Multigram-Scale Asymmetric Hydrogenation Reactions Using Ru-SYNPHOS® and Ru-DIFLUORPHOS® Catalysts

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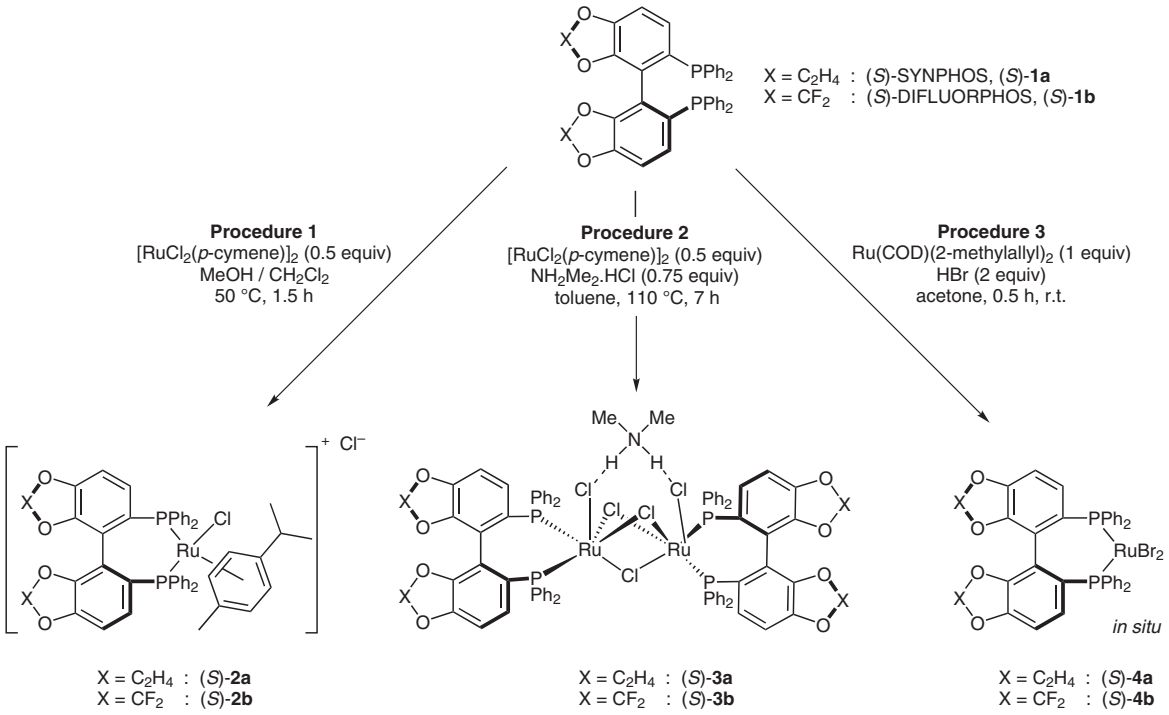
Abstract: The detailed procedure for the synthesis of Ru-SYNPHOS® and Ru-DIFLUORPHOS® catalysts are described. These catalysts displayed high rates and are quite effective for the large-scale hydrogenation reactions of unsaturated compounds.

Key words: ruthenium catalysts, asymmetric catalysis, hydrogenation, ligands, atropisomerism



Scheme 1

Ruthenium(II) complexes incorporating enantiomerically pure atropisomeric diphosphines played a crucial role in transition-metal catalyzed asymmetric transformations, thereby making the design and synthesis of chiral Ru(II)-catalysts an active area of research.[1] The pioneering work of Noyori et al. led to the discovery of the first mononuclear hexacoordinated ruthenium complex $Ru(O_2CCH_3)_2$(BINAP).[2–4] Since the initial reports in this field,[5,6] a wide variety of chiral Ru(II)-catalysts isolated or prepared in situ from Ru(COD)(η^3-methylallyl)$_2$[7] (COD = cycloocta-1,5-diene), $Ru(acac)_3$,[8] $[RuX_2(arene)]_2$,[9] $Ru(RCp)(PPh_3)_2Cl$,[10] have emerged in the literature.[11] Notable achievements are based upon ruthenium catalysts derived from atropisomeric biaryl-diphosphine ligands[12,13] which are useful catalysts for the industrial production of fine chemicals.[14]

As part as our continuing interest in homogeneous hydrogenation reactions,[15–17] we reported general synthetic methods for the preparation of chiral ruthenium(II)-catalysts such as Ru(P*P)(η^3-methylallyl)$_2$[7b]and in situ generated Ru-catalysts from Ru(COD)(η^3-methylallyl)$_2$,[7a,b] $[RuCl_2(COD)]_n$[18] and $RuCl_3$[19] bearing various chiral diphosphines. We also described the preparation of a cationic monohydride ruthenium complex [Ru{(*R,R*)-Me-DuPHOS}(H)(η^6-1,3,5-cyclooctatriene)][BF_4], which

