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Efficient preparation of an *N*-aryl β-amino acid via asymmetric hydrogenation and direct asymmetric reductive amination en route to Ezetimibe

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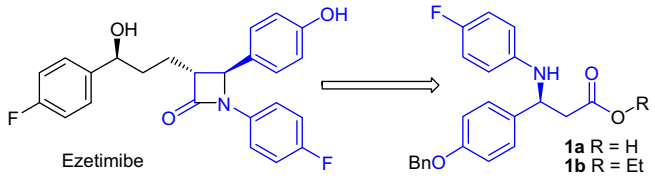
This article is dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

Two routes for the preparation of an *N*-aryl β-amino acid, an important precursor for the cholesterol-lowering drug Ezetimibe, were investigated. The first pathway proceeds via an Rh- or Ir-catalyzed asymmetric hydrogenation of *N*-aryl enamine giving the desired product with up to 82% ee. The other pathway involves a direct asymmetric reductive amination (DARA) of the β-keto ester which yielded the β-amino ester in high yield and 97% ee. Subsequent copper-catalyzed N-arylation gave the target compound.

1. Introduction

Enantiomerically pure β-amino acid derivatives are recurring structural motives in many important biologically active compounds such as β-peptides and β-lactams. The *N*-aryl β-amino acid derivative **1** described here is an attractive building block en route to Ezetimibe (Scheme 1). Ezetimibe is a member of a class of lipid-altering agents known as cholesterol absorption inhibitors.[1,2] In contrast to other drugs that reduce blood cholesterol levels by inhibiting its biosynthesis, Ezetimibe exerts its activity by limiting the intestinal absorption of both dietary and biliary cholesterol.[3]



Scheme 1.

Many methods have been reported for the preparation of enantiopure β-amino acids.[4] In this article we describe the preparation of *N*-aryl β-amino acid **1a** via two short and efficient pathways, that is, asymmetric hydrogenation of the *N*-aryl enamine **3** and direct asymmetric reductive amination (DARA) of the β-keto ester **2** followed by N-arylation (Scheme 2).

Asymmetric hydrogenation of prochiral *N*-aryl enamines can be considered as a cost-efficient and atom-economic method to synthesize *N*-aryl β-amino acids. Although many catalysts are known for hydrogenation of the structurally related *N*-acyl enamide analogues,[5] the N-substituted and unsubstituted enamines have been much less studied.[6–8,13b] This is probably related to the conviction that the presence of the amido group is a prerequisite for bidentate binding of the substrate with the metal, leading to high reactivity and selectivity.[9,10] Very few reports exist on the asymmetric hydrogenation of *N*-aryl β-enamino esters.[11] Bruneau et al. also described the preparation of a wide range of similar substrates but reported only their non-enantioselective hydrogenation.[12] Herein we report on our screening efforts leading to the discovery of a hydrogenation catalyst for the conversion of **3** into **1** (Scheme 2, pathway A).

Another approach to obtain β-amino acids is via direct asymmetric reductive amination of the corresponding β-keto esters. In spite of its attractiveness there are only a limited number of reports on this method.[13] Recently, Takasago and Merck jointly applied this technology to obtain Sitagliptin.[14] In this article we also explored the use of this route to obtain the chiral primary amine **4** starting from keto ester **2** and its further conversion into the *N*-aryl β-amino acid **1a** by Cu-catalyzed N-arylation (Scheme 2, pathway B).[15]

2. Results and discussion

2.1. Asymmetric hydrogenation, pathway A

The synthesis started from the inexpensive and readily available *p*-hydroxy-acetophenone **5**. *O*-Benzylation followed by a

