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A consecutive process for C-C and C-N bond formation with high enantio- and diastereo-control: Direct Reductive Amination of chiral ketones using hydrogenation catalysts.

Sophie H Gilbert,^a Virginie Viseur^a and Matthew L. Clarke^a

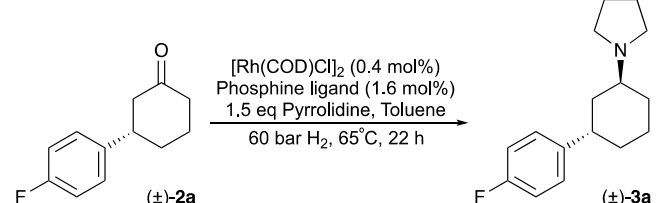
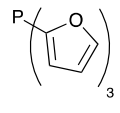
High diastereoselectivity was observed in the Rh-catalysed reductive amination of 3-aryl cyclohexanones to form tertiary amines. This was incorporated into a one-pot enantioselective conjugate addition and diastereoselective reductive amination, including an example of assisted tandem catalysis.

The synthesis of enantiomerically pure amines is of special significance in Organic Synthesis: it is estimated that chiral amines are present in around 40% of pharmaceuticals.¹ Direct reductive amination is a particularly appealing method to prepare amines since it avoids the generation of waste salts inherent in alkylation methods, or the alternative of isolation of imine or enamine intermediates. Direct reductive amination is also potentially quite general in being applicable to many combinations of carbonyl compounds and primary or secondary amines as substrates. Some useful enantioselective and diastereoselective direct reductive amination processes have been reported.² The most industrially important method to make any chiral compounds with chemo-catalysts is catalytic hydrogenation, due to economic and environmental considerations. Hydrogenations that are also direct reductive aminations are at the cutting edge of what is possible to do with current hydrogenation catalysts and need further research.^{3,4} Reductive aminations that produce tertiary amines are the least well developed of all, and particularly need a breakthrough to become useful procedures.^{5,6} Tertiary amines appear in many bio-active compounds and launched drugs,⁵ so a hydrogenation-based method for their synthesis could have broad application.

Direct reductive amination of secondary amines with ketones would likely involve a common reduction step, whether that be an enamine or iminium ion hydrogenation. Either of these are very challenging hydrogenations, as is clear from the literature.⁶ Effective alkene hydrogenations generally make use of alkenes with a coordinating groups such as enamides. This restricts rotation and enhances association. Without this the substrates are hindered

electron rich alkenes of low reactivity. Iminium ions are readily reduced, but there is a challenge in controlling chemoselectivity when made *in situ*, and stereochemistry in an outer-sphere reaction. Rh catalysts derived from a combination of a Rh source and weakly donating phosphine were recently found to be very active achiral enamine hydrogenation catalysts.^{6e} Here we show that simple Rh catalysts can promote direct reductive amination using H₂ gas on a range of chiral ketone substrates. Apart from furthering this challenging topic in the hydrogenation field, this provides a solution for reactions that are actually problematic using any classical procedure using reducing agents. Finally a rare example of assisted tandem catalysis is presented:⁷ catalyst speciation is altered during a consecutive process that needs two different catalysts.

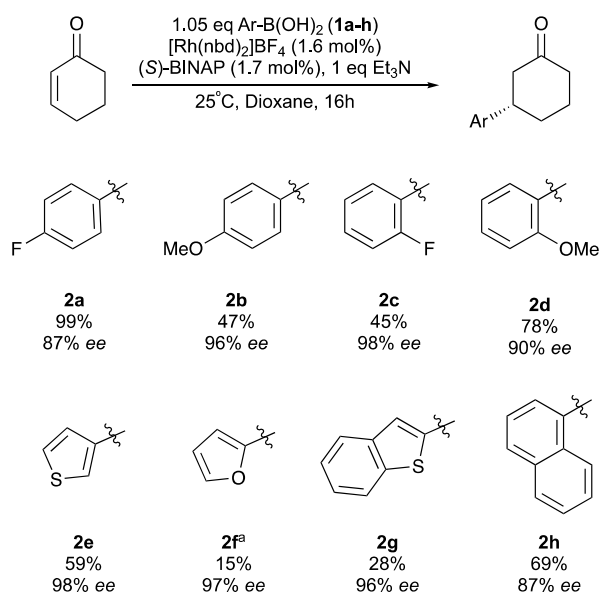
Table 1 Ligand effects on catalytic reductive amination^a

