RESEARCH ARTICLE doi.org/10.1002/adsc.202200777

Advanced Synthesis & Catalysis

Merging Gold(I) Catalysis with Amine Transaminases in Cascade Catalysis: Chemoenzymatic Transformation of Propargylic Alcohols into Enantioenriched Allylic Amines

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Manuscript received: July 14, 2022; Revised manuscript received: September 19, 2022;
Version of record online: October 26, 2022

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202200777

Abstract: The compatibility between gold(I) catalysts and amine transaminases has been explored to transform racemic propargylic alcohols into enantioenriched allylic amines in a straightforward and selective manner. The synthetic approach consists of a gold(I)-catalysed Meyer-Schuster rearrangement of a series of 2-arylpent-3-yn-2-ols and a subsequent stereoselective enzyme-catalysed transamination of the resulting α,β-unsaturated prochiral ketones. The design of cascade processes involving sequential or concurrent approaches has been studied in our search for ideal reaction conditions to produce the desired amines. Thus, the N-heterocyclic carbene complex [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]-[bis(trifluoromethanesulfonyl)-imide]gold(I) ([Au(IPr)(NTf_2)] (**A**) in aqueous medium was found to be an ideal catalyst, while selective, made-in-house and commercial amine transaminases permitted the asymmetric synthesis of both (*E*)-4-arylpent-3-en-2-amine enantiomers in good isolated yields (53–84%) and excellent stereoselectivities (97 to >99% enantiomeric excess).

Keywords: Chiral amines; Gold catalysis; Meyer-Schuster rearrangement; N-Heterocyclic carbene; Transaminases

Introduction

The impact of chiral amines in the preparation of drugs and bioactive compounds is continuously increasing. Recent studies consider that around 40 to 45% of small pharmaceutical products on the market contain this nitrogenated core.[1] Additionally, optically active amines display a pivotal role in asymmetric synthesis due to their versatility as building blocks, chiral auxiliaries, and ligands for synthetic purposes.[2] Nowadays, biocatalysis provides useful solutions to obtain optically active amines from racemic mixtures or carbonyl compounds. The development of enantioselective desymmetrisation with imine reductases (IREDs), reductive aminases (RedAms), amine dehydrogenases (AmDHs) or transaminases (ATAs), replacing the traditional role played by lipases in (dynamic) kinetic resolutions represent state-of-the-art developments.[1,3]

One-pot chemoenzymatic strategies allow for the introduction of molecular complexity with simultaneous chiral induction.[4] However, the combination of metal catalysts and enzymes is particularly challenging when primary amine syntheses are targeted due to metal-catalyst deactivation and/or amine coordination and cross-reactivity issues. Therefore, the compatibility

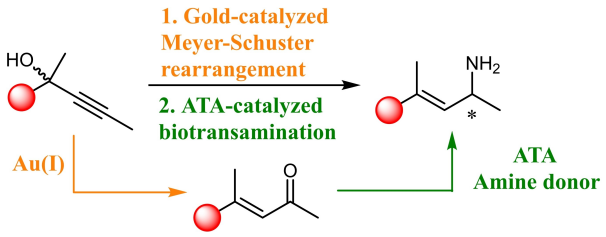
of reaction conditions found for metal-only and biocatalysed-only transformations limit the design of general and efficient routes to produce chiral amines. Additionally, metalloenzymatic approaches towards the synthesis of chiral amines have been less investigated than reactions yielding alcohols, amides and esters.[4,5] In this context, a limited number of examples have been described involving mainly palladium-catalysed transformations (hydrogenation, Wacker-Tsuji oxidation or Suzuki-Miyaura cross-coupling, among others).[6] One notable example is the ruthenium-catalysed isomerisation of allylic alcohols[7] in combination with enzymes (with a selection of ATAs) for selective transformation of ketones into chiral amines. In fact, these metal-ATA combinations were developed in a sequential manner due to incompatibilities between the amine donor and the metal catalyst, precluding the development of these processes in a one-pot cascade mode.

The combination of gold catalysts and enzymes has attracted recent attention, disclosing elegant examples for multi-step transformations. Among the biocatalysts used, lipases and esterases from the hydrolase family,[8] and redox enzymes including monoamine oxidases (MAOs),[9] and alcohol dehydrogenases (ADHs),[10] have provided access to different families of organic compounds, although the performance of concomitant strategies has been scarcely demonstrated using either lipases[8a] or ADHs.[10d,e] Very recently, two one-pot alkyne amination strategies have been reported based on the gold hydration of terminal alkynes to produce methyl ketones as amine precursors.[11,12] On one hand, Rueping and co-workers identified gold(I) chloride, which was employed at low loading, to synthesise a series of aryl ketones at 60 °C, requiring principally an organic reaction medium for 25 mM alkyne concentration.[11] Once the hydration step was complete, the reaction was diluted five times by addition of the ATA preparation, and the enzymatic step was carried out at 30 °C, that are more suitable conditions for the enzyme stability. Excellent stereoselectivities and a range of yields were achieved using commercial enzymes, pyridoxal-5'-phosphate (PLP) and isopropylamine (^{i}PrNH$_2$) as amine donor. On the other hand, Liu and co-workers prepared an encapsulated Au/carbene mediating the hydration of propargylic ethers,[12] employing an ammonia source together with an amine dehydrogenase and a cofactor regeneration system for the second step. This approach led to 25 aliphatic amines bearing in all cases the 2-aminopropan-1-oxy core with good to very high conversions and excellent selectivity.

Encouraged by the previous development of the Meyer-Schuster rearrangement[13] of a series of racemic propargylic alcohols using a N-heterocyclic carbene (NHC)-gold(I) catalyst, and since it can be compatible with the enzyme reaction as previously described with ADHs,[10d] herein the possibility to combine a gold(I) catalyst with ATAs has been investigated, to obtain a series of allylic amine enantiomers using a one-pot approach (Scheme 1). In addition to the reactivity of both catalysts, special efforts have been made in the design and optimisation of sequential or concurrent approaches.