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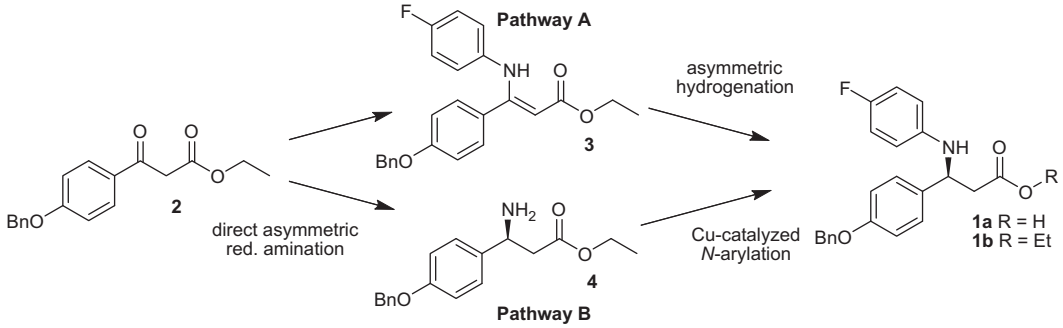
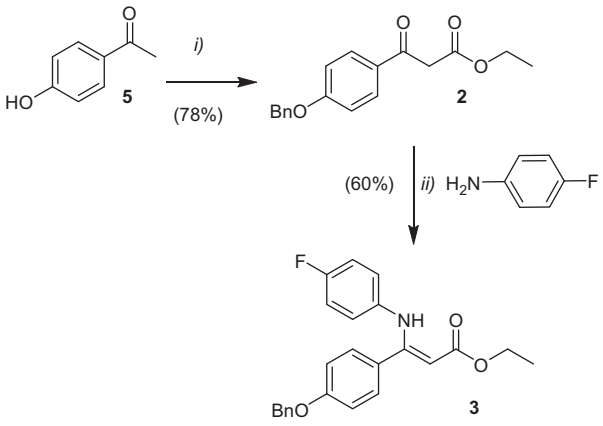
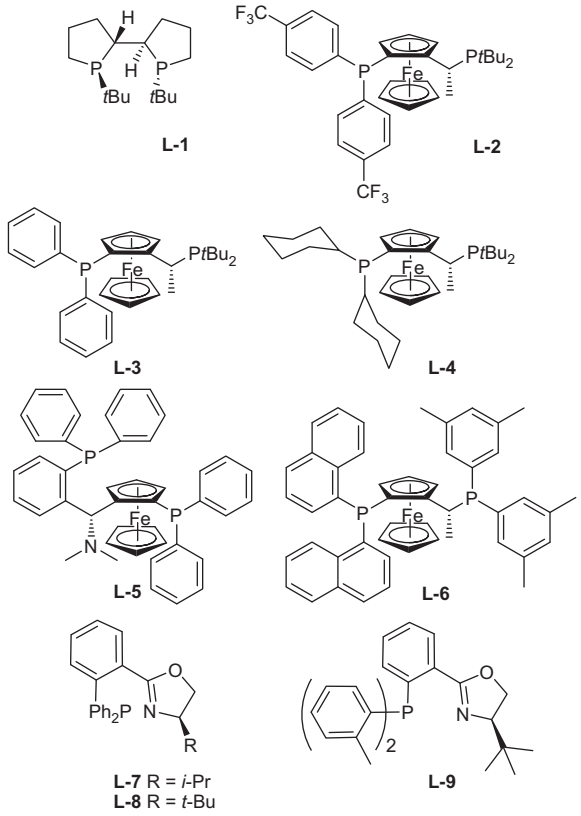


Scheme 2.



Scheme 3. Synthesis of the enamine **3**. Reagents: (i) BnBr, K_2CO_3, acetone, (95%) then $(EtO)_2CO$, NaH, THF, (83%); (ii) *p*-TsOH, molecular sieves (60%).

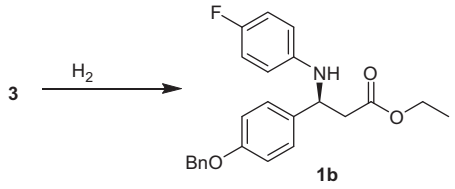


Scheme 4. Ligands used for the asymmetric hydrogenation of **3**.

Claisen condensation[16] afforded the β-keto ester **2** in high yield (Scheme 3). Subsequent reaction with *p*-fluoro-aniline in the presence of molecular sieves and *p*-toluenesulfonic acid yielded the hydrogenation substrate, that is, enamine **3**.

We started our screening by applying the Rh/TangPhos catalyst developed by Zhang et al. (**L-1**, Scheme 4).[11b] This led to formation of the desired product **1b** with an acceptable enantiomeric access (81%, Table 1, entry 1). The hydrogenation proceeds in various solvents (CH_2Cl_2, 2,2,2-trifluoroethanol (TFE), MeOH, entries 1–3) but in all cases the activity is rather low, possibly due to product inhibition.[17] An extensive screening of solvents and additives (Brönsted acids (CH_3COOH), Lewis acids (La, Cu, Sc, Mg, Fe, Ti), NH_4Cl, phenol, iodine) did not improve the activity of the Rh/TangPhos catalyst. We then tested some ligands from the Josiphos family, **L-2** to **L-4** (Scheme 4), as this class of ligands had been used successfully in the rhodium-catalyzed hydrogenation of an unprotected enamine.[8] Higher yields were obtained (Table 1, entries

