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Asymmetric Amination of Tetralone and Chromanone Derivatives Employing ω-Transaminases

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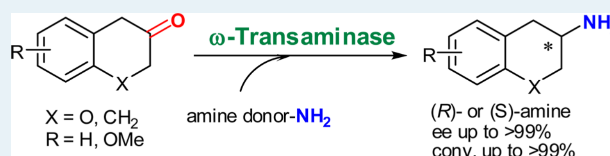
Supporting Information

ABSTRACT: Various (*S*)-selective and (*R*)-selective *ω*-transaminases were investigated for the amination of 1- and 2-tetralone and derivatives as well as of 3- and 4-chromanone. All ketones tested were aminated to give the corresponding enantiopure amines (*ee* > 99%) employing at least one of the enzymes investigated. In most of the cases the (*S*)- as well as the (*R*)-enantiomer was obtained in optically pure form. The amination of 3-chromanone was performed on a 100 mg scale leading to optically pure (*R*)-3-aminochromane (*ee* > 99%) with complete conversion and 78% isolated yield.



KEYWORDS: *asymmetric catalysis, biocatalysis, amination, ω-transaminase, aminochromane, aminotetraline*

INTRODUCTION

Chiral amine moieties are ubiquitously found in a vast number of natural products and bioactive compounds, like pharmaceuticals and agro chemicals.[1−5] For instance, the 1-aminotetraline backbone can be found in various pharmaceuticals such as the antidepressiva Sertraline[6−11] or Norsertraline.[12] 2-Aminotetraline represents the scaffold of Rotigotine, a drug employed for the treatment of Parkinson as well as Willis-Ekbom diseases.[13] Furthermore, (*S*)-3-aminochromane shares the same backbone as the antidepressant and anxiolytic drug Alnespirone,[14] whereas its enantiomeric form is a part of the antihypertensive Etamicastat[15,16] and the 5-HT1A receptor antagonist Robalzotan.[17,18]

Aminotetraline and aminochromane derivatives have been obtained previously by resolution of racemic mixtures using fractional crystallization[19−22] or chiral auxiliaries[12] as well as via organic synthesis from chiral precursors.[23−25] Dynamic kinetic resolution (DKR) (i.e., Ru, Pd, Ni catalyzed racemization combined with a lipase catalyzed resolution) afforded the amines in high optical purity (>99% *ee*) and good yields.[26,27] The DKR of amines was plagued by the low racemization rate (up to 3 days) even at higher temperature (70 °C) and the often not perfect chemoselectivity.[28−30] Adding gaseous hydrogen (ca. 0.1 bar)[31] or applying microwave irradiation accelerated the racemization rate.[32] The asymmetric hydrogenation using metal-catalysts at high pressure (i.e., up to 100 bar) of enamides, imines, and oximes furnished optically active amines.[1−3,33] Interestingly, the asymmetric hydrogenation of the enamide analogues of the ketones **2b** and **2e** led to high *ee*'s (98% and >99%, respectively),[34−37] whereas the enamides of **2a** and **2f** were hydrogenated with 92−94% *ee*.[38−40]

A metal-free biocatalytic amination of prochiral ketones can be performed employing *ω*-transaminases (*ω*TAs).[1,41−45] *ω*TAs have been recently investigated with increased efforts for asymmetric synthesis,[46−63] leading also to the launch of an industrial process.[64]

RESULTS AND DISCUSSION

Various (*S*)-selective and (*R*)-selective *ω*-transaminases were investigated for the asymmetric amination of 1- and 2-tetralone and derivatives as well as of 3- and 4-chromanone. The *ω*TAs were employed as freeze-dried cell powder of *E. coli* containing the overexpressed enzyme. The amination of the ketones was conducted using alanine as amine donor and removing the coproduct pyruvate by either a lactate dehydrogenase (LDH, Scheme 1, LDH-system) or alanine dehydrogenase (AlaDH, AlaDH-system). The cofactor NADH required by the LDH/AlaDH was recycled employing GDH-glucose or FDH-formate. Depending on the stereoselectivity of the *ω*TA, either L- or D-alanine was supplied.

As an alternative, the bioamination was performed using 2-propylamine as amine donor employing the engineered variant from *Arthrobacter* sp. (ArRmut11-*ω*TA)[64] in aqueous phase at pH 11 leading to acetone as a coproduct (Scheme 2, 2-PrNH$_2$ system). This variant was designed for the amination of sterically hindered ketones bearing to bulky substituents (bulky-bulky ketones) on an industrial scale.[64] Dimethylsulfoxide (DMSO) was added as cosolvent in few selected cases (20% v v^{-1}) for transformations employing (*R*)-selective *ω*TAs.