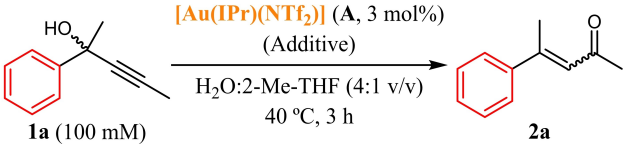
Results and Discussion

The determination of suitable reaction conditions in aqueous medium to permit the action of gold catalysts and ATAs is crucial, especially in the case of concurrent cascade approaches. Shifting the equilibrium in the biotransamination of ketones represents one of the major challenges, since the reaction equilibrium is highly favoured in the opposite direction.[3g,h,14] Therefore, the use of easily accessible and inexpensive amine donors is required, and nowadays two main strategies are employed, the use of a large excess of ^{i}PrNH$_2$ (forming acetone as by-product), or using a small excess of alanine (Ala) with *in situ* removal of the resulting pyruvate,[15] although other possibilities such as the use of the so-called "smart" amine donors in almost equimolecular amounts with regard to the carbonyl substrate can be an alternative.[16] The addition of various reactants needed for the enzymatic step was explored taking as an initial set of conditions our previously optimised gold-catalysed Meyer-Schuster rearrangement of racemic alcohol **1a** to provide preferentially the ketone isomer (*E*)-**2a**.[10d] This included different amine donors (^{i}PrNH$_2$ and L-Ala), an ATA and PLP required as enzyme cofactor (Table 1). A clear incompatibility between the metal reactivity and the use of ^{i}PrNH$_2$ was observed, even when reducing the amount of the amine donor from 1 to 0.1 M (entries 2 and 3). Importantly, L-alanine appears to be compatible with the gold(I) catalyst leading to the formation of the (*E*)-unsaturated ketone **2a** in a similar ratio than in the absence of any additive (entries 1 and 4).[10d] The use of an enzyme such as commercial ATA-415 and PLP did not impede the development of a cascade approach (entries 5 and 6).



Scheme 1. One-pot Meyer-Schuster rearrangement of propargylic alcohols and enzyme-catalysed stereoselective transamination of α,β-unsaturated ketone intermediates.

Table 1. Influence of additives in the Meyer-Schuster rearrangement of racemic alcohol **1 a**.



1a (100 mM) **2a**

Entry	Additive	**1 a** [%][a]	(*E*)-**2 a** [%][a]	(*Z*)-**2 a** [%][a]
1[b]	–	< 1	89	11
2	^{i}PrNH$_2$ (1 M)	> 99	< 1	< 1
3	^{i}PrNH$_2$ (0.1 M)	96	3	1
4	L-Ala (0.1 M)	< 1	87	13
5	ATA-415	< 1	85	15
6	PLP (1 mM)	< 1	86	14

[a] Product percentages measured by GC analyses.
[b] Data reported in reference 10d.

Searching for an efficient and compatible gold(I) catalyst for this cascade,[17] a screening of NHC-gold catalysts was performed (Table S1 in SI).[18] Interestingly, apart from [Au(IPr)(NTf$_2$)] (**A**) (87% conversion), the dinuclear gold(I) hydroxide complex {[Au(IPr)]$_2$(μ-OH)}[BF$_4$] (**B**)[19] also provided a remarkable 84% conversion, which provided us with two adequate catalysts to study the process in both sequential and cascade manners.

As possible cosolvents, 2-methyltetrahydrofuran (2-Me-THF), tetrahydrofuran, *tert*-butyl methyl ether (MTBE), 2-propanol (^{i}PrOH), acetonitrile (MeCN) and *n*-heptane were tested (Figure 1 and Table S2 in SI). All led to complete conversions with variable amounts of the ketone (*E*)-**2 a** isomer, attaining 87–89% with 2-Me-THF, THF and ^{i}PrOH. The use of the eutectic mixture choline chloride:glycerol (1:2 mol/mol) was also studied, but a lower total conversion was found (85%), with a poor selectivity towards (*E*)-**2 a** formation (44%). At this point, the use of lower amounts (5–15% vol) of 2-Me-THF was studied in more detail, but

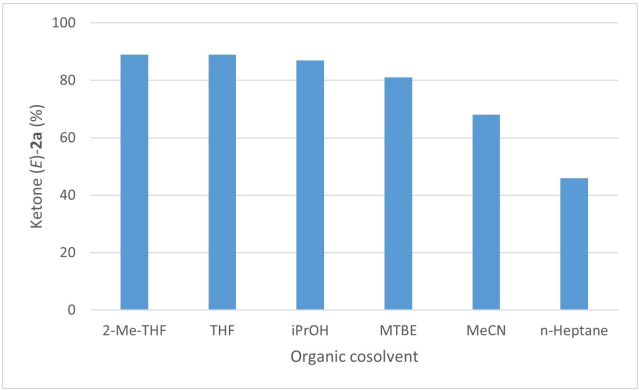


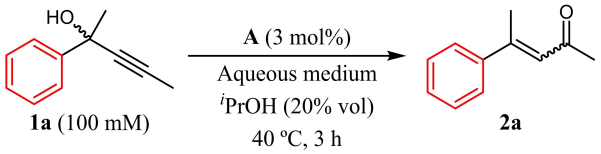
Figure 1. Influence of the cosolvent (20% vol) in the Meyer-Schuster rearrangement of **1 a** (100 mM) using [Au(IPr)(NTf$_2$)] (3 mol%) in water for 3 h at 40 °C.

no improvement of the reaction outcome (82–88%, Table S3 in SI) was observed. Interestingly, higher 2-Me-THF ratios (50% vol) achieved a remarkable 92% to (*E*)-**2 a**, although this condition will not be suitable for the action of the ATA in the second step of the chemoenzymatic sequence, so it was not further considered.

Higher temperatures usually favoured this transformation, but in a chemoenzymatic cascade context, the use of elevated temperatures is deleterious for the enzymatic step. For this reason, the Meyer-Schuster rearrangement of **1 a** was performed at 40 °C or 45 °C using 2-Me-THF, THF and ^{i}PrOH as cosolvents, but no significant differences were observed towards (*E*)-**2 a** formation (87–90%, Table S4 in SI) under these conditions. Finally, the use of different aqueous media was explored, since the control of the pH is a key parameter in biotransaminations, especially after addition of an amine donor such as ^{i}PrNH$_2$ which can affect both the final pH value and the enzyme activity. Apart from distilled water, different buffers were examined ranging from phosphate (KPi) to derivatives of 2-(*N*-morpholino)ethanesulfonic acid (MES) or 3-(*N*-morpholino)propanesulfonic acid (MOPS). These results are displayed in Table 2. The use of water and MOPS buffer resulted in the most beneficial results for the gold(I) species (entries 1 and 7), while the use of different concentrations of KPi or MES buffers (entries 2–5), commonly accepted by ATAs, led to lower conversion values.

Moving to the biotransamination step and considering the screening, six lyophilised *E. coli* whole-cell preparations heterologously expressing different ATAs were used. These are the (*S*)-selective ATAs from *Chromobacterium violaceum* (*Cv*TA),[20] *Arthrobacter citreus* (*Ar*STA),[21] wild type[22] and a variant[23] from *Vibrio fluvialis* (*Vf*TA and *Vf*TA mutant), the (*R*)-selective ATAs from *Aspergillus terreus* (*At*TA),[24] *Arthrobacter* sp. (*Ar*RTA)[25] and its engineered variant

Table 2. Effect of the aqueous medium in the Meyer-Schuster rearrangement of racemic alcohol **1 a**.



