VIP *Very Important Publication*

Gold and Biocatalysis for the Stereodivergent Synthesis of Nor(pseudo)ephedrine Derivatives: Cascade Design Toward Amino Alcohols, Diols, and Diamines

Sergio González-Granda,[a] Georg Steinkellner,[b] Karl Gruber,[b] Iván Lavandera,[a,*] and Vicente Gotor-Fernández[a,*]

[a] Organic and Inorganic Chemistry Department, Universidad de Oviedo
   Avenida Julián Clavería 8, 33006 Oviedo, Asturias (Spain)
   E-mail: lavanderaivan@uniovi.es; vicgotfer@uniovi.es
[b] Institute of Molecular Biosciences, University of Graz
   Humboldtstraße 50/3, 8010 Graz (Austria)

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202300140

Abstract: The combination of gold(I) and enzyme catalysis has provided access to a series of nor(pseudo)ephedrine derivatives in a regio- and stereoselective manner. The approach involves developing IPrAuNTf$_2$-catalyzed hydration of 1-phenylprop-2-yn-1-yl acetate or *N*-(1-phenylprop-2-yn-1-yl)acetamide, followed by (dynamic) asymmetric biotransamination or bioreduction of the corresponding keto ester or keto amide intermediates. Enzyme actions were completely selective towards the modification of the methyl ketones in a highly stereoselective manner, allowing the synthesis of enantio- and diastereomerically enriched products using either racemic or optically active starting materials. Thus, a series of amino alcohol, diol, and diamine derivatives were produced from propargyl esters or amides (57 to 86% isolated yield), the biocatalyst of choice determining the (stereo)selectivity of the overall cascade process (70–99% diastereomeric excess and >98% enantiomeric excess), and providing access to nor(pseudo)ephedrine compounds in a straightforward manner.

Keywords: Biotransamination; Enzymes; Gold catalysis; Hydration; Nor(pseudo)ephedrine

Introduction

Alkaloids are naturally occurring chemical compounds produced by a large variety of organisms such as animals, bacteria, fungi, or plants, most of which display remarkable pharmacological activities.[1] The presence of at least a nitrogen atom with a basic character was included in the original definition of the alkaloid term. However, more recently, the neutral or even weakly acidic character of this chemical motif has also been considered when classifying other families of nitrogen-containing secondary metabolites. Another important structural key element is their chirality; the presence of one or more stereogenic centers determines the biological response of this family of compounds.

Isolation from crude extracts of natural sources is the preferred strategy to obtain alkaloids. However, the chemical syntheses of many of them have also been achieved even on an industrial scale. Remarkably, the use of enzymes for their asymmetric synthesis has been gaining major attention in recent years,[2] with various enzyme families providing straightforward access by means of stepwise chemoenzymatic strategies or multienzymatic cascades.[3]

Ephedrine-type alkaloids, also known as phenyl-propylamino alkaloids (Figure 1A), constitute a representative family of these naturally nitrogen-containing compounds, which can mimic the action of adrenaline, therefore finding multiple applications in medicinal chemistry (anesthesia, bronchial dilation, nasal congestion…). In addition, ephedra constituents have served as valuable building blocks and chiral auxiliaries with remarkable applications in stereoselective synthesis.[4] Importantly, the absolute configuration of their stereogenic centers and the substituents present in key residues determine their biological profiles,[5] including in this ephedrine alkaloid family (1R,2S)-norephedrine, (1S,2S)-norpseudoephedrine, (1R,2S)-ephedrine, (1S,2S)-pseudoephedrine, (1R,2S)-N-methylephedrine and (1S,2S)-N-methylpseudoephedrine, among others (Figure 1B). In addition, the position of the nitrogen and oxygen atoms is another engineering vector, with the 1-amino-1-arylpropan-2-ol family being useful building blocks in organic synthesis as

occurs with other 1,2-amino alcohol families (Figure 1C).

In this context, the use of multienzymatic cascades provides access to a wide number of products, highlighting the stereoselective action of alcohol dehydrogenases (ADHs), carboligases, amine transaminases (ATAs), and amine dehydrogenases to produce optically active amino alcohols.[3] Few research groups have been especially active in this field, reporting stereocontrolled domino reactions combining the use of ATAs either with ADHs or carboligases to prepare all four possible diastereoisomers of nor(pseudo)ephedrine (Schemes 1A and 1B).[6] More recently, Mutti and co-workers have reported the use of a fused styrene monooxygenase and an epoxide hydrolase to stereoselectively transform β-methylstyrene into the corresponding diol, to later develop the efficient combination of the regioselective oxidation of one of the hydroxyl groups, and the formation of the corresponding chiral amino alcohols using either amine dehydrogenases (Scheme 1C)[7] or ATAs.[8] These strategies are commonly developed in a sequential manner to avoid simultaneous enzyme inactivation for both steps, and in general require low substrate concentrations or a dilution at the intermediate stage.

The combination of transition metal catalysis and biotransformations has opened a myriad of possibilities, expanding the repertoire of the synthetic chemist, especially in the last decade due to the synergy between both technologies under similar reaction conditions.[9] In this context, gold species have emerged as ideal catalysts of cycloisomerization, hydration, and rearrangement reactions in an aqueous medium, which can be successfully coupled with the action of stereoselective lipases,[10] ADHs,[10b,11] ATAs,[12] amine dehydrogenases,[13] and aldolases[14] to
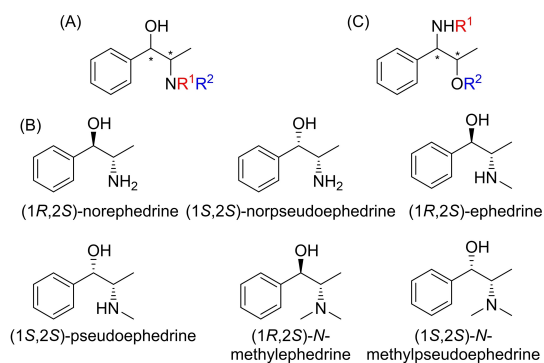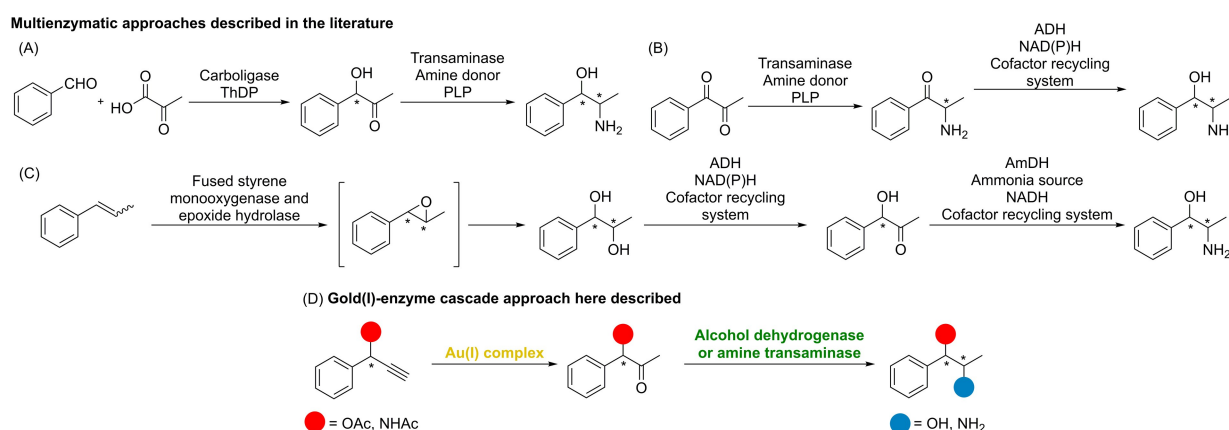

Figure 1. Ephedrine-type alkaloids: (A) General structure. (B) Representative examples. (C) General structure of related 1-amino-1-phenylpropan-2-ol derivatives.

Scheme 1. Multienzymatic approaches toward ephedrine derivatives combining: (A) A carboligase with a transaminase.[6] (B) A transaminase with an alcohol dehydrogenase.[6d] (C) A monooxygenase, an epoxide hydrolase, an alcohol dehydrogenase, and an amine dehydrogenase.[7,8] (D) Gold(I)-enzyme cascade approach proposed in this contribution through alkyne hydration and subsequent biotransformation using an alcohol dehydrogenase or an amine transaminase.

produce chiral furans, alcohols, amines, and hydroxy ketones. Herein, we present our latest results to expand the cooperative action between gold complexes and enzymes for the synthesis of nor(pseudo)ephedrine derivatives starting from easily accessible starting materials through concurrent catalysis. Initially, we will look for adequate conditions to merge gold(I) N-heterocyclic carbenes (NHCs) with ATAs to expand later the potential of this chemoenzymatic approach using ADHs (Scheme 1D). The possibility to work at least at 100 mM substrate concentration for the hydration step, the simple scalability of the processes, and starting from easily accessible propargylic amides or esters in both racemic and enantiopure forms, will pave the way to design (dynamic) regio- and stereo-divergent processes in an efficient manner.

