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Practical, Catalytic Enantioselective Hydrogenation to Synthesize *N*-Unprotected β-Amino Esters

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ABSTRACT: Practical and simple catalytic enantioselective hydrogenation reactions to synthesize *N*-unprotected β-amino esters have been developed: (1) asymmetric hydrogenation of *N*-unprotected β-enamine ester and (2) asymmetric direct reductive amination of β-keto esters using ammonium salts. A Ru−DM-SEGPHOS complex was used as the catalyst in both cases and gave high enantioselectivity, high reactivity, and wide substrate applicability. These protocols greatly reduced reaction time and waste compared to conventional synthetic routes. The direct reductive amination route was demonstrated on a >100 kg scale.

1. INTRODUCTION

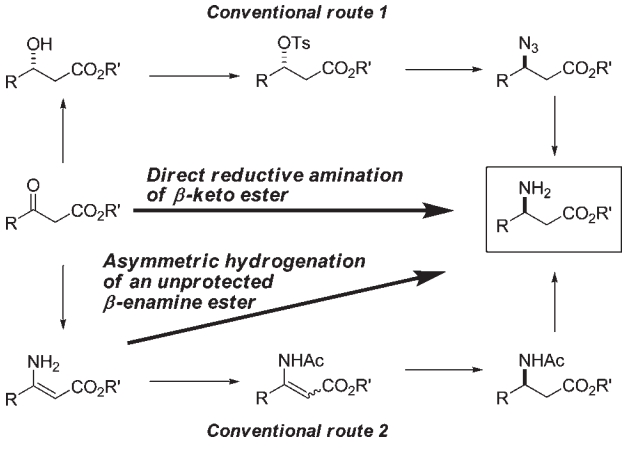
β-Amino acids are attracting increasing attention as chiral building blocks, especially in the pharmaceutical industry.[1] Several methods for the synthesis of this class of compounds have been developed.[2] In large-scale synthesis, optical resolution[3] and derivation from chiral pool[4] are commonly employed methods, and biocatalytic approaches are also becoming promising recently.[5] Catalytic asymmetric hydrogenation is also a potentially powerful method because it has intrinsic operational efficiency (feasibility of a high substrate concentration) and is highly atom economical (low waste). However, despite a large number of reported studies,[6] asymmetric hydrogenation has never been considered a mainstream technology in this field. The main reason has been the lack of a direct method for obtaining β-amino acids using hydrogenation, which has required circuitous synthetic routes involving extra functional group interconversion steps.

The starting material for the synthesis of β-amino acids by asymmetric hydrogenation are β-keto esters, and conventional approaches are classified into two types (Scheme 1): (1) after asymmetric hydrogenation of a β-keto ester, the hydroxyl group is converted to an amino group (conventional route 1), and (2) a β-enamide, prepared from the β-keto ester, is subjected to asymmetric hydrogenation (conventional route 2).

In the first step of conventional route 1, an optically active β-hydroxyl ester is prepared by the asymmetric hydrogenation of a β-keto ester. The β-hydroxyl group is then converted to an appropriate leaving group, which is subjected to nucleophilic substitution by a nitrogen source. Methods via azide[7] and β-lactam[8] intermediates have been reported. Our old synthetic route to methyl 3-aminobutyrate (**1a**) via an azide intermediate (**5a**) is shown as an example in Scheme 2. In this route, the asymmetric hydrogenation step itself was near perfect in terms of the enantioselectivity and the catalytic activity,[9] and the yield of each step was high. However, the route suffered from two disadvantages: it used an azide intermediate that requires special care in handling, and more importantly, it was too long.

Conventional route 2 is more straightforward because it can circumvent the stepwise conversion of hydroxyl group to the amino group. In most examples, substrates are *N*-acetylated since it was strongly believed that acyl group protection of the enamine was necessary for efficient asymmetric hydrogenation. While this reaction has a long history[10] and has been the subject of many studies,[2,11] there are still some unsolved problems. Asymmetric hydrogenation of (*E*)- and (*Z*)-enamides often results in different reaction rates and enantioselectivities.[12,13] Thus, the synthesis of pure (*E*)- or (*Z*)-substrate has been necessary to obtain high enantioselecticity. However, selective synthesis of (*E*)-enamide is difficult, and chromatographic separation of the (*E*)/(*Z*) mixture has been required.[14] In recent years, this issue has been addressed by the emergence of catalysts that are highly enantioselective for both geometric isomers.[15] Nonetheless, when unprotected β-amino acids are targeted, there remains the inherent

Scheme 1. Strategy to develop a synthetic route to β-amino ester



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Scheme 2. Synthetic route via an azide compound

