When Alcohol Dehydrogenases and N-Heterocyclic Carbene Gold(I) Catalysts Meet: Design of a Chemoenzymatic Cascade towards Optically Active β,β-Disubstituted Allylic Alcohols

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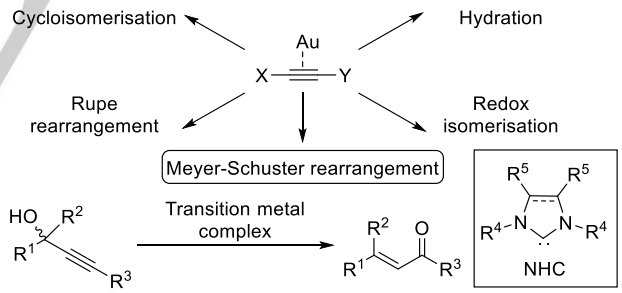
Supporting information (SI) for this article is given via a link at the end of the document.

Abstract: The combination of gold(I) and enzyme catalysis has been exhaustively analysed aiming to develop a two-step concurrent approach. This strategy consists of a Meyer-Schuster rearrangement of a series of easily available propargylic alcohols followed by the stereoselective bioreduction of the corresponding allylic ketone intermediates, providing optically pure β,β-disubstituted allylic alcohols. Thus, the first concurrent cascade example involving the use of a gold N-heterocyclic carbene and an enzyme is described, demonstrating the compatibility of both catalyst types in aqueous medium under very mild conditions. The combination of [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene][bis(trifluoromethanesulfonyl)-imide]gold(I) (IPrAuNTf$_2$) and a selective alcohol dehydrogenase (ADH-A from *Rhodococcus ruber*, KRED-P1-A12 or KRED-P3-G09), has allowed the synthesis of a series of optically active (*E*)-4-arylpent-3-en-2-ols in good isolated yields (65-86%). The chemoenzymatic approach was also successfully extended to various 2-hetarylpent-3-yn-2-ol, hexynol and butynol derivatives. Remarkably, the use of alcohol dehydrogenases of opposite selectivity has allowed the straightforward production of both allyl alcohol enantiomers (93->99% *ee*) for a broad panel of substrates bearing different substitutions in the aromatic ring.

Introduction

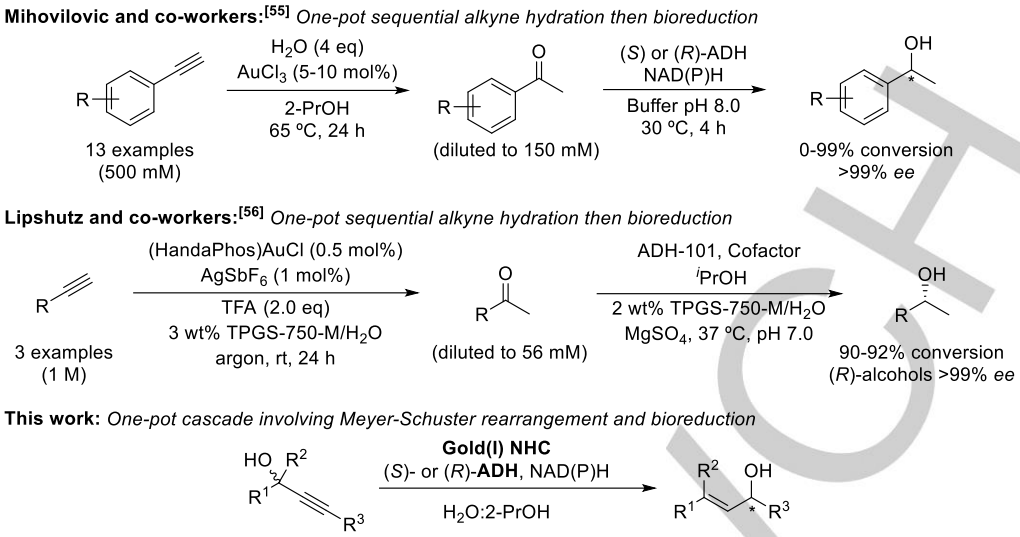
One-pot synthesis provides nowadays multiple advantages over traditional stepwise approaches, avoiding the isolation and purification of unstable intermediates, simplifying the reaction set-up, reducing time and costs associated with the chemical process, and generally leading to higher isolated yields.[1-4] Focusing on the field of Biocatalysis, apart from multienzymatic transformations,[5-10] one-pot chemoenzymatic syntheses represent elegant alternatives to traditional conventional organic multi-step strategies, combining biotransformations with other (un)catalysed processes.[11-14] Interestingly, the compatibility of organo-, photo- or metal-catalysts with enzymes has been intensively investigated in the last decade,[15-19] and many efforts have been put in the setup of environmentally friendly media where the different (bio)catalysts can be compatible, ranging from aqueous systems to neoteric solvents.[20,21]

