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Stereoselective synthesis of γ -hydroxy- α -amino acids through Aldolase-Transaminase recycling cascades

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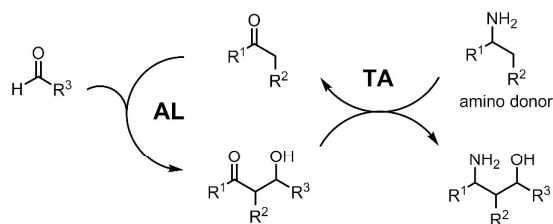
Efficient bienzymatic cascades combining aldolases and α -transaminases were designed for the synthesis of γ -hydroxy- α -amino acids. These recycling cascades provide high stereoselectivity, atom economy, and an equilibrium shift of the transamination. *L*-syn or *anti*-4-hydroxyglutamic acid and *D*-*anti*-4,5-dihydroxynorvaline were thus isolated in 83-95% yield in one step from simple substrates.

Biocatalysis is now fully recognized as a cornerstone of green and sustainable chemistry. Enzymes offer catalytic ways to valuable molecules with exclusive chemo- regio- and stereoselectivity, high atom economy and limited waste.¹ Exploring biodiversity to discover new biocatalysts is a key issue to allow biocatalytic methods to become standard retrosynthetic choices.² Moreover, finding new ways to combine enzymes in cascades is a prerequisite to build up highly efficient bioinspired processes and to respond to the new challenges of the chemical industry.³

Aldolases (ALs) form a large and diverse enzyme family which provides solutions to the chemo- regio- and stereoselectivity of crossed-aldol reactions.⁴ Within AL family, pyruvate-aldolases (PyrALs) offer access to γ -hydroxy- α -keto acids through a reaction between pyruvic acid (PA) and a variety of aldehydes.⁵ For their part, transaminases (TAs) catalyse the highly stereoselective conversion of prochiral ketones into chiral amines, using an amino donor substrate. TAs were proven to be useful catalysts to access a wide range of bioactive molecules.⁶ Notably, enzymes belonging to the *L*- or *D*- α -TA family were used to prepare a large range of rare or unnatural α -amino acids of the *L*- or *D*- series, whereas ω - and amine-TAs offered access to a variety of chiral amines lacking an α -carboxylic acid moiety. However one major drawback of transamination reactions lies in their reversibility resulting in

limited yields and purification problems. Hence, various equilibrium shift strategies are often required, complicating the synthetic processes.⁷ The design of new irreversible processes thus constitutes today a major challenge in the TA application domain.

The combination of ALs and TAs in bi-enzymatic linear cascades is of high synthetic potential with very few examples reported to date.⁸ Indeed, aldols produced by AL-catalysis are converted with TA into γ -amino alcohols which are widely represented in natural products and pharmaceuticals and constitute useful chiral synthons. In order to optimize the combination of AL and TA in synthetic processes, we designed innovative AL-TA recycling cascades described in scheme 1. The basic idea is to use as amino donor, the precursor of the nucleophile substrate of the AL-catalysed reaction. In addition to complete atom economy, the thermodynamically favoured aldolisation is expected to afford the equilibrium shift of the transamination reaction. To our knowledge, this recycling concept was applied only twice: firstly, 1,2-amino alcohols norephedrine and nor-pseudoephedrine were prepared by combining a thiamine-diphosphate carboligase and two amine-TA.⁹ However, due to a side transamination of the aldehyde used as substrate in the carboligation, the reaction was done in two steps and an excess of amino donor was required. Secondly, *L*- and *D*-Homoserine were efficiently prepared in one step from *L*- or *D*-Alanine (Ala) and formaldehyde in the presence of a catalytic amount of PA (50 mol %) by combining a PyrAL with two *L*- and *D*- α -TA.^{8c} In this communication, we report new examples of AL-TA recycling cascades combining



