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Highly Efficient Asymmetric Hydrogenation of 2-Methylenesuccinamic Acid Using a Rh-DuPHOS Catalyst

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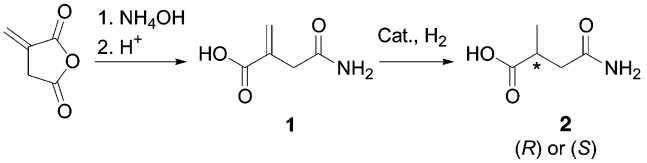
Abstract:

An extremely efficient route to highly enantiomerically enriched 2-methylsuccinamic acid via asymmetric hydrogenation has been developed. By using [(*S,S*)-Et-DuPHOS Rh COD]BF_4 as the precatalyst under a set of broadly optimised process parameters, (*R*)-2-methylsuccinamic acid was obtained in 96% ee at a substrate-to-catalyst ratio (S/C) of 100000 (average turnover frequency ~13000 h^{-1}). The exclusion of chloride-containing contaminants in the substrate was found to be crucial in obtaining exceptionally low catalyst loadings. This material could be upgraded with a single-crystal digestion to yield (*R*)-2-methylsuccinamic acid in >99.5% ee containing less than 1 ppm rhodium.

Introduction

Both enantiomers of 2-methylsuccinamic acid (**2**) are important chiral building blocks for the synthesis of numerous biologically active compounds.[1,2] A synthetic approach to enantiomerically enriched **2** via asymmetric hydrogenation of 2-methylenesuccinamic acid (Scheme 1) has potentially the combined advantages of high selectivity, high efficiency, and the availability of both enantiomers by using opposite enantiomers of the chosen catalyst.[3,4] Such an approach has been previously reported, albeit with moderate enantioselectivities, high catalyst loadings, and long reaction times (75−77% ee with a molar substrate-to-catalyst ratio (S/C) of 100 to 1000 over 20 h).[5] Herein we report a study performed to identify a more efficient asymmetric hydrogenation catalyst for the preparation of **2** together with initial investigations into process optimisation.

Scheme 1. **Synthesis of (*R*) or (*S*)-methylsuccinamic acid via asymmetric hydrogenation**



Results and Discussion

The hydrogenation substrate, 2-methylenesuccinamic acid (**2**), was obtained by treatment of itaconic anhydride with aqueous ammonium hydroxide followed by neutralization of excess base with dilute hydrochloric acid (Scheme 1).[5] Analysis of the substrate thus obtained indicated a retention of chloride of approximately 1 wt %. Replacement of hydrochloric acid by sulfuric acid produced a chloride-free product. As will be described below, the presence or absence of this chloride-containing impurity was found to have a dramatic effect on the overall reaction rates obtainable.

Having chosen a set of standard conditions that we have found to be routinely applicable for early-stage catalyst screening (18 h at 60 psi H_2, 0.2 M solution of substrate in MeOH, room temperature, and S/C of 100), the hydrogenation study commenced with an initial screen of several [(diphosphine)Rh(COD)]BF_4 precatalysts containing the diphosphines shown in Figure 1.[6−8] All reactions gave complete conversion, and the resulting enantioselectivities are represented in Figure 2. Interestingly, under these conditions, the presence of the chloride-containing impurity had no overall effect on the general trend observed for enantioselectivity.

With these initial results in hand, four precatalysts were identified as candidates worthy of further examination,

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(1) For an example of the use of (*R*)-2-methylsuccinamic acid, see: (a) Ikeura, Y.; Doi, T.; Fujishima, A.; Natsugari, H. *Chem. Commun.* **1998**, 2141−2142. (b) Natsugari, H.; Ikeura, Y.; Kamo, I.; Ishimaru, T.; Ishichi, Y.; Fujishima, A.; Tanaka, T.; Kasahara, F.; Kawada, M.; Natsugari, H. *J. Med. Chem.* **1999**, *42*, 3982−3993.

(2) For an example of the use of (*S*)-2-methylsuccinamic acid, see: Fuji, T.; Ogawa, N. *Tetrahedron Lett.* **1972**, *13*, 3075−3078.