Hence, the search for active metal complexes in aqueous medium is a consolidated synthetic possibility, since water soluble complexes made from gold, indium, iridium, nickel, palladium, ruthenium, rhodium, osmium or zinc among many others have been successfully applied in a plethora of organic reactions.[22-26] Considering that gold catalysis has emerged in the last decades as a powerful tool for chemical synthesis through the activation of unsaturated systems and formation of gold carbenes and vinylidenes,[27-36] herein it was envisaged the possible combination of gold complexes and enzymes. With that purpose and due to the large π-acidic character of Au complexes, the selection of alkynes as benchmark substrates flourish as a wise choice based on the diverse chemical possibilities of this pair Au-alkyne.[37-41] Interestingly, a broad number of organic transformations can be successfully accomplished such as cyclisation, hydration, redox isomerisation or rearrangements such as the Rupe or Meyer-Schuster ones (Scheme 1),[42-46] gold N-heterocyclic carbenes (NHCs) playing a relevant role in the catalysis of these type of chemical processes.[47-49]



Scheme 1. Activation of alkynes with gold for the development of diverse chemical transformations including Meyer-Schuster rearrangements. General structure of N-heterocyclic carbenes appears in the box.

The Meyer-Schuster rearrangement consists in the transformation of propargylic (acetylated) alcohols into the corresponding α,β-unsaturated carbonyl compounds, requiring metal catalysis (Cu, Sc, Hg, Ag, Au, In...) and traditionally performed under harsh reaction conditions (organic solvent, acidic catalysis, high temperature...).[42,46,50] This is a highly atom economy process occurring via formal 1,3-hydroxyl shift and tautomerisation, that has attracted great attention in the last decades questing for more sustainable solutions. Therefore, a key point of this study is the replacement of conventional organic solvents by aqueous media, making the process compatible with a second enzymatic reaction, foreseeing the use of NHC gold(I) complexes as a solution for the performance of this selective transformation under milder reaction conditions.



Scheme 2. One-pot combinations of gold catalysis involving hydration or Meyer-Schuster rearrangement of alkynes and an alcohol dehydrogenase-catalysed bioreduction for the production of chiral alcohols.

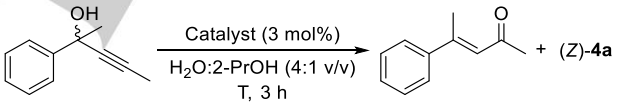
Particularly, the gold-enzyme pair has been successfully applied in a concurrent cascade fashion combining gold(I) or gold(III) species with hydrolases[51,52] and monoamine oxidases.[53] Among them, the only stereoselective application was demonstrated by Asikainen and Krause, who reported the synthesis of optically active 2,5-dihydrofurans through a tandem hydrolytic kinetic resolution/cycloisomerisation employing *Pseudomonas cepacia* lipase and $HAuCl_4$.[51] On the other hand, approaches involving gold catalysis and alcohol dehydrogenases (ADHs) have also been described, but through sequential transformations due to the incompatibility of individual catalytic systems and reaction conditions.[54-56] In this context, the one-pot two-step synthesis of chiral *sec*-alcohol derivatives in high conversions and enantiomeric excess was described via gold-catalysed hydration of terminal aryl- or alkyl acetylenes using either gold(III) chloride at 65 ºC in a water/2-propanol (2-PrOH) mixture,[55] or HandaPhos-gold(I) chloride, a silver salt and a surfactant in water that formed micelles under argon atmosphere,[56] both followed by the ketone intermediate bioreduction with external addition of the corresponding ADH and auxiliary reagents (Scheme 2, top).

Encouraged by the synthetic possibilities that α,β-unsaturated ketones offer, and considering the great applicability of the Meyer-Schuster rearrangement,[42,46,50] herein we propose the development of a concurrent cascade process to get access to a series of enantioenriched β,β-disubstituted allylic alcohols, by combining an active NHC gold(I) catalyst in aqueous medium with alcohol dehydrogenases (ADHs) of opposite selectivity (Scheme 2, bottom), by considering 2-propanol as a key element due to its compatibility with NHC gold complexes and simultaneous key role in the enzyme cofactor recycling action.

