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Selective oxidations of activated alcohols in water at room temperature

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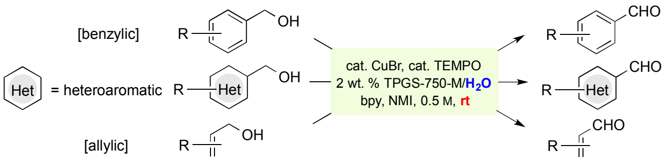
Allylic and benzylic alcohols can be selectively oxidized to their corresponding aldehydes or ketones in water containing nanoreactors composed of the designer surfactant TPGS-750-M. The oxidation relies on catalytic amounts of CuBr, bpy, and TEMPO, with N-methyl-imidazole; air is the stoichiometric oxidant.

Mild and selective methods for the oxidation of alcohols to aldehydes and ketones are among the most valuable processes in organic chemistry. While many feature use of catalytic quantities of metal-based reagents, catalysis alone may not be sufficient to anticipate widespread use, especially on an industrial scale. Indeed, today there is an increasing level of concern as to the environmental impact of such methodologies, most notably from the standpoint of the stoichiometric oxidant, which ideally is air. But even when a process is tailored to involve catalysis and a benign oxidizing agent, these together can be overshadowed by a single parameter that represents the main contributor to organic waste: solvent.[1] Hence, an oxidation that relies not only on the virtues of a catalysis/air combination, but also that further adheres to the *12 Principles of Green Chemistry*[2] should enhance the appeal from the environmental perspective of such a process.

In this report, we describe an oxidation protocol for activated alcohols that uses catalytic amounts of a base metal (Principle 9), involves air as the stoichiometric oxidant (Principle 7), relies on an innocuous and recyclable reaction medium (Principle 5), and offers conditions leading to a very low E Factor[3] based on solvent usage (Principle 3) indicative of the level of greenness associated with this new technology (Scheme 1).



Scheme 1 Oxidations of activated alcohols under green conditions: in water at room temperature.

The overarching concept behind the oxidation developed herein is the far greater dissolution properties of gases, such as oxygen, in organic solvents rather than in water.[4] Thus, when air is presented with the option in an aqueous micellar medium as to where to localize, the concentration of oxygen within the hydrophobic inner core of a nanomicelle is expected to be much higher than in the surrounding water.[5] When taken together with the much higher concentrations of reactants and catalysts typically found within these nanoreactors,[6] the major parameters are well positioned to potentially arrive at a relatively environmentally benign oxidation.

We opted to focus on a base metal such as copper, rather than palladium or other transition metals[7] that have also been used for similar oxidations. There are several published procedures that utilize copper salts in the presence of catalytic amounts of TEMPO, as summarized in Table 1. Among those that can be utilized at ambient temperature, we were led to investigate the application of Stahl's conditions: $[Cu(MeCN)_4]X$ where X = TfO^-, BF_4^-, or PF_6^-, catalytic TEMPO (5 mol %), air, *N*-methylimidazole (NMI), and 2,2'-bipyridine (bpy) as ligand.[8] Screening both copper salts

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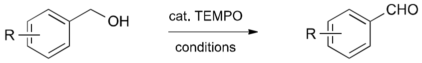
† Electronic Supplementary Information (ESI) available: Experimental procedures and details, copies of ^1H and ^{13}C NMR characterization data for all new compounds: See DOI: 10.1039/b000000x/

$[Cu(MeCN)_4]OTf$ and $[Cu(OTf)_2]$•PhMe[9] in water containing two weight percent TPGS-750-M did afford the desired product aldehyde based on *p*-methoxybenzyl alcohol as educt, albeit in modest yields (Table 2). Far better results were achieved with CuBr, affording the targeted benzaldehyde in virtually quantitative yield within four hours at room temperature. Other sources of copper (*e.g.,* CuCl, copper metal) gave lower levels of conversion, although $CuBr_2$ led to roughly comparable results.

