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Selective Aerobic Oxidation of Alcohols in Low Melting Mixtures and Water and Use for Telescoped One-Pot Hybrid Reactions

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An efficient, selective and sustainable protocol was developed for the $CuCl_2$/TEMPO/TMEDA-catalyzed aerobic oxidation of activated alcohols to the corresponding carbonyl compounds using water or the environmentally friendly low melting mixture (LMM) D-fructose-urea as the reaction medium. Such oxidation reactions proceed under mild (room temperature or 40 °C) and aerobic conditions, with the carbonyl derivatives isolated in up to 98% yield and within 4 h reaction time when using the above-mentioned LMM. The potential application of this methodology is demonstrated by setting up useful telescoped, one-pot two-step hybrid transformations for the direct conversion of primary alcohols either into secondary alcohols or into valuable nitroalkenes, by combining oxidation processes with nucleophilic additions promoted by highly polarized organometallic compounds (Grignard and organolithium reagents) or with nitroaldol (Henry) reactions, respectively.

Introduction

Oxidation reactions of alcohols are cornerstone transformations in organic chemistry, and the controlled oxidation of primary alcohols to aldehydes is especially crucial for the synthesis of fine chemicals, perfumes, organic intermediates, and pharmaceutical compounds.[1] These reactions have been traditionally carried out with stoichiometric amounts (or even a large excess) of toxic/expensive inorganic oxidants (basically, permanganate or dichromate salts), thereby generating unwanted chemical waste.[2a–c] In this regard, during the past years, several *greener* methodologies have been developed making use of both molecular oxygen as the oxidant and several (supported) transition metals (e.g., Pt, Ru, Cr, Pd, Au) as reusable catalysts, sometimes in form of nanoparticles.[2d–h] Both heterogeneous and homogeneous conditions have been explored, usually in the presence of ligands (e.g., salen, diimine, (pyridyl)imine, triazines), and employing either volatile organic compounds (VOCs) (e.g., toluene, CH_2Cl_2) or aqueous mixtures as solvents.[3]

Recent studies have revealed the usefulness of the synergistic combination of copper salts with stable organic nitroxyl radicals such as TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) to promote the mild oxidation of alcohols to the corresponding carbonyl compounds.[4] Interestingly, detailed cyclic voltammetry studies have also disclosed the key role played by ligands such as TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) in decreasing the redox potential ($E_{1/2}$) of the couple $E_{1/2}$ Cu^{2+}/Cu^{+} to $E_{1/2}$ Cu^{2+}/Cu^{+}-TMEDA by 454 mV in the redox system.[5] These transformations have been accomplished with a catalytic amount of TEMPO as a redox mediator jointly with a stoichiometric amount of a terminal oxidant such as $Fe(NO_3)_3{\cdot}9H_2O$, NaOCl, molecular oxygen or even air, and often involve the use of VOCs (e.g., 1,2-dichloroethane, dichloromethane, MeCN), thereby exerting a very strong impact on the environment.[5,6] One notable exception is represented by the employment of ionic liquids (ILs) as solvents, liquid supports or catalysts.[7]

Deep eutectic solvents (DESs) are an emerging class of neoteric solvents with several properties mirroring those of ILs (e.g., negligible vapor pressures, high thermal stability, non-flammability, easy recycling). They are eutectic mixtures of Lewis or Brønsted acids and bases strongly associated with each other, exhibiting a significant depression of freezing points far below that of ideal mixtures (each component has a higher melting point than the mixture).[8] Owing to their minimal ecological footprint, ease of preparation, cheapness and biodegradability of their constituents (many of them extractable from biomass matrices), and tunability of their physicochemical properties, DESs have been finding increasing and successful

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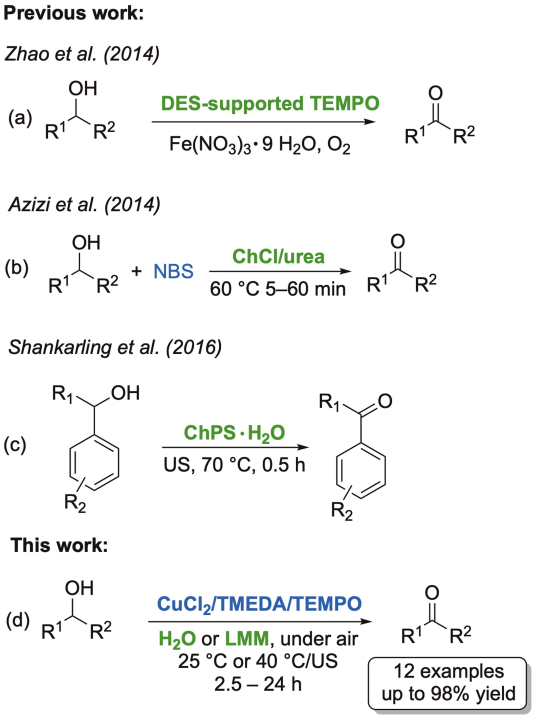
applications in several scientific fields of current interest (e.g., metal-, bio- and organocatalysis, main group chemistry, photosynthesis, crystallization).[9] Low-melting mixtures (LMMs), introduced in 2005 by König and co-workers, are closely related to DESs.[10] They are stable eutectic mixtures of neutral compounds, usually based on carbohydrates or sugar alcohols, urea (derivatives) and inorganic salts, which melt around 70 °C.

