Birch reduction of Heterocycles

Ruben Eckermann

Gaich-Group Seminar

06.01.2014

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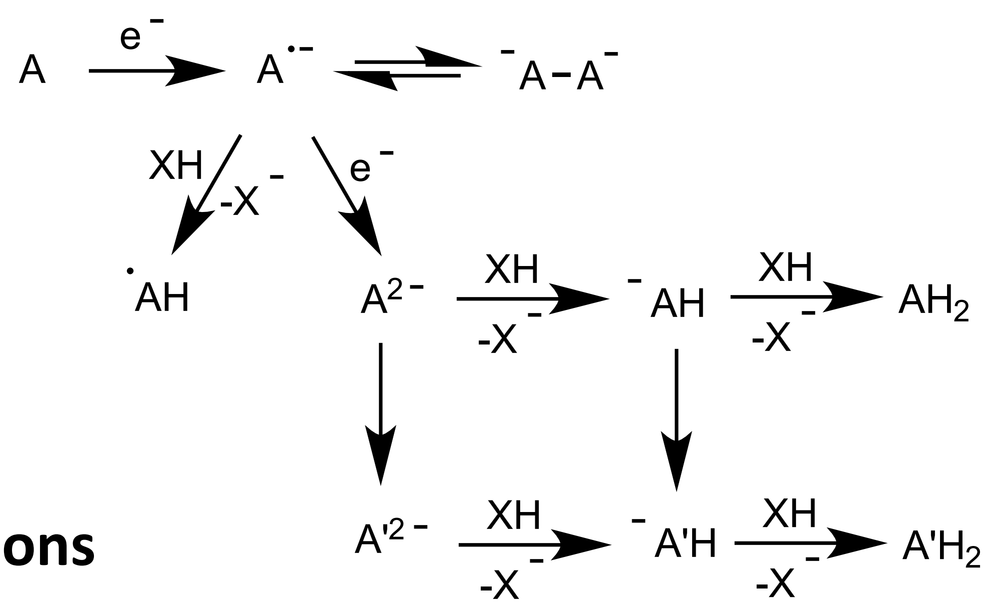

General Informations

Review:

"Reduction of heterocyclic compounds by metal-ammonia solutions and related reagents"

Arthur J. Birch, Jacob Slobbe, *Heterocycles* **1976**, *5*, 905-944

Solvent system

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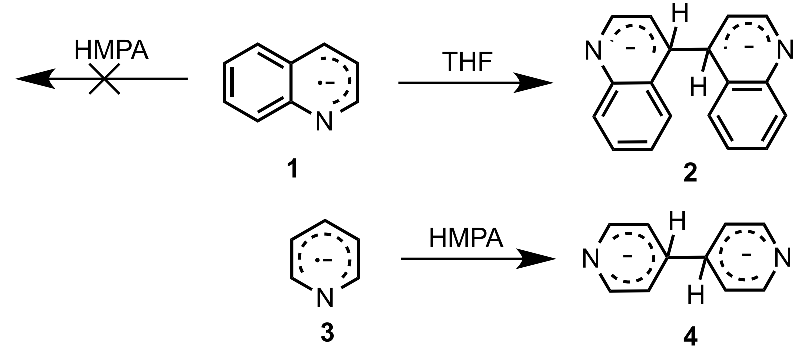
- e^- best solved in NH_3, more reactive in amines
- A^{*-} best solved & stabalized in amines
- Dielectric constant of co-solvent:

  THF: 7.6 HMPA: 30



- Co-solvents: THF, DME, dioxanes, HMPA → decreases metal solubility
- Temperature range:

NH_3	-80° → -33°C	Li best soluble in amines
H_2NEt	-81° → 17°C	Na/K alloy soluble in ethylene diamine
$H_2N\text{-}(CH_2)_2\text{-}NH_2$	8° → 116°C	

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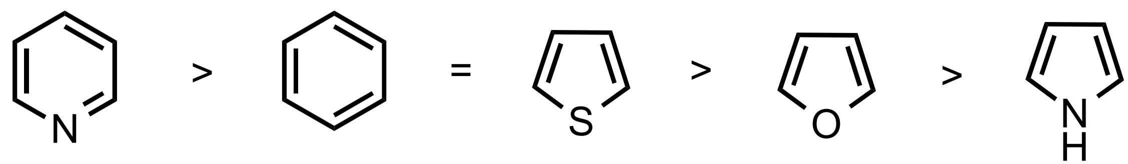
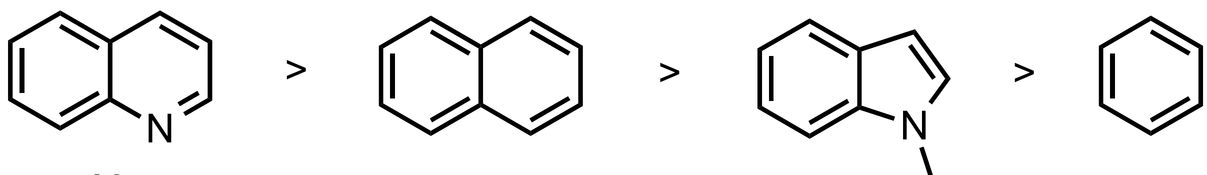
Reducibility

Lower LUMO → more rapid reduction



5 6 7 8 9

low LUMO high LUMO



10 11 12 6

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Reducibility

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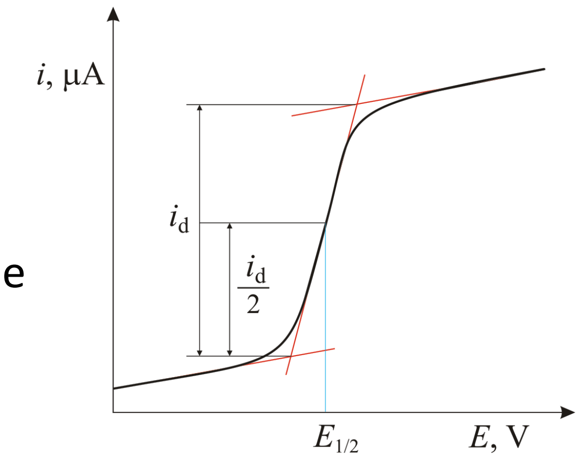
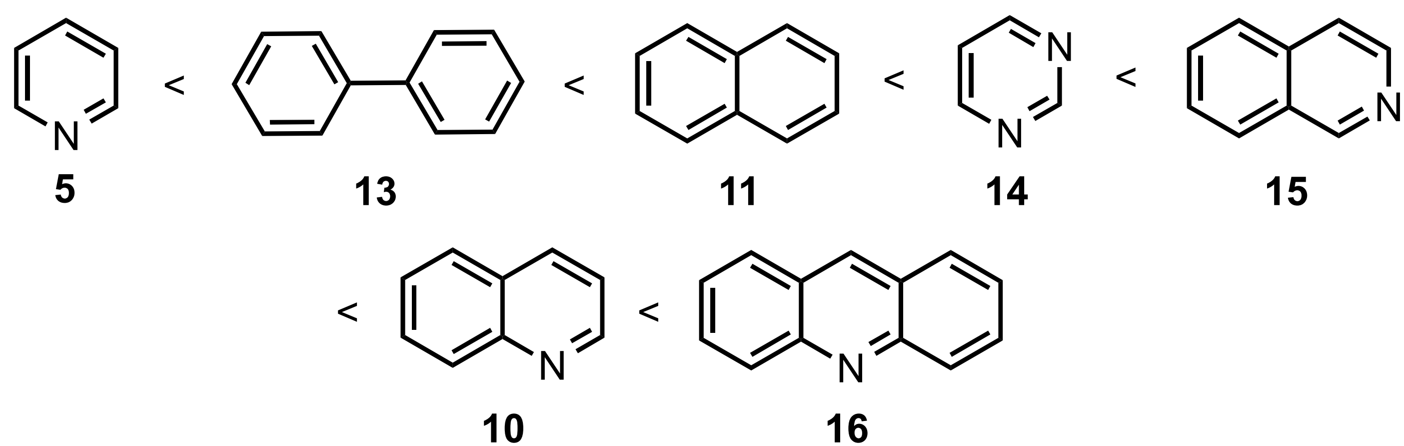
Reduction potentials → half wave potential ($E_{1/2}$)

in NH_3 not given for most cases → DMF or MeCN comparable

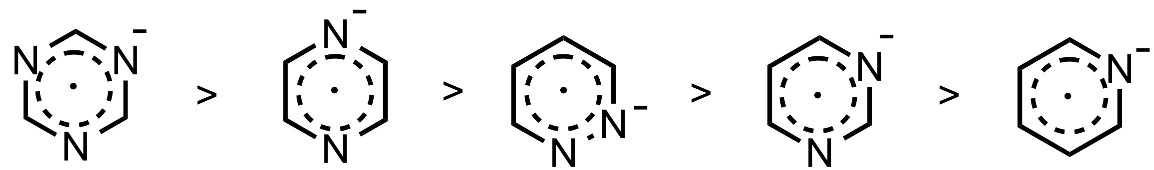




ease of first electron addition

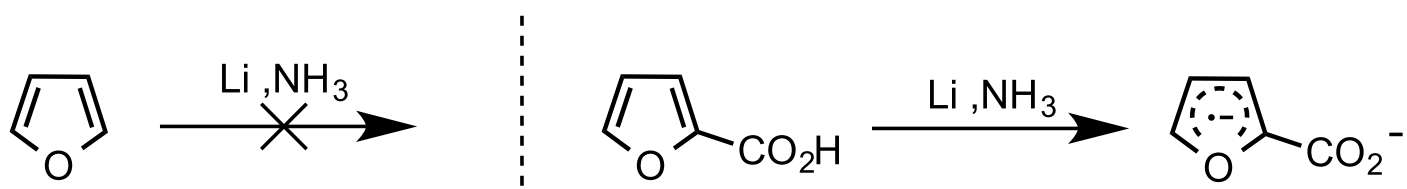
Reducibility

Stabilisation of A^{*-}



17 **18** **19** **20** **21**

→ More delocalization favours reduction
→ Benzyl groups (quinolines, indoles) & carboxyl substituents favours reduction

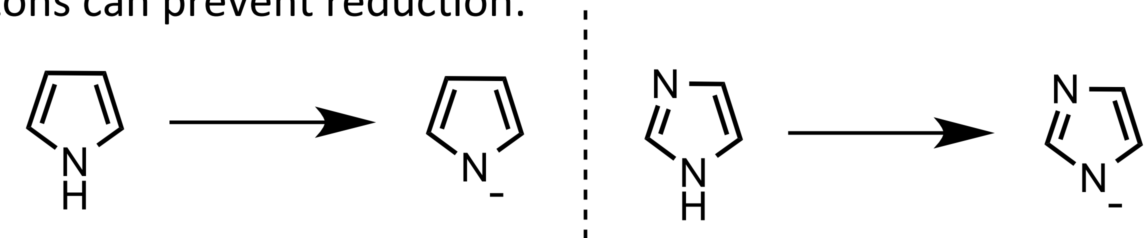


8 **23** **24**

Arthur J. Birch, Jacob Slobbe, *Heterocycles* **1976**, *5*, 905-944

Reducibility

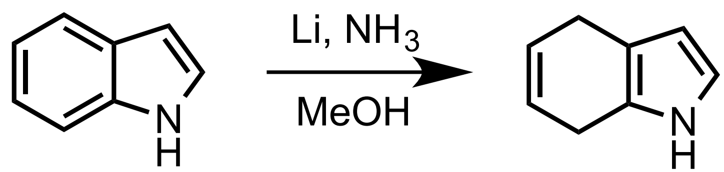
Acidic protons can prevent reduction:



9 **25** **26** **27**

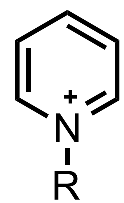
→ *N*-alkyl substituents!