Table 1. Previous work on air/oxygen-based benzylic oxidations.



author	year	catalyst system	ligand	solvent	atm	temp. (°C)
Semmelhack [10]	1984	CuCl	--	DMF	O_2	rt
Knochel [11]	2002	CuBr•SMe_2	**1**	$C_8F_{17}Br/PhCl$	O_2	90
Sheldon [12]	2003	$CuBr_2$/*t*-BuOK	bpy	$MeCN/H_2O$	air	rt
Falk [13]	2005	Cu°/NaOH	bpy	$MeCN/H_2O$	O_2	rt
Ragauskas [14]	2006	$Cu(ClO_4)_2$	TMDP	DMSO	O_2	100
Repo [15a]	2007	$CuSO_4/NaOH$	phen	H_2O	O_2 (10 atm)	100
Sekar [16]	2007	DABCO-CuCl/K_2CO_3	--	PhMe	O_2	80
Repo [15b]	2009	$CuSO_4/K_2CO_3$	**2**	H_2O	O_2	100
Stahl [8]	2011	$[Cu(MeCN)_4]OTf/NMI$	bpy	MeCN	air	rt
Ding [17]	2013	CuI/*t*-BuOK	L-proline	DMF	air	rt
Zhang [18]	2013	$Cu(OAc)_2$•H_2O/Na_2CO_3	**3**	H_2O	air	100
this work	2014	CuBr/NMI	bpy	**TPGS-750-M, 2 wt. % in H_2O**	**air**	**rt**

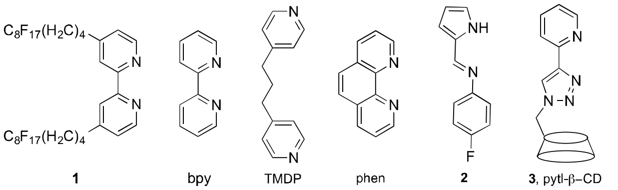
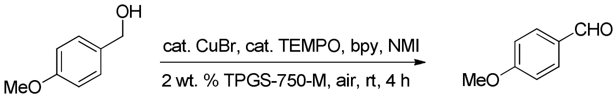


Table 2. Screening of copper salts for the oxidation.

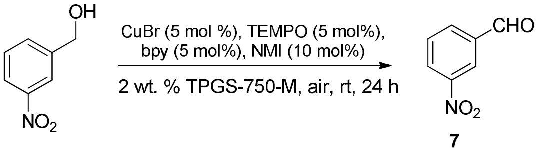


Entry	Conditions[a]	Conversion (%)[b]
1	$[Cu(CH_3CN)_4]OTf$	64
2	$[Cu(OTf)]_2$•PhMe	58
3	CuCl	63
4	Cu^0 powder	35
5	$CuBr_2$	97
6	**CuBr**	**100(98)[c]**
7	CuBr[d]	43
8	CuBr[e]	84

[a] Alcohol (0.5 mmol), copper source (0.025 mmol), TEMPO (0.025 mmol), bpy(0.025 mmol), NMI (0.05 mmol), TPGS-750-M (1.0 mL). [b] Determined by GC analysis.[c] Isolated yield. [d] Reaction concentration 2.0 M. [e] Reaction run "on water".

The role of the surfactant was studied using several alternatives to TPGS-750-M (Table 3). As noted in previous work,[19] particle size can play a significant role in determining the extent and quality of a given reaction, and here again, the amphiphile engineered to provide particles in the 50-60 nm range was the surfactant of choice.[20] That the reactions are mainly happening within the nanomicellar core is evident from the competing "on water" [21] background reaction, which, as noted previously,[22] oftentimes does not lead to synthetically useful results (Scheme 2).

Table 3. Impact of surfactant on a benzylic oxidation.



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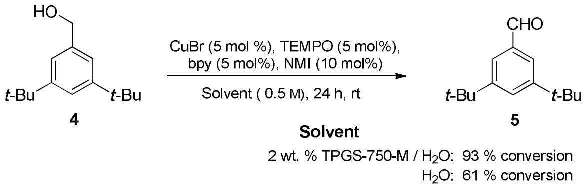
run	surfactant[a,b]	particle size (nm)[c]	conversion (%)[d]
1	Brij 30	110	58
2	**TPGS-750-M**	**53**	**100**
3	Cremophor EL	9	83
4	SDS	17	46
5	CTAB	10	34

[a] See SI for structures of surfactants. [b] Used as a 2 wt. % solution in water. [c] Determined by Dynamic Light Scattering. [d] Determined by GC.



Scheme 2 Comparison between an oxidation 'on water' *vs.* under micellar conditions.

