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Research Article

Unmasking the Hidden Carbonyl Group Using Gold(I) Catalysts and Alcohol Dehydrogenases: Design of a Thermodynamically-Driven Cascade toward Optically Active Halohydrins

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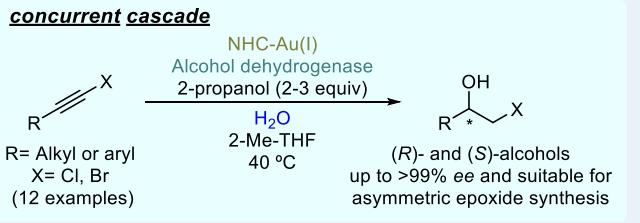
ABSTRACT: A concurrent cascade combining the use of a gold(I) N-heterocyclic carbene (NHC) and an alcohol dehydrogenase (ADH) is disclosed for the synthesis of highly valuable enantiopure halohydrins in an aqueous medium and under mild reaction conditions. The methodology consists of the gold-catalyzed regioselective hydration of easily accessible haloalkynes, followed by the stereoselective bioreduction of the corresponding α-halomethyl ketone intermediates. Thus, a series of alkyl- and aryl-substituted haloalkynes have been selectively converted into chloro- and bromohydrins, which were obtained in good to high yields (65−86%). Remarkably, the use of stereocomplementary commercial or made-in-house overexpressed alcohol dehydrogenases in *Escherichia coli* has allowed the synthesis of both halohydrin enantiomers with remarkable selectivities (98 → 99% *ee*). The outcome success of this method was due to the thermodynamically driven reduction of the ketone intermediates, as just a small excess of the hydrogen donor (2-propanol, 2-PrOH) was necessary. In the cases that larger quantities of 2-PrOH were applied, higher amounts of other by-products (e.g., a vinyl ether derivative) were detected. Finally, as an extension of this cascade transformation and exploration of the synthetic potential of chiral halohydrins, the synthesis of both enantiomers of styrene oxide has been developed in a one-pot sequential manner in very high yields (88−92%) and optical purities (97 → 99% *ee*).



KEYWORDS: *alkyne hydration, biocatalysis, bioreduction, cascade reactions, enzymes, gold catalysis, halohydrins*

INTRODUCTION

α-Halomethyl ketones constitute one of the most important classes of organic intermediates based on their multiple synthetic possibilities due to the susceptibility of the carbonyl group to be reduced with reducing agents, react with different nucleophile classes,[1−3] and also their ability to become carboxylic acid precursors through the Favorskii rearrangement.[4] Two traditional approaches have been described for their synthesis, consisting of the development of α-halogenation of the corresponding ketones[1] or alternatively the chemical modification of olefins and alkynes.[5] Unfortunately, the halogenation of ketones with molecular halogens, metal halides, or *N*-halosuccinimides usually suffers from serious drawbacks due to the occurrence of low regiospecificity or polyhalogenation transformations, and therefore special efforts have been made in recent years toward the selective modification of C−C multiple bonds under mild reaction conditions.

Remarkably, alkynes are adequate carbonyl surrogates, their hydration receiving considerable attention because it proceeds with a complete atom efficiency for terminal alkynes, dialkylalkynes, diarylalkynes, arylalkylalkynes and even hetero-substituted ones.[5−11] Interestingly, haloalkynes are easily accessible through C−H metalation or deprotonation of the corresponding terminal alkynes and subsequent halogenation employing different halogenation reagents. On the other hand, the catalytic addition of water to these unsaturated compounds involves the tautomerization of initially formed enol-type species that is especially favored when considering these haloalkynes as substrates because the C−X bond is highly polarized.[8] In this context, the production of α-halomethyl ketones through regioselective haloalkyne hydration has been traditionally catalyzed by Brønsted acids[12] and metal species, the latter being considered as the first choice strategy (Scheme 1). Thus, the usefulness of a wide range of metal species has been reported to accelerate this transformation, including cerium,[13] copper,[14] indium,[15] iron,[16] or silver[17] catalysts.

Au(I) catalysts have emerged in the past decade as valuable tools[18] for alkyne hydration,[19] allowing chemoselective transformations when other functional groups are present.[20−24] In

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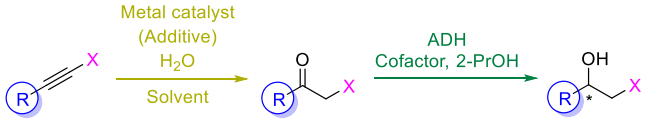
Scheme 1. Alkyne Hydration−Stereoselective Bioreduction Sequence for the Synthesis of Enantioenriched Halohydrins



