

PERCH-CIC CONGRESS X:

2018 INTERNATIONAL CONGRESS FOR INNOVATION IN CHEMISTRY

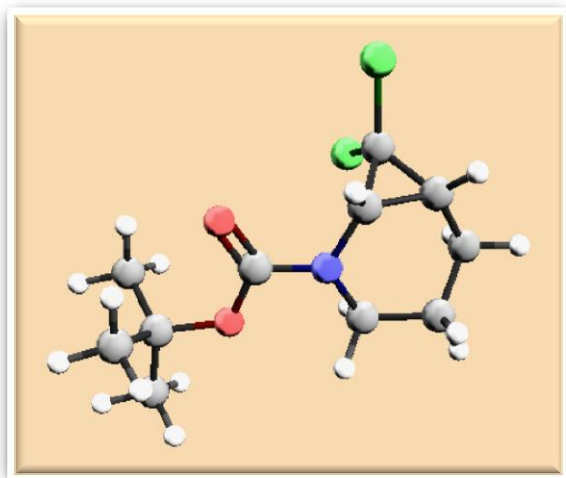
Contributing Expertise for THAILAND 4.0

July 4 - 7, 2018

Jomtien Palm Beach Hotel & Resort, Pattaya, Thailand



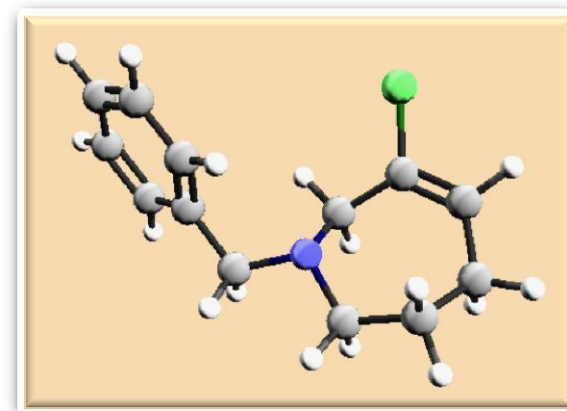
Bicyclic halogenated aminocyclopropanes as versatile precursors for the synthesis of functionalized azepanes and piperidines



Yvan Six

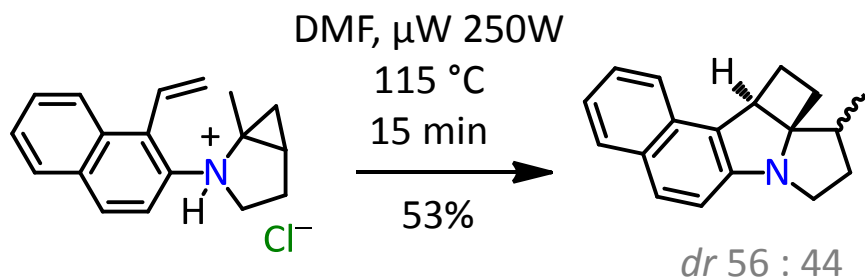
Laboratoire de Synthèse Organique
UMR 7652
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E-mail: yvan.six@polytechnique.edu

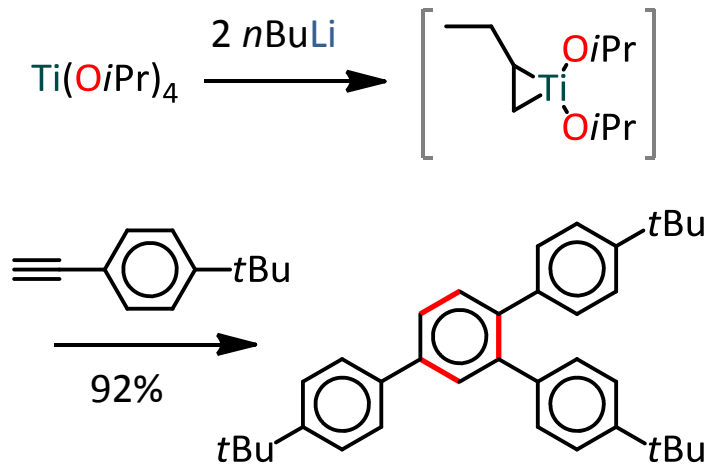


Research topics investigated in our group

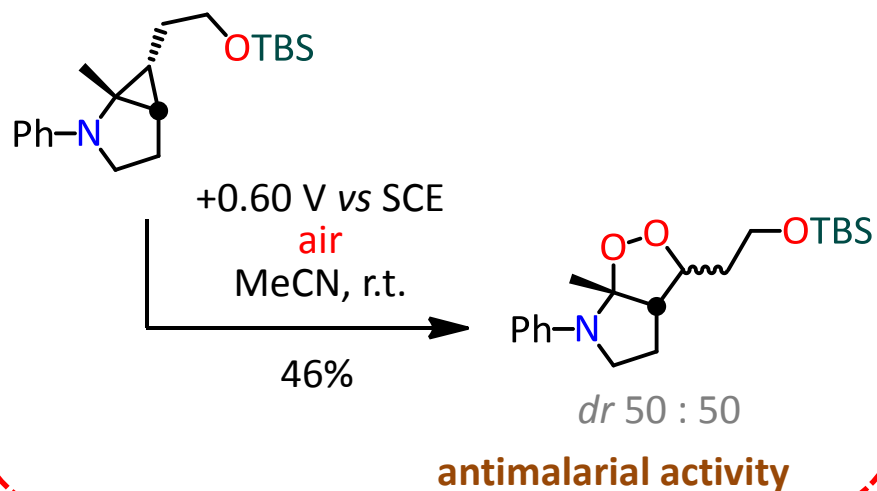
Aminocyclopropane chemistry



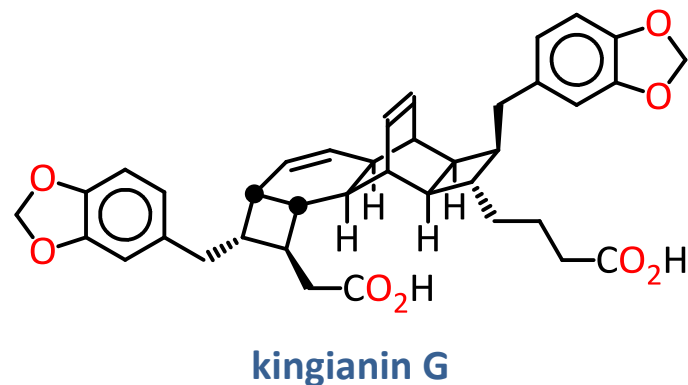
Transmetalation reactions with $\text{Ti}(\text{O}i\text{Pr})_4$



Synthesis of peroxides by aerobic oxidation



Natural product total synthesis



Contents of this talk

I. Background: some aminocyclopropane chemistry

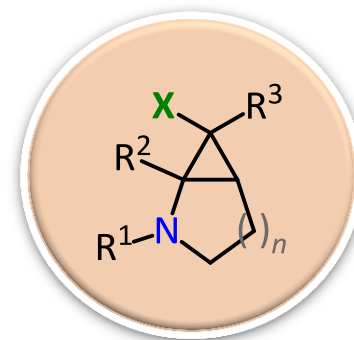
II. Preparation of bicyclic 2-halocyclopropane derivatives

III. Reductive alkylation / ring expansion

IV. Selectivity aspects

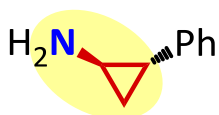
Summary

Acknowledgements



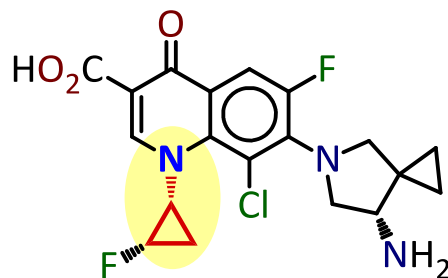
I. Background: some aminocyclopropane chemistry

Marketed aminocyclopropane drugs



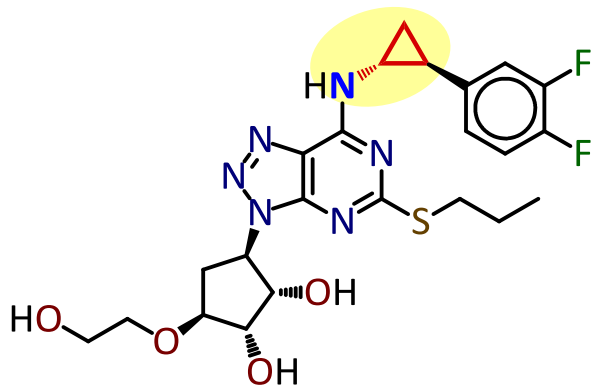
(±)-tranylcypromine

monoamine oxidase inhibitor
(major depressive disorder)



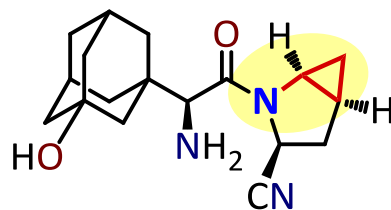
sitafloxacin

antibiotic (Buruli ulcer)



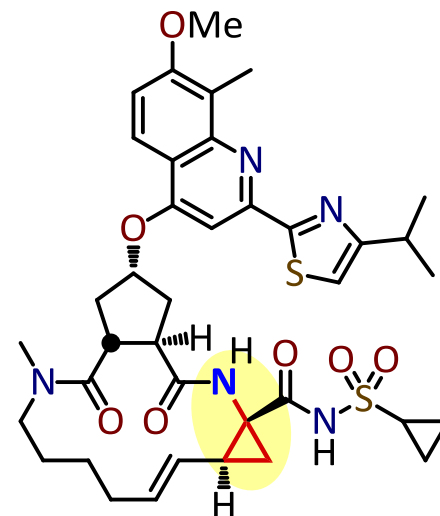
ticagrelor

platelet aggregation inhibitor
(acute coronary syndrome)



saxagliptin

DPP4-inhibitor
(type II diabetes)



