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Asymmetric Synthesis of (*S*)-3-Amino-4-methoxy-butan-1-ol by Way of Reductive Amination

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ABSTRACT: A new synthesis of (*S*)-3-amino-4-methoxy-butan-1-ol is reported. The synthesis is based on the preparation of the primary, nonprotected enamine of the commercially available β-keto ester methyl 4-methoxy-3-oxo-butanoate and asymmetric catalytic enamine hydrogenation using a Ru-MeOBIPHEP catalyst. Alternatively, the process is performed by asymmetric catalytic reductive amination of the β-keto ester with ammonium acetate and hydrogen using a similar Ru catalyst. Both process versions provided initial ee values of 97−98% which were upgraded to ≥99% by product crystallization. Ester to alcohol conversion was best accomplished by $LiBH_4$ reduction after transitory Boc protection of the amino group.

1. INTRODUCTION

(*S*)-3-Amino-4-methoxy-butan-1-ol (**1**, Figure 1) was required in multigram quantities for a medicinal chemistry program. This β-amino alcohol, and *N*-protected derivatives thereof, served as useful starting materials for the preparation of diamines of type **2** by reductive alkylation at the amino group and reductive amination at the alcohol derived aldehyde function.

Precedent for the synthesis of **1** and derivatives thereof comprises their preparation from aspartic acid derivatives. Thus, starting from Z-Asp(O*t*-Bu)-OH, Cbz-protected **1** was prepared by a sequence of borane reduction, Ag_2O-mediated *O*-methylation, *tert*-butyl ester cleavage, and acid reduction via a mixed anhydride (Scheme 1).[1] In a related approach, starting from Boc-Asp(OBn)-OH, the *O*-methylation step was performed with trimethylsilyldiazomethane/BF_3.[2] The route starting from Z-Asp(O*t*-Bu)-OH proved difficult in our hands due to concurrent *N*-methylation in the *O*-methylation step leading to substantial formation of the *O*,*N*-dimethylation product, hence requiring chromatographic purification.

Concurrent *N*-methylation was also observed in an alternative route which started from L-homoserine benzyl ether (**7**) and which involved a sequence of borane reduction to amino alcohol **8**, Boc protection of the amino group, Ag_2O-mediated *O*-methylation, and final debocylation and debenzylation to provide the acetate salt of **1** (Scheme 2, **7** → **8** → **9** → **10** → **1**·**HOAc**). Therefore, in a further version, phthalimido protection of the amino function was chosen (Scheme 2, **8** → **11** → **12** → **10** → **1**·**HOAc**). *N*-methylation was thus prevented, but insufficient selectivity in these transformations resulted again in the necessity of chromatographic purification.

From a scale-up perspective these routes appeared problematic due not only to the required chromatographic purifications but also to the use of Ag_2O, which was deemed impractical for larger scale. Moreover, homoserine benzyl ether **7** could not be readily obtained in kilogram quantities within a reasonable time frame. Accordingly, synthetic approaches using other starting materials were considered.

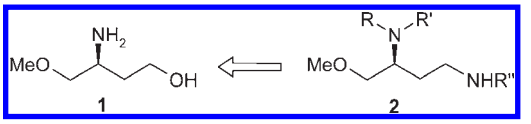
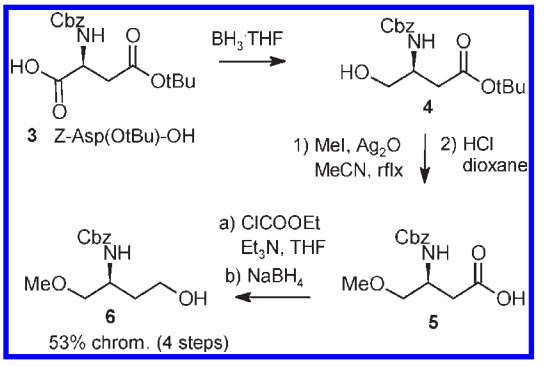


Figure 1. β-Amino alcohol **1**.

Scheme 1. Aspartic acid derivative as starting material



2. REDUCTIVE AMINATION-BASED SYNTHESIS

Rh- and Ru-catalyzed asymmetric hydrogenation of unprotected primary enamines derived from β-keto esters as well as Ru-catalyzed asymmetric reductive amination of β-keto esters recently has been reported for the preparation of β-amino acid derivatives.[3−5] A new synthesis of **1** therefore was envisioned to start from methyl 4-methoxyacetoacetate (**13**). This readily available β-keto ester incorporates already the methyl ether moiety, hence eliminating the need to establish this functionality at a later stage. Treatment of neat **13** with ammonia gas afforded the enamine **14** in high yield

