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An Efficient Catalytic Asymmetric Synthesis of a β^2-Amino Acid on Multikilogram Scale

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Supporting Information

ABSTRACT: We describe herein a scalable catalytic asymmetric hydrogenation process for the multikilogram-scale production of a β^2-amino acid. A short and efficient synthesis of the starting unsaturated *N*-Boc-protected β^2-enamide was developed followed by extensive catalysis screening and optimization studies that identified a simple Ru-BINAP catalyst system to directly afford the (*S*) product in high enantiomeric excess and yield. The final process enabled the multikilogram production in >99% ee, to be used as a key component for one of our clinical candidates.

INTRODUCTION

The efficient synthesis of chiral β^2-amino acid derivatives, as key components of medicinally active compounds, remains a challenge especially for kilogram-scale production.[1] Several methods are known for the synthesis of these types of amino acids, and a few examples are illustrated in Figure 1. One of the most widely used methods includes the asymmetric aminomethylation, or Mannich reaction, that employs chiral auxiliaries such as the Evans oxazolidinone to efficiently set the stereochemistry.[2a] More recent advances include a report by Davies and co-workers of an enantioselective intermolecular C−H insertion reaction of amino methyl derivatives with aryl diazoesters and catalytic chiral dirhodium complexes, that shows high utility.[2b] Also noteworthy is the organocatalytic asymmetric transfer hydrogenation reactions of β-nitroacrylates reported by List and co-workers.[2c] New methodologies continue to be developed for the synthesis of this important class of compounds. From a process perspective, however, the catalytic asymmetric hydrogenation (CAH)[3] of β^2-enamide derivatives was envisioned to be the most efficient method for accessing β^2-amino acid (*S*)-**2** (Figure 2). Installation of the chirality in the last step of the synthesis is a strategic advantage to minimize the loss of chiral product. In addition, numerous chiral transition metal catalysts are available for asymmetric hydrogenation on large scale, and this became the focus of our development efforts starting with the β^2-enamide precursor (*E*)-**1**.

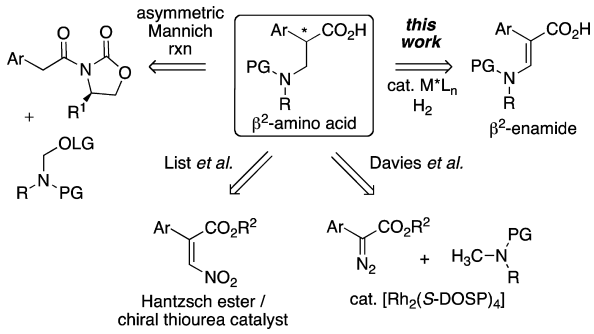

Figure 1. Selected asymmetric methods to access β^2-amino acid derivatives.

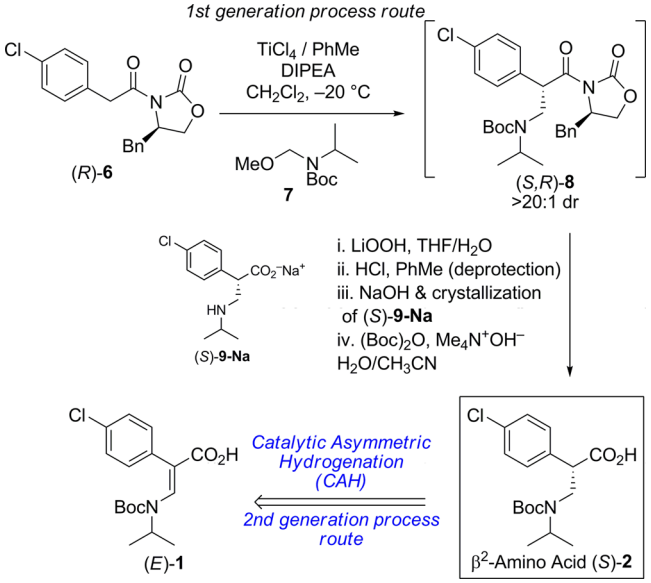

Figure 2. Process chemistry routes for scale-up of β^2-amino acid (*S*)-**2**.

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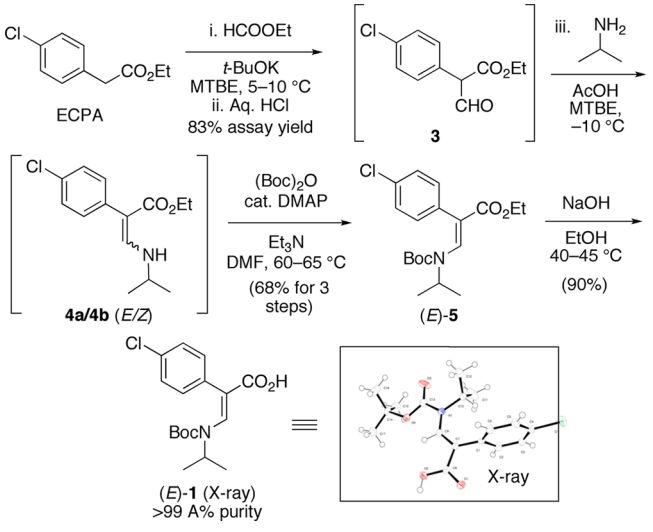
RESULTS AND DISCUSSION