1a (100 mM) **2a**

Entry	Aqueous medium[a]	**1 a** [%][b]	(*E*)-**2 a** [%][b]	(*Z*)-**2 a** [%][b]
1	**H_2O**	**<1**	**89**	**11**
2	KPi (100 mM)	42	50	8
3	KPi (50 mM)	38	54	8
4	KPi (25 mM)	30	63	7
5	MES (50 mM)	35	59	6
6	MOPS (50 mM)	16	75	9
7	**MOPS (50 mM)[c]**	**<1**	**87**	**13**

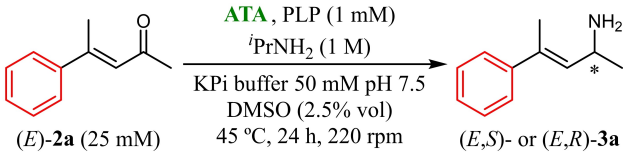
[a] The pH values for all the tested buffers were 7.5.
[b] Product percentages measured by GC analyses.
[c] Reaction time was extended to 24 h.

*ArRmut11*TA.[26] Additionally, a commercial kit from Codexis Inc. was employed containing 28 ATAs. For simplicity, all the biotransformations were carried out using $^{i}PrNH_2$ (1 M) to identify active enzyme hits, which could be later examined with alanine to design the concomitant chemoenzymatic approach.

Parameters such as temperature and the addition of a cosolvent were investigated. On the one hand, biotransaminations were carried out at 30 °C (Table S6 in SI), 40 °C and 45 °C (Table S7 in SI), leading to the best conversions at 45 °C, while the selectivity remained unaffected at the highest temperature. The best results are summarised in Table 3. The selection of this temperature is advantageous since it is also suitable for the metal-catalysed step. On the other hand, DMSO and ^{i}PrOH (2.5% vol) led to better outcomes than 2-Me-THF for the formation of (*E*)-**3 a** for a representative number of ATAs, considering both (*R*)- and (*S*)-selective ones (82–92% yield, Table S8 in SI). Remarkably, in no case was (*Z*)-**2 a** accepted by ATAs since the amine (*Z*)-**3 a** was not observed in the reaction crude analyses, a situation similarly found for reactions involving ADHs,[10d] likely due to steric hindrance.

Notably, some enzymes proved able to accept alanine as an amine donor (5 equiv., 125 mM) in lieu of $^{i}PrNH_2$, using the lactate dehydrogenase, glucose and glucose dehydrogenase system (LDH/Glu/GDH) for the transformation of pyruvate into lactate (Table S9 in SI). This was the case for ATA-251 (64%) to obtain the enantiopure (*E*,*S*)-**3 a**, while *At*TA, that was inactive with $^{i}PrNH_2$, displayed the highest activity giving access to the opposite enantiomer in an outstanding 90% (Figure 2).

Table 3. ATA screening for the biotransamination of (*E*)-**2 a** under standard conditions.



(*E*)-**2a** (25 mM) (*E*,*S*)- or (*E*,*R*)-**3a**

Entry	Enzyme	*c* [%][a]	(*E*)-**3 a** *ee* [%][b]
1	*Ar*STA	85	99 (*S*)
2[c]	*Vf*TA mutant	84	>99 (*S*)
3	ATA-237	86	99 (*S*)
4	ATA-251	90	99 (*S*)
5	ATA-254	90	99 (*S*)
6	ATA-260	89	99 (*S*)
7	ATA-415	89	97 (*R*)
8	ATA-024	91	99 (*R*)
9	ATA-025	89	99 (*R*)
10	ATA-033	92	99 (*R*)

[a] Conversion values were measured by GC analyses.
[b] Enantiomeric excess values were measured by chiral HPLC after chemical acetylation of the reaction crude.
[c] Reaction was carried out at 30 °C instead of 45 °C.

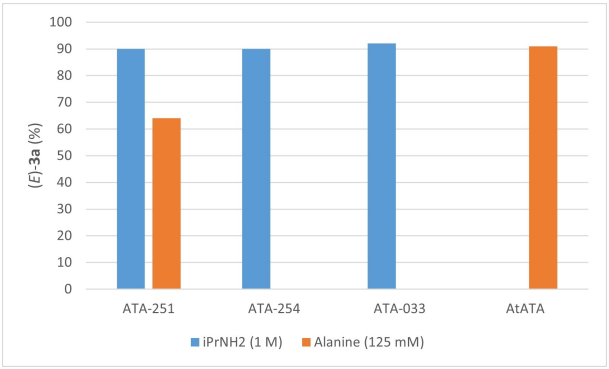


Figure 2. Influence of the amine donor in the biotransamination of (*E*)-**2 a** (25 mM) using a KPi buffer pH 7.5 and DMSO (2.5% vol) for 24 h at 45 °C and 220 rpm.

The compatibility between [Au(IPr)(NTf_2)] and alanine already displayed in Table 1 (entry 4), deserved a deeper study of the enzymatic step, in order to achieve an efficient cascade sequence. The most remarkable results about the use of the LDH/Glu/GDH system and different temperatures with ATA-251 and the use of ^{i}PrOH as cosolvent in *At*TA-catalysed reactions are highlighted in Table 4.

On the one hand, ATA-251 suffered a significant loss of activity at 30 °C compared to the reaction at 45 °C (57–64%, entries 1 and 2), while changing the amount of amine donor and enzyme related to the pyruvate removal did not lead to any improvement (entries 3–5). On the other hand, ^{i}PrOH was explored as possible cosolvent of the *At*TA-catalysed reactions

Table 4. ATA-catalysed biotransamination of (*E*)-**2 a** (25 mM) using alanine as amine donor.[a]

Entry	Enzyme	Ala [mM]	LDH [U]	GDH [U]	T [°C]	Cosolvent [% vol]	*c* [%][b]	(*E*)-**3 a** *ee* [%][c]
1	ATA-251	125	45	15	45	DMSO (2.5)	64	>99 (*S*)
2	ATA-251	125	45	15	30	DMSO (2.5)	57	>99 (*S*)
3	ATA-251	125	60	15	45	DMSO (2.5)	62	>99 (*S*)
4	ATA-251	200	45	15	45	DMSO (2.5)	65	>99 (*S*)
5	ATA-251	125	45	20	45	DMSO (2.5)	63	>99 (*S*)
6	*At*TA	125	45	15	45	DMSO (2.5)	90	>99 (*R*)
7	*At*TA	125	45	15	45	^{i}PrOH (2.5)	91	>99 (*R*)
8	*At*TA	125	45	15	45	^{i}PrOH (2.5)[d]	65	>99 (*R*)
9	*At*TA	125	45	15	45	^{i}PrOH (2.5)[e]	61	>99 (*R*)
10	*At*TA	125	45	15	45	^{i}PrOH (5)	68	>99 (*R*)
11	*At*TA	125	45	15	45	^{i}PrOH (10)	15	n.d.
12	*At*TA	125	45	15	45	^{i}PrOH (15)	<1	n.d.

