The impact of substituents and cycle size on the regioselectivity of the Beckman rearrangement in annulated cyclic ketones

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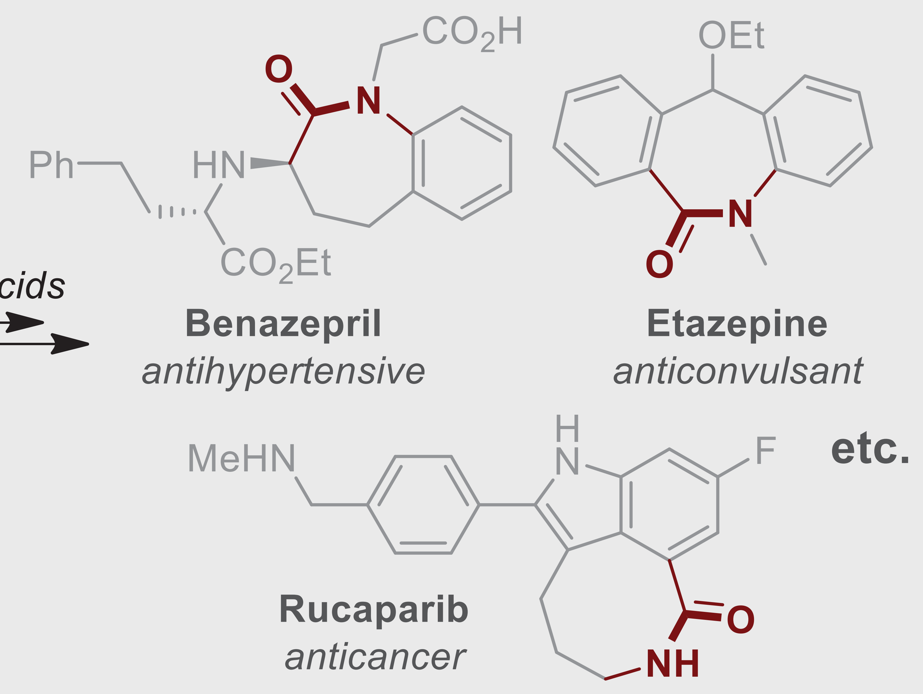
Background of the project

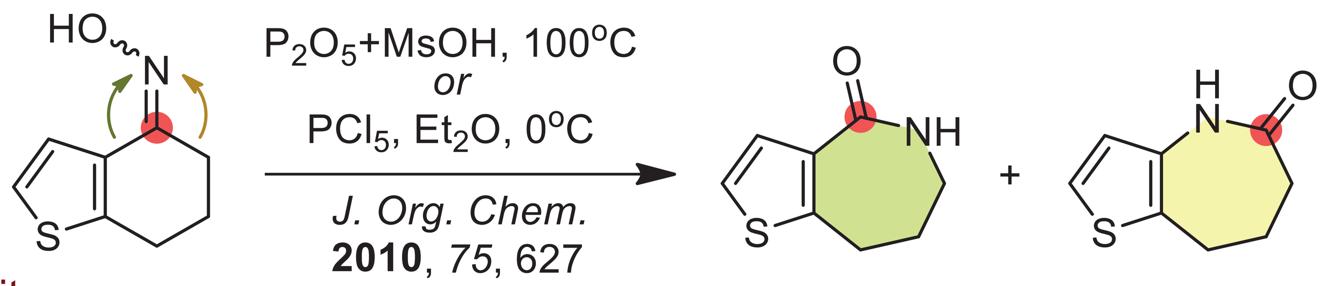
The Beckmann rearrangement is a highly versatile and industrially important reaction that plays a crucial role in the production of polymers & pharmaceuticals due to its ability to efficiently produce lactams and amides.

