

# Robust multigram protocol to access diazасpiroalkanes featuring azetidine moiety



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## Background of the project

### THE 15-YEAR-OLD EQUATION OF CLINICAL SUCCESS

Article Views | Altmetric | Citations  
58K | 87 | 3154

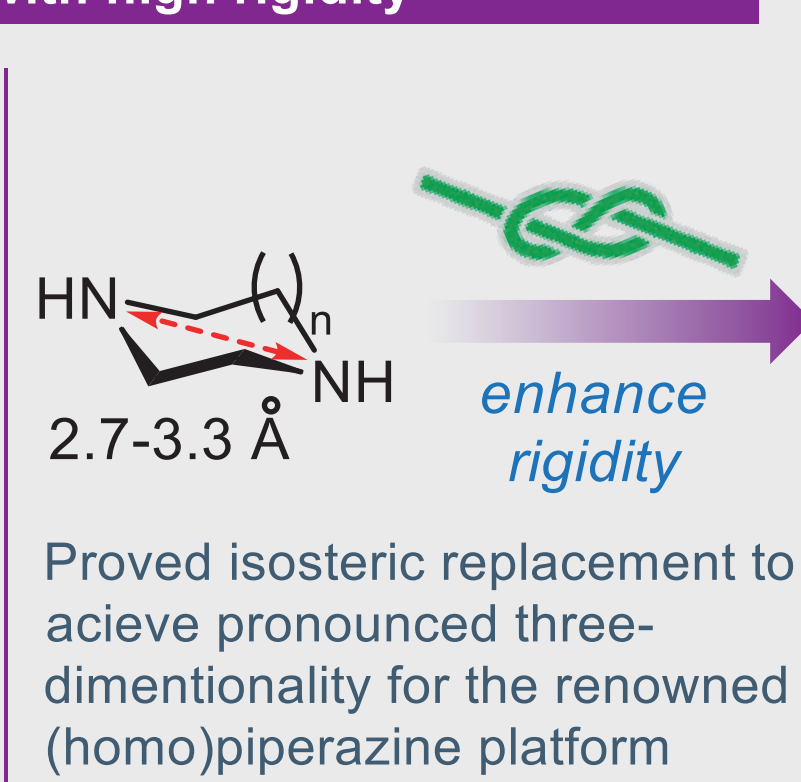
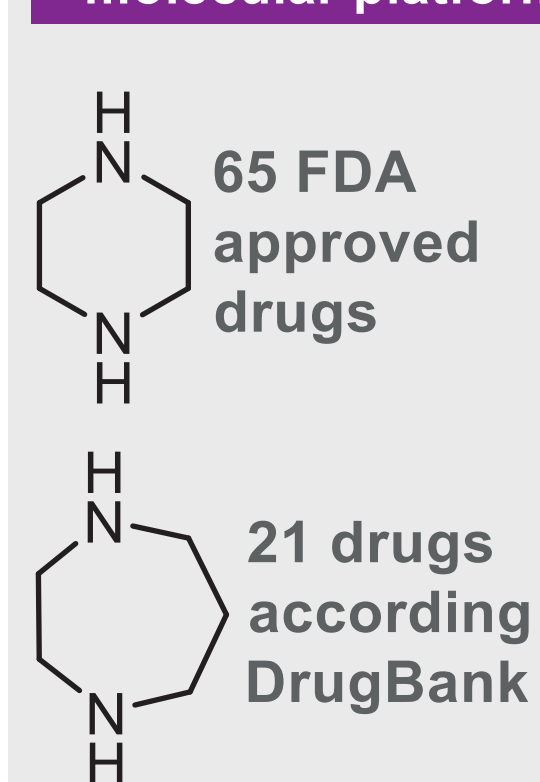
### SATURATION + THREE-DIMENSIONALITY + CONFORMATIONAL RESTRICTION

