Get Involved with the DCHAS and the safety community at ACS by becoming a division member!

Become a Member!

Visit our website: dchas.org

Connect with us on LinkedIn

Follow us on Instagram

Email membership@dchas.org for information on how to become a member!

Check out these Articles from Journal of Chemical Health and Safety!



Challenges of Legacy Chemicals

ACS Chem. Health Saf. 2025, 32, 1, 16–21

Craig A. Merlic, Imke Schröder, and Christopher M. Kolodziej



Gist of the List

ACS Chem. Health Saf. 2025, 32, 1, 3–4

Lauren Goulding

Interested in submitting a paper? Check out these call for papers using the QR code below!

2YC CHAS Chat: Green Chemistry Resources and Solvent Alternatives

- ACS Green Chemistry Institute
- ACS Green Chemistry 12 Principles
- ACS Reagents Guides
- ACS Acid-Base Selection Tool
- Beyond Benign: Green Chemistry Teaching and Learning Community
- GCTLC Methylene Chloride Replacements

Other links and resources shared during the chat:

- Stanford Storage Groups
- Laboratory Safety Institute – Methylene Chloride webinar series
- Stephen Taylor LinkedIn article: The Silent Hazard: A Pandemic of Legacy Chemicals in Our Schools

ACS Chemistry for Life®

American Chemical Society

Reagent Guides and Acid-Base Selection Tool

Dr. Edmond Lam

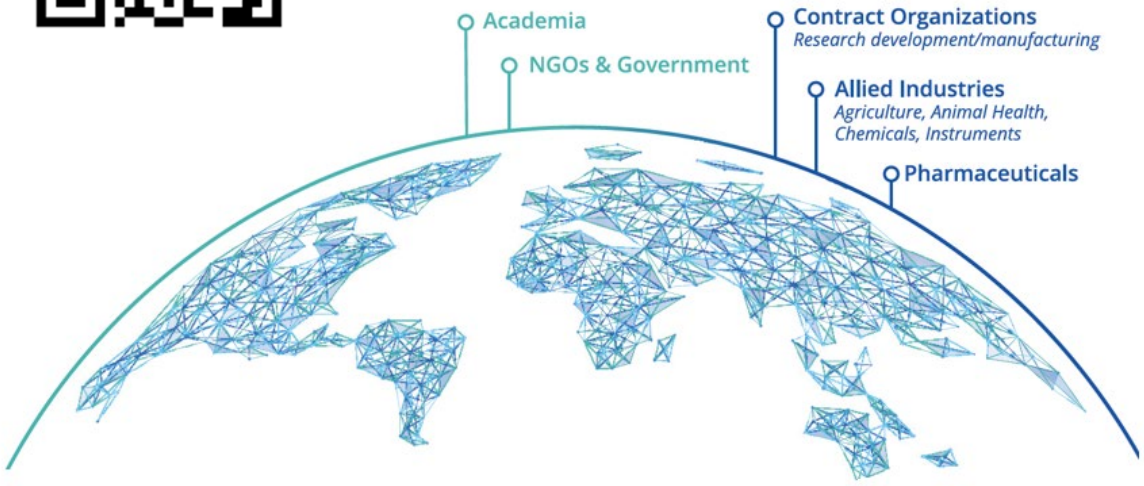
Green Chemistry Institute

August 21, 2025



Catalyzing Green Chemistry & Engineering in the Global Pharma Industry

- Advancing the Research Agenda
- Tools and Metrics for Innovation
- Influencing present and future leaders



ACS Chemistry for Life®

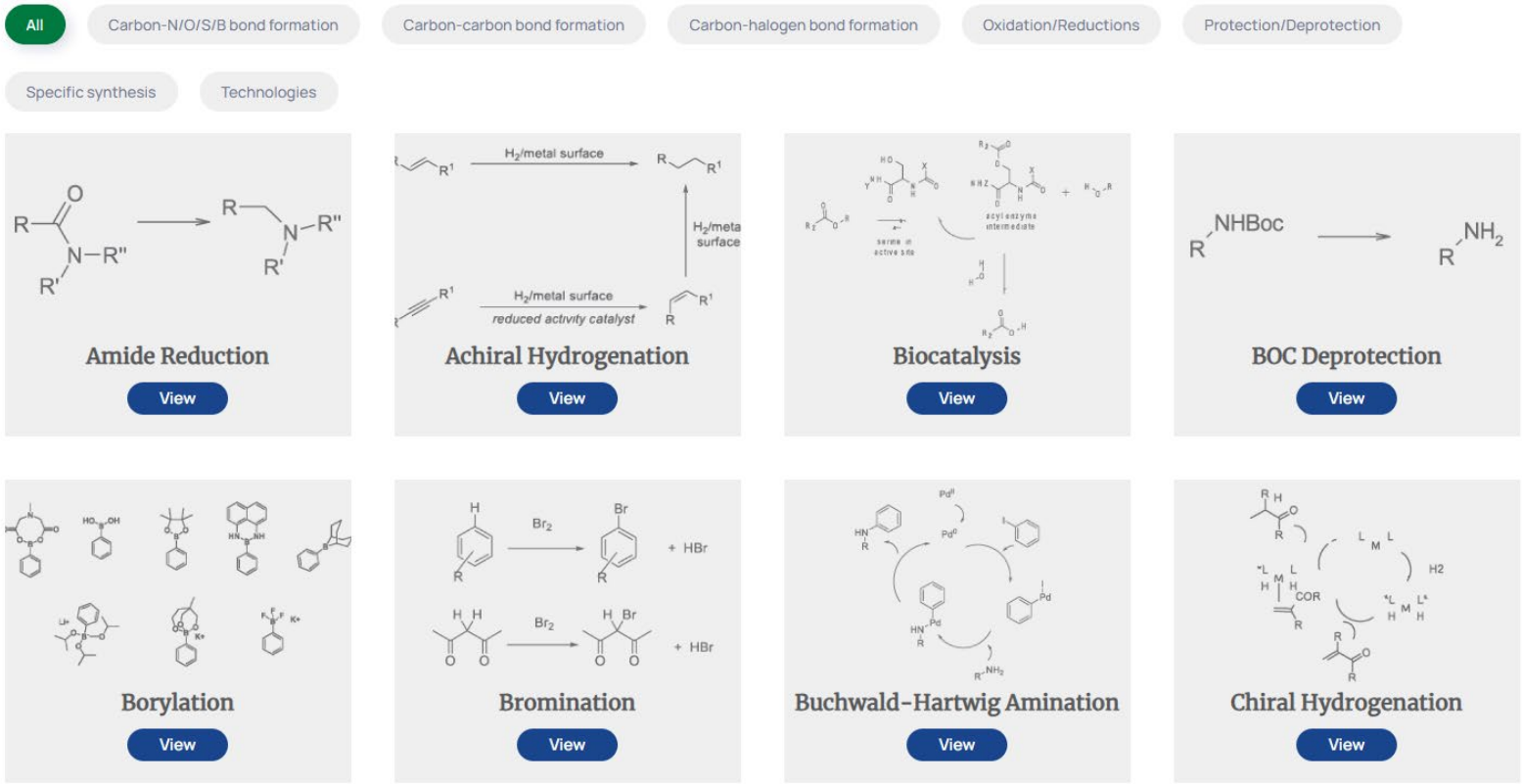
© 2025 American Chemical Society. All rights reserved.

Reagent Guides

https://reagents.acsgcipr.org/reagent-guides/

Aim: To encourage chemists to choose a ‘greener’ choice of reaction conditions.

The guides aim to achieve this by providing transparency using **Venn diagrams** in addition to improving understanding by discussion and up to date references.



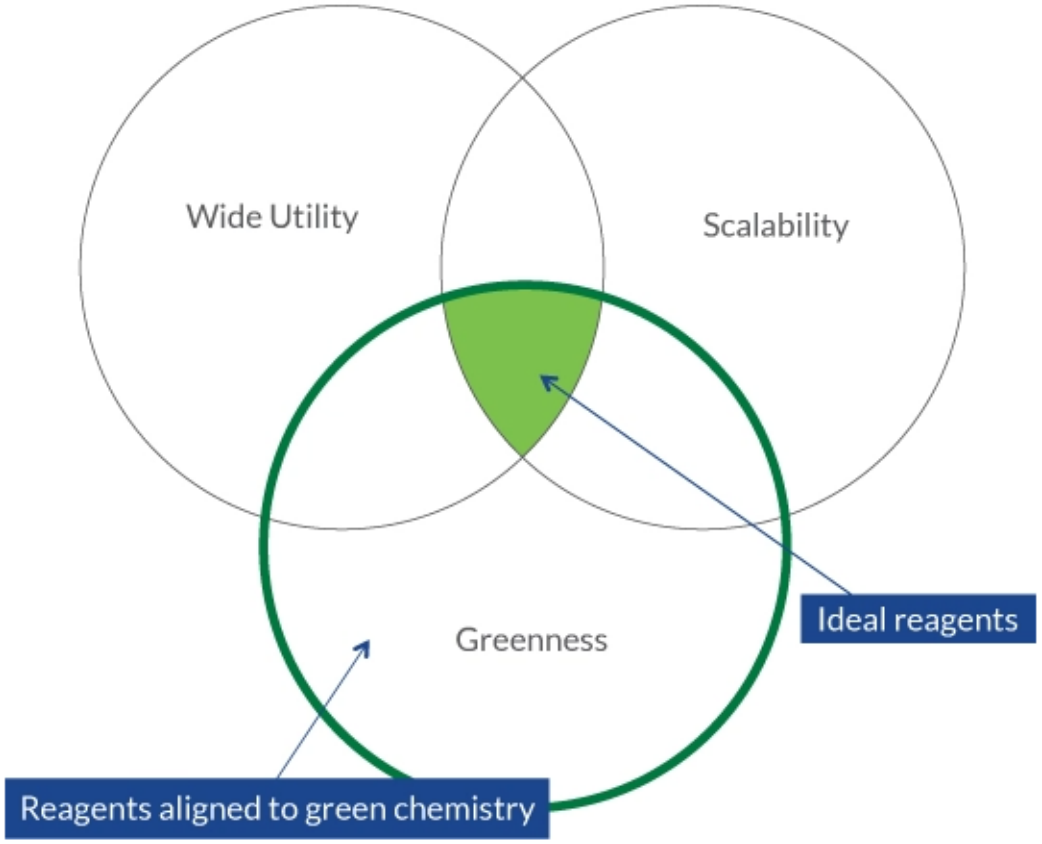
© 2025 American Chemical Society. All rights reserved.

Interpret Venn Diagrams

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.

