Neglected Cage Compounds from Rare Structures to Available Chemicals

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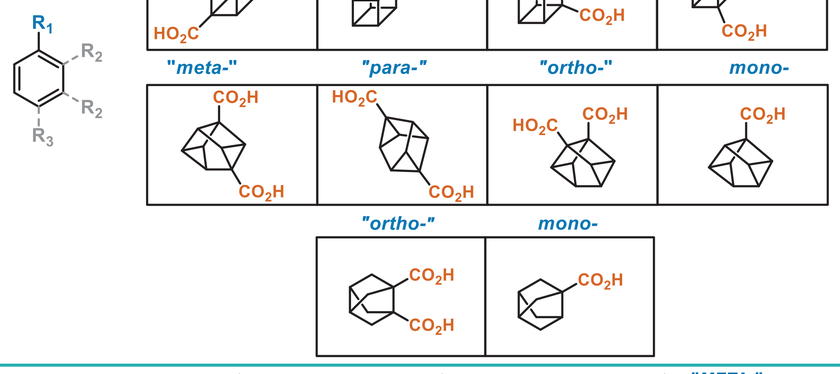
Background of the project

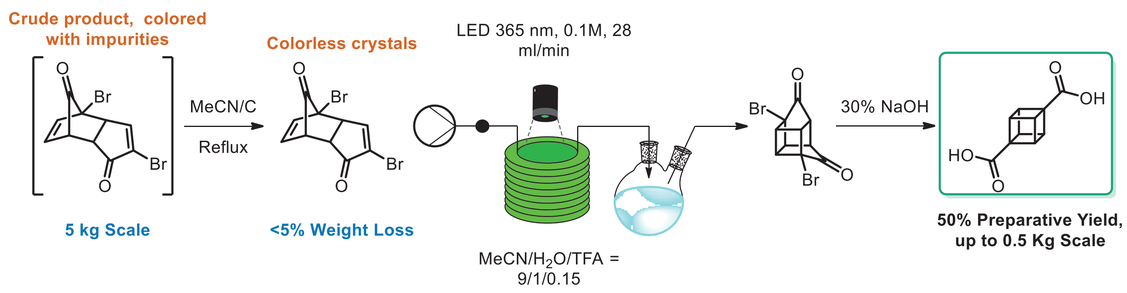
“Escape from Flatland” to 3D Cages: an Evolution

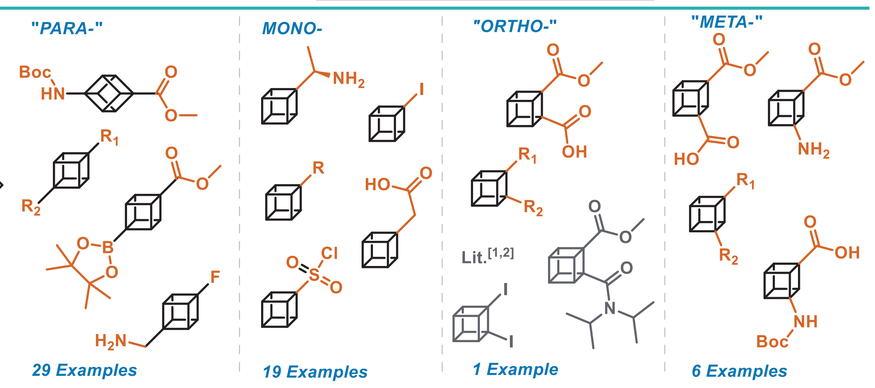
- High-Fsp³ scaffolds now serve as bioisosteric alternatives to planar aromatic cores.
- Stellanes, cubanes, and cuneanes offer compact, rigid, and uniquely three-dimensional frameworks.
- Development of preparative and scalable synthetic protocols remains to be the core issue on the way to establishing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



