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Enantioselective hydrolysis of (*RS*)-2-fluoroarylacetonitriles using nitrilase from *Arabidopsis thaliana*[1]

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Abstract—The enzymatic resolution of 2-fluoroarylacetonitriles (*RS*)-**3** using nitrilase from the plant *Arabidopsis thaliana* is described. Racemic 2-fluoronitriles **3** are easily accessible from *O*-silylated aromatic cyanohydrins **2** by reaction with DAST. The nitriles (*RS*)-**3** were hydrolysed with the nitrilase as a catalyst, not to the expected 2-fluoroarylacetic acids but to the corresponding (*R*)-2-fluoroarylacetamides (*R*)-**5** as the main products. After optimization of reaction conditions (pH 9, 7°C), the enantiomeric excesses of (*R*)-**5a**,**c** and **f** (R = H, 3-Me, 3-OMe) could be improved to >99% by one recrystallization. The acid catalysed hydrolysis of (*R*)-**5a**,**5c** and **5f** afforded the corresponding (*R*)-2-fluoroarylacetic acids (*R*)-**4a**,**4c** and **4f** without racemization.

1. Introduction

Since C–H and C–F bonds are comparable in their steric demands but markedly different in their electronic properties, organofluorine compounds play an important role in a variety of applications including medicinal diagnostics, nuclear magnetic resonance tomography, positron emission tomography (PET) and so on.[2–4] Organofluorine compounds have attracted particular attention in biologically active compounds.[5] Thus optically active α-fluorocarboxylic acids and their derivatives are highly potent as analogues of pheromones,[6] antirheumatics[7] and as analgesics.[8]

Stereoselective syntheses have been developed especially for α-fluorocarboxylic acids because of their biological activity.[5] The kinetic resolution of ethyl α-fluorohexanoate[9a] and alkyl 2-fluorodecanoates[9b] is reported for the application of enzymes in the preparation of optically active α-fluorocarboxylic acids. For the preparation of optically active α-fluorophenylacetic acids, however, neither an efficient enzymatic nor efficient chemical procedure is so far known which affords enantiopure fluoro acids. Because racemic α-fluoronitriles are readily accessible by reaction of unprotected or *O*-silylated cyanohydrins with diethylaminosulfur trifluoride (DAST),[10] the kinetic resolution of α-fluoronitriles appears to offer an easy approach to the enantiopure α-fluorocarboxylic acids. Nitrilases can be classified, depending on their substrate specificity, into 'aromatic nitrilases', 'arylacetonitrilases' and 'aliphatic nitrilases'.[11] The nitrilases from *Alcaligenes faecalis* ATCC 8750,[12] *Alcaligenes faecalis* JM3[13] and *Pseudomonas fluorescens* DSM 7155[14] were unambiguously identified as arylacetonitrilases.[14] Nitrilases derived from plants have not yet been investigated systematically with respect to their substrate specificities.

To date, the nitrilase from *Arabidopsis thaliana* is the only plant nitrilase known to be cloned, sequenced and functionally expressed in *E. coli*,[15] hence, this enzyme is available in amounts sufficient for preparative applications. In a comprehensive investigation of the substrate range of *A. thaliana* nitrilase[16] α-fluoroarylacetonitriles were found to be possible substrates for this enzyme.

Herein, we report the kinetic resolution of α-fluoroarylacetonitriles using nitrilase from *A. thaliana* and the study of the reaction under a number of reaction conditions.

2. Results and discussion

2.1. Preparation of 2-fluoroarylnitriles 3

The racemic 2-fluoronitriles **3** were prepared analogously to the methodology developed by Le Tourneau et al.[10] In a one-pot reaction the starting aldehydes **1** were reacted with trimethylsilylcyanide to

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give the corresponding silylated cyanohydrins **2**, which subsequently gave the 2-fluoronitriles **3** with diethylaminosulfur trifluoride (DAST) (Scheme 1).[10a] 2-Fluoro-2-(methylphenyl)ethanenitriles **3b**,**c**,**d**, which have not been described so far, could be isolated by this route in 66–79% yield. For the synthesis of 2-fluoro-2-(3-methoxyphenyl)ethanenitrile **3f** the method was modified to improve the yield. The silylated cyanohydrin **2f**[17] was first distilled and subsequently fluorinated with DAST at −78°C, giving **3f** in 70% yield.