			
Entry	Ligand	Yield ^b (%)	dr ^c (%)
1	 (TFP)	64	96
2	Ph ₃ P	Trace	90
3	(4-FC ₆ H ₄) ₃ P	21	92
4	(3,4,5-C ₆ F ₃ H ₃) ₃ P	56	96
5	(C ₆ F ₅) ₃ P	58	75
6	(4-ClC ₆ H ₄) ₃ P	49	91
7	(PhO) ₃ P	70	82
8	(rac)-BINAP	Trace	82
9	Ph ₃ P-CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ PPh ₂	0	-
10	dppf	0	-
11 ^d	TFP	57	93

^a General catalytic conditions: 3-(4-fluoro-phenyl)-cyclohexanone (0.5 mmol), pyrrolidine (0.75 mmol), [Rh(COD)Cl]₂ (0.4 mol%), ligand (1.6 mol%), in toluene (1 mL) under 60 bar H₂ at 65°C for 22 hours. ^b Isolated yields. ^c dr values were determined by ¹⁹F{¹H} NMR. ^d 1 atm of H₂.

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A range of ligands in combination with $[\text{RhCl}(\text{COD})]_2$ deliver catalysts for directive reductive amination of racemic ketone **2a** (Table 1). The selectivity always favours the trans relative stereochemistry shown, as determined by ^1H NMR spectroscopy (see ESI for stereochemical assignment). The weakly donating ligands such as those described in entry 1, 3 and 4 give increased amine formation and diastereoselectivity. It has already been noted that weakly donating phosphines are associated with increased catalyst activity in enamine hydrogenations.⁸ The $(\text{C}_6\text{F}_5)_3\text{P}$ ligand is associated with a decrease in diastereoselectivity when compared to the other substituted triarylphosphines, even though it is the weakest electron donor of all the phosphine examples. This may have to do with unfavourable sterics – $(\text{C}_6\text{F}_5)_3\text{P}$ has a tolmán angle of 184° , whereas the other ligands in entries 1-4 and 6 have angles of 145° .⁹ One of the preferred ligands is weakly donating and commercially available tri(2-furyl)phosphine (TFP), as it displays both high activity and selectivity. Various bidentate ligands were tested (entries 8-10) but none of these showed any activity. It was also found that the protocol is tolerant of a wide range of conditions; the experiment described in entry 11 shows that this reaction works at atmospheric pressures. This reaction tolerates a range of solvents including EtOAc and MeTHF. Full details are provided in the supporting information.



Scheme 1 Enantioselective synthesis of 3-substituted cyclohexanones and piperidones^a. Yields quoted are isolated yields. ee values were determined by HPLC. ^a Uses 1.5 eq of boronic acid.

Rh catalysed conjugate additions are a powerful method to produce ketones of this type.¹⁰ Expanding a known protocol for the conjugate addition to cyclohexenone using an achiral catalyst enabled us to prepare further racemic chiral ketones **2a-i** (see ESI for details).¹¹ Racemic ketones were used for the majority of the hydrogenation studies (d.r. is expected to be the same for racemic or single enantiomer compounds). In

order that the process could produce enantiomerically and diastereomerically pure isomers of the desired amines, we also investigated conditions to produce the chiral ketones in enantiomerically rich form. Adapting a known protocol¹² for reactions with the aryl boronic acids shown delivers the desired enantiomerically enriched ketones in varying yields, but generally high ee (Scheme 1). Heteroaryl boronic acids nucleophiles are more challenging, as they are more prone to protodeborylation.¹³ For example, **2f** has only been synthesised in a couple of publications using aryl-boron reagents, and these gave poor yields.¹⁴ These procedures needed to use alternative boronates such as Ar-B(MIDA) and Ar-Bpin. These ketone substrates (**2a-i**) could all be applied to the reductive amination protocol and form the corresponding amines with high diastereoselectivity and good yield (Table 2).

Table 2 Catalytic reductive amination of several ketone substrates

Entry	Ketone	Yield ^b (%)	dr ^c (%)
1	2a	89	93
2	2b	88	94
3	2c	89	97
4	2d	86	96
5	2e	82	89
6	2f	89	63
7	2g	99	99
8	2h	72	94
9	Ar = Ph 2i	79	87

^a General catalytic conditions: ketone (0.5 mmol), pyrrolidine (0.75 mmol), $[\text{Rh}(\text{COD})\text{Cl}]_2$ (0.4 mol%), TFP (1.6 mol%), in dioxane (1 mL) under 40 bar H_2 at 80°C for 22 hours. ^b Isolated yields. ^c dr values were determined by NMR.