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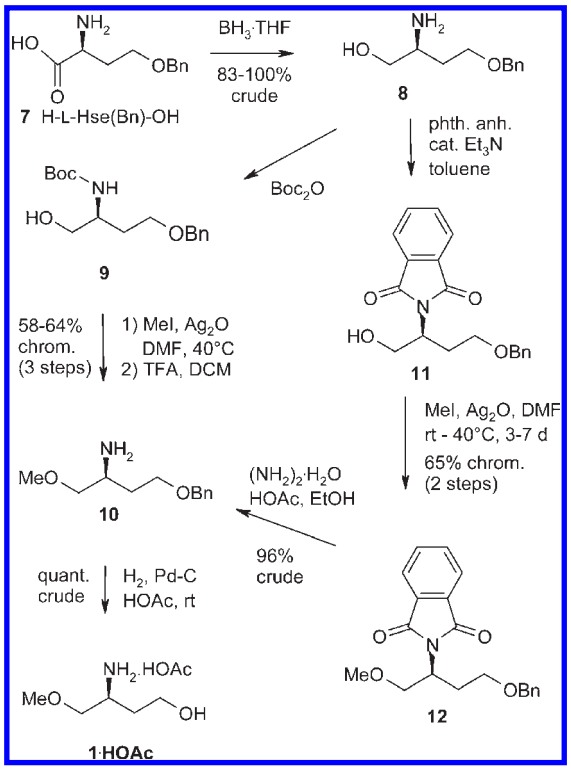
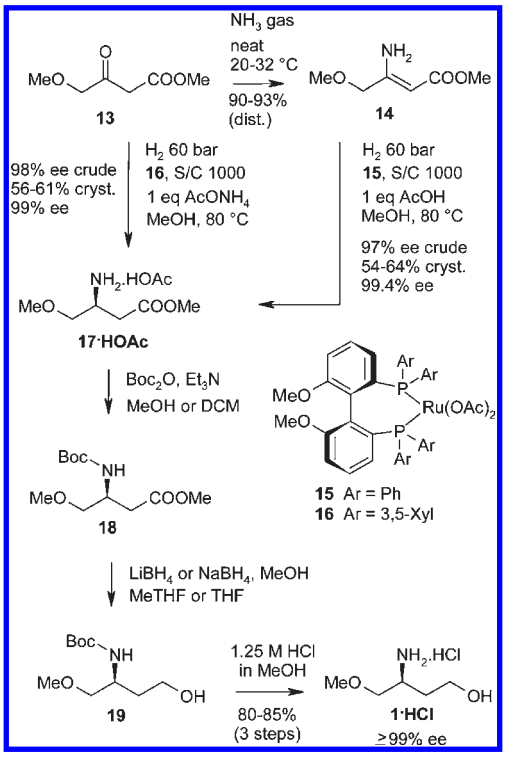
Scheme 2. L-Homoserine benzyl ether as starting material



Scheme 3. Asymmetric reductive amination-based synthesis



(90−93% after distillation) and high purity (GC >99%).[6] The enamine **14** consists of a single geometric isomer of *Z*-configuration based on ^{1}H NMR (NOE measurement). No evidence was found for the presence of the *E*-isomer (Scheme 3).

Asymmetric catalytic hydrogenation of **14** in the presence of 1 equiv of acetic acid (HOAc) using [Ru(OAc)$_2$((*R*)-MeOBIPHEP)] (**15**) as catalyst (MeOH, 60 bar, 80 °C, S/C 1000) produced crude amino ester acetate salt **17·HOAc** with high enantioselectivity (97% ee) and with a chemoselectivity of ∼85%. Crystallization from ethyl acetate/heptane provided the salt **17·HOAc** with 99.4% ee in 54−64% yield based on **14**. Alternatively, **17·HOAc** was obtained by asymmetric reductive amination of the β-keto ester **13**. Thus, hydrogenation of **13** in the presence of 1 equiv of ammonium acetate using [Ru(OAc)$_2$((*R*)-3,5-Xyl-MeOBIPHEP)] (**16**) as the catalyst (MeOH, 60 bar, 80 °C, S/C 1000) produced **17·HOAc**, again with high enantioselectivity (98% ee) and with a chemoselectivity of ∼85%. Crystallization provided pure **17·HOAc** of 99.0% ee in yields of 56−61% based on β-keto ester **13**. Hence, enamine isolation was rendered obsolete. Moreover, the yield of **17·HOAc** based on **13** was higher in the direct conversion by about 5%. It is assumed that in both process versions the primary imine of the keto ester is the reactive species undergoing hydrogenation.[3a,5b]

Conversion of amino ester acetate salt **17·HOAc** to the required amino alcohol **1** was achieved by Boc protection (Boc$_2$O, Et$_3$N, rt) in methanol or dichloromethane (DCM) to afford Boc-protected amino ester **18** followed by ester reduction with LiBH$_4$ (1.2 equiv, 2 equiv MeOH, THF, or 2-methyltetrahydrofuran, 0 °C to rt) to provide Boc-protected amino alcohol **19**. The reduction can also be performed with NaBH$_4$ under slightly forcing conditions (2.5 equiv NaBH$_4$, 5 equiv MeOH, THF, 40−45 °C) leading to somewhat lower yields. Final deprotection (HCl/MeOH) gave the amino alcohol hydrochloride **1·HCl** in 80−85% yield based on **17·HOAc** over three steps. The enantiomeric purity was fully conserved over these three steps. The overall yield of **1·HCl** based on β-keto ester **13** amounted to ∼40% (via enamine **14** over five steps) or to ∼45% over four steps via direct reductive amination. Assignment of absolute configuration was established by correlation with a sample of **1** previously prepared from **7**, hence also confirming the expected sense of asymmetric induction in the catalytic reduction processes.[4,5]

