

Rh-Catalyzed Nitrene Insertionen towards Oxazolidinones

Presentation about my Spezialisierungsmodul
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C-H Functionalization

- Origins of Nitrene-Chemistry

- The „Du Bois-Reaction“ for Rh-Catalyzed C-H Amination

- Nitrenoid Selectivity

- Motivation & Aim

Results

- Synthesis of Carbamates

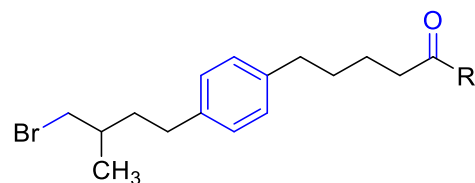
- Rh-Catalyzed Nitrene Insertion

Summary

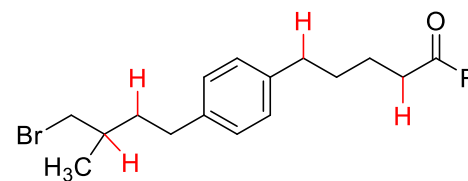
Outlook (Masterthesis)



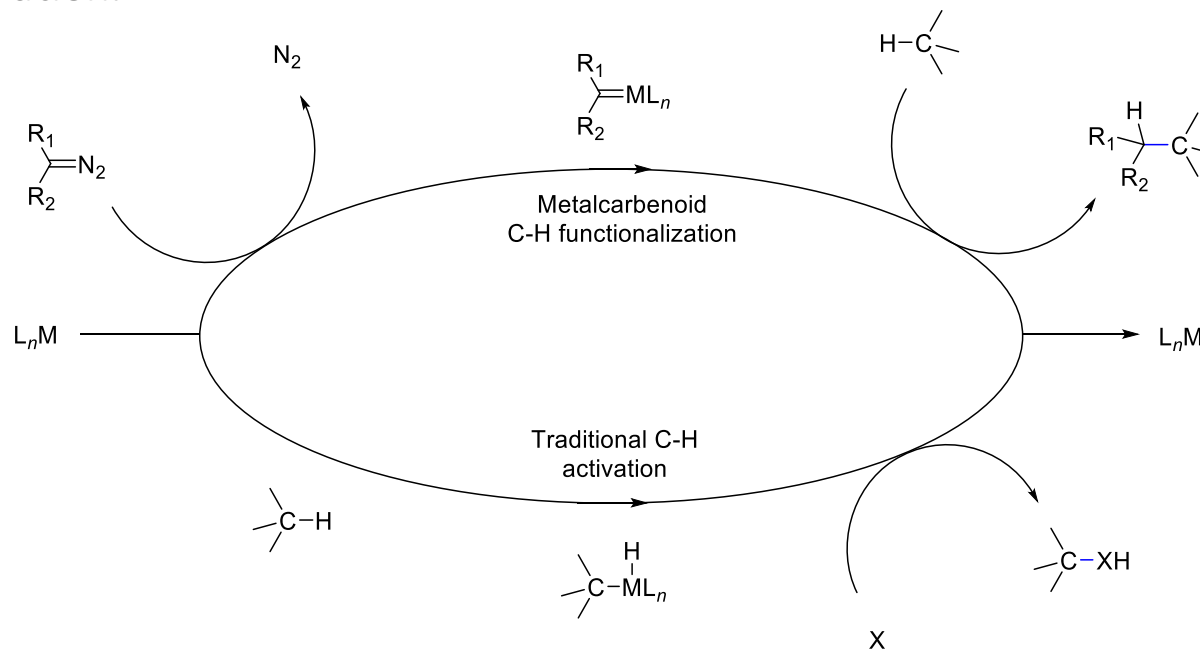
Functional group modification



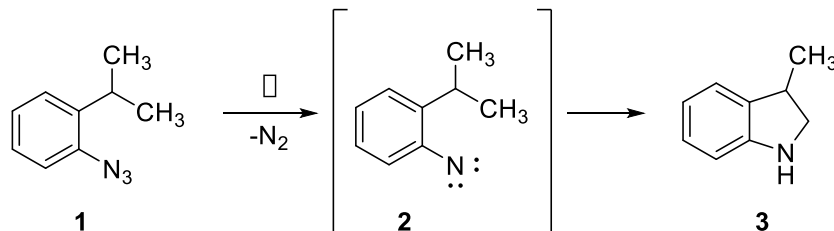
Direct C-H functionalization



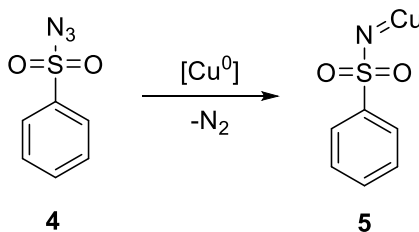
C-H functionalization:



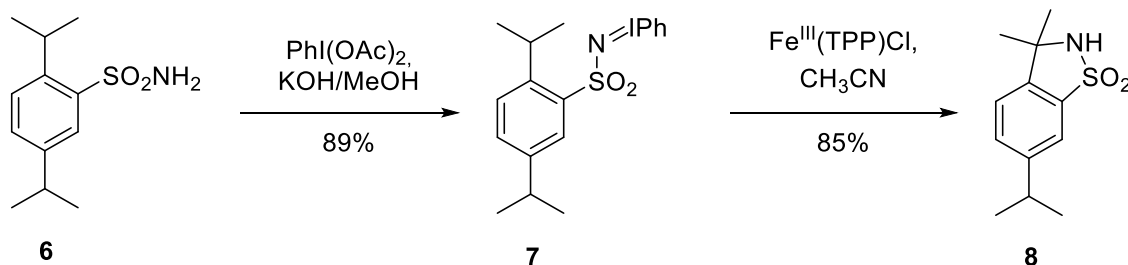
Smolinsky, Lwowski, Edwards, Breslow: Generation of nitrenes



Kwart & Kahn: Metal catalyzed generation of nitrenes



Breslow: Metal catalyzed intramolecular nitrene insertion

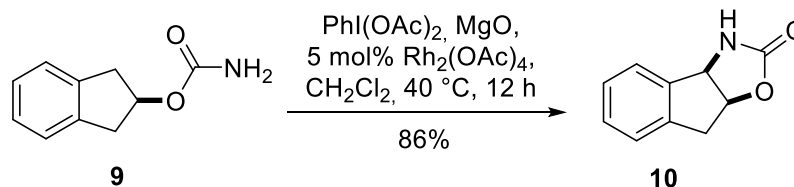


G. Smolinsky, *J. Org. Chem.* **1961**, 26, 4108–4110, D. S. Breslow, M. F. Sloan, N. R. Newburg, W. B. Renfrow, *J. Am. Chem. Soc.* **1969**, 91, 2273–2279, H. Kwart, A. A. Kahn, *J. Am. Chem. Soc.* **1967**, 89, 1950–1951, R. Breslow, S. H. Gellman, *J. Am. Chem. Soc.* **1983**, 105, 6728–6729.

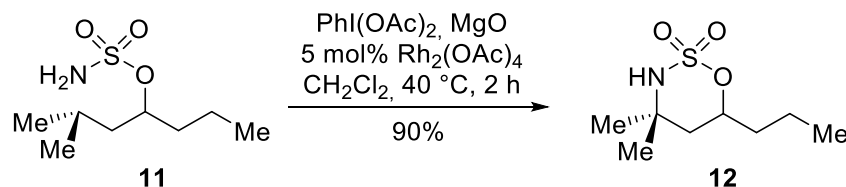


2001: Espino & Du Bois

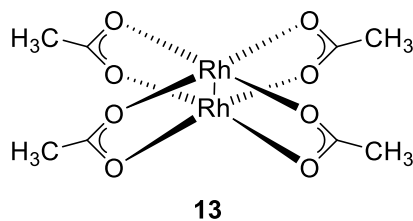
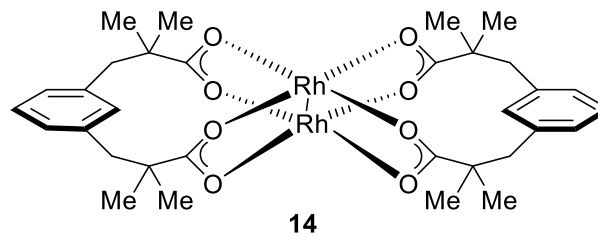
„Du Bois Reaction“



Nitrene precursor: Carbamates (5-membered rings)
Sulfamates (6-membered rings)

