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Advanced Synthesis & Catalysis

β,β-Disubstituted Alkan-2-ones from Propargylic Alcohols Combining a Meyer-Schuster Rearrangement and Asymmetric Alkene Bioreduction

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Abstract: The combination of a gold(I) N-heterocyclic carbene complex and an ene-reductase (ERED) has made possible the synthesis of enantiopure β,β-disubstituted ketones in a one-pot concurrent approach. The protocol consists of the Meyer-Schuster rearrangement of racemic propargylic tertiary alcohols using [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]-[bis(trifluoromethanesulfonyl)-imide]gold(I) ($IPrAuNTf_2$), followed by an asymmetric alkene reduction of the α,β-unsaturated ketone intermediate using the *Zymomonas mobilis* ERED (NCR-ERED). The chemoenzymatic cascade was optimised with a model substrate, where *E*/*Z*-isomers both generated the (*R*)-ketone, which was rationalised using *in silico* molecular docking experiments. The cascade was then applied towards the production of a series of (*R*)-4-substituted-alkan-2-ones in enantiopure form in a straightforward manner.

Keywords: Alkene bioreduction; Chemoenzymatic cascades; Ene-reductase; Gold catalysis; Meyer-Schuster rearrangement

Introduction

Several enzyme families have demonstrated their versatility in synthetic chemistry due to their high levels of activity and selectivity for a myriad of organic transformations.[1] In addition to the use of biocatalysts for single transformations, the possibility to work with other catalysts is now well-established. In this context, the use of multienzymatic systems can be valuable, but this requires the compatibility of different enzyme (sub)classes under similar reaction conditions.[2] There has also been a rapid growth in the area of merging biocatalysis with other types of catalysis, such as metal-, organo-, photo and electrocatalysis for developing cascade reactions.[3] From a synthetic point of view, transition metals offer multiple possibilities for enhancing organic transformations including C–C bond formation, and their combination with enzymes is possible due to the adaptation of these two catalytic methods to work together productively.[4]

Gold chemistry is an established method for the activation of unsaturated systems, such as the transformation of alkynes into valuable synthetic intermediates through cyclisation, hydration, isomerisation or carbon-carbon bond rearrangement under mild conditions.[5] The combination of gold- and enzyme-

catalysed transformations has notably been achieved using hydrolases, such as lipases and esterases,[6] monoamine oxidases,[7] alcohol dehydrogenases (ADHs),[8] amine dehydrogenases,[9] transaminases[10] and aldolases.[11] We envisioned exploring a combination of gold catalysis with ene-reductases (EREDs), that are biocatalysts able to catalyse the asymmetric reduction of alkenes bearing electron-withdrawing groups (acid, ester/lactone, aldehyde, ketone, nitro and nitrile).[12] In particular, the development of a Meyer-Schuster rearrangement of a racemic propargylic alcohol followed by a stereoselective alkene reduction of the corresponding α,β-unsaturated ketone intermediate. This combination has no precedent in the literature, although there are scarce examples accounting for the combination of EREDs with metals, such as palladium and rhodium complexes.[13] However, all of these approaches have been reported in a sequential manner, as well as the use of light irradiation allowing the discovery of novel reactivities of these flavoproteins.[14]

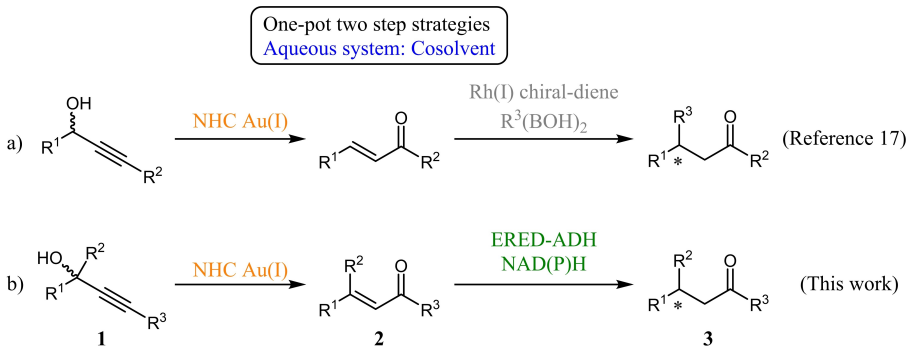
One century ago, the Meyer-Schuster rearrangement of propargylic alcohols was described for the first time,[15] involving a 1,3-shift of the hydroxyl group in the presence of a Brønsted or Lewis acid, and furnishing the corresponding α,β-unsaturated carbonyl compounds. The high atom economy and selectivity of this reaction, together with the synthetic potential of the enal and enone products, motivated interest in this approach.[16] In this context, the use of transition-metal catalysts has gained considerable attention, with gold chemistry as an ideal method due to its ability to activate π-systems. For instance, the combination of catalytic strategies to transform racemic propargylic secondary alcohols to β,β-disubstituted ketones has been previously described by studying the compatibility of two metal complexes of gold and rhodium.[17] To achieve this, an N-heterocyclic carbene Au(I) complex $IPrAuNTf_2$ efficiently catalysed the Meyer-Schuster rearrangement at room temperature, while a chiral diene ligand bound to Rh(I) facilitated the boronic acid 1,4-addition to access the desired saturated ketones at 50 °C (Scheme 1A). Inspired by this work, and due to the difficulty in accessing these types of compounds in a stereoselective manner, we hypothesised about the synergistic combination of gold(I) species to promote the Meyer-Schuster rearrangement of a racemic tertiary propargylic alcohol, and the use of EREDs to catalyse the asymmetric reduction of the C=C double bond. Encouraged by the excellent results obtained in the combination of gold NHCs with ADHs,[8d,e] the design of a one-pot concurrent approach starting from propargylic alcohols **1** followed by a chemoselective reduction of the enone intermediates **2** was envisioned (Scheme 1B).