Results and Discussion

Gold-Catalyzed Hydration of Propargylic Ester 1 and Amide 2

Gold species are powerful catalysts for the electrophilic activation of alkynes towards a broad family of nucleophiles,[15] the hydration of propargylic derivatives representing a straightforward reaction to prepare carbonyl compounds that are ideal substrates for enzymes in the quest for novel optically active derivatives. Herein, we ambition the gold-catalyzed hydration of 1-phenylprop-2-yn-1-yl acetate (**1**) and *N*-(1-phenylprop-2-yn-1-yl)acetamide (**2**) to obtain 2-oxo-1-phenylpropyl acetate (**3**) and *N*-(2-oxo-1-phenylpropyl)acetamide (**4**), respectively, opening a wide range of possibilities for the regio- and stereo-divergent synthesis of nor(pseudo)ephedrine derivatives by using ADHs or ATAs in a cascade manner (Scheme 1D).

To develop a regioselective access towards ketone derivatives **3** and **4**, the gold(I) NHC complex [1,3-bis(2,6-diisopropylphenyl)imidazole-2-

ylidene][bis(trifluoromethanesulfonyl)imide] gold(I) (IPrAuNTf$_2$) was selected as catalyst for the hydration of propargylic acetate **1** and acetamide **2** (Scheme 2). Initial reaction conditions involved the use of propan-2-ol (2-PrOH, 20% vol) as organic cosolvent but also as hydrogen donor in the subsequent ADH-catalyzed bioreduction step for cofactor recycling purposes, and a compromise temperature of 40 °C since both gold(I) and enzyme can be simultaneously active under these conditions.[11d,e] Interestingly, after studying the influence of the gold(I) catalyst loading (2–6 mol%) and the reaction time (2–6 h), the amount of IPrAuNTf$_2$ could be reduced to 2 mol% for the synthesis of racemic keto ester **3** requiring just 6 h to achieve a quantitative conversion (see Table S1 in the SI for more details), expanding the potential of gold(I) catalysis previously disclosed using other species.[16] The reaction could be scaled at 2 mmol of **1**, isolating **3** in 89% yield.

Remarkably, under identical conditions, the hydration of enantiopure (*R*)- or (*S*)-**1**, obtained after lipase-catalyzed enantioselective acetylation of the propargylic alcohol precursor, occurred with full conversion and without any loss of optical activity (>99% *ee*, see Table S2), thus obtaining enantiopure (*S*)- and (*R*)-**3** and opening the possibility to obtain nor(pseudo)ephedrine derivatives with two stereogenic centers.

Development of a Chemoenzymatic Hydration-Biotransamination Sequence Towards Amido Ester 5 b

A total of 37 ATAs were screened with keto ester *rac*-**3** to prepare amino ester **5 a** in a highly stereoselective manner using either alanine enantiomers (Ala) or isopropylamine (2-PrNH$_2$) as amine donors (see Table S3). The use of ATAs with 2-PrNH$_2$ provided a number of enzyme candidates to attempt the gold-ATA cascade strategy; for instance, the one from *Chromobacterium violaceum* (*E. coli*/*Cv*TA)[17] provided (after
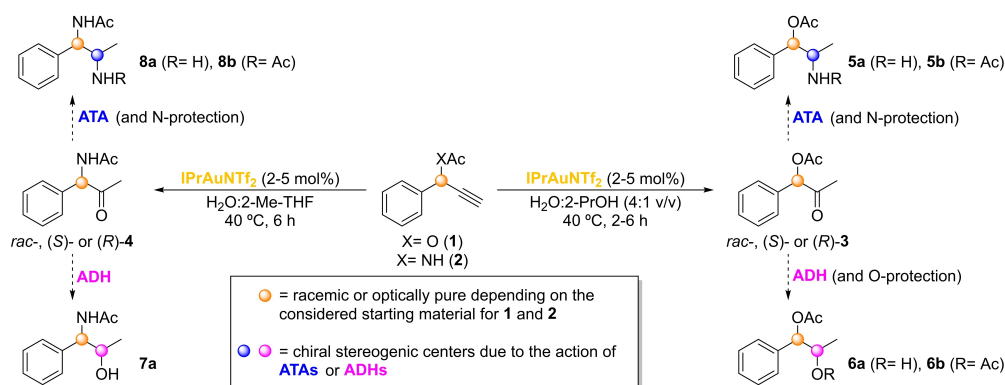
Scheme 2. IPrAuNTf$_2$-catalyzed hydration of propargylic ester **1** and amide **2** (continuous arrows) and subsequent asymmetric enzymatic reactions (dashed arrows).

chemical acetylation) an equimolecular mixture of *syn*-(1*S*,2*S*) and *anti*-(1*R*,2*S*)-**5b** diastereoisomers in enantiopure form, while the commercial ATA-025, ATA-303, and ATA-412 led to the stereocomplementary antipodes [*syn*-(1*R*,2*R*) and *anti*-(1*S*,2*R*)-**5b**] with the same ratio and conversions over 90% (Scheme 3A). It was observed that no racemization occurred at the benzylic position under these mild reaction conditions.

(*S*)-Selective *Cv*TA and (*R*)-selective ATA-303 were chosen as suitable candidates for the gold(I)-ATA cascades to produce all possible diastereoisomers of amino ester **5a**. Before developing them, as depicted in Scheme 3B, biotransamination reaction conditions were optimized (Tables S4 and S5 for *Cv*TA, and Table S7 for ATA-303), considering the influence of the cosolvent percentage (10–20% vol of 2-PrOH), enzyme loading (1.5–38 mg of *Cv*TA for 0.05 mmol of **3**) and the amine donor concentration (50–1000 mM of 2-PrNH$_2$). This strategy allowed us to produce all four possible enantiopure diacetylated 1,2-amino alcohols **5b** after chemical protection of the intermediate **5a**, to simplify the analytical measurement of the final mixture obtained, due to the intra- and intermolecular migration of the acetyl group from the ester to the amino group.

The cascade approach was developed sequentially, performing the hydration step of acetate enantiomer (*R*)- or (*S*)-**1** (100 mM) for 6 h at 40 °C,[18] while for the biotransamination of enantiopure keto ester intermediate **3**, its dilution to 25 mM was necessary for the quantitative conversion into enantiopure **5b** after chemical acetylation (Scheme 3B and Tables S6 and S8).

This procedure was successfully performed on a preparative scale (100 mg) from (*S*)-**1** to isolate (1*R*,2*S*)-**5b** and (1*R*,2*R*)-**5b** in 79 and 85% isolated yield, respectively, after liquid-liquid extraction and column chromatography. The assignment of the absolute configuration of all diastereoisomers was performed based on the selectivity of CAL–B towards the preferential acetylation of the (*R*)-enantiomer,[19] while for the second stereocenter, ^{1}H-NMR analysis of the reaction crudes allowed to unequivocally assign the stereochemistry of the so-obtained compounds.

Development of a Hydration-Bioreduction Cascade Towards Diesters 6b

The possibility of achieving all possible diastereoisomers of **5b** encouraged us to propose a complementary approach towards diacetylated diol **6b**, in this case, replacing the ATA-catalyzed biotransamination step with an ADH-catalyzed bioreduction. Therefore, 26 ADHs were screened towards the reduction of keto ester **3** (Table S9), finding 4 suitable enzymes to obtain the *syn*- and *anti*-**6b** diester diastereoisomers after chemical acetylation, which were (*S*)-selective *E. coli*/ADH-T,[20] *E. coli*/ADH-A,[21] and commercial KRED–P1-A12, while to access the opposite enantiomer, commercial evo.1.1.200 was required (Scheme 4A). After optimization of the reaction conditions in terms of pH (7.5–9.0) and temperature (30–45 °C), it was observed that for ADH-T, pH 9.0 and 40 °C were necessary to attain a quantitative conversion, while for ADH-A, the use of 45 °C at pH 7.5 was sufficient to furnish an equimolecular mixture of both *syn* and *anti*-diastereoisomers of diester **6b**, obtained after chemical O-acetylation, with total enantioselectivity (Table S10).

