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A one-pot two-step synthesis of tertiary alcohols combining the biocatalytic laccase/TEMPO oxidation system with organolithium reagents in aerobic aqueous media at room temperature†‡

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The one-pot/two-step combination of enzymes and polar organometallic chemistry in aqueous media is for the first time presented as a proof-of-concept study. The unprecedented combination of the catalytic oxidation of secondary alcohols by the system laccase/TEMPO with the ultrafast addition (3 s reaction time) of polar organometallic reagents (RLi/RMgX) to the *in situ* formed ketones, run under air at room temperature, allows the straightforward and chemoselective synthesis of tertiary alcohols with broad substrate scope and excellent conversions (up to 96%).

Polar *s*-block organometallic reagents (mainly organolithium[1] and organomagnesium[2] reagents) are well known to have a pivotal role in the functionalisation of organic molecules both in the chemical industry and in academia. However, owing to the high polarity of their metal–carbon bonds, their use in organic synthesis traditionally requires restricted reaction conditions *i.e.*, low temperatures (up to −78 °C), protecting atmosphere (N_2 or Ar) and meticulous dry volatile and hazardous organic solvents],[1,2] in order to minimize undesired side reactions (*e.g.*, hydrolysis, oxidations, rearrangements and attack to sensitive functional groups). Thanks to the recent work by different research groups worldwide,[3] the conventional wisdom that RLi/RMgX reagents need to be used under the aforementioned Schlenk-type conditions is now changing. In this sense, we have recently reported on the effective use of protic and biorenewable solvents [like H_2O, glycerol and the so-called *Deep Eutectic Solvents* (*DESs*)[4]] as privileged reaction media to promote: (i) the addition of RLi/RMgX reagents to different organic electrophiles;[5] (ii) *ortho*- and lateral litiations of aromatic substrates;[6] (iii) anionic living polymerisation of styrenes;[7] (iv) Pd-catalysed cross-couplings involving organolithium and organozinc reagents as nucleophiles;[8] and (v) formation of C–X (X = P or N) bonds by using lithium-amides or -phosphides.[9] These recent findings pave the way to design new sustainable and hybrid[10] one-pot tandem protocols,[11] which could conveniently combine the aforementioned highly efficient main-group-mediated organic transformations with other synthetic procedures available in the general toolbox of organic chemists, for which a core of knowledge under more sustainable conditions has been already achieved.[12] In this vein, some of us have pioneered this field by describing the successful combination between RLi/RMgX reagents and transition-metal (Ru,[13a] Pd[6c,8a]) or organo-catalysed[13b] transformations in water or in *DESs* under bench-type reaction conditions. However, as far as we are aware, the possibility to promote *s*-block organometallic chemistry (RLi/RMgX) in the presence of enzymes/co-factors has been totally neglected, probably as a consequence of the common assumption that these polar reagents rapidly decompose under the conditions usually employed in enzymatic protocols (using water or *DESs* as solvent, under air and at room temperature).[14] Thus, trying to finish with this discontinuity, a new hybrid one-pot tandem protocol that combines (in a two-step fashion without the need of isolation/purification protocols) the commercially available laccase from *Trametes versicolor*[15] with RLi/RMgX reagents is herein reported as a proof-of-concept study. The described methodology has been set in aqueous media, under air and at room temperature (rt), a trio of conditions regarded as completely incompatible with these highly reactive organometallic compounds[1] (Scheme 1). Importantly, the targeted tertiary alcohols are among the most useful and versatile building blocks for the synthesis of pharmaceuticals and natural products.[16]

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† In memory of Prof. Victor Riera, a leading authority in Spanish Organometallic Chemistry.

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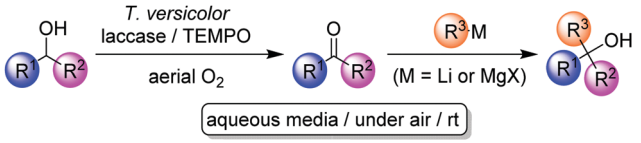
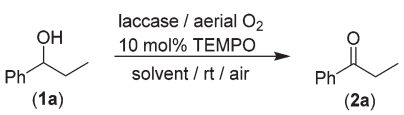


Scheme 1 Design of an unprecedented hybrid one-pot tandem protocol through the successful combination of *s*-block reagents (RLi/RMgX) and enzymes (laccase from *Trametes versicolor*) in aqueous media, at room temperature and under air.