Results and discussion

As a starting point, the (racemic) propargylic alcohols **3a-x** were synthesised in 59-92% yield from commercially available carbonyl compounds **1** and the corresponding Grignard or organolithium reagent (**2**, see Section III in SI). Then, 2-phenylpent-3-yn-2-ol (**3a**) was selected as benchmark substrate for the study and optimisation of the Meyer-Schuster rearrangement to explore the influence of the gold catalyst type and the reaction temperature in a medium composed of a mixture of water and 2-propanol.

Table 1. Meyer-Schuster rearrangement optimisation (catalyst and temperature).



3a (100 mM) (*E*)-**4a**

Entry	Catalyst	T (ºC)	(*E*)-ketone **4a** (%)[a]	(*Z*)-ketone **4a** (%)[a]
1	IPrAuNTf2	30	85	15
2	JhonPhosAuNTf2	30	75	25
3	IPrAuNTf2	20	80	20
4	IPrAuNTf2	25	80	20
5	IPrAuNTf2	40	87	13
6	IPrAuNTf2	45	94	6

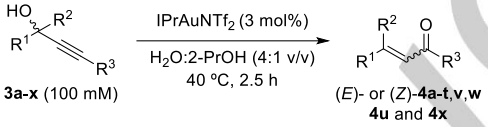
[a] Percentage of products measured by GC analyses of the reaction crudes. See the SI for detailed reaction conditions and GC methods. Complete conversions were attained in all cases.

Hence, two commercially available gold(I) catalysts were initially tested (3 mol%, Table 1) containing the bis(trifluoromethanesulfonyl)imidate moiety (NTf_2^-) as a weakly coordinating counteranion (entries 1 and 2). These are [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] [bis(trifluoromethanesulfonyl)imide]gold(I) (IPrAuNTf2) and (2-di-*tert*-butylphosphinobiphenyl)gold(I) [bis(trifluoromethanesulfonyl)imide] (JhonPhosAuNTf2).[49] The reactions were carried out in a water:2-propanol (4:1 v/v) mixture, which would increase the solubility of the substrate and the gold catalyst in the reaction medium, and at the same would facilitate the use of an ADH in a concurrent manner since 2-propanol is

commonly used as hydrogen donor for ADH-catalysed bioreduction processes.[57] Satisfyingly, complete conversions were attained in both cases after 3 h, finding a higher selectivity for the IPrAuNTf$_2$ catalyst (85:15, *E vs Z*). At this point, different temperatures were studied leading at 45 ºC to the best selectivity towards (*E*)-allylic alcohol **4a** (94:6, entry 6). Higher temperatures were not tested due to the potential enzyme deactivation using harsher conditions. Bearing in mind this fact, 40 ºC was selected as upper limiting conditions, and the Meyer-Schuster rearrangement reaction was next studied with the previously synthesised propargylic alcohols **3a**-**x**.

For the substrate scope, three molecular engineering vectors were selected (R^1, R^2 and R^3, Scheme of Table 2) including 2-(het)arylpent-3-yn-2-ols (**3a**-**q**), hexynols **3r**,**t**,**v** and butynols **3s**,**u**,**w**,**x** bearing different pattern substitutions for a total of 24 substrates. Complete conversions were achieved in all cases, resulting in a highly selective strategy for most of the substrates under these conditions, 14 out of 22 (*E*)-allylic alcohols **4a**-**f**,**j**,**k**,**m**,**n**,**p**-**s** being obtained with over 85% conversion (Table 2).

Table 2. Meyer-Schuster rearrangement of (racemic) propargylic alcohols **3a**-**x**.



3a-x (100 mM) (*E*)- or (*Z*)-**4a-t**,**v**,**w** **4u** and **4x**

Entry	Alcohol **3a**-**x**	R^1	R^2	R^3	(*E*)-**4a**-**x** (%)[a]	(*Z*)-**4a**-**x** (%)[a]
1	**a**	Ph	CH_3	CH_3	87	13
2	**b**	4-F-C_6H_4	CH_3	CH_3	90	10
3	**c**	4-Cl-C_6H_4	CH_3	CH_3	86	14
4	**d**	4-Br-C_6H_4	CH_3	CH_3	85	15
5	**e**	3-F-C_6H_4	CH_3	CH_3	91	9
6	**f**	2-F-C_6H_4	CH_3	CH_3	90	10
7	**g**	2-Br-C_6H_4	CH_3	CH_3	59	41
8	**h**	4-CH_3-C_6H_4	CH_3	CH_3	55	45
9	**i**	4-OCH_3-C_6H_4	CH_3	CH_3	43	57
10	**j**	4-NO_2-C_6H_4	CH_3	CH_3	96	4
11	**k**	3-NO_2-C_6H_4	CH_3	CH_3	94	6
12	**l**	2-NO_2-C_6H_4	CH_3	CH_3	10	90
13	**m**	4-CF_3-C_6H_4	CH_3	CH_3	92	8
14	**n**	3-CF_3-C_6H_4	CH_3	CH_3	89	11
15	**o**	2-OCH_3-C_6H_4	CH_3	CH_3	58	42
16	**p**	2-thienyl	CH_3	CH_3	>97	<3
17	**q**	3-thienyl	CH_3	CH_3	86	14
18	**r**	^{t}Bu	CH_3	CH_3	96	4
19	**s**	Ph	H	CH_3	>97	<3
20	**t**	Ph	CH_3CH_2	CH_3	54	46
21	**u**	Ph	Ph	CH_3	>97[b]	
22	**v**	Ph	CH_3	CH_3CH_2	57	43
23	**w**	Ph	CH_3	Ph	29	71
24	**x**	CH_3	CH_3	Ph	>97[b]	