Our first-generation process route to (*S*)-**2** involved use of the Evans' chiral (*R*)-4-benzyloxazolidinone auxiliary in compound (*R*)-**6** (Figure 2) to direct the asymmetric Mannich reaction with the iminium ion derived from *N*-(alkoxymethyl)carbamate **7**.[4] Using this approach, the initial kilogram quantities of enantiomerically pure (*S*)-**2** was produced in ~20% overall yield from 2-(4-chlorophenyl)-acetic acid. Although the key asymmetric Mannich reaction provided alkylation product (*S*,*R*)-**8** in high diastereoselectivity (>20:1 dr) this route required the use of stoichiometric auxiliary, and undesirable reagents such as MOMBr, $TiCl_4$, H_2O_2, etc. In addition, purification of the crude **2** was laborious and required Boc-deprotection and formation of the sodium carboxylate salt (*S*)-**9-Na** which was key for purification as well as crystallization to increase the enantiopurity from ~98% ee to >99% ee. Finally, the Boc group had to be put back on in the last step. This was a fit-for-purpose route to supply our initial kilogram quantities of (*S*)-**2**; however, it was not a practical long-term manufacturing synthesis.

Retrosynthetically, the second-generation approach we investigated was the catalytic asymmetric hydrogenation of Boc-protected enamide (*E*)-**1** illustrated in Figure 2. A very large number of catalysts are available for the asymmetric hydrogenation of α-aminoesters(acids) and β-substituted-β-aminoesters(acids).[5a] A more limited number of examples are available for the hydrogenation of α-methylaminoacrylates leading to β^2-type amino acids.[5b] At the start of our work, there were no reported examples for the asymmetric hydrogenation of a hindered Boc-protected alkyl amine substrate possessing an unsaturated α-aryl carboxylic acid of the type **2**.[5c] It was also unclear how important the olefin bond geometry would be and if the hindered amino group would be detrimental to finding a practical catalyst system to apply on large scale.

Synthesis of Boc-Enamide Substrate (*E*)-1. Preparation of enamide (*E*)-**1** substrate from commercially available ethyl 4-chlorophenyl acetate (ECPA) is illustrated in Scheme 1. Formylation of ECPA with *tert*-butoxide and ethyl formate gave the known Claisen product **3** in 83% HPLC assay yield.[6] Treatment of crude **3** with isopropylamine and acetic acid afforded a ~70:30 mixture of enamine products **4a**/**4b** (*E*- and *Z*-olefin geometries) as determined by HPLC analysis. Boc protection of the vinylogous carbamate was performed at this stage of the process since attempted ester hydrolysis with NaOH resulted in a retro-Claisen/hydrolysis byproduct.[7] Reaction of the enamine with Boc anhydride was sluggish and required up to 8 equiv of this reagent in the presence of catalytic DMAP and with heating in order to completely consume the mixture of enamine esters **4a**/**4b**.[8] Interestingly, during the Boc-protection step, both isomers **4a**/**4b** were consumed, but only one olefin isomer of **5** was isolated. Presumably, this is a result of isomerization of the less reactive *Z*-isomer and concomitant protection of the *E*-isomer although this was not confirmed.[9] The unsaturated ester (*E*)-**5** was isolated in 68% yield overall from the starting material ECPA. The final step in the synthesis of (*E*)-**1** was hydrolysis of the ethyl ester group with aqueous NaOH to afford the unsaturated carboxylic acid product in 90% yield and >99 A% purity by HPLC as a single geometrical isomer. The *E*-olefin geometry was confirmed by single-crystal X-ray structural analysis, and this substrate was used for all catalyst screenings and development work leading up to the scale-up of (*S*)-**2**.

Scheme 1. Preparation of Boc-enamide (*E*)-1



Chiral Catalyst Screening. A catalyst screen was designed to examine common and readily available chiral metal complexes of Rh, Ru, and Ir that would produce β^2-amino acid **2** in high enantiomeric excess. Over 70 experiments with >25 different Rh and Ru metal complexes were performed, and a representative subset of these experiments is shown in Table 1 (illustrated in eq 1). At this preliminary stage the screen was

