Enantioselective Hydrogenation of Imines Using a Diverse Library of Ruthenium Dichloride(diphosphine)(diamine) Precatalysts

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Abstract: A range of aromatic and cyclic imines were subjected to asymmetric hydrogenation with catalysts derived from complexes of the type $RuCl_2$(diphosphine)(diamine). Good to high enantioselectivities were observed. For each imine, a library of chiral complexes based on different diphosphine and diamine combinations was screened. A different combination of diphosphine and diamine was required each time to obtain the optimum enantioselectivity.

Keywords: Asymmetric hydrogenation; DuPHOS; imine hydrogenation; ruthenium

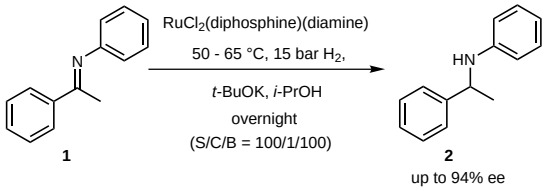
Introduction

Enantiomerically pure amines are highly important building blocks for biologically active molecules and the discovery of new and efficient methods for their preparation is a matter of continued interest. Although numerous methods are available for their preparation, the catalytic asymmetric hydrogenation of imines offers a cheap and industrially viable process as demonstrated by the multi-ton synthesis of (*S*)-metolachlor.[1] This area, however, is still under development with progress being centred around catalysts based on complexes of Rh, Ir, Ru and Ti.[2] Our own[3] recent experience in the area of non-olefinic hydrogenation has focused on the use of Noyori's ruthenium(II) dichloride(diphosphine)(diamine) complexes (**3**).[4] In *i*-PrOH and in the presence of a strong base, these complexes generate catalysts capable of reducing ketones with very high enantioselectivities even at extremely low catalyst loadings (e.g., molar substrate to catalyst ratio, S/C = 100,000/1).[5] Therefore, we sought to investigate their use in the catalytic asymmetric hydrogenation of imines. We were specifically interested in this class of complex as large libraries of structurally diverse diphosphine and diamine ligands could be used to rapidly generate an array of catalysts with very different stereoelectronic domains.

Results and Discussion

The precatalysts used were readily prepared under inert conditions by reaction of $[RuCl_2C_6H_6]_2$ with a diphosphine in hot DMF followed by treatment with a diamine at room temperature yielding air stable, easily handled solids.[5] The imines were purchased or prepared by reaction of the requisite ketones and amines in toluene at room temperature in the presence of 4 Å molecular sieves.[2i] It should be noted that we observed hydrogenation at lower pressures than reported, but for consistency in screening higher pressures were used. In a preliminary hydrogenation reaction using a molar substrate-to-catalyst-to-base ratio (S/C/B) of 100/1/100 of *N*-(phenylethylidene)aniline (**1**), $RuCl_2$[(*S*)-Tol-BINAP][(*S*,*S*)-DPEN] and *t*-BuOK (1 M solution in *t*-BuOH) in *i*-PrOH at 50 °C under 15 bar H_2 provided quantitative conversion to amine **2** with 49% ee (Scheme 1). As will be described, we were ultimately able to increase the enantioselectivity to 94% ee (*vide infra*) by choice of appropriate catalyst and conditions.

Concurrent to this work, Morris et al.[6] reported the hydrogenation of a range of simple ketones and two imines using $RuH_2(PPh_3)_2$[(*R*,*R*)-DACH] or $RuHCl(PPh_3)_2$[(*R*,*R*)-DACH] but no enantioselectivities were reported. Very recently the same authors reported the use of complexes of the type RuHCl(chiral



Scheme 1. Hydrogenation of *N*-(phenylethylidene)aniline (**1**).