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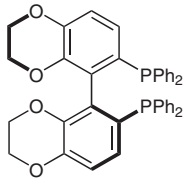
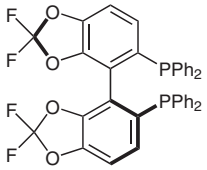


(*S*)-SYNPHOS : (*S*)-**1a**

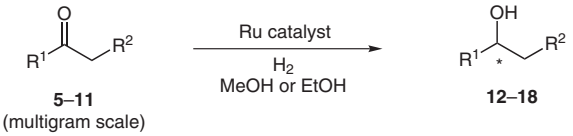


(*S*)-DIFLUORPHOS : (*S*)-**1b**

Figure 1 (*S*)-SYNPHOS [(*S*)-**1a**] and (*S*)-DIFLUORPHOS [(*S*)-**1b**]

was successfully used for the synthesis of (+)-*cis*-methyl dihydrojasmonate (paradisone®) in an industrial enantioselective hydrogenation process on a multi t/year scale.[20] Recently, we designed new atropisomeric diphosphines named SYNPHOS[21] and DIFLUORPHOS[22] with relevant stereoelectronic properties (Figure 1). In this paper, we report the synthetic procedures for the preparation of ruthenium catalysts based upon the SYNPHOS (**1a**) or DIFLUORPHOS (**1b**) ligands and their applications in multigram-scale asymmetric hydrogenation reactions.

The chiral Ru(II)-catalysts bearing SYNPHOS or DIFLUORPHOS ligands were prepared on large scale through standard procedures[23] involving reaction between each of the chiral ligand and the precursor complex $[RuCl_2(p\text{-cymene})]_2$ or $Ru(COD)(\eta^3\text{-methylallyl})_2$ (Scheme 1). The isolated complexes [Ru(*p*-cymene){(*S*)-SYNPHOS}Cl]$^+$Cl$^-$ [(*S*)-**2a**] and [Ru(*p*-cymene){(*S*)-DIFLUORPHOS}Cl]$^+$Cl$^-$ [(*S*)-**2b**] were conveniently synthesized quantitatively by mixing respectively the (*S*)-SYNPHOS and (*S*)-DIFLUORPHOS ligands with $[RuCl_2(p\text{-cymene})]_2$ in a mixture of MeOH–CH_2Cl_2 at 50 °C for 1.5 hours (Scheme 1, Procedure 1). When $[RuCl_2(p\text{-cymene})]_2$ was treated with SYNPHOS or DIFLUORPHOS in the presence of $NH_2Me_2{\cdot}HCl$ in toluene at 100 °C for 7 hours, large amount of $[(RuCl\{(S)\text{-SYNPHOS}\})_2(\mu\text{–}Cl)_3][NH_2Me_2]$ [(*S*)-**3a**] and $[(RuCl\{(S)\text{-DIFLUORPHOS}\})_2(\mu\text{–}Cl)_3][NH_2Me_2]$ [(*S*)-**3b**] catalysts were obtained in 77 and 76% yields, respectively (Scheme 1, Procedure 2). The structure of these Ru-SYNPHOS [(*S*)-**3a**] and Ru-DIFLUORPHOS [(*S*)-**3b**] Ikariya–Mashima's catalysts were assigned according to NMR in comparison with literature data.[23,24] The in situ generated $[RuBr_2\{(S)\text{-SYNPHOS}\}]$ [(*S*)-**4a**] and $[RuBr_2\{(S)\text{-DIFLUORPHOS}\}]$ [(*S*)-**4b**] were prepared from a mixture of $Ru(COD)(\eta^3\text{-methylallyl})_2$ and the diphosphine in acetone by addition of 2.2 equivalents of HBr according to our convenient procedure[7a] (Scheme 1, Procedure 3). Next, our studies involving the chiral Ru-SYNPHOS and Ru-DIFLUORPHOS catalysts focused upon asymmetric catalytic hydrogenation reactions. Once prepared, these chiral catalysts have been screened for the synthesis of representative building blocks **12**–**18** (Scheme 2). Most of the chiral alcohols **12**–**18** have been used as key intermediates for the preparation of target molecules in fine chemical production.[14] All the catalytic tests were carried out in a TOP 45 stainless steel autoclave which was connected to a 1590 000 TOP INDUSTRIE[25] parallel hydrogenation system equipped with a central mechanical stirrer. Hydrogen uptake was monitored to follow the conversion of the substrate.