Table 1

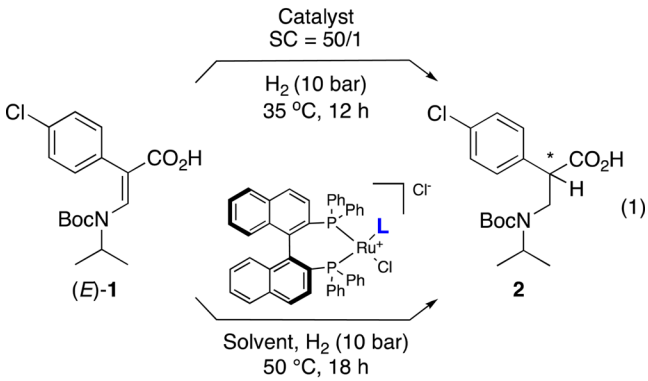


Table 2

performed using either CH_2Cl_2 or MeOH as solvent in the presence, or absence, of triethylamine as a base additive under mild reaction conditions (35 °C, 10 bar H_2 with substrate to catalyst (S/C) loading = 50:1 mol/mol). Among the rhodium catalysts tested, [Phanephos Rh(COD)]BF_4[10a] and [Ph-BPE Rh(COD)]BF_4[10b] catalysts gave complete conversion in MeOH in the presence of 0.7 equiv of triethylamine, with modest enantioselectivities (entries 1 and 2, Table 1). The rhodium complex [(*R*,*R*)-BDPP-RhCOD]BF_4[10c] gave 80% ee of (*R*)-**2** in complete conversion (entry 3, Table 1). Higher enantioselectivities were observed using the chiral ruthenium BINAP complexes with both enantiomers of [BINAP-$RuCl_2$]-$(DMF)_n$[10d] to give (*R*)- or (*S*)-**2** in >95% ee with complete conversion (entries 4B, 4C and 5, Table 1). Contrary to the case of rhodium catalysts, the addition of Et_3N to the carboxylic acid substrate was found to be detrimental to both conversion and ee. Chiral ruthenium BINAP complexes provided the highest enantioselectivity among the catalysts tested.[11] They

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Table 1. Representative Rh and Ru catalysts screened for conversion of (*E*)-1 to (*S*)- or (*R*)-2.[a]

entry	catalyst	solvent	Et_3N, equiv	conv., %	ee, %[b]
1	[(*R*)-Phanephos-Rh(COD)]BF_4	A. CH_2Cl_2	0.7	72	53 (*S*)
		B. MeOH	0.7	>99	40 (*S*)
2	[(*R*,*R*)-Ph-BPE-Rh(COD)]BF_4	MeOH	A. 0.7	>99	57 (*R*)
			B. none	17	37 (*R*)
3	[(*R*,*R*)-BDPP-Rh COD]BF_4	MeOH	0.7	>99	80 (*R*)
	[(*S*,*S*)-BDPP-Rh COD]BF_4	CH_2Cl_2	0.7	12	52 (*S*)
4	[(*S*)-BINAP-$RuCl_2$]$(DMF)_n$	A. MeOH	0.7	35	35 (*S*)
		B. MeOH	**none**	**>99**	**>95 (*S*)**
		C. CH_2Cl_2	none	>99	>95 (*S*)
5	[(*R*)-BINAP-$RuCl_2$]$(DMF)_n$	MeOH	none	>99	>95 (*R*)

[a]All reactions were conducted in a Biotage Endeavor. [b]The (*S*) configuration was confirmed by comparison to a reference standard prepared from the first-generation synthesis of (*S*)-**2**, illustrated in Figure 2.

also had the advantage of providing lower catalysts' cost contribution to the process over other catalysts.

After having identified ruthenium-BINAP as the most promising chiral catalyst in Table 1, the nature of the ruthenium precatalyst, the catalyst loading, and effect of substrate concentration were examined using the (*R*)-enantiomer of the catalyst. Table 2 shows representative examples from eq 1, of reactions at 50 °C and 10 bar hydrogen in MeOH and EtOH, both solvents having emerged from a solvent screen as leading to the highest reactivity.[12] Cationic complexes of the type [(*R*)-BINAP-RuCl (L)]Cl (L= benzene or *p*-cymene)[13] gave a slight improvement in enantioselectivity relative to the less characterized [BINAP-$RuCl_2$]$(DMF)_n$ complex at a S/C = 100/1 and substrate concentration of 0.05 M (entry 1A vs entries 2A and 3A, Table 2). In the case of the [(*R*)-BINAP-RuCl (*p*-cymene)]Cl complex, the use of MeOH gave lower enantioselectivities and yields than the use of EtOH (entries 3A and 3E, Table 2). In general, lower catalyst loadings (S/C >100/1) required the use of higher pressures (30 bar) and temperatures (up to 80 °C; entry 2D, Table 2) to achieve decent conversions and to obtain lower enantioselectivities. Increased substrate concentration up to 0.5 M with lower catalyst loading (entry 2C, Table 2) led to complete conversion to product at S/C = 1000/1 but with only 92% ee. The results from Table 2 suggest there were significant differences in performance among different ruthenium complexes with increasing S/C ratio. We concluded that the ligands on the ruthenium precatalysts would lead to higher conversion and enantioselectivity in the order of benzene > *p*-cymene > DMF.

Having identified [BINAP-RuCl(benzene)]Cl as the most active and selective catalyst, optimization continued with this system to determine the effectiveness of additives to improve both reactivity and enantioselectivity. The addition of various salts including NaOTf, AgOTf, $LiBF_4$, $AgBF_4$, and KPF_6 was examined to evaluate the potential for catalyst activation by displacing the chloride anion from the coordination sphere of the cationic ruthenium complex.[14] These additives led to an increase of reactivity by the catalyst and allowed for lower catalyst loadings (up to 2500/1) and higher concentrations of substrate (up to 0.6 M). The results in Table 3 show that, at 0.375 M substrate concentration and S/C = 1000/1, three additives gave identical conversion and enantioselectivity (entries 1−3, Table 3). Of these three salts, $LiBF_4$ was

