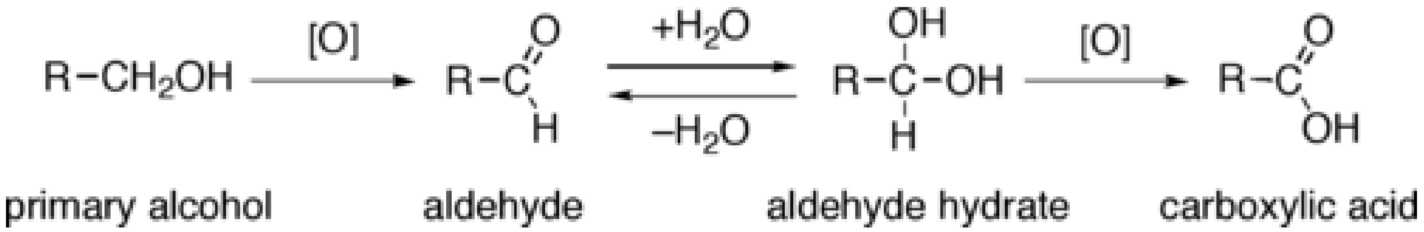
Modern Oxidation Methods

Dr. M. R. Naimi-Jamal, Chemistry Department, IUST, Nov. 2012

Part 1:

Modern Oxidation of Alcohols using Environmentally Benign Oxidants



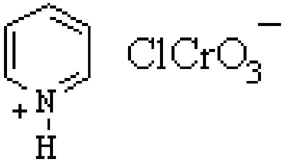
Common reagents:

Aqueous Oxidants

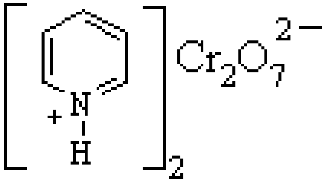
Chromic acid	H_2CrO_4
Chromate salts	CrO_4^{2-}
Dichromate salts	$Cr_2O_7^{2-}$
Permanganate	MnO_4^-

Anhydrous Oxidants

Pyridinium **c**hloro**c**hromate (PCC)

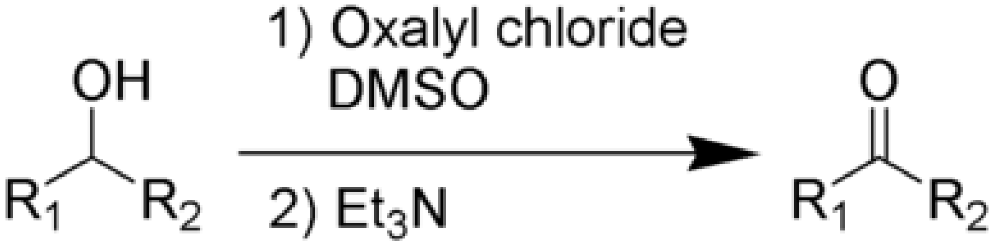


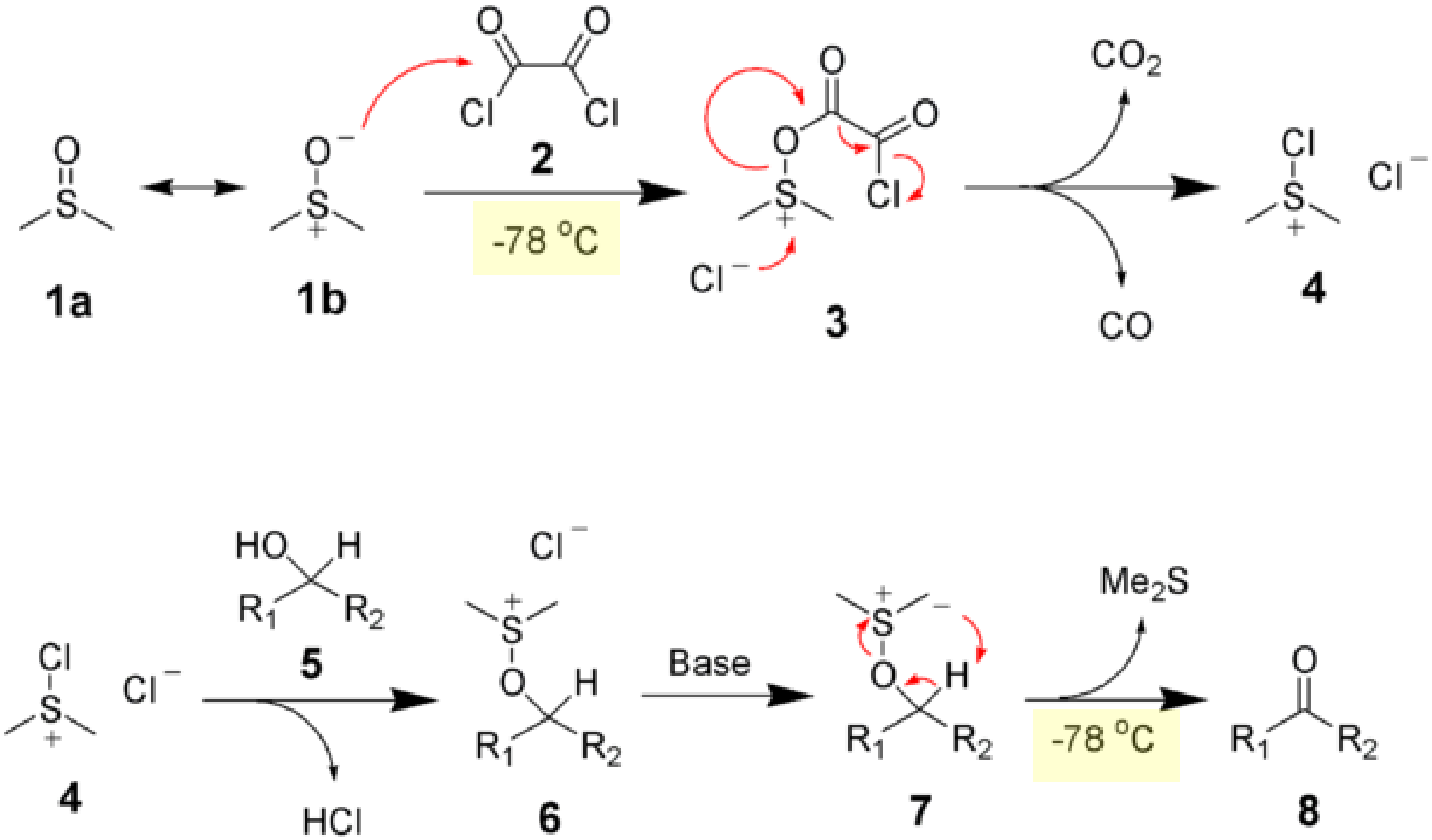
Pyridinium **di** **c**hromate (PDC)



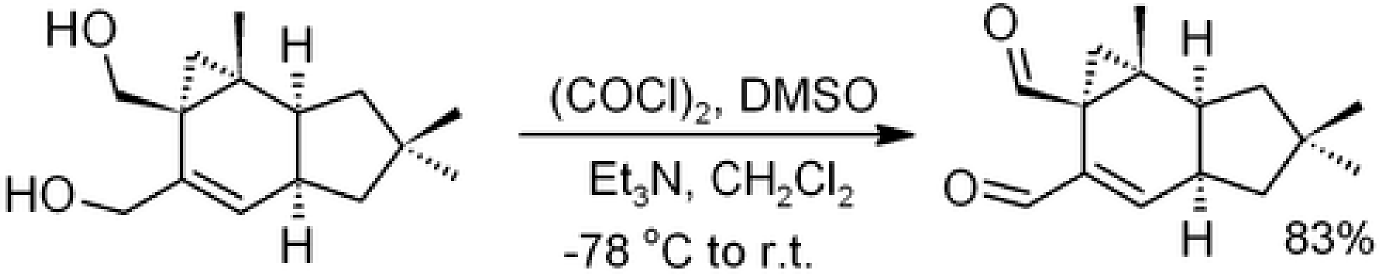
MnO_2

Swern oxidation



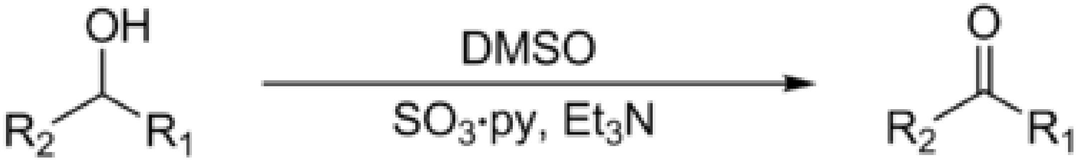

1a
1b
2
-78 °C
3
CO_2
CO
4
5
Base
6
HCl
7
Me_2S
-78 °C
8

The reaction conditions allow oxidation of acid-sensitive compounds, which might decompose under the acidic conditions of a traditional method such as Jones oxidation. For example, in Thompson & Heathcock's synthesis of the sesquiterpene isovelleral, the final step uses the Swern protocol, avoiding rearrangement of the acid-sensitive cyclopropanemethanol moiety.

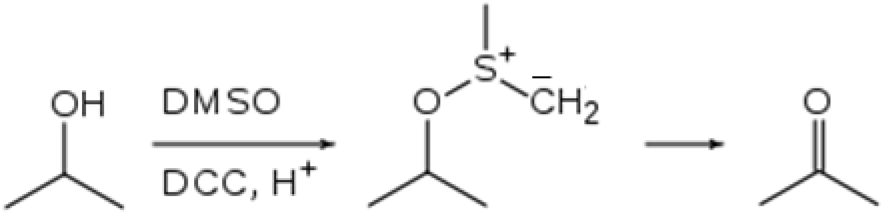


Thompson, S. K.; Heathcock, C. H. (1992). "Total synthesis of some marasmane and lactarane sesquiterpenes". *J. Org. Chem.* **57** (22): 5979–5989. doi:10.1021/jo00048a036.

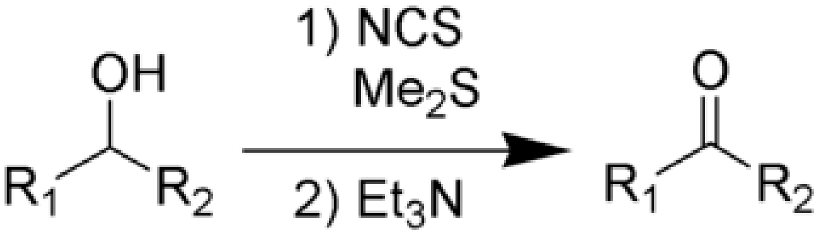
The **Parikh-Doering oxidation** is an oxidation reaction that transforms primary and secondary alcohols into aldehydes and ketones, respectively. The procedure uses dimethyl sulfoxide (DMSO) as the oxidant, activated by the sulfur trioxide pyridine complex in the presence of triethylamine base.



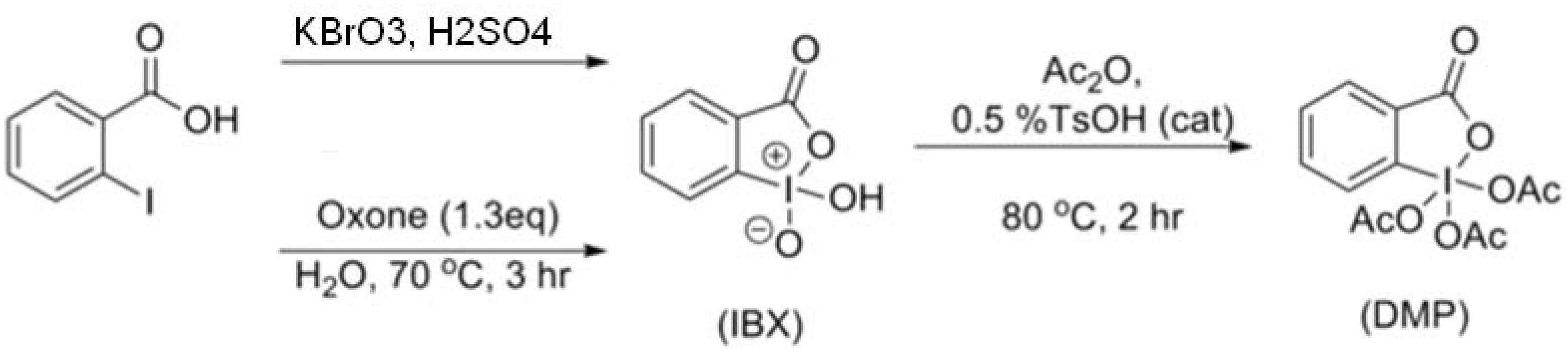
The **Pfitzner–Moffatt oxidation**, sometimes referred to as simply the **Moffatt oxidation**, is a chemical reaction which describes the oxidation of primary and secondary alcohols by dimethyl sulfoxide (DMSO) activated with a carbodiimide, such as dicyclohexylcarbodiimide (DCC). The resulting alkoxysulfonium ylide rearranges to generate aldehydes and ketones, respectively.

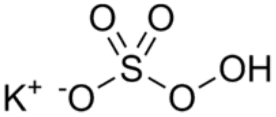


The **Corey–Kim oxidation** is an oxidation reaction used to synthesise aldehydes and ketones from primary and secondary alcohols. It is named for American chemist and Nobelist Elias James Corey and Korean-American chemist Choung Un Kim

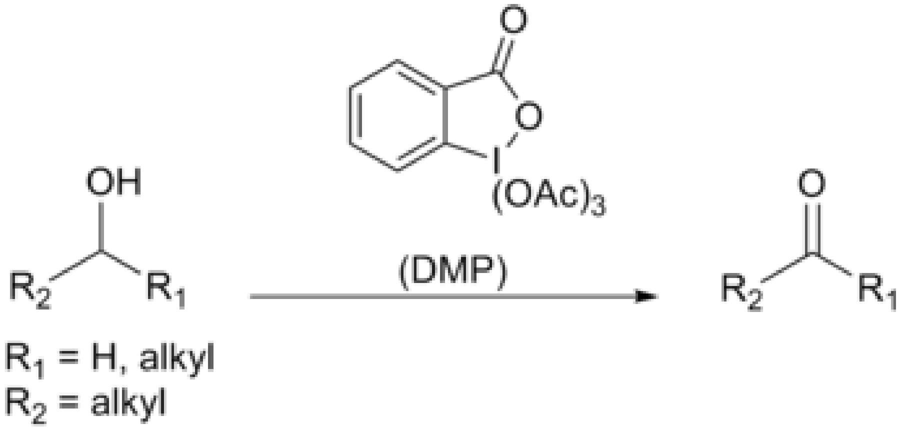


Dess–Martin periodinane (DMP)