3. COMMENTS TO INDIVIDUAL STEPS

3.1. Enamine Formation. The primary enamine **14** was best prepared by passing gaseous ammonia through neat β-keto ester **13**. The reaction is slightly exothermic. Conversions >99% were readily achieved after 5−6 h. GC−MS analysis of the crude reaction product indicated the presence of the enamine amide byproduct **20** (Figure 2), which is slowly formed in 1−2% in a secondary reaction. Being partially water-soluble and less volatile, **20** was readily removed during workup and distillation. Likewise the enamine "dimer" **21**, also being slowly formed in a secondary reaction in up to 0.5%, is removed in the distillation. The enamine **14** was also prepared by treatment of **13** with ammonium formate in methanol under reflux[4] or with NH$_3$ gas in methanol at rt,[7] but partial hydrolysis back to **13** occurred during workup.[8] Scale-up of the enamine formation proceeded straightforwardly to the 1-kg scale. Distilled materials were obtained in yields of 90−93% with excellent GC purity (>99%). Ammonia consumption was reduced from ∼4 equiv in lab-scale reactions to ∼2 equiv by employing cooling and slower ammonia feeding rates at the kilogram scale.

3.2. Asymmetric Enamine Reduction. The investigation of the asymmetric hydrogenation of **14** focused on [Ru(OAc)$_2$-(bisphosphine)] catalysts containing Roche proprietary MeO-BIPHEP-type ligands.[9,10] The hydrogenations were performed

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Table 1. [Ru(OAc)$_2$(bisphosphine)]-catalyzed asymmetric hydrogenation of 14 in methanol[a]

no.	bisphosphine	conv. %	17[b] %	ee %
1	(*R*)-MeOBIPHEP	>99	89	97.2
2	(*R*)-*p*-Tol-MeOBIPHEP	>99	89	97.2
3	(*R*)-3,5-Xyl-MeOBIPHEP	>99	89	97.0
4	(*R*)-3,5-*i*-Pr-MeOBIPHEP	99	90	96.2
5	(*R*)-3,5-*t*-Bu-MeOBIPHEP	66	33	80

[a] Reagents and conditions: MeOH, S/C 1000, 60 bar H_2, 1 equiv HOAc, 80 °C, 22 h, 5-g scale. [b]GC area %.

in methanol at 80 °C and 60 bar hydrogen pressure at S/C ratios of 1000. The most pertinent results are given in Table 1. Catalysts containing MeOBIPHEP and sterically moderately demanding MeOBIPHEP ligands such as (*R*)-*p*-Tol-MeOBIPHEP or (*R*)-3,5-Xyl-MeOBIPHEP performed well, providing ee values of 97%. They were more active and more enantioselective than catalysts containing bulky bisphosphines such as (*R*)-3,5-*i*-Pr-MeOBIPHEP and (*R*)-3,5-*t*-Bu-MeOBIPHEP. The latter ligand in particular led to a substantial drop in activity and enantioselectivity.

The chemical selectivity of the hydrogenations was in the order of 85−90%. Major byproducts, as proposed by GC−MS analysis, were **22** (∼4%), **23** (∼0.5%), and **24** (∼5%) (Figure 2), indicating deamination as well as dimerization was occurring under the hydrogenation conditions. The use of 1 equiv of HOAc was crucial for a high catalyst performance. In the absence of HOAc almost no conversion was observed. Hydrochloric, trifluoroacetic, *p*-toluenesulfonic, and methanesulfonic acids led to very poor chemoselectivity (5−20%). The use of HOAc was also beneficial because the acetate salt of **17** formed in the reaction could easily be isolated by distillation from the dark-brown reaction residue to afford the white crystalline salt **17·HOAc** in up to 78% yield. The distillation process, however, proved nonscalable because of the limited thermal stability of **17·HOAc**.[11] Therefore, crude **17·HOAc** was finally purified by crystallization from ethyl acetate/heptane yielding crystalline **17·HOAc**.[12] A single crystallization allowed for enantiomeric purity enhancement of the product to ≥99% ee, albeit with some loss of yield. An investigation towards lower catalyst loading showed that at S/C 2000 either the reaction time (1 → 3 days) or the reaction temperature (80 → 100 °C) had to be increased to achieve complete conversion. Thereby, the product formed was exposed longer to thermal stress which led to a lower yield. Eventually, reaction conditions using a S/C ratio of 1000 were chosen. Under the optimized conditions (catalyst **15**, S/C 1000, 60 bar H_2, 1 equiv of HOAc, MeOH, 80 °C, 24 h) the hydrogenation of **14** was successfully performed at the 100-g scale to yield **17·HOAc** in 54−64% yield and with an ee of 99.4% after crystallization.

3.3. Asymmetric Reductive Amination. Results of the screening of reductive aminations of **13** with various Ru bisphosphine complexes are shown in Table 2.[10] The screening was performed in 2,2,2-trifluoroethanol (TFE) in the presence of 2.5 equiv NH_4OAc as ammonia source at S/C 100, 60 bar H_2 and 80 °C, conditions similar to reported ones.[5b] Conversions were >99% in all experiments. The selectivity for **17** varied from 30 to 88%. Alcohol **25** was formed as the major byproduct due to the competitive hydrogenation of the keto group. In addition, the same set of byproducts (**22**, **23**, **24**) was formed as already observed in the enamine hydrogenation. Ru catalysts derived

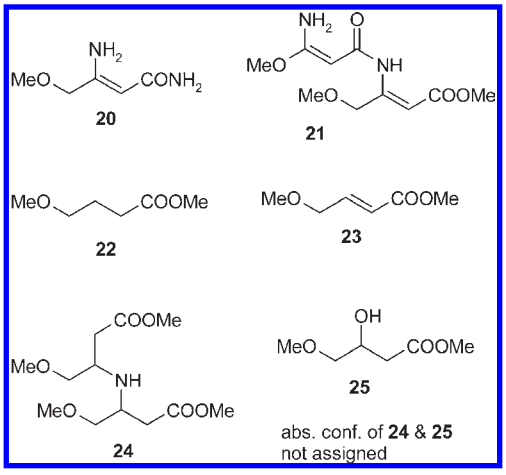

Figure 2. Byproducts.

