Versatile Synthetic Pathways to Heteroadamantane Cages: Enhancing Accessibility and Functionality

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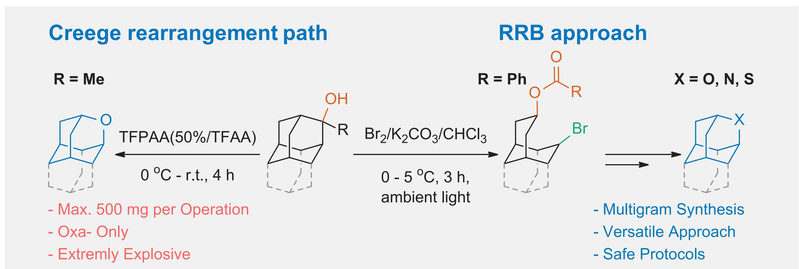
Background and aim of the project

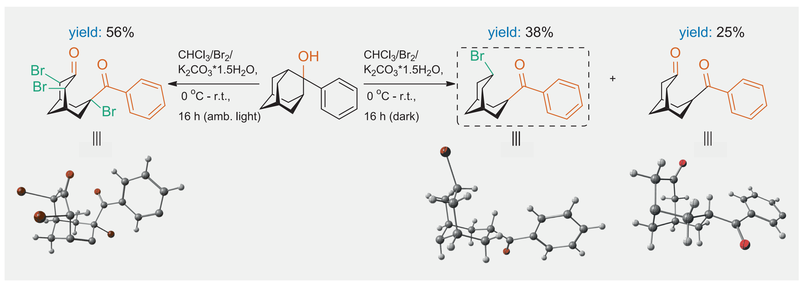
Difficulties in the Synthesis of Heteroatom-Doped Adamantanes:

- Heteroadamantanes are privileged structures for drug discovery due to their enhanced ADME-profile, restricted topology, high *f*-sp^3, rigidity, and metabolic stability. However, **these compounds are barely accessible synthetically.**
- Previous methods[1] limit to oxygen doped cages, and have a number of disadvantages, meanwhile approach to heterodiamantanes via **Retro-Barbier reaction[2] (RRB) looks promising** for translating it to adamantanes.



RRB approach: the straightforward effort

- We have prepared RRB product however **in case of adamantane substrate it did not go further to haloester** as it was with diamantane.
- At the same time, we obtained t**he unexpected diketone** product as well as its *alfa*-brominated derivative (in harsher conditions) with notable yields.



- We have synthesized [3.3.1]bicyclononane bromoester in multigram quantity with good preparative yield.
- Further studies showed significant differences in its reactivity compared to diamantane analogue.

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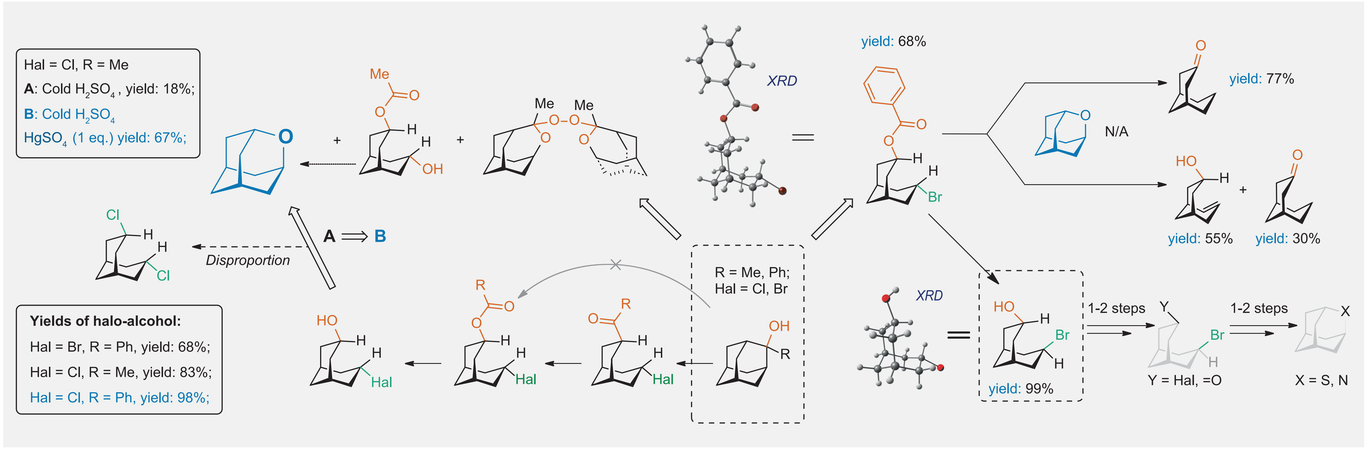
Further probing RRB on adamantanes: in search for the optimal path

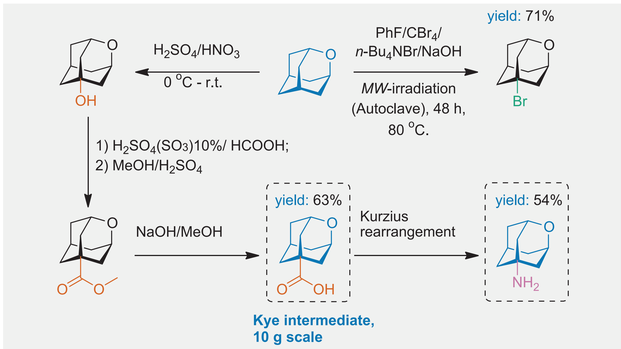
The $HgSO_4$ additive fixes the disproportion issue entirely



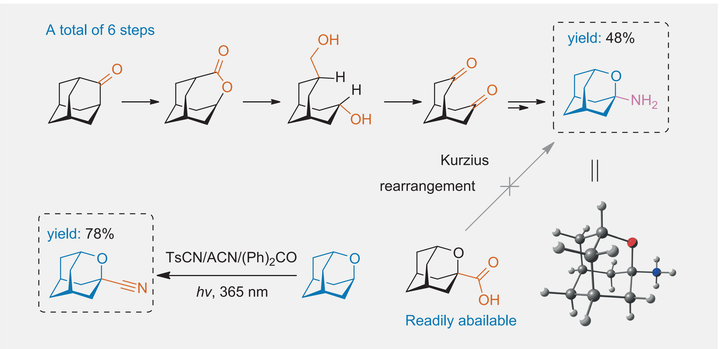
Rigorous study of the possible RRB conditions and comprehensive products analysis led to finding optimal setup

2-Oxaadamantane derivatization: accessing 1- and 5-substituted derivatives

Key precursors to 5-substituted oxaadamantanes



Filling the gaps in 1-substituted oxaadamantane derivatives



Preparative yields given as total over multiple steps

Primary functionalization of 2-oxaadamantane is a necessary step for further studies on its derivatives, however it ramains significant challenge due to extremely low reactivity of the substrate. However, we managed to:

- Develop a new protocol for 2-oxadiamantane bromination, hydroxylation (at 5-th atom) and cyanation (at position-1);
- Synthesize the key, previously unavailable 2-oxaadamantane-5-carboxylic acid in 10-th of grams quantity.

References

1. Fokin, A. A. et al., *Org. Lett.* **2009,** 11 (14), 3068-71;
2. Fokin, A. A. et al., *Org. Lett.* **2022,** 24 (27), 4845-4849.