(3) (a) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley-Interscience: New York, 1994. (b) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1. (c) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

(4) For industrial examples of asymmetric hydrogenation, see: Blaser, H. U.; Spindler, F.; Studer, M. *Appl. Catal. A: Gen.* **2001**, *221*, 119−143.

(5) Takeda, H.; Tachinami, T.; Hosokawa, S.; Aburatani, M.; Inoguchi, K.; Achiwa, K. *Chem. Pharm. Bull.* **1991**, *39*, 2706−2708.

(6) 5-Fc = 1, 1′-bis(2,5-dialkylphospholano)ferrocene

(7) COD = 1,5-cyclooctadiene

(8) (a) Burk, M. J.; Gross, M. F. *Tetrahedron Lett.* **1994**, *35*, 9363−9666. (b) Berens, U.; Burk, M. J.; Gerlach, A.; Hems, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 1981. (c) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207−6208. (d) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363−372 and references therein; (e) Henschke, J. P.; Burk, M. J.; Malan, C. J.; Herzberg, D.; Peterson, J. A.; Wildsmith, A. J.; Cobley, C. J.; Casy, G. *Adv. Synth. Catal.* **2003**, *345*, 300−307.

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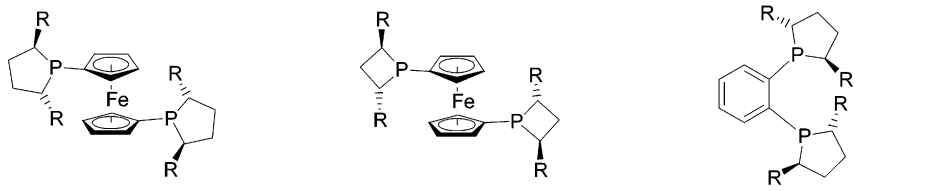
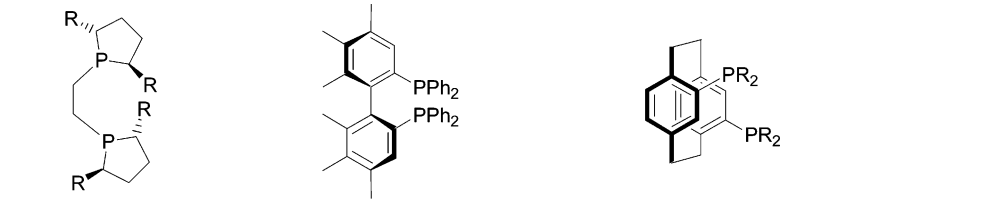


(*R*,*R*)-Me-5-Fc[6] R = Me
(*R*,*R*)-Et-5-Fc R = Et
(*S*,*S*)-*i*-Pr-5-Fc R = *i*-Pr

(*R*,*R*)-Me-FerroTANE R = Me
(*R*,*R*)-Et-FerroTANE R = Et
(*S*,*S*)-*i*-Pr-FerroTANE R = *i*-Pr
(*S*,*S*)-*t*-Bu-FerroTANE R = *t*-Bu

(*R*,*R*)-Me-DuPHOS R = Me
(*R*,*R*)-Et-DuPHOS R = Et
(*S*,*S*)-*i*-Pr-DuPHOS R = *i*-Pr



(*R*,*R*)-Me-BPE R = Me
(*R*,*R*)-Et-BPE R = Et
(*S*,*S*)-*i*-Pr-BPE R = *i*-Pr

(*S*)-HexaPHEMP

(*R*)-PhanePhos R = Ph
(*R*)-*i*-Pr-PhanePhos R = *i*-Pr
(*R*)-Xyl-PhanePhos R = 3,5-dimethylphenyl
(*R*)-MeOXyl-PhanePhos R = 3,5-dimethyl-4-methoxyphenyl

Figure 1. **Diphosphines screened for the asymmetric hydrogenation of 2-methylenesuccinamic acid.**