Table 3. Additives screened with [BINAP-RuCl(benzene)]Cl[a]

entry	additive	S/C	[S]/M	pressure, bar	conv., %	ee, %
1	$LiBF_4$ (4 mol %)	1000/1	0.375	10	>99	96 (*R*)
2	NaOTf (2 mol %)	1000/1	0.375	10	>99	96 (*R*)
3	$AgBF_4$ (2 mol %)	1000/1	0.375	10	99	96 (*R*)
4	AgOTf (2 mol %)	1000/1	0.375	20	>99	94 (*R*)
5	KPF_6 (2 mol %)	1000/1	0.375	10	95	95 (*R*)
6	$LiBF_4$ (5 mol %)	1000/1	0.6	5	93	94 (*S*)
7	NaOTf (5 mol %)	1000/1	0.6	5	64	94 (*S*)
8	$LiBF_4$ (2 mol %)	2500/1	0.6	20	61	97 (*S*)
9	$LiBF_4$ (2 mol %)	5000/1	0.6	20	15	96 (*S*)
10	**$LiBF_4$ (5 mol %)**	**2500/1**	**0.5**	**25**	**>99**	**96 (*S*)**

[a]Reaction temperature = 65 °C and analyzed after 24 h in a Parr autoclave.

Table 2. Optimization experiments with BINAP-ruthenium catalysts to afford (*R*)-2[a]

entry	catalyst	S/C	[S]/M	solvent	conv.,%	ee, %
1	[(*R*)-BINAP-$RuCl_2$]**(DMF)**$_n$	A. 100/1	0.05	A. EtOH	>99	95
		B. 250/1	0.13	B. MeOH	>99	90
2	[(*R*)-BINAP-RuCl **(benzene)**]Cl	**A. 100/1**	**0.05**	**EtOH**	**>99**	**98**
		B. 500/1	0.37	EtOH	>99	95[b]
		C. 1000/1	0.5	EtOH	>99	92[b]
		D. 1000/1	0.2	EtOH	>99	88[c]
3	[(*R*)-BINAP-RuCl **(*p*-cymene)**]Cl	**A. 100/1**	**0.05**	**EtOH**	**>99**	**99**
		B. 250/1	0.13	EtOH	>99	98
		C. 500/1	0.25	EtOH	63	96[d]
		D. 1000/1	0.5	EtOH	30	84[b]
		E. 100/1	0.05	MeOH	32	73

[a]All reactions were conducted in a Biotage Endeavor. [b]Hydrogen reaction pressure = 30 bar and reaction temperature 65 °C using a Parr autoclave. [c]Hydrogen reaction pressure = 30 bar and reaction temperature 80 °C using a Parr autoclave. [d]Hydrogen pressure = 30 bar.

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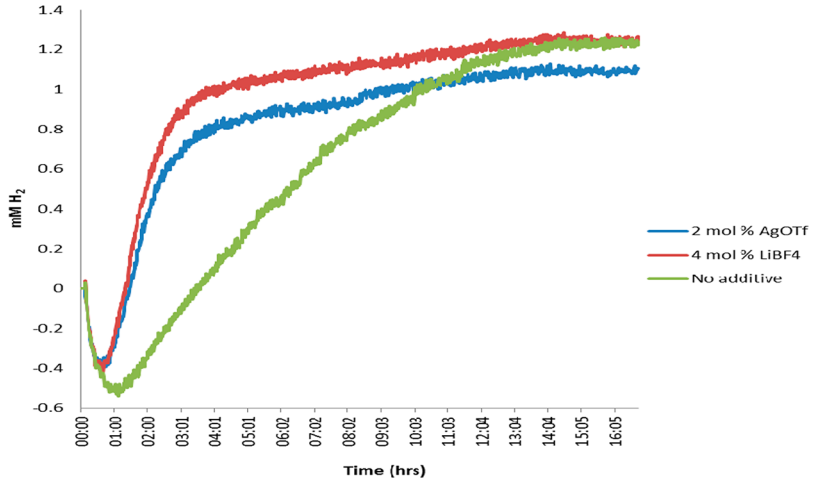

Figure 3. Hydrogen update curves for conversion of (*E*)-**1** to (*S*)-**2**. S/C = 1000/1 mol/mol, EtOH (0.375 M), H_2 (20 bar), 60 °C, 16 h, 2−4 mol % additive.

shown to be superior to NaOTf at [S]/M = 0.6 M (entries 6 and 7, Table 3) and was favored over the use of the silver salts. Upon further optimization of S/C loading and substrate concentration, the limit using $LiBF_4$ additive was found to be S/C = 2500/1 at 0.5 M, 65 °C, and 25 bar pressure of hydrogen to afford complete conversion and 96% ee. The hydrogen uptake was also measured at 60 °C and 20 bar hydrogen to visualize the effect of the additives on reaction profiles, and the plots from the addition of 2 mol % AgOTf (blue) and 4 mol % $LiBF_4$ (red) are shown in Figure 3.[15] There was a significant increase in the rate of hydrogen uptake with these additives relative to no additives added (green curve).

