Chapter 4. Stereoselective Synthesis

- chiral solvents and chiral solvating agents
- chiral reagents
  - reduction of C=O
  - hydroboration
- chiral modification of the substrate (chiral auxiliaries)
- radical reactions
- chiral catalysts

Stereoselective synthesis

- diastereoselective: Reaction gives one diastereomer preferentially

  (covered under "asymmetric induction")

- enantioselective: Reaction gives one enantiomer preferentially
- Problem: Establish the first C*
- Solution: Provide chiral information in one of various ways

1. Chiral solvents, chiral solvating agents
   - just as discussed earlier in NMR spectroscopy:
     - differentiation is not great, not very high %ee
     - too expensive
   - dependence of %ee on T ($\Delta G^{\ddagger} = f(T)$)

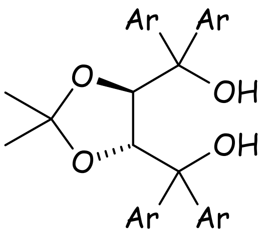
T (°C)	0	-78	-120
% ee	8.5	15	25

BUT!:

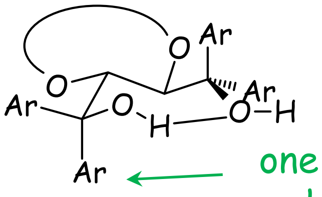
1. Chiral solvents continued

- development from Rawal, University of Chicago (2003)
- chiral alcohol activates aldehydes through H-bonding

TADDOL: TetraArylDioxolaneDiOL: C_2

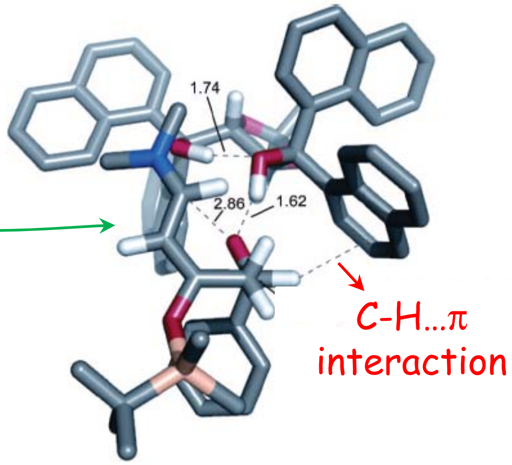


TADDOL



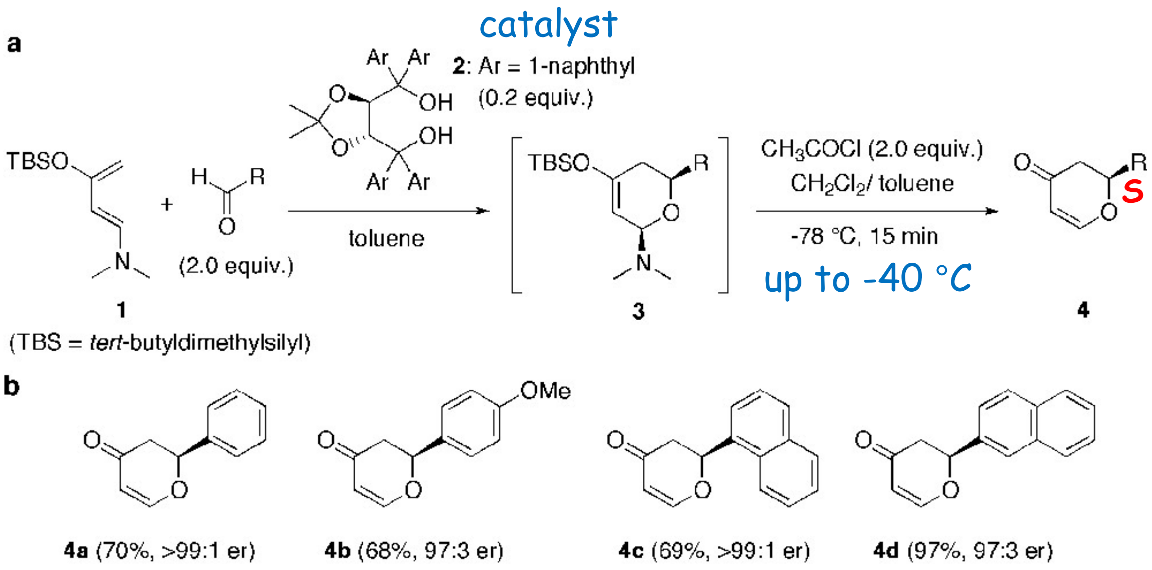
one face
more hindered

TADDOL + substrates



C-H…π
interaction

Anderson, Dudding, Gordillo, Houk, Org. Lett. **10**, 2749 (2008)

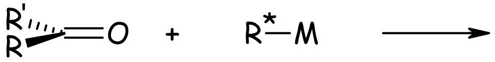


Huang, Unni, Thadani, Rawal, Nature **424**, 146 (2003)

2. Chiral reagents

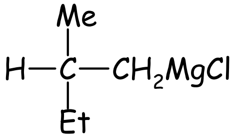
- just two examples

A. Reduction with chiral reducing agent



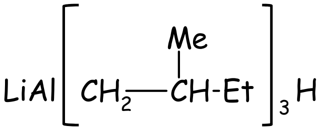
up to 100 %ee alcohol

R*-M: Grignard reagent:



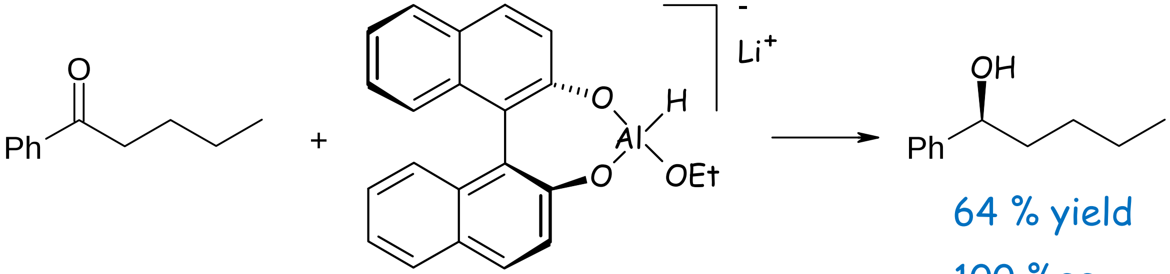
$$\mathrm{H{-}\overset{Me}{\underset{Et}{C}}{-}CH_2MgCl}$$

Al-organic reagent:



$$\mathrm{LiAl}\left[\mathrm{CH_2{-}\overset{Me}{C}H{-}Et}\right]_3\mathrm{H}$$

example



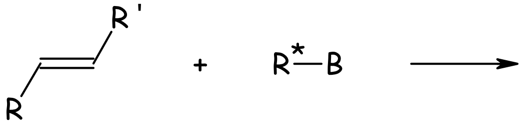
binaphthyl-Al-hydride

64 % yield

100 %ee

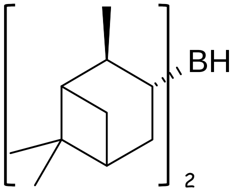
2. Chiral reagents continued

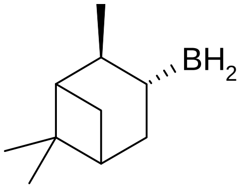
B. Hydroboration with chiral borane (H.C. Brown, Perdue, 1979 Nobel Prize, with G. Wittig)



high %ee alcohol

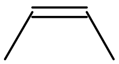
R*-B: α-pinene-modified BH_3:

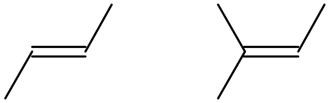




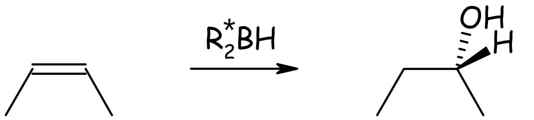
for Z-alkenes

for other alkenes



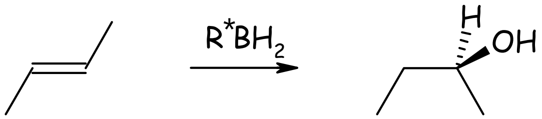


examples



(R)-2-butanol 98.4 %ee

Brown, Yoon, Isr. J. Chem. **15**, 12 (1976)



(S)-2-butanol 73 %ee

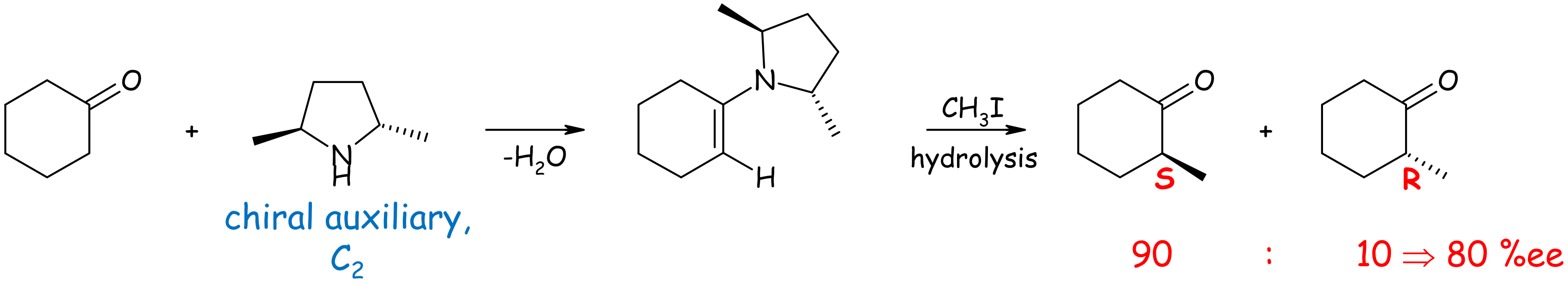
⇒ R^*BH_2 is more reactive, gives better yields, but gives poorer %ee

3. Chiral modification of the substrate

- use of a chiral auxiliary: introduces chiral information, gets removed
- α-alkylation of ketones: not addition to C=O (focus is ***not*** on faces)

  but substitution at α-C (focus is on ligands)

Through chiral enamines (Stork enamine reaction)



- diastereomeric differentiation in the TS for addition to C=C
- addition from the Si face is less hindered

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