ARTICLE

Combination of gold and redox enzyme catalysis to access valuable enantioenriched aliphatic β-chlorohydrins

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The synthesis of enantioenriched β-chlorohydrins is highly appealing due to their relevance as building-blocks in organic synthesis. However, the approximation to aliphatic derivatives is particularly challenging due to the difficulties to get access to the α-chloroketone precursors. Herein, we propose a straightforward and scalable approach combining in a concurrent manner gold(I) and redox enzyme catalysis through a hydration-bioreduction cascade. A total of nine aliphatic β-chlorohydrins bearing different functional groups were obtained with very high yields (63-88%) and stereoselectivities (>99% *ee*).

Introduction

The search for general, simple, and environmentally-friendly synthetic strategies to obtain chiral synthons and derivatives is nowadays a must in the chemical industry. This is the case, for instance, of β-chlorohydrins, highly appreciated compounds due to their enormous possibilities as intermediates of different valuable and biologically active targets.[1] However, it is undeniable that in the literature one can find many possibilities to get access to (hetero)aromatic β-chlorohydrins, while the number of described methodologies to obtain the aliphatic counterparts is much more limited.[2] In part, this is due to the different accessibility to the α-chloroketone precursors which, through direct reduction, would render the desired chiral halohydrins (Scheme 1a). While for aromatic derivatives the monochlorination of the corresponding ketone can be easily performed under acidic conditions, this straightforward method cannot be implemented towards aliphatic substrates, since the internal and more nucleophilic carbon reacts preferentially with the chlorinating agent, thus rendering a complex mixture of (poly)halogenated compounds (Scheme 1a).[3]

The synthesis of racemic aliphatic β-chlorohydrins is relatively well resolved by mainly using three different general approaches (Scheme 1b): a) by reaction of an aldehyde with a "$ClCH_2X$" reagent in the presence of a metal or a strong base;[4] b) through oxirane ring-opening using a metal chloride,[5a,b] the trichloroisocyanuric acid (TCA)-triphenylphosphine pair,[5c] or trichloroacetonitrile under light conditions,[5d] or reacting a chlorinated epoxide with an alcohol derivative;[6] and c) *via* hydrochlorination addition to an alkene using, e.g. chloramine T[7a] or TCA[7b] in the presence of water. However, limitations still exist to find general and selective high-yielding protocols to obtain enantioenriched aliphatic chlorohydrins (Scheme 1c). In fact, most of the described methodologies rely on: a) the kinetic resolution (KR) of a racemic oxirane in the presence of hydrochloric acid,[8] or epichlorohydrin with an oxygenated nucleophile[9] employing cobalt complexes with chiral ligands, and the KR of a racemic halohydrin using a lipase and an acylating agent;[10] b) the chemical modification of a commercially available enantiopure synthon (e.g. epichlorohydrin);[11] and c) the bioreduction of the corresponding α-chloroketone precursor with whole-cells[12a,b] or isolated/heterologously expressed alcohol dehydrogenases (ADHs).[12c,d] Unfortunately, these methods present a series of disadvantages such as low yields and moderate stereoselectivities (approach a), use of extremely low temperatures and elevated cost of the chiral synthon[13] (approach b), and requirement to access the α-chloroketone through multi-step and low-yielding procedures (approach c). In addition, the opening of epoxides usually provides a regioisomeric mixture of compounds which is not easily separable.

With these precedents, and based on our previous experience in the combination of gold(I) and enzyme redox catalysis,[14] we envisaged the use of easily accessible aliphatic chloroalkynes as starting materials to directly synthesize the corresponding enantioenriched (*R*)- or (*S*)-β-chlorohydrins *via* concomitant gold-catalyzed hydration and ADH-catalyzed asymmetric reduction of the α-chloroketone intermediate (Scheme 1d). In fact, it has been described the exquisite selectivity of Au species (3-5 mol%) to mediate the highly regioselective hydration of haloalkynes in an organic solvent adding few equivalents of water,[15] and the possibilities to combine this protocol with a Ru-catalyzed hydrogen transfer reaction[16] or an ADH-catalyzed reduction[14b] to obtain aromatic chiral β-halohydrins.

