



Sustainable Organic Synthesis

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What is sustainability?

Environment



Maintain or support
a process over time



Economy



Society

Environmental hazards



Organic synthesis



Renewable
feedstock



Chemical
hazards

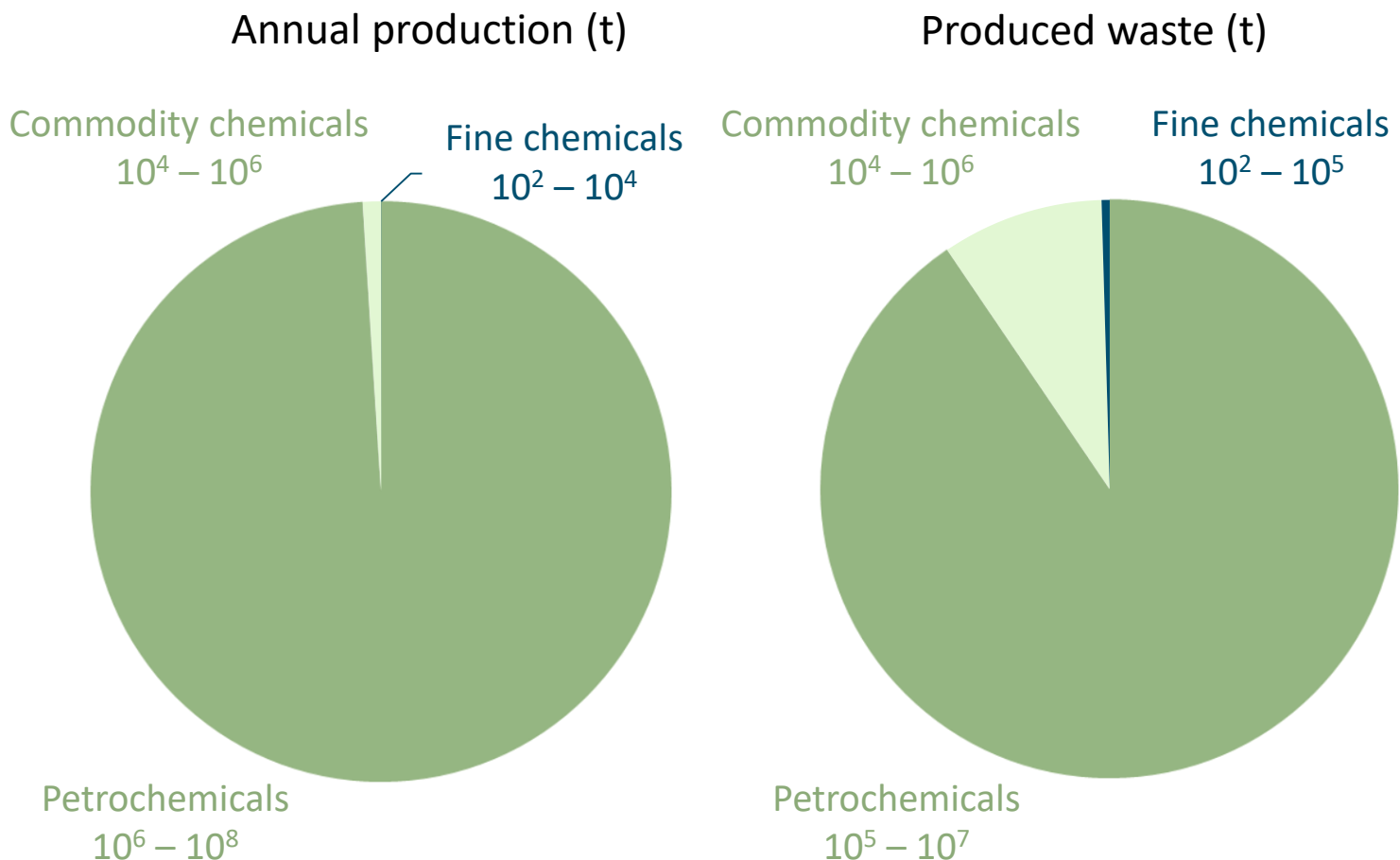


Costs



Health
hazards

Why should we care about sustainable chemistry?