The 2-furyl substituted ketone gives the lowest selectivity; perhaps unsurprising given it is the smallest aryl substituent tested. Fig. 1 shows a comparison on the dr obtained in this atom-efficient approach relative to the dr of the classical process using $\text{NaBH}(\text{OAc})_3$. Thus not only is this reaction more atom efficient, but it benefits from significantly higher selectivity.

Different amines were explored in this catalytic system. Pyrrolidine is a sterically unhindered nucleophilic amine, so is especially good at forming enamines *in situ*. The other amines studied do not so readily undergo enamine formation so molecular sieves and trifluoroacetic acid was required as additives to allow workable yields. We note the unsuccessful *tert*-butyl methyl amine did not undergo reductive amination using reducing agents or hydrogenation catalysts. Pleasingly even an aniline derivative does undergo the reaction

(Scheme 3). Preliminary studies using a cyclopentyl ketone and a 4-piperidinone type substrate show that the procedures could extend to other quite different substrates (see ESI).

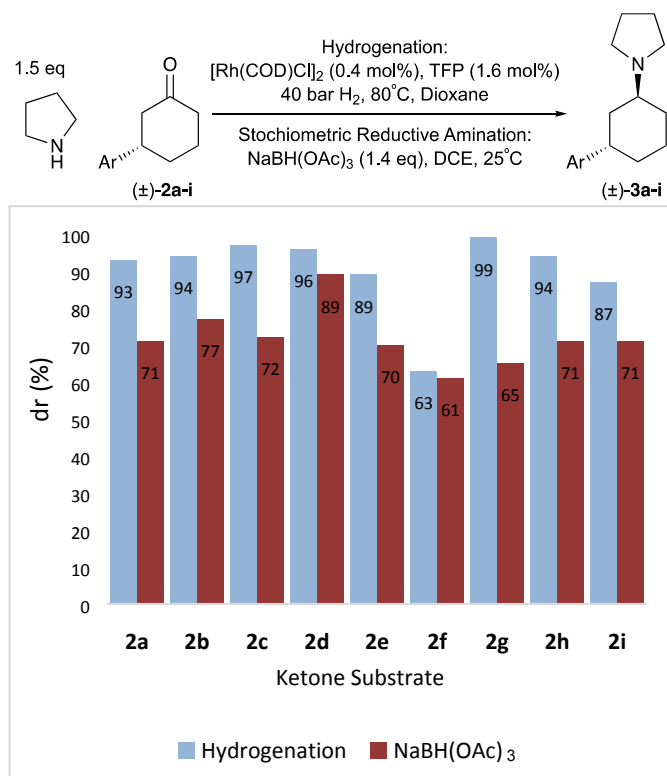
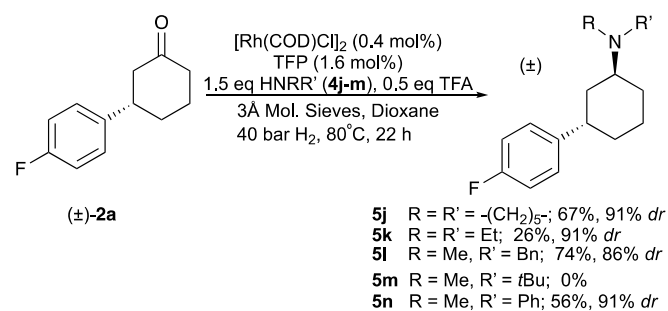


Figure 1 A comparison of diastereoselectivity between the catalytic hydrogenation and the classical reductive amination using stoichiometric NaBH(OAc)₃. *dr* values were determined by NMR.

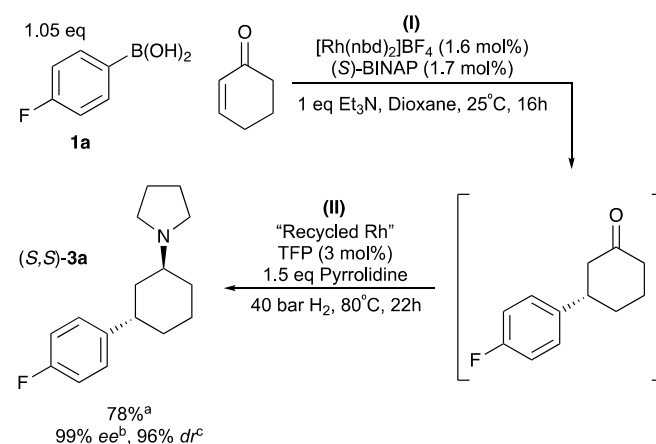


Scheme 3 Catalytic reductive amination for less nucleophilic secondary amine substrates. Yields quoted are isolated yields, and *dr* values were determined by ¹⁹F{¹H} NMR.