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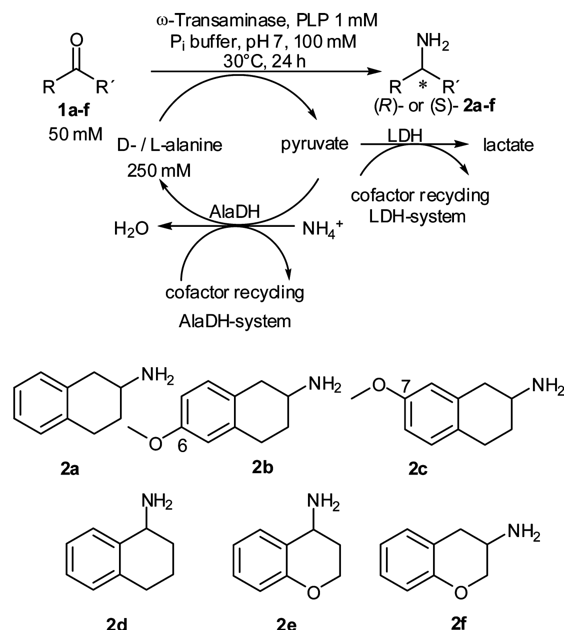
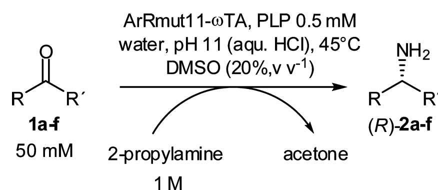
Scheme 1. Asymmetric Reductive Amination of Prochiral Ketones (1a–f) Employing ω-Transaminases (ωTAs) with Alanine as Amine Donor



Scheme 2. Asymmetric Bioamination Employing 2-Propylamine as Amine Donor (2-PrNH$_2$ System)



The (*S*)-selective ωTAs from the following strains were tested: *Vibrio fluvialis* (VF-ωTA),[65] *Chromobacterium violaceum* (CV-ωTA),[66] *Bacillus megaterium* (BM-ωTA),[67] *Paracoccus denitrificans* (PD-ωTA),[68] *Pseudomonas fluorescens* (PF-ωTA)[69] as well as a variant from *Arthrobacter citreus* (ArS-ωTA).[70] The (*R*)-selective ωTAs originated from *Aspergillus terreus* (AT-ωTA),[59] *Hyphomonas neptunium* (HN-ωTA),[59] *Arthrobacter* sp. (ArR-ωTA)[71] as well as its variant ArRmut11-ωTA.[64]

β-Tetralone **1a** was in general very well accepted by most of the (*S*)-selective transaminases leading to high or even complete conversion. Interestingly, only ArS-ωTA performed the amination with *ee* > 99% (Table 1, entry 1). The (*R*)-selective ArR-ωTAs and the variant from *Arthrobacter* sp. (ArRmut11-ωTA) aminated ketone **1a** yielding the amine with only moderate *ee*'s (76 and 54%, entries 3–4), while AT-ωTA and HN-ωTA were not active at all.

Introducing a substituent in 6-position, 6-methoxy substituted *β*-tetralone **1b** was aminated with slightly higher stereoselectivities compared to **1a** by various ωTAs (see Supporting Information). For instance, (*S*)-6-methoxy-2-aminotetraline **2b** was obtained in enantiopure form using ArS-ωTA as well as BM-ωTA (entries 5–6) while ArRmut11-ωTA yielded (*R*)-**2b** with perfect stereoselectivity (>99% *ee*, entry 8). On the other hand CV-ωTA led to (*S*)-**2b** with moderate *ee* (79%, entry 7). The stereoselectivity of CV improved significantly when the methoxy substituent was in 7-position (substrate **1c**). Actually five (*S*)-selective ωTAs out of six, namely, VF, PD, BM, CV, and PF converted (*S*)-7-methoxy-2-tetralone (**1c**) with perfect *ee* (>99%). Additionally quantitative conversion could be achieved in four cases (>99%, entry 10–13). ArRmut11-ωTA was also for this substrate the only applicable (*R*)-selective ωTA giving (*R*)-**2c** with perfect conversion and stereoselectivity (>99% conv., >99% *ee*, entry 13).