Green Chem. **2007**, 9, 1273

Environmental factor (E):

$$E = \frac{\text{mass of waste}}{\text{mass of product}}$$

| Industry sector | E factor |
|--------------------|----------|
| Petrochemical | 0.1 |
| Commodity chemical | 1 - 5 |
| Fine chemical | 5 - 100 |

Organic synthesis on small scale?

Hazardous chemicals **are** and **will be** regulated by laws

Such compounds less attractive as starting material or reagents

Green vs. sustainable chemistry

Green chemistry adheres to 12 principles:

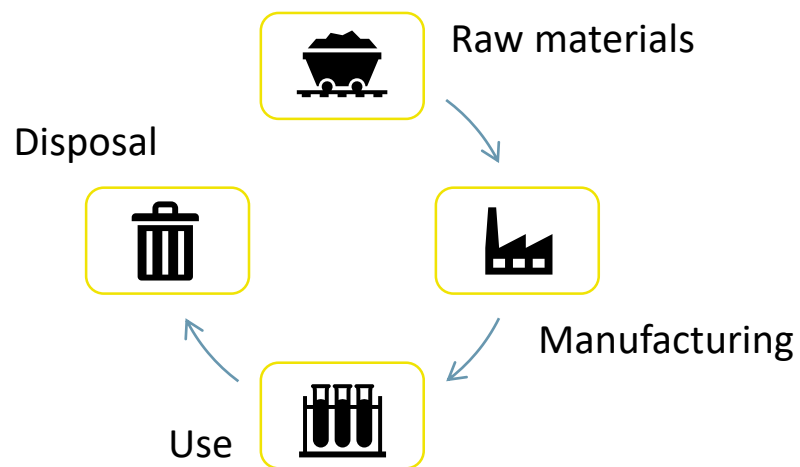
1. Preventing waste
2. Atom economy
3. Less hazardous chemical syntheses
4. Designing safer chemicals
5. Safer solvents and auxiliaries
6. Design for energy efficiency
7. Use of renewable feedstocks
8. Reduce derivatives (protecting groups)
9. Catalysis over stoichiometric reagents
10. Design for degradation
11. Real-time analysis for pollution prevention
12. Safer chemistry for accident prevention

Green chemistry: deliverance or distraction?

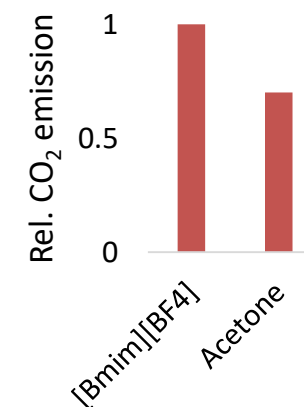
- Critique of each principle
- Questions if these principles are good guidelines to develop sustainable processes
- Principles neglect process economics, feedstock supply, function of markets and regulation

Clean Tech Environ Policy **2016**, 18, 991

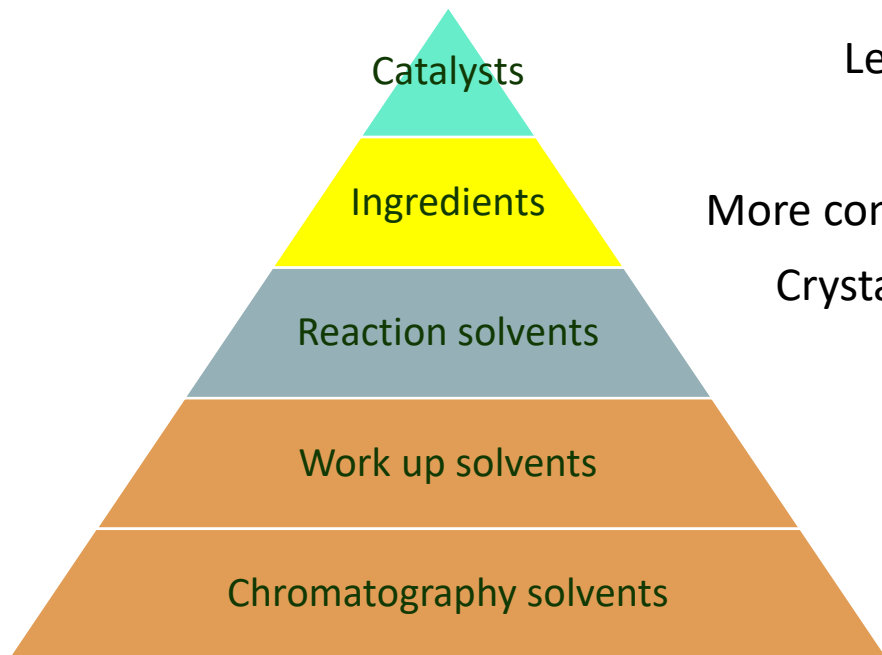
Sustainability looks at the broader picture, e.g., life cycle analysis (LCA):