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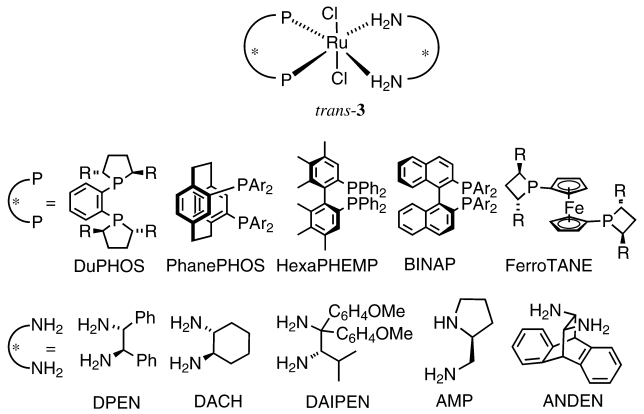


Figure 1. Diphosphines and diamines used to generate the precatalyst library.

diphosphine)(chiral diamine) for the stereoselective hydrogenation of ketones and imines.[7] Only a limited range, however, of chiral diphosphines and chiral diamines was tested for the hydrogenation of imines and at best moderate selectivities obtained (up to 71% ee). The hydrogenation of cyclic imines was not reported.

We therefore wish to report the use of a diverse library of the related $RuCl_2$(diphosphine)(diamine) complexes in the enantioselective catalytic hydrogenation of a range of structurally different imines and observations concerning the effect of different diphosphine/diamine combinations. Crucially, we have found that for a given imine the most appropriate diphosphine/diamine combination is best identified by extensive screening and is difficult to predict.

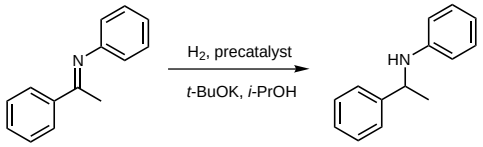
With the successful preliminary result in hand we screened a range of precatalysts and rapidly identified the Et-DuPHOS/DPEN ligand system as a more selective combination, providing an 89% ee for imine **1**. In an effort to optimise conditions before extending the precatalyst screen further, we examined the reaction parameters in the hydrogenation of **1**. While increased temperatures led to decreasing selectivities, optimum conversion was achieved at *ca.* 65 °C over a 20 h period. At room temperature over 20 h, 48% conversion and 90% ee were achieved. Although hydrogenation occurred over a range of pressures from 1.5 to 15 bar, with a small improvement in selectivity at higher pressures, quantitative conversion was only realised at 15 bar over the reaction times studied. At 5 bar a 96% conversion was achieved at 65 °C over 20 h. A solvent screen using the optimised conditions (15 bar, 65 °C, 20 h) revealed that quantitative hydrogenation could be achieved in *i*-PrOH, PhMe and THF. Methanol proved to be a poor solvent for this reaction with 78% ee and 22% conversion being obtained. A series of reactions was conducted with differing amounts of base (*t*-BuOK in *t*-BuOH from 0.1 to 2.0 equivalents) but no significant differences in the conversion or ee was observed. When the base was omitted no reaction occurred.

Having identified optimal conditions for the hydrogenation of **1**, we proceeded to test a larger range of precatalysts based on different combinations of the chiral diphosphines and chiral diamines shown in Figure 1 (see Table 1). In entries 1 – 10, the DuPHOS family of diphosphines was tested more extensively. Although Me-DuPHOS (entry 1) gave good selectivity it was inferior to Et-DuPHOS (entry 2) and *i*-Pr-DuPHOS (entry 8) in conjunction with DPEN. A marked stereochemical matching/mismatching effect was observed for diphosphine/diamine combinations (*cf.* entries 2 and 3). Comparison of different diamines revealed that although DACH (entry 4) provided a slight improvement in selectivity over DPEN (entry 2), DAIPEN (entry 5), ANDEN (entries 6 and 7) and AMP (entry 9) were less selective.