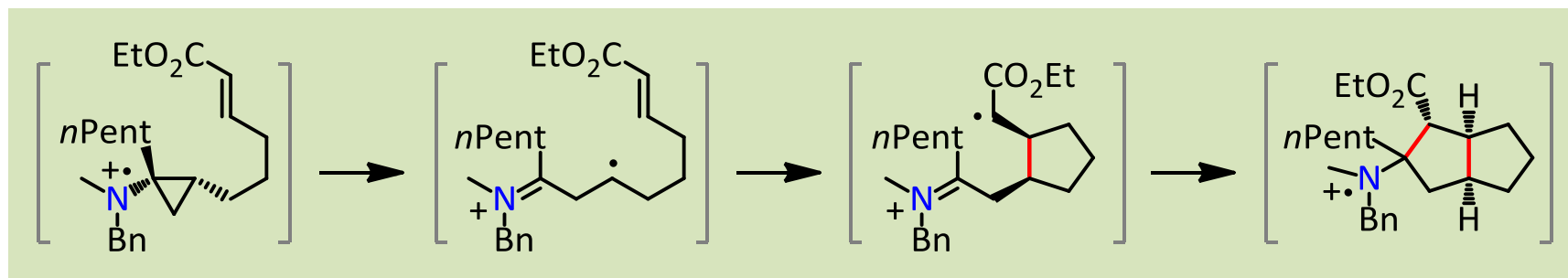
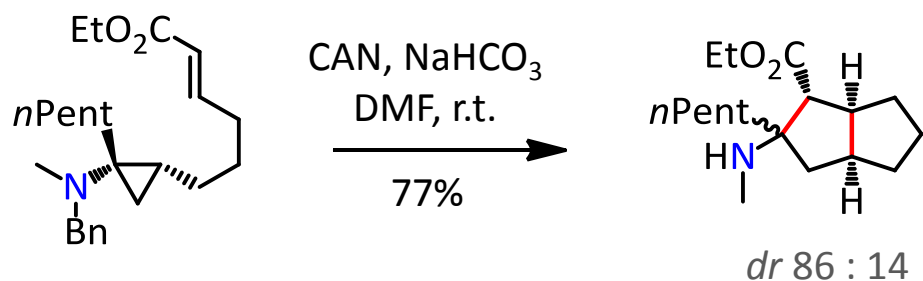
simeprevir

HCV protease inhibitor
(hepatitis C)

I. Background: some aminocyclopropane chemistry

Bicyclic aminocyclopropanes as precursors to nitrogen-containing systems

Single-electron oxidation

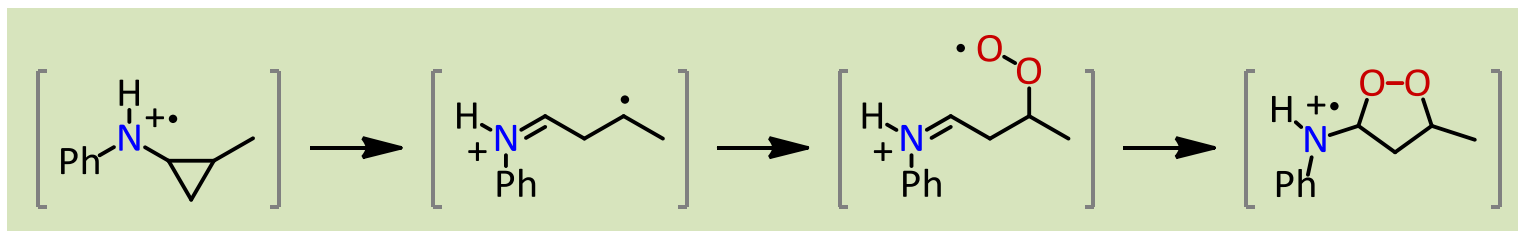
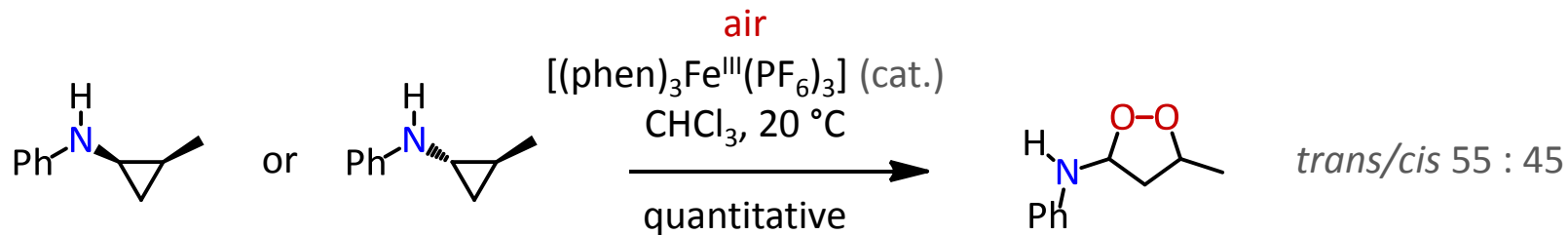


distonic cation radical

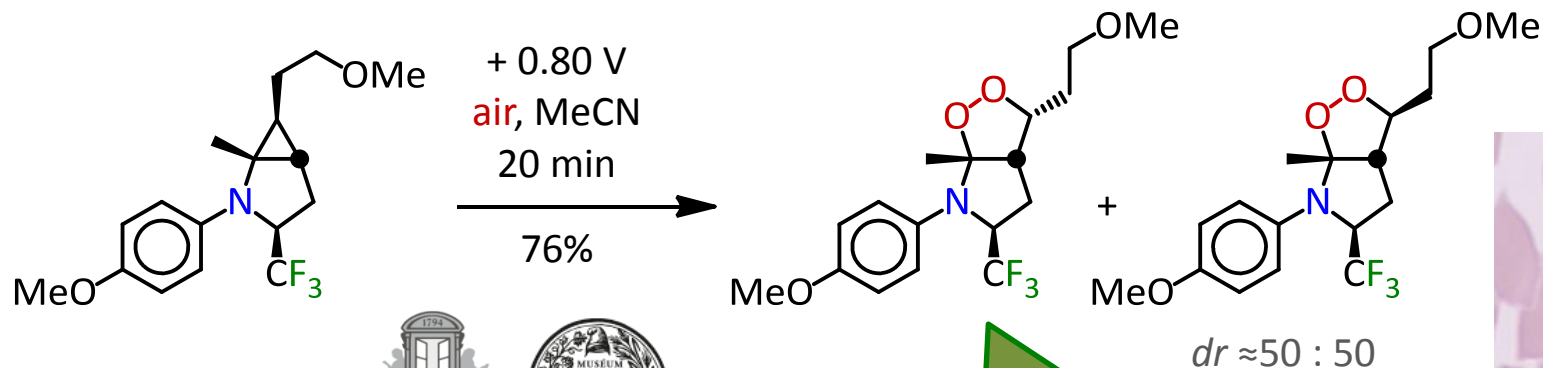
Y. Takemoto, S. Yamagata, S. Furuse, H. Hayase, T. Echigo, C. Iwata, *Chem. Commun.* **1998**, 651

See also: J. D. Ha, C. S. Blackstock, J. K. Cha, *J. Org. Chem.* **1998**, 63, 8510

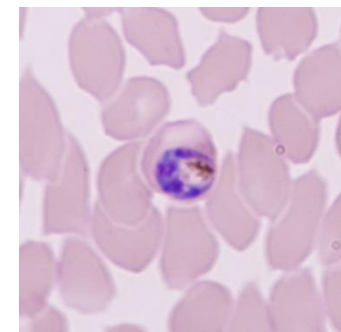
I. Background: some aminocyclopropane chemistry



K. Wimalasena, H. B. Wickman, M. P. D. Mahindaratne, *Eur. J. Org. Chem.* **2001**, 3811



IC₅₀ 1.1 μM



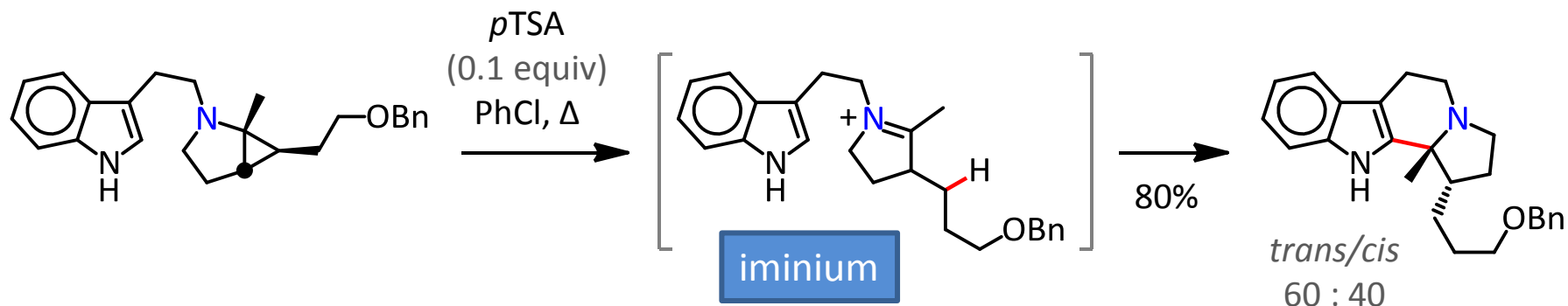
Plasmodium falciparum

C. Madelaine, Y. Six, O. Buriez, *Angew. Chem. Int. Ed.* **2007**, 46, 8046

C. Madelaine, O. Buriez, B. Crousse, I. Florent, P. Grellier, P. Retailleau, Y. Six, *Org. Biomol. Chem.* **2010**, 8, 5591

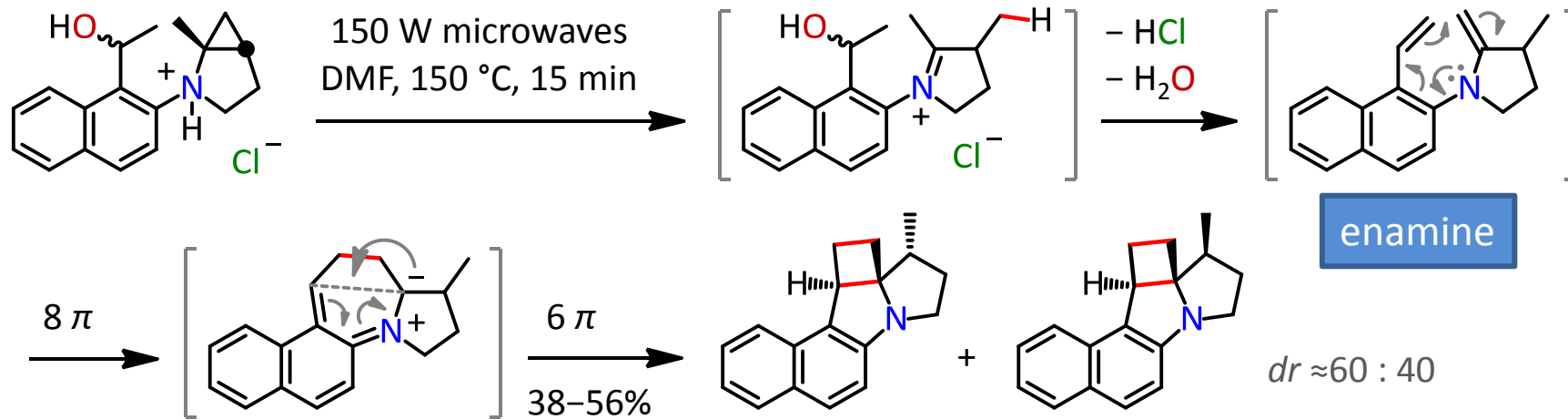
I. Background: some aminocyclopropane chemistry