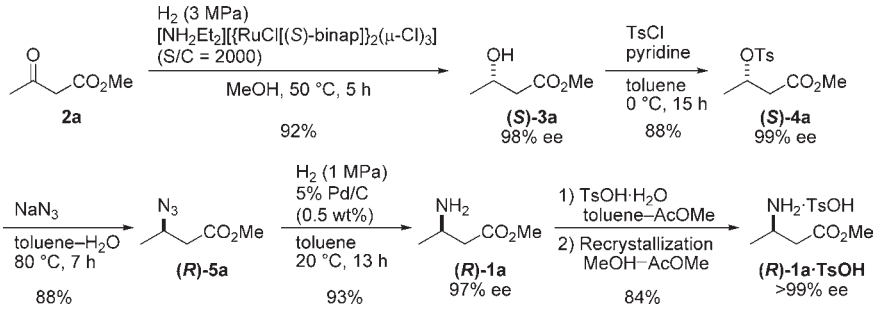
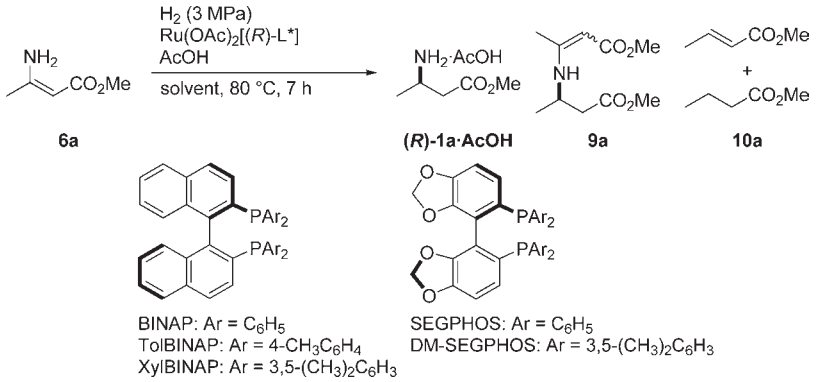


Table 1. Asymmetric hydrogenation of 6a[a]



					1a		GC area %			
entry	L*	S/C[b]	solvent	AcOH (equiv)	% yield[c]	% ee[d]	1a	6a	9a	10a
1	TolBINAP	100	MeOH	none	trace					
2	TolBINAP	100	TFE	none	76	92	76	0	8	5
3	TolBINAP	200	MeOH	1	90	82	88	0	5	2
4	BINAP	200	MeOH	1	84	83	79	1	12	2
5	XylBINAP	200	MeOH	1	89	82	87	0	9	2
6	SEGPHOS	200	MeOH	1	77	95	70	3	24	1
7	DM-SEGPHOS	200	MeOH	1	93	93	93	0	2	3

[a] Unless otherwise stated, reactions were conducted under 3 MPa of H_2 for 7 h at 80 °C using **6a** in solvent (5 mL/g of **6a**) containing a Ru complex. [b] Substrate-to-catalyst molar ratio. [c] Assayed by GC analysis of the *N*-Boc derivative or HPLC analysis of the acetamide derivative. [d] Assayed by chiral HPLC analysis of the *p*-nitrobenzamide derivative.

problem of step counts due to protection and deprotection. In addition, amide hydrolysis is a troublesome reaction that requires heating under strongly acidic conditions.[15b]

We envisioned that a fundamental improvement could be realized by identifying a new catalyst system that can mediate the asymmetric hydrogenation of unprotected β-enamine esters. Furthermore, even more ambitiously, we wished to develop a direct reductive amination of β-keto esters (Scheme 1). Similar to our strategy, several direct syntheses of unprotected β-amino acids using asymmetric hydrogenation have been reported.[7,16,17] For example, Merck and Solvias that reported the Rh–Josiphos complexes catalyze the asymmetric hydrogenation of unprotected β-enamine esters and amides with excellent enantioselectivity, which is an important breakthrough.[16a]

In this report, we present the results of our efforts to develop a new direct synthetic route leading to β-amino acids. The new asymmetric direct reductive amination of methyl acetoacetate was conducted on a >100-kg scale.

2. RESULTS AND DISCUSSION

2.1. Asymmetric Hydrogenation of Unprotected β-Enamine Esters. We used the structurally simplest methyl 3-aminocrotonate (**6a**)[18] as a starting motif of investigation.[16b] The first attempt conducted under typical conditions for Ru-catalyzed asymmetric hydrogenation (MeOH as a solvent, initial hydrogen pressure of 3 MPa, reaction temperature of 80 °C and reaction time of 7 h) resulted in trace conversion (Table 1, entry 1).

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Table 2. Screening of acid additives under the condition in Table 1, entry 7[a]

		1a		GC area %			
entry	additive (pK_a)	yield (%)[b]	% ee[c]	1a	6a	9a	10a
1	$ClCH_2CO_2H$ (2.86)	87	93	65	0	0	2
2	HCO_2H (3.77)	41	94	47	11	27	6
3	$PhCO_2H$ (4.20)	95	91	96	0	0	3
4	*p*-anisic acid (4.47)	98	93	91	0	4	1
5	AcOH (4.76)	93	93	93	0	2	3
6	propionic acid (4.88)	88	92	89	0	7	1

[a] Unless otherwise stated, reactions were conducted under 3 MPa of H_2 for 7 h at 80 °C using **6a** in methanol (5 mL/g of **6a**) containing $Ru(OAc)_2$[(*R*)-dm-segphos] (S/C = 200). [b] Assayed by GC analysis of the *N*-Boc derivative or HPLC analysis of the acetamide derivative. [c] Assayed by chiral HPLC analysis of the *p*-nitrobenzoylated derivative.

