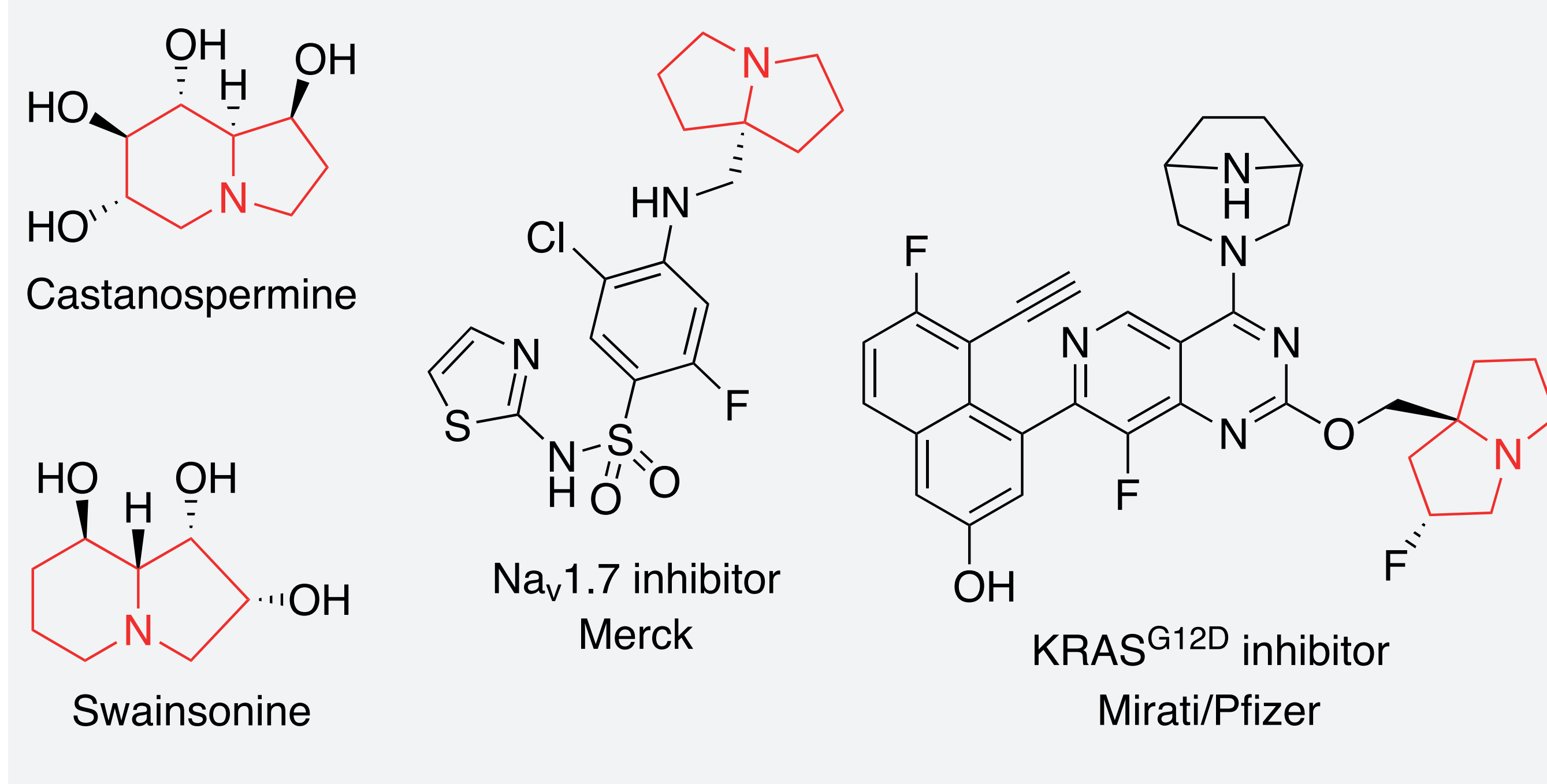


## 2-Substituted [1,2]-cycloannelated pyrrolidines and piperidines in the focus of medicinal chemistry

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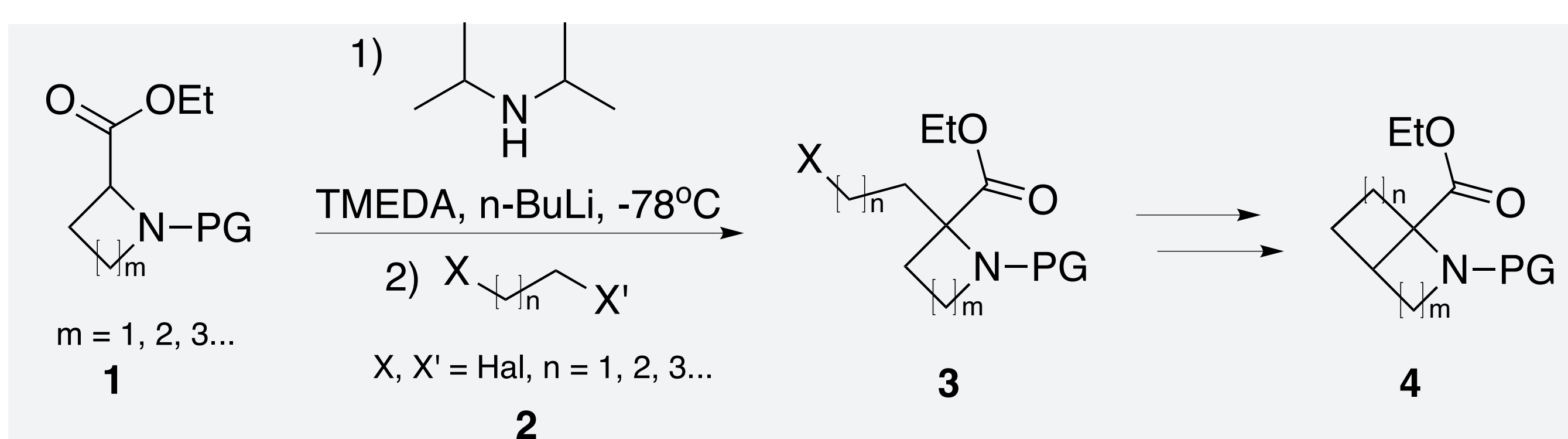
### Background of the research

- **Functionalized bicycloamines** occur frequently in Nature and drug discovery.
- Natural glucomimetic alkaloids swainsonine and castanospermine are important **pharmacophores** for treatment of cancer and hepatitis C, respectively.
- **Tetrahydro-pyrrolizidine** core was incorporated into Merck's voltage-gained **sodium ion channel Nav1.7 inhibitor**.
- A similar **fluorine-substituted block** was incorporated into the Mirati/Pfizer's drug, an **inhibitor of KRAS G12D proto-oncogene**.