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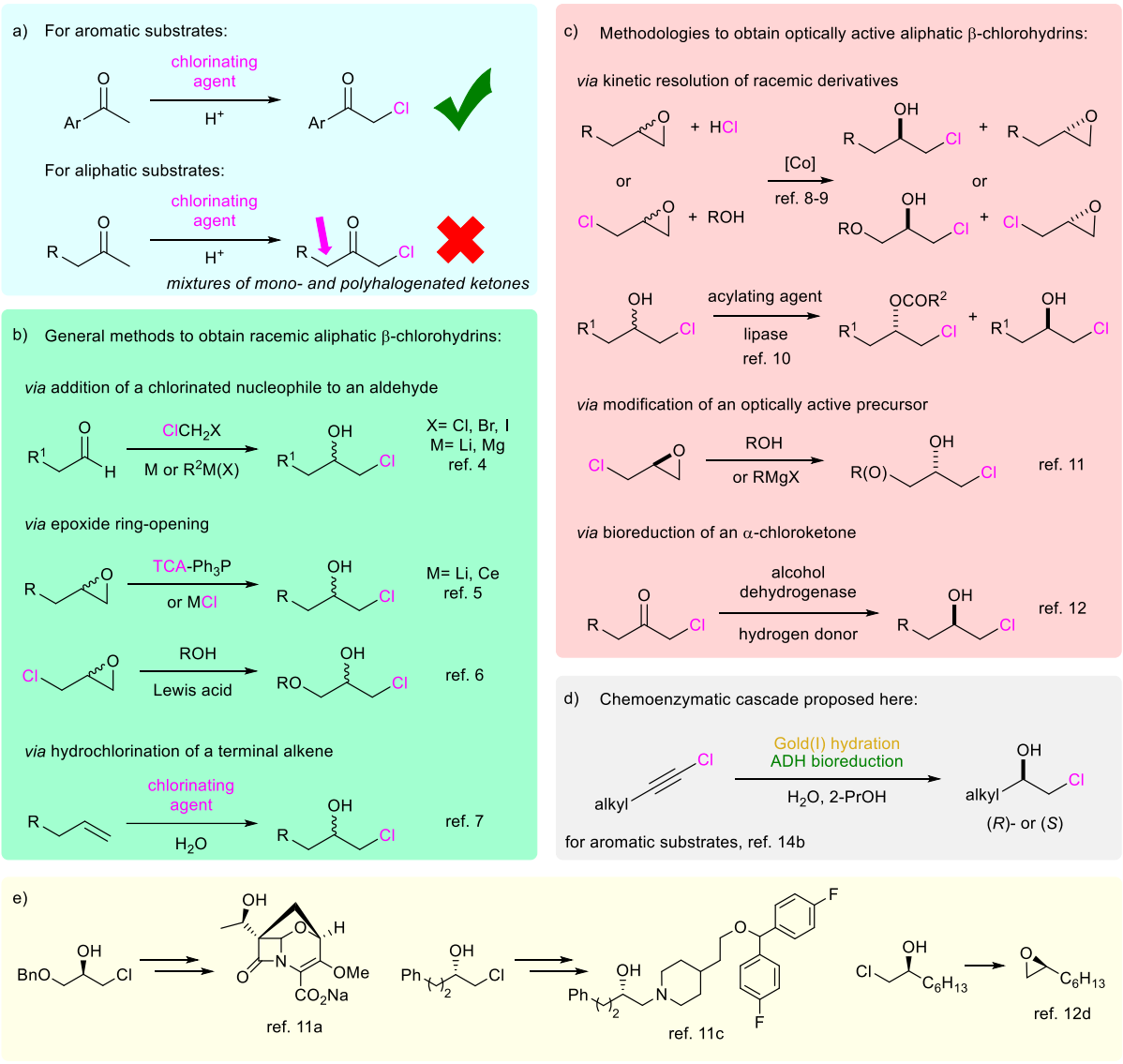


Scheme 1 Synthetic general approaches to obtain racemic and enantioenriched aliphatic halohydrins (a-d). Relevance of some of the β-chlorohydrins synthesized in this contribution (e).

Results and discussion

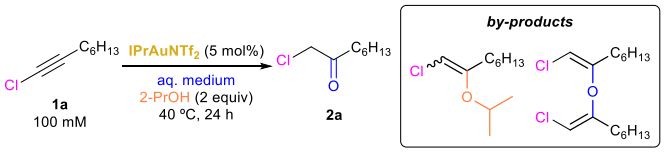
As a first step, 1-chlorooct-1-yne (**1a**) was synthesized from oct-1-yne using *N*-chlorosuccinimide (NCS) in the presence of AgOAc[17] (89%, Scheme S1 in the ESI). The next stage was to optimize both chemoenzymatic processes, in order to find compatible reaction conditions that would allow us to achieve the desired cascade transformation. While we previously used N-heterocyclic carbene (NHC)-gold (I) complexes in aqueous medium for the hydration of **1a**,[14b] the formation of different by-products (*vide infra*), prompted us to perform an optimization of this process. Hence, a first screening of Au catalysts including NHC derivatives (5 mol%) was performed at 40 °C with **1a** (100 mM). A mixture of water and 2-Me-THF (4:1 *v*/*v*) was selected as solvent including the presence of 2-PrOH (2 equiv), since this alcohol would act as hydrogen donor in the bioreduction process (Table 1 and Table S1 in ESI). After 24 h, [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) [bis(trifluoromethanesulfonyl)imide] (IPrAuNTf$_2$, entry 2),[18] afforded optimum results in terms of conversion (>99%) and selectivity (99%) towards 1-chlorooctan-2-one (**2a**). For other catalysts poorer results were observed, as the formation of two by-products resulting from the addition of 2-PrOH or the enol tautomer of ketone **2a** towards the alkyne moiety (obtaining a dimer compound in this last case) was observed at significant extent.