The 2-fluorocarboxylic acids **4**, required as reference compounds, were prepared by acid hydrolysis of the nitriles **3**. In the hydrolysis of **3a** with concentrated HCl, halogen exchange was observed and 2-chloro-2-phenylacetic acid[18] formed, as well as the desired 2-fluoro-2-phenylacetic acid **4a**. By using 49% sulfuric acid instead of HCl, the fluoroacetic acids **4** were obtained as the sole products in 26–64% yield.

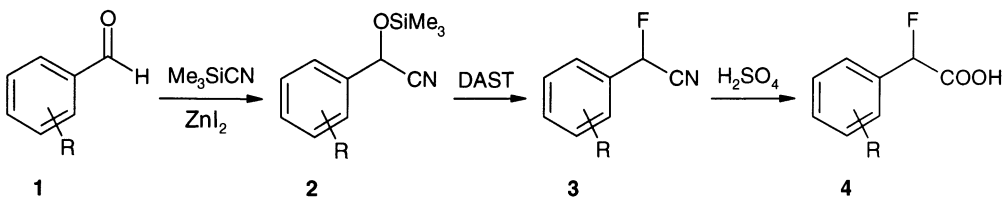
2.2. Enzymatic hydrolysis of 2-fluoroarylnitriles 3 using the nitrilase from *Arabidopsis thaliana*

Preliminary investigations of the nitrilase catalysed hydrolysis of 2-fluorobenzyl cyanide **3a**, as depicted in Scheme 2, surprisingly resulted in the formation of 2-fluoro-2-phenylacetamide **5a** as the main product with acid **4a** obtained as a side product. Normally the nitrilase of *A. thaliana* reacts as nitrilase to give only the carboxylic acid and not as hydratase/amidase yielding the amide in the first step and the acid in the second step.[16] The acid **4a** was extracted with sodium bicarbonate solution, while the mixture of nitrile and amide can be separated by chromatography on silica gel with different eluents. The enantiomers of both the remaining nitrile and acid (as methyl ester) could be separated directly by gas chromatography. The enantiomeric excess of the amide **5a** was determined by gas chromatography after hydrolysis and subsequent esterification of the intermediate acid with diazomethane. Conversion and amide/acid ratio were determined by HPLC. The configuration of the products was assigned by comparison of specific rotation values of acid **4a** and nitrile **3a** with literature data.[10b,19]

At 41% conversion, nitrile **3a**, acid **4a** and amide **5a** were obtained in a ratio of 59:6:35. The amide **5a** is (*R*)-configured, with an e.e. of 76% (Table 1), whereas the acid **4a** (with an e.e. of 13%) and the main enantiomer of the remaining nitrile **3a** (with an e.e. of 36%) were found to have (*S*)-configuration.

At higher conversion rates, the e.e.s of the (*S*)-nitrile and the (*S*)-acid did not increase as expected. After 24 h and 84% conversion, nitrile **3a**, acid **4a** and amide **5a** were obtained in a ratio of 16:22:62 with e.e.s of 47, 42 and 59%, respectively. This result is caused by racemization of the nitrile **3a** under the reaction conditions, as was demonstrated by using isolated (*S*)-**3a**.

Additional substrates (*RS*)-**3b**–**3f** have been hydrolysed and investigated using the nitrilase of *A. thaliana* with respect to the influence of aromatic ring substituents, R, on the rates and enantioselectivities of the conversions (Scheme 2, Table 1).