5–11
(multigram scale)

12–18

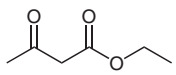
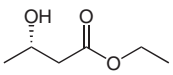
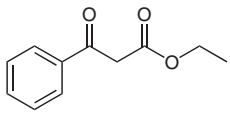
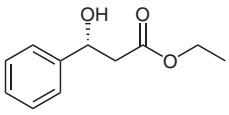
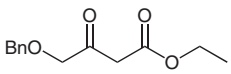
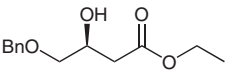
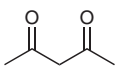
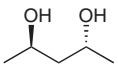
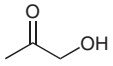
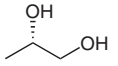
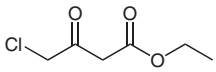
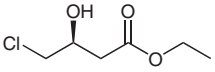
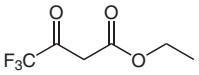
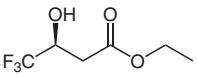
5,12: $R^1 = CH_3$, $R^2 = CO_2Et$
6,13: $R^1 = Ph$, $R^2 = CO_2Et$
7,14: $R^1 = CH_2OCH_2Ph$, $R^2 = CO_2Et$
8,15: $R^1 = CH_3$, $R^2 = COCH_3$
9,16: $R^1 = CH_3$, $R^2 = OH$
10,17: $R^1 = CH_2Cl$, $R^2 = CO_2Et$
11,18: $R^1 = CF_3$, $R^2 = CO_2Et$

Scheme 2

Table 1 summarizes our results. The hydrogenation of ethyl acetoacetate (**5**) to (*S*)-**12** was first performed with a complete conversion in ethanol under 20 bar at 50 °C for 40 hours by using the in situ generated $[RuBr_2\{(S)\text{-SYNPHOS}\}]$ [(*S*)-**4a**] at a high substrate/catalyst ratio (S/C = 7000) and with excellent enantiofacial discrimination (Table 1, entry 1, ee = 99.4%).

Afterwards, most of the reactions were optimized regarding both catalyst loading and reaction times. The in situ generated $[RuBr_2\{(S)\text{-SYNPHOS}\}]$ [(*S*)-**4a**] catalyst was also found to be very effective for the hydrogenation of ethyl 3-oxo-3-phenylpropionate (**6**) in ethanol allowing an excellent conversion to (*R*)-**13** (entry 2, 97% conversion) over a very short reaction time of 15 minutes at S/C = 200 with high level of chiral induction (entry 2, 98.3% ee) under 4 bar and 80 °C. The cationic Ru-SYNPHOS catalytic system [Ru(*p*-cymene){(*R*)-SYNPHOS}Cl]$^+$Cl$^-$ [(*R*)-**2a**] ensured very high enantiomeric excess (entry 3, 98.9% ee) and a complete conversion under a standard set of mild conditions (4 bar, 80 °C, S/C = 200, 45 min) in ethanol for the hydrogenation reaction of ethyl 4-benzyloxy-3-oxobutyrate (**7**) to (*S*)-**14**, which is an essential building block for HMG-CoA reductase inhibitors.[26] Our overall objective was to demonstrate that the Ru-SYNPHOS complexes could be broadly effective catalysts for hydrogenations on multigram scale. In this context, the $[(RuCl\{(R)\text{-SYNPHOS}\})_2(\mu\text{-}Cl)_3][NH_2Me_2]$ catalyst (*R*)-**3a** induced in methanol the highly enantio- and diastereoselective 600 mmol-scale hydrogenation of pentane-2,4-dione (**8**) to the *anti*-diol (*S*)-**15** (entry 4, >99% ee and de) at 20 bar, 50 °C and S/C = 1000 over 9 hours reaction time. The hydrogenation

Table 1 Asymmetric Hydrogenations Based upon Ru-SYNPHOS and Ru-DIFLUORPHOS Catalysts

Entry	Substrate		Solvent	Ru-Catalyst	H_2 Pressure/ Temp. (°C)	Time (h)	S/C Ratio	TOF (h^{-1})	Conv (%)[a]	Product		ee (%)
1		**5**		(*S*)-**4a**	20 bar/50	40	7000	175	100		(*S*)-**12**	99.4
2		**6**	EtOH	(*S*)-**4a**	4 bar/80	0.25	200	800	97		(*R*)-**13**	98.3
3		**7**	EtOH	(*R*)-**2a**	4 bar/80	0.75	200	270	100		(*S*)-**14**	98.9
4		**8**	MeOH	(*R*)-**3a**	20 bar/50	9	1000	110	100		(*R,R*)-**15**	>99[b]
5		**9**	MeOH	(*S*)-**4a**	30 bar/80	40[c]	2000	–	100		(*S*)-**16**	96
6		**10**	EtOH	(*R*)-**3b**	100 bar/100	3[c]	1000	–	100		(*S*)-**17**	97
7		**11**	EtOH	(*R*)-**2b**	10 bar/110	0.04	100	2500	100		(*S*)-**18**	77

[a] Conversions were measured by ^{1}H NMR spectral data of the crude reaction mixture.
[b] De >99% *anti*.
[c] Reaction time not optimized.