Then, different reaction media were tested (Table 1 and Table S2 in the ESI), noticing that the use of other miscible (entries 3 and 4) or immiscible (entry 5) organic solvents did not lead to any improvement. As expected, the use of a higher amount of 2-PrOH as cosolvent was deleterious for the selectivity of the process, as the percentage of the enol ether from the addition

of the alcohol to the gold activated haloalkyne increased (entry 6). The employment of a typical buffer for ADH-mediated transformations (entry 7) negatively influenced the hydration reaction. A lower amount of 2-Me-THF (entry 8) or the usage of plain water as medium (entry 9), led to complete conversions but also to the formation of higher amounts of the undesired by-products. Also, different temperatures (20-45 °C) compatible with the action of the enzyme were tried (entry 10 and Table S2 in the ESI), finding 40 °C as optimum value (entry 2). Finally, higher substrate concentrations (150-200 mM) were tested, however lower selectivities were attained (Table S2).

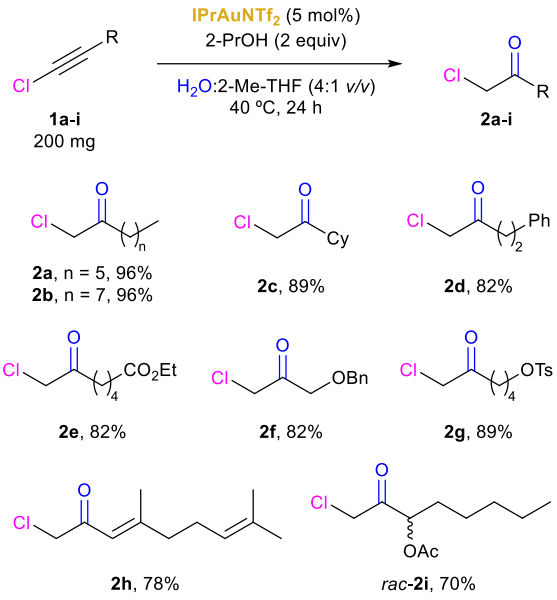
Afterwards, we synthesized other aliphatic chloroalkynes **1b**-**i** (Figure S1 in the ESI) using the same methodology as the one described for **1a**,[17] employing the NCS/*n*-BuLi system,[19] or starting from an aldehyde through a Corey-Fuchs reaction.[20] These protocols afforded the desired products in moderate to very high yields (48-93%, for further details, see Schemes S1-S7 in the ESI). The selection of the substrates was made due to the relevance of the final halohydrins (Scheme 1e) and searching for substrates bearing different functional groups such as ester (**1e** and **1i**), ether (**1f**), or tosylate (**1g**), including a derivative (**1h**) from natural product geraniol, to demonstrate the possibilities of our method. Once obtained, we applied the best reaction conditions found for **1a** to the other chloroalkynes. Transformations were performed at 200-mg scale, obtaining in all cases good to excellent yields of the desired α-chloroketones **2a**-**i** (70-96%, Scheme 2). Independently on the functional group present in the starting material (ester, ether, tosylate, or alkene), reactions afforded the carbonyl compounds in a very selective and clean manner. Moreover, this set-up is perfectly compatible with the action of, e.g. alcohol dehydrogenases, opening the door for a possible chemoenzymatic cascade transformation.

Table 1 Optimization of the Au(I)-catalyzed hydration of chloroalkyne **1a**[a]



entry	reaction medium	*c* (%)[b]	selectivity (%)[b]
1[c]	H_2O:2-Me-THF (4:1 *v*/*v*)	<1	n.a.
2	H_2O:2-Me-THF (4:1 *v*/*v*)	>99	99
3	H_2O:THF (4:1 *v*/*v*)	>99	72
4	H_2O:MeCN (4:1 *v*/*v*)	88	76
5	H_2O:*n*-heptane (4:1 *v*/*v*)	97	80
6	H_2O:2-PrOH (4:1 *v*/*v*)	>99	35
7	KPi buffer 50 mM pH 7.5: 2-Me-THF (4:1 *v*/*v*)	46	74
8	H_2O:2-Me-THF (9:1 *v*/*v*)	>99	48
9	H_2O	>99	86
10[d]	H_2O:2-Me-THF (4:1 *v*/*v*)	>99	91

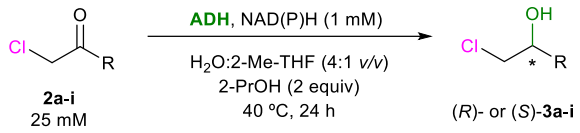
[a] For reaction conditions, see Experimental Section and ESI. [b] Total conversion and selectivity values were determined by GC analysis. The selectivity refers to the formation of **2a** in comparison with the total amount of products. n.a. Not available. [c] Without catalyst. [d] Reaction at 30 °C.



Scheme 2 Synthesis of α-chloroketones **2a**-**i**.