BECKMANN REARRANGEMENT
- pharmaceuticals
- natural products
- industrial application

amides
lactams
amino acids



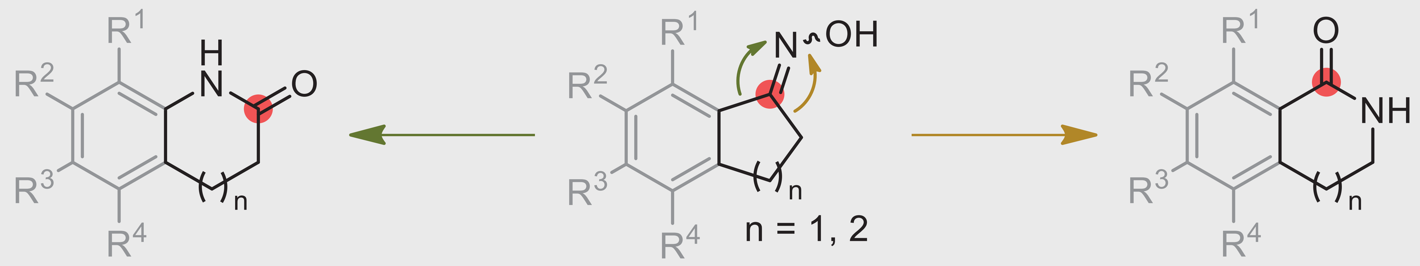
OBSTACLE: Low regioselectivity of the Beckmann rearrangement of bicyclic aryl ketones poses a great problem to its wide application in synthetic organic and process chemistry:



regioselectivity is usually unclear

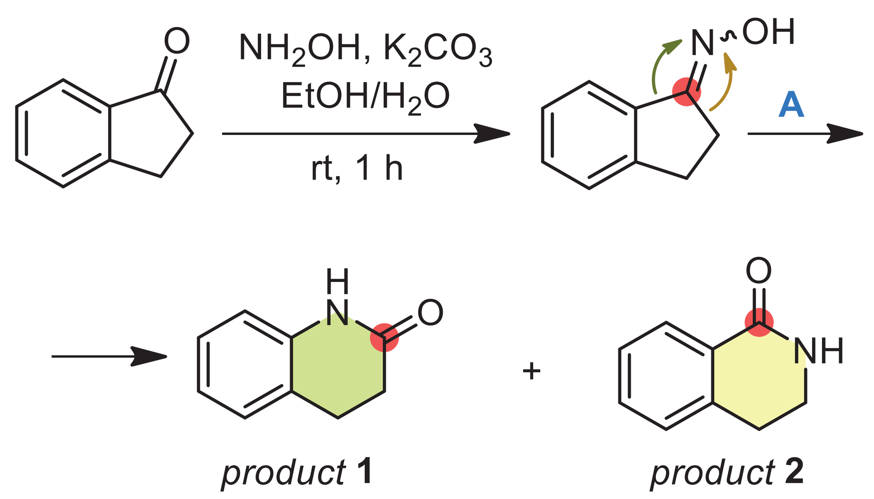
Regiochemical problem		
P_2O_5+MsOH	60%	30%
PCl_5	8%	32%

THIS PROJECT:
- **bicyclic aryl ketones** with cyclopentane and cyclohexane moieties
- A wide range of **EWG, 'neutral', and EDG substituents** placed in the aromatic ring in different positions
- thoroughly **optimized rearrangement conditions**



- **n = 1:** 162 starting ketones were tested
- **n = 2:** 136 starting ketones were tested

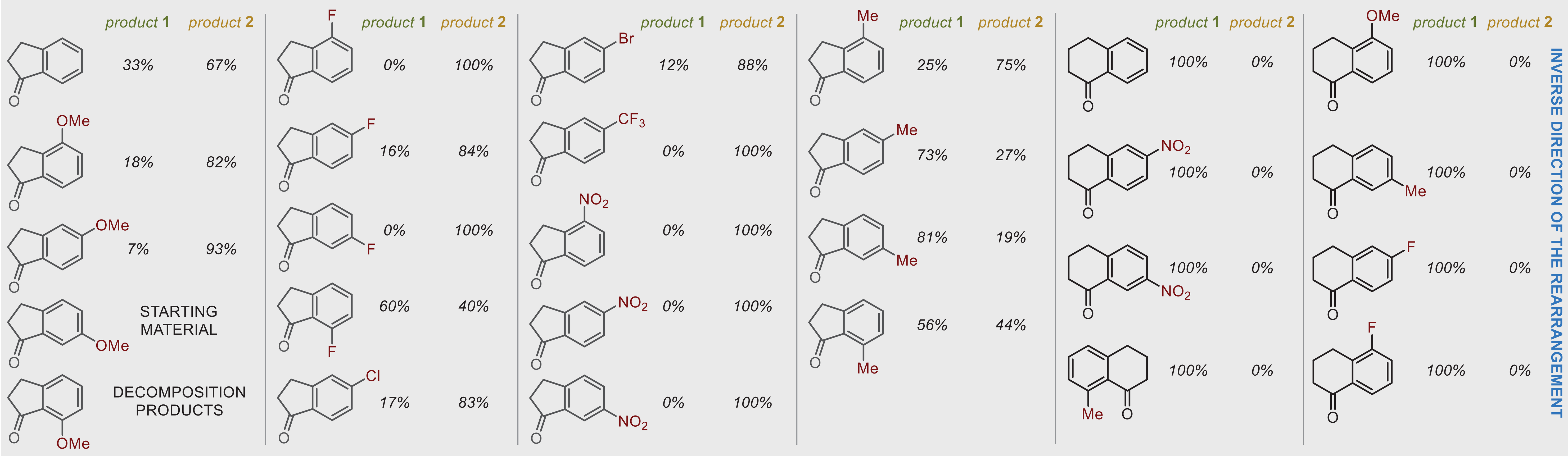
Optimization of the rearrangement conditions and 'structure/direction' relationships