• solubility  
• complexity

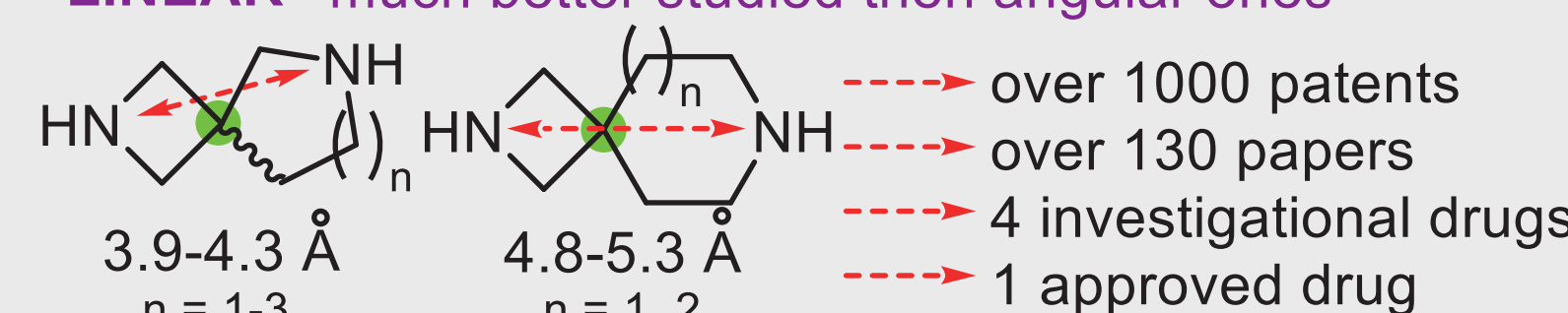
• receptor/ligand complementarity

• reducing entropy penalty  
• well-defined vectorization

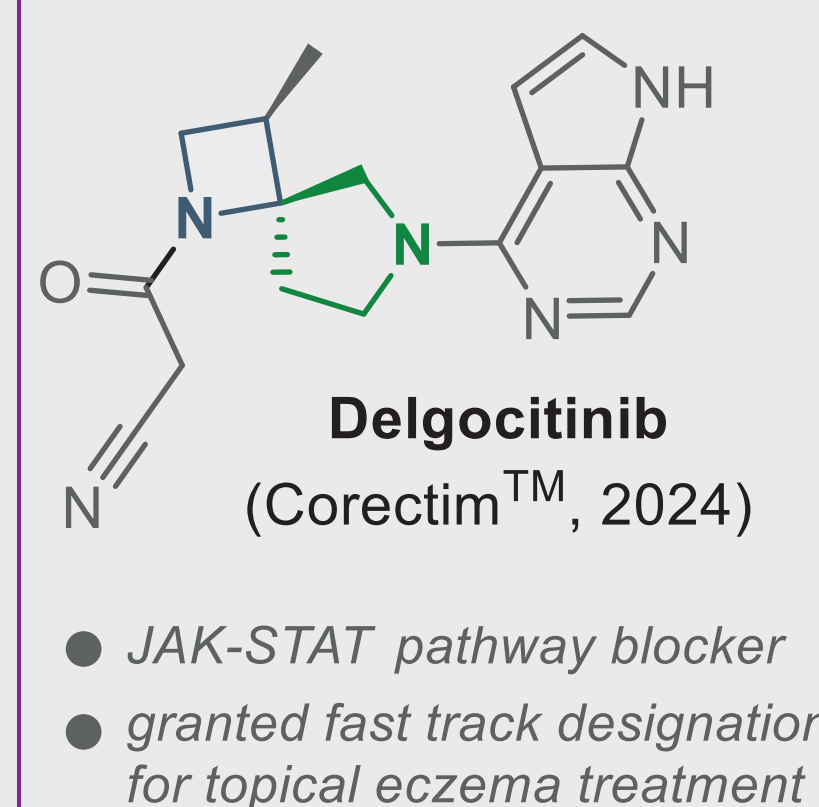
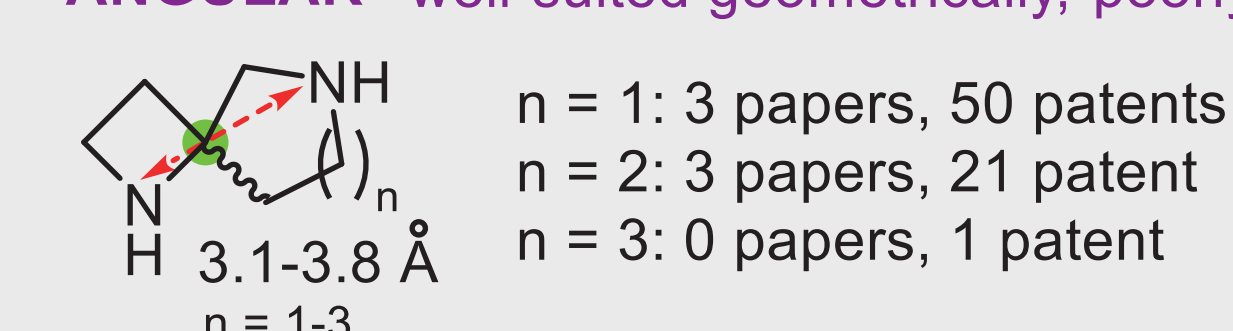
### MedChem relevant diamine molecular platforms with high rigidity



