

# Paving Rout to Soluble Cage Compounds: in Search for Accessible 2-Heteroadamantanes Source

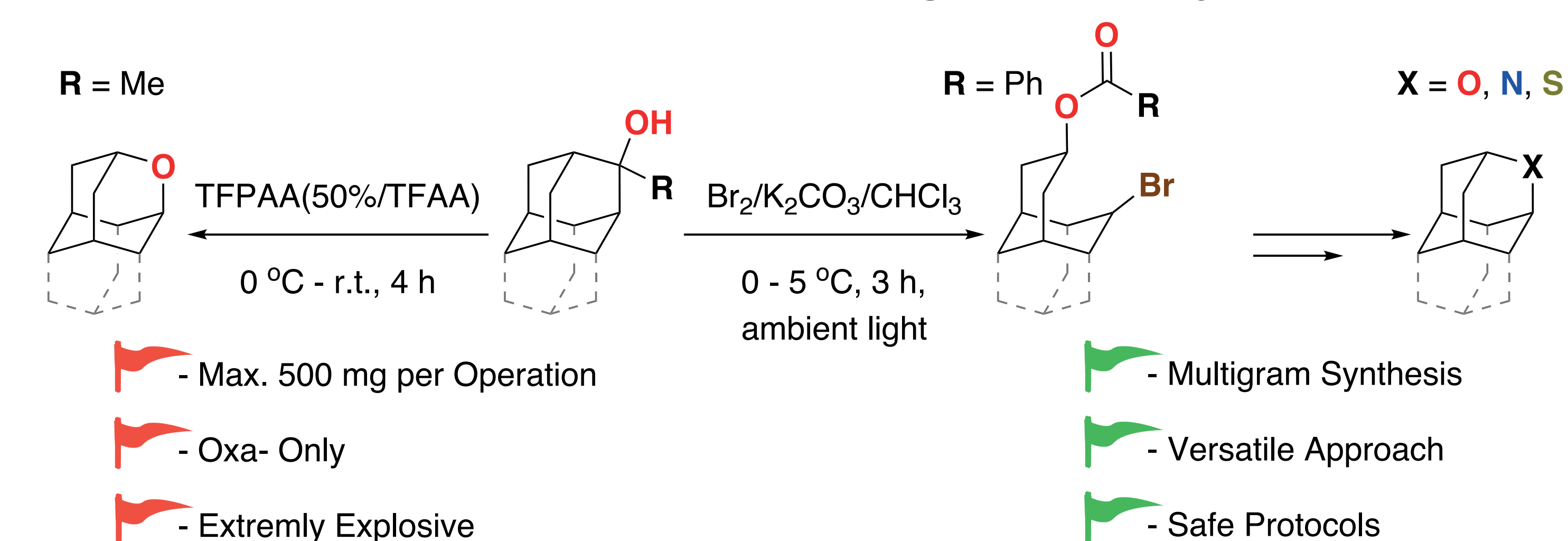


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## Background and aim of the project

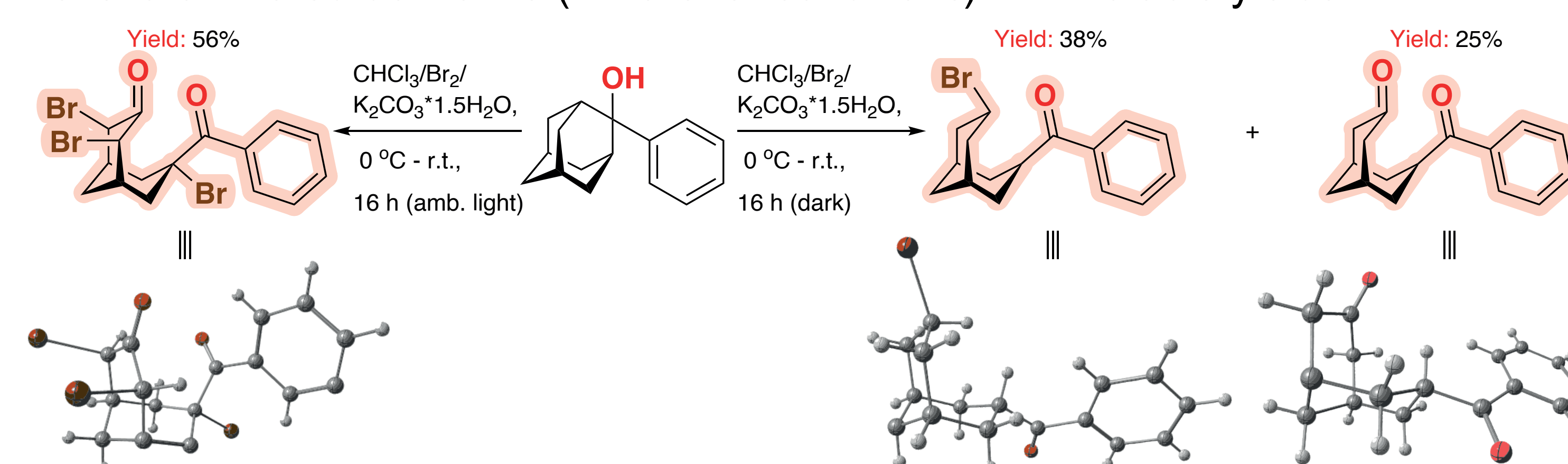
### Difficulties in the Synthesis of Heteroatom-Doped Adamantanes:

- Heteroadamantanes are privileged structures for drug discovery due to their enhanced ADME-profile, restricted topology, high f-sp<sup>3</sup>, rigidity, and metabolic stability. However, the **entire class of these compounds is barely accessible from the standpoint of preparative synthesis.**
- Previous methods<sup>1</sup> limit to oxygen doped cages, and have a number of disadvantages, meanwhile recently developed approach to heterodiamantanes via **Retro-Barbier reaction<sup>2</sup>** looks promising for translating it to adamantanes.



## Preliminary Results

- We have prepared Retro-Barbier 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 **the unexpected diketone** product as well as its alfa-brominated derivative (in harsher conditions) with notable yields.



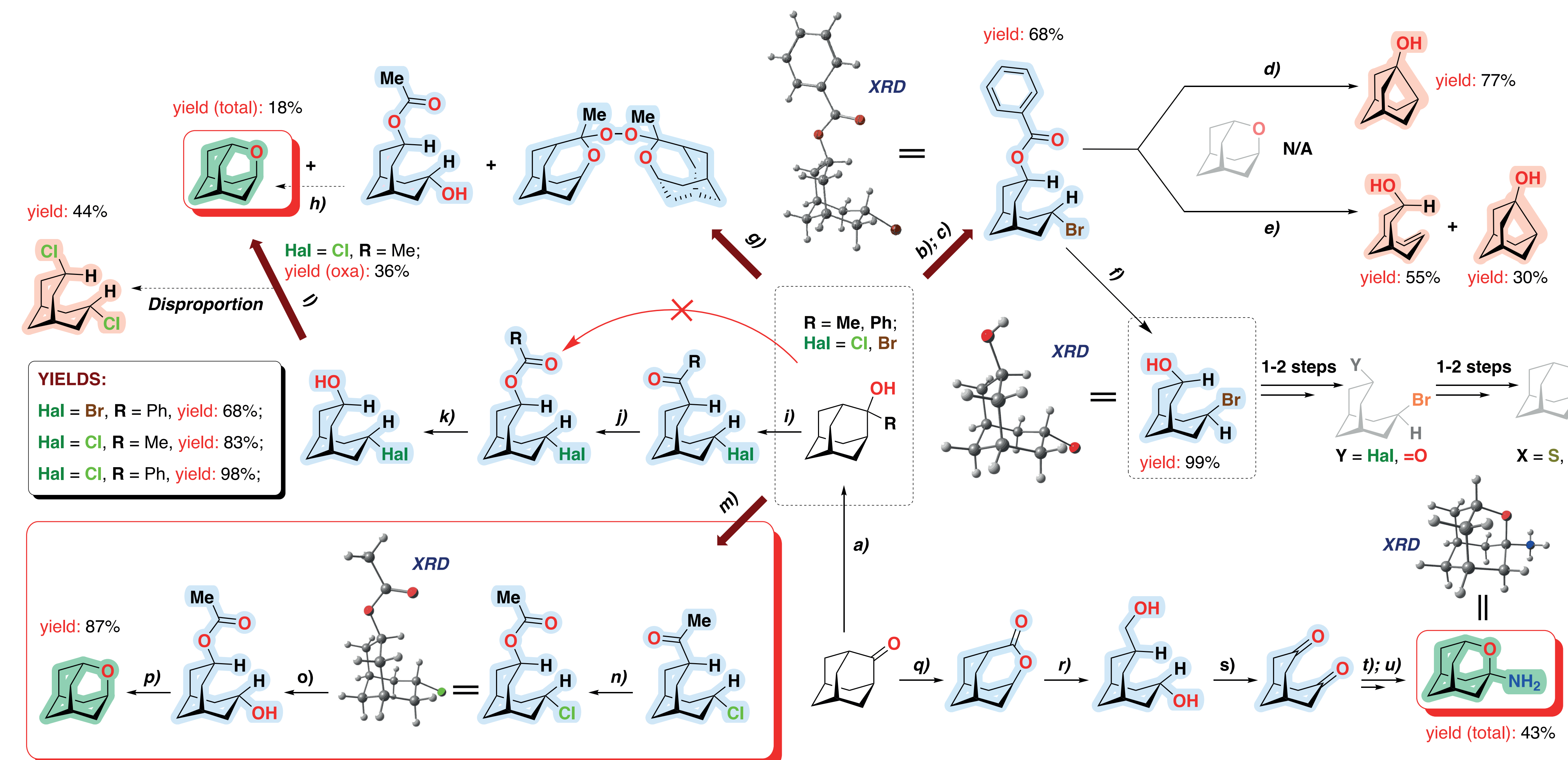
### Preparation of [3.3.1]bicyclononane bromoether and its reactivity studies:

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

## Contact

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## Probing Retro-Barbier reactions (RRB) on Adamantanes: in Search for the Optimal Path

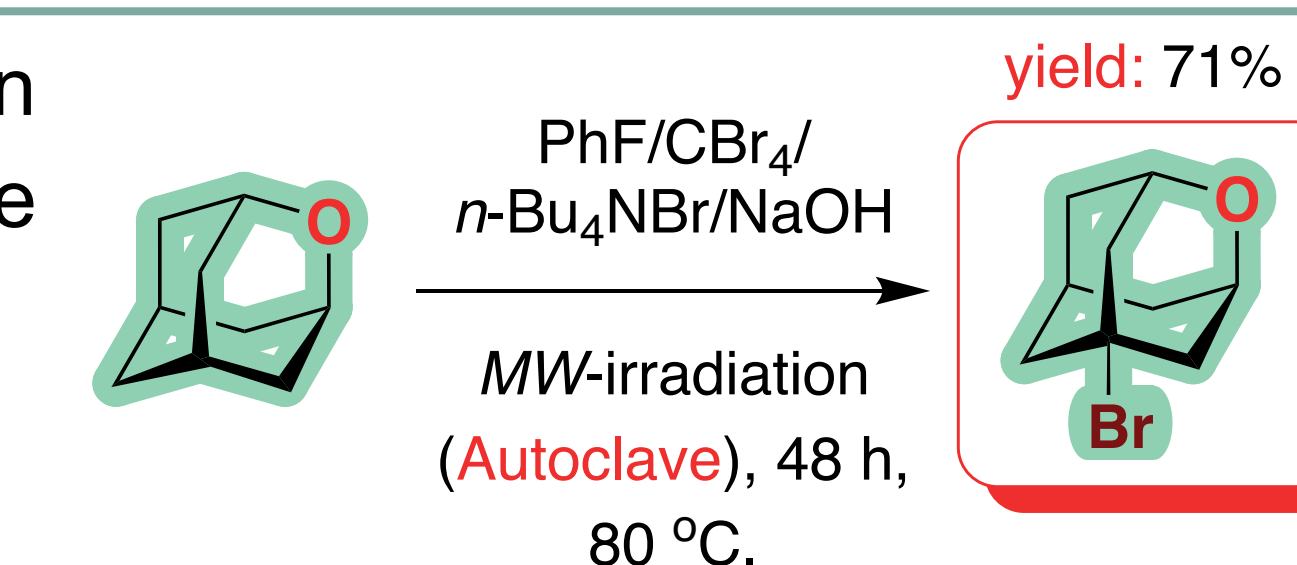


**Experimental conditions:** a) RMgX/THF r.t. 24 h; H<sub>2</sub>O/HCl/EtoAc, yields: 81-99%; b) Br<sub>2</sub>/K<sub>2</sub>CO<sub>3</sub>/H<sub>2</sub>O/CHCl<sub>3</sub>, 3h, 0 °C to r.t.; NaHSO<sub>3</sub>/H<sub>2</sub>O/CHCl<sub>3</sub>, 68% yield; c) m-CPBA/CH<sub>2</sub>Cl<sub>2</sub>, 4h, 0 °C to r.t.; NaHSO<sub>3</sub>/H<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>, 99.8% yield; d) NaOH/MeOH/H<sub>2</sub>O, 24 h, 65 °C; 77% yield; e) Dioxane/5M HCl, 24 h, 80 °C; f) LiAlH<sub>4</sub>/Et<sub>2</sub>O, 1h, 0 °C; H<sub>2</sub>O/NaOH/MBE, 99% yield; g) TFAA/H<sub>2</sub>O<sub>2</sub>(30%), 6 h, -10 °C, yield: trace; h) H<sub>2</sub>SO<sub>4</sub>, 0.5 h, -10 - 0 °C, yield 99%; i) NaOH/CCl<sub>4</sub>/H<sub>2</sub>O, 3 h, 0 °C; yields: 69 - 99% ; j) m-CPBA/CH<sub>2</sub>Cl<sub>2</sub>, 4h, 0 °C to r.t.; NaHSO<sub>3</sub>/H<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>, 99% yield; k) LiAlH<sub>4</sub>/Et<sub>2</sub>O, 1h, 0 °C; H<sub>2</sub>O/NaOH/MBE, 99% yield; l) H<sub>2</sub>SO<sub>4</sub>, 0.5 h, -10 - 0 °C, yields: 22 - 36%; m) NaOCl/CCl<sub>4</sub>/H<sub>2</sub>O, 3 h, 0 °C; 