Scale-up of β^2-Amino Acid (*S*)-2. On initial 20 g scale, the optimized reaction conditions were used with minor modifications to suit the available equipment: S/C = 2000/1, EtOH (0.6 M, 5 vol), H_2 (35 bar), and 5 mol % $LiBF_4$, the hydrogenation of (*E*)-**1** proceeded in 95% conversion after 17 h and gave (*S*)-**2** in 98.9% ee. After recrystallization from heptane, the optical purity of (*S*)-**2** increased to >99% and 86% yield.[16] With increasing scale, a similar catalyst loading was found to achieve similar full conversion. Six batches ranging from 4−35 kg of (*E*)-**1** (Table 4) were subjected to reaction conditions similar to those above, with S/C = ∼2000/1. All six reactions proceeded smoothly with complete conversion to afford crude **2** with 97−98% ee. The combined batches of crude product were treated with SiliaMetS thiol to scavenge residual ruthenium and were crystallized from heptane to produce a total of 126 kg of (*S*)-**2** in >99.9% ee and >99A% purity by HPLC (Scheme 2).

Table 4. Scale-up batches of crude (*S*)-2[a]

	(*E*)-**1** (kg)	(*S*)-**2** in EtOH (kg)	purity (HPLC area) (%)	purity (w/w assay) (%)	% ee
1	4	20	98.8	20	98
2	15	75	98.2	20	97
3	35	178	98.6	21	97
4	33	163	98.2	21	97
5	33	167	98.7	20	97
6	15.2	76	98.4	21	98

[a]Reactions were performed under identical conditions as described in Scheme 2 and gave ∼100% yield of crude product. See Supporting Information for analytical methods.

Process Mass Intensity (PMI).[17] The process mass intensity (PMI) defined as the total mass (kg) of materials that go into each step divided by the mass of product (kg) was used to compare our first- and second-generation process routes to (*S*)-**2**. In the first-generation auxiliary route, a total of 8.9 kg of (*S*)-**2** was produced (in seven synthetic steps) and required on average 575 kg of materials input to produce one kilogram of product (blue bar in Figure 4). In contrast, the second-generation catalytic asymmetric hydrogenation (CAH) route (six synthetic steps) used on average 146 kg of input for every kilo of product. The lower PMI for the CAH route represents an overall 4-fold reduction in mass input (and waste stream) leading to a greener process. A major factor contributing to the higher PMI in the chiral auxiliary route was the purification of (*S*)-**2** for ee enhancement. As described earlier, Boc deprotection, formation of the sodium salt (*S*)-**9-Na**, crystallization, and Boc protection was required that added significant processing. In contrast, purification of crude (*S*)-**2** in the CAH route was achieved by an efficient crystallization. Although the CAH route required up to 8 equiv of Boc_2O to prepare compound (*E*)-**5**, further optimization is ongoing to reduce the number of equivalents which could further reduce the overall PMI of this route.[18] In a direct route comparison of the organic solvents used (defined as preferred, usable, undesirable, and excluding water), there is an overall 6-fold reduction in solvents used in the second generation hydrogenation process.[19]

CONCLUSION

In summary, we have reported an efficient and robust catalytic enantioselective hydrogenation process to generate hundred kilogram quantities of (*S*)-**2** in high optical purity using a readily available BINAP-Ru catalyst. Production of the penultimate (*E*)-**1** olefin substrate was achieved in a four-step, two-pot process from commercially available ethyl 4-chloro phenylacetate in ∼50% overall yield. Obtaining (*E*)-**1** as a single geometric isomer and developing hydrogenation conditions suitable for the use of BINAP-Ru at acceptably low catalyst loadings were key to the success of this project.

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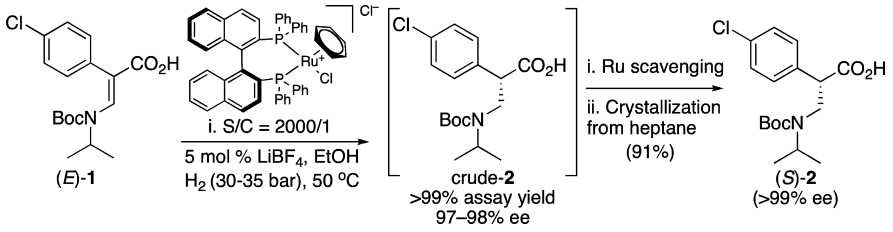
Scheme 2. Kilogram scale-up synthesis of (*S*)-2



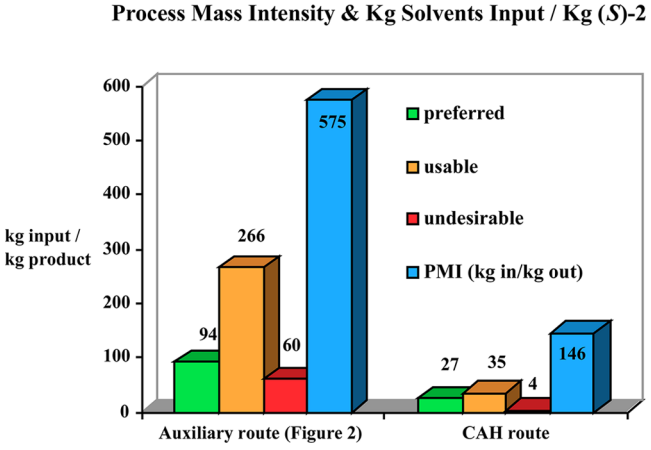


Figure 4. Solvent usage and PMI for auxiliary and catalytic asymmetric hydrogenation routes.

