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Flexible Response Lab Automation in Medicinal Chemistry

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Role and Goals

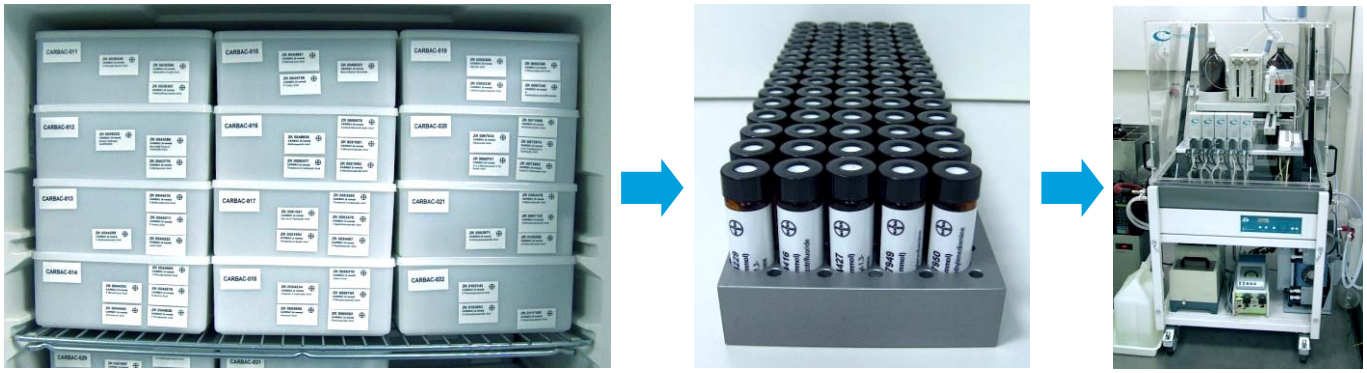
- Current screening library size of 2.5 million+ compounds reduces need for intense library build-up activities
- Strong focus on project support, mainly Hit-to-Lead but also Lead Optimization phase

General Approach

- Balance between flexibility (effort, scope) and standardization (efficiency, limitation)
- Complementary automated synthesizer systems enable preparation of a large diversity of chemotypes
- Automated HPLC-MS platform can adapt to a variety of purification problems
- Highly automated robotic reformatting system supports a standardized compound submission scheme

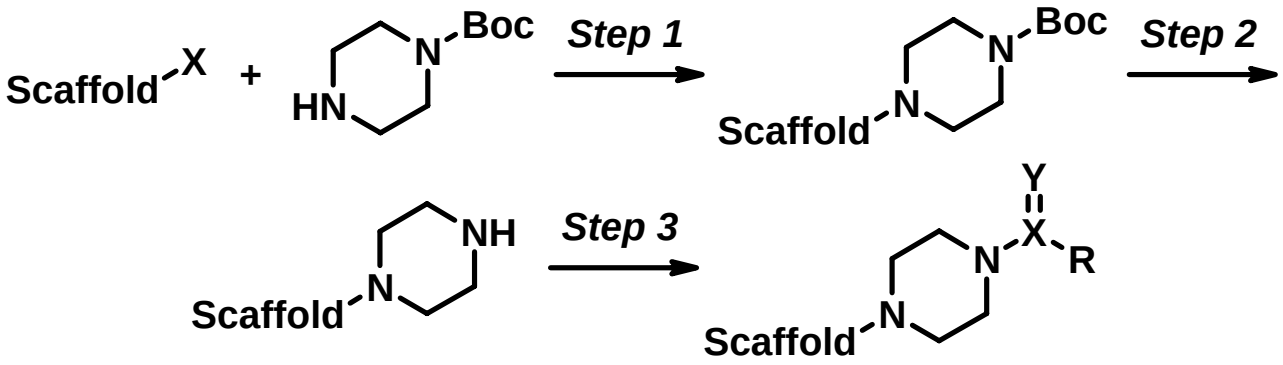
Building Block Collection

- **Comprehensive Inventory**
  Significant time savings, all major compound classes, selection based on SAR considerations and MedChem know-how
- **Proprietary Building Blocks**
  Strengthening of patent and SAR position by adding examples not synthesized otherwise, driven by custom synthesis programs
- **Prepacked Building Block Sets**
  Ready-to-use, weighed into standardized vials, multiple copies available, quick assembly of selected sets