Ionic liquids LCA:



Waste and environmental hazards

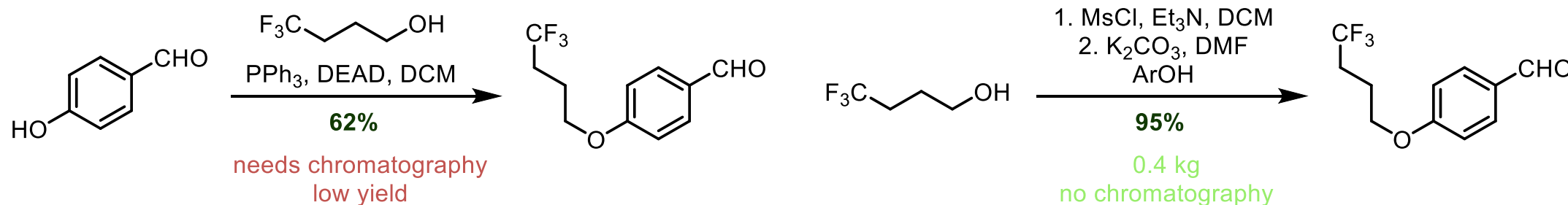


- Less steps, less waste
- Direct isolation
- More concentrated reactions
- Crystallization/distillation
- Alternative solvents
- 'New' technologies
- Reagent selection

| Solvent | Alternative |
|-----------------------------|----------------|
| Benzene | Toluene |
| Pent, Hex | Heptane |
| Et ₂ O, THF, DME | 2-MeTHF, TBME |
| DCM, DCE | No direct alt. |
| DMF, NMP | Acetonitrile |

Desired: H₂O, Acetone, EtOH, EtOAc

Synthesis of BMS-963272:

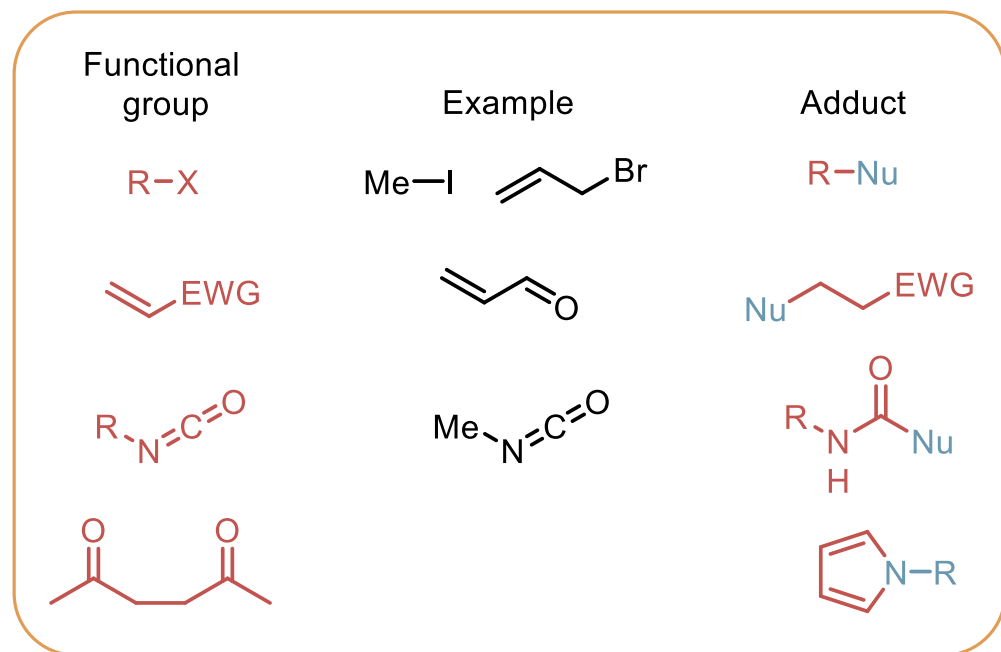


Health hazards

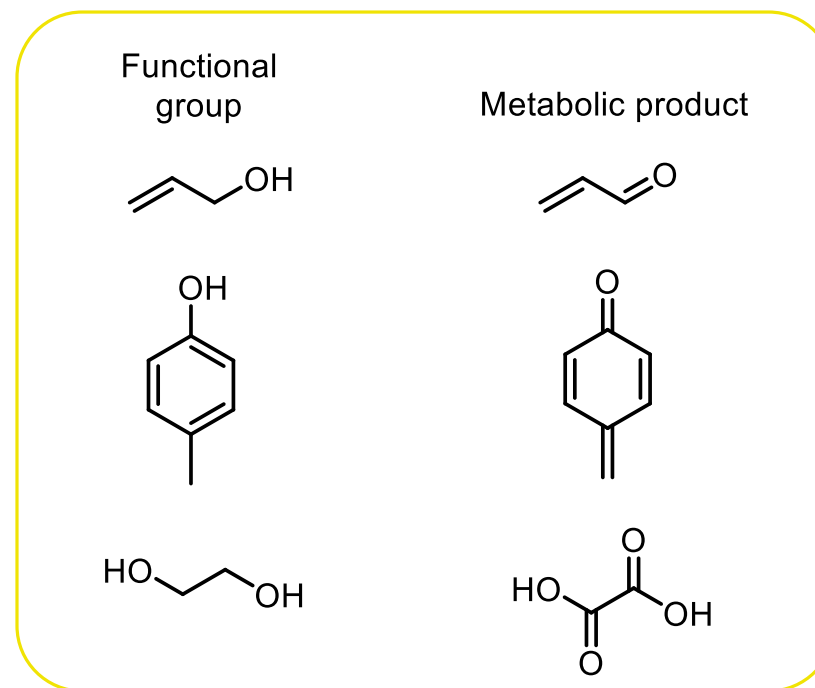


Familiar toxicity: HCl, NaOH, CO, HCN, H₂S

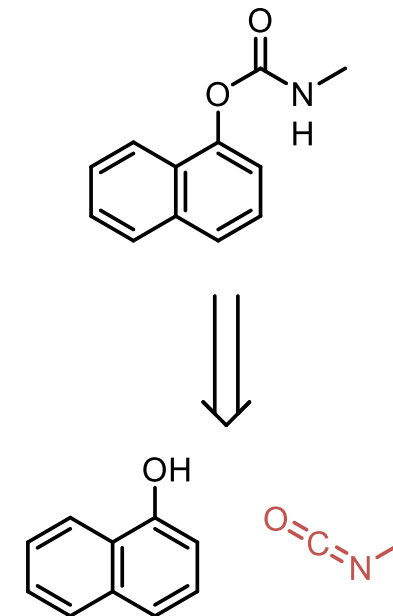
Directly toxic



Toxic through metabolic oxidation



How would you sustainably synthesize Carbaryl?



