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Dynamic Kinetic Resolution of α-Amino Acid Esters in the Presence of Aldehydes

Daniel A. Schichl,[a] Stephan Enthaler,[a] Wolfgang Holla,[b] Thomas Riermeier,[c] Udo Kragl,[a] and Matthias Beller*[a]

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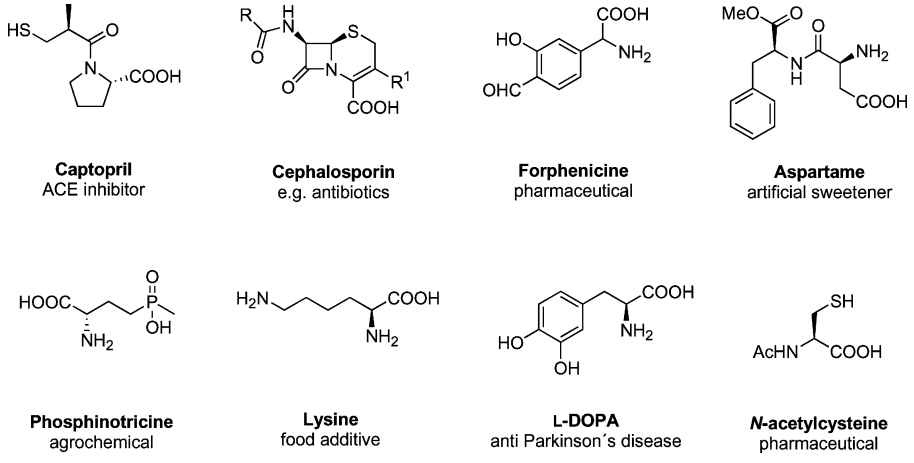
A convenient procedure for the racemization of α-amino acid esters in the presence of catalytic amounts of salicylaldehydes is described. The combination of this racemization protocol with lipase-catalyzed ester hydrolysis allows successful dynamic kinetic resolution of various α-amino acid esters. The corresponding α-amino acids are obtained in high yield and optical purity.

Introduction

Optically pure amino acids and their derivatives are probably the most important chiral compounds due to their biochemical significance. In addition, α-amino acids are used as pharmaceuticals, agrochemicals, artificial sweetener, food additives, chiral intermediates for fine chemicals and pharmaceuticals, etc.[1] In Scheme 1, a few examples of industrially important amino acid derivatives are shown.

In general, naturally occurring α-amino acids are produced on large scale either from the chiral pool or by fermentation.[2,3] The synthesis of optically active nonnatural α-amino acids has been extensively studied for several decades.[3] Despite various "classic" developments of, for example, Evans,[4] Schöllkopf,[5] Seebach,[6] Corey,[7] and many others,[8] there is still a demand for improved practical approaches to amino acids. With respect to kilogram-scale synthesis, catalytic asymmetric hydrogenations,[9] and the well-known Strecker synthesis in combination with resolution techniques, are the industrial methods of choice. Additionally, attention was directed to enzyme-catalyzed kinetic resolution techniques to produce chiral amino acids on industrial scale.[2b] Although a maximum yield of 50% in the resolution step is attainable, this approach is still attractive because of low-cost starting materials and simple process technology.



Scheme 1. Selection of industrially important α-amino acids.

Obviously, dynamic kinetic resolution (DKR) of abundantly available and less costly amino acid precursors is an

[a] Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany
Fax: +49-381-1281-5000
E-mail: matthias.beller@catalysis.de
[b] Sanofi-Aventis, 65926 Frankfurt, Germany
[c] Evonik-Röhm GmbH, Kirschenallee, 64293 Darmstadt, Germany

efficient alternative to the classical resolution of *N*-acyl amino acids, because complete conversion of the racemic mixture to the desired enantiomer is feasible.[10] However, certain requirements have to be fulfilled to gain the complete set of advantages of DKR. First of all, the resolution step must be irreversible and no product racemization should occur under the reaction conditions. In order to obtain products with high optical purity, the selectivity E (k_A/k_B) of the resolution step should be at least 20 (Figure 1). Furthermore, the rate constant for the racemization process (k_{inv}) should be faster than the rate constant of the resolution step (k_A) otherwise a very high selectivity E has to be ensured.[11,12]