Table 2. [Ru(OAc)$_2$(bisphosphine)]-catalyzed reductive amination of 13 in TFE[a]

no.	bisphosphine	25[b] %	17[b] %	ee %
1	(*R*)-TMBTP	21	68	92
2	(*R*)-MeOBIPHEP	16	81	90
3	(*R*)-SEGPHOS	6	76	90
4	(*R,S*)-NMe$_2$-PR$_2$-Mandyphos[c]	1	74	90
5	(*R*)-BIBFUP	4	71	90
6	(*R,S*)-PPF-P*t*-Bu$_2$[d]	24	60	88
7	(*R*)-3,5-Xyl-MeOBIPHEP	23	66	84
8	(*R*)-3,5-*t*-Bu-MeOBIPHEP	4		76
9	(*R,R*)-Ph$_2$PPhFcCHMePXyl$_2$[d]	–	34	54
10	(*R*)-[2,2]-PHANEPHOS	–	13	54
11	(*S,S,S*)-BICP[e]	–	9	6
12	(*R,R*)-NORPHOS	–	5	6
13	(*S,S*)-SKEWPHOS	–	9	4

[a] Conditions: TFE, S/C 100, 60 bar H_2, 2.5 equiv NH_4OAc, 80 °C, 22 h, 250-mg scale; conversion >99%. [b]GC area %. [c] R = 3,5-Me-4-MeO-C_6H_2; [Ru(2H$^+$-bisphosphine)(NCMe)(η^5-2,4-dimethylpentadienyl)]-[BF_4]$_3$ used as catalyst. [d] [Ru(bisphosphine)(NCMe)(η^5-2,4-dimethylpentadienyl)]BF_4 used as catalyst. [e] (1*S*,1′S,2S,2′S)-2,2′-Bis-(diphenylphosphino)-1,1′-bicyclopentyl.

from the atropisomeric parent bisphosphines TMBTP, MeOBIPHEP, SEGPHOS, and BIBFUP performed best in terms of the enantioselectivity providing ee values of 90−92%, as did a catalyst derived from a (*R,S*)-Mandyphos ligand. Catalysts derived from sterically hindered MeOBIPHEP ligands performed with slightly lower enantioselectivity.

A remarkable improvement of the enantioselectivity as well as of the chemical selectivity was achieved with these catalysts when the reaction was run in methanol rather than in TFE (Table 3). Among the catalysts tested, [Ru(OAc)$_2$((*R*)-3,5-Xyl-MeOBIPHEP)] (**16**), i.e. a catalyst derived from a sterically moderately demanding bisphosphine, performed now best, yielding at S/C 250 **17·HOAc** with 98.0% ee and with high 97% chemoselectivity.

Progressing development work with **16** as catalyst revealed that the amount of NH_4OAc could be reduced from 2.5 to 1 equiv without affecting chemical selectivity and yield but that at lower catalyst loading (S/C 1000) the chemical selectivity started to decrease (88−90%). The extended reaction times required due to

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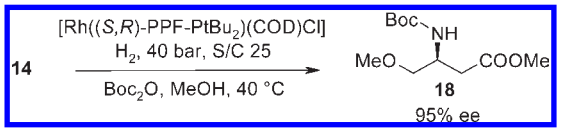
Table 3. [Ru(OAc)$_2$(bisphosphine)]-catalyzed reductive amination of 13 in methanol[a]

no.	bisphosphine	14[b] %	17[b] %	ee %
1	(*R*)-3,5-Xyl-MeOBIPHEP	–	97	98.0
2	(*R*)-MeOBIPHEP	5	86	97.0
3	(*R*)-DM-SEGPHOS	3	94	96.6
4	(*R*)-SEGPHOS	–	96	94.6
5	(*R*,*S*)-NMe$_2$-PR$_2$-Mandyphos[c]	5	91	95.2
6	(*R*)-3,5-*t*-Bu-MeOBIPHEP	3	95	75.2

[a] MeOH, S/C 250, 60 bar H_2, 2.5 equiv NH_4OAc, 80 °C, 22 h, 500-mg scale; [b] GC area %. [c] R = 3,5-Me-4-MeO-C$_6$H$_2$; [Ru(2H$^+$-bisphosphine)-(NCMe)(η^5-2,4-dimethylpentadienyl)][BF$_4$]$_3$ used as catalyst.

Scheme 4. Asymmetric hydrogenation of enamine 14 with in situ product Boc protection



the reduced catalyst loading led again to increased formation of byproducts, as already observed in the asymmetric hydrogenation of **14**. Under technically feasible reaction conditions (catalyst **16**, S/C 1000, 60 bar H_2, 1 equiv of NH_4OAc, MeOH, 80 °C, 22 h), an ee of 97.8% was achieved, and after crystallization, **17·HOAc** of 99.0% ee was isolated in 56−61% yield.[12] The process as far as examined is considered robust and scalable. Nevertheless, identification of catalysts and/or conditions leading to improved chemoselectivity as well as elaboration of improved product crystallization conditions would be desirable.