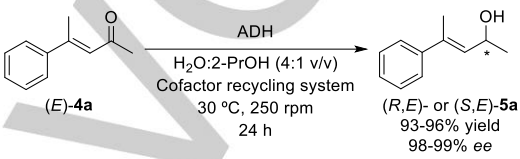
[a] Percentage of products measured by ^{1}H NMR analyses of the reaction crudes. See the SI for detailed reaction conditions. Complete conversions to ketones **4a**-**x** were attained in all cases. [b] Not applicable the *E*/*Z* isomerism.

In general, good results were found with 2-arylpent-3-yn-2-ols **3a**-**o**, only attaining poor selectivities for substrates bearing electron-donating substitutions at the *para* position (methyl and methoxy, entries 8 and 9), or electron-donating and electron-withdrawing groups at the *ortho*-position (entries 7 and 15), highlighting the preference change when the nitro functionality at the *ortho*-position was subjected to investigation (10:90 *E* vs *Z*, entry 12). Trying to expand the possibilities of our methodology, 2-hetarylpent-3-yn-2-ols were considered, for instance containing a thienyl moiety at C-2 or C-3 (**3p** and **3q**), and good selectivities were found (entries 16 and 17), being especially noticeable the exclusive formation of (*E*)-4-(thiophen-2-yl)pent-3-en-2-one (**4p**). Next, the reaction was performed with the propargylic alcohol bearing a furyl group substituted at C-2 position, but a complex mixture was found. This is in accordance with the already described reactivity of furan derivatives in combination with gold catalysis, occurring e.g., furan-alkyne intramolecular cyclisations or other rearrangements.[58] At this point, the use of pyridine derivatives was omitted since it is well known that the basic nitrogen atom coordinates to the gold catalyst leading to a dramatic loss of the metal activity,[59] requiring therefore higher reaction temperatures[60] that on the other hand would not be compatible with a second enzymatic reaction.

This strategy was also applicable when developing the rearrangement over the aliphatic derivative **3r** (R^1= ^{t}Bu) with very high preference towards the recovery of (*E*)-4,5,5-trimethylhex-3-en-2-one (96:4 *E*/Z, entry 18). Next, the influence of the substitution at the carbon bearing the hydroxyl functionality was studied, in comparison with our model substrate (R^2= CH_3, **3a**, entry 1), and 3 different substitutions (R^2= H, Et, or Ph, **3s**-**u**) were also considered, obtaining ketones **4s**-**u** with complete conversion, although a significant decrease of the *E*/*Z* selectivity was observed when moving from the formation of the less bulky substrate (*E*)-**4s** (R^2= H, >97%, entry 19) to the ones bearing aliphatic moieties **4a** (R^2= Me, 87%) and **4t** (R^2= Et, 54%) of the *E*-isomer (entries 1 and 20). Obviously, for 4,4-diphenylbut-3-en-2-one (**4u**, entry 21), *E*/*Z* isomerism was not applicable.

The replacement of the methyl substitution at the terminal alkyne position by an ethyl or a phenyl group (R^3= Et or Ph, entries 22 and 23) was also considered, achieving also a complete transformation into ketones **4v** and **4w**, but observing a decrease or even an inversion of the *E*/*Z* selectivity when enlarging the size of the terminal substitution, favoring the formation of the (*Z*)-ketones (43 and 71%, entries 22 and 23), in contrast to the preferred formation of (*E*)-**4a** (entry 1, only 13% of the *Z* isomer). Finally, maintaining the terminal aromatic ring but replacing the phenyl ring by a methyl group at the R^1 substitution, 3-methyl-1-phenylbut-2-en-1-one (**4x**, entry 24) was also obtained in full conversion. Overall, a very general methodology was developed for the straightforward synthesis of allylic ketones from propargylic alcohols in aqueous medium, and next all the efforts were focused on the accomplishment of a bioreduction process under similar reaction conditions.