EXPERIMENTAL SECTION

Preparation of *N*-Boc-enamide Ethyl Ester (*E*)-5. A mixture of MTBE (766.7 kg) and *t*-BuOK (114.6 kg, 1023 mol, 2.0 equiv), was cooled to −5 °C. A solution of ethyl formate (93.6 kg, 1263.2 mol, 2.5 equiv), MTBE (142 kg), and ethyl 4-chlorophenylacetate (100 kg, 503 mol, 1.0 equiv) was charged ≤5 °C. The mixture was stirred between 0−10 °C for 1.5 h and deemed complete by HPLC analysis: **3** = 0.8 A% by HPLC.[20] The reaction mixture was added to aqueous HCl (35%, 114.6 kg in 454 L H_2O) at ≤10 °C. The mixture was stirred for 30 min between 0−10 °C (pH = 1.5). The layers were separated, and the organic layer was washed with 25% aqueous NaCl solution (500 kg). HPLC analysis showed starting material and a mixture of keto−enol tautomers of compound **3** corresponding to 79.7% assay yield.

The reaction mixture was cooled to −5 °C, and isopropylamine (62 kg, 1051 mol, 2.0 equiv) was charged followed by the slow addition of AcOH (62 kg, 1033 mol, 2.0 equiv) at a rate to maintain internal temperature <10 °C. The mixture was stirred for 3 h between 0−10 °C and then monitored for consumption of *β*-formyl ester **3**. In-process analysis of the reaction mixture by HPLC showed **3**/**4a**+**4b** = 0.9 A%. The organic layer was washed consecutively with H_2O (640 kg), 15% aqueous Na_2CO_3 (350 kg), and then 25% aqueous NaCl (500 kg). The separated organic layer was analyzed by HPLC: **4a**+**4b** = 92.7A% purity.

The organic layer was concentrated by vacuum distillation to ∼250 L (<50 °C), and then the reactor was charged with DMF (299 kg), and the organics were concentrated again to ∼250 L (<50 °C). The reaction mixture was charged with DMAP (12 kg, 98.4 mol, 0.2 equiv) and triethylamine (152.7 kg, 1512 mol, 3 equiv) and heated to 60 °C. A solution of $(Boc)_2O$ (755 kg, 3457 mol, 7 equiv) and DMF (165 kg) were slowly added over 24 h at this temperature. In-process analysis by HPLC showed **4a**+**4b**/**5** = 8.7 A%. Additional triethylamine (54 kg, 535 mol), $(Boc)_2O$ (95 kg, 436 mol) and DMF (43 kg) were added over 3 h at 60 °C, resulting in **4a**+**4b**/**5** = 5.4 A% by HPLC.

The reaction mixture was cooled to 25 °C and charged with MTBE (900 kg), water (840 kg), and 10% aqueous citric acid (800 kg) with agitation for 1.5 h. The aqueous layer was separated, and the organic layer was washed with 25% aqueous NaCl (820 kg) with agitation for 1.5 h. The aqueous layer was removed, and the solution was concentrated *via* vacuum distillation to a minimum working volume of ∼250 L (<50 °C). Heptane (80 kg) was charged to the reactor, and the solution was cooled to ∼5 °C and stirred for 5 h. The crystallized product was filtered and washed with heptane (12 kg) and dried under vacuum to afford (*E*)-**5** (155.95 kg, 96.1 A% purity by HPLC) in 68% yield (over three steps) as white solid. Loss in the mother liquors was ∼9%. ^{1}H NMR (500 MHz, DMSO-d_6) 7.76 (s, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.74 (h, *J* = 6.8 Hz, 1H), 1.32 (s, 9H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) 166.7, 152.0, 138.8, 133.8, 132.0, 131.5 (2C), 128.0 (2C), 116.7, 81.6, 60.4, 49.7, 27.5 (3C), 19.9 (2C), 14.0; HRMS: *m*/*z* calculated for $C_{19}H_{26}ClNO_4$ $[M + H]^+$ = 368.1623; found 368.1616; mp = 88.6 °C (onset) by DSC.

Preparation of *N*-Boc-Enamide Carboxylic Acid (*E*)-1. A 20% solution of NaOH (88 kg in 370 kg H_2O) was charged to a solution of (*E*)-**5** (200.0 kg, 543.6 mol) and EtOH (450 kg) with agitation at 25 °C. The mixture was warmed to 45 °C and maintained until a clear solution was formed (∼3 h). In-process analysis by HPLC showed **1**/**5** = not detected. The mixture was concentrated under vacuum to a minimum working volume at ≤60 °C. The mixture was cooled to ∼20 °C and charged with EtOAc (1375 kg) and aqueous 2 N HCl (880 kg) to obtain a pH between 4−5. The aqueous layer was separated, and the organic layer was washed with 25% aqueous NaCl (1210 kg). The organic layer was concentrated under vacuum (<50 °C) and then charged with *n*-heptane (280 kg); this process was then repeated. The solids were filtered, washed with *n*-heptane (3 × 24 kg), and then dried under vacuum at ∼45 °C for 10 h to afford (*E*)-**1** (133 kg, 87% yield, 99.9A% purity by HPLC) as white solid. Losses in the mother liquor were found to be 7.6%. ^{1}H NMR (500 MHz, DMSO-d_6) 12.38 (bs, 1H), 7.70 (s, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 3.78 (h, *J* = 6.8 Hz, 1H), 1.30 (s, 9H), 1.08 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) 168.1, 152.0, 138.3, 134.3, 131.8, 131.4 (2C), 127.9 (2C), 118.0, 81.3, 49.5, 27.5 (3C), 20.0 (2C); KF = 0.1%; ROI = 0.02%). HRMS: *m*/*z* calculated for $C_{17}H_{22}ClNO_4$ $[M - H]^-$ = 338.1165; found 338.1161; mp = 163.8 °C (onset) by DSC.