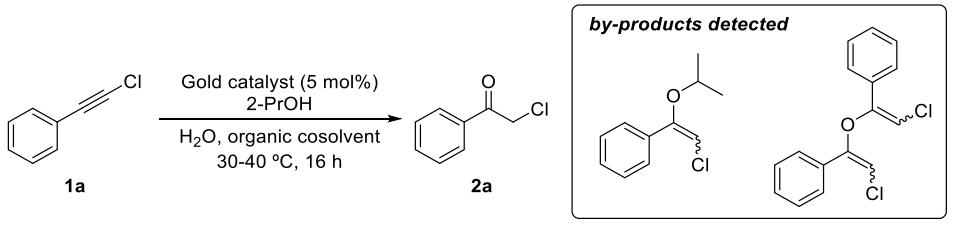
an inspiring work, He and co-workers reported the first general hydration of aliphatic and (hetero)aromatic 1-haloalkynes using XPhosAuNTf$_2$ and 3 equiv of water.[20] The hydration of similar haloakynes (X = Br, Cl, and I) was later successfully achieved by using an immobilized gold(I) catalyst (MCM-41-PPh$_3$AuNTf$_2$).[21] Terminal halo-substituted propargyl carboxylates have also become adequate hydration substrates using a Ph$_3$PAuNTf$_2$/AgSbF$_6$ catalytic system and also 3 equiv of water.[22] More recently, Cazin and co-workers described the hydration of aromatic 1-iodoalkynes using IPrAuNTf$_2$ and 2 equiv of water as part of a one-pot sequential iodination−hydration sequence,[23] results that complement the investigations previously reported by Sheppard and co-workers in a similar multistep synthesis.[24] Also, Liu and co-workers have demonstrated the potential of this methodology combining the gold(I)-mediated hydration of haloalkynes with a Ru-catalyzed hydrogen transfer reaction to obtain enantioenriched halohydrins in 1,2-dichloroethane at 20 °C.[25,26]

Chiral halohydrin derivatives are extremely versatile intermediates in organic chemistry, as they can be easily functionalized to provide different families of biologically active compounds and synthetic drugs.[27−30] Among the reported synthetic approaches to obtain these derivatives in enantioenriched form, enzyme-catalyzed reactions represent an elegant sustainable strategy.[31] In fact, the bioreduction of α-halomethyl ketones using alcohol dehydrogenases (ADHs) can be highlighted[32−36] since it is a highly thermodynamically favored reaction, requiring just a small excess of the hydrogen donor, 2-propanol (2-PrOH), used as a cosubstrate for cofactor recycling purposes.[37−39] Therefore, shifting the reaction toward alcohol formation is highly favored, to the detriment of the reverse alcohol oxidation.

The quest for cooperative multicatalytic transformations presents the combination of metal and enzyme catalysis as an advantageous strategy for increasing molecular complexity at the same time that chirality can be induced under mild reaction conditions,[40−44] including transformations involving ADHs.[45] Thus, finding suitable reaction conditions for the combined action of gold and enzyme catalysis would make plausible the development of a straightforward synthesis of chiral halohydrins starting from haloalkynes in an aqueous medium under very mild conditions, as depicted in Scheme 1.

In this field, the development of multicatalytic transformations involving gold species and enzymes such as lipases, ADHs, monoamine oxidases, and transaminases has received increasing attention in recent years. Groundbreaking findings have covered the development of various multicatalytic approaches, including a nonselective alkynylation of tetrahydroisoquinolines catalyzed by the combined action of an evolved monoamine oxidase and HAuCl$_4$,[46] and also a few stereoselective multistep transformations using Au(I) or Au(III) catalysts. For instance, cycloisomerization transformations have been elegantly implemented together with lipase-catalyzed hydrolytic kinetic resolution procedures,[47,48] or ADH-mediated bioreduction processes.[49] Interestingly, hydration−bioreduction routes have also been reported, transforming terminal alkynes in optically active 1-arylethan-1-ols and aliphatic alcohols in sequential protocols.[50,51] In this

Table 1. Hydration of 1a Using 2-PrOH and a Gold(I) Catalyst under Different Reaction Conditions (Solvent, 2-PrOH Concentration, and Temperature)[a]



entry	catalyst	cosolvent[b] (%)	2-PrOH[b]	T (°C)	**1a**[c] (%)	**2a**[c] (%)	by-products[c] (%)
1	IPrAuNTf$_2$	MeCN (16.7)	16.7%	40	1	35	64
2	IPrAuNTf$_2$		20%	40	<1	15	85
3	IPrAuNTf$_2$		2 equiv	40	<1	88	12
4	IPrAuNTf$_2$	MeCN (20)	2 equiv	40	1	82	17
5	JohnPhosAuNTf$_2$	MeCN (20)	2 equiv	40	<1	81	19
6	BrettPhosAuNTf$_2$	MeCN (20)	2 equiv	40	<1	85	15
7	IPrAuNTf$_2$	THF (20)	2 equiv	40	<1	99 (93)	1
8	IPrAuNTf$_2$	THF (20)	2 equiv	30	3	96 (85)	1
9	IPrAuNTf$_2$	2-Me-THF (20)	2 equiv	40	<1	99 (94)	1
10	IPrAuNTf$_2$	THF (15)	2 equiv	40	<1	99 (91)	1
11	IPrAuNTf$_2$	THF (10)	2 equiv	40	<1	99 (93)	1
12	IPrAuNTf$_2$	2-Me-THF (10)	2 equiv	40	<1	99 (93)	1
13	IPrAuNTf$_2$	2-Me-THF[d] (10)	2 equiv	40	<1	99 (89)	1

[a]Reaction conditions: **1a** (100 mM), gold catalyst (5 mol %), H_2O (66.6−98.4% v/v), cosolvent (0−20% v/v), 2-PrOH (1.6−20% v/v) for 16 h. [b]Percentages of cosolvents are given in % v/v, while for 2-PrOH they are either as % v/v or equivalents with respect to the haloalkyne. [c]Percentages of product were measured by GC analysis of the reaction crude. Isolated yields of ketone **2a** in parentheses after column chromatography purification. [d]A 2% w/v of TPGS-750-M surfactant was added.