[a] Reaction conditions: (*E*)-**2 a** (25 mM), KPi buffer (pH 7.5, 50 mM), cosolvent (2.5–15% vol), 30–45 °C, 24 h, 220 rpm, ATA-251 (1:1 w/w), L-Ala, GDH (15–20 U) and D-Glucose (75 mM); or *At*TA (4:1 w/w), D-Ala, GDH (15 U) and D-glucose (75 mM).
[b] Conversion values were measured by GC analyses.
[c] Enantiomeric excess values were measured by chiral HPLC after chemical acetylation of the reaction crude. Major amine enantiomer appears in parentheses. n.d.: Not determined.
[d] Distilled water was used instead of KPi buffer.
[e] MOPS buffer (pH 7.5, 50 mM) was used instead of KPi buffer.

since it was previously demonstrated that DMSO is not adequate for the [Au(IPr)(NTf_2)] catalysed step.[10d] Satisfyingly, conversion values were similar and practical for synthetic purposes (entries 6 and 7). Additional experiments using other aqueous systems (entries 8 and 9), or higher cosolvent concentrations (entries 10–12) led to poorer results. With *At*TA as the unique enzyme capable to fulfil the requirements for the chemoenzymatic approach, the development of the concurrent cascade was next explored (Table 5).

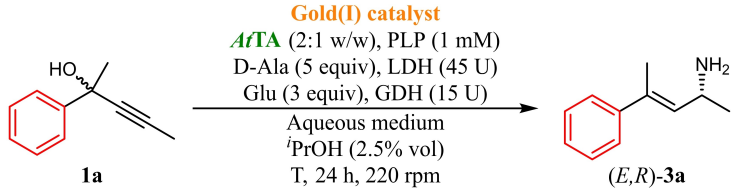
Reactions were initially carried out in phosphate buffer or water as the aqueous medium, finding in both cases at 100 mM substrate concentration, that there remained a significant amount of unreacted propargylic alcohol (33–35%, entries 1 and 2), but also that the reactions just produced the α,β-unsaturated ketone intermediate **2 a**. Therefore, the substrate concentration was decreased to 25 mM (entries 3 and 4), which slightly favoured the ketone transformation into the amine but still to a low extent, and a lower concentration (10 mM) only led to 9% conversion (entry 5). The use of 40 °C allowed to increase the amine formation to 29%, but lower temperatures led again to poor results (entries 6 and 7).

Better results were found with the use of higher [Au(IPr)(NTf_2)] (**A**) loadings (7.5 mol%), and prolonging the reaction time to 48 h allowed the formation of enantiopure (*E*,*R*)-**3 a** to 41% conversion (entries 8 and 9). Finally, the use of another gold(I) catalyst, the dinuclear species {[Au(IPr)]$_2$(μ-OH)}[BF_4] (**B**) was explored, considering its addition in portions along the process and running it for one or two days (entries 10–12), providing the highest conversion of 48%, although the optical purity of the amine slightly decreased (97% *ee*) in comparison with the **A**-catalysed reactions.

Bearing in mind that conversions did not reach a 50% yield in the concomitant approach, we studied a sequential approach, by adding the ATA, the amine donor, PLP and ^{i}PrNH$_2$ once the first metal-mediated step was completed. In this case, two active and selective ATAs were selected (Table 3), one (*S*)-selective and overexpressed in *E. coli* (*ArS*TA) and another (*R*)-selective and commercially available (ATA-024), and their reactions were optimised obtaining up to 89% and 94% conversion, respectively (Table 6). Before studying the sequential approach, the influence of the presence of the gold catalyst **A** (3 mol%) on the *ArS*TA and ATA-024 was studied, finding that both ATAs were not affected by the presence of the metal (Table S19). These results prompted us to study the sequential approach more in depth.

This optimisation was based on the study of different gold(I) species, dilutions of the ketone intermediate, reaction times and amounts of ATA. Thus, starting from a concentration of 100 mM of the propargylic alcohol **1 a**, the best results were found when the gold reaction was allowed to proceed for 3 h, and following dilution of the reaction content to 15 mM ketone concentration for the second step by addition of the KPi buffer (entries 1–4). In this case, the amount of *ArS*ATA did not have an impact on the process outcome, while longer reaction times (48 h) allowed the formation of (*E*,*S*)-**3 a** with the highest conversion. Both, **A** and **B** displayed good catalytic performance (entries 4 and 5), although to extend the

Table 5. Optimisation of the one-pot Meyer-Schuster rearrangement and biotransamination of **1 a** conducted in concurrent mode.[a]

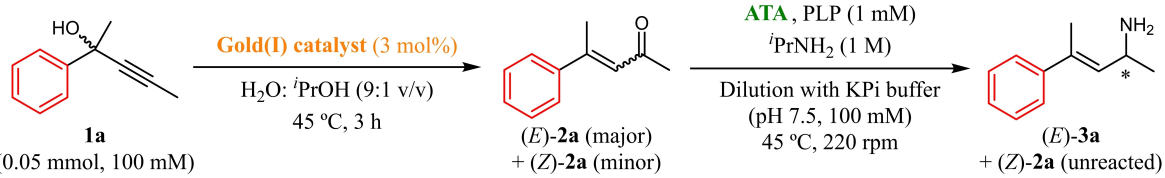


1a (*E*,*R*)-**3a**

Entry	Aqueous medium	Gold(I) catalyst [mol%]	T [°C]	[**1 a**] [mM]	**1 a** [%][b]	(*E*)-**2 a** [%][b]	(*Z*)-**2 a** [%][b]	(*E*,*R*)-**3 a** [%][b]	(*E*,*R*)-**3 a** *ee* [%][c]
1	KPi pH 7.5 50 mM	**A** (5)	45	100	35	57	2	6	n.d.
2	H_2O	**A** (5)	45	100	33	59	2	6	n.d.
3	KPi pH 7.5 50 mM	**A** (5)	45	25	35	39	1	25	n.d.
4	H_2O	**A** (5)	45	25	41	46	1	12	n.d.
5	KPi pH 7.5 50 mM	**A** (5)	45	10	87	4	< 1	9	n.d.
6	KPi pH 7.5 50 mM	**A** (5)	40	25	53	18	< 1	29	n.d.
7	KPi pH 7.5 50 mM	**A** (5)	30	25	67	19	1	13	n.d.
8	KPi pH 7.5 50 mM	**A** (7.5)	45	25	35	28	1	36	> 99
9	KPi pH 7.5 50 mM	**A** (7.5)	45[d]	25	28	25	6	41	> 99
10	KPi pH 7.5 50 mM	**B** (5 + 5)[e]	45	25	35	43	3	19	n.d.
11	KPi pH 7.5 50 mM	**B** (7.5)	45	25	36	29	1	34	97
12	KPi pH 7.5 50 mM	**B** (7.5)	45[d]	25	25	22	5	48	97

