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Technical Notes

Industrially Viable Syntheses of Highly Enantiomerically Enriched 1-Aryl Alcohols via Asymmetric Hydrogenation

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Abstract:

The practicalities of the asymmetric hydrogenation of acetophenone derivatives are addressed. The catalysts used, derived from the precatalysts [(xylylPhanePhos)RuCl$_2$(DPEN)] (*S*)-(*R*,*R*)-1 and (*R*)-(*S*,*S*)-1, were shown to possess very high reactivity. 4′-Fluoroacetophenone was hydrogenated at a molar substrate-to-catalyst ratio (S/C) of 100,000 with complete conversion effected in as little as 80 min (average turnover ~1200 min^{-1}, peak turnover ~2500 min^{-1}). The catalysts are tolerant of a range of commercial grade substrates, in most cases a S/C of 5000−10000 was achieved without the need to purify the ketone. Using precatalyst 1 enantioselectivities of 95 → 99% ee were achieved. The high selectivity and catalyst activity, plus the simplicity of the process, offers significant advantages over other enantioselective ketone reductions.

Introduction

A wide range of methodologies have been developed for the synthesis of chiral alcohols in high enantiomeric excess via the reduction or hydrogenation of prochiral ketones.[1] Catalytic hydrogenation offers potentially significant advantages over other approaches. Only a small amount of high-value catalyst is required to facilitate the reaction, the more active and selective the catalyst, the greater the amplification of this value in the product. The reagent, hydrogen, is cheap and can be used in excess as all unreacted hydrogen is very easily removed at the end of the reaction, leaving a solution of the product containing trace quantities of the catalyst residue. The most effective catalysts available for the asymmetric hydrogenation of ketones to date are those derived from diphosphine ruthenium dichloride diamine complexes.[2,3] They were shown to be effective for the asymmetric hydrogenation of a wide range of prochiral ketones. The catalysts are tolerant of various functionalities within the substrate and offer excellent enantioselectivity. Molar substrate-to-catalyst ratio as high as 2,400,000 (low catalyst loading) have been reported.[4] To demonstrate the utility of these types of catalyst we sought to carry out some larger-scale transformations than have typically been reported to date. Our primary concern was whether we could effect the hydrogenation of a range of prochiral ketones, easily purify the chiral product, and meet an acceptable quality standard, for example, >95% chemical purity, ≥98% ee. We also wished to examine to what extent it is possible to avoid extensive purification of the ketones prior to hydrogenation.

Results and Discussion

The precatalysts used throughout this study were [((*S*)-xylyl-PhanePhos)Ru((*R*,*R*)-DPEN)Cl$_2$] (*S*)-(*R*,*R*)-**1** and [((*R*)-xylyl-PhanePhos)Ru((*S*,*S*)-DPEN)Cl$_2$] (*R*)-(*S*,*S*)-**1**[5] (Figure 1).

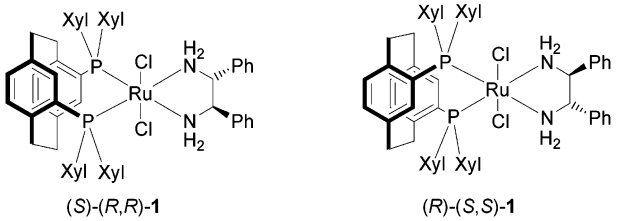

Figure 1.

By variation of the diamine and the diphosphine it is possible to access a wide range of precatalysts of this type, offering a variety of chemoselectivities and selectivities for different substrate types. Catalysts derived from **1** have been shown to offer high selectivity and reactivity for the ketones examined in this current study.[3] The focus of this work is primarily on catalyst utilization rather than catalyst selection.

A range of acetophenone substrates **2a**−**i** (Figure 2) were hydrogenated using (*S*)-(*R*,*R*)-**1** and (*R*)-(*S*,*S*)-**1** on a 20 mmol scale in a 50-mL pressure vessel. In these reactions, using

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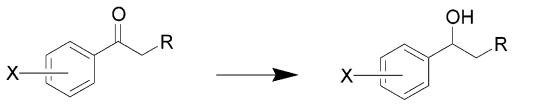


2a R = H, X = H
2b R = CH_3, X = H
2c R = Ph, X = H
2d R = H, X = 2'-Br
2e R = H, X = 3'-Br
2f R = H, X = 4'-Br
2g R = H, X = 4'-NH_2
2h R = H, X = 4'-F
2i R = H, X = 3'-CF_3

3a R = H, X = H
3b R = CH_3, X = H
3c R = Ph, X = H
3d R = H, X = 2'-Br
3e R = H, X = 3'-Br
3f R = H, X = 4'-Br
3g R = H, X = 4'-NH_2
3h R = H, X = 4'-F
3i R = H, X = 3'-CF_3

Figure 2.