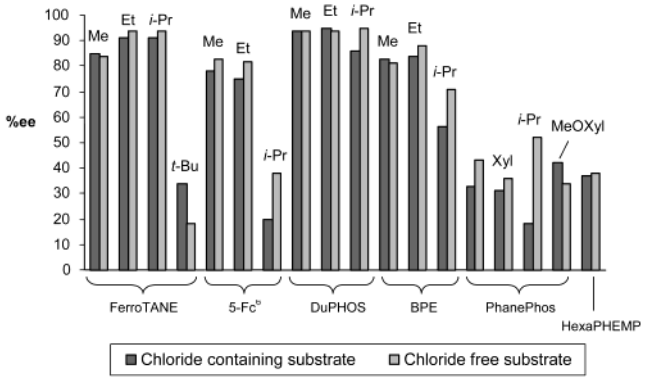
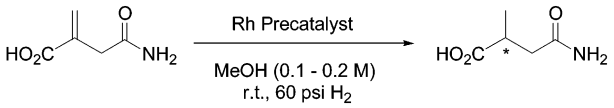


Figure 2. **Enantioselectivities obtained with a series of rhodium-based catalysts.**

namely [(*R*,*R*)-Me-DuPHOS Rh COD]BF_4, [(*S*,*S*)-Et-DuPHOS Rh COD]BF_4, [(*S*,*S*)-Et-FerroTANE Rh COD]BF_4, and [(*S*,*S*)-*i*-Pr-FerroTANE Rh COD]BF_4. The next phase in the investigation was to determine the effect on enantioselectivity when reducing the catalyst loading to S/C = 1000 for each promising precatalyst (Table 1). At this stage of the project, only the chloride-containing substrate was available and this was used in subsequent small-scale development work. All reactions were performed overnight, and although complete conversion was achieved in each case, the (*S*,*S*)-Et-DuPHOS-containing rhodium catalyst was the only candidate to retain a high level of enantioselectivity (94% ee).

Further studies revealed that the hydrogenation with [(*S*,*S*)-Et-DuPHOS Rh COD]BF_4 remained highly enantioselective under a variety of conditions (Table 2). As expected, an increase in temperature or pressure or both resulted in a faster reaction, but the reaction was found to be very slow at lower temperatures (entry 1, Table 2). It is debatable if variations in pressure or temperature could offer any marked improvement on enantioselectivity, but it may be possible

Table 1. **Effect of reduced precatalyst loadings**



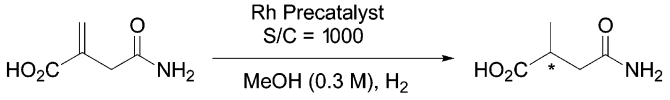
entry	precatalyst	S/C	conv. (%)[a]	ee (%)[b]
1	[(*R*,*R*)-Me-DuPHOS Rh COD]BF_4	100	>98	94 (*S*)
2	[(*R*,*R*)-Me-DuPHOS Rh COD]BF_4	1000	>98	87 (*S*)
3	[(*S*,*S*)-Et-DuPHOS Rh COD]BF_4	100	>98	95 (*R*)
4	[(*S*,*S*)-Et-DuPHOS Rh COD]BF_4	1000	>98	94 (*R*)
5	[(*S*,*S*)-Et-FerroTANE Rh COD]BF_4	100	>98	93 (*R*)
6	[(*S*,*S*)-Et-FerroTANE Rh COD]BF_4	1000	>98	87 (*R*)
7	[(*S*,*S*)-*i*-Pr-FerroTANE Rh COD]BF_4	100	>98	91 (*S*)
8	[(*S*,*S*)-*i*-Pr-FerroTANE Rh COD]BF_4	1000	>98	83 (*S*)

[a] Determined by ^{1}H NMR on the crude reaction mixture (d_6-DMSO). [b] Determined by chiral GC on the methyl ester derivative.[9]

that higher pressures have a positive effect (cf. entries 2 and 4, Table 2). In order not to discard at this early development stage an electronically and structurally different catalyst, [(*S*,*S*)-Et-FerroTANE Rh COD]BF_4[8b] was also included in this brief study of the effect of temperature and pressure. Although this complex resulted in a more active catalyst than [(*S*,*S*)-Et-DuPHOS Rh COD]BF_4 (cf. reaction times for entries 2 and 6, and entries 5 and 8, Table 2), variations in both temperature and pressure did not improve the enantioselectivity (entries 6−8, Table 2).

