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Stereoselective Synthesis of 1-Arylpropan-2-amines from Allylbenzenes through a Wacker-Tsuji Oxidation-Biotransamination Sequential Process

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Abstract. Herein, a sequential and selective chemoenzymatic approach is described involving the metal-catalysed Wacker-Tsuji oxidation of allylbenzenes followed by the amine transaminase-catalysed biotransamination of the resulting 1-arylpropan-2-ones. Thus, a series of nine optically active 1-arylpropan-2-amines were obtained with good to very high conversions (74-92%) and excellent selectivities (>99% enantiomeric excess) in aqueous medium.

The Wacker-Tsuji reaction has been exhaustively optimised searching for compatible conditions with the biotransamination experiments, using palladium(II) complexes as catalysts and iron(III) salts as terminal oxidants in aqueous media. The compatibility of palladium/iron systems for the chemical oxidation with commercially available and made in house amine transaminases was analysed, finding ideal conditions for the development of a general and stereoselective cascade sequence. Depending on the selectivity displayed by selected amine transaminase, it was possible to produce both 1-arylpropan-2-amines enantiomers under mild reaction conditions, compounds that present therapeutic properties or can be employed as synthetic intermediates of chiral drugs from the amphetamine family.

Keywords: allylbenzenes; amphetamine derivatives; one-pot processes; transaminases; Wacker-Tsuji oxidation

Introduction

Optically active amines are key building blocks in the synthesis of chiral pharmaceuticals and drug intermediates.[1] Within this broad group of nitrogen-containing organic compounds, 1-arylpropan-2-amines, also known as amphetamines (Figure 1), are privileged motifs due to their powerful and diverse effects on the central nervous system. In fact, a wide set of them are present in commercial drugs used for the treatment of the attention deficit hyperactivity disorder, narcolepsy or binge eating disorder (Dextroamphetamine and Lisdexamphetamine), obesity (Benzphetamine) or other diseases including Parkinson (Selegiline), benign prostatic hyperplasia (Tamsulosin) and asthma ((*R*,*R*)-Formoterol).

Traditional chemical methods for the synthesis of enantiopure (un)substituted 1-arylpropan-2-amines involved the use of (stereoselective) reductive processes including the hydrogenation of chiral vicinal amino alcohols[2] and 1,3-oxazolidin-2-ones,[3] prochiral enamides [4] and nitroalkenes,[5] the reductive amination of prochiral ketones,[6] or the regioselective nucleophilic addition of aryl cuprates to substituted chiral azirdines,[7] among others.

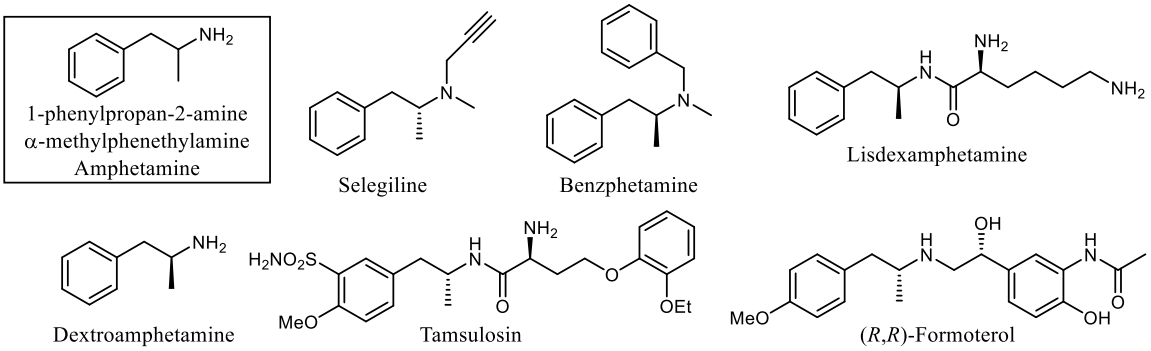


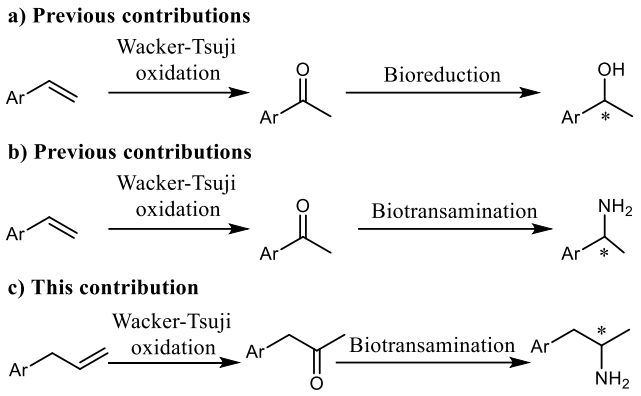
Figure 1. Chemical structure of 1-phenylpropan-2-amine and related chiral compounds used as drugs.

Nowadays, Biocatalysis is considered a practical and mature technology for the synthesis of optically active compounds,[8] providing several elegant (chemo)enzymatic strategies for the synthesis of chiral amines.[9] Thus, various families of biocatalysts have been efficiently employed in the asymmetric preparation of 1-arylpropan-2-amines using amine transaminases (ATAs),[10] amine dehydrogenases (AmDHs),[11] imine reductases (IREDs),[12] reductive aminases (RedAms)[13] or hydrolases such as lipases and proteases.[14]

Particularly attractive are those methods developed through chemoenzymatic and multienzymatic approaches, which allow to introduce higher molecular complexity.[15] For instance, Rebolledo and co-workers have reported the catalytic chemical oxidation of 1-arylpropan-2-ols mediated by AZADO to produce the corresponding 1-arylpropan-2-ones, which were later subjected to asymmetric biotransamination using ATAs.[16] Multienzymatic strategies for the synthesis of optically active 1-arylpropan-2-amines from alcohols rely on the combination of two stereocomplementary alcohol dehydrogenases (ADHs) for the oxidation of racemic 1-arylpropan-2-ols to subsequently perform the biotransamination reaction[17] or the reductive amination catalysed by an AmDH.[18] Alternatively, a redox-neutral cascade has been described starting from racemic 1-phenylpropan-2-ol based on the use of a single non selective ADH for alcohol oxidation and subsequent reductive amination employing the reductive aminase from *Aspergillus oryzae*.[19]

The Wacker-Tsuji reaction consists in the metal-catalysed aerobic oxidation of alkenes for the production of carbonyl compounds.[20] This transformation involves the Pd(II)-catalysed oxidative nucleophilic addition of water to olefins in the presence of a co-catalyst and/or a terminal oxidant, which allows the reoxidation of Pd(0) to Pd(II) species, typically Cu(II) salts and molecular oxygen. However, the use of different oxidative reagents (benzoquinone, DDQ, $Fe_2(SO_4)_3$, CrO_3…) has also received great attention due to their successful role in these oxidation reactions.[21] Recently, Gröger and co-workers have described the compatibility of the Wacker-Tsuji reaction of styrenes with selected biotransformations for the development of chemoenzymatic one-pot sequential transformations, including ADH-catalysed bioreductions for a formal hydration of styrenes (Scheme 1a)[22] and ATA-catalysed biotransaminations towards the production of optically active α-methylbenzylamines (Scheme 1b)[23]. Both works were initially hampered by the enzyme deactivation due to the presence of copper ions but the design of compartmentalisation approaches solved the initial limitations to achieve successful one-pot transformations.

Based on the importance of optically active 1-arylpropan-2-amines, herein we propose to extend the possibilities of one-pot chemoenzymatic transformations by focusing on the development of a sequence involving the palladium-catalysed Wacker-Tsuji oxidation of allylbenzenes followed by an asymmetric biotransamination step (Scheme 1c).



Scheme 1. Chemoenzymatic sequences combining the Wacker-Tsuji oxidation of styrenes and allylbenzenes with selected biocatalysts for the production of: (a) 1-arylethanols; (b) α-methylbenzylamines; (c) 1-arylpropan-2-amines.