Subsequently, an enzymatic screening was developed in order to find suitable ADHs that could work under the previously optimized conditions for the hydration step, and could provide both halohydrin enantiomers in high enantiomeric excess (*ee*). Thus, non-purified commercial biocatalysts and lyophilized whole-cells heterologously expressing ADHs were tested to obtain chiral **3a**-**i** (Table 2 and Tables S3-S11 in the ESI). In most cases we found suitable stereocomplementary enzymes to obtain both halohydrin antipodes in excellent conversions and *ee* values, just with the exception of substrates **2c** (entry 5) and **2h** (entry 14). As can be noticed, usually the best candidates were ADHs from *Rhodococcus ruber* (ADH-A),[12c] *Thermoanaerobacter* sp. (ADH-T),[21] and *Lactobacillus brevis* (*Lb*ADH),[22] displaying opposite selectivities. For racemic ketone **2i** (entries 15 and 16), we also discovered two commercial ADHs which were able to provide reductions at high extent, therefore affording a mixture of two out of four diastereoisomers since were perfectly selective towards position 2. It must be remarked that just employing 2 equiv of the hydrogen donor (2-PrOH) was enough to recycle the nicotinamide cofactor [NAD(P)H, 1 mM] and accomplish quantitative conversions, due to the fact that these transformations are thermodynamically favored towards the β-chlorohydrin formation,[23] with the exception of α,β-unsaturated ketone **2h**, where a higher amount of 2-PrOH (10% *v*/*v*) was necessary. This fact is again related to the thermodynamics of the process, as it is known that this type of substrate cannot be easily reduced, in comparison to its saturated counterparts.[24]

Table 2 Selection of the best ADHs to perform the stereoselective bioreduction of α-chloroketones **2a-i**[a]

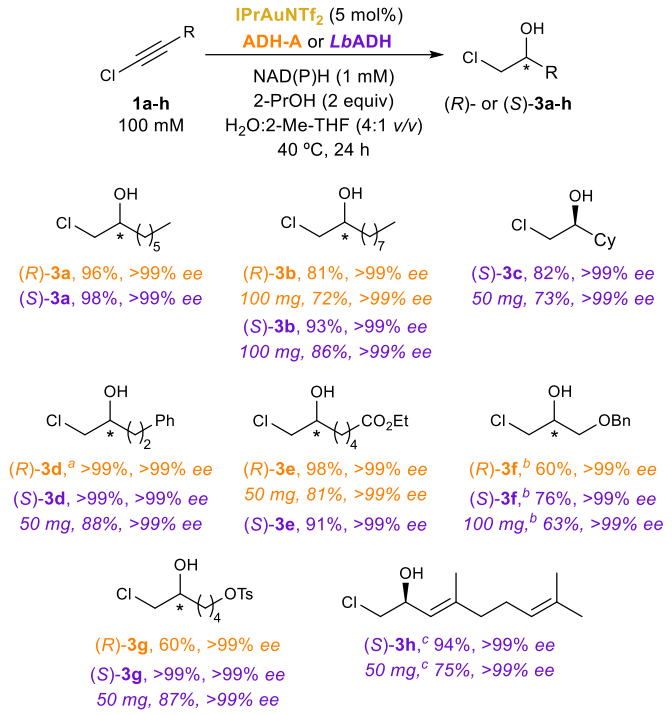


entry	substrate	ADH[b]	*c* (%)[c]	*ee* (%)[d]
1	**2a**	*E. coli*/ADH-A	>99	>99 (*R*)
2	**2a**	*E. coli*/*Lb*ADH	>99	>99 (*S*)
3	**2b**	*E. coli*/ADH-A	>99	>99 (*R*)
4	**2b**	*E. coli*/*Lb*ADH	>99	>99 (*S*)
5	**2c**	*E. coli*/*Lb*ADH	98	>99 (*S*)
6	**2d**	*E. coli*/ADH-T	>99	>99 (*R*)
7	**2d**	*E. coli*/*Lb*ADH	99	>99 (*S*)
8	**2e**	*E. coli*/ADH-A	>99	>99 (*R*)
9	**2e**	*E. coli*/*Lb*ADH	99	>99 (*S*)
10	**2f**	*E. coli*/ADH-A	99	>99 (*R*)
11	**2f**	*E. coli*/*Lb*ADH	>99	>99 (*S*)
12	**2g**	*E. coli*/ADH-A	99	>99 (*R*)
13	**2g**	*E. coli*/*Lb*ADH	>99	>99 (*S*)
14[e]	**2h**	*E. coli*/*Lb*ADH	93	>99 (*S*)
15	*rac*-**2i**	KRED-P2-B02	94	96 (2*R*,3*S*)[f]; >99 (2*R*,3*R*)[f]
16	*rac*-**2i**	evo.1.1.200	>99	95 (2*S*,3*R*)[g]; >99 (2*S*,3*S*)[g]

[a] For reaction conditions, see ESI. [b] Enzymatic preparation:substrate loading: for heterologously expressed ADHs (4:1 wt); for commercial ADHs (1:1 wt). [c] Conversions were determined by GC analysis. [d] Enantio- and diastereomeric excess (*de*) values were determined by chiral GC or HPLC. Major isomer appears in brackets. [e] 10% (*v*/*v*) of 2-PrOH was added. [f] *de* = 18. [g] *de* <1.

After selecting the catalysts that could work under similar reaction conditions, we studied in detail the cascade transformation starting from chloroalkyne **1a** (Table S14 in the ESI). It was noticed that the vessel type (glass vial or Eppendorf tube for small-scale reactions) and the stirring mode (orbital or magnetic), could influence the outcome of the process. Furthermore, taking advantage from the thermostability of ADH-A,[12c] we partially purified it by heat treatment, achieving superior results than those attained with the lyophilized whole-cell preparation. Thus, for the case of ADH-A and ADH-T magnetic stirring gave better results, while for the case of *Lb*ADH orbital shaking showed improved conversions, in all cases using glass vials.

