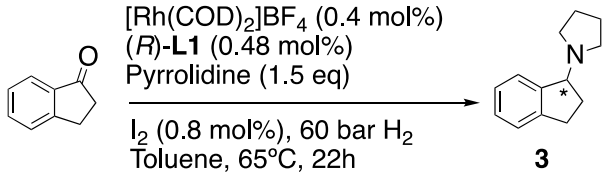
This tandem reaction worked well – giving quantitative yields and similar enantioselectivity to the isolated enamine hydrogenation (Table 3, entries 1 and 2). No additives were required to assist in enamine formation *in situ*. Table 3 also explores a range of modifications to this reductive amination reaction. This catalytic reaction operates using very mild conditions – decreasing the temperature to 25 °C, or the pressure to 1 atm did not significantly depreciate the yield or the enantioselectivity.

Different modifications were attempted to improve the enantioselectivity. The solvent was changed to chlorobenzene, but again, this solvent change does not assist with the enantioselectivity, similar to the enamine hydrogenation described in Table 1. We tested molecular sieves and trifluoroacetic acid as additives to see if their presence would improve the enantioselectivity, but in both cases this was ineffective. It appears that increasing the rate of enamine formation does not lead to higher enantioselectivity, at least for this example.

This reductive amination was carried out at the catalyst loading of 0.1 mol% (Table 3, entry 6) while still achieving high yields and moderate enantioselectivity. TurnOver Numbers

approaching 1000 have rarely been achieved in unfunctionalised enamine hydrogenation before, even without the potential complication of DARA where two reactions occur and compatibility with water and second amines is required.[8,10]

Table 3. Enantioselective reductive amination of 1-indanone and pyrrolidine.



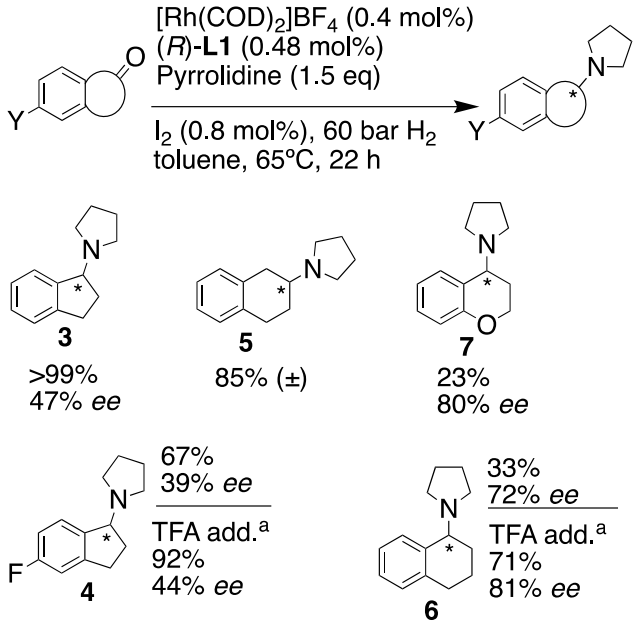
3

Entry	Variation from 'standard conditions'[a]	[Yield][b]	*ee* [c] (%)
1	-	>99	47
2[d]	Enamine Hydrogenation	98	47
3	No I_2	85	40
4[e]	Mol. Sieves additive	97	49
5[f]	TFA additive	>99	47
6[g]	0.1 mol% catalyst loading	92	40
7	1 bar H_2	84	39
8	25 °C	88	48
9	C_6H_5Cl as solvent	96	43

[a] For standard conditions, see equation. [b] Isolated yield. [c] *ee* determined by chiral HPLC. [d] Result from Scheme 1 included for comparison of enamine hydrogenation with reductive amination.[e] 3Å molecular sieves (30 mg). [f] Trifluoroacetic acid (0.25 mmol). [g] Loadings of $[Rh(COD)_2]BF_4$ (0.1 mol%), and (*R*)-**L1** (0.12 mol%) and Iodine (0.2 mol%).

