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Easy Access to Enantiopure (*S*)- and (*R*)-Aryl Alkyl Alcohols by a Combination of Gold(III)-Catalyzed Alkyne Hydration and Enzymatic Reduction

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Chemoenzymatic one-pot processes based on the combination of metal catalysis and biocatalysis open up highly attractive perspectives regarding the production of enantiopure compounds. By combining a gold-catalyzed hydration reaction with an enzymatic reduction, we present a straightforward and atom-economical chemoenzymatic method for the synthesis of secondary alcohols with excellent optical purity. Efficient cofactor recycling exploits the solvent of the metal-catalyzed step as an auxiliary substrate for the enzymatic step.

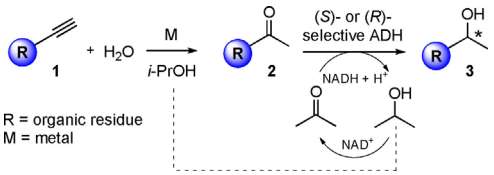
In addition to general feasibility, the preparation of chiral molecules is also assessed by environmental and sustainable aspects within modern synthetic chemistry.[1–3] In this regard, the combination of several reaction steps within one pot is an attractive strategy, as the number of workup and purification steps can be substantially reduced.[4–9] During the past decades, biocatalysis was established as a highly potent method for the introduction and manipulation of stereochemistry, in particular on the basis of improved access to versatile enzymes of natural origin or by enzyme engineering.[10–15] Linking enzyme-mediated reactions with metal-assisted catalysis is generally understood as a highly prospective approach, as both areas offer complementary functional group interconversions. Whereas the incorporation of metal-assisted catalysis in a protein framework has been proven to be highly successful,[16–22] this specific combination has proven particularly challenging in cascade processes on the basis of limited compatibility or the reaction conditions.

Critical obstacles are encountered by differences in concentration of the reactants, reaction temperature, solvent, pH value, and, in particular, the envisaged coexistence of a metal catalyst and biocatalyst in one pot. Consequently, most of these processes need a form of compartmentalization to separate the metal catalyst from the biocatalyst, thereby avoiding poisoning effects.[23–25]

There are only very few examples without any form of compartmentalization; for example, a recent concurrent ruthenium-catalyzed allylic alcohol isomerization and asymmetric bioreduction[26] and the combination of metathesis with the biocatalytic aromatizing activity of monoamine oxidases.[27] Furthermore, an iridium-catalyzed oxidation was combined concurrently to an asymmetric biocatalytic reduction,[28] and the combination of biocatalysts with artificial metalloenzymes enabled synthetic cascades.[29,30] Thus, the most challenging task is to arbitrate the reaction environments of the individual steps by identifying consensus conditions with minimal detrimental effects. In addition to spatial separation, temporal separation provides a simple alternative; the addition of the biocatalyst at a later stage may avoid temperature issues and limits problems associated with solvent and metal compatibility. Nevertheless, the choice of the catalytic metal species is crucial for a successful chemoenzymatic one-pot process. Gold as an inert metal species is known to be well tolerated by microorganisms to a certain amount.[31–33] Gold salts, on the other hand, are often exploited as Lewis acids, typically coordinating to C–C double and triple bonds, functionalities rarely present in enzymes.[34–37]

In this contribution, we report on the combination of Au-catalyzed ketone formation with subsequent enzymatic reduction to secondary alcohols (Scheme 1), in which the metal-catalyzed step is performed in a solvent that serves as an auxiliary substrate for cofactor recycling in the subsequent biotransformation.

A similar transformation was reported recently by Rodríguez-Álvarez et al.[38] In this contribution, $KAuCl_4$ was used as the gold source, and pentynoic acid was used as the substrate. After converting the alkyne into a keto group, the latter was reduced by a ketoreductase (KRED), and the obtained alcohol cyclized spontaneously to the corresponding lactone. Alkynes can be considered as surrogates for the ketone functionality, as they can be readily converted into the latter by simple addition of water.[39] This can be exploited several ways, for example, by access to specific structural motifs such as 1,4-dike-



Scheme 1. Chemoenzymatic reaction sequence in which the solvent of the metal-catalyzed step serves as the auxiliary substrate for the enzymatic step.