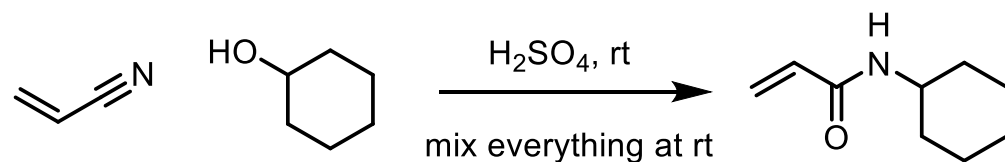
Highly volatile and toxic compounds should be avoided on scale:
methyl iodide vs. dimethyl sulfate

Chemical hazards



Runaway reactions

- High temperatures and gas release (BH₃·THF, NaH + DMF)
- Poor understanding of reaction kinetics



mixture ejected from the flask after 2 h (2 mol scale)

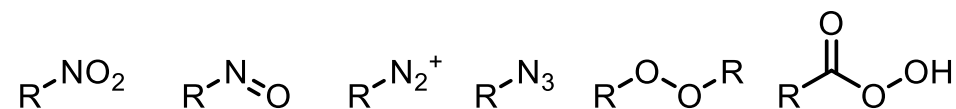
Simultaneous addition of H₂SO₄ (1.77 eq.) and substrates to H₂SO₄ (0.25 eq) at 45–55 °C

- Delayed initiation (Grignard reagents)

Volatile flammable compounds

| Solvent | bp (°C) | fp (°C) |
|-------------------|---------|---------|
| Acetone | 56 | -20 |
| MeOH | 65 | 11 |
| Et ₂ O | 35 | -45 |
| Pentane | 36 | -49 |