Other cyclic ketones were selected to see if any selectivity could be achieved with other substrates. The results from these reactions are described in Scheme 2. Enantioselective reductive amination was achieved for a range of cyclic ketone substrates. This catalyst tolerates the presence of electron-withdrawing groups on the aryl ring, as seen in the production of **4**, although it shows a significant depreciation in yield and enantioselectivity compared to its unsubstituted counterpart **3**. The yield can be improved to reach 92% by addition of TFA as a promoter. The β-tetralone-derived amine **5** was formed with high yields by this reductive amination. However, no enantioselectivity was induced, perhaps as the ketone substrate (and the prochiral reactive intermediates) are likely to have relatively indistinguishable *re* and *si* faces, compared to the other substrates studied. Conversely the other six-membered ring products **6** and **7** had moderately high enantioselectivity, demonstrating that it is the position of substitution, and not ring size responsible for the lack of enantioselectivity observed in product **5**.

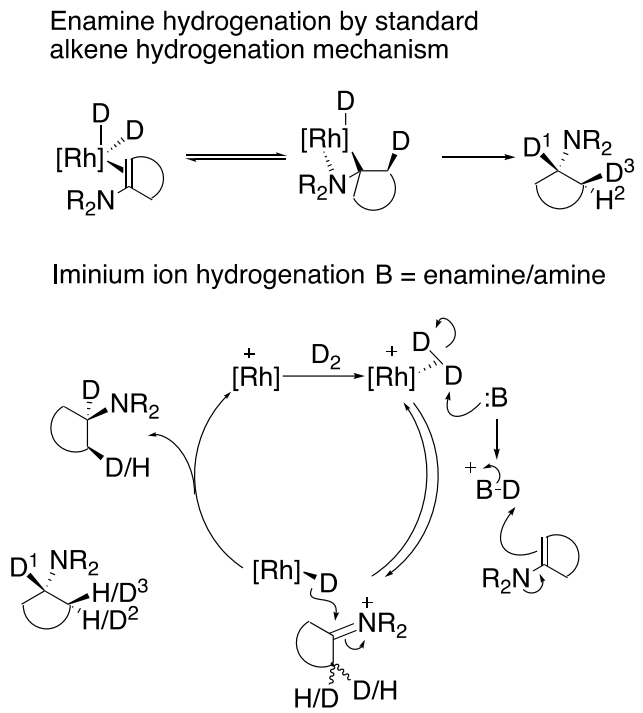
Scheme 2. General conditions: See equation. Yields quoted are isolated yield. *ee* determined by chiral HPLC or by ^{1}H NMR after addition of excess of (*R*)-(-)- α-methoxyphenylacetic acid. [b] Trifluoroacetic acid (0.25 mmol) was added after the ketone.



This reductive amination for the products **6** and **7** proceeds with low yields without any promoter. The yield of α-tetralone-derived amine **6** is significantly improved by using TFA as an additive. This suggests that the *in situ* formation of the enamine intermediate is challenging, and its slow formation has an adverse effect on the yield and enantioselectivity. The Brønsted acid helps catalyse the enamine formation. For **7**, the use of TFA as an additive did not improve the reaction (see ESI). The main organic impurity present after reductive amination was the ketone substrate, so the cause for this low yield was low catalytic activity as opposed to the ketone substrate being used up in competing side reactions. When the catalyst loading is doubled, it does not significantly affect the substrate conversion (see ESI). This is suggestive of the substrate or product poisoning the catalyst.