1-4	a	b	c	d	e	f
R	H	2-Me	3-Me	4-Me	4-NO_2	3-OMe

Scheme 1.

Table 1. Enantioselective hydrolysis of 2-fluoronitriles (*RS*)-**3** to 2-fluoroacetamides (*R*)-**5** and 2-fluoroacetic acids (*S*)-**4** catalysed by the nitrilase from *Arabidopsis thaliana*

Substrate	Rel. activity (%)[a]	Conversion (%)[b]	Ratio **5**:**4**	2-Fluoro acids		2-Fluoroamides	
				(*S*)-**4**	% E.e.	(*R*)-**5**	% E.e.
3a	26	41	85:15	**4a**	13	**5a**	76
3b	<0.1	–	–	**4b**	–	**5b**	–
3c	35	33	80:20	**4c**	14	**5c**	76
3d	4.3	21	70:30	**4d**	<5	**5d**	22
3e	2.8	34	85:15	**4e**	<5	**5e**	<5
3f	23	21	82:18	**4f**	11	**5f**	80

[a] Activity referred to butyronitrile.
[b] Conversion is defined as: conversion = [amide]+[acid]/[nitrile]$_0$.

Table 1 shows that the substituent R sterically influences the enzyme activity. While 2-fluoro-2-(2-methylphenyl)benzyl cyanide **3b** was not accepted by the nitrilase from *A. thaliana*, nitriles **3d** and **3e**, carrying *para*-substituted phenyl rings, were hydrolysed 6–10 times slower than **3a**. The 2-fluorobenzyl cyanides **3c** and **3f** with *meta*-substituted phenyl rings, however, were converted with rates similar to compound **3a**. In all cases, the ratio (*R*)-amide **5**/(*S*)-acid **4** is comparable, with the amide as the main product.

With respect to the amide (*R*)-**5**, the stereoselectivity is satisfactory only for the nitriles **3a**, **3c** and **3f**, yielding the amides (*R*)-**5a**, **5c** and **5f** with an e.e. of approximately 80%. The enantiomeric excesses determined for the acids (*S*)-**4** are low in all cases (Table 1). In order to improve the enantiomeric excess of the (*R*)-amides, the reaction conditions have been varied, using 2-fluorobenzyl cyanide **3a** as substrate. The results are summarized in Table 2.

As can be seen from Table 2, the variation of the pH value from 8.0 to 9.5 at 20°C has almost no influence on the enantiomeric excess. The best result at this temperature, an e.e. of 82%, was obtained at pH 9.0, the pH optimum of the nitrilase.[16,20] The temperature, however, had a very significant influence on the observed e.e. An increase in e.e. from 40 to 82% was seen on lowering the reaction temperature from 30 to 20°C. Lowering the temperature further to 7°C led to a further increase in the e.e., which increased to 94% at 39% conversion.

On a preparative scale under optimized reaction conditions (pH 9.0 at 7°C), (*R*)-2-fluoro-2-phenylacetamide (*R*)-**5a** was isolated at 53% conversion with an e.e. of 92%. After recrystallization from petroleum ether/chloroform enantiomerically pure (*R*)-**5a** was obtained in 72% yield (referred to conversion) (see Scheme 3, Table 3).

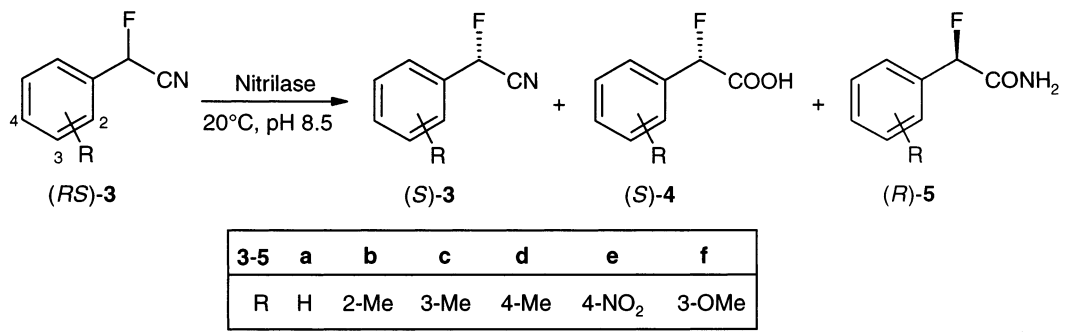
Table 2. Optimization of the reaction conditions using 2-fluoro-2-phenylethanenitrile **3a** as substrate

