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Enantioselective Hydrogenation and Transfer Hydrogenation of Bulky Ketones Catalysed by a Ruthenium Complex of a Chiral Tridentate Ligand

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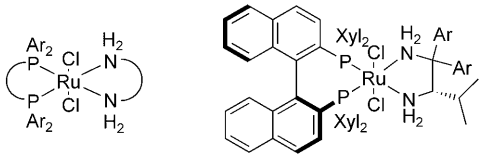
Abstract: A study on the enantioselective hydrogenation of tertiary alkyl ketones catalysed by a novel class of tridentate–Ru complex is reported. In contrast to the extensively studied [$RuCl_2$(diphos)(di-primary amine)] complexes, this new class of hydrogenation catalyst smoothly reduces these less reactive bulky ketones with up to 94% *ee*. The same catalyst system can also selectively reduce other potentially problematic substrates such as bulky heterocyclic ketones. Unusually for a pressure hydrogenation catalyst, similar enantioselectivity can be obtained under transfer hydrogenation conditions. The transfer hydrogenations are somewhat slower than the pressure hydrogenations, but this drawback is readily overcome, since we have discovered that a microwave accelerated transfer hydrogenation of the above ketones occurs within 20 min at about 90 °C with similar selectivity to that obtained in the pressure hydrogenation system.

Keywords: asymmetric catalysis · heterocyclic ketones · hydrogen transfer · hydrogenation · N,P ligands

Introduction

Reduction of C=O and C=N double bonds using molecular hydrogen is a very important process in industrial organic syntheses, due to its low cost and complete atom efficiency.[1–4] There has consequently been a massive research effort aimed at developing homogeneous catalysts that can carry out this goal with high efficiency, chemoselectivity and, in the case of prochiral ketones, enantioselectivity. Asymmetric hydrogenation of β-keto esters and related substrates has been an industrial process for some time.[3,4] Homogeneous hydrogenation of unfunctionalised ketones could not be carried out with sufficient efficiency or chemoselectivity until Noyori's pioneering research on ruthenium complexes containing both diphosphine and diamine ligands.[5,6] These catalysts are highly chemoselective for C=O bonds, show industrially relevant turnover numbers, and if the catalyst shown in Scheme 1 is used, extremely high enantioselectivity for a range of acetophenone derivatives. Since Noyori's original publications, there has been intense interest in [$RuCl_2$(diphos)(diamine)] systems, with several structurally related catalysts also showing similarly excellent selectivity and reactivity for reduction of acetophenone derivatives.[7,8] The key to the massively enhanced reactivity relative to simple Ru–phosphine catalysts is proposed to be a unique mechanism in which the substrate hydrogen bonds to the NH functionality in the diamine ligand.[9]



Scheme 1. General structure of Noyori catalysts and the most selective catalyst known

However, [$RuCl_2$(BINAP)(DAIPEN)] (BINAP = 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl, DAIPEN = 1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine) and related catalysts do have some important limitations and are far less effective for the hydrogenation of tetralones,[7j,k] dialkylke-

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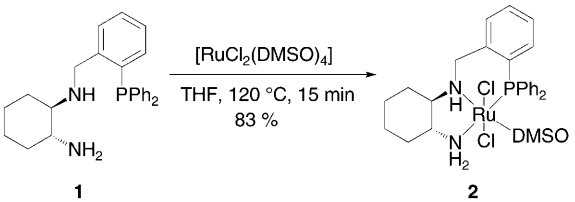
tones,[10] bulky ketones,[11] some heterocyclic ketones,[12] and imines.[13] Given that so many drugs, agrochemicals, materials, and natural products can be disconnected back to enantiopure secondary alcohols, it is of significant importance to extend asymmetric hydrogenation chemistry such that it is effective for every major class of substrate. We therefore initiated a project aimed at successfully hydrogenating these difficult substrates, with the general impression that a departure from the [$RuCl_2$(diphosphine)(diamine)] blueprint may offer the best chance of some success in this challenging goal. In our preliminary communication,[14] we reported that a ruthenium complex of a chiral tridentate ligand is an active hydrogenation catalyst for a very wide range of carbonyl substrates and provided two examples of highly enantioselective hydrogenation of the highly challenging tertiary alkyl ketones. Herein, we report a more extensive study into the enantioselective hydrogenation and microwave-accelerated transfer hydrogenation of two classes of poorly reactive ketones using the new tridentate Ru system.