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context, Mihovilovic and co-workers have sequentially combined the action of $AuCl_3$ in 2-PrOH using 4 equiv of water for alkyne hydration at 65 °C with the bioreduction of the resulting 1-arylethan-1-one intermediates at 30 °C,[50] while Lipshutz' group described a one-pot sequential protocol including the use of (HandaPhos)AuCl in the presence of a silver salt, trifluoroacetic acid, and a surfactant in water for the hydration step, adding the ADH, cofactor, buffer, and additional surfactant for the reductive step once the alkyne was consumpted.[51] Very recently, Rueping and co-workers have developed a hydration−biotransamination sequential approach to transform terminal arylacetylenes into optically active 1-arylethan-1-amines, combining gold(I) chloride and a stereoselective transaminase in a sequential manner since the substrate concentration had to be diminished and the temperature decreased after the hydration step.[52]

Being aware of the difficulties to develop multicatalytic transformations when considering an alkyne hydration and biotransformation sequences in a concurrent cascade mode,[50−52] herein we have focused on the exploitation of the compatibility of an N-heterocyclic carbene (NHC)−gold(I) complex, namely, [1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene] [bis(trifluoromethanesulfonyl)imide]gold-(I) ($IPrAuNTf_2$) with ADHs, recently reported as the first example of a concurrent cascade involving a gold species and these oxidoreductases.[53] In that case, the Meyer-Schuster rearrangement of various racemic propargylic alcohols followed by stereoselective bioreduction of the α,β-unsaturated ketone intermediates was reported to afford enantiopure allylic alcohols. Now the exploitation of this synergic combination of a NHC−gold(I) catalyst and stereoselective ADHs is expanded, searching for adequate conditions to develop a novel one-pot approach for the straightforward synthesis of pharmaceutically relevant optically active halohydrins from haloalkynes.

RESULTS AND DISCUSSION

Herein, the most representative results are presented: (i) the gold(I)-catalyzed hydration process of (chloroethynyl)benzene (**1a**) and the scope of the reaction using other haloalkynes **1b**-**1l**; (ii) the bioreduction of 2-chloro-1-phenylethan-1-one (**2a**) using different ADHs; (iii) next, the development and scope of the stereodivergent concurrent cascade consisting in the alkyne-hydration sequence; (iv) and finally an application of this methodology for creating new molecular diversity in a one-pot sequential transformation toward an optically active epoxide.

NHC−Gold(I) Catalyzed Hydration of (Chloroethynyl)benzene (1a) and Reaction Scope. For this study, (chloroethynyl)benzene (**1a**) was selected as a benchmark substrate since it can be prepared in a straightforward manner through selective halogenation at the terminal position of phenylacetylene with *N*-chlorosuccinimide.[54] On the basis of the excellent reactivity displayed by $IPrAuNTf_2$ in the Meyer-Schuster rearrangement of propargylic alcohols in an aqueous medium,[53] the hydration of haloalkyne **1a** was investigated using 5 mol % of the gold catalyst at 40 °C in water as a reaction medium (Table 1). The addition of 2-PrOH was considered at this point with a dual role, first as an organic cosolvent to improve the substrate solubility but also as a cosubstrate for cofactor recycling purposes in a coupled-substrate fashion when considering the subsequent bioreduction process.

First, variable amounts of 2-PrOH were considered (1.6−20%, see also Table S1 of the Supporting Information), leading to the desired 2-chloro-1-phenylethan-1-one (**2a**) with the concomitant formation of some by-products in significant amounts. These side-reaction products were identified as a mixture of the vinyl ether resulting from the gold-catalyzed nucleophilic addition of 2-PrOH to the chloroalkyne[55] and the dimeric product displayed in the scheme from Table 1 obtained after the addition of the enol tautomer from **2a** to **1a**. High 2-PrOH contents preferably favored the formation of the vinyl ether, but unfortunately a complex mixture was identified in the NMR analyses, from this point focusing exclusively on the optimization of the reaction conditions to the formation of ketone **2a**.

Usually, when bioreductions are performed using 2-PrOH as the cosubstrate, a huge molar excess regarding the ketone substrate is necessary to drive the equilibrium into the desired alcohol product. However, when carbonyl compounds present an electron-withdrawing group at the α position such as a halogen atom, the reduction is highly thermodynamically favored.[37−39] Taking advantage of this singularity, the hydration reaction of **1a** was carried out in the presence of only 2 equiv of 2-PrOH at 40 °C, finding high percentages of ketone **2a** either in the absence or presence of acetonitrile as the cosolvent (82−88%, entries 3 and 4) due to the drop of the by-product formation.