pH	Temp. (°C)	Conversion (%)	Ratio **5a**:**4a**	(*R*)-**5a** % e.e.
8.0	20	18	87:13	75
8.5	20	24	85:15	81
9.0	20	21	82:18	82
9.5	20	11	82:18	71
9.0	30	46	71:29	40
9.0	7	39	84:16	94

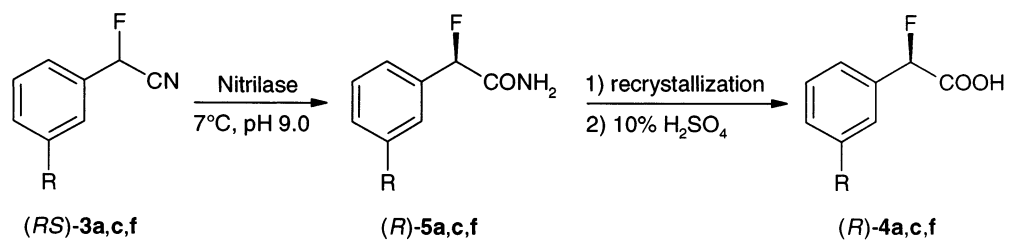
The optimized reaction conditions were also applied to substrates **3c** and **3f** (Scheme 3, Table 3). The nitrilase catalysed hydrolysis gave the (*R*)-amides **5c** and **5f** with e.e.s of 88 and 91%, respectively, and about 50% conversion. E.e.s were improved by recrystallization from petroleum ether/chloroform to afford **5c** with an e.e. of 97% and **5f** with e.e. of >99%. The total yield of both amides after enzymatic hydrolysis and recrystallization was in the range of 60–70%, referred to the conversion of nitriles (*R*)-**3c** and (*R*)-**3f**.

The acid catalysed hydrolysis of (*R*)-**5a**, **5c** and **5f** with 10% sulfuric acid proceeded without racemization, giving the (*R*)-2-fluoroacetic acids (*R*)-**4a**, **4c** and **4f** in 80–90% yield with enantiomeric excesses of 98 to >99% (Table 3). Because both the sign of optical rotation values and the retention order of **4c** and **4f** correspond with those of acid (*R*)-**4a**, the (*R*)-configuration was also assigned to **4c** and **4f**.

In summary, enantiomerically pure (*R*)-2-fluoroarylacetamides **5** are accessible for the first time by the kinetic resolution of racemic 2-fluoroarylnitriles (*RS*)-**3** cat-



Scheme 2.



Scheme 3.

Table 3. Enzymatic hydrolysis of 2-fluoronitriles (*RS*)-**3a**,**3c**,**3f** to (*R*)-2-fluoroacetamides (*R*)-**5a**,**5c**,**5f** and their hydrolysis to 2-fluoroacetic acids (*R*)-**4a**,**4c**,**4f**

Substrates (*RS*)-**3**	Conv. (%)[a]	2-Fluoroacetamides (*R*)-**5**				2-Fluoroacetic acids (*R*)-**4**		
			% E.e.	Yield (%)[b]	% E.e.[c]		Yield (%)	% E.e.
3a	53	**5a**	92	72	>99	**4a**	91	>99
3c	56	**5c**	88	61	97	**4c**	90	98
3f	48	**5f**	91	67	>99	**4f**	88	>99