84% yield; n) m-CPBA/CH<sub>2</sub>Cl<sub>2</sub>, 4h, 0 °C to r.t.; NaHSO<sub>3</sub>/H<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>, 99% yield; o) SiO<sub>2</sub>/acetone/AgClO<sub>4</sub>, 48 h, 70 °C (autoclave), 88% yield; p) H<sub>2</sub>SO<sub>4</sub>, 0.5 h, -10 - 0 °C, yield 99%; q) m-CPBA/CH<sub>2</sub>Cl<sub>2</sub>, 4h, 0 °C to r.t.; NaHSO<sub>3</sub>/H<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>, 99% yield; r) LiAlH<sub>4</sub>/Et<sub>2</sub>O, 1h, 0 °C; H<sub>2</sub>O/NaOH/MBE, 99% yield; s) CH<sub>2</sub>Cl<sub>2</sub>/PCC/SiO<sub>2</sub>, 48 h, 38 °C (reflux), 79% yield; t) THF/BnNH<sub>2</sub>, 65 °C, 0.5 h; THF/LiAlH<sub>4</sub>, 24h, 0 °C - r.t., 56% yield; u) Pd/C/THF/H<sub>2</sub>, 1 h, r.t., yield 98%.

## Progression Towards 2-Oxaadamantane Derivatization

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

- Develop a new protocol for 2-oxadamantane bromination;
- Improve literature yield and make it scalable by avoiding the MW irradiation step.



## References

- Fokin, A. A.; Zhuk, T. S.; Pashenko, A. E.; Dral, P. O.; Gunchenko, P. A.; Dahl, J. E.; Carlson, R. M.; Koso, T. V.; Serafin, M.; Schreiner, P. R., *Org. Lett.* **2009**, 11 (14), 3068-71.
- Fokin, A. A.; Reshetlyova, O. K.; Bakhonsky, V. V.; Pashenko, A. E.; Kivernik, A.; Zhuk, T. S.; Becker, J.; Dahl, J. E. P.; Carlson, R. M. K.; Schreiner, P. R., *Org. Lett.* **2022**, 24 (27), 4845-4849.