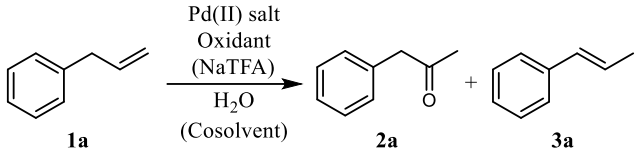
Results and Discussion

Wacker-Tsuji oxidation of allylbenzene 1a

The Wacker-Tsuji oxidation of allylbenzenes in combination with the transaminase-catalysed biotransamination of the resulting 1-arylpropan-2-ones deals with three main inherent problems associated to the proposed method, which are the: (i) competitive Pd-catalysed isomerisation of the C=C bond; (ii) oxidative side-reactions; and (iii) enzyme inhibition effects due to the presence of metal species involved in the chemical oxidation step. Taking into account this items, allylbenzene (**1a**) was selected as model substrate, studying the behaviour of palladium(II) catalysts in combination with different reoxidation systems using water as reaction medium.[24]

On one hand, a series of palladium salts was considered including palladium(II) chloride, palladium(II) acetate, palladium(II) trifluoroacetate and bis(triphenylphosphine)palladium(II) dichloride, although the latest led in all cases to the recovery of the starting material. On the other hand, and in the search for compatible conditions for the sequential biotransamination step, several oxidants were attempted such as molecular oxygen,[24,25] Dess-Martin periodinane,[26] iron(III) chloride, iron(III) nitrate, iron(III) sulfate,[27] or even a chemoenzymatic system composed by the laccase *Trametes versicolor* and the *N*-oxy radical TEMPO.[28] After preliminary screenings (Tables S5-S6), the use of palladium(II) trifluoroacetate and an iron(III) salt as terminal oxidant were found to be the best catalytic systems in terms of yields and selectivities, so extensive optimisation with these oxidative systems has been summarised in the Supporting Information (Tables S7-S9), while in the main text the most remarkable results are displayed in Table 1 to be later discussed.

Table 1. Palladium-catalysed Wacker-Tsuji oxidation of allylbenzene **1a**.



Entry	[**1a**] (mM)	Pd(II) (mol%)[a]	NaTFA (mM)	Fe(III) (equiv.)[a]	Cosolvent[b]	t (h)	T (ºC)	**1a** (%)[c]	**2a** (%)[c]	**3a** (%)[c]
1	25	$Pd(OAc)_2$ (2.5)	----	$FeCl_3$ (1.0)	----	24	60	3	92	<1
2	25	$Pd(TFA)_2$ (2.5)	50	$FeCl_3$ (1.0)	----	14	60	3	87	3
3	50	$Pd(TFA)_2$ (5.0)	----	$Fe_2(SO_4)_3$ (6.0)	----	24	45	9	77	4
4	50	$Pd(TFA)_2$ (2.5)	----	$Fe_2(SO_4)_3$ (2.0)	----	24	60	9	83	1
5	25	$Pd(TFA)_2$ (5.0)	50	$FeCl_3$ (1.0)	MeCN	4	45	2	87	6
6	25	$Pd(TFA)_2$ (5.0)	50	$Fe_2(SO_4)_3$ (2.0)	MeCN	4	45	5	84	6
7	25	$Pd(TFA)_2$ (5.0)	50	$FeCl_3$ (1.0)	Hexane	16	60	9	83	1
8	25	$Pd(TFA)_2$ (5.0)	50	$Fe_2(SO_4)_3$ (3.0)	Hexane	24	30	8	90	2
9	25	$Pd(TFA)_2$ (5.0)	50	$Fe_2(SO_4)_3$ (4.0)	Hexane	24	30	11	88	1
10[d]	25	$Pd(TFA)_2$ (2.5)	5	$Fe_2(SO_4)_3$ (3.0)	MeCN	20	30	<1	88	2
11[d]	25	$Pd(TFA)_2$ (1.0)	5	$Fe_2(SO_4)_3$ (2.0)	MeCN	3	45	3	86	2
12[d]	25	$Pd(TFA)_2$ (1.0)	5	$FeCl_3$ (1.1)	MeCN	3	45	3	83	6

[a] The amount of Pd^{2+} and Fe^{3+} complexes are given in reference to 1-allylbenzene as the limiting reagent. [b] The cosolvent was used in a 5% v/v ratio. [c] Percentages of the remaining starting material **1a** and the products **2a** and **3a** were calculated by GC analyses of the reaction crudes using anisole as internal standard. [d] Transformations were scaled-up to a 10 mL scale.

First of all, it must be mentioned that depending on the reaction conditions two main products were formed in these oxidative processes, which are the expected Markovnikov addition product 1-phenylpropan-2-one (**2a**) and the *trans*-β-methylstyrene (**3a**) resulting from the C=C bond isomerisation. This process only occurs in the presence of the palladium catalyst and was found to be reversible, so the internal olefin **3a** could evolve to the desired product **2a** at certain temperatures, which was confirmed studying the oxidation products obtained in the reaction of *trans*-β-methylstyrene with the Pd(II)/Fe(III) system (Table S10). In addition, other products were detected in some cases depending on the reaction conditions, although always as minor components, that are propiophenone (**4a**) due to the oxidation of **3a**, and the anti-Markovnikov regioselectivity products 3-phenylpropanal (**6a**) and cinnamaldehyde (**7a**).[29] Also the formation of benzaldehyde (**5a**) was detected in variable amounts due to an oxidative radical cleavage of the internal olefin **3a**.[30]

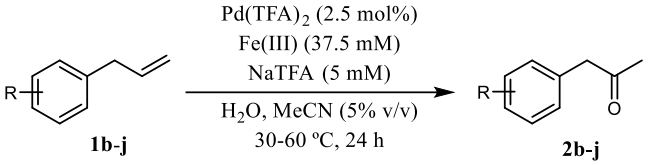
Noteworthy, when examining the reaction conditions reported by Gröger and co-workers for the Wacker-Tsuji oxidation of styrene ($PdCl_2$, CuCl and molecular oxygen in a MeOH-water mixture) to the oxidation of allylbenzene (**1a**), only the C=C isomerisation product **3a** was observed after 16 h at room temperature.[21] Besides that, an almost equimolar mixture of **1a** and the desired ketone **2a** was obtained when following the protocol described by Fernandes and co-workers[26] that uses $PdCl_2$ as catalyst and $Fe_2(SO_4)_3$ as oxidant. Both methods employ high organic solvent concentrations so based on the requirements to accomplish efficient biotransamination processes, from here reactions were deeply studied in mostly aqueous medium (Table 1).

Oxidations were performed in the absence of light and air to minimise the formation of the benzaldehyde side-product. Palladium(II) acetate and trifluoroacetate acted as highly efficient catalysts for the Wacker-Tsuji oxidation of **1a** in the presence of Fe(III) sulfate or chloride salts, allowing the formation of the ketone **2a** as the main product in yields over 75% (entries 1-4).

The acidity of the aqueous solution provided by the Fe(III) salts is a key issue in the reaction, since adjusting the pHs to values above 3.5 led to the precipitation of the oxidant, therefore causing a complete loss of reactivity. In order to improve the reaction conversion, sodium trifluoroacetate (NaTFA, 5-50 mM, entries 2, 5-12) was tested as an additive[24c] in the presence of different organic cosolvents (MeCN, TBME, MeOH, 1,4-dioxane, toluene and hexane, Table S7), since their use could have a benefit effect as solubilisation agents of the alkenes in aqueous medium, thus enhancing the reproducibility and outcome of the oxidation reaction (entries 5-12).

The best and mildest reaction conditions were found with a 25 mM allylbenzene concentration using $Pd(TFA)_2$ (2.5 mol%), $Fe_2(SO_4)_3$ (3.0 equiv., 37.5 mM), NaTFA (5 mM) and MeCN as cosolvent (5% v/v), leading to **2a** with 88% yield after 20 h at 30 ºC (entry 10), although, interestingly, the loading of the Pd(II) salt was decreased to 1 mol% without significant detriment on the ketone yield (entries 11 and 12).