Results and Discussion

Given the absence of data on hydrogenation catalysis using tridentate ligands,[15] ruthenium complexes of tridentate P^N^NH_2 type ligands seemed worthy of investigation. This type of ligand could form octahedral ruthenium complexes with a more open co-ordination environment, thus increasing substrate scope or reactivity in hydrogenation. The use of a single ligand to play the roles carried out by both diphosphine and diamine ligands in Noyori catalysts is also a topic of considerable recent interest.[8f,g]

After some optimisation, we found that heating readily available compound **1**[16] with [$RuCl_2$(DMSO)$_4$] in THF at 120 °C in a microwave gave a quantitative yield of ruthenium complex **2** in sufficient purity (≈90–95 %) for the applications described here (Scheme 2). On the other hand, complexation reactions carried out using conventional heating always gave a significant amount of side products. Completely pure samples of complex **2** can be obtained by column chromatography or by recystallisation from acetonitrile to form the MeCN–solvate. (All samples gave similar selectivity in catalysis.) Samples of complex **2** have remained unchanged in air for extended periods of time, and in the majority of the hydrogenations reported here, autoclaves were loaded under a non-inert atmosphere, prior to flushing with hydrogen, which is a desirable feature for a catalyst.



1 2

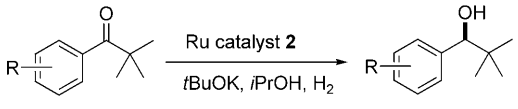
Scheme 2. Synthesis of the ruthenium catalyst **2.**

The X-ray crystal structure of this pre-catalyst has already been discussed in our communication.[14]

One of our main goals when we initiated this research was to hydrogenate unreactive ketones using the new catalysts, ideally with some asymmetric induction. The enantiopure variant, (*R, R*)-**2** was used for the experiments below. Noyori and co-workers have reported that 1,1′,1″-trimethylacetophenone **3** gave only a 6 % yield when hydrogenated using [$RuCl_2$(BINAP)(DPEN)] (DPEN = 1,2-Diphenylethylenediamine). When this work was initiated, there were no effective ruthenium catalysts for asymmetric hydrogenation of this substrate,[6,11] so it was therefore selected as a challenging example of a bulky ketone. We were therefore delighted to find that the hydrogenation proceeds smoothly at 50 °C to give the (*S*)-alcohol in quantitative yield and up to 77 % *ee* using (*R*,*R*)-**2** as catalyst (Table 1). A series of experiments with varied solvents and temperature show that running reactions in *i*PrOH with a base/Ru ratio of 2 at temperatures between 50 and 70 °C give the best results for this substrate (Table 1).

Alternative *tert*-butyl ketones **5a**–**5d**, readily available as shown in Scheme 3, were also tested in this general protocol. These gave very similar enantioselectivity showing that sub-

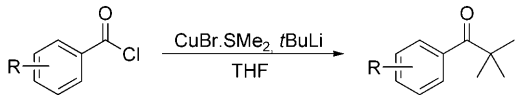
Table 1. Hydrogenation of *tert*-butyl ketones using catalyst **2**.



3 R = H
5a R = *p*-OMe **5c** R = *p*-CF_3
5b R = *o*-OMe **5d** R = *p*-Cl

Entry[a]	Ketone	[cat] mol %	[base] mol %	*T* °C	Solvent	Conversion (Yield) [%][b]	*ee* [%][c]
1	**3**	1.0	2.0	50	*i*PrOH	>99 (>99)	74 (*S*)
2	**3**	1.0	2.0	50	EtOH	>99 (>99)	53 (*S*)
3[d]	**3**	1.0	2.0	50	*i*PrOH	>99 (>99)	74 (*S*)
4[e]	**3**	1.0	2.0	50	*i*PrOH	>99 (>99)	74 (*S*)
5[f]	**3**	0.5	1.0	70	*i*PrOH	>99	77 (*S*)
6[g]	**3**	1.0	2.0	70	*i*PrOH	19	61 (*S*)
7[h]	**3**	1.0	2.0	50	*i*PrOH	>99 (>99)	71 (*S*)
8	**5a**	0.5	1.0	50	*i*PrOH	>99 (79)	77 (*S*)
9	**5b**	0.5	1.0	50	*i*PrOH	>99 (97)	69 (*S*)[c]
10	**5c**	0.5	1.0	50	*i*PrOH	>99 (84)	76 (*S*)[c]
11	**5d**	0.5	1.0	50	*i*PrOH	>99 (69)	80 (*S*)[c]