Before exploring the possible compatibility of $IPrAuNTf_2$ and ADHs under certain conditions, the bioreduction of (*E*)-4-phenylpent-3-en-2-one (**4a**) was screened using a series of ADHs. Among them, some ketoreductases were made in house and overexpressed in *E. coli*, while others were purchased from commercially available sources (Evoxx Technologies GmbH and Codexis Inc). Thus, a wide biocatalyst screening is disclosed in Table S2 of the SI, some of them providing enantioenriched allylic alcohol (*E*)-**5a** with above 90% conversion and enantiomeric excess (Scheme 3). Ten ADHs allowed the synthesis of the alcohol (*R*)-**5a** (93-96% conversion and 98-99% *ee*), while only two Prelog enzymes led to its (*S*)-**5a** antipode (94-96% conversion and 98-99% *ee*). Satisfyingly, complementary stereoselective overexpressed ADHs on *E. coli* such as the one from *Rhodococcus ruber* (ADH-A)[61,62] and the one from *Lactobacillus brevis* (LBADH)[63,64] were found, and also various commercially available enzymes from the Codexis Inc. kit. Absolute configurations were assigned based on the known selectivity of the overexpressed ADHs on *E. coli* and confirmed by comparing the measured specific optical rotations with those previously described in the literature, such as the allylic alcohol (*S*,*E*)-**5a**.[65,66]



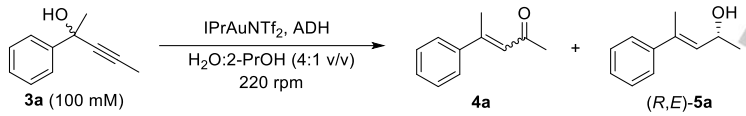
Scheme 3. Screening of ADHs for the bioreduction of ketone (*E*)-**4a** for the synthesis of (*E*)-**5a** alcohol enantiomers depending on the ADH of choice.

The coupling of gold species and biocatalysts is still in its infancy,[51-56] and as mentioned before only sequential attempts have been reported when considering ADHs,[54-56] mainly caused due to the high temperatures required by gold(I) and gold(III) catalysts in aqueous media. For that reason, the search for adequate reaction conditions with model substrate **3a** (100 mM) was next chased, selecting the overexpressed LBADH on *E. coli* and commercial KRED-P1-A12 for the design of an efficient concurrent cascade approach. An exhaustive analysis can be found in the SI (Table S8), displaying the influence of experimental parameters that affect to the gold and ADH catalysts reactivity, including different loading of $IPrAuNTf_2$ and enzyme, the use of additives, different temperatures and reaction times. Among these data, a few experiments are highlighted in Table 3.

Reactions were carried out in an orbital shaker at 220 rpm since the use of higher speeding rates usually led to a conversion decrease as the reactants spilled around the glass vial. Over 60% conversion for the global process was reached when using lyophilised cells of *E. coli*/LBADH (2:1 w/w enzyme:substrate) at 30 and 40 ºC during 24 and 72 h, respectively (entries 1 and 2) without significant increasing the reaction yield at prolonged reaction times. It must be highlighted that in this case, the use of higher loadings of $IPrAuNTf_2$ catalyst (10 mol%) was required to obtain the mentioned conversion levels. The reaction was also studied with the commercial KRED-P1-A12 (entries 3-8), that provided higher conversions and very high selectivities towards (*R*,*E*)-**5a** (>96% *ee*). Remarkably, the use of lower $IPrAuNTf_2$ loadings resulted in an efficient transformation at 7.5 mol% ratio, isolating the desired enantiopure allylic alcohol in 78% yield after column chromatography purification (entry 8).

At this point, the extension of the cascade approach to 18 propargylic alcohols **3** was undertaken to get access to both (*R*)- and (*S*)-allylic alcohol enantiomers **5** (Table S9 in SI and Figure 1).

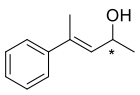
Table 3. Optimisation of the Meyer-Schuster rearrangement and bioreduction concurrent cascade for the production of allylic alcohol (*R*,*E*)-**5a**.