BINAP in combination with a variety of diamines gave low enantioselectivities and conversions (entries 11 – 14) for this substrate, whilst the more electron-rich Tol-BINAP gave full conversion (entry 15). Conversely, Noyori reported[8] that the parent ketone, acetophenone, was hydrogenated in 91% ee using $RuCl_2$[(*S*)-Tol-BINAP][(*S*)-DAIPEN]. Generally, we observed lower selectivities for imines as compared to those achieved in ketone hydrogenation using Noyori-type precatalysts. Moreover, diphosphine/diamine combinations that were good for ketone hydrogenation (e.g., Tol-BINAP/DPEN and PhanePHOS/DPEN) were poor for imine hydrogenation and *vice versa* (e.g., Et-DuPHOS/DPEN). Several other biaryldiphosphines, including the electron-rich HexaPHEMP[9] ligand were tested (entries 16 – 18) and although conversions were generally high, enantioselectivities were moderate. The PhanePHOS-based family of diphosphines, that we have shown[10] to be as effective as BINAP-based ligands in ketone hydrogenation using Noyori-type precatalysts, provided poor results for imine hydrogenation (entries 19 – 21). It was evident from this precatalyst screen that even small electronic and steric changes in related ligands were critical to the selectivities and activities obtained. Interestingly $RuCl_2$[(*R*,*R*)-Et-DuPHOS](DMF)$_n$, which is an intermediate in the synthesis of the $RuCl_2$[(*R*,*R*)-Et-DuPHOS](diamine), and which has been reported[11] to effect styrene hydrogenation in conjunction with *t*-BuOK in *i*-PrOH, provided 8% conversion and 16% ee under our standard conditions. In theory, the complex $RuCl_2$[(*R*,*R*)-Et-DuPHOS](**2**)$_2$ could be formed under these reaction conditions by displacement of the diamine ligand with the product **2**, however, separate experiments using this prepared separately showed it was only slightly active giving 26% conversion and 8% ee.

We proceeded to optimise the reaction conditions for a more industrially acceptable molar substrate-to-catalyst-to-base ratio of 1000/1/100, with the preferred

Table 1. Precatalyst screening against *N*-(phenylethylidene)aniline (**1**).[a]



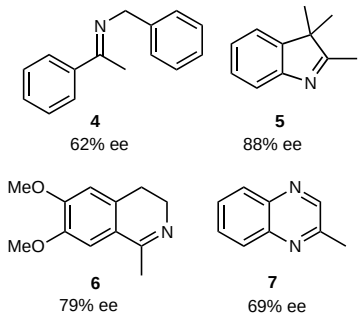
1 **2**

Entry	$RuCl_2$(diphosphine)(diamine)	Conversion [%][b]	ee [%][c]
1	(*R*,*R*)-Me-DuPHOS/(*R*,*R*)-DPEN	94	85 (*S*)
2	(*R*,*R*)-Et-DuPHOS/(*R*,*R*)-DPEN	100	91 (*S*)
3	(*S*,*S*)-Et-DuPHOS/(*R*,*R*)-DPEN	60	11 (*R*)
4	(*R*,*R*)-Et-DuPHOS/(*R*,*R*)-DACH	92	92 (*S*)
5	(*R*,*R*)-Et-DuPHOS/(*R*)-DAIPEN	43	48 (*S*)
6	(*R*,*R*)-Et-DuPHOS/(*R*,*R*)-ANDEN	11	8 (*R*)
7	(*R*,*R*)-Et-DuPHOS/(*S*,*S*)-ANDEN	9	9 (*R*)
8	(*S*,*S*)-*i*-Pr-DuPHOS/(*R*,*R*)-DPEN	99	89 (*S*)
9	(*R*,*R*)-*i*-Pr-DuPHOS/(*S*)-AMP	3	11 (*R*)
10	(*R*,*R*)-*i*-Pr-DuPHOS/(*S*)-BINAM	9	–
11	(*R*)-BINAP/EDA	3	24 (*S*)
12	(*R*)-BINAP/(*R*,*R*)-DPEN	22	49 (*S*)
13	(*S*)-BINAP/(*S*)-AMP	6	23 (*R*)
14	(*R*)-BINAP/(*S*)-AMP	4	19 (*R*)
15	(*S*)-Tol-BINAP/(*S*,*S*)-DPEN	99	49 (*R*)
16	(*S*)-HexaPHEMP/(*S*,*S*)-DACH	78	56 (*R*)
17	(R)-HexaPHEMP/(*R*,*R*)-DPEN	98	45 (*S*)
18	(*R*)-MeO-BIPHEP/(*R*,*R*)-DPEN	98	50 (*S*)
19	(*R*)-*i*-Pr-PhanePHOS/(*S*,*S*)-DPEN	16	37 (*R*)
20	(*R*)-Xylyl-PhanePHOS/(*S*,*S*)-DPEN	26	11 (*R*)
21	(*S*)-CF_3-Ph-PhanePHOS/(*R*,*R*)-DPEN	2	35 (*S*)
22	(*R*,*R*)-Me-FerroTANE/(*S*,*S*)-DPEN	20	–