of oxopropanol **9** to (2*S*)-propane-1,2-diol (**16**), which is a key intermediate in the synthesis of levofloxazine,[27] proceeded smoothly with 96% ee in methanol under 30 bar and 80 °C by using the in situ generated [$RuBr_2$\{(*S*)-SYNPHOS\}] [(*S*)-**4a**] at S/C = 2000 (entry 5, 100% conversion). We next endeavored to explore the scope of the Ru-DIFLUORPHOS catalysts. Hydrogenation of more challenging substrates such as ethyl 4-chloro-3-oxobutyrate (**10**) to (*S*)-**17** was performed in ethanol with complete conversion and high selectivity (entry 6, 97% ee) by using [(RuCl\{(*R*)-DIFLUORPHOS\})$_2$(μ-Cl)$_3$][NH_2Me_2] [(*R*)-**3b**] at high pressure and temperature for 3 hours reaction time. Finally, when [Ru(*p*-cymene)\{(*R*)-DIFLUORPHOS\}Cl]$^+$Cl$^-$ [(*R*)-**2b**] was used, 4,4,4-trifluoro-3-oxobutyrate (**11**) was reduced to (*S*)-**18** with an extremely short reaction time of only 2 minutes and good selectivity (entry 7, 77% ee) in ethanol under 10 bar and 110 °C at S/C = 100.

Finally, we performed a comparative examination of the [Ru(*p*-cymene)\{(*S*)-SYNPHOS\}Cl]$^+$Cl$^-$ [(*S*)-**2a**], [(RuCl\{(*S*)-SYNPHOS\})$_2$(μ–Cl)$_3$][NH_2Me_2] [(*S*)-**3a**] and in situ generated [$RuBr_2$\{(*S*)-SYNPHOS\}] [(*S*)-**4a**] in the hydrogenation of ethyl 3-oxo-3-phenylpropionate (**6**) to (*R*)-**13** under strictly the same reaction conditions (Figure 2). In this case, the in situ generated [$RuBr_2$\{(*S*)YNPHOS\}] [(*S*)-**4a**] offered extremely high rates and the highest enantioselectivity (ee = 98.3%) compared to both [Ru(*p*-cymene)\{(*S*)-SYNPHOS\}Cl]$^+$Cl$^-$ [(*S*)-**2a**] (ee = 91.9%) and [(RuCl\{(*S*)-SYNPHOS\})$_2$(μ-Cl)$_3$][NH_2Me_2] [(*S*)-**3a**] (ee = 94.2%) allowing a complete conversion to (*R*)-**13** within 15 minutes at S/C = 200.

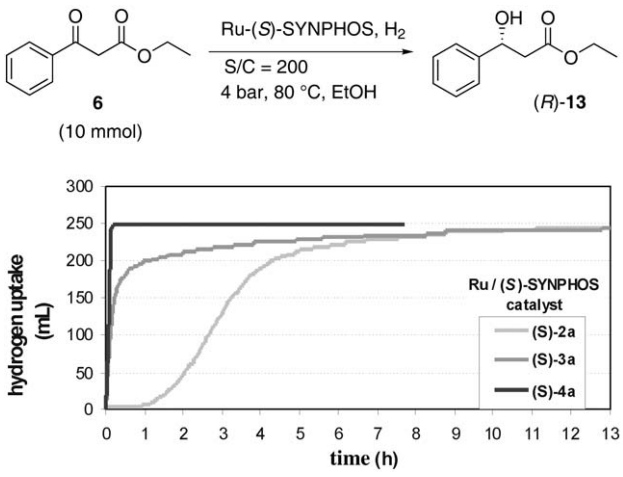


Figure 2 Kinetics of hydrogen uptake in asymmetric hydrogenation of substrate **6** using Ru-SYNPHOS catalysts (*S*)-**2a** (ee = 91.9%), (*S*)-**3a** (ee = 94.2%) and (*S*)-**4a** (ee = 98.3%).

In conclusion, the Ru(II)-catalysts derived from SYNPHOS and DIFLUORPHOS are effective for the hydrogenation reaction of a representative range of unsaturated compounds. The results obtained in this work demonstrated that high reaction rates and selectivities were achieved at low catalyst loading on multigram scale by using the Ru-SYNPHOS and Ru-DIFLUORPHOS catalytic systems. As far as asymmetric hydrogenation is concerned, these results confirm that each prochiral substrate requires an accurate optimization of reaction conditions (pressure, temperature, reaction time) but also an appropriate choice of ruthenium catalyst and chiral diphosphine ligand (SYNPHOS or DIFLUORPHOS), so as to obtain the most effective system in terms of catalytic activity and selectivity.

^{1}H NMR spectra were recorded at 200 MHz or 300 MHz on a Bruker AC 200 or AC 300 instrument, respectively. Chemical shifts (δ) are expressed in ppm with trimethylsilane (TMS) as external standard. ^{31}P NMR spectra were recorded at 121 MHz on a Bruker AC 300 instrument. Chemical shifts (δ) are expressed in ppm with an 85% solution of H_3PO_4 as external standard. ^{19}F NMR spectra were recorded at 282 MHz on a Bruker AC 300 instrument. Chemical shifts (δ) are expressed in ppm with a 1% solution of trichlorofluoromethane in $CDCl_3$ as external standard. GC analyses were performed on a Hewlett-Packard 5890 series II instrument connected to a Merck D-2500 or D-2000 integrator with a flame-ionization detector. Chiral HPLC analyses were conducted on a Waters 600 system with Daicel chiral stationary-phase columns.