[a] Conversion for the enzymatic reaction of (*RS*)-**3**.
[b] Total yield of enzymatic reaction and recrystallization referred to reacted nitrile (*R*)-**3**.
[c] E.e. values after recrystallization.

alysed by a nitrilase from *A. thaliana*. (*R*)-2-Fluoroarylacetamides can easily be hydrolysed in 10% sulfuric acid to give the corresponding (*R*)-2-fluoroarylacetic acids **4** without any racemization. The enzymatic hydrolysis of arylacetonitriles to the corresponding amides is superior to chemical hydrolysis because no decomposition products are found. The isolated nitrile starting material can be easily racemized by heating at 50°C for 1 h in the buffer applied for the enzymatic conversion and thus can be returned to the resolution. Because racemic 2-fluoroamides are known to be fungitoxic,[21] the optically pure forms are also expected to have biological activity.

3. Experimental

3.1. Materials and methods

Melting points were determined on a Büchi SMP-20 and are uncorrected. Unless otherwise stated, ^{1}H NMR spectra were recorded on a Bruker AC 250 F (250 MHz) and ARX 500 (500 MHz) in $CDCl_3$ with TMS as internal standard. Chromatography was performed using silica gel S (Riedel-de Haen), grain size 0.032–0.063 mm. HPLC was performed on a Pharmacia LKB with VWM 2141 detector using an RP-C18 Vertex column (25 cm×4 mm) with Nucleosil 100, 5 μm (Knaur). Optical rotations were measured in a thermostated polarimeter with $l=10$ cm. Enantiomeric excesses: GC separations were conducted with a Chiraldex G-TA (ICT) column (30 m×0.32 mm), carrier gas hydrogen. All solvents were dried and distilled.

3.2. Preparation of 2-fluoroethanenitriles 3b,c and d; general procedure

According to a known procedure,[10a] to the respective methylbenzaldehyde **1b–d** (2.40 g, 20 mmol) and ZnI_2 (10 mg, 0.031 mmol) at 0°C under an inert gas atmosphere, trimethylsilyl cyanide (1.98 g, 20 mmol) was slowly added dropwise with stirring. After warming to room temperature, the reaction mixture was stirred for a further 20 min. The reaction mixture was mixed with anhydrous dichloromethane (25 mL), cooled to 0°C, and a solution of DAST (3.55 g, 22 mmol) in dichloromethane (10 mL) was slowly added dropwise. The reaction mixture was allowed to warm to room temperature, stirred for a further 20 min, poured on ice (100 mL) and vigorously stirred for 5 min. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2×100 mL). The combined organic phases were washed with a 5% aqueous $NaHCO_3$ solution and water to neutralize, dried (Na_2SO_4) and concentrated. The crude products were chromatographed on silica gel with petroleum ether/ethyl acetate (90:10 for **3b**, **3d**, 93:7 for **3c**).

3.2.1. 2-Fluoro-2-(2-methylphenyl)ethanenitrile 3b. Yield: 79% (light yellow oil). ^{1}H NMR (250 MHz): δ 2.46 (s, 3H), 6.19 (d, $J=46.4$ Hz, 1H), 7.25–7.58 (m, 4H). Anal. calcd for C_9H_8FN (149.2): C, 72.47; H, 5.41; N, 9.39. Found: C, 72.42; H, 5.47; N, 9.34%.

3.2.2. 2-Fluoro-2-(3-methylphenyl)ethanenitrile 3c. Yield: 72% (light yellow oil). ^{1}H NMR (250 MHz): δ 2.41 (s, 3H), 6.00 (d, $J=47.1$ Hz, 1H), 7.29–7.37 (m, 4H). Anal. calcd for C_9H_8FN (149.2): C, 72.47; H, 5.41; N, 9.39. Found: C, 72.68; H, 5.40; N, 9.24%.

