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Kilogram-Scale Asymmetric Ruthenium-Catalyzed Hydrogenation of a Tetrasubstituted Fluoroenamide

Andreas Stumpf,[a,*] Mark Reynolds,[a] Daniel Sutherlin,[a] Srinivasan Babu,[a] Erhard Bappert,[b] Felix Spindler,[b] Michael Welch,[c] and John Gaudino[c]

[a] Genentech Inc., 1 DNA Way, South San Francisco, CA 94080, USA
Fax: (+1)-650-467-8382, phone: (+1)-650-467-7461; e-mail: stumpf.andreas@gene.com
[b] Solvias AG, Mattenstrasse 22, 4002 Basel, Switzerland
[c] Array Biopharma, 2620 Trade Center Avenue, Longmont, CO 80503, USA

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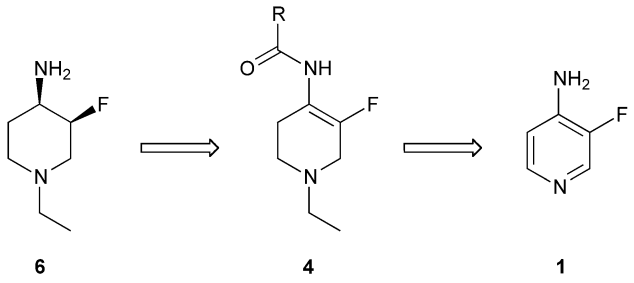
Abstract: Ruthenium-catalyzed asymmetric homogeneous hydrogenation (AHH) is used as the key step of a multi-kilogram scale synthesis of an enantiomeric fluoropiperidine. The AHH of a tetrasubstituted β-fluoroenamide is carried out under mild conditions using a Ru/Josiphos catalyst with high *ee* (98%).

Keywords: amines; enantioselectivity; fluorine; high-throughput screen (HTS); homogeneous catalysis; hydrogenation; ruthenium; tetrasubstituted β-fluoroenamides

Enantiomerically pure fluorine-containing molecules are useful intermediates for the synthesis of active pharmaceutical ingredients (APIs).[1] As part of development activities for a drug candidate, we needed kilogram amounts of enantiomerically enriched (3*S*,4*R*)-1-ethyl-3-fluoropiperidin-4-amine (**6**) as a key API intermediate (Scheme 1).

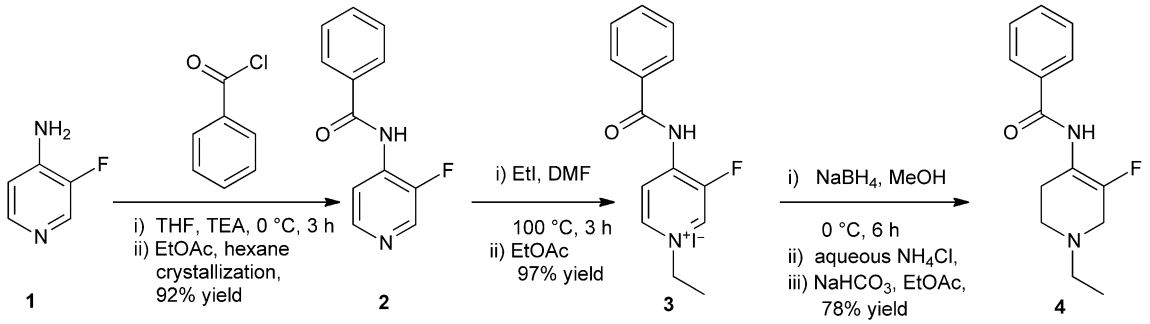


Scheme 1. Retrosynthetic analysis of **6**.

The target compound **6** might be elaborated in multiple steps by conventional methods such as enantioselective fluorination,[2] catalytic enantioselective decarboxylation,[3] and diastereomeric salt resolution of racemates.[4]

Due to the *cis* configuration of the piperidine substituents, AHH of a tetrasubstituted dehydropiperidine was an attractive approach to **6**. Thus, AHH of the cyclic enamide **4** would allow introduction of the two stereocenters in one step from an achiral starting material. We hoped to access enamide **4** from the regioselective reduction of commercially available 3-fluoro-4-amino pyridine (**1**).