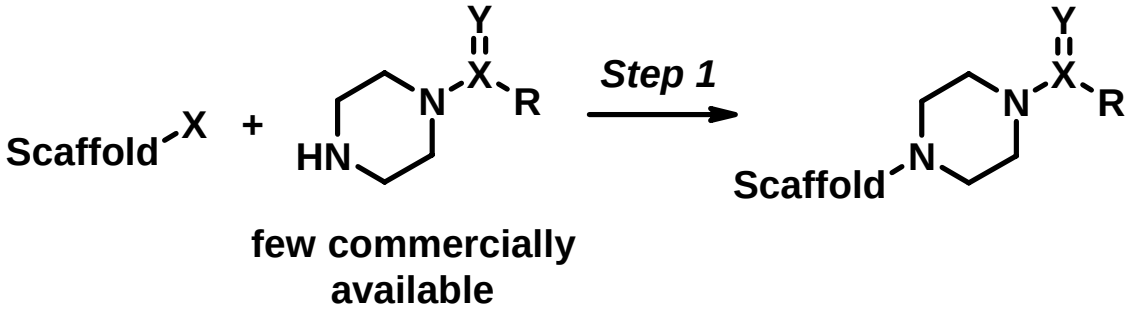


Building Block Library Concept

- Longer synthetic pathway when using commercially available building blocks only (e.g. coupling, deprotection, acylation)



- Shorter synthetic pathway when using custom building blocks (direct coupling to scaffold)