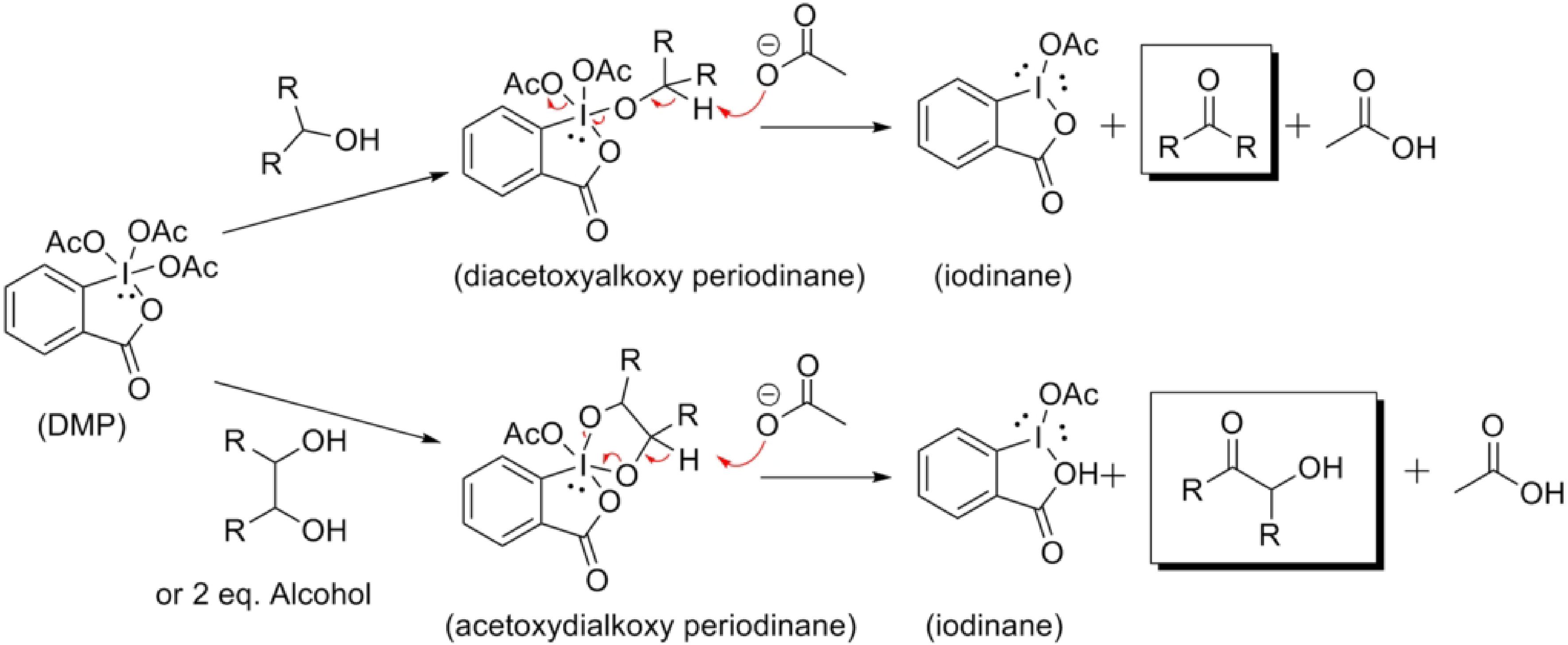


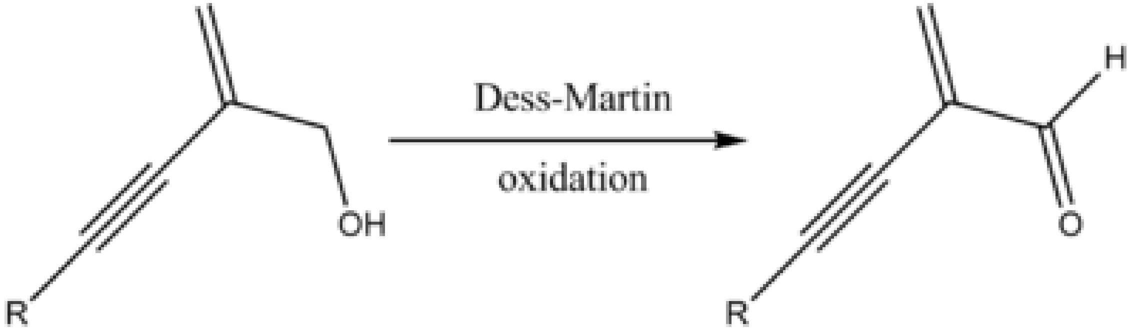


Potassium peroxymonosulfate (also known as MPS, potassium monopersulfate, and the trade names Caroat and Oxone



milder conditions (room temperature, neutral pH), shorter reaction times, higher yields, simplified workups, high chemoselectivity, tolerance of sensitive functional groups, and a long shelf life


(DMP)
or 2 eq. Alcohol
(diacetoxyalkoxy periodinane)
(iodinane)
(acetoxydialkoxy periodinane)
(iodinane)

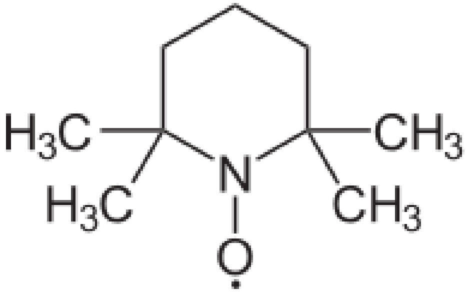


Thongsornkleeb, C., Danheiser, R.L. (2005). "A Practical Method for the Synthesis of 2-Alkynylpropenals". *J. Org. Chem.* **70**: 2364. doi:10.1021/jo047869a

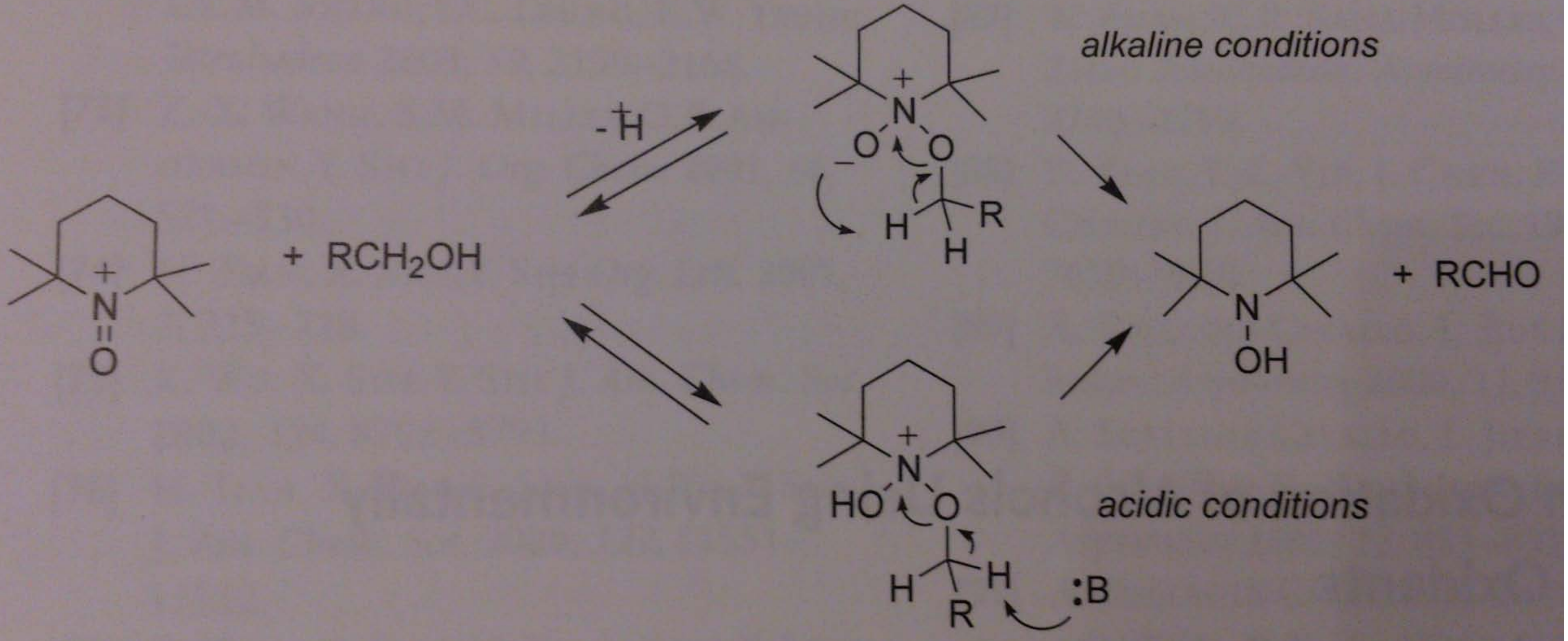
Chemistry of Polyvalent Iodine

Viktor V. Zhdankin and Peter J. Stang
*Chemical Reviews***2008** *108* (12), 5299-5358

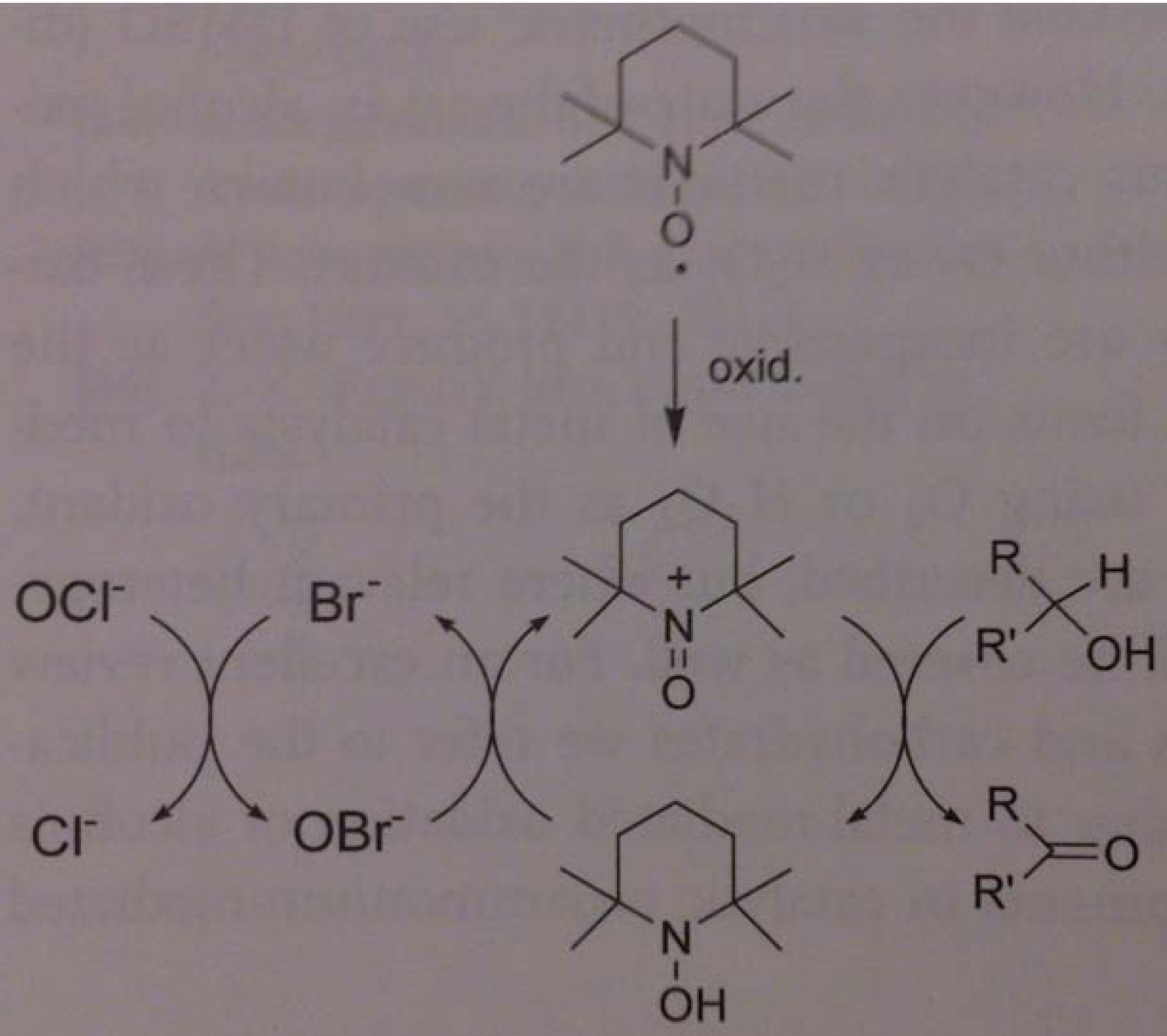
Oxoammonium-based Oxidation of Alcohols



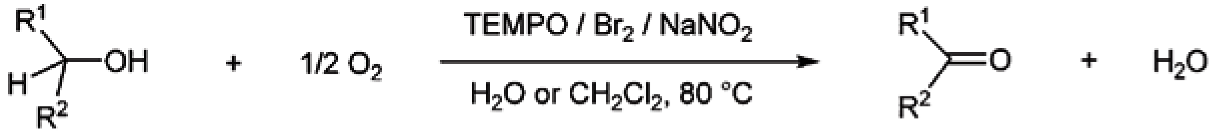
(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl ,TEMPO



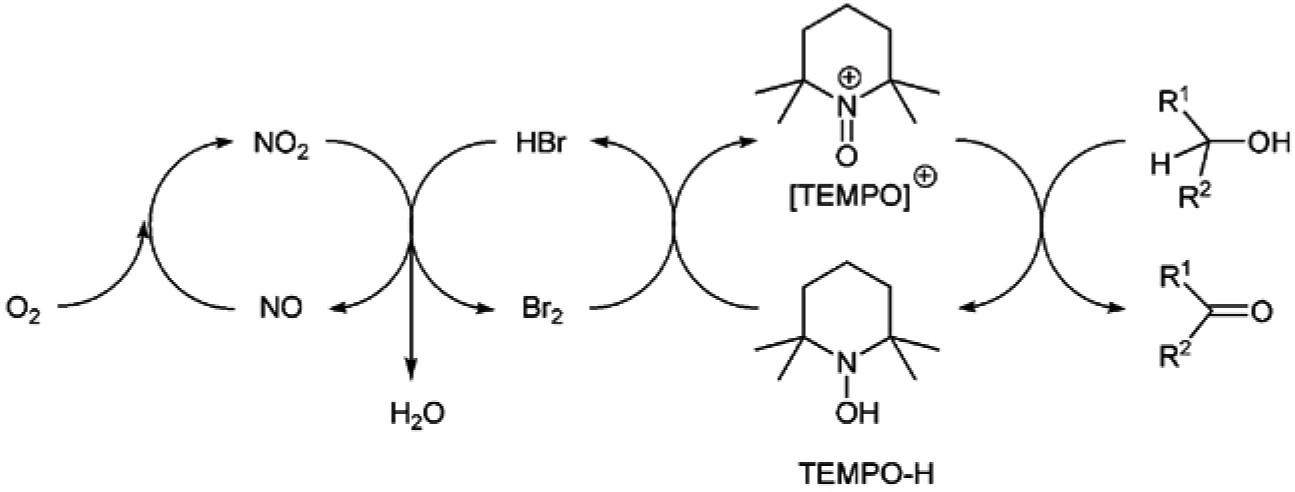
Scheme 4.1 Mechanism for the oxoammonium catalyzed oxidation



Scheme 4.2 TEMPO catalyzed oxidation of alcohols using hypochlorite as the oxidant

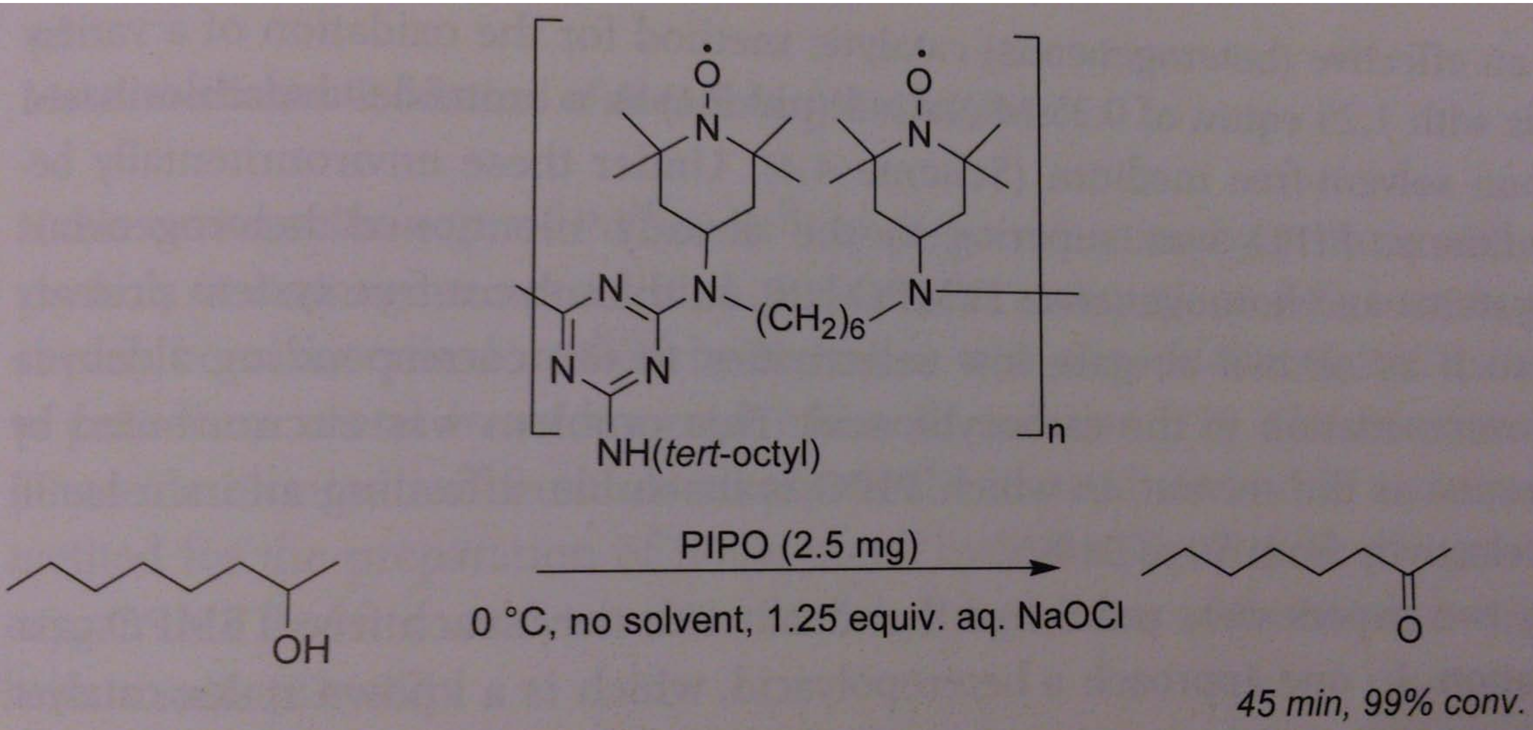


Scheme 1. Selective oxidation of alcohols with the system TEMPO/Br_2/$NaNO_2$.[6]