3a (100 mM) **4a** (*R*,*E*)-**5a**

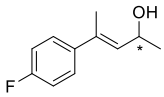
Entry	ADH[a]	IPrAuNTf$_2$ (mol%)	T (ºC)	t (h)	Alcohol **3a** (%)[b]	Ketone **4a** (%)[b]	Alcohol (*E*)-**5a** (%)[b]	(*E*)-**5a** *ee* (%)[c]
1	*E. coli*/LBADH (46)	10	40	72	35	23	42	n.d.
2	*E. coli*/LBADH (46)	10	30	24	38	18	44	94
3	KRED-P1-A12 (22)	10	30	72	<1	14	86	98
4	KRED-P1-A12 (22)	5	30	24	7	25	68	97
5	KRED-P1-A12 (16)	7.5	30	24	<1	15	85	98
6	KRED-P1-A12 (16)	10	30	24	<1	15	85	98
7	KRED-P1-A12 (8)	10	30	24	<1	20	80	97
8	KRED-P1-A12 (22)	7.5	40	24	<1	15	85 (78)	99

[a] Amount of ADH in mg for 0.1 mmol of racemic substrate **3a**. [b] Percentage of products was measured by GC analyses. Isolated yield after liquid-liquid extraction and column chromatography purification on silica gel appears in parentheses. See the SI for additional analytical and experimental details. [c] Enantiomeric excess values of (*R*,*E*)-**5a** were measured by GC analyses.



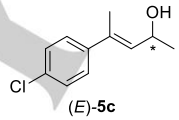
(*E*)-**5a**

KRED-P1-A12: 78% yield, 99% *ee* (*R*)
KRED-P3-G09: 70% yield, 99% *ee* (*S*)
***E. coli*/ADH-A:**[a] 51% yield, 97% *ee* (*S*)



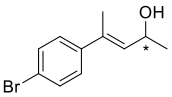
(*E*)-**5b**

KRED-P1-A12: 74% yield, 99% *ee* (*R*)
KRED-P3-G09: 70% yield, >99% *ee* (*S*)
***E. coli*/ADH-A:**[a] 58% yield, 99% *ee* (*S*)



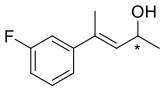
(*E*)-**5c**

KRED-P1-A12: 73% yield, >99% *ee* (*R*)
KRED-P3-G09: 65% yield, >99% *ee* (*S*)
***E. coli*/ADH-A:**[a] 62% yield, >99% *ee* (*S*)



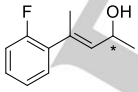
(*E*)-**5d**

KRED-P1-A12: 71% yield, >99% *ee* (*R*)
KRED-P3-G09: 70% yield, 99% *ee* (*S*)
***E. coli*/ADH-A:**[a] 61% yield, 99% *ee* (*S*)



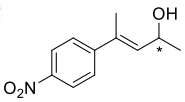
(*E*)-**5e**

KRED-P1-A12: 80% yield, 99% *ee* (*R*)
KRED-P3-G09: 78% yield, 99% *ee* (*S*)
***E. coli*/ADH-A:**[a] 76% yield, >99% *ee* (*S*)



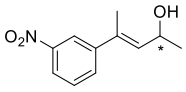
(*E*)-**5f**

KRED-P1-A12: 77% yield, >99% *ee* (*R*)
KRED-P3-G09: 38% yield, 99% *ee* (*S*)
***E. coli*/ADH-A:**[a] 76% yield, 98% *ee* (*S*)



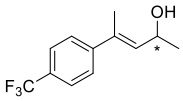
(*E*)-**5j**

KRED-P1-A12:[b] 70% yield, >99% *ee* (*R*)
KRED-P3-G09: 80% yield, >99% *ee* (*S*)
***E. coli*/ADH-A:**[a] 68% yield, >99% *ee* (*S*)



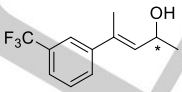
(*E*)-**5k**

KRED-P1-A12:[b] 86% yield >99% *ee* (*R*)
KRED-P3-G09: 72% yield, >99% *ee* (*S*)
***E. coli*/ADH-A:**[a] 78% yield, >99% *ee* (*S*)



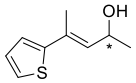
(*E*)-**5m**

KRED-P1-A12:[b] 76% yield, >99% *ee* (*R*)
KRED-P3-G09: 72% yield, >99% *ee* (*S*)
***E. coli*/ADH-A:**[a] 78% yield, >99% *ee* (*S*)



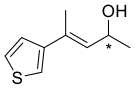
(*E*)-**5n**

KRED-P1-A12:[b] 78% yield, >99% *ee* (*R*)
KRED-P3-G09: 61% yield, >99% *ee* (*S*)
***E. coli*/ADH-A:**[a] 78% yield, >99% *ee* (*S*)