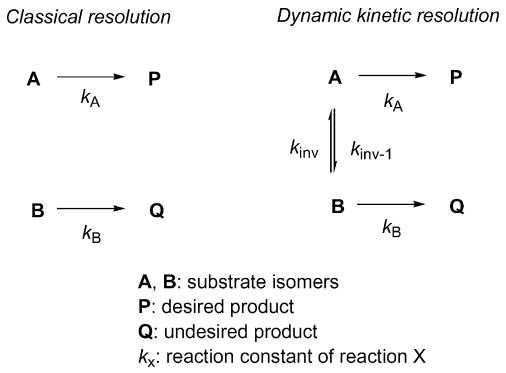


Figure 1. Comparison of classical resolution and dynamic kinetic resolution.

So far, enzymes, as well as organo- or organometallic catalysts, have been proven to be enantioselective catalysts for this purpose.[11,13] Noteworthy, various nonenzymatic efforts were reported on the resolution of racemic α-acetamido β-keto esters by efficient hydrogenation in the presence of ruthenium–phosphane complexes by Noyori et al. and Genêt et al.[13a,14] Later on, this method was extended also by other groups to approach pharmaceutical intermediates in excellent enantioselectivities.[15] More recently, and especially the group of Berkessel, described DKR methods catalyzed by organocatalysts.[16,17]

In case of enzymatic DKR reactions for the synthesis of α-amino acids, the *Hydantoinase*-catalyzed resolution of racemic hydantoins substituted with aryl groups in the 5-position to yield the corresponding D-*N*-carbamoyl α-amino acids in slight alkaline media (pH: 7.5–10) is known.[18] However, this process is limited to aryl hydantoin derivatives, as alkyl representatives required *Hydantoin racemase* for efficient resolution, which is relatively scarce.[18b,19] Similarly, oxazolones undergo fast base-catalyzed racemization in alkaline media.[18b,20] Unfortunately, these compounds are highly sensitive towards unselective chemical hydrolysis in aqueous solution.

Notably, Sheldon and coworkers reported the successful dynamic kinetic resolution of racemic phenylglycine methyl ester by lipase-catalyzed ammonolysis in the presence of pyridoxal, which mediates in situ racemization.[21] Careful adjustment of the reaction conditions gave (*R*)-phenylglycine amide in 88%*ee* and 85% conversion. To ensure high selectivity, the reaction was performed at low temperature (–20 °C), which resulted in longer reaction times (66 h). On the basis of naturally occurring pyridoxal-5-phosphate, Chen and Wang et al. developed an alcalase®-catalyzed DKR of amino acid esters.[22] Here, the free amino acids were obtained in high yields (87–95%) and excellent optical purities (90–98%). However, the impact of this method is lowered, because the desired L/D-amino acid esters are often accessible only in moderate yield and because of the necessity of an expensive racemization catalyst.[23] More recently, the group of Kanerva reported the DKR of *N*-heterocyclic amino acid esters catalyzed by aldehydes, for example, acetaldehyde (racemization step) and *Candida antarctica* lipase A (resolution step by *N*-acylation).[24] A combination of two different enzymes (D-aminopeptidase, α-amino-ε-caprolactam racemase) for racemization and resolution of alanine amide to yield D-alanine was demonstrated to be useful by Asano et al.[25]

Recently, we studied the kinetics of dynamic kinetic resolutions in the presence of substituted salicylaldehydes.[26] Herein, we describe a full account of our synthetic work and demonstrate that catalytic amounts of various aldehydes allow for smooth racemization of α-amino acid esters under mild conditions. Combination with enantioselective ester cleavage by enzymes gives efficient access to diverse enantiopure α-amino acids.