Table 2. Oxidation of allylbenzenes **1b-j** (25 mM) after optimisation of the reaction conditions.



Entry	R	Fe(III)	T (ºC)	*c* (%)[a]	**2b-i** (%)[b]
1	2-CH_3 (**b**)	$Fe_2(SO_4)_3$	30	>99	96
2	3-CH_3 (**c**)	$Fe_2(SO_4)_3$	30	97	95
3	4-CH_3 (**d**)	$Fe_2(SO_4)_3$	30	98	94
4	4-CF_3 (**e**)	$Fe_2(SO_4)_3$	45	97	87
5	2-OCH_3 (**f**)	$FeCl_3$	60	>99	95
6	4-OCH_3 (**g**)	$FeCl_3$	30	97	92
7	3,4-OCH_2O- (**h**)	$FeCl_3$	60	98	91
8	3,4-$(OCH_3)_2$ (**i**)	$FeCl_3$	60	98	83
9	3-OCH_3 and 4-OH (**j**)	$FeCl_3$	45	89	77

[a] Conversion values measured by GC analyses of the reaction crudes. [b] Yields of **2b-j** measured by GC analyses.

Wacker-Tsuji oxidation of allylbenzenes 1b-j

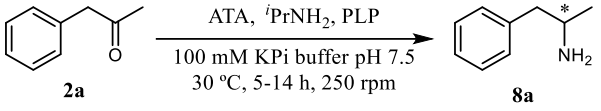
Once optimal conditions were obtained for the Wacker-Tsuji oxidation of **1a**, the reaction outcome was explored with commercially available allylbenzenes **1b-f** and naturally occurring compounds from essential oils such as estragole (**1g**), safrole (**1h**) and methyl eugenol (**1i**), the latest being readily synthesised through methylation of eugenol (**1j**). The results are summarised in Table 2.

Excellent conversions and selectivities into ketones **2b-d** bearing a methyl substituent at the aromatic ring (entries 1-3) were obtained at 30 ºC, requiring a higher temperature (45 ºC) for the effective oxidation of the trifluoromethyl derivative **1e** (entry 4). After optimisation of the reaction conditions for the oxidation of estragole (**1g**, Table S11), the use of $FeCl_3$ as oxidant provided better results for those allylbenzenes **1f-j** bearing oxygenated substituents on the aromatic ring, and the best temperatures (30-60 ºC) were selected for each substrate to prevent the accumulation of the internal olefins **3f-j** by enabling the reversibility of the isomerisation (entries 5-9).

Biotransamination of 1-arylpropan-2-ones 2a-i

Amine transaminases (ATAs) are valuable stereoselective enzymes able to transfer an amine group from an amine donor, typically L- or D-alanine, isopropylamine or diamines, to an acceptor (ketones or aldehydes) for the production of enantiopure amines in theoretically 100% yield.[31] Herein, a total of 31 ATAs were screened in the biotransamination of 1-phenylpropan-2-one (**2a**, 20 mM) for 5 h at 30 ºC. Some of them derived from *Chromobacterium violaceum*, *Arthobacter citreus* and *Arthrobacter* species were overexpressed in *E. coli*,[32] and others were used as received from commercial sources (Table S12). A large excess of isopropylamine ($^{i}PrNH_2$, 50 equiv.) as amine donor was used in order to shift the equilibrium towards amine synthesis, and the most interesting results are displayed in Table 3.

Table 3. Biotransamination of **2a** (20 or 50 mM) using $^{i}PrNH_2$ as amine donor.[a]



Entry	ATA	[**2a**] (mM)	*c* (%)[b]	**8a** *ee* (%)[c]
1	*E. coli*/Cv-TA	20	92	96 (*S*)
2	ATA-237	20	92	>99 (*S*)
3	ATA-251	20	95	>99 (*S*)
4	TA-P1-A06	20	90	>99 (*S*)
5	TA-P1-G06	20	94	>99 (*S*)
6	TA-P2-B01	20	96	>99 (*R*)
7	*E. coli*/Cv-TA	50	92	96 (*S*)
8	ATA-237	50	85	>99 (*S*)
9	ATA-251	50	90	>99 (*S*)
10	TA-P1-A06	50	91	>99 (*S*)
11	TA-P1-G06	50	94	>99 (*S*)
12	TA-P2-B01	50	81	>99 (*R*)

[a] Reaction conditions: Ketone **2a** (0.01 mmol, 1.3 µL or 0.025 mmol, 3.3 µL), ATA (2.0 mg for commercial enzymes, 10.0 mg for *E. coli*/Cv-TA whole cells), PLP (1 mM), 100 mM phosphate buffer pH 7.5 (500 µL) and $^{i}PrNH_2$ (1.0 M) at 30 °C and 250 rpm for 5 h (20 mM **2a**) or 14 h (50 mM **2a**). [b] Conversion values measured by GC analyses of the enzymatic reaction crudes. [c] Enantiomeric excess values were measured by HPLC analyses after derivatisation of the reaction crudes with acetic anhydride. The major amine enantiomer is shown in parentheses.

Interestingly, 12 enzymes allowed the production of amine **8a** in enantiopure form finding complementary ATAs in terms of stereoselectivity, while 5 of them led to **8a** pure enantiomers with conversions over 90% (entries 2-6). Selected commercially available enzymes provided the best results, leading to the

amine (*S*)-**8a** in 90-94% conversion with the ATA-237, ATA-251, TA-P1-A06 and TA-P1-G06, while the TA-P2-B01 produced in 96% conversion the (*R*)-counterpart. Searching for a more productive system, ketone concentrations were increased to 50 mM (entries 7-12 and Table S13) leading to similar but usually lower yields in spite of increasing the reaction time from 5 to 14 h.

The use of organic cosolvents improves the substrate solubilisation in ATA-catalysed transformations, favouring higher reaction conversion values as the enzyme activity is usually completely maintained at low volumes of organic solvent (typically DMSO, DMF or MeCN)[33] and, besides, showed a beneficial effect on the Wacker-Tsuji step. For this reason, MeCN (2.5-10% v/v) was selected for further optimisation of the biotransamination experiments over ketone **2a** (Table 4). In addition, efforts were made in the reduction of the isopropylamine amount trying to achieve a better atom-economy reaction.

For TA-P1-G06 the use of a ratio higher than 5% v/v of MeCN led to a considerable decrease in the conversion (entries 1-6). Fixing a MeCN 5% v/v ratio, it was observed that the amount of isopropylamine can be reduced by a half without a significant decrease of the amine yield when using TA-P1-G06, (entries 7-11). Similar conversion values were attained with other (*S*)-selective enzymes using only 5 equiv. of the amine donor (74-76%, entries 11-13), while with the tested (*R*)-selective (TA-P2-B01, entry 14) the conversion was significantly reduced when using this low amine donor loading (34% conversion).

The moderate excess of isopropylamine (5-10 equiv) required for shifting the equilibrium towards high conversions into the amine **8a** encouraged us to perform energy calculations in order to have a deeper understanding of the enzymatic processes (Table S18). For that reason, Gibbs free energies of the ketone/amine pairs were calculated at the M06-2X/6-311++G(3df,2p) level,[32b,34] to compare the predicted ΔG of the global amination reactions of 1-phenylpropan-2-one (**2a**) and a reference substrate such as acetophenone with isopropylamine. The thermochemical study reflects that the equilibrium shift of the (bio)transamination of **2a** is highly favoured (ΔG= -12.0 kJ/mol), while the formation of α-methylbenzylamine is unfavourable (ΔG= +5.4 kJ/mol), explaining in this manner the large excess required for the biotransamination of acetophenone in comparison with 1-phenylpropan-2-one (**2a**).

