Neglected Cage Compounds – Transitioning From Rare Molecules to Casual MedChem Tools

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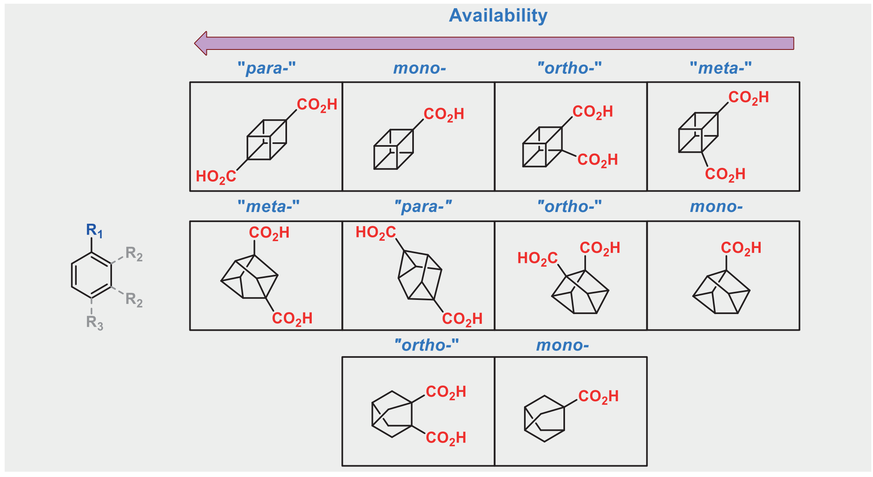
Background of the project

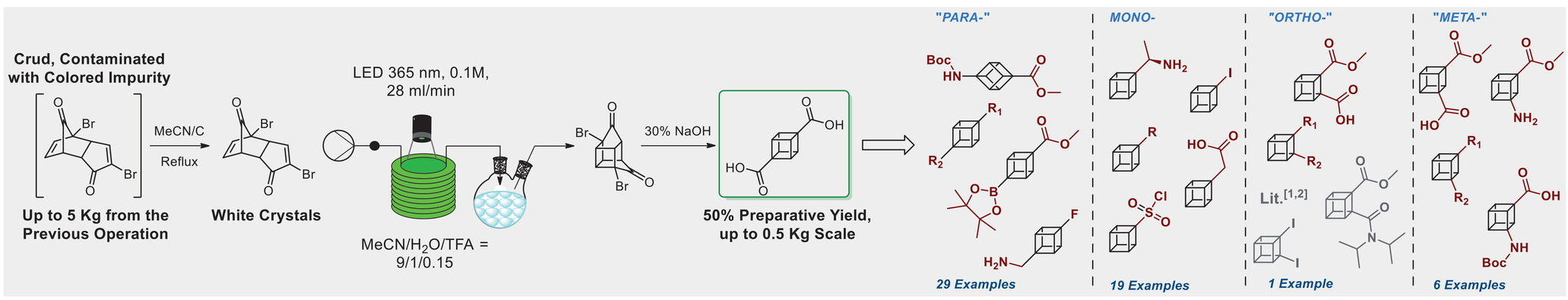
"Escape from Flatland" to 3-D Cages: an Evolution

- High-Fsp³ scaffolds now serve as bioisosteric alternatives to planar aromatic cores.
- Stellanes, cubanes, and cuneanes offer compact, rigid, and uniquely three-dimensional frameworks.
- Development of preparative and scalable synthetic protocols remains to be the core issue on the way to establishing these cages as standard MedChem tools.



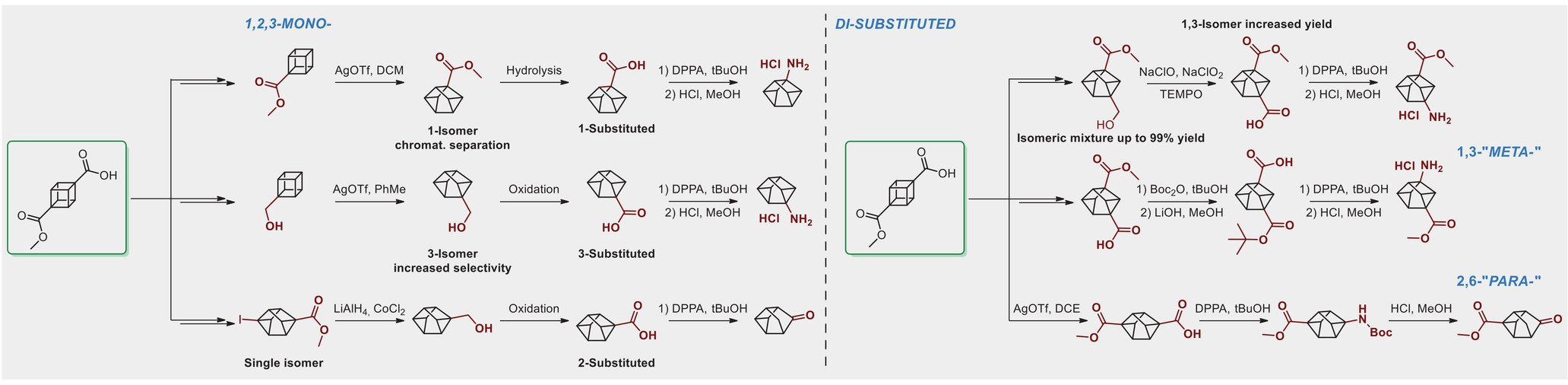
Cubanes: Recent Advances and Challenges

Improved Protocol: Less Steps, Better Yields, Tunable Scale



Cuneane Derivatives: Free Access to Cubane-1,4-Dicarboxylic Acid Facilitates the Study