We reasoned that the nucleophilic amine moiety of the substrate and/or product blocked the coordination site of Ru and functioned as a catalyst poison.[19] On the basis of this working hypothesis, we decided to acidify the reaction media to reduce the nucleophilicity of the amino group.[20] The reaction gave the corresponding β-amino ester (**1a**) in 76% yield and 92% ee by the use of 2,2,2-trifluoroethanol (TFE)[20] as an acidic solvent, although it was accompanied by a small amount of dimer-like byproduct (**9a**) and deaminated byproduct (**10a**) (entry 2). Independently, Merck and Solvias reported a similar protocol using a Rh−Josiphos catalyst system.[16a] The use of TFE as a solvent was critical in their system too, which confirmed that the presence of acid was essential in the hydrogenation of unprotected β-enamine esters.

Although TFE gave excellent results, its use on a manufacturing scale was not desirable because of its relatively high cost. Since we were convinced that the acidity within the reaction system was the key, we thought we could replace TFE with more process-friendly media by using an acidic reagent. The use of acetic acid (1 equiv) and methanol as an additive and solvent, respectively, gave **1a**·AcOH salt in 90% yield, albeit with a 10% drop in enantioselectivity (entry 3). This drop in ee was recovered by the proper choice of chiral diphosphine ligands. Careful ligand screening revealed that DM-SEGPHOS gave **1a** in both high yield (93%) and high enantioselevtivity (93% ee) (entries 4−7).

Screening of acid additives identified an ideal range of acidity. Acids with a wide range of pK_a values were tested (Table 2). The results showed that a pK_a range of 4.2 (benzoic acid)−4.8 (acetic acid) was ideal for high yield (>90%) and high enantioselectivity (93−94% ee) (entries 3−6). On the other hand, stronger acids such as chloroacetic acid (pK_a = 2.86) and formic acid (pK_a = 3.77) led to a decrease in yield (entries 1 and 2). On the basis of a consideration of selectivity, handling, and price, acetic acid was still judged to be the best. This success in the asymmetric hydrogenation of an unprotected β-enamine ester realized a two-step synthetic route to a β-amino ester from a β-keto ester.

2.2. Direct Reductive Amination. Direct reductive amination of a β-keto ester was a bigger challenge because of competing hydrogenation of the ketone. In order to obtain the amine in high yield, the formation of the alcohol needed to be minimized. We envisioned that Ru diacetate complexes might be useful, since they had been reported to be inactive in the asymmetric hydrogenation of β-keto esters,[9a] while they mediate the hydrogenation of unprotected enamines (see section 2.1.). As expected, the asymmetric hydrogenation of β-keto ester **2a** catalyzed by the Ru diacetate complex **Ru−I** in the presence of ammonium acetate (NH_4OAc) as a nitrogen source led to selective formation of the desired product **1a**, and β-hydroxyl ester **3a** was scarcely detected (Table 3, entry 1). A considerable amount of dimer-like byproduct **9a** derived from condensation between **2a** and **1a** (or **6a**) was formed. Fortunately, **9a** was inert to hydrogenation, and gradually dissociated back to **2a** and **1a** (or **6a**) with a prolonged reaction time. As a result, the yield of **1a** was ultimately improved (entry 2). The addition of acid was also found to accelerate the dissociation of **9a**, which led to completion of the reaction in a shorter period of time (entry 3). An investigation of catalysts revealed that the anionic dimer complex **Ru−III** gave performance similar to that of **Ru−I** (entry 5) while the cationic complex **Ru−II** resulted in low conversion (entry 4). The catalyst solution **Ru−IV** that was prepared in situ from $[RuCl_2(p\text{-cymene})]_2$, (*R*)-DM-SEGPHOS, and ammonium acetate in 1,4-dioxane, also gave the acceptable performance (entry 6).

Optimization of the major reaction parameters (initial hydrogen pressure and temperature) is presented in Figure 1. With regard to hydrogen pressure, higher pressure was essential for a faster reaction, and 3 MPa was sufficient to reach higher conversion (Figure 1(a)). With respect to the reaction temperature, the reaction was accelerated at a higher temperature, but excessive temperature led to the formation of deaminated byproducts **10a**. The optimal temperature was around 80 °C.

This catalytic reaction has been scaled up without any troubles. Direct reductive amination of **2a** (66.6 kg) under the conditions in Table 3, entry 6, gave **1a** in 86% yield and 95% ee. Subsequent crystallization as a *p*-toluenesulfonic acid salt allowed the isolation of 117.2 kg of **1a**·TsOH in >99% ee (Scheme 3).

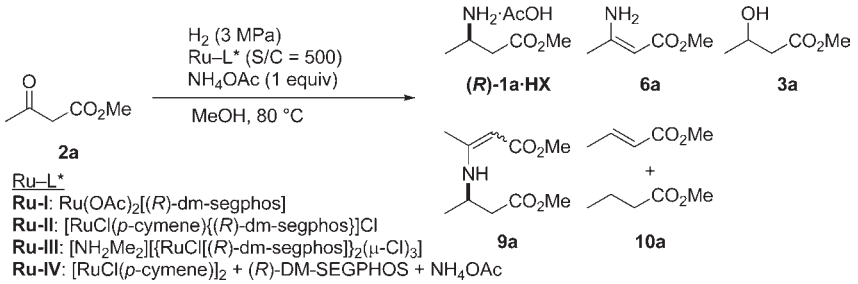
The substrate scope of the reaction was expanded by careful choice of the type of ammonium salt. The results of the substrate scope study are summarized in Table 4. As has been reported regarding the reductive amination of β-keto amides,[17f] the use of ammonium salicylate (NH_4SA) was key to achieving a higher yield in the reductive amination of methyl benzoylacetate (**2b**) (entry 1 vs 2).[17g] The addition of 2 equiv of ammonium salicylate led to a higher yield (entry 3). The use of ammonium salicylate generally resulted in a faster reaction with high chemo- and enantioselectivities (entries 4−7). However, when R of the substrate was a methyl group (**2a**), the enantioselectivity was reduced (entry 8).

