

Astex Pharmaceuticals

Enabling synthesis in FBDD

Dial-a-Molecule Annual Meeting 2018

Rachel Grainger



- **Fragments:**

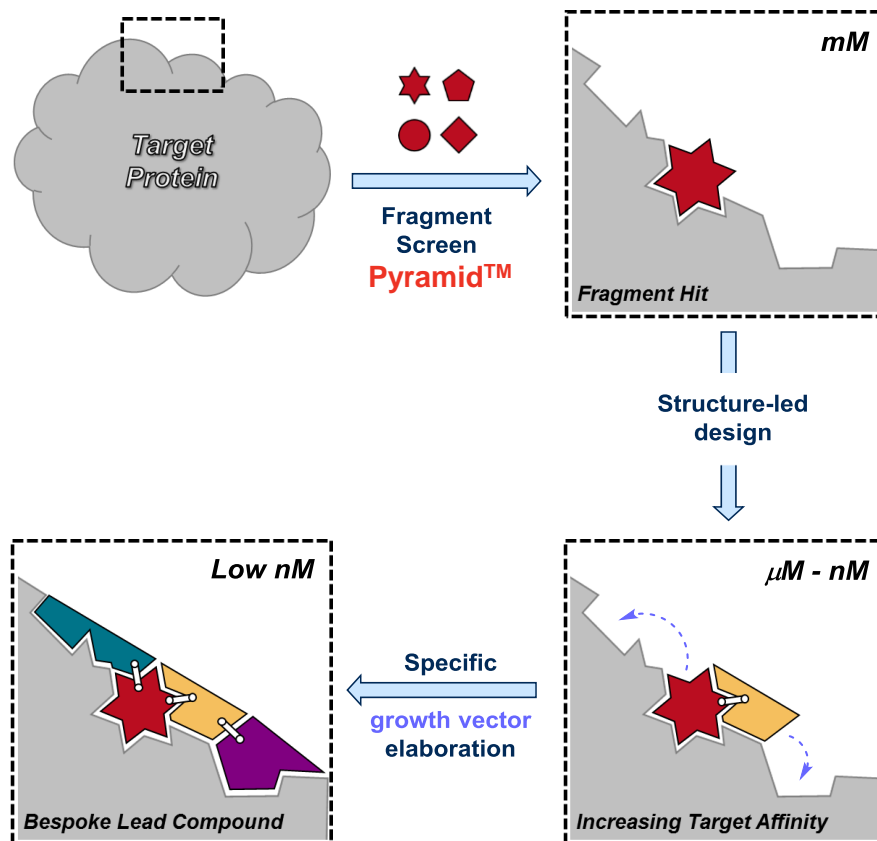
- **Low MW, polar molecules** are used to identify binding pockets on a target protein

- **Structure-led design:**

- Increased target affinity is achieved by designing chemical probes to interrogate protein architecture

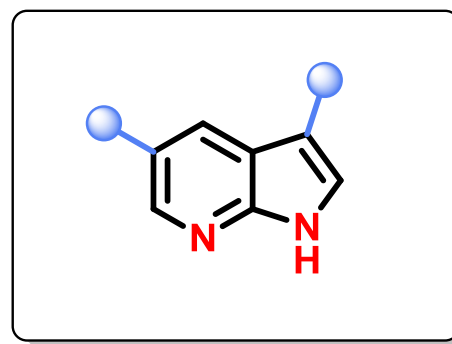
- **Specific growth vector elaboration:**

- Fragments are elaborated in **specific directions** along well-defined **vectors** to generate **bespoke** lead compounds