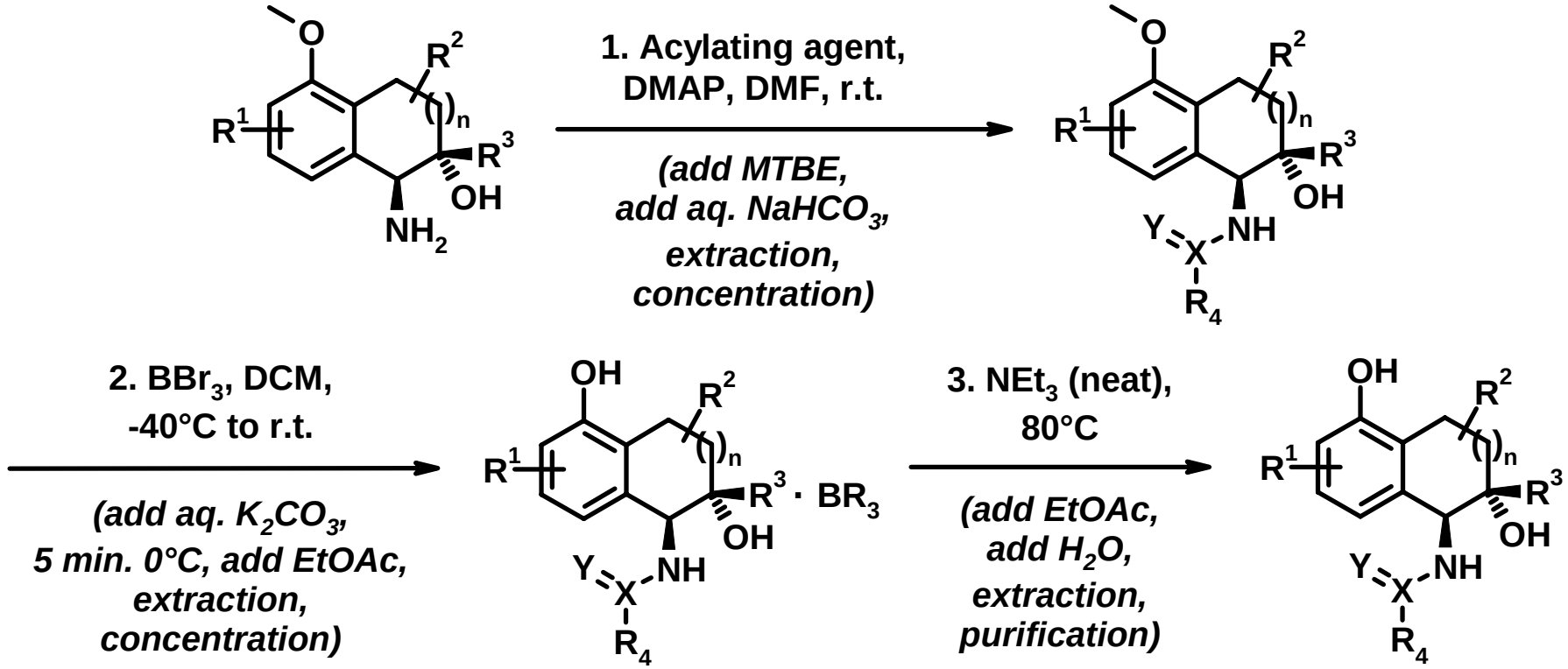


Automated Synthesis

- **Flexibility**
  Required to adress a large variety of chemotypes, no artificial limitation to 'simple' chemistry
- **Solution-Phase Synthesis**
  Quick adaption of procedures, aqueous work-up and multistep synthesis, *Chemspeed* platform (three ASWs, two Accelerators, also used as liquid handlers for simple MTP-based syntheses)
- **Microwave Synthesis**
  Difficult thermal reactions, *CEM* platform (Explorer 96 monomode, Mars multimode)
- **Solid-Phase Synthesis**
  Multiple R-groups or very long sequences, *Myriad* platform (Core System, two Discoverers)

Chemistry Scope

- Acylation followed by OMe deprotection and BR_3 adduct removal (three aqueous work-ups, two concentrations, low temperature)



'One-Minute' Synthesis Programming

- Ready-to-use synthesizer setup enables the use of pre-programmed procedures to reduce effort
- Macro approach introduced with the Chemspeed AutoSuite software allows for simplied programming using variables
- Parameters including setup, reaction and work-up time, temperature, solvents can quickly be specified to modify the procedure

Variable	Value	Unit
Vortex_speed	550	rpm
Preparation_temperature	0	°C
Preparation_time	10	min
Incubation_temperature	20	°C
Incubation_time	12	h
BulkReag1_volume	0	ml
BulkReag2_volume	0.2	ml
BulkReag3_volume	0	ml
DiversityReag1_volume	0.44	ml

Variable	Value	Unit
Extraction_speed	1000	rpm
Extraction_time	1	min
Wait_time	20	min
UseEvaporation	0	
Discard_volume	9	ml
Vacuum_start	400	mbar
UseDistribution	1	
Distribution_volume	5	ml
UseExtraction	0	

Low-Solubility Reagent Handling

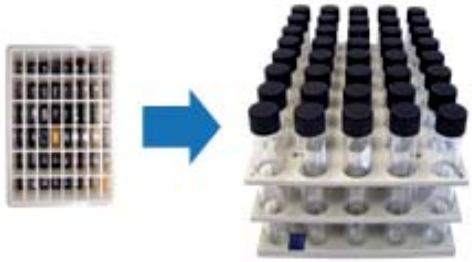
- Frequently reagents of interest show limited solubility in reaction solvents at the concentrations required
- Utilization of solid dosing is complicated, unavailable on the ASW platform and reduces overall synthesis efficiency
- Suspensions can be used instead, if adequate particle distribution can be achieved by shaking or stirring
- An 80-well stirrer constructed by the BSP lab engineering group is used to solve this issue for diversity reagents

Microwave Synthesis Support

- For maximum efficiency, preferably the same upstream (synthesis assembly) and downstream (purification) workflows are employed
- This should also include aqueous work-up and unattended follow-up synthesis steps (as in heat-driven synthesis)
- The ASW platform is used to support the full microwave synthesis workflow on an external CEM Explorer 96 system

Purification and Analysis

- **Flexibility**
  Separation of complex mixtures required, *Corona* detector for broad applicability
- **Pre-analysis**
  Standard conditions (*Waters* Acquity UPLC-MS system), determination of initial purity and retention time to select gradient
- **Purification**
  Individualized gradient (*Waters* 4-channel parallel HPLC-MUX-MS, two systems), pooling of fractions into vials for reformatting (*Hamilton* Microlab 4200 and SWAP 420)
- **Re-analysis**
  After reformatting, determination of molpeak, purity and retention time for documentation



Summary

- Quick adaptation of lab procedures is required for optimal Hit-to-Lead and Lead Optimization project support
- A reasonable balance between flexibility and standardization avoiding artificial limitation helps to achieve this goal
- A comprehensive reagent collection utilizing pre-weighed ready-to-use and proprietary building blocks reduces response times
- Using this approach turnaround times of 2-4 weeks can routinely be achieved for prioritized libraries, resulting in significant project impact

Acknowledgement

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