A plausible mechanism for this reaction is depicted in Scheme 4. In addition to the desired reaction pathway (**2**→**6**→**1**), three other pathways leading to byproducts can be considered: (1) competitive reduction of ketone (**2**→**3**), (2) formation of dimer-like byproduct (**1** + **2** (or **6**)→**9**), and (3) formation of elimination products (**1**→**10**). Our observations on these side reactions made during this study are summarized below.

(1) Competitive reduction of ketone (**2**→**3**)

In this study, this concern about chemoselectivity was shown to be unfounded. This is attributed to the reluctance of a Ru diacetate complex to hydrogenate β-keto esters. Although the anionic dimer complex **Ru−III** which smoothly hydrogenates β-keto esters[9] gave the same results as Ru diacetate **Ru−I**, its selectivity can be explained considering the presence of acetate ions in the reaction system and the likelihood of the in situ formation of Ru diacetate. The ability of acetate to suppress the

Table 3. Initial screening results for the asymmetric reductive amination of 2a[a]



			1a		GC area %				
entry	Ru−L*	time (h)	% yield[b]	% ee[c]	1a	2a + 3a	6a	9a	10a
1	**Ru−I**	7	70	96	70	<1	3	26	1
2	**Ru−I**	10	92	95	87	<1	<1	7	3
3[d]	**Ru−I**	7	95	93	93	1	0	0	0
4	**Ru−II**	10	26	96	22	3	30	43	1
5	**Ru−III**	10	92	96	81	<1	1	15	2
6	**Ru−IV**[e]	9	84	95	91	<1	1	5	3

[a] Unless otherwise stated, reactions were conducted under 3 MPa of H_2 at 80 °C using **2a** in methanol (10 mL/g of **2a**) containing a Ru complex (**2a**/catalyst (Ru atom) = 500). [b] Assayed by HPLC analysis of the acetamide derivative. [c] Assayed by chiral HPLC analysis of the *p*-nitrobenzoylated derivative. [d] AcOH (2 equiv was added). [e] The mixture of $[RuCl_2(p\text{-cymene})]_2$ (**2a**/Ru = 500), (*R*)-DM-SEGPHOS (1 equiv to Ru), and ammonium acetate (5 equiv to Ru) in 1,4-dioxane was refluxed for 5 h, and then the resulting mixture was cooled to room temperature and used as a catalyst.

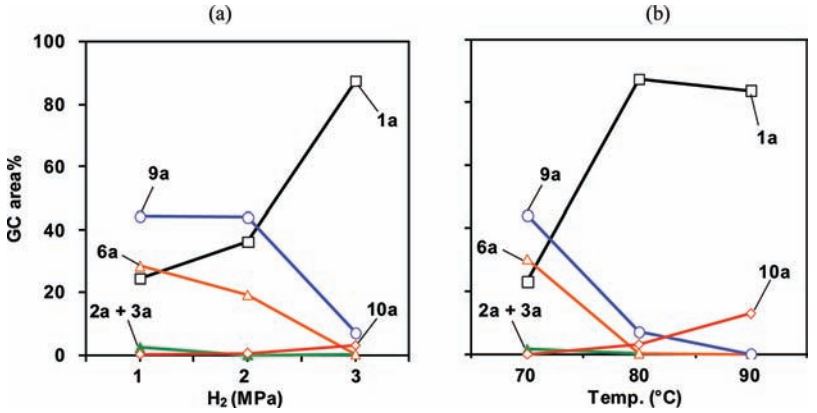
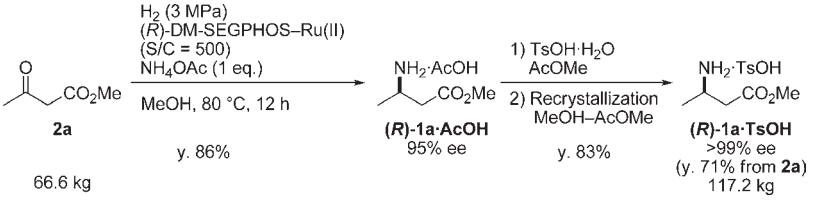


Figure 1. Effects of hydrogen pressure (a) and temperature (b) in the asymmetric reductive amination of **2a**. Conditions: 4.3 mmol of **2a** in 5 mL of methanol, **Ru−I** (S/C = 500), 10 h, reactions were conducted using a 100-mL autoclave. (a) 80 °C. (b) H_2 (3 MPa).

Scheme 3. Scalable synthesis of (*R*)-1a·TsOH via direct asymmetric reductive amination



hydrogenation of β-keto ester was supported by a control experiment. When sodium acetate was added to the typical conditions for the hydrogenation of methyl acetoacetate (**2a**), the catalytic activity of **Ru−III** decreased drastically (Scheme 5). Presumably, the anionic dimer complex **Ru−III** was converted to the Ru acetate complex **Ru−I** in the presence of sodium acetate.