[a] Unless otherwise indicated in these footnotes, reactions were carried out using 0.33 mmol mL^{-1} ketone at 50 bar of hydrogen pressure with a 24 h reaction time using *t*BuOK as base. [b] Conversions were determined by ^{1}H NMR analysis of the crude reaction mixtures (all peaks assigned). Yields are for pure alcohols after short-path silica gel chromatography or filtration through alumina. [c] The *ee* value was determined by chiral HPLC (see Supporting Information). Configuration for alcohols from hydrogenation of ketones **3** and **5a** were determined to be (*S*) by comparison of optical rotation to those in the literature. The closely related alcohols derived from ketones **5b–d** have the same negative sense of rotation of polarised light, and are therefore tentatively also assigned as *S*. [d] 0.033 mmol ketone per mL *i*PrOH. [e] 1.66 mmol ketone per mL *i*PrOH and reaction time reduced to 5 h. [f] Reaction time reduced to 38 min (hydrogen uptake monitored at constant pressure). [g] Reaction was run in the absence of hydrogen for 38 min. [h] Reaction was run in the absence of hydrogen for 24 h.



4 5

a R = *p*-OMe, 65 % **c** R = *p*-CF_3, 49 %

b R = *o*-OMe, 70 % **d** R = *p*-Cl, 67 %

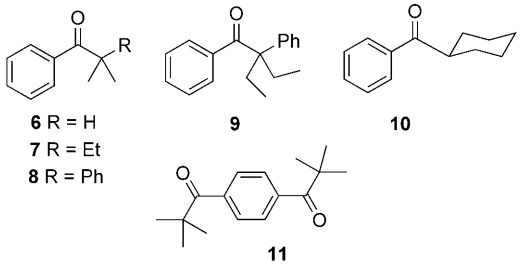
Scheme 3. Preparation of *tert*-butyl ketones.

strate electronic effects on the selectivity of these hydrogenations are minimal.

To explore the scope of the new catalyst, a range of other ketones were hydrogenated using catalyst **2**, including **6**–**11**, which are even more sterically demanding than the tertiary alkyl ketones studied recently by the Noyori group. As can be seen from Table 2, all ketones are essentially quantitatively reduced to alcohols, and as the steric bulk of the substrate increases, so does enantioselectivity. The (*R*,*R*) catalyst generally gives *S* alcohols in cases where the bulky group is of lower Cahn–Ingold priority to phenyl, although for this new catalyst, it is not known if the Noyori NH-bifunctional mechanism is in operation or an inner sphere mechanism. For the first member of a new class of ketone hydrogenation catalysts, the enantioselectivities observed (up to 94% *ee*) for a class of ketone hydrogenation that were reported to be unreactive to reduction with standard Noyori-type catalysts (or other Ru–phosphine hydrogenation catalysts) are very promising. One ketone that was not reduced was the extremely bulky 1,1,1-triphenylacetophenone. However, we note that with this substrate no reduction occurred with $NaBH_4$ and incomplete reduction occurred with $LiAlH_4$. Using the first member of this new class of catalyst, asymmetric hydrogenation of simple acetophenones gives essentially racemic alcohols.