Table 1. Selected Results for the Asymmetric Amination of 1- and 2-Tetralones and Derivatives

entry	ωTA	substr.	system[a]	conv. (%)[b]	*ee* (%)[c]
1	ArS	**1a**	LDH	>99	>99 (*S*)
2	CV	**1a**	LDH	>99	74 (*S*)
3	ArRmut11	**1a**	2-PrNH2	>99	54 (*R*)
4	ArR	**1a**	AlaDH	14	76 (*R*)
5	ArS	**1b**	AlaDH	90	>99 (*S*)
6	BM	**1b**	AlaDH	88	>99 (*S*)
7	CV	**1b**	LDH	67	79 (*S*)
8	ArRmut11	**1b**	2-PrNH2	>99	>99 (*R*)
9	VF	**1c**	AlaDH/LDH	>99	>99 (*S*)
10	PD	**1c**	AlaDH/LDH	>99	>99 (*S*)
11	CV	**1c**	AlaDH/LDH	>99	>99 (*S*)
12	PF	**1c**	AlaDH/LDH	>99	>99 (*S*)
13	ArRmut11	**1c**	2-PrNH2	>99	>99 (*R*)
14	VF	**1d**	LDH	22	98 (*S*)
15	PD	**1d**	LDH	8	>99 (*S*)
16	ArRmut11	**1d**	2-PrNH2	26	>99 (*R*)[56]

[a]Substrate (50 mM), freeze-dried *E. coli* cells containing overexpressed ωTA (20 mg), LDH-system: L-/D-alanine (250 mM), phosphate buffer (pH 7, 100 mM), PLP (1 mM), LDH (90 U), GDH (30 U), NAD$^+$ (1 mM), glucose (150 mM). AlaDH-system: L-/D-alanine (250 mM), phosphate buffer (pH 7, 100 mM), PLP (1 mM), AlaDH (12 U), FDH (11 U), NAD$^+$ (1 mM), ammonium formate (150 mM). 2-PrNH$_2$ system: water, 2-propylamine (1 M), PLP (0.5 mM), adjusted to pH 11 with aqueous 3 N HCl. [b]24 h reaction time, 30 °C, shaking 120 rpm. [c]Determined by GC on a chiral stationary phase.

Although 1-tetralone **1d** led in general to low conversions, the analogous 4-chromanone **1e** was transformed with higher conversion using (*S*)-selective as well as (*R*)-selective ωTAs (Table 2). For instance, VF-, PD-, and BM-ωTA aminated **1e** with perfect stereoselectivity (*ee* > 99%) (entries 2–4). The mirror image (*R*)-**2e** was also obtained with perfect *ee* (>99%) and 54% conversion using ArRmut11-ωTA (entry 5).

The amination of 3-chromanone **1f** led to the formation of (*R*)-3-aminochromane (*R*)-**2f** employing the (*S*)-selective ωTAs due to a switch in the CIP priority. Particularly, ArS-ωTA afforded (*R*)-**2f** in optically pure form (>99% *ee*) and quantitative conversion (entry 7). (*R*)-**2f** is described as a building block for a medication for treating chronic heart disorders.[71] All other (*S*)-selective ωTAs showed lower stereoselectivity (see Supporting Information). Surprisingly, a switch of the stereopreference for the amination of **1f** was observed for ArRmut11-ωTA as well as HN-ωTA. Both enzymes led to the formation of (*R*)-**2f**, thus the same enantiomer as obtained with the (*S*)-selective ωTAs: HN-ωTA even gave (*R*)-**2f** in optically pure form (>99% *ee*, entry 8), whereas ArRmut11-ωTA led to 67% *ee* (*R*). In contrast, AT-ωTA retained the expected stereopreference yielding (*S*)-**2f** with 56% *ee* and excellent conversion (94%) when DMSO was added as cosolvent (20% v v^{-1}) (entry 10).

Finally, the bioamination of **1f** with ArS-ωTA was shown on a 100 mg scale leading to (*R*)-**2f** with full conversion and perfect optical purity (*ee* > 99%); after extraction the amine

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Table 2. Selected Results for the Asymmetric Amination of 3- and 4-Chromanone

entry	ωTA	substr.	system[a]	conv. (%)[b]	*ee* (%)[c]
1	PF	**1e**	AlaDH	13	85 (*S*)
2	VF	**1e**	LDH	56	>99 (*S*)
3	PD	**1e**	LDH	45	>99 (*S*)
4	BM	**1e**	AlaDH	11	>99 (*S*)
5	ArRmut11	**1e**	2-PrNH_2	54	>99 (*R*)
6	ArS	**1e**	AlaDH	25	88 (*S*)
7	ArS	**1f**	LDH	>99	>99 (*R*)[d]
8	HN	**1f**	AlaDH	22	>99 (*R*)[d,e]
9	ArRmut11	**1f**	2-PrNH_2	>99	67 (*R*)[d,e]
10	AT	**1f**	LDH	94[f]	56 (*S*)[d]