3.4. Asymmetric Enamine Reduction with in Situ Product Boc Protection. As a shorter, one-pot process from enamine **14** to Boc-amino ester **18**, the [Rh((*S*,*R*)-PPF-P*t*-Bu$_2$)(COD)Cl]-catalyzed enamine hydrogenation in the presence of di-*tert*-butyl dicarbonate was briefly examined (Scheme 4).[13] At a S/C ratio of 25 and in the presence of 1 equiv of Boc$_2$O in methanol at 40 °C and 40 bar H_2, **18** was obtained with 90% chemoselectivity and with 95% ee. However, the moderate catalyst activity (98% conversion at S/C 25) was considered to be too low to warrant further development of this approach.

3.5. Ester to Alcohol Conversion. In principle, direct conversion of the amino ester salt **17·HOAc** to the amino alcohol **1** should be possible. Preliminary experiments showed that $LiAlH_4$ reduction indeed worked, but they also indicated that substantial investment into the development of a suitable workup and isolation protocol for the highly water-soluble product would have had to be performed. In the interest of a rapid development of a scalable process, and due to project time constraints, protection of the amino group therefore was envisioned, and Boc-, Cbz- and dibenzyl protection were explored. Boc protection eventually was selected because it provided the best results.

Reduction of the Boc-amino ester **18** was most favorably performed with $LiBH_4$ in the presence of methanol as activating agent.[14] In the optimized protocol, the reaction was run in THF or 2-methyltetrahydrofuran at 0 °C to rt with 1.2−1.3 equiv of $LiBH_4$ and with addition of 2 equiv of methanol over a period of 1 h. Quantitative conversion and high selectivity were obtained in this way, and the exothermic reaction was easily controlled. The yields of Boc-amino alcohol **19** were quantitative for crude material and 92−97% after filtration over silica gel.

The reduction with $NaBH_4$ was slower and proved slightly inferior in terms of yield.[15] Under optimized conditions (suspension of 2.5 equiv $NaBH_4$ in THF, 5 equiv of methanol added at 40−45 °C over 1 h), a 90% yield was achieved after filtration over silica gel. The elevated reaction temperature was chosen in order to avoid accumulation of reactive hydride species formed from $NaBH_4$ and methanol and hence to reduce the potential for runaway reactions under the heterogeneous conditions. At the same time foaming due to gas evolution was readily controlled. It is also important to note that the Ru content of the substrate **18** may have an influence on the required hydride equivalents.[16] Although Ru contents have not been determined systematically, it is safe to note that Ru contents ≤20 ppm had no influence on the hydride reductions. A silica gel filtration of crude substrate **18** proved necessary in case the Ru content in the hydrogenation product **17·HOAc** was high.

4. CONCLUSION

A new synthesis of (*S*)-3-amino-4-methoxy-butan-1-ol (**1**) starting from β-keto ester **13** has been found and developed. It provides **1·HCl** with ≥99% ee in 40% overall yield via enamine **14** over five steps and in 45% overall yield over four steps by reductive amination. Ru-MeOBIPHEP catalysts proved efficient in introducing the stereogenic center, either by enamine reduction or by reductive amination. An attractive feature of the new process is that there is no need to perform an *O*-methylation reaction. Areas for improvement in the catalytic processes are the currently still unsatisfactory chemoselectivity of ∼85% and the product crystallization protocol for **17·HOAc**.

5. EXPERIMENTAL SECTION

5.1. General Remarks. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Reactions generally were carried out under argon atmosphere. Gas chromatography (GC, area %) was performed on Agilent 6890 instruments using fused silica capillary columns (25−30 m × 0.32 mm, 0.25 μm) with hydrogen or helium as carrier gas. Enantiomeric purity determinations were performed by GC analyses on chirally supported columns: BGB-176-SE (BGB Analytics, fused silica, 30 m × 0.25 mm, 25 μm) for **17** and **18**, Lipodex-E (Macherey Nagel, 25 m × 0.25 mm, 25 μm) for **19** and BGB-172 (BGB Analytics, 30 m × 0.25 mm, 25 μm) for **1**. ^{1}H NMR spectra were recorded using tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ) and coupling constants (J) are reported in hertz (Hz). Mass spectra were obtained as electron impact spectra at an ionization voltage of 70 eV (EI-MS) or by positive or negative ion spray ionization (ESI-MS). Data are reported in the form of m/z (intensity relative to base =100). Gases used in the hydrogenations were of following qualities: hydrogen (99.99990%, <0.1 ppm O_2), argon (99.99990%, <0.1 ppm O_2). Methanol used in the hydrogenations was distilled under argon. The Ru catalysts **15** and **16** were prepared according to reported procedures.[17]

5.2. (*Z*)-3-Amino-4-methoxy-but-2-enoic Acid Methyl Ester (14). A 2.5-L jacketed glass reactor was charged with methyl