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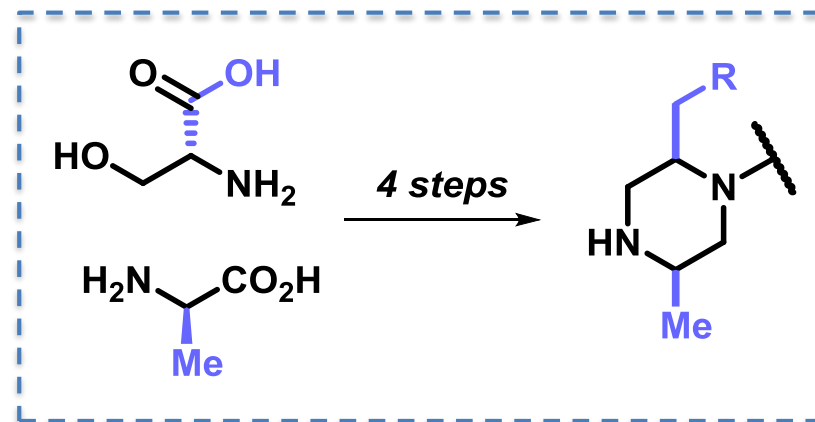
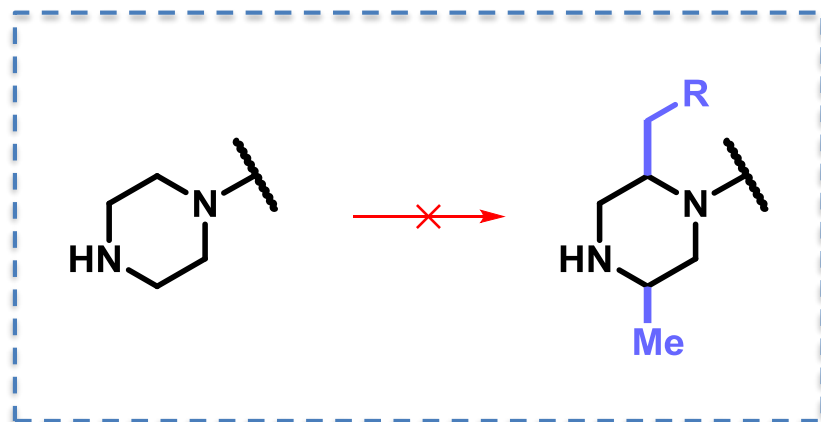
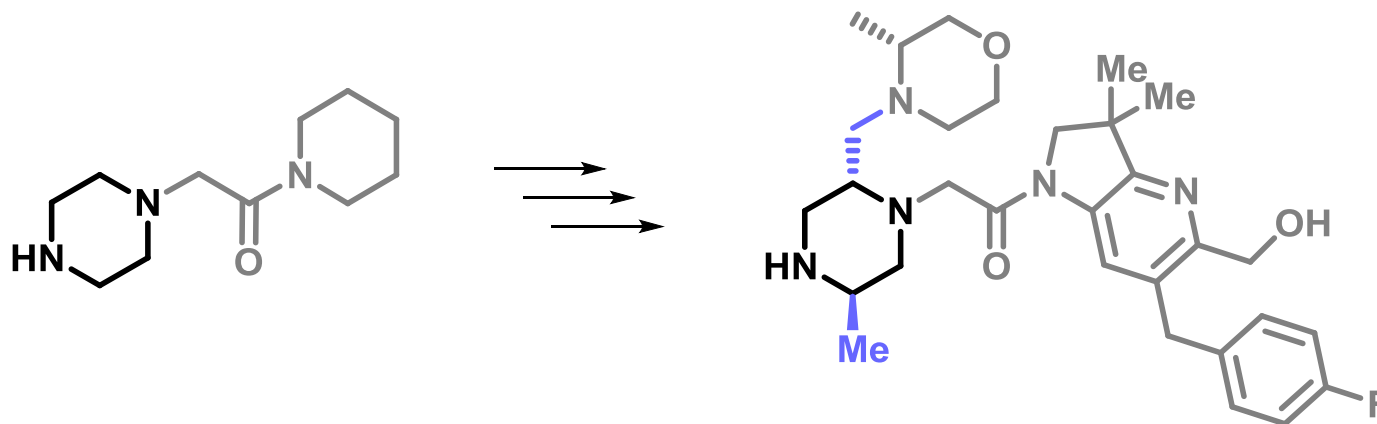
Minimal pharmacophore can present regioselectivity and reagent compatibility issues