The two most plausible mechanisms for this reductive amination are either a standard alkene (enamine) hydrogenation mechanism, or via iminium ion reduction (illustrated in Scheme 3). There have been reported examples of both enamine and iminium hydrogenations, and previously evidence supporting an iminium ion hydrogenation in the hydrogenation of isolated enamines has been found.[7d,21] To gain further insight into the mechanism of this enantioselective reductive amination, we carried out deuterium labelling experiments. The reductive amination protocol for the formation of **3** was repeated with deuterium gas at different pressures (Scheme 4). The percentage of deuterium labelling was measured using ^{1}H NMR integration. Partial deuteration is seen at the hydrogen sites labeled D^1-D^3. Diastereotopic hydrogens D^2 and D^3 have equal levels of deuteration. Mass spectrometry shows the presence of tertiary amine products with 0-to-3 deuterium atoms. Scheme 3 presents the deuterium labelling expected for each likely mechanism.

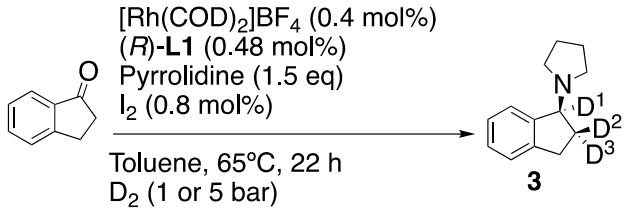
Scheme 3. Two probable mechanisms, and predicted deuterium-labelling products. Other Rh-coordinating ligands are excluded.



As D^1 shows incomplete labelling, this tells us that D/H exchange on the metal center is taking place. To ensure the entire cycle isn't reversible, product **3** was placed under these catalytic conditions with deuterium gas. As no deuterium labels were introduced to the returned amine, this confirms that the final step is irreversible. To obtain the d-labelling shown in Scheme 4 using an iminium ion reduction step is very readily explained, as will be discussed shortly. In contrast, a standard alkene hydrogenation mechanism would require a number of observations that are inconsistent with this type of mechanism. Since the addition of Rh-H/D to an alkene and its microscopic reverse are *syn* processes, then for a cyclic alkene, this should not be a mechanism for deuterating the enamine. Therefore, even in a standard alkene hydrogenation mechanism, enamine and iminium would have to interconvert in order to form some deuterated enamine (~24% or ~66% of the products would be formed from a deuterated enamine at 1 or 5 bar respectively). An exchange process between Rh-D and Rh-H, combined with the impact of any kinetic isotope effect, would then have to coincidentally incorporate the same degree of deuterium in the first C-H/D bond forming step as the unrelated enamine-iminium exchange process incorporated i.e. using an enamine mixture containing 66% deuterated enamine, it would have to fortuitously react with Rh-D/Rh-H to coincidentally give 66% deuteration at D^3. Finally, there would need to be further fast exchange occurring prior to the second C-H/D bond forming process in order to give different amounts of deuterium incorporation at D^1 to that observed at D^3. The similar amounts of deuteration at D^1 at different pressures when pressure influenced the amount of deuteration at D^2 and D^3 significantly is also hard to explain using a simple hydrogenation of the enamine.

In contrast, the iminium ion reduction option can easily fit the d-labelling data. For the iminium ion reduction mechanism, an even ratio of deuteration is expected so long as the D^2/D^3 ratio is at equilibrium before hydride (deuteride) addition occurs to the iminium ion. As D^2/D^3 ratio is 1 at both pressures, and increases with increasing pressure, this fits the mechanism shown in the lower part of Scheme 3. A simple pathway can be envisaged in which a deuteron is removed from $Rh(D_2)$ complex by either the enamine or an amine acting as base. In this way, the deuteron is then directly or indirectly transferred to the enamine to form the deuterated iminium ion. This process can reverse with loss of the remaining proton H^2 or H^3 until both D^2/D^3 have an even level of deuteration. The deprotonation of a $Rh(D_2)$ complex would form a Rh-monodeuteride that would then reduce the iminium ion. We therefore propose that this is dominant pathway for reductive amination to take place.

