An innovative Green Chemistry Methodology for Selective Aerobic Oxidation of Primary Alcohols

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Green Chemistry

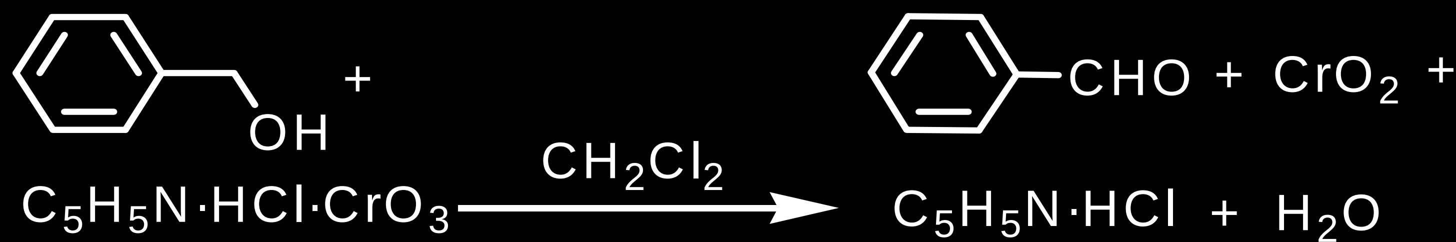
- prevent waste before created
- be atom efficient
- use benign substrates
- make benign products
- use less or benign solvent
- use less energy
- avoid protecting groups
- use renewables
- use catalysts
- analyze in real time
- make things biodegradable
- be safe

P. T. Anasta, J. C. Warner, *Green Chemistry: Theory and Practice*. Oxford University Press: New York, 1998.

Atom Economy

$$\text{Atom Economy} = \frac{\text{mass of atoms in desired product}}{\text{mass of atoms in reactants}} \times 100\%$$

Oxidation

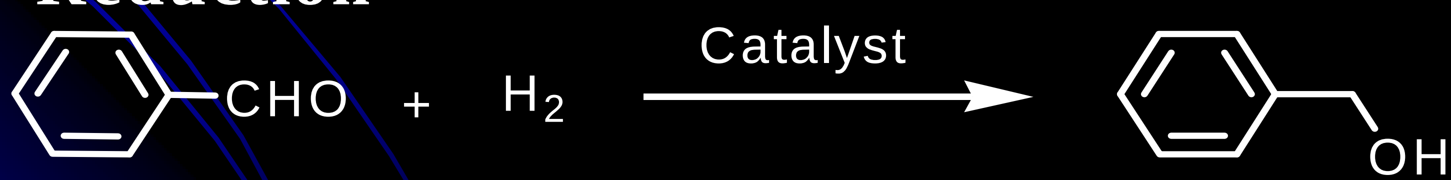


PCC

Atom efficient 33%

85% atom efficient

Reduction



100% atom efficient

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Reaction Solvents

- **Molecular Organic Solvents**

  1. Volatile Organic Compounds (VOCs): MeOH, EtOH, Ether, Chlorinated Solvents, Benzene, etc.

  2. High Polar Aprotic Solvents: DMF, DMA, DMSO, etc.

- **Alternative Reaction Media**

  1. Water or aqueous media

  2. Supercritical CO_2

  3. Poly(ethyleneglycol) (PEG) and aqueous PEG solution

  4. Ionic Liquids

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Ionic Liquids (ILs)

- **Definition:** composed entirely of ions with a melting point below 100 ºC.
- **Properties:** low volatility, high polarity, thermal stability, good solubility, 'designer solvents' by a proper choice of cation and anion.
- **'Green Solvents':** this is highly contentious:

  1. they have not been fully tested;

  2. some ILs are made from highly toxic ions and could cause great harm when spilt .