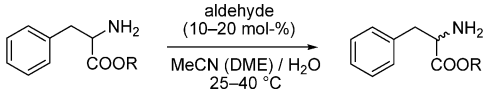
Results and Discussion

Racemization of α-Amino Acids

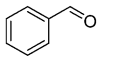
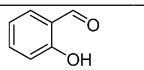
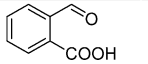
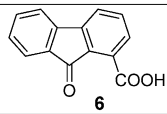
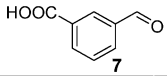
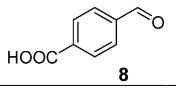
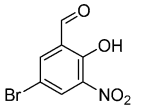
In a first set of experiments, we searched for an efficient amino acid ester racemization catalyst. More than 30 functionalized aldehydes and ketones were tested for the racemization of enantiomerically pure phenylalanine esters, which were generated from the corresponding HCl salts. Owing to the easy determination of the corresponding enantiomers, benzyl and ethyl esters were used as model substrates. Notably, these amino acid esters are not activated towards racemization relative to other amino acid esters, for example, arylglycine derivatives. Selected results are shown in Table 1. In preliminary experiments, the optical stability of both esters was tested in the absence of catalyst under the described reaction conditions, but no racemization was observed after 24 h. Initial runs with benzaldehyde (**3**) as catalyst showed complete stability of the model systems. However, the utilization of salicylaldehyde (**4**) as catalyst under identical conditions showed some ability to racemize the substrate. 2-Carboxybenzaldehyde (**5**) and 9-fluorenone-1-carboxylic acid (**6**) were also active for the racemization of the model substrate.

Interestingly, the variation of pH demonstrated that racemization at pH 7.0 (12%*ee* and 2%*ee* within 120 h) is significantly improved to that obtained at pH 5.0 and 9.0. Nevertheless, the overall space–time yield is outside the practical range. The addition of salts did not improve the racemization activity in comparison to experiments without

Table 1. Racemization of phenylalanine esters in the presence of different aldehydes.[a]



1: R = Et
2: R = Bn

Entry	R	Aldehyde	pH	*t* [h]	*ee* [%][b]
1[c]	Bn		8.5	24	96
2	Et		8.5	24	>99
3[d]	Et	**3**	8.5	24	>99
4[e]	Et		8.5	24	>99
5	Bn		8.5	24	93
6	Et		8.5	24	68
7[d]	Et	**4**	8.5	24	60
8[e]	Et		8.5	24	64
9	Et		5.0	120	46
10	Et		7.0	120	12
11	Et		7.7	24	54
12	Et	**5**	9.0	120	40
13	Et		5.0	120	62
14	Et		7.0	120	2
15	Et	**6**	9.0	120	36
16	Et	 **7**	7.5	24	>99
17[c]	Bn	 **8**	8.5	24	98
18[c]	Bn	 **9**	8.5	24	<1

[a] Reaction conditions: L-Phe-OEt (10 mmol), catalyst (10 mol-%), MeCN/H_2O (9:1), 40 °C. [b] The enantiomeric excess was determined by chiral GC (25 m Chirasil-Val, Alltech, 120 °C, isotherm) of the corresponding perfluoropropionyl *O*-methyl ester. [c] D-Phe-OBzl (0.7 mmol), catalyst (20 mol-%), dimethoxyethane (DME)/H_2O (4:1), 25 °C. [d] Additive: LiBr. [e] Additive: $Sc(OTf)_3$.

tained results were related to pyridoxal-5-phosphate (**10**), which has been proven to be an efficient racemization catalyst.[22] All aldehydes racemized D-**2** fast and continuously to lead to nearly complete racemization within 8 h. 5-Nitrosalicylaldehyde (**12**; 2%*ee* in 4 h) was found to be a highly active catalyst, and it was even more reactive than the naturally occurring **10** (16%*ee* in 4 h). To control the selectivity of the process, experiments with the free enantiopure amino acid phenylalanine were carried out. To our delight, no racemization was observed under identical reaction conditions, which indicates a high selectivity for amino acid ester racemization.