Results and Discussion

EREDs have been used for applications in the industrial sector, participating in highly chemo-, regio- and/or enantioselective transformations, enabling the formation of up to two stereogenic centres.[18] The presence of electron-withdrawing groups directly linked to the olefin, is essential to achieve high levels of activity. Among these redox catalysts, a nicotinamide-dependent reductase from *Zymomonas mobilis* (NCR-ERED), a member of the Old Yellow Enzyme (OYE) class I EREDs,[19] was selected for this study to potentially combine with [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]-[bis(trifluoromethanesulfonyl)-imide]gold(I) ($IPrAuNTf_2$)[20] under cascade conditions.

Bioreduction Studies

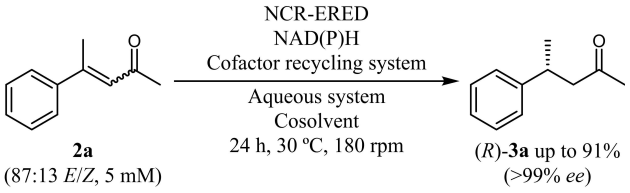
For these redox enzymes, there is a requirement for efficient nicotinamide cofactor regeneration, such as coupling a glucose/glucose dehydrogenase-based system,[21] or alternatively the use of an ADH such as the one from *Thermanaerobacter ethanolicus* (*Te*SADH)[22] with isopropanol (2-PrOH), and both were considered here. Moreover, the target redox



Scheme 1. One-pot combination of the Meyer-Schuster rearrangement of racemic propargylic alcohols towards β,β-disubstituted ketones including: a) Rh-catalysed boronic acid 1,4-addition; b) ERED-catalysed alkene reduction.

bienzymatic system needs to fulfil the necessity to selectively reduce the alkene, while maintaining the integrity of the carbonyl group. The initial aim was to establish suitable reaction conditions for the metal- and enzyme-catalysed processes, selecting an aqueous medium and ethanol (EtOH) or 2-PrOH as organic cosolvents to favour substrate solubility and cofactor recycling without significantly affecting the reactivity of $IPrAuNTf_2$ and NCR-ERED (Table S1).

4-Phenylpent-3-en-2-one (**2 a**) was used as benchmark substrate in a *E*/*Z* ratio 87:13 obtained after a Meyer-Schuster rearrangement from propargylic alcohol **1 a**.[8d,e] In all cases, the formation of enantiopure ketone (*R*)-**3 a** was observed suggesting the formation of the same reduced product from both geometric alkene isomers (Scheme 2).



Scheme 2. Bioreduction of ketone **2 a** using NCR-ERED.

Better conversions were found using the *Te*SADH system rather the glucose/GDH one, attaining a 79% conversion when using a 100 mM phosphate buffer pH 7.0 and 2-PrOH (10% vol). The higher product formation was finally found moving to water as the main solvent and a 10% vol of 2-PrOH, reaching a 91% conversion after 24 h at 30 °C.

To better understand the observed selectivity towards generating (*R*)-**3 a**, molecular docking experiments were carried out using Autodoc Vina (v.1.2.0),[23] using the protein structure of *Zymomonas mobilis* NCR (PDB: 4A3U).[24] Analysis of the docking results (Figure 1), revealed that both (*E*)- and (*Z*)-**2 a** orientated into a similar productive conformation in the catalytic site of NCR, positioned above the cofactor flavin mononucleotide (FMN) $FMNH_2$. The carbonyl group can bind to Asn175 (2.89 Å for (*E*)-**2 a** and 2.82 Å for (*Z*)-**2 a**), with the larger aromatic moiety orientated towards Tyr177 (right hand side in Figures 1A and B). As highlighted in Figures 1C and D, the $FMNH_2$ sits at an acute angle of the planes in both (*E*/*Z*)-**2 a**. Hydride transfer from $FMNH_2$ can then occur on the *Si* face of the benzylic carbon for both the *E*/*Z* alkenes, yielding product **3 a** with the (*R*)-configuration as the preferred stereoisomeric product. This is a nice example where a substrate does not undergo the typical