[a] Reaction conditions: **1 a** (10–100 mM), KPi buffer (pH 7.5, 50 mM, 696 µL), ^{i}PrOH (25 µL, 2.5% vol), gold catalyst (5–10 mol%), *At*TA (2:1 w/w), PLP (1 mM), D-Ala (5 equiv.), D-glucose (3 equiv.), LDH (45 U), GDH (15 U), 24 h, 220 rpm.
[b] Conversion values were measured by GC analyses.
[c] Enantiomeric excess values measured by chiral HPLC after acetylation of the reaction crude. n.d.: Not determined.
[d] Reaction was run for 48 h.
[e] Catalyst added in two portions (5 mol% at the beginning plus 5 mol% after 6 h).

Table 6. Optimisation of the one-pot Meyer-Schuster rearrangement and biotransamination of **1 a** carried out in a sequential mode.



1a (0.05 mmol, 100 mM) (*E*)-**2a** (major) + (*Z*)-**2a** (minor) (*E*)-**3a** + (*Z*)-**2a** (unreacted)

Entry	Gold(I) cat.	ATA[a]	Dilution [mM]	t [h]	**1 a** [%][b]	(*E*)-**2 a** [%][b]	(*Z*)-**2 a** [%][b]	(*E*)-**3 a** [%][b]	(*E*)-**3 a** *ee* [%][c]
1	**A**	*Ar*STA (20 mg)	25	24	< 3	33	< 3	63	99 (*S*)
2	**A**	*Ar*STA (30 mg)	25	24	< 3	30	3	65	99 (*S*)
3	**A**	*Ar*STA (20 mg)	15	24	< 3	15	5	79	99 (*S*)
4	**A**	*Ar*STA (20 mg)	15	48	< 3	7	4	89	99 (*S*)
5	**B**	*Ar*STA (20 mg)	15	48	< 3	17	7	76	96 (*S*)
6	**A**	ATA-024 (8 mg)	15	48	< 3	6	< 3	94	> 99 (*R*)
7	**A**	ATA-024 (4 mg)	15	48	< 3	6	< 3	94	> 99 (*R*)
8	**A**	ATA-024 (8 mg)	15	24	< 3	16	< 3	84	> 99 (*R*)

[a] Weight of lyophilised cells of *E. coli* overexpressed (entries 1–5) or commercial (entries 6–8) ATA appear in parentheses.
[b] Percentage of products were determined after liquid-liquid extraction and ^{1}H-NMR analysis of the corresponding reaction crude.
[c] Enantiomeric excess values were measured by chiral HPLC after chemical acetylation of the reaction crude. Major amine enantiomer appears in parentheses.

reaction scope, **A** was selected. To obtain the amine (*E*,*R*)-**3 a** using ATA-024, the use of longer reaction times (48 h) proved crucial to achieve the optimal results (entries 6–8).

After enzyme screening of the biotransamination of ketones **2b–h** (Tables S10 to S16 in SI), the scope of the sequential chemoenzymatic cascade was next explored using seven additional propargylic alcohols **1b–h** bearing different pattern substitutions at the aromatic ring, which were selected since they are known to be good substrates for their [Au(IPr)(NTf_2)]-catalysed Meyer-Schuster rearrangements (Figure 3).[10d] The best [Au(IPr)(NTf_2)]-ATA pairs were identified (Table S18 in SI), allowing the preparation of both amine enantiomers **3b–h** (97 to >99% *ee*) in good to excellent conversions (70–95%). Absolute configurations were assigned based on the known ATA stereoselective preference,[20–26] finding that the (*R*)-enantiomers released first in the HPLC analyses (see Section X in SI). The reaction was also extended to the 2-thiophene derivative (**1i**) as an example of a heteroaromatic substrate, although the low conversions achieved in the biotransamination step of ketone **2i** (<45%, Table S17 in SI) hampered the development of the chemoenzymatic approach.

Sequential reactions were scaled-up on semipreparative scale (100 mg of substrate), producing the enantioenriched amines **3a–g** in moderate to high isolated yields (53–84%) and excellent *ee* values, after liquid-liquid extraction and column chromatography purification. Importantly, the obtained amines were recovered with the same optical purity as the ones attained in the cascade reactions previously carried out on smaller analytical scale. Additionally, the reaction with 0.5 g of **1a** was performed with *Ar*SATA and $^{i}PrNH_2$, producing (*S*)-**3a** in 79% isolated yield and 99% *ee*.

Conclusions

After identifying a smooth access to chiral allylic amines from propargylic alcohols, the gold(I)-catalysed Meyer-Schuster rearrangement and the stereoselective biotransamination of the unsaturated ketone intermediates have been optimised, exploring the possibility of obtaining high-yielding sequential and cascade processes. From the different parameters affecting catalyst activities, for instance catalyst loadings, (co)solvent, temperature or substrate concentration, the use of an adequate amine donor has proved crucial to develop an efficient chemoenzymatic strategy. Although the use of alanine has allowed for the first time the synthesis of an optically active amine through a gold-enzyme concurrent strategy, the conversions into (*E*)-4-phenylpent-3-en-2-amine (**3a**) did not exceed 50% conversion (at 25 mM substrate concentration). While still low, it is a remarkable value since the deactivation of metals in the presence of highly nucleophile species such as amine derivatives is known (in this case, both the amine donor and the final product), as demonstrated in previous metalloenzymatic approaches to synthesise amines.[6,7,9,11,12] Thus,

