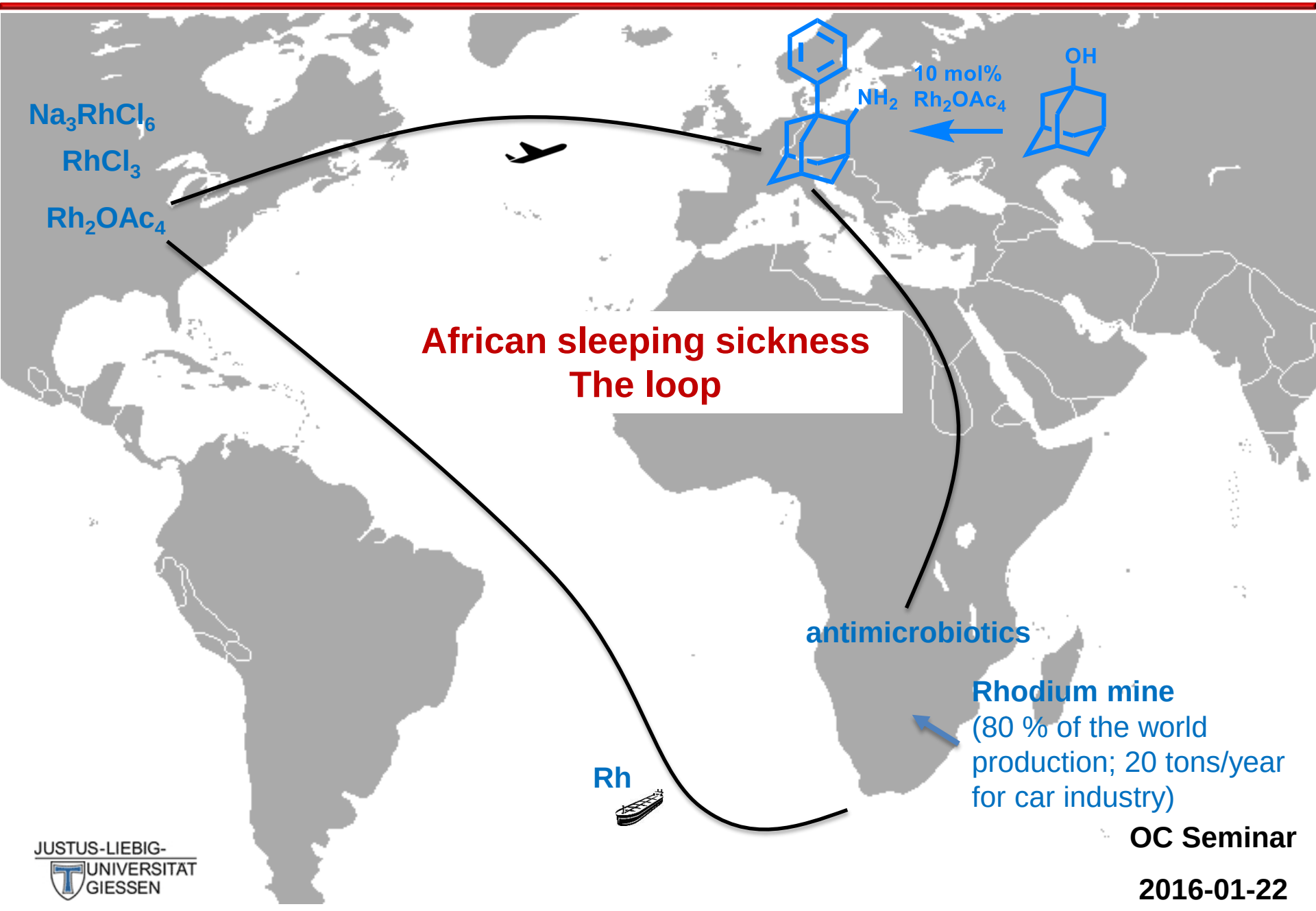
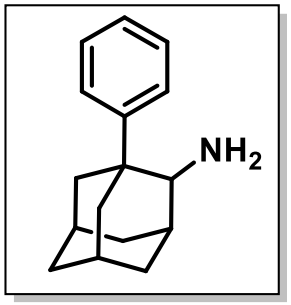
Directed 1,2-Functionalizations of Diamondoids

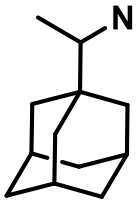


Bio-active compounds with aryl-adamantane motif

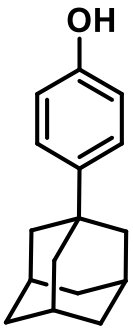
Cointaining aromatic ring in the structure:



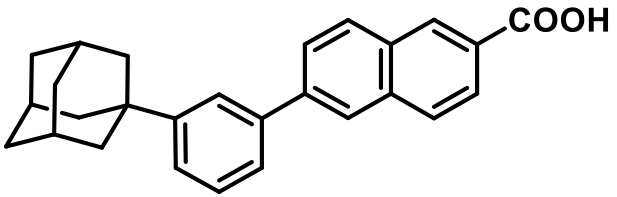
Aminoadamantanes with Trypanocidal activity (African sleeping sickness)
(*this compound is as potent as commercial rimantadine*)



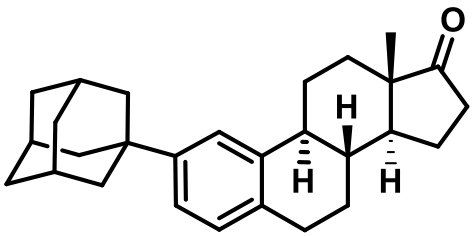
Sigma receptors (opioid receptors)