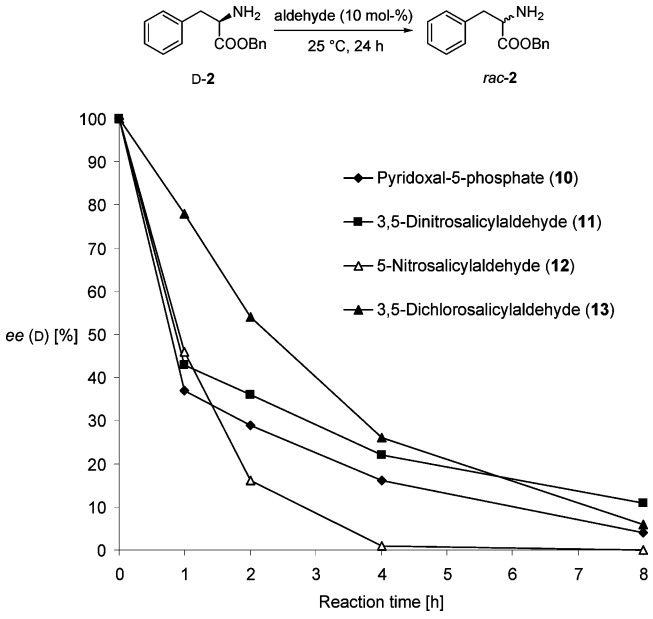


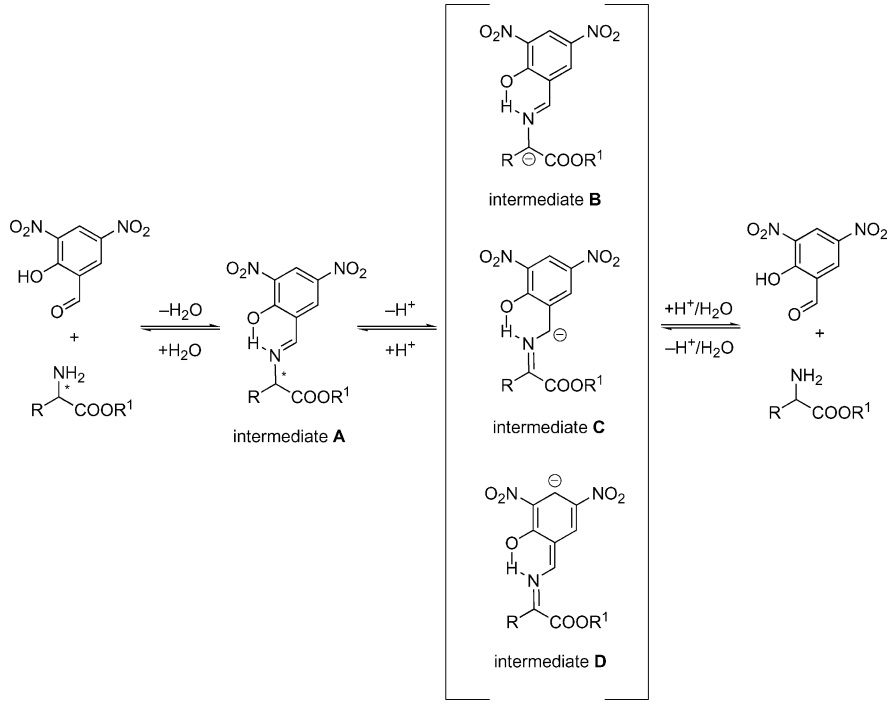
Figure 2. Comparison of enantioselectivity–time dependency of several salicylaldehydes and pyridoxal-5-phosphate (**10**).

salts (Table 1, Entries 3, 4, 7, and 8). Noteworthy is that the catalyst activity is related to the *ortho* substituent, and to confirm this fact, 3-carboxy- and 4-carboxybenzaldehyde (**7**, **8**) were tested as catalysts. Indeed, no racemization occurred under similar reaction conditions. Furthermore, 2-hydroxy-1-naphthaldehyde, 1-carboxyl-8-naphthaldehyde, 2,2′-dihydroxybenzophenone, 9-fluorenone, 5-chloro-2-hydroxybenzophenone, 1*H*-indole-2,3-dione, and 4-nitrobenzaldehyde were tested under slightly basic conditions, but no significant racemization was observed.

A more promising result was obtained with 3-nitro-5-bromosalicylaldehyde (**9**) as catalyst. Complete racemization of the model substrate D-phenylalanine benzyl ester (**2**) was observed at pH 8.5 within 24 h at 25 °C. On the basis of this result, the catalytic activity of several electron-deficient salicylaldehydes, for example, 3,5-dinitrosalicylaldehyde (**11**), 5-nitrosalicylaldehyde (**12**), and 3,5-dichlorosalicylaldehyde (**13**) was studied in more detail (Figure 2). The ob-

Regarding the structure–activity relationship for effective racemization, it is important that electron-withdrawing groups in the 3-and 5-positions of the aromatic ring are combined with a hydroxy group in the 2-position. Treatment of aldehydes, on the basis of these structural features, with phenylalanine esters results in the immediate formation of the intermediate Schiff bases at room temperature. On the basis of this fact, we propose the mechanism presented in Scheme 2 for the aldehyde-catalyzed racemization.[21,27]

After condensation reaction of the amino acid ester with 3,5-dinitrosalicylaldehyde (**11**), the acidity of the α-hydrogen atom at the chiral center is remarkably increased. Hence, rapid protonation–deprotonation at the α-carbon atom takes place, which causes racemization. Notably, the stabilization of the imine through hydrogen bonding enhances the opportunity for the protonation–deprotonation sequence. After hydrolysis of the intermediate Schiff base, the racemized amino ester and the aldehyde are liberated.