Growth vectors can be difficult to access synthetically

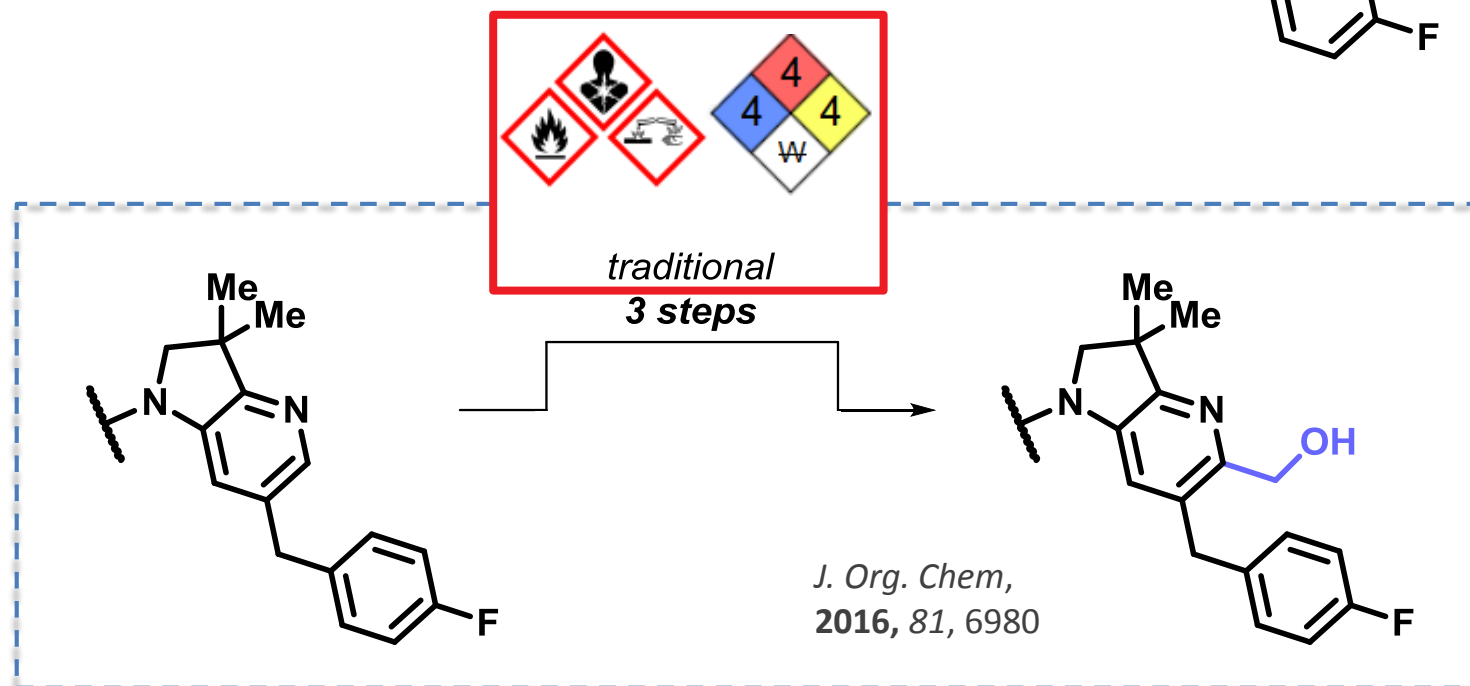
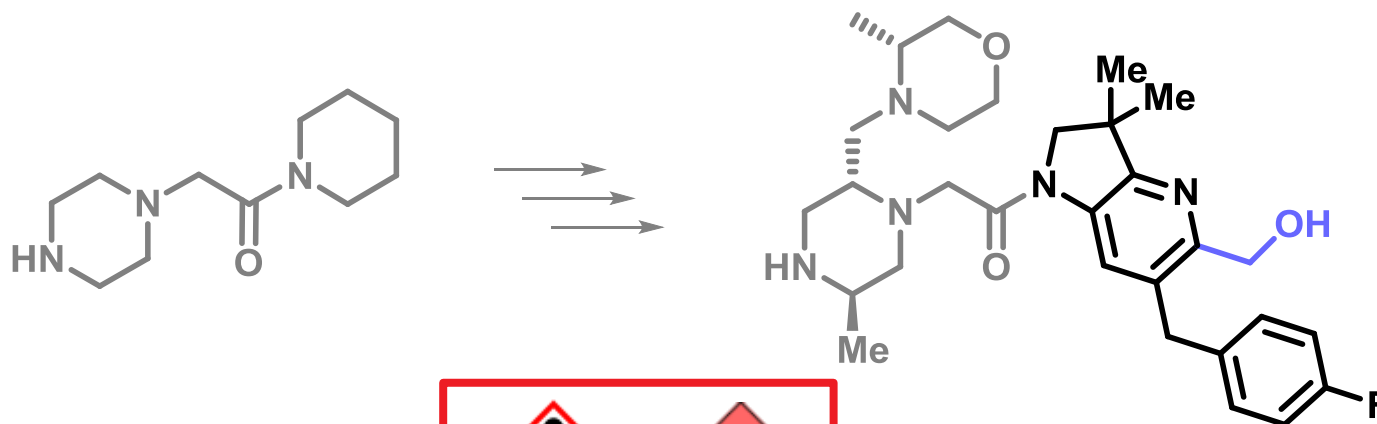
**Design rationale
vs
Synthetic tractability**

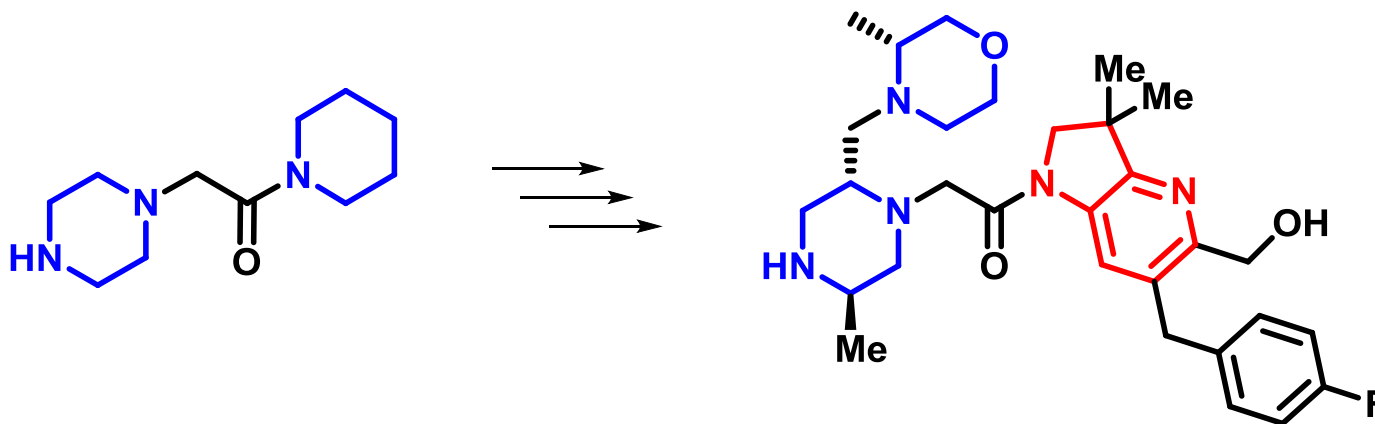
Traditional vs cutting edge synthesis techniques