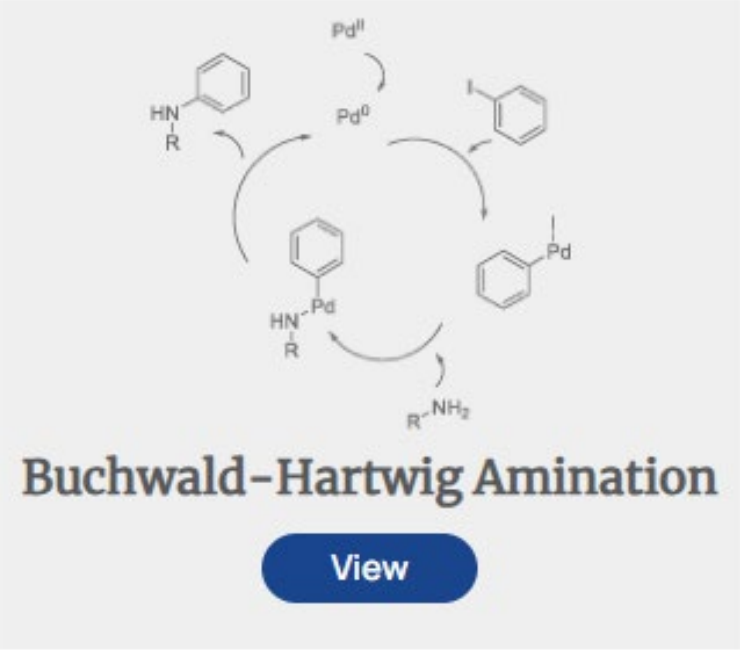
Placements within the Venn can change with many variables (solvent, catalyst, treatment of wastes etc). As outlined they are a good estimate but not final with discussion actively encouraged.

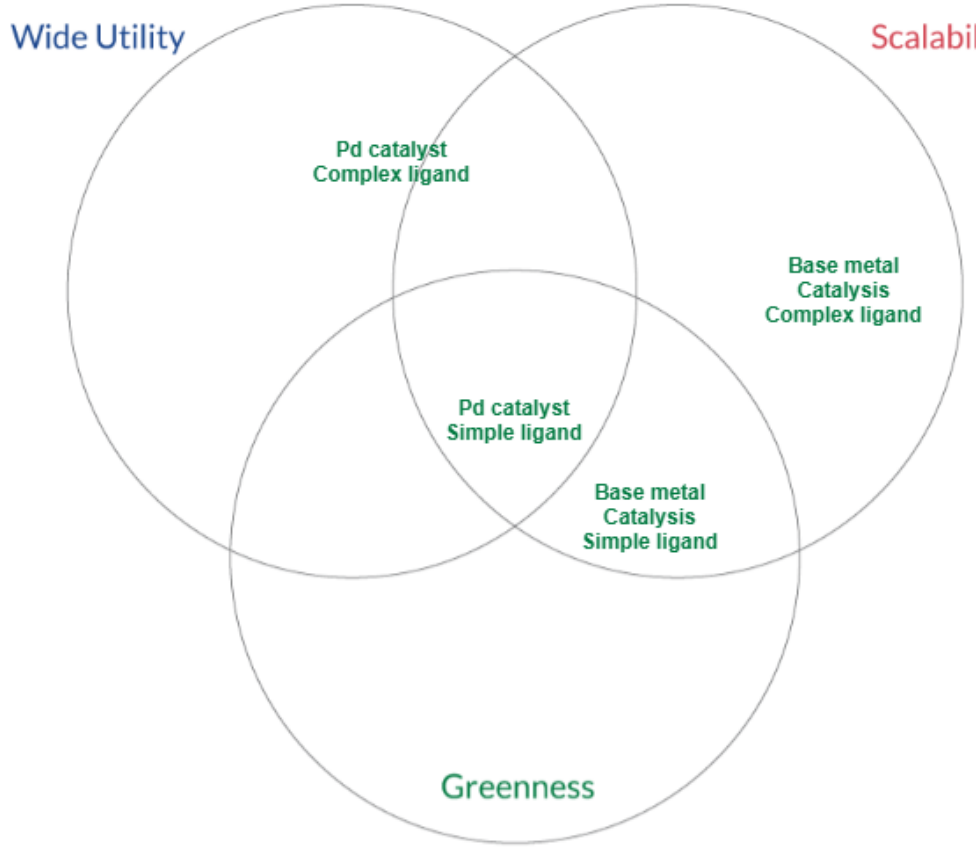


© 2025 American Chemical Society. All rights reserved.

Buchwald-Hartwig Amination

The inclusion of an article in this document does not give any indication of safety or operability. Anyone wishing to use any reaction or reagent must consult and follow their internal chemical safety and hazard procedures and local laws regarding handling chemicals





© 2025 American Chemical Society. All rights reserved.

Acid-Base Selection Tool

https://acsgcipr.org/tools/acid-base-selection-tool/

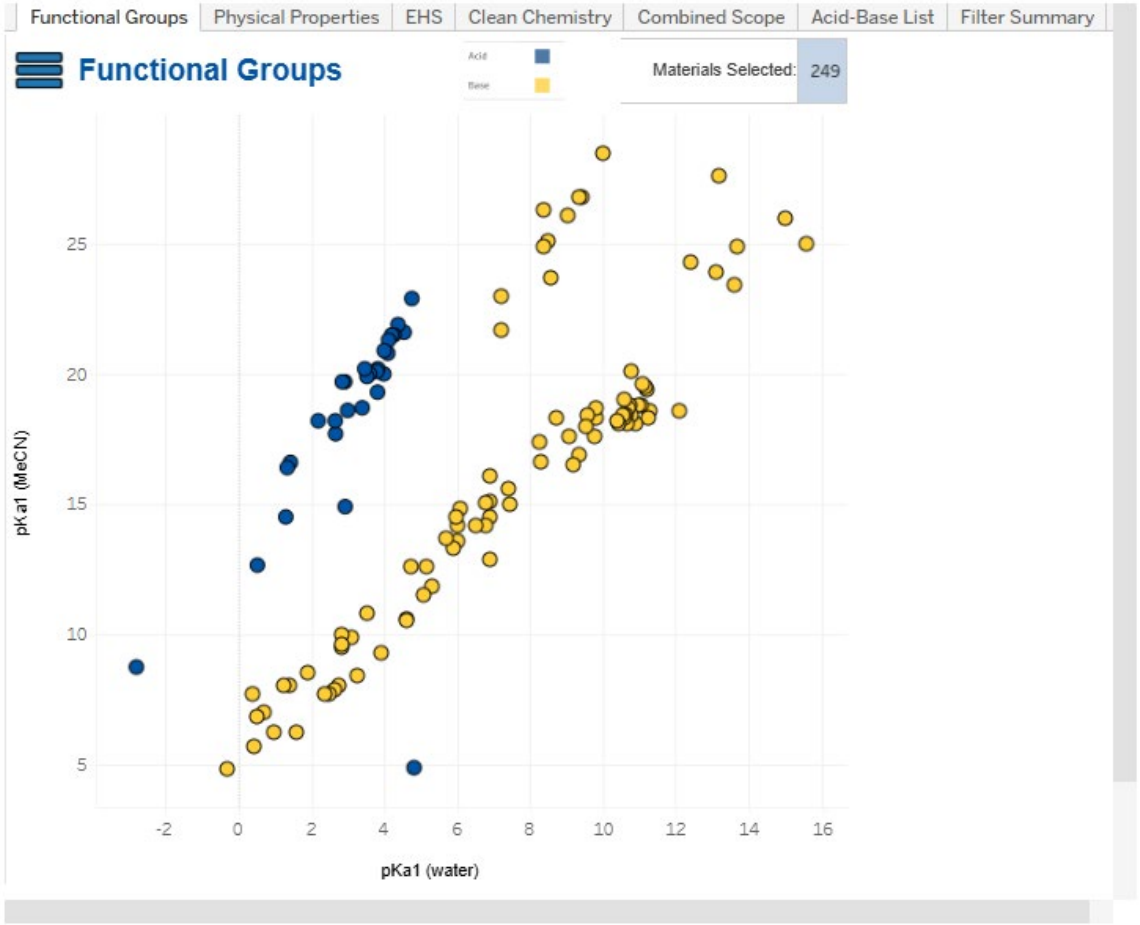
Aim: To enable industrial and academic scientists to choose more sustainable acids and bases.

The tool contains over 200 acids and bases, which the user can filter by parameters including:

- pKa (in water or acetonitrile)
- Functional groups
- Melting point
- Boiling point

The tool contains scoring for acids and bases on:

- Environment, health, and safety (EHS)
- Clean chemistry aspects



Green Chem., **2015**, *17*, 945-949.
Green Chem., **2013**, *15*, 1542-1549. (definitions of the scores)

© 2025 American Chemical Society. All rights reserved.

GREEN CHEMISTRY CHALLENGE

ACS Chemistry for Life®

Green Chemistry Challenge Awards Ceremony & Reception



Please join us to recognize the 2025 Green Chemistry Challenge Award winners. Drinks and appetizers will be provided at a reception following the ceremony.

RSVP TODAY

September 3, 2025 | 4:00 – 6:15 pm | Washington, D.C.



ACS
Chemistry for Life®

AMERICAN CHEMICAL SOCIETY

Green Chemistry

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

Published on 22 April 2013. Downloaded by McGill University on 8/21/2025 9:26:09 PM.

Cite this: *Green Chem.*, 2013, **15**, 1542

Development of GSK's reagent guides – embedding sustainability into reagent selection†

Joseph P. Adams,[a] Catherine M. Alder,[a] Ian Andrews,[a] Ann M. Bullion,[b] Matthew Campbell-Crawford,[a] Michael G. Darcy,[b] John D. Hayler,[a] Richard K. Henderson,[c] Catriona A. Oare,[a] Israil Pendrak,[b] Anikó M. Redman,[d] Leanna E. Shuster,[e] Helen F. Sneddon*[a] and Matthew D. Walker[a]

Received 30th January 2013,
Accepted 22nd April 2013

DOI: 10.1039/c3gc40225h

www.rsc.org/greenchem

Reagent guides ranking commonly used reagents for 15 transformations have been developed to reduce the environmental impact of drug discovery and development. Reagents have been scored by a combination of health, safety and environmental risk phrases, life cycle analysis (where possible) and an assessment of the chemistry including considerations of atom efficiency, stoichiometry, work-up and other issues. Guides covering alkene reduction, amide formation, C–H bromination, C–H chlorination, deoxychlorination, epoxidation, ester formation, ether formation, fluorination, iodination, ketone reduction, nitro reduction, oxidation of alcohols to aldehydes and ketones, reductive amination and sulfur oxidation are shared, with an explanation of the methodology behind their generation.