Ligands for estrogen receptors

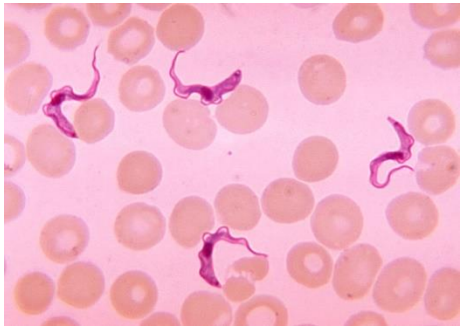


Adamantane-substituted retinoids



L. Wanka, K. Igbal, P. R. Schreiner *Chem. Rev.* **2013**, *133*, 3516-3604.

Sleeping sickness



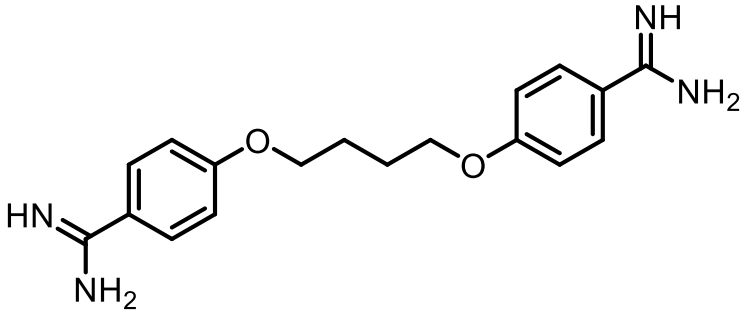
Disease:

African trypanosomiasis or **sleeping sickness** is a parasitic disease of humans and other animals. It is caused by protozoa of the species *Trypanasoma brucei* transmitted by the bite of an infected tse tse fly.

Treatment:

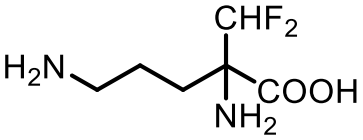
First stage:

Pentamidine

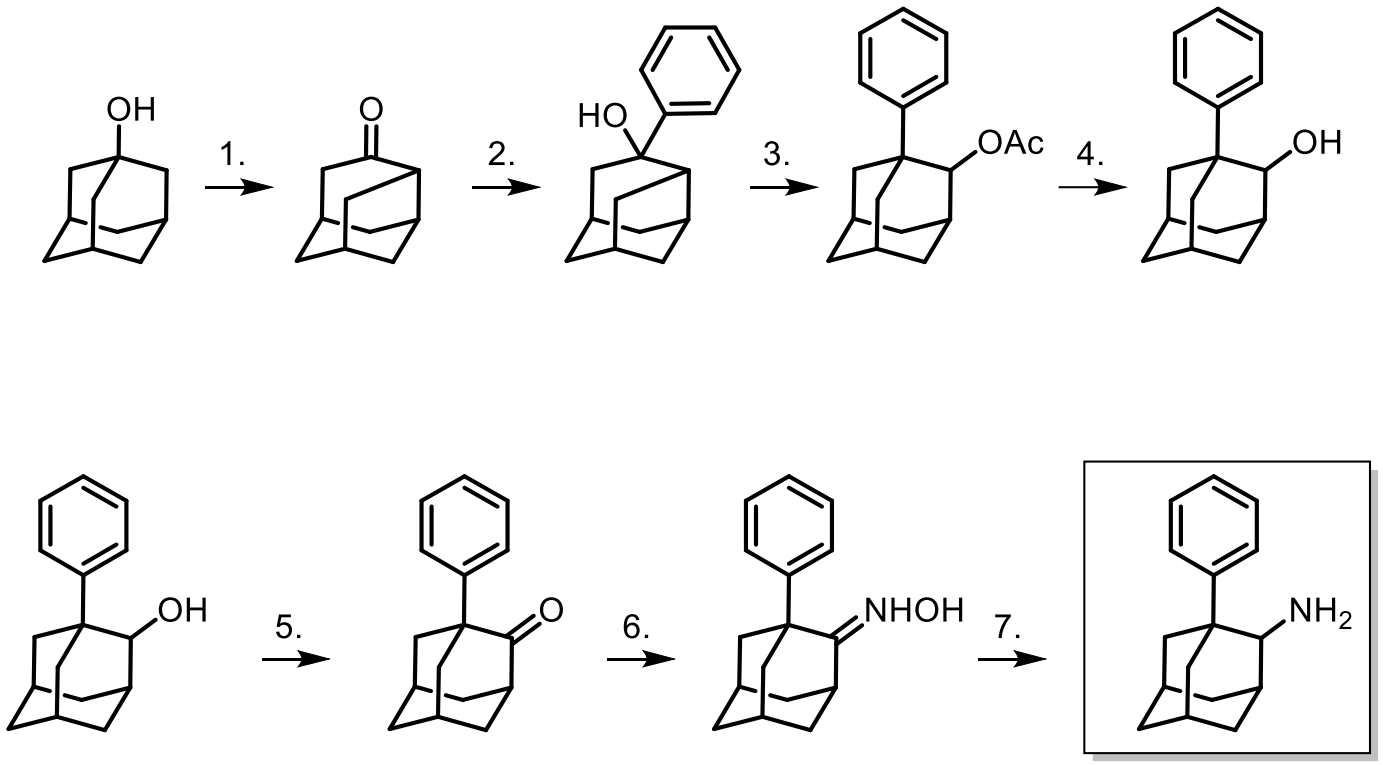


Second stage:

Eflornithine (α-difluoromethylornithine or DFMO) is a drug found to be effective in the treatment of sleeping sickness. Manufactured by **Sanofi Aventis** and sold under the brand name Ornidyl in the USA.