### "LINEAR" much better studied than angular ones

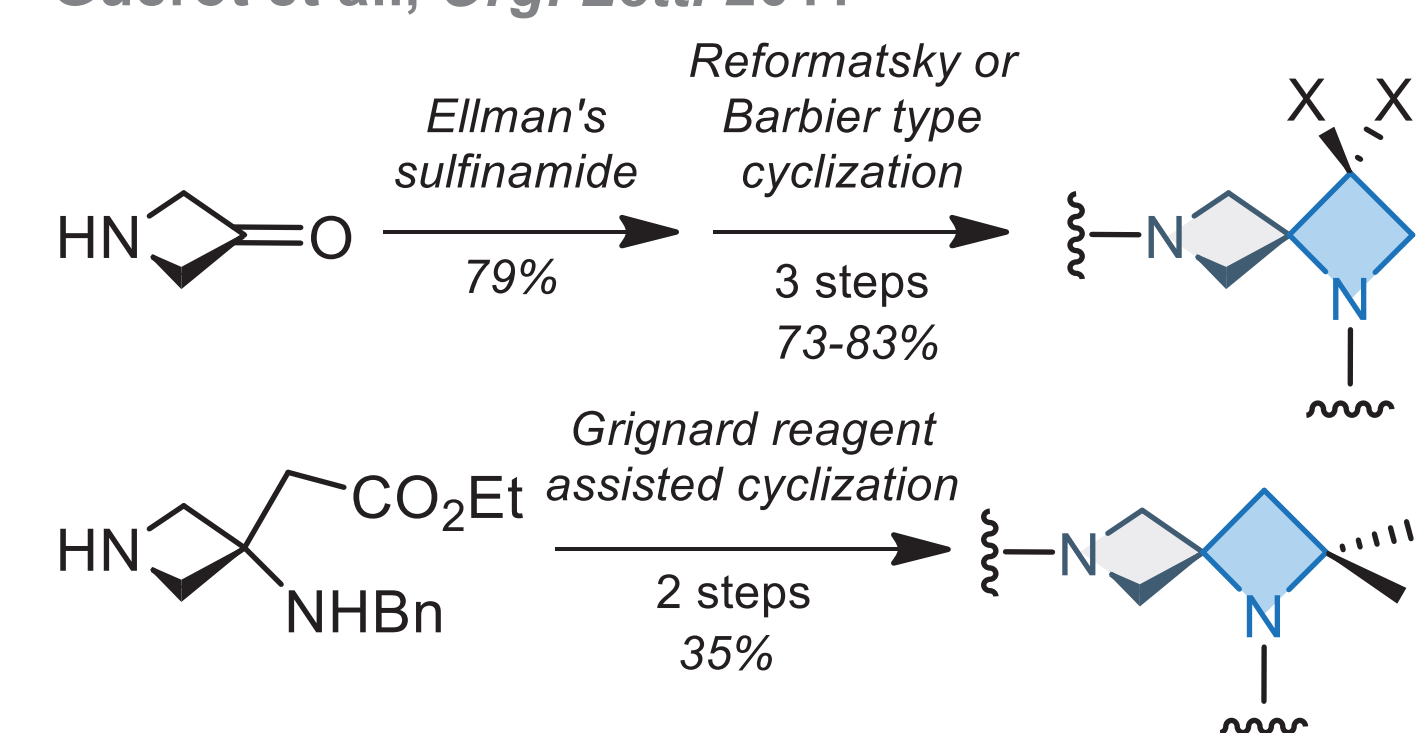


### "ANGULAR" well-suited