Although the synthesis of chiral amines *via* asymmetric hydrogenation of enamides, using Ru, Rh and Ir catalysts has been widely investigated by numerous groups from both academia and industry,[5] we found no examples of enantioselective hydrogenation of α- or β-substituted fluoroenamides. Only a few examples of enantioselective hydrogenation of vinyl fluorides have been reported.[6] For example, an enantioselective Rh-catalyzed hydrogenation of a vinyl fluoride possessing an allylic alcohol was described.[7] The allylic alcohol presumably acts as metal coordinating group to achieve excellent *ee*. In our case the carbonyl function of the enamide would take over this coordinating function to hopefully result in a high chiral induction. However, enantioselective hydrogenation of tetrasubstituted enamides has been challenging and plagued by low conversion and enantioselectivity.[5a,b,8] Furthermore it is known that fluoro-substituted olefins can suffer from defluorination, leading to by-products and the formation of fluoride ions, that could poison the catalyst and decrease the yield.[6d,e] These obstacles were considered as we attempted to develop a successful protocol.



Scheme 2. Synthesis of tetrasubstituted cyclic enamide **4**.

We set out to synthesize our key intermediate **4** from 4-amino-3-fluoropyridine (**1**) (Scheme 2). Usually the *N*-acetyl group is used as protecting group for enamines[5], but instead we decided to introduce a benzoyl group, because it provided a chromophore that would simplify HPLC analysis of the process.

Benzoylation of **1** with benzoyl chloride in THF and triethylamine at 0 °C went to completion in 2 h in presence of triethylamine (TEA), and **2** was isolated in 92% yield after crystallization from ethyl acetate (EtOAc)/hexane. Ethylpyridinium species **3** was obtained from alkylation of compound **2** with iodoethane in DMF. After reaction completion, **3** was precipitated by pouring the reaction mixture into EtOAc and then isolated after filtration in 97% yield. Intermediate **3** was used without further purification into the sodium borohydride reduction in MeOH.[7] We were delighted to find that treatment of **3** with $NaBH_4$ in MeOH at 0 °C gave exclusively the desired regioisomer **4** after reaction quench with aqueous NH_4Cl. Extractive work-up and crystallization with EtOAc following $NaHCO_3$ pH adjustment, furnished key intermediate **4** in 78% yield (99% purity by HPLC). The reduction of **3** was completely selective and no regioisomers of **4** were detected. The overall transformation of **1** to **4** proceeded in 68% yield over 3 steps and was successfully demonstrated on scale to provide a total of 20 kg of enamide **4**.

Enamide **4** was then subjected to an asymmetric homogeneous hydrogenation micro-scale screen [0.04 mmol scale; substrate/catalyst ratio (S/C) of 25; 4 mol% catalyst loading; hydrogen pressure of 60 bar; 40 °C; 16 h].

For these screening experiments, 5 types of Ru, Rh and Ir metal precursors in combination with 22 different chiral diphosphine ligands to generate the active chiral catalysts and five isolated Rh and Ir catalyst precursors were used (Figure 1). All evaluated Rh and Ir catalysts were of the type [M(diene)(Lig)]A (M: Rh, Ir; diene COD, NBD; Lig: chiral diphosphine or phosphino-oxazoline; A: BF_4, CF_3SO_3, BARF). For the *in-situ* generation of the Ru catalysts, $[RuCl_2(p\text{-cymene})]_2$ and $[Ru(COD)(CF_3COO)_2]$ were used as precursors in combination with diphosphine ligands (PP). The performance of these catalysts was examined in both protic and aprotic solvents (methanol, THF, 1,2-dichloroethane) with TFA as an additive in some cases to improve solubility and catalyst performance.