At this point, the overall gold(I)-ADH cascade was attempted to produce the four diastereoisomers in full conversion, starting from the corresponding enantio-
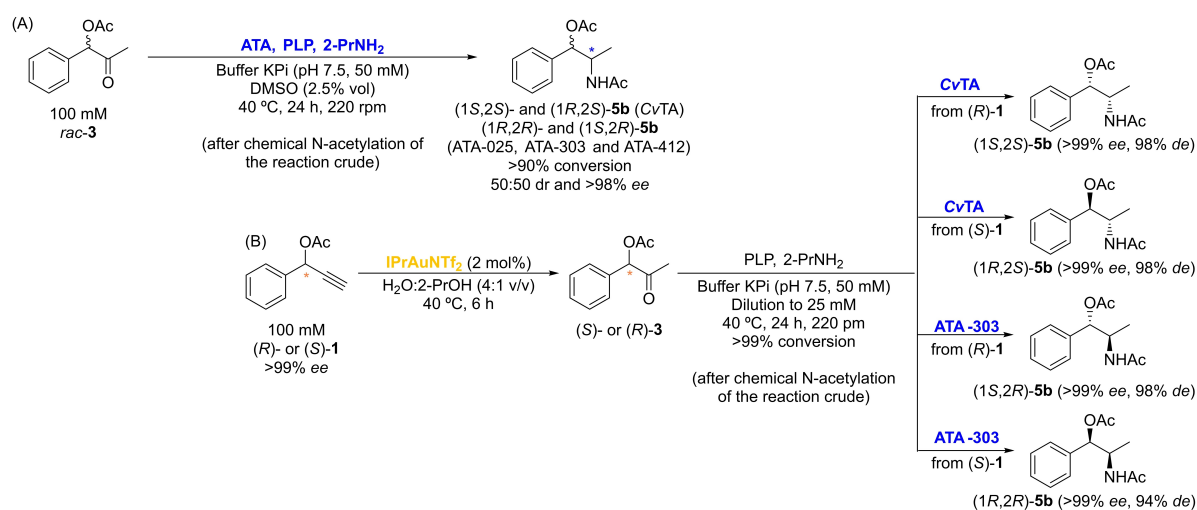
Scheme 3. (A) Best results in the ATA screening for the biotransamination of racemic keto ester **3**. (B) IPrAuNTf$_2$-ATA sequential cascade from enantiopure (*R*)- or (*S*)-**1** for the stereodivergent syntheses of nor(pseudo)ephedrine derivatives **5b**.
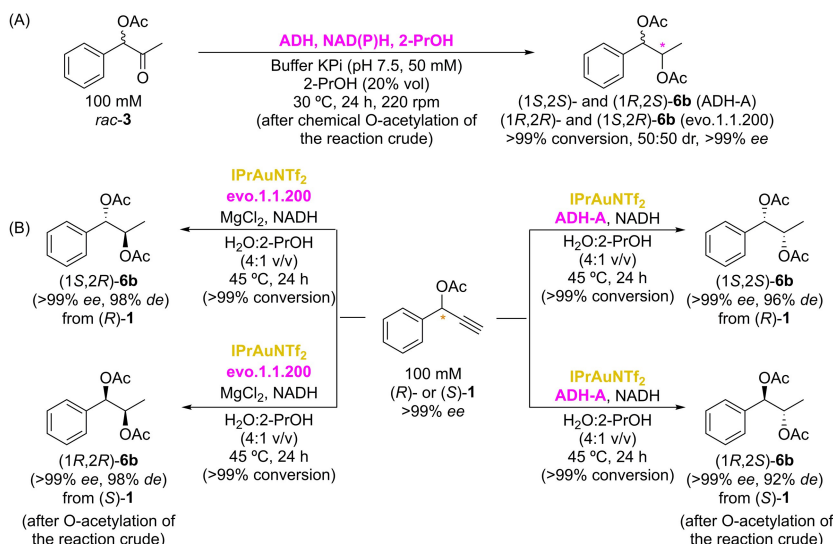
Scheme 4. (A) Best results of the ADH screening with *rac*-**3**. (B) IPrAuNTf₂-ADH cascade for the stereodivergent syntheses of nor(pseudo)ephedrine diester analogs **6 b** starting from (*R*)- or (*S*)-**1**.

pure propargyl ester (*S*)- and (*R*)-**1**. Optimization of the reaction conditions in terms of substrate concentration (75 or 100 mM), IPrAuNTf₂ (5.0 or 7.5 mol%) and ADH loading (9 or 18 mg for 0.05 mmol of **1**), shaking type (magnetic or orbital), reaction vessel (1.5 or 2.5 cm diameter), temperature (40 or 45 °C), and reaction time (24 or 48 h), led to the successful achievement of the overall cascade process for the (*S*)-selective ADH-A (Tables S11 and S12) and (*R*)-selective evo.1.1.200 (Table S13). Remarkably, the concurrent stereodivergent approach adding all the reagents from the beginning was achieved, without modification of the reaction conditions along the multicatalytic strategy, in contrast to the previous sequential gold(I)-ATA cascade (Scheme 4B). Semi-preparative transformations at a 100 mg substrate scale were demonstrated to obtain enantio- and diastereomerically pure **6 b**, yielding the (1*S*,2*R*)-diastereoisomer in 93% conversion (81% isolated yield) and the (1*R*,2*R*) isomer in quantitative conversion (86% isolated yield) after 24 h at 40 °C, and purification by column chromatography. Absolute configurations were assigned by comparison with the optical rotation values and HPLC retention times detailed in the literature using other alternative synthetic strategies.[22]

Propargylic acetamide 2 as Substrate for Chemo-enzymatic Cascades

Once the versatility of racemic and enantiopure forms of propargyl acetate **1** was demonstrated for synthesizing amino alcohol and diol ephedrine derivatives, the next step was to explore the possibility of employing propargyl acetamide **2** for the preparation of structural amino alcohol regioisomers and diamine derivatives. Compared to the gold-catalyzed hydration of esters, the transformation over N-protected amines has been unexplored, with the use of amides currently remaining a challenge.[23] Therefore, the IPrAuNTf₂-catalyzed hydration of racemic amide **2** (100 mM) was studied in water using different catalyst loadings (2–5 mol%) and organic cosolvents (2-PrOH and 2-Me-THF, Scheme 5 and Table S14). As expected, the amount of catalyst allowed to increase the conversion when using 2-PrOH (15–43%), although far from being synthetically useful due to the low solubility of the amide in this cosolvent. However, adding 2-Me-THF highly improved the solubility of **2** and, therefore, the conversion, being quantitative at 10% vol after 6 h at 40 °C, and allowing to recover the racemic keto amide **4** in 87% yield after
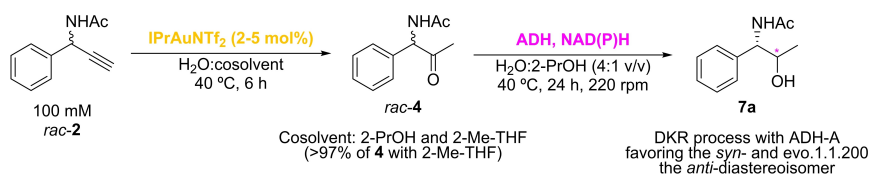
Scheme 5. Optimization of the gold-ADH cascade from propargylic amide **2** via IPrAuNTf₂-catalyzed hydration of *rac*-**2** and ADH-catalyzed dynamic asymmetric reduction of keto amide *rac*-**4**.

extraction and chromatography purification on a 2 mmol-substrate scale.

In this case, the bioreduction using 26 ADHs was not as successful as the one achieved for the keto ester **3** since only ADH-A and evo.1.1.200 were active under standard conditions (19% and 40%, respectively, Table S15), although gratifyingly with outstanding stereoselection, the *syn*-diastereoisomer being favored for ADH-A (75:25) and the *anti*-isomer for evo.1.1.200 (3:97).

Docking Studies

We docked compounds **3** and **4** -both enantiomers in each case- into the structure of ADH-A from *Rhodococcus ruber* (Section XXVI in the SI),[24] using the program AutoDock-Vina[25] and the Catalobase platform (www.innophore.com). For both compounds, the calculations predicted the lowest energy binding modes to have the carbonyl oxygen atom of the ester or amide moiety bound to the active site zinc, thereby precluding the reduction of the keto-group. Arguably productive binding modes with the keto group attached to the metal ion (Figure 2) had slightly less favorable binding energies. However, these values were at most 0.7 kcal/mol above the minimum.