Building on our recent study on the one-pot/two-step combination of the laccase-promoted oxidation of primary alcohols in water with a palladium-catalysed cycloisomerisation/hydrolysis of pentynols,[17] we selected as a model reaction the oxidation of the secondary benzylic alcohol **1a** by the laccase/TEMPO system which demands O_2 as the oxidant and generates only water as a by-product (Table 1). Firstly, we compared the oxidative catalytic activity of this system in different aqueous environments in order to find the right conditions compatible with the second step of our targeted one-pot/two-step tandem protocol, that is the addition of RLi/RMgX reagents to the *in situ* formed ketones (entries 1–3, Table 1). In addition to the usually employed reaction medium in previously reported oxidations promoted by laccase/TEMPO (*i.e.*, citrate buffer 50 mM with pH = 5.5; entry 1, Table 1),[15] we also investigated the use of bulk water or brine as solvents (entries 2 and 3, Table 1).[8a] We found quantitative formation of the desired ketone **2a** when either citrate buffer or bulk water were used as the reaction media after 24 h, at rt and in the presence of air. The formation of ketone **2a** was ascertained by means of its isolation and characterisation by NMR (see ESI‡). Conversely, when brine was employed as the solvent, a total shut down of the oxidation reaction was observed (entry 3).[18] Finally, the effectiveness of other commercially available laccases was also studied: (i) *T. Versicolor*, but with a different activity (0.5 U mg^{-1} *vs.* 10 U mg^{-1}, entry 4, Table 1); and (ii) *Rhus vernicifera* (50 U mg^{-1}, entry 5, Table 1), but no improvement in the oxidation process was observed.

Since the buffer citrate and bulk water displayed the best results in terms of both reaction time and conversion, we decided to investigate a tandem combination of the oxidation of alcohol **1a** by the system laccase/TEMPO in the presence of aerial O_2 with the chemoselective addition of RLi/RMgX reagents to the intermediate ketone **2a**, at rt and in the presence of air (Table 2). This unprecedented one-pot tandem transformation, which first describes the possibility to promote polar organometallic chemistry in the presence of enzymes, cofactors and buffers, would open the door to the design of new and straightforward hybrid protocols granting access to tertiary alcohols under mild, simple and environmentally friendly reaction conditions. To this end, the laccase/TEMPO oxidation of 1-phenylpropan-1-ol (**1a**) into the corresponding ketone **2a** was followed by the direct addition of *n*-BuLi to the resulting aqueous-based reaction mixture (no isolation/purification of any intermediate was required).[19] Firstly, the reaction mixture containing the alcohol **1a** and the oxidation system (laccase/TEMPO) was allowed to react in the buffer citrate (entry 1, Table 2) or bulk water (entry 2, Table 2), at rt and in the presence of air for 24 h, to trigger the desired oxidation. As soon as the conversion of **1a** into propiophenone (**2a**) was complete (24 h, GC analysis),[19] *n*-BuLi was directly added to the reaction mixture in the absence of any protecting

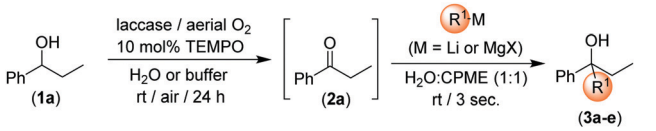
Table 1 Oxidation of 1-phenylpropan-1-ol (**1a**) into propiophenone (**2a**) promoted by the system laccase/TEMPO in different aqueous media, at room temperature and under air[a]



Entry	Laccase	U/mg[bc]	Time (h)	Solvent	Conv.[d] (%)
1	*T. Versicolor*	10	24	Buffer citrate	99
2	*T. Versicolor*	10	24	H_2O	99
3	*T. Versicolor*	10	24	Brine	2
4	*T. Versicolor*	0.5	96	H_2O	88
5	*Rhus Vernicifera*	50	24	H_2O	2

[a] General conditions: reactions performed in an open vessel (the required O_2 oxidant is taken from the air), at rt using 0.73 mmol (0.1 mL) of the alcohol **1a**, 10 mol% (12 mg) of TEMPO, and 1 mL of the desired solvent. Buffer citrate 50 mM and pH = 5.5. [b] U mg^{-1} = Units of activity per mg of protein. [c] 14 mg of *T. Versicolor* 10 U mg^{-1} or 280 mg of *T. Versicolor* 0.5 U mg^{-1} or 2.8 mg of *Rhus Vernicifera* 50 U mg^{-1} were employed. [d] Conversions were determined by GC analysis.