There is currently an urgent demand to develop environmentally benign oxidation reactions.[11] However, there are still very few case studies of selective oxidation of alcohols to aldehydes performed in DESs: (a) in 2014, Zhao et al. demonstrated that a DES-supported TEMPO, based on a quaternary ammonium salt and urea, in combination with $Fe(NO_3)_3$ as co-catalyst, showed excellence catalytic performances in the oxidation of various alcohols to the corresponding carbonyl compounds with molecular oxygen as the oxidant (Scheme 1a);[12] (b) in 2014, Azizi's group reported a fast and selective oxidation of primary and secondary alcohols when using *N*-bromosuccinimide (NBS) in a choline chloride (ChCl)/urea eutectic mixture (Scheme 1b);[13] whereas (c) in 2016, Shankarling et al. showed that the oxidation of benzylic alcohols to aldehydes was feasible in an aqueous eutectic mixture of choline peroxydisulfate (ChPs), and using ultrasound (US) as the energy source (Scheme 1c).[14]

As part of our ongoing research program aimed at setting up more sustainable and safer chemical transformations by replacing toxic VOCs with more environmentally responsible, bio-inspired solvents (e.g., water, DESs), we recently embarked on a project for the synthesis of tertiary alcohols by combining either a ruthenium(IV)-catalyzed isomerization of allylic alcohols in DESs[15a] or a biocatalytic laccase/TEMPO oxidation system of secondary alcohols in aqueous media with the chemoselective nucleophilic addition of polar organometallic reagents to the in situ formed ketones.[15b]



Scheme 1. (a) DES-supported TEMPO for oxidation of alcohols; (b) oxidation of alcohols with NBS in DES; (c) choline peroxydisulfate (ChPS)-promoted oxidation of benzylic alcohol derivatives to aldehydes and ketones; (d) copper/TEMPO/TMEDA-mediated oxidation of alcohols to carbonyl compounds under air in water (25 °C) or in LMM (40 °C/US).

The synthesis of highly enantiomerically enriched secondary alcohols has also been achieved by coupling the Ru-catalyzed isomerization of racemic allylic alcohols with an enantioselective bioreduction of the resulting ketones in DES-buffer mixtures.[15c]

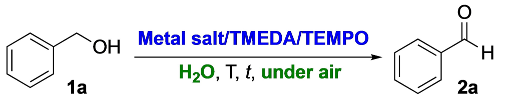
At this point, it is important to mention that our one-pot two-step protocols[15a–c] showed the possibility to achieve the fruitful combination of different synthetic organic utensils from the organic synthetic toolbox (transition metals, enzymes or s-block organometallic chemistry) in the same reaction media (no intermediate isolation/purification steps were needed), thereby designing new hybrid protocols under greener reaction conditions en route to highly-added value organic compounds starting from raw materials.[16]

Herein, we first describe a sustainable, selective copper/TEMPO-catalyzed oxidation of primary alcohols to the corresponding aldehydes comparing the outcome of the transformations both in DESs/LMMs and water (Scheme 1d). Notably, this oxidation proceeds: (a) under mild conditions (room temperature or 40 °C) with air as the terminal oxidant, and (b) with activated benzylic and allylic alcohols, with the corresponding carbonyl derivatives being obtained in up to 98 % yield and within 4 h when using LMMs. Moreover, the robustness of the reported protocol was displayed by setting up effective hybrid tandem reactions by assembling oxidation processes with either nucleophilic addition reactions promoted by organometallic reagents of s-block-elements or nitroaldol (Henry) reactions for the synthesis of valuable nitroalkenes both in LMM and water.