In considering what might be useful design features of catalyst **2**, the presence of a labile solvent molecule in one of the co-ordination sites seemed potentially advantageous for functionalised substrates that might otherwise inhibit the catalyst. Certain heterocyclic ketones have been found to be either completely unreactive[12a] or unreactive unless Lewis acid additives are added to the hydrogenations.[12b] This is presumably due to deactivation of the catalyst by the heterocycle, through hydrogen bonding, deprotonation, or co-ordination to Ru. It seemed possible that co-ordination of a heterocycle to Ru could occur to complex **2**, but still allow the ketone to reach a transition state where hydride transfer could occur. A small selection of heterocyclic substrates was therefore investigated in this reduction (Table 3). Imidazole-functionalised aryl alcohols are intermediates to a group of compounds known to exhibit anti-fungal activity, and a pre-

Table 2. Enantioselective hydrogenation of other bulky-aryl ketones using catalyst **2**.



6 R = H
7 R = Et
8 R = Ph

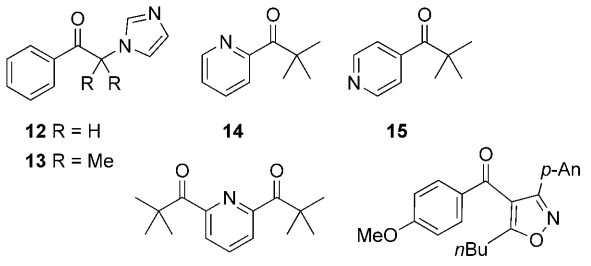
9 **10**

11

Entry[a]	Ketone	*T* [°C]	Conversion (Yield) [%][b]	*ee* [%][c]
1	**6**	50	(>99)	48 (*S*)
2	**7**	50	(>99)	90
3[d]	**8**	70	>99 (79)	84
4[d]	**9**	70	>99 (62)	75
5[e]	**10**	70	(>99)	46 (*S*)
6	**11**	50	>99 (98)	94[f]

[a] Unless otherwise indicated in these footnotes, reactions were carried out using 0.5 mol% catalyst and 1 mol% *t*BuOK at 50 bar of hydrogen pressure in propan-2-ol as solvent with a 24 h reaction time. [b] Conversions were determined by ^{1}H NMR analysis against an internal standard. Yield refers to yield of isolated pure alcohols after chromatography (or in the case of those quoted as >99 refer to a quantitative yield after removal of catalyst by filtration through a pad of alumina). [c] The *ee* value was determined by chiral HPLC (see Supporting Information), configuration for alcohols of entries 1 and 5 was determined to be (*S*) by comparison of optical rotation to those in the literature. [d] Hydrogenation carried out at 40 bar of hydrogen pressure. [e] Hydrogenation carried out at 70 bar of hydrogen pressure. [f] Estimated diastereomeric ratio of 83:17 ((*S*,*R*)+(*R*,*S*):*meso*) based on uncorrected HPLC data assuming equal absorbance for both diastereomers (in agreement with those determined by ^{1}H NMR integration).

Table 3. Enantioselective hydrogenation of bulky heterocyclic ketones using catalyst **2**.



12 R = H
13 R = Me

14 **15**

16 **17**

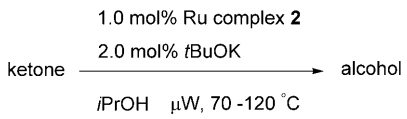
Entry[a]	Ketone	*T* [°C]	Conversion (Yield) [%][b]	*ee* [%][c]
1[d]	**12**	50	>99	61 (*R*)
2	**13**	70	>99 (86)	53
3	**14**	70	>99 (55)[e]	60 (*S*)
4	**15**	70	>99 (61)[e]	69
5	**16**	100	(>99)	70
6	**17**	70	>99 (98)	67

[a] Unless otherwise indicated in these footnotes, reactions were carried out using 0.5 mol% catalyst and 1 mol% *t*BuOK at 40 bar of hydrogen pressure in propan-2-ol as solvent with a 24 h reaction time. [b] Conversions were determined by ^{1}H NMR analysis against an internal standard, with yields of isolated pure alcohols after chromatography. [c] The *ee* value was determined by chiral HPLC (see Supporting Information), configuration for alcohol of entry 1 was determined to be (*R*) and for alcohol of entry 4 was determined to be (*S*) by comparison of optical rotation to those in the literature. [d] Hydrogenation carried out at 50 bar of hydrogen pressure. [e] The alcohol products from ketones 14 and 15 do not elute well on silica hence reducing yields significantly below the quantitative conversions.

vious paper has reported these substrates to be unreactive to pressure hydrogenation by [$RuCl_2$(diphos)(diamine)] catalysts.[12a] It was therefore gratifying to find that **12** and **13** are readily hydrogenated by catalyst **2**, even if enantioselectivities are only moderate. The pyridyl ketones **14**, **15** and **16**, which also contain a deactivating bulky alkyl group, were none-the-less hydrogenated readily enough with moderate enantioselectivity. The tolerance of the catalyst to bulky isoxazole rings was evaluated using ketone **17**[17]; no sign of inhibition was caused by this heterocycle either, and reasonably good *ee* was observed.