1. Introduction

The pharmaceutical industry has taken a leading role in finding ways to embed more sustainable chemical process design and development into the manufacture of Active Pharmaceutical Ingredients (API). GSK first developed a guide to green solvent selection in 1998[1] and have revised and enhanced it in subsequent years[2,3] making the latest version widely available. The American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR) published an industry-wide mass efficiency benchmarking study to understand the typical composition of the materials used to manufacture an API[4,5] with the aim of driving down over time the amounts of materials needed to manufacture an API.

In 2008, Pfizer published a green reagent guide concept to influence their scientists to use greener reagents while taking into account the differing needs of laboratory scale discovery chemistry and pilot plant scale development chemistry.[6] GSK has taken a complementary approach encouraging green reagent selection across a wide range of transformations. The approach adopted and the resultant reagent guides for the first fifteen reaction classes are presented in this paper.

The aim is both to encourage chemists to use greener reagents by first intent, and to provide a simple, easy-to-use reference for greener alternatives that might be considered when reactions are repeated, and/or scaled up.

2. Selection of the reaction classes

Reviews[7] have been published highlighting that despite the wide variety of chemistry which is conducted as part of drug discovery and development, the majority of reactions fall into a relatively small number of categories.

It was decided that initial efforts would focus on those reactions where guidance would be most useful and as such the first batch of guides produced comprised the following common transformations: alkene reduction, amide formation, C–H bromination, C–H chlorination, deoxychlorination, epoxidation, ester formation, ether formation, fluorination, iodination, ketone reduction, nitro reduction, oxidation of alcohols to aldehydes and ketones, reductive amination and sulfur oxidation.

3. Encouraging use of the guides

To ensure the guides were readily accessible, an internal website was prepared. The website has one page per transformation, and is colour coded into green, amber and red

[a]*GSK, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts., UK, SG1 2NY. E-mail: helen.f.sneddon@gsk.com; Fax: +44 (0)1438 768302; Tel: +44 (0)1438 763645*
[b]*GSK, 709 Swedeland Road, King of Prussia, PA 19406, USA*
[c]*GSK, Park Road, Ware, Herts., UK, SG12 0DP*
[d]*GSK, 5 Moore Drive, Research Triangle Park, NC 27709, USA*
[e]*GSK, 1250 South Collegeville Road, Collegeville, PA 19426, USA*

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c3gc40225h

This journal is © The Royal Society of Chemistry 2013

Published on 22 April 2013. Downloaded by McGill University on 8/21/2025 9:26:09 PM.

sections (*cf.* traffic lights). Clicking on a given reagent takes the user to the relevant page for the reagent, which contains information on:

- Common name of reagent, Full name, CAS number
- Structure
- Scope and utility of the reagent
- In-house protocols
- Literature references – hyperlinked to the relevant journal article, with procedures highlighted
- Environment score, Health score, Safety score
- Overall Environment, Health and Safety score
- Molecular Weight, Atom Efficiency and Stoichiometry scores
- Work-up, Co-reagent and "Other" scores with comments
- Overall Chemistry score
- Risk phrases
- Whether or not a legislation flag[8] has been noted
- Life Cycle score and comment

Learning from the success of the Medicinal Chemistry version of the solvent selection guide,[3] a similar two page schematic of each guide was drawn up to enable simple visualisation of the data. This promoted the information which could be accessed *via* the website and laminated copies of the schematic were provided for easy and timely reference at desks and in the laboratory.

The first page of each schematic shows the overview of which reagents fall into which categories (green, amber, red), with reagents listed in rank order. A reminder is included that the guide should only be used by the competent chemist, and before using any reagent listed on this guide, a complete risk assessment must be performed. Links are also provided to the online version of the guide within the GSK intranet.

The reverse of each guide shows the Material; Full name; CAS number; Environment, Health and Safety score; Clean Chemistry score and combined "Greenness" score, along with comments to help explain the scoring of a particular reagent, or provide further information to the user.

In order to encourage the use of the recommended reagents, it was checked that these were readily available in-house.

We would like to share an overview of the methodology used with the wider chemistry community, with three guides exemplified here and all 15 guides available in the ESI.†

4. Methodology behind the guides – selection and scoring of reagents

A standardised approach to assessing each reagent was adopted. It was then necessary to define the scope of each transformation. It was decided, for example, that alkene reduction would refer only to isolated carbon–carbon double bonds rather than incorporating α,β-unsaturated carbonyls or styrenes. Related reactions which we felt lay outside of the scope were addressed in reviews attached to the internal online version of each guide.

Reagents for inclusion in the guide were identified by a combination of use of search engines, specifically SciFinder® and Reaxys®, and canvassing GSK scientists to share their experience, thereby capturing both up to date academic literature as well as years of organisational and personal knowledge.

Information on each of the reagents was entered into an Excel spreadsheet to enable comparison of the sustainability criteria of each reagent for a given transformation, on a scale of 1 (most issues) to 10 (least issues).

Reagent data

For each reagent the following basic information was entered:

- Transformation category (*e.g.* Alkene Reduction)
- Common Name
- Full Name
- CAS Number
- Molecular Formula
- Molecular Weight
- EU risk phrases

When compiling the data on reagents it rapidly became apparent that there were occasional discrepancies between the risk phrases recorded by different suppliers. In the interests of consistency two sources (generally Aldrich and Acros) were checked, and if any differences were noted then the more severe phrases were used. In a few cases[9] (mainly solid supported reagents and reagents which had to be prepared in house) risk phrases were not available, and these cases were discussed and judged individually.

Assessment of health score

EU risk phrases[10] and available Occupational Exposure Limits (OEL) were combined using a set of rules to assign each reagent a Health score.

If any of the following risk phrases were present: R26, R27, R28, R45, R49, R60, R61, R64 or R68 or the OEL was <0.5 ppm or <0.01 mg m^{-3} then the material was assigned a Health score of 1.

If any of the following risk phrases were present: R23, R24, R25, R34, R35, R39, R40, R41, R42, R43, R48, R62 or R63, or the OEL was ≤5 ppm or ≤0.1 mg m^{-3} then the material was given a Health score of 4.

If a reagent had one of R20, R21, R22 or R33 or the OEL was ≤50 ppm or ≤1 mg m^{-3} then the material was given a Health score of 7.

Any other reagent was scored 10.

Assessment of safety score

EU risk phrases that address process safety hazards were used to develop a simple set of rules to categorise and score the reagents. Where specific hazard data was known, this was used to override the categorisation score.

Reagents with EU risk phrases R1, R2, R3, R4, R5, R6, R7, R9, R16, R17 or R44 were given a score of 1. Reagents with EU risk phrases R8, R11, R12, R14, R15, R18, R19, R29, R30, R31, or R32 were given a score 4. Reagents with EU risk phrase R10 scored 7 and reagents with no identified process safety hazard scored 10.

Published on 22 April 2013. Downloaded by McGill University on 8/21/2025 9:26:09 PM.

Assessment of environment score

The environmental score was assessed using EU risk phrases which indicate adverse environmental impact as well as those that indicate carcinogens, mutagens or reproductive hazards. Reagents with EU risk phrases R50 and R53, or one of R40, R45, R49, R60, R61, R64, R68 scored 1. Reagents with risk phrases R51 and R53, or any of R50, R62 or R63, scored 4. Reagents with R52 and R53 scored 7. Everything else scored 10.

Assessment of FLASC™ score

GSK has developed a tool called FLASC™ (Fast Lifecycle Assessment for Synthetic Chemists),[11] for assessing simplified life cycles of compounds that we prepare. The FLASC™ database provides reduced life cycle data for materials from arriving at GSK sites, through processing and finally leaving the factory gates (cradle-to-gate). We used the environmental impact factors for chemicals (or the appropriate FLASC™ category average) to assign an environmental life cycle score for each reagent. The FLASC™ score is presented for information only at present.

Overall environment, health and safety score

In order to present the complex results of these analyses in a manner that is easy to understand, the Environment score, Health score and Safety score were combined into an overall Environment, Health and Safety (EHS) score using weighted averages. Since there is a danger of inadvertently masking some significant EHS hazard information when applying averages, an extra weighting[12] was applied to reagents which had one of the Environment, Health or Safety scores in the red zone (score <3.5), to keep the final overall score in the red.

Assessment of chemistry score

A team of chemists spanning medicinal chemistry and development reviewed the most typical procedures to assess stoichiometry, work-up, co-reagents and other issues. Comments were added where necessary to support the assessment. Atom efficiency and stoichiometry were scored using simple algorithms.

Work-up: A work-up was scored 1 for very difficult, 4 for difficult, 7 for normal/average, 10 for easy.

These classifications are inevitably subjective, but care was taken to get input from experienced chemists within medicinal chemistry, process and pilot plant teams to ensure that as comprehensive a perspective as possible was taken into account. Typically 'Very Difficult' was taken to be consistent with 'toxic and/or difficult to remove by-products', 'Difficult' was consistent with 'gaseous products need abating' or 'acids are generated that may attack protecting groups', a 'Normal/Average' work-up may require a column on a medicinal chemistry scale, and 'Easy' referred to products which could be isolated by a simple filtration, or filtering off a heterogeneous catalyst and concentrating the filtrate.

Co-reagents: For many transformations only the principal reagent is classified for the EHS score, so this score gives an opportunity to account for co-reagents, their inherent hazards and stoichiometry. Co-reagent in large stoichiometric excess was scored 1, co-reagent in stoichiometric amounts or catalytic co-reagent with serious EHS issues was scored 4, co-reagent in catalytic amounts was scored 7, and no co-reagent was scored 10.

Other issues: This category allowed stench, low reaction temperature, air sensitivity or other factors to be evaluated. Score 1 was reserved for those reactions which were air sensitive, had decomposition issues, were run at very low temperature or required significant extra attention for other reasons. A transformation with issues such as stench/pungent smell, moisture sensitivity or similar scored 4. A transformation where some precautions might need to be taken to account for moisture sensitivity scored 7, and a transformation with no issues was scored 10.

Atom Efficiency was assessed using molecular weight as a surrogate. Whilst an approximation, if a reagent has a molecular weight of greater than 250 it scored 1, if greater than 175 but less than or equal to 250 it scored 4, if greater than 140 but less than or equal to 175 it scored 7, if less than or equal to 140 it scored 10.

Stoichiometry was scored to give a boost to catalysts and penalise reagents which relied upon high stoichiometric equivalents. The stoichiometry judged to be most commonly used was assessed, and 1 was scored for anything used in over 3 equivalents, 3 for ≤3, 5 for ≤1.55, 7 for ≤1, and 10 was scored for a stoichiometry of ≤0.2 equivalents. A default of 1.1 was used when no information was available to give a score of 5.