Table 1. **Hydrogenation of acetophenone derivatives with (*S*)-(*R*,*R*)-1 and (*R*)-(*S*,*S*)-1**

ketone	specified purity (%)	(*S*)-(*R*,*R*)-**1** yield %	(*S*)-(*R*,*R*)-**1** ee %[a]	(*R*)-(*S*,*S*)-**1** yield %	(*R*)-(*S*,*S*)-**1** ee %[b]
2a	99	88	96.8	n/a[c]	98.5[d]
2b	99	73	98.5	94	98.8[d]
2c	98	93	98.9	96	98.2
2d	98+	77	98.8	88	98.5
2e	97	86	98.8	90	98.3
2f	98	91	98.0	85	98.1
2g	99	82	94.0	99	89.3
2h	99 distilled	n/a[c]	99.0	n/a[c]	99.0
2i	99	–	–	n/a[c]	98.7

[a] (*S*)-aryl alcohol. [b] (*R*)-aryl alcohol. [c] Not isolated. [d] Molar S/C = 10,000. (20 mmol input) molar S/C = 5000.

typical conditions (8 atm hydrogen, 1−5 mol % *t*-BuOK, room temperature in propan-2-ol) these ketones underwent complete conversion to the corresponding alcohol **3a**−**i** with a S/C ratio of 5000−10000 in 2−6 h. The hydrogenation of 4′-fluoroacetophenone proved to be more problematic as some commercially available materials (99% purity) showed very little reactivity. However, after distillation of the ketone the hydrogenation was very rapid. In small-scale reactions (20 mmol) at S/C of 10,000 the reaction was complete in less than 2 h.

When hydrogen uptake had ceased, the crude reaction mixture was treated with 1 equiv of hydrochloric acid (with respect to *t*-BuOK), solvent was removed in vacuo, and the residue was partitioned between water and dichloromethane. After drying, removal of solvent gave a coloured oil or solid, Kugelrohr distillation gave a colourless product. Analysis of this product indicated clean conversion in all cases, and the enantioselectivities were uniformly high (Table 1).

Design of Experiment. Before embarking on larger-scale experiments with these substrates the profile of a typical hydrogenation reaction was examined in more detail. The hydrogenation of acetophenone **2a** with (*R*)-(*S*,*S*)-**1** under of a range of temperatures (10, 20, and 30 °C), pressures (3, 8, and 13 atm H_2) and substrate concentrations (0.2, 0.3, and 0.4 g/mL) were examined. The effect of these factors on reaction selectivity and rate are shown in Table 2.

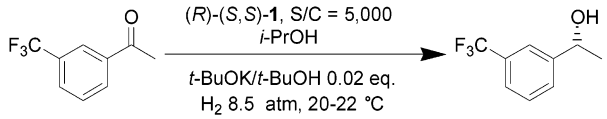
The data were analysed using the MODDE 6 software package.[6] Computer-based analysis of the data confirmed what a cursory examination of the crude data would

Table 2. **Design of experiment matrix for the hydrogenation of acetophenone 2a with (*R*)-(*S*,*S*)-1**

entry	pressure (atm)	temp (°C)	ketone (concn g/mL)	selectivity ee	rate[a] (mol s^{-1})
1	13	30	0.4	98.1	6.2×10^{-6}
2	3	30	0.4	97.5	2.1×10^{-6}
3	3	30	0.2	97.5	3.0×10^{-6}
4	13	30	0.2	98.4	11.1×10^{-6}
5	3	10	0.2	98.8	0.8×10^{-6}
6	13	10	0.2	98.8	2.9×10^{-6}
7	3	10	0.4	98.4	0.7×10^{-6}
8	13	10	0.4	98.7	3.2×10^{-6}
9	8	20	0.3	98.3	2.9×10^{-6}
10	8	20	0.3	98.3	4.0×10^{-6}
11	8	20	0.3	98.7	3.4×10^{-6}

[a] Approximate rate based on time to 50% conversion.