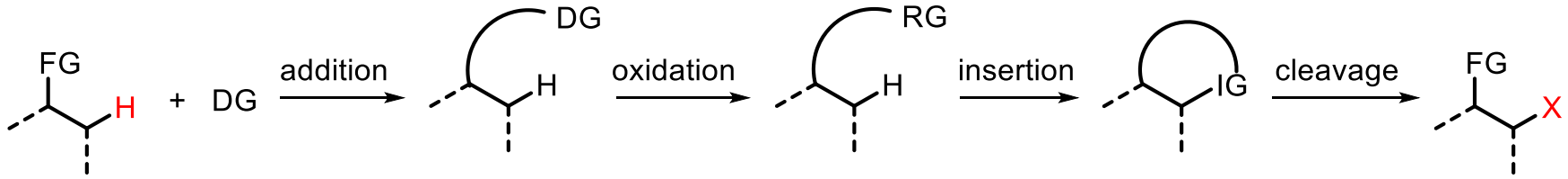
Current synthesis



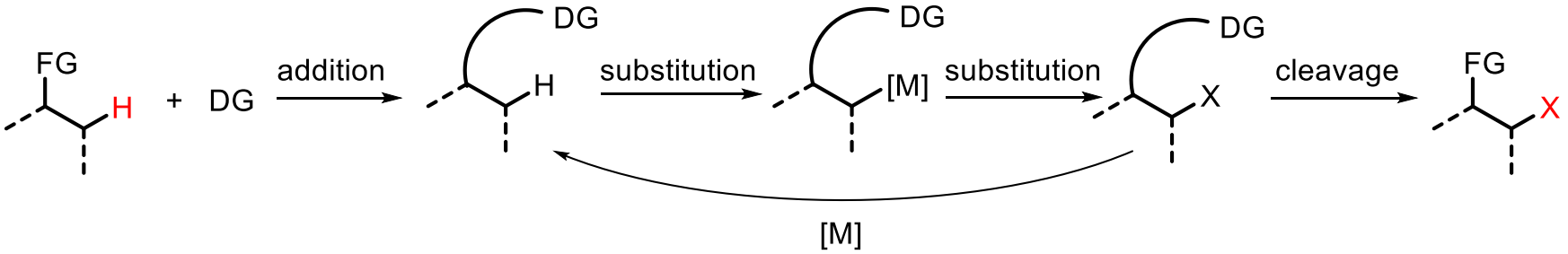
Zoidis, G.; Kolocouris, N.; Kelly, J.M.; Prathalingam, S. R.; Naesens, L.; De Clercq, E. *Eur. J. Med. Chem.* **2010**, *45*, 5022-5030.

Two general approaches to 1,2-disubstitution pattern

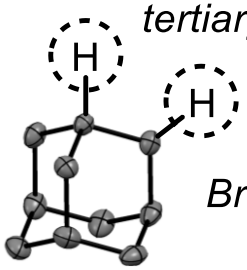
Directed C-H oxidations



C−H functionalisation by metal



Features of adamantane framework



tertiary C-H (electrophilic oxidations)

secondary C-H (rather unreactive)

Bredt´s system (double bond cannot be formed)

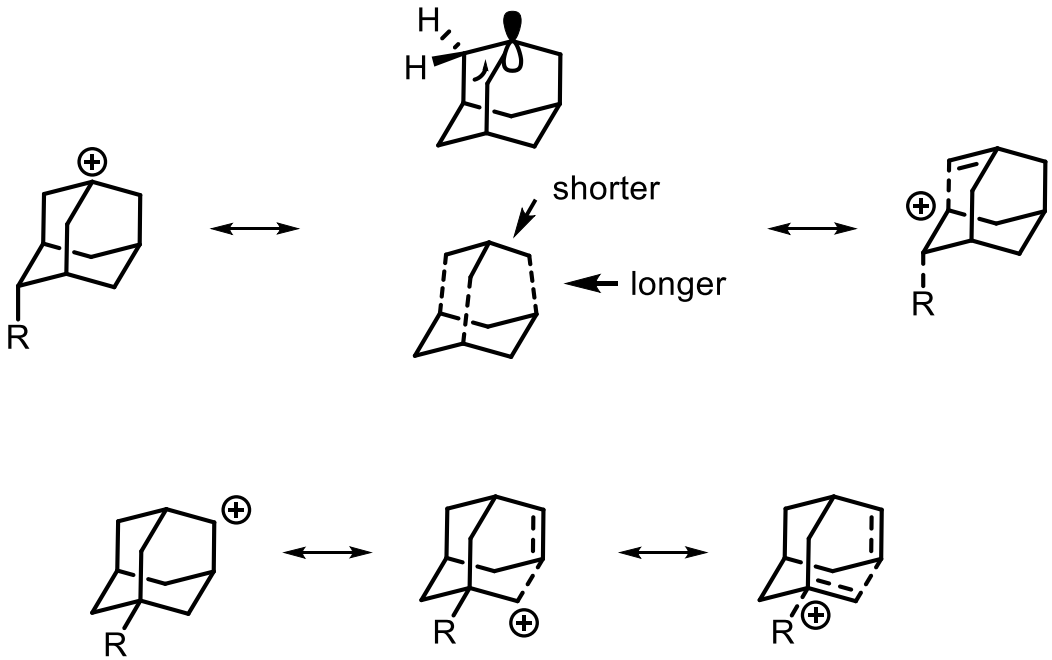
C−H bond dissociation energies:

tertiary C−H 96 kcal/mol

secondary C−H 98 kcal/mol

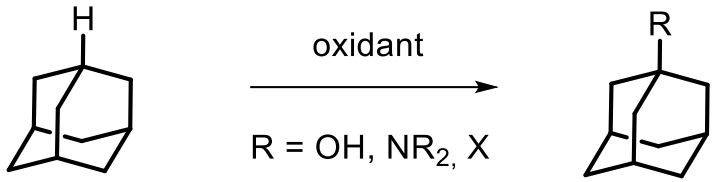
For comparison:
methane C−H 105 kcal/mol
toluene (benzyl C−H) 90 kcal/mol
tertbutane (tertiary C−H) 96 kcal/mol