3.2.3. 2-Fluoro-2-(4-methylphenyl)ethanenitrile 3d. Yield: 66% (light yellow oil). ^{1}H NMR (250 MHz): δ 2.40 (s, 3H), 6.00 (d, $J=47.3$ Hz, 1H), 7.25–7.46 (m, 4H). Anal. calcd for C_9H_8FN (149.2): C, 72.47; H, 5.41; N, 9.39. Found: C, 72.76; H, 5.60; N, 9.22%.

3.3. 2-Fluoro-2-(3-methoxyphenyl)ethanenitrile 3f

To a solution of **2f**[17] (4.71 g, 20.0 mmol) in dichloromethane (50 mL) at −78°C under an inert gas atmosphere DAST (3.55 g, 22.0 mmol) was slowly added dropwise, and the reaction mixture was stirred for 1 h at −78°C. The mixture was poured on ice (100 mL) and was vigorously stirred for 5 min. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2×100 mL). The combined organic phases were washed with a 5% aqueous $NaHCO_3$ solution to neutralize, and water. The organic extract was then dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel with petroleum ether/ethyl acetate (85:15) to give **3f** as a light yellow oil (2.32 g, 70%). ^{1}H NMR (250 MHz): δ 3.84 (s, 3H), 6.02 (d, $J=46.9$ Hz, 1H), 7.06–7.42 (m, 4H).

Table 4. Physical data and elemental analysis of 2-fluoroacetic acids **4**

Compd	Mp (°C)	^{1}H NMR (250 MHz, $CDCl_3$) δ	Elemental analysis (calcd/found)			
			Mol. formula (mol. weight)	C	H	N
4a	103	5.81 (d, J=47.4 Hz, 1H), 7.37–7.49 (m, 5H), 11.50 (br s, 1H)	$C_8H_7FO_2$ (154.1)	62.34 62.52	4.58 4.68	–
4c[a]	83–85.5	2.30 (s, 3H), 5.70 (d, J=47.8 Hz, 1H), 7.14–7.22 (m, 4H)	$C_9H_9FO_2$ (168.2)	64.28 64.27	5.39 5.53	–
4d[a]	108–109	2.34 (s, 3H), 5.95 (d, J=47.7 Hz, 1H), 7.26–7.37 (m, 4H), 13.50 (br s, 1H)	$C_9H_9FO_2$ (168.2)	64.28 64.44	5.39 5.45	–
4e[b]	92–94	6.27 (d, J=46.9 Hz, 1H), 7.72–8.33 (m, 4H)	$C_8H_6FNO_4$ (199.1)	48.25 48.25	3.04 3.07	7.03 6.96

[a] 500 MHz spectra.
[b] In DMSO-d_6.

3.4. Acid hydrolysis of 2-fluoronitriles 3 to the 2-fluoroacetic acids 4; general procedure

A vigorously stirred emulsion of **3** in a 49% aqueous solution of sulfuric acid (50 mL/g of **3**) was heated at 80°C for at least 3 h. After being cooled to room temperature, the aqueous phase was extracted twice with the double volume of diethyl ether. Acids **4** were extracted from the combined organic phases with a sat. $NaHCO_3$ solution (1/10 volume referred to the ethereal phase). The aqueous phase was acidified to pH 4 and extracted twice with the double volume of diethyl ether. The combined extracts were dried (Na_2SO_4) and concentrated. The residue was recrystallized from chloroform/petroleum ether (Table 4).

3.5. Crude extract preparation and enzymatic hydrolysis of 2-fluoronitriles (*RS*)-3 using the nitrilase from *Arabidopsis thaliana*; general procedure

Cells were separated from the nutrient medium by centrifugation for 30 min at 4°C (5700×g) and washed with Tris/HCl buffer (70 mM, pH 8.0–9.5). The pellet was re-suspended in Tris/HCl buffer (100 mL/10 g wet weight), sonicated with ice cooling (3×5 min), and centrifuged for 40 min (186 000×g). The supernatant containing the crude enzyme was diluted with Tris/HCl buffer (to reach 15–40% conversion after 2–4 h), and a 1 M solution of **3** in methanol (10 mM end concentration) was added. After being stirred for 2–4 h, samples of 6 mL volume were taken and analyzed as described in Section 3.6.