The study of the ATA-catalysed transamination was then extended to other 1-arylpropan-2-ones **2b-i** (see Tables S14-S17 for the complete enzyme screenings), finding in all cases complementary enzymes for the production of the corresponding optically active amphetamine derivatives in high to excellent conversions (79-99%) and with excellent optical purities (>97% *ee*) after 24 h at 30 ºC (Table 5). Remarkably, overexpressed enzyme from *Chromobacterium violaceum* (Cv-TA) led to several amine (*S*)-enantiomers with synthetically useful results (93% yield and 97% *ee* for **8e**, 73% yield and >99% *ee* for **8f**, 98% yield and >99% *ee* for **8g**, 97% yield and 97% *ee* for **8h** and 70% yield and 97% *ee* for **8i**).

Table 4. Biotransamination of **2a** (25 mM) using MeCN as cosolvent and different amounts of amine donor.[a]

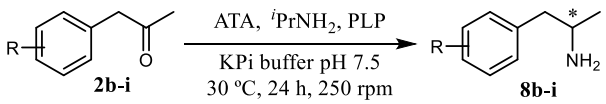
Entry	ATA	MeCN (%)	t (h)	[^{i}PrNH$_2$] (M)	*c* (%)[b]
1	TA-P1-G06	2.5	10	1.0	89
2	TA-P1-G06	2.5	24	1.0	95
3	TA-P1-G06	5.0	10	1.0	88
4	TA-P1-G06	5.0	24	1.0	92
5	TA-P1-G06	10.0	10	1.0	59
6	TA-P1-G06	10.0	24	1.0	87
7	TA-P1-A06	5.0	12	1.0	95
8	TA-P1-A06	5.0	12	0.5	93
9	TA-P1-A06	5.0	12	0.25	86
10	TA-P1-A06	5.0	12	0.125	77
11	TA-P1-A06	5.0	24	0.125	75
12	TA-P1-G06	5.0	24	0.125	74
13	ATA-251	5.0	24	0.125	76
14	TA-P2-B01	5.0	24	0.125	34

[a] Reaction conditions: Ketone **2a** (0.0125 mmol, 1.6 µL), TA (2.0 mg), PLP (1 mM), 100 mM phosphate buffer pH 7.5 (500 µL) and ^{i}PrNH$_2$ (0.125-1.0 M) at 30 °C and 250 rpm. [b] Conversion values measured by GC analyses of the enzymatic reaction crudes.

Design of the Wacker-Tsuji oxidation-biotransamination cascade

Because of the different pH values required for the chemical oxidation and enzymatic transamination, the design of a sequential cascade was developed to convert allylbenzenes into optically active 1-arylpropan-2-amines, adjusting the pH after consumption of the allylbenzene by addition of the amine donor as a mixture of isopropylammonium phosphate and isopropylamine. Firstly, the influence of the Pd(II) and Fe(III) salts in the activity of (*S*)-selective TA-P1-G06 and the (*R*)-selective TA-P2-B01 was analysed, in order to have a deeper knowledge of the reaction trying to avoid enzyme inhibition effects. From Figure 2 it seems evident that both Pd^{2+} and Fe^{3+} species cause a partial or almost complete deactivation of both enzymes, the effect of Fe(III) being highly dramatic with the (*R*)-selective TA-P2-B01.

Table 5. Biotransamination of ketones **2b-i** under optimised conditions.[a]



Entry	R	ATA	*c* (%)[b]	Amine **8b-i** *ee* (%)[c]
1	2-CH_3 (**b**)	ATA-251	93	>99 (*S*)
2	2-CH_3 (**b**)	ATA-412	88	>99 (*R*)
3	3-CH_3 (**c**)	TA-P1-G06	92	>99 (*S*)
4	3-CH_3 (**c**)	TA-P2-B01	99	>99 (*R*)
5	4-CH_3 (**d**)	TA-P1-G06	97	99 (*S*)
6	4-CH_3 (**d**)	TA-P2-B01	99	>99 (*R*)
7	4-CF_3 (**e**)	TA-P1-F03	96	>99 (*S*)
8	4-CF_3 (**e**)	ATA-412	96	>99 (*R*)
9	2-OCH_3 (**f**)	ATA-251	95	>99 (*S*)
10	2-OCH_3 (**f**)	ATA-412	93	>99 (*R*)
11	4-OCH_3 (**g**)	ATA-113	98	>99 (*S*)
12	4-OCH_3 (**g**)	TA-P2-B01	98	>99 (*R*)
13	3,4-OCH_2O- (**h**)	ATA-251	98	>99 (*S*)
14	3,4-OCH_2O- (**h**)	TA-P2-B01	97	>99 (*R*)
15	3,4-$(OCH_3)_2$ (**i**)	TA-P1-F03	79	>99 (*S*)
16	3,4-$(OCH_3)_2$ (**i**)	ATA-412	91	>99 (*R*)

[a] Reaction conditions: Ketone **2a-i** (0.01 mmol), TA (2.0 mg), PLP (1 mM), 100 mM phosphate buffer pH 7.5 (500 µL) and ^{i}PrNH$_2$ (1.0 M) at 30 °C and 250 rpm for 24 h. [b] Conversion values measured by GC analyses of the enzymatic reaction crudes. [c] Enantiomeric excess values were measured by HPLC or GC analyses after derivatisation of the reaction crudes with acetic anhydride. The major amine enantiomer is shown in parentheses.

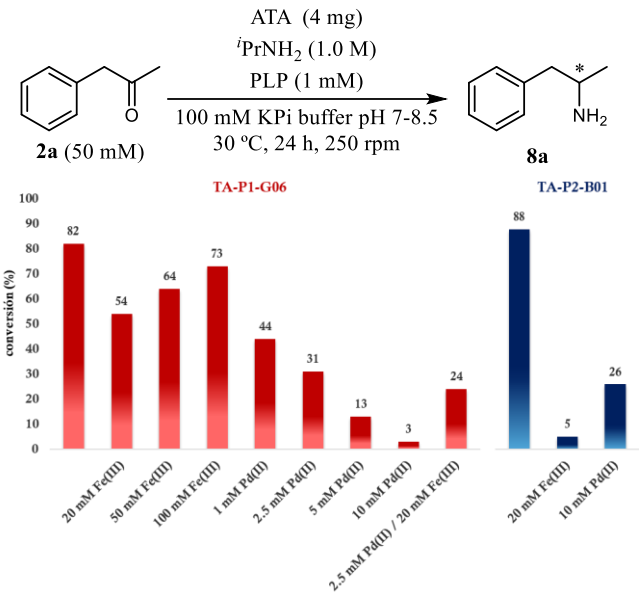


Figure 2. Preliminary study of the enzyme inhibition in the biotransamination due to the presence of metal salts.

Nonetheless, when investigating the sequential process using hexane as cosolvent, a surprisingly high ATA activity was detected with several complementary enzymes, attaining 94-95% conversion in the biotransamination step catalysed by (*S*)-selective TA-P1-G06 and ATA-251, and (*R*)-selective TA-P2-B01 (Figure 3). This suggests that, once the Fe(III) has been consumed in the Wacker-Tsuji reaction, the resulting iron species with lower oxidation state do not display significant enzyme inhibitory effects, while the use of low catalyst loading leads to a negligible concentration of remnant Pd^{2+} after the first reaction step.