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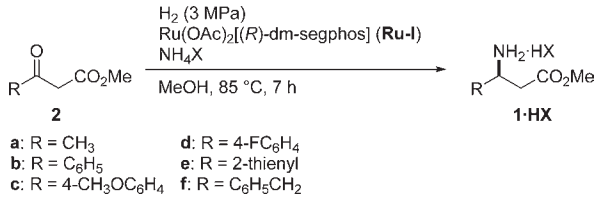
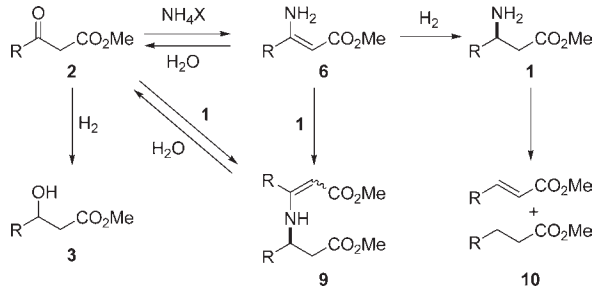
Table 4. Asymmetric reductive amination of β-keto esters 2[a]



entry	2	NH_4X (equiv)	% yield[b]	% ee[c]	config.[d]
1	**2b**	NH_4OAc (1)	19	99	*S*
2	**2b**	NH_4SA (1)	69	96	*S*
3	**2b**	NH_4SA (2)	84	98	*S*
4	**2c**	NH_4SA (2)	83	98	*S*
5	**2d**	NH_4SA (2)	89	97	*S*
6	**2e**	NH_4SA (4)	75	98[e]	*S*[f]
7	**2f**	NH_4SA (2)	88	97	*R*
8	**2a**	NH_4SA (2)	95[g]	83[e]	*R*

[a] Unless otherwise stated, reactions were conducted under 3 MPa of H_2 for 7 h at 85 °C using **2** in methanol (5 mL/g of **2**) containing **Ru−I** (S/C = 500). [b] Isolated yield of the free amine. [c] Assayed by chiral HPLC analysis. [d] Determined by the sign of rotation. [e] Assayed by chiral HPLC analysis of the *p*-nitrobenzoylated derivative. [f] Determined by the sign of rotation of the corresponding HCl salt. [g] Assayed by GC analysis of the *N*-Boc derivative.

Scheme 4. Plausible mechanism for the asymmetric reductive amination of β-keto esters

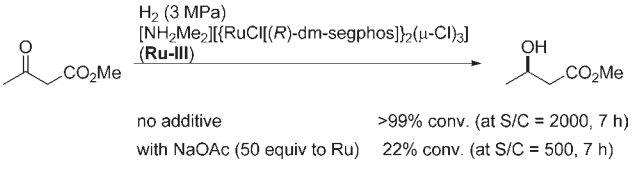


(2) Formation of dimer-like byproduct (**1** + **2** (or **6**)→**9**)

Significant amount of dimer-like byproduct **9** was formed initially in the reaction, but its concentration gradually decreased with the progress of the reaction (**6**→**1**) as a result of equilibrium shift. The acidic additive is considered to accelerate the equilibrium, and the type of acid is dependent on the substrate. In the case of methyl acetoacetate (**2a**), the reaction proceeded with formation of **9** without acid additive (Table 3, entries 1 and 2). On the other hand, the addition of 2 equivalents of acetic acid effectively suppressed the formation of **9**. The role of the acid is presumably the suppression of the dimer formation and/or the promotion of the dimer dissociation, releasing **1** and **2** (or **6**) (Table 3, entry 3). In the case of methyl benzoylacetate (**2b**), the addition of more acidic ammonium salicylate (pK_a of salicylic acid = 2.98) was found to suppress the formation of **9** most effectively.

(3) Formation of elimination products (**1**→**10**)

Scheme 5. Effect of acetate anion on the asymmetric hydrogenation of methyl acetoacetate (2a)



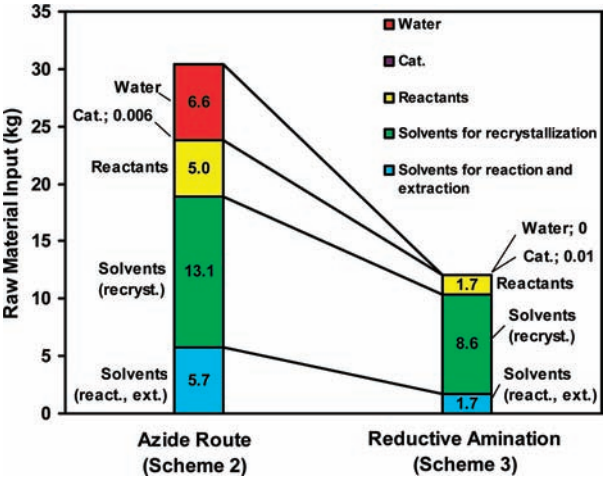


Figure 2. PMI (raw materials input per kilogram of (*R*)-**1a**·TsOH produced) of the conventional azide route (Scheme 2) versus the reductive amination (Scheme 3).

A prolonged reaction time and high reaction temperature are the likely causes of the formation of **10** through β-elimination. The addition of an acid additive is effective to suppress the formation of **10**, although enantioselectivity tends to be slightly lower (Table 3, entry 3). To obtain **1** in high yield, it is essential to appropriately control the reaction time, hydrogen pressure, and reaction temperature.