Table 3. **Effect of substrate concentration on the hydrogenation of 3′-trifluoroacetophenone with (*R*)-(*S*,*S*)-1**



entry	ketone concn (v/v)	reaction time(min)[a]	selectivity ee
1	100	>310[b]	72.9
2	83	119	93.0
3	71	87	94.6
4	55	36	97.4
5	38	20	98.3
6	19	25	98.9
7	11	24	98.7
8	6	38	98.7

[a] Time for uptake of hydrogen to cease. [b] 80% of hydrogen uptake after 5 h, reaction left overnight.

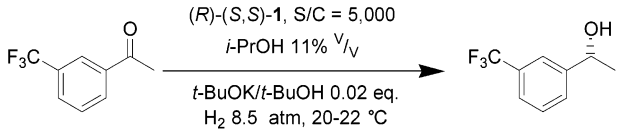
suggest: the variation in selectivity is very slight. In general lower concentrations and higher pressures enhance reaction rate and selectivity. Higher temperatures increase the rate of the reaction but afford lower selectivity. As the target selectivity is ≥98% ee conditions were chosen that should give reasonably high selectivity and a reasonable reaction rate while still allowing a suitably high substrate concentration to confer high-volume efficiency. Consequently, most of the subsequent work was carried out at ∼20 °C, 0.3 g/mL (30% w/v) and 8 atm H_2 pressure.

The hydrogenation of a similar substrate, 3′-trifluoromethylacetophenone **2i**, was examined over a wider range of concentration and pressures (Tables 3 and 4). In Table 3 the effect of a range of ketone concentration from 6 to 100% on reaction time and selectivity are shown. Even at high concentration of substrate a reasonable rate and high selectivity are maintained. At very high concentration selectivity deteriorates as does the reactivity of the system. In the absence of propan-2-ol the reaction is very sluggish, and the selectivity falls dramatically.

As the hydrogen pressure is increased, the reaction rate increases (Table 4). At very high pressure there was no

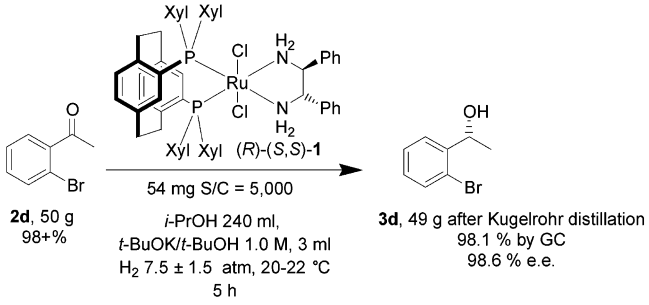
(6) MODDE 6, Umetric AB, http://www.umetrics.com.

Table 4. **Effect of pressure the hydrogenation of 3′-trifluoroacetophenone with (*R*)-(*S*,*S*)-1**



entry	H_2 pressure atm	conversion (time) 12 min	conversion (time) 45 min	selectivity ee
1	1.7	16	99	98.6
2	6.9	76	100	98.7
3	12.4	99.5	100	98.7
4	27.6	92.3	100	98.6

Scheme 1



improvement in rate; under these conditions the rate of reaction is probably limited by the rate at which hydrogen can be dispersed into the reaction medium rather than the pressure of hydrogen over the reaction.[7]

Preparative Scale Hydrogenations, 0.25−0.5 mol. The asymmetric hydrogenation of ketones **2a**−**g** were repeated at a 50−80-g scale using conditions similar to those developed in the design of experiment study (Scheme 1). The reactions were conducted in a 600-mL glass-lined pressure vessel equipped with an overhead stirrer. All the reactions proceeded smoothly; using a molar S/C of 5000 complete conversion was achieved for all the substrates. The ketones were used as supplied without any purification. After a similar workup as described for the 20 mmol reactions, the crude products were isolated by Kugelrohr distillation, giving the alcohols as colourless oils or solids in good-to-excellent yields (86−99%). GC, HPLC, and water content analysis (Karl Fisher) showed that all the samples were of ≥98% purity and ≥98% ee. The only exception was in the case of (*S*)- and (*R*)-1-(4-aminophenyl)ethanol **3g**. The ee of the crude product of the hydrogenation reactions was lower than required: ∼95% ee. After the product slurried in MTBE, the ee had increased to ≥98% ee. The alcohols (*S*)-**3g** and (*R*)-**3g** were isolated as a hydrate in yields of 69 and 71%, respectively.