Scheme 4. Deuterium-labelling in the reductive amination of indanone with pyrrolidine



Level of deuteration:

Pressure: 1 bar
D^1: 36%, D^2: 24%, D^3: 24%
Pressure: 5 bar
D^1: 40%, D^2: 66%, D^3: 66%

3. Conclusions.

In summary, a new catalyst has been shown to form tertiary amines by hydrogenation of isolated enamines, and in some cases it can also catalyse reductive amination. The Rh catalyst derived from the electron-deficient **L1** ligand is highly active, and moderately selective and can achieve catalyst loadings closer to industrially viable conditions than most enamine hydrogenations reported thus far.[7,8] Prior to this work, we had reported monophosphines with electron-withdrawing substituents to deliver unusually active catalysts. The fact that the same trend holds for a diphosphine/Rh catalyst seems to rule out a change in speciation in the mono-phosphine example and implicates a strong ligand electron-effect on a step in the catalytic cycle. This Rh/**L1** catalytic system appears to catalyse reductive aminations through an iminium ion reduction mechanism. It is plausible that a less electron-donating ligand could make the deprotonation of dihydrogen to a Lewis acidic Rh(III) centre an easier process. Until earlier this year, there were no reported examples of tertiary amines being formed through DARA of any secondary amines,[10] presumably due to the challenging nature of this reaction. The identification of a distinct and highly reactive Rh catalyst should aid future catalyst development. We have not pursued the scope of this reaction further since the *ee* of the products is only moderate, but we have proven that useful reactivity is observed when fluorinated chiral

ligands are used. This will hopefully lead to new catalysts that combine activity and high selectivity and hence provide greener routes to making fine chemicals and pharmaceuticals.

4. Experimental.

4.1 General Experimental Techniques

Commercially available starting materials were purchased from Sigma Aldrich, Alfa Aesar, Acros or Apollo scientific and were used without further purification. (*R*)-F_{24}-Phanephos was synthesised in house according to published procedures.[14] Enamines *N,N*-diethyl-1-phenylethen-1-amine,[11] and 1-(1-phenylvinyl)pyrrolidine[22] were made according to published procedures. All catalytic reactions and all air sensitive procedures were carried out under inert conditions or under hydrogen pressure using standard schlenk techniques. All solvents used for these reactions were dry and degassed (either: taken from solvent stills, solvent purification systems, or commercially supplied anhydrous solvents). The reactor used for hydrogenation reactions was a high-pressure autoclave (max pressure: 140 bar, max temperature: 200°C) with magnetic stirring. Work-ups of all amines were done aerobically using an acid/base wash technique. Removal of solvent was assisted by Heidolph Laborota 4001 or a BÜCHI 461 rotatory evaporator. Analytical thin layer chromatography (TLC) was performed on pre-coated alumina plates (Kieselgel 60 F254 silica), before analysing under ultraviolet light (254 nm). TLC plates were stained, then gently heated to aid visualisation. Stains used includes $KMnO_4$ dip, vanillin stain, ninhydrin dip. These stains were all made in house. All SiO_2 column chromatography was performed with Kieselgel 60 silica. For some flash chromatography systems, the silica was neutralised with NH_3 solutions before loading the sample. All spectra were taken at room temperature. NMR spectra (^1H, $^{13}C\{^1H\}$, $^{19}F\{^1H\}$, ^2H and 2D spectra) were acquired on Bruker Avance 500 (500 MHz ^1H and 126 MHz ^{13}C), Bruker Avance 400 (400 MHz ^1H and 100 MHz ^{13}C), or Bruker Avance 300 (300 MHz ^1H and 75 MHz ^{13}C). Mass spectroscopy and high-resolution mass spectroscopy were carried out by the University of St. Andrews Mass Spectrometry facility, using electronspray ionisation (ESI), or EI. High resolution ESI was carried out on a Micromass LCT spectrometer. Infrared spectra (ν_{max}) were recorded using a MIRacle^{TM} single reflection horizontal ATR accessory from Pike (ZnSe single crystal). Only characteristic absorbances were assigned. Melting points were measured on Stuart SMP30 melting point apparatus. Optical rotations were measured in $CHCl_3$ on a PerkinElmer Model 341 Polarimeter with a 10 cm cell (c given in g/100 mL).