In the course of these studies, we also tested whether catalyst **2** could promote transfer hydrogenation.[18] It has been reported by Morris and co-workers that some hydrogenation catalysts can also promote transfer hydrogenation, but in these examples, good hydrogenation catalysts were generally poorly selective transfer hydrogenation catalysts and vice versa.[19] Catalyst **2** does promote transfer hydrogenation of the above substrates with very similar selectivity to the pressure hydrogenation described above. Transfer and pressure hydrogenations run side-by-side suggest that the rate of transfer hydrogenation is significantly slower (Table 1 entries 5 and 6), and a labelling experiment was consistent with this. A hydrogenation carried out in [D_8]isopropanol at 50 bar H_2 presssure gave >99% conversion with 23% of the alcohol product incorporating the deuterium in the C-H(D) position. A general catalyst for both pressure hydrogenation and transfer hydrogenation of ketones is a sought-after goal, since hydrogenation is preferred at commercial scale, and transfer hydrogenation is more convenient in a research laboratory. The fact that catalyst **2** does seem to give similar *ee* values in transfer hydrogenation is encouraging.

The transfer hydrogenations were clearly slower than the pressure hydrogenations, and as such we investigated if faster reactions could be achieved at higher temperatures using microwave heating (Scheme 4). Other reports on microwave-accelerated transfer hydrogenation[20] generally show some eroding of the enantioselectivity at higher temperatures, but the high degree of control offered by modern microwaves should allow an optimum temperature where the fastest rates are observed with no losses of enantioselectivity. This did indeed prove to be the case, and in optimisation using ketone, **3**, it was found that temperatures of 90°C and below all gave similar enantioselectivity to the pressure hydrogenation of this substrate. In addition, at 90°C, the reaction was complete in just 20 min (Table 4; entry 5), making the procedure highly convenient. A selection of the other ketones studied in Tables 1–3 was also investigated. Enantioselectivity of the reduction is very similar to that observed in pressure hydrogenation, and, in most cases the ketones could be reduced selectivity in short reaction times. Surprisingly, the imidazole containing ketones seemed to be more reluctant to transfer hydrogenation[18g] using our catalyst (ketone **12** was not reduced, and ketone **13** give a moderate yield as shown in entry 14 of Table 4).



Scheme 4. Enantioselective transfer hydrogenation of some bulky ketones.

Table 4. Enantioselective transfer hydrogenation of bulky ketones using catalyst **2**.

Entry[a]	Ketone	*T* [°C]	*t* [min]	Conversion (Yield) [%][b]	*ee* [%][c]
1	**3**	70	38	98	76 (*S*)
2	**3**	80	38	98	76 (*S*)
3	**3**	90	38	>99	77 (*S*)
4	**3**	100	38	>99	68 (*S*)
5	**3**	90	20	98	77 (*S*)
6	**5a**	120	20	>99 (75)	85 (*S*)
7	**5b**	120	20	62	79
8	**5c**	120	20	>99 (89)	72
9[d]	**5d**	90	20	>99 (82)	77
10	**7**	120	20	87	91
11	**8**	120	20	>99 (82)	84
12	**9**	120	20	18	83
13	**11**	90	20	70	92[f]
14	**13**	120	20	41	64
15[d]	**14**	120	20	>99 (56)	57 (*S*)
16[d]	**15**	120	20	>99 (57)	61

[a] Unless otherwise indicated in these footnotes, reactions were carried out using 1.0 mol% catalyst and 2.0 mol% *t*BuOK in a microwave. [b] Conversions were determined by ^{1}H NMR analysis against an internal standard, with yields of isolated pure alcohols after chromatography. [c] The *ee* value was determined by chiral HPLC (see Supporting Information). [d] Reactions carried out using 0.5 mol% catalyst and 1.0 mol% *t*BuOK solution. [e] Estimated diastereomeric ratio of 87:13 ((*S*,*S*)+(*R*,*R*):*meso*) based on uncorrected HPLC data assuming equal absorbance for both diastereomers (in agreement with those determined by ^{1}H NMR integration).