In addition to the coordination to zinc, the carbonyl oxygen was hydrogen bonded to Ser-40 in these structures. The methyl group was located near the indole ring of Trp-295. This amino acid residue

restricts the available space in this active site region and rules out the binding of substrates with larger substituents. On the other hand, the bulkier phenyl ring occupied a larger pocket created by residues Phe-43, Val-44, Met-47, Tyr-54, and Leu-119. The ester and amide groups pointed towards residues Ile-271, Phe-281, Phe-286, and Tyr-294. The distances between the C4 atom of the nicotinamide and the carbonyl carbon atom of the substrate ranged from 3.1 to 3.4 Å, which was well compatible with hydride transfer to the ketone *Re*-face. The resulting *S*-configuration of the secondary alcohols was consistent with the experimentally determined stereoselectivity of the enzyme. Regarding the distinction between both ketone enantiomers by the enzyme, the docking calculations did not provide any clear differences since reasonable binding modes with comparable binding energies were obtained for both enantiomers of compound **3** (Figures 2A and 2B), which is consistent with the good activities found for both enantiomers. However, the inability of ADH-A to convert amide **4** could unfortunately not readily be explained by these binding modes (Figures 2C and 2D). Also, the Gibbs free energies for the isodesmic transformations between the 2-propanol/acetone and the alcohol/ketone counterpart were studied to check if the different reactivity of ketones **3** and **4** could be attributed to the thermodynamics of the reactions. Still, in aqueous solution and the gas phase, the free energy differences estimated for all these processes indicated a thermodynamically favored reduction of both ketone substrates (Section XXVII in the SI).
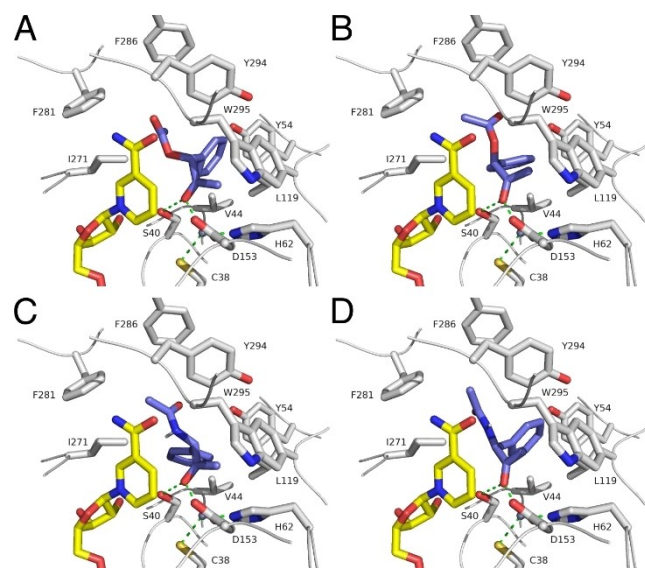
Development of a Stereoselective Dynamic Strategy Towards Hydroxy Amide 7a and Diamide 8b

Interestingly, quick racemization of the substrate was observed when incubating the enantiopure (*S*)-**4** at different pH values in a 100 mM Tris·HCl buffer (with 2.5% vol of 2-Me-THF) along the time. Thus, while at pH 5 negligible racemization was observed, almost racemic **4** was recovered at higher pHs (7.5–9.5), even after only 1 h at pH 9.5 (Table S16). This effect has already been observed in the metal-catalyzed hydrogenation of similar substrates,[26] although no explanation for this effect was provided. Since at first sight the hydrogen at the benzylic position of the keto ester should be slightly more acidic than the one from the keto amide (confirmed by *ab initio* calculations, see SI), the simple acidic character of this hydrogen atom was discarded as the only explanation for the racemization occurrence, so we hypothesize that the enol form of the ketone in **4** could be stabilized by internal hydrogen bonding with the NH group of the amide that would not be possible in compound **3**, thus favoring the racemization of the amide. Although these results hampered the possibility of accessing all

Figure 2. Predicted binding modes of (*R*)-**3** (A), (*S*)-**3** (B), (*R*)-**4** (C), and (*S*)-**4** (D) to the enzyme ADH-A from *Rhodococcus ruber*. Substrate molecules are shown in dark blue, the nicotinamide cofactor in yellow, and the surrounding amino acid residues in white. The zinc ion is depicted as a grey sphere. Interactions are indicated by dashed lines. This figure was generated using the program PyMOL (https:/pymol.org).

possible diastereoisomers of **7a**, a dynamic kinetic resolution (DKR) can be accomplished, allowing the use of the racemic propargylic amide as substrate. Using evo.1.1.200 (Table S17), the DKR was analyzed in depth by varying the pH (8.5 and 9.5), temperature (30 and 45 °C), reaction time (24 and 48 h), and amide **4** concentration (15 and 25 mM) leading to a conversion slightly superior to 50% and furnishing both *syn*- and *anti*-**7** diastereoisomers in enantiopure form (>99% *ee*), although clearly favoring the formation of the *anti* isomer (up to 94:6 ratio). In this particular case, the final acetylation protocol was not necessary

since the migration of the acetyl moiety from the amide towards the alcohol was not observed, remaining as a stable compound.

All these results encouraged us to explore the chemoenzymatic dynamic strategy towards the hydroxy amide **7a** and the diamide **8b**, combining the IPrAuTf$_2$-catalyzed hydration of **2** for 6 h, and the subsequent addition of an ADH (evo.1.1.200) as depicted in Scheme 6 (right side). The results can be found in Table 1. A 51% conversion was reached when adding the enzyme in portions since the reduction step stopped at 26% after 48 h when using 10 mg of the ADH for 0.05 mmol of substrate (entries 1 and 2). Also, the dilution of the intermediate to 10 mM instead of 15 mM provided a significant conversion improvement (67%, entry 3).

On the other hand, two ATAs formed the corresponding amino amide **8a** that was isolated after derivatization as diacetamide (1*S*,2*R*)-**8b** (ATA-024 and ATA-033, 99% *ee*, 19:81 *syn*:*anti* ratio, Table S18), and ATA-033 at pH 9.5 led to 96% conversion and 14:86 dr with complete enantioselectivity (Table S19), with a high dependence of the amount of the amine donor, since 50 equiv. provided the best conversion (0.1–1.0 M 2-PrNH$_2$, 54–96% after 24 h at 45 °C, Table S20).

The approach gold-ATA was performed sequentially (Scheme 6, left side), the hydration being completed after 6 h, while the biotransamination could be performed at the same temperature or at 30 °C for additional 48 h after dilution of **4** (25 mM, Table 2),
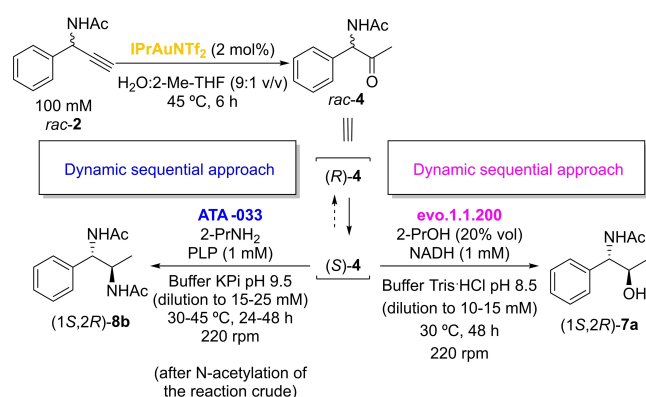
Scheme 6. IPrAuNTf$_2$-catalyzed hydration of *rac*-**2** followed by ADH-catalyzed bioreduction (right) or ATA-catalyzed biotransamination (left) with concomitant racemization of keto amide **4**.

Table 1. IPrAuNTf$_2$-enzyme cascade for the chemoenzymatic synthesis of hydroxy amide (1*S*,2*R*)-**7a** from racemic propargylic acetamide **2** (100 mM) at 30 °C for 48 h.

Entry	evo.1.1.200 (mg)[a]	Dilution (mM)[b]	4 (%)[c]	7a (%)[c]	7a syn:anti[c]	ee$_{syn}$ (%)[d]	ee$_{anti}$ (%)[d]
1	10	15	74	26	6:94	99 (1*R*,2*R*)	99 (1*S*,2*R*)
2	10 + 5	15	49	51	5:95	>99 (1*R*,2*R*)	>99 (1*S*,2*R*)
3	10 + 5	10	33	67	5:95	>99 (1*R*,2*R*)	>99 (1*S*,2*R*)

[a] Amount of evo.1.1.200 per 0.05 mmol of racemic **2**, when necessary, the second addition was done after 24 h of reaction.
[b] Concentration of keto amide **4** for the enzymatic step once the reagents and enzyme were added to develop the biocatalytic step.
[c] Percentage of products and diastereomeric ratios were measured by HPLC analyses.
[d] Enantiomeric excess values were measured by HPLC analyses (see SI for further information).

Table 2. IPrAuNTf$_2$-enzyme cascade for the chemoenzymatic synthesis of diacetamide (1*S*,2*R*)-**8b** from racemic propargylic acetamide **2** (100 mM) using ATA-033.

Entry	Dilution (mM)[a]	T (°C)	t (h)	4 (%)[b]	8b (%)[b]	8b syn:anti[b]	ee$_{syn}$ (%)[c]	ee$_{anti}$ (%)[c]
1	25	45	24	4	96	15:85	99 (1*R*,2*R*)	>99 (1*S*,2*R*)
2	25	45	48	3	97	25:75	99 (1*R*,2*R*)	>99 (1*S*,2*R*)
3	25	30	48	3	97	17:83	99 (1*R*,2*R*)	>99 (1*S*,2*R*)
4	15	45	48	5	95	15:85	99 (1*R*,2*R*)	>99 (1*S*,2*R*)

[a] Concentration of keto amide **4** for the enzymatic step once the reagents and the enzyme were added.
[b] Percentage of products and diastereomeric ratios were measured by HPLC analyses (after chemical acetylation for **8b**).
[c] Enantiomeric excess values were measured by HPLC analyses (see SI for further information).

finding in all cases very high conversions (95–97%), with a slight better diastereoselectivity when the enzymatic step was performed at 30 °C (entry 3, 17:83 *syn*:*anti*).

