DOI: 10.1002/ejoc.200700345

Selective Synthesis of Unnatural α-, β- and γ-Amino Esters

Thomas C. Nugent*[a] and Abhijit K. Ghosh[a]

Keywords: Asymmetric reductive amination / Amino esters / Heterogeneous hydrogenation

Reductive amination of keto esters **1** with α-methylbenzylamine (α-MBA) in the presence of hydrogen and Raney-Ni allows direct access to diastereomeric amino esters **2** in good to high *de* (72–94 %). For the α-keto ester **1d** and the β-keto esters **1a**, **1b** and **1c** the reaction is optimally performed in the presence of AcOH, while the γ-keto ester **1h** requires $Ti(OiPr)_4$. The reductive amination product of **1d** is an advanced homophenylalanine building block for Angiotensin Converting Enzyme (ACE) inhibitor drugs. The reductive amination product of **1h** is converted in two additional steps to a protected chiral 2-methylpyrrolidine **4h**, which is an advanced amine intermediate for pharmaceutical drugs, e.g. ABT-239. The strategy presented here obviates the need for preforming enamine or imine intermediates for amino ester synthesis.

Introduction

Natural and unnatural amino acids are indispensable for pharmaceutical drug development and receptor research, the latter being exemplified by the unprecedented access to new protein targets through advances in proteomics research. Novel α- and β-amino acids are particularly useful for designing peptides with controlled conformation and thus targeted function, e.g. enhanced enzymatic stability.[1] Furthermore, the incorporation of unnatural amino acids into pharmaceutical drug products is well established. For example (*S*)-homophenylalanine is a key building block for no less than 10 unique drugs that are classified as ACE inhibitors, of which Lisinopril is a multibillion-dollar (per year) example.[2]

Because of the wide application potential of α- and β-amino acids, innumerable methodologies for their synthesis, and the corresponding ester derivatives, have been described.[3] Regarding α-amino acids, a noteworthy example is the reductive amination of α-keto acids using cationic Rh(deguphos) catalysts in exceptional overall yield and *ee*.[4] Another example is the preparation of homophenylalanine derivatives starting from acetophenone and diethyl oxalate.[2b] Unnatural α-amino acids have also been prepared in enantiopure form utilizing palladium-catalyzed Suzuki cross-coupling reactions.[5] Versatile methodologies are also available for the asymmetric synthesis of β-amino acids. Among them the Arndt–Eistert homologations of α-amino acids,[3a] the 1,4-addition of homochiral lithium amides to α-,β-unsaturated esters,[6] and the highly diastereoselective addition of enolates to *tert*-butylsulfinylimines stand out as very useful.[7] Additionally, access to amino acids through enzymatic pathways are in use by industry and actively pursued by academic researchers.[8]

The industrial preoccupation with generating stereocenters by catalytic enantioselective hydrogenation is well justified based on the afforded atom economy,[9] and this methodology has been extensively examined for the synthesis of both α-[10] and β-[11]amino acids as championed by Burke, Zhang, and Boaz. In this regard, very high enantioselectivity has been obtained when reducing *N*-acetyl-protected dehydro-α- or -β-amino acid derivatives in the presence of Ru or Rh homogeneous chiral hydrogenation catalysts;[12] but the precursor syntheses are lengthy and the chiral ligands must be optimized on a case-by-case basis. Hsiao et al. have begun to seriously address the Achilles heel of lengthy *N*-acetyl-dehydroamino acid synthesis by showing that non-acetylated dehydro-β-amino acid derivatives are excellent substrates for β-amino acid synthesis.[11b] Further modifications have since come forth.[13]

Chiral auxiliary approaches utilizing inexpensive chiral amine sources for amino acid synthesis are not common, only a few examples are reported in the literature and then mainly for β-amino acid formation. To this end, (*R*)-α-MBA has been used in several stepwise processes employing preformed enamines, that were subsequently reduced with $NaHB(OAc)_3$ to form acyclic or cyclic β-amino esters in moderate diastereoselectivity and yield,[14] in another example a cyclic β-amino acid was generated in low overall yield (29 %) but high *de* (99 %) after enrichment.[15] The reduction of (*S*)-phenylglycine dehydro-β-amino esters or dehydro-β-

[a] Department of Chemistry, School of Engineering and Science, Jacobs University Bremen (formerly International University Bremen),
Campus Ring 1, 28759 Bremen, Germany
Fax: +49-421-200-3229
E-mail: t.nugent@jacobs-university.de

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

aminoamides with PtO_2 has been reported on and proceeds in very good *ee*, but in low overall yield from the starting β-keto esters.[16] Herein, we report on the reductive amination of keto esters **1** with (*R*)- or (*S*)-α-MBA to generate amino esters **2** using heterogeneous hydrogenation catalysts (optimally Raney-Ni) with a Brønsted acid (optimally AcOH) for α- and β-keto esters, and with a Lewis acid [optimally Ti(O*i*Pr)$_4$] for a γ-keto ester.

