Reaction Development: A Student's Checklist

- Take Stock
- Kinetics & Thermodynamics
- Mechanism
- Optimisation
- Catalysis
- Scope
- Applications

Take Stock

Have you made the desired compound?
- Have you obtained a range of characterisation data?
- Have you obtained the X-ray crystal structure?

Have you determined where all the atoms go?
- Can you write out a balanced equation?
- Where do all of the atoms in the product come from?
- What are the byproducts and side-products?
- Is there involvement from solvent, water or oxygen?

Are all reaction conditions necessary?
- How long does it take to reach full conversion?
- Are you operating at the lowest feasible temperature?
- What is the lowest equivalency of reagent that can be used?
- Are all reagents required to achieve product formation?

Is the reaction reproducible and robust?
- Can you reproduce the yield of the reaction?
- Can the purification conditions be reliably reproduced?
- Have you performed a sensitivity screen?

Have you found the minimal synthon and retron?
- Can the substrate or reagents be simplified?
- Can the reactivity be extended to intermolecular systems?
- Is the minimal retron found in natural products?

Kinetics & Thermodynamics

Can the rate law be determined?
- What reagents are involved in the rate-determining step?
- Can you calculate the rate constant?

Can you increase the rate?
- What is the effect on the rate of increasing temperature?
- Can you harness the Thorpe-Ingold effect?

Have you established the steric sensitivity?
- What are the steric limits of the reaction?
- Can you favour reactivity using intramolecularisation?

Have you identified the reaction driving force?
- What is the thermodynamic driving force?
- Can you estimate the value of ΔH and ΔS?
- Can you run the reaction at a higher pressure?
- Can you destabilise the starting materials?

Can you bias an equilibrium?
- Can you stabilise an intermediate at equilibrium?
- Can you evolve or precipitate the product or byproduct?

Is the intended product stable?

Mechanism

Do you have evidence for the mechanism?
- Can you measure kinetic isotope effects?
- Can you monitor the reaction with in situ spectroscopy?
- Are the bond forming steps concerted or stepwise?
- Can you conceive of a radical clock experiment?
- Can you measure the quantum yield of the reaction?
- Can you estimate the frontier molecular orbitals?
- Can you probe the reaction with UV-vis spectroscopy?
- Can you calculate the triplet energy of the substrates?
- Can you perform a Hammett analysis?
- Can you analyse the kinetic profile of the reaction?
- Can you measure redox potentials with cyclic voltammetry?
- Can you perform a Stern-Volmer quenching study?

Have the intermediates be identified?
- Can an intermediate be isolated or detected by spectroscopy?
- Can you intercept an intermediate using a trapping agent?

Can the reaction pathway be computed?
- Are the proposed transition state energies feasible?
- Can you rationalise selectivity using computation?

Is there a better route to the active species?
- Can the route to the active species be simplified?
- How does the method compare to similar transformations?

Optimisation

Has the yield been fully maximised?

Have you optimised the...
- Reaction time
- Temperature
- Stoichiometry
- Concentration
- Catalyst loading
- Solvent
- Mixing rate
- Reagent addition rate
- Pressure
- Solution pH

Have you considered...
- Reagent addition order
- Additives
- Reaction atmosphere
- Wavelength of light
- Light intensity
- Number of light sources
- Waste production
- Electrode material
- Current density
- Inter-electrode distance
- Residence time
- Flow rate
- Sustainability
- Reaction cost

Can reaction selectivity be achieved?
- Can chemo-/regio/or diastereoselectivity be achieved?
- Can the reaction be rendered enantioselective?
- Can the conditions access divergent reactivity?

Can the protocol be more efficient?
- Can you compare PMI and E-Factor to similar syntheses?
- Can the reaction be run in air or at ambient temperature?
- Can any step of the procedure be automated?
- Can the reaction be performed with less toxic reagents?

Catalysis

Can the reaction be catalysed?
- Can the reaction be catalysed by an enzyme?
- Can a reagent be turned over using a redox agent?
- Can the reaction be catalysed in the excited state?
- Have you confirmed the existence of a catalytic cycle?

Have you identified the catalytically active species?
- Can you detect the active species using spectroscopy?
- Can you find a relationship between pre and active catalysts?
- Are nanoparticles responsible for catalytic activity?
- Can a better strategy to form the active catalyst be conceived?

Can you catalyse the reaction enantioselectively?
- Can the reaction be used for desymmeterisation?
- Can an organocatalyst be employed?
- Is there a relationship between sterics and enantioselectivity?
- Have you identified the enantiodetermining step?

Is the catalyst turnover optimal?
- Can Turnover Number (TON) be calculated?
- Can catalyst deactivation pathways be suppressed?
- Can you reduced the use of precious metals?
- Is there a relationship between ligand identity and TON?

Scope

Is the substrate scope diverse?
- Have you explored a wide range of substrates?
- Have you attempted to eliminate selection and reporting bias?
- Can complex substrates be tolerated?
- Have a variety of steric environments been explored?
- Have you reported the 'negative' results?
- Can a standardised scope selection model be used?

Have you shown functional group tolerance?
- Can the reaction tolerate nucleophiles or electrophiles?
- Can you tolerate substrates that can be oxidised or reduced?
- Can you tolerate Lewis acids and Lewis bases?
- Can you tolerate fragments found frequently in drugs?
- Can the reaction be performed in a range of solvents?
- Have you employed a robustness screen?

Have you defined the parameters of reactivity?
- Can you define a pKa range in which reactivity is observed?
- Is there a steric limit to reactivity?
- Can you define a redox window for the starting materials?
- Have you considered the mechanistic implications of the scope?
- Can the Mayr scale be used to define the limits of electrophilicity, nucleophilicity and radical philicity?

Applications

Can it be used to access target compounds?
- Can the reaction be applied to natural product synthesis?
- Can the reaction be used to access motifs found in drugs?
- Can you access building blocks for functional materials?

Can it be used for late-stage transformations?
- Can the reaction tolerate dense functionality?
- Can the reaction be used for skeletal editing?

Can the products be derivatised?
- Do you form a linchpin group that can be further reacted?
- Can functional group interconversion be demonstrated?
- Can the reaction be used as part of a cascade?

Can it be used for bioconjugation?
- Are the conditions suitably mild for in vivo functionalisation?
- Can the reaction target a native amino acid side chain?
- Can the reaction be run in a cell or in an organism?
- Can click-type reactivity between biomolecules be achieved?

Can it be used in materials chemistry?
- Can the reaction be used to depolymerise plastics?
- Can the functionalisation of a plastic be achieved?

Note: Given the significant number of variables associated with individual synthetic methodology studies, all of the themes displayed above are not directly applicable to every new reaction or are a necessity for publication.