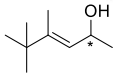
(*E*)-**5p**

***E. coli*/LBADH:**[a,c] 74% yield, >99% *ee* (*R*)
***E. coli*/ADH-A:**[a,c] 69% yield, >99% *ee* (*S*)



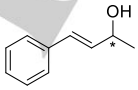
(*E*)-**5q**

***E. coli*/LBADH:**[a,c] 73% yield, 99% *ee* (*R*)
***E. coli*/ADH-A:**[a,c] 37% yield, 99% *ee* (*S*)



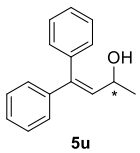
(*E*)-**5r**

KRED-P3-H12: 48% yield, 98% *ee* (*R*)
KRED-P2-H07: 43% yield, 99% *ee* (*S*)
***E. coli*/LBADH:**[a] 47% yield, >99% *ee* (*R*)
***E. coli*/ADH-A:**[a] 49% yield, >99% *ee* (*S*)



(*E*)-**5s**

KRED-P2-G03: 69% yield, 98% *ee* (*R*)
KRED-P3-G09: 62% yield, 93% *ee* (*S*)
***E. coli*/LBADH:**[a] 60% yield, 99% *ee* (*R*)
***E. coli*/ADH-A:**[a] 63% yield, 94% *ee* (*S*)



5u

KRED-P1-B02:[c] 82% yield, 98% *ee* (*R*)
***E. coli*/ADH-A:**[a,c] 80% yield, >99% *ee* (*S*)

[a] Sequential approach

[b] A H_2O:2-PrOH:MeCN (4:1:1 v/v) mixture was used

[c] Reactions times of 48 h instead of 24 h were considered

Figure 1. Summary of the best results obtained in terms of isolated yield and optical purity for the production of a series of allylic alcohols through a one-pot Meyer-Schuster rearrangement and bioreduction concurrent cascade using a commercial ADH or in a sequential approach when employing *E. coli*/ADH-A or *E. coli*/LBADH.

Compounds bearing bromo, nitro or methoxy substitutions at the *ortho*-position of the aromatic ring at the R^1 position (**3g**, **3l** and **3o**), an ethyl group at R^2 (**3t**), or the ones bearing an ethyl or phenyl rest at the terminal alkyne position (**3v** and **3w**) were omitted from the cascade reaction scope due to the low selectivities achieved for the production of the corresponding ketones (*E*)-**4** (41-46% *Z*-**4g**,**o**,**t**,**v**), or the preferred formation of the (*Z*)-isomers (10:90 and 29:71, **4l** and **4w**). It is important to remark that (*Z*)-allylic ketones **4** are not converted by the tested ADHs. In spite of the almost negligible selectivity achieved in the Meyer-Schuster rearrangement for compounds substituted with electron donating groups such as 4-methyl (**h**, 55:45) and 4-methoxy (**i**, 43:57), these were considered in the study to broaden the scope of the presented cascade methodology. Unfortunately, low conversions into the allylic alcohols (<25%, Table S9 in SI) were observed.

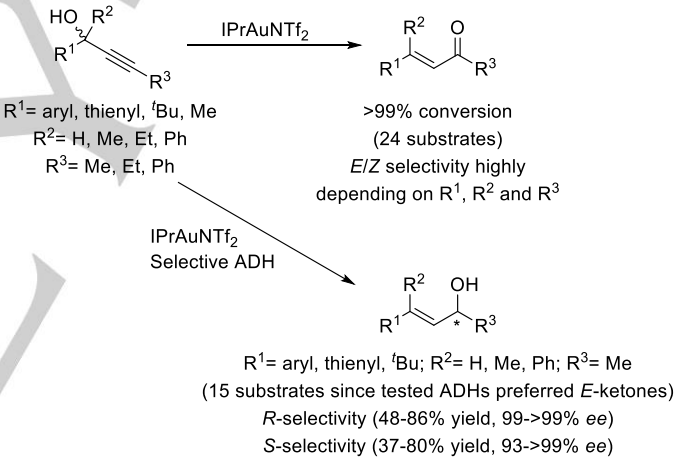
Overall, the Au(I)-ADH chemoenzymatic strategy resulted feasible in a concurrent manner using commercial ketoreductases, especially KRED-P1-A12 and KRED-P3-G09 for the synthesis of 2-arylpent-3-yn-2-ols, while better results in terms of activity were found through a sequential approach when employing enzymes overexpressed in *E. coli*. For instance, ADH-A was found as a suitable biocatalyst for the synthesis of alcohols (*S*,*E*)-**5a**-**f**,**j**,**k**,**m**,**n**,**p**-**s** and (*S*)-**5u** requiring the addition of the metal catalyst in two portions along the process. Both sequential and cascade approaches provided the desired alcohols in very high to excellent optical purities (93->99% *ee*), compounds that were recovered in moderate to high isolated yields (up to 86% for the (*R*)-alcohols and up to 80% for the (*S*)-alcohols), obtaining lower yields for alcohol **5r** due to the high volatility of this aliphatic substrate. The reaction resulted unsuccessful for the synthesis of alcohol **5x** due to the spontaneous 1,3-rearrangement of the final product in aqueous medium[67] forming the achiral (*E*)-2-methyl-4-phenylbut-3-en-2-ol and therefore hampering the development of a stereoselective process. In fact, when the chemically synthesised racemic **5x** was incubated in the bioreduction medium without enzyme, the isomerization reaction occurred.