3. CONCLUDING REMARKS

In this study, ruthenium catalyzed asymmetric hydrogenation of an *N*-unprotected β-enamine ester was realized with the addition of acid. As a further advanced protocol, direct reductive amination of a β-keto ester catalyzed by Ru diacetate complex was developed. Especially, the latter made it possible to synthesize a β-amino ester in a single step from the corresponding β-keto ester. This new short-cut method helps to dramatically reduce the time and waste associated with the reaction. Figure 2 compares the process mass intensity (PMI, defined as the raw material input per kilogram of the product)[22] for (*R*)-**1a**·TsOH for both the conventional azide route (Scheme 2) and the reductive amination route (Scheme 3). Compared to the azide route, the reductive amination route reduced PMI by ~60%, which indicates that it is a green protocol. Most strikingly, the amount of aqueous waste produced in the process was reduced to zero. Moreover, the reductive amination route reduced the total reaction time by ~70%, which contributes to operational efficiency. This direct reductive amination is not only applicable to a wide range of substrates through the appropriate choice of the ammonium salt but can also be easily scaled up. Asymmetric

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hydrogenation of unprotected β-enamine esters and direct reductive amination reactions are becoming a new standard for β-amino acid synthesis.[7,16,17]

4. EXPERIMENTAL SECTION

General Remarks. All reactions and manipulations were conducted under a nitrogen atmosphere unless otherwise noted. Reagents and solvents were used as received from commercial suppliers. Hydrogen of 99.99% purity (Showa Denko) was used. GC analysis was performed on Agilent 6890 instruments. HPLC analysis was performed on GL Science 7400 instruments. The content of **1a**, **6a**, **9a**, and **10a** were determined GC analysis (column, HP-1, df = 0.25 μm, 0.32 mm i.d. × 30 m; carrier gas, helium (100 kPa); column temperature, 40 °C, 5 min hold, heating to 100 °C at a rate of 5 °C/min, then heating to 250 °C at a rate of 10 °C/min; detection, FID; t_R of **1a**·AcOH, 5.6 min; t_R of **6a**, 10.8 min; t_R of **9a**, 23.1 min, t_R of **10a**, 2.2 and 2.6 min). The assay yield of **1a** was determined by HPLC analysis of the corresponding acetamide (column, YMC J'sphere ODS-H80, 4.6 mm i.d. × 250 mm, 4 μm particles; eluent, 10 mM K_2HPO_4 in water (pH adjusted to 6.8 with H_3PO_4):methanol = 90:10; flow, 1.0 mL/min; column temperature, 35 °C; detection, 220 nm; t_R of the acetylated **1a**, 13.0 min) or GLC analysis of the corresponding *tert*-butyl carbamate (column, HP-1, df = 0.25 μm, 0.32 mm i.d. × 30 m; carrier gas, helium (100 kPa); column temperature, 40 °C, 5 min hold, heating to 100 °C at a rate of 5 °C/min, then heating to 250 °C at a rate of 10 °C/min; detection, FID; t_R of the *N*-Boc-**1a**, 20.7 min; t_R of tetraglyme (internal standard), 22.9 min). The enantiomeric excess of **1a** was determined by HPLC analysis of the *p*-nitrobenzoylated derivative (column, CHIRALCEL OD-H, 4.6 mm i.d. × 250 mm, 5 μm particles; eluent, hexane:2-propanol = 80:20; flow, 0.5 mL/min; column temperature, 30 °C; detection, 254 nm; t_R of the *p*-nitrobenzoylated (*R*)-**1a**, 19.9 min; t_R of the *p*-nitrobenzoylated (*S*)-**1a**, 24.7 min). NMR spectra were measured on a Bruker AVANCE III 500 (^{1}H: 500 MHz, ^{13}C: 126 MHz) and Varian Mercury 200 (^{1}H: 200 MHz). NMR chemical shifts are reported in ppm relative to $CHCl_3$ (7.26 ppm for ^{1}H, and 77.0 ppm for ^{13}C) or DMSO (2.50 ppm for ^{1}H, and 39.5 ppm for ^{13}C). Optical rotation was measured on a Jasco P-1020. Melting points were measured on a Yanaco MP500D. HRMS was recorded on a Shimadzu LC/MS-IT-TOF.

Methyl (3*R*)-3-Aminobutyrate *p*-toluenesulfonate ((*R*)-1a·TsOH). Under a nitrogen atmosphere, a mixture of $[RuCl_2(p\text{-cymene})]_2$ (0.351 kg, 0.574 mol), (*R*)-DM-SEGPHOS (0.850 kg, 1.176 mol), and ammonium acetate (0.442 kg, 5.74 mol) in 1,4-dioxane (6.7 L) was refluxed for 5 h and then cooled to room temperature. The resultant mixture was added to a mixture of methyl acetoacetate (**2a**, 66.6 kg, 574 mol), ammonium acetate (44.2 kg, 574 mol) and methanol (666 L) in a 1-M^3 stainless steel autoclave. The air present in the gas inlet tube was removed by flushing with a stream of hydrogen. Hydrogen was initially introduced into the autoclave at a pressure of 0.3 MPa, before being reduced to 0.1 MPa by carefully releasing the stop valve. After this procedure was repeated three times, the hydrogen pressure was set to 2.3 MPa and heating was started. After a reaction temperature of 80 °C was reached, the pressure was slightly increased to 3.0 MPa. During hydrogenation, the hydrogen pressure was maintained within the range of 2.9−3.0 MPa. A conversion of 92% (determined by GC area%, conversion (%) = (**1a**/(**1a** + **6a** + **9a**)) × 100) was reached after 11 h. After a total reaction time of 12 h, the autoclave was cooled and the hydrogen was carefully vented. The mixture was concentrated (40 °C/5.3 kPa) to give as the crude **1a**·AcOH (111 kg). The crude product was assayed to contain 87.2 kg (492 mol, 85.8% assay yield) of **1a**·AcOH which was 95.0% ee.