Next, the scope of the cascade transformation at 0.05 mmol scale (Scheme 3 and Table S15 in the ESI) was studied in detail, finding excellent results in terms of conversion (60->99%) and stereoselectivity (>99%) towards the formation of the desired enantiopure aliphatic β-chlorohydrins (*R*)- or (*S*)-**3a**-**h** (100 mM). Just in the case of oxygenated derivative **3f**, a slightly higher amount of the gold catalyst (7.5 mol%) and a higher temperature (45 °C) were necessary to achieve better conversions. Reactions could be easily scaled-up to 50-100 mg, isolating the final enantiopure products with high yields (63-88%), demonstrating the potential and robustness of this chemoenzymatic approach (Scheme 3 and Table S16 in the ESI).



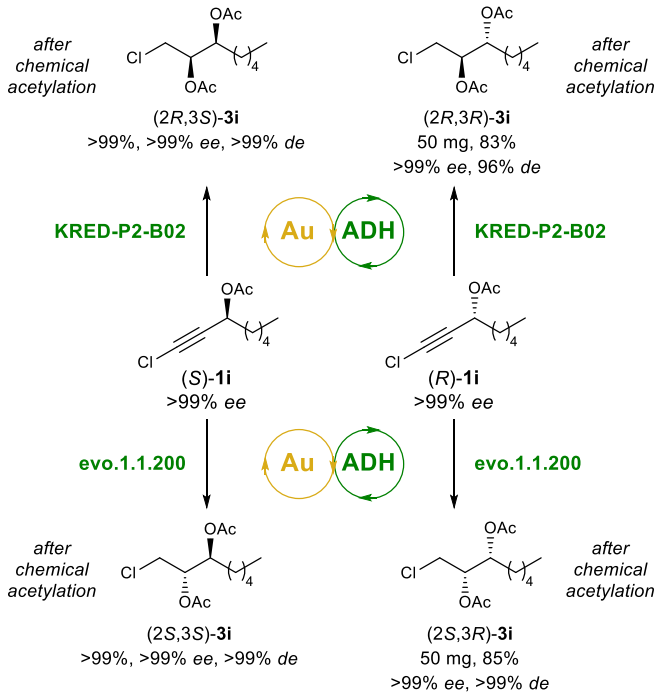
[a] ADH-T; [b] 7.5 mol% $IPrAuNTf_2$ and 45 °C; [c] 10% (*v*/*v*) of 2-PrOH

Scheme 3 Synthesis of enantioenriched **3a**-**h** through hydration-bioreduction cascade.

As a final application of this synthetic method, enantiopure esters (*R*)- and (*S*)-**1i** (obtained *via* KR after lipase-catalyzed acetylation of oct-1-yn-3-ol[25] and chlorination of the alkyne, see Scheme S8 in the ESI), were also submitted to the gold(I)-ADH cascade protocol with two stereocomplementary commercial ADHs, attaining the four possible diastereoisomers of the hydroxy ester, which after chemical acetylation afforded the final chlorinated diacetate **3i** with excellent conversion, enantio- and diastereoselectivity values (Scheme 4). Interestingly, these derivatives are precursors of highly valuable natural products such as (+)-petromyroxol.[26]

Conclusions

It is undeniable that in the last years there is a growing interest in the development of chemoenzymatic cascades combining the use of metals and enzymes,[27] as it is possible to increase molecular complexity in a straightforward manner under mild reaction conditions. Recently, bulky NHC-gold(I) complexes have demonstrated to stabilize the metal center under aqueous conditions, therefore allowing possible combinations with different biological catalysts in a cascade manner.[14,28] Herein, we have implemented this methodology to provide a general and simple synthetic chemoenzymatic approach to enantioenriched aliphatic β-chlorohydrins, building-blocks of important derivatives, which otherwise are not easily accessible using traditional methods.



Scheme 4 Stereodivergent synthesis of valuable chlorinated diester **3i** using this cascade approach as the key step. See Experimental section for reaction conditions.

Experimental section

General information. Chemical reagents and nicotinamide cofactors ($NADP^+$ and NAD^+) were purchased from commercial sources. The following gold(I) catalysts were also obtained from commercial sources: $IPrAuNTf_2$, (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (JohnPhosAu(MeCN)SbF_6), [2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl]gold(I) bis(trifluoromethanesulfonyl)imide ($BrettPhosAuNTf_2$), and chloro(triphenylphosphine)gold(I) [$(Ph_3P)AuCl$], while the syntheses of the other two gold(I) complexes have been performed from the corresponding chloride derivatives, (acetonitrile)[1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I) hexafluoroantimonate [IPrAu(MeCN)SbF_6] and [(2-biphenyl)di-*tert*-butylphosphine]gold(I) [bis(trifluoromethanesulfonyl)imide] (JohnPhosAuNTf_2).