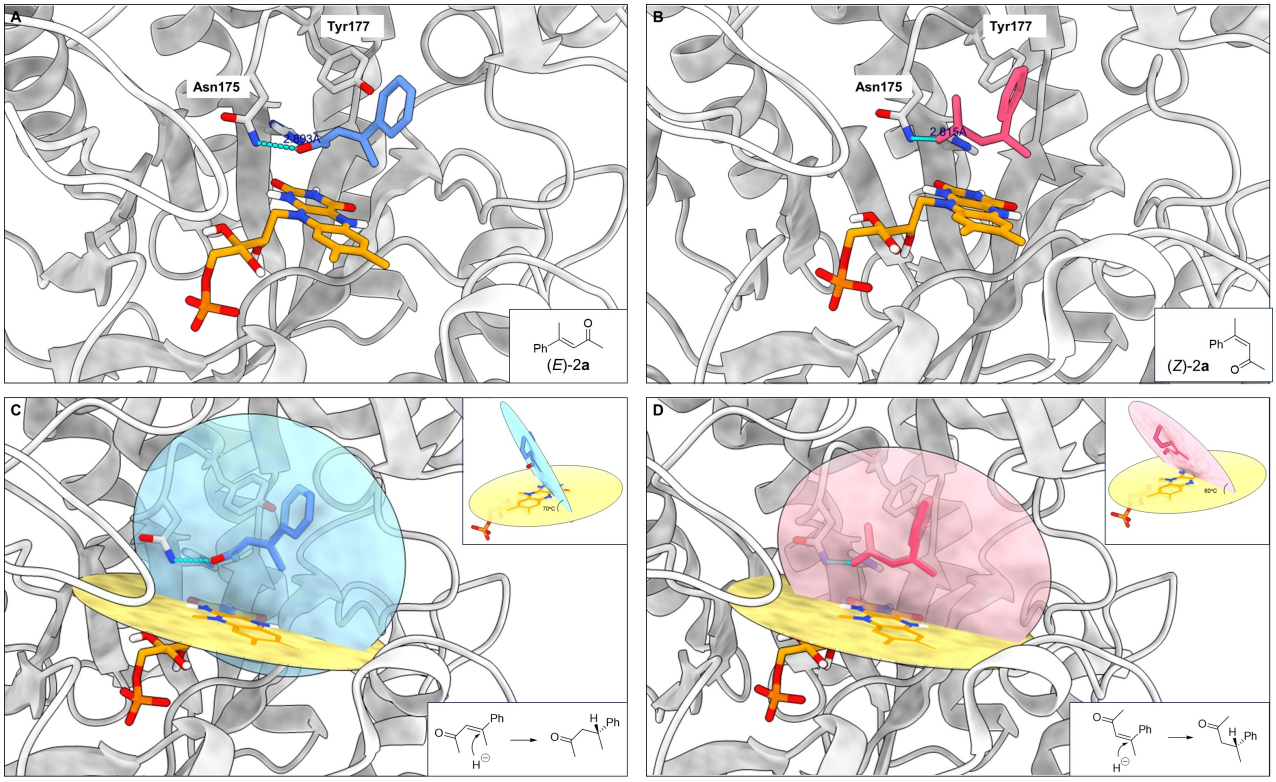
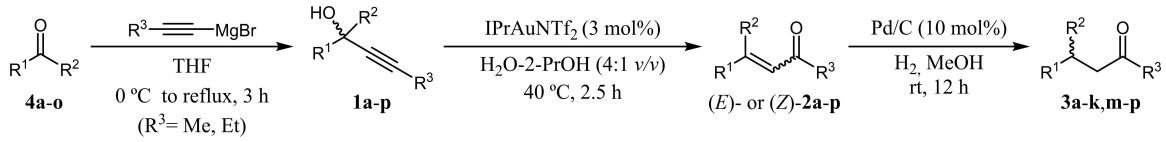


Figure 1. Docking study of NCR and (*E*)/(*Z*)-**2 a**. **A**. NCR and (*E*)-**2 a**, NCR is shown in greyscale, and the cofactor $FMNH_2$ and (*E*)-**2 a** in orange and blue, respectively. **B**. NCR and (*Z*)-**2 a**, with (*Z*)-**2 a** in pink. **C**. Planes of the cofactor $FMNH_2$ and (*E*)-**2 a**. **D**. Planes of the cofactor $FMNH_2$ and (*Z*)-**2 a**. Figures were generated using ChimeraX(1.6.1).[25]

"flipping" mode inside the active centre of the enzyme,[12b,e] maintaining both phenyl and methyl groups at β-position in similar dispositions.

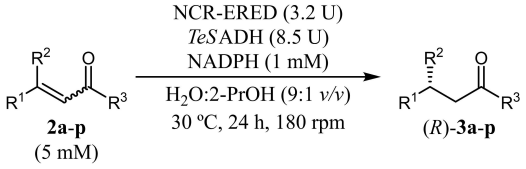
Before expanding the reaction scope of the NCR-ERED catalysed reduction of enones **2 a–p**, the corresponding alcohols **1 a--p**, enones **2 a--p** and ketones **3 a–p** were synthesised using conventional transformations (Scheme 3). The strategy consisted of the reaction between the corresponding ketones **4 a–o**, including (hetero)aryl (R^1) and alkyl (R^2) groups, with a 1-propynyl- or 1-butynylmagnesium bromide solution in THF (Table S4),[8d, e,26] followed by a gold-catalysed Meyer-Schuster rearrangement as previously described by our group (Table S5),[8d] and finally palladium-catalysed hydrogenation in methanol (Table S6). This also enabled robust analytical methods to be established for the measurement of conversions and (enantio)selectivities for the single and cascade transformations.

At this point, the bioreduction of the synthesised enones **2 a–p** obtained from the gold-catalysed Meyer-Schuster rearrangement was undertaken (Table 1). Independently of the *E*/*Z* ratio of the unsaturated substrate **2 a–p**, in all cases the enantiopure saturated



Scheme 3. Synthesis of racemic alcohols **1 a--p**, prochiral enones **2 a--p** and racemic ketones **3 a–p**.