Scheme 1 General model of Aldolase-Transaminase recycling cascade

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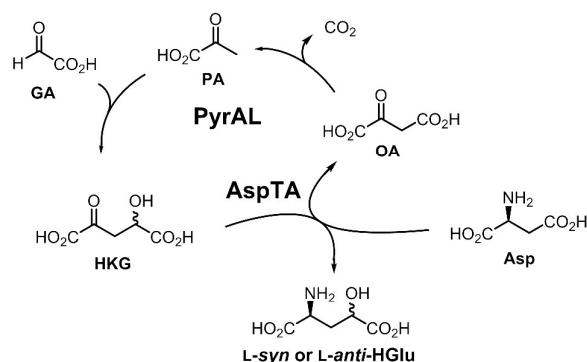
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PyrALs and L- or D- α -TAs to prepare γ -hydroxy- α -amino acids *i.e.* 4-hydroxy glutamic acids (HGlu) and 4,5-dihydroxynorvaline (DHNv).

HGlu isomers are naturally occurring amino acids identified in several plants¹⁰ and the L-*anti* isomer was shown to be an intermediate in mammals hydroxyproline metabolism.¹¹ HGlu was also found in the structure of various natural compounds including several bioactive γ -amide derivatives,¹² α -N-glycosides,¹³ cyclo- and lipopeptides.¹⁴ Moreover, cyclic 4-hydroxy-pyrroglutamic or other protected derivatives of HGlu were prepared following various routes and revealed valuable building blocks for the synthesis of several complex molecules.¹⁵ Our laboratory already reported a two-step chemoenzymatic synthesis of both L-*syn*- and L-*anti*-HGlu combining a base-catalysed aldolisation between oxaloacetic (OA) and glyoxylic acids (GA) and a transamination catalysed by an aspartate transaminase (AspTA).¹⁶ This L- α -TA catalysed the efficient conversion of both enantiomers of 4-hydroxy-2-ketoglutaric acid (HKG) into the mixture of L-*syn* and L-*anti*-HGlu. Here, the recycling AL-TA cascade using a stereoselective PyrAL offers access to enantiomerically pure HKG which can then be converted to one stereochemically pure HGlu isomer. Hence, all four stereoisomers of HGlu might be produced by combining one AL producing selectively (*R*)- or (*S*)-HKG with one TA specific for L- or D-series of amino acids.

In order to identify suitable biocatalysts, 19 PyrALs were tested. These enzymes previously identified by screening of an aldolase collection from the biodiversity, were shown to display a broad substrate spectrum including various aldehydes as electrophile and at least two nucleophile substrates: PA and hydroxypyruvic acid.¹⁷ These 19 PyrALs were assayed on analytical scale in combination with AspTA from *Escherichia coli* to produce HGlu from PA (10 mM) and GA (10 mM). As AspTA does not accept L-alanine (Ala) as amino donor, we used instead its natural substrate L-aspartic acid (Asp, 10 mM). Moreover, we took advantage of the general property of PyrALs to catalyse the decarboxylation of OA, formed from Asp, to give PA, their own nucleophile substrate. We thus implemented the AL-TA recycling cascade described in scheme 2. All the assayed PyrALs catalysed an aldolisation reaction between PA and GA, with activities from 0.5 to 7 U.mg⁻¹ and the decarboxylation of OA with activities



Scheme 2 PyrAL-AspTA recycling cascade for the synthesis of L-*syn*- and L-*anti*-HGlu

from 0.7 to 3.2 U.mg⁻¹ (see ESI). For each experiment with the various PyrAL, the amino acids (Asp, *syn*- and *anti*-HGlu) present in the reaction mixture after 24 h were isolated through selective adsorption on a sulfonic resin and ¹H NMR analysis was used to determine conversion and selectivity. As shown in Fig. 1, conversions above 60% were obtained with 6 PyrALs and two of them, AL1 and AL2 (Uniprot Id. A0A081HJP9 from *Pseudomonas aeruginosa* and B7NJZ1, GarL from *E. coli*, respectively) offered an almost exclusive access to *syn* or *anti* isomer of HGlu. This high selectivity was presumed to result from the selective formation of (*R*)- or (*S*)-enantiomer of HKG with AL1 and AL2 respectively, followed by the conversion of both enantiomers into L-*syn*- or L-*anti*-HGlu, in accordance with AspTA strict stereoselectivity always observed in favour of amino acids of the L-series.¹⁸