2-Methylenesuccinamic acid has low solubility in MeOH; therefore, the effect of adding triethylamine to aid dissolution was investigated together with variations in concentration. It is evident from the results shown in Table 3, that the addition of triethylamine increased the rate of the reaction, but at the expense of selectivity. The observed increase in

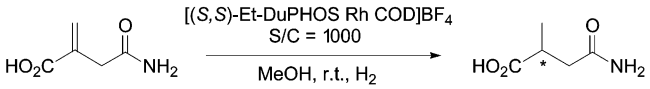
Table 2. **Effect of pressure and temperature**



entry	precatalyst	temp (°C)	H_2 pressure (psi)	time[a] (min)	conv.[b] (%)	ee[c] (%)
1	[(*S*,*S*)-Et-DuPHOS Rh COD]BF_4	0	60	>18 h	33	93 (*R*)
2	"	20	60	240	>98	94 (*R*)
3	"	45	60	140	>98	96 (*R*)
4	"	20	140	120	>98	97 (*R*)
5	"	45	140	90	>98	95 (*R*)
6	[(*S*,*S*)-Et-FerroTANE Rh COD]BF_4	20	60	120	>98	87 (*R*)
7	"	20	140	45	>98	72 (*R*)
8	"	45	140	20	>98	86 (*R*)

[a] Maximum time within which the reaction was complete. [b] Determined by ^{1}H NMR on the crude reaction mixture (d_6-DMSO). [c] Determined by chiral GC on the methyl ester derivative.[9]

Table 3. **Effect of substrate concentration and addition of triethylamine**



entry	H_2 pressure (psi)	concentration (M)	time[a] (h)	additive	conv.[b] (%)	ee[c] (%)
1	60	0.3	4	–	>98	94 (*R*)
2	60	0.3	2.5	NEt_3	>98	74 (*R*)
3	60	1.0	<10	–	>98	94 (*R*)
4	60	1.0	5	NEt_3	>98	69 (*R*)
5	140	0.3	2	–	>98	97 (*R*)
6	140	0.3	2	NEt_3	>98	72 (*R*)
7	140	1.0	<8	–	>98	97 (*R*)
8	140	1.0	5	NEt_3	>98	68 (*R*)

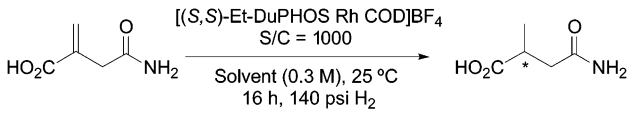
[a] Maximum time within which the reaction was complete. [b] Determined by ^{1}H NMR on the crude reaction mixture (d_6-DMSO). [c] Determined by chiral GC on the methyl ester derivative.[9]

activity may be due to triethylamine either reducing the detrimental effect that the chloride containing contaminant has on the reaction (see below for further discussions) or by simply aiding dissolution of the substrate. It may also be argued that the observed decrease in enantioselectivity is due to carboxylate formation, which competes with the amide carbonyl as the metal binding site.[10] Although the reaction was somewhat slower when run as a slurry (1.0 M without NEt_3, entry 7, Table 3), the enantioselectivity remained unaffected, hence making this procedure preferable.

A study of alternative solvents confirmed MeOH to be the solvent of choice (Table 4). The same level of enantioselectivity was obtained in *i*-PrOH but with a concomitant decrease in the reaction rate as shown by the lower conversion.

Having broadly identified favourable reaction conditions, a direct comparison between the chloride-containing and the chloride-free substrates was made (entries 1 and 2, Table 5). It was at this stage that the dramatic effect of the chloride contaminant on reaction rates was realized. The turnover frequency increased from 500 h^{-1} to an average of over

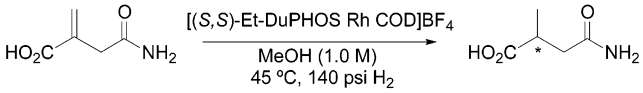
Table 4. **Solvent screen for the asymmetric hydrogenation of 2-methylenesuccinamic acid**



entry	solvent	conv. (%)[a]	ee (%)[b]
1	MeOH	>98	97 (*R*)
2	EtOH	37	84 (*R*)
3	*i*-PrOH	87	97 (*R*)
4	CF_3CH_2OH	5	–
5	THF	24	17 (*S*)
6	EtOAc	21	*c*
7	CH_2Cl_2	2	–
8	acetone	9	*c*
9	toluene	0	–
10	α,α,α-trifluorotoluene	0	–

[a] Determined by ^{1}H NMR on the crude reaction mixture (d_6-DMSO). [b] Determined by chiral GC on the methyl ester derivative.[9] [c] Unable to obtain due to coeluting impurity.