Results and Discussion

We initiated our investigation using benzylic alcohol (**1 a**) (1.5 mmol) as the model substrate, which was subjected to oxidation in water (1 mL), working under air, in the presence of $CuCl_2$/TMEDA/TEMPO as a homogeneous catalytic system. After careful evaluation of all the reaction parameters (time, temperature and loading of the co-catalysts), we found that the treatment of **1 a** at room temperature (RT, 25 °C) afforded benzaldehyde (**2 a**) in 95 % yield with 7 mol % $CuCl_2$, TMEDA and TEMPO, after 2.5 h reaction time (Table 1, entries 1–4). By reducing the Cu^{II}/TMEDA loading from 7 to 1 mol %, we observed a dramatic decrease of the catalytic activity. It happened the same even when the loading of TEMPO was increased from 7 to 10 mol % (Table 1, entry 5). Under these conditions ($CuCl_2$ (1 mol %), TEMPO (7 mol %), TMEDA (1 mol %)), quantitative conversion (98 % yield) of benzylic alcohol (**1 a**) into the desired benzaldehyde (**2 a**) occurred only after 23 h when pure O_2 atmosphere was used in place of air. Other copper(I) (Cu_2O) or copper(II) ($Cu(OAc)_2$) salts proved to

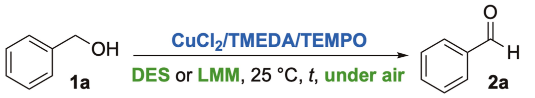
Table 1. Optimization of oxidation of benzylic alcohol (**1a**) to benzaldehyde (**2a**) working under air and in water.[a]



Entry	Metal salt (Amount [mol %])	TEMPO [mol %]	TMEDA [mol %]	T (°C)	*t* [h]	**2a** yield [%][b]
1	$CuCl_2$ (4)	4	4	40	2.5	69
2	$CuCl_2$ (4)	4	4	25	4	80
3	$CuCl_2$ (5)	5	5	25	2.5	88
4	**$CuCl_2$ (7)**	**7**	**7**	**25**	**2.5**	**95**
5	$CuCl_2$ (1)	7 or 10	1	25	22	46[c]
6	Cu_2O (7)	7	7	25	2.5	31
7	$Cu(OAc)_2$ (7)	7	7	25	2.5	69
8	$FeCl_3$ $6H_2O$ (7)	7	7	100	4	NR[d]
9	$CuCl_2$ (7)	7	–	25	4	22

[a] Reaction conditions: 1.0 mL H_2O per 1.5 mmol of **1a**. [b] Calculated by ^1H NMR analysis of the crude reaction mixture using an internal standard technique (NMR internal standard: CH_2Br_2). [c] Quantitative conversion (98 % yield of **2a**) was observed after 23 h of reaction when using a O_2 balloon (1 atm) under the same catalytic conditions [$CuCl_2$ (1 mol %), TEMPO (7 mol %), TMEDA (1 mol %)]. [d] NR = no reaction.

Table 2. [VC1]
Optimization of oxidation of benzylic alcohol (**1a**) to benzaldehyde (**2a**) working in air and in DES or LMM.[a]



Entry	DES or LMM[b]	$CuCl_2$ [mol %]	TEMPO [mol %]	TMEDA [mol %]	*t* [h]	**2a** yield [%][c]
1	$FeCl_3 \cdot 6H_2O$/urea	7	7	7	4	12
2	$FeCl_3 \cdot 6H_2O$/Gly	7	7	7	4	20
3	ChCl/urea	7	7	7	4	90
4	ChCl/sorbitol	7	7	7	4	95
5	ChCl/ᴅ-glucose	7	7	7	4	98
6	ChOAc/urea	7	7	7	4	NR[d]
7	**ᴅ–fructose/urea**	**7**	**7**	**7**	**4**	**98**[e]
8	ᴅ-fructose/urea	7	7	–	4	NR[d,e]
9	ᴅ-fructose/urea	[f]	7	[g]	4	NR[d,e] or 24[e]
10	ᴅ-fructose/urea	7	7	7	2	30[e]
11	ᴅ-fructose/urea	4	4	4	4	65[e]
12	ᴅ-fructose/urea	5	5	5	4	96[e]