The ability of complex **2** to catalyse pressure hydrogenation and transfer hydrogenation with very similar enantioselectivity suggests a common pathway for the enantioselectivity-determining step of these two processes. This is no surprise, but there does not seem to be a common pathway for [$RuCl_2$(BINAP)(DPEN)] and related catalysts as discussed by Morris and co-workers.[19] Future studies using new catalysts of the [$RuCl_2$(P^N^N)(L)]-type could lead to a highly selective and reactive catalyst for both types of reduction.

Conclusion

In summary, a study on the enantioselective pressure and transfer hydrogenation of some poorly reactive ketones that are not reduced with established ketone hydrogenation catalysts is presented. The mechanism of the reduction with this new type of catalyst is currently unknown. The lack of C_2 symmetry and presence of both NH_2 and NH functions in the catalyst could mean that either of these are involved in the hydrogenation or that a completely different inner-sphere process takes place. A project aimed at unravelling this mechanism to aid the design of new derivatives will be

underway shortly. By using this first-generation catalyst, synthetically useful selectivity has been obtained for hydrogenation and transfer hydrogenation of some challenging ketones. In addition, the catalyst used in this study forms a new alternative class of catalyst for future development in other types of reductions.

Experimental Section

All research chemicals were obtained from commercial sources and used as received unless otherwise stated. Dry, degassed solvents were used for reactions that were carried out under an N_2 atmosphere unless otherwise indicated. Normal grade solvents were used for chromatography and work-up procedures under aerobic conditions. Solvents were removed by rotary evaporation on a Heidolph labrota 4000. All microwave syntheses were carried out in a Biotage Initiator Microwave reactor using 5 mL heavy-walled vials equipped with an air tight septum. Melting points were determined with a Gallenkamp melting point apparatus N° 889339 and are uncorrected. ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and ^{19}F NMR spectra were recorded on Bruker Avance 300 instruments (^{1}H 300.1 MHz, ^{13}C 75.5 MHz, ^{31}P 121.4 MHz and ^{19}F 282 MHz). Chemical shifts are reported in ppm from tetramethyl silane (TMS) with the solvent resonance as the internal standard. Chemical shift values for ^{31}P spectra are reported downfield of phosphoric acid, and chemical shifts values for ^{19}F spectra are relative to $CFCl_3$. Proton resonance multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) or a combination of these. When appropriate, coupling constants (J) are quoted in Hz and are reported to the nearest 0.1 Hz. All spectra were recorded at room temperature, and the solvent for a particular spectrum is given in parentheses. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 Spectrum GX FT-IR system. Mass spectra were recorded on Waters Micromass GCT (Time of flight) fitted with lockspray for accurate mass (ESI) or GCT (CI) instruments. Only major peaks are reported, and intensities are quoted as percentages of the base peaks. Optical rotations were measured on an Optical Activity Ltd AA-1000 digital polarimeter using a 5 mL cell with a 1 cm path length at room temperature using the sodium D-line and a suitable solvent, reported along with the concentration (c: g per 100 mL). Microanalysis for carbon, hydrogen and nitrogen were performed using an EA 1110 CHNS CE instruments elemental analyser at the University the St Andrews. HPLC analysis has been determined using a Varian Prostar operated by Galaxie workstation PC software. Experimental procedures and spectroscopic details for known compounds produced by the methods described here can be found in the Supporting Information.