geometrically, poorly studied

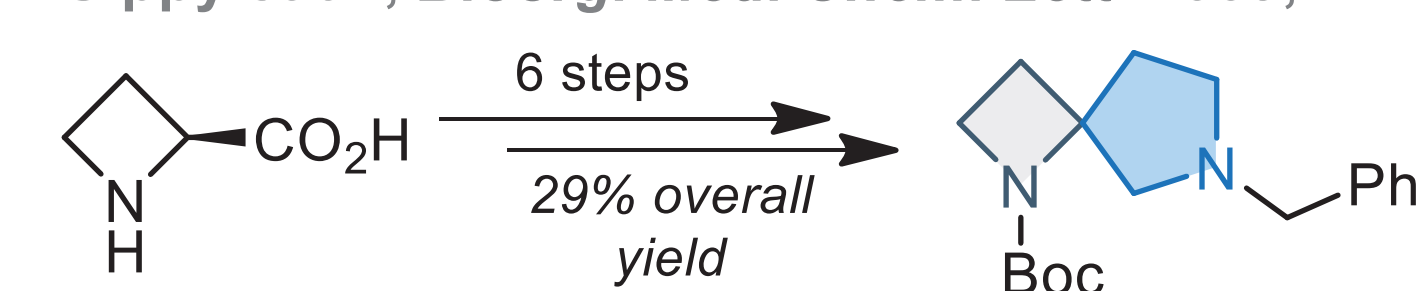


## SYNOPSIS OF EXISTING APPROACHES TO ANGULAR SPIROAZETIDINES