3.6. Analytical procedure for the determination of conversion, acid/amide ratios and enantiomeric excesses

3.6.1. Ratio of 3:4:5 determined by HPLC. The sample (1 mL) was acidified with a 5 M HCl solution (50 μL) and extracted with diethyl ether (5 mL). After centrifugation (2000×g) and cooling at −30°C for 30 min to freeze the aqueous phase, the organic phase was decanted and concentrated in vacuo. The residue was taken up in 1 mL of phosphate buffer (50 mM, pH 2.3)/acetonitrile (70:30) and analyzed by HPLC (flow 1 mL/min, detection wavelength 210 nm).

3.6.2. Determination of enantiomeric excesses of compounds 3–5. A 5 M aqueous Na_2CO_3 solution (250 μL) was added to the remaining 5 mL of the sample. The reaction mixture was extracted with diethyl ether. The aqueous phase was separated, acidified with a 5 M HCl solution (500 μL) and extracted with diethyl ether. After esterification with diazomethane,[22] the enantiomeric excess of acid **4** was determined by gas chromatography.

The ethereal phase was concentrated, and the mixture of nitrile **3** and amide **5** was separated by chromatography on a silica gel column (5×0.5 cm). Compound **3** was eluted with petroleum ether/ethyl acetate (90:10) (3×5 mL) and the e.e. value was determined by gas chromatography directly from the filtrate. Compound **5** was eluted with ethyl acetate (5 mL), concentrated, and hydrolysed to the corresponding acid in half-conc. sulfuric acid by heating at 60°C for 3 h. After extraction with diethyl ether (5 mL) and esterification with diazomethane,[22] the enantiomeric excess was determined by gas chromatography.

3.7. Enzymatic hydrolysis of (*RS*)-3a,c and f using the nitrilase of *Arabidopsis thaliana* on a preparative scale; general procedure

To a solution of crude enzyme (156 U) in Tris/HCl buffer (370 mL, 70 mM, pH 9) at 7°C was added **3a**,**c** or **f** (0.5 g each) as a 1 M solution in methanol, and the reaction mixture was stirred for 9.5 h. Then it was acidified to pH 4 with a 5 M HCl solution and extracted with diethyl ether. In order to separate the formed acid **4**, the combined organic phases were extracted twice with a 10% (v/v) sat. aqueous $NaHCO_3$ solution. The organic phase, containing nitrile **3** and amide **5**, was dried (Na_2SO_4) and concentrated. The mixture of **3** and **5** was separated by chromatography on silica gel with petroleum ether/ethyl acetate (90:10) (for **3**), followed by ethyl acetate (for **5**). After concen-

tration, (*R*)-amides **5** were recrystallized from petroleum ether/chloroform. The amides **5d**,**e**, required as reference compounds, were prepared analogously.

3.7.1. (*R*)-2-Fluoro-2-phenylacetamide (*R*)-5a. White needles; mp 144–145°C; $[\alpha]_D^{20}=+122.3$ (*c* 0.9, $CHCl_3$), e.e. = >99%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.76 (d, $J=48.4$ Hz, 1H), 6.26, 6.47 (br s each, 2H), 7.46–7.48 (m, 5H). Anal. calcd for C_8H_8FNO (153.2): C, 62.74; H, 5.26; N, 9.15. Found: C, 62.61; H, 5.27; N, 9.14%.

3.7.2. (*R*)-2-Fluoro-2-(3-methylphenyl)acetamide (*R*)-5c. White needles; mp 125–126°C; $[\alpha]_D^{20}=+107.3$ (*c* 0.7, $CHCl_3$), e.e. = 97%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.32 (s, 3H), 5.73 (d, $J=48.1$ Hz, 1H), 7.21–7.31 (m, 4H), 7.56, 7.85 (br s each, 2H). Anal. calcd for $C_9H_{10}FNO$ (167.2): C, 64.66; H, 6.03; N, 8.38. Found: C, 64.50; H, 6.00; N, 8.36%.