Overall clean chemistry score

As in the case of the overall EHS score there was a desire to combine all the chemistry factors, into one overall score, and accordingly the overall Clean Chemistry score represents the geometric mean of the Atom Efficiency, Stoichiometry, Work-up, Co-reagent and Other scores.

Overall "Greenness" score

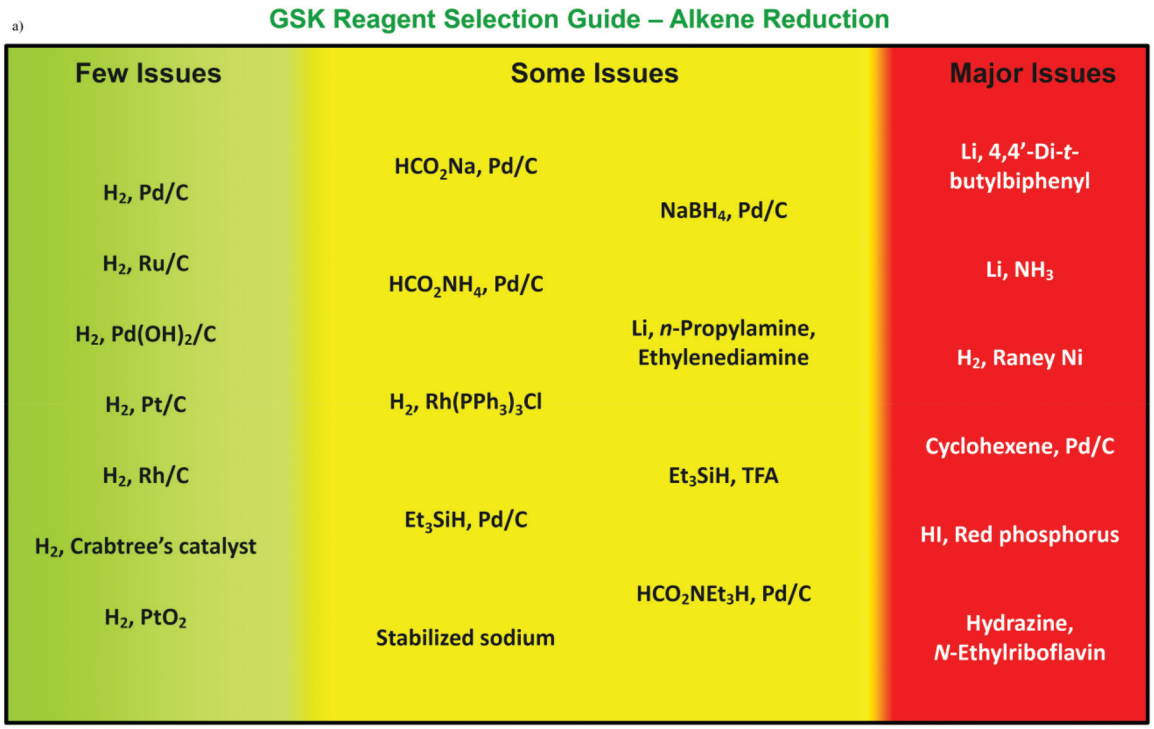
Whilst we believed the main benefit of the guides lay in highlighting the individual issues associated with certain reagents, and in making it as simple as possible for chemists to make informed choices about the reagents based on the full assessments provided, we acknowledged that there was a drive for at-a-glance classification (Fig. 1–3).

Accordingly a "Greenness" score was then created as the geometric mean of the overall EHS score and the overall Clean Chemistry score.[13] This was then used to place the reagents in colour coded bands for publishing on websites and on handouts (Fig. 4). Whilst acknowledging that the reagents assessed fell on a continuum of "greenness", some arbitrary boundaries were chosen. A reagent was scored as "red" if its overall greenness score was below 4 (or any one of the E, H or S scores were 3.5 or less, or the Clean Chemistry score was 3.5 or less).

 This journal is © The Royal Society of Chemistry 2013

Published on 22 April 2013. Downloaded by McGill University on 8/21/2025 9:26:09 PM.

a)



This guide should only be used by the expert trained chemist. Before using any reagent listed on this guide, a complete risk assessment must be carried out.

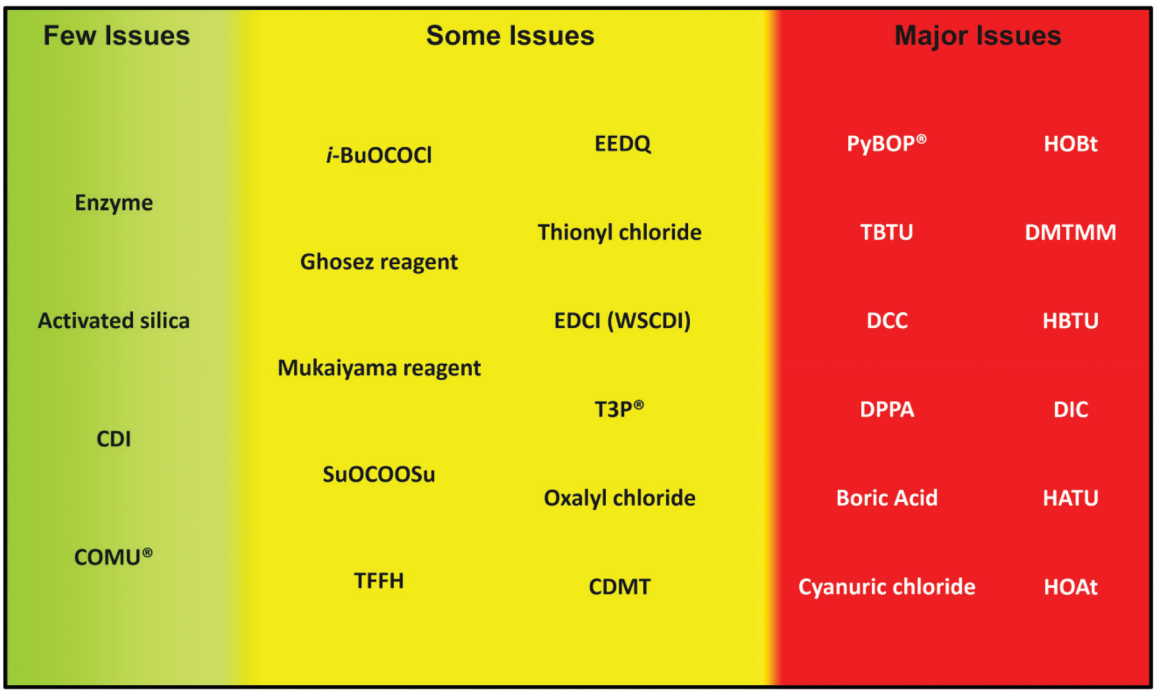
b)

Material	Full name	CAS / MFCD number	EHS	Clean chemistry	Greenness	Comment
H_2, Pd/C	Hydrogen, Palladium on Carbon	1333-74-0/7440-05-3	7	7	7.2	Flammable. Relative cost cheap. Catalyst can be recycled.
H_2, Ru/C	Hydrogen, Ruthenium on Carbon	1333-74-0/7440-18-8	7	7	7.2	Flammable. Relative cost cheap. Catalyst can be recycled.
H_2, $Pd(OH)_2/C$	Hydrogen, Palladium hydroxide	1333-74-0 12135-22-7	7	7	7.2	Flammable. Slightly more expensive than Pd/C. Catalyst can be recycled.
H_2, Pt/C	Hydrogen, Platinum on Carbon	1333-74-0 7440-06-4	7	7	7.2	Flammable. Relative cost expensive. Catalyst can be recycled.
H_2, Rh/C	Hydrogen, Rhodium on Carbon	1333-74-0/7440-16-6	7	7	7.1	Flammable. Relative cost extremely expensive.
H_2, Crabtree's catalyst	Hydrogen, (1,5-Cyclooctadiene)(pyridine) (tricyclohexylphosphine)-iridium(I) hexafluorophosphate	1333-74-0 64536-78-3	7	6	6.8	Flammable. Relative cost of iridium very expensive. Catalyst can be recycled.
H_2, PtO_2	Hydrogen, Platinum oxide	1333-74-0 1314-15-4	5	7	6.1	Flammable. Relative cost expensive. Catalyst can be recycled.
HCO_2Na, Pd/C	Sodium Formate, Palladium on Carbon	141-53-7 7440-05-3	7	5	5.9	Hydrogen transfer. Reaction rates, off-gassing rates may be a concern on some systems.
Ammonium formate, Pd/C	Ammonium Formate, Palladium on Carbon	540-69-2 7440-05-3	7	5	5.8	Hydrogen transfer. Reaction rates, off-gassing rates may be a concern on some systems.
H_2, $Rh(PPh_3)_3Cl$	Hydrogen, Chlorotris(triphenylphosphine)rhodium(I)	1333-74-0/14694-95-2	5	6	5.8	Flammable. Relative cost of rhodium extremely expensive.
Et_3SiH, Pd/C	Triethylsilane, Palladium on Carbon	617-86-7/7440-05-3	7	5	5.5	Hydrogen transfer.
Stabilized sodium	Sodium on Silica gel	MFCD01941718	5	5	5.3	Used in Birch reduction, no need for ammonia.
$NaBH_4$, Pd/C	Sodium borohydride, Palladium on Carbon, Acetic acid	16940-66-2 7440-05-3/64-19-7	5	5	5.3	Acetic acid required.
Li, *n*-Propylamine, $NH_2CH_2CH_2NH_2$	Lithium, *n*-Propylamine, Ethylenediamine	7439-93-2/107-10-8 107-15-3	5	5	5.0	Flammable.
Et_3SiH, TFA	Triethylsilane, Trifluoroacetic acid	617-86-7 76-05-1	5	5	4.9	Higher stoichiometry of Et_3SiH may be required for less electron rich alkenes.
HCO_2NEt_3H, Pd/C	Triethylammonium formate, Palladium on Carbon	585-29-5 7440-05-3	5	4	4.9	Hydrogen transfer. Reaction rates, off-gassing rates may be a concern on some systems.
Li, 4,4'-Di-*t*-butylbiphenyl	Lithium, 4,4'-Di-*tert*-butylbiphenyl	7439-93-2 1625-91-8	5	2	3.5	Causes burns. Reacts violently with water.
Li, NH_3	Lithium, Ammonia	7439-93-2 7664-41-7	4	3	3.3	Causes burns. Very toxic to aquatic organisms. Danger of serious irreversible effects by exposure.
H_2, Raney Ni	Hydrogen, Raney nickel	1333-74-0 7440-02-0	1	6	3.0	Highly flammable. Potential carcinogen and sensitizer.
Cyclohexene, Pd/C	Cyclohexene, Palladium on Carbon	110-83-8 7440-05-3	1	6	3.0	Benzene (known carcinogen) forms as by-product.
HI, Red phosphorus	Hydroiodic acid, Red phosphorus	10034-85-2 7723-14-0	2	3	2.7	Highly flammable. Red phosphorus is a controlled substance.
Hydrazine, *N*-Ethylriboflavin	Hydrazine, *N*-Ethylriboflavin	302-01-2 N/A	1	4	2.4	Hydrazine is a material of concern. May cause cancer.