Results and Discussion

We have recently demonstrated that unfunctionalized ketones are optimally reductively aminated in the presence of Ti(O*i*Pr)$_4$. Depending on the ketone substrate category, Raney-Ni, Pt-C, or Pd-C hydrogenation catalysts are required and provide good to excellent yield and diastereoselectivity for the amine products.[17] This prompted us to investigate the reductive amination of keto esters, and we chose to begin our studies with β-keto ester **1a** (*tert*-butyl acetylacetonate). The reaction was performed in EtOH using a combination of Ti(O*i*Pr)$_4$, Raney-Ni, and α-MBA (1.5 equiv.) in the presence of hydrogen (8.3 bar) at 22 °C, but these conditions failed to produce the desired product. When the hydrogen pressure was increased to 20 bar and the temperature increased to 65 °C, β-amino ester **2a** was observed in 67 area% (GC) and in 81% *de* after 19 h of reaction (Scheme 1). This level of diastereoselectivity was encouraging but the low GC yield prompted us to screen a variety of alternative acids (Table 1). Of the Brønsted acids examined, AcOH provided the best reaction profile (diastereoselectivity and yield). Examination of further achiral and chiral carboxylic acids, e.g. L-mandelic acid (Entry 2) and L-tartaric acid (Entry 3), in addition to stronger mineral acids, e.g. HCl (Entry 4), H_2SO_4 (Entry 5), confirmed the superiority (Table 1, Entry 9) of AcOH (1.00 equiv.). Other researchers have previously shown that acetic acid, trifluoroacetic acetic acid, and formic acid can be useful for the synthesis of enamines from β-keto esters.[18]

We were able to further optimize our initial AcOH result (90% *de* and 76% GC yield) for **1a** (Table 1, Entry 8) by adding $MgSO_4$ (1.10 equiv.) (Table 1, Entry 9). The $MgSO_4$ likely only facilitates faster in situ enamine, dehydro-β-amino ester, formation by sequestration of the eliminated H_2O. A solvent screen (tetrahydrofuran, dichloromethane, *tert*-butyl methyl ether, hexane, toluene) carried out under these optimal conditions (AcOH/$MgSO_4$, 65 °C, 20 bar hydrogen) corroborated EtOH as the appropriate choice regarding reaction rate (19 h), isolated yield (70%), and *de* (91%). Binary solvent mixtures with EtOH proved fruitless.

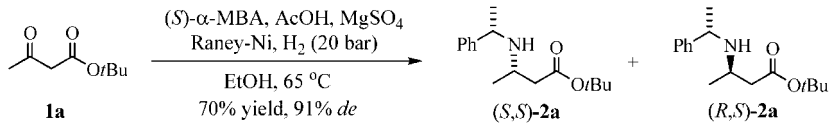
Table 1. Reductive amination of keto ester (**1a**); Lewis and Brønsted acid screening.[a]

Entry	Brønsted or Lewis acid	Equiv.	*de* (GC area%)	Product (GC area%)
1	BF_3·THF	1.0	84	26
2	L-mandelic acid	2.0	78	41
3	L-tartaric acid	0.2	88	12
4	HCl	0.05	88	49
5	H_2SO_4	0.05	88	53
6	Ti(O*i*Pr)$_4$	1.25	81	67
7	AcOH	2.0	90	74
8	AcOH	1.0	90	76
9[b]	**AcOH**	**1.0**	**91**	**88**
10	no acid	–	57	16

[a] **1a** (2.50 mmol), α-MBA (1.50 equiv.), EtOH (3.0 mL), Raney-Ni (100 wt.-%), H_2 (20 bar), 65 °C, the remainder of the product profile was mainly the hydroxy ester by-product. Concentrated HCl (12 N) and H_2SO_4 (18 M) were diluted in EtOH to the appropriate molarity. [b] $MgSO_4$ (1.1 equiv.) added (vacuum-dried at 22 °C).

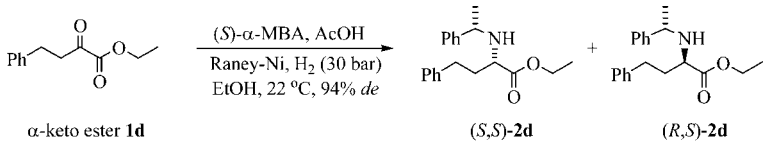
Before settling on Raney-Ni as optimal (yield and *de*) for all keto ester substrates, we probed for a link between the heterogeneous hydrogenation catalyst used and the steric and/or electronic properties of various substrates. For this purpose, β-keto ester **1a** (Scheme 1) and α-keto ester **1d** (Scheme 2) were examined with several heterogeneous hydrogenation catalysts. In the event, a temperature of 65 °C was required for β-keto ester **1a**, while 22 °C was sufficient for the α-keto ester **1d**. Regardless, PtO_2 (Table 2, Entry 3 and 5) and Pd-C (Entry 6) provided low diastereoselectivity (51–62%) regardless of the starting substrate. For β-keto ester **1a**, Pd-C (Table 2, Entry 1) failed to produce the desired product, and only the intermediate enamine was noted. The effect of double stereo-differentiation was very briefly examined by investigating the use of Pt/Al_2O_3 with adsorbed cinchonidine, but no influence on the diastereoselectivity of the product was noted (Table 2, Entry 2). Rh and Ru catalysts, supported on carbon, were also examined; under the mild conditions of 22 °C and 8.3 bar of H_2, <65% *de* was observed and unreacted starting material was always noted. Under more forcing conditions (>20 bar of H_2, 65 °C) an intolerable amount of what is presumed to be the benzene ring hydrogenated product was noted. These studies confirmed Raney-Ni as the catalyst of choice for good yield and high diastereoselectivity (Table 2, Entries 4 and 7), and was used in 100 wt.-% loading which is not uncommon for reductive amination.[19] It should be noted that the Raney-Ni catalyst loading had no influence on the diastereoselectivity of the observed products.

The scope and versatility of the reductive amination method, from the perspective of yield and diastereoselectivity, was then examined by screening various keto esters



1a (*S*,*S*)-**2a** (*R*,*S*)-**2a**

Scheme 1. Reductive amination of β-keto ester **1a**.



Scheme 2. Reductive amination of ethyl 2-oxo-4-phenylbutanoate (**1d**).

Table 2. Reductive amination of keto esters **1a** and **1d**; heterogeneous hydrogenation catalyst screening.