From a total of six gold(I) catalysts comprising the presence of different ligands and anions (see Table S2 for gold catalyst screening), $JohnPhosAuNTf_2$ and $BrettPhosAuNTf_2$ also turned out to be efficient species leading to **2a** as the main product (81−85%, entries 5 and 6). Further optimization of the reaction conditions was performed with $IPrAuNTf_2$ because of its lower price in comparison to that of $BrettPhosAuNTf_2$, focusing on the selection of a suitable cosolvent to favor the solubility of the starting material (entries 7−13) and minimize the side product formation. After optimization of the organic cosolvent and reaction temperature (see further experiments in Table S3), the use of ethers such as water-miscible tetrahydrofuran (THF, entry 7) and also the more environmentally benign, renewable, and water-immiscible 2-methyltetrahydrofuran (2-Me-THF, entry 9)[56] turned out to be the best choice, exclusively leading to the formation of **2a**. Interestingly, the reaction maintained its perfect regioselectivity in THF at 30 and 40 °C, but was faster at a higher temperature (96−99%, entries 7 and 8), being also synthetically useful at different cosolvent ratios (10−20%, entries 9−12), while its combination with a surfactant[51] also allowed the isolation of **2a** in very high yields (entry 13).

In Table 2 the hydration of **1a** was further studied, analyzing now the influence of the catalyst loading (2−5 mol %, entries 1−4) and the amount of 2-propanol (2−10 equiv, entries 1 and 5−8). On the one hand, a significant formation of by-products was observed when reducing the $IPrAuNTf_2$ loading from 5 to 2 mol % (up to 17% of undesired products, entry 4), so 5 mol % of $IPrAuNTf_2$ was selected to favor the main hydration reaction. On the other hand, higher amounts of 2-PrOH favored the progressive formation of by-products (up to 6%), finding the best reaction conditions when combining 5 mol % $IPrAuNTf_2$ and 2 equiv of 2-PrOH (93% isolated yield of **2a**). Therefore, these conditions were selected for the design of a one-pot hydration−bioreduction cascade.

Next, haloalkynes **1b**−**1l** were synthesized following the reported procedures[54,57] to explore the scope of the

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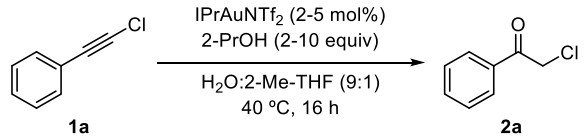
Table 2. Effect of $IPrAuNTf_2$ and 2-Propanol Amounts in the Hydration of 1a at 40 °C for 16 h



1a 2a

entry	$IPrAuNTf_2$ (mol %)	2-PrOH (equiv)	2a[a] (%)	by-products[a] (%)
1	5	2	99 (93)	1
2	4	2	97 (89)	3
3	3	2	85 (80)	15
4	2	2	83 (74)	17
5	5	3	98 (91)	2
6	5	5	97 (91)	3
7	5	7	95 (87)	5
8	5	10	94 (84)	6

[a]Percentages of products were measured by GC analysis of the reaction crude. Isolated yields of ketone **2a** in parentheses after chromatographic purification.

$IPrAuNTf_2$-catalyzed hydration reaction under a compatible setup with a bioreduction process. The use of 5 mol % $IPrAuNTf_2$, 2 equiv of 2-propanol, and 2-Me-THF as cosolvent (10% v/v) was selected for the synthesis of a total of 12 α-halomethyl ketones **2a**–**2l**, which occurred with high to excellent selectivities in over 85% conversion (Figure 1) and isolated after column chromatography in very high yields (79–96%). It must be stated that a column chromatography purification was required for the separation of the remaining starting material and resulting by-products, although they appeared to a low extent.

Bioreduction of 2-Chloro-1-phenylethan-1-one (2a). A total of 23 alcohol dehydrogenases were screened to find stereoselective enzymes that were able to produce both 2-chloro-1-phenylethan-1-ol (**3a**) enantiomers under suitable conditions for the gold(I)-catalyzed hydration step previously optimized. To this aim, 2-Me-THF (20% v/v), 40 °C, and only 2 equiv of 2-PrOH (Table S5) were selected. On the one hand, 4 reductases led to the enantiopure (*S*)-**3a** in quantitative conversions: (a) Commercially available KRED-P1-A04, KRED-P1-A12, and KRED-P2-H07 from a Codexis screening kit; (b) lyophilized cells of *E. coli* overexpressing ADH from *Lactobacillus brevis* (*Lb*ADH),[58,59] an enzyme that was already described as an efficient catalyst in the bioreduction of α-halomethyl ketones.[60] On the other hand, only the ADH from *Rhodococcus ruber* (ADH-A)[61,62] led to the enantiopure (*R*)-**3a** in 98% conversion, which was also previously found to be a good candidate for the production of optically active halohydrins.[63−66]

Design of a Stereodivergent Concurrent Chemoenzymatic Cascade toward Halohydrins 3a–3l through a Hydration–Bioreduction Sequence. Encouraged by the excellent results obtained in the individual gold-catalyzed hydration of alkynes **1a**–**1l** and the bioreduction of α-chloromethyl ketone **2a**, and on the basis of our recent successful experience in the combination of $IPrAuTf_2$ and ADHs,[53] the concurrent hydration–bioreduction cascade was next attempted. Because of the requirements of both catalysts, a few parameters were considered in selecting the formation of **3a** as the final goal. Importantly, the use of an aqueous system was pursued with the addition of few 2-propanol equivalents since both possess a decisive role in the global process and do not present serious drawbacks for the metal-catalyzed alkyne hydration, as demonstrated before. The concomitant use of stereocomplementary *Lb*ADH and ADH-A together with the NHC–gold(I) catalyst was next investigated, a selection of the most important results of this combination with *Lb*ADH being described in Table 3.