Kilogram-Scale Hydrogenation (8−10 mol). Next we focused on scaling up the reaction to ∼1 kg input, utilising a 10-L pressure reactor. During the synthesis of the 50 g samples it had become clear that the hydrogenation reaction was exothermic; thus, prior to scaling up the reaction further

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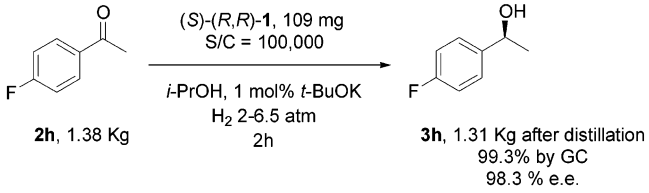
Scheme 2



a calorimetric study was carried out. By using a 50-mL calorimetric pressure vessel,[8] the hydrogenation of 4′-fluoroacetophenone was examined, using the conditions identified previously. It was found that the reaction reached a maximum heat output of 12.3 W mol^{-1} and a total energy flow of −77 kJ mol^{-1}. Interestingly, the maximum power output occurred approximately 1 h after the reaction was initiated. This also corresponded to the period of the reaction where the rate of hydrogen uptake was at a maximum. This ties in with previous observations where reactions of this type have been seen to have an induction period between addition of the base required to activate the catalysts and uptake of hydrogen.

Judging that the cooling capacity of the reactor was greater than the heat output of the reaction, the hydrogenation of acetophenone **2a** and 4′-fluoroacetophenone **2h** were carried out on 1−1.4 kg input. The process was straightforward: the vessel was charged with the ketone, solvent, and a solution of base. To achieve an oxygen-free environment the vessel was charged to 6 atm with nitrogen while being stirred, the vessel was then vented to atmospheric pressure. The process was repeated several times. The precatalyst was dissolved in deoxygenated toluene, and the solution was introduced into the vessel. The vessel was charged with hydrogen to between 1 and 3 atm, and the reaction proceeded. During the course of the reaction the hydrogen pressure was increased to 6.5 atm (∼100 psi). The maximum hydrogen uptake achieved was ∼6 L min^{-1} using 0.1 mmol of catalyst; this corresponds to a turnover frequency of ∼2,500 min^{-1}. The workup was relatively simple: treatment with hydrochloric acid to neutralise the excess base used to activate the catalyst, filtration of the precipitated potassium chloride, and removal of solvent followed by wiped film evaporation of the crude product. The chiral alcohols **3a** and **3h** were thus obtained as colourless liquids. In the case of the hydrogenation of 4′-fluroacetophenone it was found that much higher S/C catalyst ratios could be achieved if the substrate was purified by distillation prior to the hydrogenation reaction. Thus, **2h** that had been purified by wiped film distillation was successfully hydrogenated using (*S*)-(*R*,*R*)-**1** at a molar S/C of 100,000 which equates to 0.109 mg of catalyst (*S*)-(*R*,*R*)-**1** required to convert 1.38 kg of **2h**. After purification 1.31 kg (94% yield) of (*S*)-1-(4-fluorophenyl)-ethanol, **3h** was obtained with a 98.3% ee (Scheme 2).

Conclusions

Asymmetric hydrogenation of prochiral ketones with a diphosphine ruthenium diamine catalyst was demonstrated up to a kilogram-scale. The key parameters that determine

(8) HEL stainless steel Automate.

the efficiency and selectivity of the reaction were examined. The catalyst system was shown to be tolerant of commercial grade substrates and high substrate-to-catalyst ratios were achieved without compromising the enantioselectivity of the product or the robust nature of the reaction.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded at 400 MHz (Bruker DPX 400). ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts (δ) are quoted in ppm, and coupling constants (J) are given in Hz. Optical rotations were determined using a Perkin-Elmer 341 Polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. Sample purity was analysed by GC [DB-5, 30 M × 0.25 μm, 60 °C for 5 min ramp 15 °C/min to 270 °C hold 5 min].