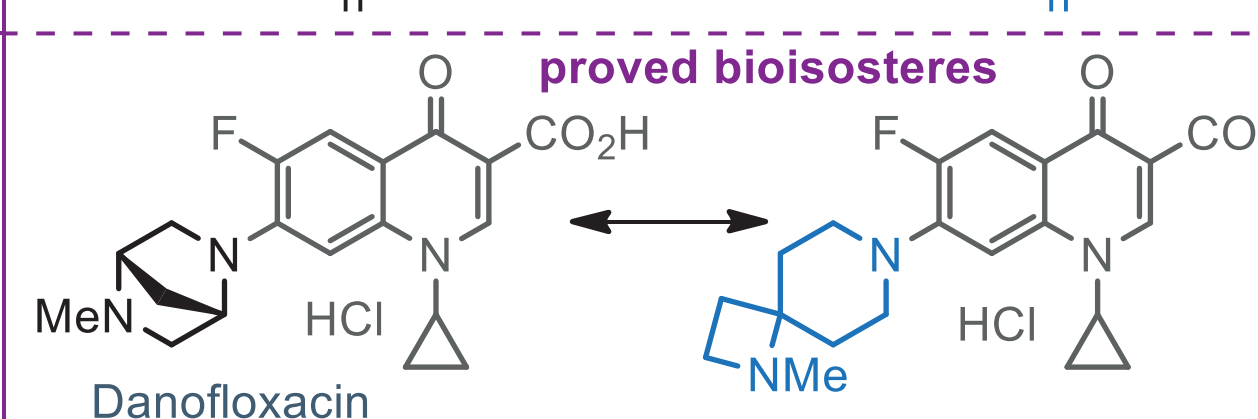
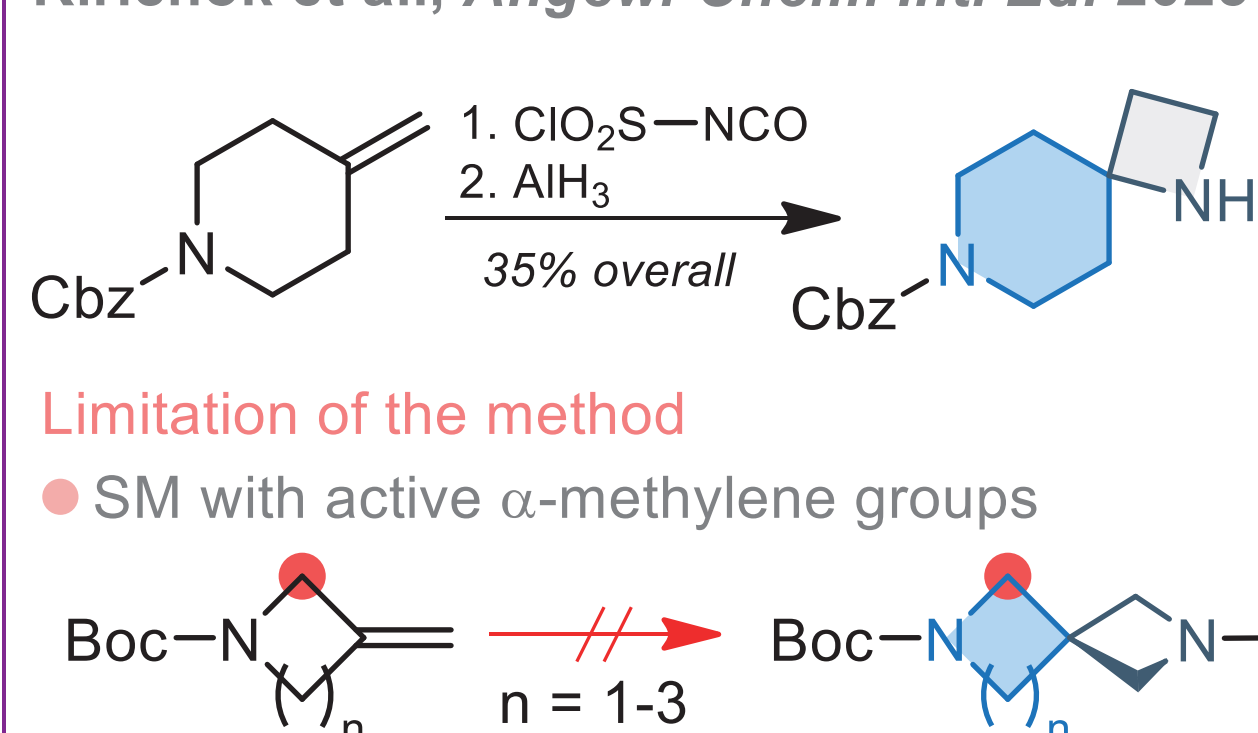
Guerot et al., *Org. Lett.* 2011