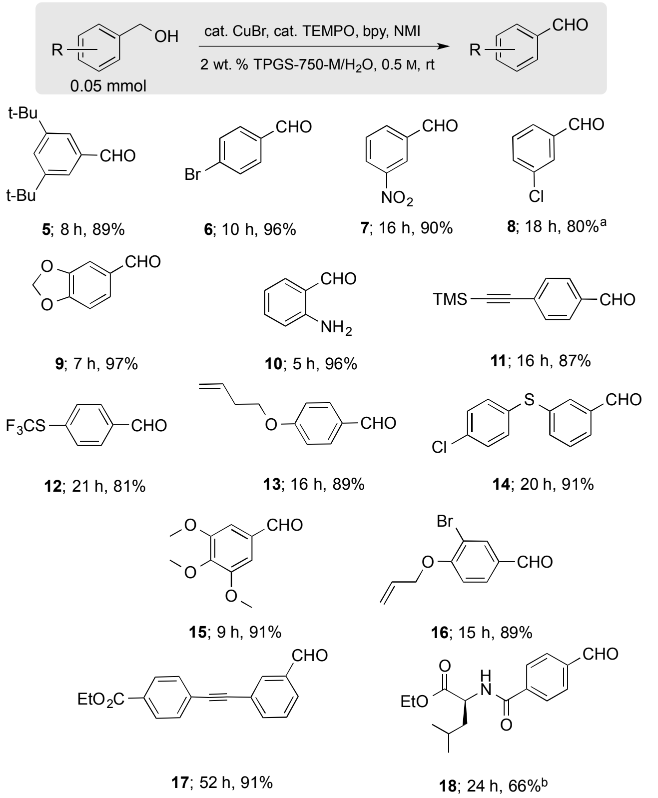
Several primary, benzylic alcohols could be smoothly oxidized to the corresponding aldehydes in water at room temperature (Table 4). Most reactions reached completion in 5 to 20 hours, and tend to be very clean, with the associated isolated yields uniformly high. There appears to be no obvious relationship between the nature of the substituents on the aromatic ring and the time required for each oxidation. Heteroatoms also seem to be well tolerated, including cases where a sulfide and primary amine substituents are present (compounds **12** and **14**, and **10**, respectively). Since the pH of the reaction mixtures is 6, these conditions do not interfere with a TMS-protected alkyne (**11**).

Secondary benzylic alcohols can also be oxidized under the aqueous micellar conditions, although they are slower than the corresponding primary cases and therefore required mild heating to 40-45 °C. Three representative examples are shown in Scheme 3. These observed differences in rate, as noted by Stahl,[8] allow for the selective oxidation of a primary over secondary benzylic alcohol, as illustrated by the conversion of **22** into **23** (Scheme 4).

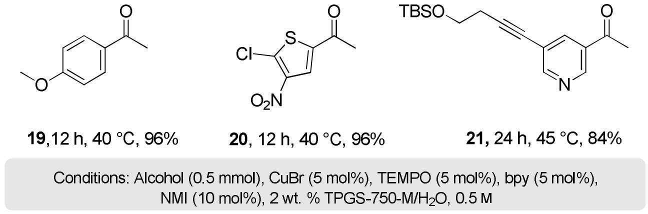
Heteroaromatic primary alcohols could also be readily oxidized under our standard room temperature conditions. The examples in Table 5, including a formylated indole **24**, a substituted furfural **25**, an acetylenic thiophene **26**, and a ferrocenyl derivative **27** suggest that functional group tolerance extends to this class of educts.

Primary, aliphatic alcohols undergo oxidation to the desired aldehydes very slowly, even when mild heating (40-45 °C) is applied. This allows for selective oxidations of activated over unactivated polyols (e.g., Scheme 5).

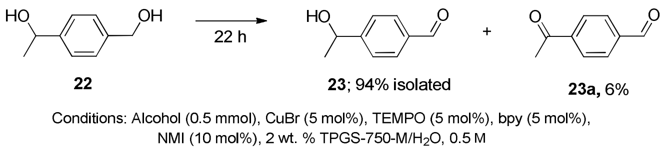
Table 4. Representative examples of benzylic oxidations in water at rt.