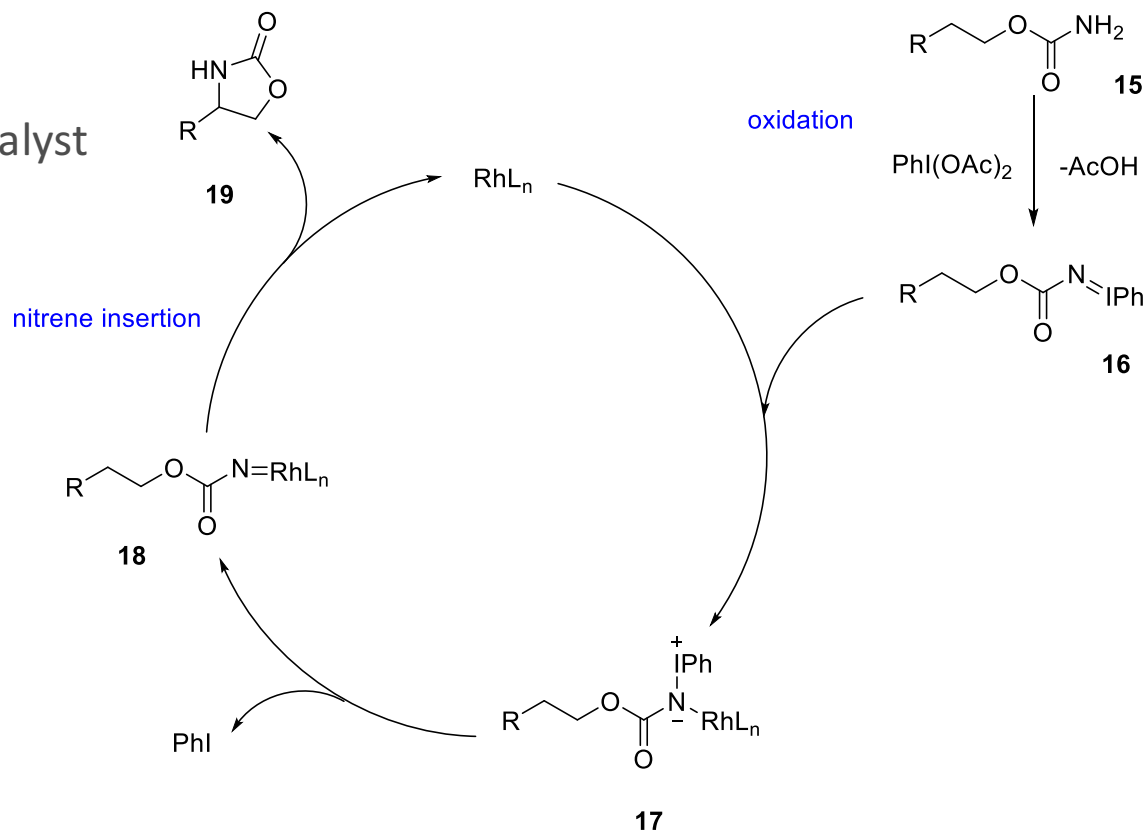


Catalysts:

 $\text{Rh}_2(\text{OAc})_4$  $\text{Rh}_2(\text{esp})_2$ 



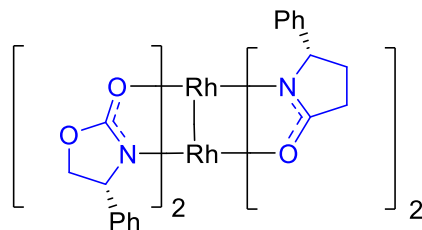
- *In-situ* oxidation with $\text{PhI}(\text{OAc})_2$
- MgO to catch AcOH
- Coordination of Rh-catalyst
- Nitrene insertion





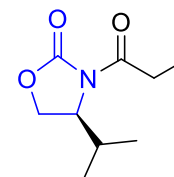
Versatile compounds:

Chiral catalysts: Doyle's Carboxamidates



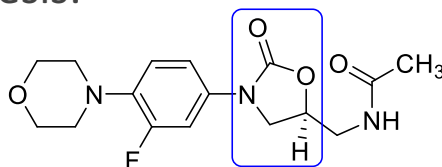
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Auxiliaries: Evans chemistry



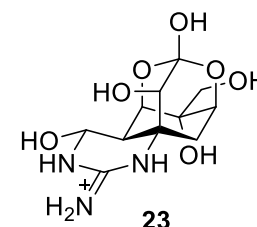
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Natural product synthesis:



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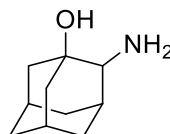
Linezolid



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Tetrodotoxin

Route to β -amino alcohols:



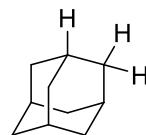
24

F. Collet, C. Lescot, P. Dauban, *Chem. Soc. Rev.* **2011**, 40, 1926–1936, D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, 103, 2109–2127, A. Hinman, J. Du Bois, *J. Am. Chem. Soc.* **2003**, 125, 11510–11511, H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, 103, 2861–2903, J. J. Rohde, M. A. Pliushchev, B. K. Sorensen, D. Wodka, Q. Shuai, J. Wang, S. Fung, K. M. Monzon, W. J. Chiou, L. Pan, *J. Med. Chem.* **2007**, 50, 149–164.