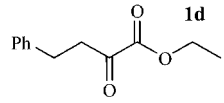
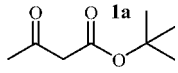
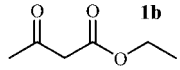
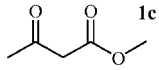
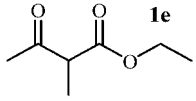
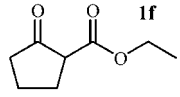
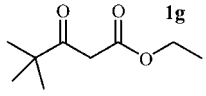
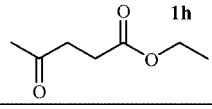
Entry	Heterogeneous catalyst	Loading	Amino esters	*de* (GC area%)
1[a]	Pd/C	0.25 mol-%	**2a**	only enamine
2[a]	Pt/Al_2O_3 (cinchonidine)	1 mol-%	**2a**	60
3[a]	PtO_2	2 mol-%	**2a**	62
4[a]	**Raney-Ni**	**100 wt.-%**	**2a**	**91**
5[b]	PtO_2	2 mol-%	**2d**	51
6[b]	Pd/C	0.25 mol-%	**2d**	60
7[b]	**Raney-Ni**	**100 wt.-%**	**2d**	**94**

[a] **1a** (2.50 mmol), α-MBA (1.50 equiv.), AcOH (1.0 equiv.), EtOH (3.0 mL), indicated hydrogenation catalyst, H_2 (20 bar), 65 °C. [b] **1d** (2.50 mmol), α-MBA (1.50 equiv.), AcOH (3.0 equiv.), EtOH (4.0 mL), indicated hydrogenation catalyst, H_2 (30 bar), room temperature.

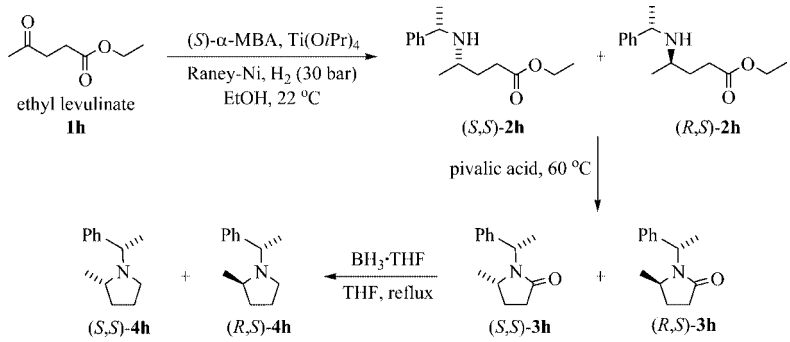
(Table 3). α-Keto ester **1d**, (Table 3, Entry 1), was chosen because reductive amination, followed by hydrogenolysis of the auxiliary, allows access to homophenylalanine esters, which are vital building blocks for many ACE inhibitor drugs.[2] Although **1d** provided **2d** in high *de* (94%), a low isolated yield (55%) was observed, and could be accounted for by keto amide by-product formation and to a smaller extent from α-hydroxy ester by-product formation. The formation of these by-products could be controlled to some extent by using a large excess of AcOH (3.00 equiv.). Replacement of AcOH by $Ti(OiPr)_4$ in the aprotic solvents tetrahydrofuran, dichloromethane, *tert*-butyl methyl ether, hexane, or toluene, resulted in appreciable transesterification, resulting in the desired product **2d** (ethyl ester) and the corresponding isopropyl ester of **2d**.[20] Prior to our investigation, the α-keto ester ethyl pyruvate (not shown) was reductively aminated with α-MBA and Pd-C/H_2, resulting in 9% *de* for the β-amino ester product.[21]

Regarding β-keto esters, as the steric bulk of the ester moiety was increased a clear trend of higher diastereoselectivity for the β-amino ester product was noted, thus *tert*-butyl acetoacetate (**1a**) provided 91% *de*, while ethyl acetoacetate (**1b**) 84% *de*, and methyl acetoacetate (**1c**) 72% *de* (Table 3, Entries 2–4). Regarding the level of induced diastereoselectivity for **1b**, Palmieri et al.[14] have previously reduced the (*R*)-α-MBA enamine of **1b** with $NaHB(OAc)_3$, achieving 58% *de* for **2b**. We verified this earlier reported two-step approach,[22] and note that our Raney-Ni reductive amination method does not require preformation of the enamine and provides superior *de* for **2b** (Table 3, Entry 3, 84% *de*). This successful outcome prompted us to examine β-keto esters with different substitution patterns. Investigation of β-keto ester **1e**, with methyl substitution at the acidic C-2 atom (Table 3, Entry 5), unexpectedly prohibited in situ enamine formation from occurring, while cyclic β-keto ester **1f** (Table 3, Entry 6) allowed high diastereoselectivity (92%) for the *cis* product but with marginal product formation noted (25 area%, GC) after 24 h. Substitution in the form of a *t*Bu group at the ketone carbonyl moiety (Table 3, Entry 7) generated none of the desired product, but did allow enamine formation. These results clearly show that dehydro-β-amino esters with tetrasubstituted alkenes are not tolerated by this methodology, nor are sterically demanding substituents (*t*Bu of **1g**) on the ketone

Table 3. A comparative reactivity study of α-, β- and γ- keto esters.