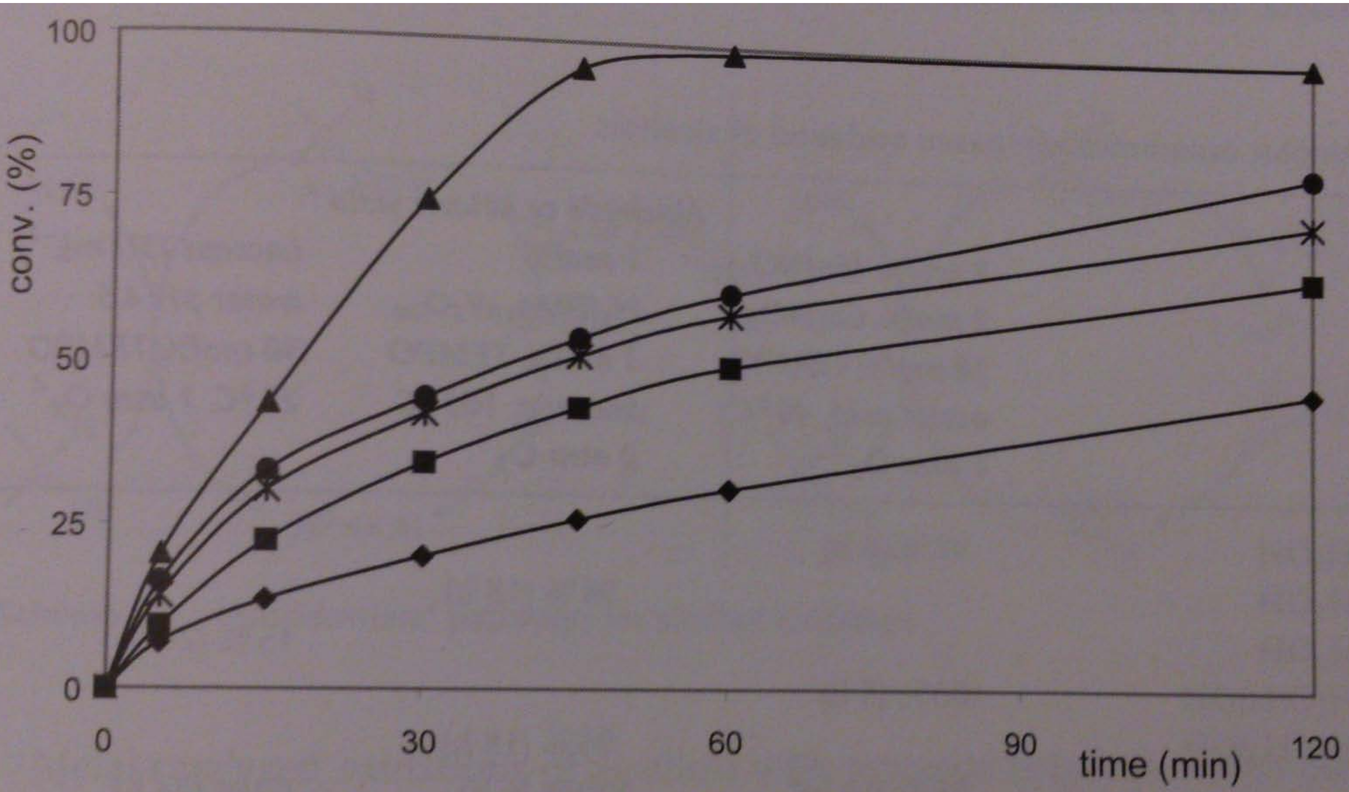


Scheme 2. Reaction cascade for the oxidation of alcohols.[6]

Angew. Chem. Int. Ed. **2006**, *45*, 3206–3210



Scheme 4.3 PIPO as heterogeneous catalyst for alcohol oxidation

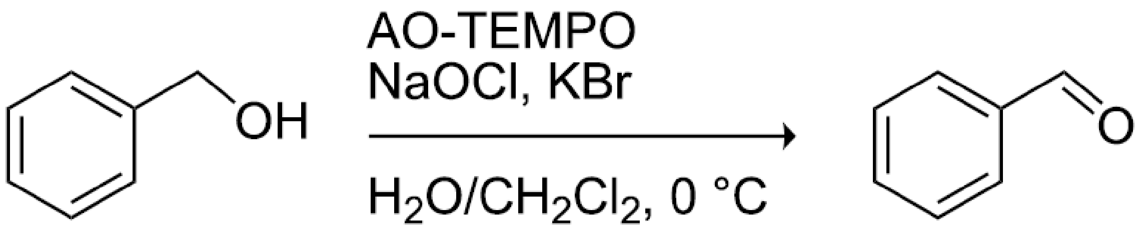


Scheme 4.4 Bleach oxidation of octan-2-ol under chlorinated hydrocarbon solvent- and bromide-free conditions using 1 mol% of nitroxyl catalyst: (▲) PIPO (3.19 mmol g^{-1}; amine linker) [17]; (•) MCM-41 TEMPO (0.60 mmol g^{-1}; ether linker) [15]; (*) SiO_2 TEMPO (0.87 mmol g^{-1}, amine linker) [13]; (■) SiO_2 TEMPO (0.40 mmol g^{-1}, amide linker) [14]; (◆) TEMPO

A biphasic oxidation of alcohols to aldehydes and ketones using a simplified packed-bed microreactor

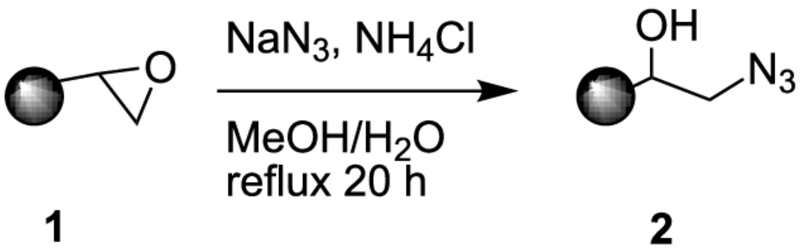
Andrew Bogdan[1] and D. Tyler McQuade*,[2]

Beilstein Journal of Organic Chemistry **2009, 5, No. 17.** doi:10.3762/bjoc.5.17

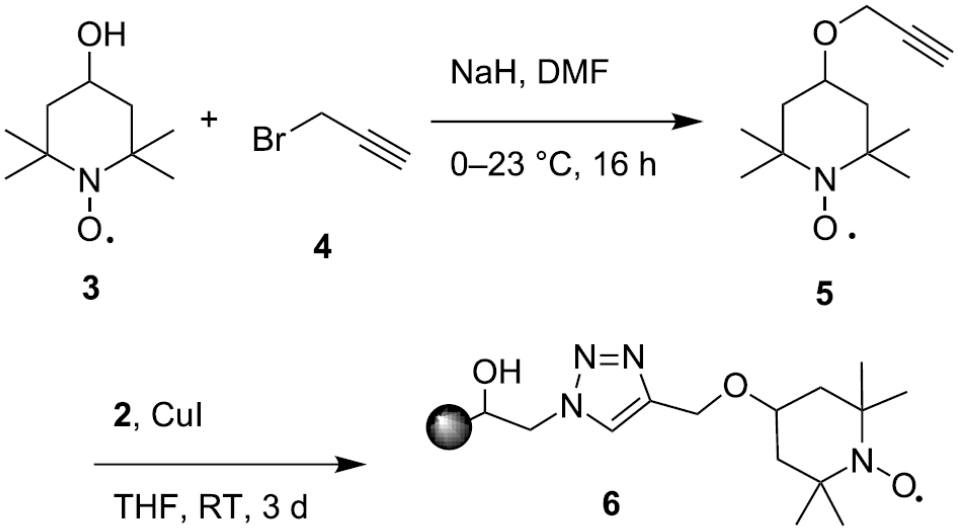


Scheme 3: The AO-TEMPO-catalyzed oxidation of benzyl alcohol.

AMBERZYME® Oxirane (AO, **1), a commercially available** resin with pendant epoxide functionalities designed for enzyme immobilization



Scheme 1: Preparation of azide-modified AO resin **2**.



Scheme 2: Preparation of AO-TEMPO **6**.

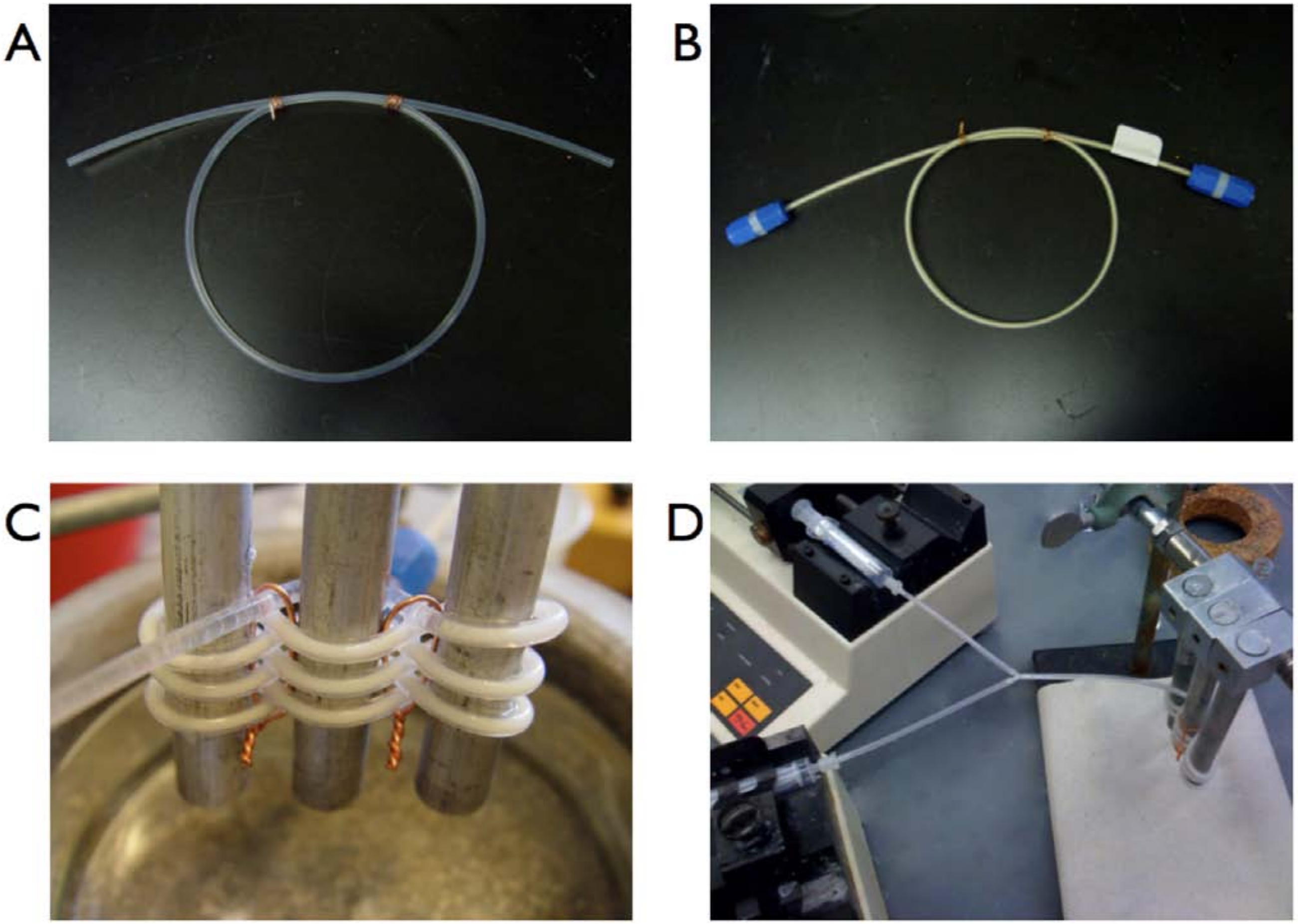


Figure 1: The simplified microreactor setup. Empty tubing (A) is packed with functionalized AO resin and attached to caps (B). The packed bed is woven between metal bars (C) and connected to syringe pumps (D).

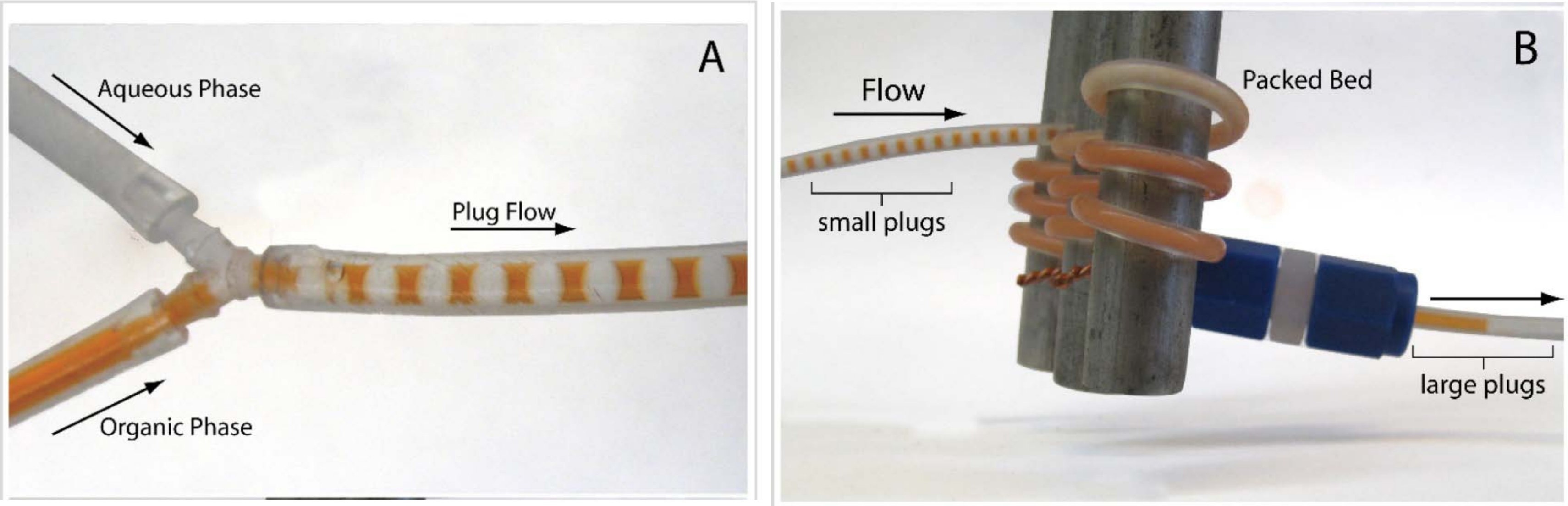
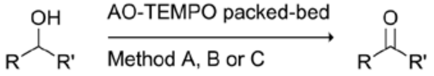
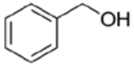
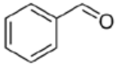
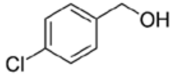
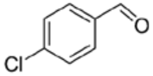
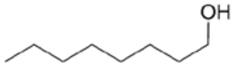
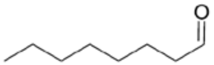
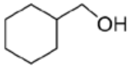
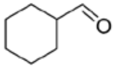
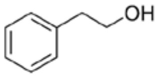
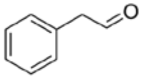
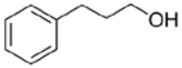
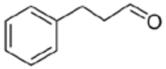
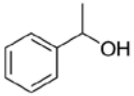
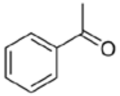
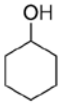
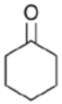
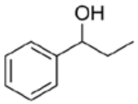
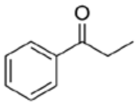
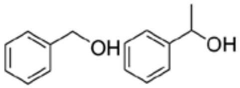
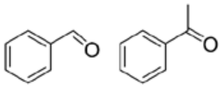
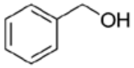
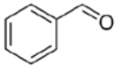


Figure 2: The organic (colored solution) and aqueous phases (colorless solution) forming plugs at the Y-junction (A). The phases mix upon reaching the packed bed, leading to a coalescence of drops at the outlet of the microchannel (B).