Energetic functional groups

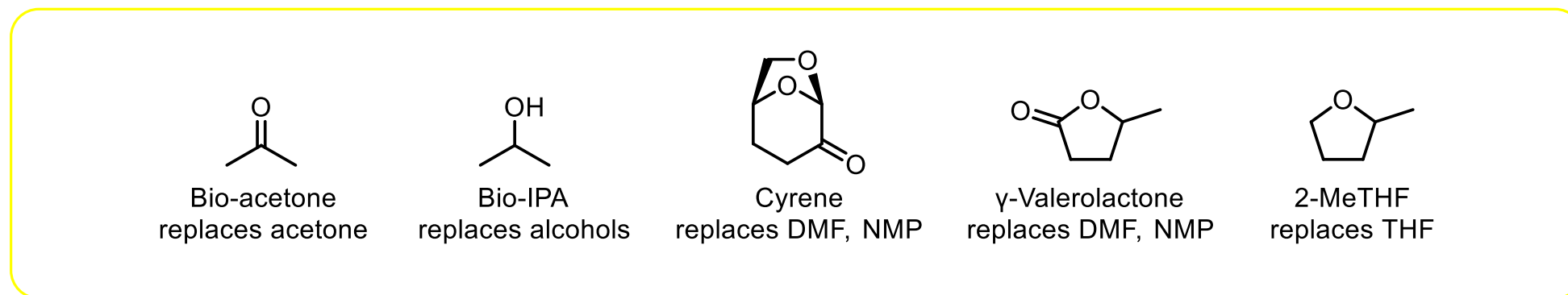


Full list: Org. Process Res. Dev. **2002**, 6, 877

Renewable feedstock

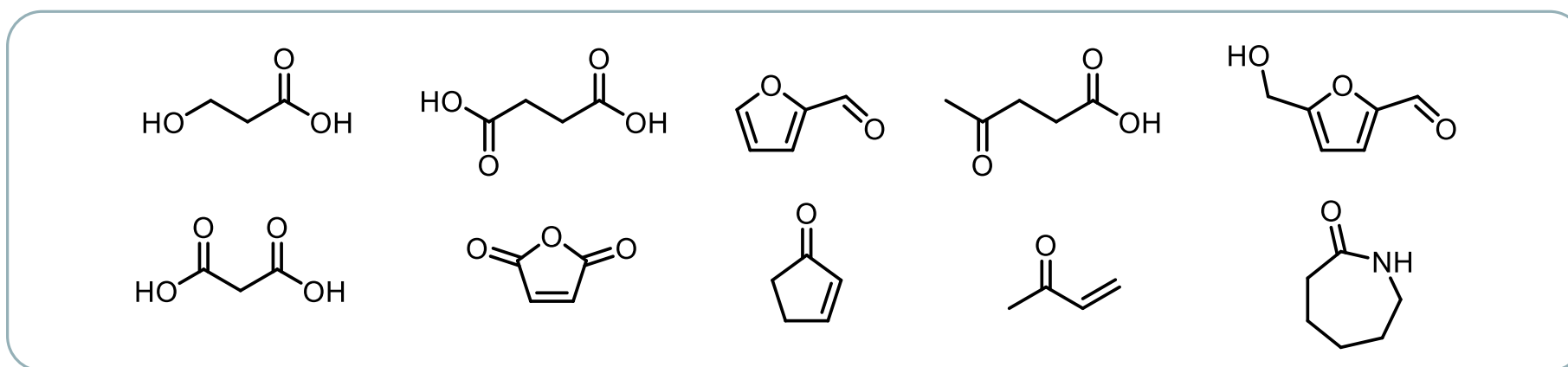


Renewable solvents



Relevant literature: Chem. Rev. **2018**, 118, 747

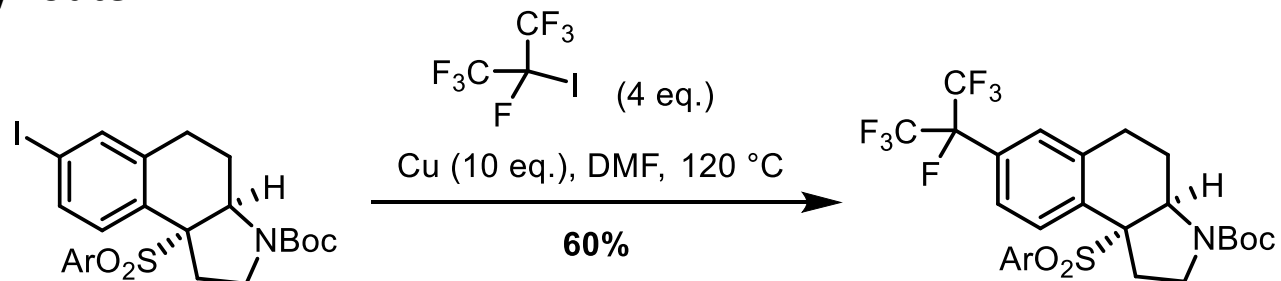
Carbohydrate based building blocks



Relevant literature: : Chem. Rev. **2018**, 118, 505

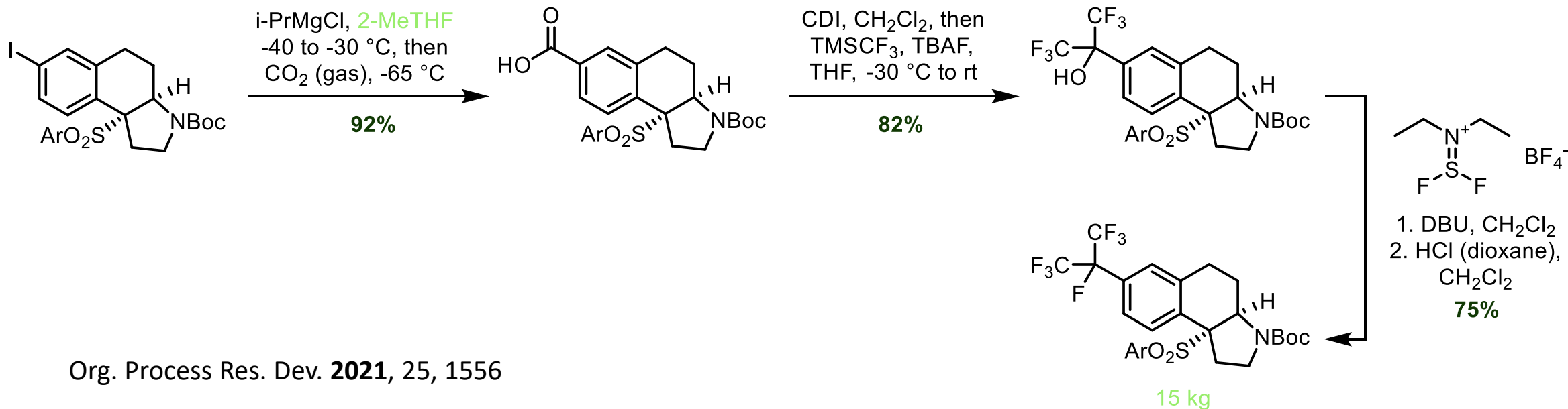
Real world application: BMS-986251

Discovery route:



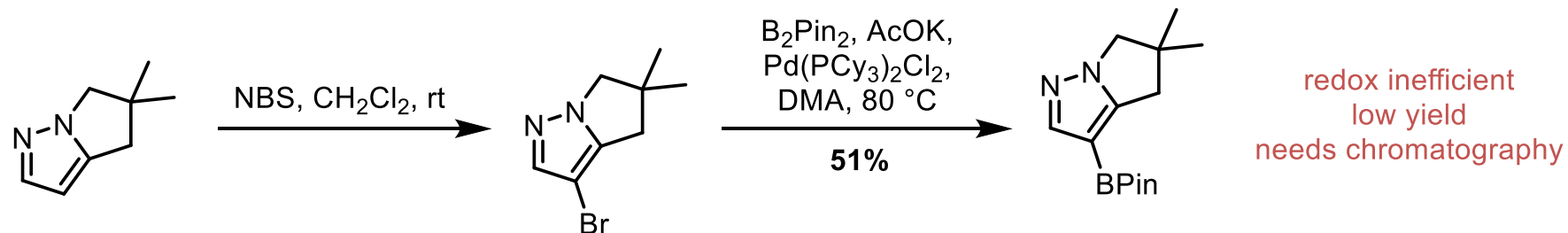
yield decreases on >10 g scale
low bp of fluoroiodide (40°C)
high temperature
sealed tube heating

Large scale route:

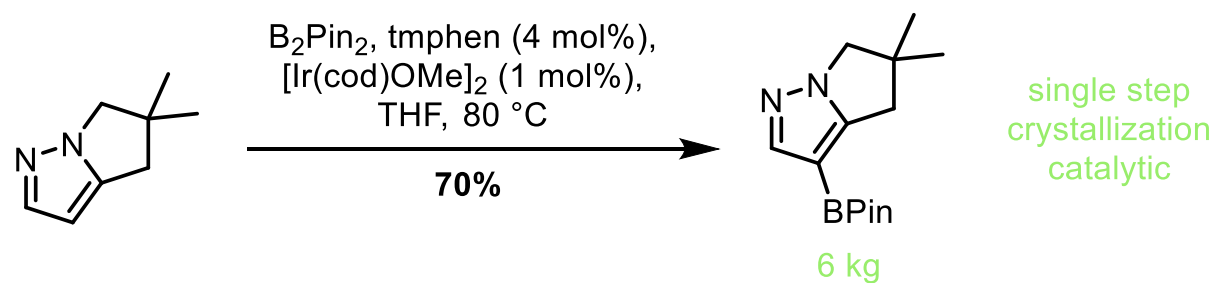


Real world application: AZD4573

Discovery route:



Large scale route:

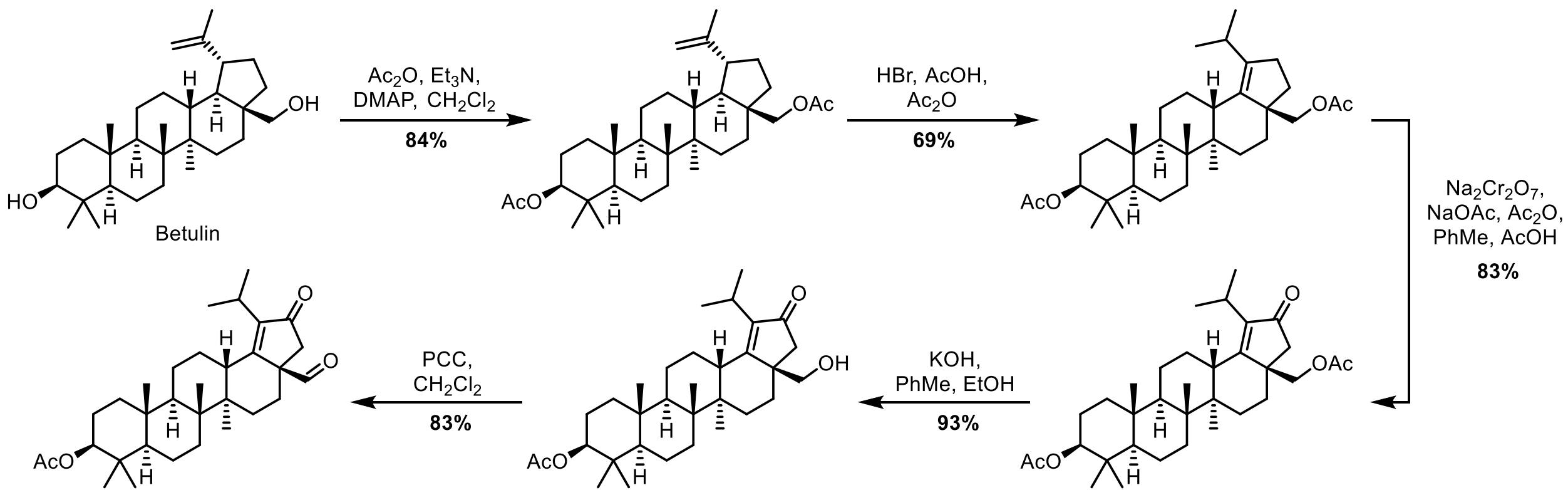


Org. Process Res. Dev. **2022**, 26, 601

Hartwig borylation guide: J. Am. Chem. Soc. **2014**, 136, 4287

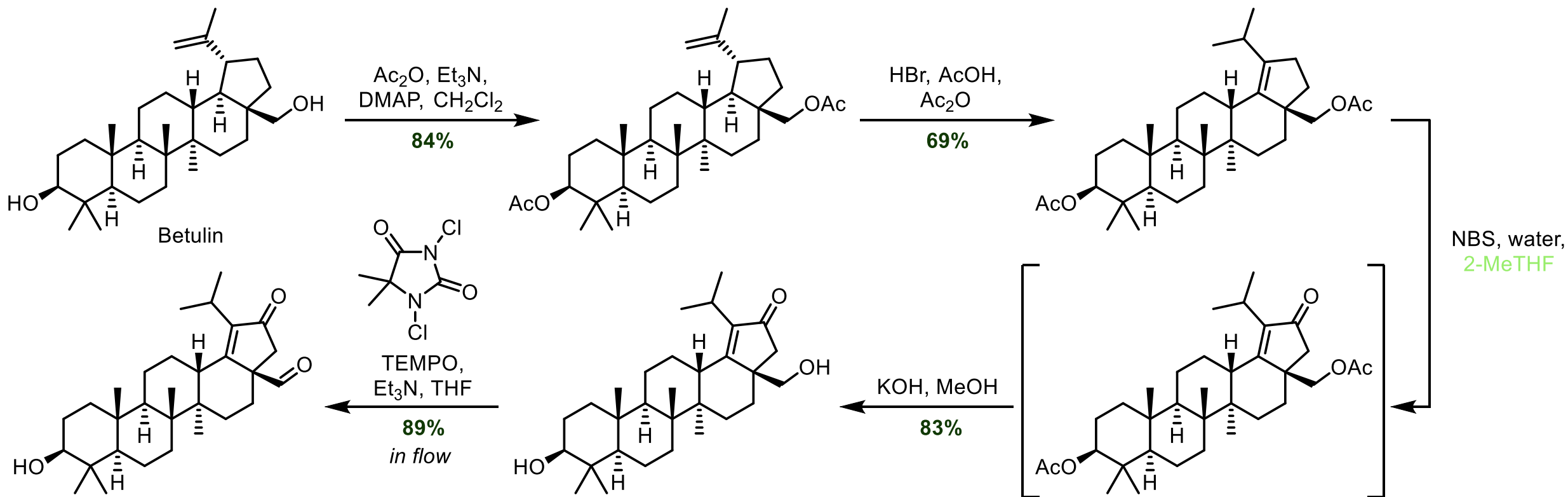
Real world application: GSK2838232

Discovery route:



Real world application: GSK2838232

Large scale route:



Elimination of two Cr(VI) steps
Selective primary alcohol oxidation allows better step efficiency
Telescoping further increases step efficiency