→ Indoles work!



28 **29**

Positive charge favours reduction:



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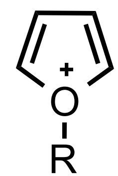


31

Arthur J. Birch, Jacob Slobbe, *Heterocycles* **1976**, *5*, 905-944

Reducibility

Experimetnal observations:

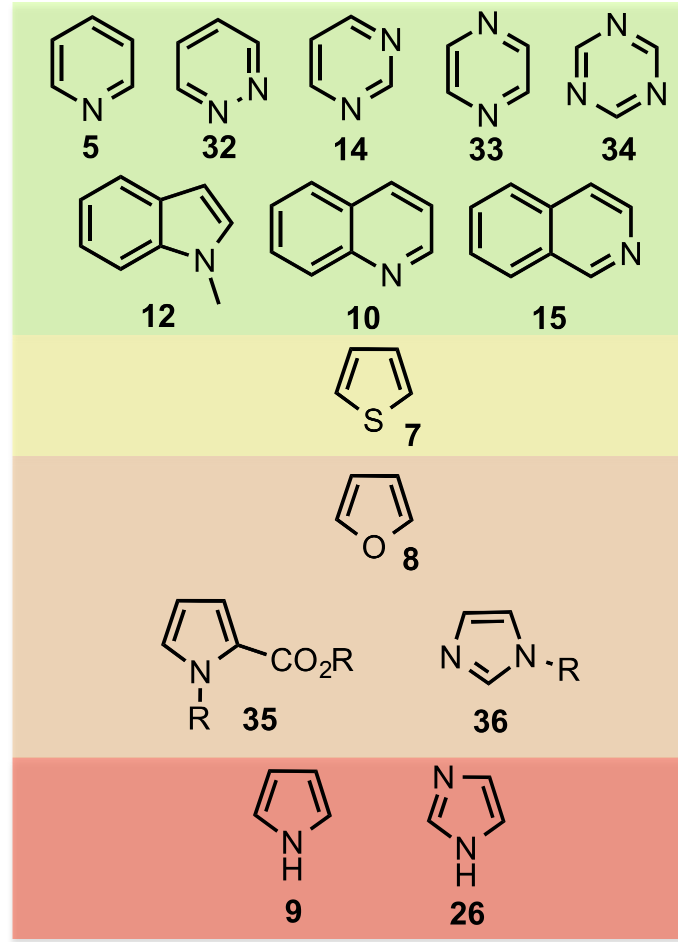
→ Triazines, Pyridines, Pyrimidines, Pyridazines, Pyrazines, Quinolines & Indoles easy reducible

→ Thiophenes reducible

→ Furanes reducible under forcing conditions

→ *N*-alkyl pyrrole carboxylic acids very slowly reducible

→ Pyrroles not reducible
Imidazoles only N-alkylated



Text

Mono-protonation

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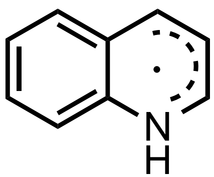
$$A^{\bullet -} \xrightarrow{ROH} {}^{\bullet}AH$$

Not irreversible like in carbocycles!

ESR studies and MO-calculations indicates protonation at position of highest electron spin density

→ Nitrogen special role!



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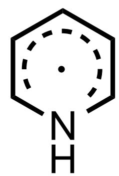
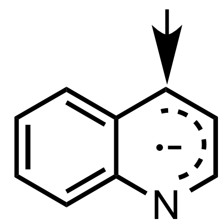


38

4-position highest density



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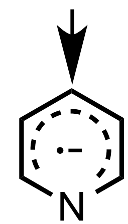
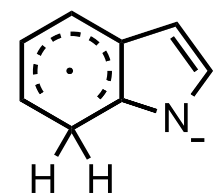


3

Protonation at nitrogen for pyridines & quinolines

Indoles protonated in benzene ring first!



39

Monoprotonated products can dimerize or add 2nd eletron

Arthur J. Birch, Jacob Slobbe, *Heterocycles* **1976**, *5*, 905-944

Dianion Formation

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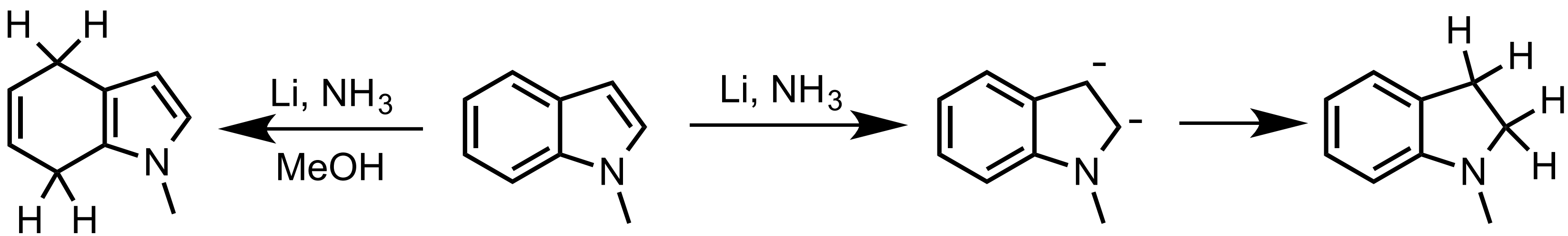
$$A^{\bullet -} \xrightarrow{e^-} A^{2-}$$

Dianion formation is hindered → reduction potential of A^{*-} and the metal crucial

Product formation in some cases indicates dianion formation, at least in small amounts of an equilibrium

→ dianions highly basic, mostly irreversible protonated, even by NH_3



40 12 41 42

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Dianion Formation

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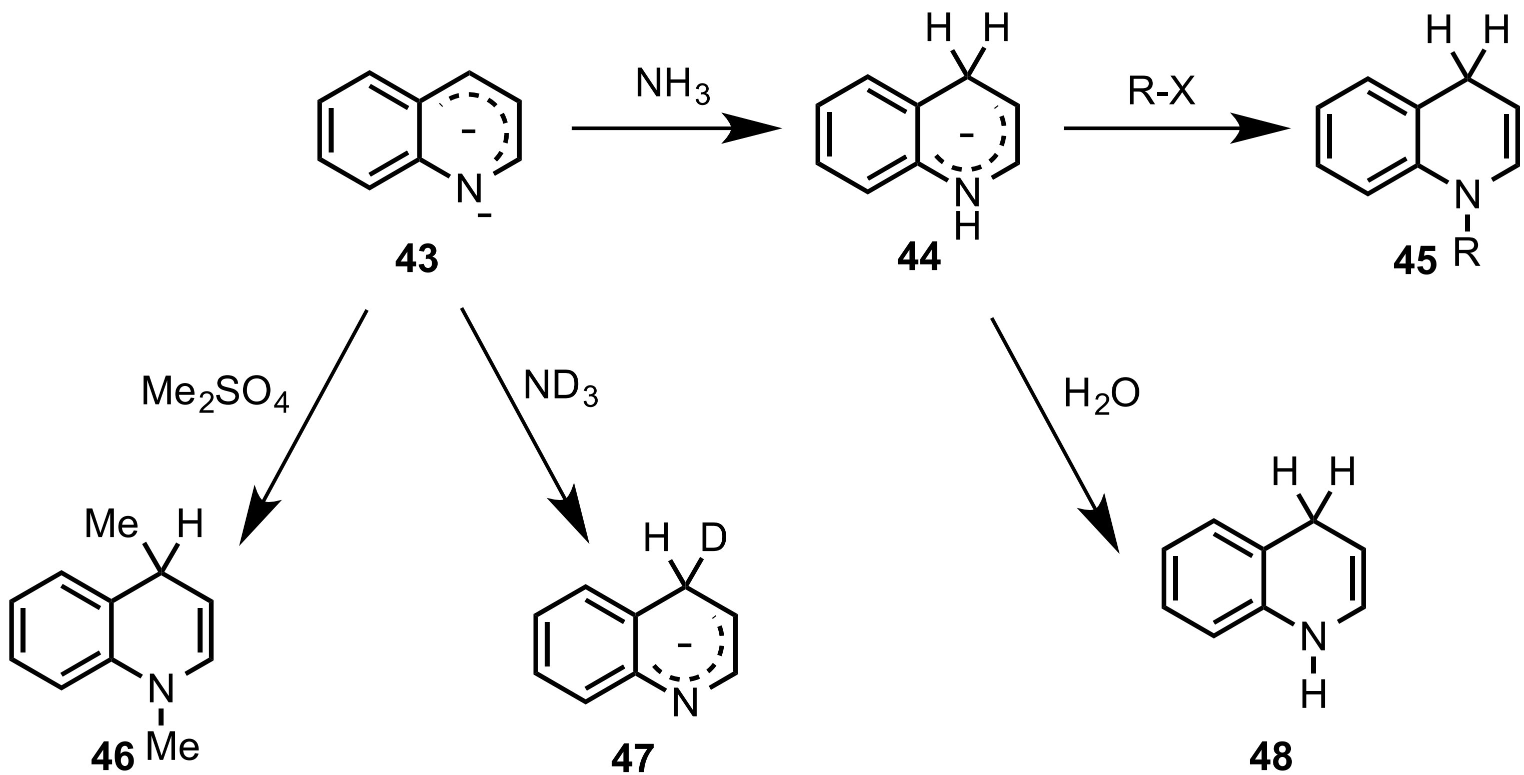