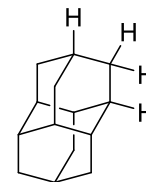


Selective functionalization of Diamandoids challenging

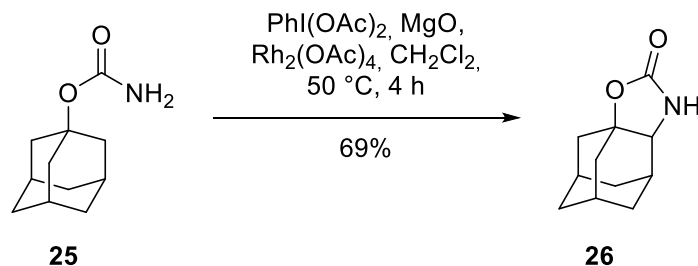
Adamantane: 3° Carbon vs. 2° Carbon



Diamantane: 3° apical Carbon vs. 3° medial Carbon vs. 2° Carbon

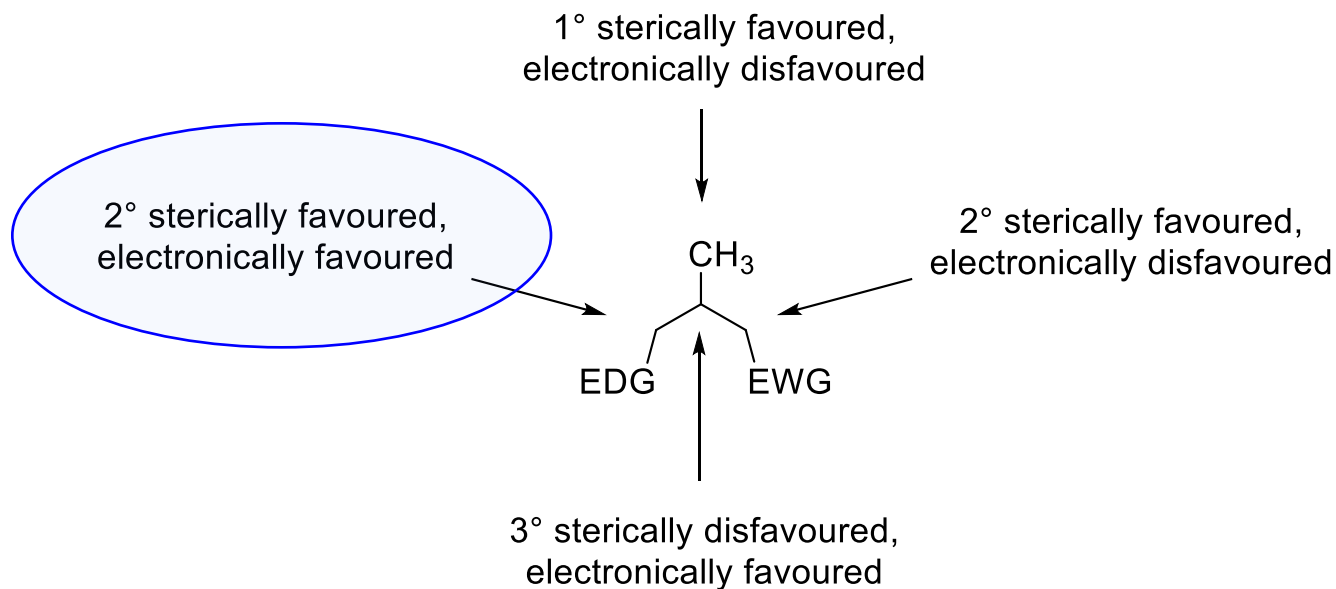
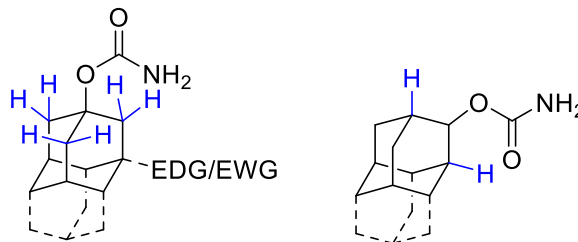


State of the Art: (Rhode *et. al*)