These two selective PyrALs were then used to validate the principle of the AL-TA recycling cascade. New experiments were run with a stoichiometric amount of Asp and GA (100 mM, 1 mmol) and a catalytic amount of PA (10 mM). Preliminary results showed an inhibition of the production of HGlu with concentrations of GA above 20 mM (see ESI). In order to circumvent enzyme inhibition, a slow addition of GA was performed over 7 h. Under these conditions, AL1 (10 mg, 0.34 μ mol) combined with AspTA (0.5 mg, 11 nmol) allowed to isolate L-*syn*-HGlu after 24 h in 92% yield and 98/2 d.r. Under similar conditions, AL2 offered access to L-*anti*-HGlu in 95% yield and > 98/2 d.r. Both isomers of HGlu were shown to belong to the L-series (see ESI) thus confirming the high L-selectivity of AspTA. These results clearly demonstrated the efficiency of PyrAL-AspTA recycling cascades using Asp as amino donor which afford an equilibrium shift of the transamination reactions without the need of excess amino donor. However, considering that PA is not a substrate of AspTA, the decarboxylation of OA accounted for the equilibrium shift of the transamination and an aldolisation-driven equilibrium shift thus remained to be demonstrated.

To that end, a collection of TAs from biodiversity was

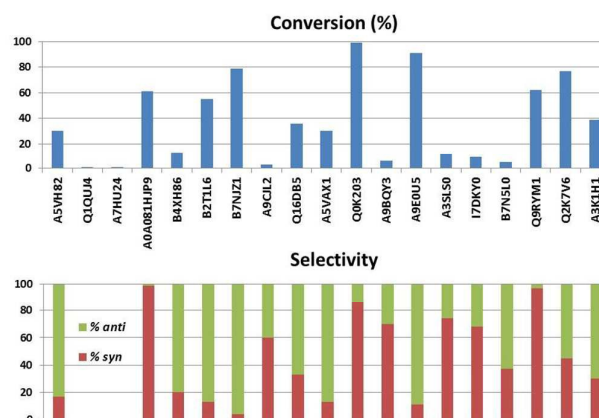


Fig. 1 Conversion and selectivity of PyrAL-AspTA recycling cascades.

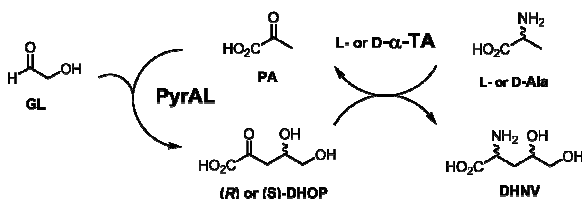
Reaction conditions: Asp, PA, and GA (10 mM, 0.1 mmol), PyrAL (1 U), AspTA (10 U), 24 h. Conversion calculated by ¹H NMR (= (HGlu)/(HGlu)+(Asp)).

screened in order to identify new TAs accepting γ -hydroxy- α -oxo acids as acceptor substrates and L- or D-Ala as amino donor substrate.¹⁹ However, the newly identified TAs proved also active towards GA and consequently, AL-TA recycling cascades with Ala as amino donor could not be implemented for the synthesis of H-Glu. Fortunately, considering the high specificity of α -TAs for α -oxo acids, this unwanted transamination reaction between Ala and the PyrAL aldehyde substrate should not be observed with any aldehyde except GA.

