

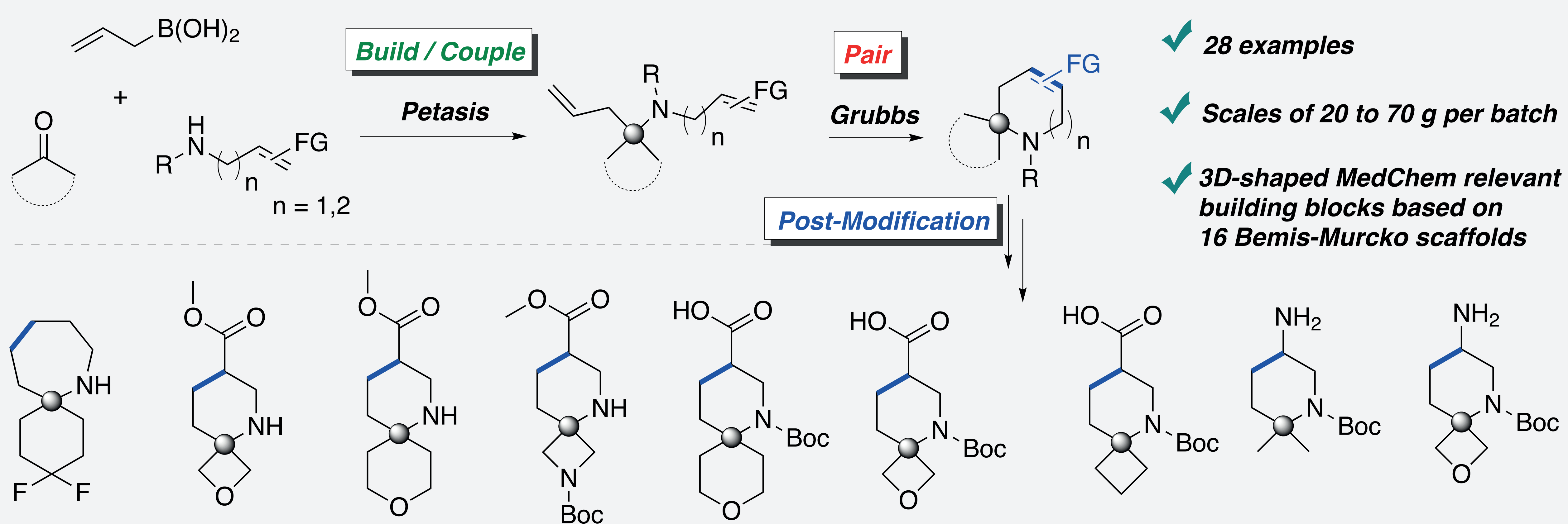
DOS-like strategy for the MedChem relevant building blocks via Petasis/Grubbs reaction

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Background and synthetic strategy

- The last two decades the Medicinal Chemistry strongly influenced on modern organic chemistry. It's clearly demonstrated by appearing of the new concepts like DOS, LOS, DTS as complimentary part to classical organic synthesis¹.
- The DOS approach was very popular at the beginning, however, it is criticized for producing "molecules with obesity" useful only for chemical genetics.
- Therefore, DOS design of "small" 3D-shaped fragments meeting the rule of 3 or even stricter requirements is a challenge for MedChem relevant building blocks synthesis.

