

Enzymatic-Organo-Catalyzed Oxidative Rearrangement of Tertiary Allylic Alcohols: Synthetic Applications and Integration into a Cascade Process

Elisabetta Brenna,^{a,b} Michele Crotti,^a Matteo De Pieri,^a Francesco G. Gatti,^{*,a,b} Gabriele Manenti,^a and Daniela Monti^c

^a Dipartimento CMIC "G. Natta", Politecnico di Milano, Via Mancinelli, 20134, Milan, Italy
Fax: (+39)-23993080; phone: (+39)-23993072; e-mail: Francesco.gatti@polimi.it

^b The Protein Factory, Politecnico di Milano Università degli Studi dell'Insubria, Via Mancinelli 7, 20131 Milano, IT

^c Istituto di Chimica del Riconoscimento Molecolare C.N.R. Via Mario Bianco, 9, 20131, Milano, IT



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Abstract: A chemo-enzymatic catalytic system, comprised of Bobbitt's salt and laccase from *Trametes versicolor*, allowed the [1,3]-oxidative rearrangement of endocyclic allylic tertiary alcohols into the corresponding enones under O₂ atmosphere in aqueous media. The yields were in most cases quantitative, especially for the cyclopent-2-en-1-ol or the cyclohex-2-en-1-ol substrates without EWGs on the side chain. Transpositions of tertiary alcohols bearing EWGs or macrocyclic alkenols were instead carried out in acetonitrile by using an immobilized laccase preparation. Dehydro-Jasmone[®], dehydro-Hedione[®], dehydro-Muscone and other fragrance precursors were directly prepared with this procedure, while a synthetic route was developed to easily transform a cyclopentenone derivative into *trans*-Magnolione[®] and dehydro-Magnolione[®].

The rearrangement of exocyclic allylic alcohols was tested as well, and a dynamic kinetic resolution was observed: α,β -unsaturated ketones with (*E*)-configuration and a high *de* were synthesized. Finally, the TEMPO⁺BF₄⁻/laccase catalysed oxidative rearrangement was combined with the ene-reductase/alcohol dehydrogenase cascade process in a one-pot three-step synthesis of *cis* or *trans* diastereoisomer of 3-methylcyclohexan-1-ol with a high optical purity.

Keywords: Oxidation; Biocatalysis; Dynamic Resolution; Laccases; Ene reductases; Birch reduction; Wacker Oxidation; Fragrances.

Introduction

The [1,3]-oxidative rearrangement or transposition of tertiary allylic alcohols is a key transformation of organic chemistry (Figure 1a),¹ especially for the synthesis of β substituted or α,β disubstituted cyclic enones, which are wide spread structural moieties in the field of fragrances chemistry,² either as key-intermediates or final products (Figure 1b).

The reaction is typically carried out in presence of a large excess of Chromium(III) based reagents such as pyridinium chloro chromate (PCC), Collins, Jones and many others. Although these oxidants are operationally simple and usually very efficient, their use on a large scale is impractical, since the wastes produced are notoriously very toxic and harmful. In this regard a significant improvement was achieved with the appearance of organic based oxidants, among which 2-iodoxybenzoic acid³ (IBX), 2,2,6,6-tetramethylpiperidine-1-oxyl⁴ (TEMPO) and its oxoammonium fluoroborate salt⁵ (TEMPO⁺BF₄⁻, also

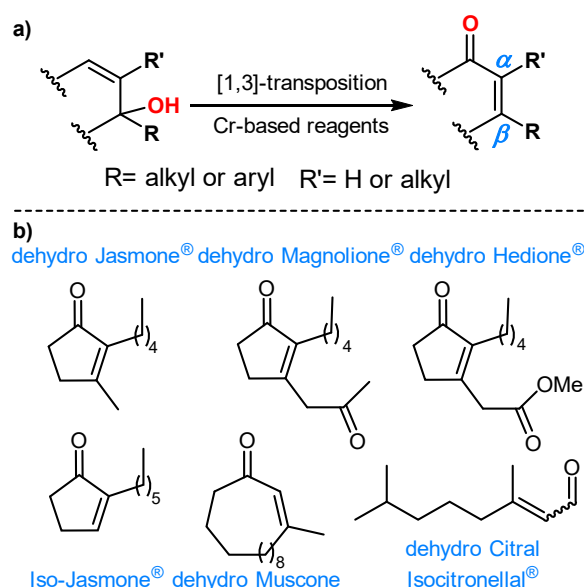


Figure 1. Oxidative [1,3]-rearrangement of tertiary allylic alcohols to give tri- or tetrasubstituted enones; b) Selected examples of cyclic enones based fragrances.

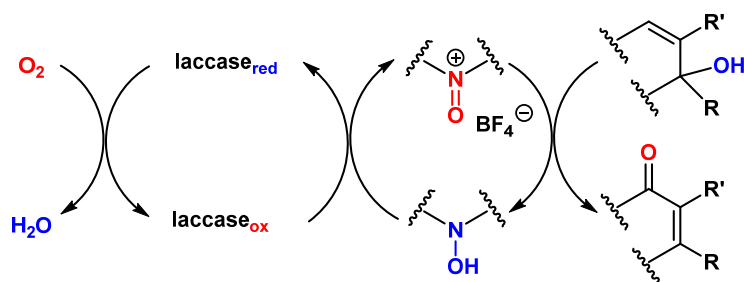


Figure 2. Proposed catalytic cycle in the oxoammonium/laccase mediated oxidative [1,3]-rearrangement of tertiary allylic alcohols to give tri- or tetrasubstituted enones.

known as Bobbitt's salt) are undoubtedly the most important. Considering the lack of a catalytic procedure^{3,5,6} in water, we feel that by combining the high efficiency of these oxidants with the typical advantages of the biotransformations might be an eye-catching goal.