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tones, which can be more readily synthesized by alkyne hydration of 3-alkynoates than by any other method.[40]

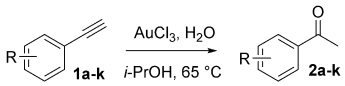
Another application in this regard is taking advantage of the different reactivities of alkynes and ketones, which allows reactions of the latter to be performed in the presence of alkynes and only later are the alkynes transformed into another ketone functionality. In this regard, the alkyne may be considered as a "masked" ketone. Interestingly, examples of this strategy in the literature remain scarce.[41–43]

As mentioned previously, nucleophilic addition of water or alcohols to alkynes delivers ketones or enols.[39] Historically, such hydrations were conducted by oxymercuration or with large amounts of mineral acids[39,44] and alcohol solvents (often methanol), but both of these methods are incompatible with modern concepts of green chemistry.[40] A newer, more environmentally benign method takes advantage of gold salts as catalysts, mainly in methanol,[45–47] but other alcohol solvents have also been tested.[48]

A substantial number of KREDs are self-sustainable, as in addition to the synthetically interesting ketone they can accept auxiliary substrates for regeneration of the redox cofactor. Such a coupled substrate strategy[49] would allow the use of *i*PrOH, as a prominent example of an economically attractive co-substrate for a bioreduction step. Specifically, regarding the combination with another catalytic system, it is highly desirable to limit the number of enzymes involved, which contrasts conventional cofactor recycling systems that employ several biocatalysts. The large excess amount of the acidic reagent (in most cases sulfuric acid) that is often required for the hydration of unactivated alkynes is clearly critical as regards potential combination with a biocatalyst.

In 2015, for the first time Das et al. demonstrated a ligand-free and acid-free procedure for the synthesis of methyl ketones through the hydration of terminal alkynes by employing gold(I) chloride as a key catalyst.[48] The presented method generated the respective Markovnikov ketones without any acid promoters or additives. We slightly varied the published protocol with regard to biocompatibility by replacing MeOH with *i*PrOH (prospectively enabling subsequent cofactor recycling) and additionally by switching to gold(III) chloride as a slightly less-expensive catalyst. Thus, by performing the hydration of phenylacetylene in *i*PrOH by applying 5 mol% $AuCl_3$ as the catalyst at 65 °C, we were pleased to observe the formation of acetophenone in 98% yield, as determined by GC analysis, after 24 h within the first model reaction (Table 1, entry 1). This result matches the outcome of Das et al., who obtained the same yield in MeOH with the use of $Au^{I}Cl$ as the catalyst. We used this result as a starting point for subsequent investigation into a future sequential chemoenzymatic one-pot process, for which the biocatalyst would be added after the formation of the ketone. After selecting representative alkynes **1a**–**k** with varying substitution patterns, the respective hydration reactions were conducted. The modified hydration procedure gave moderate to excellent yields (49–99%, determined by GC analysis) of corresponding acetophenones **2a**–**k** (Table 1). Notably, for all cases that could be directly compared with the Das protocol (Table 1, entries 1, 2, 4, 6, and 8), the yields were the same within experimental error. Electron-withdrawing substituents led to decreased yields, which was particularly evident for substrates in which the strongly electron-withdrawing trifluoromethyl group was incorporated in the alkyne scaffold (Table 1, entries 10 and 11).

Table 1. Ketone synthesis.[a]



Entry	Substrate	$AuCl_3$ [mol%]	Product	Yield[b] [%]
1	**1a**	5	**2a**	98
2	**1b**	5	**2b**	98
3	**1c**	5	**2c**	99
4	**1d**	10	**2d**	71
5	**1e**	10	**2e**	86
6	**1f**	10	**2f**	72
7	**1g**	10	**2g**	76
8	**1h**	10	**2h**	70
9	**1i**	10	**2i**	79
10	**1j**	10	**2j**	49
11	**1k**	10	**2k**	57

[a] Reaction conditions: substrate (0.5 mmol), $AuCl_3$, H_2O (4 equiv.), *i*PrOH, 65 °C. [b] Measured by GC analysis after a reaction time of 24 h.