- As the protein-binding conformation is 'locked', **conformationally limited drugs** tend to show higher potency and selectivity.
- Scalability is the key criterion for incorporating the compound for drug discovery, so we propose a **concise** and **scalable** approach to **2-substituted [1,2]-cycloannelated saturated azaheterocycles**.



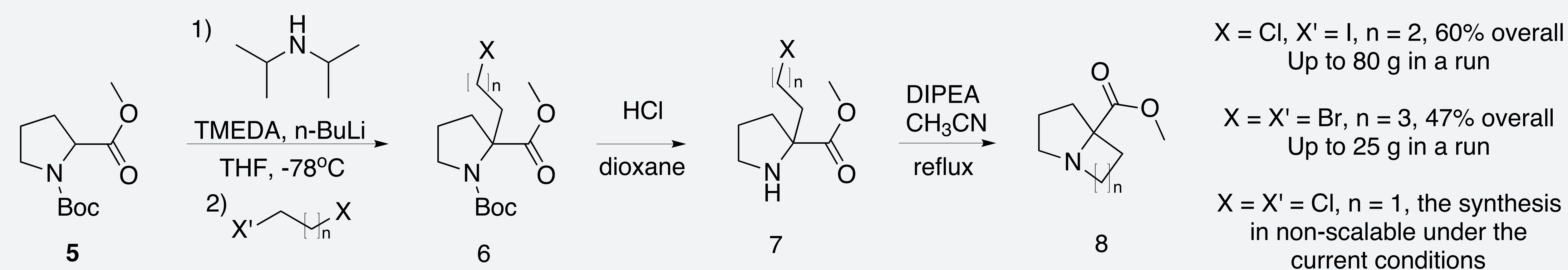
### Synthetic strategy

- **Scope and limitations** for different size of cycles (n, m) was analyzed.
- Cyclization efficiency was demonstrated as a dependent from the **n value** and **saturation degree** of **2**.
- Synthetic sequence is **atom-efficient** and **shorter** than analogous attempts.