→ The more basic anion gets alkylated / protonated

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Dimerization

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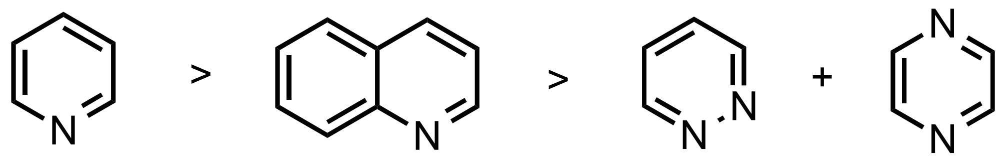
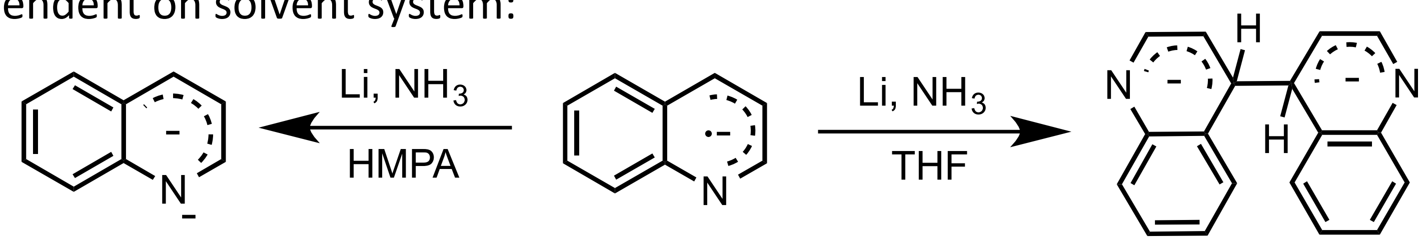
$$2\,A^{\bullet -} \rightleftharpoons {}^{-}A{-}A^{-} \quad \text{vs.} \quad A^{\bullet -} + A \longrightarrow {}^{-}A{-}A^{\bullet}$$

Occurs especially with nitrogen containing heterocycles



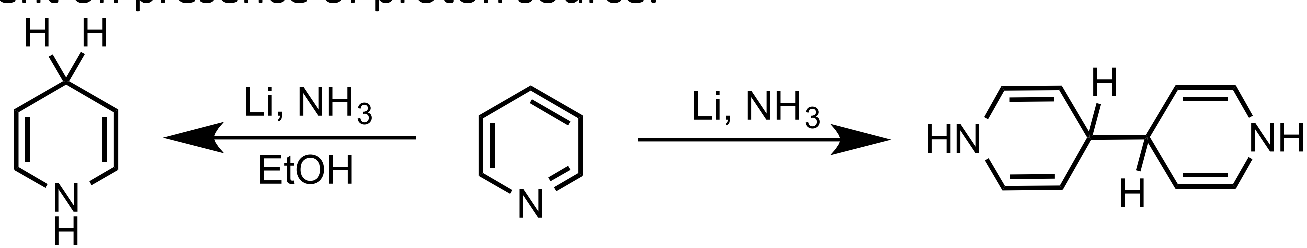
5 **10** **32** **33**

Dependent on solvent system:



49 **1** **2**

Dependent on presence of proton source:



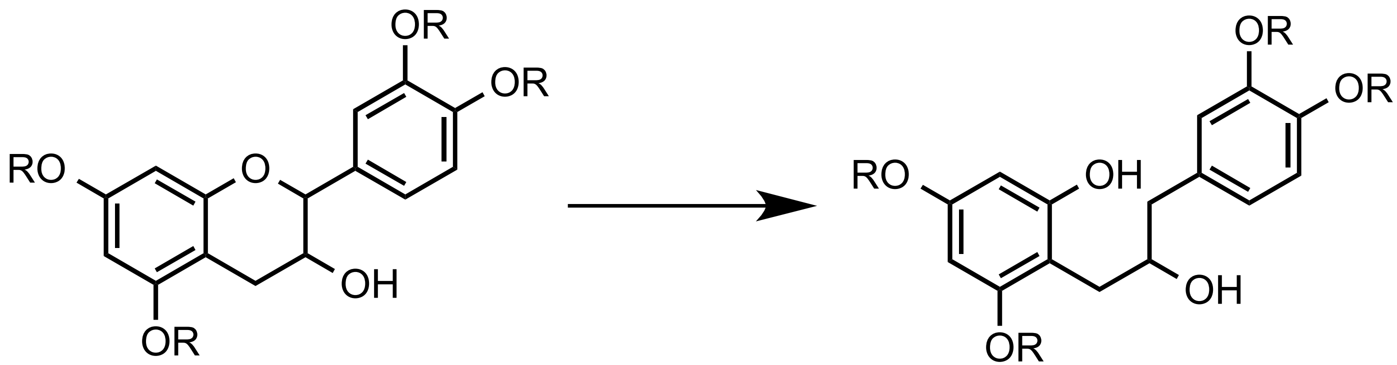
50 **5** **51**

Arthur J. Birch, Jacob Slobbe, *Heterocycles* **1976**, *5*, 905-944

Cleavage processes

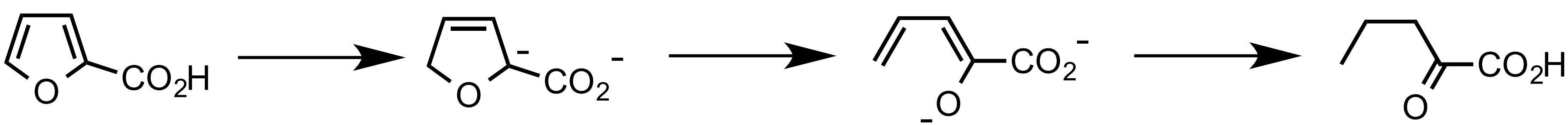
Important for oxygen- and sulfur-containing heterocycles: S > O >> N

1. **Direct cleavage:** stabilisation of negative charge on hetero-atom
   diaryl ethers, allyl ehters, benzyl ethers



52 53

2. **Elimination:** $^{-}C-C-X \longrightarrow C{=}C + X^{-}$



54 55 56 57

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Cleavage processes: furanes

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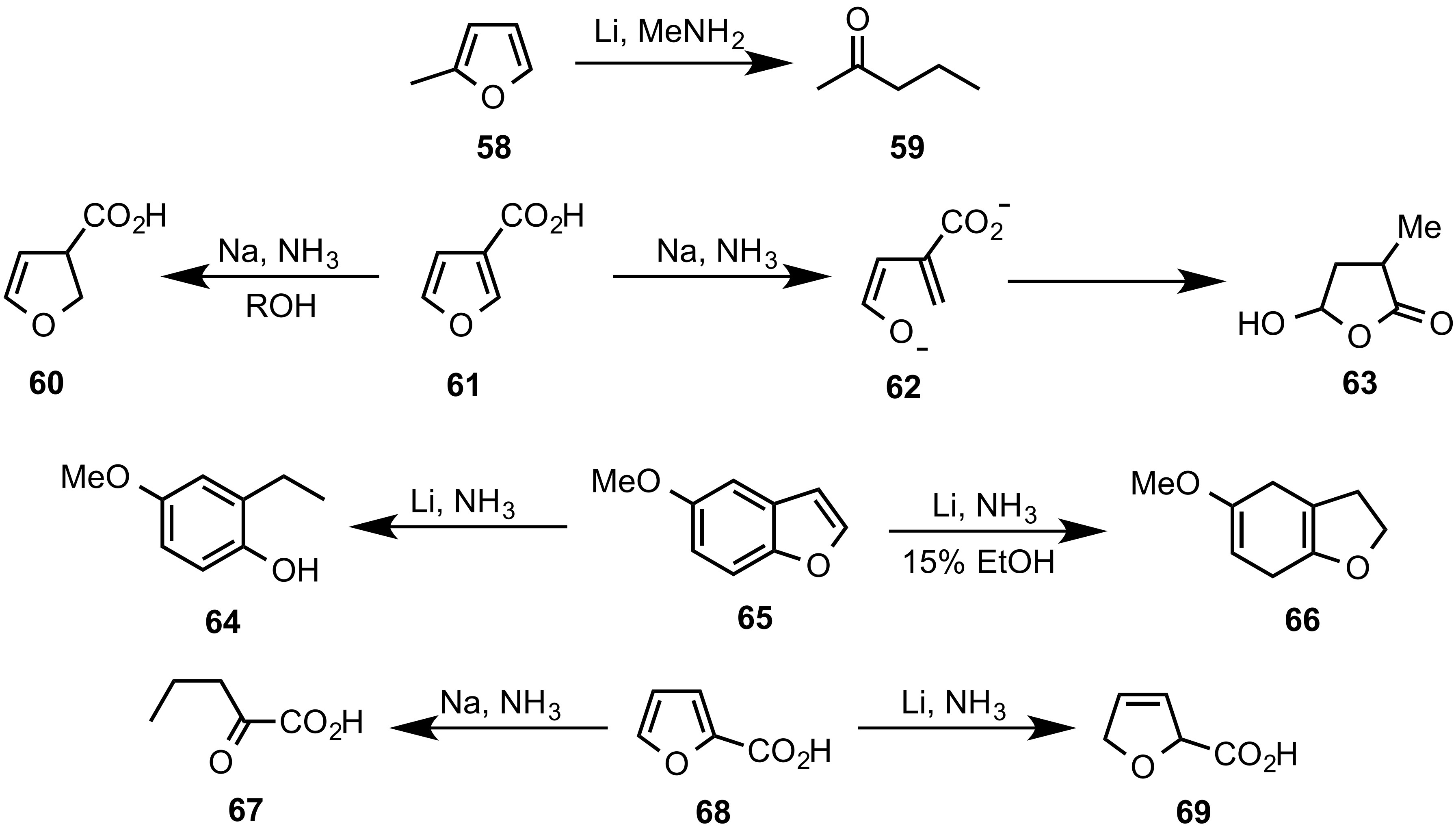