Table 5. **Effects of reducing the substrate-to-catalyst ratio**



entry	S/C	substrate input (g)	time[a] (min)	conv. (%)[b]	ee (%)[c]
1[d]	1000	15 g	117	>98	97 (*R*)
2	1000	15 g	4	>98	96 (*R*)
3	5000	15 g	24	>98	97 (*R*)
4	10000	15 g	46	>98	96 (*R*)
5	20000	15 g	102	>98	97 (*R*)
6	50000	40 g	242	>98	97 (*R*)
7	100000	40 g	447	>98	96 (*R*)

[a] Maximum time within which the reaction was complete. [b] Determined by ^{1}H NMR on the crude reaction mixture (d_6-DMSO). [c] Determined by chiral GC on the methyl ester derivative.[9] [d] Reaction performed with substrate batch containing 1% chloride impurity.

(9) To assign the enantiomer elution order, a reaction mixture corresponding to 92% ee was recrystallised from MeOH {$[\alpha]^{20}_D = +18.2$ (c 2.0, MeOH)}. By comparison to a literature value for (*S*)-2-methylsuccinamic acid {$[\alpha]^{22}_D = -17.7$ (c 2.0, MeOH)},[5] the major product for this reaction was assigned as (*R*)-2-methylsuccinamic acid. This corresponds to the first eluting enantiomer in the GC method used.

(10) (a) Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Gerosa, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1931−1933. (b) Burk, M. J.; Bienewald, F.; Challenger, S.; Derrick, A.; Ramsden, J. A. *J. Org. Chem.* **1999**, *64*, 3290−3298.

13000 h^{-1}, the reaction being 26 times faster for the chloride-free substrate, with the enantioselectivity being unaffected. Interestingly, when the chloride-free substrate was hydrogenated under the same conditions and using a precatalyst prepared from $[RhCl(COD)]_2$ and 2 equiv of (*R,R*)-Et-DuPHOS at S/C = 1000, the reaction took 31 min to go to completion (turnover frequency $\approx$ 2000 h^{-1}) with 97% ee, supporting the hypothesis that the lower reaction rates are due to the presence of chloride ions. With this information in hand, the substrate-to-catalyst ratio was systematically reduced with the chloride-free material to explore the process limitations (entries 2−7, Table 5). Ultimately, the high activity of this catalyst for the asymmetric hydrogenation of this substrate was demonstrated by performing the reaction at the extremely low catalyst loading of S/C = 100000 (entry 7, Table 5).

A sample of the crude product was purified by crystal digestion in *i*-PrOH (50 wt %) at 40 °C, cooling to −5 °C, filtering, and drying in vacuo (20 °C). This gave the desired (*R*)-2-methylsuccinamic acid as an off-white, crystalline solid (77% recovery) in >99.5% ee.

When using homogeneous catalysis for the manufacture of active pharmaceutical ingredients, the presence of residual metal in the final product is of great concern. Current guidelines from The European Agency for the Evaluation of Medicinal Products[11] suggest that concentration levels for the platinum group metals should be less than 5 ppm for orally delivered pharmaceuticals. In light of this, rhodium content analyses of both the crude and the upgraded material from the reaction performed at S/C 100000 were carried out, giving 9.0 ± 0.4 and 0.88 ± 0.05 ppm, respectively. Furthermore, analysis of both crude and upgraded material from the reaction performed at S/C 20000 showed that the rhodium content could be decreased from 36 ± 1 to 9.8 ± 0.4 ppm with a single crystal digestion. This demonstrates that the recommended rhodium concentration levels can be achieved using standard processing techniques.