Both this conjugate addition and reductive amination use similar rhodium sources. It seemed feasible that these two steps could be done consecutively to allow the rhodium to be recycled in the second step. This could be achieved by carrying out the conjugate addition under inert conditions, then adding pyrrolidine and charging the system with hydrogen. While BINAP was a great ligand for the conjugate addition, this proved to be almost inactive for the reductive

amination step (Table 1, Entry 8). To get around this issue, TFP was added after the conjugate addition had gone to completion, prior to putting the reaction mixture under hydrogenation conditions. (Scheme 4)

This process effectively contains 3 steps within the same pot. From simple starting materials, a complex product with multiple chiral centers is formed with good yields, high diastereoselectivity and enantioselectivity. This is an example of assisted tandem catalysis.^{7,15} Once the initial reaction step is complete, the original catalyst is converted into a new catalytic species, with the latter converting the new intermediate into the desired final product. Ligand exchange is perhaps an underutilised method to achieve assisted tandem catalysis, and hence increase the value delivered by a precious metal precatalyst.



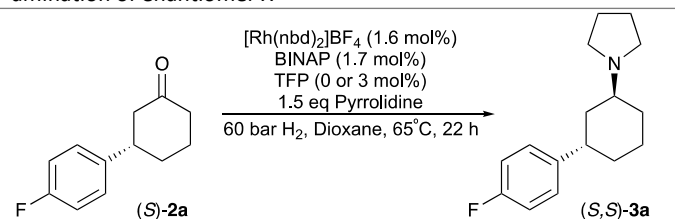
Scheme 4 The one-pot reaction of sequential enantioselective conjugate addition followed by diastereoselective reductive amination. ^a Isolated yield from cyclohexanone. ^b ee was determined using ¹⁹F{¹H} NMR analysis on the chiral salts made *in situ* from (R)-α-methoxyphenylacetic. ^c *dr* was determined by ¹⁹F NMR.

The active catalyst in Scheme 4, step II was formed by addition of the TFP. This active hydrogenation catalyst could contain just TFP phosphorus containing ligands, similar to the active catalyst of Table 2, or this particular active catalyst may also include a BINAP ligand. ³¹P NMR experiments (see ESI) are suggestive of both Rh-TFP complexes and Rh-TFP-BINAP complexes within the reaction mixture in step II. As this was inconclusive, a further experiment was done replicating the conditions for step II with (S)- 2a to see if any difference in performance between the catalyst enantiomers could be seen (Table 3). While a Rh-BINAP complex shows a matched/mismatched interaction and expected low yields (entry 1 and 2), the active catalyst formed in step II does not show any significant effects (entry 3 and 4). While these results are far from entirely conclusive, it may suggest the chiral catalyst is an achiral Rh-TFP complex, as the enantiomer of BINAP used has no effect on the *dr*.

The reaction mechanism could potentially proceed through the catalyst hydrogenating either the enamine or iminium ion intermediate. Deuterium labelling experiments were carried out using deuterium gas. If there was no exchange

and a clean C=C reduction took place, d labelling would confirm this. However, unfortunately fast exchange occurred between the protons alpha to the C-N bond, resulting in mixed labeling at 5 different protons, a scenario that is possible with either enamine or iminium ion intermediate (see ESI).

Table 3 Enantiomer ligand effects on diastereoselective reductive amination of enantiomer X



Entry	BINAP	eq. of TFP (mol%)	Yield ^b (%)	dr ^c (%)
1	(S)-BINAP	0	15	83
2	(R)-BINAP	0	13	93
3	(S)-BINAP	3	51	90
4	(R)-BINAP	3	53	91

^a see experimental in ESI for reaction details. ^b Isolated yields. ^c dr values were determined by ¹⁹F{¹H} NMR.

In conclusion, an atom-efficient way of synthesising tertiary chiral amines has been developed. We have demonstrated some of the potential of this reaction; adapting it to both a consecutive process and a range of substrates. Further developments of reactions such as this will lead to a broader range of scaleable tertiary amine syntheses than are currently available.

Conflicts of interest

There are no conflicts to declare

Notes and references

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A Rh catalyst derived from tri-(2-furyl)phosphine enables the direct reductive amination of 1,3-substituted ketones to occur in high yield and diastereoselectivity