Arthur J. Birch, Jacob Slobbe, *Heterocycles* **1976**, *5*, 905-944

Cleavage processes: thiophenes

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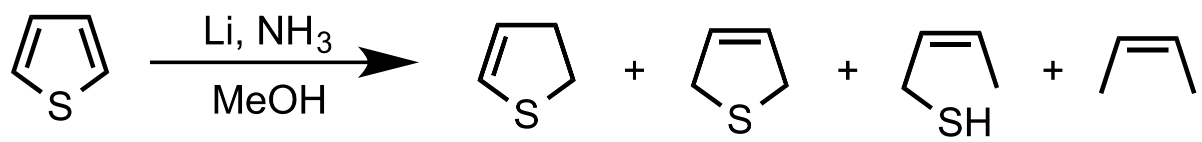
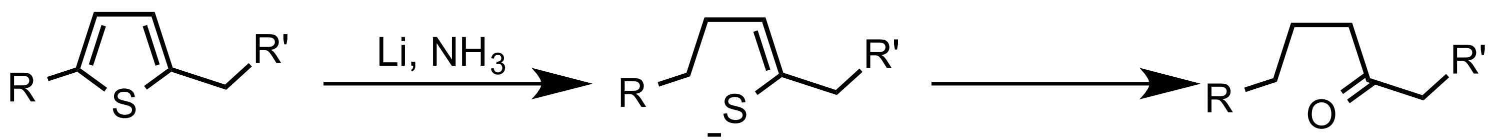
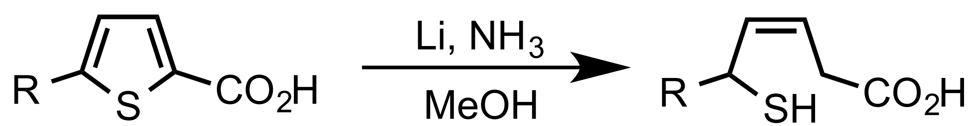




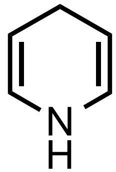


Arthur J. Birch, Jacob Slobbe, *Heterocycles* **1976**, *5*, 905-944

Examples/Applications

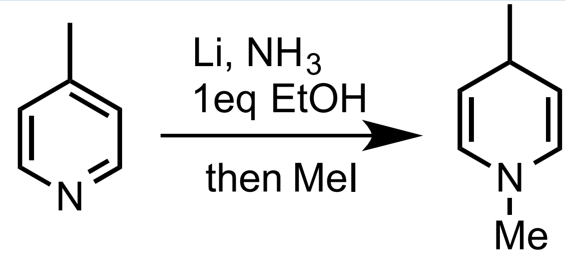
1) **Pyridines**
2) **Pyrroles**
3) **Furanes**
4) **Thiophenes**

1) Pyridines

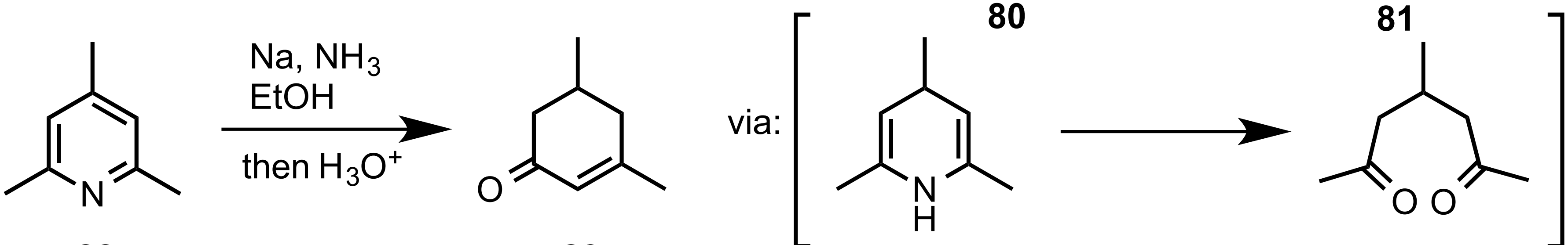


79

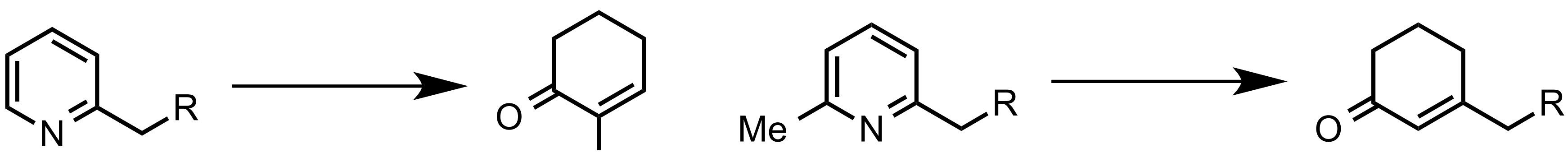
Dihydropyridine derivatives tend to autoxidation and rearomatization
→ in-situ alkylation