In this regard, the TEMPO/laccase catalytic system⁷ has been one of the first examples of chemo-enzymatic procedures applied to the oxidation of several classes of organic compounds such as benzyl alcohols⁸ and diols.⁹ In addition, this catalytic system has been proficiently integrated with other biotransformations either in sequential multi-step¹⁰ or cascade processes.¹¹

Laccases are metallo-proteins belonging to the family of oxidase enzymes, catalyse the reduction of O₂ into H₂O at the expense of sacrificial substrates, typically phenol derivatives, but also TEMPO is a substrate well accepted by laccases.^{7b,12}

Thus, keeping this in mind, we devised a new laccase-organo-catalytic system, consisting of an oxoammonium salt and *Trametes versicolor* laccase, using O₂ as co-oxidant for the oxidative rearrangement of tertiary allylic alcohols (Figure 2).

Results and Discussion

First, we studied the oxidative rearrangement of 1-methylcyclohex-2-en-1-ol, *i.e.* **1a**, which was chosen as model compound for the optimization of reaction parameters. The oxidation at pH 4.0, at which the *T. versicolor* laccase exhibits its highest activity,¹² under O₂ atmosphere and in presence of a substoichiometric amount of TEMPO⁺BF₄⁻ (20% in mol. eq.) gave, after 24 hours, a mixture of enone **1b**, secondary allylic alcohol **1c** and starting material in the ratio of 37:38:25 (conversions by GC-MS), respectively (Table 1).

At this pH, **1a** partially isomerizes to the more thermodynamically stable alcohol **1c** (disubstituted alkene *vs.* trisubstituted alkene), reaching the equilibrium after 3 hours (**1a/1c**, 4:6 by ¹H-NMR, for the kinetic measurement see SI). Since, even after prolonged reaction times, just a small amount of secondary allylic alcohol **1c** was oxidised into enone **1b** (≈ 3%, by GC-MS) we increased the pH with the scope of slowing down the detrimental acid catalysed 1,3-allylic isomerizing side-reaction.¹³ Table 1 reports conversions at different pH and reaction times.

Overall these results lead to the following conclusions: i) in the pH range 5.2-6.0, the laccase activity is still sufficiently high to catalyse the regeneration of the oxoammonium mediator; ii) in the same pH range, the isomerization rate decreases drastically and it is much slower than the oxidative rearrangement, since no allylic alcohol **1c** was anymore present in the reaction mixture; iii) TEMPO⁺BF₄⁻ oxidizes the secondary allylic alcohol **1c** very slowly; iv) the oxidative rearrangement of **1a** needs an acid environment, since the conversion was less than 10% when using 0.2 molar equivalents of TEMPO⁺BF₄⁻ at neutral pH.

Table 1. Optimization of pH and reaction time for the oxidative rearrangement of **1a** using TEMPO⁺BF₄⁻.^[a]

Time (h)	pH	Reaction Mixture (%) ^[b]		
		1a	1b	1c
12	4.0	26	34	40
	5.2	11	89	–
	6.0	29	71	–
	7.0	94	2	4
24	4.0	25	37	38
	5.2	–	100	–
	6.0	–	100	–
	7.0	90	3	7

^[a] Screening conditions on 1 mL scale: [substrate]= 50 mM, *T. versicolor* laccase: 200 μg/mL, TEMPO⁺BF₄⁻ 20% in mol. eq., 1% DMSO co-solvent, under O₂ atmosphere (balloon), buffers (50 mM): pH 7.0, phosphate; pH 6.0, 5.2, or 4.0, acetate; 30 °C; ^[b] By GC-MS.

Due to the great success of TEMPO mediated oxidations, in the last decades we have assisted to the development of many similar reagents, which in several cases have proved to be more efficient than their progenitor. However, since their reactivity applied to the oxidative transposition of tertiary allylic alcohols is practically unknown, especially in water, we decided to test some of them, *i.e.* keto-ABNO, ABNO¹⁴ and its oxoammonium¹⁵ tetrafluoroborate salt together with the progenitor TEMPO (Figure 3, for the

preparation of oxoammonium salts see SI); the results of this screening are shown in Table 2.

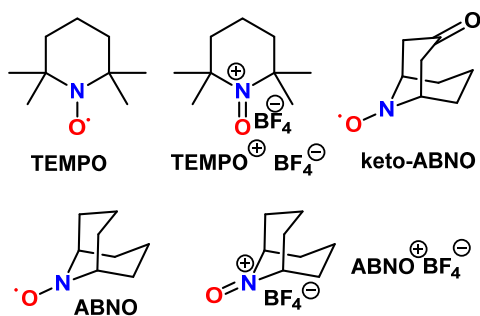


Figure 3. Mediators screened in the [1,3]-oxidative rearrangement of **1a**.

Noteworthy, at pH 5.2, in the TEMPO series the oxoammonium salt was significantly more efficient than the nitroxyl radical (100% vs. 19%, respectively). The trend was reversed for the ABNO based oxidants, the radical ABNO being significantly more performing than its oxoammonium tetrafluoroborate salt (60% vs. 4% conversion). For the keto-ABNO, it was not possible to prepare the tetrafluoroborate oxoammonium salt, however, both oxidative rearrangement and direct oxidation of the secondary allylic alcohol gave the enone in a very low yield.

Table 2. Mediator screening for the oxidative rearrangement of **1a** at pH 5.2. ^[a]

Mediator	Reaction Mixture (%) ^[b]		
	1a	1b	1c
TEMPO	33	19	48
keto-ABNO	40	<1	60
ABNO	16	60	24
ABNO ⁺ BF ₄ ⁻	39	4	57

^[a] Screening conditions on 1 mL scale: [substrate]= 50 mM, *T. versicolor* laccase: 200 µg/mL, mediator 20% in mol. eq., 1% DMSO co-solvent, under O₂ atmosphere (balloon), buffer: 50 mM acetate, pH = 5.2, 30 °C, 24 h; ^[b] By GC-MS.

In conclusion the optimal set-up for the oxidative rearrangement of **1a** resulted to be: laccase (200 µg/mL), TEMPO⁺BF₄⁻ (20% in mmol), at room temperature and pH 5.2 under a static O₂ atmosphere (Method A).