[a] Conducted in a multi-well hydrogenation apparatus at 15 bar H_2, 65 °C, for *ca.* 20 h, with 1 mol % $RuCl_2$(diphosphine)(diamine) and 100 mol % 1 M *t*-BuOK in *t*-BuOH.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by GC analysis using a chiral DEX-CB column. Absolute configuration is in parentheses.

$RuCl_2$[(*R*,*R*)-Et-DuPHOS][(*R*,*R*)-DACH] precatalyst. At this loading, 20% conversion and 88% ee were obtained at 65 °C, 20 h at 20 bar H_2 at 0.5 M substrate concentration in *i*-PrOH. Although an increase in the hydrogen pressure to 100 bar had little effect, increasing the temperature to 100 °C had a detrimental effect on the selectivity (80% ee) and produced only a modest increase in conversion (48%). The two most important factors leading to an increase in the conversion were time and concentration. Thus, when the reaction was conducted for 69 h at 65 °C in *i*-PrOH (4.1 M) with 5 mol % *t*-BuOK 97% conversion and 94% ee were obtained. This compares favourably (*ca.* 23% higher ee) to that which Morris[7] reported using a smaller set of Noyori-type precatalysts and to the literature using other catalysts.[2a,c,i,12]

A similar screening approach to that presented in Table 1 was applied to imines **4**, **5**, **6**, and **7** (Figure 2). Hydrogenation of benzylimine **4** with a range of precatalysts proceeded with low selectivities (2–29% ee) when the reaction was conducted in the presence of 100 mol % *t*-BuOK. A control experiment indicated that under these conditions an equilibrium mixture of **4** and its aldimine tautomer was generated (which would hydrogenate to give a racemic product) accounting for the low selectivities. When the amount of base was reduced to 5 mol % the selectivities were greatly enhanced and 62% ee (97% conversion) was obtained using $RuCl_2$[(*S*)-Tol-BINAP][(*S*,*S*)-DPEN].



4 62% ee **5** 88% ee

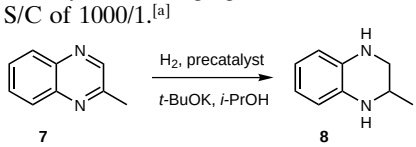
6 79% ee **7** 69% ee

Figure 2. Other imines reduced and the ees of the corresponding amine products.

In our studies we also investigated the enantioselective hydrogenation of cyclic imines. Catalyst screening (15 precatalysts tested in a multi-well vessel) against 2,2,3-trimethylindolenine (**5**) revealed that $RuCl_2$[(*S*)-MeO-BIPHEP][(*S*,*S*)-ANDEN] provided the highest selectivity (88% ee). Although the dihydroisoquinoline (**6**) was screened against a smaller set of precatalysts a large difference in selectivities was observed. Whereas $RuCl_2$[(*R*,*R*)-Et-DuPHOS][(*R*,*R*)-DACH] provided 79% ee and 80% conversion, with $RuCl_2$[(*S*)-HexaPHEMP][(*S*,*S*)-DPEN] 8% ee and 47% conversion were obtained. The conversion with the former precatalyst was improved to near quantitative by raising the reaction temperature to 80 °C.