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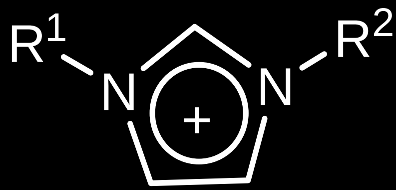
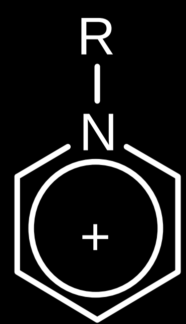
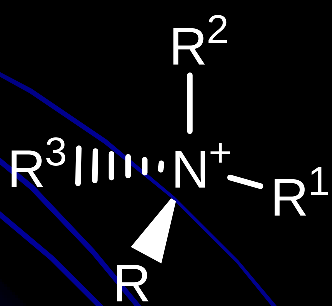
Some Ions in Ionic Liquids

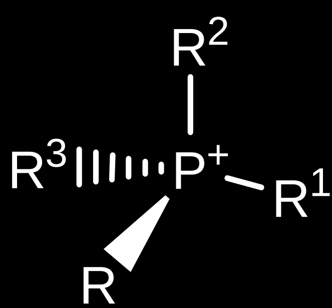
Cations





Imidazolium   Pyridinium





Ammonium   Phosphonium

Anions

PF_6^-

BF_4^-

$CF_3SO_3^-$

$(CF_3SO_3)_2N^-$

$MeOSO_3^-$

$AlCl_4^-$

$Cl(Br)^-$

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Oxidation of Alcohols

$$PhCH_2OH + C_5H_5N\cdot HCl\cdot CrO_3 \xrightarrow{CH_2Cl_2} PhCHO + CrO_2 + C_5H_5N\cdot HCl + H_2O$$

PCC

Atom efficient 33%

$$PhCH_2OH + O_2 \xrightarrow{\text{catalyst}} PhCHO + H_2O$$

Atom efficient 85%

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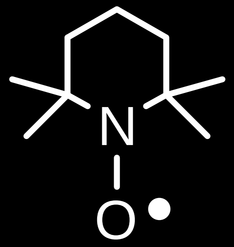
TEMPO Catalyzed Selective Oxidation of Primary Alcohols

2,2,6,6,-tetramethyl-piperidyl-1-oxy Nitroxy Radical TEMPO



TEMPO

$PhCH_2OH + NaOCl \xrightarrow[\text{10 mol\% NaBr, } CH_2Cl_2\text{, 0 ºC}]{\text{1 mol\% TEMPO}} PhCHO + NaCl + H_2O$

Atom efficient 58%

P. L. Anelli et al *J. Org. Chem.* **1987**, *52*, 2559.

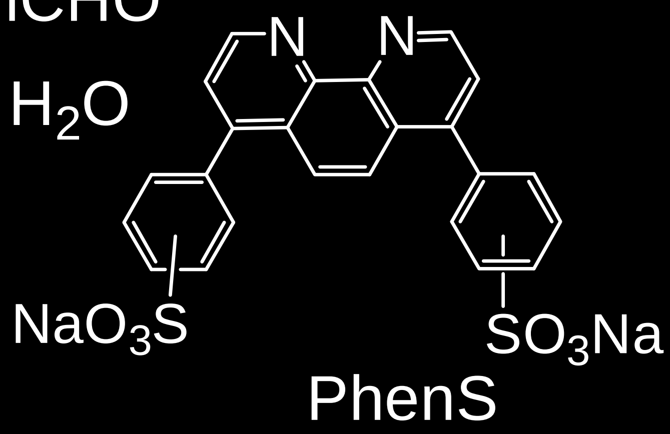
$PhCH_2OH \xrightarrow[\text{4-8 mol\% } NaNO_2\text{, 0.4 MPa Air, } CH_2Cl_2\text{, 80 ºC}]{\text{1 mol\% TEMPO/4 mol\% } Br_2} PhCHO + H_2O$

Atom efficient 85%

X. Hu et al *J. Am. Chem. Soc.* **2004**, *126*, 4112.

Transition-Metal Catalyzed Selective Aerobic Alcohol Oxidation

$PhCH_2OH$ —[0.5 mol% $Pd(OAc)_2$/ PhenS; air (30 bar), 10 mol% NaOAc, 2 mol% TEMPO, H_2O, 100 ºC]→ $PhCHO + H_2O$



R. A. Sheldon et al *Science* **2000**, *287*, 1636.

$PhCH_2OH$ —[0.5% $RuCl_2(PPh_3)_3$, 1.5 mol% TEMPO; PhCl, 100 ºC, 1 atm O_2, 2.5 h]→ PhCHO