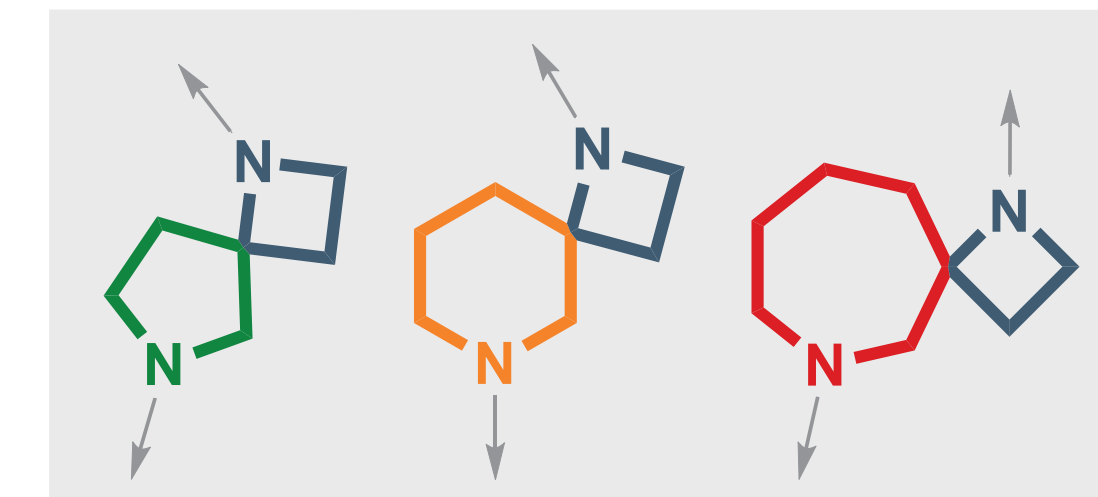
Sippy et al., *Bioorg. Med. Chem. Lett.* 2009,



Kirichok et al., *Angew. Chem. Int. Ed.* 2025



## MOLECULAR CARCASSES IN FOCUS

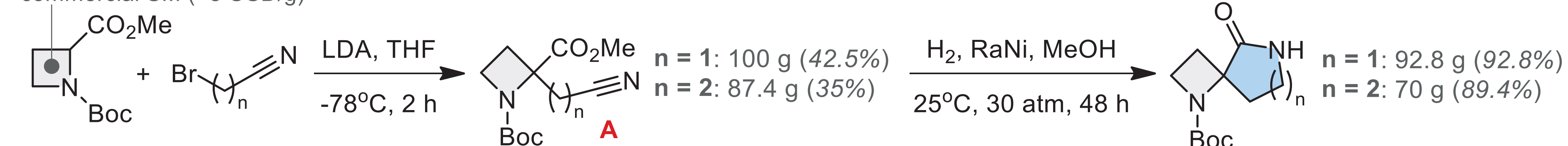


- bioisosters of venerable piperazine core
- rare or no protocols for the preparation
- can yield novel patent-free analogs with similar physicochemical properties and activity as parent compounds

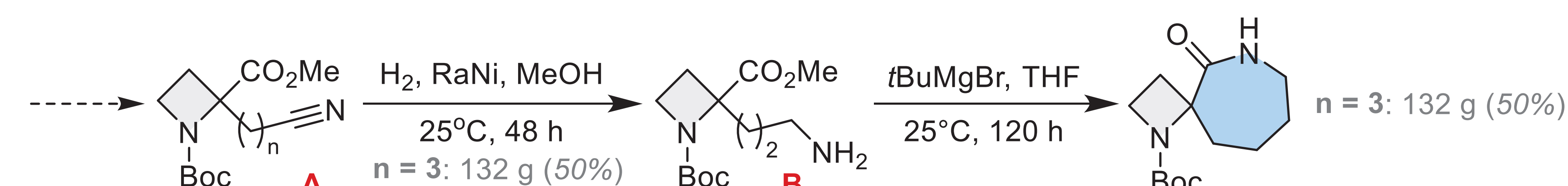
Aim: to elaborate reliable, concise & scalable protocol toward rare angular piperazine mimics

## STEP 1. Optimization of the protocol toward the key lactam

commercial SM (~8 USD/g)