Table 1. Bioreduction of unsaturated ketones **2 a--p** using the bienzymatic NCR-ERED and *Te*SADH.[a]



Entry	**2 a–p**[b]	R^1	R^2	R^3	**3 a–p** (%)[c]	*ee* (*R*)-**3 a-p** (%)[c]
1	**2 a**	Ph	Me	Me	> 99	> 99
2	(*E*)-**2 a**	Ph	Me	Me	> 99	> 99
3	(*Z*)-**2 a**	Ph	Me	Me	74	> 99
4	**2 b**	4-F-C_6H_4	Me	Me	> 99	> 99
5	**2 c**	4-Cl-C_6H_4	Me	Me	> 99	> 99
6	**2 d**	4-Br-C_6H_4	Me	Me	70	> 99
7[d]	**2 d**	4-Br-C_6H_4	Me	Me	77	> 99
8	**2 e**	4-NO_2-C_6H_4	Me	Me	46	> 99
9[d]	**2 e**	4-NO_2-C_6H_4	Me	Me	64	> 99
10	**2 f**	4-CF_3-C_6H_4	Me	Me	> 99	> 99
11	**2 g**	4-OMe-C_6H_4	Me	Me	82	> 99
12	**2 h**	3-F-C_6H_4	Me	Me	76	> 99
13	**2 i**	3-NO_2-C_6H_4	Me	Me	7	> 99
14[d]	**2 i**	3-NO_2-C_6H_4	Me	Me	15	> 99
15	**2 j**	3-CF_3-C_6H_4	Me	Me	> 99	> 99
16	**2 k**	2-F-C_6H_4	Me	Me	> 99	> 99
17	**2 l**	2-NO_2-C_6H_4	Me	Me	12	> 99
18[d]	**2 l**	2-NO_2-C_6H_4	Me	Me	24	> 99
19	**2 m**	2-Thienyl	Me	Me	79	> 99
20	**2 n**	Ph	Et	Me	77	> 99
21	**2 o**	Ph	^{n}Pr	Me	74	> 99
22	**2 p**	Ph	Me	Et	95	> 99

[a] A general procedure can be found in the Experimental Section.
[b] The *E*/*Z* ratio of the starting enones **2 a–p** is displayed in Table S5.
[c] Percentages of **3 a–p** and enantiomeric excess values were determined by GC or HPLC analyses depending on the substrate (see SI for further details).
[d] A H_2O:2-PrOH:MeCN (87.5:10:2.5 *v*/*v*) mixture was used.

ketones **3a--p** were exclusively detected, thus displaying an excellent stereoselectivity towards the (*R*)-enantiomers with the enzymatic paired system composed of NCR-ERED and *Te*SADH. Experiments with the model substrate as a 87:13 *E*/*Z* mixture (entry 1), and the single (*E*)- and (*Z*)-isomers (entries 2 and 3) were also performed, confirming the preferred selectivity of this enzyme for both isomers, giving the enantiopure ketone (*R*)-**3a**, although the reaction appeared to be slower for the (*Z*)-isomer. However, due to the fact that this was the minor compound in the mixture obtained after the Meyer-Schuster rearrangement reaction, it was not an issue to achieving an excellent conversion (entry 1).

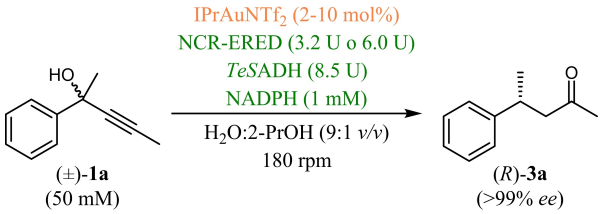
In terms of reactivity, at least 70% conversions were reached for all substrates except for the nitro compounds that led to lower values (entries 8, 13 and 17, 7–46%), although by-products were not observed for compounds **2e**, **2i** and **2l**. In these cases, higher conversion values were obtained when performing the reactions in the presence of acetonitrile as a solubilising cosolvent (2.5% vol), which gave better results (entries 9, 14 and 18, 15–64%). An increase in the alkyl chain length at the β-position was also not a problem with the ERED selectivity slightly, decreasing the conversion values to 77% for **2n** (R^2 = Et) and 74% for **2o** (R^2 = ^{n}Pr), compared to the full conversion attained with ketone **2a** (entries 1, 20 and 21). At this point, all the substrates considered were methyl ketones, so the bioreduction of the ethyl ketone **2p** was carried out, also giving an excellent conversion (95%, entry 22) with total selectivity. Additionally, 1,3-diphenylbut-2-en-1-one (R^1 = Ph, R^2 = Me and R^3 = Ph) was chemically synthesised, although it resulted to be a poor substrate for the NCR ERED-*Te*SADH system in terms of reactivity.

Optimisation of the Chemoenzymatic Cascade

Next, the design of a concurrent approach for the one-pot cascade consisting of the Meyer-Schuster rearrangement and the stereoselective bioreduction was developed, selecting alcohol **1a** as model substrate. Table 2 summarises the parameters explored that can influence the performance of the gold and enzyme-mediated catalysis, with the aim of identifying conditions compatible for both catalysts in one-pot.