2-Methylquinoxaline (**7**), a challenging aromatic diimine, was hydrogenated using a range of Noyori-type precatalysts under our standard hydrogenation conditions (15 bar H_2, 65 °C, *i*-PrOH, S/C/B = 100/1/100) with good conversions and a range of ees being obtained. Bianchini et al.[13] have addressed the asymmetric hydrogenation of this aromatic diimine using iridium-based catalysts. Although a high selectivity (90% ee) was achieved by these workers for this substrate at 54% conversion, a lower ee (73%) was obtained at higher conversion (97%). In our work, biaryl BINAP-like systems gave the highest selectivity. Given that 2-methylquinoxaline (**7**) and its reduced product were not solids under the reaction conditions we saw the opportunity to conduct the hydrogenation in the absence of solvent. Indeed, when the reaction was conducted neat with $RuCl_2$[(*R*,*R*)-Et-DuPHOS][(*R*,*R*)-DACH] (entry 1, Table 2) at S/C/B = 1000/1/50, at 50 °C and 30 bar H_2 40% ee and 98% conversion were obtained. This was very pleasing because we have observed severe retardation of reaction rate in the hydrogenation of ketones using Noyori-type precatalysts when conducted neat, or at very high concentration.[14] The use of $RuCl_2$[(*S*)-Tol-BINAP][(*S*,*S*)-DPEN] (entry 2) provided quantitative conversion and improved selectivity (68% ee) suggesting that biaryldiphosphines were better for this particular substrate. A screen against HexaPHEMP and BINAP precatalysts (entries 3–12) revealed an unexpected lack of diphosphine/diamine matching/mismatching effects. Only relatively small differences in selectivity were observed between the two enantiomers of either DPEN or DACH. This was unexpected given previous observations with imine **1**, which showed a marked matching/mismatching effect between the stereochemical elements of the chiral diphosphine and diamine ligands. This is also a characteristic of ketone hydrogenation.[10] More surprisingly, there appeared to be a reversal in the usual matching/mismatching for the HexaPHEMP precatalysts bearing the DACH ligand (entries 5 and 6). These results suggested that these diamines had little steric interaction with the imine substrate. When the chiral diamine was substituted for ethylenediamine (EDA), however, markedly lower selectivity (entry 11) was observed suggesting an electronic influence. The ee obtained for the product represented by entry 3 was upgraded to 96% upon single crystallisation from *i*-PrOH. When precatalysts based on DAIPEN were tested (entries 12 and 13) the expected diphosphine/diamine matching effect was observed.

Table 2. Precatalyst screening against neat 2-methylquinoxaline (**7**) at S/C of 1000/1.[a]