Fig. 1 GSK alkene reduction green reagent guide. (a) Front of guide with overview, (b) reverse of guide with more detail.

Published on 22 April 2013. Downloaded by McGill University on 8/21/2025 9:26:09 PM.

a)



This guide should only be used by the expert trained chemist. Before using any reagent listed on this guide, a complete risk assessment must be carried out.

b)

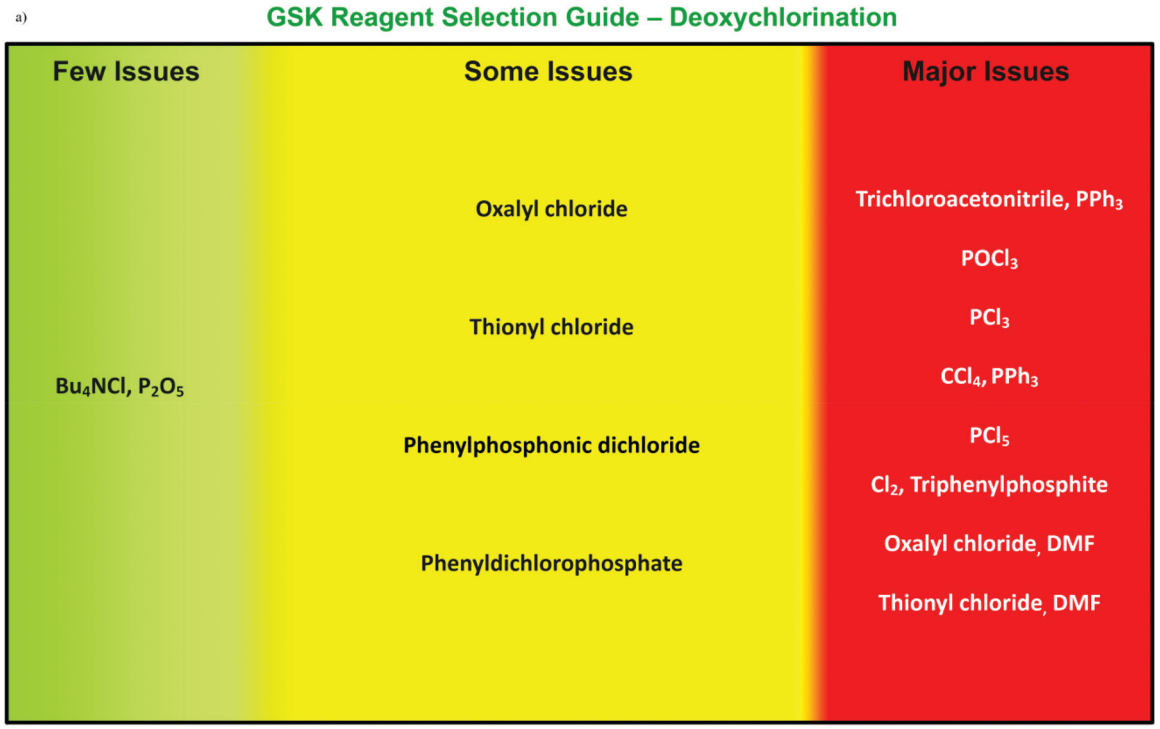
Material	Full Name	CAS number	EHS	Clean Chemistry	Greenness	Comments
Enzyme	Enzyme	N/A	10	8	8.8	
Activated silica	Thermally activated Kieselgel 60	7631-86-9	10	8	8.7	Activated at > 600 °C.
CDI	1,1-Carbonyl diimidazole	530-62-1	7	7	6.5	Gaseous and water soluble byproducts.
COMU®	(1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino morpholino-carbenium hexafluorophosphate	1075198-30-9	10	4	6.5	Water soluble byproduct.
i-BuOCOCl	Isobutyl chloroformate	543-27-1	7	6	6.4	Lachrymator, gaseous byproducts. Recommended storage at +4 °C. Activated species forms quickly.
Ghosez reagent	1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine	26189-59-3	7	6	6.4	Recommended storage at +4 °C.
Mukaiyama reagent	2-Chloro-1-methylpyridinium iodide	14338-32-0	10	4	6.3	Recommended storage at +4 °C.
SuOCOOSu	*N*,*N*′-Disuccinimidyl carbonate	74124-79-1	9	4	6.3	Water sensitive. Recommended storage at +4 °C.
TFFH	Fluoro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate	164298-23-1	10	4	6.0	Fluoride byproduct may limit vessel choice. Avoid acidic work-up.
EEDQ	2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline	16357-59-8	9	4	5.6	Odour. Recommended storage at +4 °C
Thionyl chloride	Thionyl chloride	7719-09-7	5	6	5.5	Lachrymator. Gaseous byproducts .
EDCI (WSCDI)	[1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride]	25952-53-8	7	4	5.3	Water soluble byproducts. Recommended storage at +4 °C. Known to test AMES positive, potential mutagen.
T3P®	2-Propanephosphonic acid anhydride	68957-94-8	5	5	5.3	Regulated chemical. Usage as 50% in EtOAc preferable to DMF solution
Oxalyl chloride	Oxalyl chloride	79-37-8	5	5	5.2	Lachrymator. Gaseous byproducts. Scored for usage on own, usage with DMF not recommended as DMCC carcinogen may be produced.
CDMT	2-Chloro-4,6-dimethoxy-1,3,5-triazine	3140-73-6	5	5	5.0	Sensitizer. Toxic to aquatic organisms.
PyBOP®	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate	128625-52-5	10	3	5.2	Cytotoxic urea byproduct.
TBTU	*O*-Benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate	125700-67-6	3	6	4.5	Risk of explosion. Urea byproduct difficult to remove.
DCC	*N*,*N*′-Dicyclohexylcarbodiimide	538-75-0	7	3	4.4	Urea byproduct is a sensitizer, also difficult to remove.
DPPA	Diphenylphosphoryl azide	26386-88-9	5	3	4.2	May form explosive hydrogen azide on contact with moisture.
Boric acid	Boric acid	10043-35-3	2	9	4.1	May damage fertility. May damage the unborn child.
Cyanuric chloride	2,4,6-Trichloro-1,3,5-triazine	108-77-0	3	6	3.8	Reacts violently with water. Causes burns. Toxic by inhalation.
HOBt	1-Hydroxybenzotriazole hydrate	123333-53-9	3	4	3.7	May cause explosion. Cytotoxic urea byproduct.
DMTMM	4-Dimethoxy-1,3,5,triazin-2-yl)-4-methyl morpholinium chloride	3945-69-5	3	5	3.6	Causes burns.
HBTU	*N*,*N*,*N*′,*N*′-Tetramethyl-*O*-(benzotriazol-1-yl)uronium hexafluorophosphate	94790-37-1	3	4	3.5	Cytotoxic urea byproduct.
DIC	Diisopropyl carbodiimide	693-13-0	3	4	3.5	Flammable. Toxic by inhalation.
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate	148893-10-1	3	4	3.3	Cytotoxic urea byproduct.
HOAt	1-Hydroxy-7-azabenzotriazole	39968-33-7	2	5	2.9	May cause explosion. Cytotoxic urea byproduct. Currently only available as DMF solution - may cause harm to the unborn child.

Fig. 2 GSK amide formation green reagent guide. (a) Front of guide with overview, (b) reverse of guide with more detail.

This journal is © The Royal Society of Chemistry 2013

Published on 22 April 2013. Downloaded by McGill University on 8/21/2025 9:26:09 PM.

a)



This guide should only be used by the expert trained chemist. Before using any reagent listed on this guide, a complete risk assessment must be carried out.

b)

Material	Full name	CAS number	EHS	Clean chemistry	Greenness	Comments
Bu_4NCl, P_2O_5	Tetrabutylammonium chloride Phosphorus pentoxide	1112-67-0 1314-56-3	7	6	6.5	Limited examples.
Oxalyl chloride	Oxalyl chloride	79-37-8	5	6	5.8	Lachrymator. Gaseous byproducts.
Thionyl chloride	Thionyl chloride	7719-09-7	5	5	5.3	Lachrymator. Gaseous byproducts.
Phenylphosphonic dichloride	Phenylphosphonic dichloride	824-72-6	5	5	5.0	Possible high temperatures needed.
Phenyldichlorophosphate	Phenyldichlorophosphate	770-12-7	5	5	5.0	Limited examples.
Trichloroacetonitrile, PPh_3	Trichloroacetonitrile Triphenylphosphine	545-06-2 603-35-0	5	3	4.2	Danger of serious damage to health by prolonged exposure through inhalation. PPh_3 is a material of concern, future regulatory impact possible.
$POCl_3$	Phosphorus oxychloride	10025-87-3	3	6	3.8	Danger of serious damage to health by prolonged exposure through inhalation.
PCl_3	Phosphorus trichloride	7719-12-2	3	5	3.7	Danger of serious damage to health by prolonged exposure through inhalation.
CCl_4, PPh_3	Carbon tetrachloride Triphenylphosphine	56-23-5 603-35-0	3	5	3.6	Limited evidence of carcinogenic effect. Dangerous for the ozone layer, PPh_3 is a material of concern, future regulatory impact possible.
PCl_5	Phosphorus pentachloride	10026-13-8	3	5	3.4	Danger of serious damage to health by prolonged exposure through inhalation.
Cl_2, Triphenylphosphite,	Chlorine, Triphenylphosphite	101-02-0 7782-50-5	3	4	3.2	Very toxic to aquatic organisms. May cause long-term adverse effects in the aquatic environment.
Oxalyl chloride, DMF	Oxalyl chloride, Dimethylformamide catalyst	79-37-8 68-12-2	1	5	2.5	DMF typically used in catalytic amounts. DMCC carcinogen may be formed if used in conjunction with DMF.
Thionyl chloride, DMF	Thionyl chloride, Dimethylformamide catalyst	7719-09-7 68-12-2	1	5	2.5	DMF typically used in catalytic amounts. Risk to unborn child.