Generation of iminium species by protonation



C. Madelaine, N. Ouhamou, A. Chiaroni, E. Vedrenne, L. Grimaud, Y. Six, *Tetrahedron* **2008**, *64*, 8878

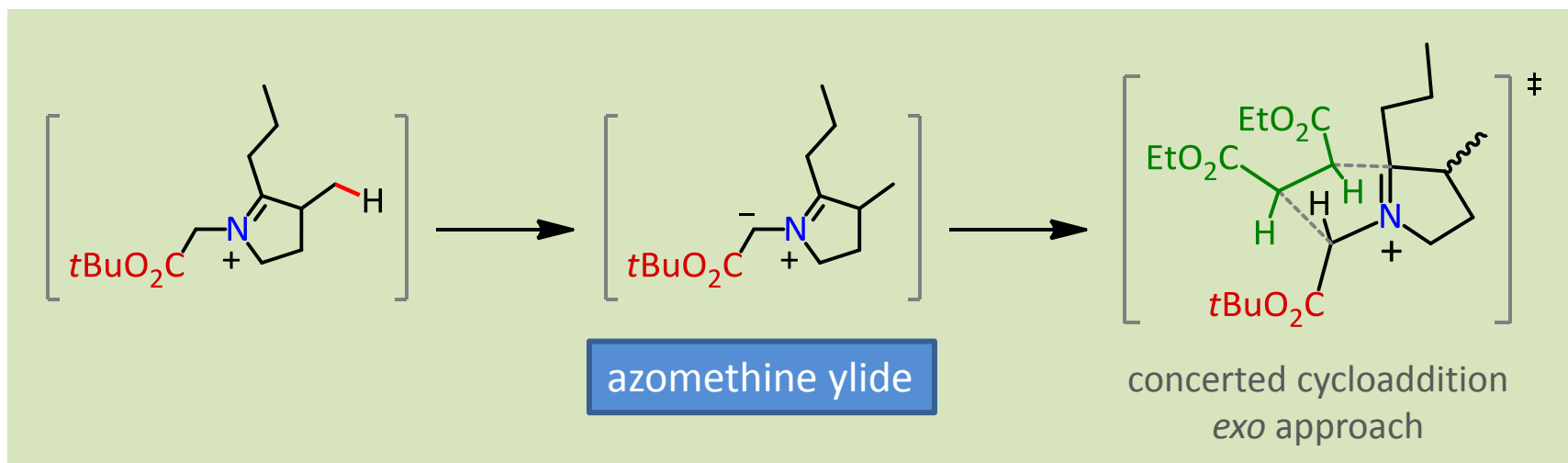
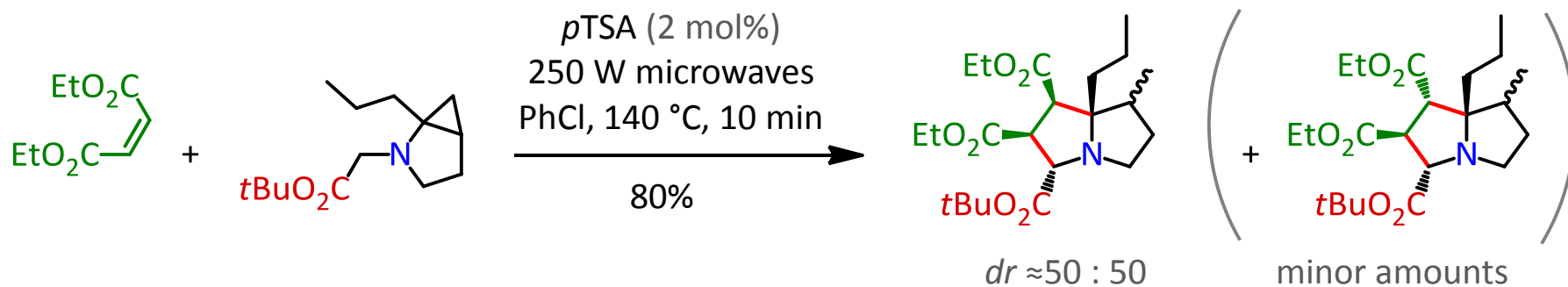
Generation of enamine intermediates



A. Wasilewska, B. A. Woźniak, G. Doridot, K. Piotrowska, N. Witkowska, P. Retailleau, Y. Six, *Chem. Eur. J.* **2013**, *19*, 11759

I. Background: some aminocyclopropane chemistry

1,3-Dipolar cycloadditions

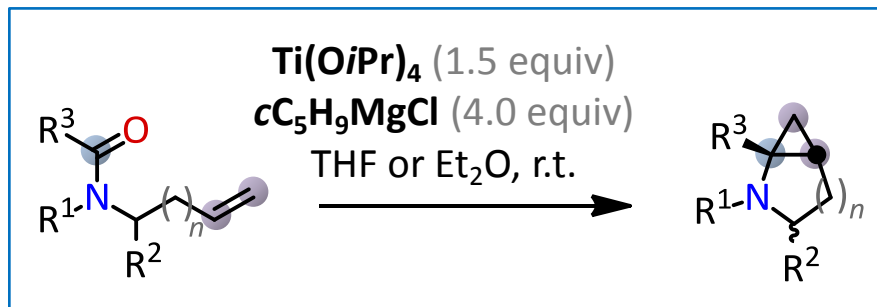


A. Wolan, J. A. Kowalska-Six, H. Rajerison, M. Césarío, M. Cordier, Y. Six,
Tetrahedron **2018**, 74, doi: 10.1016/j.tet.2018.05.082

I. Background: some aminocyclopropane chemistry

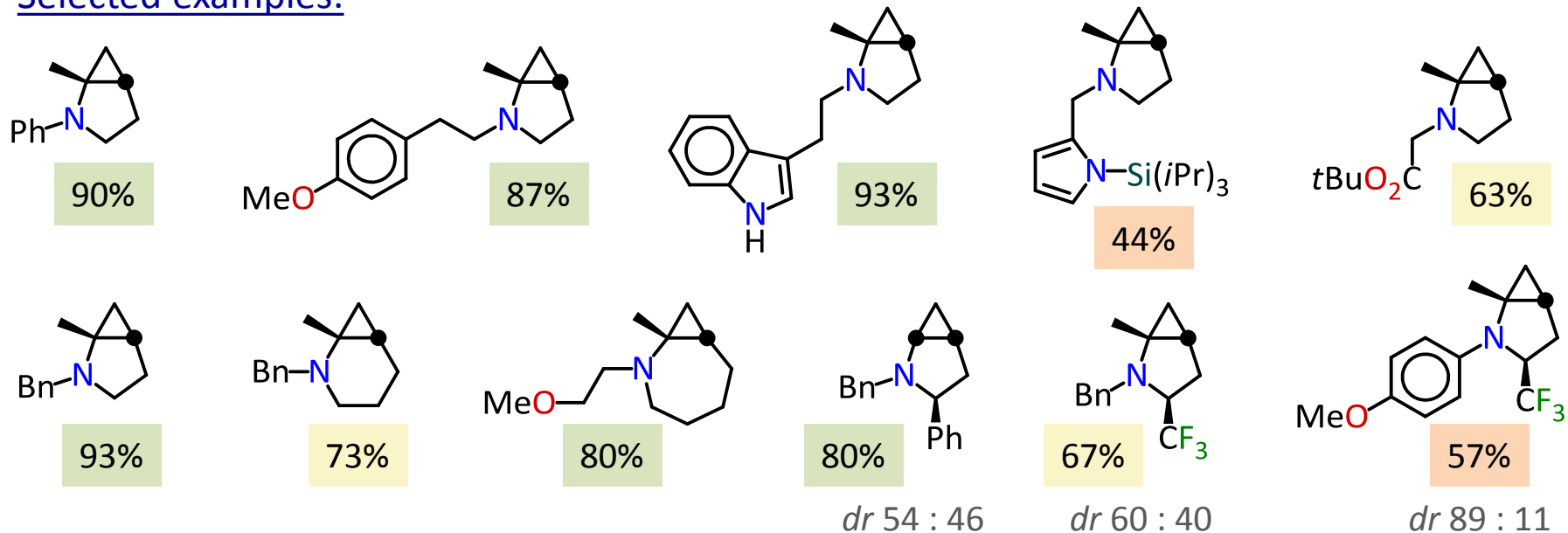
Synthesis of the substrates

Kulinkovich- de Meijere reaction (intramolecular)