The best overall performances were obtained using a Ru complex of the Josiphos ligands SL-J011-1 and SL-J002-1 (Figure 2) made by mixing $[RuCl_2(p\text{-cymene})]_2$ precursor with the ligand in MeOH. These two catalysts provided high levels of enantiomeric excess (97%), small amounts of the de-fluoro compound **5c** (2–3%), and gratifyingly, no *trans*-**5b** was detected (Table 1, entries 7 and 8). The Ru/SL-J002-1 catalyst generated from $[Ru(COD)(CF_3CO_2)_2]$ under aprotic conditions in DCE (entry 9), in combination with TFA (0.5 equiv./**4**) as additive, delivered a comparable conversion and selectivity, but the enantiomeric excess was significantly lower (88%). In the reaction with catalyst Ru/SL-J301-1 in MeOH (Table 1, entry 10) the de-fluorinated product **5c** was formed in a significant amount (19%).

The Rh and Ir catalysts were not as effective in hydrogenation of **4** (Table 1, entries 1–6) as the Ru catalyst, resulting in lower *ee* and higher de-fluorination. The Ir catalysts also suffered from low conversions. Based on these results, a further scale-up using 2 mmol of **4** was undertaken with the Ru/SL-J011-1 and Ru/SL-J002-1 catalyst systems, which were identified as the best metal-ligand combinations. Although the conversion (92% after 1 day) was lower for the Ru/SL-J011-1 catalyst (Table 2, entry 1), a high enantiomeric excess (96.5% *ee*) could be obtained, and almost full conversion was achieved after 2 days. The Ru/SL-J002-1 catalyst (Table 2, entry 2) displayed higher reactivity, but the enantioselectivity was lower (91.6% *ee*).

With respect to the planned production, we desired the higher reactivity of the Ru/SL-J002-1 catalyst, but needed to increase the enantioselectivity of the reaction. Further optimization raised the S/C ratio from 25 to 100 (Table 2, entry 3), by lowering the hydrogenation pressure to 20 bar, and decreasing the reaction

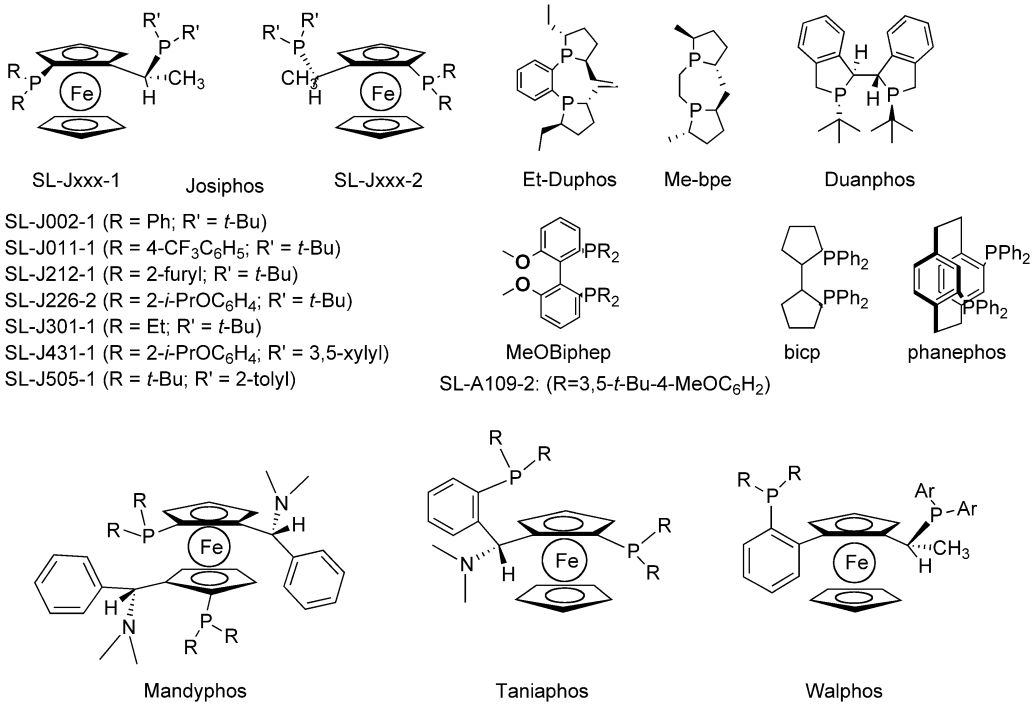


Figure 1. Selected chiral diphosphine ligands used in HTS.