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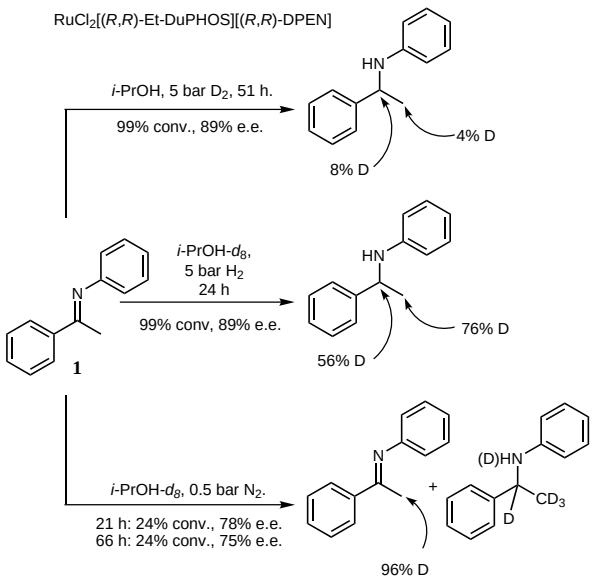
Entry	$RuCl_2$(diphosphine)(diamine)	Conversion [%]	ee [%]
1	(*R*,*R*)-Et-DuPHOS/(*R*,*R*)-DACH	98	40 (*S*)
2	(*S*)-Tol-BINAP/(*S*,*S*)-DPEN	100	68 (*R*)
3	(*S*)-HexaPHEMP/(*S*,*S*)-DPEN	100	69 (*R*)
4	(*S*)-HexaPHEMP/(*R*,*R*)-DPEN	100	64 (*R*)
5	(*S*)-HexaPHEMP/(*S*,*S*)-DACH	100	65 (*R*)
6	(*S*)-HexaPHEMP/(*R*,*R*)-DACH	100	69 (*R*)
7	(*R*)-BINAP/(*R*,*R*)-DPEN	99	66 (*S*)
8	(*R*)-BINAP/(*S*,*S*)-DPEN	99	66 (*S*)
9	(*S*)-BINAP/(*S*,*S*)-DACH	100	61 (*R*)
10	(*R*)-BINAP/(*S*,*S*)-DACH	100	60 (*S*)
11	(*R*)-BINAP/EDA	99	39 (*S*)
12	(*R*)-BINAP/(*R*)-DAIPEN	94	62 (*S*)
13	(*S*)-BINAP/(*R*)-DAIPEN	96	37 (*R*)

[a] Reactions were conducted with neat **7** (5.6 M), at 30 bar H_2, 50 °C, S/C/B 1000/1/50, 20 h, 0.05 equiv. 1.0 M *t*-BuOK in *t*-BuOH. Conversion and ees were determined by GC analysis using a chiral DEX-CB column. Absolute configuration is in parentheses.

Finally, some deuterium labelling experiments were performed in order to obtain a better understanding of the reaction (Scheme 2). When imine **1** was treated with deuterium under the standard reaction conditions (5 bar, S/C/B = 100/1/100, *t*-BuOK, 65 °C, 51 h) using $RuCl_2$[(*R*,*R*)-Et-DuPHOS][(*R*,*R*)-DPEN], 8% deuterium was observed to have been incorporated into the benzylic position and 4% into the methyl group. 89% ee and 99% conversion were obtained as for the standard hydrogenation. These results suggest that solvent is the source of hydrogen. Although we had initially expected almost complete deuterium incorporation into the benyzlic position of **2**, it appears that hydrogen or deuterium is rapidly transferred between the solvent (e.g., *i*-PrOH) and ruthenium species as previously suggested in the literature.[15] When the reaction was repeated using *i*-PrOH-d_8 in the presence of hydrogen gas, 56% deuterium was incorporated (determined by ^{1}H NMR spectroscopy) into the benzylic position, with once again an 89% ee and 99% conversion. The reproducible selectivity indicated that no hydrogen/deuterium exchange occurred at the ben-



Scheme 2. Deuterium labelling experiments.

zylic position after reduction had occurred. The methyl group was shown to have undergone a 76% hydrogen/deuterium exchange. When the reaction was conducted under a positive pressure of nitrogen gas under otherwise standard conditions in *i*-PrOH-d_8, a 24% conversion of an essentially fully deuterated (benzylic and methyl groups) amine with a 78% ee was produced. The remainder of the product mixture was composed of the starting imine **1** that was shown to have 96% deuterium incorporated into the methyl group. The latter observation was due to base-catalysed hydrogen/deuterium exchange and accounts for the deuterium incorporated in the methyl position in the previous experiment. Upon conducting the same experimental procedure for 66 hours, a 24% conversion and 75% ee were obtained suggesting that both reactions had attained equilibrium. These results together suggest the activated DuPHOS-ruthenium complex catalyses both hydrogenation as well as transfer hydrogenation, the latter being slower and apparently providing lower selectivities. This has not been reported for ketone hydrogenation, most likely due to the greater reaction rates observed for hydrogenation at the milder conditions employed. The competing and lower selectivity of the transfer hydrogenation could account for some erosion in enantioselectivity.