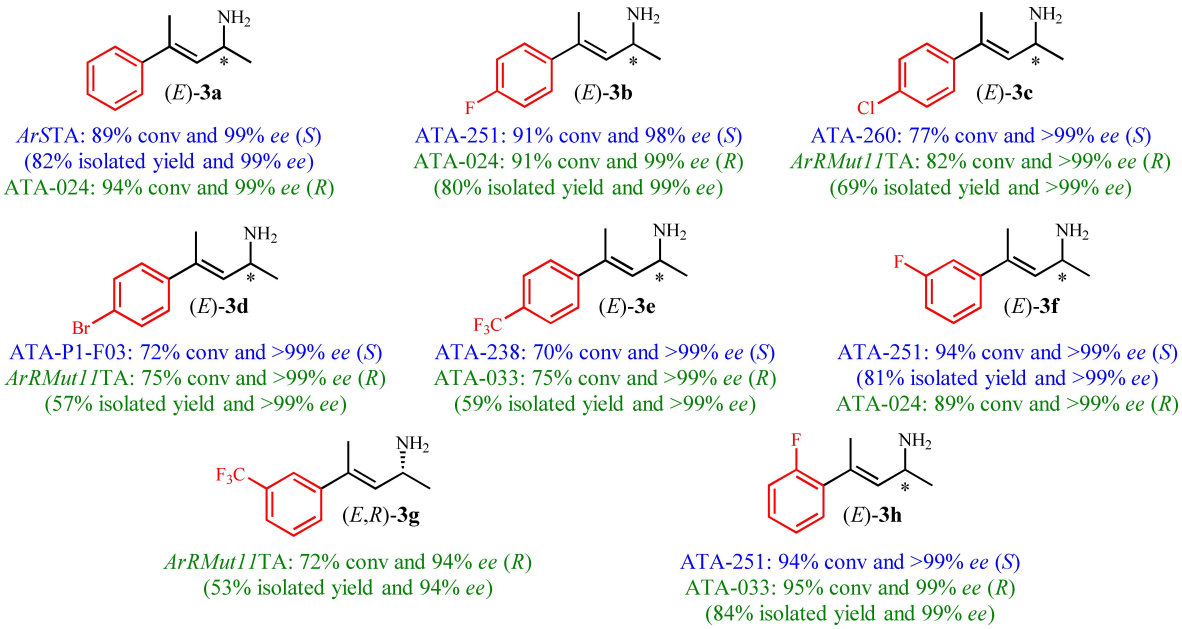


Figure 3. One-pot sequential **A**-catalysed Meyer-Shuster rearrangement followed by stereoselective biotransamination: Au(IPr)(NTf_2)] (3 mol%), H_2O:$^{i}PrOH$ (9:1 v/v), 45 °C, 3 h and magnetic stirring; then dilution to 15 mM with KPi buffer pH 7.5 100 mM, $^{i}PrNH_2$ (1 M), PLP (1 mM), ATA (see the experimental section for individual enzyme details), 45 °C, 48 h and 220 rpm. Blue and green data for (*S*)- and (*R*)-selective ATAs, respectively, including preparative experiments in parentheses for 100 mg of substrate.

both enantiomers of a series of (*E*)-4-arylpent-3-en-2-amines (**3 a**–**h**) were produced in good conversions (67–95%) and excellent selectivities (>97% *ee*), the scalability of these processes being also demonstrated by recovering the target enantiopure amines in good to high isolated yields (53–84%).

Experimental Section

Lyophilised made in house ATAs heterologously expressed in *E. coli* from *Cv*TA, *Ars*TA, *Vf*TA, *Vf*TA mutant), *At*TA, *ArR*TA and its mutant *ArRmut11* were obtained as already described,[20–26] while commercially available ATAs were obtained from Codexis Inc. GDH-105 (48 U/mg) was obtained from Codexis Inc. and LDH (300 U/mg) was purchased from Sigma-Aldrich. All other reagents for chemical transformations and product recovery were obtained from Sigma-Aldrich and used as received.

Thin layer chromatographies (TLCs) were conducted with silica gel precoated plates and visualised with UV and potassium permanganate stain. Column chromatographies were performed using silica gel (230—400 mesh). NMR spectra were recorded on a Bruker 300 MHz spectrometer. All chemical shifts (δ) are given in parts per million (ppm) and referenced to the residual solvent signal as internal standard. IR spectra were recorded on a spectrophotometer on NaCl pellets.

Gas chromatography (GC) analyses were performed on standard gas chromatograph apparatus equipped with a FID detector. High performance liquid chromatography (HPLC) analyses were carried out in a chromatograph with UV detector at a 210 nm wavelength. GC and HPLC analyses served to calculate conversion, enantiomeric excess and diastereomeric excess values. High resolution mass spectra (HRMS) were obtained in a spectrometer using the ESI-TOF positive mode. Measurement of the optical rotation was carried out at 590 nm in a standard polarimeter. Typical procedures for the Meyer-Schuster rearrangement of alcohols **1 a**–**h** and ATA-catalysed transamination of ketone (*E*)-**2 a**–**h** appear in the Supporting Information.

Typical procedure for the one-pot Meyer-Schuster and biotransamination performed in a concurrent manner at analytical scale using *At*TA overexpressed in *E. coli*. Propargylic alcohol **1 a** was dissolved in ^{i}PrOH (25 µL) inside a glass vial (2.5×4 cm), and then a 50 mM KPi buffer pH 7.5 or distilled water (696 µL), containing PLP (1 mM) and D-alanine (125 mM), LDH (45 U), glucose (75 mM), GDH (15 U) and NADH (1 mM) were successively added. Finally, the gold(I) catalyst (5 or 7.5 mol%) and lyophilised cells of *E. coli* overexpressing *At*TA (30 mg) were added. The mixture was shaken at the corresponding temperature (30–45 °C) and 220 rpm for 24 h, and after this time the reaction was stopped with the addition of a NaOH 10 M aqueous solution (200 µL). The mixture was extracted with EtOAc (3×750 µL) and the organic phases were combined, dried over Na_2SO_4 and filtered. Conversions were determined by GC and ^{1}H-NMR analyses, and enantiomeric excess values were determined by HPLC after chemical acetylation using DMAP and acetic anhydride.

Typical procedure for the one-pot Meyer-Schuster and biotransamination performed in a sequential manner at analytical scale using enzymes overexpressed in *E. coli*. Propargylic alcohol **1 a** (0.05 mmol, 8.0 mg) was dissolved in ^{i}PrOH (50 µL) inside a glass vial (2.5×4 cm), and then distilled water (450 µL) and the gold(I) catalyst (3 mol%, 0.0015 mmol) were added. The mixture was stirred at 45 °C for 3 h. After this time, 100 mM KPi buffer pH 7.5 (2.83 mL) containing PLP (1 mM) and $^{i}PrNH_2$ (1 M), and *E. coli* overexpressing *Ars*TA or *ArRmut11*TA (20 mg), were then added. The mixture was stirred for 48 h at 45 °C, after this time the reaction was stopped by the addition of a NaOH 10 M aqueous solution (400 µL). The mixture was extracted with EtOAc (3×2 mL) and the organic phases were combined, dried over Na_2SO_4 and filtered. The conversion values were determined by ^{1}H-NMR analyses, and enantiomeric excess values were determined by HPLC after chemical acetylation using DMAP and acetic anhydride.