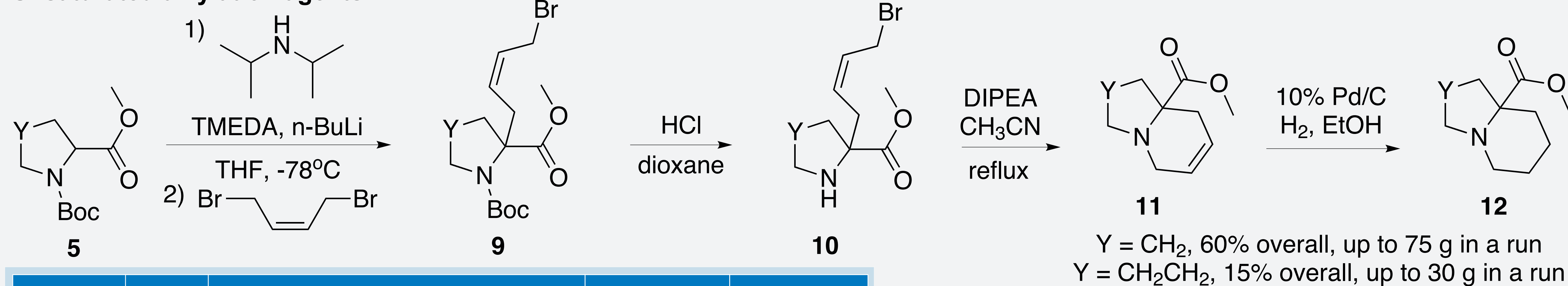


### Diversity of the products

#### Saturated alkylation agents

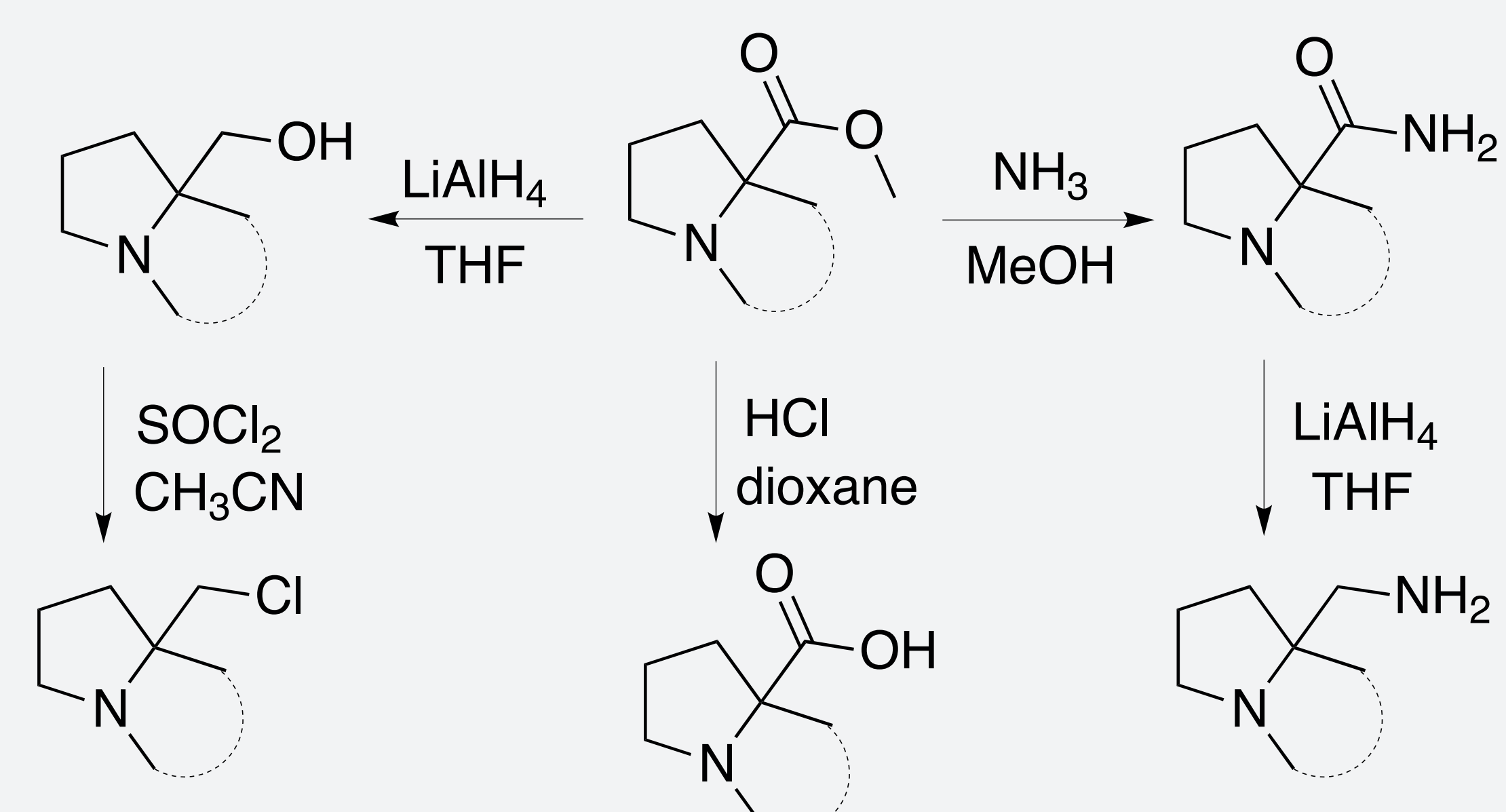


#### Unsaturated alkylation agents



m	n	Alkylation agent	Yield of alkylation	Yield of cyclization
4	2	1,2-dibromoethane	Traces	NA
4	3	1-chloro, 3-iodopropane	Traces	NA
4	4	1,4-dibromobuth-2-ene	Traces	NA
5	2	1,2-dibromoethane	84%	32%
5	3	1-chloro, 3-iodopropane	95%	64%
5	4	1,4-dibromoethane	88%	54%
5	4	1,4-dibromobuth-2-ene	80%	75%
6	2	1,2-dibromoethane	78%	traces
6	4	1,4-dibromobuth-2-ene	30%	54%

#### Functionalization of pyrrolizidines and indolizidines



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