On the basis of these promising results for the metal-catalyzed step, we investigated the overall chemoenzymatic process by using phenylacetylene (**1a**) as a model substrate for alkyne hydration and the solvent-tolerant, NADH-dependent, and (*S*)-selective ADH-A (alcohol dehydrogenase A) from *Rhodococcus ruber* for the subsequent enzymatic reduction.[50] After conducting the Au-mediated hydration at 65 °C, the reac-

tion mixture was cooled to room temperature. Next, we directly supplemented the mixture of the hydration step (Table 1, entry 1) (30%, *v*/*v*) with 50 mg whole-cell lyophilisate of ADH-A resuspended in Tris-HCl buffer (350 mM, pH 8, 70%, *v*/*v*) at 30 °C without any other manipulation. To our delight, within this model reaction, the enzymatic step gave the product in 93% yield (determined by GC analysis), which resulted in an overall yield of 91% (determined by GC analysis) to (*S*)-phenylethanol (**3a**) with 99% *ee* over two steps. This finding indicated that the gold catalyst does not deactivate the (*S*)-selective ADH-A at the concentration used.

A high buffer concentration of 350 mM was required to neutralize HCl generated during the hydration to avoid any detrimental effect on the whole-cell biocatalyst.

To demonstrate the general applicability of the cascade transformation, we chose an enantiocomplementary enzyme with a largely overlapping substrate profile: the (*R*)-selective and NADPH-dependent KRED from *Lactobacillus kefir*.[51] Upon repeating the one-pot reaction by using 50 mg whole-cell lyophilisate of the KRED from *Lactobacillus kefir*, we observed a comparable yield of (*R*)-phenylethanol (**3a**) of 93% (determined by GC analysis) over two steps with >99% *ee* (Table 2, entry 1). Thus, neither the relatively high *i*PrOH content of 30% (*v*/*v*) nor the metal catalyst displayed any detrimental effect on the enzymatic reduction.

We aimed, in particular, to develop a simple and straightforward method that could be used in a facile fashion by researchers without a pronounced biocatalytic background; hence, we used both alcohol dehydrogenases as "easy-to-prepare" whole-cell lyophilisates.

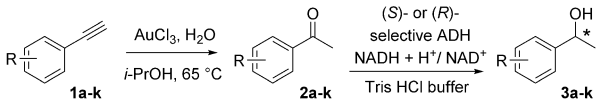
On the basis of the established conditions, we performed the enzymatic reduction of a substrate library (Table 2, entries 2–11) to generate both enantiodivergent alcohols **3b**–**k**. The yields of the cascade procedure, as determined by GC analysis, ranged from 49 to 99% for the (*S*)-selective ADH-A. Employing the (*R*)-selective KRED, yields up to 93% were achieved (Table 2). Both alcohol dehydrogenases delivered the respective secondary alcohols with excellent *ee* values. The KRED from *Lactobacillus kefir* was less efficient for *meta*-substituted aromatic ketone substrates, presumably as a result of the steric hindrance of the substituent, which impeded access to the active site of the enzyme (Table 2, entries 3, 7, 9, and 11).

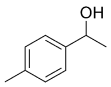
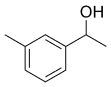
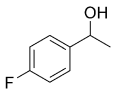
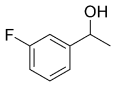
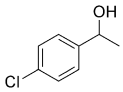
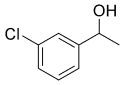
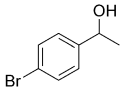
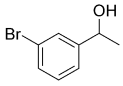
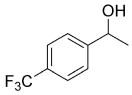
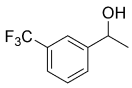
To demonstrate the synthetic utilization of the developed process, two preparative-scale experiments were conducted by using the (*S*)-selective ADH-A to generate alcohols (*S*)-**3d** and (*S*)-**3g**, which were isolated in yields of 71 (50 mg) and 64% (50 mg) respectively, both with an optical purity of >99% *ee*.

In summary, we presented a straightforward sequential chemoenzymatic one-pot process for the production of enantiopure (*S*)- and (*R*)-aryl alkyl alcohols. The complete reaction mixture from the metal-catalyzed step could be used in the subsequent enzymatic reduction without any spatial separation of the metal species and biocatalyst. Furthermore, we successfully designed a process that would be feasible for researchers from fields other than biocatalysis.