KREDs were received from Codexis Inc. and used as received. Made in house ADHs were heterologously expressed in *E. coli*, these are, horse liver alcohol dehydrogenase (*Hl*ADH), *Sphingobium yanoikuyae* (*Sy*ADH), *Thermoanaerobacter* species (ADH-T), *Lactobacillus brevis* (*Lb*ADH), *Thermoanaerobacter ethanolicus* (*TeS*ADH) and *Rhodococcus ruber* (ADH-A) and used as lyophilized whole-cell preparations. The activity of these preparations is approximately 0.5-1 U/mg using benzaldehyde (*Hl*ADH), propiophenone (*Sy*ADH), octan-2-one (ADH-T and *TeS*ADH), or acetophenone (*Lb*ADH and ADH-A) as substrates. Additional information about these alcohol dehydrogenases can be found in the main text of the manuscript and its reference section. Non-commercially available terminal alkynes were chemically synthesized, exhibiting physical and spectral data in agreement with those reported in the literature (see Section II in the ESI for synthetic procedures and full characterization). Cascade reactions were performed in a glass vial tube (1.5 x 4 cm).

^1H, ^{13}C and bidimensional NMR experiments 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. Gas chromatography (GC) analyses were performed on a Hewlett-Packard 7890 GC chromatograph equipped with a FID detector using a DB-1701 (30 m x 0.23 mm x 0.25 μm) or HP-1 column (30 m x 0.32 mm x 0.25 μm) for the determination of conversion values, while the CP-Chirasil-DEX CB column (30 m x 0.32 mm x 0.25 μm) was employed for the determination of enantiomeric excess values. High performance liquid chromatography (HPLC) analyses were performed on an Agilent Infinity 1260 HPLC chromatograph equipped with a VIS-UV detector using Chiralcel OD-H (25 cm x 4.6 mm, 5 μm particle size) or Chiralpak AD-H column (25 cm x 4.6 mm, 5 μm particle size) for the measurement of enantiomeric excess values. See Section X in the ESI for analytical conditions and recorded chromatograms. Infrared (IR) spectra were recorded on a Jasco FT/IR-4700 spectrometer in neat form, and ν_{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^+). Thin-layer chromatography (TLC) analyses were conducted with silica gel 60 F254 precoated plates and visualized with a UV lamp, plus either potassium permanganate or vanillin stains. Column chromatographies were performed using silica gel 60 (230-240 mesh).

Synthesis of α-halomethyl ketones 2a-i obtained through gold(I)-catalyzed hydration. To the corresponding haloalkyne **1a-i** (200 mg, 100 mM), 2-Me-THF (20% *v/v*), water (80% *v/v*) and the catalyst $IPrAuNTf_2$ (5 mol%) previously dissolved in propan-2-ol (2 equiv) were added. The mixture was stirred at 40 °C for 24 h, and after this time the reaction was extracted with Et_2O (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude was purified by chromatographic column on silica gel (mixtures of EtOAc/hexane or Et_2O/pentane).

(*E*)-1-Chloro-4,8-dimethylnona-3,7-dien-2-one (2h): Yellowish oil (171 mg, 78%). R_f (10% Et_2O/pentane): 0.52. IR: ν 3052, 2929, 2859, 1701, 1682, 1611, 1280, 1264, 1099, 892, 763, 749, 733, 699 cm^{-1}. ^1H-NMR (300.13 MHz, $CDCl_3$): δ 6.20 (*s*, 1H), 5.04 (*m*, 1H), 4.06 (*s*, 2H), 2.16 (*m*, 7H), 1.66 (*s*, 3H), 1.58 (*s*, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 191.8 (C), 163.9 (C), 133.1 (C), 123.1 (CH), 119.6 (CH), 49.8 (CH_2), 41.8 (CH_2), 26.4 (CH_2), 26.1 (CH_3), 20.3 (CH_3), 18.1 (CH_3). HRMS (ESI^+, m/z): calcd for $(C_{11}H_{18}ClO)^+$ $(M+H)^+$: 201.1041; found 201.1046.

1-Chloro-2-oxooctan-3-yl acetate (2i): Yellowish oil (152 mg, 70%). R_f (20% Et_2O/pentane): 0.69. IR: ν 2954, 2929, 2859, 1738, 1457, 1373, 1276, 1222, 1029, 762, 757, 753, 745 cm^{-1}. ^1H-NMR (300.13 MHz, $CDCl_3$): δ 5.17 (*dd*, *J* = 8.0, 4.7 Hz, 1H), 4.25 (*d*, *J* = 2.5 Hz, 2H), 2.12 (*s*, 3H), 1.82–1.72 (*m*, 2H), 1.39–1.26 (*m*, 6H), 0.86 (*t*, *J* = 6.4 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 199.8 (C), 171.0 (C), 77.1 (CH), 46.7 (CH_2), 31.7 (CH_2), 31.0 (CH_2), 25.1

(CH_2), 22.7 (CH_3), 20.9 (CH_2), 14.3 (CH_3). HRMS (ESI^+, m/z): calcd for $(C_{10}H_{18}ClO_3)^+$ $(M+H)^+$: 221.0939; found 221.0943. After gold-catalyzed hydration of (*R*)-**1i**: (*R*)-**2i**, *ee* >99%, $[\alpha]_D^{20}$: +8.5 (*c* 1.0, $CHCl_3$).