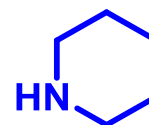
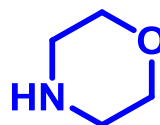
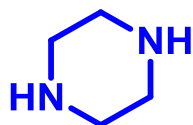
J. Med. Chem., **2015**, 58, 6574; *J. Med. Chem.*, **2017**, 60, 4611

Traditional vs cutting edge synthesis techniques

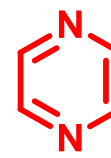
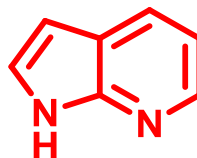
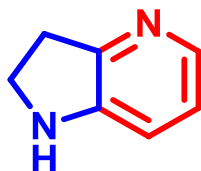


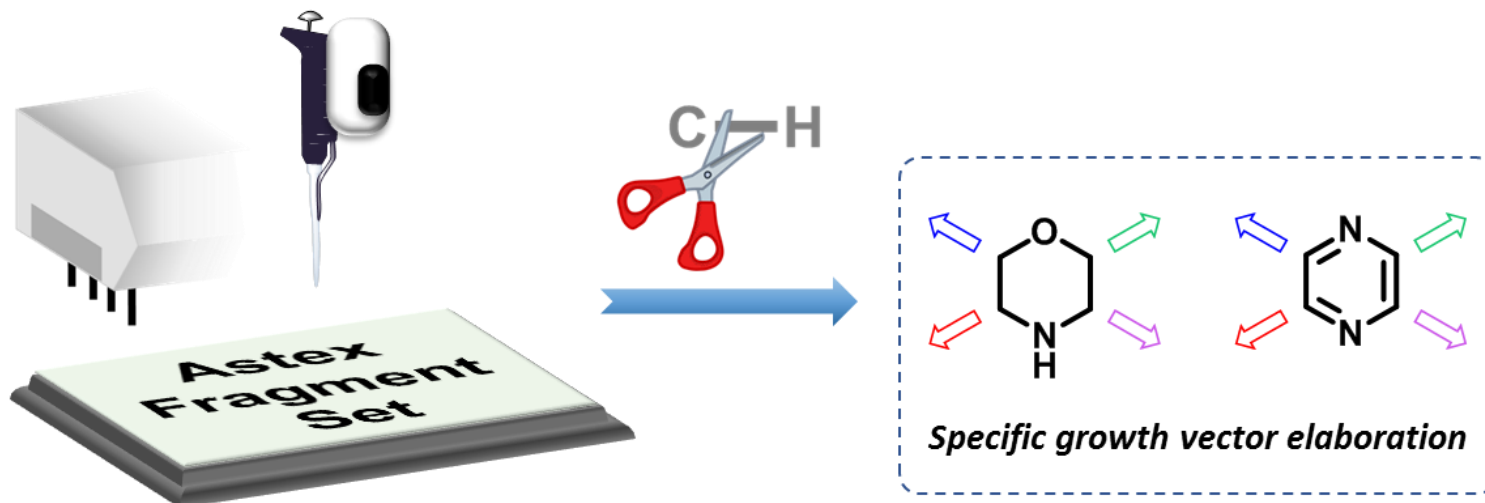


- Aliphatic heterocycles

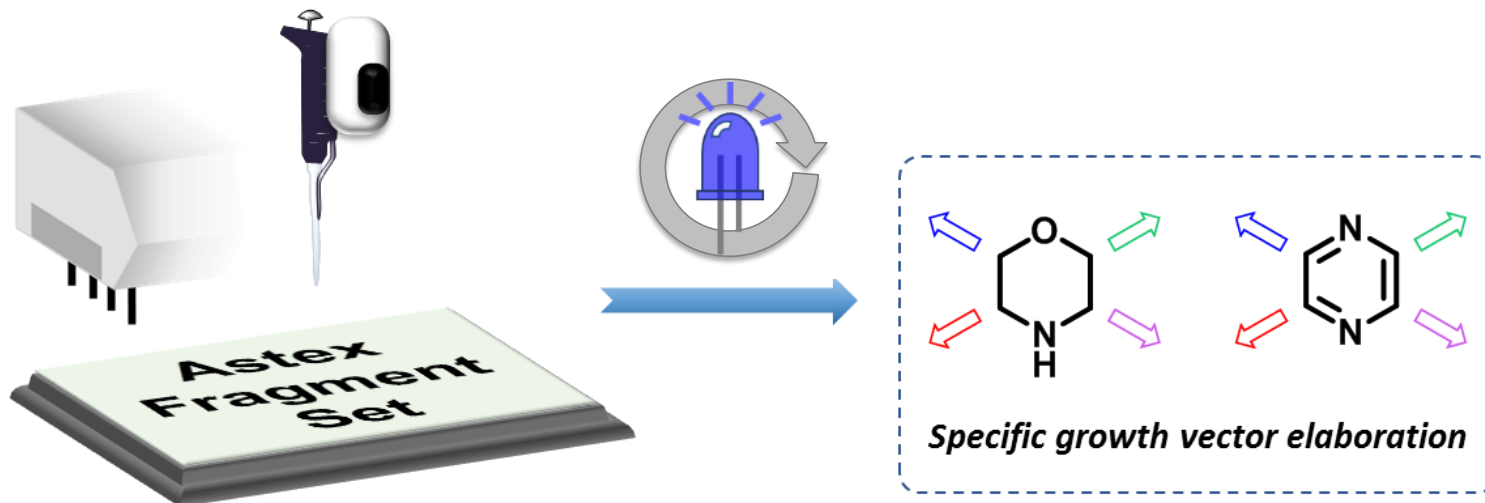


- Nitrogenous heteroarenes





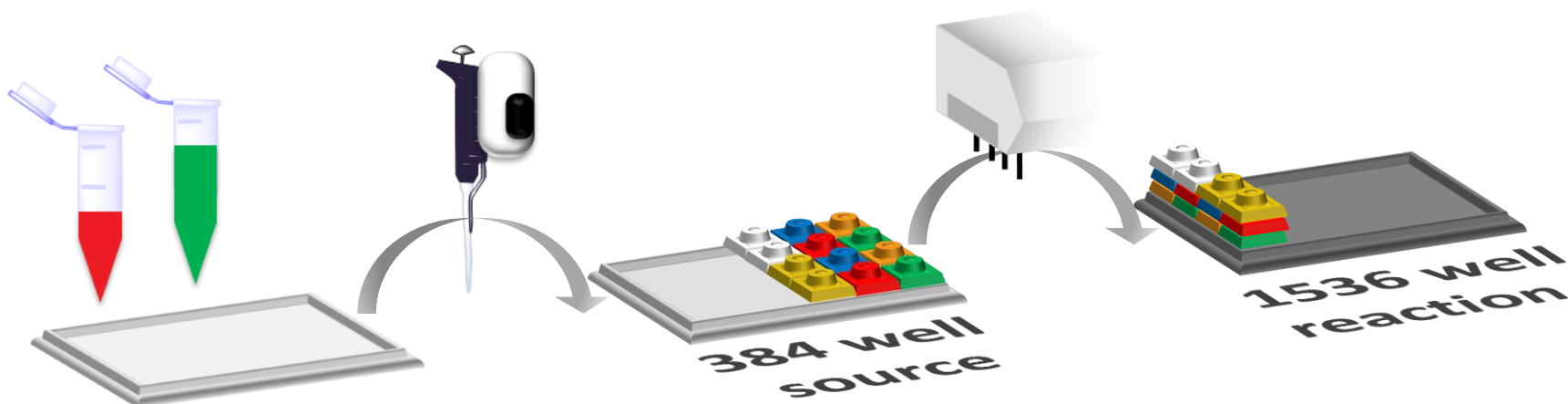
- At Astex we are exploring the use of liquid handling robots for optimisation and reaction discovery
- C-H functionalisation techniques e.g. Hydrogen Atom Transfer (HAT) catalysis can permit direct elaboration on native fragments



Single electron transfer processes:

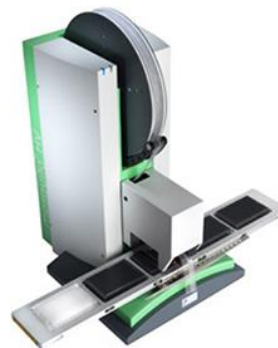
- Tolerate polar motifs – good for heterocycles!
- Performed in polar solvents – good for liquid handling robots
- Ambient temperature – good functional group tolerance
- High value couplings (e.g. sp^2 - sp^3 coupling, nitrogen-rich compounds)

Highly accessible thanks to revolution in photoredox catalysis!