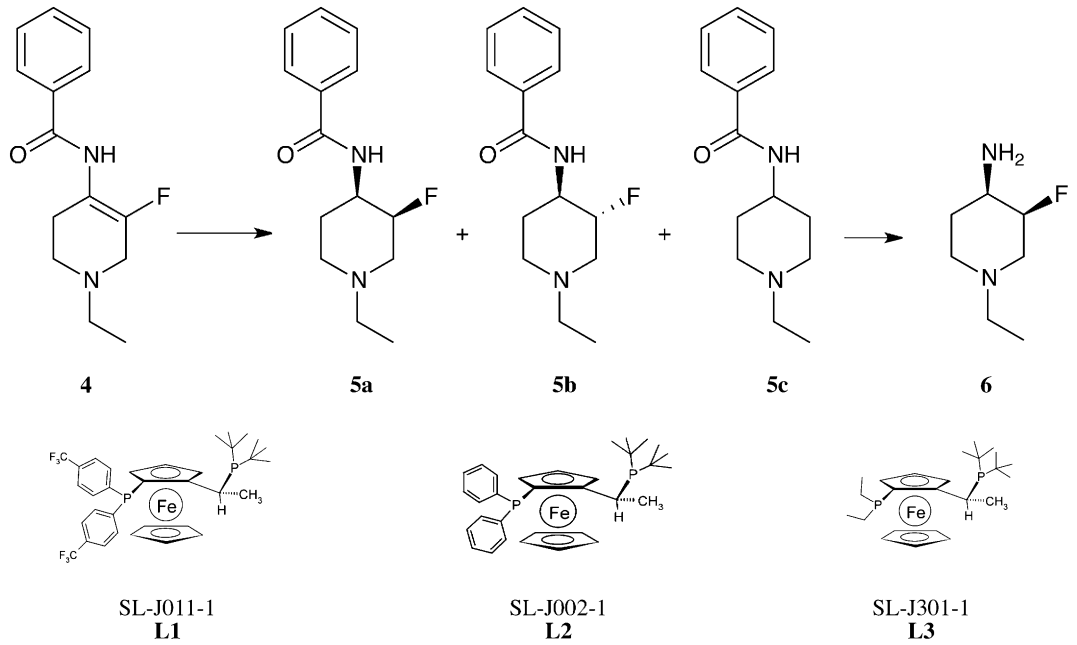


Figure 2. Asymmetric hydrogenation of **4**.

temperature from 40 °C to room temperature. Consequently, the enantioselectivity for **5a** was improved to 98.2% *ee*, and the reaction was complete after 16 h.

We then investigated $[Ru(COD)(CF_3CO_2)_2]$ as metal precursor, which delivered a slightly higher reactivity compared to $[RuCl_2(p\text{-cymene})]_2$. This allowed us to increase the S/C ratio to 200, and use an MeOH/DCE mixture (4/1) as solvent on a 10-mmol scale. Almost full conversion was reached even at room temperature after 16 h (Table 2, entry 4).

This difference can be rationalized by the fact that different catalyst precursors are formed depending on the metal precursors. Specifically, treatment of $[Ru(COD)(CF_3CO_2)_2]$ with 1 equiv. of a josiphos

Table 1. Asymmetric hydrogenation of enamide **4**: selected results from micro-scale screening experiments.