Hydrogenation of *N*-Boc-(*E*)-Enamide Acid 1. *Hydrogenation Screen in Biotage Endeavor.* Catalyst and substrate **1** were weighed into glass Endeavor reaction vials. The vials were purged with nitrogen, and solvent (anhydrous, Fluka) was added. The reaction was purged with hydrogen and run at the

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required temperature and pressure for 18 h. A drop of the reaction mixture was diluted in EtOH and analyzed by HPLC. Column: Diacel Chiralpak AD-H, 0.46 cm × 25 cm, eluent: *n*-hexane/*i*-PrOH 97/3, 1 mL/min, T = 30 °C, wavelength detection = 223 nm, R_t of (*R*)-**2** = 9.8 min; R_t of (*S*)-**2** = 12.1 min.

Hydrogenation in Parr Autoclave. [(*R*)-BINAP-RuCl-(benzene)]Cl (2.5−5 mg) and substrate **2** (1.0 g, 2.9 mmol) were weighed into a 25 mL Parr autoclave fitted with overhead stirrer. The autoclave was sealed and purged with nitrogen. EtOH (6−8 mL) was added *via* syringe, and the reaction was purged with hydrogen and heated to 65 °C under 30 bar H_2 pressure for 18 h with stirring. The vessel was then cooled to room temperature, vented, and sampled for HPLC analysis. The reaction mixture was filtered through a short pad of Celite and washed with EtOAc (10−5 mL), and the solvents were removed *in vacuo*. Drying at 50−60 °C under high vacuum (<5 mbar) gave the product as a viscous oil.

Large-Scale Hydrogenation Representative Procedure. A mixture of (*E*)-**1** (15.0 kg, 44.1 mol), EtOH (56 kg), $LiBF_4$ (0.21 kg, 2.2 mol, 5 mol %), and [(*S*)-BINAP-RuCl(benzene)]Cl (0.020 kg, 0.023 mol; S/C = 1919:1 mol/mol = 750/1 wt/wt) were charged to a reactor.[21] The agitated mixture was vacuum degassed with nitrogen (evacuated to ≤−0.08 MPa and bleeding nitrogen to atmospheric pressure) for five times, evacuated to ≤−0.08 MPa and bleeding hydrogen to ∼34 bar once, then evacuated to ≤−0.08 MPa again and pressurized with hydrogen gas at ∼34 bar and maintained at ∼55 °C for ∼26 h. In-process analysis by HPLC showed complete consumption of enamide (*E*)-**1**. The mixture was cooled to ∼25 °C and transferred to a holding drum and then analyzed by HPLC to have an assay = 20.3%, purity = 98.2%, and 97.4% ee.

A total of six batches were processed under identical reaction conditions described above, and the results are summarized in Table 4. All reactions proceeded to ≥100% assay yield and totalled 138.7 kg in EtOH solution. The six batches of crude (*S*)-**2** were combined, scavenged for Ru, and crystallized to produce one batch as described below.

Metal Scavenging and Purification of Combined Batches of Crude (S)-2. An EtOH solution of crude (*S*)-**2** (∼20% assay in EtOH solution = 138.7 kg in 680 kg EtOH) was concentrated under vacuum *via* distillation (<50 °C) to ∼250 L to which was then added EtOAc (999 L). The mixture was washed with 25% aqueous NaCl (3 × 700 L) and then the organic layer concentrated under vacuum to ∼600 L at ≤40 °C. To the solution was charged SiliaMetS thiol (8.30 kg), and the mixture was agitated for 14 h at ∼50 °C. After cooling to ∼30 °C the mixture was filtered and washed with EtOAc (40 L). The filtrate was concentrated to ∼140 L at ≤42 °C and *n*-heptane (2 × 485 L) was charged in portions with continuous distillation to form a suspension. The suspension was agitated for 1.5 h at ∼50 °C and then for 16 h at ∼0 °C. The product was collected by filtration and washed with *n*-heptane (4 × 229 L). The filter cake was dried under vacuum at ∼45 °C for 10 h to afford compound β^2-amino acid (*S*)-**2** (126.24 kg, 91% yield, 99.6A% purity by HPLC and >99.9% ee) as white solid. The filtrate contained (*S*)-**2** product in ∼80% ee; attempted recrystallization from EtOAc afforded (*S*)-**2** with 86% ee and 40% yield recovery. ^{1}H NMR (500 MHz, DMSO-d_6) 12.60 (bs, 1H), 7.40 (d, J = 8.46, 2H), 7.31 (d, J = 8.46, 2H), 3.86 (bs, 1H), 3.63 (dd, J = 6.8, 14.2 Hz, 1H), 3.35 (dd, J = 7.2, 14.0 Hz, 1H), 1.36 (s, 9H), 1.01 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) 173.4, 154.1, 136.8, 131.8, 130.1 (2C), 128.3 (2C), 78.7, 51.0, 48.4, 47.8, 27.9 (3C), 20.2 (2C); Metal analysis for Ru: <10 ppm; ROI = 0.04%; HRMS: m/z calculated for $C_{17}H_{24}ClNO_4$ $[M - H]^-$ = 340.1321; found 340.1316; $[\alpha]^{24}_D$ = −97.63 (c 0.2, MeOH).