Table 1: Oxidation of alcohols using AO-TEMPO packed-bed microreactor.



Entry	Alcohol	Method	Solvent	Product	Conversion[d]	Yield[d]
1		A[a]	CH_2Cl_2		>99%	95%
2		A	CH_2Cl_2		>99%	93% (86%)[e]
3		A	CH_2Cl_2		88%	85%
4		A	CH_2Cl_2		89%	86%
5		A	CH_2Cl_2		88%	71%
6		A	CH_2Cl_2		80%	74%
7		B[b]	CH_2Cl_2		>99%	95%
8		B	CH_2Cl_2		95%	84%
9		B	CH_2Cl_2		89%	85%
10	 1:1 mixture	C[c]	CH_2Cl_2		79%/16%	71%/11%
11		A	EtOAc		84%	81%

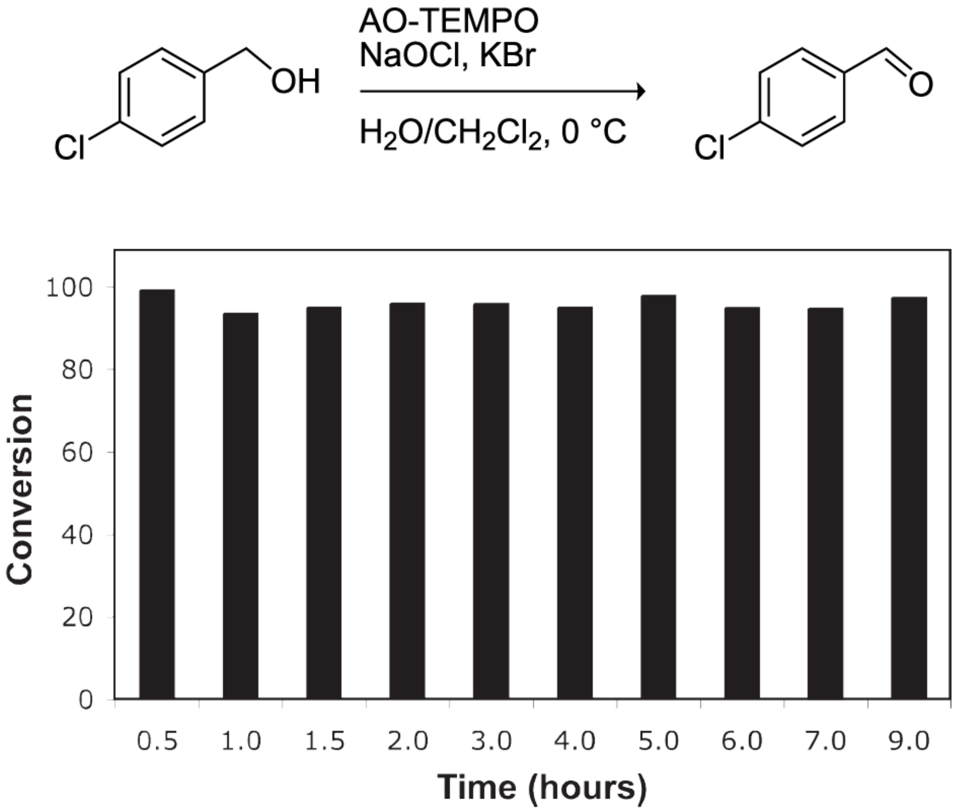
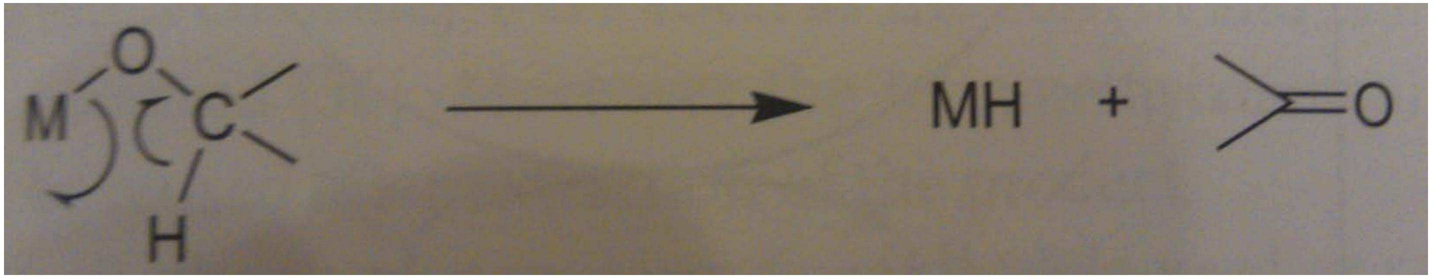
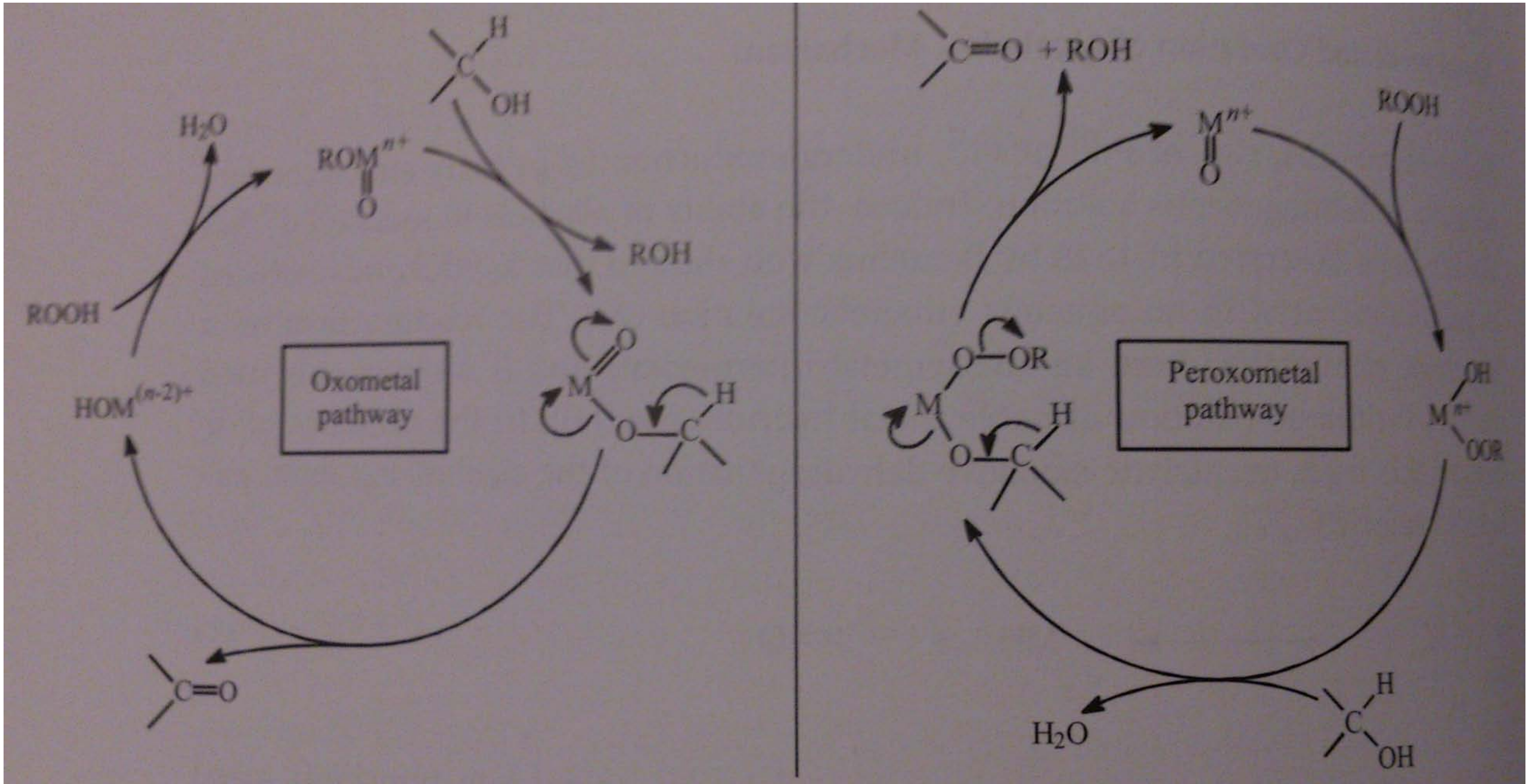


Figure 3: The long-term activity of AO-TEMPO packed beds in the oxidation of 4-chlorobenzyl alcohol. A solution of 4-chlorobenzyl alcohol (0.2 M in CH_2Cl_2) set to 44 μL min^{-1} (8.8 μmol min^{-1}, 1.0 equiv min^{-1}) and an aqueous solution consisting of NaOCl (0.25 M), adjusted to pH 9.1 with $NaHCO_3$, and KBr (0.5 M, 30 μL per mL NaOCl) set to 56 μL min^{-1} (1.5 equiv NaOCl min^{-1}, 0.10 equiv KBr min^{-1}) were passed through the AO-TEMPO packed bed for 9 h. Fractions were collected and analyzed by GC using an internal standard.

Metal-mediated Oxidation of Alcohols

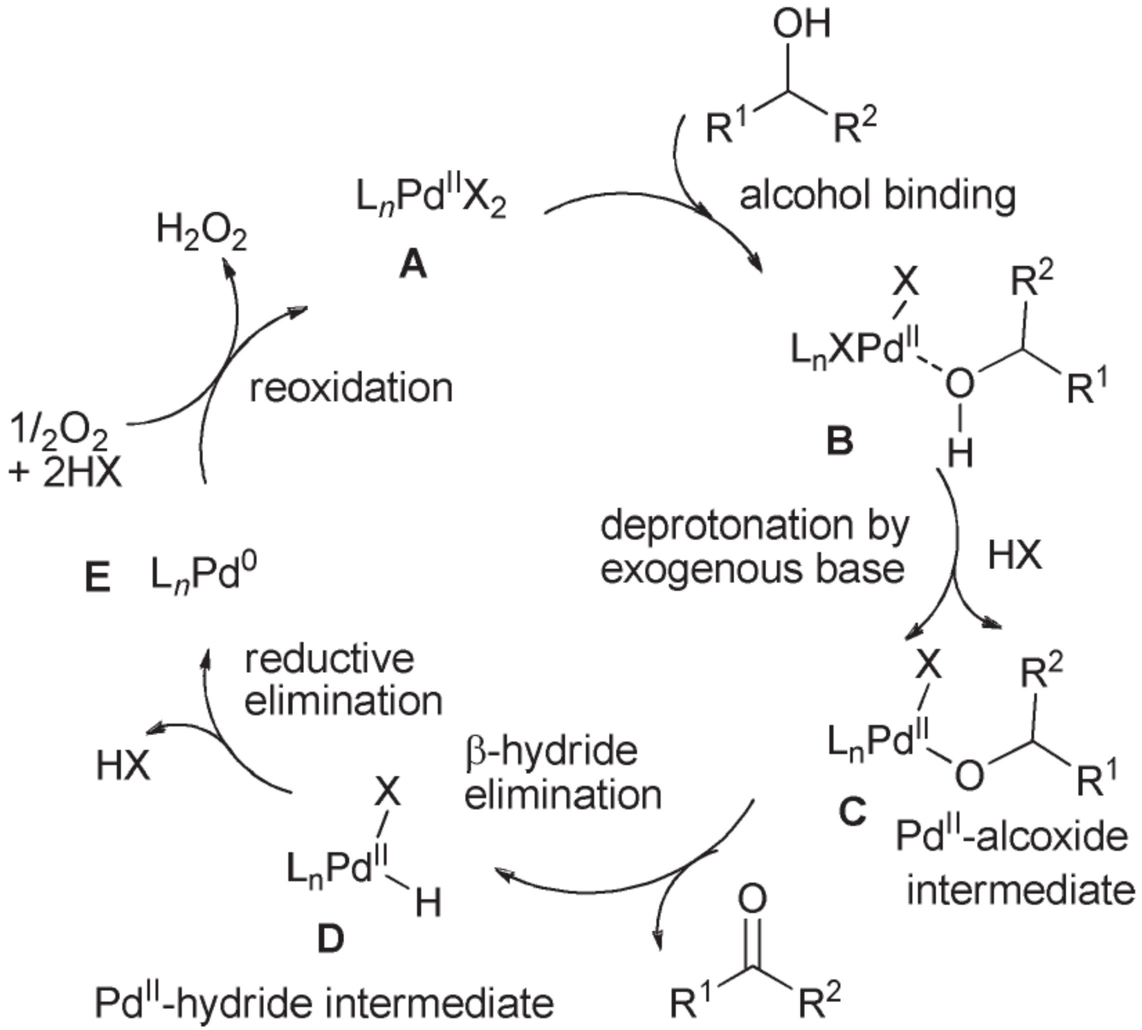




Scheme 4.6 Oxometal *versus* peroxometal pathways in metal catalyzed alcohol oxidations

In contrast, oxometal pathways involve a two-electron change in oxidation state of the metal ion. Typically observed with string oxidants, e.g. Cr(VI), Mn(V), Os(VIII), Ru(VI) and Ru(VIII).

In the peroxometal pathway the metal ion remains in the same oxidation state. Typically observed with weak oxidants d^0 metal ions, e.g. Mo(VI), W(VI), Ti(IV), Re(VII).



Scheme 17 The generally accepted mechanism of the aerobic Pd^{II}-catalyzed oxidation of alcohols.