Hyperconjugation

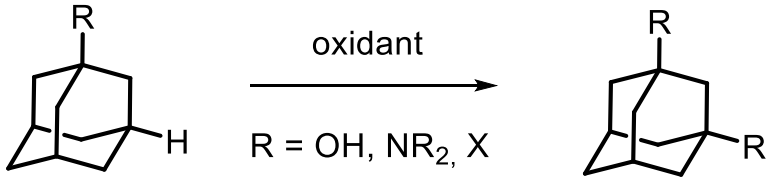


Undirected oxidations

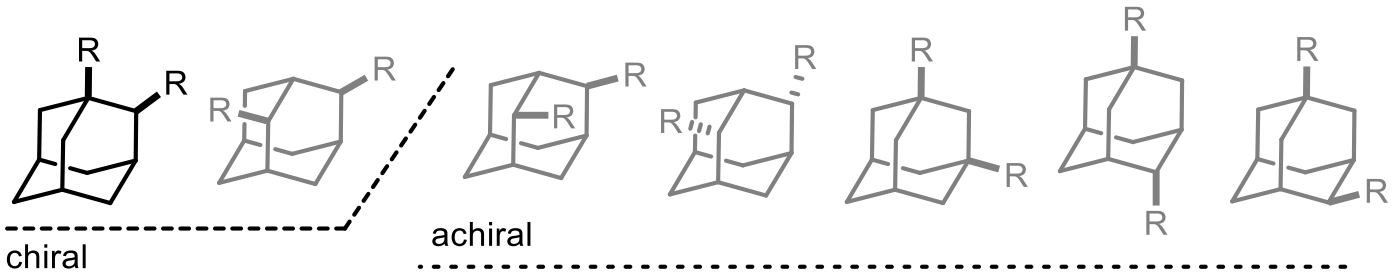
First oxidation:



Second oxidation:



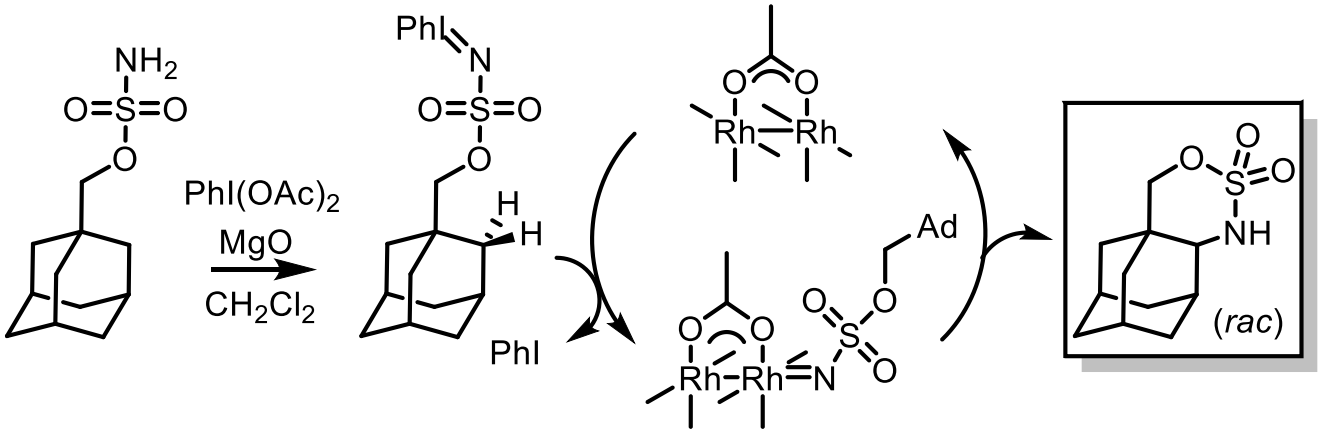
All possible stereoisomers:



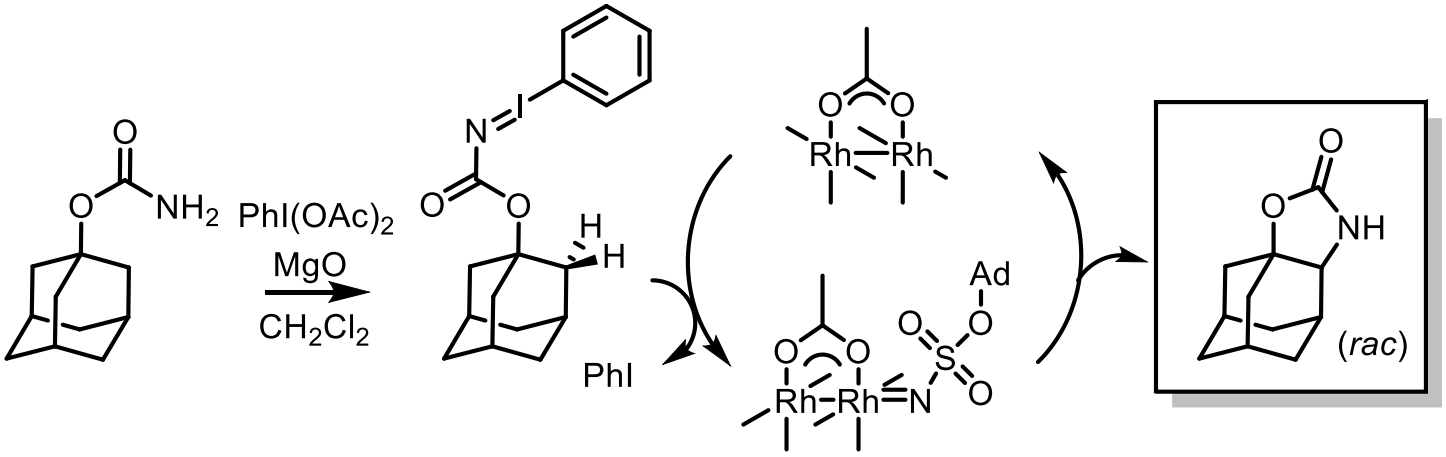
Gunawan, M. A.; Hierso, J. C.; Poinsot, D.; Fokin, A. A.; Fokina, N. A.; Tkachenko, B. A.; Schreiner, P. R. *New J. Chem.* **2014,** *38*, 28-41.
Schwertfeger, H.; Fokin, A. A.; Schreiner, P. R. *Angew. Chem.-Int. Edit.* **2008,** *47*, 1022-1036.