Table 1
Asymmetric hydrogenation of enamine **3**



Entry	Catalyst	S/C	Solvent	*P* (bar)	*T* (°C)	**1b**[a]	ee[b] (%)
1	**L-1**[c]	50	TFE	25	50	45	81
2	**L-1**[c]	50	CH_2Cl_2	25	50	32	87
3	**L-1**[c]	50	MeOH	25	50	49	67
4	**L-2**[c]	50	TFE	25	50	62	38
5	**L-3**[c]	50	TFE	25	50	99	74
6	**L-4**[c]	50	TFE	25	50	93	39
7	**L-5**[c]	50	TFE	25	50	80	82
8	**L-6**[c]	50	TFE	25	50	82	80
9	**L-5**[c]	50	TFE	25	30	69	73
10	**L-5**[c]	50	TFE	25	40	75	74
11	**L-5**[c]	50	TFE	5	50	88	81
12	**L-5**[c]	50	TFE	5	70	89	53
13	**L-6**[c]	50	TFE	5	50	75	67
14	**L-6**[c]	50	TFE	25	40	91	78
15	**L-6**[c]	50	TFE	25	30	81	80
16	**L-7**[d]	1000	TFE	25	50	100	45
17	**L-8**[e]	80	TFE	25	50	94	42
18	**L-8**[d]	80	TFE	25	50	100	42
19	**L-9**[e]	80	TFE	25	50	74	41
20	**L-9**[d]	80	TFE	25	50	93	36

[a] HPLC area%.
[b] Determined by chiral HPLC using a Chiralcel AD-H column.
[c] Rh-precursor = $[Rh(COD)_2]BF_4$.
[d] Ir-precursor = $[Ir(COD)_2]PF_6$.
[e] Ir-precursor = $[Ir(COD)Cl]_2$. Reaction time 18 h.

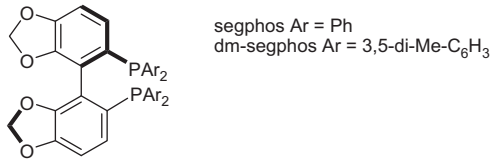
4–6) although the ee's were lower than those achieved with Tang-Phos. Stimulated by these results, we decided to screen a wide range of commercially available ligands using our high throughput screening equipment (HTE).[18] Among the 32 ligands tested, two new ligands that induced a high enantiomeric excess were identified, that is, **L-5** Taniaphos 001-1 (82% ee, Table 1, entry 7) and **L-6** Josiphos 404-1 (80% ee, Table 1, entry 8). Next, we examined the effect of the hydrogen pressure and the temperature using these two ligands. Unfortunately, the variations of these two parameters did not result in any improvement, of the activity or of the enantioselectivity (entries 9–15).

Since the activity of all rhodium systems we tested so far remained low (incomplete conversions at S/C = 50–100), we decided to turn toward another metal, that is, iridium. Inspired by the work of Pfaltz et al.,[6g] we included chiral P,N-ligands in the large library of ligands (monodentate and bidentate phosphines) tested with this metal. Again we used our HTE set-up in order to screen many ligands and conditions at the same time. Gratifyingly, we found out that the use of Ir combined with P,N-ligand **L-7** led to full conversion at S/C = 1000 (entry 16). Encouraged by this result, we performed an extensive screening of P,N-ligands in combination with iridium as a metal. The best results were obtained with phosphine–oxazoline ligands for which we made the following observations: changes in the hydrogen pressure (5–25 bar) or the temperature (25–50 °C) (not shown in Table 1) had little effect. Good conversions were only obtained in TFE; much lower conversions were found in most common solvents such as CH_2Cl_2, MeOH, EtOH, *i*-PrOH, toluene, TFE/CH_2Cl_2 mixture, and TFE/EtOH mixture even at S/C = 40. We found no influence of the counter-ions having tested PF_6, Cl (entry 17), and BArF (not shown). A summary of the best results obtained from the screening of the P,N-ligands is shown in Table 1 (entries 16–20). Although the Ir/phosphine–oxazoline catalysts were highly active, the ee remained too low.

2.2. Direct asymmetric reductive amination, pathway B

Next, the direct asymmetric reductive amination of β-keto ester **2** into chiral primary amine **4** was investigated (pathway B, Scheme 2). This approach in which ammonium salts are used as a nitrogen source was pioneered by Takasago[13a] using ruthenium-based catalysts.