Scheme 2. Proposed mechanism for the aldehyde-catalyzed racemization of α-amino acid esters.

Dynamic Kinetic Resolution of α-Amino Acids

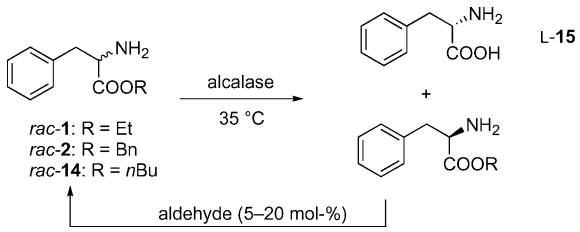
With a convenient racemization protocol under biological conditions in hand, we focused our attention on the development of in situ coupling of the racemization step with a resolution step. Thereby, the resolution step would be based on enzyme-catalyzed ester cleavage to yield the enantiopure amino acids. Here, commercially available alcalase®, an endoproteinase of the serine type, offers the opportunity for large-scale synthesis, as it is inexpensive and has a high stability in organic solvents even at low water concentrations.[28] The key element in alcalase®, which is accessible from *Bacillus licheniformis*, is subtilisin Carlsberg (E.C. 3.4.21.62, alkaline protease A).

By using the crude enzyme extract in preliminary experiments, we observed a crucial solvent–reactivity dependency; hence, several solvent combinations were investigated. The most efficient solvent mixture for the DKR of *rac*-phenylalanine benzyl ester (**2**) was found to be acetonitrile/water (4:1).

In more detail, the reactions were carried out on a 20-mmol scale by using 2.0 mL alcalase® (0.6 AU) at 35 °C in acetonitrile/water (4:1). The pH value was kept constant during the reaction by the addition of 2-N solution of sodium hydroxide by an autotitrator. The end point of the reaction was determined by HPLC and subsequent workup by cooling to 0 °C and setting the pH to 5.5 within 60 min. The addition of 1,2-dimethoxyethane led to nearly quantitative precipitation of the free amino acid.

The results presented in Table 2 underline the successful combination of alcalase®-mediated resolution of *rac*-phenylalanine benzyl ester (**2**) with in situ racemization. Depending on the racemization catalyst, L-phenylalanine (**15**) was isolated in 71 and 79% yield with an optical purity of 83 and 70%*ee*, respectively. Because the *ee* value of the product was significantly higher by using 3,5-dichlorosalicylaldehyde (**13**), we chose this catalyst for our ongoing purposes.

Table 2. Dynamic kinetic resolution of several phenylalanine esters.[a]



Entry	R	Aldehyde	pH	*t* [d]	Yield [%]	*ee* [%] (L)
1	Bn	20 mol-% **13**	8.5	1	71	83
2	Bn	20 mol-% **11**	8.5	1	79	70
3	Bn	10 mol-% **13**	8.5	1	87	88
4	Et	5 mol-% **13**	7.5	5	72	**98**
5	*n*Bu	5 mol-% **13**	8.0	7	63	92

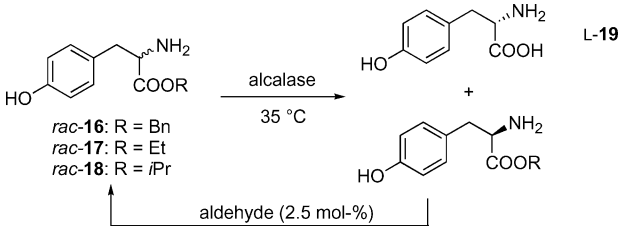
[a] Reaction conditions: alcalase® (2.0 mL, 0.6 AU), substrate (20 mmol), acetonitrile/water (4:1, 50 mL), 35 °C; aldehyde **11**: 3,5-dinitrosalicylaldehyde; aldehyde **13**: 3,5-dichlorosalicylaldehyde. The enantiomeric excess was determined by chiral GC (25 m Chirasil-Val) of the corresponding perfluoropropionyl *O*-methyl ester.