Entry	Keto ester	*de* (GC area %)	Yield (%) (isolated)
1[a]	 **1d**	94	55
2[b]	 **1a**	91	70
3[b]	 **1b**	84	74[f]
4[b]	 **1c**	72[d]	56
5[b]	 **1e**	fails to form enamine	–
6[b]	 **1f**	92	25[f]
7[b]	 **1g**	only enamine forms	–
8[c]	 **1h**	74[e]	51[g]

[a] Keto ester (2.50 mmol), α-MBA (1.50 equiv.), AcOH (3.00 equiv.), EtOH (4.0 mL), Raney-Ni (100 wt.-%), H_2 (30 bar), room temperature. [b] Keto ester (2.50 mmol), α-MBA (1.50 equiv.), AcOH (1.00 equiv.), EtOH (3.0 mL), Raney-Ni (100 wt.-%), H_2 (20 bar), 65 °C. [c] Keto ester (2.50 mmol), α-MBA (1.50 equiv.), $Ti(OiPr)_4$ (1.50 equiv.), EtOH (5.0 mL), Raney-Ni (100 wt.-%), H_2 (30 bar), 22 °C. [d] Solvent: MeOH; T = 55 °C. [e] Diastereoselectivity verified by ^1H NMR and GC (area%) of **4h**. [f] GC (area%). [g] This represents the overall yield of **4h** from **1h**, see Scheme 3.



Scheme 3. Conversion of γ-keto ester **1h** to the protected 2-methylpyrrolidine **4h**.

moiety tolerated. The assignment of stereochemistry has been made by direct comparison with the previously published amino ester structures **2**.[14,15]

In an attempt to broaden the substrate breadth, we next chose to examine a γ-keto ester, levulinic ester (**1h**). The carbonyl group in a γ-keto ester is too remote from the ester moiety to promote tautomerization of the initially formed imine. Because of this, the carbonyl moiety would be expected to react like a non-functionalized ketone substrate, it was therefore not surprising that our previously established method for ketone reductive amination using $Ti(OiPr)_4$ and Raney-Ni was optimal.[17] With acetic acid, an undesirable mixture of the product (**2h**), the corresponding ring-closed lactam (**3h**), and larger quantities of the hydroxy ester were noted. $Ti(OiPr)_4$ reductive amination of γ-keto ester **1h** was optimally performed in EtOH at a hydrogen pressure of 30 bar (22 °C); these conditions allowed full consumption of **1h** within 18 h with smooth formation of **2h** in 74% *de*. Interestingly, the optimal conditions for 2-octanone, which is structurally similar although not further functionalized, were the following: tetrahydrofuran, Raney-Ni/H_2 (8 bar), and α-MBA (1.1 equiv.) at 22 °C, providing 72% *de*.[17] In other polar (dichloromethane or EtOAc) or non-polar (hexane or toluene) aprotic solvents, 2-octanone provided similar results, but these aprotic solvents significantly slowed down the rate of reaction for γ-keto ester **1h**.

The difficulty of separating the product diastereomers of **2h**, (*S*,*S*)-**2h** and (*R*,*S*)-**2h**, and the importance of 2-methylpyrrolidine, an advanced intermediate for the synthesis of histamine H_3 receptor antagonist ABT-239 used in the treatment of Alzheimer disease,[23] encouraged us to further convert it into the substituted pyrrolidine **4h**. The synthesis (Scheme 3) relies on commercially available starting materials and inexpensive reagents to provide the methylbenzyl protected pyrrolidine.[24] Thus, crude reaction product **2h** was heated with pivalic acid (1.50 equiv.) to produce the γ-lactam **3h**. In turn, crude product **3h** was then reduced with BH_3·THF to obtain **4h** in 51% overall yield from **1h** in 74% *de* (GC area%). Attempts to replace $Ti(OiPr)_4$ with pivalic acid, acetic acid, trifluoroacetic acid, or benzoic acid for a one-pot reductive amination/lactamization of **1h** to **3h** resulted in significantly larger quantities of the hydroxy ester by-product in addition to the desired lactam **3h** under various conditions of time, temperature, and H_2 pressure. The more acidic carboxylic acids, trifluoroacetic acid and benzoic acid, produced the largest quantities of the γ-hydroxy ester by-product (>20%). The use of substoichiometric quantities (5 mol-%) of a strong Brønsted acid (HCl or H_2SO_4) or more equiv. of α-MBA for the reductive amination of **1h** did not solve the problems associated with the use of a Brønsted acid. Instead, the mild Lewis acid $Ti(OiPr)_4$ optimally facilitates the reductive amination, but unlike α-keto ester **1d**, no transesterification was noted.

Conclusions

The reductive amination of α-, β- and γ-keto esters with the chiral ammonia equivalent (*R*)- or (*S*)-α-methylbenzylamine has been demonstrated, allowing the time-consuming and sometimes tedious task of enamine or ketimine synthesis to be avoided. The presented strategy allows the one-step synthesis of unnatural methylbenzylamine-protected α- or -β-amino esters in high *de* (91–94%) and can thus be considered as an alternative to using *N*-acetyl-protected dehydro-α- or -β-amino acid derivatives for amino acid synthesis. The latter method requires four reaction steps from a ketone to produce an amino acid; by comparison, our methodology would require two steps to arrive at α-, -β, or γ-amino esters. Although substrate limitations clearly exist for the presented methodology, the pharmaceutically important keto esters **1d** and **1h**, underwent smooth reductive amination. The method is of future potential use because it is stepwise efficient and provides a low-cost entry into either enantiomeric series of α-, β- or γ-amino esters.