4.2 General procedures for Amine Formation

General Procedure: Enamine Hydrogenation

A high pressure autoclave with 4 internal 10 mL vials was used. Each pre-dried vial was filled with $[Rh(COD)_2]BF_4$ (1.6 mg, 4 μmol), the ligand (4.8 μmol, 4.8 mol%), a magnetic stirring bead, and the vials were sealed with crimped caps. The vials were purged with argon 3 times. A solution of iodine (8 nM, 8 μmol) in toluene (1.0 mL) was added to the vial. If iodine was not used, toluene (1.0 mL) was added instead. This was left to stir for 10 minutes. A solution of the desired enamine in toluene, also containing methyl naphthalene internal standard was

added (1.0 mL, 1 M, 1.0 mmol, an NMR of a small portion was taken to calibrate the standard to the enamine). The vials were equipped with open gas inlet needles and sealed in the autoclave, which was purged with H_2 three times before being charged with H_2 at the desired pressure. The vessel was heated to the desired temperature for 16 hours. After this, the reaction vessel was cooled, the pressure was released and the vessel was opened. NMR analysis was carried out on the crude mixture. The reaction mixture was worked up and purified using the general amine workup described below.

*General Procedure A: Catalysed Reductive Amination using **L1***

A high pressure autoclave with 4 internal 10 mL vials was used. Each pre-dried vial was filled with $[Rh(COD)_2]BF_4$ (0.8 mg, 2 μmol), **L1** (2.4 mg, 2.4 μmol), a magnetic stirring bead, and the vials were sealed with crimped caps. The vials were purged with argon 3 times. A solution of iodine (8 nM, 4 μmol) in toluene (0.5 mL) was added to the vial. If iodine was not used, toluene (0.5 mL) was added instead. This was left to stir for 10 minutes. A solution of the desired ketone in toluene (1.0 mL, 0.5 M, 0.5 mmol) was added, followed by the addition of pyrrolidine (63 μL, 0.75 mmol). For reactions which include the additive TFA, it would also be added to the reaction at this time (19 μL, 0.25 mmol). The vials were equipped with open gas inlet needles and sealed in the autoclave, which was purged with H_2 three times before being charged with H_2 at 60 bar. The vessel was heated to 65°C for 22 hours. After this, the reaction vessel was cooled, the pressure was released and the vessel was opened. The reaction mixture was worked up and purified using the general amine workup described below.

General Procedure B: Catalysed Reductive Amination using TFP

A high pressure autoclave with 4 internal 10 mL vials was used. Each pre-dried vial was filled with $[Rh(COD)Cl]_2$ (1 mg, 2 μmol), tri(2-furyl)phosphine (1.9 mg, 8 μmol), a magnetic stirring bead, and the vials were sealed with crimped caps. The vials were purged with argon 3 times. Toluene (0.5 mL) was added to the vial. This was left to stir for 10 minutes. A solution of the desired ketone in toluene (1.0 mL, 0.5 M, 0.5 mmol) was added, followed by the addition of pyrrolidine (63 μL, 0.75 mmol). For reactions which include the additive TFA, it would also be added to the reaction at this time (19 μL, 0.25 mmol). The vials were equipped with open gas inlet needles and sealed in the autoclave, which was purged with H_2 three times before being charged with H_2 at 60 bar. The vessel was heated to 65°C for 22 hours. After this, the reaction vessel was cooled, the pressure was released and the vessel was opened. The reaction mixture was worked up and purified using the general amine workup described below.