R. A. Sheldon et al *J. Am. Chem. Soc.* **2001**, *123*, 6826.

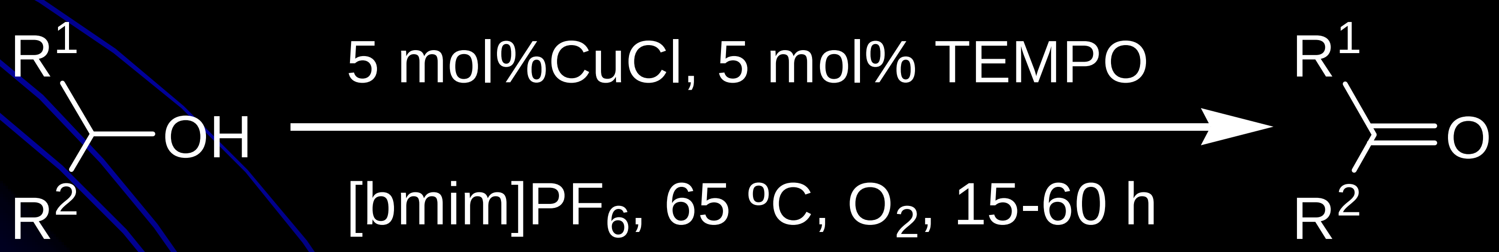
Limitations: unreactive alcohols with heteroatoms (**N**, **S**, **O**)

$ArCH_2OH$ —(10 mol% CuCl, 10 mol% TEMPO / DMF, rt, O_2, 1-7 h)→ $ArCHO$

M. F. Semmelhack et al *J. Am. Chem. Soc.* **1984**, *106*, 3374.

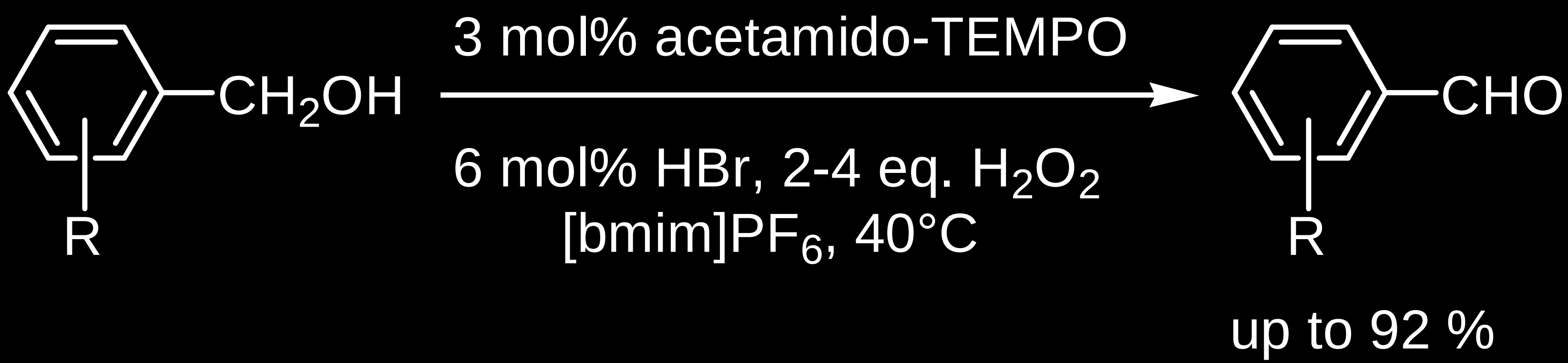
RCH_2OH —(5 mol% [$CuBr_2$(2,2'-bipyridine)] / 5 mol% TEMPO, 5 mol% *t*-BuOK / MeCN/H_2O (2:1), rt, Air, 2.5-24 h)→ $RCHO$

R. A. Sheldon et al *Chem. Commun.* **2003**, 2414.

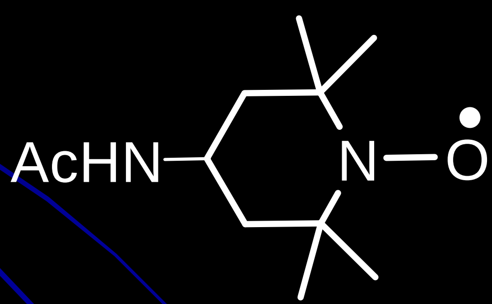


I. A. Ansari and R. Gree *Org. Lett.* **2002**, *4*, 1507.

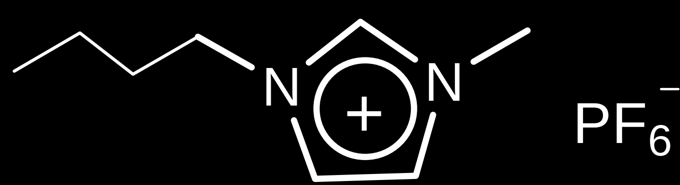
Recovery and Reuse of TEMPO



Acetamido-TEMPO can be recycled and reused for 5 runs.