First of all, the type of agitation (magnetic vs orbital mode) was considered, employing different amounts of $IPrAuNTf_2$ and a fixed 5 mM concentration

Table 2. Concurrent cascade approach involving the Meyer-Schuster rearrangement of (±)-**1a** and the stereoselective bioreduction of intermediate **2a** for the formation of ketone (*R*)-**3a**.[a]



(±)-**1a** (50 mM) → (*R*)-**3a** (>99% *ee*)

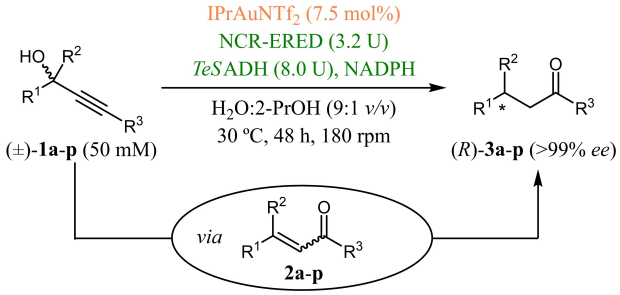
Entry	[**1a**] (mM)	$IPrAuNTf_2$ (mol%)	Stirring	t (h)	T (°C)	NCR (U)	**1a** (%)[b] (*S*)	(*R*)	**2a** (%)[b] (*E*)	(*Z*)	(*R*)-**3a** (%)[b]
1	5	2	Magnetic	24	30	3.2	13	13	<1	<1	74
2	5	5	Magnetic	24	30	3.2	5	5	6	<1	84
3	5	7.5	Magnetic	24	30	3.2	<1	<1	7	<1	93
4	5	10	Magnetic	24	30	3.2	<1	<1	8	<1	92
5	5	10	Orbital	24	30	3.2	2	2	13	<1	82
6	10	10	Magnetic	24	30	3.2	<1	<1	24	<1	76
7	25	10	Magnetic	24	30	3.2	<1	<1	42	<1	58
8	50	10	Magnetic	24	30	3.2	<1	<1	52	<1	48
9	75	10	Magnetic	24	30	3.2	<1	<1	55	<1	45
10	100	10	Magnetic	24	30	3.2	<1	<1	59	<1	41
11	25	10	Magnetic	48	30	3.2	<1	<1	11	<1	89
12	50	10	Magnetic	48	30	3.2	<1	<1	15	<1	85
13	100	10	Magnetic	48	30	3.2	<1	<1	57	<1	43
14	50	10	Magnetic	24	35	3.2	<1	<1	51	<1	49
15	50	7.5	Magnetic	48	30	6.0	<1	<1	4	<1	96

[a] A general procedure can be found in the Experimental Section.
[b] Percentages of **1a**, **2a** and **3a** were determined by HPLC analyses. Enantiomeric excess values of ketone **3a** were >99% *ee* in all cases, also determined by HPLC analyses (see SI for further details).

of **1 a** (entries 1–5). A 7.5 mol% of the gold(I) catalyst was required to achieve a 93% conversion into enantiopure (*R*)-**3 a**, proving that the chemobiocatalytic approach in a concurrent mode was possible (entry 3). Lower $IPrAuNTf_2$ loadings (up to 5 mol%, entries 1 and 2) were not sufficient to transform all the starting alcohol **1 a**, while higher amounts of chemocatalyst (10 mol%, entry 4) did not improve the results at 7.5 mol%. Better results were obtained with the magnetic stirring (entries 4 and 5), so this type of agitation was selected for further improvements. Unfortunately, the use of higher substrate concentrations (10–100 mM, entries 6–10) led to significantly lower overall conversions (41–76%), caused by the inferior reactivity of the bioreduction system. In order to design a more productive system, the reaction time was increased from 24 to 48 h, achieving 89% and 85% formation of (*R*)-**3 a** at 25 and 50 mM substrate concentrations (entries 11 and 12), respectively, with a decreased conversion at 100 mM (43%, entry 13). The necessity of longer reaction times even at higher temperatures was confirmed at 50 mM **1 a** concentration (entry 14), identifying the possibility to improve the conversion to 96% when running the reaction for 48 h (entry 15), maintaining constant the *Te*SADH loading and increasing the amount of NCR-ERED (6.0 U).

Next, the scope of the one-pot concurrent approach was evaluated using 15 other racemic alcohols (**1 b–p**) at a 50 mM substrate concentration and without requiring a high enzyme loading (Table 3). Thus, reactions were run for 48 h with 7.5 mol% of $IPrAuNTf_2$, 3.2 U of NCR-ERED and 8.5 U of *Te*SADH at 50 mM **1 a--p** concentration (0.025 mmol), and the results agreed with the results of each substrate in single gold- and enzyme-catalysed transformations. As observed for the bioreduction study, variable conversions were attained from 35–85% for the

Table 3. Scope of the one-pot concurrent cascade for the synthesis of enantiopure β,β-disubstituted ketones **3 a–p**.[a]