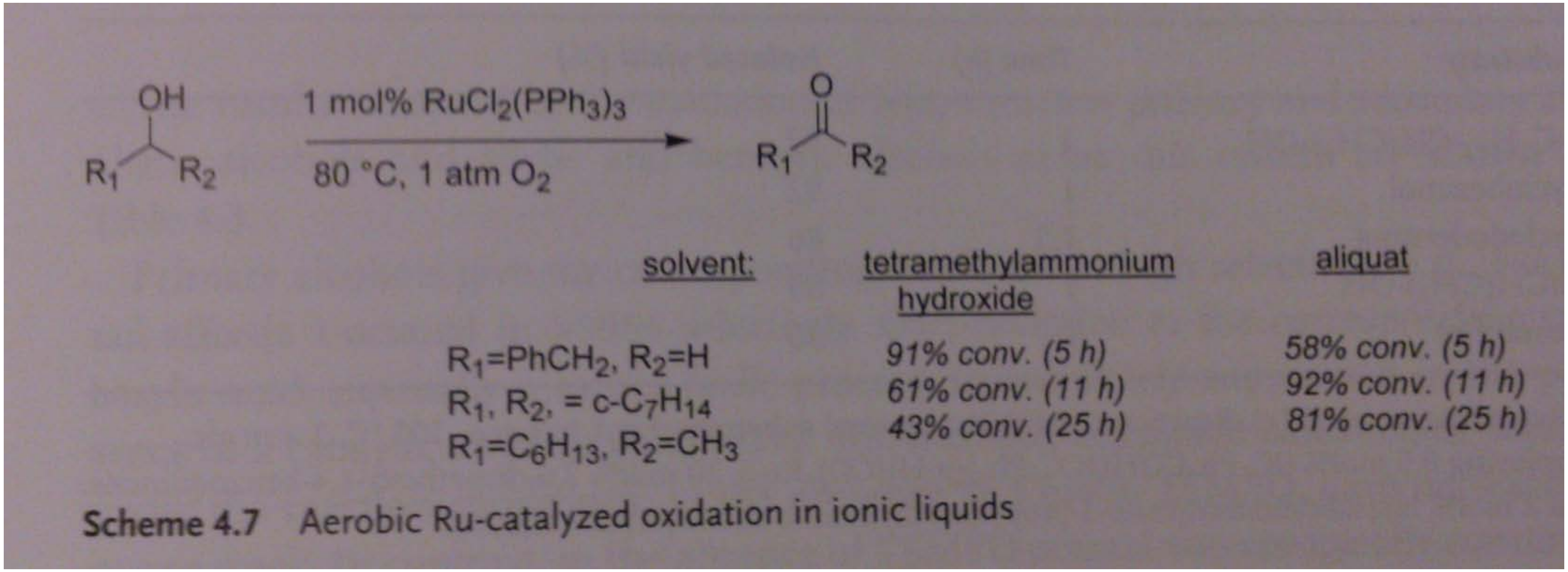
Green Chem.
2012,

Transition metal based catalysts in the aerobic oxidation of alcohols

Camilla Parmeggiani*[a,b] **and Francesca Cardona***[a]

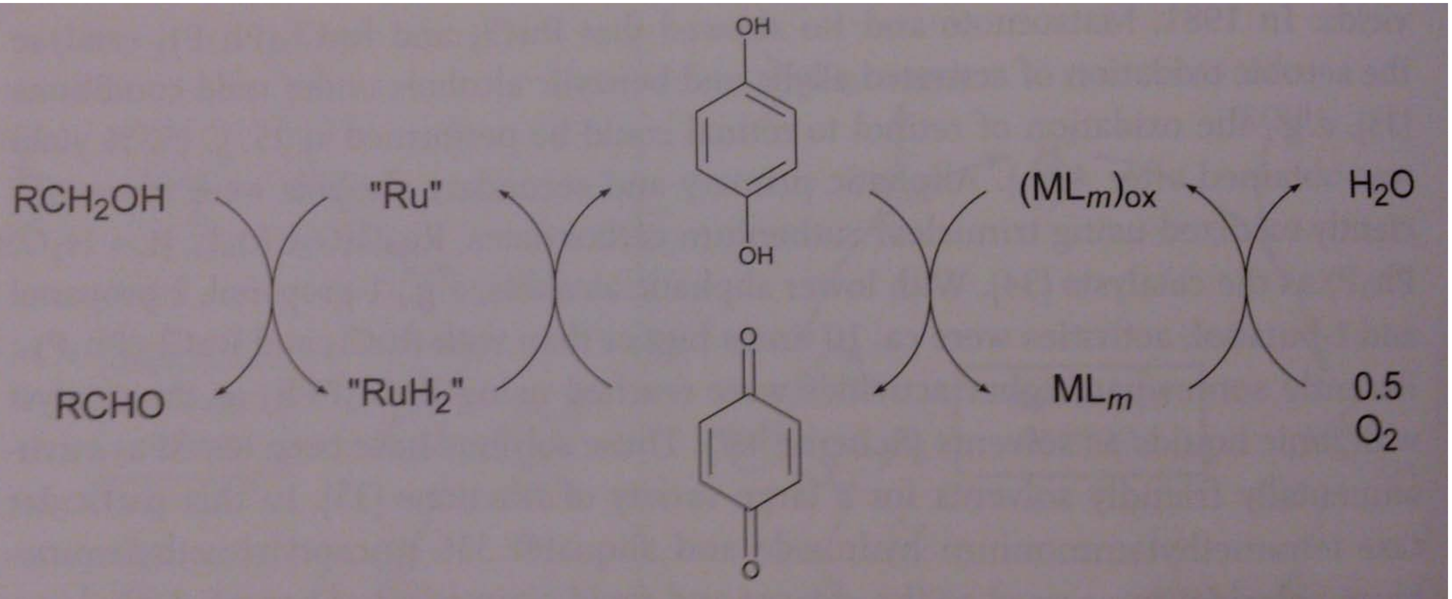
Received 27th October 2011, Accepted 19th December 2011
DOI: 10.1039/c2gc16344f

Ruthenium-catalyzed Oxidations with O_2.

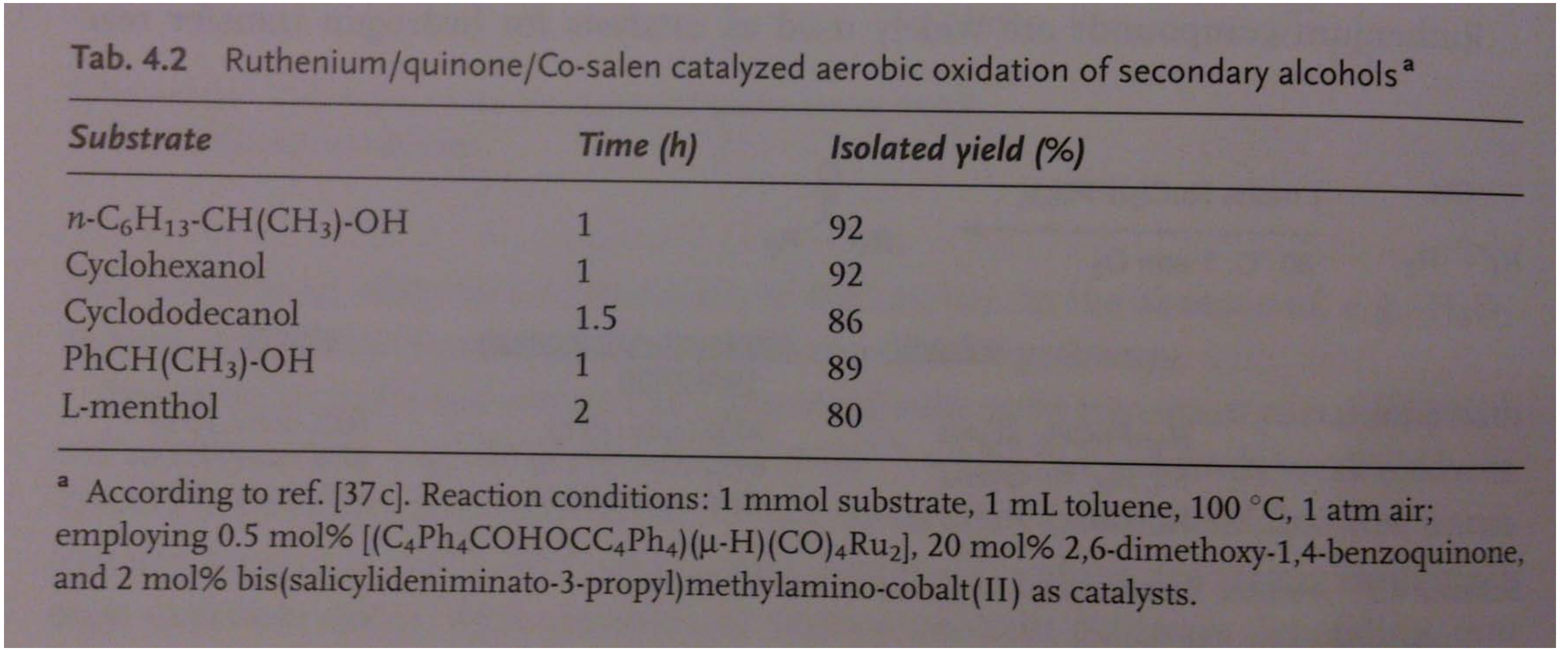


solvent:	tetramethylammonium hydroxide	aliquat
R_1=$PhCH_2$, R_2=H	*91% conv. (5 h)*	*58% conv. (5 h)*
R_1, R_2, = c-C_7H_{14}	*61% conv. (11 h)*	*92% conv. (11 h)*
R_1=C_6H_{13}, R_2=CH_3	*43% conv. (25 h)*	*81% conv. (25 h)*

Scheme 4.7 Aerobic Ru-catalyzed oxidation in ionic liquids



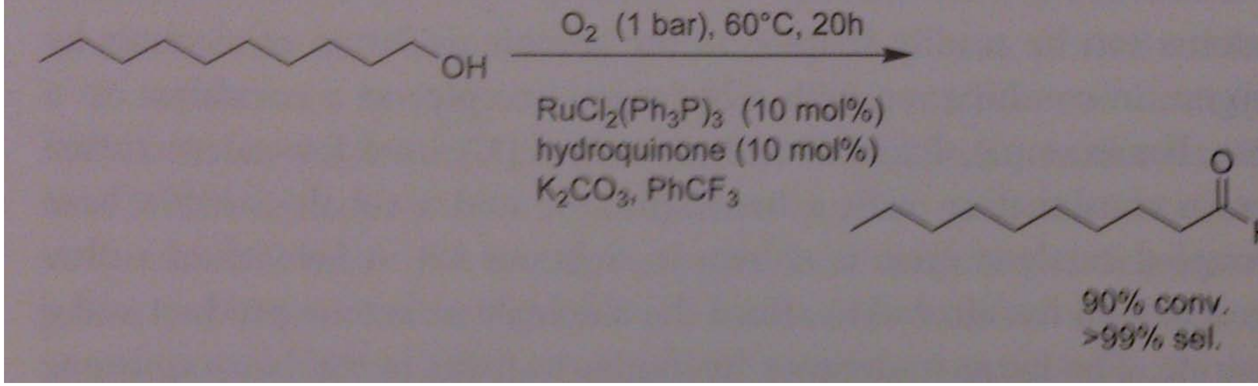
Scheme 4.8 Ruthenium catalyst in combination with a hydrogen acceptor for aerobic oxidation



Tab. 4.2 Ruthenium/quinone/Co-salen catalyzed aerobic oxidation of secondary alcohols[a]

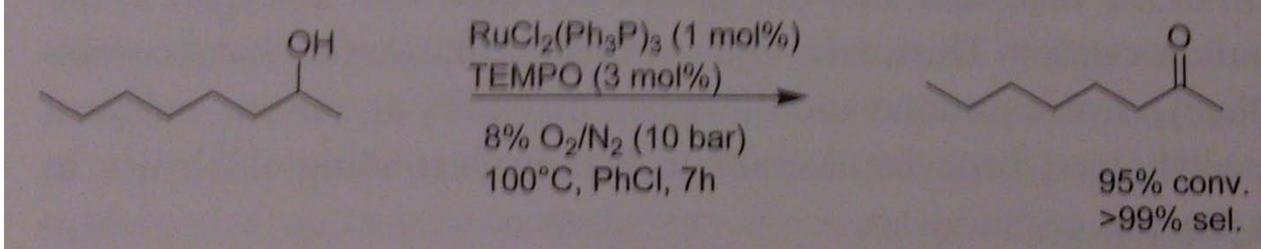
Substrate	*Time (h)*	*Isolated yield (%)*
n-C_6H_{13}-CH(CH_3)-OH	1	92
Cyclohexanol	1	92
Cyclododecanol	1.5	86
PhCH(CH_3)-OH	1	89
L-menthol	2	80

[a] According to ref. [37c]. Reaction conditions: 1 mmol substrate, 1 mL toluene, 100 °C, 1 atm air; employing 0.5 mol% [($C_4Ph_4COHOCC_4Ph_4$)(μ-H)(CO)$_4$Ru$_2$], 20 mol% 2,6-dimethoxy-1,4-benzoquinone, and 2 mol% bis(salicylideniminato-3-propyl)methylamino-cobalt(II) as catalysts.

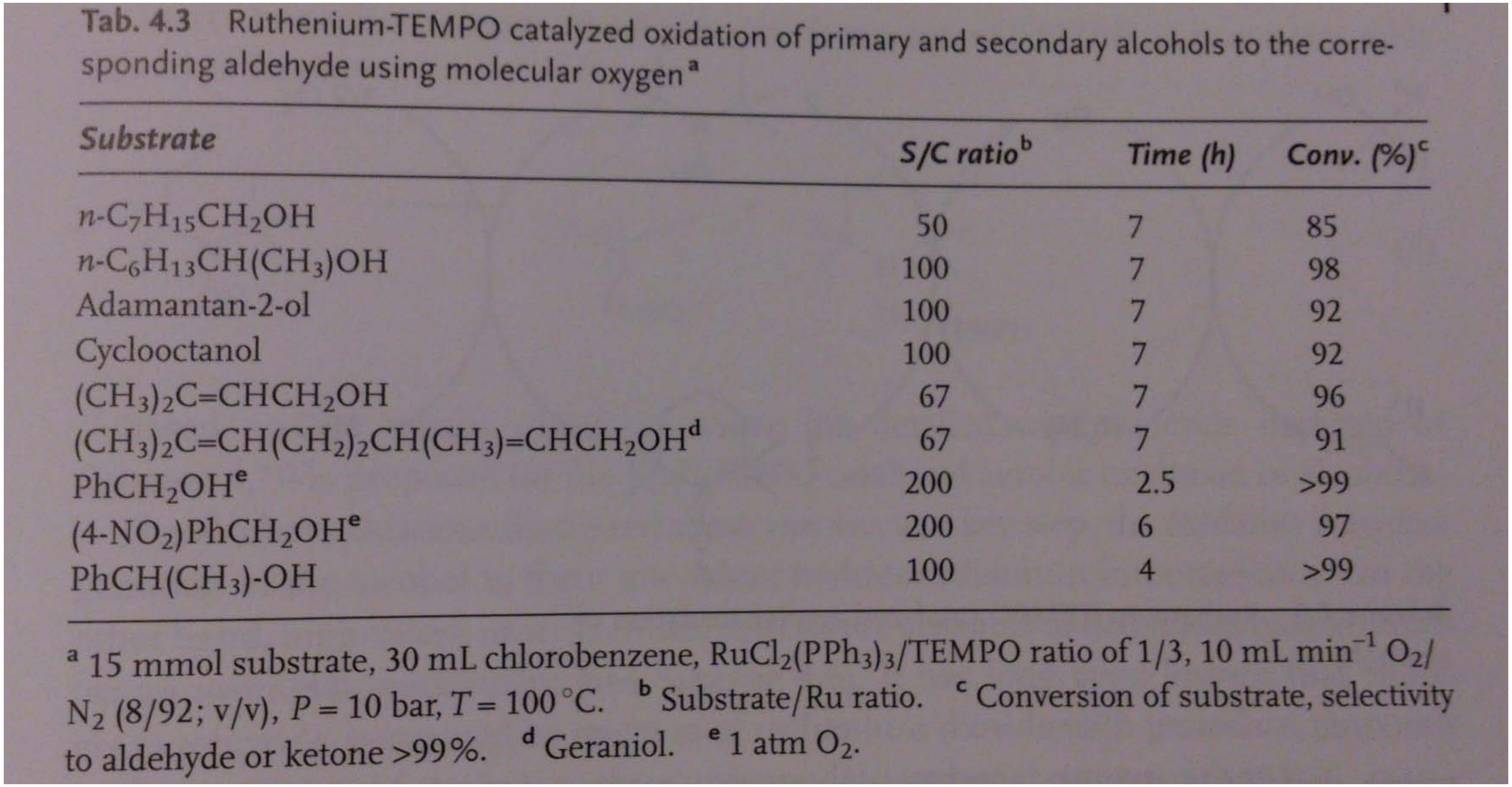


(2)

The regeneration of Benzoquinone can also be achieved with dioxygen in the absence of the co-cotalayst