Satisfyingly, the semi-preparative transformations were next performed, allowing the synthesis of the hydroxy amide (1*R*,2*S*)-**7a** (95:5 dr, >99% *ee*) in 69% conversion with 57% isolated yield, by addition of evo.1.1.200 in portions and developing the bioreduction at 30 °C and a final dilution of **4** to 10 mM. Also, the diamide (1*R*,2*S*)-**8b** could be attained in 96% conversion and 77% isolated yield (85:15 dr, 99% *ee*, after chemical N-acetylation), performing the biotransamination for 24 h at 45 °C with a dilution of **4** to 25 mM. Both products were isolated by liquid-liquid extraction and purified through column chromatography, the stereopreference of evo-1.1.200 and ATA-033 allowed us to assign the absolute configurations of the products (see the SI for further details).
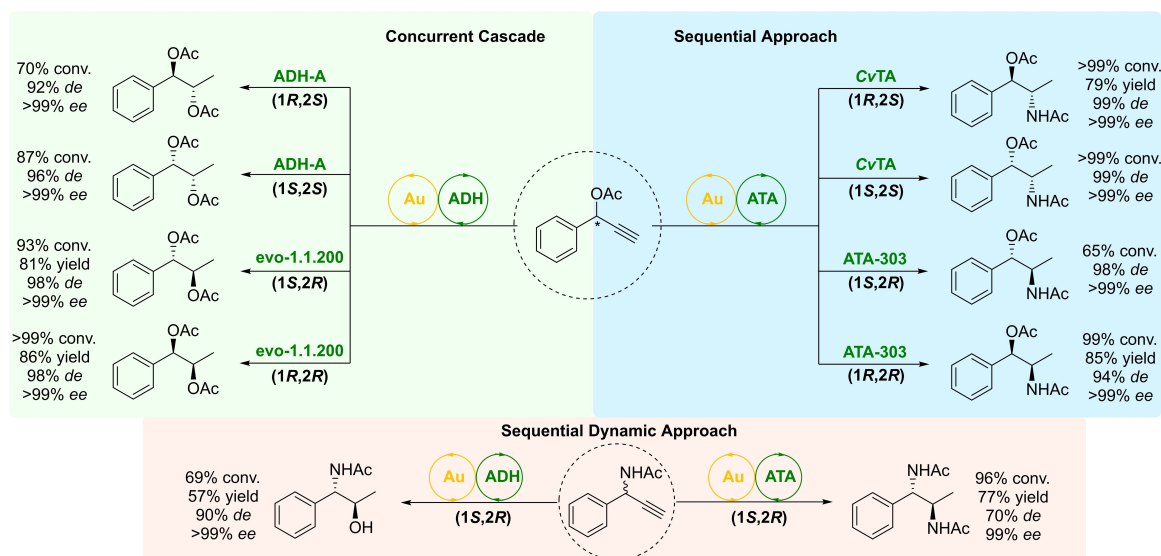
Conclusions

The combined use of an N-heterocyclic carbene gold(I) species and enzymes from the alcohol dehydrogenase and amine transaminase classes has been designed and optimized, starting from easily accessible materials, to obtain nor(pseudo)ephedrine derivatives in a highly selective manner (Scheme 7). Firstly, IPrAuNTf$_2$ catalyzes the highly regioselective and straightforward syntheses of a keto ester and a keto amide intermediate, starting from racemic or enantiopure propargylic esters or amides, obtained by simple chemical methods, under reaction conditions that are compatible with the development of one-pot sequential or concurrent chemoenzymatic cascades.

The finding of active and stereoselective enzymes provided stereodivergent access to a series of protected diol, amino alcohol, or diamine derivatives, the stereo-discrimination being dependent on the enzyme of choice. Remarkably, using a propargylic ester precursor led to the formation of all possible four diastereoisomers of the protected diol and amino alcohol following a concurrent or a sequential approach, respectively, with excellent conversions and stereoselectivities (Scheme 7 top).

In the case of the propargylic amide, its racemization under suitable conditions for the gold- and enzyme-catalyzed steps opened the possibility of performing a one-pot sequential transformation under dynamic conditions, favoring the formation of one diastereoisomer of the corresponding N-protected regiocomplementary amino alcohol or diamine, using either an alcohol dehydrogenase or an amine transaminase, respectively (Scheme 7 bottom). Overall, a wide panel of nor(pseudo)ephedrine derivatives and analogs bearing two chiral centers has been achieved in a straightforward manner taking advantage of the best features of two worlds, gold and enzyme catalysis, in aqueous medium and under mild reaction conditions, highlighting the tremendous potential that this combination can provide to the selective synthesis of high-added value compounds.

Experimental Section

Scheme 7. Sum-up of the gold(I)-enzyme cascades designed to synthesize nor(pseudo)ephedrine derivatives and analogs.

while KRED and ATA kits, and GDH-105 (48 U/mg) were obtained from Codexis Inc. LDH (300 U/mg) was purchased from Sigma-Aldrich. Made in house ADHs and ATAs were heterologously expressed in *E. coli*.

NMR spectra were recorded on a Bruker AV300 MHz spectrometer including ^{1}H and ^{13}C NMR monodimensional experiments. All chemical shifts (δ) are given in parts per million (ppm) and referenced to the residual solvent signal as internal standard. Melting points were measured in a Gallenkamp apparatus, introducing the samples in open capillary tubes and the measurements are uncorrected. IR spectra were recorded on a Jasco FT/IR-4700 spectrophotometer, and v_{max} values are given in cm^{-1} for the main absorption bands. High resolution mass spectra (HRMS) experiments were carried out by electrospray ionization in positive mode (ESI$^+$) using a Micro Tof Q spectrometer. Thin-layer chromatography (TLC) was conducted with Merck Silica Gel 60 F254 precoated plates and visualized with a UV lamp, plus either potassium permanganate, vanillin, or ninhydrin stains. Column chromatographies were performed using silica gel 60 (230–240 mesh).

Gas chromatography (GC) analyses were performed on an Agilent HP6890 GC chromatograph equipped with a FID detector using an HP-5 column (30 m × 0.32 mm × 0.25 μm) for the determination of conversion values, and a CP-Chirasil-DEX CB (30 m × 0.32 mm × 0.25 μm) for the determination of enantiomeric excess values. High-performance liquid chromatography (HPLC) analyses were performed on an HP 1100 chromatograph equipped with a VIS-UV detector for the measurement of enantiomeric excess values.

General Procedure for the Gold-Catalyzed Hydration of Propargylic Ester 1

Distilled water (400 μL) and IPrAuNTf$_2$ were added to a solution of racemic acetate **1** (0.05 mmol, 8.7 mg) in 2-PrOH or 2-Me-THF (100 μL), and the mixture was stirred at 40 °C for 2 or 6 h. Then, the reaction was extracted with EtOAc (3 × 1 mL), and the organic phases were combined, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The conversion was measured by GC analysis.

The reaction was scaled-up as follows (Scheme 3; entry 5 of Table S1): H$_2$O (16 mL) and IPrAuNTf$_2$ (0.04 mmol, 34 mg) were added to a solution of racemic acetate **1** (2 mmol, 348 mg) in 2-PrOH (4 mL), and the mixture was stirred at 40 °C for 6 h. Then, the reaction was extracted with EtOAc (4 × 25 mL), the organic phases were combined, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The reaction crude was purified by column chromatography on silica gel (25% EtOAc/hexane), obtaining racemic acetate **3** (342 mg, 89% isolated yield).

***rac*-2-Oxo-1-phenylpropyl acetate (*rac*-3)**: Yellowish oil (89% yield). R_f (25% EtOAc/hexane): 0.56. IR: 2601, 1744, 1732, 1371, 1232, 1044 cm^{-1}. ^{1}H-NMR (300.13 MHz, CDCl$_3$): δ 7.41 (*s*, 5H), 5.97 (*s*, 1H), 2.19 (*s*, 3H), 2.11 (*s*, 3H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): δ 201.7 (C), 170.3 (C), 133.2 (C), 129.4 (CH), 129.1 (2CH), 128.1 (2CH), 81.0 (CH), 26.2 (CH$_3$), 20.7 (CH$_3$). HRMS (ESI$^+$, m/z): calcd for (C$_{11}$H$_{12}$NaO$_3$)$^+$ (M + Na)$^+$: 215.0679; found 215.0684.