Source plate dosing

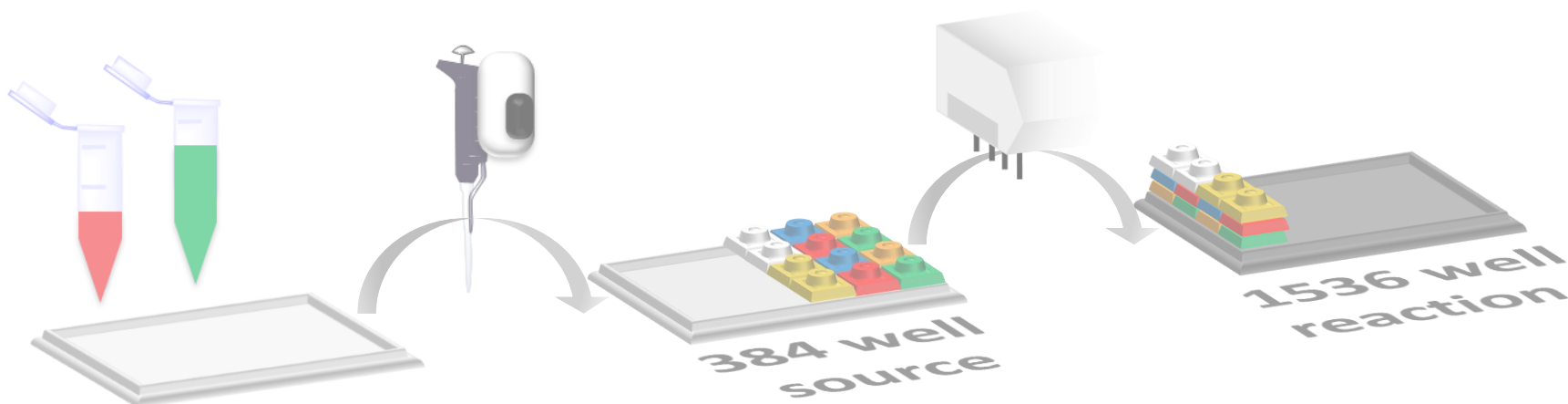
- Andrew Alliance LHR
- Flexibility of Consumables
- Free X,Y, Z movement



Reaction plate dosing

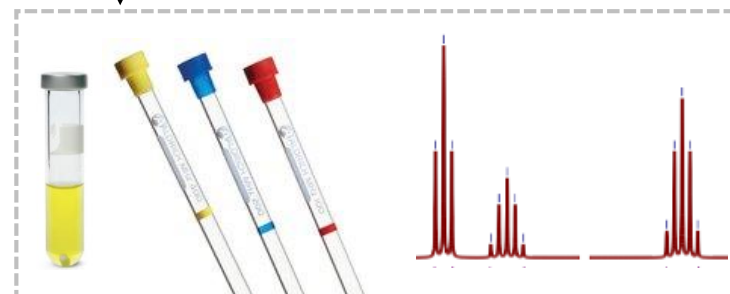
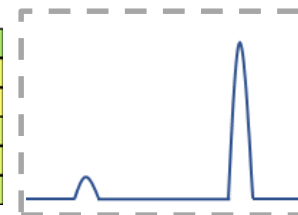
- Mosquito® LHR
- 125 nmol scale
- 2.5 μ L reaction volume
- ~40 mg substrate/plate
- 100-1000s combinations

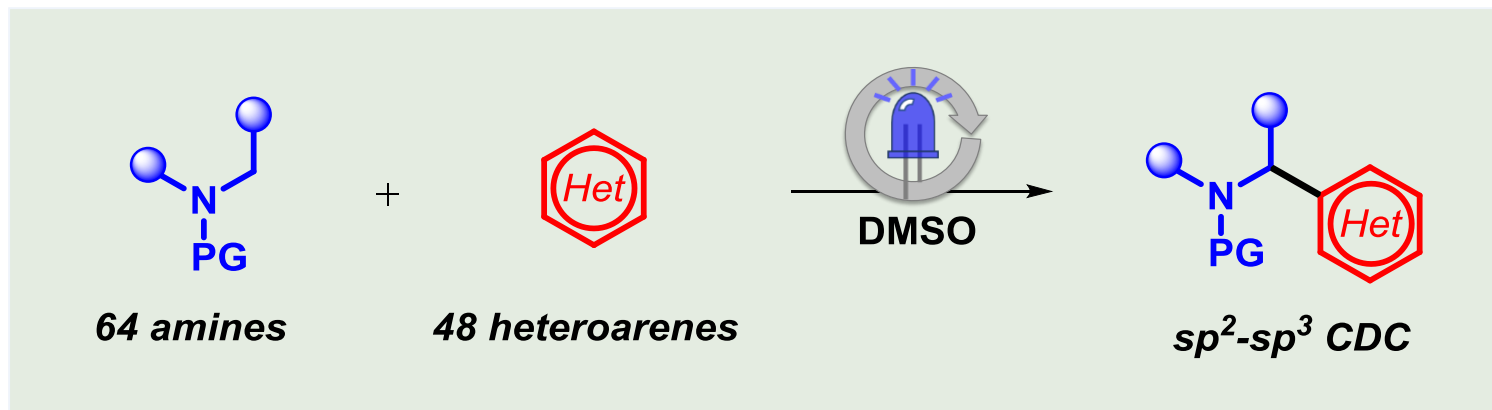
Science, 10.1126/science.aar6236 (2018); *Science*, 2015, 347, 49