Next, the reaction was carried out with a decreased catalyst loading (10 mol-%) in order to minimize the amount of intermediate Schiff base products at the end of reaction and make the process more economical. Indeed, the reduction

of catalyst led to an increased yield (87%) and optical purity (88%*ee*). After having demonstrated that dynamic kinetic resolution of the model benzylic ester can be carried out successfully, we focused our attention on phenylalanine derivatives with other ester functionalities. In general, benzyl esters are problematic to prepare in quantitative yields; thus, the DKR of aliphatic esters would constitute an important improvement. In our test reaction, the catalytic amount of aldehyde was reduced to 2.5 mol-% and all other reaction conditions remained unchanged. Although the reaction times increased for the ethyl and *n*-butyl ester of phenylalanine (Table 2), which is in agreement with the literature, as alcalase® hydrolyses benzyl esters about three times faster than aliphatic counterparts,[29] the new substrates were obtained in comparable yields and superior enantioselectivities up to 98%*ee* with respect to the benzyl ester! As a result of the instability of the aliphatic esters towards unselective chemical hydrolysis, the best results were obtained at a nearly neutral pH value of 7.5.

Similar to phenylalanine, tyrosine esters can be efficiently racemized in the presence of 3,5-dinitrosalicylaldehyde (**11**) or 3,5-dichlorosalicylaldehyde (**13**) and resolved at very mild conditions (25–35 °C; pH 7.5–8.5). Notably, even aliphatic esters give yields up to 90% and enantioselectivities >98%. In the case of aliphatic esters, we recommend to not run the DKR reaction above pH 8, because of the increased chemical hydrolysis of the ester groups. Selected results with the use of tyrosine esters are outlined in Table 3. In the case of D,L-TyrO-*i*Pr (**18**; Table 3, Entry 6) a significantly longer reaction time (5 d) was needed due to the slow enzymatic hydrolysis of the sterically hindered isopropyl ester.

Table 3. Dynamic kinetic resolution of racemic tyrosine esters.[a]

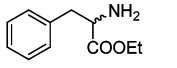
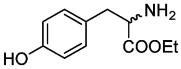
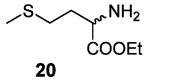
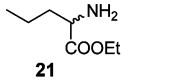
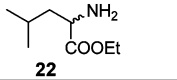


Entry	R	*T* [°C]	pH	*t* [h]	Yield [%]	*ee* [%] (L)
1[b]	Bn	35	8.5	24	95	**99**
2	Bn	35	8.5	24	87	97
3	Bn	35	8.5	48	92	97
4	Et	25	8.0	20	85	98
5	Et	35	7.5	72	92	98
6	*i*Pr	35	8.0	120	92	99

[a] Reaction conditions: alcalase® (2.0 mL, 0.06 AU), substrate (20 mmol), acetonitrile/water (4:1, 50 mL), 3,5-dichlorosalicylaldehyde (**13**; 2.5 mol-%). The enantiomeric excess was determined by chiral GC (25 m Chirasil-Val) of the corresponding perfluoropropionyl *O*-methyl ester. [b] 3,5-Dinitrosalicylaldehyde (**11**) instead of 3,5-dichlorosalicylaldehyde (**13**).

Finally, the established method was used for a range of aliphatic amino acid esters of alanine, leucine, norleucine, norvaline, and methionine. However, the corresponding amino acids were obtained only in moderate yields and enantioselectivities. The main problem of these reactions is the solubility of the amino acid esters and the enzyme in the reaction medium. Hence, we did some additional fine tuning. After some experimentation, it turned out that a lower amount of acetonitrile led to improved DKR reactions. In general, a 1:1 mixture of acetonitrile/water furnished excellent results with these aliphatic amino acid esters. Here, only 2.5 mol-% of 3,5-dinitrosalicylaldehyde as catalyst at room temperature was sufficient to maintain good racemization activity (Table 4).