General Procedure C: Reductive amination using stoichiometric hydride $NaBH(OAc)_3$

The desired ketone (1 mmol) was dissolved in DCE (1.5 mL), followed by pyrrolidine (125 μL, 1.5 mmol) and then the addition of sodium triacetoxyborohydride (178 mg, 1.4 mmol). This was stirred for 18 hours. The reaction mixture was worked up and purified using the general amine work-up described below.

General amine work-up and purification

The reaction mixture was diluted with toluene (8 mL), and the amine was extracted with HCl (1M, 3 x 20 mL). Combined aqueous fractions were treated with NaOH (1M) until the pH >7, and the amine was further extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to afford the desired product. Further purification was carried out in some cases by column chromatography (details are

provided in the Supported Information). The yield was calculated, and the enantiomeric excess was determined by either HPLC analysis or by NMR resolution of the diastereoisomeric salts formed with (*R*)-(-)-α-methoxyphenylacetic acid.

***N,N*-diethyl-1-phenylethanamine 1**: This compound has been synthesised in the literature by another route.[11] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.31-7.07 (m, 5H), 3.70 (q, $^{3}J_{HH}$ = 6.7 Hz, 1H), 2.57-2.33 (m, 4H), 1.25 (d, $^{3}J_{HH}$ = 6.7 Hz, 3H), 0.90 (t, $^{3}J_{HH}$ = 7.1 Hz, 6H) ppm. $^{13}C\{^{1}H\}$ NMR (75.5 MHz, $CDCl_3$) δ = 145.3, 128.1, 127.6, 126.5, 59.2, 42.9, 18.5, 12.2 ppm. HRMS (ES^+) *m/z*: 178.1586 $[M+H]^+$, [$C_{12}H_{19}N$+H] requires 176.1590.

1-(1-phenylethyl)pyrrolidine 2: This compound has been synthesised in the literature by another route.[8] ^{1}H NMR (500 MHz, C_6D_6) δ = 7.39 (d, $^{3}J_{HH}$ = 7.3 Hz, 2H), 7.20 (*app*. t, $^{3}J_{HH}$ = 7.6 Hz, 2H), 7.10 (t, $^{3}J_{HH}$ = 7.3 Hz, 1H), 3.06 (q, $^{3}J_{HH}$ = 6.6 Hz, 1H), 2.44-2.40 (m, 2H), 2.33-2.29 (m, 2H), 1.60-1.55, 1.33 (d, $^{3}J_{HH}$ = 6.6 Hz, 3H) ppm. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ = 145.7, 128.3, 127.2, 126.8, 66.1, 52.93, 23.4, 23.2 ppm. HRMS (ES^+) *m/z*: 176.1430 $[M+H]^+$, [$C_{12}H_{17}N$+H] requires 176.1434.

1-(2,3-dihydro-1*H*-inden-1-yl)pyrrolidine 3: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, $^{3}J_{HH}$ = 7.3 Hz, 1H), 7.27-7.17 (m, 3H), 4.24 (*app*. t, $^{3}J_{HH}$ = 6.0 Hz, 1H), 3.07 (*app*. dt, J_{HH} = 15.9, 7.7 Hz, 1H), 2.87-2.79 (m, 1H), 2.71-2.61 (m, 4H), 2.22-2.12 (m, 2H), 1.83-1.76 (m, 4H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 144.4, 143.5, 127.4, 125.8, 125.7, 124.8, 67.3, 50.3, 30.9, 28.5, 23.5 ppm. IR (neat) ν, cm^{-1}: 2960.7, 2941.4, 2789.1, 1477.5,, 1458.2, 1352.1, 1321.2, 1195.9, 1124.5, 1105.2, 1022.3, 887.3 ppm. HRMS (EI^+) *m/z*: 187.1363 $[M]^+$, $C_{13}H_{17}N$ requires 187.1361. HPLC (Chiralpack OD-H, hexane/isopropanol/diethylamine 99:1:0.04, 0.5 mL/min, RT): t_R = 9.0 min (-), 9.9 min (+).