[a]Substrate (50 mM), freeze-dried *E. coli* cells containing overexpressed ωTA (20 mg); LDH System: L-/D-alanine (250 mM), phosphate buffer (pH 7, 100 mM), PLP (1 mM), LDH (90 U), GDH (30 U), NAD^+ (1 mM), glucose (150 mM). AlaDH-system: L-/D-alanine (250 mM), phosphate buffer (pH 7, 100 mM), PLP (1 mM), AlaDH (12 U), FDH (11 U), NAD^+ (1 mM), ammonium formate (150 mM). 2-PrNH_2 system: reaction conditions: water, 2-propylamine (1 M), PLP (0.5 mM), adjusted to pH 11 with aqueous 3 N HCl. [b]24 h reaction time, 30 °C, shaking 120 rpm. [c]Determined by GC on a chiral stationary phase. [d]Switch in CIP priority compared to amines **2a−e**. [e]HN- and ArRmut11-ωTA displayed opposite stereopreference than expected. [f]20% v v^{-1} DMSO employed as cosolvent.

product was precipitated and isolated as its hydrochloride salt (*R*)-**2f**·HCl with 78% isolated yield.

■ CONCLUSION

In summary, various (*S*)- and (*R*)-selective ω-transaminases were employed for the asymmetric reductive amination of 1- and 2- tetralone and derivatives as well as 3- and 4-chromanone. In all the cases investigated, the (*S*)-selective ω-transaminase enabled amine formation in enantiopure form using at least one of the tested (*S*)-ωTAs. The in general (*R*)-selective transaminases HN-ωTA and ArRmut11 displayed for 3-chromanone **1f** an inverted stereopreference compared to the other substrates in this paper as well as to published substrates; thus it led for this single substrate to the same amine enantiomer as the (*S*)-selective transaminases. The corresponding (*R*)-enantiomers were also accessible in optically pure form in most of the cases, the only exception being substrates **1a**. The bioamination was successfully exemplified on a preparative scale (100 mg) for substrate **1f**.

■ EXPERIMENTAL SECTION

Ketones **1a−e**, racemic amine *rac*-**2d** and enantiopure amine (*R*)-**2d** were commercially available from Sigma-Aldrich (Vienna, Austria). Racemic amines *rac*-**2a,c,e** and enantiopure amines (*S*)-**2c**, (*S*)-**2d**, and (*R*)-**2d** were a gift from BASF. Ketone **1f** was synthesized according to literature.[72,73] Racemic amine *rac*-**2b** was synthesized according to literature.[72,73] Solvents were purchased from Roth and used as received unless otherwise stated. PureLinkTM Quick Plasmid Mini-preparation Kit (K2100−10) and One Shot TOP10 chemically competent *E. coli* cells (SKU# C6000-03) were obtained from Invitrogen (Karlsruhe, Germany). L-Lactate dehydrogenase from rabbit muscle (lyophilized powder, 136 U mg^{-1} protein, one unit will reduce 1.0 μmol of pyruvate to L-lactate per min at pH 7 at 25 °C, catalog no. 61309) was purchased from Sigma-Aldrich (Vienna, Austria). Glucose dehydrogenase (lyophilized powder, 25 U mg^{-1}, one unit will oxidize 1 μmol of β-D-glucose to D-glucono-δ-lactone per min at pH 8.0 and 37 °C, catalog no. B-4) was purchased from X-zyme (Düsseldorf, Germany). Formate dehydrogenase from *Candida boidinii* (lyophilized crude enzyme, 2.2 U mg^{-1}, one unit will oxidize 1.0 μmole of formate to CO_2 per min at pH 7.6 at 37 °C, catalog no. FDH-101) and β-NAD free acid were purchased from Codexis (Redwood City, CA, U.S.A.).

The conversions to amines were measured by GC using an Agilent 7890 A GC system, equipped with a FID detector and using an Agilent J&W DB-1701 column (30 m, 250 μm, 0.25 μm). Helium was used as carrier gas and EtOAc was used as solvent. The *ee*'s of amines were measured by GC using an Agilent 7890 A GC system, equipped with a FID detector and using a Varian Chrompack Chirasel Dex-CB column (25 m, 320 μm, 0.25 μm). Hydrogen was used as carrier gas. All GC-MS measurements were carried out with an Agilent 7890A GC system, equipped with an Agilent 5975C mass-selective detector (electron impact, 70 eV) and using an Agilent HP-5 ms capillary column (5%-phenyl-methylpolysiloxane phase, 30 m, 250 μm, 0.25 μm). Helium was used as carrier gas.