Metal catalysed nitrenoid insertion

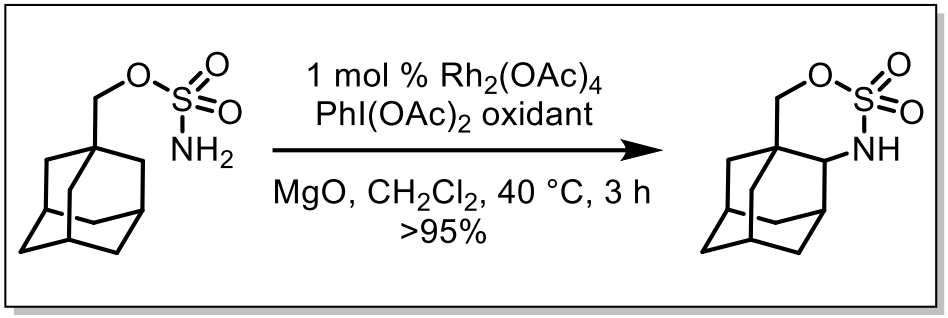
Catalytic cycle 1:

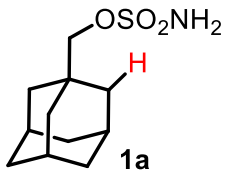


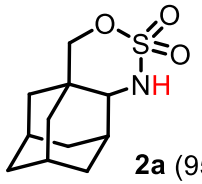
Catalytic cycle 2:

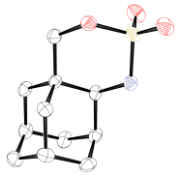


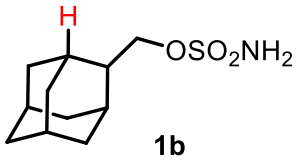
Scope

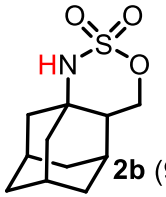


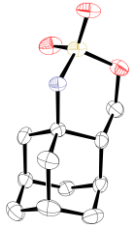

1a

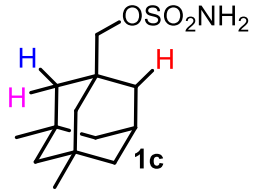

2a (95%)

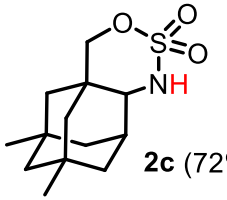


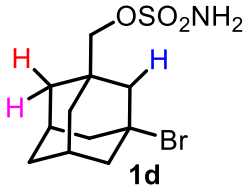

1b

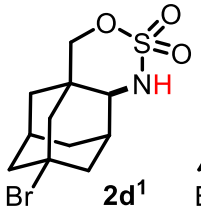

2b (90%)

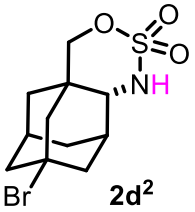



1c

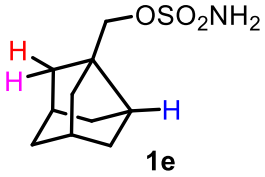

2c (72%)

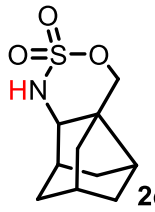

1d

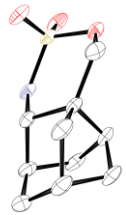

2d[1]

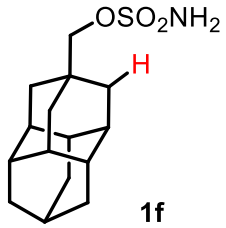

2d[2]

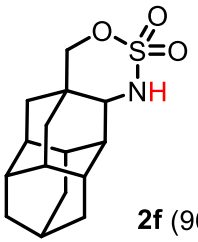
(92% combined, 1.1:1)

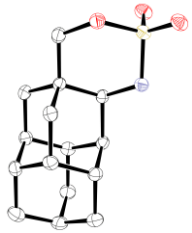

1e

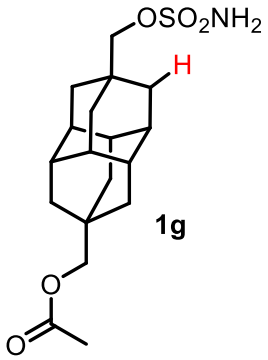

2e (85 %)

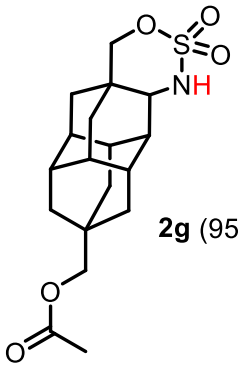


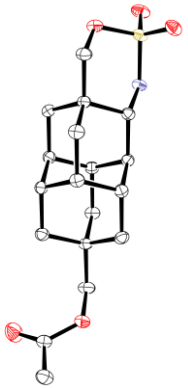

1f

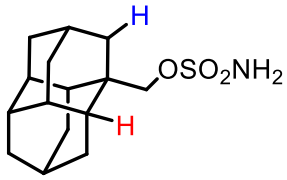

2f (96 %)

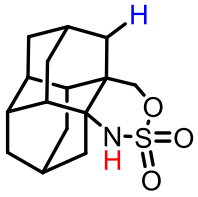


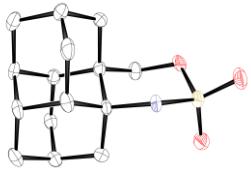

1g


2g (95 %)