Experimental Section

General: NMR spectra were recorded with a JEOL ECX 400 spectrometer, operating at 400 MHz (^1H) and 100 MHz (^{13}C), respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from TMS (δ = 0 ppm) or relative to $CHCl_3$ (δ = 7.26 ppm) for ^1H NMR spectroscopy. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CHCl_3$ (δ =77.0 ppm) as an internal reference. Multiplicities are abbreviated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad. The coupling constants are given in Hertz (Hz). FTIR spectra were obtained with a Nicolet Avatar 370 spectrometer. Mass spectra were recorded with a Finnigan MAT 95 (EI) instrument with an ionization

potential of 70 eV. Elemental analysis was performed at the Analytische Laboratorien, Lindlar, Germany, with an Elementar Vario EL III instrument. For the amine products **2**, reaction progress and diastereomeric ratio measurements were measured with a Shimadzu GC-2010 instrument on an Rtx-5 amine column (Restec, 30 m × 0.25 mm); T_{inj} = 300 °C and T_{det} = 300 °C were always constant; program A: 50→160 °C at 20 °C/min then →280 °C at 20 °C/min, 1 min at 280 °C; program B: 50→215 °C at 20 °C/min then →280 °C at 20 °C/min, 1 min at 280 °C; program C: 50→150 °C at 5 °C/min and then at 150 °C for 40 min. Column chromatography was performed using silica gel 60 (0.040–0.063 mm). Thin-layer chromatography (TLC) was performed using precoated plates of silica gel 60 F_{254} and visualized under ultraviolet irradiation (254 nm) or by potassium permanganate staining [2 g of $KMnO_4$, 13.3 g of K_2CO_3, 3.3 mL of 5% (w/w) NaOH, 200 mL of H_2O]. All reagents were obtained from Sigma–Aldrich and used without further purification unless stated. 99.999% grade Ti(O*i*Pr)$_4$ was purchased from Sigma–Aldrich (catalog number 377996) and AcOH was purchased from Fluka (catalog number 45740, > 99%). (*S*)-α-Methylbenzylamine was purchased from Aldrich (catalog number 115568, 98% pure and 97.5% *ee*). The Raney nickel (in water) was purchased from Fluka (catalog number 83440). Pd/C [≤ 50% water, 5 wt.-% loading (dry basis)] was purchased from Aldrich (catalog number 276707). PtO_2 was purchased from Aldrich (catalog number 206032). $MgSO_4$ was purchased from Aldrich (catalog number 246972) and dried under high vacuum at 22 °C for 4 h before use. All reactions were performed under argon and under anhydrous conditions.

General Procedure for the Reductive Amination of α- and β-Keto Esters: Keto ester (1.00 equiv., 2.50 mmol), AcOH (1.00–3.00 equiv., 0.14–0.43 mL), and (*S*)-α-methylbenzylamine (1.50 equiv., 3.75 mmol, 0.48 mL) in EtOH (3.0–5.0 mL) were combined. This mixture was prestirred for 1 h and then hydrogenated at 20–30 bar in the presence of Raney-Ni (100 wt.-% based on the limiting reagent, the keto ester) [prewashed with EtOH (3×)] at 22 °C. The reactions were monitored by GC. At complete conversion, the reaction mixture was treated with a saturated aqueous solution of Na_2CO_3 (15 mL) and stirred for 10 min. The solution was then filtered through Celite and the Celite washed with EtOH (3 × 20 mL). The filtrate was concentrated in a rotary evaporator ($T \leq 35$ °C) to remove most of the EtOH and the remaining aqueous solution, then extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were then treated with aqueous saturated NaCl (20 mL), dried with Na_2SO_4, filtered, and concentrated (rotary evaporator, $T \leq 25$ °C). The diastereomeric excess of the crude product was then assessed by GC using either program A or B. The yield of the diastereomers was recorded after flash chromatography and drying to constant weight under high vacuum of their hydrochloride salts.

(*S*)-*tert*-Butyl 3-{[(*S*)-1-Phenylethyl]amino}butanoate [(*S*,*S*)-2a]: Reaction details: 2.50 mmol scale of *tert*-butyl acetylacetonate (395 mg, 0.41 mL, 1.00 equiv.); AcOH (2.50 mmol, 0.14 mL, 1.00 equiv.); solvent: EtOH (3.0 mL, 0.83 M); $MgSO_4$ (331 mg, 1.10 equiv.); prestirred at room temperature for 1 h; hydrogen pressure 20 bar; Raney-Ni (400 mg, 100 wt.-%); 65 °C. Reaction time: 16 h; 91% *de*. The mixture of diastereomers was isolated as a colorless liquid using flash chromatography (hexane/EtOAc/NH_4OH, 79:20:1) then converted to a free-flowing white solid by ethereal HCl (525 mg, 70% yield). The diastereomers were separated after further flash chromatography (hexane/EtOAc/NH_4OH, 94:5:1) of the free base. GC (program A): retention time: 23.9 [major (*S*,*S*) isomer]; 22.9 min [minor (*R*,*S*) isomer].

(*S*,*S*)-2a (Major Isomer): R_f = 0.42 (hexane/EtOAc/NH_4OH, 72:24:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.20–7.32 (m, 5 H), 3.88 (q, J = 6.4 Hz, 1 H), 2.94 (sext, J = 6.2 Hz, 1 H), 2.34 (dd, J = 5.6, J = 14.4 Hz, 1 H), 2.28 (dd, J = 6.4, J = 14.4 Hz, 1 H), 1.51 (br. s, 1 H), 1.45 (s, 9 H), 1.32 (d, J = 6.4 Hz, 3 H), 1.04 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.7, 146.2, 128.4, 126.8, 126.6, 80.3, 55.2, 48.1, 42.1, 28.2, 24.6, 21.4 ppm. HRMS (70 eV): calcd. for $C_{16}H_{25}NO_2$ [M^+] 263.1885; found 263.1889. LRMS (EI): *m*/*z* (%) = 263 (2), 248 (68), 206 (42), 192 (94), 148 (52), 132 (20), 120 (64), 105 (100). IR (KBr): $\tilde{\nu}$ = 3320, 1726, 1157 cm^{-1}.