Asymmetric Hydrogenation of Acetophenone (2a) To Provide (*S*)-1 Phenylethanol (3a). A 600-mL pressure reactor equipped with a thermostatically controlled cooling loop and fitted with a glass liner was charged with acetophenone (60 mL, 0.50 mol) and propan-2-ol (175 mL). The reactor was placed in a heating mantle, and the temperature was set to 20 °C. A nitrogen atmosphere was established by charging the vessel to 10 bar with nitrogen while stirring and then gently venting the vessel to 1 atm. This was repeated three times. A solution of [((*S*)-xylyl-PhanePhos)Ru((*R*,*R*)-DPEN)Cl$_2$] (*S*)-(*R*,*R*)-**1** (21 mg, 20 μmol, molar S/C = 25,000) in propan-2-ol (25 mL) was prepared under nitrogen using standard Schlenk techniques. This solution was transferred to the pressure reactor via syringe. The vessel was charged to 3 bar of nitrogen and vented three more times. A solution of potassium *tert*-butoxide in *tert*-butanol (1.0 M, 5 mL, 5 mmol) was added via syringe. The vessel was charged to 4.5 bar with hydrogen. As hydrogen was consumed, the pressure in the vessel was maintained at 2.5−4.5 bar. After 2.5 h hydrogen uptake appeared to have stopped. The hydrogen was vented from the vessel which was then flushed with nitrogen. Hydrochloric acid (1 N, 5 mL, 5 mmol) was added, and the solvents were removed in vacuo. The crude product was dissolved in dichloromethane (300 mL) and washed with brine (200 mL, ∼18%). The organic layer was dried ($MgSO_4$) and filtered, and solvent was removed to give a brown liquid. The crude product was purified by wiped film distillation (WPD) (bp 55 °C 3 mbar) to give a clear, colourless liquid (59.3 g, 96% yield). (lit. bp 81−82 °C, 6 Torr[9]); $[\alpha]_D^{23} = -44.4$ (*c* 1, MeOH) [lit. $[\alpha]_D^{25} = -45$ (*c* 1, MeOH)[10]]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.32 (4H, m, ArH), 7.30−7.24 (1H, m, ArH), 4.89 (1H, dq, 3.2 and 6.5 Hz, C*H*OH), 1.90 (H, br) and 1.49 (3H, d, 6.5 Hz, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 70.8, 125.8, 127.8, 128.9 and 146.2; 99.0% ee, [GC, Chirasil Dex CB, 25 M × 0.25 mm, 120 °C, hold for 9.5 min, ramp to 200 °C at 15 °C/min, retention time: 9.83 min (+)-(*R*); 10.10 min (−)-(*S*)]. 99.5% purity (GC), moisture (Karl Fischer) 0.09 wt %/wt.

(*R*)-1-Phenylethanol (*R*)-(3a). In a similar fashion [((*R*)-xylyl-PhanePhos)Ru((*S*,*S*)-DPEN)Cl$_2$] (*R*)-(*S*,*S*)-**1** and acetophenone gave (*R*)-1-phenylethanol **(*R*)-(3a)** as a clear, colourless liquid; bp 52 °C 4 mbar (WPD); $[\alpha]_D^{23} = +44.2$ (*c* 1.3, MeOH); 99.0% ee, >99.4% purity (GC), moisture (Karl Fischer) 0.09 wt %/wt.

Asymmetric Hydrogenation of 4′Aminoacetophenone (2g) To Provide (*R*)-1-(4-Aminophenyl)ethanol (*R*)-(3g). 4′-Aminoacetophenone (66.8 g, 494 mmol) was hydrogenated with (*R*)-(S,S)-(**1**) (106 mg, 98.8 μmol) as previously described. Hydrochloric acid (1 N, 27 mL, 27 mmol) was added, and the solvents were removed in vacuo. The crude product was dissolved in ethyl acetate (200 mL) and washed with a mixture of water and saturated sodium chloride (200 mL, 1:1). The aqueous fraction was re-extracted with ethyl acetate (100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to ∼300 mL. This solution was filtered through a pad of silica gel (∼180 g) and eluted with ethyl acetate (3 × 300 mL). The solvent was removed in vacuo to provide a cream-coloured solid that was charged to a 250-mL round-bottomed flask equipped with a stirrer bar and a condenser. MTBE (120 mL) was charged to the flask, and the stirred suspension was heated to a gentle reflux. After stirring for 17 h, the suspension was filtered to provide (*R*)-1-(4-aminophenyl)ethanol as an off-white solid (57.1 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (2H, d, 8.4 Hz, ArH), 6.63 (2H, d, 8.4 Hz, ArH), 4.75 (1H, q, 6.4 Hz, C*H*OH), 3.6 (2H, br, N*H*$_2$), 2.1 (1H, br, CHO*H*), and 1.43 (3H, d, 6.4 Hz, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 70.4, 115.5, 127.0, 136.4, and 146.1; 96.8% ee [HPLC Chiracel OD, heptane 70%, propan-2-ol 30% 1 mL/min: detector 254 nm, retention times, 13.4 min and 19.2 min]. Karl fisher analysis showed this material to contain 13% water, and attempts to dry this material led to extensive decomposition.