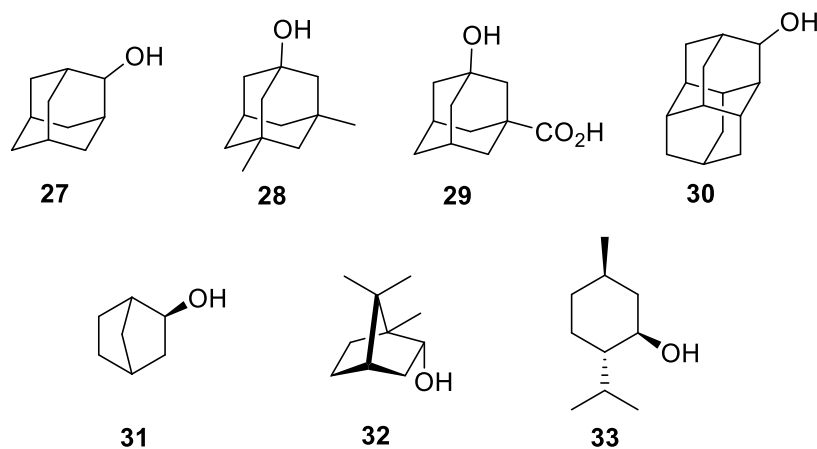


Carbenoid & Nitrenoid reactivity & selectivity

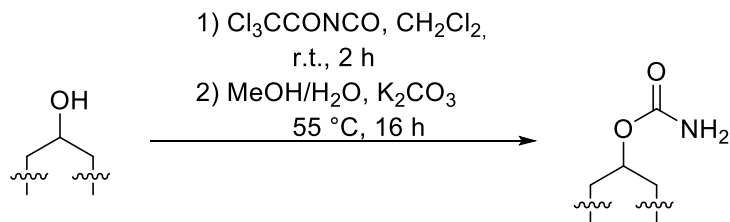




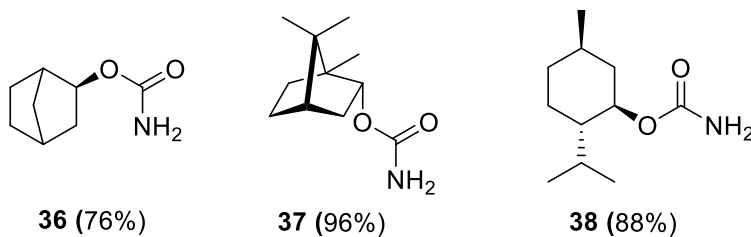
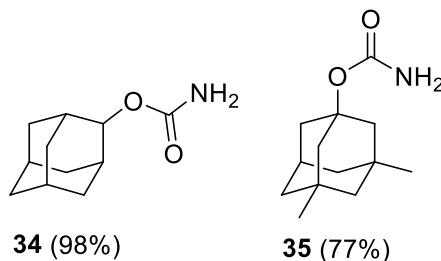
Rh-catalyzed Nitrene insertions starting from different substrates



- Optimization of reaction parameters (solvent, temperature,...)
- Selectivities
- Catalysts: $\text{Rh}_2(\text{OAc})_4$ vs. $\text{Rh}_2(\text{esp})_2$

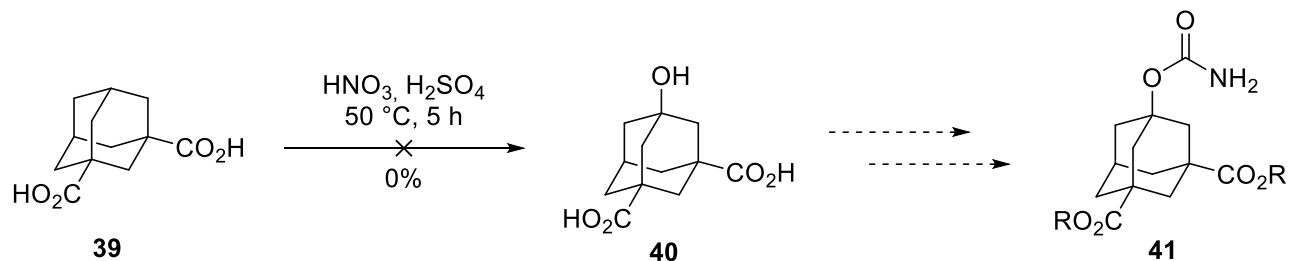


- Formation of the isocyanate
- Subsequent basic hydrolysis to the carbamate

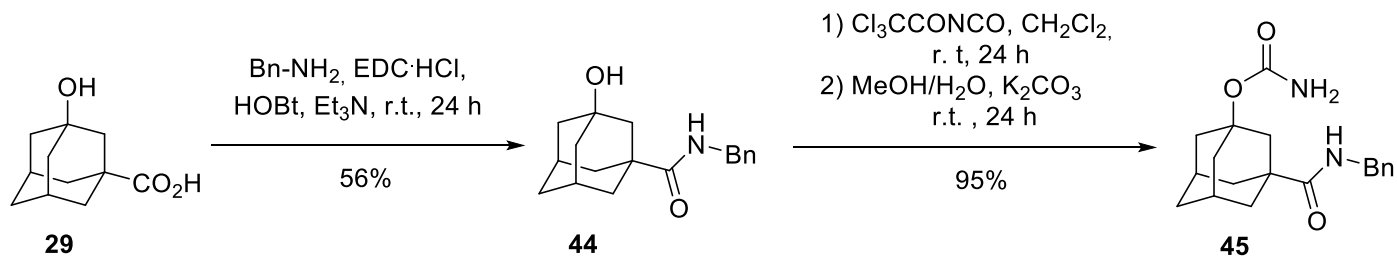
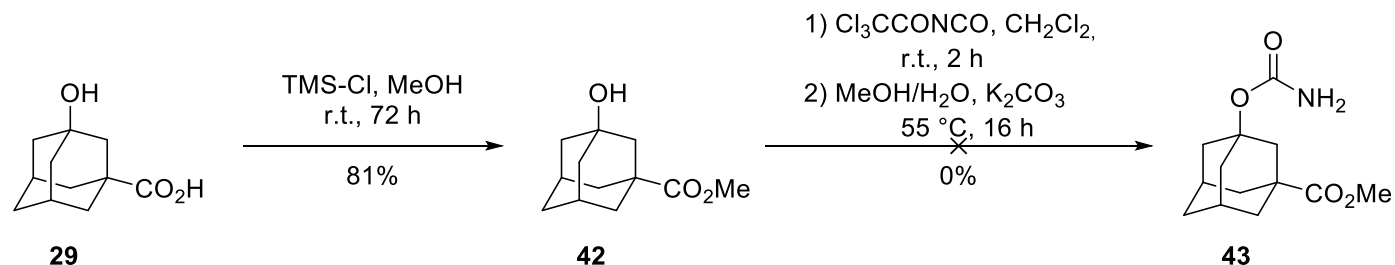