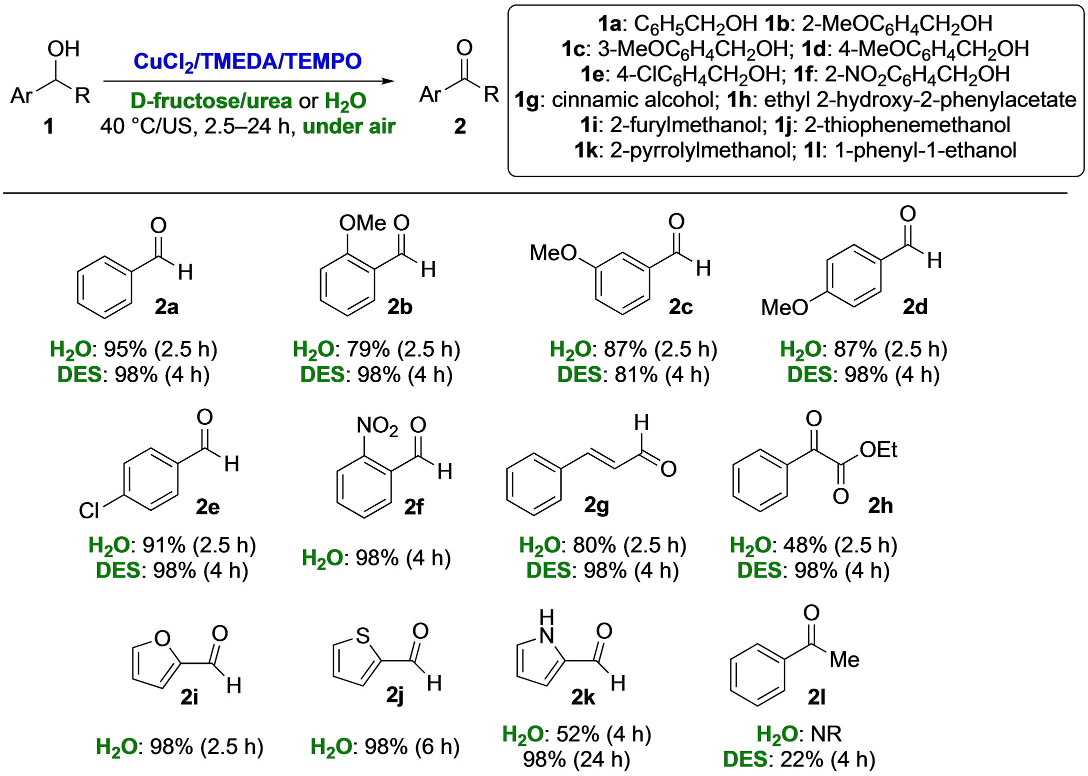
[a] Reaction conditions: 1.0 g DES or LMM per 1.5 mmol of **1a**. [b] DES: $FeCl_3 \cdot 6H_2O$/urea (2:1 mol mol^{-1}); $FeCl_3 \cdot 6H_2O$/glycerol (Gly) (3:1 mol mol^{-1}); choline chloride (ChCl)/urea (1:2 mol mol^{-1}); ChCl/sorbitol (1:1 mol mol^{-1}); ChCl/ᴅ-glucose (1:1 mol mol^{-1}); choline acetate (ChOAc)/urea (1:2 mol mol^{-1}). LMM: ᴅ-fructose/urea (3:2 w w^{-1}). [c] Calculated by ^1H NMR analysis of the crude reaction mixture using an internal standard technique (NMR internal standard: CH_2Br_2). [d] NR = no reaction. [e] Temperature: 40 °C with the assistance of ultrasound. [f] Copper salts used in place of $CuCl_2$ in 7 mol %: CuI (no reaction), CuO (no reaction), Cu_2O (**2a**: 24 % yield). [g] Ligands used in place of TMEDA in 7 mol %: no reaction with 1,10-phenantroline, ʟ-proline, ʟ-histidine, ʟ-alanine, ethylenediamine, *N*,*N*-ethylenediamine, and neocuproine.

be less effective (**2a**: 31–69 % yield), whereas the employment of iron salts ($FeCl_3 \cdot 6H_2O$) led to a quantitative recovery of **1a** (Table 1, entries 6–8). The presence of TMEDA as a basic co-catalyst ligand was crucial for the reaction effectiveness, as in its absence the yield of **2a** dropped down to 22 % even after 4 h reaction time, with only starting material remaining in the mixture beyond the product (Table 1, entry 9).