General Procedure for the Gold-Catalyzed Hydration of Propargylic Amide 2

Distilled water (400 μL) was added to a solution of racemic amide **2** (0.05 mmol, 8.6 mg) in 2-Me-THF (100 μL). Then, IPrAuNTf$_2$ (2 mol%, 0.001 mmol, 1 mg) was added, and the mixture was stirred at 40 °C for 6 h. After this time, the reaction was extracted with EtOAc (3 × 1 mL), the organic phases were combined, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The conversion was measured by ^{1}H-NMR analysis of the reaction crude.

The reaction was scaled-up as follows (Scheme 5): Distilled water (16 mL) was added to a solution of racemic amide **2** (2 mmol, 346 mg) in 2-Me-THF (4 mL). Then, IPrAuNTf$_2$ (0.04 mmol, 34 mg) was added, and the mixture was stirred at 40 °C for 6 h. After this time, the reaction was extracted with EtOAc (4 × 25 mL), the organic phases were combined, dried over Na$_2$SO$_4$, filtered and concentrated under vacuum. The reaction crude was purified by column chromatography on silica gel (70% EtOAc/hexane), obtaining *rac*-**4** as a white solid (333 mg, 87% isolated yield).

***rac*-N-(2-Oxo-1-phenylpropyl)acetamide (*rac*-4)**. White solid (87% yield). R_f (70% EtOAc/hexane): 0.25. Mp: 98–100 °C. IR: 2714, 1692, 1603, 1371 cm^{-1}. ^{1}H-NMR (300.13 MHz, CDCl$_3$): δ 7.39–7.28 (*m*, 5H), 6.83 (*br s*, 1H), 5.55 (*d*, J = 6.6 Hz, 1H), 2.10 (*s*, 3H), 1.99 (*s*, 3H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): δ 203.6 (C), 169.3 (C), 136.4 (C), 129.3 (2CH), 128.6 (CH), 128.0 (2CH), 63.5 (CH), 27.2 (CH$_3$), 23.1 (CH$_3$). HRMS (ESI$^+$, m/z): calcd for (C$_{11}$H$_{13}$NNaO$_2$)$^+$ (M + Na)$^+$: 214.0838; found 214.0842.

General Procedure for the Gold-ATA Cascade of Propargylic Ester 1 and *Cv*TA

The acetate (*S*)-**1** (0.58 mmol, 100 mg) was dissolved in 2-PrOH (0.58 mL) inside a 50 mL-round bottom flask, and distilled water (5.23 mL) and IPrAuNTf$_2$ (10 mg, 0.012 mmol, 2 mol%) were successively added. The mixture was stirred at 40 °C for 6 h and after this time, first a 100 mM phosphate buffer pH 7.5 (17.4 mL) containing PLP (1 mM), isopropylamine (250 mM), and later *E. coli* heterologously expressing *Cv*TA (35 mg) were added. The mixture was stirred for 24 h at 40 °C, quenching the reaction by addition of an aqueous NaOH 10 M solution (2.5 mL). The amino ester intermediate was extracted with CH$_2$Cl$_2$ (4 × 30 mL), the organic phases were combined, dried over Na$_2$SO$_4$, filtered and concentrated under vacuum. Then, the crude containing **5 a** was dissolved in CH$_2$Cl$_2$ (15 mL), DMAP (0.06 mmol, 7.2 mg), and acetic anhydride (2.61 mmol, 246 μL) were added, and the mixture was stirred for 4 h at 40 °C. After this time, H$_2$O (50 mL) was added, and the mixture was stirred for 20 min. The organic phase was separated, dried over Na$_2$SO$_4$ and filtered. Purification of the reaction crude by column chromatography on silica gel (EtOAc) led to (1*R*,2*S*)-**5 b** as a white solid (108 mg, 79% isolated yield, 99% *de*, > 99% *ee*).

(1*R*,2*S*)-2-Acetamido-1-phenylpropyl acetate [(1*R*,2*S*)-5 b]: White solid (79% yield). R_f (EtOAc): 0.32. Mp: 98–99 °C. IR: 1730, 1367, 1256 cm^{-1}. ^{1}H-NMR (300.13 MHz, CDCl$_3$): δ 7.30–7.23 (*m*, 5H), 6.22 (*d*, J = 9.0 Hz, 1H), 5.81 (*d*, J = 3.8 Hz,

1H), 4.36 (*ddd*, *J* = 8.8, 6.7, 3.9 Hz, 1H), 2.08 (*s*, 3H), 1.86 (*s*, 3H), 1.01 (*d*, *J* = 6.9 Hz, 3H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): δ 170.8 (C), 170.1 (C), 137.7 (C), 128.8 (2CH), 128.4 (CH), 126.8 (2CH), 77.8 (CH), 49.0 (CH), 23.6 (CH$_3$), 21.5 (CH$_3$), 15.4 (CH$_3$). HRMS (ESI$^+$, m/z): calcd for (C$_{13}$H$_{18}$NO$_3$)$^+$ (M + H)$^+$: 236.1281; found 236.1277. [α]$_D^{20}$ = −99.7 (*c* 1.0, CHCl$_3$, > 99% *ee* and 99% *de*). Literature data for (1*R*,2*S*)-**5 b**: [α]$_D^{20}$ = −79.4 (*c* 1.34, CHCl$_3$, 96% *ee* and 90% *de*).[27]

General Procedure for the Gold-ADH Cascade of Enantiopure Propargylic Ester 1 and evo.1.1.200

Acetate (*S*) or (*R*)-**1** (0.57 mmol, 100 mg) was dissolved in 2-PrOH (4.64 mL) inside a 50 mL-round bottom flask. Then, distilled water (16.13 mL), IPrAuNTf$_2$ (35 mg, 0.043 mmol, 7.5 mol%), NADH (9.7 mg), an aqueous 10 mM MgCl$_2$ solution (2.33 mL) and evo-1.1.200 (60 mg) were added. The mixture was stirred at 220 rpm for 24 h at 40 °C, and after this time the reaction containing **6 a** was extracted with EtOAc (4 × 20 mL), the organic phases were combined and dried over anhydrous Na$_2$SO$_4$ and filtered. Then, CH$_2$Cl$_2$ (15 mL), DMAP (0.06 mmol, 7.34 mg), and acetic anhydride (0.87 mmol, 83 μL) were added, and the mixture was stirred for 12 h at 45 °C. After this time, H$_2$O was added (4 mL) and the mixture was stirred for 20 min. The organic phase was separated, dried over Na$_2$SO$_4$ and filtered. The conversion and diastereomeric ratios were measured by GC analysis, while the enantiomeric excess values were determined by HPLC (see SI). Then, the reaction crude was purified by column chromatography on silica gel (20% EtOAc/hexane), affording the corresponding isomer [(1*S*,2*R*)-**6 b**, 109 mg, 81% isolated yield, 98% *de*, > 99% *ee*; (1*R*,2*R*)-**6 b**, 115 mg, 86% isolated yield, 98% *de*, > 99% *ee*]

(1*S*,2*R*)-1-Phenylpropane-1,2-diyl diacetate (1*S*,2*R*)-6 b: Yellowish oil (81% yield). R_f (20% EtOAc/hexane): 0.43. IR: 1735, 1495, 1370 cm^{-1}. ^{1}H-NMR (300.13 MHz, CDCl$_3$): δ 7.33 (*m*, 5H), 5.92 (*d*, *J* = 4.2 Hz, 1H), 5.22 (*dq*, *J* = 6.5, 4.3 Hz, 1H), 2.14 (*s*, 3H), 2.00 (*s*, 3H), 1.18 (*d*, *J* = 6.5 Hz, 3H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): δ 170.3 (C), 169.9 (C), 136.6 (C), 128.3 (2CH), 128.2 (CH), 126.9 (2CH), 76.1 (CH), 71.7 (CH), 21.1 (CH$_3$), 21.0 (CH$_3$), 14.6 (CH$_3$). HRMS (ESI$^+$, m/z): calcd for (C$_{13}$H$_{16}$NaO$_4$)$^+$ (M + Na)$^+$: 259.0941; found 259.0939. [α]$_D^{20}$ = +38.1 (*c* 1.0, CHCl$_3$, > 99% *ee* and 98% *de*). Literature data for (1*R*,2*S*)-**6 b**: [α]$_D^{22}$ = −46.4 (*c* 5.6, CHCl$_3$, 96% *ee* and > 99% *de*).[28]