Finally, to demonstrate the practical applicability of both concurrent and sequential approaches, the reaction with racemic 2-(3-fluorophenyl)pent-3-yn-2-ol (**3e**) was scaled-up to 100 mg using KRED-P1-A12 or *E. coli*/ADH-A, yielding (*R*,*E*)- and (*S*,*E*)-**5f** enantiomers, respectively, with excellent conversions (84-85%) and isolated yields (78-79%, Table S10 in SI).

Conclusions

A novel chemoenzymatic cascade is described for the stereoselective synthesis of a series of β,β-disubstituted allylic alcohols, compounds which are not easily accessible by other chemical means, and that have been used as precursors of, e.g. aroma compounds.[65] Initially, both (*E*)-4-(het)arylpent-3-en-2-ol enantiomers were synthesised by properly combining the action of a gold(I) N-heterocyclic carbene complex and a stereoselective alcohol dehydrogenase in aqueous medium, using 2-propanol to improve the substrate solubility and acting as hydrogen donor in the bioreduction process. In general, high selectivities were achieved in the Meyer-Schuster rearrangement to fully transform 2-(het)arylpent-3-yn-2-ols into the corresponding (*E*)-4-(het)arylpent-3-en-2-ones using $IPrAuNTf_2$ at 40 ºC, conditions that were compatible with the use of made in house overexpressed and commercial ketoreductases. Depending on the enzyme of choice, the desired optically active allylic alcohols (96->99% *ee*) were obtained in good to high isolated yields (65-86%). The cascade reaction was successfully achieved in a concurrent mode with the commercial enzymes and worked better through a sequential approach for the overexpressed enzymes.

Satisfyingly, the synthetic possibilities of the Meyer-Schuster rearrangement and the metal-enzyme combination were extended by considering various molecular engineering vectors at both sides of the triple carbon-carbon bond as depicted in Scheme 4, including hexynol and butynol derivatives, thus replacing for instance the (het)aromatic ring by aliphatic chains (methyl or *tert*-butyl) at R^1, considering different substitutions at the carbon directed linked to the hydroxyl group of the propargylic alcohol (hydrogen, methyl, ethyl or phenyl) or even with different moieties at the terminal alkyne position (methyl, ethyl or phenyl). In addition, a semi-preparative transformation was successfully accomplished using racemic 2-(3-fluorophenyl)pent-3-yn-2-ol (100 mg) as starting material. Overall, we believe that this first example of a concurrent cascade combining NHC gold(I) species and enzymes under mild conditions can be envisaged as a powerful tool to get access to highly valuable molecules through complementary and selective catalyst reactivities.



Scheme 4. Overall representation of the Meyer-Schuster rearrangement and bioreduction cascade strategy including their substrate scope.

Acknowledgements

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Keywords: Alcohol dehydrogenases • Cascade reactions • Gold catalysis • Meyer-Schuster rearrangement • Stereoselective synthesis

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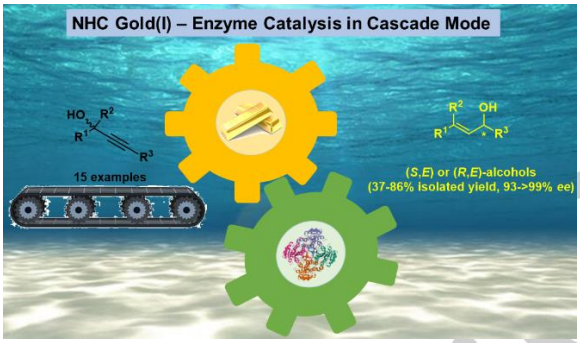

A concurrent process involving a golden N-heterocyclic carbene ($IPrAuNTf_2$) and an enzyme (alcohol dehydrogenase) has been described for the first time. This cascade approach has allowed the development of a Meyer-Schuster rearrangement for the transformation of racemic propargylic alcohols, mostly with good selectivities towards the corresponding (*E*)-allylic ketone intermediates in aqueous medium, which were subsequently reduced to obtain the desired alcohol enantiomers with excellent optical purities.