Conclusion

In conclusion, we have shown that the readily prepared Noyori-type chiral ruthenium(II)dichloride (diphosphine)(diamine) complexes, once activated *in situ* with *t*-BuOK, reduce a range of aromatic and activated non-aromatic imines to amines in the presence of hydrogen gas. For a given imine substrate a diverse range of diphosphine/diamine combinations needs to be tested to determine the optimum catalyst system. The imines can be hydrogenated neat with good S/C loadings and at reasonable pressures. In contrast to ketone reduction using the same precatalysts, more forcing conditions for reduction are required.

Experimental Section

General Remarks

Commercially available diamines, DPEN (Fluka), AMP (Aldrich), DAIPEN (Strem), BINAM (Strem), EDA (Aldrich), were used as received. ANDEN[16] and DACH[17] were prepared according to literature procedures. Tol-BINAP (Strem), BINAP (Strem) and MeO-BIPHEP (Roche) were purchased and used as received. Me-DuPHOS, Et-DuPHOS and *i*-Pr-DuPHOS were prepared as previously described.[18] Me-FerroTANE was prepared as previously published.[19] HexaPHEMP was prepared as described in a patent application.[9] 2-Methylquinoxaline (**7**) (Aldrich), 2,3,3-trimethylindolenine (**5**) (Aldrich) and 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**6**) (Acros) were purchased and distilled before use except for the latter which was used as received. *N*-(1-Phenylethylidene)aniline (**1**) and *N*-(1-phenylethylidene)benzylamine (**4**) were prepared as described in the literature.[2i] Racemic amines required for development of analytical methods were prepared as described in the literature.[2i] Deuterium gas (99.98%) was purchased from Aldrich. All imines and their corresponding amines are known compounds and reported in the literature.

Precatalysts

The precatalysts were prepared as described in the supporting information and as published by Noyori et al.,[5] however, the diphosphines were generally allowed to react with the ruthenium dimer for *ca.* 30 – 60 min for BINAP and BIPHEP derivatives, and 2 – 3.5 h for DuPHOS and PhanePHOS derivatives. Diamines were then reacted with the ruthenium-diphosphine intermediates at room temperature overnight.

Hydrogenations

All hydrogenations were carried out in 50 mL Parr hydrogenation vessels or in a Baskerville multi-welled hydrogenation vessel equipped with injection ports with a rubber septum for the addition of the solvent *via* syringe, a pressure gauge, a tightly fitting removable internal glass liner and a magnetic stirring bar. Commercially available anhydrous *i*-PrOH (Fluka) was degassed prior to use by sparging with nitrogen for at least 30 minutes. A commercially available 1.0 M solution of *t*-BuOK in *t*-BuOH (Aldrich) was used following degassing.

General Procedure

The catalyst (0.01 mmol) and imine substrate (1 mmol) were placed in a glass liner and the vessel assembled. This was purged with nitrogen and then with hydrogen at least three times, by pressurising to 5 bar and releasing the pressure. *i*-PrOH (4 mL) was added and the reaction was purged a further three times with hydrogen. A solution of *t*-BuOK in *t*-BuOH (1.0 M, 1.0 mL, 1.0 mmol) was added and the reaction purged a further three times with hydrogen. Finally, the vessel was pressurised to 15 bar of hydrogen and stirred at 50 – 65 °C (oil bath) for 18 – 21 h. The hydrogenations conducted in the mutliwelled vessel were conducted on half this scale. When the pressure was released a sample of the crude reaction was analysed (derivatised or underivatised) by chiral GC (DEX-CB column) for conversion and enantiomeric purity. Conversions were supported by ^{1}H NMR spectroscopy. Liquid imines were added to the catalyst in the purged vessel as a solution in *i*-PrOH. The absolute configurations of the hydrogenation products of *N*-(1-phenylethylidene)aniline **1** were determined by optical rotation on a doubly distilled sample of the product prepared using $RuCl_2$[(*R*,*R*)-Et-DuPHOS][(*R*,*R*)-DACH]. $[\alpha]_D^{25}$: +18.0° (*c* 1.0, MeOH)) {lit.[20] $[\alpha]_D^{24}$: −16° (*c* 1.0, MeOH) for (*R*)-2-phenyl-(1-phenylethyl)amine (**2**)}.