Cubanes: Recent Advances and Challenges

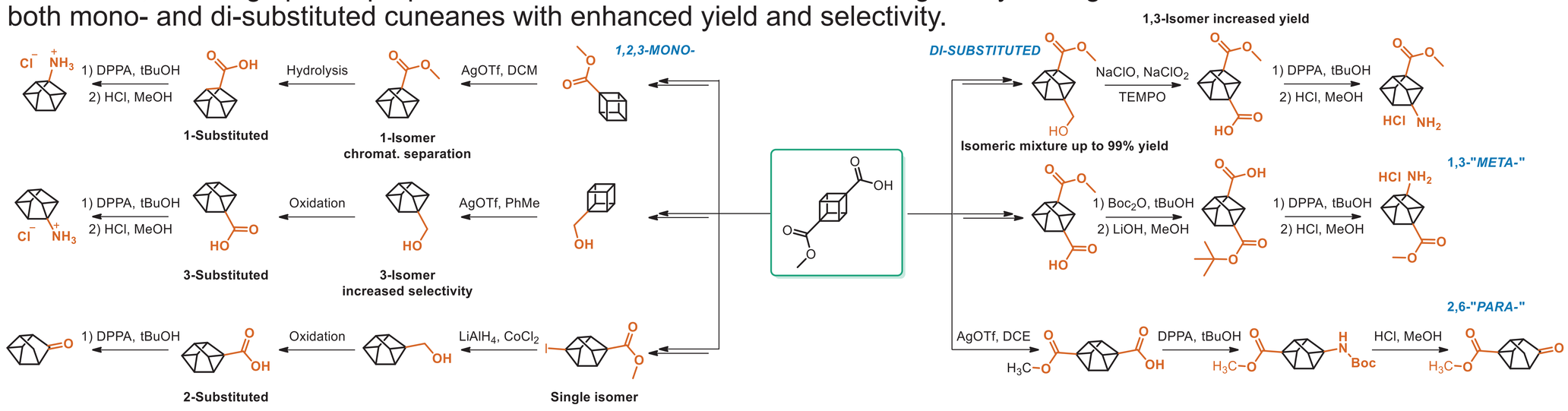
Improved Protocol: Less Steps, Better Yields, Tunable Scale





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

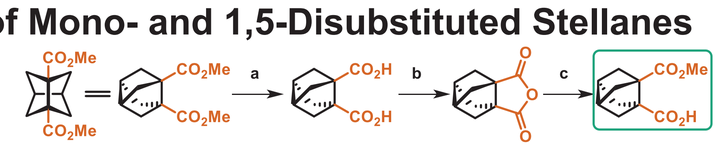
The development of improved protocols for large-scale synthesis of cubane-1,4-dicarboxylic acid grants access to cuneane derivatives, enabling optimal preparation studies. Our methods reduced Ag catalyst usage tenfold versus literature and deliver both mono- and di-substituted cuneanes with enhanced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