(*R*,*S*)-2a (Minor Isomer): R_f = 0.35 (hexane/EtOAc/NH_4OH, 72:24:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.20–7.32 (m, 5 H), 3.91 (q, J = 6.8 Hz, 1 H), 2.87 (sext, J = 6.4 Hz, 1 H), 2.29 (dd, J = 7.6, J = 14.8 Hz, 1 H), 2.21 (dd, J = 5.2, J = 14.8 Hz, 1 H), 1.43 (s, 9 H), 1.34 (d, J = 6.4 Hz, 3 H), 1.05 (d, J = 6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.8, 145.4, 128.4, 126.8, 126.6, 80.4, 54.7, 47.2, 43.5, 28.1, 25.1, 19.8 ppm.

(*S*)-Ethyl 4-Phenyl-2-{[(*S*)-1-phenylethyl]amino}butanoate [(*S*,*S*)-2d]: Reaction details: 2.50 mmol scale of ethyl 2-oxo-4-phenylbutanoate (516 mg, 0.48 mL, 1.00 equiv.); solvent: EtOH (5.0 mL, 0.5 M); prestirred at room temperature for 1 h; hydrogen pressure 30 bar; AcOH (7.50 mmol, 0.43 mL, 3.00 equiv.); Raney-Ni (500 mg, 100 wt.-%); room temperature. Reaction time: 20 h; 94% *de*. The mixture of diastereomers was isolated as a colorless liquid using flash chromatography (hexane/EtOAc/NH_4OH, 79:20:1), then converted to the hydrochloride salt (semi-solid) by ethereal HCl (478 mg, 55% yield). The diastereomers were separated after further flash chromatography (hexane/EtOAc/NH_4OH, 94:5:1) of the free base. GC (program B): retention time: 23.9 [major (*S*,*S*) isomer]; 25.8 min [minor (*R*,*S*) isomer].

(*S*,*S*)-2d (Major Isomer): R_f = 0.52 (hexane/EtOAc/NH_4OH, 76:20:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.07–7.34 (m, 10 H), 4.17 (q, J = 7.2 Hz, 2 H), 3.70 (q, J = 6.4 Hz, 1 H), 3.03 (dd, J = 5.2, J = 8 Hz, 1 H), 2.75–2.82 (m, 1 H), 2.50–2.57 (m, 1 H), 1.76–1.9 (m, 3 H), 1.35 (d, J = 6.8 Hz, 3 H), 1.26 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.9, 145.1, 141.7, 128.4, 128.3, 127.1, 125.8, 60.6, 58.8, 56.8, 35.8, 32.2, 25.4, 14.4 ppm. HRMS (70 eV): calcd. for $C_{20}H_{25}NO_2$ [M^+] 311.1885; found 311.1886. LRMS (EI): *m*/*z* (%) = 311 (4), 238 (100), 134 (44), 105 (79). IR (KBr): $\tilde{\nu}$ = 3330, 1730, 1179 cm^{-1}.

(*R*,*S*)-2d (Minor Isomer): R_f = 0.47 (hexane/EtOAc/NH_4OH, 76:20:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.18–7.31 (m, 10 H), 3.98–4.11 (m, 2 H), 3.74 (q, J = 6.6 Hz, 1 H), 3.30 (t, J = 6.6 Hz, 1 H), 2.71 (t, J = 8 Hz, 2 H), 1.83–2.01 (m, 3 H), 1.33 (d, J = 6.4 Hz, 3 H), 1.21 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 171.8, 145.4, 128.4, 126.8, 126.6, 80.4, 54.7, 47.2, 43.6, 28.1, 25.1, 19.8 ppm.

(*S*)-2-Methyl-1-[(*S*)-1-phenylethyl]pyrrolidine [(*S*,*S*)-4h]: Ethyl 4-oxopentanoate (**1h**, 360 mg, 0.35 mL, 2.50 mmol, 1.00 equiv.), Ti(O*i*Pr)$_4$ (3.75 mmol, 1.10 mL, 1.50 equiv.), and (*S*)-α-MBA (3.75 mmol, 0.48 mL, 1.50 equiv.) in EtOH (5.0 mL) were combined. This mixture was prestirred for 30 min and then hydrogenated at 30 bar (H_2) in the presence of Raney-Ni (360 mg, 100 wt.-%) [prewashed with EtOH (3×)] at 22 °C. The reaction was monitored by GC. At complete conversion, after 18 h, the reaction mixture was treated with a saturated aqueous solution of Na_2CO_3 (15 mL) and stirred for 1 h. The solution was then filtered through Celite and the Celite washed with EtOH (3 × 20 mL). The filtrate was concentrated in a rotary evaporator ($T \leq 35$ °C) to remove most of the EtOH and the remaining aqueous solution then extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were then

treated with aqueous saturated NaCl (20 mL), dried with Na_2SO_4, filtered and concentrated (rotary evaporator, $T \leq 25$ °C). To this crude mixture pivalic acid (383 mg, 1.50 equiv.) was added in EtOH (5.0 mL) and the mixture stirred at 60 °C. After 6 h, the reaction mixture was worked up as above, and the crude product **3h** was then treated with BH_3·THF (2 mL, 1.0 M) in THF (5.0 mL) at 0 °C for 15 min and then heated at reflux for 1 h. The refluxing solution was cooled to room temperature, and aqueous hydrochloric acid (10 mL, 1.0 M) was added. After removal of the THF, the neutral organic compounds were removed by washing the aqueous layer with Et_2O (2 × 20 mL). The aqueous layer was basified with NaOH (20 mL, 1.0 M) to pH = 10–12. This was then further extracted with Et_2O (3 × 20 mL), the diethyl ether layer washed with saturated aqueous NaCl, dried with Na_2SO_4, and filtered to obtain the crude diastereomeric mixture which can be isolated as a colorless liquid using flash chromatography (hexane/EtOAc/NH_4OH, 59:40:1). Ethereal HCl was then added to the pure diastereomers and the mixture concentrated (rotary evaporator) to obtain a hydrochloride salt of (*S*)-2-methyl-1-[(*S*)-1-phenylethyl]pyrrolidine which is semi-solid (288 mg, 51% overall yield from the keto ester **1h**, 74% *de*). The major diastereomer can be separately obtained by further flash chromatography (hexane/EtOAc/NH_4OH, 86:12:6). GC (program C): retention time: 24.3 [major (*S*,*S*) isomer]; 23.7 min [minor (*R*,*S*) isomer].