Complex 2 $[RuCl_2(DMSO)_4]$ (29 mg, 5.92×10^{-2} mmol) was added to a solution of (1*R*,2*R*)-*N*-(2-dphenylphosphanylbenzyl)cyclohexane-1,2-diamine (23 mg, 5.92×10^{-2} mmol) in dry THF prepared in a microwave tube. The solution was then heated in the microwave at 120 °C for 15 min. The solvent was removed under vacuum and the product was obtained as a brown solid in quantitative yield and >95% purity. Recrystallisation by slow evaporation of MeCN gave crystals of the bis-acetonitrile adduct (25 mg, 65%). The complex can also be purified by chromatography on silica gel (75:25 to 100:0 ethyl acetate/hexane) and isolated as a brown powder. Crystals, powder and crude material gave similar results in hydrogenation experiments. m.p. 169–171 °C; $[\alpha]_D^{20}$ + 60 (c=0.5, $CHCl_3$); $\tilde{\nu}_{max}$=432 (w), 3282 (s), 3214 (s), 3136 (s), 3053 (s), 2929 (w), 2856 (s), 1648 (s), 1587 (s), 1483 (s), 1434 (w), 1092 (w, $R_2S=O$), 1047 (w), 1018 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H=7.59–7.09 (14H, m, $C_{Ar}H$), 4.41–3.91 (2H, m, ArCH_2NH), 3.64–3.74 (1H, m, NH), 3.47–3.26 (2H, m, C*H*NH, C*H*NH_2), 2.99 (6H, s, $SO(CH_3)_2$), 2.72–2.52 (1H, m, cyclohexyl-H), 1.55 (2H, br, NH_2), 1.29–0.91 (4H, m, cyclohexyl-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_C=135.0–126.0 (12 Ar*C*H + 4 ArC_{ipso}), 62.7 (CH-NH), 56.1 (CH-NH_2), 51.5 (d, $^3J_{C,P}$=7.7 Hz, NH*C*H_2Ar,), 45.8 ($SO(CH_3)_2$), 44.2 ($SO(CH_3)_2$), 35.1 (cyclohexyl-CH_2), 29.5 (cyclohexyl-CH_2), 23.8 (cyclohexyl-CH_2), 23.4 (cyclohexyl-CH_2); ^{31}P NMR (121.4 MHz, $CDCl_3$): δ_P= +43.6 ppm; (ES+): m/z (%): 644 ([M−Cl+MeCN], 100%), 603 (58); HRMS (ES+): found: 644.1205 ([M−Cl+MeCN]), $C_{29}H_{38}N_3OPS^{35}ClRu$ requires 644.1212. The acetonitrile solvate was also characterised by X-ray crystallography as discussed in reference [14]. Elemental analysis calcd (%) for $C_{27}H_{35}Cl_2N_2OPRuS$ + 1 DMSO + 2 CH_3CN: C 49.6, H 5.9, N 7.0; found: C 49.3, H 5.5, N 6.7.

Example procedure for preparation of ketones using Cu^I-promoted alkylation of acid chlorides: **1-(4-Methoxyphenyl)-2,2-dimethylpropan-1-one (5a)**: A 1.7 M solution of *tert*-butyllithium in pentane (4.33 mL, 6.49 mmol) was added to a suspension of copper bromide dimethyl sulfide complex (1.33 g, 6.49 mmol) in tetrahydrofuran (20 mL) at −78 °C. After the mixture had been stirred for 30 min, a solution of 4-methoxybenzoyl chloride (1.00 g, 5.86 mmol) in tetrahydrofuran (5 mL) was added slowly by cannula. After the mxiture had been stirred for 4 h, the reaction was quenched by addition of saturated ammonium chloride solution and the organic layer separated. The aqueous layer was extracted with diethyl ether, and the organic fractions combined, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by short-path distillation to yield the pure product as a colourless oil (0.73 g, 65%). $\tilde{\nu}_{max}$=2969 (s), 2907 (m), 2872 (w), 2840 (w), 1667 (s), 1602 (s), 1462 (s), 1477 (m), 1307 (m), 1258 (s), 1167 (s), 1029 (m), 960 (s), 842 (s), 769 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H=7.81–7.74 (2H, m, $C_{Ar}H$), 6.85–6.79 (2H, m, $C_{Ar}H$), 3.78 (3H, s, OCH_3), 1.30 (9H, s, $C(CH_3)_3$) ppm; ^{13}C NMR (75.5 MHz $CDCl_3$): δ_C=206.3 (C=O), 162.0 (COC_{ipso}), 131.0 ($C_{Ar}H$), 130.1 (C_{ipso}OMe), 113.2 ($C_{Ar}H$), 55.4 (OCH_3), 43.9 ($C(CH_3)_3$), 28.4 ($C(CH_3)_3$) ppm; (CI+) m/z (%): 193.1 ([M+H]$^+$, 100), 135.1, 109.1, 85.1; HRMS (CI+): found: 193.1229 (±0.9 ppm), $C_{12}H_{16}O_2$ requires 193.1230.