First example:
J. Lee, J. K. Cha,
J. Org. Chem. **1997**, 62, 1584

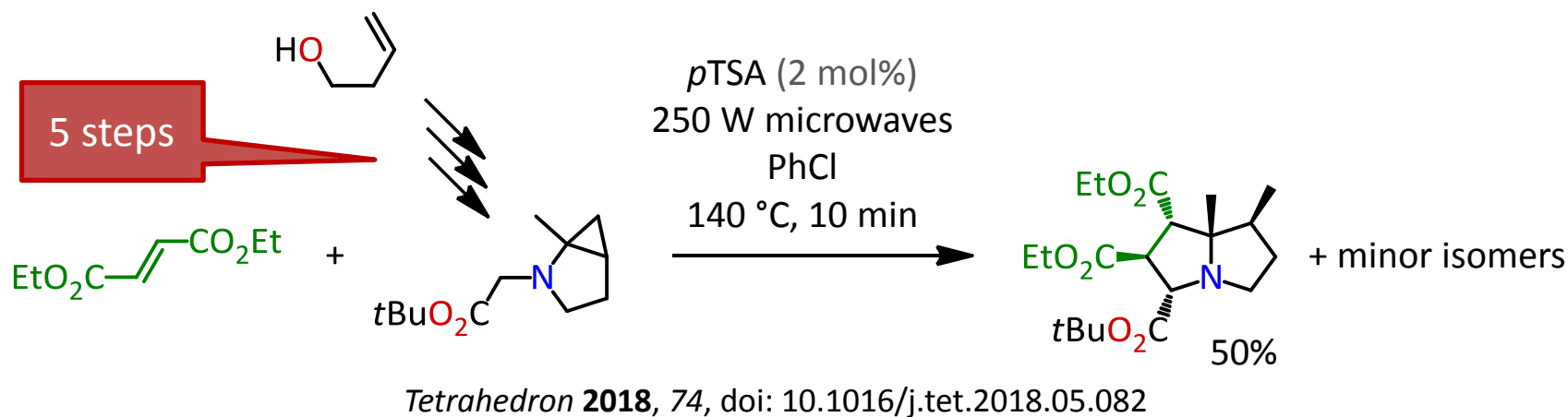
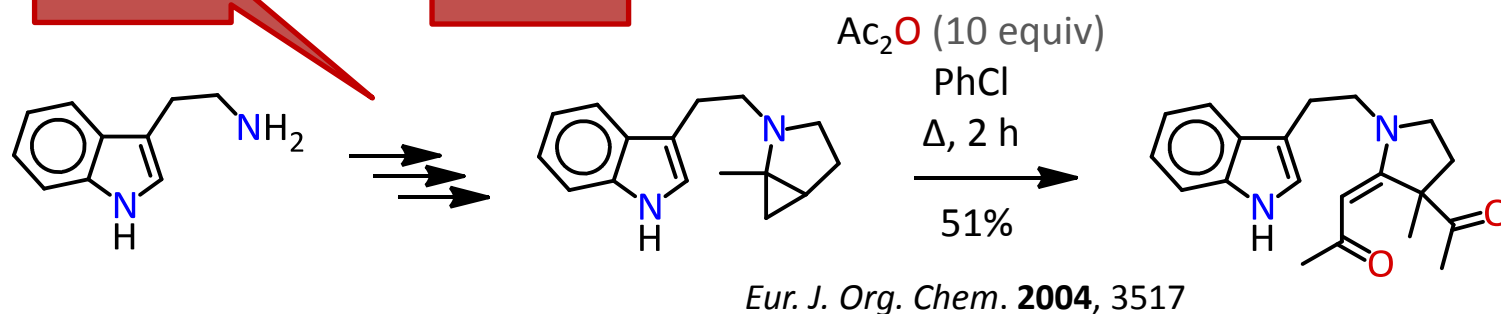
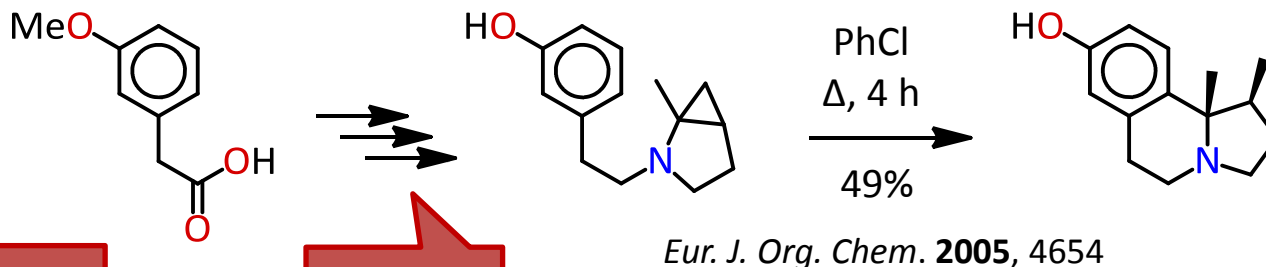
Selected examples:



Selected references from our group: *Org. Biomol. Chem.* **2003**, 1, 3007; *Angew. Chem. Int. Ed.* **2007**, 46, 8046;
Org. Biomol. Chem. **2010**, 8, 5591; *Chem. Eur. J.* **2013**, 19, 11759; *Tetrahedron* **2018**, 74, doi: 10.1016/j.tet.2018.05.082

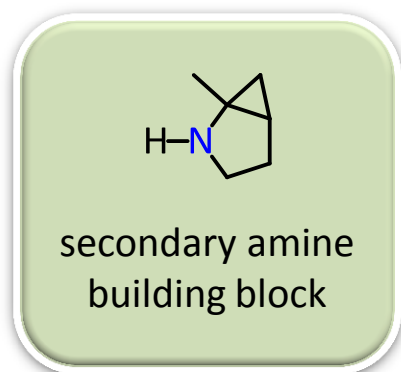
I. Background: some aminocyclopropane chemistry

The potential advantages of a modular approach

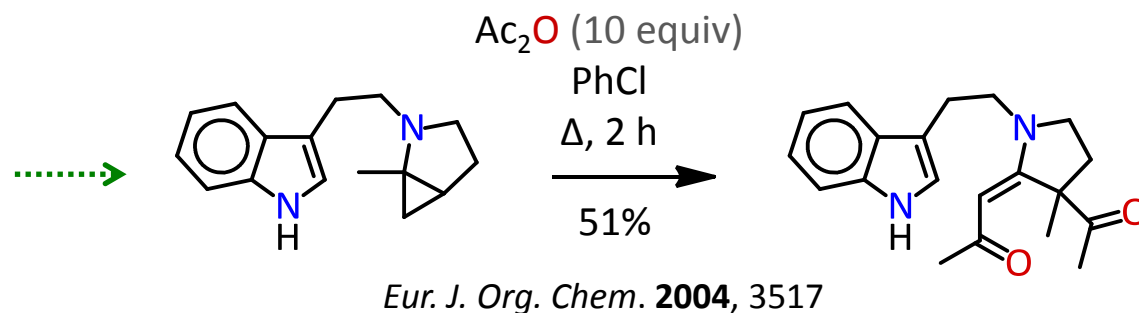
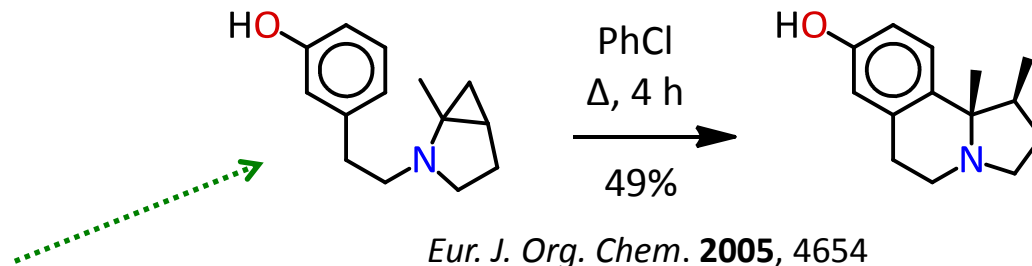


I. Background: some aminocyclopropane chemistry

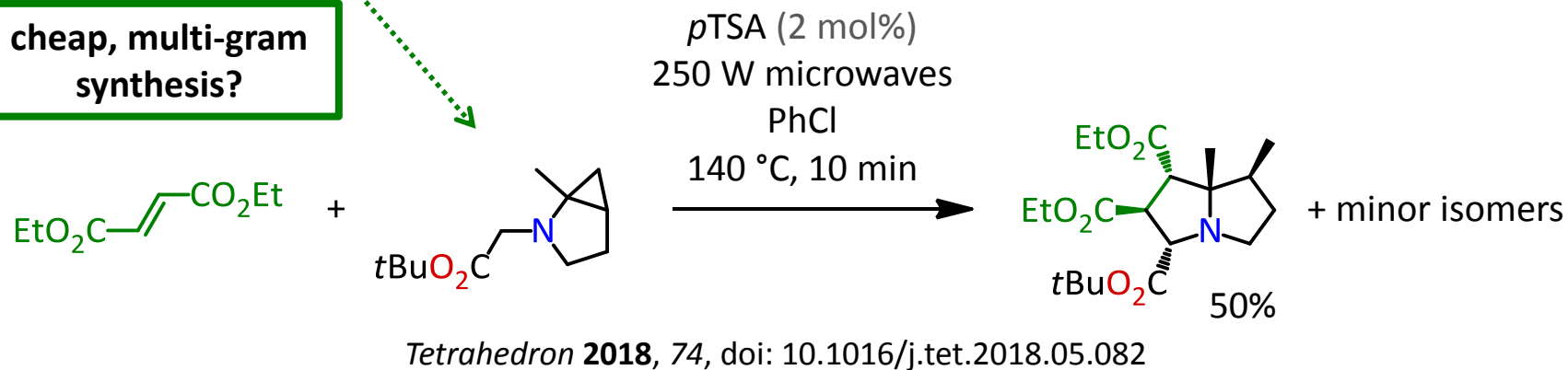
The potential advantages of a modular approach



cheap, multi-gram
synthesis?

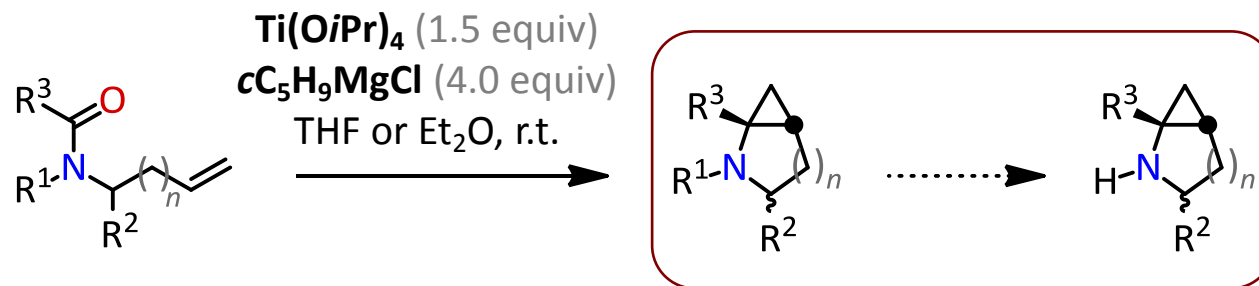


cheap, multi-gram
synthesis?