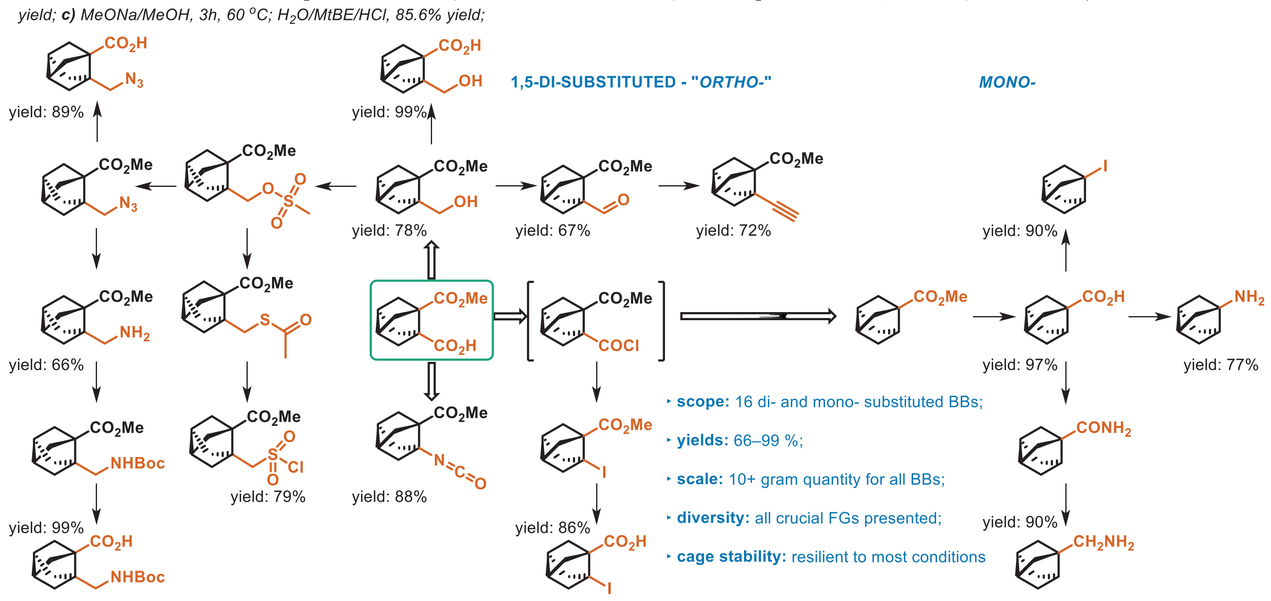
Stellane Derivatives: Novel C8-Scaffolds With Unique Ortho-Isosteric Potential

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.

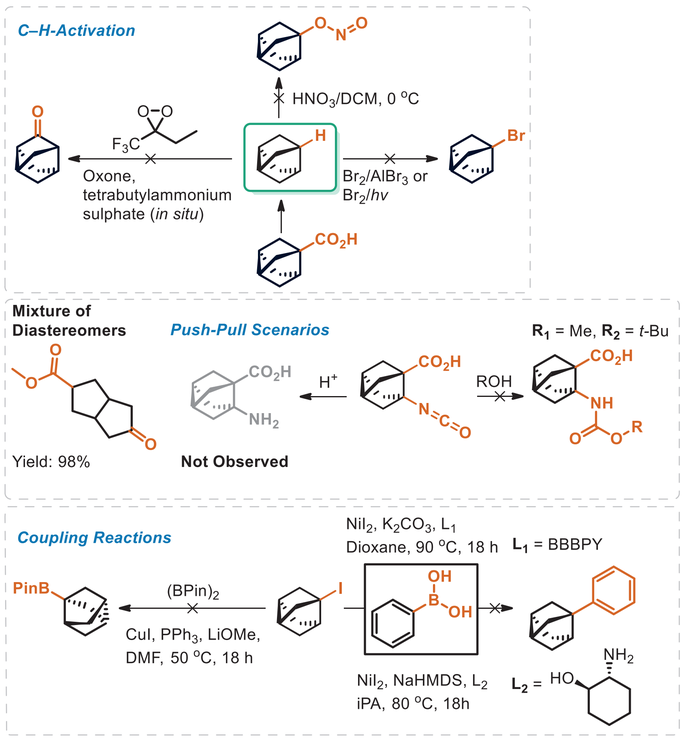
Preparation of Mono- and 1,5-Disubstituted Stellanes



Experimental conditions: ***a)*** *MeOH/H_2O/NaOH r.t., overnight; MeOH/HCl/EtoAc, 87.5% yield;* ***b)*** *Ac_2O, 3h reflux; evaporation, crystallization CCl_4, 84.9% yield;* ***c)*** *MeONa/MeOH, 3h, 60 °C; H_2O/MtBE/HCl, 85.6% yield;*



Challenges in Current Stellane Chemistry



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References

1. Smyrnov, *et al., Chem. Eur. J.*, **2023**, *29* (70), e202302454.
2. Smyrnov, O. K. *et al., Org. Lett.* **2024**, *26* (22), 4808-12.