Conclusions

In conclusion, an initial screen to identify a suitable precatalyst and subsequent investigations into the effects of various process parameters determined an extremely efficient route to highly enantiomerically enriched (*R*)-2-methylsuccinamic acid via asymmetric hydrogenation with [(*S,S*)-Et-DuPHOS Rh COD]BF_4. Substrate purity was found to be crucial in obtaining extremely low catalyst loadings. Eliminating trace amounts of chloride contaminant by using H_2SO_4 in place of HCl during substrate preparation enabled us to achieve complete conversion to (*R*)-2-methylsuccinamic acid in 96% ee with S/C 100000:1 (w/w $\approx$ 21400, reaction time 7.5 h, TOF $\approx$ 13000 h^{-1}). Purification of the crude reaction product by crystal digestion in *i*-PrOH enabled (*R*)-2-methylsuccinamic acid to be obtained in >99.5% ee with less than 1 ppm rhodium content.

(11) See draft guidelines from the European Agency for the Evaluation of Medicinal Products, 27 June 2002, http://www.emea.eu.int/pdfs/human/swp/444600en.pdf

Experimental Section

General Methods. Unless otherwise stated, all chemicals and reagents were purchased from commercial sources and used without further purification. Ammonium hydroxide, 28% aqueous solution, and itaconic anhydride were purchased from Aldrich and 4 M sulfuric acid from Fisher Scientific. Standard HPLC grade MeOH, purchased from Fisher Scientfic, was used throughout the hydrogenation studies. Standard HPLC grade *i*-PrOH, purchased from Fisher Scientific, was used for the crystal digestions.

Analytical Methods. ^1H and ^{13}C NMR were recorded on a Bruker WH-400 spectrometer. Spectra were recorded in d_6-DMSO at ambient temperature. Chloride content was analysed via titration with silver nitrate. Rhodium content was determined for the Rh-104 isotope using neutron activation. GC analysis was performed on a Perkin-Elmer Autosystem XL equipped with a FID detector. Enantioselectivity determinations for the hydrogenation reactions were performed on the methyl ester of 2-methylsuccinamic acid[12] by derivatisation of a sample with trifluoroacetic anhydride and MeOH (Varian Chirasil Dex CB column, 25 m × 0.25 mm, 0.25 μm). A temperature program of 105 °C for 5 min, then 5 °C/min to 150 °C was used with carrier gas helium at 20 psi (retention times 12.74 min for the (*R*) enantiomer and 12.85 min for the (*S*) enantiomer).

Preparation of 2-Methylenesuccinamic Acid. To a 1-L round-bottomed flask equipped with a mechanical stirrer was loaded 28% NH_4OH in water (154 g, 1.2 mol). After cooling the solution to 0 °C, itaconic anhydride (98.0 g, 0.87 mol) was added slowly, keeping the reaction temperature below 5 °C. When the addition of the anhydride was complete, the mixture was allowed to warm to room temperature. After stirring for 2 h the reaction was cooled to 0 °C. The pH of the reaction mixture was adjusted to below 1 by dropwise addition of 4 M H_2SO_4 (250 mL) and then left to stir at room temperature for 18 h. The slurry was cooled to 0 °C before filtration through a sintered glass frit. The wet cake was washed with 100 mL of dilute H_2SO_4 (pH < 3). The solid was dried at room temperature in a vacuum oven to yield 70 g of crude 2-methylenesuccinamic acid which contained 13 mol % of the undesired 3-methylenesuccinamic acid (^1H NMR). Crystal digestion in ethanol (120 mL) yielded 59.2 g of the desired 2-methylenesuccinamic acid (53% yield), mp 137−138 °C (lit.[5] mp 150−152 °C for material prepared with HCl).

When 2-methylenesuccinamic acid was prepared using hydrochloric acid, as described in the literature,[5] the material obtained was found to contain 1% chloride by weight.

General Hydrogenation Procedure. Unless stated otherwise, all reactions were carried out in either a 50-mL Parr microreactor or a Baskerville multiwell reactor, both modified with an injection port allowing introduction of solutions via syringe. The reactors were used with a suitable glass liner and a magnetic stirrer. All solvents were deoxygenated prior to use by sparging with nitrogen for 1 h.

(12) 2-Methylsuccinamic acid methyl ester: ^1H NMR (400 MHz, d_6-DMSO) δ ppm 7.35 (1H, NH, br s), 6.83 (1H, NH, br s), 3.61 (3H, CH_3O, s), 2.79 (1H, C*H*CH_3 m), 2.45 (1H, C*H*HC(O)NH_2, dd, J = 7.3 and 15.3), 2.21 (1H, C*H*HC(O)NH_2, dd, J = 7.3 and 15.3), and 1.10 (3H, CH_3, d, J = 7.0).