Substrate Scope and Synthetic Application

We focused our attention on three different sub-set of substrates: i) endocyclic allylic alcohols of medium/large rings; ii) endocyclic allylic alcohols bearing substituents with electron withdrawing groups (EWGs) and lastly iii) the more challenging exocyclic allylic alcohols. Most of tertiary allylic alcohols were prepared by addition of an organometallic reagent to a ketone (Grignard, organo- Lithium or Zinc reagents, see SI).

Initially, the substrates were oxidized on a preparative scale (2.5 mmol) using the above established reaction conditions (Method A); the yields of the isolated products for starting materials of type i) and ii) are reported in Table 3.

The oxidation of cyclohexenol derivatives **2a-7a** proceeded smoothly. Most of products were afforded in a nearly quantitative yield, especially the enones with an aliphatic or an aromatic substituent. The reaction condition set-up resulted successful also for substrates bearing a vinyl or an allyl substituent (**6a-7a**). More remarkable, the isolation of the products was column chromatography-free.

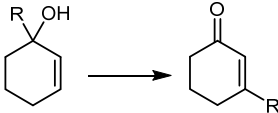
In contrast, for substrates with a propargyl or an ethyl acetate side chain (**8a-9a**) no product was detected, even after prolonged reaction times (72 hours). However, in the seminal work of Iwabuchi,⁵ some tertiary alcohols were better oxidized in anhydrous acetonitrile, whereas for others the conversions were improved simply by adding a small amount of water to the reaction mixture. Apparently, depending upon to the type of mechanism, water can have a beneficial or detrimental effect on the reaction yield. Keeping this in mind, we took in account the possibility of using our catalytic system in organic solvents too. To this aim, the *T. versicolor* laccase was adsorbed on porous glass beads¹⁶ and tested in the oxidative transposition of model compound **1a** in anhydrous MeCN, keeping unchanged the other reaction conditions (Method B, Table 3). The conversion of **1a** into **1b** was slightly worse than that achieved in water, (84% vs. 95%) and required a much longer reaction time (3 days vs. 24 h). However, by adopting method B, it was possible to oxidize **9a** into cyclohexenone **9b** in a satisfactory yield of 70%. Instead, the oxidation of **8a** gave an unforeseen result, *i.e.*, the formation of cyclic enone **8b**, even if in a low yield. Surprisingly, in addition to the expected oxidative rearrangement an alkyne/allene isomerization occurred as well.¹⁷

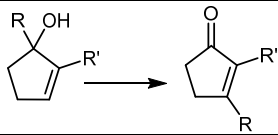
Subsequently, we moved to the more appealing five-membered ring substrates (**10a-18a**, Table 3), since many fragrances are derivatives of cyclopentenone. Analogously to the cyclohexenol based substrates, the tertiary cyclopentenols were smoothly oxidized into the corresponding enones; even in this case the conversions were quantitative, and the product isolation was again very simple, with the only exception of **10b**, likely due to its high volatility.

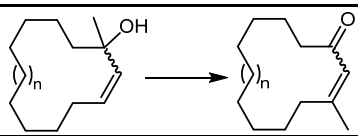
Tetrasubstituted cyclopentenols **13a-16a** underwent to oxidative rearrangement always in quantitative yields but in much shorter reaction times (3 hours instead of 1 day). This result is not surprising, being due to the higher strain of the tetrasubstituted cyclopentenols with respect to that of their trisubstituted homologues that facilitates the oxidative rearrangement.

Especially interesting was the oxidation of **17a**, which gave information about the chemoselectivity of the laccase/TEMPO⁺BF₄⁻ catalytic system. The oxidative rearrangement resulted prevailing over the

Table 3. Substrate scope of laccase/TEMPO⁺BF₄⁻ catalytic oxidative rearrangement. ^[a]

					
R	Sub.	Prod.	Met.	Yield (%) ^[b]	
Et	2a	2b	A	>99 ^[c]	
			B	84	
<i>n</i> -Pr	3a	3b	A	97 ^[c]	
<i>n</i> -Bu	4a	4b	A	98 ^[c]	
Ph	5a	5b	A	>99 ^[c]	
CH=CH ₂	6a	6b	A	>99 ^[c]	
CH ₂ CH=CH ₂	7a	7b	A	>99 ^[c]	
CH ₂ C≡CH	8a	8b	A	-	
			B	15	
CH ₂ CO ₂ Et	9a	9b	A	-	
			B	70	

					
R	R'	Sub.	Prod.	Met.	Yield (%) ^[b]
Me	H	10a	10b	A	70 ^[c]
<i>n</i> -Bu	H	11a	11b	A	92 ^[c]
Ph	H	12a	12b	A	>99 ^[c]
Me	<i>n</i> -Pent	13a	13b	A	>99 ^[c,d]
<i>n</i> -Bu	Me	14a	14b	A	>99 ^[c,d]
Ph	Me	15a	15b	A	>99 ^[c,d]
CH ₂ CH=CH ₂	<i>n</i> -Pent	16a	16b	A	>99 ^[c,d]
				B	
Me	CH ₂ OH	17a	17b 17d	A	>99 (85:15) ^[e]
				B	
CH ₂ CO ₂ Et	<i>n</i> -Pent	18a	18b	A	-
				B	91

					
n	Sub.	Prod.	Met.	Yield (%) ^[b]	
1	19a	19b	A	20	
			B	50	
2	20a	20b	A	-	
			B	23	

^[a] Typical exp. cond. on 50 mL scale. Met. A in H₂O: [Sub.] = 50 mM, [TEMPO⁺BF₄⁻] = 10 mM, *T. versicolor* laccase: 200 μg/mL, 1% DMSO co-solvent, under O₂ atmosphere (balloon), buffer 50 mM: pH = 5.2 acetate, 30 °C, reaction time 24 h; Met. B in MeCN: same cond. of A, except 2.5 gr of immobilized laccase (glass beads/laccase 50:1 in weight), no buffer, reaction time 72 h, 300 mg of MS 3 Å; ^[b] After work-up; ^[c] No column chromatography; ^[d] Reaction time 3 h; ^[e] Ratio **17b**/**17d**.