Acetamido-TEMPO



[bmim]PF_6

N. Jiang and A. J. Ragauskas *Tetrahedron Lett.* **2005**, *46*, 3323.

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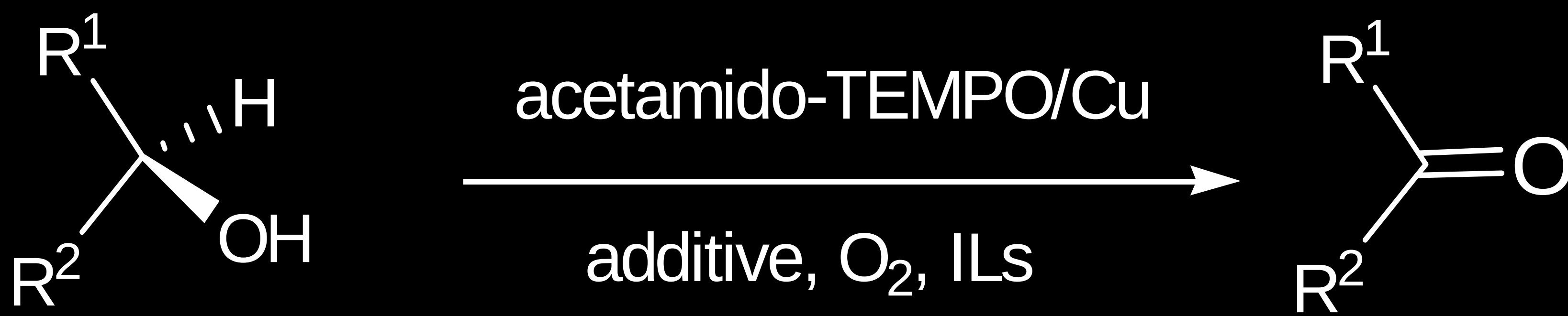
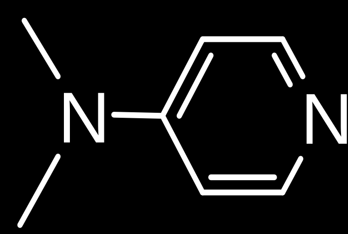
Can Acetamido-TEMPO Work as Recyclable Catalyst in Ionic Liquid for Aerobic Alcohol Oxidation?

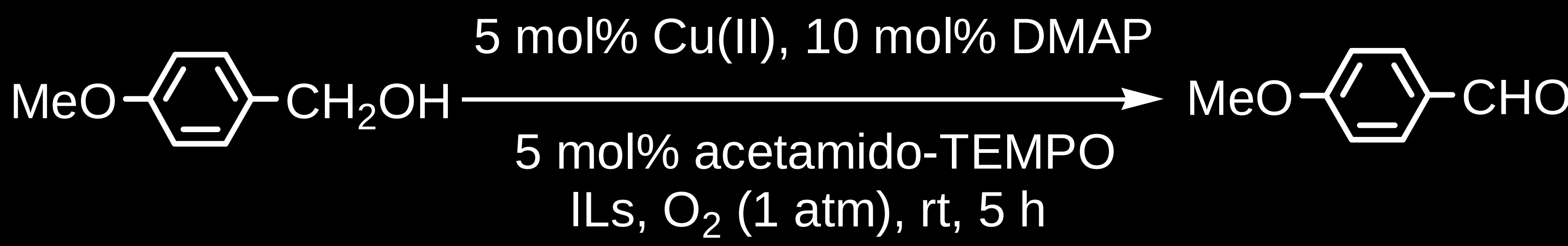


additive = 4-(dimethylamino)pyridine (DMAP)