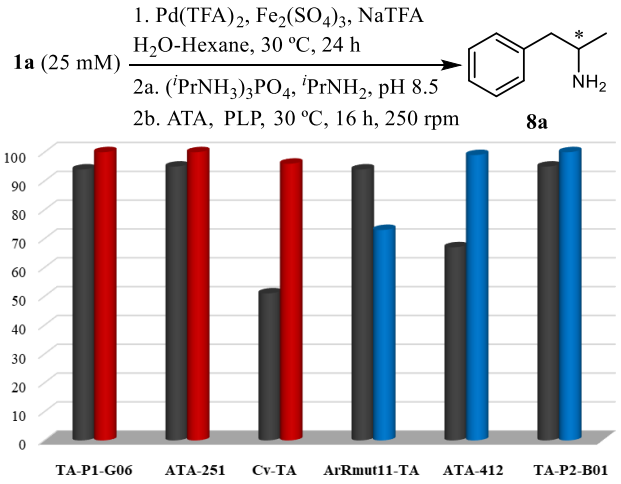
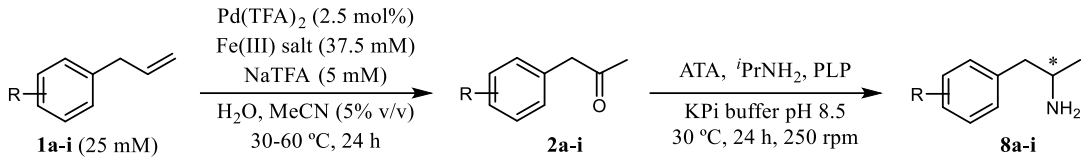


Figure 3. Study of the enzyme activity in the sequential cascade for the transformation of allylbenzene (**1a**) into 2-phenylpropan-2-amine (**8a**) using different ATAs (conversion values of the biotransamination step appear in black, *ee* for (*S*)-**8a** in red and *ee* for (*R*)-**8a** in blue): **1a** (25 mM), $Pd(TFA)_2$ (5 mol%), $Fe_2(SO_4)_3$ (37.5 mM), NaTFA (50 mM), hexane (5% v/v).

Table 6. Sequential cascade process for the transformation of allylbenzenes **1a-i** into optically active 1-arylpropan-2-amines **8a-i**.[a]



1a-i (25 mM) **2a-i** **8a-i**

Entry	R	T (ºC)	Yield **2a-i** (%)[b]	ATA	*c* (%)[c]	Yield **8a-i** (%)[d]	Amine **8a-i** *ee* (%)[e]
1	H (**a**)	30	88	TA-P1-G06	94	83 (78)	>99 (*S*)
2				TA-P2-B01	94	83	>99 (*R*)
3	2-CH_3 (**b**)	30	97	ATA-251	89	86 (85)	>99 (*S*)
4				ATA-412	81	79	>99 (*R*)
5	3-CH_3 (**c**)	30	95	TA-P1-G06	92	87	>99 (*S*)
6				TA-P2-B01	97	92 (92)	>99 (*R*)
7	4-CH_3 (**d**)	30	94	TA-P1-G06	89	84	99 (*S*)
8				TA-P2-B01	97	92 (90)	>99 (*R*)
9	4-CF_3 (**e**)	45	87	TA-P1-F03	85	74	>99 (*S*)
10				ATA-412	92	80 (70)	>99 (*R*)
11	2-OCH_3 (**f**)	60	95	ATA-251	94	89 (87)	>99 (*S*)
12				ATA-412	92	87 (82)	>99 (*R*)
13	4-OCH_3 (**g**)	30	92	TA-P1-G06	95	87 (84)	>99 (*S*)
14				TA-P2-B01	96	88 (86)	>99 (*R*)
15	3,4-OCH_2O- (**h**)	60	91	TA-P1-G05	89	81 (76)	>99 (*S*)
16				TA-P2-B01	95	86 (85)	>99 (*R*)
17	3,4-$(OCH_3)_2$ (**i**)	45	83	TA-P1-F03	84	75	>99 (*S*)
18				ATA-412	95	79 (79)	>99 (*R*)

[a] Reaction conditions: Allylbenzene **1a-i** (25 mM), $Pd(TFA)_2$ (2.5 mol%), Fe(III) (37.5 mM, $Fe_2(SO_4)_3$ for **1a-e** or $FeCl_3$ for **1f-j**), NaTFA (5 mM), MeCN (5% v/v) in water were stirred for 24 h under inert atmosphere. Then isopropylammonium phosphate (0.25 M), isopropylamine (0.15 M), PLP (0.5 mM) and the corresponding ATA (1:1 w/w enzyme:substrate) were successively added. The mixture was shaken at 250 rpm and 30 °C for 24 h. [b] Yields for the oxidation reaction were calculated by GC analyses. [c] Conversions of the enzymatic process were calculated by GC analyses. [d] Yields of the amines were calculated by GC analyses, displaying in parentheses the isolated yields after acid-basic extraction. [e] Enantiomeric excess values were measured by HPLC or GC analyses after derivatisation of the reaction crudes with acetic anhydride. The major amine enantiomer is shown in parentheses.

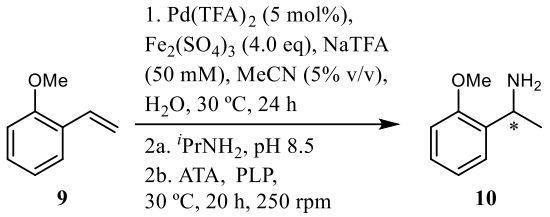
At this point, the sequential cascade was attempted using a moderate excess of amine donor (5 or 10 equivalents) using the ATA-251 and TA-P1-G06, leading after 24 h of oxidation and subsequent 16 h of biotransamination to conversions in the range of 40-56% for the production of (*S*)-**8a** in enantiopure form. These results encouraged us to apply this procedure to the Wacker-Tsuji oxidation/biotransamination sequential cascade of allylbenzenes **1b-i** using a large excess of amine donor and MeCN as cosolvent (Table 6). Interestingly, this approach resulted very general as the proper selection of allylbenzenes, metal species, additives, reaction medium and amine transaminase led to the formation of both 1-arylpropan-2-amines enantiomers (>99% *ee*) in high to excellent conversions (81-96%) and good to very high yields after an acid-basic extraction (70-92%). Thereby, several pharmaceutically relevant products could be synthesised such as Dextroamphetamine ((*S*)-**8a**) and Levoamphetamine ((*R*)-**8a**, precursor of Selegiline), (*S*)- and (*R*)-**2f** (immediate precursors of the bronchodilator methoxyphenamine), (*R*)-**2g** (precursor of Tamsulosin and Formoterol) or (*S*)- and (*R*)-**8h** (immediate precursors of the entactogen drug MDMA).[35]

The use of another common amine donor such as L-alanine was also attempted in similar reaction conditions, which implies the use of a multienzymatic method composed by alanine dehydrogenase to shift the equilibrium of the transamination reaction and formate dehydrogenase for the cofactor recycling. In these conditions, the biotransamination of ketones **2a**,**g**,**h** was also successfully demonstrated, observing a good compatibility between the employed redox enzymes and the presence of metals, yielding (*S*)-**8a** in a 97% conversion and (*S*)-**8g** in a 92% with the TA-P1-G06, and (*S*)-**8h** in a 87% using the TA-P1-G05.

Finally, to prove the generality of the proposed chemoenzymatic strategy, the Wacker-Tsuji oxidation/biotransamination sequence was applied to the synthesis of 1-(2-methoxyphenyl)ethan-1-amine, since it has been demonstrated that 2'-methoxyacetophenone is a suitable substrate in biotransamination reactions catalysed by ATAs such as ATA-024, ATA-033, ATA-251 and TA-P1-

G06.[36] Starting from 2-vinylansiole (**9**), the ketone intermediate was obtained in a 90% yield in the oxidation step, which was subsequently transformed into optically amine **10** with good overall conversion (Table 7, 87-88%) and excellent selectivities (≥95% *ee*).

Table 7. Transformation of 2-vinylanisole (**9**) into 1-(2-methoxyphenyl)ethan-1-amine (**10**) using different ATAs.



Entry	ATA	2nd step *c* (%)[a]	Global *c* (%)[a]	*ee* (%)[b]
1	ATA-024	97	87	96 (*R*)
2	ATA-033	97	87	98 (*R*)
3	ATA-251	97	87	>99 (*S*)
4	TA-P1-G06	98	88	95 (*S*)

[a] Conversion values for the biotransamination reaction and the Wacker-Tsuji oxidation-biotransamination sequence were measured by GC analyses of the enzymatic reaction crudes. [b] Enantiomeric excess values were measured by HPLC analyses after derivatisation of the reaction crudes with acetic anhydride. The major amine enantiomer is shown in parentheses.