Metallic precursor $[RuCl_2(p\text{-cymene})]_2$ was purchased from Strem Chemicals. [Ru(cycloocta-1,5-diene)(2-methylallyl)$_2$] was synthesized from $RuCl_3{\cdot}nH_2O$ (Strem Chemicals). Toluene and CH_2Cl_2 were distilled over CaH_2. Absolute EtOH or MeOH (>99% purity) were used as solvent in the hydrogenation reactions. Hydrogenation substrates **5**, **6** and **8**–**11** were commercially available. Substrates **5** and **6** were distilled before use. Substrate **7** was synthesized from commercially available ethyl 4-chloro-3-oxobutyrate (**10**) using a reported procedure.[26]

[RuCl{(*S*)-SYNPHOS}(*p*-cymene)]$^+$Cl$^-$ [(*S*)-2a]; Typical Procedure 1

$[RuCl_2(p\text{-cymene})]_2$ (122 mg, 0.2 mmol) and of (*S*)-SYNPHOS (256 mg, 0.4 mmol, 2 equiv) were placed in a 50-mL Schlenk tube equipped with a magnetic stirrer bar and a condenser. The system was connected to a supply of vacuum/argon. The mixture was degassed by three vacuum/argon cycles at r.t. Degassed EtOH (15 mL) and anhyd CH_2Cl_2 (6 mL) were added to the mixture. The orange mixture was refluxed (50 °C) for 1.5 h and then cooled to r.t. The deep orange solution was filtered through a short pad of Celite under argon, eluting with degassed EtOH (5 mL) and anhyd CH_2Cl_2 (5 mL). The solvents were evaporated under vacuum to give (*S*)-**2a** as an orange solid (378 mg, ~100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.8 Hz, 3 H), 1.35 (d, *J* = 6.9 Hz, 3 H), 1.99 (s, 3 H), 3.04 (sept, *J* = 6.8 Hz, 1 H), 3.78–3.90 (m, 4 H), 3.96–4.06 (m, 4 H), 4.27 (d, *J* = 6.7 Hz, 1 H), 4.44 (m, 1 H), 5.92 (d, *J* = 7.0 Hz, 1 H), 6.45 (dd, *J* = 1.7, 8.8 Hz, 1 H), 6.57 (dd, *J* = 2.0, 8.6 Hz, 1H), 6.85 (dd, *J* = 8.8, 10.5 Hz, 1 H), 6.94 (dd, *J* = 8.6, 10.3 Hz, 1 H), 7.02 (d, *J* = 6.8 Hz, 1 H), 7.20–7.33 (m, 4 H), 7.35–7.54 (m, 8 H), 7.63–7.71 (m, 4 H), 7.76–7.80 (m, 2 H), 7.85–8.00 (m, 2 H).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 26.1 (d, *J* = 63 Hz), 40.7 (d, *J* = 63 Hz)

MS (ESI): *m*/*z* = 909 ([RuCl(SYNPHOS)(*p*-cymene)]$^+$).

[Ru(*p*-cymene){(*S*)-DIFLUORPHOS}Cl]$^+$Cl$^-$ [(*S*)-2b]

Following the typical procedure 1, $[RuCl_2(p\text{-cymene})]_2$ (122 mg, 0.2 mmol) and (*S*)-DIFLUORPHOS (273 mg, 0.4 mmol) gave (*S*)-**2b** as an orange solid (395 mg, ~100%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.2 Hz, 3 H), 1.36 (d, *J* = 6.2 Hz, 3 H), 2.02 (br s, 3 H), 2.95–3.13 (m, 1 H), 3.60–3.79 (m, 1 H), 4.30–4.52 (m, 1 H), 4.52–4.78 (m, 1 H), 5.95–6.17 (m, 1 H), 6.71 (d, *J* = 8.8 Hz, 1 H), 6.79 (d, *J* = 8.8 Hz, 1 H), 7.01–8.30 (m, 22 H).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 27.5 (d, *J* = 62 Hz), 42.8 (d, *J* = 62 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –50.2 (d, *J* = 91 Hz), –49.4 (d, *J* = 91 Hz), –48.7 (d, *J* = 91 Hz), –47.1 (d, *J* = 91 Hz).

MS (ESI): *m*/*z* = 953 ([RuCl(DIFLUORPHOS)(*p*-cymene)]$^+$).