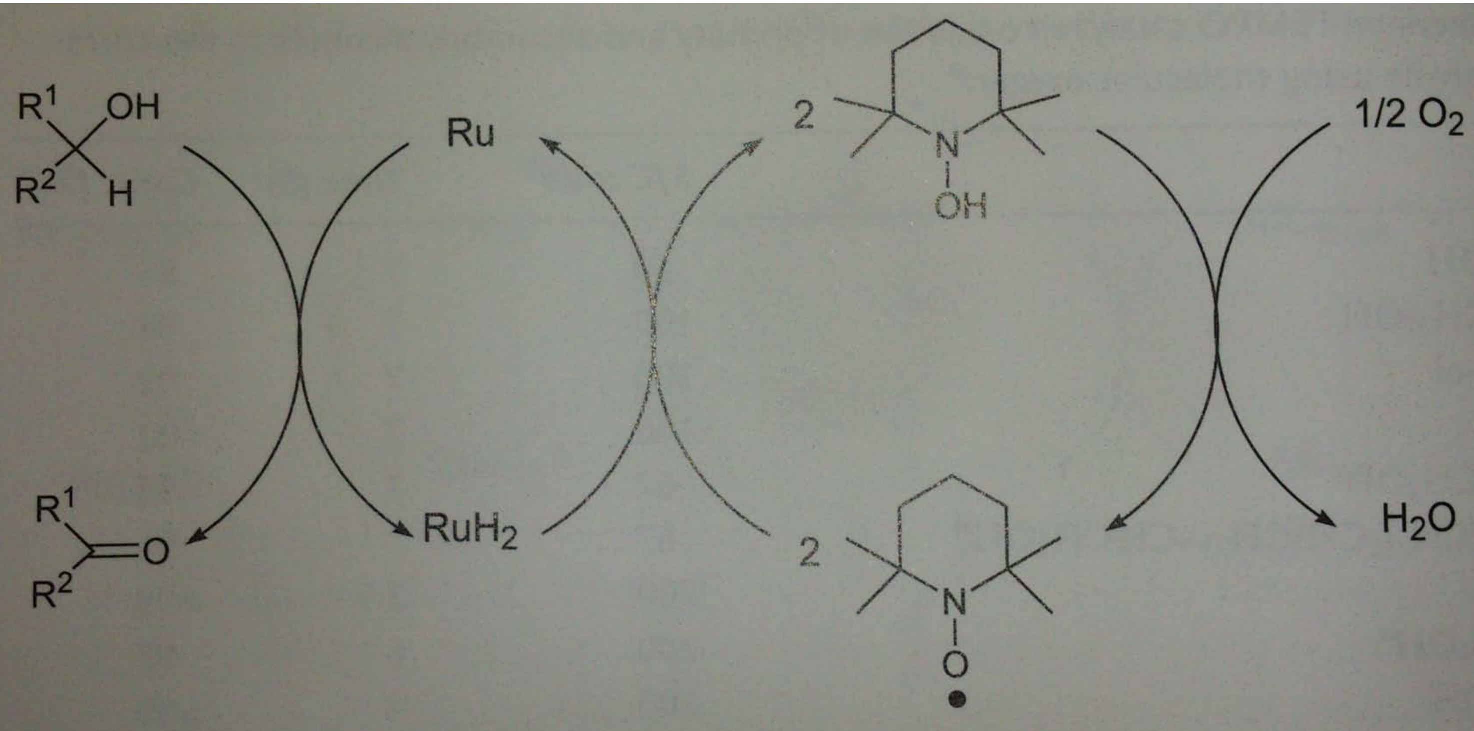
(3)



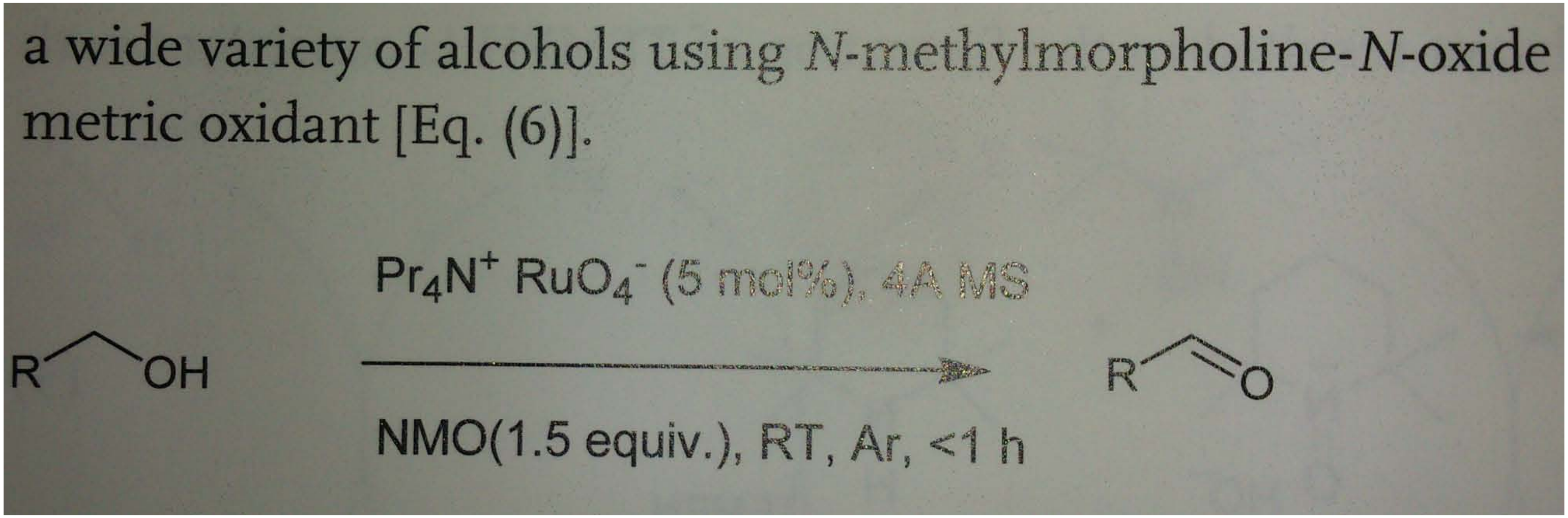
Tab. 4.3 Ruthenium-TEMPO catalyzed oxidation of primary and secondary alcohols to the corresponding aldehyde using molecular oxygen[a]

Substrate	S/C ratio[b]	Time (h)	Conv. (%)[c]
n-$C_7H_{15}CH_2OH$	50	7	85
n-$C_6H_{13}CH(CH_3)OH$	100	7	98
Adamantan-2-ol	100	7	92
Cyclooctanol	100	7	92
$(CH_3)_2C{=}CHCH_2OH$	67	7	96
$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3){=}CHCH_2OH$[d]	67	7	91
$PhCH_2OH$[e]	200	2.5	>99
$(4\text{-}NO_2)PhCH_2OH$[e]	200	6	97
$PhCH(CH_3)\text{-}OH$	100	4	>99

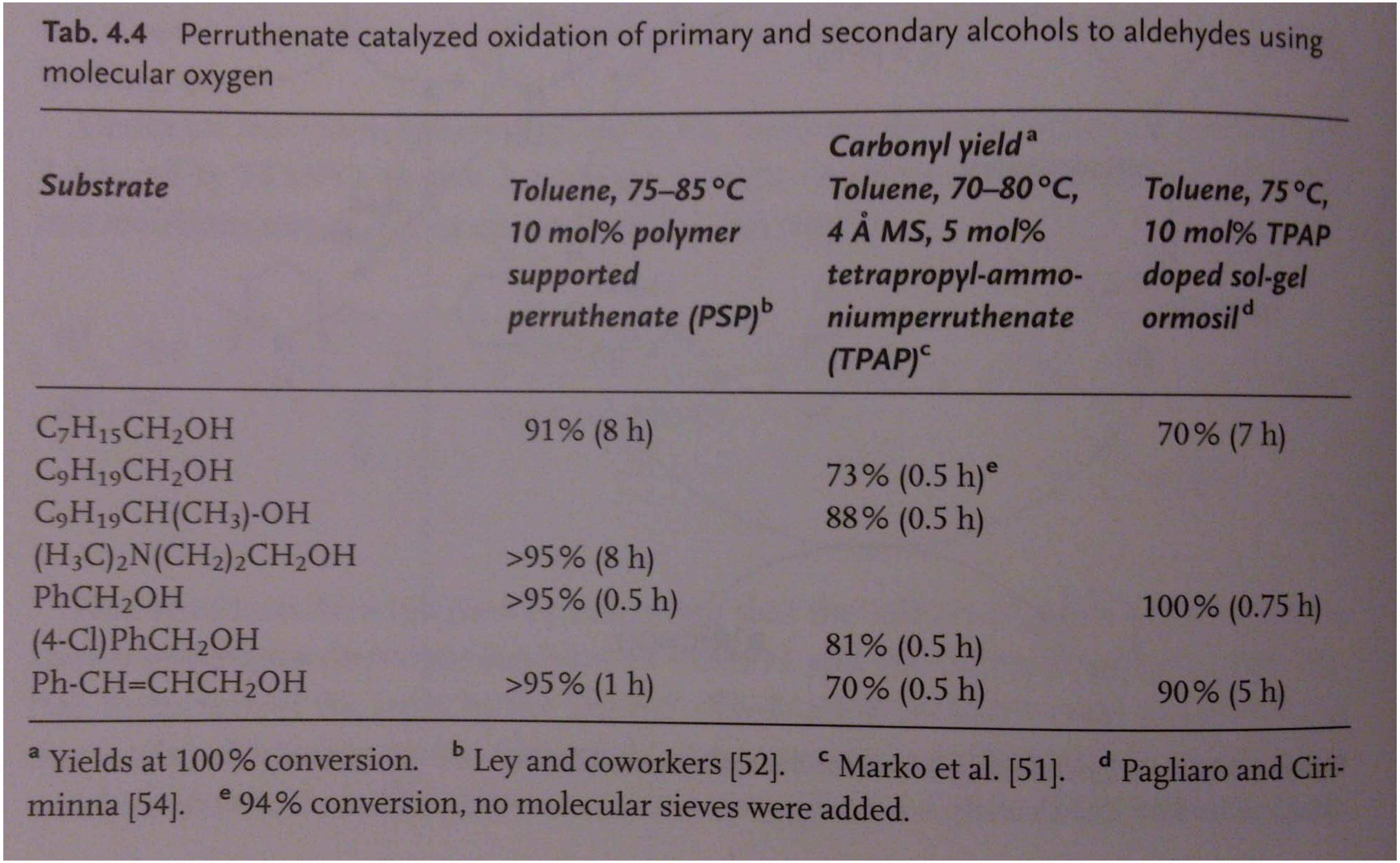
[a] 15 mmol substrate, 30 mL chlorobenzene, $RuCl_2(PPh_3)_3$/TEMPO ratio of 1/3, 10 mL min^{-1} O_2/N_2 (8/92; v/v), $P = 10$ bar, $T = 100$ °C. [b] Substrate/Ru ratio. [c] Conversion of substrate, selectivity to aldehyde or ketone >99%. [d] Geraniol. [e] 1 atm O_2.



Scheme 4.9 Ruthenium/TEMPO catalyzed aerobic oxidation of alcohols



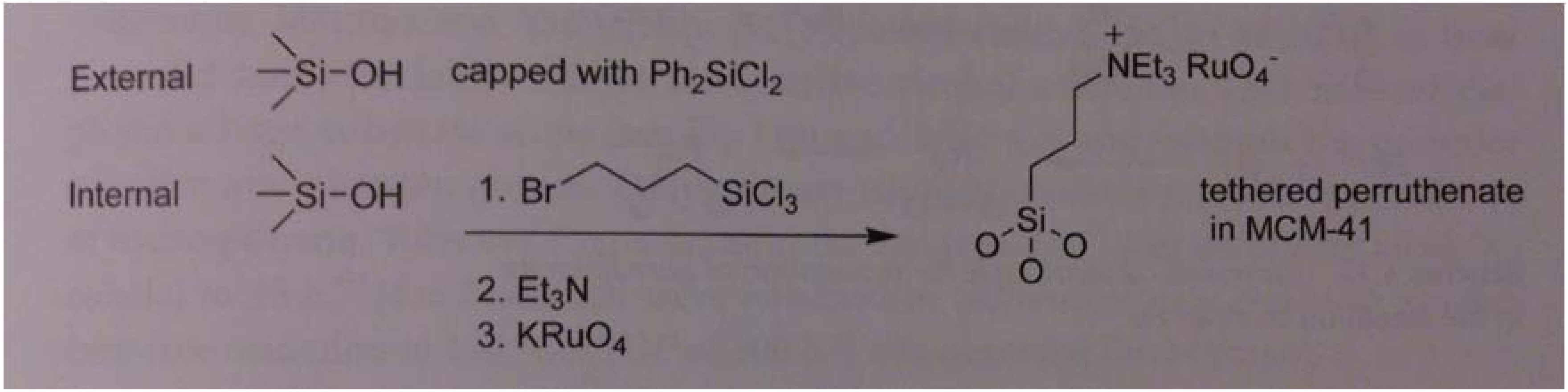
a wide variety of alcohols using *N*-methylmorpholine-*N*-oxide
metric oxidant [Eq. (6)].

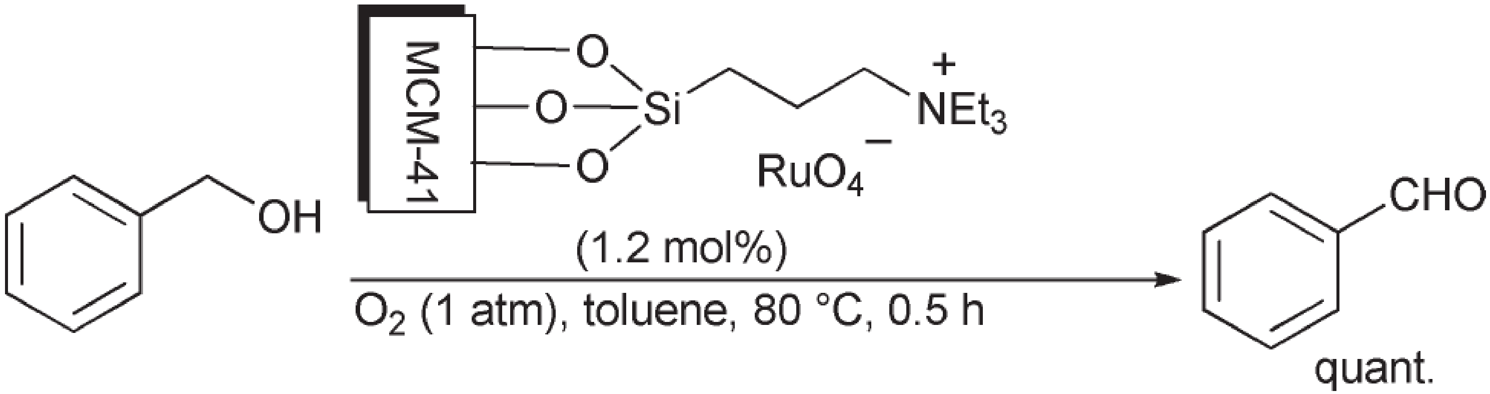


Tab. 4.4 Perruthenate catalyzed oxidation of primary and secondary alcohols to aldehydes using molecular oxygen