Reactions run with CuBr (5 mol %), TEMPO (5 mol %), bpy (5 mol %), NMI (10 mol %), and 0.5 mL TPGS-750-M/H_2O. All yields are isolated. [a] Run on 1 mmol scale, 0.75 M 2 wt. % TPGS-750-M/H_2O solution; [b] Average of two runs.

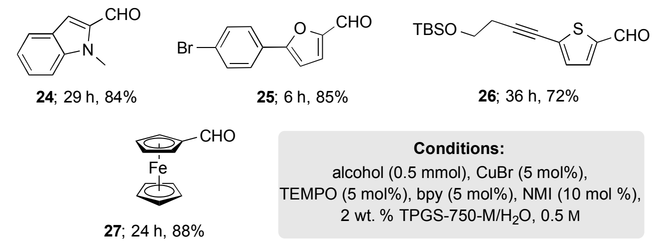


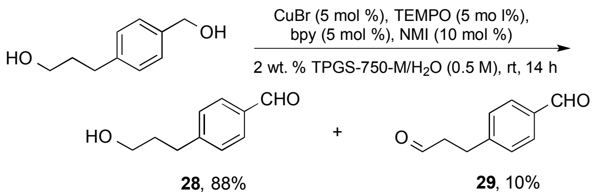
Scheme 3. Representative examples of secondary benzylic/benzylic-like oxidations.



Scheme 4. Selective oxidation of a 1° over 2° benzylic alcohol (conditions as in Scheme 3).

Table 5. Oxidations of heteroaromatic benzylic-like alcohols to their corresponding aldehydes.





Scheme 5. Selective oxidation of a benzylic over aliphatic alcohol.

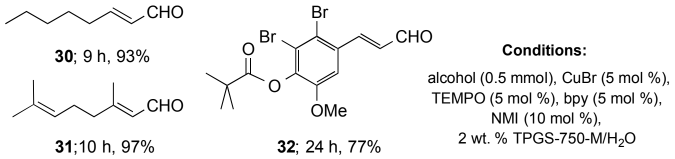
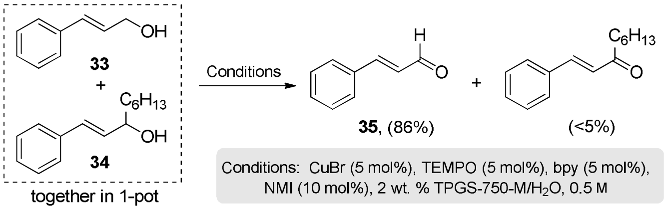


Figure 1. Representative examples of 1° allylic alcohol oxidations.

In addition to benzylic and benzylic-like substrates, primary allylic alcohols are also amenable to oxidation. Representative examples (**30-32**) are illustrated in Figure 1. Secondary allylic alcohols were essentially unreactive under these conditions, thereby allowing for selective oxidation of **33** over the secondary analog **34**, with both educts in the pot (Scheme 6).

Recycling of the aqueous reaction mixture could be smoothly achieved using educt **4** as a model case (Scheme 8). With an "in-flask" workup, **5** was obtained with very low E Factors,[23] suggestive of an overall environmentally attractive process, unlike literature methods to date, although flow chemistry is becoming increasingly competitive in this regard.[24]



Scheme 6. Selective oxidation of 1° **33** over 2° **34** at rt.

Conclusions

In summary, methodology for selective oxidation of activated alcohols to aldehydes has been developed that relies on the greater solubility of gases, specifically oxygen, inside the hydrophobic pockets associated with aqueous nanomicelles. This allows for air to function as the stoichiometric oxidant, rather than traditional oxidizing agents.

Acknowledgements

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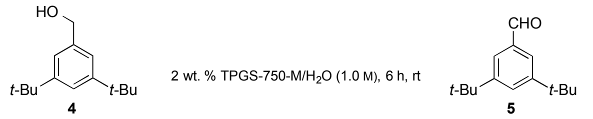

run	yield (%)
1	92
2	89
3[a]	83
4	93
5	87

[a] Added CuBr (5 mol %) to run 3

E Factors

single run		with recycling	
organic solvent only:	1.1	organic solvent only:	1.2
organic solvent + water:	6.1	organic solvent + water:	2.2

Scheme 7. Potential for recycling of the aqueous reaction mixture, and determination of E Factors

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