Conclusion

The Wacker-Tsuji oxidation of allylbenzenes catalysed by Pd(II) complexes and using Fe(III) salts as terminal oxidants has been carefully optimised in aqueous media using organic cosolvents. Special attention has been paid to the detection and identification of all by-products generated in the oxidation in order to develop effective and compatible methods with the sequential biotransamination of the corresponding 1-arylpropan-2-ones. The system composed by a $Pd(TFA)_2$ as catalyst and $FeCl_3$ or $Fe_2(SO_4)_3$ as terminal oxidant has allowed the oxidation of allylbenzenes with good to excellent yields (77-96%) in mild reaction conditions. Later, a variety of ATAs with complementary selectivities have been identified as ideal candidates for biotransamination experiments over 1-arylpropan-2-ones.

For the first time, the compatibility of a Pd(II)/Fe(III) oxidative system and a enzyme-catalysed step has been demonstrated, observing that transaminases retain their activity in the resulting reaction medium after the Wacker-Tsuji oxidation, so an efficient sequential cascade has been designed to transform allylbenzenes into the corresponding amphetamine derivatives, several of them with remarkable properties as chiral drugs or precursors of pharmaceuticals with a broad set of medical applications. Thus, (*S*)- and (*R*)-1-arylpropan-2-amines were obtained in good isolated yields (70-92%) and high optical purity (>99% *ee*) starting from commercially available allylbenzenes. The extension of the methodology to a representative component of the family of styrenes such as 2-vinylanisole has been also demonstrated, revealing that the sequential approach here proposed could give access also a wide set of valuable optically active 1-arylethanamines.

Experimental Section

General methods

Codex Transaminase ATA Screening Kit (ATASK-000250) and pyridoxal 5'-phosphate (PLP) were purchased from Codexis Inc. Amine transaminases (ATAs) from *Chromobacterium violaceum* (Cv-TA), *Arthrobacter citreus* (ArS-TA) and *Arthrobacter* sp. (ArR-TA and ArRmut11-TA) were provided by Prof. Wolfgang Kroutil (University of Graz) and were overexpressed in *E. coli* and used as lyophilised cells.[32] All other reagents were obtained from commercial sources (Sigma-Aldrich, Acros, and Fluka) and used as received except dry methanol that was previously distilled under nitrogen using calcium hydride as desiccant. Thin-layer chromatography (TLC) analyses were conducted using Merck Silica Gel 60 F254 precoated plates and visualised with UV and potassium permanganate stain. Column chromatography purifications were performed using Merck Silica Gel 60 (230-400 mesh).

^1H, ^{13}C, DEPT and ^{19}F NMR spectra were recorded on a Bruker AV300 MHz spectrometer (see the Electronic Supporting Information). All chemical shifts (δ) are given in parts per million (ppm) and referenced to the residual solvent signal as internal standard. Measurement of the optical rotation values was carried out at 590 nm on a PerkinElmer 241 polarimeter.

Gas chromatography (GC) and high performance liquid chromatography (HPLC) analyses were performed to analyse chemical oxidation and biotransamination experiments to measure conversion and enantiomeric excess values (see the Electronic Supporting Information for method descriptions and employed columns). GC analyses were performed on an Agilent HP6860 GC chromatograph equipped with a FID detector. HPLC analyses were carried out in a Hewlett Packard 1100 chromatograph UV detector at 210, 215 and 254 nm.

Synthesis of 4-allyl-1,2-dimethoxybenzene (1i). Potassium carbonate (9.0 mmol, 1.24 g) and methyl iodide (12.0 mmol, 747 µL) were added to a solution of eugenol (**1j**, 6.0 mmol, 929 µL) in acetone (10 mL). The reaction was refluxed for 12 h, and after this time the mixture was filtered and the solvent distilled under reduced pressure. The resulting reaction crude was purified by column chromatography on silica gel (10% EtOAc/hexane), yielding **1j** as a colourless oil (995 mg, 93%). R_f (10% EtOAc/Hexane): 0.65. ^1H NMR (300.13 MHz, $CDCl_3$): δ 3.34 (d, $^3J_{HH}$ = 6.6 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 5.03-5.13 (m, 2H), 5.96 (ddt, $^3J_{HH}$ = 16.8 Hz, $^3J_{HH}$ = 10.1 Hz, $^3J_{HH}$ = 6.7 Hz, 1H), 6.69-6.88 (m, 3H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 39.9 (CH_2), 55.9 (CH_3), 56.1 (CH_3), 111.4 (CH), 112.0 (CH), 115.7 (CH), 120.5 (CH_2), 132.7 (C), 137.8 (CH), 147.5 (C), 149.0 (C) ppm.

General procedure for the Wacker-Tsuji oxidation of allylbenzenes 1a-i. A solution of allylbenzene **1a-i** (0.25 mmol) in acetonitrile (0.5 mL, 5% v/v) was added under nitrogen atmosphere to a Schlenk flask containing a mixture of $Pd(TFA)_2$ (2.5 mol%, 2.0 mg), NaTFA (0.05 mmol, 7.0 mg) and the corresponding Fe(III) salt (37.5 mM; 150 mg $Fe_2(SO_4)_3 \cdot H_2O$ for **2a-e**, 61 mg $FeCl_3$ for **2f-j**) in water (9.5 mL). The reaction was stirred at 30-60 °C for 16 h in the absence of light and with the closed flask using crystal cap. After this time, the mixture was extracted with EtOAc (2 x 10 mL) and the organic phases

were combined, dried over Na_2SO_4 and filtered-off. The solvent was distilled under reduced pressure and the resulting reaction crude purified by column chromatography on silica gel (10% EtOAc/hexane), yielding ketones **2a-i** as oil products.

1-Phenylpropan-2-one (2a) Colourless oil (29 mg, 85% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.15 (s, 3H), 3.70 (s, 2H), 7.17-7.24 (m, 2H), 7.26-7.38 (m, 3H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 29.3 (CH_3), 51.1 (CH_2), 127.1 (CH), 128.8 (2CH), 129.5 (2CH), 134.3 (C), 206.7 (C) ppm.

1-(2-Methylphenyl)propan-2-one (2b). Colourless oil (36 mg, 96% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.14 (s, 3H), 2.25 (s, 3H), 3.71 (s, 2H), 7.09-7.23 (m, 4H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 19.8 (CH_3), 29.4 (CH_3), 49.3 (CH_2), 126.4 (CH), 127.5 (CH), 130.5 (CH), 130.6 (CH), 133.3 (C), 137.0 (C), 206.6 (C) ppm.

1-(3-Methylphenyl)propan-2-one (2c). Colourless oil (35 mg, 95% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.16 (s, 3H), 2.35 (s, 3H), 3.67 (s, 2H), 6.98-7.12 (m, 2H), 7.09 (d, J_{HH} = 7.5 Hz, 1H), 7.23 (t, J_{HH} = 7.4 Hz, 1H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 21.5 (CH_3), 29.4 (CH_3), 51.1 (CH_2), 126.5 (CH), 128.0 (CH), 128.8 (CH), 130.3 (CH), 134.1 (C), 138.6 (C), 207.5 (C) ppm.

1-(4-Methylphenyl)propan-2-one (2d). Colourless oil (35 mg, 94% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.14 (s, 3H), 2.34 (s, 3H), 3.65 (s, 2H), 7.06-7.19 (m, 4H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 21.2 (CH_3), 29.3 (CH_3), 50.8 (CH_2), 129.4 (2CH), 129.6 (2CH), 131.3 (C), 136.8 (C), 206.9 (C) ppm.

1-[4-(Trifluoromethyl)phenyl]propan-2-one (2e). Colourless oil (39 mg, 78% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.20 (s, 3H), 3.78 (s, 2H), 7.31 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 7.60 (d, $^3J_{HH}$ = 8.1 Hz, 2H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 29.7 (CH_3), 50.4 (CH_2), 125.7 (q, $^3J_{CF}$ = 3.8 Hz, 2CH), 124.2 (q, $^1J_{CF}$ = 271.7 Hz, C), 129.6 (q, $^2J_{CF}$ = 32.6 Hz, C), 130.0 (2CH), 138.1 (C), 206.2 (C) ppm. ^{19}F NMR (282.35 MHz, $CDCl_3$): δ –62.57 ppm.