Table 2 Hybrid one-pot tandem protocol merging oxidation of 1-phenylpropan-1-ol (**1a**) promoted by the laccase/TEMPO system with the chemoselective addition of RLi/RMgX in biphasic aqueous media, at room temperature and in the presence of air[a]



Entry	R-M[b]	Equiv.	Solvent	Product	Conv. (%)[e]
1	*n*-BuLi	3	Buffer citrate	**3a**	28
2	*n*-BuLi	3	H_2O	**3a**	22
3	*n*-BuLi	3	H_2O/NaCl	**3a**	28
4	*n*-BuLi	3	H_2O/Ultrasound[c]	**3a**	29
5	*n*-BuLi	3	H_2O/CPME[d]	**3a**	83
6	*n*-BuLi	2	H_2O/CPME[d]	**3a**	78
7	MeLi	3	H_2O/CPME[d]	**3b**	83
8	*s*-BuLi	3	H_2O/CPME[d]	**3c**	85
9	*t*-BuLi	3	H_2O/CPME[d]	**3d**	80
10	PhLi	3	H_2O/CPME[d]	**3e**	91
11	PhMgBr	3	H_2O/CPME[d]	**3e**	33

[a] General conditions: reactions performed in an open vessel (the required O_2 oxidant is taken from the air), at rt using 0.365 mmol (0.05 mL) of the alcohol **1a**, commercially available laccase from *T. Versicolor* (10 U mg^{-1}; 7 mg) with 10 mol% (6 mg) of TEMPO, and 0.5 mL of the desired solvent. [b] Commercially available 2.5 M solution of *n*-BuLi in hexanes, 1.6 M solution of MeLi in Et_2O, 1.4 M solution of *s*-BuLi in cyclohexane, 1.7 M solution of *t*-BuLi in pentane, 1.9 M solution of PhLi in dibutyl ether and 1.0 M solution of PhMgBr in THF were directly added at rt and under air after 24 h of reaction. [c] Conventional ultrasound bath operating at 35 KHz and 160 W was used. [d] 0.5 mL of CPME were added (H_2O/CPME ratio 1 : 1). [e] Conversions determined by GC analysis.

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atmosphere and at rt. Thus, under these biocatalytic conditions usually forbidden for RLi reagents,[1] we found that *n*-BuLi added instantaneously (within 3 s) to the *in situ* formed ketone **2a** to furnish the desired tertiary alcohol **3a**, both in pure water and in the citrate buffer, though conversions were only modest (22–28%, entries 1 and 2, Table 2). Chemoselectivity, however, in both cases was remarkable as no by-products were detected in the reaction crudes, aside from ketone **2a** and tertiary alcohol **3a**.[20,21] Here, we should mention that the expected side reaction between *n*-BuLi and TEMPO was not detected,[22] thus demonstrating that the use of RLi reagents under these "biocatalytic" conditions can change the expected selectivity of a given reaction. No beneficial effects were observed either by running the transformation in the presence of NaCl (saturated solution; entry 3, Table 2)[8a] or by making use of ultrasound in place of magnetic stirring (conversion increased up to 29%, entry 4, Table 2). With our delight, the employment of a biphasic mixture such as water/cyclopentyl methyl ether (CPME)[23] as the reaction medium impacted positively on the outcome of the process, with alcohol **3a** being now obtained in higher conversion (83%; entry 5, Table 2).[24] By lowering the equivalents of *n*-BuLi from 3 to 2, the addition reaction proved to be less effective leading to lower conversions (78%) of the desired alcohol **3a** (entry 6, Table 2).

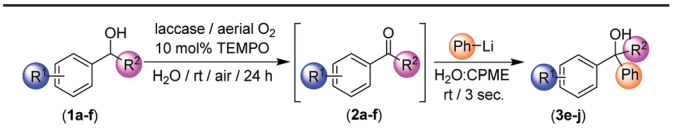
Under these optimised reaction conditions, the scope of this one-pot/two-step tandem hybrid transformation was investigated by using other organolithium and organomagnesium reagents as nucleophiles. In this sense, both aliphatic (MeLi, *s*-BuLi or *t*-BuLi) and aromatic (PhLi) organolithium reagents led to the expected tertiary alcohols **3b–e** with excellent conversions and chemoselectivities (80–91%; entries 7–10, Table 3) at rt and in the absence of protecting atmosphere (under air). These results are particularly remarkable in the case of highly reactive organolithium compounds like *s*-BuLi and *t*-BuLi, as these reagents have a greater tendency to undergo β-hydride elimination (*s*-BuLi and *t*-BuLi are usually stored and employed at low temperatures).[1] It is worth mentioning that different organic solvents coming from the used commercially available solutions of RLi reagents (hexanes for *n*-BuLi, diethyl ether for MeLi, cyclohexane for *s*-BuLi, pentane for *t*-BuLi and dibutyl ether for PhLi) are at the same time present in the aqueous mixture during the addition step. However, contrasting with our previous studies,[5] we have observed similar conversions for all the cases under study in the presence of CPME. Thus, no direct relationship between the miscibility of these organic solvents in water and the final conversion into the tertiary alcohols can be established. Finally, as for the less reactive Grignard reagents, PhMgBr was found to exhibit a reduced reactivity in the biphasic aqueous mixture producing alcohol **3e**, but in 33% conversion only (entry 11, Table 2).[25]