II. Preparation of bicyclic 2-halocyclopropane derivatives

Dealkylation of a tertiary amine

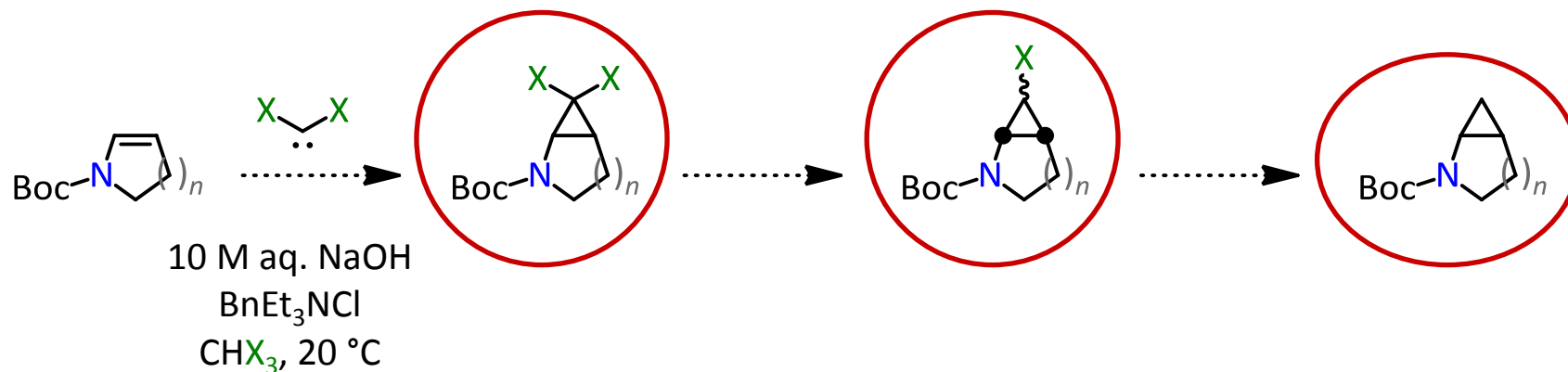


Tricky!

No general solution found.

A. Wolan, M. Soueidan, A. Chiaroni, P. Retailleau, S. Py, Y. Six, *Tetrahedron Lett.* **2011**, 52, 2501

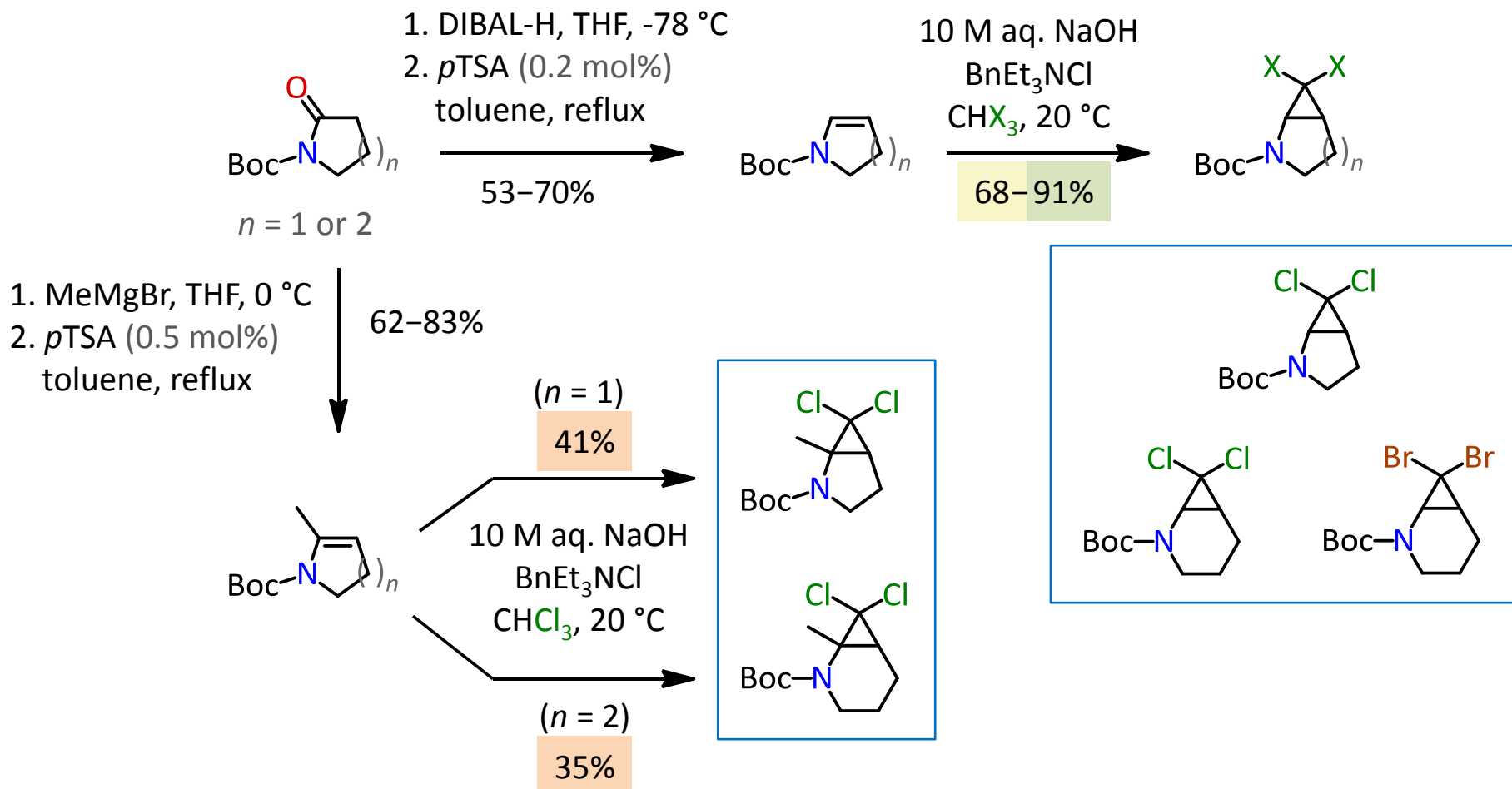
Cyclopropanation with dihalocarbene species



M. Mąkosza, M. Wawrzyniewicz, *Tetrahedron Lett.* **1969**, 10, 4659

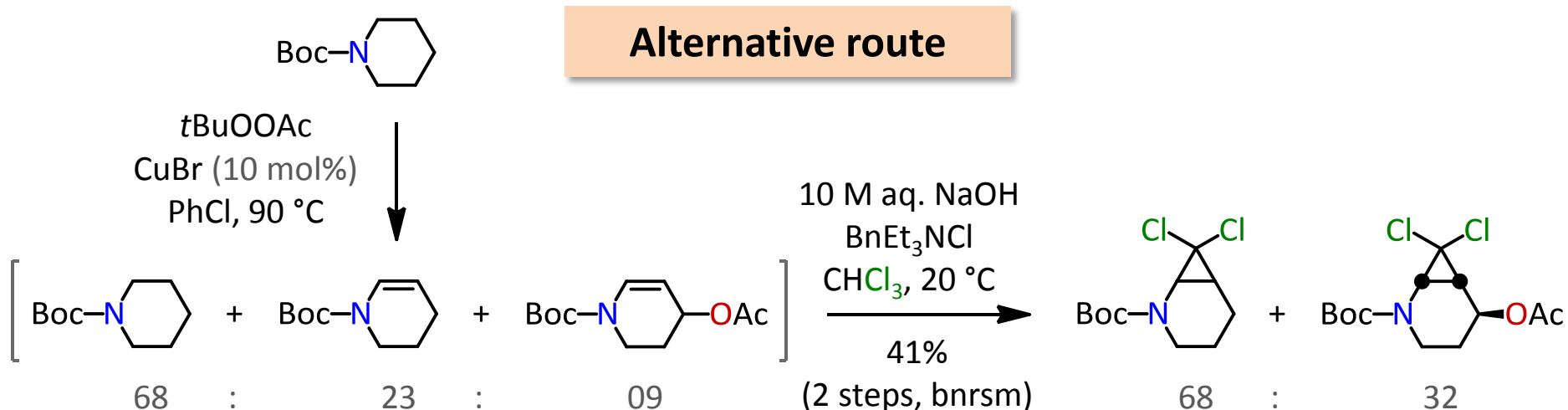
II. Preparation of bicyclic 2-halocyclopropane derivatives

Synthesis of the dihalo compounds

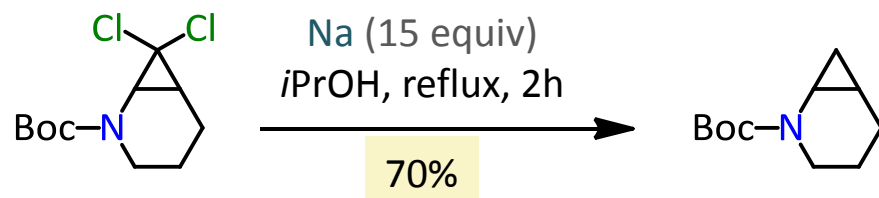
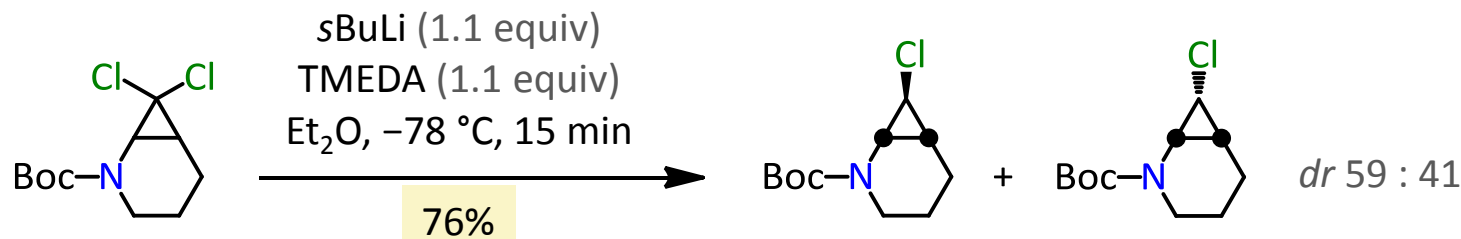


C. Chen, P. Kattanguru, O. A. Tomashenko, R. Karpowicz, G. Siemiaszko, A. Bhattacharya, V. Calasans, Y. Six,
Org. Biomol. Chem. **2017**, *15*, 5364