Hydrogenation of Neat 2-Methylquinoxaline 7

The catalyst (0.008 mmol) was placed in a glass liner and the vessel assembled. This was purged with nitrogen and then with hydrogen at least three times, by pressurising to 5 bar and releasing the pressure. 2-Methylquinoxaline **7** (1.15 g, 8.0 mmol) was added and the mixture was purged three times with hydrogen. A solution of *t*-BuOK in *t*-BuOH (1.0 M, 0.40 mL, 0.40 mmol) was added and the reaction was purged a further three times with hydrogen. Finally, the vessel was pressurised to 30 bar of hydrogen and stirred at 50 °C (oil bath) for 20 hours. The absolute configurations of the enantiomeric products were determined by optical rotation measurements of upgraded (crystallised from *i*-PrOH) product samples prepared by hydrogenation of 2-methylquinoxaline (**7**) using $RuCl_2$[(*S*)-HexaPHEMP][(*S*,*S*)-DACH] {$[\alpha]_D^{24}$: +23.1° (*c* 1.0, EtOH)} and $RuCl_2$[(*R*)-BINAP][(*R*)-DAIPEN] [$[\alpha]_D^{24}$: −23.1° (*c* 1.0, EtOH)} {lit.[21] $[\alpha]_D^{24}$: −35.8° (*c* 1.0, EtOH) for (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline (**8**)}.

Deuterium Labelling

The deuteration experiment using D_2 in *i*-PrOH was conducted as for the general procedure except the reaction was conducted under 5 bar deuterium gas pressure. After 50.5 h the reaction was analysed by GC and shown to have undergone 99% conversion with an enantioselectivity of 89% for (*S*)-2-phenyl-(1-phenylethyl)amine (**2**). ^{1}H NMR ($CDCl_3$) spectroscopy showed that the methine and methyl proton integrations were 92% and 96% of that expected indicating 8% and 4% incorporation of deuterium, respectively.

The deuteration experiment using H_2 in *i*-PrOH-d_8 was conducted as for the general procedure except the reaction was conducted under 5 bar hydrogen gas pressure in *i*-PrOH-d_8 (2 mL) and *t*-BuOK (112 mg, 1.0 mmol) in *i*-PrOH-d_8 (2 mL). After 24 h the reaction was analysed by GC and shown to have undergone 99% conversion with an enantioselectivity of 89% for (*S*)-2-phenyl-(1-phenylethyl)amine (**2**). ^{1}H NMR ($CDCl_3$) spectroscopy showed that the methine and methyl proton integrations were 44% and 24% of that expected, indicating 56% and 76% incorporation of deuterium, respectively.

The deuteration experiments using *i*-PrOH-d_8 were conducted as for the general procedure except the reaction was conducted under 0.5 bar nitrogen gas pressure in *i*-PrOH-d_8 (2 mL) and *t*-BuOK (112 mg, 1.0 mmol) in *i*-PrOH-d_8 (2 mL). After 21 h, the reaction was analysed by GC and shown to have undergone 24% conversion with an enantioselectivity of 78% for (*S*)-2-phenyl-(1-phenylethyl)amine (**2**). ^{1}H NMR ($CDCl_3$) spectroscopy showed that the methine and methyl positions had essentially full incorporation of deuterium. The methine proton integration was 4% of that expected, indicating 96% incorporation of deuterium.

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