1-(2-Methoxyphenyl)propan-2-one (2f). Colourless oil (39 mg, 94% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.14 (s, 3H), 3.67 (s, 2H), 3.81 (s, 3H), 6.88 (d, J_{HH} = 8.1 Hz, 1H), 6.93 (td, J_{HH} = 7.4, 1.0 Hz, 1H), 7.13 (dd, J_{HH} = 7.3, 1.6 Hz, 1H), 7.26 (td, J_{HH} = 7.8, 1.8 Hz, 1H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 29.4 (CH_3), 45.6 (CH_2), 55.4 (CH_3), 110.5 (CH), 120.8 (CH), 123.7 (C), 128.7 (CH), 131.2 (CH), 157.4 (C), 207.2 (C) ppm.

1-(4-Methoxyphenyl)propan-2-one (2g). Colourless oil (38 mg, 92% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.15 (s, 3H), 3.65 (s, 2H), 3.81 (s, 3H), 6.83-6.90 (m, 2H), 7.08-7.15 (m, 2H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 29.2 (CH_3), 50.2 (CH_2), 53.4 (CH_3), 114.3 (2CH), 126.4 (C), 130.5 (2CH), 158.8 (C), 207.1 (C) ppm.

1-(1,3-Benzodioxol-5-yl)propan-2-one (2h). Colourless oil (41 mg, 91% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.15 (s, 3H), 3.61 (s, 2H), 5.95 (s, 2H), 6.66 (m, 2H), 6.78 (d, J_{HH} = 7.9 Hz, 1H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 29.2 (CH_3), 50.6 (CH_2), 101.1 (CH_2), 108.5 (CH), 109.8 (CH), 122.6 (CH), 127.9 (C), 146.7 (C), 148.0 (C), 206.6 (C) ppm.

1-(3,4-Dimethoxyphenyl)propan-2-one (2i). Colourless oil (40 mg, 83% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.12 (s, 3H), 3.60 (s, 2H), 3.84 (s, 6H), 6.68 (d, J_{HH} = 2.0 Hz, 1H), 6.72 (dd, J_{HH} = 8.1, 2.0 Hz, 1H), 6.81 (d, J_{HH} = 8.1 Hz, 1H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 29.1 (CH_3), 50.6 (CH_2), 55.9 (CH_3), 55.9 (CH_3), 111.4 (CH), 112.4 (CH), 121.6 (CH), 126.7 (C), 148.2 (C), 149.1 (C), 206.9 (C) ppm.

General procedure for the biotransamination of ketones 2a-j. In a 1.5 mL Eppendorf tube with a phosphate buffer (100 mM, pH 7.5, 500 µL) containing ^{i}PrNH$_2$ (1.0 M) and PLP (1 mM), 1-arylpropan-2-one (**2a-i**, 0.01 mmol) was added. Then the ATA (10.0 mg of those overexpressed in *E. coli* or 2.0 mg of the commercially available ATAs) was added, and the mixture was shaken at 30 °C and 250 rpm for 24 h. The reaction was quenched by addition of a NaOH 4 M aqueous solution (200 µL) and extracted with EtOAc (3 x 500 µL). The combined organic phases were washed with H_2O (500 µL), dried over Na_2SO_4, filtered-off and the resulting solution was analysed by GC or/and HPLC (see Electronic Supporting Information).

General procedure for the synthesis of 1-arylpropan-amines 8a-i through a chemoenzymatic cascade sequence using ^{i}PrNH$_2$ as amine donor. A solution of allylbenzene **1a-i** (0.0625 mmol) in acetonitrile (125 µL) was added under inert atmosphere to a Schlenk flask containing a mixture of $Pd(TFA)_2$ (2.5 mol%, 0.5 mg), NaTFA (0.0125 mmol, 1.7 mg) and the corresponding Fe(III) salt (37.5 mM) in water (2.4 mL). The reaction was stirred (see main manuscript for temperature and reaction times), and after this time isopropyl ammonium phosphate (0.25 M, 172 mg) and isopropylamine (0.15 M, 31 µL) for a final amine donor concentration of 0.9 M and pH 8.5, PLP (1 mM) and the ATA (1:1 w/w enzyme:allylbenzene ratio) were successively added. This suspension was shaken at 250 rpm at 30 ºC for 24 h, quenching the reaction by acidification with a HCl 0.5 M aqueous solution, which was extracted with EtOAc (2 x 2.5 mL). The aqueous phase was collected, basified with a NaOH 4 M aqueous solution (1 mL) and extracted with EtOAc (3 x 2.5 mL). The organic phases were combined, dried over Na_2SO_4 and filtered-off, finally distilling the solvent under reduced pressure, yielding optically active 1-arylpropan-2-amines **8a-j** as colourless oils.

1-Phenylpropan-2-amine (8a). Colourless oil (26 mg, 78% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.12 (d, J_{HH} = 6.2 Hz, 3H), 1.54 (brs, 2H), 2.44 (dd, J_{HH} = 13.5, 8.0 Hz, 1H), 2.65 (dd, J_{HH} = 13.5, 5.4 Hz, 1H), 3.10-3.23 (m, 1H), 7.14-7.35 (m, 5H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 23.5 (CH_3), 46.6 (CH_2), 48.6 (CH), 126.3 (CH), 128.5 (2CH), 129.3 (2CH), 139.7 (C) ppm. $[\alpha]_D^{20}$= +45.0 (*c* 0.2, $CHCl_3$, >99% *ee* (*S*)-**8a**), lit. $[\alpha]_D^{20}$= +40.0 (*c* 1.0, $CHCl_3$, 98% *ee*).[14c]

1-(2-Methylphenyl)propan-2-amine (8b). Colourless oil (8 mg, 85% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.42 (brs, 2H), 2.62 (dd, J_{HH} = 13.5, 7.8 Hz, 1H), 2.74 (dd, J_{HH} = 13.5, 6.0 Hz, 1H), 3.14-3.27 (m, 1H), 7.08-7.23 (m, 4H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 19.7 (CH_3), 23.2 (CH_3), 43.4 (CH_2), 47.6 (CH), 126.0 (CH), 126.5 (CH), 130.2 (CH), 130.5 (CH), 136.5 (C), 137.6 (C) ppm. $[\alpha]_D^{20}$= +23.3 (*c* 0.35, MeOH, >99% *ee* (*S*)-**8b**).

1-(3-Methylphenyl)propan-2-amine (8c). Colourless oil (9 mg, 92% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.13 (d, J_{HH} = 6.3 Hz, 3H), 1.83 (brs, 2H), 2.33 (s, 3H), 2.49 (dd, J_{HH} = 13.3, 8.1 Hz, 1H), 2.69 (dd, J_{HH} = 13.3, 5.3 Hz, 1H), 3.10-3.24 (m, 1H), 6.95-7.06 (m, 3H), 7.19 (t, J_{HH} = 7.4 Hz, 1H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 21.5 (CH_3), 23.5 (CH_3), 46.5 (CH_2), 48.6 (CH), 126.4 (CH), 127.1 (CH), 128.4 (CH), 130.1 (CH), 138.1 (C), 139.6 (C) ppm. $[\alpha]_D^{20}$= +29.4 (*c* 0.2, MeOH, >99% *ee* (*S*)-**8c**).