(*S*)-1-(4-Aminophenyl)ethanol (*S*)-(3g). Following an identical procedure outlined for (*R*)-**3g**, (*S*)-**3g** was isolated in 95.6% ee. After the product was slurried in MTBE, the enantiopurity had been increased to 98.4% ee. Again, Karl Fisher analysis showed a high water content (13%), and attempted drying led to decomposition.

(*R*)-1-Phenylpropanol (*R*)-(3b): clear colourless liquid; bp 62−68 °C 0.9−1.3 mbar (lit. 110 °C, 6 Torr[11]); $[\alpha]_D^{23} = +47.6$ (*c* 1, $CHCl_3$) [lit. $[\alpha]_D^{25} = +48.5$ (*c* 1.2, $CHCl_3$)[12]]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.31 (4H, m, ArH), 7.38−7.24 (1H, m, ArH), 4.59 (1H, dt, 3.4 and 6.6 Hz, C*H*OH), 1.89 (1H, d, 3.4 Hz, CHO*H*),1.86−1.69 (2H, m, C*H*$_2$CH$_3$) and 0.91 (3H, t, 7.4 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 32.3, 76.3, 126.4, 127.8, 128.8 and 145.1; 98.1% ee, [GC, Chirasil Dex CB, 25 M × 0.25 mm, 120 °C, hold for 9.5 min, ramp to 200 °C at 15 °C/min, retention time: 10.97 min (+)-(*R*); 11.05 min (−)-(*S*)]. 99.6% purity (GC) Retention time 8.6 min, moisture Karl Fischer 0.05 wt %/wt

(*S*)-1-Phenylpropanol (*S*)-(3b): clear colourless liquid; bp 123 °C 1.6 mbar; $[\alpha]_D^{23} = -48.4$ (*c* 1.6, $CHCl_3$). 98.8% ee (GC), 99.6% purity (GC), moisture (Karl Fischer) 0.04 wt %/wt.

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(*R*)-1,2-Diphenylethanol (*R*)-(3c): white solid; mp 66−70 °C (lit. 67 °C[13]); $[\alpha]_D^{23} = -52.9$ (*c* 1, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.11 (10H, m, ArH), 4.80 (1H, m, C*H*OH), 3.05−2.90 (2H, m, CH_2Ph), and 2.12 (1H, d, 2.8 Hz, CHO*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.5, 75.8, 126.4, 127.0, 128.0, 128.8, 128.9, 130.0, 138.5, and 144.3; >98% ee, HPLC Chiracel OD, heptane 96% propan-2-ol 4% 1 mL/min: detector 254 nm, retention times, 12.65 min (*R*)-(+); 16.81 min (*S*)-(−) >99% purity (GC) 14.3 min, moisture Karl Fischer <0.1 wt %/wt.

(*S*)-1,2-Diphenylethanol (*S*)-(3c): white solid; $[\alpha]_D^{23} = +53.6$ (*c* 1, EtOH) [lit. $[\alpha]_D^{23} = +53$ (*c* 1, EtOH)[14]]. 98.6% ee. (HPLC), 99.0% purity (GC), moisture (Karl Fischer) 0.03 wt %/wt.

(*R*)-1-(2-Bromophenyl)ethanol (*R*)-(3d): white solid; bp 140 °C, 2.3 mbar (Kugelrohr) (lit. 102−105 °C, 2−3 Torr[15]) mp 53−54 °C; $[\alpha]_D^{23} = +55.7$ (*c* 1, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (1H, dd, 7.6, 2 Hz, ArH), 7.51 (1H, dd, 8.8, 1 Hz, ArH), 7.34 (1H, ddd, 7.6, 7.6, 1.2 Hz, ArH), 7.12 (1H, ddd, 7.6, 7.6, 1.6 Hz, ArH), 5.230 (1H, q, 6 Hz, C*H*OH), 2.07 (1H, s, CHO*H*), and 1.43 (3H, t, 6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 69.5, 122.1, 127.1, 128.2, 129.1, 133.0, and 145.1; 98.6% ee, [GC, Chirasil Dex CB, 25 M × 0.25 mm, 120°C, hold for 20 min, ramp to 200 °C at 15 °C/min, retention time: 22.2 min (*R*)-(+); 23.6 min (*S*)-(−)]. >99% purity (GC) retention time: 10.4 min, moisture (Karl Fischer) 0.1 wt %/wt.