General protocol for the synthesis of racemic derivatives 3a-i. Sodium borohydride ($NaBH_4$, 11.6 mg, 0.3 mmol) was added in portions at 0 °C to a stirred solution of the corresponding α-halomethyl ketone **2a**-**i** (0.2 mmol) in dry THF (4 mL). The reaction was slowly warmed to room temperature and stirred for additional 3 h. Then, an aqueous saturated NH_4Cl solution (6 mL) was added, and the mixture extracted with Et_2O (3 x 5 mL). The organic phases were combined and washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The corresponding reaction crudes were purified by column chromatography (SiO_2, mixtures EtOAc/hexane or Et_2O/pentane), obtaining the derivatives **3a**-**i** with excellent purity (68-92% yield). Optical rotation values of chlorohydrins have been here included, although they were obtained after hydration-bioreduction sequence of alkynes **1**.

Ethyl 7-chloro-6-hydroxyheptanoate (3e): Yellowish oil (35 mg, 83%). R_f (50% Et_2O/pentane): 0.35. IR: ν 3509, 3472, 3448, 2926, 2857, 1726, 1374, 1265, 1179, 763, 731, 647 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 4.13 (*q*, *J* = 7.1 Hz, 2H), 3.82 (*br s*, 1H), 3.64 (*dd*, *J* = 11.1, 3.4 Hz, 1H), 3.49 (*dd*, *J* = 11.1, 7.0 Hz, 1H), 2.33 (*t*, *J* = 7.4 Hz, 2H), 1.70–1.43 (*m*, 6H), 1.26 (*t*, *J* = 7.2 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 173.7 (C), 71.1 (CH), 60.3 (CH_2), 50.2 (CH_2), 34.1 (CH_2), 33.8 (CH_2), 25.0 (CH_2), 24.7 (CH_2), 14.2 (CH_3). HRMS (ESI^+, m/z): calcd for $(C_9H_{18}ClO_3)^+$ $(M+H)^+$: 209.0939; found 209.0943. (*R*)-**3e**, *ee* >99%, $[\alpha]_D^{20}$: +0.7 (*c* 1.0, $CHCl_3$).

6-Chloro-5-hydroxyhexyl 4-methylbenzenesulfonate (3g): Yellowish oil (56 mg, 92%). R_f (50% EtOAc/hexane): 0.44. IR: ν 3399, 2951, 2923, 1598, 1354, 1189, 1175, 1097, 930, 749, 665, 557 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 7.81 (*d*, *J* = 8.1 Hz, 2H), 7.37 (*d*, *J* = 8.0 Hz, 2H), 4.06 (*t*, *J* = 6.3 Hz, 2H), 3.76 (*m*, 1H), 3.60 (*dd*, *J* = 11.1, 3.4 Hz, 1H), 3.45 (*dd*, *J* = 11.1, 7.0 Hz, 1H), 2.47 (*s*, 3H), 1.76–1.65 (*m*, 3H), 1.55–1.42 (*m*, 4H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 144.8 (C), 133.1 (C), 129.9 (2CH), 127.9 (2CH), 71.1 (CH), 70.2 (CH_2), 50.3 (CH_2), 33.4 (CH_2), 28.7 (CH_2), 21.6 (CH_2), 21.5 (CH_3). HRMS (ESI^+, m/z): calcd for $(C_{13}H_{19}ClNaO_4S)^+$ $(M+Na)^+$: 329.0585; found 329.0590. (*S*)-**3g**, *ee* >99%, $[\alpha]_D^{20}$: –78.2 (*c* 1.0, $CHCl_3$).

1-Chlorooctane-2,3-diyl diacetate (3i): Yellowish oil (46 mg, 86%). R_f (50% Et_2O/pentane): 0.83. IR: ν 2957, 2931, 2861, 1742, 1371, 1216, 1026, 751, 603, 411 cm^{-1}. ^{1}H-NMR (300.13 MHz, $CDCl_3$): δ 5.21–5.09 (*m*, 2H), 3.70–3.45 (*m*, 2H), 2.12–2.06 (*m*, 6H), 1.55 (*m*, 2H), 1.30 (*m*, 6H), 0.86 (*t*, *J* = 6.6 Hz, 3H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ. 170.2 (C), 170.1 (C), 73.6 (CH, *anti*), 72.9 (CH, *syn*), 72.3 (CH, *anti*), 71.9 (CH, *syn*), 42.4 (CH_2, *anti*), 42.1 (CH_2, *syn*), 31.4 (CH_2), 30.4 (CH_2, *anti*), 30.0 (CH_2, *syn*), 24.8 (CH_2, *syn*), 24.6 (CH_2, *anti*), 22.4 (CH_2), 20.8 (CH_2), 20.7 (CH_3), 20.6 (CH_3), 13.9 (CH_3). HRMS (ESI^+, m/z): calcd for $(C_{12}H_{21}ClNaO_4)^+$ $(M+Na)^+$: 287.1021; found 287.1026. (2*S*,3*R*)-**3i**, *de* >99%, *ee* >99%, $[\alpha]_D^{20}$: +1.2 (*c* 1.0, $CHCl_3$); (2*R*,3*R*)-**3i**, *de* >99%, *ee* >99%, $[\alpha]_D^{20}$: +8.9 (*c* 1.0, $CHCl_3$).