[(RuCl{(*S*)-SYNPHOS})$_2$(μ-Cl)$_3$] [NH_2Me_2] [(*S*)-3a] (Large-Scale Preparation); Typical Procedure 2

$[RuCl_2(p\text{-cymene})]_2$ (7.84 g, 12.8 mmol), (*S*)-SYNPHOS (16.35 g, 25.6 mmol, 2 equiv) and dimethylamine hydrochloride (1.57 g, 19.2 mmol, 1.5 equiv) were charged in a 500-mL reactor equipped with a condenser. The system was connected to a supply of vacuum/N_2. Degassed anhyd toluene (250 mL) was added. The mixture was degassed by three vacuum/N_2 cycles at r.t. The mixture was refluxed for 7 h and then cooled to r.t. The red-orange suspension was homogenized by adding degassed CH_2Cl_2 (200 mL). The dark orange solution was filtered to eliminate excess dimethylamine hydrochloride crystals. CH_2Cl_2 was distilled off and orange solids were collected by filtration of the toluene solution. The solids were dried under reduced pressure at 45 °C for 18 h to give (*S*)-**3a** as an orange-red powder (16.87 g, 77%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66 (s, 6 H), 3.89–3.97 (m, 8 H), 4.08–4.14 (m, 6 H), 4.24–4.28 (m, 2 H), 5.99 (dd, *J* = 8.7, 10.4 Hz, 2 H), 6.29 (dd, *J* = 1.5, 8.7 Hz, 2 H), 6.45 (dd, *J* = 1.5, 8.6 Hz, 2 H), 6.56 (t, *J* = 1.8, 7.7 Hz, 4 H), 6.88 (t, *J* = 7.4 Hz, 2 H), 7.00 (td, *J* = 7.3, 1.6 Hz, 8 H), 7.06–7.27 (m, 14 H), 7.29–7.34 (m, 2 H), 7.48 (t, *J* = 8.8 Hz, 4 H), 7.70–7.84 (m, 8 H).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 51.1 (d, *J* = 39 Hz), 52.9 (d, *J* = 39 Hz). [The complex was obtained with a slight contamination (8–10%) with an unidentified compound that showed another AB quartet signal at δ = 53.7 and 56.6 (*J* = 42 Hz)[23a]].

[(RuCl{(*S*)-DIFLUORPHOS})$_2$(μ–Cl)$_3$][NH_2Me_2] [(*S*)-3b]

Following the typical procedure 2, (*S*)-**3b** was obtained from $[RuCl_2(p\text{-cymene})]_2$ and (*S*)-DIFLUORPHOS as an orange powder (76%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.67 (s, 6 H), 6.24 (dd, *J* = 8.8, 9.4 Hz, 2 H), 6.50 (d, *J* = 8.4 Hz, 2 H), 6.64 (d, *J* = 8.6 Hz, 2 H), 6.58–6.67 (m, 4 H), 6.94 (t, *J* = 7.6 Hz, 2 H), 7.01–7.35 (m, 24 H), 7.41 (t, *J* = 8.6 Hz, 4 H), 7.50 (t, *J* = 8.5 Hz, 4 H), 7.78 (t, *J* = 8.4 Hz, 4 H).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –51.0 (d, *J* = 95 Hz), –49.5 (d, *J* = 95 Hz), –48.4 (d, *J* = 95 Hz), –45.7 (d, *J* = 95 Hz).

^{31}P NMR (121 MHz, $CDCl_3$): δ = 51.6 (d, *J* = 38 Hz), 52.1 (d, *J* = 38 Hz). [The complex was obtained with a slight contamination (9%) with an unidentified compound that showed another AB quartet signal at δ = 53.5 and 56.2 (*J* = 41 Hz)[23a]].

In situ Generated [RuBr$_2$(*S*)-SYNPHOS}] [(*S*)-4a]; Typical Procedure 3

A dry 10-mL Schlenk tube was equipped with a magnetic stirrer bar, a stopper and connected to a supply of vacuum/argon. The flask was charged with [Ru(cycloocta-1,5-diene)(2-methylallyl)$_2$] (3.2 mg, 0.01 mmol) and of (*S*)-SYNPHOS (6.9 mg, 0.011 mmol, 1.1 equiv), then evacuated and filled with argon. Degassed anhyd acetone (1 mL) was introduced via syringe under a stream of argon. Methanol-

ic HBr (122 μL, 0.18 mol·L^{-1}, 2.2 equiv) was added dropwise to the solution. The mixture was degassed with three vacuum/argon cycles and stirred for 30 min at r.t. under a stream of argon. The orange precipitate was concentrated under vacuum. The crude orange-brown solid (*S*)-**4a** was used as catalyst in the hydrogenation reaction without further purification.

[$RuBr_2$\{(*S*)-DIFLUORPHOS\}] [(*S*)-4b]

Following the typical procedure 3, [Ru(cycloocta-1,5-diene)(2-methylallyl)$_2$] (3.2 mg, 0.01 mmol), (*S*)-DIFLUORPHOS (7.5 mg, 0.011 mmol) and methanolic HBr (122 μL, 0.18 mol·L^{-1}) afforded crude (*S*)-**4b** as an orange solid, which was used as catalyst in the hydrogenation reaction without further purification.