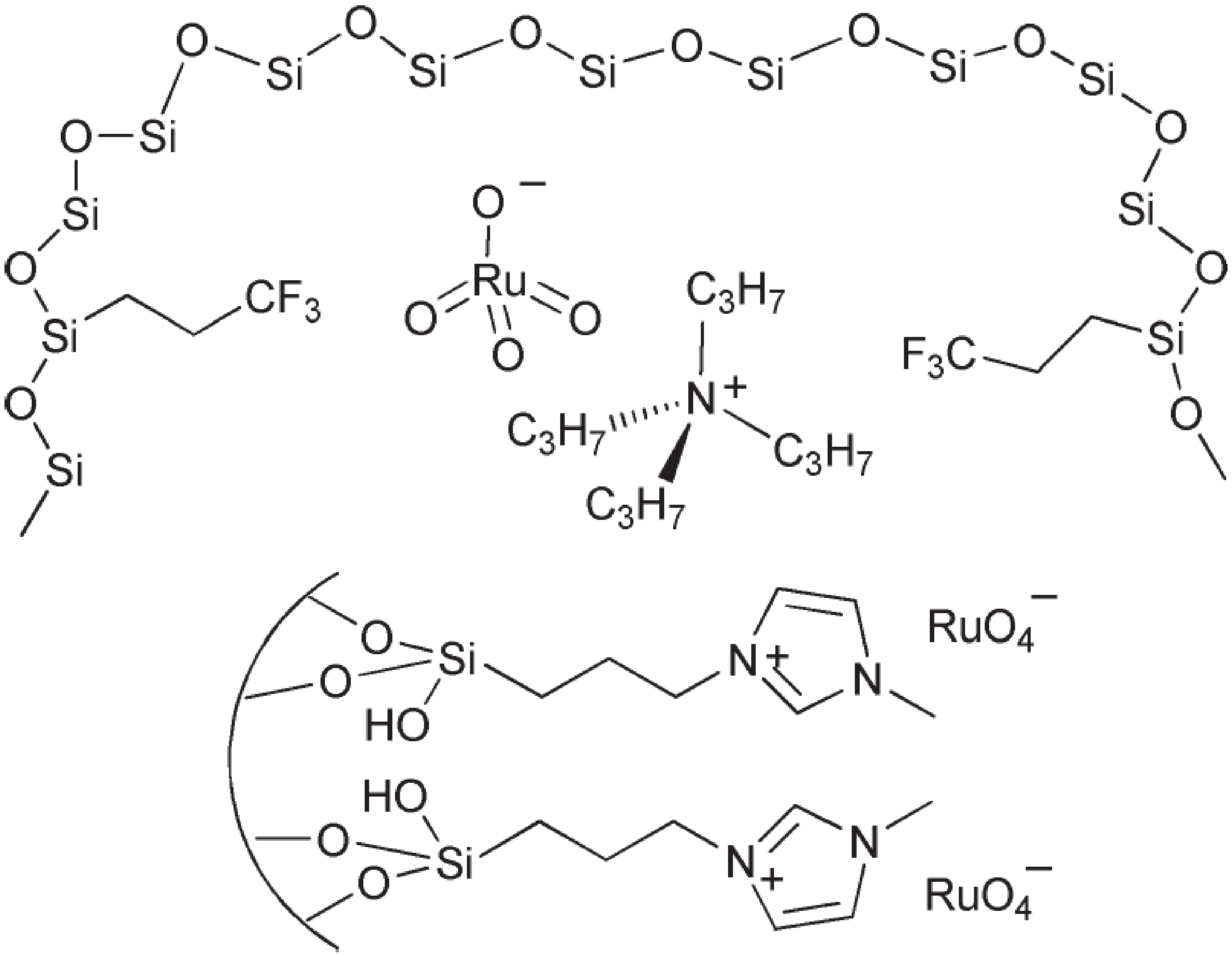
Substrate		*Carbonyl yield*[a]	
	Toluene, 75–85 °C 10 mol% polymer supported perruthenate (PSP)[b]	*Toluene, 70–80 °C, 4 Å MS, 5 mol% tetrapropyl-ammoniumperruthenate (TPAP)*[c]	*Toluene, 75 °C, 10 mol% TPAP doped sol-gel ormosil*[d]
$C_7H_{15}CH_2OH$	91% (8 h)		70% (7 h)
$C_9H_{19}CH_2OH$		73% (0.5 h)[e]	
$C_9H_{19}CH(CH_3)$-OH		88% (0.5 h)	
$(H_3C)_2N(CH_2)_2CH_2OH$	>95% (8 h)		
$PhCH_2OH$	>95% (0.5 h)		100% (0.75 h)
(4-Cl)$PhCH_2OH$		81% (0.5 h)	
Ph-CH=$CHCH_2OH$	>95% (1 h)	70% (0.5 h)	90% (5 h)

[a] Yields at 100% conversion. [b] Ley and coworkers [52]. [c] Marko et al. [51]. [d] Pagliaro and Ciriminna [54]. [e] 94% conversion, no molecular sieves were added.

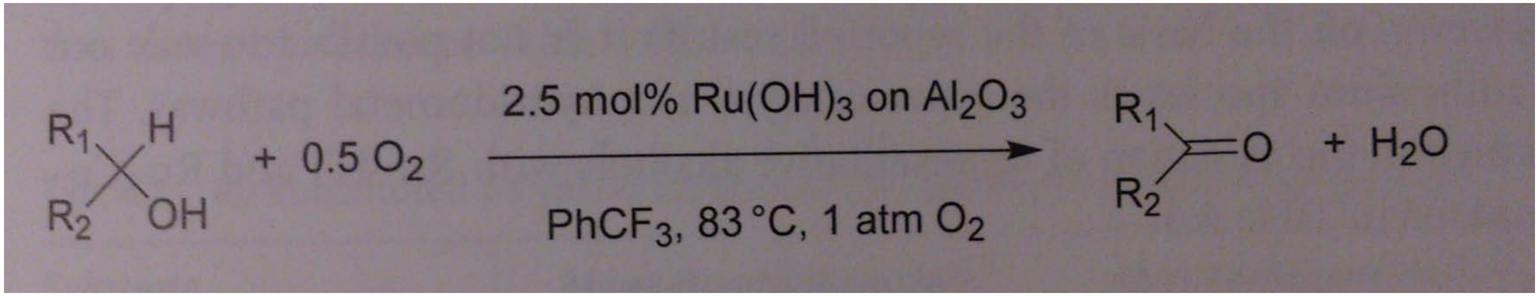

External
Si-OH
capped with Ph2SiCl2
Internal
Si-OH
1. Br
SiCl3
2. Et3N
3. KRuO4
+NEt3 RuO4-
Si
O
O
O
tethered perruthenate
in MCM-41

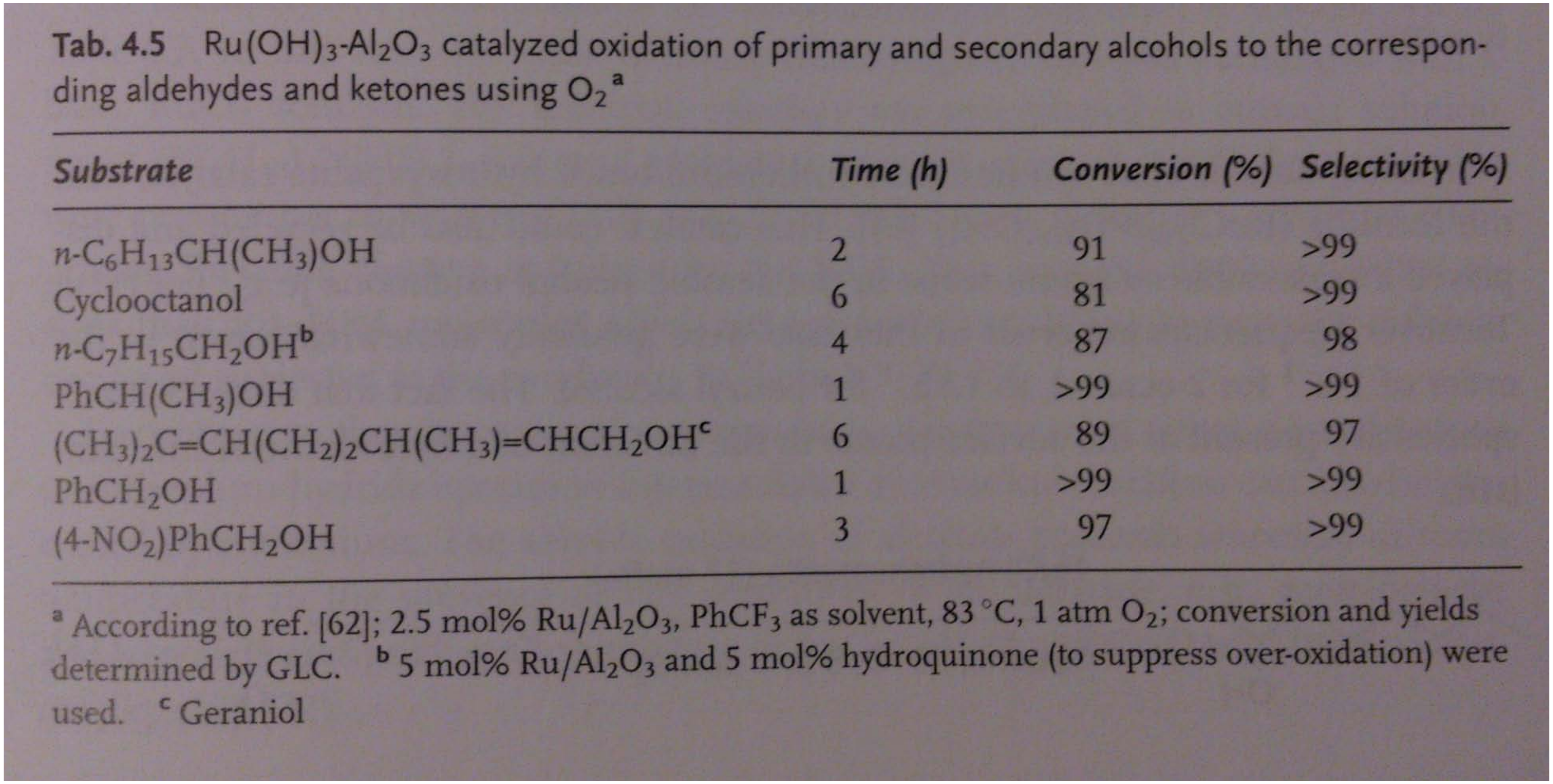


Scheme 12 Ley's modified mesoporous silicate materials MCM-41.



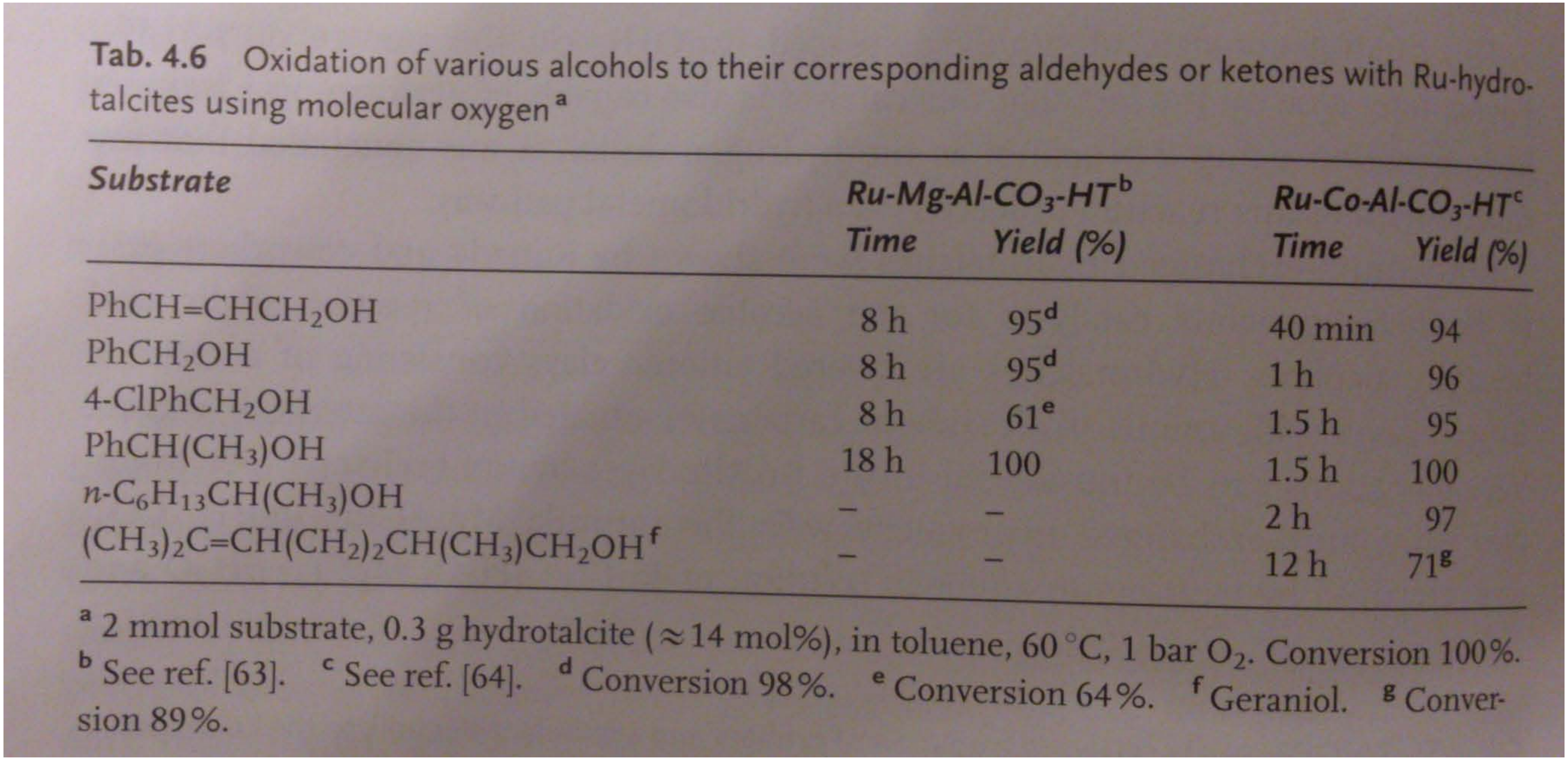
Scheme 13 TPAP-heterogeneous catalysts developed by Pagliaro and co-workers.




Tab. 4.5 $Ru(OH)_3$-Al_2O_3 catalyzed oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones using O_2[a]

Substrate	*Time (h)*	*Conversion (%)*	*Selectivity (%)*
n-$C_6H_{13}CH(CH_3)OH$	2	91	>99
Cyclooctanol	6	81	>99
n-$C_7H_{15}CH_2OH$[b]	4	87	98
$PhCH(CH_3)OH$	1	>99	>99
$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3){=}CHCH_2OH$[c]	6	89	97
$PhCH_2OH$	1	>99	>99
$(4\text{-}NO_2)PhCH_2OH$	3	97	>99

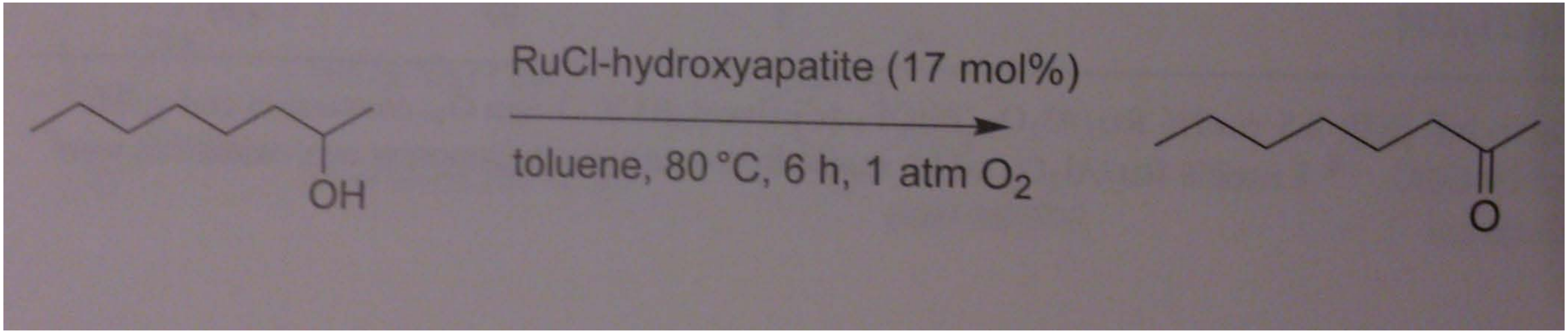
[a] According to ref. [62]; 2.5 mol% Ru/Al_2O_3, $PhCF_3$ as solvent, 83 °C, 1 atm O_2; conversion and yields determined by GLC. [b] 5 mol% Ru/Al_2O_3 and 5 mol% hydroquinone (to suppress over-oxidation) were used. [c] Geraniol