As shown in scheme 3, in a second model cascade, we used glycolaldehyde (GL) to access 2,5-dihydroxynorvaline (DHNV), an uncommon amino acid found in peptidonucleosides polyoxins²⁰ and used as intermediate for the synthesis of clavalanine and echinocandin antibiotics.²¹

Both AL1 and AL2 which previously showed complementary stereoselectivities for HKG synthesis, proved also to be efficient catalysts to access 4,5-dihydroxy-2-oxopentanoic acid (DHOP) from PA and GL. Small scale synthesis experiments allowed to estimate activities around 10 and 1 U.mg⁻¹ for AL1 and AL2 respectively. These 2 PyrALs were combined with 2 newly identified α -TAs: L-TA1 and D-TA2 (Uniprot Id. G0VQA2 from *Megasphaera elsdenii* and E6LHY8 from *Enterococcus italicus* respectively).¹⁹ Both L-TA1 and D-TA2 were shown active towards DHOP and L- or D-Ala with specific activities of 0.9 and 57 U.mg⁻¹, respectively (see ESI). Experiments were first run with the 4 AL-TA combinations using a stoichiometric amount of GL and L- or D-Ala (50 mM, 0.1 mmol) and a catalytic amount of PA (5 mM). As described above for H-Glu synthesis, the amino acids (L- or D-Ala, L- or D-*syn* or *anti*-DHNV) present in the reaction mixture were isolated and ¹H NMR analysis was used to determine conversion and selectivity. Results are summarised in table 1.

Firstly, considering that a catalytic amount of PA (10 mol%) was used in these experiments, the conversions obtained after 4 h (42–65%) demonstrated the recycling nature of the cascades. Secondly, higher selectivities were obtained with AL1 (entries 1 and 2). In accordance with the high selectivity of α -TAs towards the L- or D-series of amino acids, L-*syn*- and D-*anti*-DHNV were assumed to be selectively formed with L-TA1 and D-TA2 respectively. These results suggested that AL1 allowed a selective access to DHOP of (*R*) configuration, as it was already observed with GA used as electrophile substrate. Conversely, AL2 showed a very low stereoselectivity for the synthesis of DHOP (entries 3 and 4) and experiments were not pursued with that enzyme. Finally, considering the low specific activity of L-TA1, we decided to limit further investigation to the recycling cascade combining AL1 and D-TA2.



Scheme 3 PyrAL- α -TA recycling cascade for the synthesis of DHNV

Table 1 Results of cascades with 4 AL-TA combinations^a

Entry	PyrAL (μ M)	α -TA (μ M)	Conv. ^b [%]	d.r. ^b [<i>syn/anti</i>]
1	AL1 (1.3)	L-TA-1 (34)	42	89/11
2	AL1 (1.3)	D-TA-2 (4)	65	8/92
3	AL2 (34)	L-TA-1 (34)	49	43/57
4	AL2 (34)	D-TA-2 (4)	52	48/52

^a Reaction conditions: L- or D-Ala and GL (50 mM, 0.13 mmol), PA (5 mM), MgCl₂ (1 mM), PLP (0.1 mM), H₂O, pH 7.5, 20 °C, 4h.

^b Determined *via* ¹H NMR.

In order to improve this recycling cascade, a second series of experiments was then run with AL1 and D-TA2 with 100 mM D-Ala and various GL concentrations, enzymes quantities and reaction times. Selected results are presented in table 2. Firstly, it appeared that an increase in GL concentration resulted in a conversion drop (entries 1–3). This could be explained by an inhibition of D-TA2 by GL. Indeed, this limitation was overcome by a slow addition of GL to the reaction mixture, leading to a conversion up to 78% after 4 h and 88% after 24 h (entries 10 and 11). It was also observed that an increase in AL1 quantity had a negative impact on stereoselectivity: although a 5:95 *syn/anti* ratio was obtained with 0.85 μ M (25 μ g) AL1 (entry 9), a 24:76 ratio was obtained in the same conditions with 13.6 μ M enzyme (entry 6). Moreover a longer reaction time also resulted in a stereoselectivity drop (see entries 1, 5, 10 and 11). This was particularly clear with 6.8 μ M of PyrAL after 24 h (entry 5) where up to 40% of *syn* isomer was isolated. Conversely, an increase in TA quantity did not significantly affect stereoselectivity (see entries 2, 4, 7 and 8). These results illustrate the propensity of aldolisation to be