Asymmetric Hydrogenation on Multigram Scale; (2*R*,4*R*)-Pentanediol [(*R*,*R*)-15]; Typical Procedure

Pentane-2,4-dione (**8**; 58 g, 580 mmol) and MeOH (90 mL) were introduced in a 500-mL round-bottomed flask equipped with a magnetic stirrer. The system was connected to a supply of vacuum/argon and the solution was carefully degassed by three vacuum/argon cycles. Solid catalyst [(RuCl\{(*R*)-SYNPHOS\})$_2$(μ-Cl)$_3$][NH_2Me_2] [(*R*)-**3a**; 496 mg, 0.29 mmol] was added in one portion. The orange solution was degassed by another vacuum/argon cycle. Under a flow of argon, the solution was introduced via cannula in a 500 mL stainless steel autoclave which was connected to a 1 590 000 TOP INDUSTRIE[25] parallel hydrogenation system equipped with a central mechanical stirrer and a gas consumption control and display system (TOP VIEW software). The atmosphere of the autoclave was purged three times with argon (8 bar) and twice with H_2 (5 bar). The temperature of the autoclave was adjusted to 50 °C under a H_2 pressure of 1 bar (stirring 200 rpm). The autoclave was then filled with H_2 (20 bar, stirring 200 rpm). The stirring rate was adjusted to 1200 rpm and the H_2 uptake was monitored. After total conversion of the substrate (end of H_2 uptake), the autoclave was adjusted to r.t. and atmospheric pressure and finally purged three times with argon (8 bar, stirring 200 rpm). The contents were drained off and the autoclave was rinsed with MeOH (20 mL). The MeOH was distilled off in vacuo to give a brown solid residue which was triturated in refluxing EtOAc (100 mL) and pentane (50 mL). The suspension was filtered to give pale yellow solids which were dried under reduced pressure for 18 h to give (2*R*,4*R*)-pentane-2,4-diol [(*R*,*R*)-**15**] (55 g, 90%, de >99% *anti*, ee >99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.3 Hz, 6 H), 1.62 (t, *J* = 5.6 Hz, 2 H), 2.82 (s, 2 H, OH), 4.18 (m, 2 H).

Enantiomeric and diastereomeric excesses were determined by ^{19}F NMR of the (*S*)-MTPA ester of (*R*,*R*)-**15** and achiral gas chromatography.

(*S*)-MTPA Ester of (*R*,*R*)-15

^{19}F NMR (282 MHz, $CDCl_3$): δ = –71.91 (*syn*), –71.72 (*S*,*S*), –71.64 (*R*,*R*).

Achiral GC: DB1701 column, flow: 1.0 mL/min (He), 200 °C (10 min), 5 °C/min, final temperature: 250 °C, t_R = 18.3 min (*R*,*R*), 18.7 min (*S*,*S*), 19.7 min (*syn*).

(3*S*)-Ethyl 3-Hydroxybutyrate [(*S*)-12]

Prepared from ethyl acetoacetate (**5**; 9.1 g, 70 mmol) according to the general hydrogenation procedure, using the in situ generated Ru/SYNPHOS catalyst (*S*)-**4a** (0.01 mmol, prepared according to procedure 3) in EtOH (10 mL). After distillation of the solvent under reduced pressure, the crude product was purified by silica gel chromatography (cyclohexane–EtOAc, 8:2), affording (*S*)-**12** as a colorless oil (7.6 g, 83%). Enantiomeric excess was measured by chiral HPLC (ee = 99.4%).

Chiral HPLC: Chiralcel OD-H column; eluent: hexane–*i*-PrOH (95:5); flow: 1.0 mL/min; λ = 215 nm; t_R = 7.3 min (*R*) and 9.2 min (*S*).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 6.2 Hz, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 2.40 (dd, *J* = 8.4, 16.5 Hz, 1 H), 2.49 (dd, *J* = 3.7, 16.5 Hz, 1 H), 3.00 (br s, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 4.13–4.20 (m, 1 H).

(3*R*)-Ethyl 3-Hydroxy-3-phenylpropionate [(*R*)-13]

Prepared from ethyl 3-oxo-3-phenylpropionate (**6**; 1.9 g, 10 mmol) according to the general hydrogenation procedure, using the in situ generated Ru/SYNPHOS catalyst (*S*)-**4a** (0.05 mmol, prepared according to procedure 3) in EtOH (8 mL). Complete conversion was observed as no other product was detected by NMR. After distillation of the solvent under reduced pressure, the crude product was purified by silica gel chromatography (cyclohexane–EtOAc, 8:2), affording (*R*)-**13** as a colorless oil (0.72 g, 90%). Enantiomeric excess was measured by chiral HPLC (ee = 98.3%). The reaction was also carried out on 330 g (1683 mmol) of ethyl 3-oxo-3-phenylpropionate using the in situ generated Ru/SYNPHOS catalyst (*S*)-**4a** with S/C = 500 under 20 bar and 80 °C for 12 h affording (*R*)-**13** (274 g, 84%, 97% ee).

Chiral HPLC: Chiralcel OD-H column; eluent: hexane–*i*-PrOH (95:5); flow: 1.0 mL/min; λ = 254 nm; t_R = 11.9 min (*S*) and 13.9 min (*R*).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, 7.1 Hz, 3 H), 2.68 (dd, *J* = 4.3, 16.2 Hz, 1 H), 2.76 (dd, *J* = 8.4, 16.3 Hz, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 5.12 (dd, *J* = 4.4, 8.5 Hz, 1 H), 7.25–7.40 (m, 5 H).