Fig. 3 GSK deoxychlorination green reagent guide. (a) Front of guide with overview, (b) reverse of guide with more detail.

Published on 22 April 2013. Downloaded by McGill University on 8/21/2025 9:26:09 PM.

Greenness Score =
Geomean{Geomean(Health, Safety, Env),Geomean(Atom Efficiency, Stoichiometry, Work-up, Co-reagent, Other)}

Green	6 to 7.3* <Greenness Score
Yellow	4 <Greenness Score < 6 to 7.3*
Red	Greenness Score < 4 (or any individual E, H or S score ≤ 3.5, or Clean Chemistry score ≤ 3.5)

*value varies for a given transformation based on team review

Fig. 4 Explanation of categorisation of reagents.

5. Conclusions and future work

We have developed and applied a methodology for reagent guidance, and here share 15 reagent guides. These guides are intended to be updated over time as additional reagents or other information on existing reagents become available. We intend to cover and publish further transformations with this current format, and to further develop these guides to include assessment of reaction mass efficiency and incorporate guidance for synthetic strategy.

Whilst GSK have taken a different approach to that of Pfizer in the preparation of reagent guides,[6] our conclusions are broadly aligned with their published guides on the oxidation of primary alcohols to aldehydes, and amide formation. Both companies scored air and metal catalyst, PIPO and co-oxidant, and TEMPO and co-oxidant as preferred conditions for oxidation. Likewise enzymatic procedures, CDI and iBuOCOCl were ranked by both as preferred conditions for amide bond formation. However, the Pfizer guide lists boric acid as a preferred reagent for amide formation, whilst risk phrases associated with potential fertility damage outweigh catalytic advantages and otherwise high ranking scores and drive this reagent into the red section in GSK's guide.

Our protocol frequently resulted in biocatalytic processes topping our lists of preferred reagents. This is consistent with the many advantages that biocatalysis can offer in terms of moderate reaction temperatures, frequent use of green solvents for reactions (often water) and high turnover numbers. This is even more apparent in cases where downstream processing does not require significant use of organic solvent for product isolation. The variety of enzymes from commercial sources is increasing rapidly, and many companies/institutions are becoming capable of producing and optimising their own biocatalysts (enzymes and whole cells). This has resulted in much more variety and greater security of supply on commercial scale. However, had we explicitly included other factors, such as demonstrated use for a particular biocatalyst on large scale, these might not have always scored as highly and there are still reaction classes that are not well served by biocatalysis.

The systematic approach to assessing reagents should allow for the updating of these guides with additional reagents, so they can continue to evolve and remain current. Information such as that provided in these guides is of increasing value to companies and other institutions to enable scientists in research and development roles to develop processes that are more sustainable based on objective assessments. This is especially important in light of increased regulatory activity (*e.g.* EU REACH Legislation) that aims to restrict the marketing and use of hazardous chemicals.

The preparation of the guides has highlighted a number of greener reagents which we believe have the potential to be more widely utilised within the pharmaceutical industry. We have started to explore the scope of some of these reagents in preferred solvents,[14,15] and will continue to do so as we validate these guides.

In addition to offering guidance for specific reaction types, the guides also allow for analysis of the overall impact of a whole transformation, highlighting areas where there are fewer robust, validated reagents in the "green section" as a target for further research. One example of this is deoxychlorination where only one reagent combination was found to occupy the green category, and in our hands this was found to have limited scope and utility.

GSK seeks to move towards more sustainable practices in all areas of its business, and these guides form part of current and future initiatives and strategies to embed sustainability into our operations as we strive to become carbon neutral by 2050.[16]

Acknowledgements

The authors wish to acknowledge Jason Ramoutar and Martin Long from GSK IT, and Stephen Montgomery from Platform Technology and Science for their continued support and collaboration in setting up and maintaining the intranet version of the reagent guides; Paul Evans, Susan Shilcrat and Bill Hinkley from Process Safety for their thoughtful contributions in reviewing and revising the safety rankings; Alan Curzons and Conchita Jiménez-González for discussions as the concept was forming and Andrew Dominey, Bing Liu, Carolyn Selenski, Gail Fisher, Graham Inglis, Lynette Oh, Marie Catherine Salaun and many colleagues in Investigational Material Supply, Product Development, Medicinal Chemistry and R&D EHS for their input and suggestions during revision of the guides.

Notes and references

1 A. D. Curzons, D. J. C. Constable and V. L. Cunningham, *Clean Products Processes*, 1999, **1**, 82–90.
2 C. Jiménez-González, A. D. Curzons, D. J. C. Constable and V. L. Cunningham, *Clean Technol. Environ. Policy*, 2005, **7**, 42–50.
3 R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks and A. D. Curzons, *Green Chem.*, 2011, **13**, 854.

 This journal is © The Royal Society of Chemistry 2013

Published on 22 April 2013. Downloaded by McGill University on 8/21/2025 9:26:09 PM.

4 R. K. Henderson, J. Kindervater and J. Manley, *American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable*, Benchmarking 2006, http://portal.acs.org/portal/PublicWebSite/greenchemistry/industriainnovation/roundtable/CTP_005585, last accessed 13th November 2009.
5 J. Manley and R. K. Henderson, American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable Benchmarking, 2008, *private communication*.
6 K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem.*, 2008, **10**, 31–36.
7 S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54** (10), 3451; J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337.
8 Highlighting existing or potential forthcoming legislation.
9 Reagents where risk phrases were not available: enzymes, solid supported reagents (PIPO and acid catalysts), iron powder, a ruthenium zeolite, dimesitylammonium pentafluorobenzenesulfonate and diphenylammonium triflate.
10 Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. Official Journal 196, 16/08/1967, 1–98. During the process of compiling these guides the form of the risk phrases was updated to the GHS system, however in the interests of consistency, R phrases have been used throughout.
11 A. Curzons, C. Jiménez-González, A. Duncan, D. Constable and V. Cunningham, *Int. J. Life Cycle Assessment*, 2007, **12**(4), 272–280.
12 If any of the Environment, Health or Safety scores is less than 3.5, the geometric mean of the three scores and the number 1 is calculated to keep the combined score in the red zone. If none of the individual scores are red, the overall Environment, Health and Safety score is the geometric mean of the three separate Environment, Health and Safety scores.
13 Note that whilst the figures show the overall EHS score and overall chemistry score to one significant figure, the more precise number was used when calculating the geometric mean, which can lead to some apparent inconsistencies.
14 D. S. MacMillan, J. Murray, H. F. Sneddon, C. Jamieson and A. J. B. Watson, *Green Chem.*, 2013, **15**, 596–600.
15 F. I. McGonagle, D. S. MacMillan, J. Murray, H. F. Sneddon, C. Jamieson and A. J. B. Watson, *Green Chem.*, 2013, DOI: 10.1039/c3gc40359a.
16 GSK Corporate responsibility report http://www.gsk.com/responsibility.html

Green Chemistry

PAPER

View Article Online
View Journal | View Issue

Published on 25 September 2014. Downloaded by McGill University on 8/21/2025 9:25:16 PM.

Cite this: Green Chem., 2015, 17, 945

Development of GSK's acid and base selection guides†

Richard K. Henderson,[a] Alan P. Hill,[b] Anikó M. Redman*[c] and Helen F. Sneddon[b]

Received 1st August 2014,
Accepted 24th September 2014

DOI: 10.1039/c4gc01481b

www.rsc.org/greenchem

Further to the introduction of solvent and reagent guides at GSK, the reagent guide methodology has been adapted to score common acids and bases for use in situations where the chemistry is tolerant of a number of options. The pK_a of each acid and base, and information as to whether they are generally recognised as safe are included to enhance the utility of such guides.

1. Introduction

Scientists at GSK have been consulting an internal base guide for over ten years to aid selection of bases as reagents. A more recent internal survey resulted in an expanded list of 63 bases, and an additional set of 23 acids. Two new guides were then compiled using methodology consistent with that applied to generate our reagent guide.[1]

Selecting the right acids or bases for a particular chemical transformation is influenced by a number of factors, including environmental, health and safety effects, reagent strength, solubility, boiling point, ease of removal and/or recovery, and ease of handling. These constraints may not always give rise to a variety of choices, but if there are multiple options, sustainability assessments can be consulted. Medicinal Chemistry timelines can sometimes hinder consideration of sustainability, but as projects progress, consulting these guides can be helpful before larger investments are made into the original Medicinal Chemistry routes and reagents.

2. Methodology

Assessments and calculations performed for the fifteen reagent guides published in early 2013 [1] were followed to generate these acid and base guides (Tables 1 and 2). As before, the European Risk Phrases were used to assign an Environmental, Health and Safety Score for each reagent.[2] Additional concerns where acids and bases have large molecular weight, or generate gaseous, flammable or toxic by-products, or give rise to disposal issues such as incineration of halogenated acids were addressed through the Chemistry Scores. When generating the reagent guides, the most typical procedures utilizing the reagents were taken into account, and the Chemistry Scores were additionally weighted based on the amounts of reagents and co-reagents used. Clearly individual acids and bases might be employed in a variety of different stoichiometries depending on the reaction being considered, so for the purpose of ranking it was assumed that 1.1 equivalents of acids or bases were being used with no additional co-reagents. Within the acid guide separate entries were created for concentrated and dilute acid in cases where using a more dilute formation resulted in a significantly higher ranking.

When acids or bases are used as solvents, other factors such as waste handling and life cycle assessment may need additional consideration. Solvent guides[3] published by various pharmaceutical companies can help evaluate the possible choices. Acids and bases as potential salt partners for *in vivo* experiments will have to undergo more rigorous health assessments, however the inclusion of information as to which acids and bases are generally recognized as safe (GRAS) by the US Food and Drug Administration as of March 2014 may assist in some decision making.

Individual pK_a values are a key consideration when selecting acids and bases. Including pK_a data in the acid/base guides increases utility and may help encourage chemists to consult these guides, and related reagent guides. Experimental pK_a data were retrieved from ACD/pK_a DB software.[4] Where a range of experimental pK_a values were available in the literature, data obtained under aqueous conditions at 25 °C with an ionic strength approaching 0 were used wherever possible.

3. The benefits of selecting more sustainable conditions

In addition to their sustainability advantages, greener acids and bases often have additional benefits. Commonly used

[a]GSK, Environmental Sustainability Centre of Excellence, Park Road, Ware, Herts, SG12 0DP, UK
[b]GSK, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts, SG1 2NY, UK
[c]GSK, 5 Moore Drive, Research Triangle Park, NC 27709, USA.
E-mail: aniko.m.redman@gsk.com; Tel: +1-919-483-4638

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c4gc01481b

Published on 25 September 2014. Downloaded by McGill University on 8/21/2025 9:25:16 PM.