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4-methoxyacetoacetate (**13**, 893 g, 6.11 mol) and a gentle stream of ammonia gas (99.99%) was introduced under the surface of the liquid at 25 °C (jacket temperature T_j 25 °C). The feeding rate was increased stepwise allowing for a temperature increase to 30 °C after 1.5 h and to 34 °C after 2.5 h. The temperature fell to 29 °C after 4 h total addition time. Ammonia addition was stopped after 5 h when the reaction temperature reached 25 °C. A total of 200 g of ammonia gas (11.74 mol, 1.92 equiv) was consumed. Argon was passed through the orange, turbid mixture for 1 h which then was transferred to an extraction vessel using methyl *tert*-butyl ether (MTBE, 1.60 L) and 20% aq sodium chloride solution (300 mL). The phases were separated and the aq phase was back-extracted with MTBE (500 mL). The combined organic phases were dried over sodium sulfate (300 g) and filtered, and the filter cake was washed with MTBE (500 mL). The combined pale-yellow organic phases were evaporated, and the residue was dried (50 °C/≥10 mbar, 1 h) to yield crude **14** (851 g, 96%; GC 99.8%) as yellow liquid. Distillation (10 cm Vigreux column, oil bath temperature ≤100 °C) afforded enamine **14** (828.2 g, 93%) as colorless liquid, bp 64−67 °C/0.2−0.1 mbar; GC 99.9%. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.36 (s, 3H, CH_3O), 3.66 (s, 3H, CO_2CH_3), 3.97 (s, 2H, OCH_2), 4.55 (s, 1H, =C*H*−)), ∼5.3 (very br, 1H, N*H*), ∼7.8 (very br, 1H, N*H*). EI-MS: 145 ($M^{\bullet+}$, 41), 113 ($[M - CH_3OH]^{\bullet+}$, 100), 98 (77), 82 (44), 68 (34).

5.3. (*S*)-2-Methoxy-1-methoxycarbonylmethyl-ethyl-ammonium Acetate (17·HOAc) . 5.3.1. By Enamine Hydrogenation. A 500-mL catalyst addition device was charged in the glovebox with a yellowish solution of 2.99 g [$Ru(OAc)_2$((*R*)-MeOBIPHEP)] (**15**, 3.72 mmol) in methanol (400 mL). The device was pressurized with 6 bar of argon and connected to a 12-L autoclave. The autoclave was charged with enamine **14** (540.7 g, 3.725 mol), methanol (6.60 L), and acetic acid (214 mL, 3.725 mol) and then was sealed and rendered inert under stirring (400 rpm, four cycles of pressurizing with 7−8 bar of argon and evacuation to 1−2 bar). The catalyst solution was introduced from the addition device into the autoclave. The autoclave was connected to a hydrogen line, which was thoroughly flushed with hydrogen. To remove residual argon and oxygen, the autoclave was pressurized with 18−20 bar of hydrogen, and the pressure was reduced to 2−3 bar (6 cycles). Then the hydrogen pressure was set to 60 bar and the heating started. After 1 h the reaction temperature of 80 °C was reached, whereas the pressure slightly increased to 62 bar. During the course of the hydrogenation, the pressure decreased slowly to the set 60 bar. A conversion of 96.2% was reached after 22 h. After a total reaction time of 25 h the autoclave was cooled and vented, and the brownish reaction solution was transferred with methanol (1.0 L) to a 20-L round-bottomed flask. The mixture was evaporated and dried to constant weight (35 °C, ≥10 mbar) to yield 760 g (98.5% by weight) of a red-brown oil which solidified upon storing at 4 °C; GC 87.5%, >99.9% conversion; ee 97.2%. In an analogous experiment starting from enamine **14** (100 g, 0.689 mol) 254 g of crude material was isolated as red-brown oil; GC 88.7%, ee 97.2%. The combined crude materials were dissolved in ethyl acetate (3.80 L), and the solution was treated with 30 g Norit SA II on the rotary evaporator (40 °C/1 h). The suspension was filtered (glass fiber paper overlaid with Hyflo filter aid), and the filter cake was washed with ethyl acetate (0.50 L). The light-brown filtrate was evaporated and dried (40 °C/≥100 mbar). The oily residue was dissolved in ethyl acetate (3.80 L) and the solution transferred to a 10-L jacketed glass reactor. Crystallization started upon cooling (T_j 0 °C), resulting in the formation of a voluminous pulp. Heptane (1.0 L) was added within 30 min, and the suspension was stirred at T_j 10 °C overnight and finally at T_j 0 °C for 2 h. The crystals were collected by suction filtration, washed with several portions of ethyl acetate (total 1.0 L) and heptane (total 1.0 L), and dried (40 °C/20 mbar) to provide 548.1 g (60% by weight) of **17·HOAc** as white crystalline powder which, by ^{1}H NMR analysis, contained ∼0.3 equiv HOAc corresponding to ∼8 wt % of HOAc; corrected yield: 55% **17·HOAc**. GC 99.7%; ee 99.4%; Ru content 20 ppm. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.04 (s, ∼3.8H, $CH_3CO_2^-$), 2.48 and 2.54 (*ABX*, J_{AB} = 16.5 Hz, J_{AX} = 8.2 Hz, J_{BX} = 4.8 Hz, 1H each, CH_2CO_2), 3.34 and 3.40 (*ABC*, J_{AB} = 9.3 Hz, J_{AC} = 6.8 Hz, J_{BC} = 4.3 Hz, 1H each, OCH_2), 3.37 (s, 3H, CH_3O), 3.48 (m, 1H, C*H*N), 3.70 (s, 3H, CO_2CH_3), 5.37 (s br, ∼4H, H_3N^+ and H_2O). ESI-MS: calcd for $C_6H_{13}NO_3$ 147.0898; found 170.0788 $(M + Na)^+$, 148.0971 $(M + H)^+$.