Interestingly, Kara and co-workers recently reported the results of a study on the feasibility of transferring dioxygen from air into DESs, while using water as a reference, demonstrating that the nature of DESs had big influences on the oxygen transfer.[17] We wondered whether the oxidation of alcohols could also be achieved directly in DESs with air as the terminal oxidant. Thus, we screened again the oxidation of **1a** to **2a** in the presence of the $CuCl_2$/TEMPO/TMEDA system in some representative DES mixtures and under the best conditions found for the oxidation in water (Table 1, entry 4). As can be seen from the results compiled in Table 2, while type-IV eutectics based on metal chlorides and hydrogen bond donors (for example, $FeCl_3 \cdot 6H_2O$/glycerol (Gly) (3:1 mol mol^{-1}), $FeCl_3 \cdot 6H_2O$/urea (2:1 mol mol^{-1})) gave poor results (**2a**: 12–20 % yield; Table 2, entries 1,2), the employment of ChCl-based type-III eutectic mixtures (for example, ChCl/urea (1:2 mol mol^{-1}), ChCl/sorbitol (1:1 mol mol^{-1}), ChCl–D-glucose (1:1 mol mol^{-1})), which led to more homogeneous mixtures, showed excellent conversion values (**2a**: 90–98 % yield) (Table 2, entries 3–5). The choline acetate (ChOAc)/urea (1:2 mol mol^{-1}) mixture represented an exception as no oxidation took place (Table 2, entry 6).

Pleasingly, switching to a sugar-based LMM like ᴅ-fructose/urea (3:2 w w^{-1}), the conversion of **1a** to **2a** was now quantitative (98 % yield) with the assistance of US as the energy source (Table 2, entry 7). At this point, the high chemoselectivity of our oxidative catalytic system is worth mentioning, as no oxidation of the primary alcohol units present in the eutectic mixture (ᴅ-fructose) took place.[18] Performing the oxidation in the absence of TMEDA or in the presence of other ligands (e.g., 1,10-phenantroline, ʟ-proline, ʟ-histidine, ʟ-alanine, ethylenediamine, *N*,*N*-diethylenediamine, neocuproine) or different copper salts (CuI, CuO, Cu_2O) did not result in a productive reaction (Table 2, entries 8,9). Moreover, as shown in entries 10–12 of Table 2, a reaction time shorter than 4 h had a detrimental impact as well; a loading of co-catalysts ($CuCl_2$/TMEDA/TEMPO) less than 7 mol % also provided lower yields.

With optimized conditions identified in water (Table 1, entry 4) and in LMM (Table 2, entry 7),[19] we next studied the generality of the alcohol substrate for this oxidation reaction. As for the reactions in water, benzylic alcohol derivatives with a MeO group at the *ortho*-, *meta*-, and *para*-positions (**1b–d**) reacted smoothly, affording the corresponding aldehydes **2b–d** in 79–87 % yield (Scheme 2). Benzylic alcohol derivatives containing electron-deficient groups (Cl, NO_2) at the *ortho*- and *para*-positions (**1e,f**) proved to be excellent substrates as well, providing carbonyl derivatives **2e,f** in 91 % and 98 % yield, respectively (Scheme 2). Cinnamic alcohol **1g**, as a representative of allylic alcohols, and ethyl 2-hydroxy-2-phenylacetate **1h** also actively participated in the oxidation process delivering cinnamaldehyde **2g** and ethyl 2-oxo-2-phenylacetate **2h** in 48–80 % yield (Scheme 2). Heterocyclic substrates like 2-furylmetha-



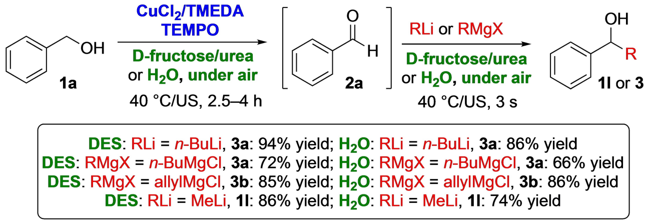
Scheme 2. Oxidation of activated alcohols **1a–l** in H_2O and in D-fructose/urea eutectic mixture (3:2 w w^{-1}) at 40 °C with the assistance of ultrasound to give carbonyl derivatives **1a–l**. Reaction conditions: 1.0 g DES or 1 mL H_2O per 1.5 mmol of **1**; $CuCl_2$: 7 mol%; TMEDA: 7 mol%; TEMPO: 7 mol%. NR = no reaction.

nol (**1 i**), 2-thiophenemethanol (**1 j**) (notoriously refractory to be oxidized by transition metal complexes under aerobic conditions),[20] and 2-pyrrolylmethanol (**1 k**) were all completely converted (98% yield) to the corresponding carboxaldehyde derivatives **2 i–k**, although an extended reaction time was required for complete consumption of **1 j,k** (6–24 h; Scheme 2). On the other hand, with the exception of **1 h**, both secondary aromatic and aliphatic alcohols (e.g., 1-phenyl-1-ethanol (**1 l**), cyclopentanol) as well as primary aliphatic alcohols (e.g., 1-butanol) proved to be difficult substrates for the aerobic oxidation under the conditions previously set up with the $CuCl_2$/TMEDA/TEMPO catalytic system in water.