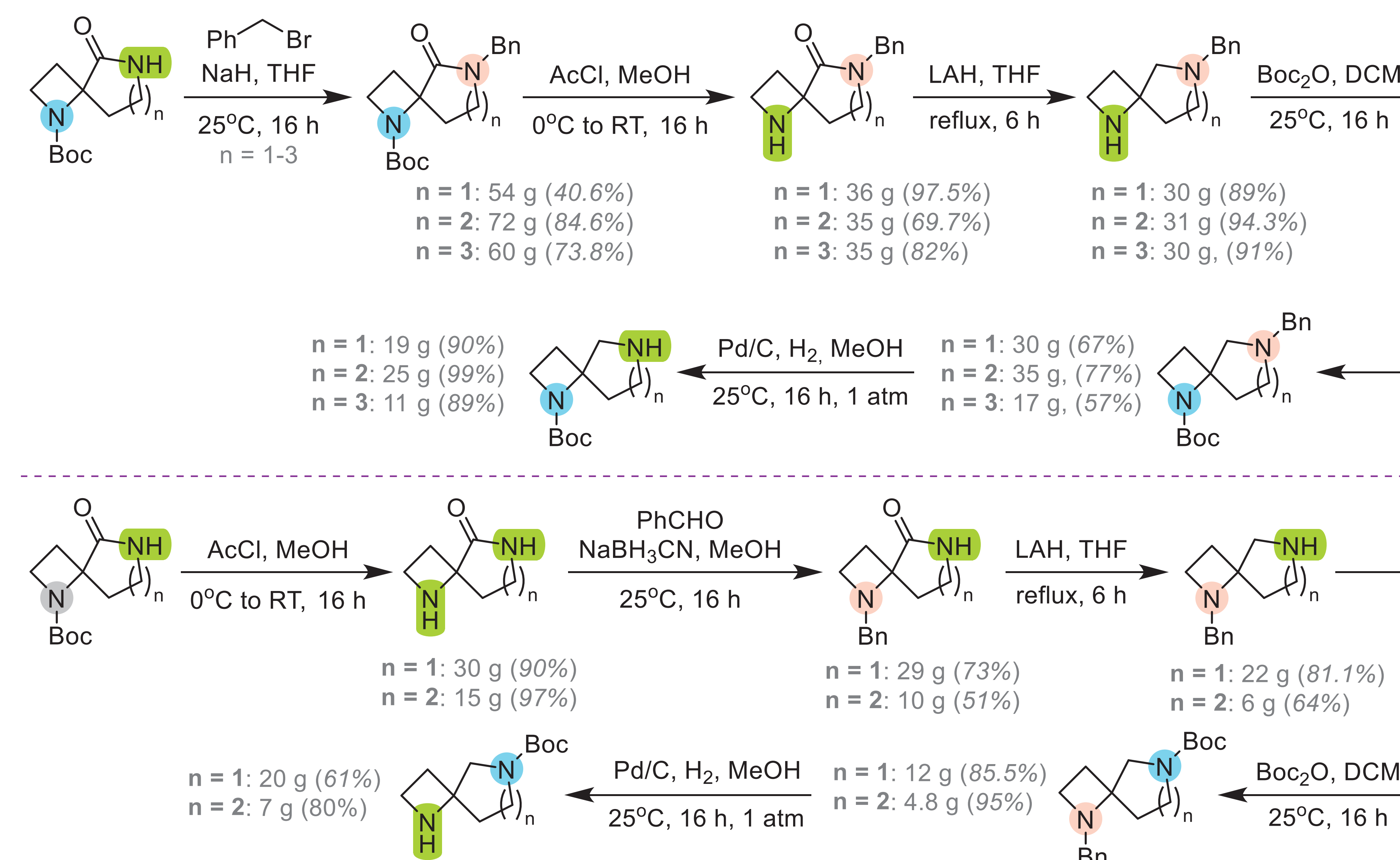


- long-chain precursor **B** to the target lactam required an additional activation to be cyclized



## STEP 2. Multigram preparation of orthogonally protected spirocyclic diazасpiroalkanes featuring azetidine moiety

- subsequent chemoselective protection provided corresponding spirocyclic building blocks on a scale of over a dozen grams
- the availability of such BBs makes further controlled functionalization on either ring nitrogen possible, hence supporting current endeavors of medicinal chemists and bringing the described chemotype of spirocyclic piperazine mimics to the forefront of drug discovery as versatile scaffolds for the development of novel therapeutic agents



## Contact

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