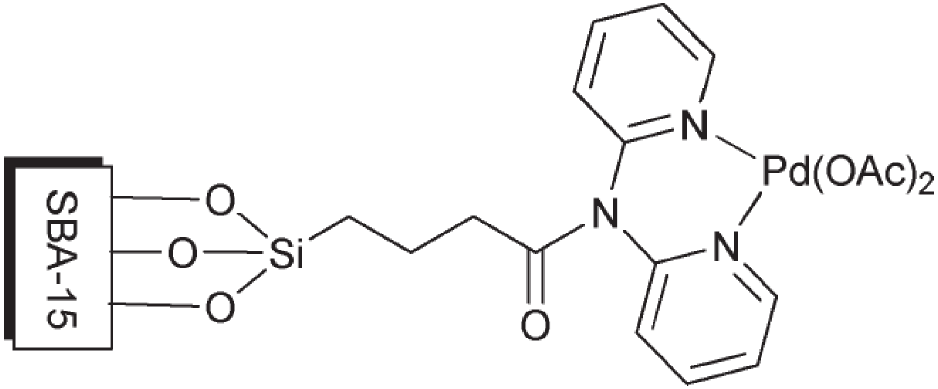
Tab. 4.6 Oxidation of various alcohols to their corresponding aldehydes or ketones with Ru-hydrotalcites using molecular oxygen[a]

Substrate	*Ru-Mg-Al-CO_3-HT*[b]		*Ru-Co-Al-CO_3-HT*[c]	
	Time	*Yield (%)*	*Time*	*Yield (%)*
$PhCH{=}CHCH_2OH$	8 h	95[d]	40 min	94
$PhCH_2OH$	8 h	95[d]	1 h	96
$4\text{-}ClPhCH_2OH$	8 h	61[e]	1.5 h	95
$PhCH(CH_3)OH$	18 h	100	1.5 h	100
$n\text{-}C_6H_{13}CH(CH_3)OH$	–	–	2 h	97
$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2OH$[f]	–	–	12 h	71[g]

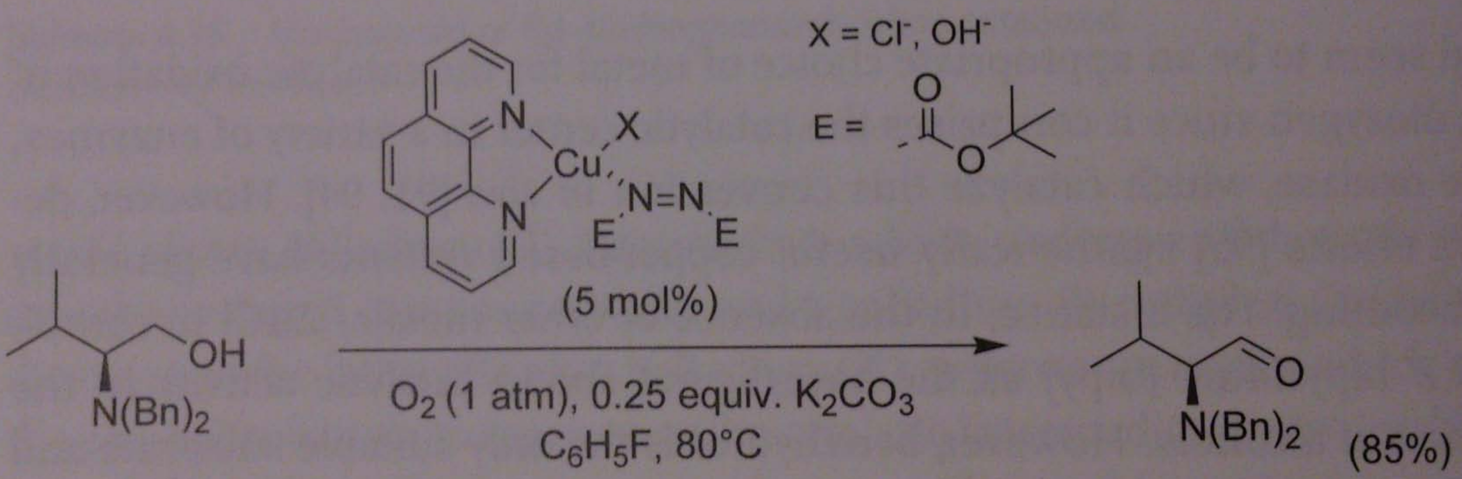
[a] 2 mmol substrate, 0.3 g hydrotalcite (≈14 mol%), in toluene, 60 °C, 1 bar O_2. Conversion 100%. [b] See ref. [63]. [c] See ref. [64]. [d] Conversion 98%. [e] Conversion 64%. [f] Geraniol. [g] Conversion 89%.


RuCl-hydroxyapatite (17 mol%)
toluene, 80 °C, 6 h, 1 atm O2
OH
O

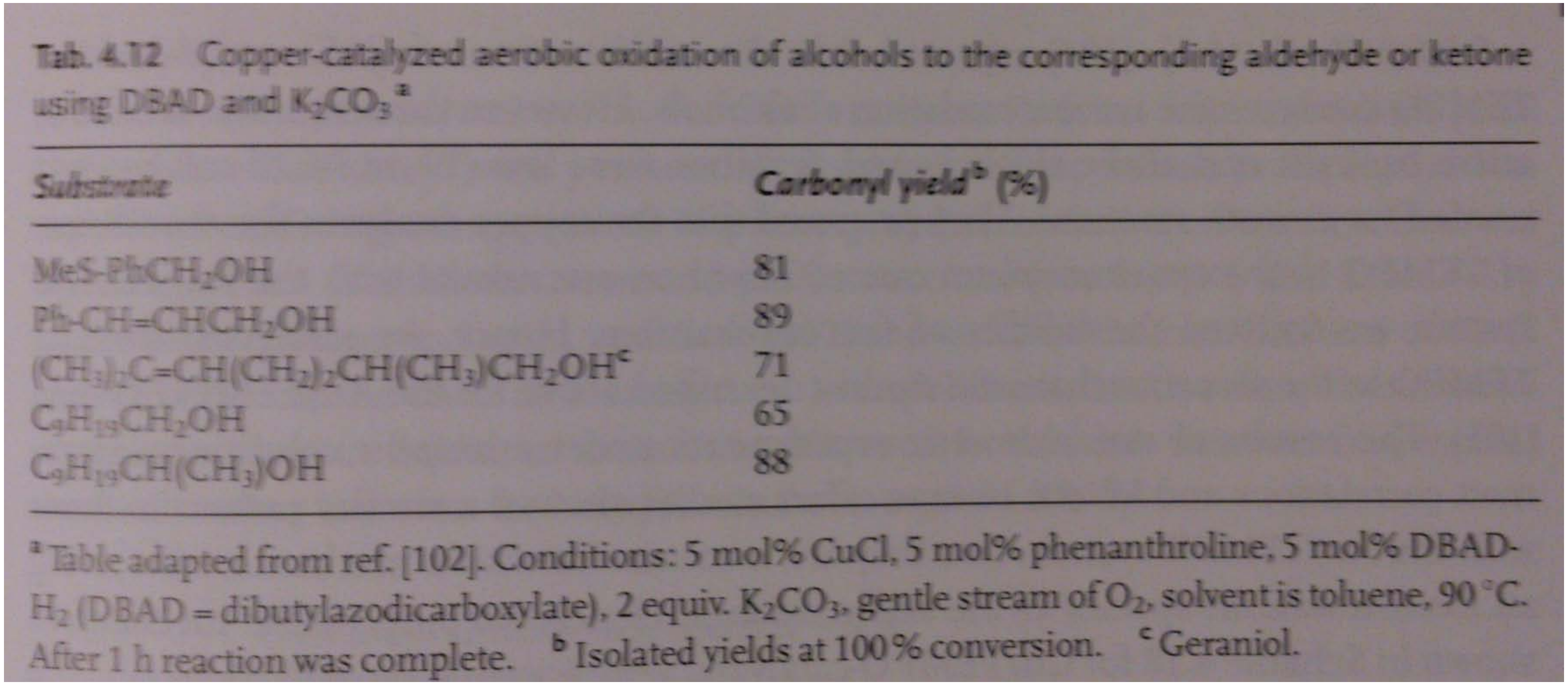
Some examples with other metals



Scheme 24 Nanoparticles stabilized on mesoporous channels of SBA-15.


X = Cl⁻, OH⁻
E =
O
O
N
N
Cu
X
N=N
E
E
(5 mol%)
OH
N(Bn)2
O2 (1 atm), 0.25 equiv. K2CO3
C6H5F, 80°C
O
N(Bn)2
(85%)

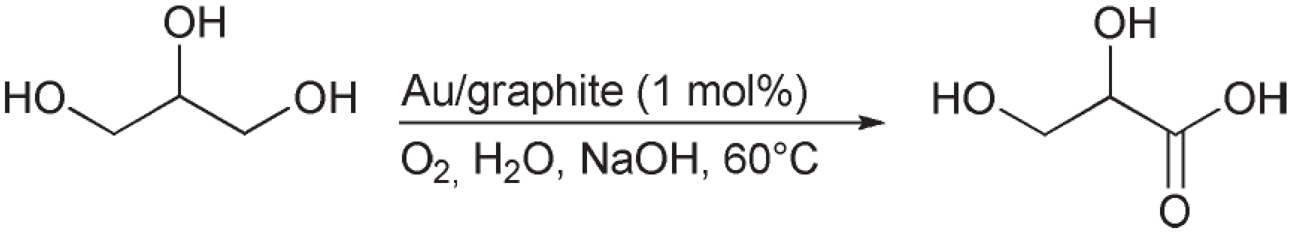
(17)



Tab. 4.12 Copper-catalyzed aerobic oxidation of alcohols to the corresponding aldehyde or ketone using DBAD and K_2CO_3 [a]

Substrate	*Carbonyl yield*[b] (%)
MeS-PhCH$_2$OH	81
Ph-CH=CHCH$_2$OH	89
$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2OH$[c]	71
$C_9H_{19}CH_2OH$	65
$C_9H_{19}CH(CH_3)OH$	88

[a] Table adapted from ref. [102]. Conditions: 5 mol% CuCl, 5 mol% phenanthroline, 5 mol% DBAD-H_2 (DBAD = dibutylazodicarboxylate), 2 equiv. K_2CO_3, gentle stream of O_2, solvent is toluene, 90 °C. After 1 h reaction was complete. [b] Isolated yields at 100 % conversion. [c] Geraniol.



Scheme 29 Oxidation of glycerol using Au/graphite catalysts.

E Factors and Atom Efficiency

The E factor is the actual amount of waste produced in the process, defined as everything but the desired product. It takes the chemical yield into account and includes reagents, solvents losses, all process aids and, in principle, even fuel (although this is often difficult to quantify). There is one exception: water is generally not included in the E factor. For example, when considering an aqueous waste stream only the inorganic salts and organic compounds contained in the water are counted; the water is excluded. Otherwise, this would lead to exceptionally high E factors which are not useful for comparing processes [8].

A higher E factor means more waste and, consequently, greater negative environmental impact. The ideal E factor is zero. Put quite simply, it is kilograms (of raw materials) in, minus kilograms of desired product, divided by kilograms of product out.

Table 1.1 The E factor.

Industry segment	Product tonnage[a]	kg waste[b]/kg product
Oil refining	10^6–10^8	<0.1
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5–>50
Pharmaceuticals	10–10^3	25–>100

a) Typically represents annual production volume of a product at one site (lower end of range) or world-wide (upper end of range).

b) Defined as everything produced except the desired product (including all inorganic salts, solvent losses, etc.).

$$3\ \mathrm{PhCH(OH)CH_3} + 2\ \mathrm{CrO_3} + 3\ \mathrm{H_2SO_4} \longrightarrow 3\ \mathrm{PhCOCH_3} + \mathrm{Cr_2(SO_4)_3} + 6\ \mathrm{H_2O}$$

$$\boxed{\text{atom efficiency} = 360\ /\ 860 = 42\ \%}$$

$$\mathrm{Ph\ CH(OH)CH_3} + 1/2\ \mathrm{O_2} \xrightarrow{\text{catalyst}} \mathrm{Ph\ COCH_3} + \mathrm{H_2O}$$

$$\boxed{\text{atom efficiency} = 120\ /\ 138 = 87\ \%}$$

Fig. 1.1 Atom efficiency of stoichiometric vs. catalytic oxidation of an alcohol.

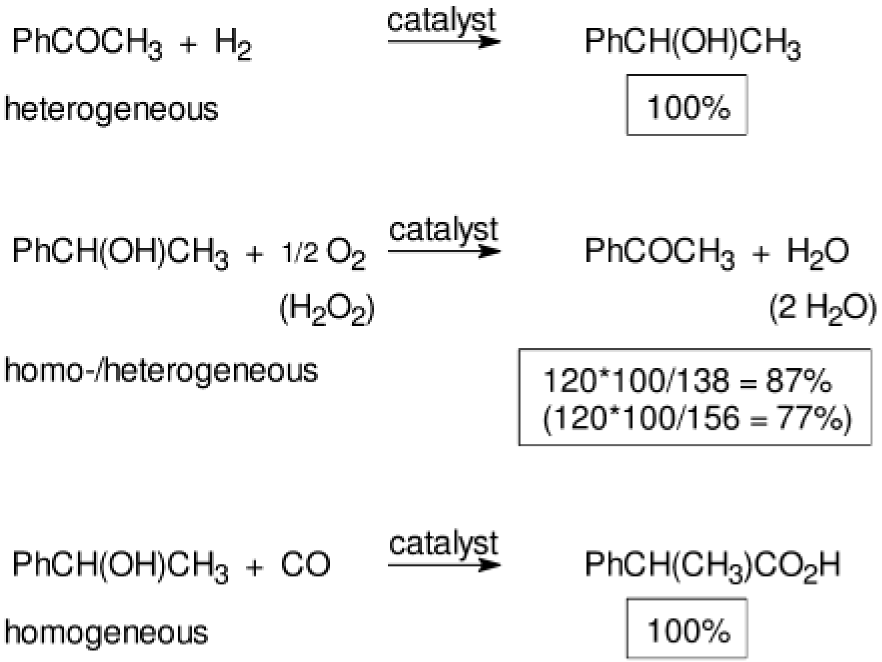
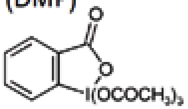


Fig. 1.3 Atom efficient catalytic processes.

Table 1: Comparison of the sustainability of eight selective oxidation methods with benzyl alcohol as example.[a]

Method	Name	Reagent	Catalyst	Solvent	*T* [°C]	Atom economy [%]	Environmental factor E [kg kg^{-1}]	Cost [€][b]	(Eco)toxicity
1[4a]	Jones oxidation	CrO_3/H_2SO_4	no	acetone	0–20	38.8	ca. 6	17	CrO_3 is carcinogenic
2[4b]	Swern oxidation	$(CH_3)_2SO$, $(COCl)_2$, $N(C_2H_5)_3$	no	CH_2Cl_2	−60	20.6	ca. 58	185	toxic reactants and products
3[4c]	Dess–Martin oxidation	periodinane (DMP) 	no	CH_2Cl_2/H_2O	−20	19.9	ca. 1800	160	DMP is unstable and explosive
4[4d]	according to Anelli et al.	NaOCl/NaBr	TEMPO[c]	CH_2Cl_2/H_2O	0	58.1	ca. 58	110	low
5[4e]	according to Sasson et al.	H_2O_2 (30%)	$RuCl_3$/phase-transfer cat.	CH_2ClCH_2Cl/toluene	80	74.7	ca. 12	20	low
6[4f]	according to Sheldon et al.	O_2	TEMPO	various	80	85.5	–	0.038	low
7[5]	see Ref. [5]	O_2	Complexes of Cu, Pd, Ru	different	80	85.5	ca. 26	0.038	none
8[6]	according to Liu et al.	O_2 or air	TEMPO, Br_2, $NaNO_2$	H_2O or CH_2Cl_2	80	85.5	ca. 15	0.038	low

[a] Stoichiometric equations can be found in Ref. [1a] and the respective literature citations. [b] Prices for pure chemicals from the Aldrich catalogue (2003), Price from the company Linde for O_2 (50 L, 99.95% purity). [c] TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy.

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