(3*S*)-Ethyl 4-Benzyloxy-3-hydroxybutyrate [(*S*)-14]

Prepared from ethyl 4-benzyloxy-3-oxo-butyrate (**7**; 5.1 g, 21.4 mmol) according to the general hydrogenation procedure, using Ru/SYNPHOS catalyst (*R*)-**2a** (101 mg, 0.107 mmol) in EtOH (20 mL). After distillation of the solvent under reduced pressure, the crude product was purified by silica gel chromatography (cyclohexane–EtOAc, 8:2), affording (*S*)-**14** as a colorless oil (4.4 g, 85%). Enantiomeric excess was measured by chiral HPLC (ee = 98.9%).

Chiral HPLC: Chiralcel OD-H column; eluent: hexane–*i*-PrOH (90:10); flow: 0.8 mL/min; λ = 215 nm; t_R: 13.1 min (*S*) and 14.8 min (*R*).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3 H), 2.54 (d, *J* = 6.3 Hz, 2 H), 2.94 (br s, 1 H), 3.48 (dd, *J* = 5.9, 9.6 Hz, 1 H), 3.52 (dd, *J* = 4.6, 9.6 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 4.22–4.26 (m, 1 H), 4.57 (s, 2 H), 7.28–7.27 (m, 5 H).

(2*S*)-Propane-1,2-diol [(*S*)-16]

Prepared from hydroxyacetone (**9**; 1.5 g, 20 mmol) according to the general hydrogenation procedure, using the in situ generated Ru/SYNPHOS catalyst (*S*)-**4a** (0.107 mmol, prepared according to procedure 3) in MeOH (1 mL). The solvent was removed under reduced pressure and the crude product was purified by distillation affording (*S*)-**16** as a colorless oil (1.37 g, 89%). Enantiomeric excess was measured by chiral GC (ee = 96.0%). The same reaction was carried out on 100 g (1351 mmol) of hydroxyacetone using the in situ generated Ru/SYNPHOS catalyst (*S*)-**4a** with S/C = 2000 under 30 bar at 50 °C for 12 h affording (*S*)-**16** (89.6 g, 87%, 96% ee).

Chiral GC: Chirasil-DEX CB column; temp: 90 °C; t_R = 3.8 min (*S*) and 3.9 min (*R*).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 9.6 Hz, 3 H), 3.00 (br s, 2 H), 3.37 (dd, *J* = 7.8 Hz, 11.1 Hz, 1 H), 3.60 (dd, *J* = 2.9, 11.2 Hz, 1 H), 3.82–3.98 (m, 1 H).

(3*S*)-Ethyl 4-Chloro-3-hydroxybutyrate [(*S*)-17]

Prepared from ethyl 4-chloro-3-oxobutyrate (**10**; 0.82 g, 5 mmol) according to the general hydrogenation procedure, using Ru-DIFLUORPHOS catalyst (*R*)-**3b** (4.4 mg, 2.5×10^{-3} mmol) in EtOH (1.8 mL). Complete conversion was observed, as no other product was detected by NMR. After distillation of the solvent under reduced pressure, the crude product was purified by silica gel chroma-

tography (cyclohexane–EtOAc, 7:3), affording (*S*)-**17** as a colorless oil. Enantiomeric excess was measured by chiral GC (ee = 97.0%).

Chiral GC: Lipodex A column; flow: 0.5 mL/min (He); temp: 70 °C; t_R = 74.5 min (*S*) and 77.8 min (*R*).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3 H), 2.56 (dd, *J* = 7.5, 16.4 Hz, 1 H), 2.64 (dd, *J* = 4.8, 16.4 Hz, 1 H), 3.58 (dd, *J* = 1.2, 5,5 Hz, 2 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 4.20–4.28 (m, 1 H).

(3*S*)-Ethyl 4,4,4-Trifluoro-3-hydoxybutyrate [(*S*)-18]

Prepared from ethyl 4,4,4-trifluoro-3-oxobutyrate (**11**; 0.37 g, 2 mmol) according to the general hydrogenation procedure, using Ru/DIFLUORPHOS catalyst (*R*)-**2b** (19.7 mg, 0.02 mmol) in EtOH (4 mL). Complete conversion was observed, as no other product was detected by NMR. After distillation of the solvent under reduced pressure, the crude product was purified by silica gel chromatography (cyclohexane–EtOAc, 7:3), affording (*S*)-**18** as a colorless oil. Enantiomeric excess was measured by chiral HPLC (ee = 77.0%).

Chiral HPLC: Chiralpak AD column; eluent: hexane–*i*-PrOH (98:2); flow: 1.0 mL/min; λ = 215 nm, t_R = 11.6 min (*S*) and 14.4 min (*R*).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3 H), 1.53 (br s, 1 H), 2.66 (dd, *J* = 7.3, 16.8 Hz, 1 H), 2.73 (dd, *J* = 3.1, 16.8 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 4.38–4.53 (m, 1 H).

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