By reacting β-keto ester **2** with ammonium acetate in the presence of Ru(OAc)$_2$((*R*)-DM-SEGPHOS) (see Scheme 5 for the ligand structures) under 30 bar hydrogen pressure, only 12% of the chiral amine **4** was formed (Table 2, entry 1). We also found several by-products such as the hydroxyl-ester **6**, the enamine ester **7**, and the elimination products **8a**,**b** (Scheme 6).



Scheme 5. SEGPHOS ligands.

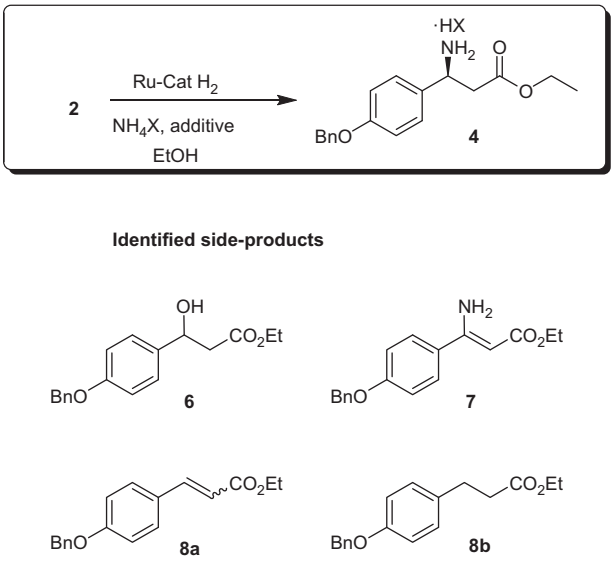
A number of other nitrogen sources were tested such as ammonium iodide, ammonium citrate, and ammonium tartrate, but this led to low yields of the desired product (<9%, not depicted). With HCO_2NH_4 or $PhCO_2NH_4$, the yields increased slightly up to 14% and 22%, respectively (entries 4 and 5). Much better results were obtained with ammonium salicylate (entries 6–11). The amount of ammonium salicylate had a strong impact on the yield of the reaction. Addition of 2 equiv of this nitrogen source led to 90% assay yield (entry 10). After having established the best nitrogen source, a ligand screening of SEGPHOS, DM-SEGPHOS, and BINAP showed that the highest yield was obtained with DM-SEGPHOS (not depicted). Variation of the hydrogen pressure from 10 to 50 bar revealed that the reaction accelerates as the hydrogen pressure increases. Varying the substrate concentration also influenced the product yield. The optimum substrate concentration of 0.2 g/mL in EtOH yielded the product in 90% yield. Further fine-tuning of the ruthenium catalyst was performed by testing two neutral ruthenium acetate complexes with SEGPHOS (Table 3, entry 1) and DM-SEGPHOS (entry 2) as ligand, one cationic arene ruthenium DM-SEGPHOS complex (entry 3) and one anionic dimeric complex (entry 4). The best results were obtained with the anionic catalyst [NH_2Me_2][{RuCl((*R*)-DM-SEGPHOS)}$_2$(μ-Cl)$_3$]. In all cases the enantiomeric excess was high (>97%). An additive screening (not shown) revealed that further addition of salicylic acid accelerates the reaction.

Having thus established the best nitrogen source, additive, and Ru-catalyst we optimized the reaction conditions to further increase the substrate to catalyst ratio. So far, all of the experiments were performed at a maximum S/C of 750. Upon careful evaluation of the effect of hydrogen pressure, temperature, and substrate concentration, we succeeded to find conditions where we could isolate compound **4** in 80% yield at an S/C ratio of 5000. This is the highest value ever obtained in a DARA. These conditions, relying on higher

Table 2
Screening of nitrogen sources in the direct reductive amination of β-keto ester **2**