primary alcohol oxidation, since at the end of the reaction we recovered a mixture of enone **17b** and aldehyde **17d** in the ratio of 85:15, respectively (by ¹H-NMR and GC-MS). The tertiary allylic alcohol **17d** was not further oxidized to the corresponding enone, since substituents bearing EWGs such as the formyl group inhibit the oxidative transposition in water. In this regard the oxidation of **18a** to give the fragrance ethyl dehydro-Jasmonate[®] **18b** was accomplished in an excellent yield of 90% but adopting the procedure in MeCN (method B). Finally, we tested our catalytic system with larger endocyclic tertiary allylic alcohols, *i.e.* **19a-20a**, but, even if these substrates do not have electron withdrawing substituents, their oxidation with method A was not satisfactory, allowing only a 20% conversion in the case of **19a** (Table 3). As macrocyclic alkenes are substantially less strained than cyclopentene and cyclohexene derivatives, these results suggest a possible crucial role of ring strain in the transposition mechanism in water. Instead, by adopting method B we afforded **19b** and the fragrance dehydro-Muscone **20b**, but the yields, especially in the case of **20b**, were not totally satisfactory.

Our results confirm that the oxidative rearrangement of tertiary allylic alcohols is a synthetic strategy particularly suitable for the preparation of medium-sized cyclic enones, also because other synthetic strategies, such as Wittig olefination or aldol condensation, are not always applicable for these compounds. However, with the aim of broadening as much as possible the synthetic scope of our catalytic system, the transposition of exocyclic allylic alcohols, *i.e.* **21a-26a** (Table 4), was investigated, even if the corresponding α,β-unsaturated products might be alternatively prepared with the above cited methodologies.

First, the oxidative rearrangement of allylic alcohols **21a-23a** with method A failed, and we managed to obtain the fragrance isocitronellal **22b** in a modest yield of 49%, but with method B.

Much more interesting was the result obtained for the rearrangement of the diastereomeric mixture of alcohol **24a** (*E/Z*, ≈ 1:1, by ¹H-NMR), which gave mainly ketone (*E*)-**24b** (*de*>95%, by GC-MS) in a yield of 77%. By repeating the reaction at a lower pH, the yield slightly improved, the same effect being observed also on the *p*-OMe derivative **25a**, which demonstrated to be a well-accepted substrate. Instead, when the hydrogen at *para* position of the phenyl ring was substituted with the electron withdrawing -NO₂ group (**26a**, Table 4), or the pH was higher than 6.0 (data not shown), no enone formation was detected. The dynamic kinetic resolution of **24a-25a** is likely due to three concomitant effects: i) the reaction goes first through the formation of the secondary allylic alcohol intermediate (for alcohols **24a-25a** the acid catalysed isomerization is occurring even at pH 5.2), and the equilibrium between the two geometrical isomers is shifted toward the most stable (*E*) diastereoisomer; ii) the (*E*)/(*Z*) interconversion is much faster than the TEMPO⁺BF₄⁻ catalysed oxidative process, and iii) the oxidation of the (*E*) secondary

alcohol is much faster than that of its (*Z*) isomer (see SI for more details on the proposed mechanism).

Table 4. Oxidative rearrangement of exocyclic tertiary allylic alcohols.^[a]

Substrate	Product	Met.	Yield (%) ^[b]
		A	–
		A B	– 49
		A	–
		A A ^[d]	77 84
		A A ^[d]	74 82
		A A ^[d]	– –

^[a] Typical exp. cond. on 50 mL scale. See Table 3 for Met. A or B; ^[b] After work-up; ^[d] At pH=4.0, acetate buffer.

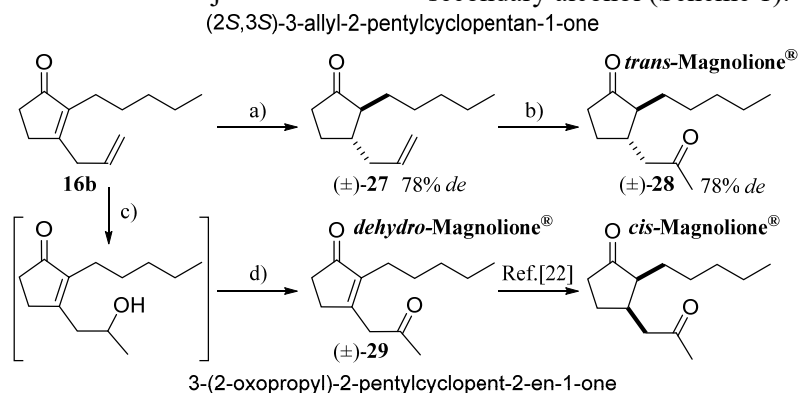
Finally, according to our ongoing research program on fragrances chemistry, we focused our attention on the development of synthetic routes for Magnolione[®] (**28**) and dehydro-Magnolione[®] (**29**) from the enone **16b** obtained in the previously described work (Scheme 1).

Magnolione[®] is a fragrance structurally very similar to the well-known Jasmonate, but in comparison to the latter it displays a more intense floral jasmine note-

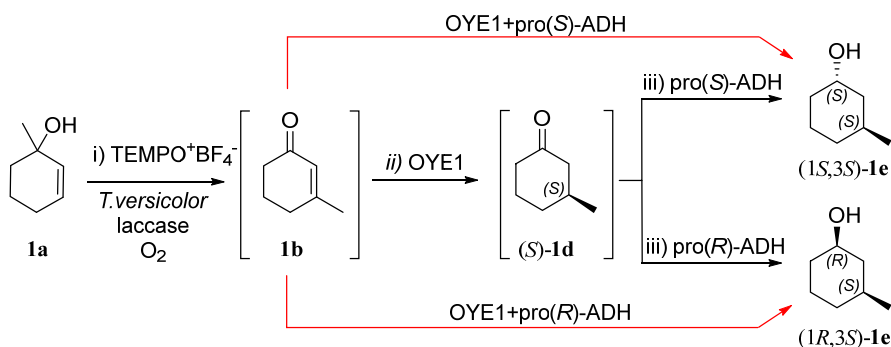
odour and an increased chemical stability. It is commercialized as a mixture of its four stereoisomers, but, as often happen for chiral odorous molecules, its olfactory properties are strongly related to its (relative and/or absolute) stereochemistry.¹⁸ Indeed, the odour of both enantiomers of the *trans* diastereoisomer is weakly floral with a metallic bottom note, while the racemic mixture of the *cis* isomer exhibits a more pleasant and floral/fruity scent,¹⁹ even if for this diastereoisomer the (2*S*,3*R*)-stereoisomer is much more intense than its enantiomer. Thus, in consideration of this odour profile, a diastereoselective synthesis might be sufficient to provide an added value to Magnolione[®] fragrance. To this end, in the following we show how intermediate **16b** is a suitable synthon for the diastereoselective synthesis of Magnolione[®].