Entry	Catalyst	Ligand	Solvent	Conversion [%][b]	**5a** [%][a]	**5a/5b**	*ee* [%][b]	**5c** [%][c]
1	$[Rh(NBD)_2]BF_4$	SL-J431-1	MeOH	100[c]	51	100/0	−87.7	33
2	$[Rh(NBD)_2]BF_4$	SL-J212-1	MeOH	100[c]	49	100/0	63.0	47
3	$[Rh(COD)]O_3SCF_3$	SL-J505-1	DCE[d]	100[c]	91	100/0	−69.2	5
4	$[Rh(COD)]O_3SCF_3$	SL-J301-1	THF	50[c]	58	94/6	6.7	27
5	[Ir(COD)BARF	SL-J226-2	DCE	74[c]	4	–/–	–	69
6	[Ir(COD)BARF	SL-A109-2	DCE	42[c]	–	–/–	–	85
7	$[RuCl_2(p\text{-cymene})]_2$	SL-J011-1	MeOH	99[c]	97	100/0	97.3	2
8	$[RuCl_2(p\text{-cymene})]_2$	SL-J002-1	MeOH	100[c]	95	100/0	97.1	3
9	$[Ru(COD)(O_2CCF_3)_2]$	SL-J002-1	DCE[d]	97[c]	93	100/0	88.9	3
10	$[Ru(COD)(O_2CCF_3)_2]$	SL-J301-1	MeOH	100[c]	77	100/0	72.6	19

[a] Determined by HPLC.
[b] S/C = 25, carried out at 40 °C and 60 bar H_2 pressure, 16 h.
[c] TFA additive (0.5 equiv./substrate).

Table 2. Selected results for catalyst optimization.

Entry	Catalyst	Ligand	S/C	Scale [mmol]	Conversion [%][a]	**5a** [%][a]	**5a/5b**	*ee* [%][a]	**5c** [%][a]
1	$[RuCl_2(p\text{-cymene})]_2$	SL-J011-1	25	2	92[b]	97	100/0	96.5	2
2	$[RuCl_2(p\text{-cymene})]_2$	SL-J002-1	25	2	100[b]	96	100/0	91.6	4
3	$[RuCl_2(p\text{-cymene})]_2$	SL-J002-1	100	10	100[c]	98	100/0	98.2	1
4	$[Ru(COD)(O_2CCF_3)_2]$	SL-J002-1	200	10	99[d,e]	98	100/0	99.1	1

[a] Determined by HPLC.
[b] Carried out at 40 °C and 60 bar H_2 pressure, MeOH.
[c] Carried out at 20 °C and 20 bar H_2 pressure, MeOH.
[d] Carried out at 20 °C and 20 bar H_2 pressure, MeOH/DCE (4/1).
[e] TFA additive (0.5 equiv./substrate).

ligand in the presence of methanol results in the formation of a Ru complex with the generic structure $[Ru(CF_3CO_2)_2(MeOH)_2(PP)]$.[9]

In contrast, treatment of $[RuCl_2(p\text{-cymene})]_2$ with josiphos affords a complex of the type $[RuCl_2(p\text{-cymene})(PP)]$.

With the optimized reaction conditions in hand the asymmetric hydrogenation of **4** was finally performed on a 24-mol scale, using the $[Ru(COD)(CF_3CO_2)_2]$/SL-J002-1 catalyst at an S/C ratio of 200 in a MeOH/DCE mixture (4/1) at 20 bar.

The reaction was run for 20 h at room temperature and then heated to 40 °C for 7 h. The desired product **5a** was obtained in excellent enantiomeric purity (98.1% *ee*) and 98.7% yield, while the de-fluorinated by-product **5c** was generated in only 1.3% yield. Finally, hydrolysis of **5a** in refluxing 6 M aqueous HCl for 9 h proceeded as expected furnishing (3*R*,4*S*)-**6** isolated as the dihydrochloride salt in 85% yield (98.7% purity), 98.7% *ee* on a 24-mol scale. Overall 12 kg of enantiomerically enriched (3*R*, 4*S*)-**6** were made using our improved protocol.

In summary, we have developed a straightforward, scaleable, and highly enantioselective (98% *ee*) process to synthesize a key pharmaceutical intermediate, (3*S*,4*R*)-1-ethyl-3-fluoropiperidin-4-amine in 5 steps and 65% yield.