Experimental protocol for the one-pot cascade reaction employing *E. coli*/ADH-A to obtain enantioenriched alcohols 3a,b,e-g. The corresponding alkyne **1a**,**b**,**e**-**g** (0.05 mmol), 2-Me-THF (100 µL), distilled water (340 µL), 2-PrOH (7.6 µL, 2 equiv), $IPrAuNTf_2$ (2.5 mg, 0.005 mmol, 5.0 mol%; 3.0 mg, 0.006 mmol, 6.0 mol% or 3.8 mg, 0.0075 mmol, 7.5 mol%), a NADH aqueous solution (60 µL, 10 mM), and overexpressed *E. coli*/ADH-A semi-purified by heat treatment (1:1 *w/w*) were placed into a glass vial. The mixture was kept under magnetic stirring at 40 or 45 °C for 24 h, and after this time, the solution was extracted with Et_2O (5 x 1 mL), the organic layers were combined, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure, measuring then the conversions into the alcohols **3a**,**b**,**e**-**g** by GC analysis, while the enantiomeric excess values were calculated by HPLC or GC.

Experimental protocol for the one-pot cascade reaction employing *E. coli*/ADH-T to obtain alcohol 3d. Alkyne **1d** (8.2 mg, 0.05 mmol), 2-Me-THF (100 µL), distilled water (340 µL), 2-PrOH (7.6 µL, 2 equiv), $IPrAuNTf_2$ (2.5 mg, 0.005 mmol, 5.0 mol%), a NADPH aqueous solution (60 µL, 10 mM), and overexpressed *E. coli*/ADH-T (10 mg) were placed into a glass vial. The mixture was kept under magnetic stirring at 40 °C for 24 h, and after this time, the solution was extracted with Et_2O (5 x 1 mL), the organic layers were combined, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure, measuring then the conversions into the alcohol **3d** and the enantiomeric excess by HPLC analysis.

Experimental protocol for the one-pot cascade reaction employing *E. coli*/*Lb*ADH to obtain enantioenriched alcohols 3a-h. The corresponding alkyne **1a**-**h** (0.05 mmol), 2-Me-THF (100 µL), distilled water (280 µL), 2-PrOH (7.6 µL, 2 equiv; 60 µL, 10% *v*/*v* for **1h**), $IPrAuNTf_2$ (2.5 mg, 0.005 mmol, 5.0 mol% or 3.8 mg, 0.0075 mmol, 7.5 mol%), a NADPH aqueous solution (60 µL, 10 mM), a $MgCl_2$ aqueous solution (60 µL, 10 mM) and overexpressed *E. coli*/*Lb*ADH (10 mg) were placed into a glass vial. The mixture was kept under orbital shaking (220 rpm) at 40 or 45 °C for 24 h, and after this time, the solution was extracted with Et_2O (5 x 1 mL), the organic layers were combined, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure, measuring then the conversions into the alcohols **3a**-**h** by GC analysis, while the enantiomeric excess values were calculated by HPLC or GC.

Experimental protocol for the one-pot cascade reaction employing Codexis KREDs to obtain 3i. Alkyne (*R*) or (*S*)-**1i** (10 mg, 0.05 mmol), 2-Me-THF (100 µL), distilled water (280 µL), 2-PrOH (7.6 µL, 2 equiv), $IPrAuNTf_2$ (2.5 mg, 0.005 mmol, 5.0 mol%), a NADPH aqueous solution (60 µL, 10 mM), a $MgCl_2$ aqueous solution (60 µL, 10 mM) and the corresponding KRED (10 mg) were placed into a glass vial. The mixture was kept under magnetic stirring at 40 °C for 24 h, and after this time, the solution was extracted with Et_2O (5 x 1 mL), the organic layers were combined, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure, and the reaction crude was acetylated with acetic anhydride and DMAP, measuring then the conversions into diester **3i** by achiral GC analysis, while the enantio- and diastereomeric excess values were calculated by GC using a chiral column.

Experimental protocol for the one-pot cascade reaction employing evo.1.1.200 to obtain 3i. Alkyne (*R*) or (*S*)-**1i** (10 mg, 0.05 mmol), 2-Me-THF (100 µL), distilled water (280 µL), 2-PrOH

(7.6 µL, 2 equiv), $IPrAuNTf_2$ (2.5 mg, 0.005 mmol, 5.0 mol%), a NADH aqueous solution (60 µL, 10 mM), a $MgCl_2$ aqueous solution (60 µL, 10 mM) and evo.1.1.200 (16 mg) were placed into a glass vial. The mixture was kept under magnetic stirring at 40 °C for 24 h, and after this time, the solution was extracted with Et_2O (5 x 1 mL), the organic layers were combined, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure, and the reaction crude was acetylated with acetic anhydride and DMAP, measuring then the conversions into diester **3i** by achiral GC analysis, while the enantio- and diastereomeric excess values were calculated by GC using a chiral column.

Author contributions

L. E. and S. G.-G. performed the experiments and analyzed the results. The study was conceptualized by V. G.-F. and I. L. All authors have contributed to the manuscript writing.

Conflicts of interest

There are no conflicts to declare.

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