(*S*,*S*)-4h (Major Isomer): R_f = 0.40 (hexane/EtOAc/NH_4OH, 59:40:1). ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.20–7.38 (m, 5 H), 3.67 (q, J = 6.8 Hz, 1 H), 2.95–2.88 (m, 1 H), 2.79–2.74 (m, 1 H), 2.45 (q, J = 8 Hz, 1 H), 1.96–1.85 (m, 1 H), 1.80–1.60 (m, 2 H), 1.45–1.35 (m, 1 H), 1.36 (d, J = 6.8 Hz, 3 H), 0.85 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 128.1, 127.7, 126.7, 60.5, 56.3, 50.0, 32.9, 22.3, 19.4, 18.4 ppm. LRMS (EI): *m*/*z* (%) = 189 (11), 174 (100), 112 (8), 105 (50), 70 (56). IR (KBr): $\tilde{\nu}$ = 3083, 3061, 3027, 2963, 2795, 1452, 1209, 1150 cm^{-1}.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra and GC chromatography (*de*) data are supplied for compounds **2a**, **2d** and **4h**.

Acknowledgments

The authors are grateful for financial support from Jacobs University Bremen. This work has been performed within the graduate program of Nanomolecular Science.

[1] a) A. Hasuoka, Y. Nishikimi, Y. Nakayama, K. Kamiyama, M. Nakao, K.-I. Miyagama, O. Nishimura, M. Fujino, *J. Antibiot.* **2002**, *55*, 322–336; b) F. A. Davis, B.-C. Chen, *Chem. Soc. Rev.* **1998**, *27*, 13–18; c) C. L. Wysong, T. S. Yokum, M. L. McLaughlin, R. P. Hammer, *Chemtech* **1997**, *27*, 26–33; d) M. Goodman, H. Shao, *Pure Appl. Chem.* **1996**, *68*, 1303–1308; e) D. Seebach, A. Jeanguenat, J. Schmidt, T. Maetzke, *Chimia* **1989**, *43*, 314–317; f) C. N. Drey, *Chemistry and Biochemistry of Amino Acids* (Ed.: G. C. Barrett), Chapman and Hall, New York, **1985**, chapter 3.

[2] a) H.-U. Blaser, M. Eissen, P. Fauquex, K. Hungerbühler, E. Schmidt, G. Sedelmeir, M. Studer, in *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions* (Eds.: H. U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**, pp. 91–104; b) H.-U. Blaser, S. Burkhardt, H. J. Kirner, T. Mössner, M. Studer, *Synthesis* **2003**, 1679–1682.

[3] For reviews, see: a) E. Juaristi, V. A. Soloshonok, *Enantioselective Synthesis of β-Amino Acids*, 2nd ed., Wiley-VCH, New York, **2005**; b) S. Abele, D. Seebach, *Eur. J. Org. Chem.* **2000**, 1–15; c) I. Ojima, *Catalytic Asymmetric Synthesis*, Wiley-VCH, New York, **2000**; d) A. F. Abdel-Magid, J. H. Cohen, C. A. Maryanoff, *Curr. Med. Chem.* **1999**, *6*, 955–970; e) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley and Sons, New York, **1994**.

[4] R. Kadyrov, T. H. Riermeier, U. Dingerdissen, V. Tararov, A. Börner, *J. Org. Chem.* **2003**, *68*, 4067–4070.

[5] M. Sabat, C. R. Johnson, *Org. Lett.* **2000**, *2*, 1089–1092.

[6] a) S. D. Bull, S. G. Davies, P. M. Kelly, M. Gianotti, A. D. Smith, *J. Chem. Soc. Perkin Trans. 1* **2001**, 3106–3111; b) S. G. Davies, D. R. Fenwick, *J. Chem. Soc. Chem. Commun.* **1995**, 1109–1110.

[7] a) T. P. Tang, J. A. Ellman, *J. Org. Chem.* **2002**, *67*, 7819–7832; b) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984–995; c) T. P. Tang, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 12–13.

[8] For enzyme catalyzed reactions, see: a) A. Liljeblad, L. T. Kanerva, *Tetrahedron* **2006**, *62*, 5831–5854; b) H. Groeger, H. Werner, J. Altenbuchner, A. Menzel, W. Hummel, WO2005093081, **2005**; c) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keseler, R. Stürmer, T. Zelinski, *Angew. Chem.* **2004**, *116*, 806–843; *Angew. Chem. Int. Ed.* **2004**, *43*, 788–824; d) H. Gröger, H. Trauthwein, S. Buchholz, K. Drauz, C. Sacherer, S. Godfrin, H. Werner, *Org. Biomol. Chem.* **2004**, *2*, 1977–1978.

[9] B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695–705.