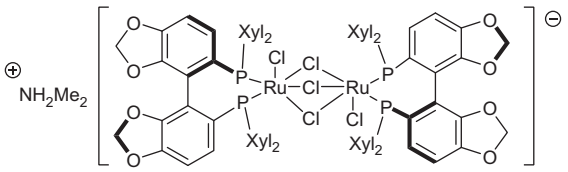
Entry	S/C	*T* (°C)	NH_4X (equiv)	Yield[a] (%)	HPLC area %					
					4	**6**	**2**	**7**	**8a**,**b**	**X**[b]
1	200	80	$AcONH_4$ (1)		12	1.5	30	39	0.9	13
2	500	95	$AcONH_4$ (2)	9	12	0.1	4.3	68	2.3	10
3	200	80	$AcONH_4$ (3)		11	0.1	4.3	74	0.6	5.8
4	500	95	HCO_2NH_4 (2)	14	18	2.8	1.4	49	11.0	10
5	500	90	$PhCO_2NH_4$ (2)	22	27	0.2	4.3	42	6	18
6	200	80	NH_4-SA[c] (1)		55	4.2	27	1.8	0.9	6.8
7	200	90	NH_4-SA[c] (1)		74	5.5	9.2	0.6	3.1	4.9
8	200	90	NH_4-SA[c] (1.5)		85	3.4	3.9	0.4	3.6	1.1
9	200	90	NH_4-SA[c] (2)		88	1.7	0.0	0.1	6.5	0.0
10	500	95	NH_4-SA[c] (2)	90	88	0.9	0.0	0.3	7.7	0.3
11	200	90	NH_4-SA[c] (3)		91	0.8	0.0	0.0	5.4	0.0

[a] Assay yield of **4**.
[b] Unidentified side product.
[c] SA = salicylate. Reaction conditions: Ru(OAc)$_2$((*R*)-dm-segphos), H_2 (30 bar), EtOH (10 mL/g).



Scheme 6. Direct reductive amination of **2** including various side products.

Table 3
Screening of Ru catalysts



$[NH_2Me_2][\{RuCl((R)\text{-dm-segphos}\}_2(\mu\text{-}Cl)_3]$

Entry	Ru-catalyst	Yield[a] (%)	ee (%)[b]	HPLC area %					
				4	**6**	**2**	**7**	**8**	**X**[c]
1	$Ru(OAc)_2((R)$-segphos)	53	98	56	0.1	14	15	0.8	1.0
2	$Ru(OAc)_2((R)$-dm-segphos)	78	98	80	0.7	5.2	4.5	1.9	4.7
3	[RuCl(p-cymene)((*R*)-dm-segphos)]Cl	38	97	42	0.4	22	22	0.3	12
4	$[NH_2Me_2][\{RuCl((R)\text{-dm-segphos})\}_2(\mu\text{-}Cl)_3]$	88	98	89	0.8	0.0	0.8	5.6	1.1

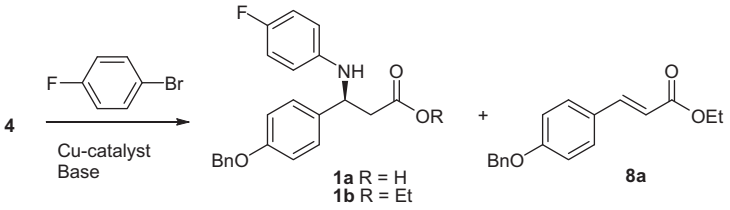
[a] Assay yield of **4**.
[b] Determined by chiral HPLC using chiralcel AS-H column.
[c] Unidentified side product. Reaction conditions: S/C = 750, ammonium salicylate (2 equiv), H_2 (30 bar), EtOH (10 mL/g), 90 °C, 15 h.

pressure (50 bar H_2 instead of 30 bar) and lower temperature (85 °C instead of 90 °C), made this step sufficiently economic for scale-up.

2.3. Copper-catalyzed arylation of 4

To achieve the final step, we investigated the copper-catalyzed N-arylation of **4** to **1**. Formation of the carbon–nitrogen bond by CuI-catalyzed coupling of aryl halides with amines is one of the typical Ullmann coupling reactions.[19] In our group we have developed the use of diketone ligands for this reaction.[15] A few years ago Ma et al. published an efficient method for the synthesis of N-arylated β-amino esters via a CuI-catalyzed coupling reaction with aryl halides.[20] However, most of the arylations described in this article were preformed with aryl iodides. Since the bromo-compound is 20 times cheaper than the related iodine compound we decided to use 4-fluoro-bromobenzene.[21] The reaction of chiral β-amino ester **4** with 4-fluoro-bromobenzene was investigated using several different copper-sources and bases with acetylacetone (acac) as ligand (Table 4).[22] In addition to the desired product **1b**, several side products such as acid **1a** and the elimination product, cinnamic ester **8a**, were formed. Although the choice of copper source had an effect on the yield, the influence of the base was much more important. Unacceptable amounts (21–44%) of undesired elimination product were obtained when K_2CO_3 was used as a base (entries 1–5). Other carbonates and amines such as