With the goal of maintaining a low gold loading, 6 mol % $IPrAuNTf_2$ was found to be the optimum one (entries 1 and 2), while the use of 2-Me-THF (entries 3 and 4) offered a slight improvement over the use of THF, leading to a 96% conversion (87% isolated yield) when the cosolvent ratio was reduced to 10% v/v and 2-PrOH to 2 equiv (entry 5). Additional experiments can be found in Table S7, where it can also be observed that the magnetic stirring represents a notable advantage in comparison to the orbital shaking, usually employed in biocatalyzed processes, while no significant improvements were observed when increasing the NADPH concentration from 1 to 2 mM. Interestingly, ADH-A allowed the stereocomplementary synthesis of the (*R*)-**3a** enantiomer,

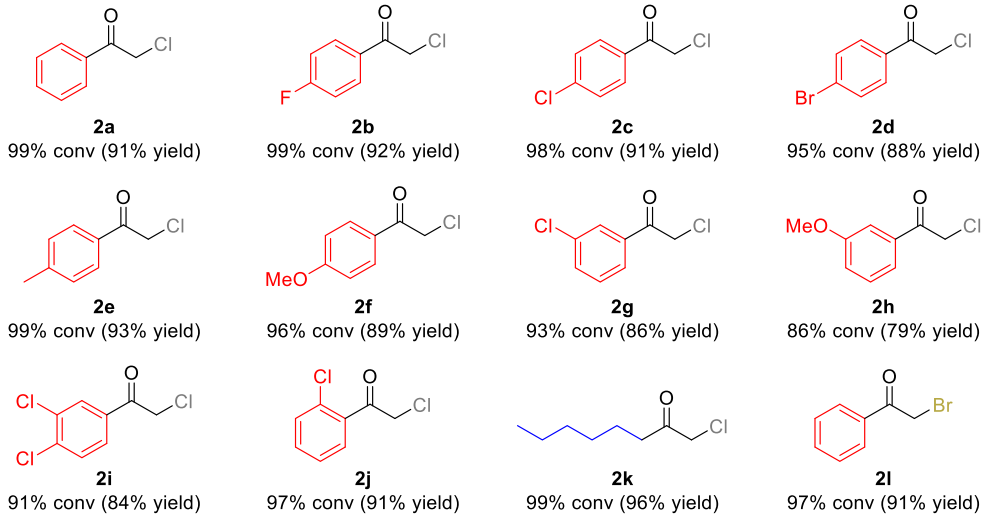


Figure 1. Scope of the gold-catalyzed hydration of alkynes **1a**–**1l**. Reaction conditions: **1a**–**1l** (100 mM in H_2O/2-Me-THF 9:1 v/v), $IPrAuNTf_2$ (5 mol %), 2-PrOH (2 equiv), 16 h, and 40 °C.

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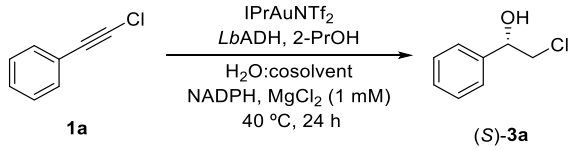
Table 3. Hydration−Bioreduction Cascade of Alkyne 1a (100 mM) Using IPrAuNTf$_2$ and *Lb*ADH[a]



entry	IPrAuNTf$_2$ (mol %)	2-PrOH (equiv)	cosolvent (% v/v)	1a[b] (%)	2a[b] (%)	by-products[b] (%)	3a[b] (%)	(*S*)-3a *ee*[c] (%)
1	5	3	THF (20)	3	<1	6	91	>99
2	6	3	THF (20)	<1	1	7	92	>99
3	6	3	2-Me-THF (20)	<1	<1	6	94	>99
4	6	2.5	2-Me-THF (10)	<1	<1	7	93	>99
5	6	2	2-Me-THF (10)	<1	<1	4	96 (87)	>99

[a]A general procedure is described in the Experimental Section. [b]Product percentages were determined by GC analysis using calibration curves. Isolated yield of (*S*)-**3a** in parentheses. [c]Enantiomeric excess values were determined by HPLC.

reaching 94% conversion and 85% of isolated enantiopure product when employing 3 equiv of 2-PrOH, 1 mM NADH, and 2-Me-THF (10% v/v) after 24 h at 40 °C.