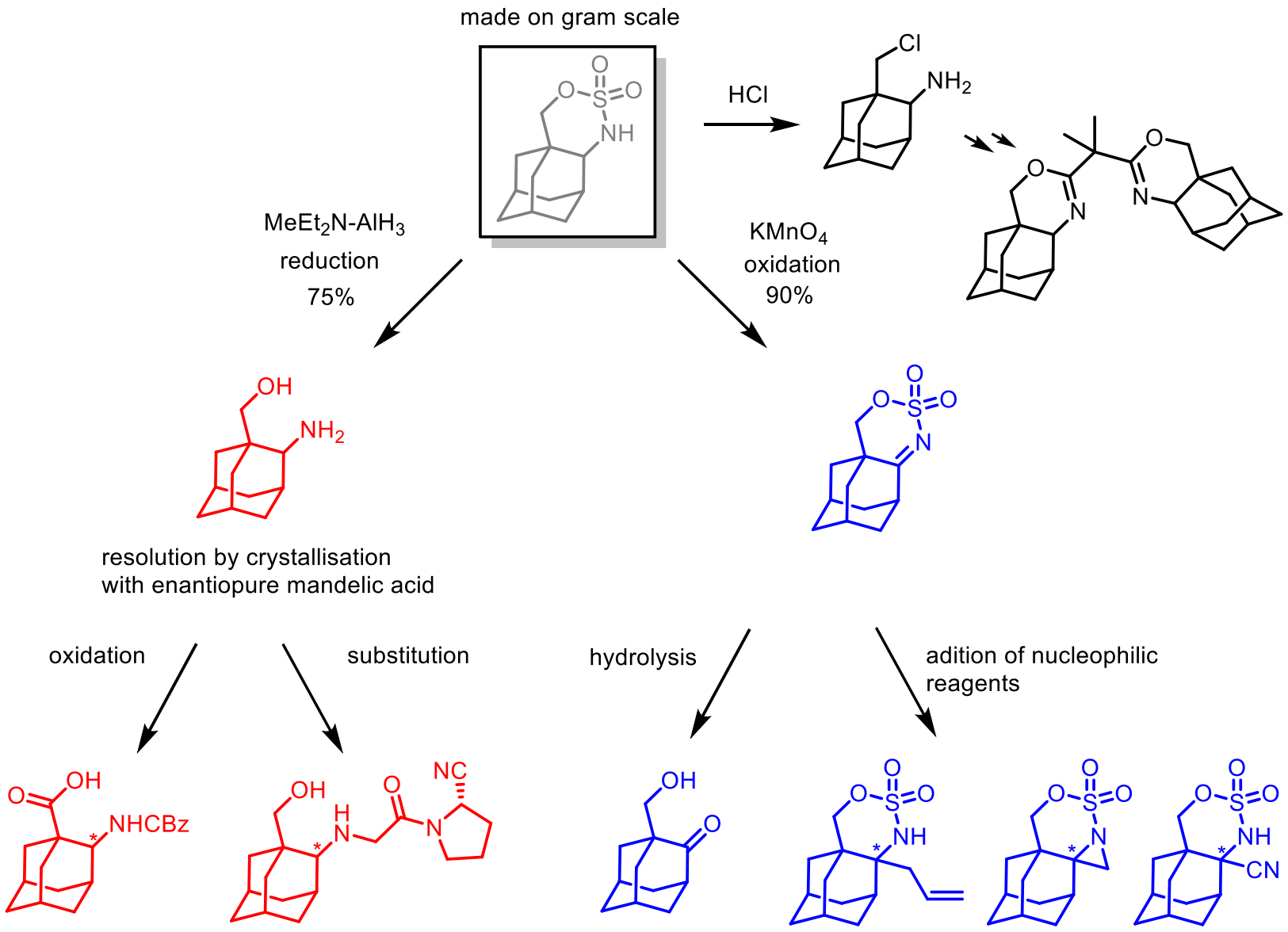



1h

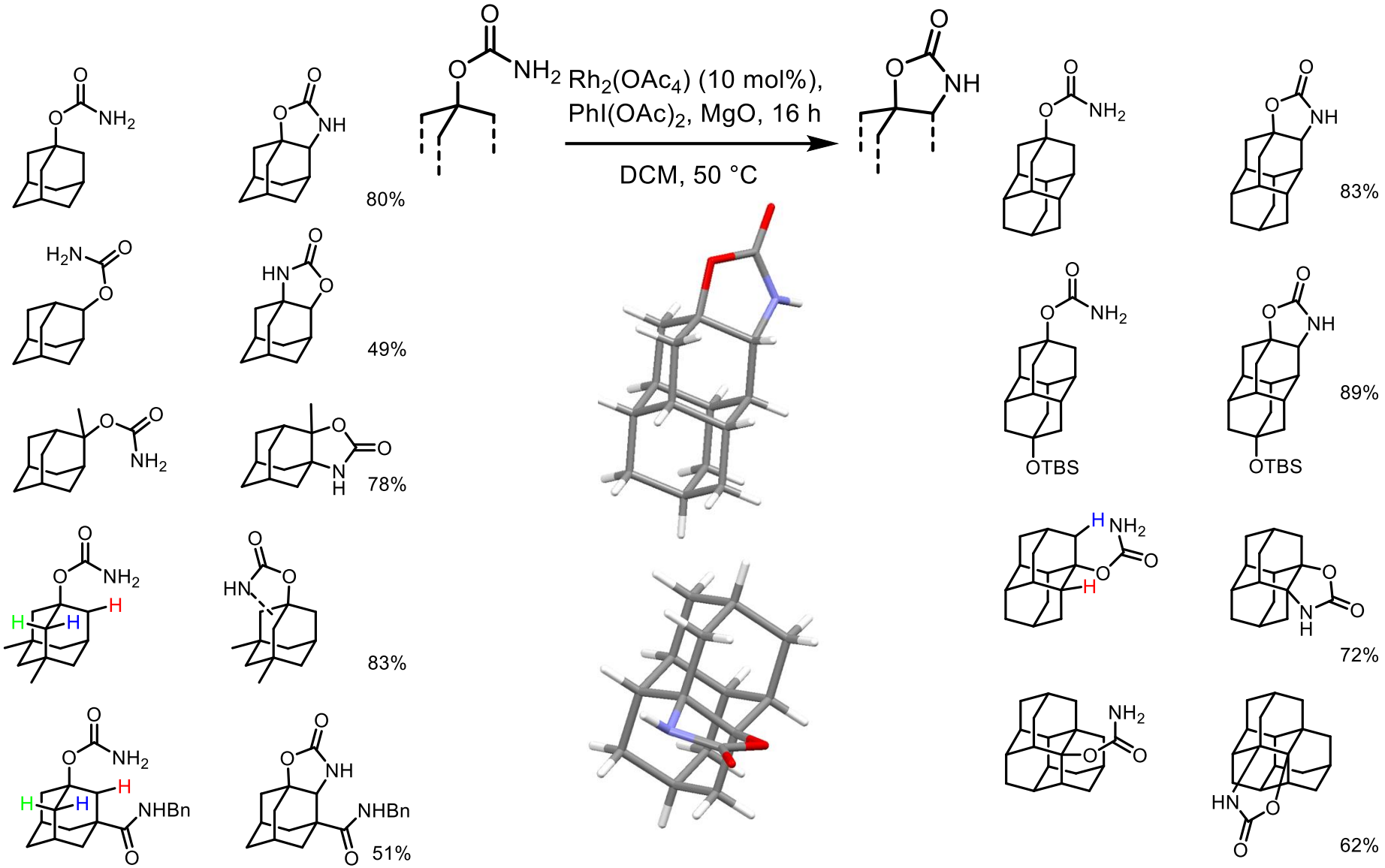

2h (67 % combined, 64%/36%)



Derivatisation

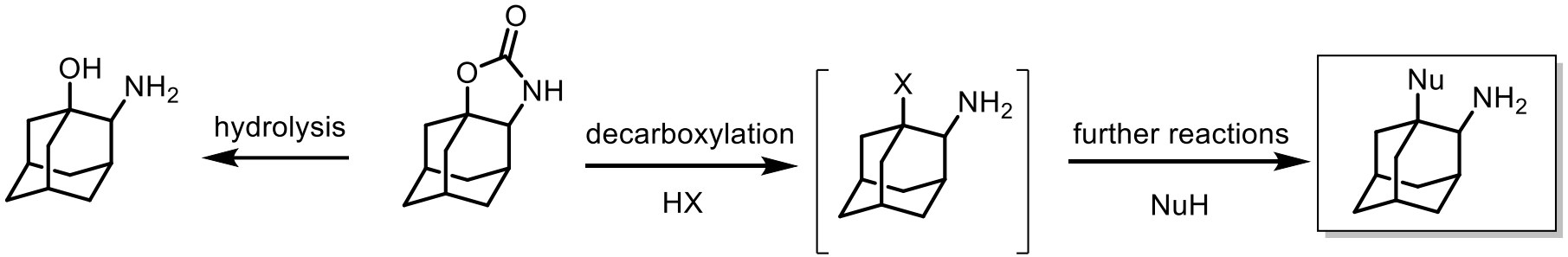


Synthesis of oxazolidinones

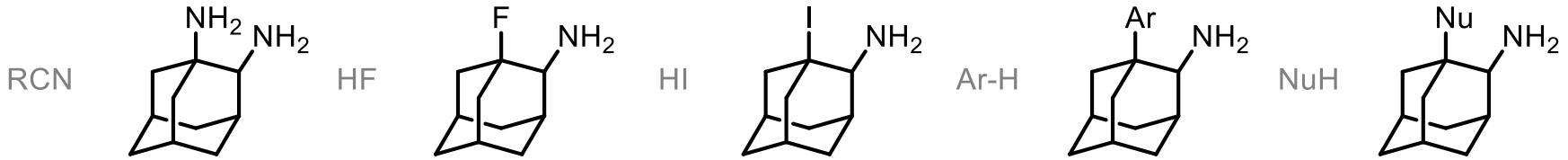


Rohde, J. J.; Pliushchev, M. A.; Sorensen, B. K.; Wodka, D.; Shuai, Q.; Wang, J. H.; Fung,S.; Monzon, K. M.; Chiou, W. J.; Pan, L. P.; Deng, X. Q.; Chovan, L. E.; Ramaiya, A.;Mullally