1-(5-fluoro-2,3-dihydro-1*H*-inden-1-yl)pyrrolidine 4: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 (dd, *J* = 8.3, 5.4 Hz, 1H), 6.95-6.85 (m, 2H, 3-H), 4.17 (*app*. t, $^{3}J_{HH}$ = 5.7 Hz, 1H), 3.07 (*app*. dt, J_{HH} = 16.2, 7.7 Hz, 1H), 2.81 (*app*. dt, J_{HH} = 16.2, 6.8 Hz, 1H), 2.70-2.59 (m, 4H), 2.24-2.15 (m, 2H), 1.85-1.75 (m, 4H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 162.7 (d, $^{1}J_{CF}$ = 244.2 Hz), 146.7 (d, $^{3}J_{CF}$ = 8.2 Hz), 126.6 (d, $^{3}J_{CF}$ = 8.6 Hz), 112.8 (d, $^{2}J_{CF}$ = 22.4 Hz), 111.6 (d, $^{2}J_{CF}$ = 21.7 Hz), 110.0, 66.6, 50.4, 31.0 (d, $^{4}J_{CF}$ = 1.9 Hz), 28.9, 23.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -116.27 ppm. IR (neat) ν, cm^{-1}: 2960.7, 2908.7, 2792.9, 1595.1, 1483.3, 1319.3, 1240.2, 1124.5, 935.5, 856.4, 806.3. HRMS (EI^+) *m/z*: 205.1269 $[M]^+$, $C_{13}H_{16}NF$ requires 205.1267. HPLC (Chiralpack OJ, hexane/diethylamine 100:0.04, 0.5 mL/min, RT): t_R = 9.2 min (+), 9.9 min (-).

1-(1,2,3,4-tetrahydronaphthalen-2-yl)pyrrolidine 5: This compound has been synthesised in the literature by another route.[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16-7.09 (m, 4H), 3.09 (ddd, J_{HH} = 15.7, 4.9, 1.7 Hz, 1H), 2.97-2.80 (m, 3H), 2.79-2.70 (m, 4H), 2.48 (*app*. tdd, $^{3}J_{HH}$ = 10.9, 4.9, 3.0 Hz, 1H), 2.28-2.20 (m, 1H), 1.90-1.85 (m, 4H), 1.77-1.66 (m, 1H) ppm. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 136.2, 135.4, 129.3, 128.5, 125.8, 125.7, 61.0, 51.8, 35.7, 28.6, 23.3 ppm. IR (neat) ν, cm^{-1}: 2960.7, 2924.1, 2777.5, 1496.8, 1452.4, 1435.0, 1346.3, 1298.1,

1143.8, 1136.1, 1039.6, 889.2. HRMS (EI^+) *m/z*: 201.1512 $[M]^+$, $C_{14}H_{19}N$ requires 201.1517. HPLC (Chiralpack OD-H, hexane/isopropanol/diethylamine 99:1:0.04, 0.5 mL/min, RT): t_R = 14.2 min, 15.9 min.

1-(1,2,3,4-tetrahydronaphthalen-1-yl)pyrrolidine 6: This compound has been synthesised in the literature by another route.[8] ^1H NMR (400 MHz, $CDCl_3$) δ = 7.41-7.38 (m, 1H), 7.20-7.09 (m, 3H), 3.59 (*app*. t, $^3J_{HH}$ = 4.9 Hz, 1H), 2.93 (*app*. dt, J_{HH} = 16.8, 6.5 Hz, 1H), 2.77 (*app*. dt, J_{HH} = 16.8, 6.9 Hz, 1H), 2.73-2.63 (m, 2H), 2.55-2.47 (m, 2H), 2.19-2.08 (m, 10.4, 6.8, 3.3 Hz, 1H), 2.03-1.94 (m, 1H), 1.86-1.69 (m, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 147.0, 137.7, 129.4, 129.0, 126.6, 124.9, 60.7, 50.3, 29.0, 24.7, 23.7, 19.3 ppm. IR (neat) ν, cm^{-1}: 2929.9, 2870.1, 2777.5, 1489.1, 1450.5, 1357.9, 1357.9, 1112.9, 993.3, 885.3, 763.8. HRMS (EI^+) *m/z*: 201.1519 $[M]^+$, $C_{14}H_{19}N$ requires 201.1517. HPLC (Chiralpack OJ, hexane/diethylamine 100:0.04, 0.5 mL/min, RT): t_R = 8.1 min (+), 8.8 min (-).