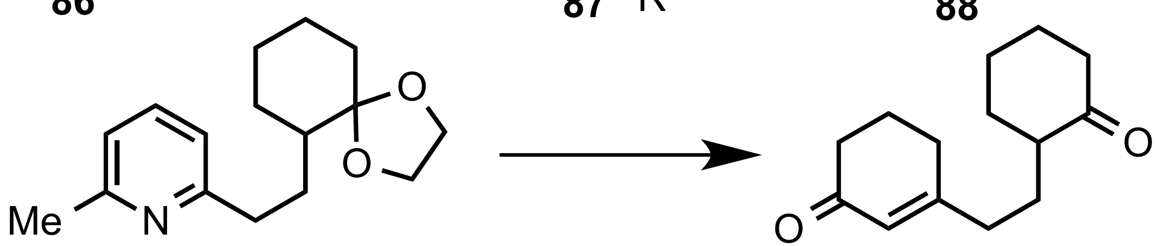
80 **81**



82 **83** **84** **85**



86 **87** **88** **89**

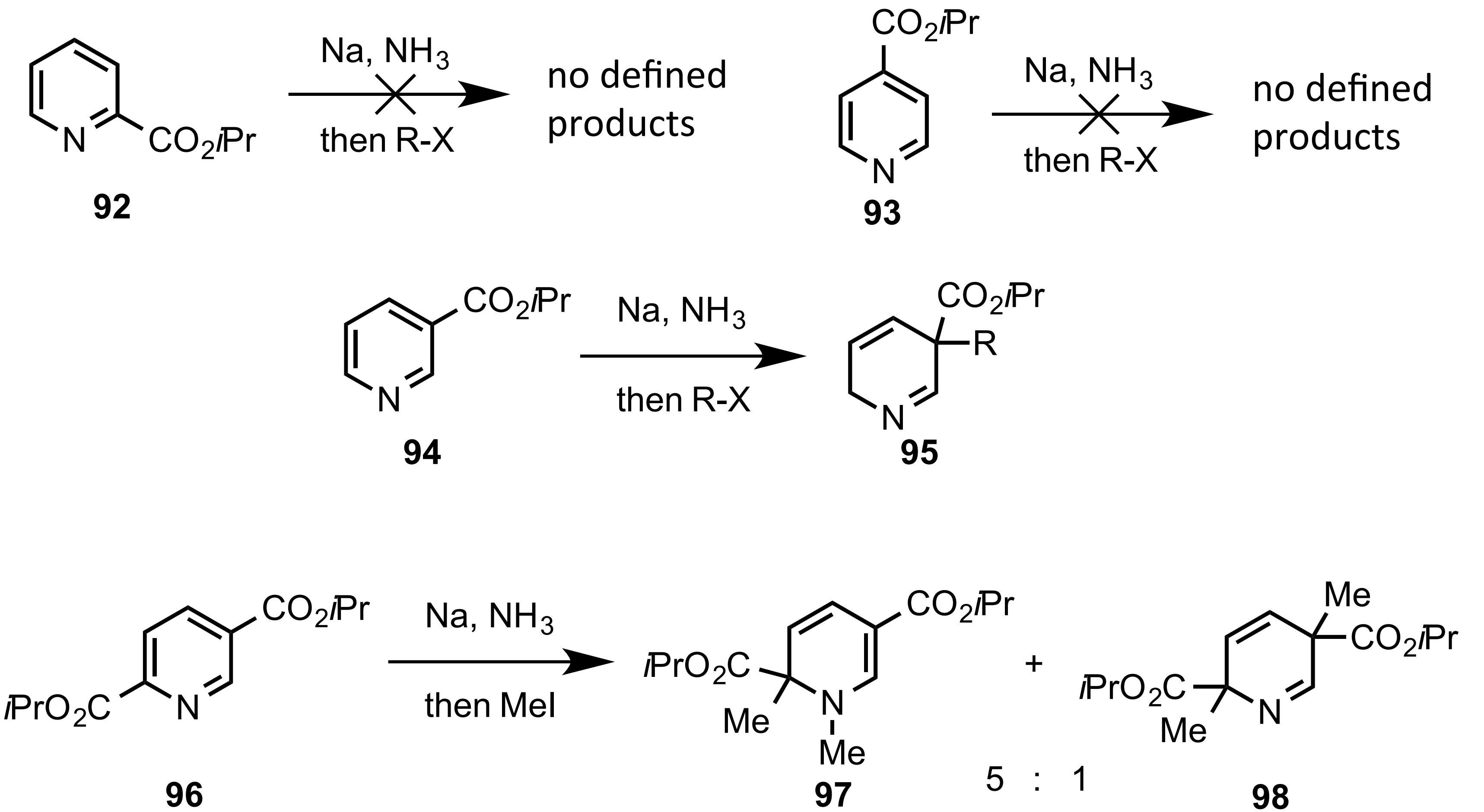


90 **91**

Pyridine access to Steroid skeletons

T. J. Donohoe, A. J. McRiner, M. Helliwell, P. Sheldrake, *J. Chem. Soc., Perk. Trans. 1* **2001**, 1435-1445

1) Pyridines



T. J. Donohoe, A. J. McRiner, M. Helliwell, P. Sheldrake, *J. Chem. Soc., Perk. Trans. 1* **2001**, 1435-1445

1) Pyridines

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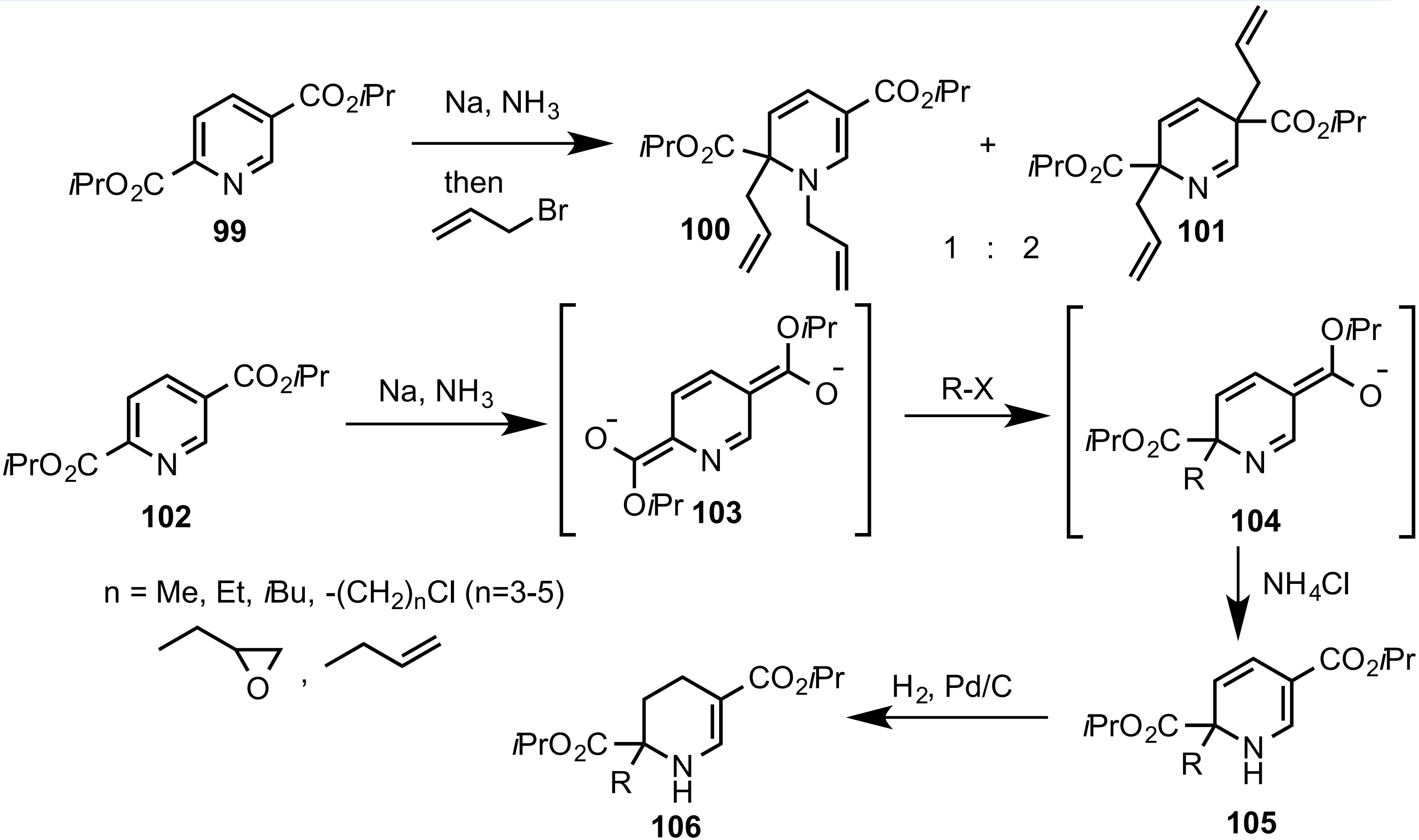
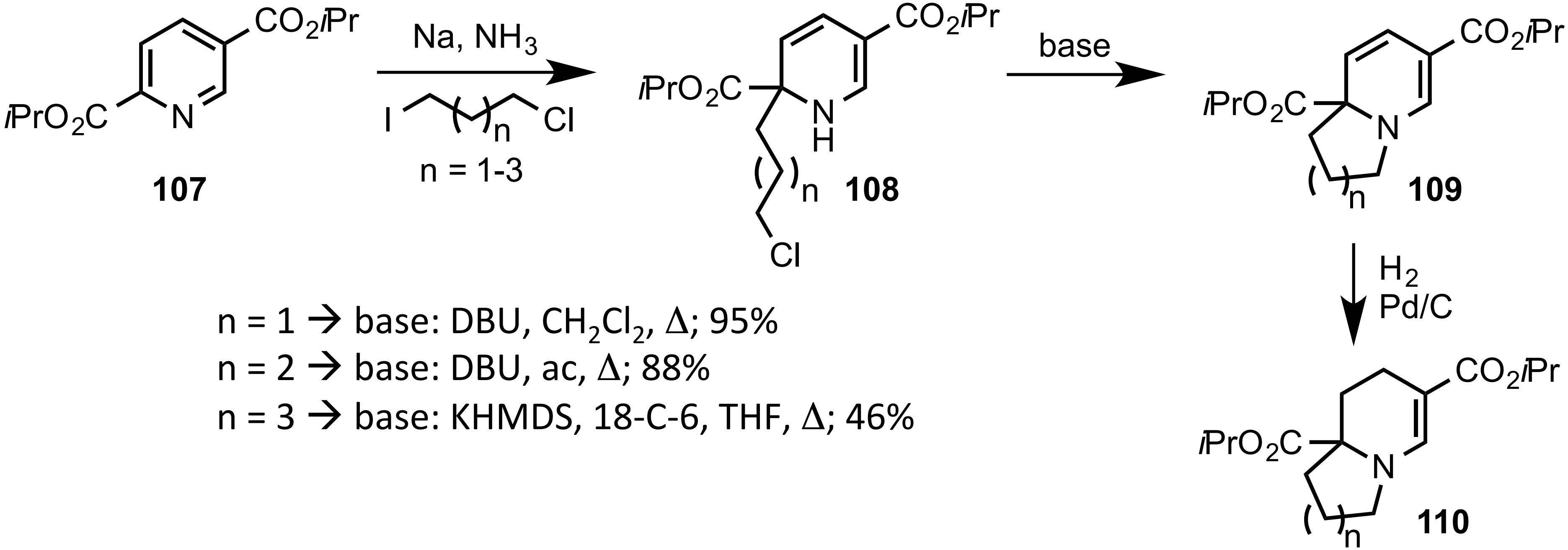
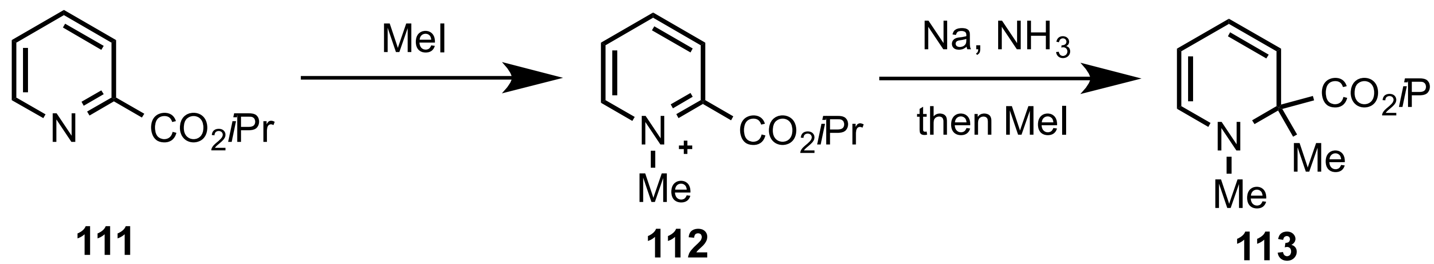


T. J. Donohoe, A. J. McRiner, M. Helliwell, P. Sheldrake, *J. Chem. Soc., Perk. Trans. 1* **2001**, 1435-1445

1) Pyridines

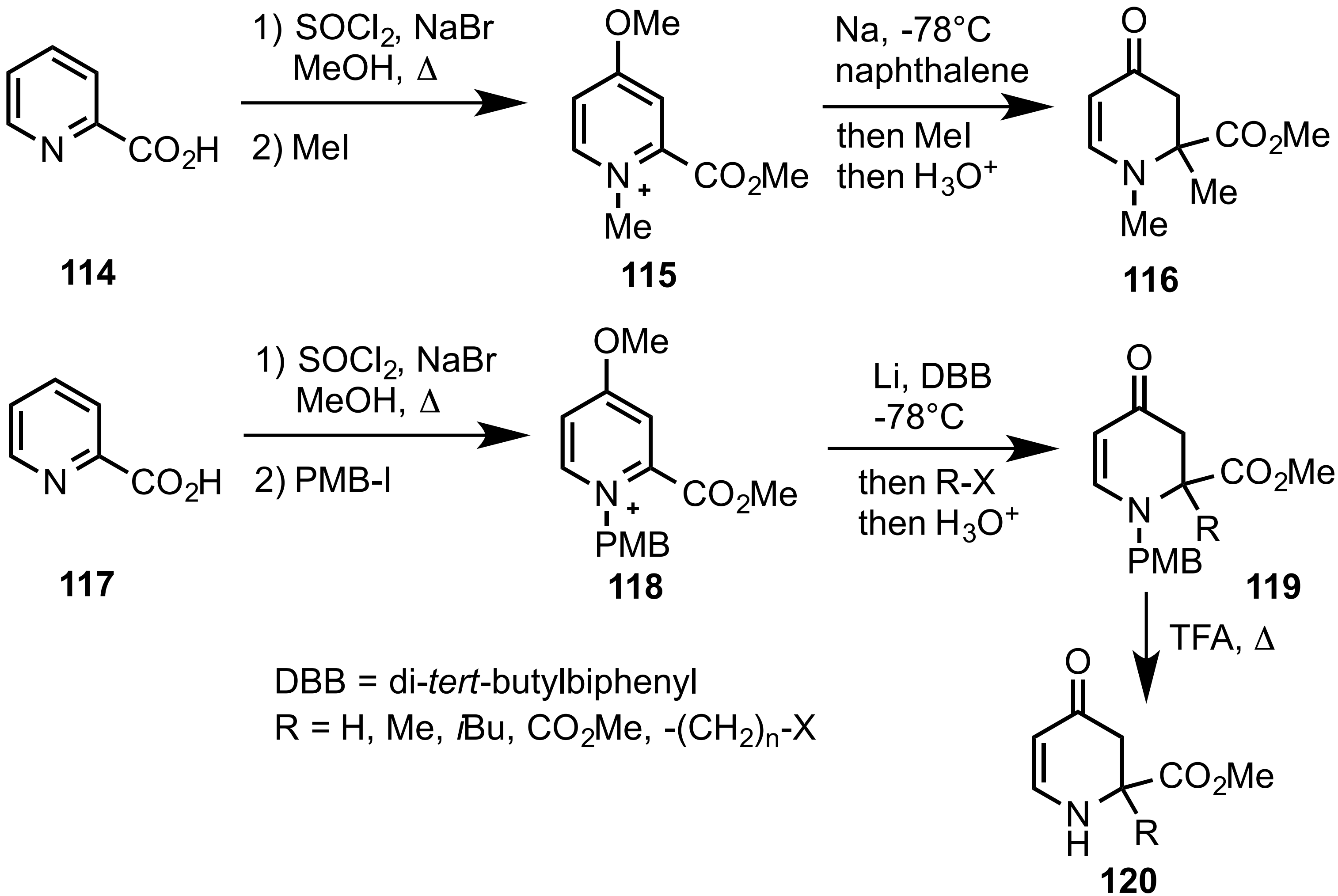


n = 1 → base: DBU, CH_2Cl_2, Δ; 95%
n = 2 → base: DBU, ac, Δ; 88%
n = 3 → base: KHMDS, 18-C-6, THF, Δ; 46%