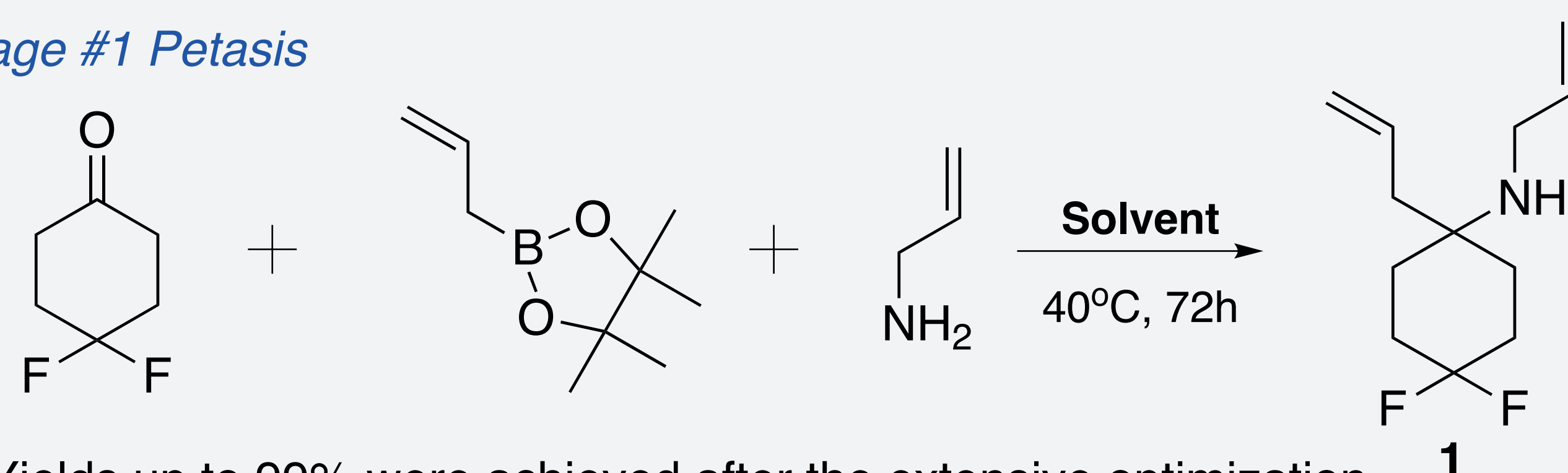
DOS strategy for BB synthesis



Synthesis Optimization and Products Diversity

- Earlier we successfully used Petasis reaction based on allylic boronic acid for the construction of quaternary center for the synthesis of spirocyclic pyrrolidines².
- In this work, we report the further development of the approach by the addition of the Grubbs reaction for the assembling of the second cycle.

Stage #1 Petasis



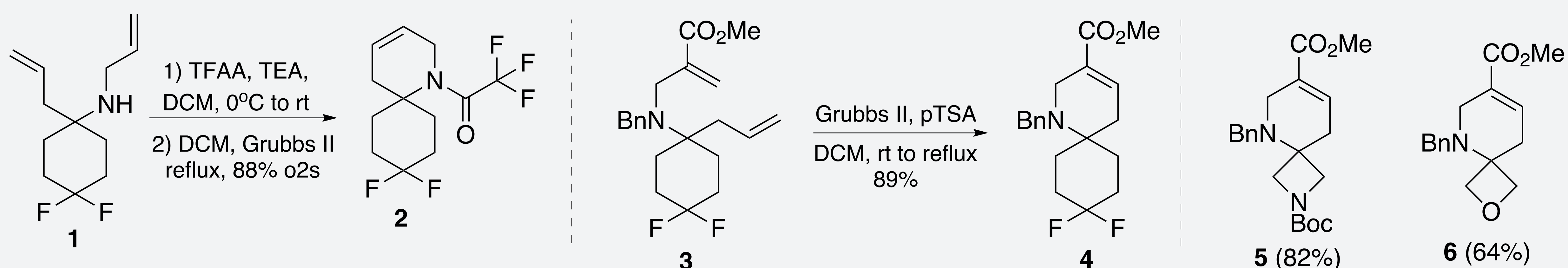
‡ Yields up to 99% were achieved after the extensive optimization.

Stage #2 Grubbs

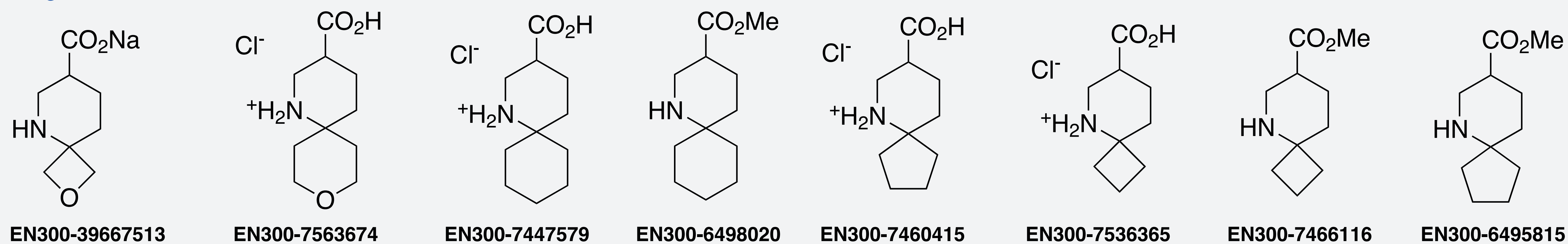
‡ TFA-protected amines were involved into metathesis under standard conditions.

‡ As tertiary amines can poison the Grubbs catalyst, pTSA (1 eq.) was added to protonate the benzyl-protected amines.

‡ 64-89% yields were reached under the optimized conditions.



Stage #3 Post-Modification



‡ A set of conformationally limited spirocyclic buildingblocks was obtained *via* common synthetic transformations such as double bond reduction, ester saponification or benzyl cleavage. The products were obtained at scales up to 70 g per run.

Solvent	SM concentration	Yield, %
Methanol	0.2 M	68
THF	0.2 M	77
CHCl ₃	0.2 M	0
EtOAc	0.2 M	75
Toluene	0.2 M	79
Toluene	0.4 M	89
Toluene	1 M	99

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References

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- Melnykov K. P. *et al. ACS Omega* **2019**, 4, 4, 7498.