II. Preparation of bicyclic 2-halocyclopropane derivatives



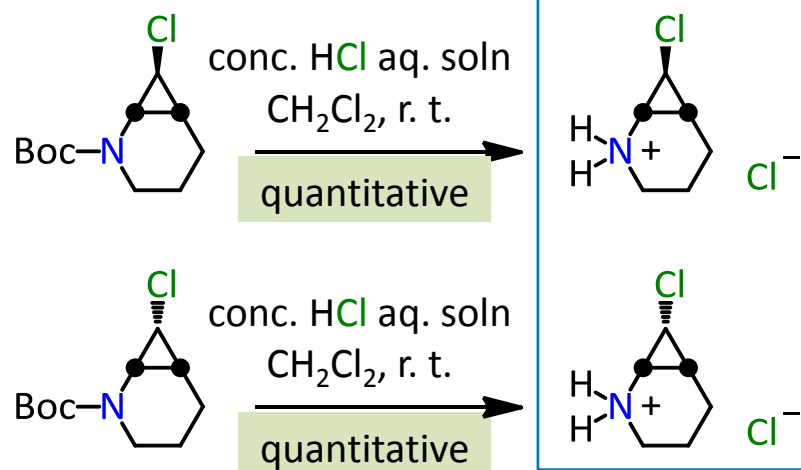
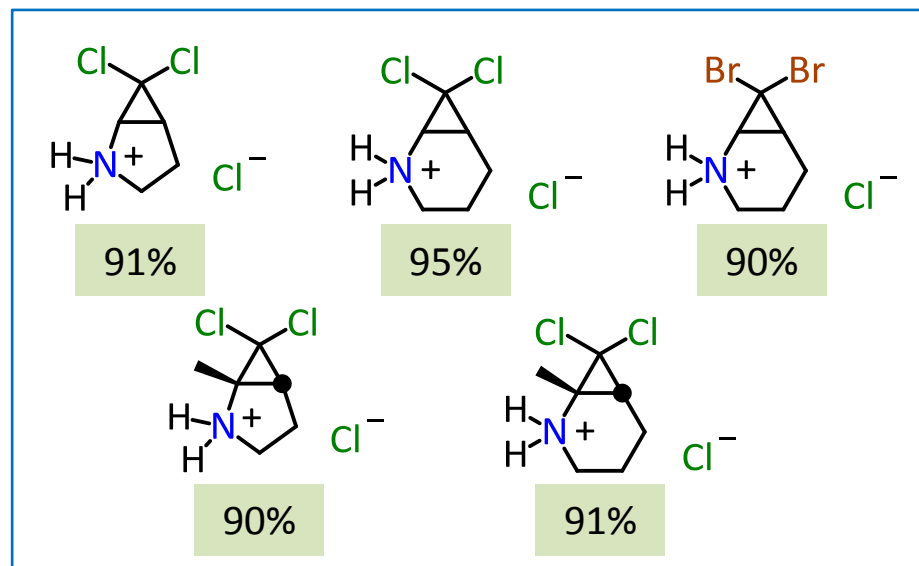
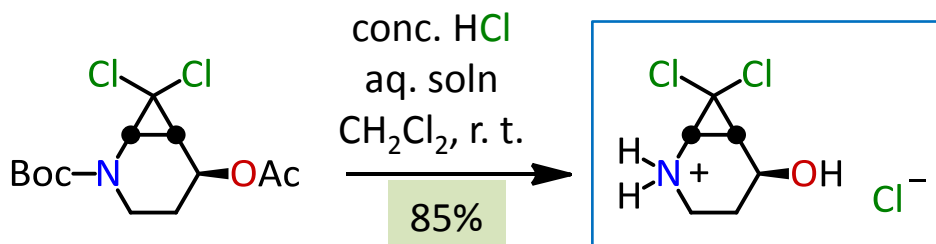
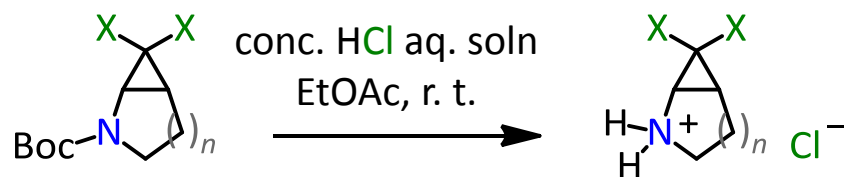
Partial / complete dehalogenation



Modified procedure adapted from
M. G. Banwell, J. H. Ryan, D. A. Winkler
Aust. J. Chem. **1991**, *44*, 593

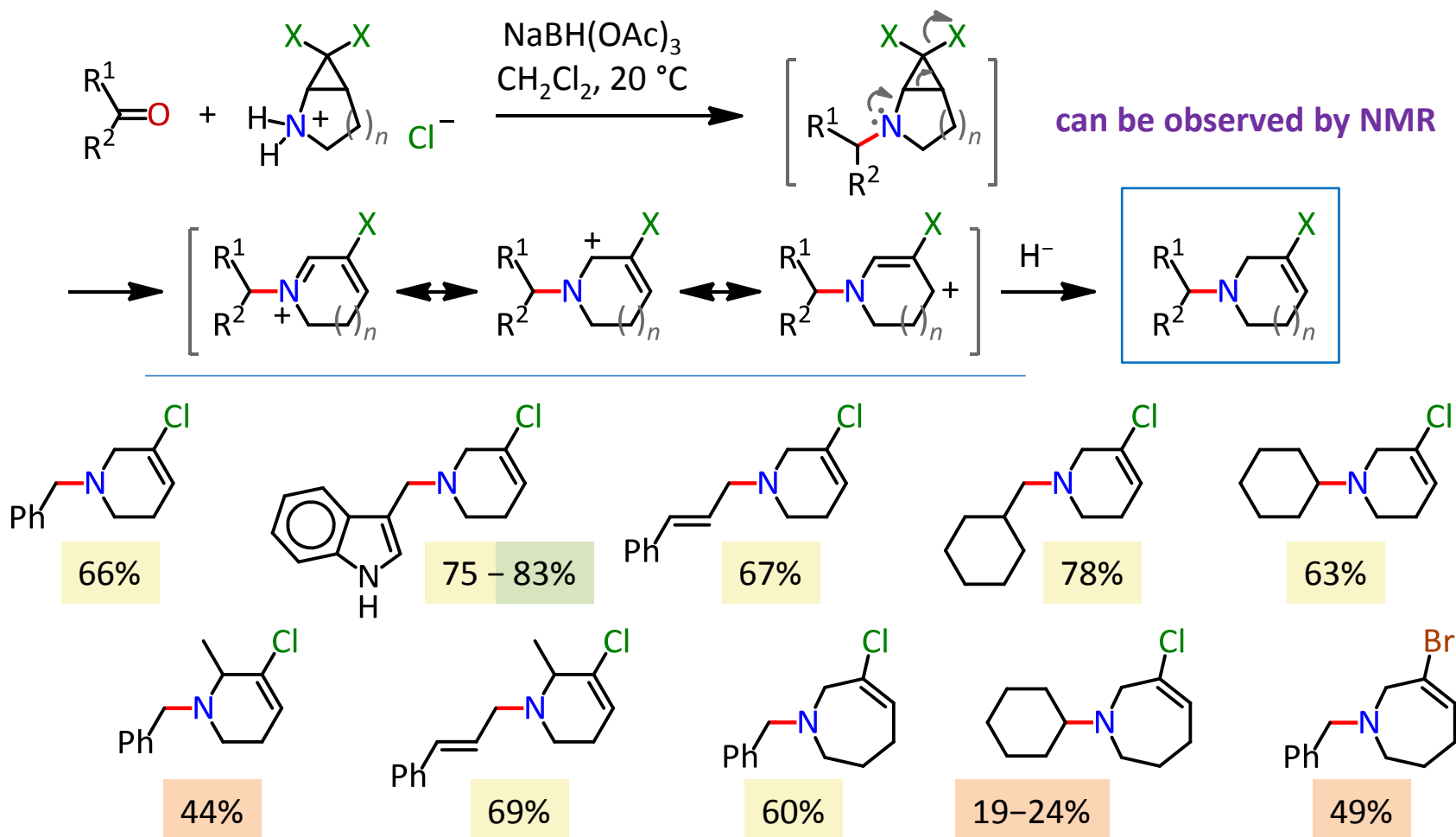
III. Reductive alkylation / ring expansion

Removal of the Boc group



III. Reductive alkylation / ring expansion

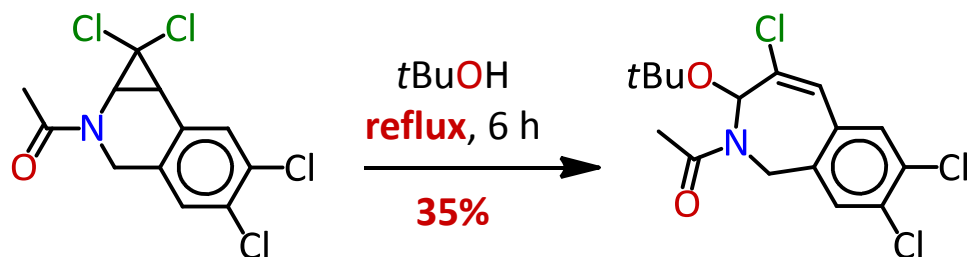
Unexpected ring-expansion under reductive alkylation conditions



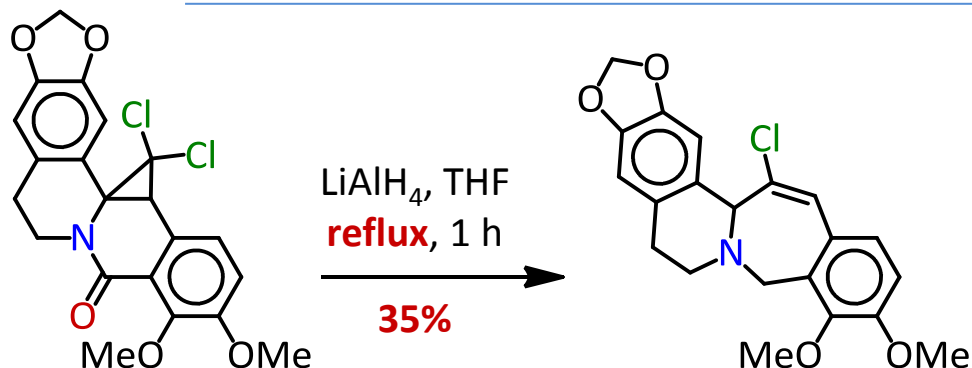
C. Chen, P. Kattanguru, O. A. Tomashenko, R. Karpowicz, G. Siemiaszko, A. Bhattacharya, V. Calasans, Y. Six, *Org. Biomol. Chem.* **2017**, *15*, 5364