(1*R*,2*R*)-1-Phenylpropane-1,2-diyl diacetate (1*R*,2*R*)-6 b: Yellowish solid (86% yield). R_f (20% EtOAc/hexane): 0.43. Mp: 50–53 °C. IR: 1737, 1495, 1372 cm^{-1}. ^{1}H-NMR (300.13 MHz, CDCl$_3$): δ 7.35–7.28 (*m*, 5H), 5.75 (*d*, *J* = 6.7 Hz, 1H), 5.26 (*apparent quint*, *J* = 6.6 Hz, 1H), 2.06 (*s*, 3H), 2.01 (*s*, 3H), 1.08 (*d*, *J* = 6.5 Hz, 3H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): δ 170.2 (C), 169.9 (C), 136.9 (C), 128.6 (CH), 128.5 (2CH), 127.4 (2CH), 76.7 (CH), 71.5 (CH), 21.1 (CH$_3$), 21.0 (CH$_3$), 16.5 (CH$_3$). HRMS (ESI$^+$, m/z): calcd for (C$_{13}$H$_{16}$NaO$_4$)$^+$ (M + Na)$^+$: 259.0941; found 259.0937. [α]$_D^{20}$ = −40.1 (*c* 1.0, CHCl$_3$, > 99% *ee* and 98% *de*). Literature data for (1*R*,2*R*)-**6 b**: [α]$_D^{22}$ = −46.6 (*c* 5.2, CHCl$_3$, 93% *ee* and > 99% *de*).[28]

General Procedure for the Gold-ADH Cascade of Propargylic Amide 2 Using evo-1.1.200

Distilled H$_2$O (3.33 mL) and IPrAuNTf$_2$ (2 mol%, 0.0074 mmol, 6.5 mg) were added to a solution of racemic amide **2** (0.37 mmol, 64 mg) in 2-Me-THF (370 μL) inside a 50 mL-round bottom flask. The mixture was stirred for 6 h at 45 °C, and after this time, a 50 mM buffer Tris·HCl pH 8.5 (25.83 mL), 2-PrOH (4.98 mL), an aqueous 10 mM MgCl$_2$ solution (2.49 mL), NADH (16 mg), and evo-1.1.200 (60 mg) were added. After stirring the reaction for 24 h at 220 rpm and 30 °C, freshly evo-1.1.200 (20 mg) was added. The reaction was stirred for additional 24 h at 30 °C, and after this time, the mixture was extracted with EtOAc (4 × 40 mL), the organic phases were combined, dried over anhydrous Na$_2$SO$_4$, filtered and the solvents were removed under vacuum. The product percentages were measured by GC analysis, while the enantiomeric and diastereomeric ratios were determined by HPLC (see SI). The reaction crude was purified by column chromatography on silica gel (70% EtOAc/hexane), affording (1*S*,2*R*)-**7 a** as a yellowish oil (40 mg, 57% isolated yield, 90% *de*, > 99% *ee*).

N-((1*S*,2*R*)-2-Hydroxy-1-phenylpropyl)acetamide (1*S*,2*R*)-7 a. Yellowish oil (57% yield). R_f (EtOAc): 0.17. IR: 3623, 1736, 1371 cm^{-1}. ^{1}H-NMR (300.13 MHz, CDCl$_3$): δ 7.36–7.23 (*m*, 5H), 6.51 (*d*, *J* = 8.3 Hz, 1H), 4.84 (*dd*, *J* = 8.3, 4.2 Hz, 1H), 4.03 (*dq*, *J* = 6.3, 4.1 Hz, 1H), 2.66 (*br s*, 1H), 2.01 (*s*, 3H), 1.17 (*d*, *J* = 6.4 Hz, 3H). ^{13}C-NMR (75.5 MHz, CDCl$_3$): δ 170.8 (C), 140.3 (C), 128.8 (2CH), 127.6 (CH), 126.7 (2CH), 71.0 (CH), 59.1 (CH), 23.3 (CH$_3$), 20.6 (CH$_3$). HRMS (ESI$^+$, m/z): calcd for (C$_{11}$H$_{15}$NNaO$_2$)$^+$ (M + Na)$^+$: 216.0995; found 216.0996. [α]$_D^{20}$ = −57.8 (*c* 1.0, CHCl$_3$, > 99% *ee* and 90% *de*).

General Procedure for the Gold-ATA Cascade of Propargylic Amide 2 Using ATA-033

Racemic acetamide **2** (0.37 mmol, 64 mg) was dissolved in 2-Me-THF (370 μL) and distilled H$_2$O (3.33 mL) inside a 50 mL-round bottom flask. Then, IPrAuNTf$_2$ (2 mol%, 0.0074 mmol, 6.5 mg) was added, and the mixture was stirred for 6 h at 45 °C. At this point, first a 100 mM phosphate buffer pH 9.5 (11.2 mL) containing PLP (1 mM) and isopropylamine (1.0 M), and later ATA-033 (60 mg) were successively added. The mixture was stirred for 24 h at 220 rpm and 45 °C, and after this time the reaction was stopped by the addition of an aqueous NaOH 10 M solution (1.0 mL). The mixture containing **8 a** was extracted with EtOAc (4 × 20 mL), the organic phases were combined, dried over Na$_2$SO$_4$ and filtered. Then, DMAP (0.037 mmol, 5 mg) and acetic anhydride (1.66 mmol, 158 μL) were added, and the mixture was stirred for 4 h at 40 °C. After this time, H$_2$O was added (15 mL) and the mixture was stirred for 20 min. The phases were separated and the combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered, and the solvent was removed under vacuum. The conversion was measured by GC, and the enantiomeric and diastereomeric ratios were measured by HPLC (see SI). Finally, diacetamide (1*S*,2*R*)-**8 b** was purified by column chromatography on silica gel (10% MeOH/EtOAc) leading to a white solid (67 mg, 77% isolated yield, 70% *de*, 99% *ee*).

N,N'-[(1*S*,2*R*)-1-Phenylpropane-1,2-diyl]diacetamide [(1*S*,2*R*)-8 b]. White solid (77% yield, 15:85 mixture of *syn*:

anti diastereoisomers). R_f (10% MeOH/EtOAc): 0.24. IR: 1783, 1370 cm^{-1}. ^{1}H-NMR (300.13 MHz, CDCl$_3$): δ 7.72 (*br s*, 1H$_{syn}$), 7.38–7.29 (*m*, 5H$_{anti}$ + 5H$_{syn}$), 6.63 (*d*, $J = 8.4$ Hz, 1H$_{anti}$), 6.14 (*d*, $J = 8.4$ Hz, 1H$_{anti}$), 5.38 (*d*, $J = 8.1$ Hz, 1H$_{syn}$), 4.89 (*dd*, $J = 6.9, 3.1$ Hz, 1H$_{syn}$), 4.73 (*dd*, $J = 10.5, 8.1$ Hz, 1H$_{anti}$), 4.41–4.24 (*m*, 1H$_{anti}$ + 1H$_{syn}$), 1.99 (*s*, 3H$_{anti}$ + 3H$_{syn}$), 1.96 (*s*, 3H$_{syn}$), 1.93 (*s*, 3H$_{anti}$), 1.15 (*d*, $J = 6.8$ Hz, 3H$_{syn}$), 0.99 (*d*, $J = 6.7$ Hz, 3H$_{anti}$). ^{13}C-NMR (75.5 MHz, CDCl$_3$): δ 171.4 (C$_{syn}$), 171.2 (C$_{anti}$), 170.5 (C$_{anti}$), 169.8 (C$_{syn}$), 139.6 (C$_{anti}$), 138.1 (C$_{syn}$), 129.0 (2CH$_{anti}$), 128.3 (2CH$_{syn}$), 128.1 (CH$_{anti}$), 127.6 (CH$_{syn}$), 127.5 (2CH$_{syn}$), 127.4 (2CH$_{anti}$), 60.3 (CH$_{anti}$), 59.5 (CH$_{syn}$), 50.2 (CH$_{anti}$), 49.4 (CH$_{syn}$), 23.4 (CH$_{3,anti}$), 23.3 (CH$_{3,anti}$), 23.2 (CH$_{3,syn}$), 18.3 (CH$_{3,anti}$), 18.2 (CH$_{3,syn}$). HRMS (ESI$^+$, m/z): calcd for (C$_{13}$H$_{18}$N$_2$NaO$_2$)$^+$ (M + Na)$^+$: 257.1260; found 257.1260. [α]$_D^{20}$ = −41.6 (*c* 1.0, CHCl$_3$, > 99% *ee* and 70% *de*).

Acknowledgements

Data Availability Statement

Electronic supporting information includes comprehensive screening and optimization of reaction conditions for gold-catalyzed reactions, biotransformations, and chemoenzymatic processes; full characterization of synthesized standards and products; docking and *ab initio* studies; analytics and copies of NMR spectra. The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

[1] a) M. M. Cassiano, *Alkaloids, Properties, Applications and Pharmacological Effects*, Nova Science Publishers, Inc., **2013**; b) T. Aniszewski, *Alkaloids: Chemistry, Biology, Ecology, and Applications*, 2nd Edition. Elsevier Science, **2014**; c) S. Funayama, G. A. Cordell, *Alkaloids: A Treasury of Poisons and Medicines*, Academic Press, **2014**.

[2] S. Simić, E. Zukić, L. Schmermund, K. Faber, C. K. Winkler, W. Kroutil, *Chem. Rev.* **2022**, *122*, 1052–1126.