3.7.3. 2-Fluoro-2-(4-methylphenyl)acetamide 5d. Mp 140–141°C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.31 (s, 3H), 5.73 (d, $J=48.2$ Hz, 1H), 7.21–7.35 (m, 4H), 7.57, 7.86 (br s each, 2H). Anal. calcd for $C_9H_{10}FNO$ (167.2): C, 64.66; H, 6.03; N, 8.38. Found: C, 64.56; H, 6.07; N, 8.35%.

3.7.4. 2-Fluoro-2-(4-nitrophenyl)acetamide 5e. Mp 111–113°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.73 (d, $J=48.2$ Hz, 1H), 7.22–8.31 (m, 4H), 7.71, 8.02 (br s each, 2H). HRMS calcd for $C_8H_7FN_2O_3$ (M^+) 198.0441. Found: 198.0443.

3.7.5. (*R*)-2-Fluoro-2-(3-methoxyphenyl)acetamide (*R*)-5f. White needles; mp 89–90°C; $[\alpha]_D^{20}=+141.8$ (*c* 1.0, $CHCl_3$), e.e. = >99%. ^{1}H NMR (250 MHz, DMSO-d_6): δ 3.73 (s, 3H), 5.76 (d, $J=48.0$ Hz, 1H), 6.95–7.56 (m, 4H), 7.56, 7.86 (br s each, 2H). Anal. calcd for $C_9H_{10}FNO_2$ (183.2): C, 59.01; H, 5.50; N, 7.65. Found: C, 59.10; H, 5.63; N, 7.45%.

3.8. Acid hydrolysis of (*R*)-2-fluoroamides 5a,c and f to (*R*)-2-fluoroacetic acids 4a,c and f; general procedure

Amide **5a**,**c** or **f** (0.82–1.31 mmol) was suspended in a 10% solution of sulfuric acid (25 mL/100 mg **5**). The vigorously stirred reaction mixture was heated at 60°C for 3 h, and extracted twice with the double volume of diethyl ether. The corresponding acid **4** was extracted from the organic phase with a sat. $NaHCO_3$ solution (1/10 volume of the organic phase). The aqueous phase was acidified to pH 4 and extracted with the double volume of diethyl ether. The combined extracts were dried (Na_2SO_4) and concentrated. Acids **4** were recrystallized from petroleum ether/chloroform.

3.8.1. (*R*)-2-Fluoro-2-phenylacetic acid (*R*)-4a. White needles; mp 104°C; $[\alpha]_D^{20}=+150.3$ (*c* 1.0, $CHCl_3$), e.e. = >99%. $[\alpha]_D^{20}=+71.4$ (*c* 1.25, $CHCl_3$), e.e. = 46%.[19] NMR data correspond to those of racemic **4a**.

3.8.2. (*R*)-2-Fluoro-2-(3-methylphenyl)acetic acid (*R*)-4c. White needles; mp 83–84°C; $[\alpha]_D^{20}=+137.4$ (*c* 1.0, $CHCl_3$), e.e. = 98%. NMR data correspond to those of racemic **4c**.

3.8.3. (*R*)-2-Fluoro-2-(3-methoxyphenyl)acetic acid (*R*)-4f. White needles; mp 67–69°C; $[\alpha]_D^{20}=+154.0$ (*c* 1.0, $CHCl_3$), e.e. = >99%. ^{1}H NMR (500 MHz): δ 3.77 (s, 3H), 5.95 (d, $J=47.6$ Hz, 1H), 6.99–7.38 (m, 4H), 13.50 (br s, 1H). Anal. calcd for $C_9H_9FO_3$ (184.2): C, 58.70; H, 4.93. Found: C, 58.91; H, 4.98%.

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