Entry	R^1	R^2	R^3	**1 a –p** (%)[b]		**2 a –p** (%)[b]		(*R*)-**3 a –p** (%)[b]
				(*S*)	(*R*)	(*E*)	(*Z*)	
1	Ph	Me	Me	< 1	< 1	15	< 1	85 (**3 a**)
2	4-F-C_6H_4	Me	Me	14	14	< 1	< 1	72 (**3 b**)
3	4-Cl-C_6H_4	Me	Me	10	12	< 1	< 1	78 (**3 c**)
4	4-Br-C_6H_4	Me	Me	11	14	17	18	40 (**3 d**)
5[c]	4-Br-C_6H_4	Me	Me	3	4	17	19	57 (**3 d**)
6	4-NO_2-C_6H_4	Me	Me	9	11	24	27	29 (**3 e**)
7[c]	4-NO_2-C_6H_4	Me	Me	4	5	26	27	38 (**3 e**)
8	4-CF_3-C_6H_4	Me	Me	16	15	< 1	< 1	69 (**3 f**)
9	4-OMe-C_6H_4	Me	Me	7	10	11	9	63 (**3 g**)
10	3-F-C_6H_4	Me	Me	17	18	17	13	35 (**3 h**)
11[c]	3-NO_2-C_6H_4	Me	Me	8	9	37	36	10 (**3 i**)
12	3-CF_3-C_6H_4	Me	Me	15	14	< 1	< 1	71 (**3 j**)
13	2-F-C_6H_4	Me	Me	11	15	< 1	< 1	74 (**3 k**)
14[c]	2-NO_2-C_6H_4	Me	Me	5	6	36	34	19 (**3 l**)
15	2-Thienyl	Me	Me	13	13	15	< 1	59 (**3 m**)
16	Ph	Et	Me	11	11	9	8	61 (**3 n**)
17	Ph	^{n}Pr	Me	10	8	12	12	58 (**3 o**)
18	Ph	Me	Et	6	4	6	6	78 (**3 p**)

[a] A general procedure can be found in the Experimental Section.
[b] Percentages of compounds and enantiomeric excess values were determined by GC or HPLC analyses depending on the substrate (see SI for further details).
[c] A H_2O:2-PrOH:MeCN (87.5:10:2.5 *v/v*) mixture was used.

formation of the saturated ketones (*R*)-**3 a--h**,**j**,**k**,**m**–**p**, which in all cases were obtained in enantiopure form (> 99% *ee*). Cascade reactions of derivatives **1 d** (R^1 = 4-BrC_6H_4 and $R^2 = R^3 = Me$) and **1 e** (R^1 = 4-$NO_2C_6H_4$ and $R^2 = R^3 = Me$) were also run in the presence of acetonitrile as cosolvent to allow a better solubility of the involved organic compounds, allowing the formation of the enantiopure products **3 d** and **3 e** at slightly higher conversions (38–57%, entries 5 and 7), in comparison to the reactions without this solvent (29–40%, entries 4 and 6). In fact, the use of acetonitrile was also needed to achieve significant conversions of nitro derivatives **3 i** and **3 l** (10–19%, entries 11 and 14).

In order to isolate and characterise the enantiopure β,β-disubstituted ketones, one-pot cascades were then performed, starting with 30 mg of those substrates that achieved good to high conversions at an analytical scale, which were **1 a--h**,**j**,**k**,**m--p**, and adjusting the amounts of enzyme to have a good agitation of the system, therefore significantly reducing the amount of *Te*SADH (Figure 2). Overall, similar yields were obtained in comparison with the experiments performed at an analytical scale (Tables 3 and S7). Enantiopure products (*R*)-**3 a**–**h**,**j**,**k**,**m**–**p** were isolated after liquid-liquid extraction and chromatographic purification (24–73% isolated yield, see Experimental Section for details). This allowed us to measure their optical rotations and compare them with those described in the literature (see SI for further details), assigning the (*R*)-configuration to all the ketones produced.[27] To demonstrate the practical applicability of this metalloenzymatic process, the concurrent cascade was performed with 100 mg of racemic alcohol **1 a**, obtaining the desired saturated ketone (*R*)-**3 a** in enantiopure form and 56% isolated yield after column chromatography.

Conclusion

Merging chemo- and biocatalysis is a challenging task that is currently receiving significant attention looking to provide straightforward solutions for the industrial sector.[28] Herein, the possibilities of gold chemistry have been expanded by describing for the first time the synergistic combination of a gold(I) N-heterocyclic carbene and an ene-reductase. Both catalysts efficiently worked in one-pot and under mild reaction conditions to transform a series of racemic tertiary alcohols into enantiopure (*R*)-β,β-disubstituted ketones.

The two-step approach consists of the Meyer-Schuster rearrangement of propargylic alcohols bearing different substituents at three positions, using a catalytic amount of $IPrAuNTf_2$ (7.5 mol%) in an aqueous medium, followed by the chemoselective asymmetric alkene reduction of the intermediate enones. Optimisation of the reaction parameters using 2-phenylpent-3-yn-2-ol as a benchmark substrate allowed the preparation of a series of (*R*)-saturated ketones, using the NCR-ERED in combination with *Te*SADH as a suitable system for the enzymatic reductive transformation. Moreover, *in silico* docking experiments were performed to rationalise the conversion of both *E*- and *Z*-**2 a** to (*R*)-**3 a**, demonstrating that no binding "flipping" mode occurred in the enzyme active site for these specific substrates.