General procedures for hydrogenation: A glass-lined stainless steel autoclave equipped with a magnetic stirring bead was charged with the catalytic solution, prepared previously in a dried and degassed Schlenk tube, containing the catalyst (0.5 mol%, 3.2 mg) dissolved in dry *i*PrOH (3 mL). The substrate (1.0 mmol) was added in air, and *t*BuOK (1 mol%, 0.01 mL of 1 M solution in *t*BuOH) was added prior to sealing the autoclave. The autoclave was flushed three times with hydrogen and finally charged with hydrogen to the specific reaction pressure. The reactions were stirred at the same speed for the desired times at the required temperature using a stainless steel heating jacket connected to a thermocouple and heater. After the desired time passed, the autoclave was cooled, opened and the solvent removed. The conversion of the reaction was calculated by NMR spectroscopy, generally using mesitylene as internal standard. The products were isolated in pure form by column chromatography (hexane/Et_2O) and characterised by comparison of NMR, IR, MS, HPLC/GCMS, optical rotation and, where appropriate, melting point data with authentic samples (see the Supporting Information). The enantiomeric excess was calculated by HPLC or using a chiral shift reagent as indicated. Racemic authentic samples of all the products from ketone and imine hydrogenation were first prepared by $NaBH_4$ or $LiAlH_4$ reduction. HPLC retention times and NMR data from hydrogenation experiments matched the authentic samples exactly.

The above method was used to prepare, for, example, 1-(4-methoxyphenyl)-2,2-dimethylpropan-1-ol (from ketone **5a**): $[\alpha]_D^{20}$ −16.3 (c=4.24, toluene) (lit[21] (S, 99% *ee*): $[\alpha]_D^{20}$ −21.6 (c=4.24, benzene)); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H=7.14–7.09 (2H, m, $C_{Ar}H$), 6.77–6.72 (2H, m, $C_{Ar}H$), 4.23 (1H, s, C*H*OH), 3.70 (s, 3H, OCH_3), 1.92 (1H, br s, CHO*H*), 0.81 ppm (9H, s, $C(CH_3)_3$); ^{31}C NMR (75 MHz, $CDCl_3$): δ_C=158.8 (C_{ipso}), 134.5 (C_{ipso}), 128.7 ($C_{Ar}H$), 112.9 ($C_{Ar}H$), 82.0 (CHOH), 55.2 (OCH_3), 35.7 ($C(CH_3)_3$), 25.9 ppm ($C(CH_3)_3$); (CI+) m/z (%): 195.1 ([M−H_2O], 100) and 177.1 ([M+H]$^+$, 33). Enantioselectivity determined by chiral HPLC. Chiralpak AD, 1.0 mL/min, 98:2 hexane:2-propanol. Retention times: 16.8 min (*R* enantiomer) and 18.0 min (*S* enantiomer).

General procedures for microwave accelerated transfer hydrogenation: A solution of substrate (ca. 1 mmol), catalyst, *t*BuOK (1 M solution) and mesitylene (ca. 1 mmol) in degassed *i*PrOH (3 mL) was prepared in a microwave vial under an atmosphere of nitrogen. The vial was then placed inside the heating cavity of the microwave and heated for the required period at the desired temperature. After the desired time passed, the microwave vial was opened and the reaction mixture passed through a plug of silica and concentrated in vacuo. The conversion of substrate to prod-

uct was calculated by ^{1}H NMR spectroscopy using mesitylene as internal standard. The products were isolated by column chromatography or short-path distillation and characterised by comparison of NMR, IR, MS, HPLC, optical rotation and, where appropriate, melting point data, with authentic samples.

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