This was realized by applying *i*PrOH as a solvent for the Au^{III}-catalyzed hydration; it served as an auxiliary substrate for cofactor regeneration in the subsequent enzymatic reduction. After resuspension of the KRED-containing whole-cell lyophilisate, the catalyst could directly be added to the hydration re-

Table 2. Combination of alkyne hydration and subsequent enzymatic reduction by using the (*S*)-selective and NADH-dependent ADH-A from *Rhodococcus ruber* and the (*R*)-selective and NADPH-dependent KRED from *Lactobacillus kefir*.[a]



Entry	Product [(*S*)/(*R*)-alcohol]		Conversion[b] [%] (*S*)-Alcohol	Conversion[b] [%] (*R*)-Alcohol	*ee*[c] [%] [(*S*)/(*R*)-alcohol]
1	**3a**		91	93	>99
2	**3b**		76	73	>99
3	**3c**		99	15	>99
4	**3d**		71	65	>99
5	**3e**		86	74	>99
6	**3f**		71	69	>99
7	**3g**		76	29	>99
8	**3h**		67	67	>99
9	**3i**		53	17	>99
10	**3j**		49	49	>99
11	**3k**		57	0	>99[d]

[a] Reaction conditions: (*R*)- or (*S*)-selective KRED whole-cell lyophilisate (50 mg, 170 mg KRED whole-cell lyophilisate for preparative-scale experiments), 70% (*v*/*v*) Tris-HCl (350 mM, pH 8), 30% (*v*/*v*) hydration reaction mixture, 30 °C. [b] Measured by GC after a reaction time of 24 h. [c] Measured by chiral-phase GC (for **3a**–**d**, **3f**–**h**, and **3j**) or HPLC (for **3e**, **3i**, and **3k**). Absolute configurations were determined by measuring [(*S*)-**3d**, (*S*)-**3j**] or comparing with the values reported in the literature (see the Supporting Information). [d] (*S*)-Alcohol product only.

action mixture. Thereby, we produced both enantiomeric alcohols in high optical purity with yields up to 99% over two steps (as determined by GC analysis) in an economically attractive fashion that provided good functional group tolerance. This operationally simple procedure is atom economical owing to the application of *i*PrOH in the gold-catalyzed step, which is fully reused in the subsequent enzymatic reduction as an auxiliary substrate.

Experimental Section

Hydration of terminal alkynes

$AuCl_3$ (0.025–0.05 mmol) and *i*PrOH (1 mL) were charged into a screw-capped vial equipped with a magnetic stirring bar. The mixture was stirred for 5 min. Then, the alkyne (0.5 mmol, 1 equiv.) and H_2O (4 equiv.) were added. The resulting mixture was heated at 65 °C for 24 h. Upon completion of the reaction, a sample of the mixture was diluted with ethyl acetate containing methyl benzoate as an internal standard, and quantitative analysis was performed by GC.

Expression of alcohol dehydrogenases and whole-cell lyophilisate preparation

Preparation of lyophilized cells of *E. coli*BL21(DE3)/pET22 b(+) *adh-A* (from *Rhodococcus ruber*): *E. coli*BL21(DE3)/pET22b(+) *adh-A* (RHRU231 470141, corresponding to Q8KLT9) was stored at −80 °C in lysogeny broth containing ampicillin (LB-amp) containing 25% (*v*/*v*) glycerol. Prior to use, cells were plated on LB-amp plates (100 μg mL^{-1} final ampicillin concentration). A single colony was used to inoculate TB-amp (200 mL, 100 μg mL^{-1} final ampicillin concentration) in a 1 L baffled shake flask. $ZnCl_2$ was added from a 100 mM stock to a final concentration of 1 mM, and cells were grown at 30 °C with shaking (120 rpm) for approximately 20 h. On the next day, the optical density at $\lambda = 590$ nm (OD_{590}) was checked ($OD_{590} \approx 6.0$) and ampicillin (50 mg mL^{-1} stock, 200 μL) was added. Protein production was induced upon the addition of isopropyl-beta-D-thiogalactopyranoside (IPTG) from a 100 mM stock to a final concentration of 2 mM, and cells were cultivated at 20 °C with shaking (120 rpm) for 24 h. Cells were harvested by centrifugation (6000 × *g*, 15 min, 4 °C). The medium was discarded, and cells were resuspended in sterile water, snap frozen in liquid nitrogen, and lyophilized.