Switching water for the D-fructose/urea LMM, we were delighted to find that conversion of substrates **1 a–e** and **1 g** to the corresponding aldehydes, which were in the range of 48–95% yield when working in water, now proved to be quantitative in almost all cases (98% yield) within 4 h reaction time with the exception of **1 c** whose carbonyl derivative **2 c** formed in 81% yield. Again, oxidation of primary and secondary non-activated aliphatic alcohols (e.g., 2-phenyl-1-ethanol, cyclopentanol, 4-phenyl-2-butanol) did not occur either in this LMM. Only in the case of **1 l**, acetophenone (**2 l**) formed, although in only 22% yield.

Finally, we sought to capitalize on these oxidation processes by investigating some telescoped and hybrid processes using water or LMM as the reaction medium. These one-pot tandem protocols are highly attractive and worth pursuing for their intrinsic practical and economic advantages, as they: (a) avoid the isolation and purification of intermediates of reactions (thereby minimizing the chemical waste and the required time and energy), and (b) allow the possibility to work with unstable, reactive intermediates (if any) as no isolation of transitory species is needed.[21]

As we have previously commented upon, the design of these hybrid one-pot transformations, which amalgamate different synthetic organic tools without the need of any intermediate isolation/purification steps, is still in its infancy.[16] Thus, we first targeted the conversion of a primary alcohol into a secondary alcohol by assembling our Cu-catalyzed oxidation reaction and main group-mediated (RLi/RMgX) organic transformations. To this end, benzylic alcohol (**1 a**) was first oxidized to benzaldehyde (**2 a**) in the D-fructose/urea LMM, working under air and at 40 °C with the assistance of US, with the catalytic system $CuCl_2$/TEMPO/TMEDA (7 mol% each). Once the conversion of **1 a** into **2 a** was completed (4 h, ^{1}H NMR analysis), a solution of *n*-BuLi in hexanes was directly added under air to the reaction mixture, which was stirred for a few seconds. Remarkably, working under aerobic conditions and at RT (which are conditions traditionally prohibitive for organolithium reagents),[22] secondary alcohol **3 a** could be isolated in 94% yield (Scheme 3). Upon exchanging *n*-BuLi for the corresponding Grignard reagent (*n*-BuMgCl), **3 a** was isolated in slightly lower yields (72%) (Scheme 3). The observed erosion on the final yield of alcohol **3 a** when changing *n*-BuLi for *n*-BuMgCl is in good agreement with our previous studies on the addition of RMgX/RLi reagents to transiently formed ketones either in other

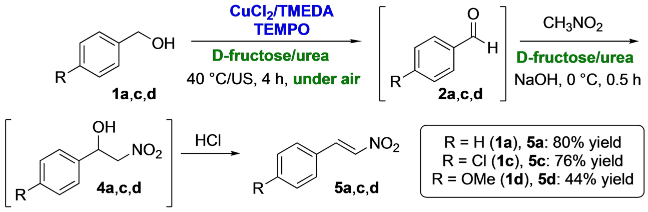


Scheme 3. Direct conversion of benzylic alcohol **1a** into secondary alcohols **1l,3a,b** through a hybrid tandem, one-pot combination of oxidation of **1a** and chemoselective nucleophilic addition of RLi/RMgX to transient aldehyde **2a** in D-fructose-urea or water under aerobic conditions. Overall yields refer to products isolated and purified by column chromatography, and were calculated with reference to the starting benzylic alcohol (see Supporting Information for details).

one-pot tandem protocols[15a,b] or in the synthesis of tertiary alcohols from esters[15d] in ChCl-based eutectic mixtures. The nucleophilic addition of other organolithiums and organomagnesium reagents like MeLi and allylMgBr to the transiently formed **2a** again smoothly yielded secondary alcohols **1l** and **3b** in 85–86% yield after 4 h in the D-fructose/urea mixture (Scheme 3). The replacement of D-fructose/urea by water provided alcohol **3a** in 66–86% yield, depending on the nature of the alkylating agent (*n*-BuMgCl or *n*-BuLi), and alcohols **1l** or **3b** in 74% and 86% yield when using MeLi or allylMgBr, respectively (Scheme 3).