Analysis

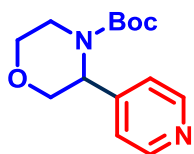
- Reformat into 384 well plate with Mosquito®
- Semi-quantitative hit analysis by LC-MS
- μmol scale up to confirm structure by NMR



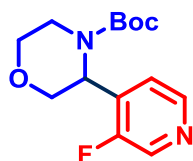


- Reaction conditions elucidated on nanogram scale in MTP
- Photoredox mediated cross-dehydrogenative coupling (CDC)
- α -amino radical Minisci-type addition to heteroarenes
- 112 substrates screened (56% hit rate)
 - explored Structure Reactivity Relationship (SRR) of methodology
- Reaction performed on gram scale in flow
 - in collaboration with Prof. Steven Ley and Dr. Fabio Lima (University of Cambridge)

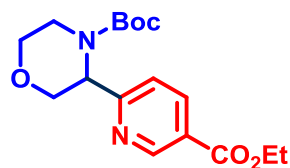
Examples of Substrate Scope



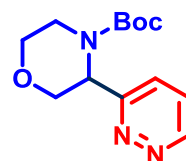
40%



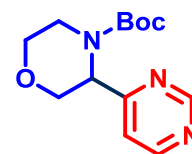
80%



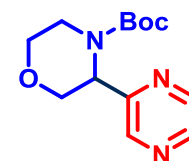
90%



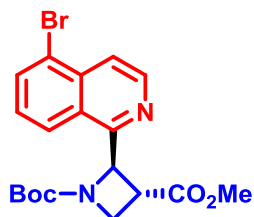
42%



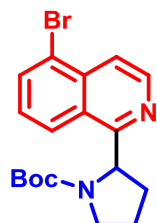
81%



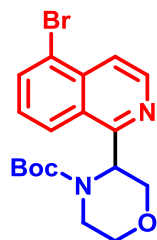
58%



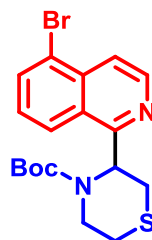
30%



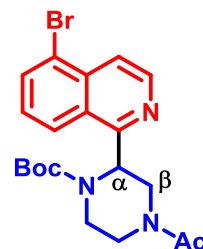
58%



83%

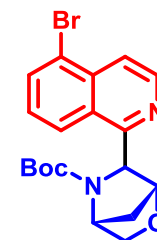


41%