III. Reductive alkylation / ring expansion

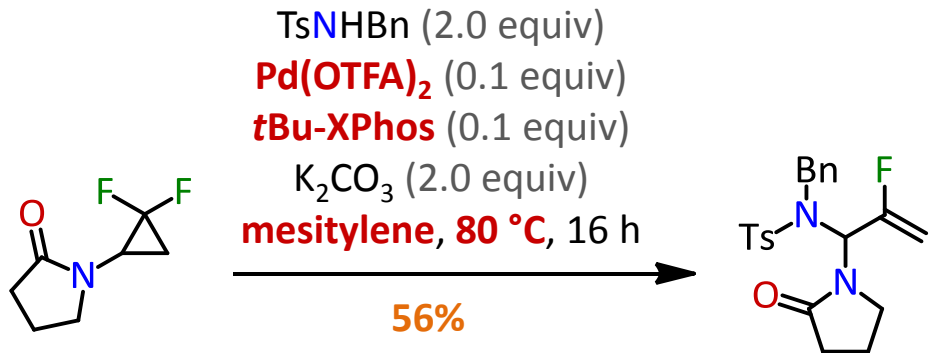
Related literature results



C. D. Perchonock, I. Lantos, J. A. Finkelstein, K. G. Holden, *J. Org. Chem.* **1980**, *45*, 1950



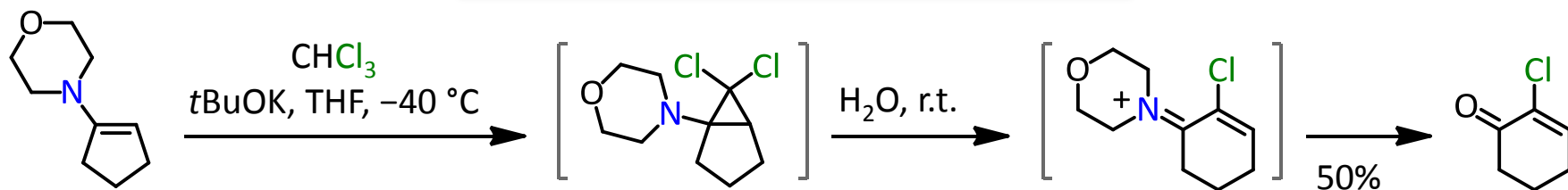
G. Manikumar, M. Shamma, *J. Org. Chem.* **1981**, *46*, 386



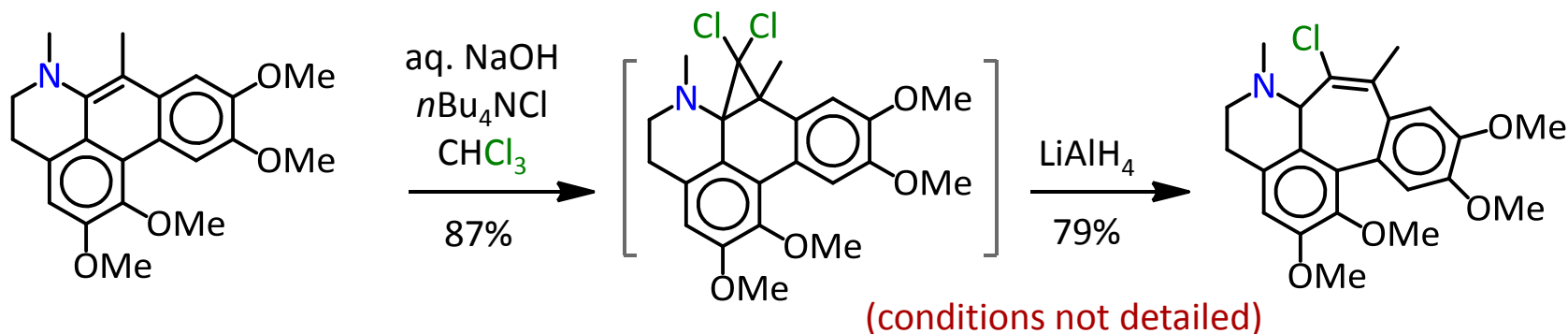
J. Xu, E.-A. Ahmed, B. Xiao, Q.-Q. Lu, Y.-L. Wang, C.-G. Yu, Y. Fu, *Angew. Chem. Int. Ed.* **2015**, *54*, 8231

III. Reductive alkylation / ring expansion

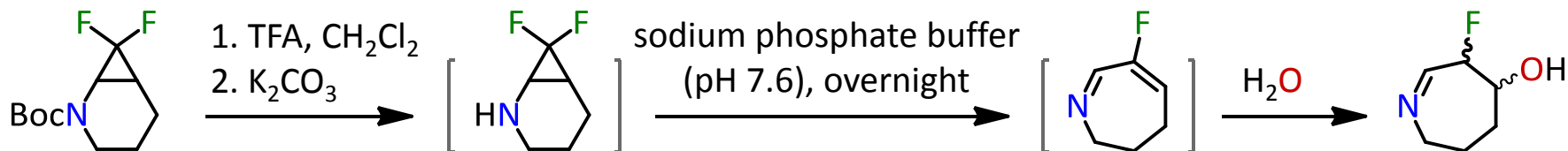
Related literature results (2)



M. Ohno, *Tetrahedron Lett.* **1963**, 1753



J. L. Castro, L. Castedo, R. Riguera, *Tetrahedron Lett.* **1985**, 26, 1561



half-life 2 days in CDCl_3

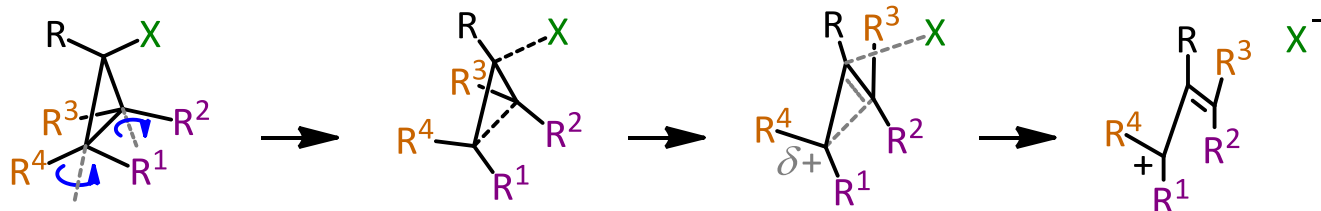
observed by NMR

V. Kubyskin, Y. Kheylik, P. K. Mykhailiuk, *J. Fluorine Chem.* **2015**, 175, 73

IV. Mechanism, selectivity aspects

Mechanism

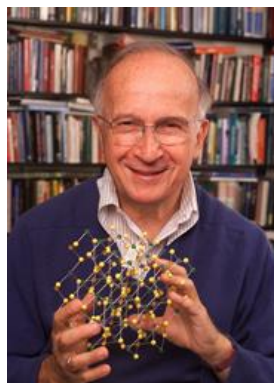
Literature background: the Woodward-Hoffmann-DePuy rule



Disrotatory electrocyclic ring-opening with simultaneous departure of X^-



Robert B. Woodward
(1917–1979)



Roald Hoffmann
(1937–)

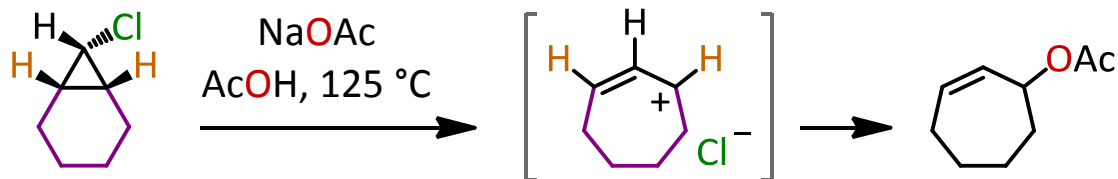
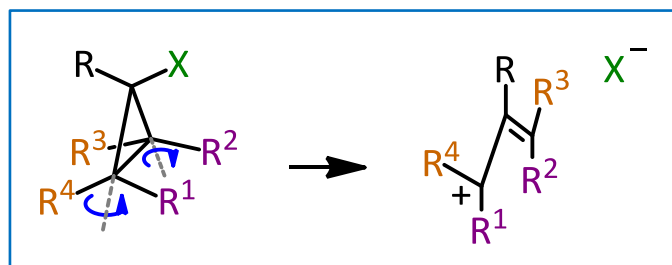


Charles H. DePuy
(1927–2013)

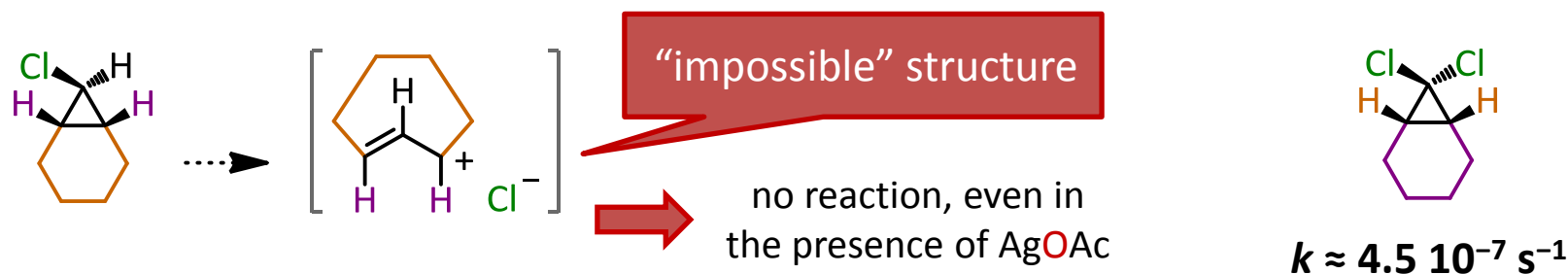
R. B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, *87*, 395

C. H. DePuy, L. G. Schnack, J. W. Hawser, W. Wiedemann, *J. Am. Chem. Soc.* **1965**, *87*, 4006

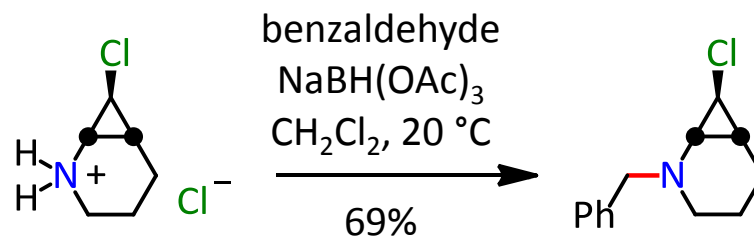
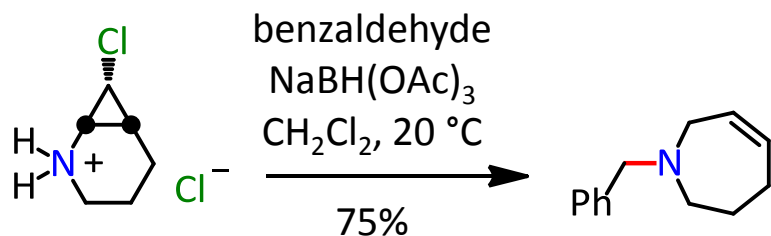
IV. Mechanism, selectivity aspects



Rate constant for the appearance of Cl^- : $k \approx 1.4 \cdot 10^{-6} \text{ s}^{-1}$