Table 4
Variation copper source



Entry	Copper source	Base	HPLC area %			
			4	**1b**	**1a**	**9**
1	CuCl	K_2CO_3	7.3	48	7.3	37
2	CuBr	K_2CO_3	13	37	13	37
3	CuI	K_2CO_3	25	40	14	21
4	$Cu(OAc)_2$	K_2CO_3	15	45	12	28
5	$Cu(acac)_2$	K_2CO_3	0.4	62	3.8	33
6	CuCl	Li_2CO_3	57	16	—	27
7	CuCl	Na_2CO_3	79	3.7	—	17
8	CuCl	Cs_2CO_3	7	—	71	22
9	CuCl	K_3PO_4	14	—	65	20
10	CuCl	Et_3N	36	2.5	—	61
11	CuCl	Imidazole	18	—	—	82
12	CuCl	K-malonate	33	45	—	21
13	CuCl	KO^{t}Bu	3	—	91	—
14	CuCl	KOH	—	—	97	—

Reaction conditions: DMF, base 2 equiv, 15 mol % copper source, 20 mol % acac, 120 °C.

Et_3N and imidazole also led to the formation of considerable amounts of the elimination product (entries 6–12). Much more rewarding results were obtained using KO^tBu and KOH, giving exclusively the hydrolyzed product **1a** (entries 13 and 14). We were able to exclude a benzyne-type mechanism which has been observed by us and others when using strong bases at high temperatures,[15,23] since in that case a mixture of 3- and 4-fluoro-aryl products would be formed. The β-amino acid **1a** is easily converted to the corresponding ester using thionyl chloride in EtOH (87% yield of **1b**). Chiral HPLC determination of the obtained amino ester showed no erosion of ee (97%).

3. Conclusions

We have demonstrated that the desired product **1b**, an intermediate en route to Ezetimibe, can be prepared by two different asymmetric pathways.[24] For pathway A, relying on the hydrogenation of enamine ester **3**, good ee's were obtained with Rh in combination with chiral bisphosphines but the activity remained relatively low. Better turnover numbers were obtained with Ir and P,N-ligands but the enantioselectivity remained moderate (ee of 45%). Pathway B, relying on the direct asymmetric reductive amination (DARA), was found to be most efficient. Using Ru in combination with DM-SEGPHOS, ammonium salicylate as ammonium source, and salicylic acid as an additive, the DARA was highly enantioselective, even at an unprecedented S/C of 5000. The β-amino ester **4** was isolated in 80% yield with 97% ee. This compound could be converted into **1a** via a copper-catalyzed arylation with 4-bromo-fluorobenzene. By careful selection of the base, this reaction was fine-tuned to yield 97% of the acid **1a** which was converted in good yield into the ester **1b** upon treatment with EtOH/$SOCl_2$.

4. Experimental section

4.1. General information

Commercially available reagents and solvents were used as delivered (reagent grade typically). Ligands were obtained from Strem or Sigma–Aldrich. All reactions were carried out under inert atmosphere of dry nitrogen. Standard syringe techniques were applied to the transfer of dry solvents and air- or moisture-sensitive reagents.

Silica Gel 60 F254 pre-coated glass plates were used for analytical thin layer chromatography (Merck KGaA). Visualization was accomplished by UV light and/or dipping the plate into an aq. solution of $KMnO_4$ and K_2CO_3 followed by heating.

Flash chromatography was performed on Silica Gel 60 (40–63 μm, Merck KGaA). Melting points were determined with a Büchi B-535 melting point apparatus. Optical rotations were determined with a Perkin–Elmer 241 polarimeter (1 dm cell). NMR spectra were recorded with a Bruker AMX-300 spectrometer. ^{1}H NMR: 300 MHz, 21 °C, residual non-deuterated solvent as internal standard ($CHCl_3$: δ_H 7.27 ppm, DMSO-d_5: δ_H 2.50 ppm). ^{13}C NMR: 75.5 MHz, 27 °C, deuterated solvent as internal standard ($CDCl_3$: δ_C 77.2 ppm, DMSO-d_6: δ_C 39.5 ppm), DEPT experiments performed additionally. Enantiomeric purities were determined on an Agilent HPLC, with indicated column and solvent mixture.