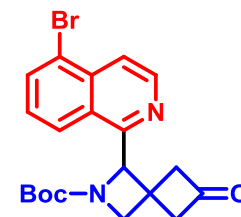


63%

(α : β) 1.5:1



69%

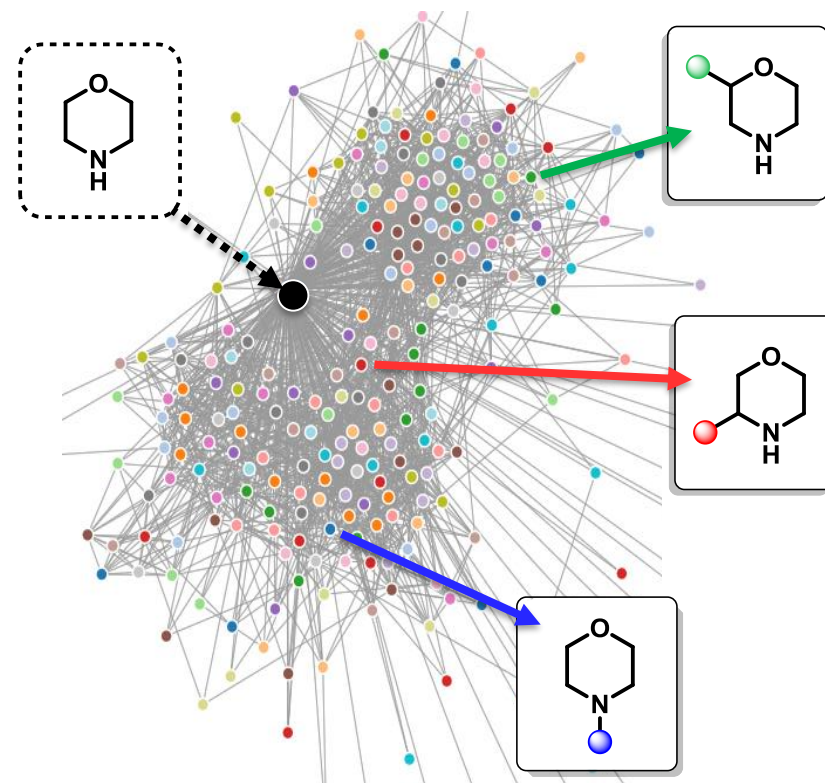


56%

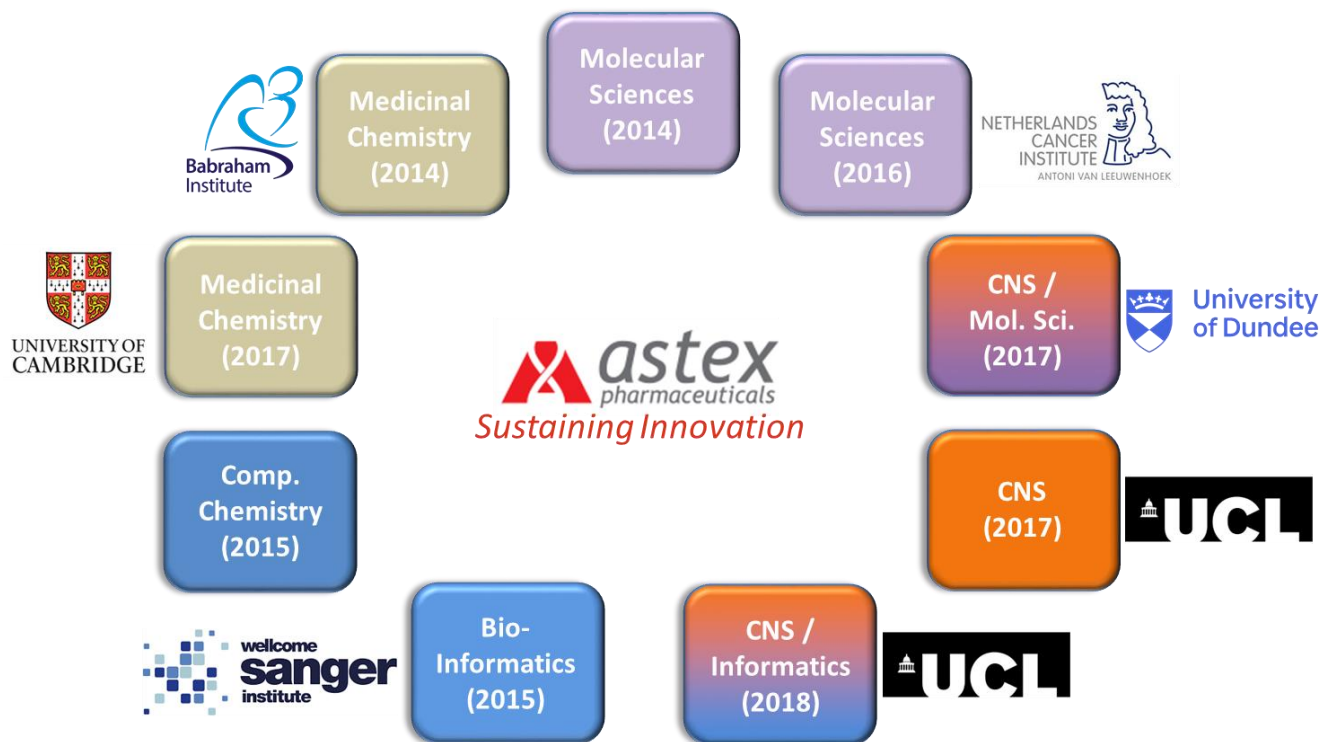
1.3g, 2h
(τ = 10min)

Manuscript in preparation

- **New synthetic methodology developed using cutting edge chemistry technologies**
 - Photoredox heteroarylation of amines
 - **HTE** screen on **ng-scale**
 - Valuable **sp²-sp³ CDC**
 - **g-scale** reaction in **flow**
- **Explore Structure Reactivity Relationships (SRR)**
 - Standardised data...reaction prediction
- **Enabling fragment growth vectors and improving fragment kinship**
- **Need to overcome analytical bottleneck!**



Sustaining Innovation Postdoc Scheme at Astex



- Propagation of Astex's scientific culture
- Exploratory research in a multi-disciplinary team
- Academia in Industry – focus on publication
- 5 postdocs/year
- 3 year contract
- Focus on internal and external collaboration

Acknowledgements



- **SI Postdoc scheme**
- **Dr Ben Cons**
- **Dr James Day**
- **Dr Tom Heightman**
- **Dr Chris Johnson**
- **Dr Nick Palmer**
- **Dr David Rees**
- **Mr Stuart Whibley**



**UNIVERSITY OF
CAMBRIDGE**

- **Prof Steven Ley**
- **Dr Fabio Lima**