Table 1 Acid selection guide

Inorganic acids	CAS number	EHS	Clean chemistry	Greenness	pK_a[a]	GRAS[b]	Comment
Hydrochloric acid	7647-01-0	7	7	7.3	*−8*[5]	YES	Waste disposal issues upon incineration. Halogenated waste.
Hydrobromic acid	10035-10-6	7	7	7.3	*−9*[5]	NO	Waste disposal issues upon incineration. Halogenated waste.
Phosphoric acid, dilute	7664-38-2	7	7	7.3	1.90, 6.74, 11.74[6]	YES	Waste disposal issues upon incineration.
Sulfuric acid, dilute	7664-93-9	7	7	7.3	*−3.19*, 1.98[7]	NO	Waste disposal issues upon incineration.
Hydroiodic acid	10034-85-2	7	5	6.4	*−9.9*[8]	NO	Causes severe burns (R35). Waste disposal issues upon incineration. Halogenated waste.
Phosphoric acid	7664-38-2	7	5	6.4	1.90, 6.74, 11.74[6]	YES	Waste disposal issues upon incineration.
Sulfuric acid	7664-93-9	7	5	6.4	*−3.19*, 1.98[7]	NO	Causes severe burns (R35). Waste disposal issues upon incineration.
Nitric acid	7697-37-2	5	3	4.3	−1.37[9]	NO	Strong oxidant (R8). Causes severe burns (R35).
Hydrogen fluoride	7664-39-3	3	5	4.2	*3.2*[8]	NO	Toxic (R26/27/28). Causes severe burns (R35). Special vessel necessary. Waste disposal issues upon incineration. Halogenated waste.
Perchloric acid	7601-90-3	3	3	3.0	~*−5*[10]	NO	Strong oxidant (R8). Causes severe burns (R35). Waste disposal issues upon incineration. Halogenated waste.

Organic acids	CAS number	EHS	Clean chemistry	Greenness	pK_a[a]	GRAS[b]	Comment
Glutaric acid	110-94-1	10	9	9.3	4.41, 5.52[11]	NO	
Citric acid	77-92-9	10	7	8.5	*2.93*[12]	YES	
Ascorbic acid	50-81-7	10	7	8.5	*4.09*[12]	YES	
p-TsOH (monohydrate)	6192-52-5	10	7	8.5	−6.57[13]	NO	
Benzoic acid	65-85-0	7	9	8.0	4.20[14]	YES	
Oxalic acid	144-62-7	7	9	8.0	1.25, 4.23[11]	NO	
Pivalic acid	75-98-9	7	9	8.0	*4.94*[12]	NO	
Succinic acid	110-15-6	7	9	8.0	*4.24*[12]	YES	
Acetic acid	64-19-7	7	9	7.5	4.76[15]	YES	Causes severe burns (R35).
Propionic acid	79-09-4	7	9	7.5	*4.79*[12]	YES	
Formic acid, dilute	64-18-6	7	9	7.5	3.75[16]	YES	
Methanesulfonic acid	75-75-2	7	7	7.3	−1.92[14]	NO	
Formic acid	64-18-6	7	7	6.9	3.75[16]	YES	Causes severe burns (R35).
Trifluoromethanesulfonic acid	1493-13-6	7	5	6.1	−12[17]	NO	Causes severe burns (R35). Halogenated waste.
Trifluoroacetic acid	76-05-1	7	5	6.0	0.50[18]	NO	Causes severe burns (R35). Waste disposal issues upon incineration. Halogenated waste.
Trichloroacetic acid	76-03-9	3	5	3.6	0.52[18]	NO	Causes severe burns (R35). Waste disposal issues upon incineration. Halogenated waste.

[a] pK_a numbers in italics are not experimentally obtained data. [b] GRAS (Generally Recognized as Safe) is an FDA designation that a chemical or substance added to food is considered safe by experts. http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm.

reactions found in the Medicinal Chemistry literature may have significant issues when employed on large scale. One such example is the use of NaH in DMF. Exposure of solid NaH to air and the release of highly flammable hydrogen gas on large scale have significant safety risks, and the combination of NaH and DMF has been implicated in runaway reactions.[42] Using alkoxides such as potassium *tert*-butoxide instead can alleviate these concerns.

When it is not feasible to replace a class of acids or bases with significantly more sustainable counterparts, the guides can still point out differences within the available choices. For example, transformation requiring the use of alkyllithiums will likely proceed as well with hexyllithium as with its short-chain analogs, and the by-product will be liquid hexane instead of flammable alkane gases. Even this is not ideal as hexane has neurotoxicity concerns.[43] Currently there is still a need for new commercially available organolithium reagents to address these safety issues.

Reactions such as BOC-deprotections are generally carried out using strong acids. Replacing TFA in dichloromethane with HCl in cyclopentyl methyl ether (CPME),[44] minimizes the safety hazard of severe skin damage, and reduces the amounts of chlorinated materials.

Choosing more sustainable conditions by first intent in Medicinal Chemistry can result in safer reaction conditions, less hazardous waste, and significant time savings during subsequent scale up campaigns.

 This journal is © The Royal Society of Chemistry 2015

Published on 25 September 2014. Downloaded by McGill University on 8/21/2025 9:25:16 PM.

Table 2 Base selection guide

Carbonates	CAS number	EHS	Clean chemistry	Greenness	pK_a^a (BH^+)	GRAS[b]	Comment
Sodium bicarbonate	144-55-8	10	9	9.3	5.95[17]	YES	
Potassium bicarbonate	298-14-6	10	9	9.3	5.95[17]	YES	
Sodium carbonate	497-19-8	10	9	9.3	9.1[17]	YES	
Potassium carbonate	584-08-7	9	9	8.8	9.1[17]	NO	
Cesium carbonate	534-17-8	10	5	7.4	9.1[17]	NO	
Phosphates	**CAS number**	**EHS**	**Clean chemistry**	**Greenness**	pK_a^a (BH^+)	**GRAS[b]**	**Comment**
Trisodium phosphate (anh.)	7601-54-9	10	8	9.0	11.74[18]	YES	
Tripotassium phosphate (anh.)	7778-53-2	7	7	7.3	11.74[18]	YES	
Hydroxides	**CAS number**	**EHS**	**Clean chemistry**	**Greenness**	pK_a^a (BH^+)	**GRAS[b]**	**Comment**
Potassium hydroxide	1310-58-3	7	9	8.0	15.74[19]	YES	Causes severe burns (R35).
Sodium hydroxide	1310-73-2	7	9	8.0	15.74[19]	YES	Causes severe burns (R35).
Calcium hydroxide	1305-62-0	7	9	8.0	15.74[19]	YES	
Barium hydroxide	17194-00-2	7	8	7.7	15.74[19]	NO	
Lithium hydroxide	1310-65-2	4	8	5.7	15.74[19]	NO	
Hydrides	**CAS number**	**EHS**	**Clean chemistry**	**Greenness**	pK_a^a (BH^+)	**GRAS[b]**	**Comment**
Sodium hydride	7646-69-7	5	5	5.0	*35.0*[20]	NO	May cause runaway reaction with certain solvents, such as DMF, DMA. Highly flammable gaseous by-product (hydrogen) needs abating. Use of mineral oil dispersions greatly reduces fire hazard.
Potassium hydride	7693-26-7	5	5	5.0	*35.0*[20]	NO	May cause runaway reaction with certain solvents, such as DMF, DMA. Highly flammable gaseous by-product (hydrogen) needs abating. Use of mineral oil dispersions greatly reduces fire hazard.
Acetates	**CAS number**	**EHS**	**Clean chemistry**	**Greenness**	pK_a^a (BH^+)	**GRAS[b]**	**Comment**
Potassium acetate	127-08-2	10	9	9.3	4.76[21]	NO	
Sodium acetate	127-09-3	10	9	9.3	4.76[21]	YES	
Alkoxides	**CAS number**	**EHS**	**Clean chemistry**	**Greenness**	pK_a^a (BH^+)	**GRAS[b]**	**Comment**
Sodium methoxide	124-41-4	5	9	6.9	15.1[22]	NO	Highly flammable (R11). Toxic (R23/24/25).
Sodium ethoxide	141-52-6	5	9	6.9	15.93[22]	NO	Highly flammable (R11).
Sodium *tert*-butoxide	865-48-5	5	9	6.9	19.2[22]	NO	Highly flammable (R11). Causes severe burns (R35).
Potassium *tert*-butoxide	865-47-4	5	9	6.9	19.2[22]	NO	Highly flammable (R11). Causes severe burns (R35).
Lithium methoxide	865-34-9	4	8	5.7	15.1[22]	NO	Highly flammable (R11). Toxic (R23/24/25).
Lithium ethoxide	2388-07-0	4	8	5.7	15.93[22]	NO	Highly flammable (R11).
Lithium *tert*-butoxide	1907-33-1	4	8	5.7	19.2[22]	NO	Highly flammable (R11).
Phosphazanes	**CAS number**	**EHS**	**Clean chemistry**	**Greenness**	pK_a^a (BH^+)	**GRAS[b]**	**Comment**
Phosphazane BEMP	98015-45-3	7	5	6.0	27.58[23]	NO	
Phosphazane P2-Et	165535-45-5	7	5	6.0	32.66[23]	NO	
Amines	**CAS number**	**EHS**	**Clean chemistry**	**Greenness**	pK_a^a (BH^+)	**GRAS[b]**	**Comment**
2-Methylpyridine	109-06-8	8	9	8.3	5.97[24]	NO	
2,6-Lutidine	108-48-5	8	9	8.3	6.75[24]	NO	
DBN	3001-72-7	7	9	8.0	*13.5*[25]	NO	
Pyridine	110-86-1	7	9	7.5	5.17[24]	NO	Highly flammable (R11).

Published on 25 September 2014. Downloaded by McGill University on 8/21/2025 9:25:16 PM.