To a solution of a crude **1a**·AcOH in methyl acetate (166 L) was added a solution of *p*-TsOH·H_2O (92.2 kg, 485 mol) in methyl acetate (332 L) dropwise for 60 min at 51−54 °C. The batch solution was then cooled to 35 °C and seeded with **1a**·TsOH (15 g). The batch was agitated for 30 min at 30−33 °C and gradually cooled to −12 °C for 16 h. The slurry was then filtered, and the wet cake was washed with cold methyl acetate (65 L × 2) to give (*R*)-**1a**·TsOH as wet white crystals (133.6 kg, 98.5% ee).

The wet cake of (*R*)-**1a**·TsOH was dissolved in methanol (63 L) and methyl acetate (313 L) at 55 °C. The batch solution was then cooled to 44 °C and seeded with **1a**·TsOH (15 g). The batch was agitated for 30 min at 42−45 °C and cooled to 23 °C for 1.5 h. The slurry was stirred over 12 h at 23 °C, and then cooled to −12 °C. The slurry was then filtered, and the wet cake was washed with cold methyl acetate (41.5 L × 2). The wet cake was dried at 40−50 °C in vacuo to give (*R*)-**1a**·TsOH (white crystals, 117.2 kg, 71% yield from **2a**, 99.6% ee). Melting point 114−116 °C. $[\alpha]_D^{24}$ −10.7 (*c* 1.01, CH_3OH), *N*-Boc-**1a**: $[\alpha]_D^{18}$ positive (CH_3OH) (lit.[23] for *N*-Boc-**1a**: $[\alpha]_D^{20}$ +8.4 (*c* 1.04, CH_3OH), 96% ee (*R*)). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.22 (d, *J* = 6.6 Hz, 3H), 2.30 (s, 3H), 2.59 (dd, *J* = 7.0, 16.5 Hz, 1H), 2.68 (dd, *J* = 6.3, 16.5 Hz, 1H), 3.49−3.56 (m, 1H), 3.65 (s, 3H), 7.11−7.13 (m, 2H), 7.49−7.51 (m, 2H), 7.77 (br s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 18.1 (CH_3), 20.6 (CH_3), 38.0 (CH_2), 43.6 (CH), 51.6 (CH_3), 125.3 (CH), 127.9 (CH), 137.5 (C), 145.6 (C), 170.1 (C). HRMS (ESI$^+$), *m*/*z* 118.0859, calcd for $[C_5H_{11}NO_2 + H]^+$: 118.0863.

Dimer-like Byproduct ***9a***. ^{1}H NMR (200 MHz, $CDCl_3$): δ; 1.24 (d, *J* = 6.4 Hz, 3H), 1.96 (s, 3H), 2.40−2.60 (m, 2H), 3.61 (s, 3H), 3.69 (s, 3H), 3.90−4.07 (m, 1H), 4.42 (s, 1H), 8.56 (br d, 1H). MS (EI$^+$) *m*/*z* 215 ([M]$^+$).

General Procedure for the Asymmetric Hydrogenation of Methyl 3-Aminocrotonate (6a) (Table 1 and 2). To a 100-mL stainless steel autoclave equipped with a glass inner lining and a Teflon-coated stirring bar were added Ru catalyst (0.017 mmol) and methyl 3-aminocrotonate (**6a**) (400 mg, 3.5 mmol). The atmosphere was replaced with nitrogen gas, and this was followed by the addition of methanol (2 mL) and an acid (3.5 mmol). Hydrogen was initially introduced into the autoclave at a pressure of 1 MPa before being reduced to 0.1 MPa by carefully releasing the stop valve. After this procedure was repeated three times, hydrogen was introduced at 3 MPa and the solution was stirred at 80 °C for 7 h. The solution was cooled to 20 °C and hydrogen gas was then carefully vented. Assay yield and enantiomeric excess of **1a** were determined by GC analysis and HPLC analysis (see General Remarks).

General Procedure for the Asymmetric Reductive Amination of β-Keto Ester 2b−2f (Table 4). To a 100-mL stainless steel autoclave equipped with a glass inner lining and a Teflon-coated stirring bar were added $Ru(OAc)_2$[(*R*)-dm-segphos] (**Ru**−**I**, 4.7 mg, 0.005 mmol), β-keto ester **2** (2.5 mmol) and ammonium salicylate (0.778 g, 5.0 mmol). The atmosphere was replaced with nitrogen gas, and this was followed by the addition of methanol (2.5 mL). Hydrogen was initially introduced into the autoclave at a pressure of 1 MPa before being reduced to 0.1 MPa by carefully releasing the stop valve. After this procedure was

repeated three times, hydrogen was introduced at 3 MPa, and the solution was stirred at 85 °C for 7 h. The solution was cooled to 20 °C, and hydrogen gas was then carefully vented.