T. J. Donohoe, A. J. McRiner, M. Helliwell, P. Sheldrake, *J. Chem. Soc., Perk. Trans. 1* **2001**, 1435-1445

1) Pyridines

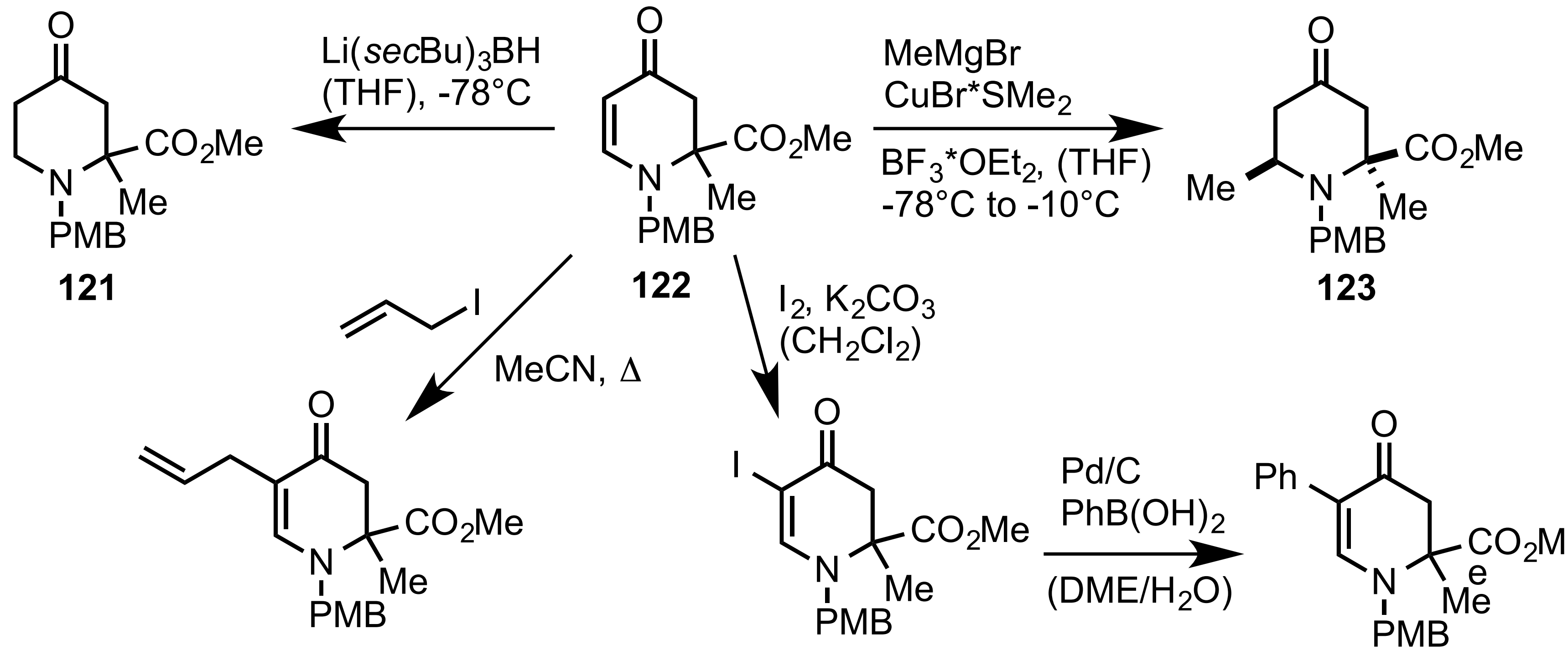


DBB = di-*tert*-butylbiphenyl
R = H, Me, *i*Bu, CO_2Me, $-(CH_2)_n$-X

T. J. Donohoe, D. J. Johnson, L. H. Mace, R. E. Thomas, J. Y. K. Chiu, J. S. Rodrigues, R. G. Compton, C. E. Banks, P. Tomcik, M. J. Bamford, O. Ichihara, *Org. Biomol. Chem.* **2006**, 1071-1084

1) Pyridines

Transformations:



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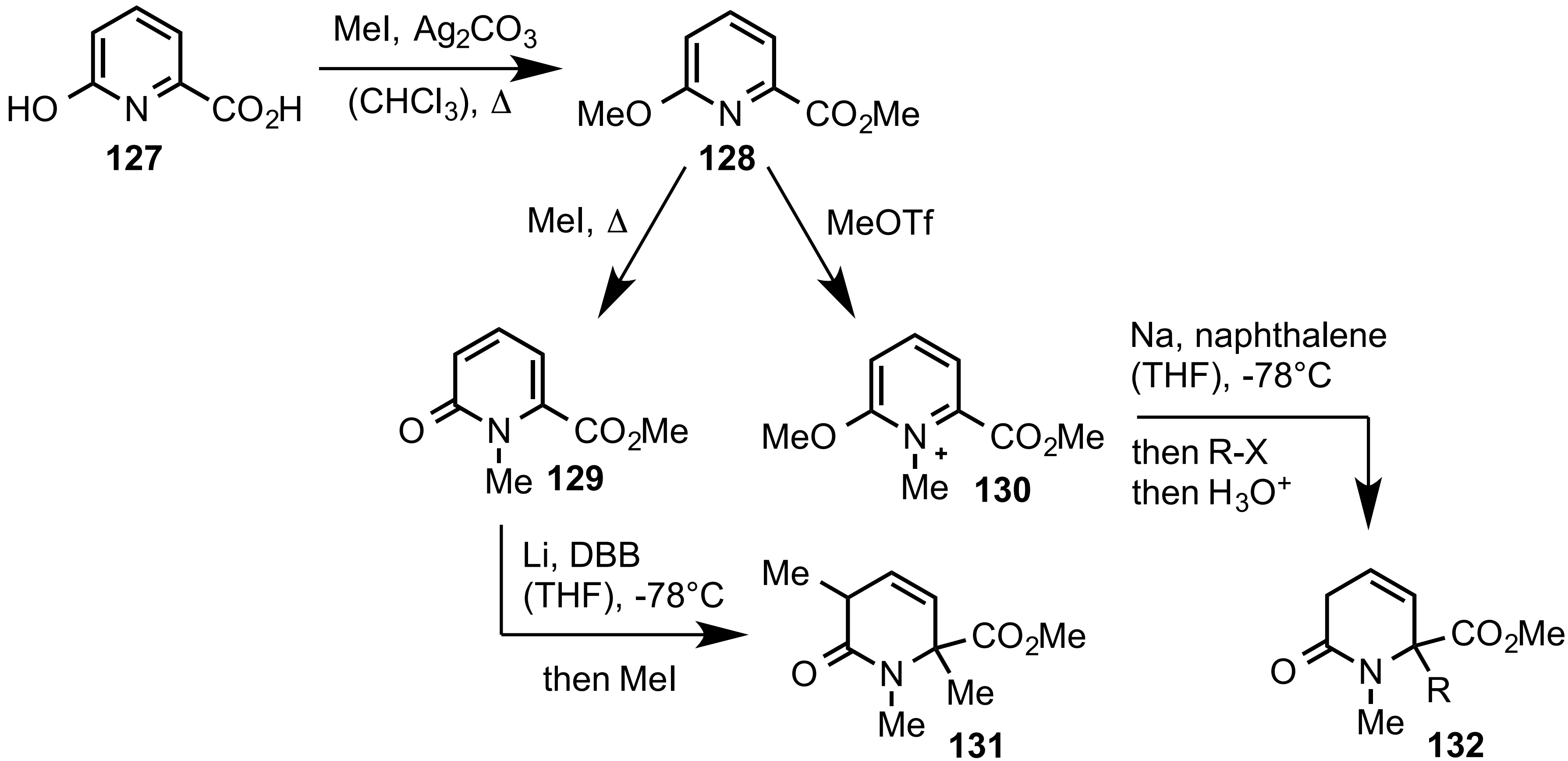
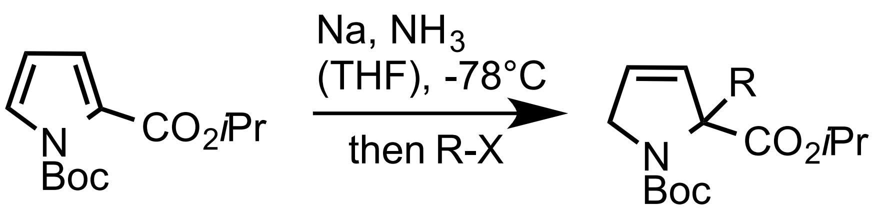
1) Pyridines

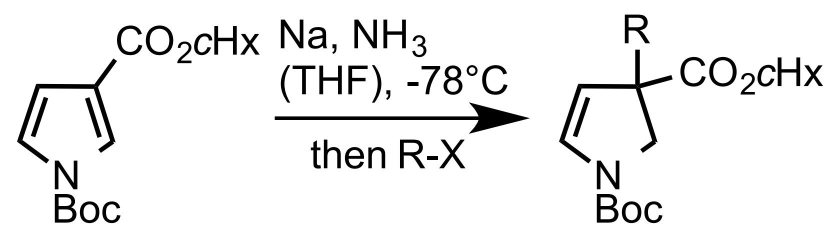


T. J. Donohoe, D. J. Johnson, L. H. Mace, R. E. Thomas, J. Y. K. Chiu, J. S. Rodrigues, R. G. Compton, C. E. Banks, P. Tomcik, M. J. Bamford, O. Ichihara, *Org. Biomol. Chem.* **2006**, 1071-1084