Table 2 *(Contd.)*

Amines	CAS number	EHS	Clean chemistry	Greenness	pK_a[a] (BH^+)	GRAS[b]	Comment
4-Methylpyridine	108-89-4	7	9	7.5	6.02[24]	NO	Toxic (R24).
Morpholine	110-91-8	7	9	7.5	8.49[26]	NO	
Diethylaminopropylamine	104-78-9	7	9	7.5	*10.48*[27]	NO	
Tetramethylguanidine	80-70-6	7	9	7.5	13.6[28]	NO	
DBU	6674-22-2	7	8	7.3	*12.5*[25]	NO	Causes severe burns (R35).
2,2,6,6-Tetramethylpiperidine	768-66-1	7	8	7.3	11.1[29]	NO	
Triethylamine	121-44-8	5	9	6.9	10.77[30]	NO	Highly flammable (R11). Toxic (R23/24). Causes severe burns (R35).
Diisopropylamine	108-18-9	5	9	6.9	11.05[36]	NO	Highly flammable (R11).
Piperidine	110-89-4	5	9	6.9	11.22[31]	NO	Highly flammable (R11). Toxic (R23/24).
Dimethylethylamine	598-56-1	5	9	6.9	10.16[32]	NO	Highly flammable (R11).
Dipropylamine	142-84-7	5	9	6.9	10.91[29]	NO	Highly flammable (R11). Causes severe burns (R35).
N-Methylmorpholine	109-02-4	5	9	6.9	7.41[29]	NO	Highly flammable (R11).
n-Butylamine	109-73-9	5	9	6.9	10.61[33]	NO	Highly flammable (R11). Causes severe burns (R35).
Diethylamine	109-89-7	5	9	6.9	10.98[36]	NO	Highly flammable (R11). Causes severe burns (R35).
Ammonia	7664-41-7	5	9	6.5	9.21[34]	NO	Toxic (R23).
Diisopropylethylamine	7087-68-5	5	9	6.5	*10.75*[35]	NO	Highly flammable (R11).
tert-Butylamine	75-64-9	5	9	6.5	10.63[30]	NO	Highly flammable (R11). Toxic (R25). Causes severe burns (R35).
DABCO®	280-57-9	5	9	6.5	*8.4*[25]	NO	Highly flammable (R11).
Cyclohexylamine	108-91-8	5	9	6.5	10.62[36]	NO	
Tributylamine	102-82-9	5	7	6.3	9.93[37]	NO	Toxic (R23/24/25).
4-(Dimethylamino)pyridine	1122-58-3	3	9	5.2	9.60[38]	NO	Toxic (R25/27).
Dicyclohexylamine	101-83-7	3	7	4.3	11.25[39]	NO	Toxic (R24/25).
Imidazole	288-32-4	2	9	3.9	6.99[39]	NO	Toxic (R61).

Disilazides	CAS number	EHS	Clean chemistry	Greenness	pK_a[a] (BH^+)	GRAS[b]	Comment
KHMDS	40949-94-8	5	7	5.9	29.5[40]	NO	Highly flammable (R11).
NaHMDS	1070-89-9	5	7	5.9	29.5[40]	NO	Highly flammable (R11).
LiHMDS	4039-32-1	4	8	5.5	29.5[40]	NO	Highly flammable (R11).

Amides	CAS number	EHS	Clean chemistry	Greenness	pK_a[a] (BH^+)	GRAS[b]	Comment
LiTMP	38227-87-1	4	8	5.5	37.3[40]	NO	
LDA	4111-54-0	3	8	4.5	35.7[40]	NO	Highly flammable (R11).
Sodium amide	7782-92-5	4	3	3.7	*35.0*[20]	NO	Forms peroxide. Toxic and flammable gaseous by-product (ammonia) needs abating.
Lithium amide	7782-89-0	4	3	3.7	*35.0*[20]	NO	Forms peroxide. Toxic and flammable gaseous by-product (ammonia) needs abating.

Alkyllithiums	CAS number	EHS	Clean chemistry	Greenness	pK_a[a] (BH^+)	GRAS[b]	Comment
n-Hexyllithium	21369-64-2	2	8	4.0	*40.0*[41]	NO	Highly flammable (R11). Causes severe burns (R35).
n-Butyllithium	109-72-8	1	7	3.1	*50.0*[41]	NO	Highly flammable (R11). Highly flammable gaseous by-product (butane) needs abating.
sec-Butyllithium	598-30-1	1	7	3.1	*51.0*[41]	NO	Highly flammable (R11). Causes severe burns (R35). Highly flammable gaseous by-product (butane) needs abating.
tert-Butyllithium	594-19-4	1	7	3.1	*53.0*[41]	NO	Highly flammable (R11). Highly flammable gaseous by-product (isobutane) needs abating.

[a] pK_a numbers in italics are not experimentally obtained data. [b] GRAS (Generally Recognized as Safe) is an FDA designation that a chemical or substance added to food is considered safe by experts. http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm

This journal is © The Royal Society of Chemistry 2015

Published on 25 September 2014. Downloaded by McGill University on 8/21/2025 9:25:16 PM.

4. Conclusion and further work

Not all acids or bases are interchangeable for every purpose, but these guides can help examine multiple choices, and can also facilitate changing a culture, encouraging people to consider sustainability as one of many criteria when planning a reaction.

Acknowledgements

The authors wish to acknowledge Catherine Alder, Weichun Chen, David Constable, Virginia Cunningham, Alan Curzons, Andrew Dominey, John Hayler, Richard Henderson, Conchita Jiménez-González, Marie Catherine Salaun, Lena Shukla and Leanna Shuster for their support of the reagent guides.

Notes and references

1 J. P. Adams, C. M. Alder, I. Andrews, A. M. Bullion, M. Campbell-Crawford, M. G. Darcy, J. D. Hayler, R. K. Henderson, C. A. Oare, I. Pendrak, A. M. Redman, L. E. Shuster, H. F. Sneddon and M. D. Walker, *Green Chem.*, 2013, **15**, 1542–1549.
2 Conversion of EU Risk Phrases to Globally Harmonized System (GHS): http://ec.europa.eu/enterprise/sectors/chemicals/files/ghs/ghs_comparison_classifications_dec07_en.pdf.
3 For example: (*a*) R. K. Henderson, C. Jiménez-González, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binksa and A. D. Curzons, *Green Chem.*, 2011, **13**, 854–862; (*b*) K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem.*, 2008, **10**, 31–36; (*c*) D. Prat, O. Pardigon, H.-W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani and P. Hosek, *Org. Process Res. Dev.*, 2013, **17**(12), 1517–1525.
4 *ACD/pKa DB Version 12.01*, Advanced Chemistry Development inc, Toronto, On, Canada, http://www.acdlabs.com, 2009.
5 F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456–463.
6 A. Avdeef and J. J. Bucher, *Anal. Chem.*, 1978, **50**, 2137–2142.
7 A. K. Covington, J. V. Dobson and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, 1965, **61**, 2057–2062.
8 W. Brown, B. Iverson, E. Anslyn and C. Foote, *Organic Chemistry*, Cengage Learning, 7th edn, 2013.
9 A. Krawetz, Thesis, Univ. of Chicago, 1955.
10 C. E. Housecroft and A. G. Sharpe, *Inorganic Chemistry*, Prentice Hall, 2nd edn, 2004, p. 171.
11 J. C. Speakman, *J. Chem. Soc.*, 1940, 855.
12 Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994–2014 ACD/Labs).
13 D. C. French and D. S. Crumrine, *J. Org. Chem.*, 1990, **55**(20), 5494–5496.
14 E. J. King and J. E. Prue, *J. Chem. Soc.*, 1961, 275–279.
15 J. R. Fisher and H. L. Barnes, *J. Phys. Chem.*, 1972, **76**, 90–99.
16 H. S. Harned and N. D. Embree, *J. Am. Chem. Soc.*, 1934, **56**(5), 1042–1044.
17 I. Hansson, *Acta Chem. Scand.*, 1973, **27**, 931–944.
18 A. Avdeef and J. J. Bucher, *Anal. Chem.*, 1978, **50**, 2137–2142.
19 E. P. Serjeant and B. Dempsey, *Ionization Constants of Organic Acids in Solution*, IUPAC Chemical Data Series No. 23, Pergamon Press, Oxford, UK, 1979.
20 M. B. Smith and J. March, *March's advanced organic chemistry*, Wiley Interscience, 6th edn, 2007.
21 J. R. Fisher and H. L. Barnes, *J. Phys. Chem.*, 1972, **76**, 90–99.
22 J. Murto, *Acta Chem., Scand.*, 1964, **18**, 1043–1053.
23 R. Schwesinger and H. Schlemper, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**(11), 1167–1169.
24 H. C. Brown and X. Mihm, *J. Am. Chem. Soc.*, 1955, **77**(7), 1723–1726.
25 T. Okuyama and H. Maskill, *Organic Chemistry: A Mechanistic Approach*, Oxford University Press, 2013, p. 130.
26 J. B. Czerminski, A. G. Dickson and R. G. Bates, Thermodynamics of the dissociation of morpholinium ion in seawater from 5 to 40 °C, *J. Solution Chem.*, 1982, **11**, 79.
27 Tissier and P. Barillier, *Comput. Rend. C.*, 1969, **268**, 1953.
28 S. J. Angyal and W. K. Warburton, *J. Chem. Soc.*, 1951, 2492–2494.
29 J. K. Hall, *J. Phys. Chem.*, 1956, **60**, 63–70.
30 D. B. Rorabacher and C. A. Melendez-Cepeda, *J. Am. Chem. Soc.*, 1971, **93**, 6071–6076.
31 S. Searles, M. Tamres, F. Block and L. Quarterman, *J. Am. Chem. Soc.*, 1956, **78**(19), 4917–4920.
32 J. Hansson, *Svensk. Kem. Tidskr.*, 1955, **67**, 256.
33 N. F. Hall and M. R. Sprinkle, *J. Am. Chem. Soc.*, 1932, **14**, 3469–3485.
34 D. B. Rorabacher, W. J. MacKellar, F. R. Shu and M. Bonavita, *Anal. Chem.*, 1971, **43**, 561–573.
35 D. D. Perrin, *Dissociation constants of organic acids and bases*, Butterworths, London, 1965. Supplement 1972.
36 R. D. Hancock, *J. Chem. Soc., Dalton Trans.*, 1980, 416–418.
37 P. Damsgard-Sorensen and A. Unmack, *Z. Phys. Chem.*, 1935, **A172**, 389–397.
38 F. Cruege, G. Girault, S. Coustal, J. Lascombe and P. Rumpf, *Bull. Soc. Chim. Fr.*, 1970, **11**, 3889–3894.
39 J. J. Christensen, R. M. Izatt, D. P. Wrathall and L. D. Hansen, *J. Chem. Soc. A*, 1969, 1212–1223.
40 R. R. Fraser and T. S. Mansour, *J. Org. Chem.*, 1984, **49**, 3442–3443.
41 Approximations based on standard alkane pK_a's.
42 (*a*) J. Buckey, *et al.*, *Chem. Eng. News*, 1982, **60**(28), 5; (*b*) G. De Wall, *Chem. Eng. News*, 1982, **60**(37), 5.
43 Toxicology Profile for *n*-Hexane, US Department of Health and Human Services Public Health Service Agency for Toxic Substances and Disease Registry, July, 1999.
44 Available from Sigma-Aldrich as a 3 M solution.