To expand even further the scope of this unique combination of enzymes and organolithium reagents in terms of the nature of the alcoholic substrate, we finally investigated the effectiveness of our hybrid one-pot/two-steps tandem protocol in the aforementioned biphasic aqueous medium with a series of secondary alcohols (**1a–f**, Table 3) by employing PhLi as the nucleophilic partner (best conversions were observed when using this organolithium reagent; see entry 10, Table 2) at rt in air. In all cases studied, the system laccase/TEMPO (in the presence of aerial O_2) was able to quantitatively produce (99% conversions, GC analysis) the desired aromatic ketones **2a–f** after 24 h reaction time.

Data collected in Table 3 also testify that our new hybrid tandem enzyme/RLi protocol tolerates a variety of functional groups in the aromatic ring, being compatible with either electron-withdrawing (Cl or Br, entries 3 and 4, Table 3) or electron-donating groups (Me, entries 5 and 6) at the *ortho*- or *para*-positions, thereby leading to the expected tertiary alcohols **3g–j** in good conversions (up to 83%) and without the need of any halfway step of isolation or purification of the intermediate ketones **2a–f**. In addition, other typical and expected competing processes when organolithium reagents are employed like: (i) the Li-halogen exchange reaction in alcohols **1c and d**; or (ii) the metalation of benzylic positions in substrates **1e and f** have not been observed. Finally, it is also remarkable that our new hybrid one-pot tandem system also works well with acetophenone-type ketones (**2b, d and f**; R^2 = Me; entries 2,4,6; Table 3) whereas previously reported addition protocols of RLi reagents proved to be totally inactive when such water-soluble substrates were subjected to alkylation/arylation with RLi reagents in bulk water.[13] This experimental observation could be related to the presence of CPME in the reaction mixture which would reduce the solubility of the starting reagents in water.

In summary, we have reported an unprecedented proof-of-concept that firstly demonstrates the feasibility to promote an organic transformation mediated by highly-polar organometallic chemistry (RLi/RMgX) under reaction conditions usually employed in biocatalytic processes [presence of enzyme/co-factors, using sustainable and protic solvents (H_2O) and under

Table 3 Hybrid one-pot tandem protocol combining the oxidation of secondary alcohols (**1a–f**) promoted by the laccase/TEMPO system with the chemoselective addition of PhLi in biphasic aqueous media, at room temperature and in the presence of air[ab]



entry	R^1	R^2	Product	Conv. (%)[c]
1	H (**1a**)	Et	**3e**	96
2	H (**1b**)	Me	**3f**	92
3	*p*-Cl (**1c**)	Et	**3g**	83
4	*p*-Br (**1d**)	Me	**3h**	65
5	*p*-Me (**1e**)	Et	**3i**	78
6	*o*-Me (**1f**)	Me	**3j**	78

[a] General conditions: reactions performed in an open vessel (the required O_2 oxidant is taken from the air), at rt using 0.365 mmol of the desired alcohols **1a–f**, commercially available laccase from *T. Versicolor* (10 U mg^{-1}; 7 mg) with 10 mol% (6 mg) of TEMPO, and 1 mL of the 1 : 1 mixture H_2O : CPME. [b] Commercially available solution of PhLi in dibutyl ether was directly added at rt and under air after 24 h. [c] Conversions determined by ^1H NMR spectroscopy.

bench-type conditions (room temperature and the absence of any protecting atmosphere) which are typically forbidden for organolithium and Grignard reagents. The reported new hybrid one-pot tandem protocol represents an operationally simple procedure that paves the way towards an effective and chemoselective synthesis (conversions up to 96%) of densely substituted tertiary alcohols through the successful combination of the oxidation of secondary alcohols (**1a–f**) promoted by the system laccase/TEMPO (in the presence of aerial O_2) with the chemoselective and ultrafast addition (3 s reaction time) of both aliphatic and aromatic organolithium (RLi) or Grignard (RMgX) reagents to the transiently-formed ketones **2a–f,** without tedious and energetic/time consuming purification/isolation intermediate steps.

Finally, it is worth noting that the role of a sustainable ethereal solvent such as CPME seems to be critical in the design of the one-pot tandem process able to cope with water-soluble intermediates (acetophenone-type ketones **2b, d and f**), thus circumventing one of the most important limitations of previously reported protocols. These results clearly demonstrate the feasibility of combining polar organometallic synthetic utensils (RLi/RMgX) with biocatalytic organic transformations under environmentally-friendly and bench-type conditions *en route* to a sustainable landscape. Further efforts devoted to the development of new hybrid one-pot tandem protocols in sustainable solvents are currently underway.

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Conflicts of interest

There are no conflicts to declare.

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