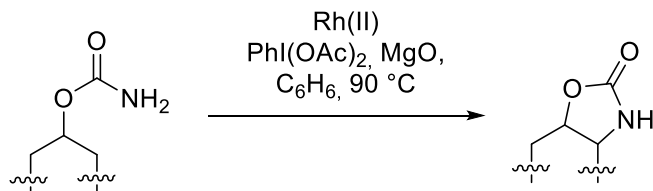


Substrate with electron withdrawing groups (EWG):

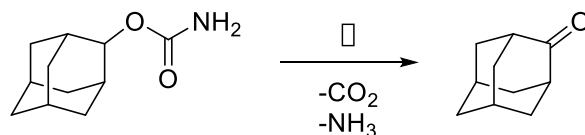


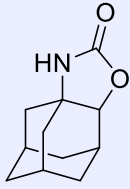
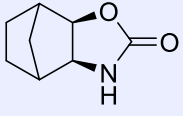
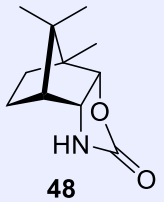
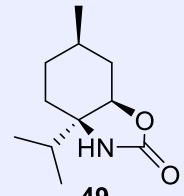
alternative:

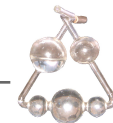




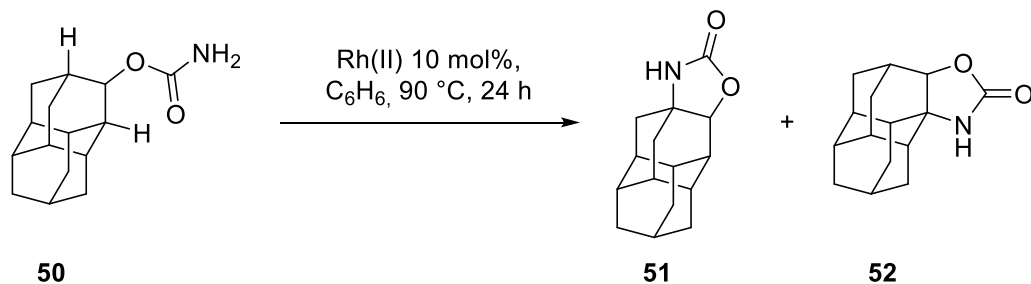
side reaction:



	 46	 47	 48	 49
$\text{Rh}_2(\text{OAc})_4$ CH_2Cl_2	0%	0%	0%	0%
$\text{Rh}_2(\text{OAc})_4$ C_6H_6	< 5%	9%	< 25%	16%
$\text{Rh}_2(\text{esp})_2$ C_6H_6	56%	24%	25%	45%

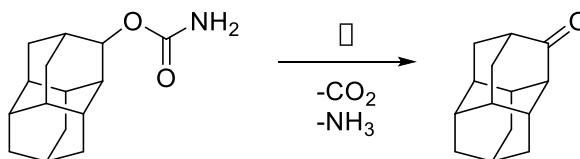


apical vs. medial:



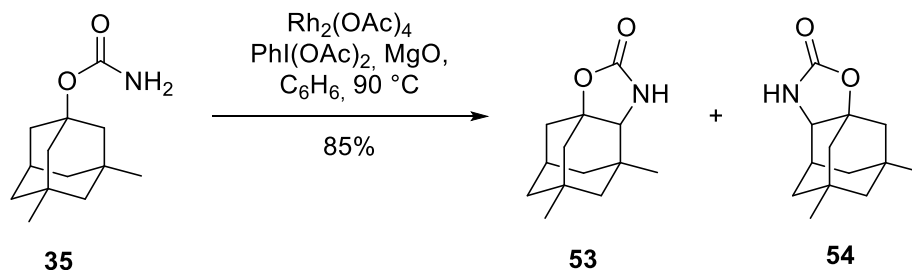
catalyst	apical : medial	conversion [%]
Rh ₂ (OAc) ₄	2:1	29
Rh ₂ (esp) ₂	2.6:1	35
Rh ₂ (S-DOSP) ₄	1.8:1	30

side reaction:

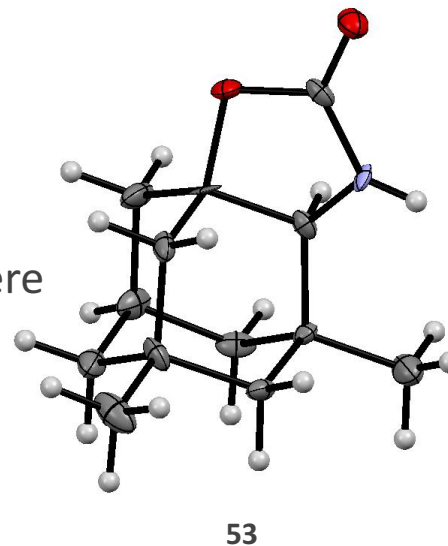




- Electron donating group

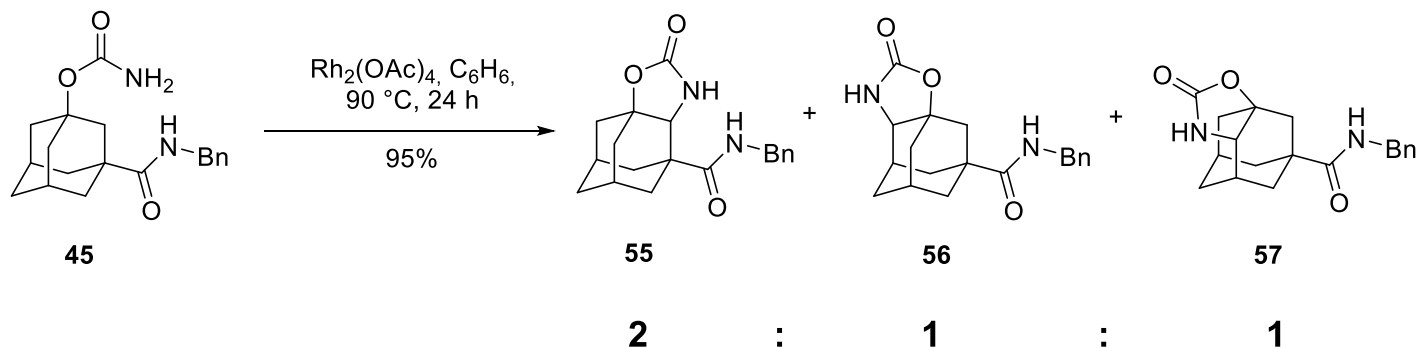


- Ratio of diastereomeres: 3:1
- Diastereomeres have not been separated
 - Main product has not been identified
- Crystal structure: electronically unfavoured diastereomere
- Separation via HPLC?

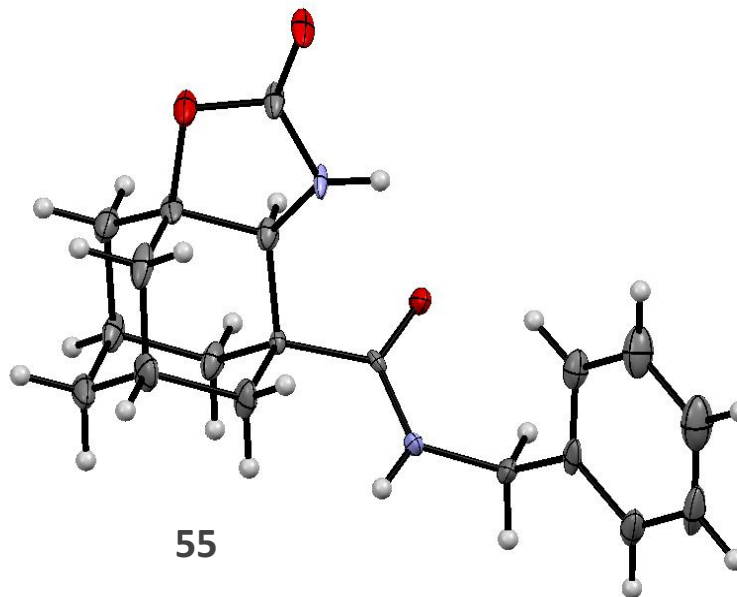


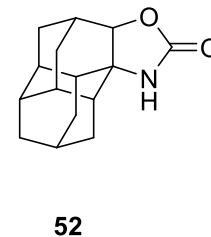
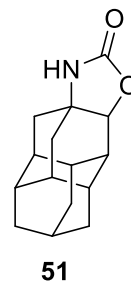
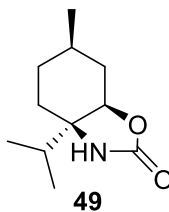
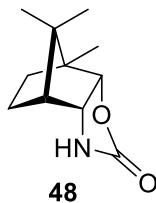
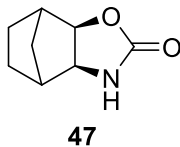
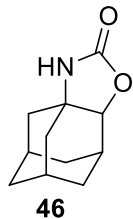


- Electron withdrawing group

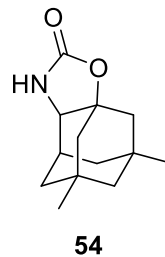
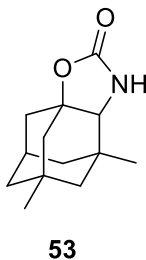


- Main product = electronically unfavoured product **55**
- Benzylamine as directing group

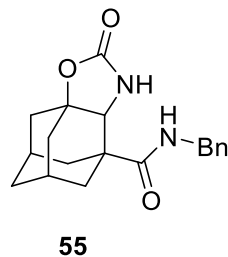




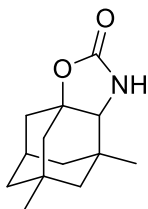
- $\text{Rh}_2(\text{esp})_2 \gg \text{Rh}_2(\text{OAc})_4$
- $\text{C}_6\text{H}_6 \gg \text{CH}_2\text{Cl}_2$
- Poor yields on secondary carbamates (side reaction)
- Apical **51** favoured product