Finally, we investigated the feasibility to run telescoped oxidation-nitro aldol (Henry) reactions for the preparation of valuable nitroalkenes. Thus, benzylic alcohols **1a** or **1c** or **1d** (1.5 mmol) were first subjected to an aerobic oxidation procedure at RT in a D-fructose/urea mixture in the presence of $CuCl_2$/TEMPO/TMEDA (7 mol% each) for 4 h. After this time, the resulting mixture containing aldehyde **2a** or **2c** or **2d** was treated with an equimolar amount (1.5 mmol) of CH_3NO_2 under basic (NaOH, 5 M) conditions, and then it was left stirring for 30 min at 0 °C. The desired nitroalkenes **5a,c,d** could be isolated in 44–80% yield after acidification with HCl (10 M) (Scheme 4).

Of note, running the whole processes above described in pure water, the final dehydration steps did not straightforwardly occur. Indeed, starting from benzylic alcohol derivatives **1c,d**, lower levels of conversions into aldehydes **2c,d** were detected, and mixtures of β-nitroalcohols **4c,d** (22–42%) and nitroalkenes **5c,d** (18-46%) formed in variable amounts. The role of DESs as catalytic active species in driving equilibrium to completeness has been suggested for several transformations.[23]



Scheme 4. Direct conversion of benzylic alcohols **1a,c,d** into nitroalkenes **5a,c,d**, via β-nitroalcohols **4a,c,d**, through a tandem, one-pot combination of oxidation of **1a,c,d** and nitroaldol (Henry) reactions of CH_3NO_2 to transient aldehydes **2a,c,d** in a D-fructose-urea mixture under aerobic conditions. Overall yields refer to products isolated and purified by column chromatography, and were calculated with reference to the starting benzylic alcohol (see Supporting Information for details).

Recycling studies of the LMM/catalytic system were also conducted. We selected the oxidation of 4-chlorobenzyl alcohol **1e** in D-fructose/urea as its conversion into aldehyde **2e** was quantitative (98% yield). After extracting the product **2e** with cyclopentyl methyl ether, fresh reagent **1e** was added to the resulting mixture, and the oxidation step was repeated. Unfortunately, the yield of **2e** dropped down to 44% after the 1st cycle. When TMEDA (7 mol%), and **1e** were added after the 1st cycle, the yield increased to 67%, and only if the mixture was supplemented by both TEMPO and TMEDA (7 mol% each), the yield of **2e** increased up to 82% after the 1st cycle. Owing to the impossibility to recycle the whole catalytic system, we decided not to proceed further.

Conclusion

In summary, we have developed a sustainable and selective $CuCl_2$/TEMPO/TMEDA-catalyzed aerobic oxidation of alcohols using a biodegradable D-fructose/urea LMM or bulk water as the reaction medium. Activated benzylic alcohols with electron-withdrawing or electron-donating groups or cinnamic alcohols or heterosubstituted benzylic-type alcohols are all smoothly and chemoselectively oxidized to the corresponding aldehydes (that have a high proclivity for further oxidation) working under mild (room temperature or 40 °C) and aerobic conditions, within 4 h in LMM or 2.5–24 h in water, in up to 98% yield. When comparing the two solvents, higher yields are generally obtained running the oxidation reaction in the LMM. A secondary alcohol like ethyl 2-hydroxy-2-phenylacetate is also quantitatively converted in the LMM, but other benzylic secondary alcohols and primary/secondary aliphatic alcohols are not oxidized under these conditions. Of note, this simple protocol allows the direct conversion of primary alcohols either into secondary alcohols or into nitroalkenes by means of telescoped, hybrid, one-pot two-step transformations in which oxidation processes are combined with main group-mediated (Grignard and organolithium reagents) nucleophilic additions or with nitroaldol (Henry) reactions, respectively. These latter reactions were found to proceed straightforwardly in LMM. Other oxidation processes and tandem reactions are currently being investigated, and results will be reported in due course.

Experimental Section

Oxidation of benzylic alcohol (1a) in water. Typical procedure. In a 20 mL vial equipped with a magnetic stirrer, $CuCl_2$ (7 mol%, 0.1 mmol, 13 mg) and TMEDA (7 mol%, 0.1 mmol, 16 μL) were added at room temperature (RT, 25 °C) to 1 mL of H_2O. To this slightly greenish solution, benzylic alcohol **1a** (1.5 mmol, 156 μL) and TEMPO (7 mol%, 0.1 mmol, 16 mg) were added, and the resulting mixture was vigorously stirred at RT and under air for 2.5 h. When conversion of **1a** was complete (TLC and ^{1}H NMR analysis), the crude was extracted with Et_2O (3×1 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solution was filtered. After removing the volatiles under reduced pressure, the desired product **2a** was isolated in 95% (151 mg) yield, and did not need further purification.