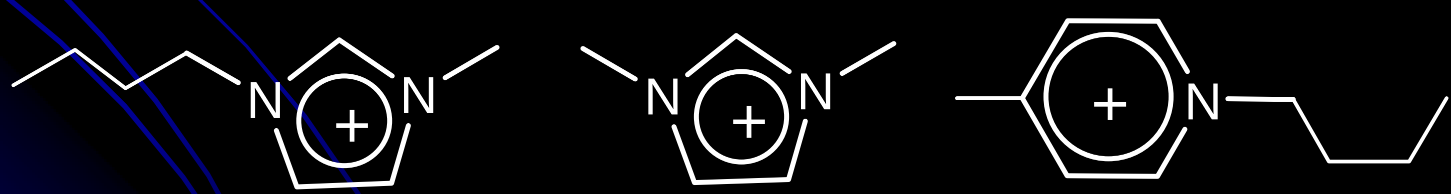


DMAP

Optimization of the Reaction Conditions[a,b]



entry	copper salt	ionic liquid	conversion (%)[c]	yield (%)[d]
1	$CuCl_2$	$[bmim]PF_6$	52	43
2	$CuCl_2$	$[bmim]BF_4$	47	45
3	$CuCl_2$	$[mmim]OSO_3Me$	44	32
4	**$CuCl_2$**	**$[bmpy]PF_6$**	**87**	**81**



[bmim] [mmim] [bmpy]

4	$CuCl_2$	$[bmpy]PF_6$	87	81
5	$Cu(OAc)_2$	$[bmpy]PF_6$	66	59
6	$CuBr_2$	$[bmpy]PF_6$	91	88
7	**$Cu(ClO_4)_2$**	**$[bmpy]PF_6$**	**99**	**91**
8[e]	$Cu(ClO_4)_2$	$[bmpy]PF_6$	4	-
9[f]	$Cu(ClO_4)_2$	$[bmpy]PF_6$	0	-
10[g]	-	$[bmpy]PF_6$	0	-

[a] 2 mmol 4-methoxybenzyl alcohol, 5 mol% acetamido-TEMPO, 5 mol% copper(II) salt, 10 mol% DMAP, 1 atm O_2, 0.50 g ionic liquid, room temperature for 5 h. [b] Selectivity is over 99% determined by ^{1}H NMR of the crude product mixture. [c] Conversion by ^{1}H NMR of the crude product mixture. [d] Isolated yield by flash chromatography. [e] No DMAP was added. [f] No acetamido-TEMPO was added. [g] No copper salt was added.

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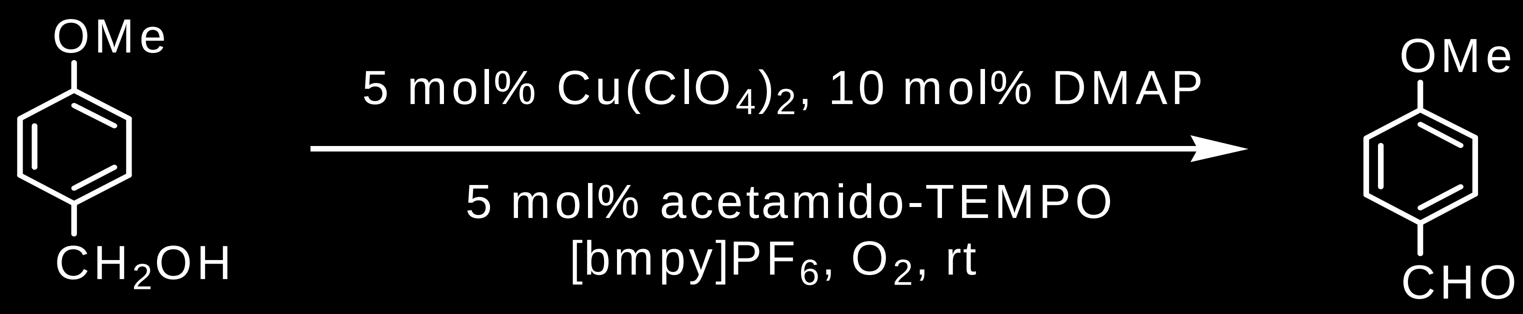
Recycling and Reuse of the Catalysts[a,b]



run	time (h)	conversion (%)[c]	yield (%)[d]
1	5	99	91
2	5	96	91
3	5	94	92
4	8	93	85
5	8	87	81

[a] 2 mmol 4-methoxybenzyl alcohol, 5 mol% acetamido-TEMPO, 5 mol% $Cu(ClO_4)_2 \cdot 6H_2O$, 10 mol% DMAP, 1 atm O_2, 0.50 g $[bmpy]PF_6$, room temperature. [b] Selectivity is over 99% determined by ^1H NMR of the crude product mixture. [c] Conversion by ^1H NMR of the crude product mixture. [d] Isolated yield by flash chromatography.