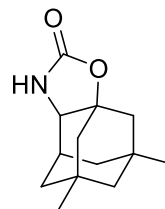
- Mixture of **53** & **54**
- **53** crystallized



- **55** main product

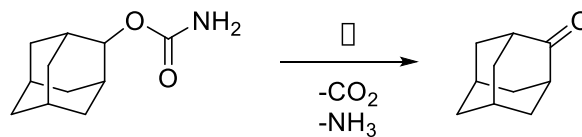


53

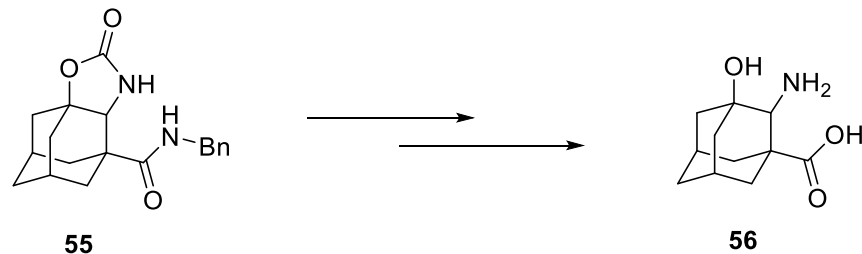


54

- Separation of diastereomers **53** & **54**
- Identification of the main product



- Conditions to suppress the side reaction

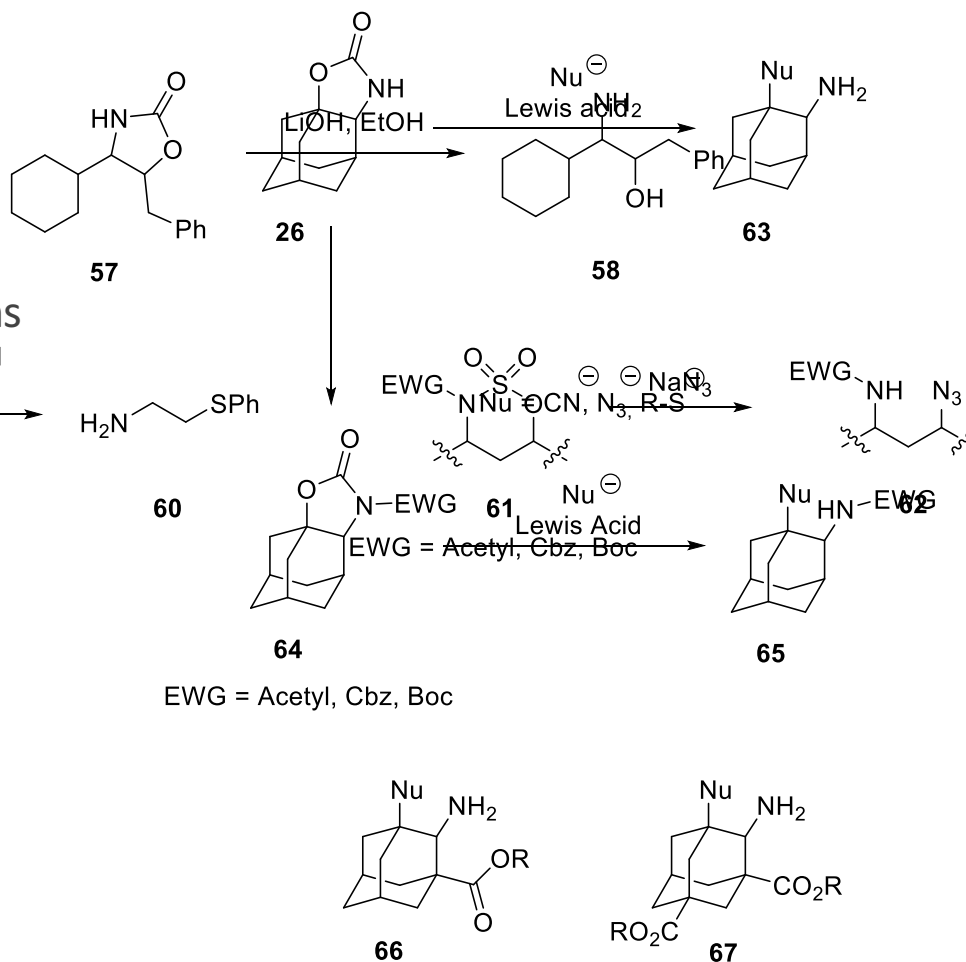


- Opening of the oxazolidinone to β -amino acid



Known ring openings of oxazolidinones & oxathiazinanes

- Soft nucleophiles
- Solvents for S_N1 reactions
- Lewis acids
- Ring activation via EWG
- Microwave synthesis
- Decarboxylation





Prof. Dr. Peter R. Schreiner,
Dr. Radim Hrdina,
Fabian Metz, Jan-Philipp Berndt
AG Schreiner

⁹⁰ Th Thorium	¹²⁴ A Adamantium	⁷ N Nitrogen	¹⁹ K Potassium	¹⁶ S Sulpher
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