Table 4. Dynamic kinetic resolution of several amino acid ethyl esters.[a]

Entry	Substrate	*t* [d]	Yield [%]	*ee* [%]
1	 **1**	1	95	99 (L)
2	 **17**	1	87[b]	97 (L)
3	 **20**	2	96	89 (L)
4	 **21**	4	98	64 (L)
5	 **22**	3	99	97 (L)

[a] Reaction conditions: alcalase® (1.0 mL, 0.6 AU; for tyrosine ester 0.06 AU), substrate (20 mmol), acetonitrile/water (1:1, 50 mL), 35 °C, 3,5-dinitrosalicylaldehyde (**11**; 2.5 mol-%). The enantiomeric excess was determined by chiral GC (25 m Chirasil-Val) of the corresponding perfluoropropionyl *O*-methyl ester. [b] Reaction was continued for an additional 1 d to give 94% yield and 95%*ee*.

Conclusions

We developed an easy and practical method to transform racemic amino acid esters to the corresponding enantiomerically pure amino acids. We showed that the salicylaldehyde-catalyzed racemization is applicable to a broad range of aliphatic amino acid esters.

Experimental Section

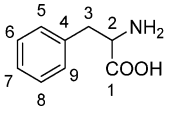
General: Alcalase® was purchased from Novo Nordisk (Denmark) as a brownish crude extract with a specific activity of 2.5 and 0.6 Anson-U mL^{-1}. Unless specified, all chemicals were commercially available and used as received. The amino acid esters were synthesized according to reported protocols by esterification of the corresponding amino acid with freshly distilled thionyl chloride or toluenesulfonic acids.[30] The optical purities of the α-amino acids were determined by chiral HPLC [CSP Crownpak CR(+) 150 × 4 DIACEL column, eluent: aqueous perchloric acid (1.63 g L^{-1})] or chiral GC analysis (Alltech Chiralsil Val column). In the case of chiral GC analysis, all amino acids were converted into the corresponding perfluoropropionate by reaction with perfluoropropionyl

chloride before measurements were carried out. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) were recorded with Bruker ARX 400 or Bruker DPX 250 instruments.

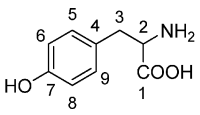
Racemization Reaction Mediated by Aldehydes: D-Phenylalanine benzyl ester hydrochloride (200 mg) was dissolved in DME/water (8.0 mL/2.0 mL) or acetonitrile/water (8.0 mL/2.0 mL). The pH value was set to 8.5 with aqueous solution of sodium hydroxide. The reaction was initiated with the addition of aldehyde (20 mol-%). If necessary, the pH value was corrected during the reaction.

Dynamic Kinetic Resolution of Phenylalanine and Tyrosine Esters: The racemic amino acid ester hydrochloride (20 mmol) was dissolved in acetonitrile/water (40 mL/10 mL). The pH of the solution was adjusted with a 2-N sodium hydroxide solution; meanwhile, phase separation occurred. The aqueous layer was removed, and the remaining organic phase was transferred into a flask connected with an autotitrator (aqueous 2 N sodium hydroxide solution). After heating to the required temperature, the reaction mixture was charged with enzyme (0.6 AU for phenylalanine esters, 0.06 AU for tyrosine esters) and aldehyde. The course of the reaction was controlled by chiral HPLC. The addition of 1,2-dimethoxyethane (100 mL) lead to nearly quantitative precipitation of the free amino acid (pH 5.5; temperature: 0 °C), which was collected by filtration.

Phenylalanine: ^{1}H NMR (400 MHz, CF_3CO_2D): δ = 7.70–7.45 (m, 5 H, 5-H, 6-H, 7-H, 8-H, 9-H), 4.88 (dd, J = 4.7 Hz, J = 8.7 Hz, 1 H, 2-H), 3.86 (dd, J = 4.7 Hz, J = 15.0 Hz, 1 H, 3-H), 3.58 (dd, J = 8.7 Hz, J = 15.0 Hz, 1 H, 3-H) ppm. ^{13}C NMR (100.6 MHz, CF_3CO_2D): δ = 174.5 (C-1), 133.3 (C-4), 131.7 (C-6, C-8), 130.9 (C-5, C-9), 130.8 (C-7), 57.3 (C-2), 37.3 (C-3) ppm. Retention time based on the corresponding perfluoropropionate (GC, 25 m Chirasil-Val, Alltech, 120 °C, isotherm): (D)-enantiomer 11.03 min and (L)-enantiomer 11.56 min.