Typical procedure for the one-pot Meyer-Schuster and biotransamination performed in a sequential manner at analytical scale using commercial enzymes. Propargylic alcohol **1 a** (0.05 mmol, 8.0 mg) was dissolved in ^{i}PrOH (50 µL) inside a glass vial (2.5×4 cm), and then distilled water (450 µL) and the gold(I) catalyst (3 mol%, 0.0015 mmol) were added. The mixture was stirred at 45 °C for 3 h. After this time, 100 mM KPi buffer pH 7.5 (2.83 mL) containing PLP (1 mM) and $^{i}PrNH_2$ (1 M), and the corresponding ATA (ATA-024, ATA-033, ATA-238, ATA-251, ATA–P1-F03 or ATA-260, 4 mg), were then added. The mixture was stirred for 48 h at 45 °C, and after this time the reaction was stopped by the addition of a NaOH 10 M aqueous solution (400 µL). The mixture was extracted with EtOAc (3×2 mL) and the organic phases were combined, dried over Na_2SO_4 and filtered. The conversion values were determined by ^{1}H-NMR analyses, and enantiomeric excess values were determined by HPLC after chemical acetylation using DMAP and acetic anhydride.

Typical procedure for the one-pot Meyer-Schuster and biotransamination performed in a sequential manner at semipreparative scale. The corresponding propargylic alcohol **1 a**–**h** (0.6 mmol) was dissolved in ^{i}PrOH (310 µL) inside an Erlenmeyer flask, and then distilled water (2.81 mL) and IPrAuNTf$_2$ (3 mol%, 0.018 mmol, 15.0 mg) were added. The mixture was stirred at 45 °C for 3 h. After this time, 100 mM KPi buffer pH 7.5 (17.54 mL) containing PLP (1 mM) and $^{i}PrNH_2$ (1 M), and the corresponding ATA (120 mg of an overexpressed *E. coli* transaminase or 25 mg of a commercial one from Codexis) were added. The mixture was stirred for 48 h at 45 °C, and after this time the reaction was stopped by the addition of a NaOH 10 M aqueous solution (5 mL). The mixture was extracted with EtOAc (4×25 mL) and the organic phases were combined, dried over Na_2SO_4, filtered and concentrated under vacuum. The conversion values were determined by ^{1}H-NMR analyses, and enantiomeric excess values were determined by HPLC after chemical acetylation using DMAP and acetic anhydride. Purification by column chromatography on silica gel (MeOH) led to the allylic amines **3 a**–**h** (53–84% isolated yields and 97->99% *ee*).

(*E*)-4-Phenylpent-3-en-2-amine (3 a). Yellowish oil (82% yield). R_f (MeOH): 0.12. IR: ν 3418, 2939, 1605, 1580, 1507, 1276 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.41–7.38 (*m*, 2H), 7.34–7.19 (*m*, 3H), 5.69 (*d*, *J*=10.1 Hz, 1H), 3.97–3.88 (*m*, 1H), 2.08 (*s*, 3H), 1.46 (*br s*, 2H), 1.22 (*d*, *J*=6.4 Hz, 3H).

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 143.4 (C), 134.6 (CH), 133.8 (C), 128.2 (2CH), 126.9 (CH), 125.7 (2CH), 45.4 (CH), 23.9 (CH_3), 15.9 (CH_3). HRMS (ESI$^+$, m/z): calcd for $(C_{11}H_{16}N)^+$ $(M+H)^+$: 162.1277; found 162.1281.

(*E*)-4-(4-Fluorophenyl)pent-3-en-2-amine (3 b). Yellowish oil (80% yield). R_f (MeOH): 0.08. IR: ν 3362, 3012, 1593, 1507, 1257 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.35–7.30 (*m*, 2H), 7.00–6.94 (*m*, 2H), 5.61 (*d*, *J* = 8.8 Hz, 1H), 3.95–3.86 (*m*, 1H), 2.03 (*s*, 3H), 1.87 (*br s*, 2H), 1.20 (*d*, *J* = 6.4 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 161.9 (*d*, *J* = 249.2 Hz, C), 139.3 (*d*, *J* = 3.8 Hz, C), 134.1 (CH), 133.1 (C), 127.2 (*d*, *J* = 7.6 Hz, 2CH), 115.0 (*d*, *J* = 21.1 Hz, 2CH), 45.4 (CH), 23.8 (CH_3), 16.1 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$): δ −116.08. HRMS (ESI$^+$, m/z): calcd for $(C_{11}H_{15}FN)^+$ $(M+H)^+$: 180.1183; found 180.1187.

(*E*)-4-(4-Chlorophenyl)pent-3-en-2-amine (3 c). Yellowish oil (69% yield). R_f (MeOH): 0.16. IR: ν 3341, 3026, 1568, 1493, 1273 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.32–7.24 (*m*, 4H), 5.66 (*d*, *J* = 9.9 Hz, 1H), 3.96–3.86 (*m*, 1H), 2.04 (*s*, 3H), 1.59 (*br s*, 2H), 1.20 (*d*, *J* = 6.3 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 141.7 (C), 134.9 (CH), 132.8 (C), 132.6 (C), 128.3 (2CH), 127.0 (2CH), 45.4 (CH), 23.8 (CH_3), 15.9 (CH_3). HRMS (ESI$^+$, m/z): calcd for $(C_{11}H_{15}ClN)^+$ $(M+H)^+$: 196.0888; found 196.0894.

(*E*)-4-(4-Bromophenyl)pent-3-en-2-amine (3 d). Yellowish oil (57% yield). R_f (MeOH): 0.16. IR: ν 3348, 3013, 1552, 1488, 1261 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.42 (*d*, *J* = 8.1 Hz, 2H), 7.25 (*d*, *J* = 8.3 Hz, 2H), 5.67 (*d*, *J* = 8.7 Hz, 1H), 3.94–3.87 (*m*, 1H), 2.04 (*s*, 3H), 1.57 (*br s*, 2H), 1.21 (*d*, *J* = 6.4 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 142.2 (C), 135.0 (C), 132.9 (C), 131.2 (2CH), 127.4 (2CH), 120.8 (CH), 45.4 (CH), 23.8 (CH_3), 15.8 (CH_3). HRMS (ESI$^+$, m/z): calcd for $(C_{11}H_{15}Br)^+$ $(M+H)^+$: 240.0382; found 240.0382.