5.3.2. By Reductive Amination. A 150-mL catalyst addition device was charged in the glovebox with a yellowish solution of [$Ru(OAc)_2$((*R*)-3,5-Xyl-MeOBIPHEP)] (**16**, 313 mg, 0.342 mmol) in methanol (100 mL). The device was pressurized with 6 bar of argon and connected to the 2-L autoclave. The 2-L autoclave was charged with β-keto ester **13** (50.0 g, 0.342 mol), ammonium acetate (26.9 g, 0.342 mol), and methanol (1.10 L). The autoclave was sealed and rendered inert under stirring (500 rpm, four cycles of pressurizing with 7−8 bar of argon and evacuation to 1−2 bar). The catalyst solution was introduced from the addition device into the autoclave. The autoclave was connected to a hydrogen line, which was thoroughly flushed with hydrogen. The hydrogen pressure was set to 60 bar and the heating started. After 45 min the reaction temperature of 80 °C was reached, whereas the pressure slightly increased to 64 bar. During the course of the hydrogenation, the pressure decreased slowly to the set 60 bar. A conversion of >99.8% was reached after 21 h. After a total reaction time of 22 h, the autoclave was cooled and vented, and the brownish reaction solution was transferred with methanol (200 mL) to a 2-L round-bottomed flask. The reaction mixture was evaporated and dried to constant weight (35 °C/≥10 mbar) to yield 72.7 g (91.4% by weight) of brownish oil; GC 89.4%; ee 97.8%. In an analogous experiment starting from **13** (50 g, 0.342 mol) 71.8 g of crude material was isolated; GC 88.2%; ee 97.8%. The combined crude residues were dissolved in ethyl acetate (600 mL) and the solution was treated with activated charcoal (10 g) on the rotary evaporator (50 °C/1 h). The suspension was filtered (glass fiber paper overlaid with 100 g of dicalite speed and diatomaceous filter-aid) and the filter cake was washed with ethyl acetate (600 mL). The light brown filtrate was evaporated and dried (40 °C/≥100 mbar). The oily residue was dissolved in ethyl acetate (800 mL). The mixture was cooled whereby crystallization spontaneously started at 0−5 °C. The white slurry was stirred at 0−5 °C for 1 h, then heptane (800 mL) was added within 30 min and the suspension stirred at 0−5 °C for another 1 h. The crystals were collected by suction filtration, washed with several portions of an ice-cold mixture of ethyl acetate (200 mL) and heptane (200 mL), and dried (25 °C, ≥0.5 mbar) to provide 95.5 g (67% by weight) of **17·HOAc** as white crystalline powder which, by ^{1}H NMR analysis, contained ∼0.33 mol equiv HOAc corresponding to ∼9 wt %; corrected yield: 61% **17·HOAc**. GC 98.9%; ee 99.0%; Ru content 96 ppm. Anal. Calcd for $C_8H_{17}NO_5 \cdot (C_2H_4O_2)_{0.33}$ (227.05): C 43.75, H 8.13, N 6.20, O 39.95; found C 44.21, H 7.97, N 6.22, O 41.95.

5.4. (*S*)-4-Methoxy-3-amino-butyric Acid Methyl Ester (17). A 2-L separation funnel was charged with **17·HOAc** (20 g, containing ∼0.1 mol equiv of HOAc and 8.1 wt % H_2O, corresponding to ∼89% purity, ∼86 mmol), DCM (500 mL) and 2 M

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$KHCO_3$ (150 mL). The layers were mixed, separated and the organic layer was washed with 2 M $KHCO_3$ (150 mL). To the combined aqueous layers, sodium chloride (300 g) and DCM (500 mL) was added, the layers were mixed, separated and the aqueous layer was extracted with DCM (500 mL). All the organic layers were combined, dried over sodium sulfate, filtered, evaporated and dried (40 °C/≤10 mbar/1 h) to yield 9.5 g (75%) of crude amino ester **17** as a light yellow oil; GC 99.9%. A sample of crude **17** (2.3 g) was purified by distillation (75 °C/2−4 mbar) to yield 2.1 g (89%) of pure **17** as colorless oil; GC 100%; ee 99.5%; $[\alpha]^{20}_D = -10.1$ (1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.65 (s very br, ∼3H, NH_2 and H_2O), 2.34 and 2.49 (*ABX*, J_{AB} = 16.1 Hz, J_{AX} = 8.7 Hz, J_{BX} = 4.3 Hz, 1H each, CH_2CO_2), 3.27 and 3.34 (*ABC*, J_{AB} = 9.1 Hz, J_{AC} = 6.9 Hz, J_{BC} = 4.6 Hz, 1H each, OCH_2), 3.37 (s, 3H, CH_3O), 3.42 (m, 1H, *CH*N), 3.70 (s, 3H, CO_2CH_3). ESI-MS: calcd for $C_6H_{13}NO_3$ 147.0896; found 148.0969 $(M + H)^+$.