Oxidation of benzylic alcohol (1a) in D–fructose/urea low-melting mixture (3:2 w/w). Typical procedure. In a 20 mL vial kept in an ultrasonic bath at 40 °C, $CuCl_2$ (7 mol%, 0.1 mmol, 13 mg) and TMEDA (7 mol%, 0.1 mmol, 16 μL) were added to 1 g of D-fructose/urea (3:2 w/w). To this slightly greenish mixture, benzylic alcohol **1a** (1.5 mmol, 156 μL) and TEMPO (7 mol%, 0.1 mmol, 16 mg) were added, and the resulting mixture was vigorously stirred at RT and under air for 4 h, until the complete conversion of **1a** (TLC and ^1H NMR analysis). Then, H_2O (5 mL) was added and the aqueous solution was extracted with Et_2O (3×1 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and the solution was filtered. After removing the volatiles under reduced pressure, the desired product **2a** was isolated in 98% (156 mg) yield.

Preparation of 1-phenylethanol (1l) in water. Typical procedure. In a 20 mL vial equipped with a magnetic stirrer, $CuCl_2$ (7 mol%, 0.1 mmol, 13 mg) and TMEDA (7 mol%, 0.1 mmol, 16 μL) were added at room temperature (RT, 25 °C) to 1 mL of H_2O. To this slightly greenish solution, benzylic alcohol **1a** (1.5 mmol, 156 μL) and TEMPO (7 mol%, 0.1 mmol, 16 mg) were added, and the resulting mixture was vigorously stirred at RT and under air for 4 h. After this time, 2.8 mL of MeLi (1.6 M Et_2O, 4.5 mmol) were rapidly spread over the homogeneous solution of benzaldehyde **2a** (153 μL, 1.5 mmol) in 1 mL of H_2O at RT and under air. After 3 s, the mixture was extracted with Et_2O (3×1 mL). The combined organic phases were dried over anhydrous Na_2SO_4, the solution was filtered and the solvent was concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc 8:2), to give 1-phenylethanol **1l** in 74% (135 mg) yield.

Preparation of 1-phenylethanol (1l) in D–fructose/urea. Typical procedure. In a 20 mL vial kept in an ultrasonic bath at 40 °C, $CuCl_2$ (7 mol%, 0.1 mmol, 13 mg) and TMEDA (7 mol% 0.1 mmol, 16 μL) were added to D-fructose/urea (3:2 w/w) (1 g). To this slightly greenish mixture, benzylic alcohol **1a** (1.5 mmol, 156 μL) and TEMPO (7 mol%, 0.1 mmol, 16 mg), were sequentially added, and the resulting mixture was vigorously stirred at RT and under air for 4 h, until the oxidation step was completed (TLC and ^1H NMR analysis). Then, 2.8 mL of MeLi (1.6 M Et_2O, 4.5 mmol) were rapidly spread over the homogeneous solution of the formed benzaldehyde **2a** (153 μL, 1.5 mmol) in D-fructose/urea (3:2 w/w, 1.0 g) at RT and under air. After 3 s, 3 mL of H_2O were added to the reaction mixture, and the aqueous solution was extracted with Et_2O (3×1 mL). The combined organic phases were dried over anhydrous Na_2SO_4, the solution was filtered, and the solvent was concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc 8:2), to give 1-phenylethanol **1l** in 86% (157 mg) yield.

Preparation of *trans*-β-nitrostyrene (5a) in D–fructose/urea. Typical procedure. In a 20 mL vial kept in an ultrasonic bath at 40 °C, $CuCl_2$ (7 mol%, 0.1 mmol, 13 mg) and TMEDA (7 mol%, 0.1 mmol, 16 μL) were added to D-fructose/urea (3:2 w/w) (1 g). To this slightly greenish mixture, benzylic alcohol **1a** (1.5 mmol, 156 μL) and TEMPO (7 mol%, 0.1 mmol, 16 mg), were sequentially added, and the resulting mixture was vigorously stirred at RT and under air for 4 h, until the oxidation step was completed (TLC and ^1H NMR analysis). Then, after cooling the vessel with an ice bath (0 °C), nitromethane (1.5 mol) was added to the mixture and an aqueous solution of NaOH (5 M, 1.5 mol, 300 μL) was added over a period of 30 min. The resulting mixture was stirred for further 30 min at 0–5 °C. Finally, HCl (10 M, 2 mL) was added to the mixture, and the yellow solid precipitated was filtered off and dried under vacuum. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc 6:1), to give *trans*-β-nitrostyrene (**5a**) in 80% (179 mg) yield.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Deep Eutectic Solvents · Water · Oxidation · Alcohols · Carbonyl compounds · Domino reactions

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