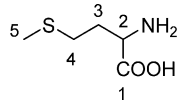


Tyrosine: ^{1}H NMR (400 MHz, CF_3CO_2D): δ = 7.45 (d, J = 8.5 Hz, 2 H, 6-H, 8-H), 7.22 (d, J = 8.5 Hz, 2 H, 5-H, 9-H), 4.84 (dd, J = 4.8 Hz, J = 8.5 Hz, 1 H, 2-H), 3.72 (dd, J = 4.8 Hz, J = 15.1 Hz, 1 H, 3-H), 3.51 (dd, J = 8.7 Hz, J = 15.1 Hz, 1 H, 3-H) ppm. ^{13}C NMR (100.6 MHz, CF_3CO_2D): δ = 172.5 (C-1), 154.2 (C-7), 130.6 (C-4), 125.1 (C-5, C-9), 116.6 (C-6, C-8), 55.1 (C-2), 34.5 (C-3) ppm. Retention time based on the corresponding perfluoropropionate (GC, 25 m Chirasil-Val, Alltech, 130 °C, isotherm): (D)-enantiomer 18.04 min and (L)-enantiomer 19.08 min.

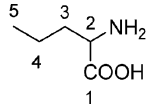


Dynamic Kinetic Resolution of Racemic Ethyl Ester of Phenylalanine, Tyrosine, Methionine, Norvaline, and Leucine: A mixture of alcalase® (0.6 AU) and 3,5-dinitrosalicylaldehyde (2.5 mol-%) in water (50 mL) were connected with an autotitrator and the pH value was set to 7.5 with aqueous sodium hydroxide solution. During a period of 2 min, a solution of amino acid ester (20 mmol) in acetonitrile (50 mL) was added. The course of the reaction was monitored by chiral HPLC. The final reaction mixture was acidified (pH 5.5), and the solvent was removed. The residue was extracted with ethyl acetate.

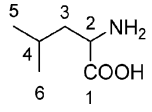
Methionine: ^{1}H NMR (400 MHz, CF_3CO_2D): δ = 8.02 (br. s, 2 H, NH_2), 4.65 (dd, J = 4.7 Hz, J = 7.4 Hz, 1 H, 2-H), 2.93 (t, J = 6.4 Hz, 2 H, 4-H), 2.62 (m, 1 H, 3-H), 2.47 (m, 1 H, 3-H), 2.24 (s, 3 H, 5-H) ppm. ^{13}C NMR (100.6 MHz, CF_3CO_2D): δ = 172.9 (C-1), 53.9 (C-2), 29.1 (C-3), 27.1 (C-4), 13.0 (C-5) ppm. Retention time based on the corresponding perfluoropropionate (GC, 25 m Chirasil-Val, Alltech, 120 °C, isotherm): (D)-enantiomer 7.57 min and (L)-enantiomer 8.06 min.



Norvaline: ^{1}H NMR (400 MHz, CF_3CO_2D): δ = 7.34 (br. s, 2 H, NH_2), 4.34 (dd ≈ t, J = 5.9 Hz, 1 H, 2-H), 2.09 (m, 2 H, 3-H), 1.54 (m, 2 H, 4-H), 1.02 (t, J = 7.4 Hz, 3 H, 5-H) ppm. ^{13}C NMR (100 MHz, CF_3CO_2D): δ = 175.6 (C-1), 56.3 (C-2), 33.8 (C-3), 19.7 (C-4), 13.5 (C-5) ppm. Retention time based on the corresponding perfluoropropionate (GC, 25 m Chirasil-Val, Alltech, 90 °C, isotherm): (D)-enantiomer 4.78 min and (L)-enantiomer 5.25 min.



Leucine: ^{1}H NMR (400 MHz, CF_3CO_2D): δ = 4.34 (m, 1 H, 2-H), 1.99 (m, 1 H, 4-H), 1.86 (m, 2 H, 3-H), 1.02 (t, J = 5.6 Hz, 6 H, 5-H, 6-H) ppm. ^{13}C NMR (100 MHz, CF_3CO_2D): δ = 173.7 (C-1), 52.7 (C-2), 38.9 (C-3), 24.2 (C-4), 20.3 (C-6), 19.7 (C-5) ppm. Retention time based on the corresponding perfluoropropionate (GC, 25 m Chirasil-Val, Alltech, 90 °C, isotherm): (D)-enantiomer 6.60 min and (L)-enantiomer 7.69 min.



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