1-(4-Methylphenyl)propan-2-amine (8d). Colourless oil (9 mg, 90% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.11 (d, J_{HH} = 6.3 Hz, 3H), 1.50 (brs, 2H), 2.32 (s, 3H), 2.47 (dd, J_{HH} = 13.3, 8.1 Hz, 1H), 2.68 (dd, J_{HH} = 13.2, 5.2 Hz, 1H), 3.06-3.21 (m, 1H), 7.03-7.16 (m, 4H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 19.4 (CH_3), 22.9 (CH_3), 42.0 (CH_2), 49.6 (CH), 129.3 (2CH), 129.5 (2CH), 133.8 (C), 136.7 (C) ppm. $[\alpha]_D^{20}$= +37.3 (*c* 0.2, MeOH, >99% *ee* (*S*)-**8d**), lit. $[\alpha]_D^{20}$= +35.0 (*c* 1.6, MeOH, 96% *ee*).[14d]

1-[4-(Trifluoromethyl)phenyl]propan-2-amine (8e). Colourless oil (9 mg, 70% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.18 (d, J_{HH} = 6.3 Hz, 3H), 2.79 (d, J_{HH} = 6.8 Hz, 2H), 3.29 (h, J_{HH} = 6.5 Hz, 1H), 3,64 (brs, 2H), 7.32 (d, J_{HH} = 8.0 Hz, 2H), 7.56 (d, J_{HH} = 8.0 Hz, 2H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 21.5 (CH_3), 23.5 (CH_3), 46.5 (CH_2), 48.6 (CH), 126.4 (CH), 127.1 (CH), 128.4 (CH), 130.1 (CH), 138.1 (C), 139.6 (C) ppm. ^{19}F NMR (282.35 MHz, $CDCl_3$): δ –62.41 ppm. $[\alpha]_D^{20}$= +33.5 (*c* 0.4, $CHCl_3$, >99% *ee* (*S*)-**8e**), lit. $[\alpha]_D^{20}$= +22.2 (*c* 1.1, $CHCl_3$, 90% *ee*).[14d]

1-(2-Methoxyphenyl)propan-2-amine (8f). Colourless oil (18 mg, 87% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.17 (d, J_{HH} = 6.4 Hz, 3H), 2.44 (dd, J_{HH} = 13.1, 7.6 Hz, 1H), 2.78 (dd, J_{HH} = 13.0, 5.8 Hz, 1H), 2.79 (brs, 2H), 3.23-3.36 (m, 1H), 3.83 (s, 3H), 6.85 (d, J_{HH} = 7.8, 1H), 6.90 (td, J_{HH} = 7.4, 1.2 Hz, 1H), 7.15 (dd, J_{HH} = 7.3, 1.6 Hz, 1H), 7.23 (td, J_{HH} = 7.8, 1.7 Hz, 1H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 22.7 (CH_3), 40.4 (CH_2), 47.4

(CH), 55.4 (CH_3), 110.5 (CH), 120.5 (CH), 127.5 (C), 127.9 (CH), 131.3 (CH), 157.8 (C) ppm. $[\alpha]_D^{20}$= +38.8 (*c* 0.4, $CHCl_3$, >99% *ee* (*S*)-**8f**), lit. $[\alpha]_D^{20}$= +31.8 (*c* 1.0, $CHCl_3$, 93% *ee*).[14b]

1-(4-Methoxyphenyl)propan-2-amine (8g). Colourless oil (17 mg, 84% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.10 (d, J_{HH} = 6.3 Hz, 3H), 1.75 (brs, 2H), 2.52 (dd, J_{HH} = 13.3, 8.1 Hz, 1H), 2.71 (dd, J_{HH} = 13.2, 5.2 Hz, 1H), 3.04-3.18 (m, 1H), 3.79 (s, 3H), 6.80-6.89 (m, 2H), 7.06-7.13 (m, 2H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 23.7 (CH_3), 45.9 (CH_2), 48.8 (CH), 55.5 (CH_3), 114.0 (2CH), 130.4 (2CH), 132.0 (C), 158.3 (C) ppm. $[\alpha]_D^{20}$= +35.3 (*c* 0.4, $CHCl_3$, >99% *ee* (*S*)-**8g**), lit. $[\alpha]_D^{20}$= +35.2 (*c* 0.95, $CHCl_3$, 99% *ee*).[14b]

1-(1,3-Benzodioxol-5-yl)propan-2-amine (8h). Colourless oil (19 mg, 85% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.12 (d, J_{HH} = 6.3 Hz, 3H), 2.41 (brs, 2H), 2.49 (dd, J_{HH} = 13.4, 7.8 Hz, 1H), 2.64 (dd, J_{HH} = 13.4, 5.7 Hz, 1H), 3.07-3.20 (m, 1H), 5.92 (s, 2H), 6.63 (dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.5 Hz, 1H), 6.68 (d, $^4J_{HH}$ = 1.4 Hz, 1H), 6.74 (d, $^3J_{HH}$ = 7.9 Hz, 1H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 22.9 (CH_3), 45.7 (CH_2), 48.7 (CH), 100.9 (CH_2), 108.3 (CH), 109.6 (CH), 122.2 (CH), 133.1 (C), 146.1 (C), 147.7 (C) ppm. $[\alpha]_D^{20}$= +16.3 (*c* 0.4, $CHCl_3$, >99% *ee* (*S*)-**8g**).

1-(3,4-Dimethoxyphenyl)propan-2-amine (8i). Colourless oil (10 mg, 79% yield). ^{1}H NMR (300.13 MHz, $CDCl_3$): δ 1.14 (d, J_{HH} = 6.3 Hz, 3H), 2.22 (brs, 2H), 2.51 (dd, J_{HH} = 13.3, 8.0 Hz, 1H), 2.68 (dd, J_{HH} = 13.3, 5.5 Hz, 1H), 3.11-3.24 (m, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 6.70-6.76 (m, 2H), 6.80 (d, J_{HH} = 7.9 Hz, 1H) ppm. ^{13}C NMR (300.13 MHz, $CDCl_3$): δ 22.1 (CH_3), 44.8 (CH_2), 48.9 (CH), 55.9 (CH_3), 56.0 (CH_3), 111.3 (CH), 112.5 (CH), 121.3 (CH), 131.3 (C), 147.7 (C), 148.9 (C) ppm. $[\alpha]_D^{20}$= +31.1 (*c* 0.2, $CHCl_3$, >99% *ee* (*S*)-**8j**), lit. $[\alpha]_D^{20}$= +31.6 (*c* 2.14, $CHCl_3$, >99% *ee*).[10b]

General procedure for the synthesis of 1-arylpropan-amines 8a,g,h through a chemoenzymatic sequence using the L-alanine/alaDH system. A solution of allylbenzene **1a**,**g**,**h** (0.075 mmol) in acetonitrile (150 µL) was added under inert atmosphere to a Schlenk flask containing a mixture of $Pd(TFA)_2$ (2.5 mol%, 0.6 mg), NaTFA (0.015 mmol, 2.0 mg) and the corresponding Fe(III) salt (37.5 mM) in water (2.85 mL). The reaction was stirred (see main manuscript for temperature and reaction times), and after this time L-alanine (180 mM, 48.1 mg) and ammonium formate (110 mM, 20.8 mg) were added. The pH of the solution was basified to a value around 8 with NaOH aqueous solutions, then PLP (1 mM) and NAD^+ (1 mM) cofactors, and finally the enzymes FDH (15 mg), alaDH (15 µL) and the corresponding ATA (20 mg) were added. This suspension was shaken at 250 rpm at 30 ºC for 24 h, quenching the reaction by addition of a NaOH 4 M aqueous solution, which was extracted with EtOAc (2 x 5 mL). If needed an acid-basic extraction was performed, combining the organic phases, dried over Na_2SO_4 and filtered-off, finally distilling the solvent under reduced pressure, yielding optically active 1-arylpropan-2-amines **8a**,**g**,**h** as colourless oils.

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Stereoselective synthesis of 1-Arylpropan-2-amines from Allylbenzenes through a Wacker-Tsuji Oxidation-Biotransamination Sequential Process

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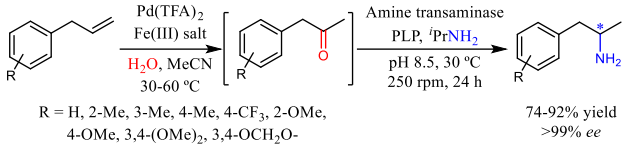
Daniel González-Martínez, Vicente Gotor and Vicente Gotor-Fernández*



R = H, 2-Me, 3-Me, 4-Me, 4-CF_3, 2-OMe, 4-OMe, 3,4-$(OMe)_2$, 3,4-OCH_2O-

74-92% yield
>99% *ee*