During a search for a higher process efficiency, additional experiments were performed at different substrate concentrations ranging from 100 to 300 mM alkyne **1a**. In all cases, the hydration of **1a** smoothly proceeded under optimized reaction conditions, reaching full conversion (Table S8), although the conversion was affected when considering the cascade approach, observing a decrease at higher concentrations moving from 96% alcohol (*S*)-**3a** at 100 mM to 84% at 250 mM (Figure 2 and Table S9) due to the formation of the

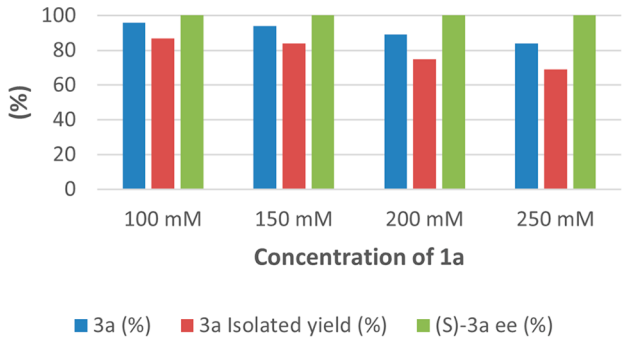


Figure 2. Influence of the alkyne **1a** (0.1 mmol) concentration in the hydration−bioreduction cascade using IPrAuNTf$_2$ (6 mol %), *E. coli*/*Lb*ADH (20 mg), 2-PrOH (2 equiv), and 2-Me-THF (10% v/v) as cosolvent for 24 h at 40 °C.

side products to a higher extent. Remarkably, the stereoselectivity remained perfect in all cases, obtaining the enantiopure halohydrin regardless of the selected conditions.

Because of the importance of chiral halohydrins as key pharmaceutical precursors,[27−30] and for the purpose of investigating the generality of the reported chemoenzymatic approach, the hydration−bioreduction cascade was attempted with a series of aryl acetylenes considering a synthetically useful 100 mM substrate concentration, and variable pattern substitutions in the aromatic ring including halogen atoms at different positions (**1b−1d**, **1g**, **1i**, and **1j**), the use of electron-donating substituents (**1e**, **1f**, and **1h**), and also the employment of (bromoethynyl)benzene (**1l**) to produce a bromohydrin. Special emphasis must be made in the selection of an aliphatic substrate such as 1-chlorooct-1-yne (**1k**) due to the difficulties to chemically develop regioselective halogenations of aliphatic ketone substrates to obtain the corresponding α-haloketone at the terminal position. The results under the optimized conditions for each substrate and enzyme are depicted in Figure 3 and Table S10, showing high to excellent conversions toward the formation of the corresponding halohydrins (78−98%), which were isolated in moderate to high yields after column chromatography (65−86%) with excellent optical purities (98 to >99% *ee*). In all cases heterologously overexpressed ADH-A and *Lb*ADH were used for the bioreduction of the ketone intermediates, except for the 2-chloro-1-(2-chlorophenyl)ethan-1-one that showed very little activity with these enzymes, so commercially available KRED-P1-A04 and KRED-P1-H08 were used in these cases (see Table S6 for a bioreduction screening with ketone **2j**).

Semipreparative transformations (100 mg) were successfully developed for the production of both 2-chloro-1-phenylethan-1-ol enantiomers (Table S11), yielding (*S*)-**3a** in 82% isolated yield with *Lb*ADH and (*R*)-**3a** in 83% isolated yield with ADH-A in enantiopure form.

Design of a Hydration−Bioreduction−Epoxidation Sequence toward Styrene Oxide Enantiomers. As described in the Introduction, halohydrins are highly valuable compounds as they can be transformed into other important derivatives. Herein, in a search to exploit the potential of this chemoenzymatic cascade, a preliminary study of styrene oxide (**4a**) formation starting from racemic chlorohydrin **3a** was developed, finding 1.2 equiv of sodium hydroxide as the minimum amount to form **4a** in a quantitative conversion (Figure 4 and Table S12), not detecting other by-products.

Then the hydration−bioreduction−cyclization sequence was performed in a one-pot sequential process, adding 1.2 equiv of sodium hydroxide to the reaction mixture once **3a** was obtained (Scheme 2). Satisfyingly, the epoxidation process just required 3 additional hours, both styrene oxide enantiomers being obtained in high purity depending on the enzyme of choice (Table S13), (*S*)-**4a** with *Lb*ADH (92% isolated yield and >99% *ee*) and (*R*)-**4a** for ADH-A (88% isolated yield and 97% *ee*). This simple protocol demonstrates that highly interesting synthetic precursors as chiral epoxides can be easily obtained by combining the action of a metal catalyst and an enzyme.

CONCLUSIONS

A one-pot concurrent cascade consisting of the NHC−gold(I)-catalyzed hydration of easily accessible haloalkynes followed by a stereoselective bioreduction has allowed the asymmetric synthesis of halohydrins with excellent conversion and stereoselectivity values. Optimization of the hydration step