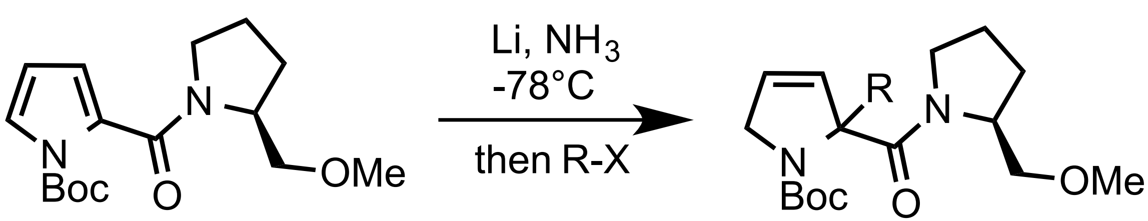
2) Pyrroles



133 R = Me, Et, *i*Bu **134**



135 R = H, Me, Bn, *i*Bu **136**

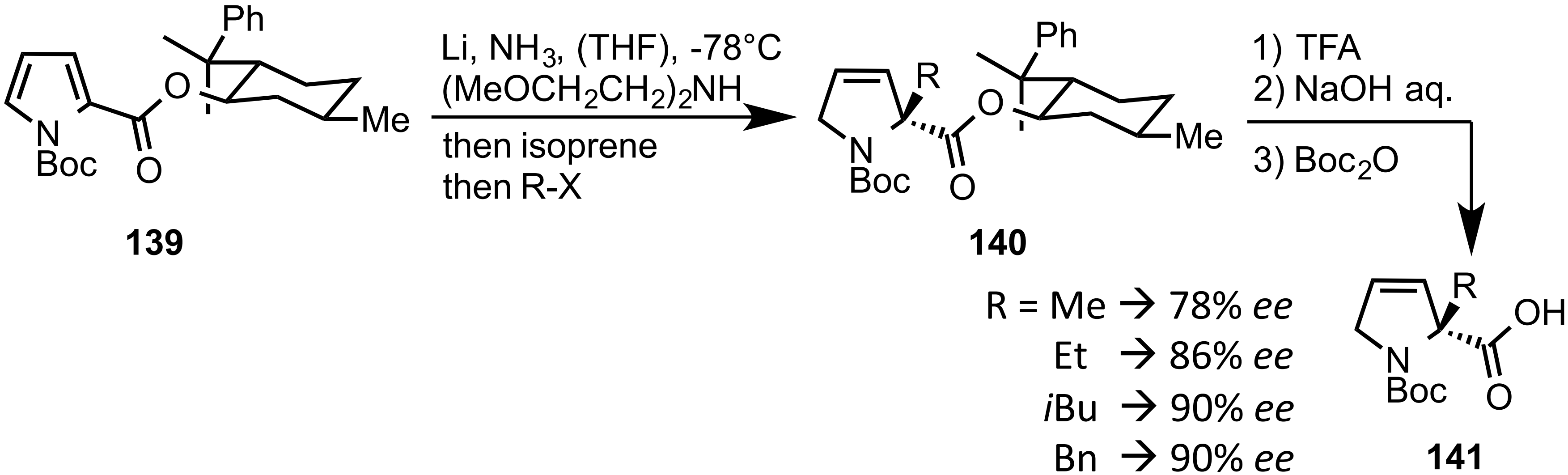


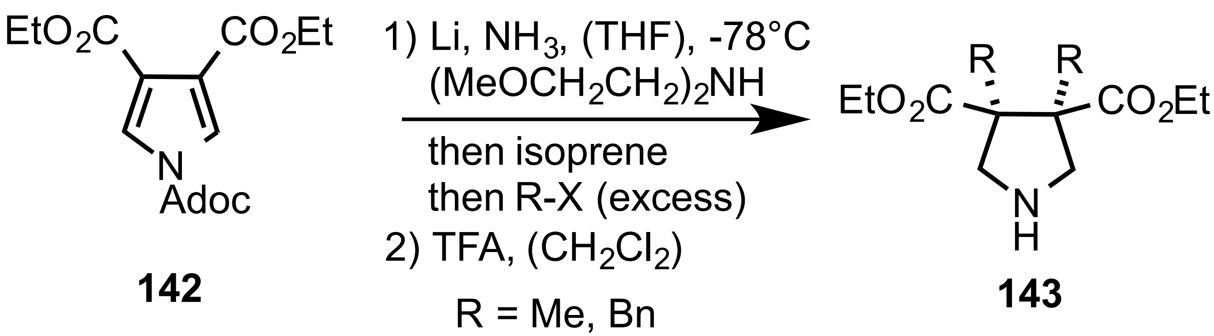
137 **138**

R = H → de = 82%
R = Me → de = 50%

A. Schäfer, B. Schäfer, *Tetrahedron.* **1999**, *55*, 12309-12312
T. J. Donohoe, P. M. Guyo, M. Helliwell, *Tet. Lett.* **1999**, *40*, 435-438

2) Pyrroles



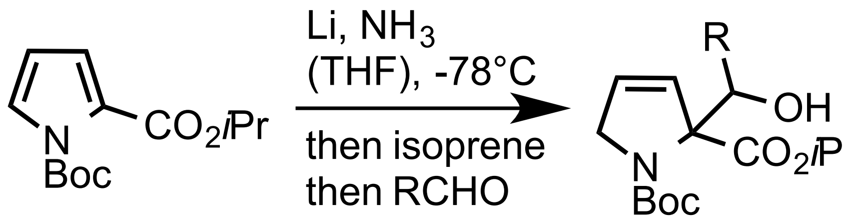


two different electrophiles also possible!

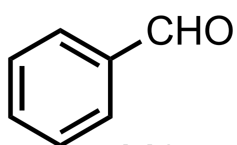
T. J. Donohoe, P. M. Guyo, M. Helliwell, *Tet. Lett.* **1999**, *40*, 435-438
T. J. Donohoe, R. R. Harji, R. P. C. Cousine, *Chem. Commun.* **1999**, 141-142

2) Pyrroles

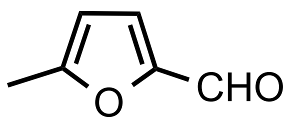
Aldol reaction:



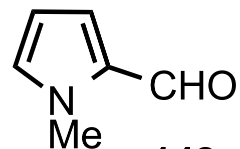
144 **145**



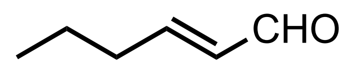
146
91%



147
90%

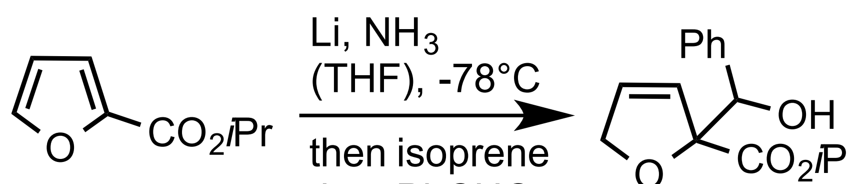


148
94%



78% **149**

Only one example with furane



150 **151**

T. J. Donohoe, K. W. Ace, P. M. Guyo, M. Helliwell, J. McKenna, *Tet. Lett.* **2000**, *41*, 989-993

3) Furanes

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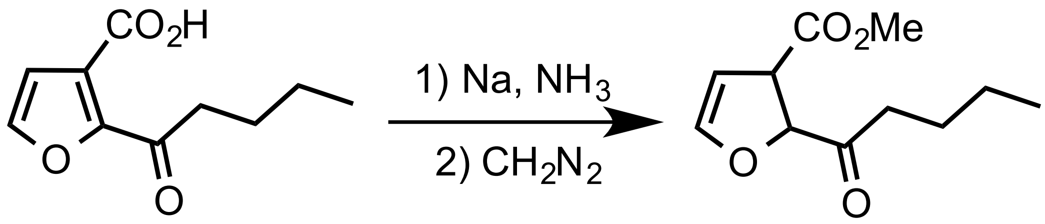
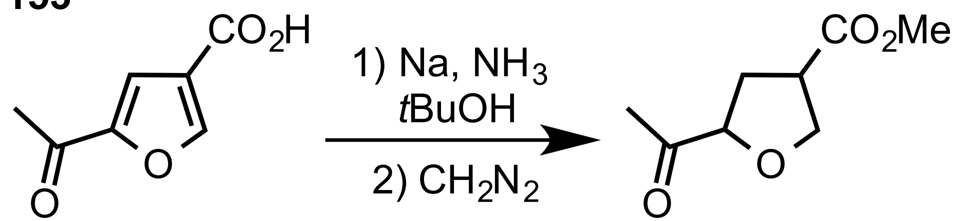


152 **153**



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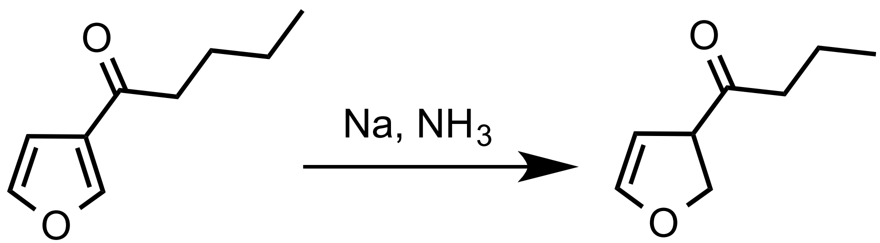

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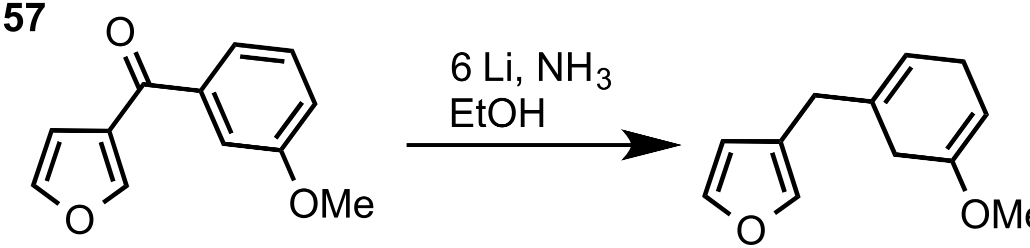