First of all, the endocyclic C=C double bond of enone **16b** was regioselectively reduced using classical Birch reaction conditions affording the *trans*-cyclopentanone **27** in 67% yield and with a *de* of 78% (by GC-MS and by ¹H-NMR). Then, to transform the terminal C=C double bond into a methyl ketone, Wacker oxidation was exploited. We tested first the classical method²⁰ (catalytic amount of PdCl₂ with a stoichiometric amount of CuCl₂ in DMF/H₂O under an O₂ atmosphere at 60 °C), but the yield was not sufficiently high due to the presence of several by-products, principally chlorinated products. Hence, we decided to switch from Cu(II) to Cu(I) salt, since the latter minimizes the concentration of chlorine and consequently the side reactions. Indeed, by using the Tsuji-Wacker variant, we managed to isolate the *trans*-Magnolione[®] **28** in a good yield of 85%, with an unaltered *de*.²¹

The attempt of transforming directly **16b** into the dehydro-Magnolione[®] **29** by Tsuji-Wacker oxidation failed, likely for the presence of the conjugated endocyclic C=C double bond, which, in our case, seemed to inhibit the generation of the methyl ketone. Thus, a two steps synthetic pathway was explored: i) Markovnikov hydration of the terminal C=C double bond of **16b**; ii) oxidation of the newly formed secondary alcohol (Scheme 1).



Scheme 1. a) Li, *t*-BuOH, NH₃(l), -78 °C, 67%; b) PdCl₂, CuCl, DMF/H₂O (7:1), O₂ bubbling, 85%; c) Hg(OAc)₂, NaBH₄, THF/H₂O (1:1); d) DMP, CH₂Cl₂, 0 °C, 74% over two steps.



Scheme 2. Integrated chemo-multienzymatic process: i) [1,3]-oxidative transposition; ii) OYE1 catalyzed reduction of C=C double bond; iii) ADH catalyzed carbonyl reduction.

Our strategy was successfully accomplished by oxymercuration of **16b**, followed by demercuration with NaBH₄ affording the alcohol intermediate, which was oxidized to **29** with Dess-Martin periodinane (DMP) in an overall yield of 74%, after column chromatography purification. We opted for a telescopic approach since the isolation of the alcohol intermediate resulted very difficult and low yielding.

Finally, the dehydro-Magnolione[®] **29** might be transformed into the most pleasant stereoisomer of Magnolione[®], *i.e.* the (2*R*,3*S*)-**28**, by Ruthenium catalysed asymmetric hydrogenation of the conjugated C=C double bond.²²

Integration of the Chemo-Enzymatic Oxidative Rearrangement in a Multienzymatic Cascade Process

In the last years, several examples of how different enzymatic activities can be simply integrated either in sequential or cascade multi-step processes have been reported.²³ Especially, we found very profitable the combination of ene-reductases (ERs, enzymes that catalyse the asymmetric reduction of electronically activated C=C double bonds) with alcohol dehydrogenases (ADHs, enzymes capable of reducing/oxidising ketones/alcohols) in the stereoselective synthesis of flavours,²⁴ fragrances,²⁵ natural products²⁶ or active pharmaceutical ingredients,²⁷ starting from α,β -unsaturated ketones. Therefore, in this regard, the TEMPO/laccase-catalysed rearrangement of a tertiary allylic alcohols could be an ideal partner of the ER-ADH catalytic system, allowing the set-up of a more complex and challenging multi-step process.

As proof of concept, the stereoselective transformation of **1a** into the *trans* alcohol (1*S*,3*S*)-**1e** or *cis* alcohol (1*R*,3*S*)-**1e** was herein investigated (Scheme 2).

Starting with, enone **1b** is one of the benchmark substrates typically used in the screening of ene-reductases activity. So far, among all ERs tested, OYE1 and OYE2 (belonging to the Old Yellow Enzymes family) achieved the best conversion of **1b** into the ketone (*S*)-**1d** (74% and 60% for OYE1 and OYE2, respectively) with an excellent

enantioselectivity (*ee* >99%),²⁸ To knowledge of the authors, for this substrate no ERs with (*R*) selectivity have been so far reported.

Preparative scale reactions (5 mM, 50 mg scale) afforded lower yields respect to those reported in literature, however we confirmed the (*S*) absolute stereochemical configuration and the high optical purity of the product. After some optimization of the reaction conditions we managed to increase the conversion, by using OYE1 under an N₂ atmosphere and a prolonged reaction time (for more details see SI). The NAD(P)H cofactor regeneration was carried out using a glucose dehydrogenase (GDH from *Bacillus megaterium*), with glucose as sacrificial co-substrate.²⁹ To complete the cascade set-up, two crucial issues of the ADH catalysed step were left: *i*) the chemoselectivity and *ii*) the stereoselectivity. To this aim we tested a set of commercially available ADHs (recombinant and/or purified) from different sources (Table 5) on the reduction of a mixture of enone **1a** and saturated ketone (*S*)-**1b** (\approx 1:1).

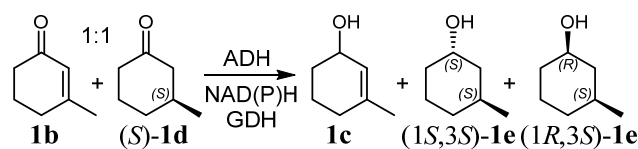
Remarkably, all the screened ADHs showed a complete chemoselectivity³⁰ towards the reduction of ketone (*S*)-**1d** with the only exception of PLADH (ADH from *Parvibaculum lavamentivorans*), which was able to reduce also a small amount of enone **1b** affording the side-product **1c**.