The key step of this synthesis sequence was the enantioselective hydrogenation of a prochiral tetrasubstituted β-fluoroenamide, which was conducted by means of a Ru-Josiphos catalyst yielding the desired intermediate with high levels of enantiomeric purity (98.7% *ee*) and small amount of de-fluorinated by-product (1.3%). To achieve this goal catalyst screening of Ru, Rh and Ir diphosphine catalysts, followed by a fast optimization program were necessary. This reaction represents a new approach to synthesize *cis* vicinal aminofluoro compounds with 2 stereogenic centers in excellent *ee* and *cis/trans* selectivity. To the best of our knowledge this is the first example for the enantioselective hydrogenation of a β-fluoroenamide.

Given the importance of this class of compound, this methodology has the potential to be of significant relevance in the development of a variety of pharmaceuticals.

Experimental Section

Synthesis of *N*-(3-Fluoropyridin-4-yl)benzamide (2)

3-Fluoropyridin-4-amine (2.20 kg, 19.6 mol) was dissolved in anhydrous THF (25 L and cooled to −5 °C. Under an atmosphere of nitrogen, triethylamine (3.99 kg, 5.5 L, 39.4 mol)

was charged followed by dropwise addition of benzoyl chloride (3.173 kg, 2.62 L, 22.6 mol) over 2 h while maintaining the internal temperature between −5 °C to 5 °C. The reaction was complete 2 h after addition. The reaction mixture was then filtered and washed with dry THF (5×20 L). The THF solution was concentrated to give crude compound **2**. Crude **2** was then dissolved in refluxing EtOAc (8.8 L) and hexane (2.9 L) was added which caused the solution to become cloudy. The mixture was cooled to 0 °C during 2 h, filtered and dried to afford compound **2**; yield: 3.90 kg (92%); mp 135.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (1 H, t, J = 5.46 Hz), 8.45 (1 H, d, J = 2.34 Hz), 8.39 (1 H, d, J = 5.46 Hz), 8.30 (1 H, s), 7.89 (2 H, d, J = 8.20 Hz), 7.62 (1 H, t, J = 7.03 Hz), 7.53 (2 H, t, J = 7.81 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.7, 149.4 (d, J = 251.73 Hz), 147.1, 147.0, 137.2, 136.9, 133.6, 133.5, 132.8, 129.1, 127.3, 114.7; ^{19}F NMR (400 MHz, $CDCl_3$): δ = −147.4 (1 F, s); HR-MS: m/z = 217.0868, calcd. for $C_{12}H_9FN_2O$; 216.0699.

Synthesis of 4-Benzamido-1-ethyl-3-fluoropyridinium Iodide (3)

Compound **2** (1.95 kg, 9.0 mol) was dissolved in anhydrous DMF (10 L). The mixture was heated to 70 °C and iodoethane was charged (1.55 kg, 0.795 L, 9.9 mol). The reaction temperature rose to 110 °C until addition was complete (*ca.* 1 h). The reaction was maintained at 100 °C for a further 2 h, then cooled to room temperature and poured into 50 L of ethyl acetate (pre-cooled to 5 °C in a 72-L reactor) causing immediate precipitation. This was aged for 1 h and the precipitate was filtered and washed with ethyl acetate (3× 10 L) to give **2** as a yellowish solid. Product **2** was dried in a tray vacuum oven at 50 °C, to provide pure compound **2**; yield: 3.25 kg (97%), mp 208.3 °C. ^{1}H NMR (400 MHz, DMSO): δ = 11.37 (1 H, s), 9.41 (1 H, dd, J = 5.86, 1.56 Hz), 8.88 (1 H, dd, J = 7.03, 1.56 Hz), 8.73 (1 H, t, J = 7.42 Hz), 7.99 (2 H, d, J = 8.20 Hz), 7.72 (1 H, t, J = 7.42 Hz), 7.61 (2 H, t, J = 8.20 Hz), 4.52 (2 H, q, J = 7.42 Hz), 1.54 (3 H, t, J = 7.42 Hz); ^{13}C NMR (101 MHz, DMSO): δ = 167.3, 149.6 (d, J = 252.57), 142.1, 141.6, 141.5, 134.1, 133.3, 132.6, 128.8, 128.6, 117.9, 117.9, 55.5, 15.9; ^{19}F NMR (400 MHz, DMSO): δ = −130.0 (1 F, s); HR-MS: m/z = 245.1277, calcd. for $C_{14}H_{14}FN_2O$ 245.1090.