After evaporation of the solvent, 5% aq Na_2CO_3 (15 mL) and ethyl acetate (15 mL) were added to the residue, and the mixture was stirred for 30 min. The ethyl acetate layer was washed with water, dried over Na_2SO_4, and then evaporated. The residue was purified by silica gel chromatography, eluted with 97:3 ethyl acetate—triethylamine to give the pure free β-amino ester **1b**—**1f**.

*Methyl (3S)-3-amino-3-phenylpropanoate ((S)-**1b**)*:[16a] $[\alpha]_D^{21}$ −21.0 (*c* 1.12, $CHCl_3$) (lit. $[\alpha]_D$ −22.4 (*c* 1.8, $CHCl_3$), 96.1% ee (*S*)), 98% ee, HPLC conditions: column, CHIRALPAK AS-RH, 4.6 mm i.d. × 150 mm, 5 μm particles; eluent, 20 mM NH_4HCO_3 in H_2O/CH_3CN = 80:20; flow, 0.5 mL/min; column temperature, 30 °C; detection, 220 nm; t_R of (*S*)-**1b**, 10.9 min; t_R of (*R*)-**1b**, 9.3 min.

*Methyl (3S)-3-amino-3-(4-methoxyphenyl)propanoate ((S)-**1c**)*:[16a] $[\alpha]_D^{21}$ +1.9 (*c* 2.09, CH_3OH) (lit. $[\alpha]_D$ +3.08 (*c* 2.1, CH_3OH), 95.0% ee (*S*)), 98% ee, HPLC conditions: column, CHIRALPAK AS-RH, 4.6 mm i.d. × 150 mm, 5 μm particles; eluent, 20 mM NH_4HCO_3 in H_2O/CH_3CN = 80:20; flow, 0.5 mL/min; column temperature, 30 °C; detection, 220 nm; t_R of (*S*)-**1c**, 15.2 min; t_R of (*R*)-**1c**, 12.5 min.

*Methyl (3S)-3-amino-3-(4-fluorophenyl)propanoate ((S)-**1d**)*:[24] $[\alpha]_D^{21}$ −18.6 (*c* 1.00, $CHCl_3$) (lit. $[\alpha]_D^{20}$ +18.5 (*c* 1.0, $CHCl_3$), 99% ee (*R*)), 97% ee, HPLC conditions: column, CHIRALPAK AS-RH, 4.6 mm i.d. × 150 mm, 5 μm particles; eluent, 20 mM NH_4HCO_3 in H_2O/CH_3CN = 80:20; flow, 0.5 mL/min; column temperature, 30 °C; detection, 220 nm; t_R of (*S*)-**1d**, 14.5 min; t_R of (*R*)-**1d**, 12.0 min.

*Methyl (3S)-3-amino-3-(thiophen-2-yl)propanoate ((S)-**1e**)*. $[\alpha]_D^{21}$ −11.6 (*c* 0.99, $CHCl_3$), HCl salt: $[\alpha]_D^{21}$ negative (CH_3OH) (lit.[16d] for HCl salt: $[\alpha]_D^{20}$ −7.6 (*c* 1.0, CH_3OH), 95% ee (*S*)), 98% ee, HPLC conditions for the *p*-nitrobenzoylated derivative: column, SUMICHIRAL 4100R, 4.6 mm i.d. × 250 mm, 5 μm particles, hexane/2-propanol = 80:20; flow, 0.5 mL/min; column temperature, 30 °C; detection, 254 nm; t_R of the *p*-nitrobenzoylated (*S*)-**1e**, 16.2 min; t_R of the *p*-nitrobenzoylated (*R*)-**1e**, 13.9 min. ^1H NMR (500 MHz, $CDCl_3$) δ 2.72 (d, *J* = 9.1, 16.0 Hz, 1H), 2.81 (dd, *J* = 4.4, 16.0 Hz, 1H), 3.70 (s, 3H), 4.69—4.71 (m, 1H), 6.94—6.96 (m, 2H), 7.19—7.21 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 44.5 (CH_2), 48.6 (CH), 51.7 (CH_3), 123.0 (CH), 124.0 (CH), 126.7 (CH), 149.2 (C), 172.0 (C). HRMS (EI^+), *m*/*z* 186.0584, calcd for $[C_8H_{11}NO_2S + H]^+$: 186.0583.

*Methyl (3R)-3-amino-4-phenylbutyrate ((R)-**1f**)*:[16a] $[\alpha]_D^{21}$ −1.1 (*c* 1.13, CH_3OH) (lit. −1.85 (*c* 0.19, CH_3OH), 93.3% ee (*R*))., 97% ee, HPLC conditions: column, CHIRALPAK AS-RH, 4.6 mm i.d. × 150 mm, 5 μm particles, eluent, 20 mM NH_4HCO_3 in H_2O/CH_3CN = 85:15; flow, 0.5 mL/min; column temperature, 30 °C; detection, 220 nm; t_R of (*S*)-**1f**, 15.4 min; t_R of (*R*)-**1f**, 17.4 min.

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