Concerning the stereoselectivity, it turned out that READH (ADH from *Rhodococcus erythropolis*) and TBADH (ADH from *Thermoanaerobium Brockii*) enzymes reduced the carbonyl group affording mainly the alcohol with (*S*) configuration at the newly generated stereogenic centre, *i.e.* (1*S*,3*S*)-**1e**, with an excellent *de*>98%; whereas PLADH and DRADH (ADH from *Deinococcus radiodurans*) showed an enantiocomplementary stereoselectivity affording mainly the *cis* diastereoisomer, (1*R*,3*S*)-**1e** (*de*>90%). The other screened ADHs gave alcohol **1e**, either *cis* or *trans*, in good yields but with modest *des*.

With the most performing ADHs and ER in our hands we tested the reductive cascade process (OYE1 + READH for the synthesis of *trans*-**1e** or OYE1 + PLADH for the synthesis of *cis*-**1e**) on a preparative scale. At the end, we managed to obtain discrete overall yields (around 80% over two steps) only by

lowering the substrate concentration from 5.0 mM to 2.5 mM (for more details see SI).

Table 5. Chemoselectivity and stereoselectivity of ADH mediated reductions. ^[a]



ADH	Reaction Mixture (%) ^[b]			
	1b	1d	1c	1e ^[c,d]
CPADH	46.9	46.6	— ^[e]	6.5 (69:31)
READH	48.7	38.8	— ^[e]	12.5(99:1)
BYADH	43.6	56.4	— ^[e]	—
HLADH	47.2	25.2	— ^[e]	27.6 (83:17)
PLADH ^[f]	38.7	0.6	5.3	55.4 (5:95)
DRADH	47.6	—	— ^[e]	52.4 (1:99)
TBADH	46.4	23.8	— ^[e]	29.8 (99:1)
KRED	46.8	0.2	— ^[e]	53.0 (84:16)

^[a] Screening conditions on 1 mL scale: [substrate] = 5 mM, **1b/1d** ≈ 1:1 mixture, ADH 100 μg mL⁻¹, GDH 4 U mL⁻¹, 4 equiv. of glucose, 0.1 mM NAD(P)⁺, 50 mM KPi buffer pH 7.0, 30 °C, 160 rpm, reaction time 12 h; ^[b] Conversion by GC-MS; ^[c] As a sum of *cis* + *trans* diastereoisomers; ^[d] Indicated in bracket the *trans/cis* ratio of the *O*-Silyl derivatives obtained by treatment with TMSiCl and NEt₃; ^[e] Not detected; ^[f] This ADH is likely contaminated with ER activity.

Lastly, we integrated the oxidative rearrangement with the reductive ER-ADH cascade process in a one-pot three-step sequence. In the first step **1a** (50 mM) was rearranged to **1b** with the TEMPO⁺BF₄⁻/laccase system at pH 5.2 under an O₂ atmosphere. After 24 h, the reaction mixture was diluted to 2.5 mM, brought at neutral pH and, under a N₂ atmosphere, OYE1 and the selected pro-(*S*) or pro-(*R*) ADH were added together with the cofactor regenerating system (GDH, NAD(P)⁺, glucose), affording the alcohol *cis*-**1e** or *trans*-**1e** in an overall yield of 85% and 82%, respectively.

Conclusion

In summary, a “green” methodology for the [1,3]-oxidative transposition of tertiary allylic alcohols has been developed: we have exploited the tetrafluoroborate oxoammonium salt of TEMPO, an established non-heavy metal oxidant, in alternative to the very toxic oxochromium(VI)-based reagents. In the catalytic cycle, the Bobbitt’s salt is efficiently regenerated by the laccase enzyme under aerobic conditions and at room temperature. The methodology is particularly suited for the preparation of cyclic enones of medium size (either five- or six-membered rings), since for this class of substrates the rearrangement’s mechanism in water is favoured by the intrinsically higher ring-strain of these substrates. Instead, the rearrangement of endocyclic tertiary alcohols either bearing EWGs on the side chain or with

rings of large size gave scarce results. For these kind of substrates, the oxidative rearrangement is usually more efficient in organic solvents. However, our catalytic system has proven to be very tolerant to both type of solvent. Indeed, by immobilizing laccase on porous glass beads we accomplished several oxidative rearrangements in MeCN.

The practical usefulness of our methodology was demonstrated by the successful preparation of several fragrances, such as dehydro-Jasmonate, dehydro-Hedione[®], dehydro-Muscone and iso-citronellal. In addition, we have shown that the cyclopentenone **16b**, bearing the allyl substituent, is a suitable intermediate for the diastereoselective synthesis of Magnolione[®] through the dehydro-Magnolione[®] intermediate.

Lastly, we have demonstrated that the oxoammonium/laccase mediated oxidative transpositions can be coupled in a sequential process with other two redox reactions: i) the OYE1 catalysed stereoselective reduction of the newly formed conjugated C=C double bond followed by ii) the ADH catalysed asymmetric reduction of the prochiral ketone. This rather complex chemo-multienzymatic catalytic system has been tested on substrate **1a** as a model; by judicious selection of a suited ADH was possible to obtain either the *trans* alcohol, *i.e.* (1*S*,3*S*)-**1e**, or the *cis* alcohol, *i.e.* (1*R*,3*S*)-**1e**, in a good overall yield and in both cases with an excellent diastereomeric excess.

Experimental Section

General Information.

Chemicals and solvents were purchased from suppliers and used without further purification, while, where required, the solvents were dried over molecular sieves (4 Å). ¹H and ¹³C NMR spectra were recorded on a 400 MHz spectrometer at room temperature, using TMS as an internal standard for ¹H and CDCl₃ for ¹³C; chemical shifts δ are expressed in ppm relative to the reference. High-resolution MS spectra were recorded with a Q-TOF mass spectrometer, equipped with an ESI source. The GC-MS analyses of all compounds were performed on a column with a low polarity stationary phase (30 m × 0.25 mm × 0.25 μm). Program temperature: 60 °C (1 min)/6 °C min⁻¹/150 °C (1 min)/12 °C min⁻¹/280 °C (5 min). TLC analyses were performed on precoated silica gel 60 F₂₅₄ plates, and spots were visualized either by UV light (254 nm) or by spraying with phosphomolybdic acid reagent. All chromatographic separations were carried out on silica gel columns (230–400 mesh). Optical rotations were determined on a digital automatic polarimeter at 589 nm (sodium D line) and are given at rt in deg cm³ g⁻¹ dm⁻¹.