Synthesis of *N*-(1-Ethyl-3-fluoro-1,2,5,6-tetrahydropyridin-4-yl)benzamide (4)

Compound **3** (6.45 kg, 17.3 mol) was dissolved in methanol (40 L) in a 72-L reactor. Sodium borohydride (1.82 kg, 43.3 mol) was charged portionwise (*ca.* 5–6 h) maintaining the internal temperature between −5 °C and 10 °C. After reaction completion, saturated aqueous ammonium chloride (10 L) was added and th mixture stirred for 1 h, followed by addition of saturated aqueous sodium bicarbonate (12 L). This was aged overnight followed by removal of methanol and extraction with ethyl acetate (3×30 L). The combined organics were washed with water and brine, then dried over sodium sulfate and concentrated to give compound **4**; yield: 3.36 kg (78%); mp 137.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (2 H, d, J = 7.7 Hz), 7.48 (4 H, dq, J = 14.9, 7.4 Hz), 3.17 (2 H, s), 2.89 (2 H, s), 2.65 (2 H, t, J = 5.6 Hz), 2.55 (2 H, q, J = 7.1 Hz), 1.13 (3H t, J = 7.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.4, 146.3, 143.8, 134.5, 131.8, 128.7, 127.1, 114.1 (d, 5.08 Hz), 51.5, 50.8, 50.5, 49.7, 25.7, 12.4; ^{19}F NMR (300 MHz, MeOD): δ = −122.8 (1 F, s); HR-MS: m/z = 249.1778, calcd. for $C_{14}H_{17}FN_2O$ 248.1325.

Preparation of Catalyst Solution

A 10-L Schlenk flask was charged with [Ru(COD)-$(CF_3CO_2)_2$] (52.6 g, 121 mmol), SL-J002–1 (68.8 g, 127 mmol), and the flask was vacuum inerted with argon 5 times. Dried and degassed methanol (4.0 L) and dichloroethane (2.5 L) were added *via* cannula under argon. The suspension was stirred for 45 min at 40 °C, and then cooled to room temperature.

Synthesis of *N*-[(3*S*,4*R*)-1-Ethyl-3-fluoropiperidin-4-yl)benzamide (5a)