(*S*)-1-(2-Bromophenyl)ethanol (*S*)-(3d): off white solid; mp 49−56 °C; $[\alpha]_D^{23} = -54.7$ (*c* 1, EtOH) [lit. $[\alpha]_D^{24} = +54.6$ (*c* 1.2, EtOH)[16]]. 98.7% ee, 98.4% purity (GC), moisture (Karl Fischer) 0.05 wt %/wt.

(*R*)-1-(3-Bromophenyl)ethanol (*R*)-(3e): clear colourless liquid; bp 145−155 °C 1.7−1.9 mbar (Kugelrohr) (lit. 106−108 °C, 2.5 Torr[17]); $[\alpha]_D^{23} = +27.3°$ (*c* 1.1, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (1H, dd, 1.6 and 1.6 Hz, ArH), 7.39 (1H, ddd, 8, 1.4, and 1.4 Hz, ArH), 7.28 (1H, ddd, 8, 1.6, and 1.6 Hz, ArH), 7.20 (1H, dd, 8 and 8 Hz, ArH), 4.85 (1H, dq, 4 and 6.4 Hz, C*H*OH), 2.00 (1H, d, 4 Hz, CHO*H*), and 1.47 (3H, d, 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 70.0, 123.0, 129.0, 130.5, 130.8, and 148.5; 98.7% ee, [GC, Chirasil Dex CB, 25 M × 0.25 mm, 120 °C, hold for 20 min, ramp to 200 °C at 15°C/min, retention time: 22.4 min (*R*)-(+); 23.1 min (*S*)-(1)], 99.4% purity GC, moisture Karl Fischer 0.05 wt %/wt.

(*S*)-1-(3-Bromophenyl)ethanol (*S*)-(3e): clear colourless liquid; bp 136 °C 1.6 mbar (Kugelrohr); $[\alpha]_D^{23} = -28.3$ (*c* 1, EtOH) [lit. $[\alpha]_D^{23} = -28.6$ (*c* 1.8, EtOH)[16]]. 99.2% ee, 99.2% purity GC, moisture (Karl Fischer) 0.03 wt %/wt. (*R*)-1-(4-bromophenyl)ethanol (*R*)-(**3f**): clear colourless liquid; bp 150−160 °C 1.2−1.4 mbar (Kugelrohr) (lit. 105−108 °C, 3 Torr[18]); $[\alpha]_D^{23} = +36.9$ (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (2H, d, 8.5 Hz, ArH), 7.25 (2H, d, 8.5 Hz, ArH), 4.86 (1H, dq, 3.4 and 6.5 Hz, C*H*OH), 1.85 (1H, d, 3.4 Hz, CHO*H*), and 1.47 (3H, d, 6.5 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 70.1, 121.5, 127.6, 131.9, and 145.2; 97.7% ee, [GC, (pyridine, Ac_2O) Chirasil Dex CB, 25 M × 0.25 mm, 100 °C, hold for 40 min, ramp to 200 °C at 15 °C/min, retention time: 45.5 min (*R*)-(+); 45.8 min (*S*)-(−)]. 98.6% purity (GC, retention time, 10.9 min), moisture (Karl Fischer) 0.36 wt %/wt.

(*S*)-1-(4-Bromophenyl)ethanol (*S*)-(3f): clear colourless liquid; bp 150−160 °C 1.2−1.4 mbar (Kugelrohr) $[\alpha]_D^{23} = -37.6$ (*c* 1, $CHCl_3$) [lit. $[\alpha]_D^{23} = -37.9$ (*c* 1, $CHCl_3$)[16]]. 98.4% ee, 99.4% purity GC, moisture (Karl Fischer) 0.04 wt %/wt.

(*R*)-1-(4-Fluorophenyl)ethanol (*R*)-(3h): clear colourless liquid; bp 52 °C 3 mbar (WPD), (lit. 70 °C, 4 Torr[19]); $[\alpha]_D^{23} = +38.4$ (*c* 1.2 MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, d, 8.7 and 5.4 Hz, ArH), 7.03 (2H, dd, 8.7 and 8.7 Hz, ArH), 4.89 (1H, dq, 3.6 and 6.4 Hz, C*H*OH), 1.82 (1H, d, 3.6 Hz, CHO*H*), and 1.48 (3H, d, 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 70.1, 115.6 (d, 21.3 Hz), 127.5 (d, 8.1 Hz), 141.9, and 162.5 (d, 245.7 Hz); 98.6% ee, [GC, Chirasil Dex CB, 25 M × 0.25 mm, 40 °C, hold for 10 min, ramp to 200 °C at 15 °C/min, retention time: 17.8 min (*R*)-(+); 18.0 min (*S*)-(−)], 99.2% purity, moisture (Karl Fischer) 0.04 wt %/wt.