Enzymes and Strains.

OYE1 from *Saccharomyces pastorianus*, OYE2 from *Saccharomyces cerevisiae* and GDH from *Bacillus megaterium* were overexpressed in *E. coli* BL21 (DE3) strains harbouring a specific plasmid, according to standard molecular biology techniques as described in ref. [29]. Protein concentrations were determined according to Bradford test, using bovine serum albumine (BSA) as a standard. CPADH from *Candida parapsilosis* and READH from *Rhodococcus erythropolis* were purchased from Julich Chiral Solutions GmbH (now CODEXIS). PLADH from *Parvibaculum lavamentivorans*, DRADH from *Deinococcus radiodurans*, BYADH from *Saccharomyces*

cerevisiae, HLADH from horse liver, TBADH from *Thermoanaerobium brockii*, KRED (ketoreductase) from an unspecified source and laccase from *Trametes versicolor* (activity ≥ 10 U mg⁻¹) were purchased from Sigma-Aldrich.

General Procedure for the Oxidative Rearrangement in Water (Method A)

To a solution of a tertiary allylic alcohol (1.0 mmol) in AcONa buffer (50 mM, pH 5.2, 20 mL, 200 μ L DMSO) were added TEMPO⁺BF₄⁻ (0.2 mmol, 49 mg) and *T. versicolor* laccase (4 mg) in a Schlenk tube. The reaction mixture was purged with pure O₂ and then stirred at 30 °C for 24 h under an O₂ atmosphere (balloon). Then, HCl (0.1 M) was added to the reaction mixture and the aqueous layer was washed with Pentane/Et₂O (7:3, 10 mL x 2). The combined organic layers was washed with brine (sat., 20 mL x 1), dried over Na₂SO₄ and concentrated under *vacuum*. Where needed, the crude material was submitted to column chromatography purification.

General Procedure for the Oxidative Rearrangement in MeCN (Method B)

To a solution of a tertiary allylic alcohol (1.0 mmol) in MeCN (15 mL) was added TEMPO⁺BF₄⁻ (0.15 mmol, 49 mg) and laccase adsorbed on glass beads (2.5 g, beads/laccase 50:1) The solution was stirred at 30 °C for 24 h under an O₂ atmosphere (balloon). Then, the reaction mixture was filtered concentrated under reduced pressure and diluted with Et₂O. The organic layer was washed with brine (sat., 20 mL x 1), dried over Na₂SO₄ and concentrated under *vacuum*. The crude material was submitted to column chromatography purification.

Synthesis of Magnolione[®] and dehydro-Magnolione[®]

3-Allyl-2-pentylcyclopent-2-enone (16b). Method A: 163.2 mg; 85% yield; 99% purity by GC (t_R = 18.48 min), ¹H NMR (400 MHz, CDCl₃): δ 5.86-5.76 (m, 1H), 5.16-5.12 (m, 2H), 3.17 (d, J = 6.64, 2H), 2.49 (t, J = 3.92, 2H), 2.36 (t, J = 4.72, 2H), 2.18 (t, J = 7.36, 2H), 1.41-1.26 (m, 6H), 0.87 (t, J = 6.56, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 209.7, 170.4, 141.0, 133.2, 117.5, 35.7, 34.2, 31.8, 29.0, 28.2, 23.0, 22.4, 13.9; MS: m/z (%) 192 [M]⁺ (38), 177 (58), 163 (12), 151 (100), 135 (46); HRMS exact mass calculated for [M+H]⁺ (C₁₃H₂₁O) requires m/z 193.1592, found m/z 193.1587.

(trans)-3-Allyl-2-pentylcyclopentanone (27). Lithium (140 mg, 20 mmol) was added to liquid ammonia (60 mL) at -78 °C. After stirring for 15 minutes, a solution of **16b** (384 mg, 2 mmol) and *t*-BuOH (0.92 μ L, 10 mmol) in THF (4 mL) were added at -78 °C and the reaction mixture was stirred for 45 minutes. Then, H₂O (40 mL) was carefully added at the same temperature and the reaction was warmed up to allow ammonia to evaporate. Hence, Et₂O (2x40 mL) was added and the combined organic layer was washed with brine (sat., 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure.³¹ The crude product was purified by column chromatography (gradient eluent: *n*-Hex/AcOEt, 95:5) to afford **27** as a colorless oil: 260 mg; 67% yield; 99% purity by GC (t_R (*trans*) = 16.77 min, t_R (*cis*) = 17.40 min), ¹H NMR (400 MHz, CDCl₃): δ 5.82 (m, 1H), 5.11-5.03 (m, 2H), 2.43-1.72 (m, 8H), 1.51 (m, 4H), 1.27 (m, 4H), 0.88 (t, J = 6.84, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 220.7, 135.9, 116.6, 54.2, 41.3, 38.7, 37.6, 32.1, 28.2, 26.6, 26.6, 22.4, 13.9; MS: m/z (%) 194 [M]⁺ (1), 153 (13), 124 (6), 109 (2), 97 (4), 83 (100).