[10] For α-amino acids, see: a) W. Zhang, X. Zhang, *J. Org. Chem.* **2007**, *72*, 1020–1023; b) M. A. Beenen, D. J. Weix, J. A. Ellman, *J. Am. Chem. Soc.* **2006**, *128*, 6304–6305; c) G. Shang, Q. Yang, X. Zhang, *Angew. Chem.* **2006**, *118*, 6508–6510; *Angew. Chem. Int. Ed.* **2006**, *45*, 6360–6362; d) N. W. Boaz, E. B. Mackenzie, S. D. Debenham, S. E. Large, J. A. Ponasik Jr, *J. Org. Chem.* **2005**, *70*, 1872–1880; e) L. Navarre, S. Darses, J.-P. Genet, *Angew. Chem.* **2004**, *116*, 737–741; *Angew. Chem. Int. Ed.* **2004**, *43*, 719–723; f) W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106–112.

[11] For β-amino acids, see: a) Q. Dai, W. Yang, X. Zhang, *Org. Lett.* **2005**, *7*, 5343–5345; b) Y. Hsiao, N. R. Rivera, T. Rosner, S. W. Krska, E. Njolito, F. Wang, Y. Sun, J. D. Armstrong III, E. J. J. Grabowski, R. D. Tillyer, F. Spindler, C. Malan, *J. Am. Chem. Soc.* **2004**, *126*, 9918–9919; c) H.-J. Drexler, J. You, S. Zhang, C. Fischer, W. Baumann, A. Spannenberg, D. Heller, *Org. Process Res. Dev.* **2003**, *7*, 355–361; d) W. Tang, S. Wu, X. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 9570–9571; e) J. Wu, X. Chen, R. Guo, C. Yeung, A. S. C. Chan, *J. Org. Chem.* **2003**, *68*, 2490–2493; f) J. Holz, A. Monsees, H. Jiao, J. You, I. V. Komarov, C. Fischer, K. Drauz, A. Börner, *J. Org. Chem.* **2003**, *68*, 1701–1707.

[12] a) W. D. Lubell, M. Kitamura, R. Noyori, *Tetrahedron: Asymmetry* **1991**, *2*, 543–554; b) J. Halpern, *Science* **1982**, *217*, 401–407.

[13] T. Bunlaksananusorn, F. Rampf, *Synlett* **2005**, *17*, 2682–2684.

[14] C. Cimarelli, G. Palmieri, *J. Org. Chem.* **1996**, *61*, 5557–5563.

[15] P. R. LePlae, N. Umezawa, H.-S. Lee, S. H. Gellman, *J. Org. Chem.* **2001**, *66*, 5629–5632.

[16] N. Ikemoto, D. M. Tellers, S. D. Dreher, J. Liu, A. Huang, N. R. Rivera, E. Njolito, Y. Hsiao, J. C. McWilliams, J. M. Williams, J. D. Armstrong III, Y. Sun, D. J. Mathre, E. J. J. Grabowski, R. D. Tillyer, *J. Am. Chem. Soc.* **2004**, *126*, 3048–3049.

[17] T. C. Nugent, A. K. Ghosh, V. N. Wakchaure, R. R. Mohanty, *Adv. Synth. Catal.* **2006**, *348*, 1289–1299.

[18] H. Ohkura, D. O. Berbasov, V. A. Soloshonok, *Tetrahedron* **2003**, *59*, 1647–1656.

[19] For a brief summary of the use of Raney-Ni for imine reduction and reductive amination applications, see the text and references within: T. C. Nugent, V. N. Wakchaure, A. K. Ghosh, R. R. Mohanty, *Org. Lett.* **2005**, *7*, 4967–4970.

[20] Some compatible functional groups with $Ti(OiPr)_4$ are, e.g., carbamates, urethanes, secondary and tertiary amides, acetonides, silyl ethers, and most esters, see: a) F. E. Janssens, F. M. Sommen, J. E. Leenaerts, Y. E. M. Van Roosbroeck, T. F. Meert (Janssen Pharmaceutica N. V.), *Combinations for opioid-*

based treatment of pain comprising 1-(1,2-disubstituted piperidinyl)-4-substituted piperazine derivatives, WO2004110451, **2004**; b) B. Miriyala, S. Bhattacharyya, J. S. Williamson, *Tetrahedron* **2004**, *60*, 1463–1471; c) K. A. Neidigh, M. A. Avery, J. S. Williamson, S. Bhattacharyya, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2527–2532; d) D. Seebach, E. Hungerbühler, R. Naef, P. Schnurrenberger, B. Weidmann, M. Züger, *Synthesis* **1982**, 138–140.

[21] G. Siedlaczek, M. Schwickardi, U. Kolb, B. Bogdanovic, D. G. Blackmond, *Catal. Lett.* **1998**, *55*, 67–72.

[22] When we performed the reaction as described in ref.[14], we obtained a 52% *de* (major diastereomer: 19.1 min; minor diastereomer: 18.7 min) using program A of the Experimental Section (General).

[23] a) Y.-M. Pu, T. Grieme, A. Gupta, D. Plata, A. V. Bhatia, M. Cowart, Y.-Y. Ku, *Org. Process Res. Dev.* **2005**, *9*, 45–50; b) G. A. Gfesser, R. Faghih, Y. L. Bennani, M. P. Curtis, T. A. Esbenshade, A. A. Hancock, M. D. Cowart, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2559–2563.

[24] a) E. Marx, M. E. Bouz, J. P. Célérier, G. Lhommet, *Tetrahedron Lett.* **1992**, *33*, 4307–4310; b) R. Sakurai, A. Yuzawa, K. Sakai, N. Hirayama, *Cryst. Growth Des.* **2006**, *6*, 1606–1610; c) D. Zhao, J. T. Kuethe, M. Journet, Z. Peng, G. R. Humphrey, *J. Org. Chem.* **2006**, *71*, 4336–4338.

Received: April 18, 2007
Published Online: June 18, 2007