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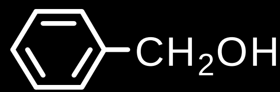
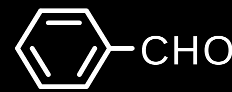
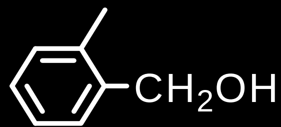
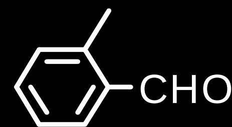
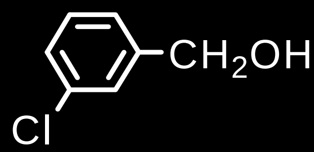
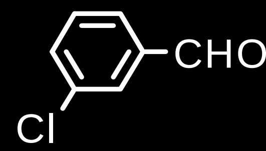
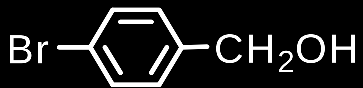
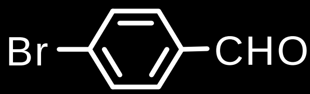
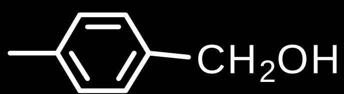
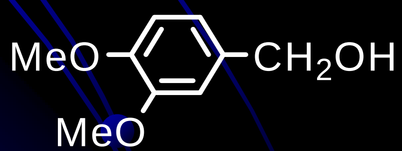
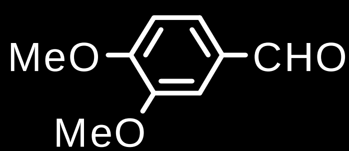
Aerobic Oxidation of Alcohols [a]

entry	alcohols	time (h)	product	convn[b]/yield[c] (%)
1		5		99/92
2		5		98/90
3		5		100/90
4		5		99/91
5		5		99/84
6		5		98/92
7		5		100/81
8		5		96/89

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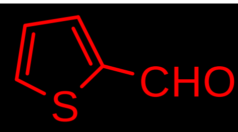
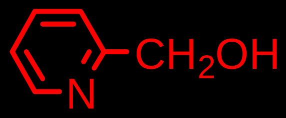
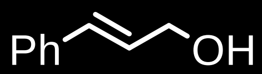
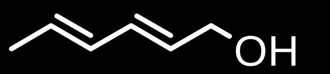
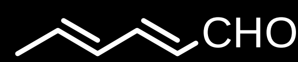
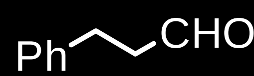
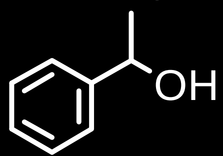
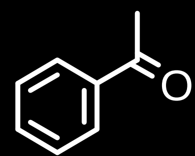
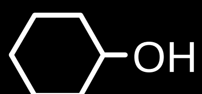
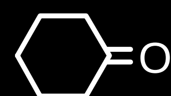
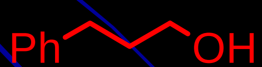
Entry	Substrate	Time (h)	Product	Conv./Yield (%)
9		5		99/88
10		5		97/79
11		5		100/89
12		5		100/77
13		24 24[d]		48/26 94/61
14		24[d]		100/54
15		24		-
16		24		-
17		4		97/75
				12/-

[a] Alcohol (2 mmol), 5 mol% acetamido-TEMPO, 5 mol% $Cu(ClO_4)_2 \cdot 6H_2O$ and 10 mol% DMAP were stirred at room temperature under 1 atm oxygen for the appropriate time. [b] Conversion by ^1H NMR. [c] Isolated yield. [d] The reaction was carried out at 40 °C.