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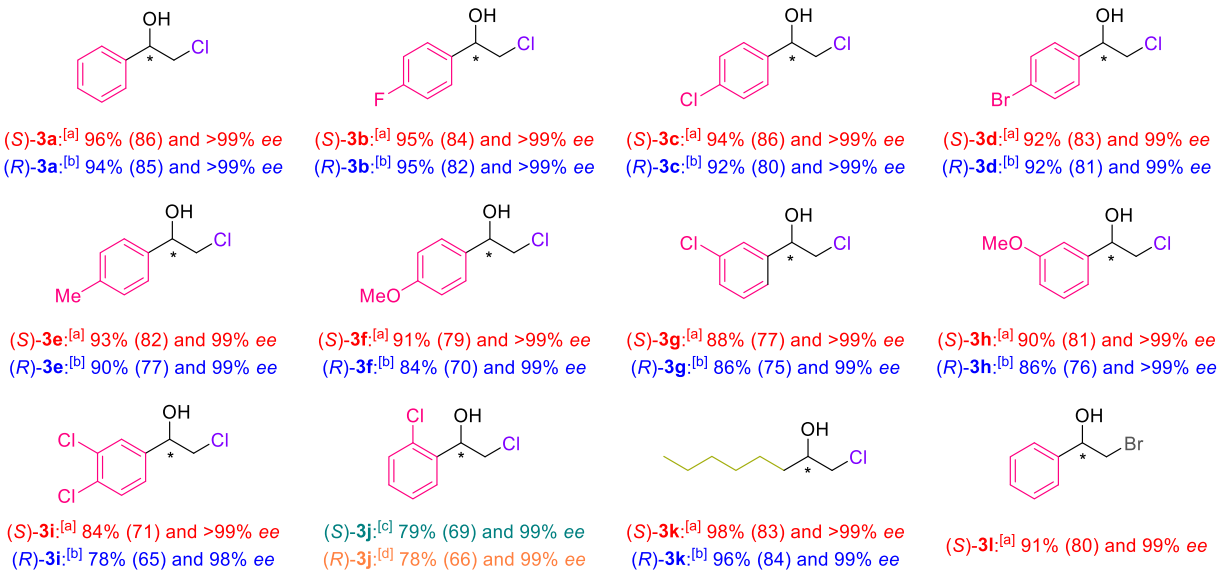


Figure 3. Scope of the concurrent hydration–bioreduction cascade of alkynes **1a–1l** (100 mM) after 16 h at 40 °C with $IPrAuNTf_2$ (6 mol %). Isolated yields appear in parentheses after the conversion values.

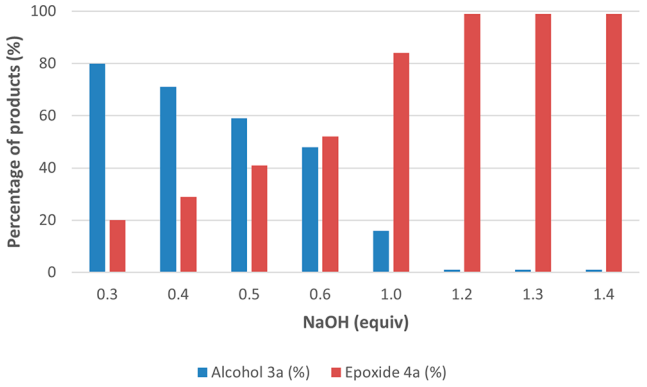
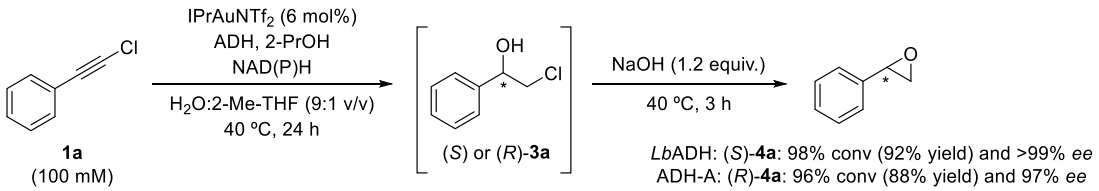


Figure 4. Influence of the NaOH amount in the epoxidation of racemic **3a** using H_2O-2-Me-THF (90:10% v/v) as the solvent in the presence of 2 equiv of 2-PrOH for 3 h at 40 °C.

was necessary to be concurrently accomplished later with the reduction of the resulting α-halomethyl ketones using stereocomplementary alcohol dehydrogenases. For that reason, the hydration of ethynylbenzene was optimized in an aqueous medium, finding tetrahydrofuran and 2-methyltetrahydrofuran as suitable cosolvents (10% v/v), while $IPrAuNTf_2$ (5–6 mol %) turned out to be an efficient catalyst for this fully atom-economy reaction. The presence and amount of 2-propanol was crucial to enable the combination of the metal and enzyme catalysts for the development of a cascade process, the use of only 2–3 equiv allowing the development of the one-pot approach without forming significant amounts of by-products due to the thermodynamically favored reduction of α-haloketones. Remarkably, alkyl- and aryl-substituted haloalkynes were isolated as the corresponding ketones in good to high yields after column chromatography (79–96%).

The screening of commercial and in-house enzymes overexpressed in *E. coli* has allowed the production of a series of pharmaceutically relevant enantioenriched chlorohydrins and a bromohydrin by employing complementary stereoselective enzymes, this biotransformation being highly selective and fully compatible in one pot with the gold-catalyzed process, even at a relevant 100 mM substrate concentration (65–86% isolated yield and >98% *ee*). The production of these valuable compounds was possible in a concurrent cascade manner, including different aromatic and aliphatic motifs, the production of 1-chlorooctan-2-ol resulting being especially attractive due to the difficulties in developing regioselective halogenation reactions over aliphatic ketone substrates to synthesize the corresponding halohydrins. Interestingly, the development of an additional cyclization transformation toward both styrene oxide enantiomers was successfully accomplished by the addition of sodium hydroxide to the reaction medium. In this way, a one-pot process allowed the preparation of styrene oxide from (chloroethynyl)benzene without loss of the stereochemical information, thus showing the potential of this methodology to be easily expanded to the synthesis of other valuable compounds.