Optical rotations were measured with a Perkin-Elmer Polarimeter 341 in a 1 mL cuvette of 10 cm length. NMR spectra were recorded on a Bruker 360 MHz spectrometer using TMS as internal standard.

L-alanine was used for the amination employing the (*S*)-selective ωTAs, while D-alanine was employed for (*R*)-selective ωTAs.

Lyophilized *E. coli* cells containing overexpressed ω-transaminases were prepared as previously reported but with elongated induction time of the enzyme (16 h).[51,56,74] Purified recombinant L-alanine dehydrogenase was prepared as described recently.[56]

Representative Example for Reductive Amination Employing the AlaDH-System. Lyophilized cells of *E. coli* BL21 (DE3) containing overexpressed ω-transaminases (20 mg) were rehydrated in an Eppendorf tube (2 mL) in phosphate buffer (0.6 mL, 100 mM, pH 7, 1 mM PLP) for 30 min at 30 °C and 120 rpm on an orbital shaker turned 90° sideward. Phosphate buffer (0.4 mL, 100 mM, pH 7, 1 mM PLP) containing ammonium formate (9.5 mg, final concentration 150 mM), alanine (22.3 mg, final concentration 250 mM), formate dehydrogenase (11 U), and NAD^+ (0.67 mg, final concentration 1 mM), as well as the ketone (50 mM) and L-alanine dehydrogenase (12 U) were added.

L- or D-alanine were used as amine donor employing either (*S*)- or (*R*)-selective ωTAs, respectively. DMSO was added in selected experiments using (*R*)-selective ωTAs (15% v v^{-1}). The mixture was shaken at 30 °C and 120 rpm. The reaction was quenched after 24 h by the addition of aqueous NaOH (200 μL, 10 N), and the reaction mixture was extracted with ethyl acetate (2 × 500 μL). The combined organic phases were dried (Na_2SO_4), and the conversion was measured by GC.

Representative Example for Amination Employing the LDH-System. Lyophilized cells of *E. coli* BL21 (DE3) containing overexpressed ω-transaminases (20 mg) were rehydrated in an Eppendorf tube (2 mL) in phosphate buffer (0.6 mL, 100 mM, pH 7, 1 mM PLP) for 30 min, at 30 °C, at 120 rpm on an orbital shaker turned 90° sideward. Phosphate buffer (0.4 mL, 100 mM, pH 7, 1 mM PLP), containing glucose (27.0 mg, final concentration 150 mM), alanine (22.3 mg, final concentration 250 mM), lactate dehydrogenase (90 U) and glucose dehydrogenase (30 U), NAD^+ (final concentration 1 mM) as well as the ketone (final concentration 50 mM), was

added. L- or D- alanine were used as amine donor employing either (*S*)- or (*R*)-selective *ω*TAs, respectively. DMSO was additionally added in selected experiments (15%, v v^{-1}). The mixture was shaken at 30 °C and 120 rpm. The reaction was quenched and worked up as described above.

Representative Example for Amination Employing the 2-Propylamine System. Lyophilized cells of *E. coli* BL21 (DE3)/pET-21a-ArRmut11-*ω*TA (20 mg) were rehydrated in a stock solution (800 *μ*L) containing PLP (0.5 mM) and 2-propylamine (1 M), adjusted to pH 11 employing 3 N HCl, for 30 min, at 30 °C and 120 rpm in a glass vial (4 mL) on an orbital shaker. Then, DMSO (200 *μ*L) and ketone **1** (50 mM) were added. The vial was closed with a cap and shaken at 45 °C and 120 rpm in an upright position. The reaction was quenched and worked up as described above.

Determination of Optical Purity. The enantiomeric excess of amines **2** was analyzed by GC on a chiral phase (see Supporting Information) after derivatization to acetoamides, which was performed by adding 4-(*N*,*N*-dimethylamino)pyridine (5 mg) dissolved in acetic anhydride (100 *μ*L). After washing with water and drying (Na_2SO_4) the *ee* value of the derivatized compound was measured. For more details see Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

Information about the *ω*-transaminases employed, procedure for the amination of ketones **1a–f** employing (*S*)- and (*R*)-selective *ω*-transaminases, chemo-enzymatic synthesis of 3-amino-chromane from *o*-hydroxy-benzaldehyde, and analytics. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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