(*E*)-4-(4-(Trifluoromethyl)phenyl)pent-3-en-2-amine (3 e). Yellowish oil (59% yield). R_f (MeOH): 0.08. IR: ν 3264, 2991, 1564, 1502, 1243 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.57 (*m*, 2H), 7.49 (*m*, 2H), 5.74 (*d*, *J* = 9.1 Hz, 1H), 3.94 (*br s*, 1H), 2.08 (*s*, 3H), 1.66 (*br s*, 2H), 1.23 (*d*, *J* = 6.2 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 146.9 (C), 136.4 (C), 132.9 (CH), 128.8 (*q*, *J* = 32.4 Hz, C), 126.0 (2CH), 125.1 (*q*, *J* = 2.8 Hz, 2CH), 124.3 (*q*, *J* = 272.3 Hz, C), 45.4 (CH), 23.8 (CH_3), 15.9 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$): δ −62.40. HRMS (ESI$^+$, m/z): calcd for $(C_{12}H_{15}F_3N)^+$ $(M+H)^+$: 230.1151; found 230.1155.

(*E*)-4-(3-Fluorophenyl)pent-3-en-2-amine (3 f). Yellowish oil (81% yield). R_f (MeOH): 0.10. IR: ν 3319, 3002, 1601, 1510, 1255 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.29–7.21 (*m*, 1H), 7.16–7.08 (*m*, 1H), 7.07 (*dd*, *J* = 10.8, 2.2 Hz, 1H), 6.91 (*td*, *J* = 8.3, 2.6 Hz, 1H), 5.70 (*d*, *J* = 8.7 Hz, 1H), 3.96–3.87 (*apparent dt*, *J* = 8.6, 6.4 Hz, 1H), 2.04 (*s*, 3H), 1.78 (*br s*, 2H), 1.21 (*d*, *J* = 6.4 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 162.9 (*d*, *J* = 245.4 Hz, C), 145.6 (*d*, *J* = 7.6 Hz, C), 135.2 (C), 133.0 (CH), 129.6 (*d*, *J* = 8.3 Hz, CH), 121.3 (*d*, *J* = 3.0 Hz, CH), 113.6 (*d*, *J* = 21.1 Hz, CH), 112.7 (*d*, *J* = 21.1 Hz, CH), 45.4 (CH), 23.7 (CH_3), 15.9 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$): δ −113.77. HRMS (ESI$^+$, m/z): calcd for $(C_{11}H_{15}FN)^+$ $(M+H)^+$: 180.1183; found 180.1189.

(*E*)-4-(3-(Trifluoromethyl)phenyl)pent-3-en-2-amine (3 g). Yellowish oil (53% yield). R_f (MeOH): 0.10. IR: ν 3239, 2989, 1562, 1508, 1253 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.61–7.38 (*m*, 4H), 5.73 (*d*, *J* = 8.6 Hz, 1H), 3.95 (*br s*, 1H), 2.08 (*s*, 3H), 1.86 (*br s*, 2H), 1.23 (*d*, *J* = 6.6 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 144.1 (C), 135.8 (C), 132.9 (CH), 130.6 (*q*, *J* = 31.8 Hz, C), 129.0 (CH), 128.6 (CH), 124.2 (*q*, *J* = 272.6 Hz, C), 123.5 (*q*, *J* = 3.8 Hz, CH), 122.5 (*q*, *J* = 3.8 Hz, CH), 45.4 (CH), 23.7 (CH_3), 15.9 (CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$): δ −62.60. HRMS (ESI$^+$, m/z): calcd for $(C_{12}H_{15}F_3N)^+$ $(M+H)^+$: 230.1151; found 230.1157.

(*E*)-4-(2-Fluorophenyl)pent-3-en-2-amine (3 h). Yellowish oil (84% yield). R_f (MeOH): 0.10. IR: ν 3271, 3029, 1588, 1513, 1241 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.26–7.17 (*m*, 2H), 7.09–6.97 (*m*, 2H), 5.50 (*d*, *J* = 8.9 Hz, 1H), 3.92 (*apparent quint*, *J* = 7.3 Hz, 1H), 2.04 (*s*, 3H), 1.80 (*br s*, 2H), 1.22 (*d*, *J* = 6.2 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 159.9 (*d*, *J* = 246.9 Hz, C), 137.5 (CH), 132.1 (*d*, *J* = 14.3 Hz, C), 130.7 (C), 129.7 (*d*, *J* = 4.6 Hz, CH), 128.3 (*d*, *J* = 8.2 Hz, CH), 123.9 (*d*, *J* = 3.8 Hz, CH), 115.6 (*d*, *J* = 22.7 Hz, CH), 45.1 (CH), 23.6 (CH_3), 17.0 (*d*, *J* = 4.6 Hz, CH_3). ^{19}F-NMR (282 MHz, $CDCl_3$): δ −115.30. HRMS (ESI$^+$, m/z): calcd for $(C_{11}H_{15}FN)^+$ $(M+H)^+$: 180.1183; found 180.1187.

Procedure for the one-pot Meyer-Schuster and biotransamination performed in a sequential manner at preparative scale. Propargylic alcohol **1 a** (3.12 mmol, 0.5 g) was dissolved in ^{i}PrOH (1.5 mL) inside an Erlenmeyer flask, and then distilled water (13.60 mL) and [Au(IPr)(NTf_2)] (3 mol%, 0.0936 mmol, 39 mg) were added. The mixture was stirred at 45 °C for 3 h. After this time, 100 mM KPi buffer pH 7.5 (84.85 mL) containing PLP (1 mM) and ^{i}PrNH$_2$ (1 M), and *Ars*TA (550 mg) were added. The mixture was stirred for 48 h at 45 °C, and after this time the reaction was stopped by the addition of a NaOH 10 M aqueous solution (25 mL). The mixture was extracted with EtOAc (4 × 70 mL) and the organic phases were combined, dried over Na_2SO_4, filtered and concentrated under vacuum. The enantiomeric excess values were determined by HPLC after chemical acetylation using DMAP and acetic anhydride. Purification by column chromatography on silica gel (MeOH) led to the allylic amine (*E*,*S*)-**3 a** (398 mg, 79% isolated yield and 99% *ee*).

Acknowledgements

Financial support from the Spanish Ministry of Science and Innovation (MCI, PID2019-109253RB–I00) and Asturian Regional Government (AYUD/2021/51542) are gratefully acknowledged. S.G.-G. thanks University of Oviedo (UNIOVI) for a predoctoral fellowship (PAPI-21-PF-14) inside the "Programa de Apoyo y Promoción de la Investigación". Technical support from the Scientific-Technical Services (UNIOVI) is acknowledged. We thank Prof. Wolfgang Kroutil (University of Graz, Austria) for the donation of heterologously expressed amine transaminases. For work performed in Ghent, we acknowledge the BOF and iBOF support as well as generous donations from Umicore AG. The Research Foundation – Flanders (FWO) is also acknowledged for a Fundamental Research PhD fellowship to N.V.T (11I6921N)

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