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The Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) Reagent Guides

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What do the Reagent Guides Hope to Achieve?

In line with the GCIPR core values, these guides aim to assist chemists in making informed decisions regarding the most sustainable reagent for the transformation to hand. They follow on from the concept of the Reagent guides introduced by Pfizer.[a]

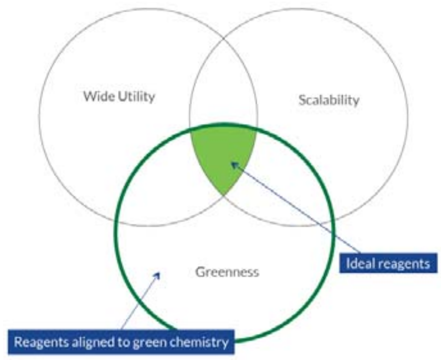
The guides are compiled by enthusiastic industrial multidisciplinary chemists who have scaled many of the methods.

Whilst the guides are designed to promote green chemistry, they also aim to be a convenient reference and, as such, are not limited to only those reagents considered 'green'.

Good green chemistry requires the chemist to look across a range of factors before making the best choice. With the inclusion of information such as atom efficiency, ecotoxicology / toxicology profiles, safety issues, waste products, sustainable feedstocks etc – we hope these guides give obvious promotion of some reagents compared to others. However a holistic approach is encouraged – i.e if a 'greener' reagent gives a much lower yield or requires multiple steps the overall benefit may be limited (i.e higher footprint in the wider context) in contrast to an initially less green reagent.

[a] Peter J Dunn *et al. Green Chem.*, **2008**, *10*, 31-36

Visual Selection using a Venn diagram



Each circle of the Venn diagram represents a criteria – those being 'Scalability', 'Greenness' and 'Wide utility'

The ideal reagent will have all three characteristics and so appear in the middle (green area), whereas some reagents have one of the traits but none of the others and some are a mix of two but not the third.

Placement within the Venn diagram can change with many variables (solvent, catalyst, treatment of wastes, etc). As outlined they are a good estimate but not final with discussion actively encouraged.

Oxidation to Aldehyde and Ketone example

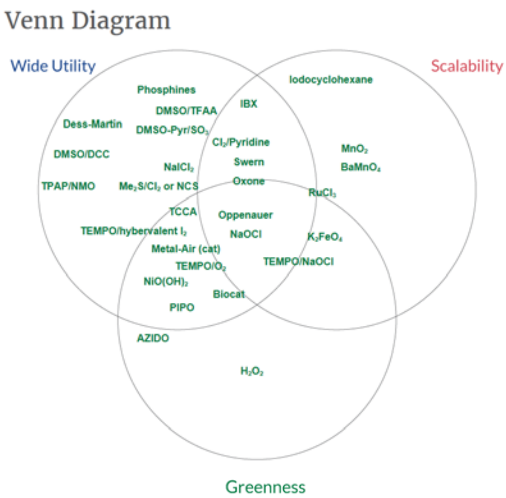
List of Reagents

Full Review

NiO_2 oxidation of alcohols
MnO_2 oxidations in organic chemistry
Hypervalent Iodine reagents – general overview
IBX 2-Iodoxybenzenesulfonic Acid
Dess Martin Periodate
$NaICl_2$ A simple system for the oxidation of alcohols
PDC Pyridium dichromate oxidations
PCC Review on Cr(VI) oxidation
Oppenauer oxidation: An Integrated Approach
DMSO –Oxalyl Chloride, Swern oxidation
DMSO/DCC Pfitzner-Moffat (also TFAA activation)
DMSO – Pyridine-SO_3 (Parikh-Doering)
DMSO activation in Pseudo-Swern reaction
Me_2S/NCS Corey - Kim oxidation
NaOCl bleach oxidation
TCA Trichloroisocyanuric Acid: A Safe and Efficient Oxidant
TPAP/NMO (tetrapropylammonium perruthenate)
TEMPO (General overview)
TEMPO-Bleach
TEMPO –air –catalyst
TEMPO-hypervalent iodine
Air-Metal catalyst transition-metal catalyzed reactions using molecular oxygen
Activated H_2O_2 hydrogen peroxide
Biocatalysis biocatalytic methods for oxidation