A 50-L autoclave was pressurized with nitrogen to 10 bar and checked for leakage, and subjected to a nitrogen inertion 3 times *via* vacuum/pressure cycles. Compound **4** (6.00 kg, 24.16 mol) was dissolved in methanol (19 L) and dichloroethane (1 L) in a 40-L reactor, and added to the autoclave. The autoclave was pressurized with nitrogen to 5 bar, depressurized, and this was repeated 3 times. The catalyst solution (6.5 L) was added to the autoclave *via* canula, pressurized with hydrogen gas to 20 bar, depressurized, repeated 3 times, then pressurized to 20 bar. This mixture was stirred at 1000 rpm for 20 h at room temperature, while hydrogen uptake was monitored. The reactor was heated to 40 °C for 7 h, and then cooled to 25 °C. The reactor was carefully depressurized, pressurized with nitrogen gas to 5 bar, depressurized, and repeated 3 times. The contents of the autoclave were transferred to a 60-L reactor under a nitrogen pressure, and the autoclave rinsed with methanol (2.0 L). Deloxan THPII (2.4 kg, 40 mass%) was charged and stirred at 500 rpm for 3 days at room temperature. The suspension was vacuum filtered over Arbocel (0.7 kg), the filter cake was washed with methanol (5.0 L), and solvent evaporated at 20 mbar and 45 °C to afford a brown solid that was used as is in the amide hydrolysis; yield: 6.58 kg; mp 154.3 °C. ^{1}H NMR (400 MHz, MeOD): δ = 7.83 (2 H, t, J = 9.1 Hz), 7.53 (1 H, t, J = 7.3 Hz), 7.45 (2 H, t, J = 7.6 Hz), 4.84 (1 H, d, J = 49.28 Hz), 4.25–3.91 (1 H, m), 3.37–3.22 (2 H, m), 3.10–2.95 (1 H, m), 2.60–2.39 (2 H, m), 2.32–2.02 (3 H, m), 1.79 (1 H, d, J = 12.3 Hz), 1.11 (3 H, t, J = 7.2 Hz); ^{13}C NMR (101 MHz, MeOD): δ = 170.2, 135.6, 132.8, 129.1 (d, J = 176.65 Hz), 89.8, 88.1, 56.4, 56.2, 53.1, 52.8, 50.9, 50.7, 26.7, 11.7; ^{19}F NMR (300 MHz, MeOD): δ = −201.7; HR-MS: m/z = 251.2293, calcd. for $C_{14}H_{19}FN_2O$ 250.1481; $[\alpha]^{26.7}$: +77.0° (589 nm, *c* 0.89, MeOH, 98% *ee*); HPLC (Chiralcel Chiralpak AD-H, 25 cm×4.6 mm, 5 mm; 20 °C; 220 nm; 1 mL min^{-1}; *n*-heptane/ethanol 90:10): retention times (min): 11.921.

Synthesis of (3*S*,4*R*)-1-Ethyl-3-fluoropiperidin-4-amine Dihydrochloride (6)

Aqueous hydrochloric acid (35 L, 209 mol) and **5a** (6.58 kg, 24.16 mol) were charged to a 60-L enamel reactor. The reactor was connected to a sodium hydroxide scrubber and heated with vigorous stirring to 130 °C jacket temperature. After 50 min the mixture reached reflux (106 °C internal

temperature). After 1.5 h a black precipitate formed. After 10 h heating was stopped and the supsension allowed to age overnight at room temperature. The precipitate was collected on a glass frit and washed with water (2 L). The light yellow mother liquor was divided between two 30-L rotary evaporator bulbs and partially concentrated, removing a total of 20 L solvent on a rotary evaporator at 30 mbar, 60 °C. Ethanol (10 L) was added to the rotary bulb, and a further 13 L ethanol/water were distilled at 30 mbar at 60 °C. The yellow oil was chased 2 more times with ethanol (10 L each) as just described. Ethanol (20 L) was added to the remaining oil and heated to 60 °C. The solution was cooled to room temperature overnight, causing crystallization. The yellow suspension was cooled to 0 °C, aged for 1 h, then isolated by filtration on a glass frit, and washed with cold ethanol (10 L, 0 °C), and diethyl ether (5 L). The tan solid was dried in a vacuum oven for 24 h at 30 mbar, 80 °C giving **6** dihydrochloride as a tan, microcrystalline powder; yield: 4.70 kg (85%); mp 245.5 °C. ^{1}H NMR (300 MHz, MeOD): $\delta = 5.35$ (d, $J = 47.2$ Hz, 1H), 3.91 (m, 1H), 3.79–3.97 (m, 6H), 2.18 (m, 2H), 1.26 (t, 3H); ^{13}C NMR (101 MHz, MeOD): $\delta = 87.4$, 87.2, 85.6, 85.4 (dd, $J = 177.02$ Hz), 64.9, 64.7 (d), 53.8, 51.0, 50.9 (d), 25.4, 25.4 (d), 23.5, 9.7; ^{19}F NMR (400 MHz, $CDCl_3$): $\delta = -204.4$; HR-MS: $m/z =$ 147.1303, calcd. for $C_7H_{15}FN_2$: 146.1219; $[\alpha]^{25.3}$: +17.0 (589 nm, *c* 1.09, DMSO, 98% *ee*).

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