3-(2-Oxopropyl)-2-pentylcyclopentanone (Magnolione[®], trans-28). To a stirred solution of DMF/H₂O (7:1, 5.6 mL), PdCl₂ (124 mg, 0.7 mmol) and CuCl (693 mg, 7 mmol, 1 eq.) were added under an O₂ atmosphere. The reaction mixture was stirred for 1 hour to allow oxygen uptake. Then, **27** (1.36 g, 7 mmol) was added dropwise. The color of the solution turned from green to black within 10 minutes and

returned gradually to green.³² After 6 hours, the reaction mixture was quenched with a solution of HCl (0.1 M, 20 mL), filtered on a pad of Celite and washed with Et₂O (30 mL). The organic layer was separated, washed with brine (sat., 20 mL), dried over Na₂SO₄, filtered and concentrated under *vacuum*. The crude product was purified by column chromatography (gradient eluent: *n*-Hex/AcOEt from 90:10 up 80:20) to afford **29** as a colorless oil: 1.25 g; 85% yield; 99% purity by GC (t_R = 20.05 min), ¹H NMR (400 MHz, CDCl₃): δ 2.76-2.09 (m, 8H), 1.73 (m, 1H); 1.53 (m, 2H); 1.45-1.24 (m, 7H); 0.88 (t, J = 6.80, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 219.5, 207.1, 54.2, 48.4, 37.6, 37.1, 32.0, 30.4, 28.0, 27.3, 26.4, 22.4, 13.9;³³ MS: m/z (%) 210 [M]⁺ (7), 195 (1), 181 (1), 167 (1), 153 (100), 140 (37), 125 (23).

3-(2-Oxopropyl)-2-pentylcyclopent-2-enone (dehydro-Magnolione[®], 29). To a stirred, completely dissolved solution of Hg(OAc)₂ (1.84 g, 5 mmol) in H₂O (5 mL) THF (5 mL) was added. The solution was bright yellow. Then, **29** (960 mg, 5 mmol) was added dropwise and the reaction mixture was stirred at room temperature till the solution faded. Thus, NaOH (6 M, 3 mL) and NaBH₄ (0.5 M, 5 mL) in 3 M NaOH were carefully added, keeping the temperature below 25 °C. The reaction was stirred for 2 hours till Hg precipitated as a shiny liquid. Hence, the reaction mixture was filtered on a Celite pad, washed with AcOEt (20 mL x 2). The organic layer was extracted, washed with brine (sat., 20 mL), dried over Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The crude, intermediate product was used in the next step without further purification.³⁴ Then, the intermediate was dissolved in CH₂Cl₂ (50 mL), trapped with a CaCl₂ valve and the reaction mixture was cooled to 0 °C. Successively, DMP (2.33 g, 5.5 mmol) was slowly added and the mixture was stirred for 24 hours. Hence, the solution was extracted with CH₂Cl₂ (30 mL), washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under *vacuum*. The titled product was purified by column chromatography (gradient eluent: *n*-Hex/AcOEt from 90:10 up 70:30) to afford **29** as a colorless oil: 770 mg; 74% yield; 99% purity by GC (t_R = 20.89 min), ¹H NMR (400 MHz, CDCl₃): δ 3.56 (s, 2H), 2.54 (t, J = 4.76, 2H), 2.39 (qt, J = 2.72, 2H), 2.24 (s, 3H), 2.16 (t, J = 7.52, 2H), 1.39-1.24 (m, 6H), 0.87 (t, J = 6.84, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 208.9, 203.0, 164.0, 143.1, 45.8, 34.3, 31.7, 30.2, 29.9, 27.9, 23.3, 22.3, 13.8; MS: m/z (%) 208 [M]⁺ (5), 193 (16), 179 (2), 165 (9), 151 (100), 137 (15); HRMS exact mass calculated for [M+H]⁺ (C₁₃H₂₁O₂) requires m/z 209.1542, found m/z 209.1548.

To a solution of **1a** (1.0 mmol) in AcONa buffer (50 mM, pH 5.2, 10 mL, 800 μ L DMSO) were added TEMPO⁺BF₄⁻ (0.15 mmol, 37 mg) and *T. versicolor* laccase (4 mg) in a Schlenk tube. The reaction mixture was purged with pure O₂ and then stirred at 30 °C under O₂ atmosphere (balloon). After 24 h the reaction mixture was purged with N₂, diluted with a phosphate buffer solution (50 mM, pH 7, 190 mL), and then glucose (720 mg, 4 mmol), NAD(P)⁺ (14 mg+14 mg), GDH (4 U/mL), OYE1 (80 μ g/mL), and PLADH (250 μ g/mL) or and READH (250 μ g/mL), were added. After 48 h, the reaction mixture was extracted with a pentane/Et₂O solvent mixture (7:3, 40 mL x 3). The combined organic layers was dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude material was submitted to column chromatography purification (Pentane/Et₂O, 9:1, SiO₂) affording alcohol **1e**.

(1S,3S)-3-Methylcyclohexanol ((1S,3S)-1e). Bioreduction with OYE1 and READH: 97 mg, 85 % isolated yield, [α]_D = + 6.7 (c 1.0, CH₂Cl₂), vs. Lit. [α]_D = 6.7 (neat).³⁵ ¹H NMR (400 MHz, CDCl₃): δ 4.06-4.01 (m, 1H), 1.72-1.57 (m, 4H), 1.53-1.46 (m, 2H), 1.32-1.17 (m, 2H), 1.01-0.91 (m, 1H), 0.88 (d, J = 6.7, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 66.9, 41.6, 34.2, 33.1, 26.5, 21.9, 20.0; MS: m/z (%) 96 [M-18]⁺ 94 (51), 81 (77), 71 (100), 57 (49).

(1R,3S)-3-methylcyclohexanol ((1R,3S)-1e). Bioreduction with OYE1 and PLADH: 93 mg, 82% isolated yield, [α]_D = < 3.0 (c 1.0, CH₂Cl₂), lit. [α]_D = +1.8 (neat).³⁶ ¹H NMR (400

MHz, CDCl₃): δ 3.56 (tt, *J*=10.9, 4.3, 1H), 1.99-1.88 (m, 2H), 1.79-1.70 (m, 1H), 1.63-1.56 (m, 1H), 1.51-1.34 (m, 2H), 1.30-1.19 (m, 2H), 1.17-1.03 (m, 2H), 0.92 (d, *J*=6.6, 3H), 0.91-0.85 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 70.4, 44.4, 35.2, 34.0, 31.3, 24.1, 22.2; MS: *m/z* (%) 96 [M-18]⁺ 94 (51), 81 (65), 71 (100), 57 (32).

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