, M.; Henry, R. F.; Stolarik, D. F.; Imade, H. M.; Marsh, K. C.; Beno, W. A.; Fey, T. A.; Droz, B. A.; Brune, M. E.; Camp, H. S.; Sham, H. L.; Frevert, E. U.; Jacobson, P. B.; Link, J. T. *J. Med. Chem.* **2007,** *50*, 149-164.

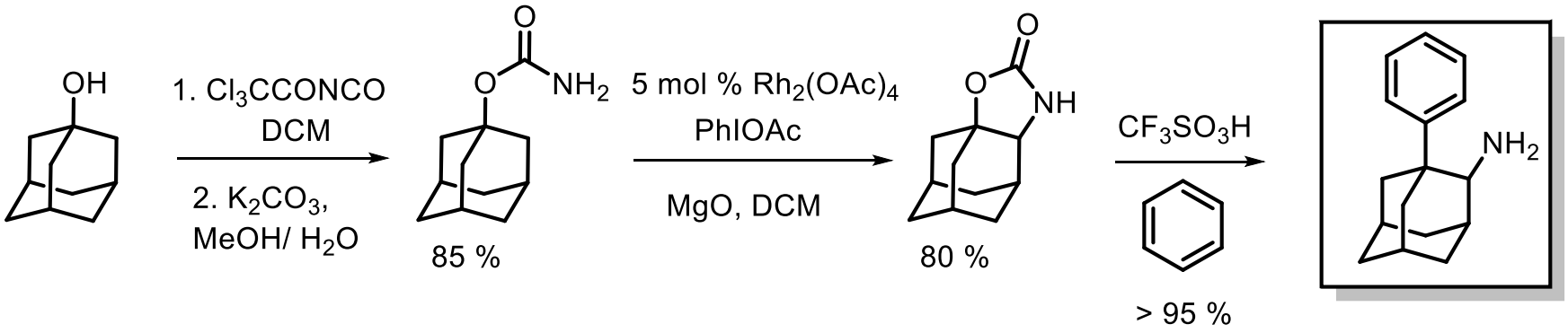
Synthetic utility of oxazolidinones



X = nonnucleophilic anion

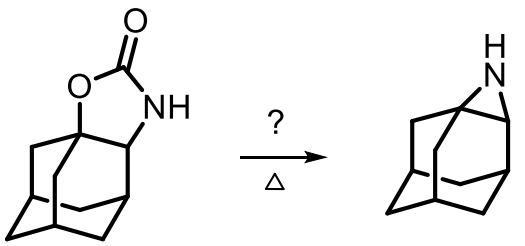


New synthesis of compound with trypanocidal activity:

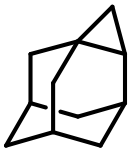


The mechanism of decarboxylation

Pyrolysis in gas phase:

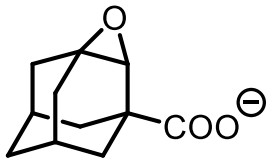


isolated



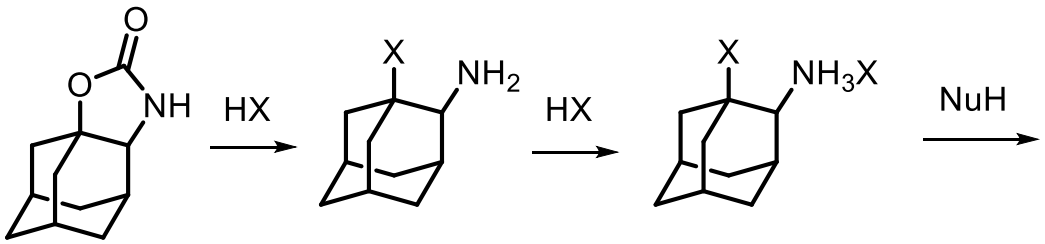
Mlinarić-Majerski, K.; Kaselj, M. *J. Org. Chem.* **1994**,*59*, 4362-4363.

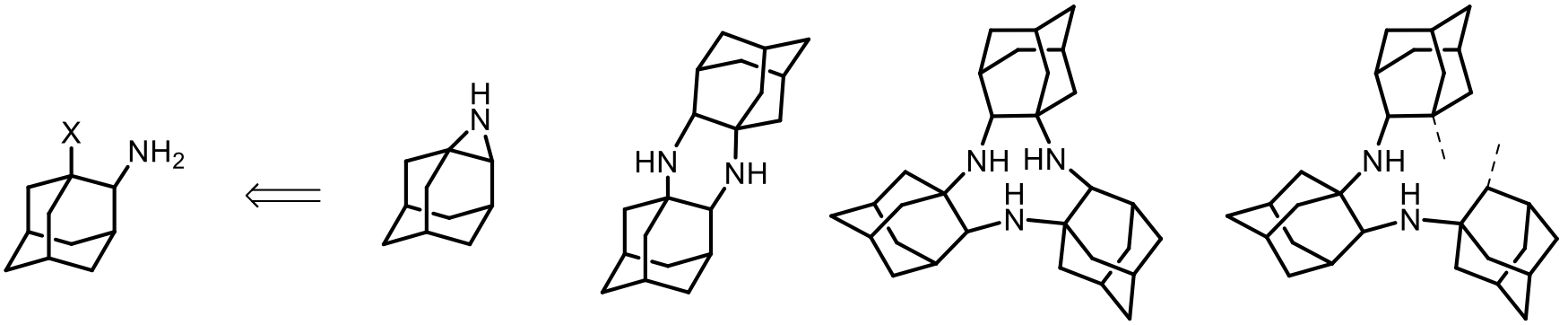
MS detection



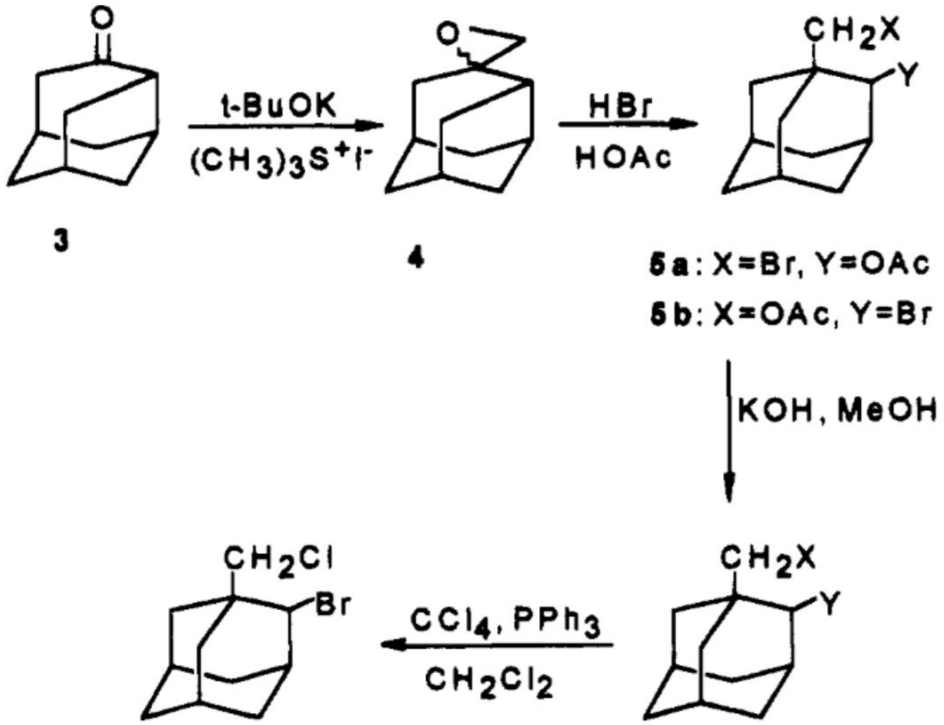
Harman, D. G.; Blanksby S. J. *Org. Biomol. Chem.* **2007**,*5*, 3495–3503.

Decarboxylation in solution:





Synthesis of cyclopropane ring



Acknowledgement

Christian Eschmann

Fabian Metz

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Funding: Loewe SynChemBio project