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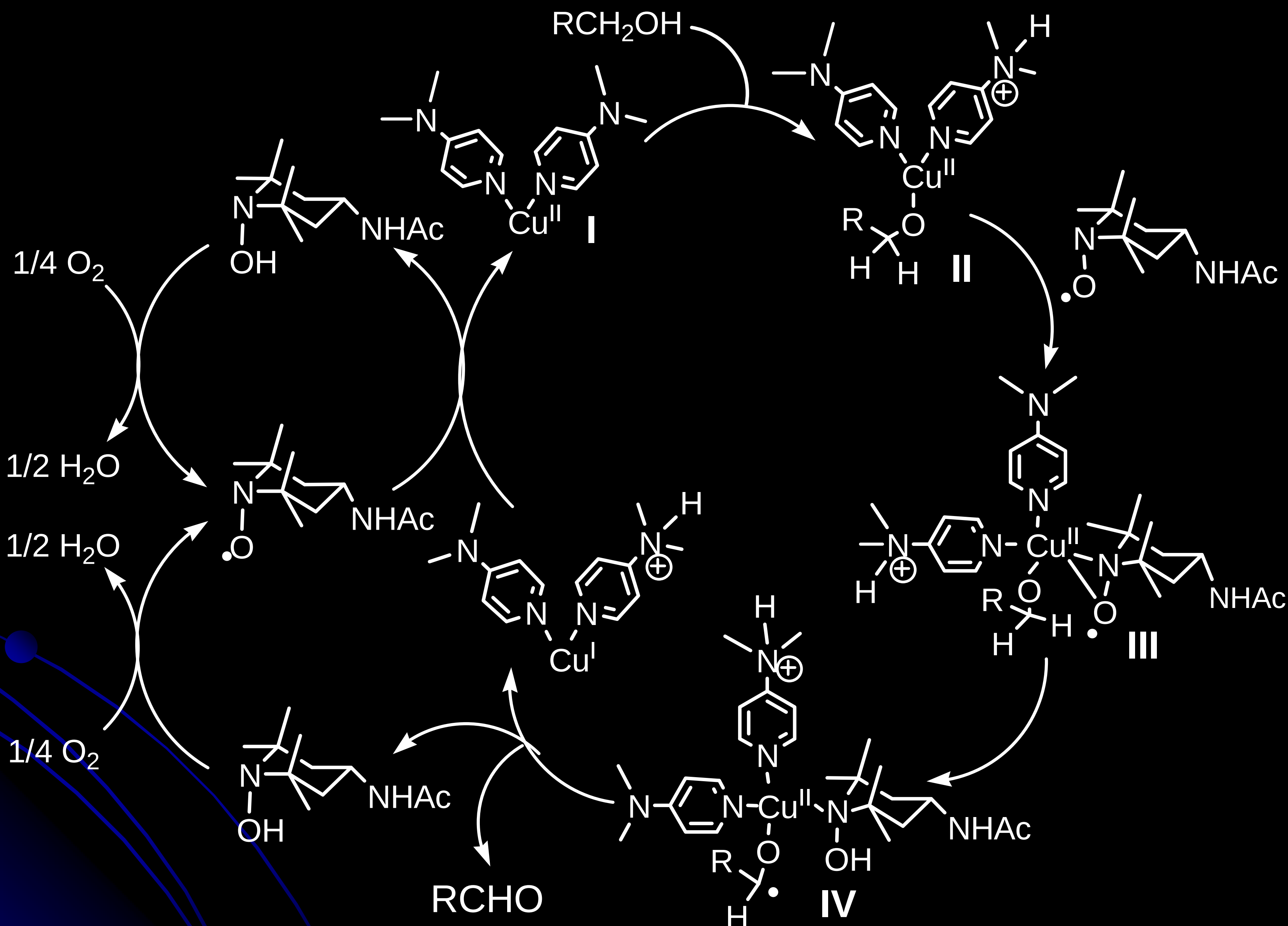
Proposed Possible Mechanism



N. Jiang, A. J. Ragauskas *Org. Lett.* **2005**, *7*, 3689

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Conclusions

- A mild and efficient aerobic oxidation of primary alcohols in ionic liquid [bmpy]PF_6.
- High selectivity to aldehydes and no over-oxidized product observed.
- Good tolerance toward heteroatom (S and N) containing compounds.
- The catalysts can be retained in ionic liquids and easily recycled and reused for five runs without significant loss of catalytic activity.

Acknowledgement

National Research Initiative of the USDA Cooperative State Research, Education and Extension Service, grant number 2003-35504-13620