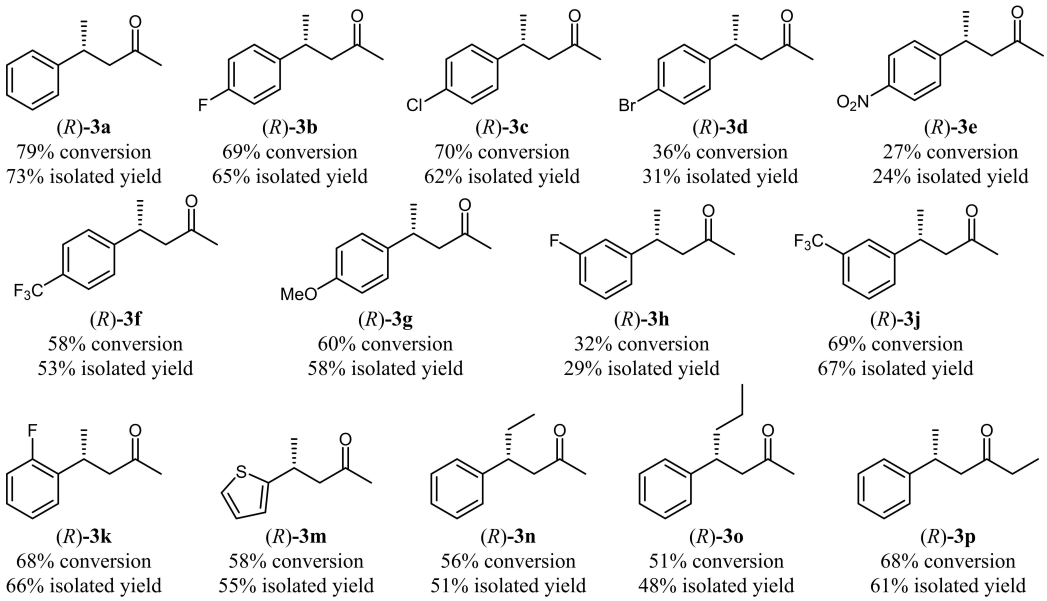


Figure 2. Semi-preparative one-pot Meyer-Schuster rearrangement and bioreduction cascades to transform alcohols (±)-**1 a**–**h**,**j**,**k**,**m--p** to enantiopure (*R*)-**3 a--h**,**j**,**k**,**m**–**p**.

Experimental Section

General Information

Chemical reagents and nicotinamide cofactor ($NADP^+$) were purchased from Sigma-Aldrich. The gold(I) catalyst [1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene] [bis(trifluoromethanesulfonyl)imide]gold(I) ($IPrAuNTf_2$) was obtained from Sigma-Aldrich. The glucose dehydrogenase GDH-105 (48 U/mg) was purchased from Codexis as cell-free lyophilised lysate and used as received. 1 unit of glucose dehydrogenase is defined as 1 micromole of gluconic acid formed from glucose per minute and mg of enzyme preparation (1 $\mu mol\,min^{-1}\,mg^{-1}$). In house NCR-ERED[19] and *Te*SADH[22] were heterologously expressed in *E. coli* as already described in the literature, and used as lyophilised lysate preparations. To quantify the amount of target enzyme in the CFE, a known quantity of the extract was subjected to purification, and the purified enzyme was quantified based on its absorbance at 280 nm. For NCR-ERED, 150 mg of CFE was purified, yielding 8.5 mL of purified enzyme solution with a concentration of 3.89 mg/mL (0.16 U/mg). 1 unit of NCR-ERED is defined as 1 micromole of cyclohexanone formed from cyclohex-2-enone per minute and mg of enzyme preparation (1 $\mu mol\,min^{-1}\,mg^{-1}$). For *Te*SADH, 179.5 mg of CFE were purified, yielding 30 mL of purified enzyme solution with a concentration of 0.85 mg/mL (0.85 U/mg). 1 unit of *Te*SADH is defined as 1 micromole of octan-2-ol formed from octan-2-one per minute and mg of enzyme preparation (1 $\mu mol\,min^{-1}\,mg^{-1}$). Non-commercially available alkynes were chemically synthesised, exhibiting physical and spectral data in agreement with those reported in the literature.[8d,, e]

General synthetic procedures and full characterisation of racemic propargylic alcohols **1 a**–**p**, α,β-unsaturated ketones **2 a--p** and racemic ketones **3 a--p** have been included in the SI file.

Cascade reactions were performed in a vial tube [(3×4) cm] under magnetic stirring, otherwise indicated. ^1H, ^{13}C and ^{19}F-NMR experiments were recorded on a Bruker 300 MHz spectrometer. All chemical shifts (δ) are given in parts per million (ppm) and referenced to the residual solvent signal as internal standard. Infrared (IR) spectra were recorded on a Jasco FT/IR-4700 spectrometer in neat form, and ν_{max} values are given in cm^{-1} for the main absorption bands. Thin-layer chromatography (TLC) analyses were conducted with silica gel 60 F254 precoated plates and visualised with a UV lamp, plus either potassium permanganate or vanillin stains. Column chromatographies were performed using silica gel 60 (230–240 mesh).

Gas chromatography (GC) analyses were performed on a Hewlett-Packard 7890 GC chromatograph equipped with a FID detector using a Restek RT-betaDEXse column (30 m×0.25 mm×0.25 µm, 12.2 psi N_2) or a CP-Chirasil-DEX CB column (30 m×0.32 mm×0.25 µm, 12.2 psi N_2) for the determination of product percentages and enantiomeric excess values. See Sections X.1 and X.2 of the SI for analytical conditions and recorded chromatograms.