1-(chroman-4-yl)pyrrolidine 7: ^1H NMR (500 MHz, $CDCl_3$) δ = 7.22 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 7.17 (*app*. td, J_{HH} = 7.7, 1.7 Hz, 1H), 6.87-6.81 (m, 2H), 4.51 (*app*. td, J_{HH} = 10.8, 2.8 Hz, 1H), 4.24 (*app*. dt, J_{HH} = 10.4, 4.2 Hz, 1H), 3.48 (br s, 1H), 2.74-2.69 (m, 2H), 2.54-2.49 (m, 2H), 2.20-2.15 (m, 1H), 1.97 (*app*. ddt, J_{HH} = 14.3, 10.9, 3.4 Hz, 1H), 1.80-1.76 (m, 4H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ = 154.6, 130.6, 128.7, 123.4, 119.1, 116.8, 62.9, 57.1, 50.9, 25.2, 23.5 ppm. IR (neat) ν, cm^{-1}: 2962.7, 2783.3, 1606.7, 1581.6, 1485.2, 1450.5, 1307.7, 1224.8, 1116.8, 1072.4, 750.3. HRMS (ES^+) *m/z*: 204.1378 $[M+H]^+$, $[C_{13}H_{17}ON+H]$ requires 204.1388.

***cis*-1-(4-(*tert*-butyl)cyclohexyl)pyrrolidine**: This compound has been synthesised in the literature by another route.[20] m.p. = 48-50 °C; Lit. for *cis* isomer = 48-50 °C (*trans* isomer = 71-73 °C).[20b] ^1H NMR (500 MHz, $CDCl_3$) δ = 2.50-2.41 (m, 4H), 2.14-2.11 (m, 1H), 1.96-1.91 (m, 2H), 1.80-1.74 (m, 4H), 1.47-1.32 (m, 6H), 1.06-0.99 (m, 1H), 0.87 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ = 59.9, 52.0, 48.6, 32.6, 31.4, 27.7, 23.7, 21.6 ppm. HRMS (ES^+) *m/z*: 210.2207 $[M+H]^+$, $[C_{14}H_{27}N+H]$ requires 210.2216

((1-(cyclopentandienyl)ethyl)pyrrolidine)cyclopentadienyliron: ^1H NMR (500 MHz, $CDCl_3$) δ = 4.22-4.20 (m, 1H), 4.16-4.15 (m, 7H), 4.12-4.11 (m, 1H), 3.37 (q, J = 6.7 Hz, 1H), 2.53-2.42 (m, 4H), 1.75-1.65 (m, 4H), 1.61 (d, J = 6.7 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ = 69.8, 68.6, 67.6, 66.9, 66.6, 57.3, 50.9, 23.1, 19.9 ppm. HRMS (ES^+) *m/z*: 284.1088 $[M+H]^+$, $[C_{16}H_{21}FeN+H]$ requires 284.1096.

Acknowledgements. We would like to thank the University of St Andrews, and the EPSRC Centre for Doctoral Training in Critical Resource Catalysis (CRITICAT) for financial support [Ph.D. studentship to SHG (PhD 2019); Grant code: EP/L016419/1], and Dr Reddys (EU Ltd.) for co-supporting a University studentship to ST (PhD 2017).
The authors have no competing interests.

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