4.1.1. Ethyl 3-(4-(benzyloxy)phenyl)-3-oxopropanoate 2

A suspension of diethyl carbonate (12.5 g, 0.105 mol, 2.4 equiv), sodium hydride (2.46 g, 0.0616 mol, 1.4 equiv, 60 wt % in mineral oil), and THF (45 mL) was heated to 60 °C. To this suspension was added *p*-BnO-acetophenone (10 g, 0.044 mol, dissolved in THF (56 mL) in 1 h. Aliquots were taken from the reaction mixture and analyzed with HPLC over time. The reaction mixture was allowed to cool to room temperature and subsequently added to 25.4 mL of an acetic acid/ water mixture (1/3, V/V) over 30 min. The phases were separated and analyzed with HPLC. The THF phase was washed with satd aq $NaHCO_3$. The THF was partially removed under reduced pressure. To the yellowish reaction mixture (14.3 g), toluene (3.6 mL) and cyclohexane (62 mL) were added and the suspension was heated to 80 °C. The resulting orange solution was allowed to cool down to room temperature and seeded with a small amount of the β-keto ester (0.17 g). The suspension was stirred for an additional 2 h and filtrated. An aliquot was taken from the filtrate and analyzed with HPLC. The yellow residue was dried at 45 °C under reduced pressure for two hours to yield the product (10.9 g, 36.6 mmol, 83% yield). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 7.92–7.95 (m, 2H, arom.), 7.37–7.47 (m, 5H, arom.), 7.02–7.05 (m, 2H, arom.), 5.15 (s, 2H), 4.18–4.26 (q, 2H), 3.94 (s, 2H), 1.24–1.27 (t, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ: 191.3, 168.1, 163.5, 136.4, 131.3, 129.8, 129.1, 128.7, 127.9, 115.2, 70.6, 61.8, 46.2, 14.5.

4.1.2. Ethyl (*Z*)-3-(4-fluorophenylamino)-3-(4-(benzyloxy) phenyl) acrylate 3

At first, ethyl 3-(-4-benzyloxy)phenyl)-3-oxopropanoate (10.0 g 33.5 mmol) was dissolved in 4-fluoro-aniline (6.36 mL, 67.2 mol). *p*-TsOH·H_2O (1.29 g, 6.68 mmol) and molecular sieves 5 Å (10 g) were added. The reaction mixture was stirred for 7 h at 100 °C until the starting material was totally consumed. Subsequently the reaction mixture was filtered, rinsed with CH_2Cl_2, washed with satd aq $NaHCO_3$, and dried with Na_2SO_4. 4-Fluoro-aniline was removed by vacuum distillation (3 mm Hg, 67 °C). The residue was dissolved in CH_2Cl_2, stirred with charcoal for a few minutes, and filtered off. The solvent was evaporated and the residue was crystallized from EtOH to give off white crystals (7.82 g, 60%). R_f 0.19 (EtOAc/*n*-heptane, 1/5). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ 10.12 (br s, 1H), 7.32–7.14 (m, 5H, arom.), 7.13–7.09 (m, 2H, arom.), 6.78–6.61 (m, 4H, arom.), 6.58–6.52 (m, 2H, arom.), 4.89 (br s, 2H), 4.87 (br s, 1H), 4.09 (q, J = 7.3 Hz, 2H), 1.19 (dt, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ: 170.2, 160.5, 159.8, 159.0, 157.2, 136.4, 129.7, 128.6, 128.1, 127.5, 124.0, 123.9, 115.5, 115.2, 114.7, 90.3, 70.0, 59.2, 14.5.

4.2. Preparation of the catalyst

Rhodium(I) tetrafluoroborate bis-1,5-cyclooctadiene complex[25] (0.255 mmol, 104 mg) and (*R,R*)-1-[1-(di-*tert*-butylphosphino)ethyl]-2-(diphenylphosphino)ferrocene (Josiphos SL-J002-1, **L-3**)[26] (0.255 mmol, 139 mg) were dissolved in degassed CH_2Cl_2 (10 mL). The reaction mixture was degassed three times and stirred for 1 h at 40 °C. After stirring, the solvent was removed in vacuo.

4.2.1. Ethyl-3-(4-fluorophenylamino)-3-(4-(benzyloxy)phenyl) propanoate 1b

Ethyl (*Z*)-3-(4-fluorophenylamino)-3-(4-(benzyloxy) phenyl) acrylate (2 g, 5.1 mmol) was added to the autoclave which was closed firmly and placed under an inert atmosphere. Next, degassed TFE (50 mL) was added via the injection port. The preformed catalyst (Rh/**L-3**) dissolved in 5 mL of degassed TFE was added via the injection port to the reaction mixture. The reaction mixture was allowed to react under 50 bar of H_2 at 50 °C overnight. The solvent was removed in vacuo and the crude compound was purified by column chromatography (EtOAc/*n*-heptane, 1/5) to yield the product (**1**) (1.69 g, 84%,) as a white solid. R_f 0.21 (EtOAc/*n*-heptane, 1/5). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 7.42–7.13 (m, 7H, arom.), 6.82 (d, J = 8.4 Hz, 2H, arom.), 6.73 (t, J = 8.8 Hz, 2H, arom.), 6.49–6.34 (m, 2H, arom.), 4.95 (s, 2H), 4.62 (t, J = 6.9 Hz, 1H), 4.06 (q, J = 6.9, 7.3 Hz, 2H), 7.72 (d, J = 6.5 Hz, 2H), 1.12 (t, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) δ:

171.5, 158.6, 158.1, 155.0, 143.17, 137.3, 134.4, 128.9, 128.4, 127.9, 116.12, 115.8, 115.5, 77.8, 77.6, 77.4, 77.0, 70.5, 61.2, 55.8, 43.1, 14.5. HPLC enantiomeric purity of 74% ee (AD-H column, 1.0 mL/min, 2-propanol/*n*-heptane, (1/9), 5 μL): retention times (min): 18.4 (major) and 23.6 (minor).

4.3. Preparation of ethyl 3-amino-3-(4-(benzyloxy)phenyl) propanoate 4 via D.A.R.A. of 2 (S/C = 5000)

A 100 mL Hastelloy autoclave was filled with $[Me_2NH_2]$ {RuCl(*R*)-dm-segphos)}$_2$(μ-Cl)$_3$][27] (6.2 mg, 0.0033 mmol), ammonium salicylate (10.4 g, 67.0 mmol), and salicylic acid (0.463 g, 3.35 mmol). The atmosphere was replaced with nitrogen (purging: 5 cycles of filling to 3 bar N_2/emptying) followed by addition of ethyl 3-(4-benzyloxy)phenyl)-3-oxopropanoate (10.0 g, 33.5 mmol) in EtOH (50 mL). The reaction mixture was stirred for 10 h at 85 °C, with 50 bar hydrogen pressure. After cooling down to ambient temperature and filtration, EtOH was evaporated and the crude reaction mixture was stirred with satd aq $NaHCO_3$ for 30 min. Next, the product was extracted with toluene (3 × 250 mL). The toluene layer was washed with satd aq Na_2CO_3. Evaporation of the toluene yielded the product as a brownish solid (8.0 g, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) δ: 7.3–7.10 (m, 7H), 6.84 (d, J = 8.4 Hz, 2H), 4.94 (s, 2H), 4.27 (t, J = 6.9 Hz, 1H), 4.02 (q, J = 6.9, 7.3 Hz, 2H), 2.53 (d, J = 7.3 Hz, 2H), 1.13 (t, J = 6.9 Hz, 3H). HPLC: enantiopurity of 96.6% ee (AS-H column, 0.5 mL/min, 2-propanol/2-hexane/diethylamine = 60/40/0.1, 5 μL): retention times (min): 12.4 (minor) and 14.0 (major).

4.3.1. Ethyl 3-(4-(benzyloxy)phenyl)-3-(4-fluorophenylamino) propanoate 1b

A round-bottomed flask was charged with CuCl (1.03 g, 10.4 mmol) and crushed KOH (17 g, 0.31 mol). Amino ester **4** (20.0 g, 66.8 mmol in 110 mL DMF), acetylacetone (1.65 mL, 16.1 mmol), and 4-fluoro-bromobenzene (12 mL, 0.11 mol) were successively added. The resulting mixture was heated at 120 °C under N_2 for 20 h. The reaction was allowed to cool down to room temperature and 100 mL of water was added. The suspension was filtered over Celite and extracted with pentane (4 × 150 mL). The aqueous layer was acidified to pH 2 with HCl (1 M) and extracted again with EtOAc (4 × 150 mL). The combined organic layers were extracted with water (10 × 175 mL). After drying over Na_2SO_4 and concentration in vacuo, **1a** was obtained as a brown oil (25 g, 96%, 96.6% ee).

A round-bottomed flask was charged with the amino acid **1a** (56.8 g, 155 mmol) and EtOH (277 mL). The solution was cooled to 5 °C and stirred for 30 min. Subsequently, $SOCl_2$ (22.2 g, 186 mmol) was added in such a way that the temperature was kept between 10 and 15 °C. The mixture was heated to 60 °C for 1.5 h and then cooled to room temperature. To the reaction mixture was added toluene (283 mL). The reaction mixture was cooled with an ice bath while $NaHCO_3$ (362 g, 9 wt %, 388 mmol) was added and stirred for one hour. After phase separation the toluene phase was concentrated in vacuo to yield the β-amino ester **1b** (53 g, 87%, 96.6% ee). Analytical data were in agreement with the data shown above.

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