(*S*)-1-(4-Fluorophenyl)ethanol (*S*)-(3h): clear colourless liquid; bp 53 °C 4 mbar (WPD); $[\alpha]_D^{23} = -37.9$ (*c* 1 MeOH) [lit. $[\alpha]_D^{23} = -37.7$ (*c* 1.1 MeOH)[16]]. 98.9% ee, (GC), 99.7% purity (GC), moisture (Karl Fischer) 0.80 wt %/wt.

1-(3-Trifluromethylphenyl)ethanol (3i): GC, Chirasil Dex CB, 100 °C, hold for 7 min, ramp to 200 °C at 15 °C/min, retention time: 10.58 min (+); 10.86 min (−)].

Kilogram Hydrogenation of 4′-Fluoroacetophenone (2h) To Provide (*S*)-1-(4-Fluorophenyl)ethanol (*S*)-(3h). A glass liner was charged with 4′-fluoroacetophenone (wipe film distilled, 1.38 kg, 10 mol) and placed in a 10-L pressure vessel equipped with a heating jacket and cooling coil. The liner was charged with propan-2-ol (3.6 L) and potassium *tert*-butoxide solution in *tert*-butyl alcohol (1.0 M, 100 mL, 100 mmol). The pressure vessel was assembled, stirring commenced, and the heating controls were set to 22 °C. A nitrogen atmosphere was established by charging the vessel to 10 bar with nitrogen while stirring and then gently venting the vessel to 0.4 bar overpressure. This was repeated three times. A solution of [((*S*)-xylyl-PhanePhos)Ru((*R*,*R*)-DPEN)-Cl_2] (*S*)-(*R*,*R*)-**1** (109 mg, 0.10 mmol, molar S/C = 100,000) in toluene (20 mL) was prepared under nitrogen using standard Schlenk techniques. This solution was transferred to the pressure reactor. The vessel was charged to 3 bar of nitrogen and vented three more times. The vessel was charged to 2 bar with hydrogen, and the reaction was allowed to proceed. Over a period of 40 min the reactor pressure was increased to 6.5 bar, ensuring that the reactor temperature was maintained at 22−23 °C. After a further 40 min hydrogen uptake was no longer apparent. The reaction was allowed to continue for a further 1 h. The contents of the

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reactor plus propan-2-ol rinses were transferred to a 10-L flask. HCl (2 N, ~50 mL) was added slowly and the pH of the mixture monitored. At pH 7 the reaction mixture changed from green to yellow. The precipitated potassium chloride was removed by filtration, and solvent was removed in vacuo to give a brown liquid. The crude product was purified by wiped film distillation (bp 77 °C 0.33 mbar) to give a clear colourless liquid (1.31 kg, 93% yield). $[\alpha]_D^{23} = -38.1$ (*c* 1.2, MeOH). 99.3% ee, (GC), 98.9% purity (GC), moisture (Karl Fischer) 0.03 wt %/wt,(*R*)-1-(4-fluorophenyl)ethanol (*R*)-(3h)0.93 kg, 91% yield. Clear colourless liquid; bp 47 °C 0.3 mbar (WPD), $[\alpha]_D^{23} = +38.4$ (*c* 0.95, MeOH). 99.1% ee, (GC), 99.6% purity (GC), moisture (Karl Fischer) 0.04 wt %/wt.

(20) About 3% acetophenone found in the product, later shown to be due to unreacted starting material contamination from a dip tube in the reactor. On subsequent runs the contents of dip tube were blown into the vessel with nitrogen once hydrogen uptake had ceased, and the reaction was allowed to run for a further 30−60 min.

(*R*)-1-Phenylethanol (*R*)-(3a): yield 1.25 kg, 93%; clear colourless liquid; bp 40 °C 0.3 mbar (WPD), $[\alpha]_D^{23} = +43.5$ (c 1.3 MeOH). 99.1% ee, (GC), 96.6% purity[20] (GC), moisture (Karl Fischer) 0.13 wt %/wt.

(*S*)-1-Phenylethanol (*S*)-(3a): yield 1.17 kg, 93%; clear colourless liquid; bp 40 °C 0.3 mbar (WPD), $[\alpha]_D^{23} = -44.3$ (*c* 1.1, MeOH). 98.9% ee, (GC), 99.5% purity (GC), moisture (Karl Fischer) 0.06 wt %/wt.

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