Preparation of lyophilized cells of *E. coli*BL21(DE3)/pET21 b(+) *LK-ADH* (from *Lactobacillus kefir*): *E. coli*BL21(DE3)/pET21b(+) *LK-ADH* (GenBank: AY267012.1) was stored at −80 °C in LB-amp containing 25% (*v*/*v*) glycerol. Prior to use, cells were plated on LB-amp plates (100 μg mL^{-1} final ampicillin concentration). A single colony was used to prepare 4 mL of an overnight culture in LB medium containing 100 μg mL^{-1} ampicillin (added from a 50 mg mL^{-1} stock). The main culture was prepared by inoculation of TB-amp (200 mL, 100 μg mL^{-1} final ampicillin concentration) in a 1 L baffled shake flask with 2 mL of the overnight culture. Cells were grown at 37 °C with shaking (120 rpm) to $OD_{590} = 0.5$. Enzyme expression was induced by the addition of IPTG (1 mM final concentration) from a 100 mM IPTG stock. Cells were cultivated at 30 °C with shaking (120 rpm) and were harvested by centrifugation (6000 × *g*, 15 min, 4 °C) after 24 h. The medium was discarded, and cells were resuspended in sterile water, snap frozen in liquid nitrogen, and lyophilized.

Chemoenzymatic one-pot reaction for the production of enantiopure alcohols 3 a–k

$AuCl_3$ (0.025–0.05 mmol, 5–10 mol%) and *i*PrOH (1 mL) were charged into a screw-capped vial equipped with a magnetic stirring bar. The mixture was stirred for 5 min, and then the starting material (0.5 mmol, 1 equiv.) and H_2O (4 equiv.) were added. The mixture was heated at 65 °C for 24 h. The reaction was monitored by GC–MS and was cooled to room temperature upon complete conversion.

Small-scale experiments

Then, the (*R*)- or (*S*)-selective alcohol dehydrogenase whole-cell lyophilisate (50 mg) was resuspended in 350 mM Tris-HCl buffer pH 8 (700 μL) in a separate vial and was shaken for 1 h at 30 °C and 200 rpm. Then, the hydration mixture (300 μL) was combined with the resuspended enzyme, which resulted in an overall *i*PrOH content of 30%. After 4 h, the chemoenzymatic one-pot reaction was complete, as monitored by GC–MS, and was extracted with EtOAc containing methyl benzoate as an internal standard, and the conversion was determined by GC or GC–MS.

Preparative-scale experiments

In the case of a preparative scale experiment, the (*R*)- or (*S*)-selective alcohol dehydrogenase whole-cell lyophilisate (170 mg) was resuspended in 350 mM Tris-HCl buffer pH 8 (2.333 mL) in a separate vial and was shaken for 1 h at 30 °C and 200 rpm. Then, the complete hydration mixture (1 mL) was combined with the resuspended enzyme. After 4 h, the chemoenzymatic one-pot reaction was complete, as monitored by GC–MS, and the overall mixture was extracted with CH_2Cl_2 (3 × 10 mL), washed with H_2O (2 × 10 mL), and dried (Na_2SO_4). The solvent was evaporated, and the product was purified by applying standard manual glass columns by using silica gel from Merck (40–63 μm) and CH_2Cl_2 (raw product/SiO_2 = 1:40). Within the preparative-scale experiments, (*S*)-**3 d** was isolated in 71% yield (50 mg) and (*S*)-**3 g** was insolated in 64% yield (50 mg).

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alcohols · alkynes · biocatalysis · enantioselectivity · enzymes

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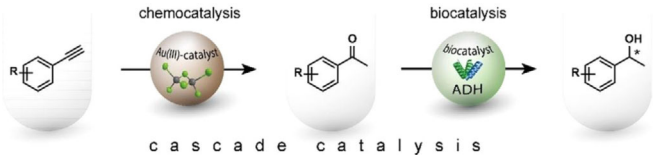
Easy Access to Enantiopure (*S*)- and (*R*)-Aryl Alkyl Alcohols by a Combination of Gold(III)-Catalyzed Alkyne Hydration and Enzymatic Reduction



What can gold not do? We present a sequential chemoenzymatic one-pot process for the production of chiral alcohols. The reaction mixture from the Au^{III}-catalyzed hydration step is used in the subsequent enzymatic reduction without separation of the metal species from the biocatalyst. *i*PrOH is used as the solvent and serves to regenerate the cofactor in the enzymatic reduction. Alcohols are obtained in high optical purity with yields up to 99% over two steps.