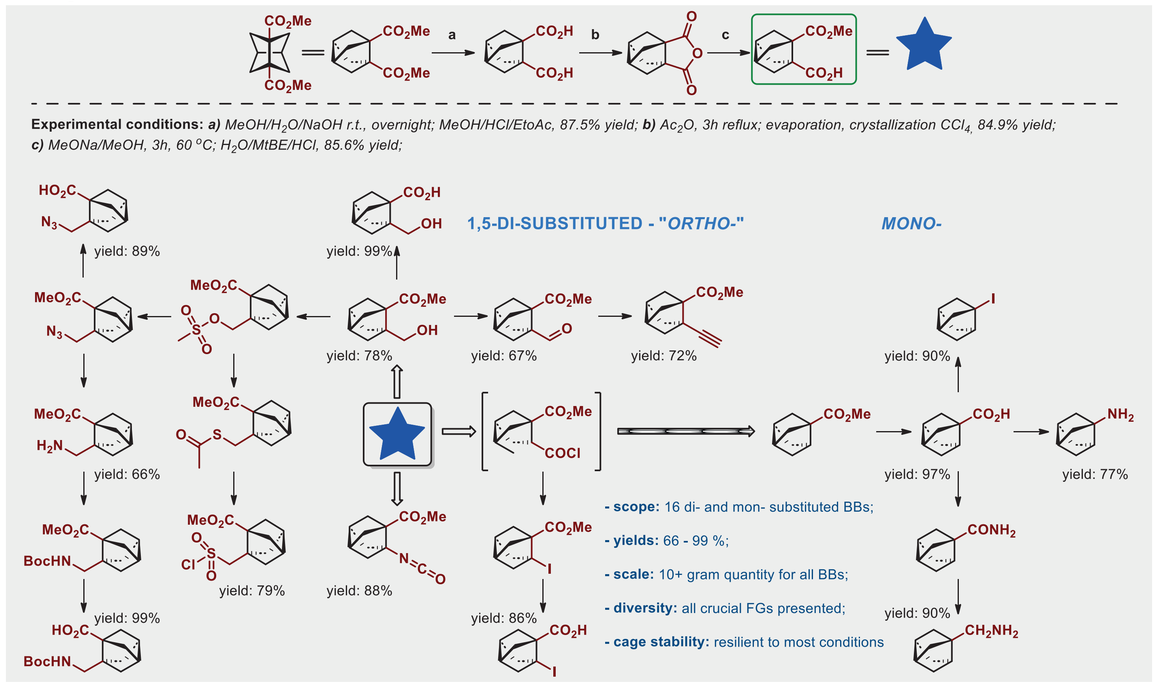
The development of improved protocols for large-scale synthesis of cubane-1,4-dicarboxylic acid grants access to cuneane derivatives, enabling optimal preparation studies. Our methods reduced Ag catalyst usage tenfold versus literature and deliver both mono- and di-substituted cuneanes with enhanced yield and selectivity.



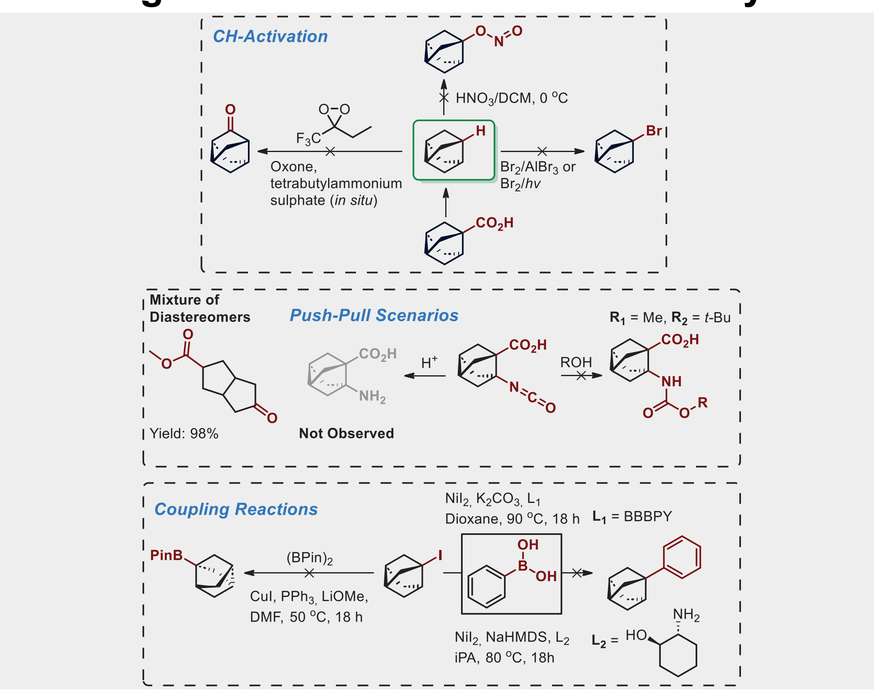
Stellane Derivatives: Novel C_8-Scaffolds With Unique *Ortho*-Isosteric Potential

Stellane derivatives offer a unique, saturated C(sp³)-rich scaffold with by far optimal geometry for *ortho*-benzene bioisosterism. Our up-scale synthesis of stellane-1,5-dicarboxylic acid[3] enables preparation of diverse scope of building blocks which cover the most important functional groups and their orthogonal combinations[4]. However, challenges in C–H activation and coupling reactions remain unresolved.

Preparation of Mono- and 1,5-Disubstituted Stellanes



Challenges in Current Stellane Chemistry



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References

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2. Pendiukh V. V. et al. *ChemRxiv* **2024**, DOI: 10.26434/chemrxiv-2024-r2knw;
3. Pendiukh V. V. et al. *ChemRxiv* **2024**, DOI: 10.26434/chemrxiv-2024-fqdl6;