Table 2 Results of AL1-D-TA2 cascades in various conditions^a

Entry	AL1 (μ M)	D-TA2 (μ M)	[GL] (mM)	Reaction time [h]	Conv. ^b [%]	d.r. ^b [<i>syn/anti</i>]
1	3.4	10	100	4	60	9/91
				24	70	33/67
2	3.4	10	120	4	44	7/93
3	3.4	10	160	4	29	5/95
4	3.4	20	120	4	77	8/92
5	6.8	20	120	4	81	12/88
				24	80	40/60
6	13.6	20	120	4	79	24/76
7	1.7	20	120	4	70	6/94
8	1.7	30	120	4	75	7/93
9	0.85	20	120	4	60	5/95
10 ^c	1.7	20	120	4	77	6/94
				24	79	19/81
11 ^c	1.7	20	160	4	78	6/94
				24	88	11/89

^a Reaction conditions: L- or D-Ala (100 mM, 0.1 mmol), GL (100–160 mM), PA (10 mM), MgCl₂ (1 mM), PLP (0.1 mM), H₂O, pH 7.5, 20 °C. ^b Determined *via* ¹H NMR. ^c GL added with a syringe pump over 3h.

thermodynamically controlled in the presence of high amount of catalyst and long reaction time favouring reaction reversibility. To confirm the interest of the recycling cascade, we then performed an AL-TA cascade in two sequential steps: DHOP was first prepared by an aldolisation between PA (100 mM, 0.1 mmol) and GL (120 mM) catalysed by AL1 (3.4 μ M) in 4 h. Consecutive transamination using D-TA2 (20 μ M) and D-Ala (100 mM) furnished DHNV with 37% conversion as a 23/77 mixture of *syn*- and *anti*-isomers. Comparison with the recycling cascade run in the same conditions (table 2, entry 4) indicated that the recycling nature of the cascade brings a large yield improvement through an equilibrium shift of the transamination, and also affords stereoselectivity enhancement. Hence, we evidenced another advantage of the recycling cascade which favours the kinetic control of the aldolisation reaction through the rapid consumption of the ketol by the transamination reaction.

Finally, a larger scale synthesis of D-*anti*-DHNV was performed using D-Ala (100 mM, 1 mmol), GL (1.6 mmol added over 4 h), PA (10 mM), AL1 (0.7 μ M) and D-TA2 (20 μ M) in 8 h. D-*anti*-DHNV and remaining D-Ala were efficiently separated by ion exchange chromatography through DHNV lactonisation and selective adsorption of the lactone on a cation exchange resin. DHNV was finally isolated after elution with NaOH in 83% yield and as a 7/93 *syn/anti* mixture. Optical rotation clearly confirmed the selective formation of D-*anti*-DHNV (see ESI).

In conclusion, a straightforward sustainable method has been established to access γ -hydroxy- α -amino acids. This method combining a PyrAL and an α -TA in a recycling cascade was exemplified through the synthesis of stereoisomers of 4-Hglu and DHNV. In this process, the PyrAL controls the configuration of the γ -position, whereas amino acids of L- or D-series are obtained depending on the choice of the TA belonging to L- or D- α -TA family. The recycling nature of the cascade brings multiple benefits: it affords complete atom economy, equilibrium shift of the transamination and also favours the kinetic control of the aldolisation reaction. In order to make this approach a general and industrially relevant, option for γ -amino alcohols synthesis, our further studies will focus on the search for new AL and TA displaying various substrate spectra and complementary stereoselectivities as well as process optimisation including biocatalyst immobilisation²² which could afford stable, recyclable and easy to handle catalysts.

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