5.5. (*S*)-3-*tert*-Butoxycarbonylamino-4-methoxy-butyric Acid Methyl Ester (18). A 2-L flask was charged with **17**·**HOAc** (100 g, containing ∼0.3 mol equiv of HOAc, ∼444 mmol) and DCM (533 mL). The solution was cooled to 5 °C and triethylamine (77.8 mL, 99.5%, 555 mmol) was added resulting in the formation of a yellowish, slightly turbid solution. A solution of di-*tert*-butyl dicarbonate (117.0 g, 99%, 531 mmol) in DCM (200 mL) was added at 5−10 °C within 20 min. The reaction was slightly exothermic and gas evolution occurred. The reaction mixture was stirred at rt for 2 h. GC analysis indicated complete conversion. 4-Dimethylamino-pyridine (1.15 g, 98%, 9.2 mmol) was added, resulting in strong gas evolution, and the mixture was stirred at rt for 1 h and then quenched with sat. sodium hydrogen carbonate solution (160 mL). The phases were separated, and the organic phase was washed with sat. sodium hydrogen carbonate solution (160 mL) and 0.1 N hydrochloric acid (330 mL), dried over sodium sulfate, filtered, evaporated, and dried to provide 117.9 g of a light-yellow oil. The material was dissolved in heptane/ethyl acetate 2:1 (50 mL) and filtered over silica gel (200 g) using heptane/ethyl acetate 2:1 (2.0 L). Evaporation (45 °C/≥15 mbar/2 h) provided 99.32 g (90% by weight) of Boc-amino ester **18** as colorless oil; GC 98.4%. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.44 (s, 9H, $C(CH_3)_3$), 2.60 (m, 2H, CH_2CO_2), 3.34 (s, 3H, CH_3O), 3.45 (m, 2H, OCH_2), 3.68 (s, 3H, CO_2CH_3), 4.11 (m br, 1H, *CH*N), 4.76 and 5.12 (m br, 0.15 and 0.85H, *NH*, rotamers). ESI-MS: calcd for $C_{11}H_{21}NO_5$ 247.14211; found 270.1313 $(M + Na)^+$, 248.1492 $(M + H)^+$.

5.6. (*S*)-3-Hydroxy-1-methoxymethyl-propyl)carbamic Acid *tert*-Butyl Ester (19). To a solution of **18** (92.0 g, 372 mmol) in 2-methyltetrahydrofuran (850 mL) was added at rt lithium borohydride (227 mL 2 M solution in THF, 435.8 mmol, 1.22 equiv). Methanol (30 mL, 748 mmol, 2.0 equiv) was added dropwise to the clear solution within 40 min (exothermic). During the addition the temperature was held in the range of 20−24 °C by occasional cooling. GC analysis after 1.5 h reaction time indicated complete conversion. The reaction mixture was stirred for an additional 1.5 h, then quenched by addition within 5 min of acetone (102 mL, *exothermic*!) followed by addition within 10 min of 2 N NaOH (900 mL). The mixture was stirred for 30 min, and the clear phases were separated. The aq phase was extracted with MTBE (2 × 350 mL). The combined organic phases were washed with sat. sodium chloride solution (2 × 290 mL), dried over sodium sulfate, filtered, evaporated, and dried to constant weight (45 °C/10 mbar) to yield 71.67 g (88% by weight) of **19** as colorless oil; GC 98.65%. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.45 (s, ∼10H, $C(CH_3)_3$ and *OH*), 1.63 (m, 1H), 1.76 (m, 1H), 3.36 (s, 3H, CH_3O), 3.40 and 3.49 (*ABC*, J_{AB} = 9.2 Hz, J_{AC} = 3.5 Hz, J_{BC} = 4.0 Hz, 1H each, CH_3OCH_2), 3.53 (m, 1H), 3.60 (m, 1H), 3.67 (m, 1H), 3.94 (m, 1H, *CH*N), 4.97 (d br, J ∼8 Hz, 1H, *NH*). ESI-MS: calcd for $C_{10}H_{21}NO_4$ 219.1475; found 242.1368 $(M + Na)^+$, 220.1551 $(M + H)^+$, 164.0922 $[(M + H) - C_4H_8]^+$.

5.7. (*S*)-3-Hydroxy-1-methoxymethyl-propyl-ammonium Chloride (1·HCl). A solution of **19** (23.87 g, 108.9 mmol) in 1.25 M hydrochloric acid in methanol (235 mL, 294 mmol) was stirred at rt for 5 h. A continuous, slow gas evolution was observed. The clear solution was further stirred at rt overnight. Evaporation and drying (20 °C/0.01 mbar/33 h) afforded 17.89 g (105% by weight) of hydrochloride **1**·**HCl** as glassy oil; GC 96.7%; ee 99.4%; residual solvents 2.5 wt % methanol, 1.2 wt % water (Karl Fischer); corrected yield: 98% **1**·**HCl**. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.84 (m, 1H), 2.08 (m, 1H), ∼2.6 (very br, ∼2H, *OH* and ∼0.5 equiv H_2O), 3.43 (s, 3H, CH_3O), 3.49 (s, ∼0.8H, ∼0.25 equiv CH_3OH), 3.63 (∼dd, J = 9.8 and 4.3 Hz, 1H), 3.68 (m, 1H), 3.72 (m br, 1H, *CH*N), 3.84 (m, 1H), 3.97 (m, 1H). Anal. Calcd for $C_5H_{14}ClNO_2$ (155.62): C 38.59, H 9.07, Cl 22.78, N 9.00; found C 37.88, H 8.98, Cl total 21.93; N 8.89; H_2O 1.55 wt % (Karl Fischer).

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