Light touch overview

$BaMnO_4$ oxidation of primary and secondary alcohols
Potassium Ferrate A Novel Oxidizing Reagent Based on Potassium Ferrate(VI
Oxidation with Chlorine /Pyridine complexes
$RuCl_3$
PIPO- Polymer immobilised TEMPO
Ce Cerium(IV) ammonium nitrate
Aqueous oxone
AZIDO (TEMPO variants)

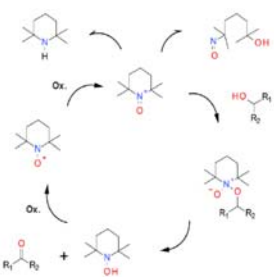


TEMPO-Bleach oxidation

Mechanism + Description

As previous for TEMPO NaOCl is often used as a co-oxidant which generates NaCl as a by-product.

NaBr or borates are often added as a promoter.



General Comments

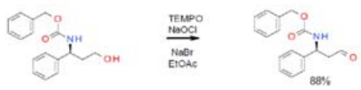
A common terminal oxidant is bleach (NaOCl) which is often employed with a Bromide or borate co-catalyst. Reactions in water of bi-phasic reactions are often helped by the addition of a phase transfer catalyst

Key References

Org. Process Res. Dev., 2005, 9 (5), 577–582 - Production of Aldehydes by Continuous Bleach Oxidation of Alcohols Catalyzed by 4-Hydroxy-TEMPO
Org. Process Res. Dev., 2008, 12 (2), 322–338– Discussion of optimisation to prevent racemisation (50 L scale)
Org. Process Res. Dev., 2010, 14 (2), 441–458 - DOE and robustness studies on TEMPO stage statin oxd'n (2000 L scale)
Org. Process Res. Dev., 2010, 14 (1), 142–151 - Use of NaI to prevent chlorination of heteroaromatic (50 L scale)

Relevant Scale up examples

Org. Process Res. Dev., 2008, 12 (2), 168–177 – 100 L oxd'n in MeOAc or THF



Org. Process Res. Dev., 2008, 12 (6), 1104–1113- 2000 L prep of Maraviroc intermediate

Green Review

1.Atom efficiency (by-products Mwt)
Generally good –the removal of H_2 generates NaCl (58) as a by-product
2.Safety Concerns
All TEMPO oxidations are exothermic and may present delayed exotherms. Compatibility of NaOCl with other reaction components needs to be considered.
3.Toxicity and environmental/aquatic impact
Generally low when used catalytically, the major concerns arising from the co-oxidant. Nitroxyl radicals like TEMPO and the hydroxylamine intermediates in the oxidation cycle give positive structural alerts as potential genotoxic impurities (PGI)
4.Cost, availability & sustainable feedstocks
The cost of TEMPO has fallen over time and is now available in bulk. Other analogs are less commercially available and much more expensive – but sometimes display far greater activity. The skeleton of TEMPO comes from acetone and ammonia.
5.Sustainable implications
With good optimisation of catalyst loading, and a low molecular weight terminal oxidant like NaOCl, this oxidation is a good choice. The major concern would be the solvent used. Many initial publications used dichloromethane, but later work has shown more sustainable solvents can be used – see references.

8 Guides Now Publically Available…

More Guides Coming

Bromination
Fluorination
Chlorination
Iodination
Metals Removal
Chiral Hydrogenation
Oxidation to Acids
Suzuki Rxn
Buchwald-Hartwig Rxn

The American Society of Chemistry Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR)

The roundtable was formed in 2005. Its mission is to catalyze the implementation of green chemistry and green engineering in the global pharmaceutical industry.

The activities of the ACS GCIPR reflect the joint belief that the pursuit of green chemistry and green engineering is imperative for a sustainable business and world environment. The ACS GCIPR aims to achieve its mission through 4 strategic priorities:

- Inform and Influence the Research Agenda
- Tools for Innovation
- Education Resource
- Global Collaboration

The roundtable is currently made up of 12 globally leading pharmaceutical companies and 1 associate member.

ACS Chemistry for Life®

ACS Green Chemistry Institute® Pharmaceutical Roundtable

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