■ ASSOCIATED CONTENT

Supporting Information

General information, analytical methods, and additional characterization data of compounds (*E*)-**5**, (*E*)-**1**, (*S*)-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(7) Attempts to hydrolyze the ethyl ester mixture of **4a**/**4b** with 20% aqueous NaOH in EtOH from 20−60 °C resulted in retro-Claisen/hydrolysis to afford 4-chlorophenyl acetic acid.

(8) Alternative solvents to DMF for the Boc protection, such as acetonitrile and THF, did not improve the conversion. Noteworthy is the Boc-protection of compound (*S*)-**9-Na** from Figure 2 that proceeded in quantitative conversion to product (*S*)-**2** using only 1.7 equiv of $(Boc)_2O$. This observation suggests the unsaturation of enamine ester **4** possesses a steric constraint for the Boc-protection, leading to enamide (*E*)-**5**.

(9) By HPLC analysis of the crude reaction mixture, there is no evidence for decomposition of isomer **4b**; see Supporting Information for the in-process control (IPC) of step 3 [**4a** and **4b**/**5** = 5.4%].

(10) (a) PhanePhos = 4,12-Bis(diphenylphosphino)-[2.2]-paracyclophane; Rh-Phanephos: 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. (b) Ph-BPE = 1,2-Bis(2,5-diphenylphospholano)ethane: Pilkington, C. J.; Zanotti-Gerosa, A. *Org. Lett.* **2003**, *5*, 1273−1275. (c) BDPP = (2*S*,4*S*)-(-)-2,4-Bis(diphenylphosphino)-pentane: Bakos, J.; Toth, I.; Marko, L. *J. Org. Chem.* **1981**, *46*, 5427−5428. (d) BINAP = 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl: Kitamura, M.; Tokunaga, M. Ohkuma, T.; Noyori, R. *Organic Syntheses*; Wiley and Sons: New York; **1998**; Collect. Vol. *9*, p 589; **1998**; Vol. *71*, p 1.

(11) Two chiral iridium catalysts, (a) ([(*R*)-*i*Pr-PHOX Ir(COD)] BAr_F and (b) [(*R*)-PPhos Ir(COD)Cl]), have also been tested under similar reaction conditions but were unreactive. For reference to (a) see: Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897−2899. For reference to (b) the catalyst was prepared mixing $[Ir(COD)Cl_2]_2$ and P-Phos: P-Phos: 2,2′,6,6′-tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridine: Pai, C.-C.; Lin, C.-W.; Lin, C.-C.; Chen, C.-C.; Chan, A. S. C.; Wong, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 11513−11514.

(12) Solvents including THF, EtOAc, and toluene were also screened with the $[BINAP\text{-}RuCl_2](DMF)_n$ catalyst under the conditions described in Table 2; however, <5% conversion to product occurred. Similar to MeOH and EtOH, CH_2Cl_2 also afforded high optical purity of the product but was not desirable to use on large scale due to the environmental impact of the waste stream.

(13) [BINAP-RuCl (L)]Cl: Mashima, K.; Kusano, K.; Sate, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064−3076.

(14) Isolated complexes of the type [BINAP-RuCl (L)]X (X = BF_4, I) are known; see ref 13.

(15) The initial negative values are attributed to equilibration of the equipment to heating, during which some gas expansion occurs before hydrogen uptake begins.

(16) The residual Ru in this lot was ∼100 ppm before crystallization from heptane and ∼30 ppm after crystallization. Metal scavenging was performed before the crystallization for all subsequent scale-up batches.

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(18) For comparison, use of only 1 equiv $(Boc)_2O$ vs 8 equiv used in the current process, would reduce the overall PMI from 146 to 142 (see Table S-3 of Supporting Information), but has a significant impact on the total cost of reagents used.

(19) (a) *ACS GCI Pharmaceutical Roundtable Solvent Selection Guide*, Version 2.0; American Chemical Society Green Chemistry Institute: Washington, D.C., Issued April 1, 2011. (b) Henderson, R. K.; Jiménez-González, C.; Constable, D. J. C.; Alston, S. R.; Inglis, G. G. A.; Fisher, G.; Sherwood, J.; Binksa, S. P.; Curzons, A. D. *Green Chem.* **2011**, *13*, 854−862.

(20) This reaction is reversible and longer reaction times did not result in complete consumption of starting material.

(21) The reactor was pretreated with an acetone/$NaHCO_3$ mixture, followed by acetone/water, and then concentrated HNO_3. The reactor was thoroughly rinsed with water until pH = 7, and then a final EtOH reflux was performed.