[3] a) J. H. Schrittwieser, V. Resch, *RSC Adv.* **2013**, *3*, 17602–17632; b) E. Cigan, B. Eggbauer, J. H. Schrittwieser, W. Kroutil, *RSC Adv.* **2021**, *11*, 28223–28270; c) R. Roddan, E. M. Carter, B. Thair, H. C. Hailes, *Nat. Prod. Rep.* **2022**, *39*, 1375–1382.

[4] a) D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–876; b) A. Cruz, I. I. Padilla-Martínez, M. E. Bautista-Ramirez, *Curr. Org. Synth.* **2018**, *15*, 38–83.

[5] R. Krizevski, E. Bar, O. Shalit, Y. Sitrit, S. Ben-Shabat, E. Lewinsohn, *Phytochemistry* **2010**, *71*, 895–903.

[6] a) T. Sehl, H. C. Hailes, J. M. Ward, R. Wardenga, E. von Lieres, H. Offermann, R. Westphal, M. Pohl, D. Rother, *Angew. Chem. Int. Ed.* **2013**, *52*, 6772–6775; *Angew. Chem.* **2013**, *125*, 6904–6908; b) X. Wu, M. Fei, Y. Chen, Z. Wang, Y. Chen, *Appl. Microbiol. Biotechnol.* **2014**, *98*, 7399–7408; c) Y.-C. Lee, Y.-Y. Chen, J.-S. Lin, Y.-W. Chen, C.-C. Li, K.-X. Liang, H.-H. Chan, W.-D. Lin, C.-H. Kao, *Process Biochem.* **2018**, *73*, 74–81; d) T. Sehl, H. C. Hailes, J. M. Ward, U. Menyes, M. Pohl, D. Rother, *Green Chem.* **2014**, *16*, 3341–3348.

[7] M. L. Corrado, T. Knaus, F. G. Mutti, *ChemBioChem* **2021**, *22*, 2345–2350.

[8] M. L. Corrado, T. Knaus, F. G. Mutti, *Green Chem.* **2019**, *21*, 6246–6251.

[9] a) F. Rudroff, M. D. Mihovilovic, H. Gröger, R. Snajdrova, H. Iding, U. T. Bornscheuer, *Nat. Catal.* **2018**, *1*, 12–22; b) T. I. Doyon, A. R. H. Narayan, *Synlett* **2020**, *31*, 230–236; c) X. Huang, M. Cao, H. Zhao, *Curr. Opin. Chem. Biol.* **2020**, *55*, 161–170; d) E. Heuson, F. Dumeignil, *Catal. Sci. Technol.* **2020**, *10*, 7082–7100; e) L. Bering, J. Thompson, J. Micklefield, *Trends Chem.* **2022**, *4*, 392–408; f) C. Ascaso-Alegre, J. Mangas-Sanchez, *Eur. J. Org. Chem.* **2022**, e202200093.

[10] a) M. Asikainen, R. Krause, *Adv. Synth. Catal.* **2009**, *351*, 2305–2309; b) Z. J. Wang, K. N. Clary, R. G. Bergman, K. N. Raymond, F. D. Toste, *Nat. Chem.* **2013**, *5*, 100–103.

[11] a) M. J. Rodríguez-Álvarez, N. Ríos-Lombardía, S. Schumacher, D. Pérez-Iglesias, F. Morís, V. Cadierno, J. García-Álvarez, J. González-Sabín, *ACS Catal.* **2017**, *7*, 7753–7759; b) P. Schaaf, V. Gojic, T. Bayer, F. Rudroff, M. Schnürch, M. D. Mihovilovic, *ChemCatChem* **2018**, *10*, 920–924; c) M. Cortes-Clerget, N. Akporji, J. Zhou, F. Gao, P. Guo, M. Parmentier, F. Gallou, J.-Y. Berthon, B. H. Lipshutz, *Nat. Commun.* **2019**, *10*, 2169; d) S. González-Granda, I. Lavandera, V. Gotor-Fernández, *Angew. Chem. Int. Ed.* **2021**, *60*, 13945–13951; *Angew. Chem.* **2021**, *133*, 14064–14070; e) S. González-Granda, L. Escot, I. Lavandera, V. Gotor-Fernández, *ACS Catal.* **2022**, *12*, 2552–2560; f) L. Escot, S. González-Granda, I. Lavandera, V. Gotor-Fernández, *Org. Biomol. Chem.* **2022**, *20*, 9650–9658.

[12] a) S. Mathew, A. Sagadevan, D. Renn, M. Rueping, *ACS Catal.* **2021**, *11*, 12565–12569; b) S. González-Granda, N. V. Tzouras, S. P. Nolan, I. Lavandera, V. Gotor-Fernández, *Adv. Synth. Catal.* **2022**, *364*, 3856–3866.

[13] F. Chang, C. Wang, Q. Chen, Y. Zhang, G. Liu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202114809; *Angew. Chem.* **2022**, *134*, e202114809.

[14] C. Gastaldi, G. Mekhloufi, C. Forano, A. Gautier, C. Guérard-Hélaine, *Green Chem.* **2022**, *24*, 3634–3639.

[15] a) W. E. Brenzovich Jr, *Angew. Chem. Int. Ed.* **2012**, *51*, 8933–8935; *Angew. Chem.* **2012**, *124*, 9063–9065; b) R.

Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028–9072; c) C. J. V. Halliday, J. M. Lynam, *Dalton Trans.* **2016**, *45*, 12611–12626.

[16] a) N. Ghosh, S. Nayak, A. K. Sahoo, *J. Org. Chem.* **2011**, *76*, 500–511; b) Y. Zhou, Q. Liu, W. Lv, Q. Pang, R. Ben, Y. Qian, Y. Zhao, *Organometallics* **2013**, *32*, 3753–3759; c) M. Kumar, G. B. Hammond, B. Xu, *Org. Lett.* **2014**, *16*, 3452–3455; d) Y. Du, F. Yao, R. Zhang, M. A. Cai, *J. Organomet. Chem.* **2020**, *910*, 121136; e) Z. Cao, A. Scalabre, S. Nlate, S. Buffière, R. Oda, E. Pouget, B. Bibal, *Chem. Eur. J.* **2021**, *27*, 427–433.

[17] U. Kaulmann, K. Smithies, M. E. B. Smith, H. C. Hailes, J. M. Ward, *Enzyme Microb. Technol.* **2007**, *41*, 628–637.

[18] Enantiopure ester (*R*)-**1** and amide (*R*)-**2** were obtained through lipase-catalyzed resolution of their corresponding racemates, while the (*S*)-antipodes were synthesized after chemical acetylation of the unreacted alcohol and amine from the CAL–B classical kinetic resolution. See SI for further details and general protocols.

[19] See, for instance: P. Chen, X. Zhu, *J. Mol. Catal. B Enzym.* **2013**, *97*, 184–188, and references cited therein.

[20] J. Peters, T. Minuth, M.-R. Kula, *Enzyme Microb. Technol.* **1993**, *11*, 950–958.

[21] a) W. Stampfer, B. Kosjek, C. Moitzi, W. Kroutil, K. Faber, *Angew. Chem. Int. Ed.* **2002**, *41*, 1014–1017; *Angew. Chem.* **2002**, *114*, 1056–1059; b) C. E. Paul, I. Lavandera, V. Gotor-Fernández, W. Kroutil, V. Gotor, *ChemCatChem* **2013**, *5*, 3875–3881.

[22] a) X. Li, M. Tanasova, C. Vasileiou, B. Borhan, *J. Am. Chem. Soc.* **2008**, *130*, 1885–1893; b) J. Zhu, X.-T. Sun, X.-D. Wang, L. Wu, *ChemCatChem* **2018**, *10*, 1788–1792.

[23] A. S. K. Hashmi, A. M. Schuster, M. Schmuck, F. Rominger, *Eur. J. Org. Chem.* **2011**, *2011*, 4595–4602.

[24] M. Karabec, A. Lyskowski, K. C. Tauber, G. Steinkellner, W. Kroutil, G. Grogan, K. Gruber, *Chem. Commun.* **2010**, *46*, 6314–6316.

[25] a) J. Eberhardt, D. Santos-Martins, A. F. Tillack, S. Forli, *J. Chem. Inf. Model.* **2021**, *61*, 3891–3898; b) O. Trott, A. J. Olson, *J. Comb. Chem.* **2010**, *31*, 455–461.

[26] J.-H. Xie, S. Liu, W.-L. Kong, W.-J. Bai, X.-C. Wang, L.-X. Wang, Q.-L. Zhou, *J. Am. Chem. Soc.* **2009**, *131*, 4222–4223.

[27] W. Oppolzer, O. Tamura, G. Sundarababu, M. Signer, *J. Am. Chem. Soc.* **1992**, *114*, 5900–5902.

[28] M. Takeshita, T. Sato, *Chem. Pharm. Bull.* **1989**, *37*, 1085–1086.