S. J. Cristol, R. M. Sequeira, C. H. DePuy, *J. Am. Chem. Soc.* **1965**, *87*, 4007

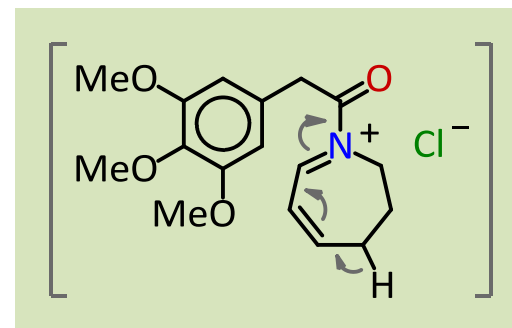
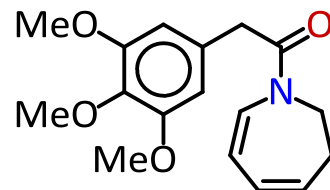
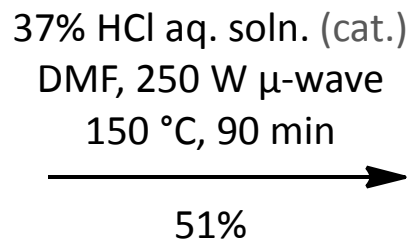
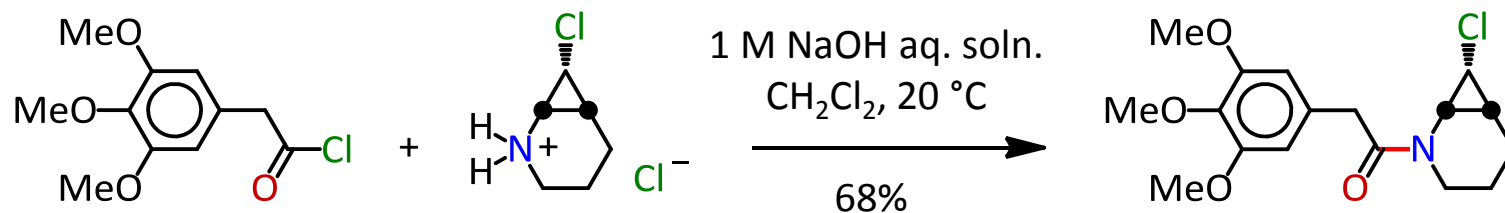
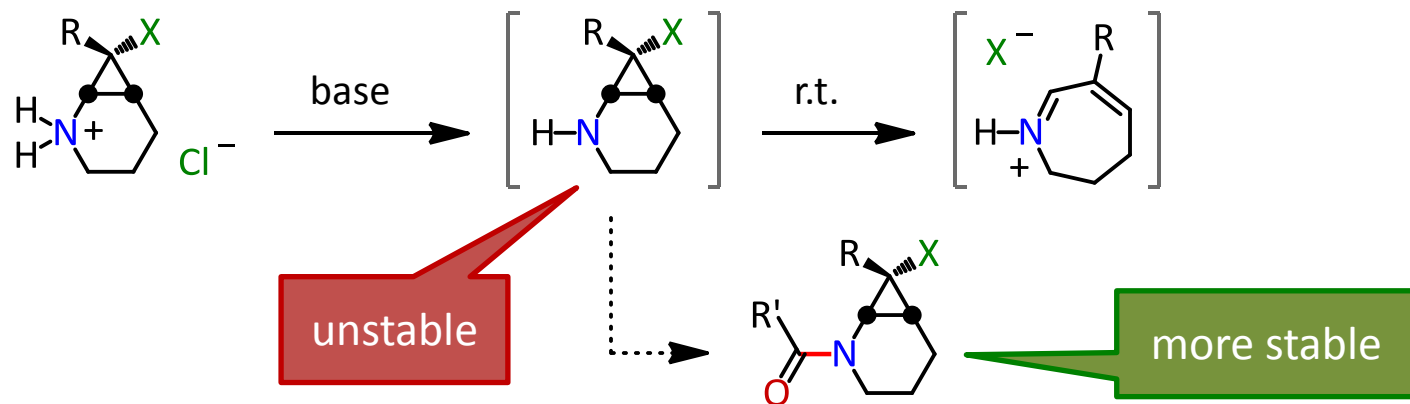


stable

C. Chen, P. Kattanguru, O. A. Tomashenko, R. Karpowicz, G. Siemiaszko, A. Bhattacharya, V. Calasans, Y. Six, *Org. Biomol. Chem.* **2017**, *15*, 5364

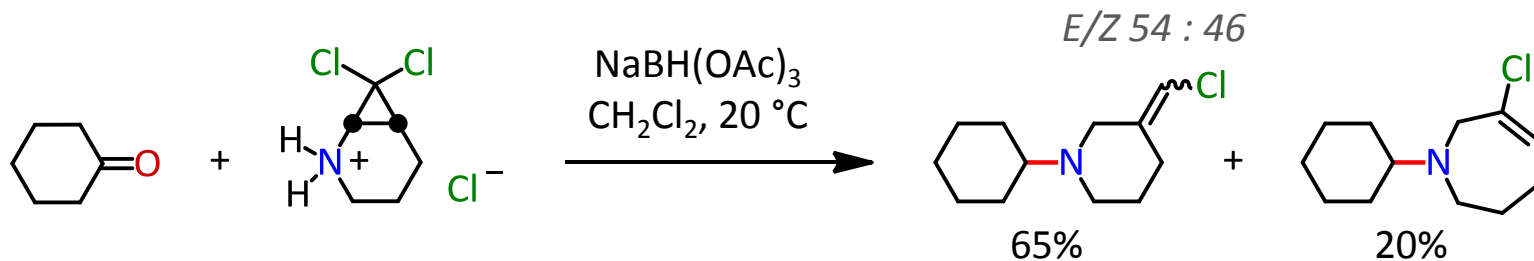
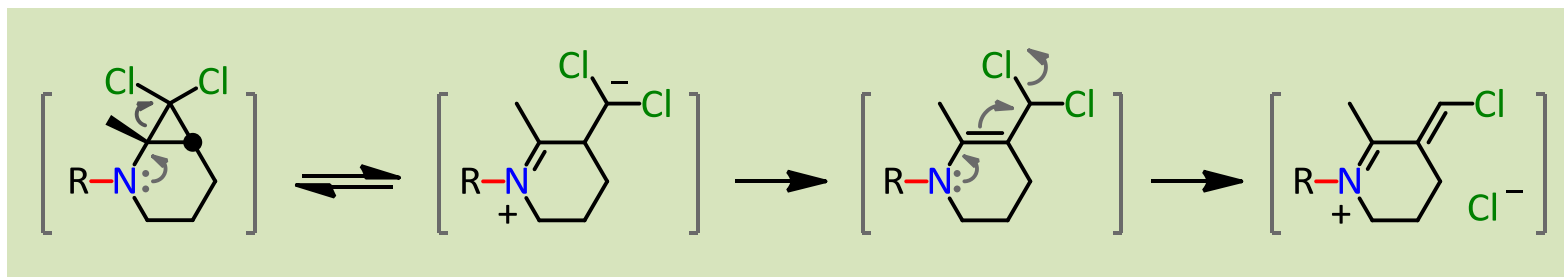
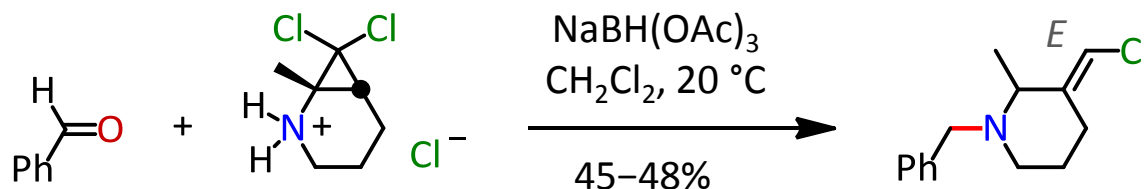
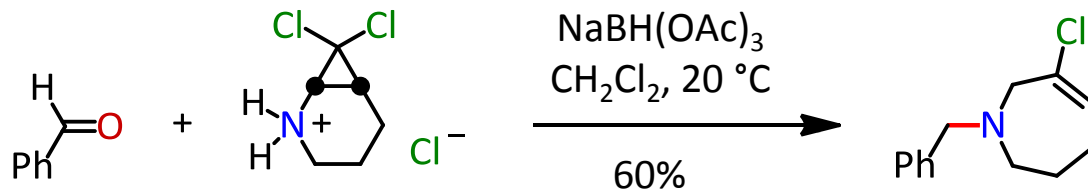
IV. Mechanism, selectivity aspects

Trapping of 2-halogenated aminocyclopropanes



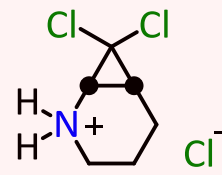
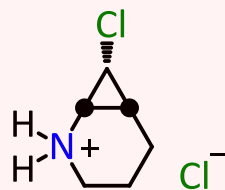
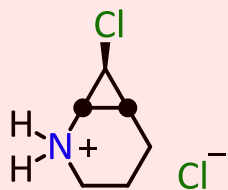
IV. Mechanism, selectivity aspects

Non-typical behaviour with certain substrates



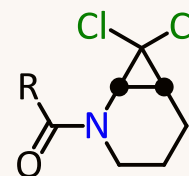
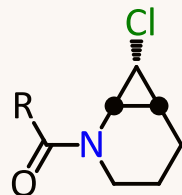
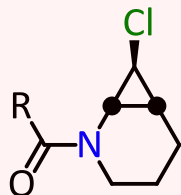
Summary

ammonium salts



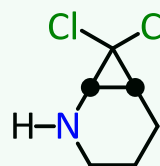
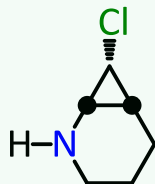
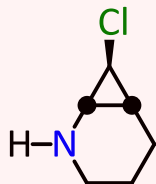
no ring-opening

amides, carbamates



ring-opening is slow; heating is typically required

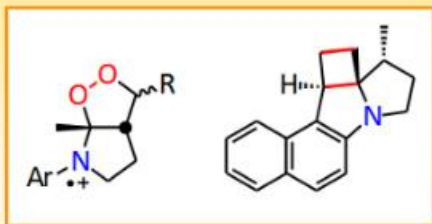
amines



ring-opening proceeds readily at r.t.



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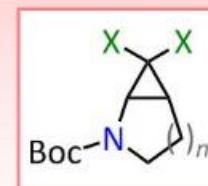
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