Typical Screen Experiment. A glass liner was charged with 2-methylenesuccinamic acid (387 mg, 3 mmol), pre-catalyst (0.03 mmol), and a cross-shaped magnetic stirrer bar. The liner was placed in a 50-mL Parr pressure vessel and the reactor assembled and flushed three times with nitrogen (100 psi). MeOH (10 mL) was added through the septum of the reactor via syringe. The reactor was purged again with nitrogen (three pressurization/release cycles to 100 psi). The reactor was finally pressurized to 60 psi with hydrogen and stirred at room temperature overnight. The hydrogen was then released and a sample submitted for ee analysis. Conversion was determined by ^{1}H NMR (d_6-DMSO). 2-Methylsuccinamic acid: ^{1}H NMR (400 MHz, d_6-DMSO) δ ppm 7.32 (1H, NH, br s), 6.79 (1H, NH, br s), 2.67 (1H, C*H*CH_3 m), 2.40 (1H, C*H*HC(O)NH_2, dd, *J* 7.3 and 15.3), 2.10 (1H, C*H*HC(O)NH_2, dd, *J* 7.3 and 15.3), and 1.06 (3H, CH_3, d, *J* 7.0). ^{13}C NMR (100 MHz, d_6-DMSO) δ ppm 177.7, 173.3, 38.7, 36.1, and 17.3.

Larger-Scale Hydrogenation. The reaction was carried out in a 600-mL pressure vessel equipped with a mechanical stirrer, a cooling/heating coil, an injection port, a temperature probe, and a pressure transducer and fitted with a glass liner. 2-Methylenesuccinamic acid (40.0 g, 0.31 mol) was added to the glass liner, followed by MeOH (306 mL). The vessel was assembled and pressurized to 140 psi with nitrogen. The reaction was stirred at the maximum rate (~750 rpm, stirrer assembly consists of two propellers, one positioned just below the solvent surface and one near the bottom of the solution) for 30 min during which time the temperature was maintained at 45 °C (internal). The pressure was then released. To ensure that an oxygen-free atmosphere was attained, the vessel was recharged with nitrogen (140 psi) and vented after stirring for 10 min. This was repeated three times. The vessel was subsequently charged and vented three times with hydrogen (140 psi). [(*S*,*S*)-Et-DuPHOS Rh(COD)]-BF_4 (3.7 mg, 0.0031 mmol, molar S/C 100000) was then added as a MeOH solution (5 mL, prepared under nitrogen using deoxygenated anhydrous solvent) via syringe. The vessel was then charged with hydrogen (140 psi). The temperature was maintained at 45 °C throughout the course of the reaction and the hydrogen pressure readjusted to 140 psi after every 4 psi of hydrogen consumed. After no further hydrogen uptake was observed, the vessel was cooled to room temperature, the hydrogen pressure released, and the system flushed once with nitrogen (140 psi) prior to vessel disassembly. The reaction mixture was transferred to a 1-L round-bottomed flask and concentrated under reduced pressure to yield the crude reaction product as an off-white solid (38.7 g, 95.3% crude yield). ^{1}H NMR spectroscopy and chiral GC were used to analyse conversion and enantioselectivity respectively (>98% conv., 96.4% ee).

Crystal Digestion of 2-Methylsuccinamic Acid. A 100-mL, three-neck, round-bottomed flask fitted with a reflux condenser and a mechanical stirrer was loaded with crude (*R*)-2-methylsuccinamic acid (27.0 g, 98.0% ee, 5% methyl ester) and *i*-PrOH (24.8 g). The resulting slurry was heated to 40 °C and stirred at that temperature for 1 h. This slurry was cooled to −5 °C over 2 h and filtered. The resulting wet cake was washed with cold 1:1 (v/v) *i*-PrOH/toluene and dried in vacuo (20 °C) to a constant weight. The final off-white solid (20.8 g, 76.8% recovery) was >99.5% ee by chiral GC analysis (derivatized as the methyl ester). Mp 131−132 °C [lit.[13] mp for (*S*)-2-methylsuccinamic acid 132−133.5 °C].

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