Scheme 2. Hydration–Bioreduction–Epoxidation Sequence To Provide Both Styrene Oxide Enantiomers from Alkyne 1a



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EXPERIMENTAL SECTION

Materials and Equipment. All the information regarding the employed instrumentation and the alcohol dehydrogenases employed in this work is extensively described in the Supporting Information, including enzyme sources and bioreduction experiments. Full characterization of α-halomethyl ketones **2a−2l**, halohydrins **3a−3l**, and styrene oxide **4a** also appears in the Supporting Information.

General Procedure for the Synthesis of α-Halomethyl Ketones 2a−2l through a NHC−Gold(I)-Catalyzed Hydration Reaction. Distilled H_2O (0.9 mL), 2-PrOH (15.3 μL, 0.2 mmol, 2 equiv), and IPrAuNTf$_2$ (4.4 mg, 0.005 mmol, 5 mol %) were successively added in this order to a solution of the corresponding haloalkyne **1a−1l** (0.1 mmol) in 2-Me-THF (0.1 mL), and the mixture was stirred at 40 °C for 16 h. After this time, the reaction was extracted with EtOAc (3 × 1 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The corresponding reaction crude was purified by column chromatography on silica gel (10% EtOAc/hexane), obtaining the α-haloketone **2a−2l** with excellent purity (79−96% isolated yield, Figure 1).

General Procedure for the Concurrent Cascade Hydration−Bioreduction of Haloalkynes 1a−1i, 1k, and 1l Using *Lb*ADH. The corresponding haloalkynes **1a−1i**, **1k**, and **1l** (0.1 mmol), 2-Me-THF (100 μL), distilled water (705 μL), 2-PrOH (15.3 μL, 2 equiv), IPrAuNTf$_2$ (5.3 mg, 0.006 mmol, 6 mol %), a NADH aqueous solution (100 μL, 10 mM), a $MgCl_2$ aqueous solution (100 μL, 10 mM), and lyophilized cells of overexpressed *E. coli*/*Lb*ADH (20 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 EtOAc (5 × 1 mL) and the organic layers were combined, dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure, measuring then the conversion into the alcohols **3a−3i**, **3k**, and **3l** by GC analysis, while the enantiomeric excess value was calculated by HPLC. Alcohols **3a−3i**, **3k**, and **3l** were purified by column chromatography on silica gel (71−86% isolated yield, Figure 3).

General Procedure for the Concurrent Cascade Hydration−Bioreduction of Haloalkynes 1a−1i and 1k Using ADH-A. The corresponding alkynes **1a−1i** and **1k** (0.1 mmol), 2-Me-THF (100 μL), distilled water (800 μL), 2-PrOH (23 μL, 3 equiv), IPrAuNTf$_2$ (5.3 mg, 0.006 mmol, 6 mol %), a NADH aqueous solution (100 μL, 10 mM), and lyophilized cells of overexpressed *E. coli*/ADH-A (20 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 EtOAc (5 × 1 mL) and the organic layers were combined, dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure, measuring then the conversion into the alcohols **3a−3i** and **3k** by GC analysis, while the enantiomeric excess value was calculated by HPLC. Alcohols **3a−3i** and **3k** were purified by column chromatography on silica gel (65−85% isolated yield, Figure 3).

General Procedure for the Concurrent Cascade Hydration−Bioreduction of Haloalkyne 1a Followed by Epoxidation with Sodium Hydroxide. To obtain each desired enantiomer of **4a**, the previously described experimental protocol has been followed depending on the enzyme employed (*Lb*ADH or ADH-A). After completion of the first part of the transformation, 40 μL of an aqueous solution of NaOH (3 M, 1.2 equiv) was added. The mixture was kept under magnetic stirring at 40 °C for 3 h, and after this time, the solution was extracted with EtOAc (5 × 1 mL) and the organic layers were combined, dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure, measuring then the conversion into styrene oxide by GC analysis and the enantiomeric excess by HPLC analysis. Epoxide **4a** was purified by column chromatography on silica gel (10% EtOAc/hexane, 88−92% isolated yield, Scheme 2).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c05216.

Structures of all chemical compounds studied here, chemical synthesis of haloalkynes **1a−1l**, extensive gold- and enzyme-catalyzed transformation screenings and optimizations, development of analytical methods (GC and HPLC) to measure enzymatic activities and selectivities, copies of chromatograms for chiral analyses, and full characterization of all novel products providing copies of ^{1}H NMR, ^{13}C NMR, DEPT, ^{19}F NMR, and selected bidimensional experiments (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

2-Me-THF, 2-methyltetrahydrofuran; ADH, alcohol dehydrogenase; *ee*, enantiomeric excess; equiv, equivalent; GC, gas chromatography; 2-PrOH, 2-propanol; KRED, ketoreductase; M, molar; NAD(P)H, nicotinamide adenine dinucleotide (phosphate) in its reduced form

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