CONDITIONS A

1) MsCl, DCM, rt, 1 h (*0%*)
2) MsCl, DCM, rt, 3 h (*3%*)
3) MsCl, DCM, rt, 12 h (*7%*)
4) MsCl, DCM, rt, 24 h (*9%*)
5) TsCl, Pyridine, rt, 3 h (*4%*)
6) TsCl, Pyridine, rt, 16 h (*15%*)
7) TsCl, Pyridine, 60 °C, 3 h (*18%*)
8) TsCl, Pyridine, 60 °C, 16 h (*34%*)
9) $SOCl_2$, THF, rt, 1 h (*7%*)
10) $SOCl_2$, THF, rt, 3 h (*13%*)
11) $SOCl_2$, THF, 50 °C, 1 h (*68%*)
12) $SOCl_2$, THF, 80 °C, 1 h (*84%*)
13) H_2SO_4 (conc.), rt, 3 h (*5%*)
14) H_2SO_4 (conc.), rt, 16 h (*8%*)
15) H_2SO_4 (conc.), 60 °C, 3 h (*15%*)
16) H_2SO_4 (conc.), 60 °C, 16 h (*33%*)
17) H_2SO_4 (conc.), 100 °C, 1 h (*68%*)
18) H_2SO_4 /H_2O (20%), rt, 16 h (*5%*)
19) H_2SO_4 /H_2O (20%), 60 °C, 3 h (*7%*)
20) H_2SO_4 /H_2O (20%), 60 °C, 16 h (*17%*)
21) PPA, 60 °C, 3 h (*4%*)
22) PPA, 60 °C, 16 h (*15%*)
23) PPA, 100 °C, 1 h (*54%*)
24) PPA, 100 °C, 3 h (*75%*)
25) PPA, 120 °C, 15 min (*86%*)
26) PPA, 150 °C, 5 min (*87%*)

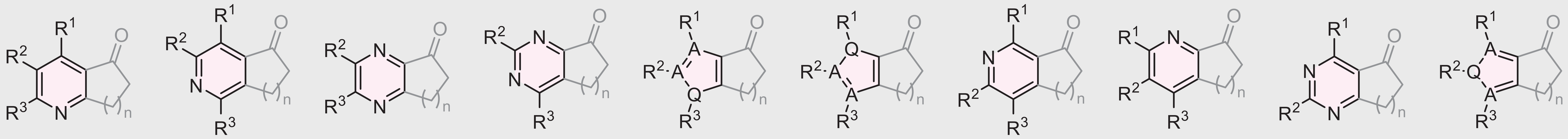
- Multiparameter optimization of rearrangement conditions includes different reagents, solvents, temperature modes, and reaction times
- Identified the three reaction conditions providing the best results, which were selected for the further substrates screening



Future horizons

- **DFT calculations and building a predicting model** for the studied aryl ketones allowing for the efficient expansion of the lactams chemical space
- To involve in the project **a wide range of heteroaromatic ketones** (208 substrates in total, n = 1, 2, Q = heteroatom, A = heteroatom or carbon)

CURENTLY ONGOING



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