High performance liquid chromatography (HPLC) analyses were performed on an Agilent Infinity 1260 HPLC chromatograph equipped with a VIS-UV detector using Chiralcel OJ–H (25 cm×4.6 mm, 5 µm particle size) or Chiralpak AD–H column (25 cm×4.6 mm, 5 µm particle size) for the measurement of enantiomeric excess values. See Section X.3 of the SI for analytical conditions and recorded chromatograms.

The associated supporting information includes all the structures of chemical compounds here studied, together with general protocols for their chemical synthesis (alcohols **1 a**–**p**, enones **2 a--p** and ketones **3 a--p**), docking studies, extensive gold- and enzyme-catalysed transformation studies, development of analytical methods (GC and HPLC) to measure enzymatic activities and selectivities, copies of chromatograms for the chiral analyses, and NMR spectra.

Bioreduction of Ketones 2 a-p Using NCR-ERED

Ketone **2 a**–**p** (0.0025 mmol, 5 mM), 2-PrOH (50 µL), a NADPH 10 mM aqueous solution (50 µL), distilled water (400 µL), lyophilised cells of *E. coli* overexpressing *Te*SADH (10 mg, 8.5 U) and lyophilised NCR-ERED (20 mg, 3.2 U) were successively added to a 1.5 mL-Eppendorf tube. The Eppendorf tube was closed and kept under orbital shaking at 30 °C and 250 rpm for 24 h. After this time, the solution was extracted with EtOAc (2×0.5 mL), the organic layers combined, dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated, measuring the reaction conversion and the enantiomeric excess by GC or HPLC analyses depending on the substrate (Tables S8, S9 and S10, see Section X of the SI for analytical studies).

One-Pot Meyer-Schuster and Bioreduction Cascade at Analytical Scale

The corresponding propargylic alcohol **1 a--p** (0.025 mmol, 50 mM), 2-PrOH (50 µL), distilled water (400 µL), $IPrAuNTf_2$ (0.15 mg, 0.0019 mmol, 7.5 mol%), a NADPH 1 mM aqueous solution (50 µL), lyophilised cells of *E. coli* overexpressing *Te*SADH (10 mg, 8.5 U) and NCR-ERED lyophilised (20 mg, 3.2 U) were placed into a glass vial. Reactions with alcohols **1 d**,**e**,**i**,**l** were also run with a H_2O:2-PrOH:MeCN (87.5:10:2.5 *v/v*) mixture achieving slightly better results. The mixture was stirred at 30 °C for 48 h, and after this time, the solution was extracted with EtOAc (2×0.5 mL), the organic layers were combined, dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure, measuring then the product percentages and the enantiomeric excess values by GC or HPLC analyses depending on the substrate (Tables S9 and S10, see Section X of the SI for analytical studies).

One-Pot Meyer-Schuster and Bioreduction Cascade at Semipreparative Scale

$IPrAuNTf_2$ (7.5 mol%) and a NADPH 1 mM aqueous solution were added to a solution of the corresponding propargylic alcohol **1 a--h**,**j**,**k**,**m--p** (30 mg, 0.14–0.21 mmol) in a mixture of distilled water and 2-PrOH (9:1 *v/v*) for a total substrate concentration of 50 mM. Then, lyophilised cells of *E. coli* overexpressing *Te*SADH (35 mg, 29.75 U) and NCR-ERED (150 mg, 24 U) were placed into a glass vial. The mixture was stirred at 30 °C for 48 h, and after this time, the solution was extracted with EtOAc (2×0.5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered, prior

distillation of the solvent under reduced pressure. Product percentages and enantiomeric excess values were measured by GC or HPLC analyses depending on the substrate (see Section X of the SI for analytical studies). Finally, the reaction crudes were purified on silica gel using mixtures of EtOAc/hexane (5% for **3 d** and **3 g**; 10% for **3 a--c**,**e**,**f**,**h**,**j**,**k**,**n--p**; and 20% for **3 m** to afford the enantiopure (*R*)-**3 a–h**,**j**,**k**,**m–p** (> 99% *ee* and 24–73% isolated yield, Figure 2).

Metalloenzymatic Cascade with 100 mg of 1 a as Substrate

$IPrAuNTf_2$ (7.5 mol%) and a NADPH 1 mM aqueous solution were added to the corresponding propargylic alcohol **1 a** (100 mg, 0.625 mmol) dissolved in a mixture of distilled water and 2-PrOH (9:1 *v/v*) for a total substrate concentration of 50 mM. Then, lyophilised cells of *E. coli* overexpressing *Te*SADH (125 mg, 106 U) and NCR-ERED (500 mg, 80 U) were placed into a round bottom flask. The mixture was stirred at 30 °C for 48 h, and after this time, the solution was extracted with EtOAc (3×10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered, prior distillation of the solvent under reduced pressure. Product percentages and enantiomeric excess values were measured by HPLC analyses. Finally, the reaction crude was purified on silica (10% EtOAc/hexane) affording (*R*)-**3 a** (56.7 mg, 56% isolated yield and > 99% *ee*).

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