158 **159**

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3) Furanes

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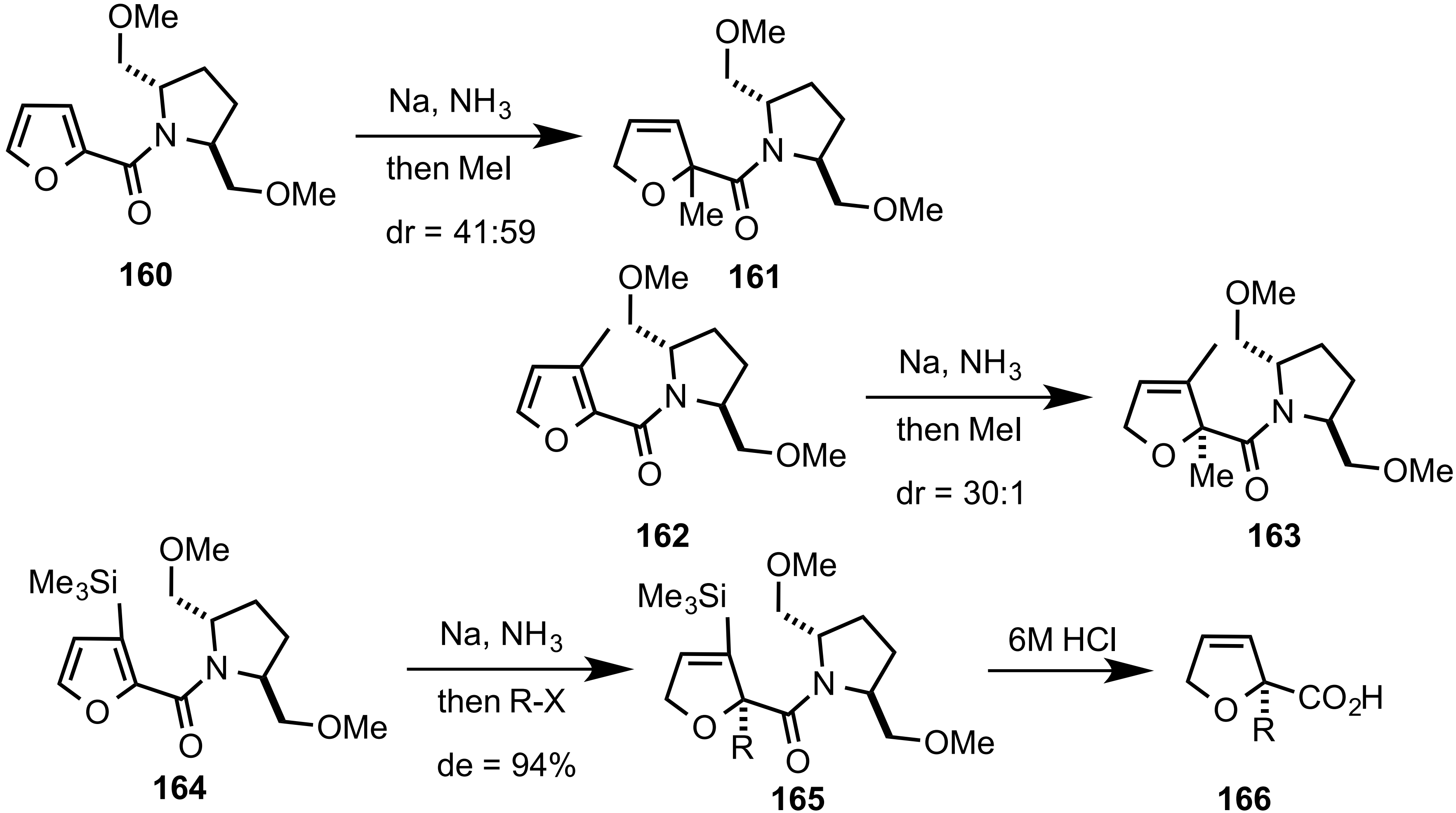

R = Me, Et, *i*Bu, Bn, CH_2OMe, $(CH_2)_3Cl$, allyl

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Thiophenes

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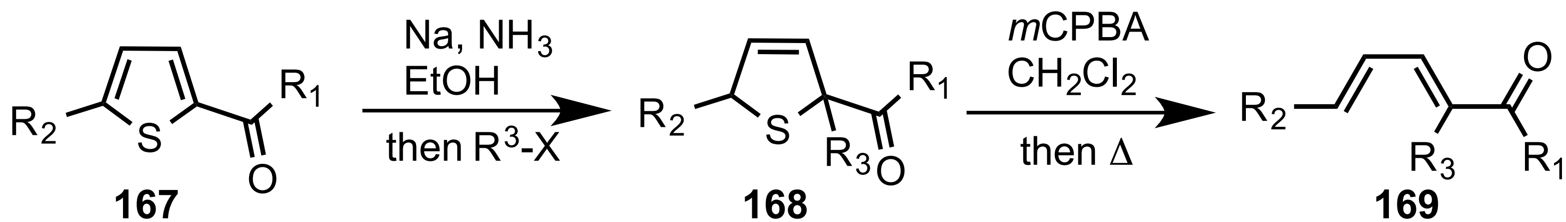
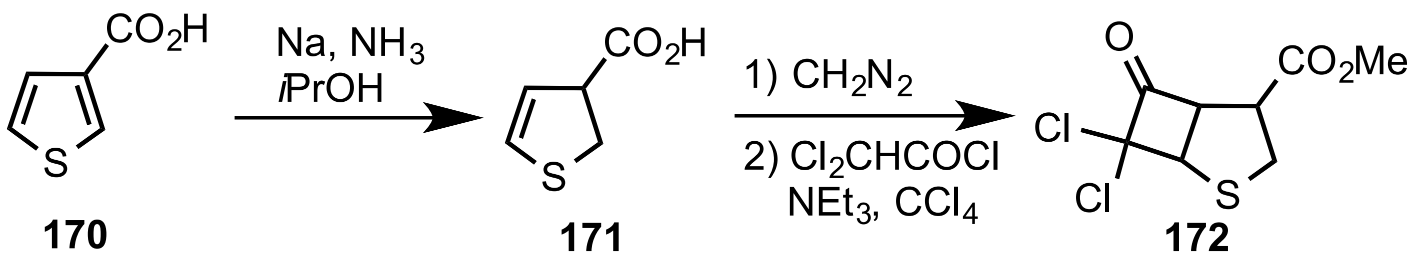


R^1 = Me, *n*Pr, *n*C_9H_{19}, *c*Hx, OH, *n*C_7H_{15}
R^2 = H, Me, Bu
R^3 = Me, Bn, allyl, Bn



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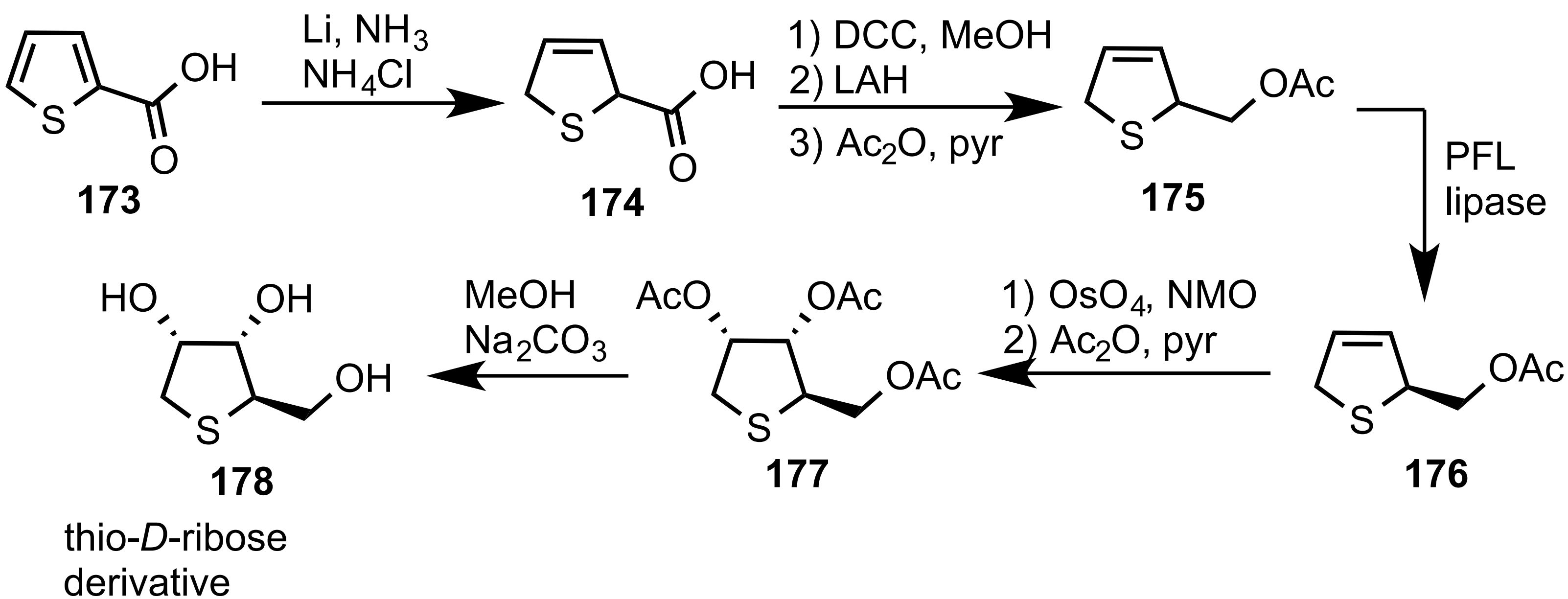
Thiophenes



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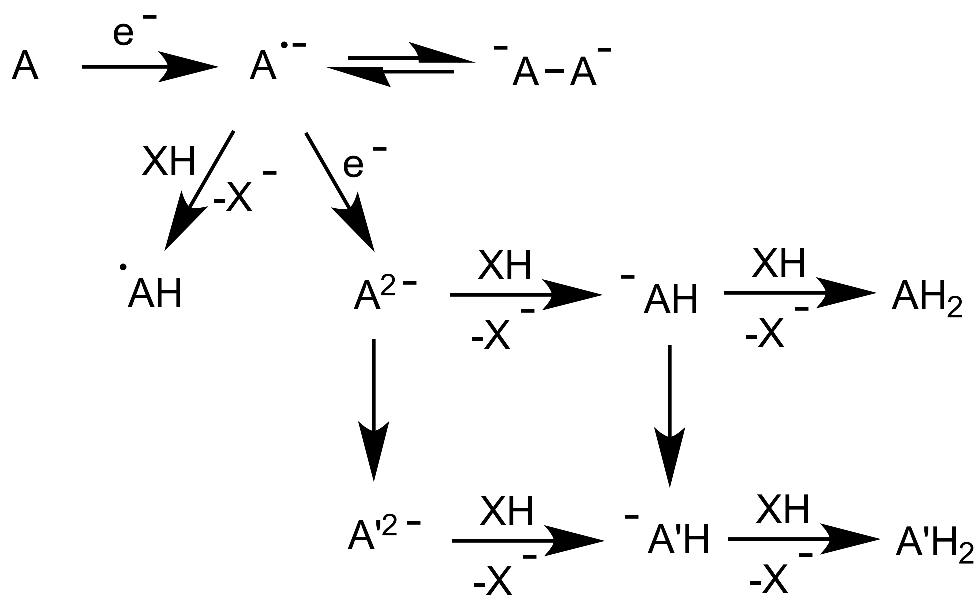
Summary

→ Birch reduction of hetero cycles much more complicated than carbocycles
→ Many variables to consider



→ Very useful procedures under right conditions, especially under alkylation conditions!