

CHEM – 750

Advanced Organic synthesis



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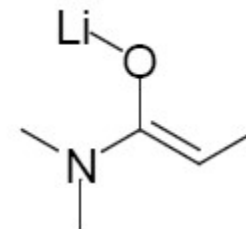
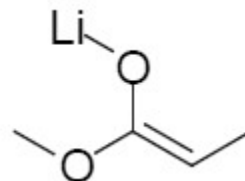
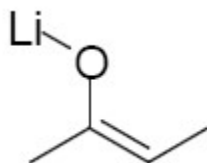
Stereoselective Enolate Formation

ketone

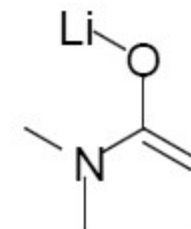
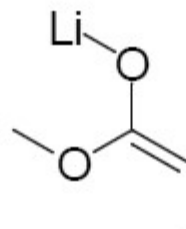
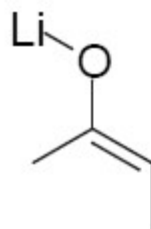
ester

amide

cis-enolates
(*Z*)-enolate



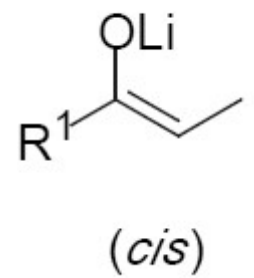
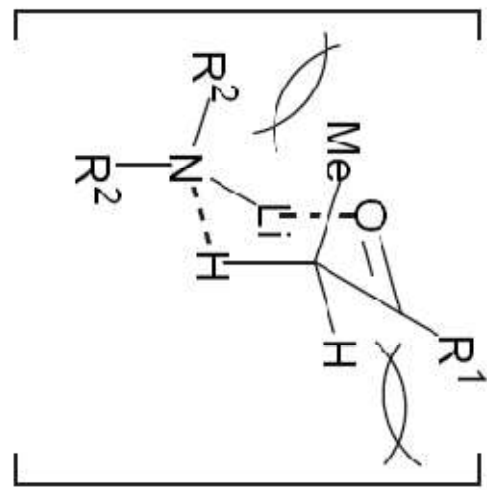
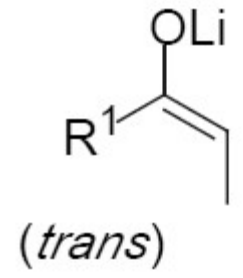
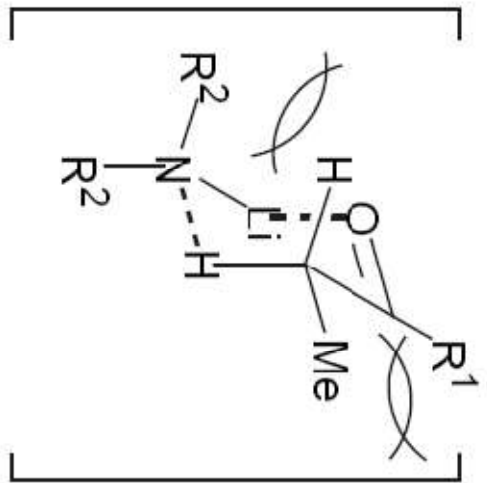
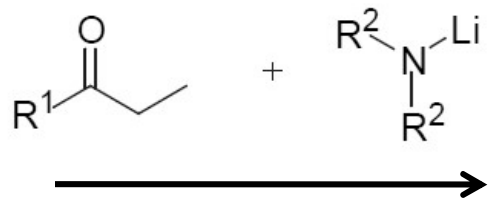
trans-enolates
(*E*)-enolate



O-metal bond of the enolate always takes priority

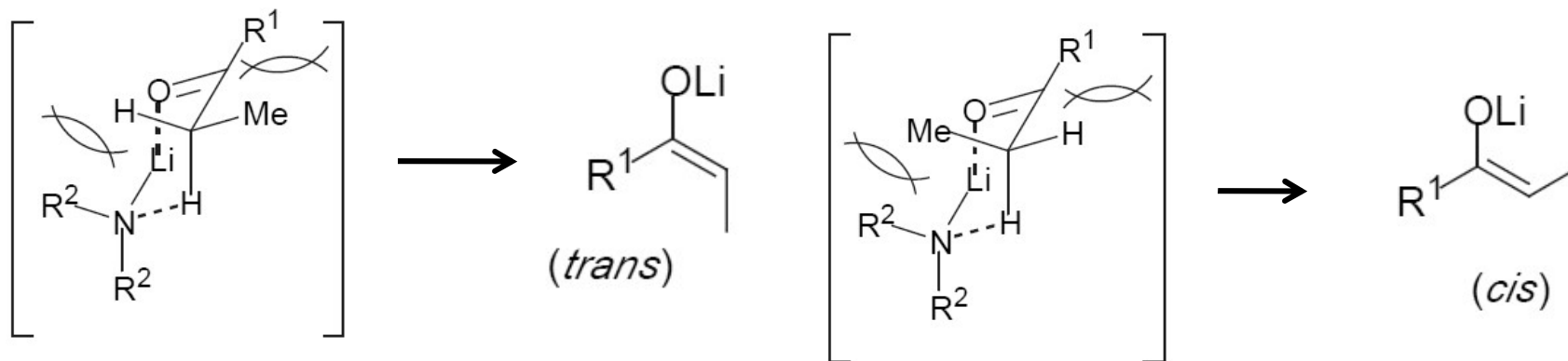


Ireland model





Ireland model

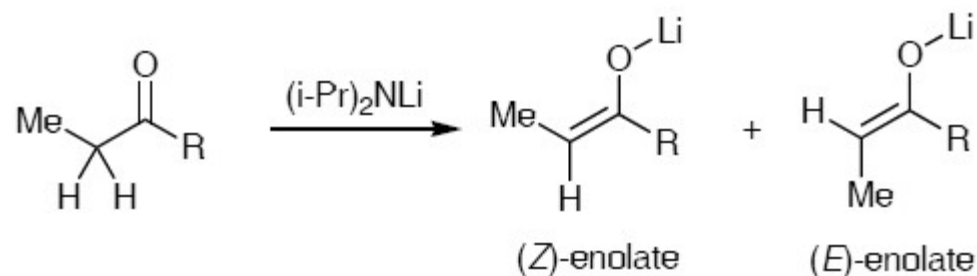


- 1) when R^1 is NOT sterically demanding and when $H \leftrightarrow R^2 \ll Me \leftrightarrow R^2$ then the *trans*-stereoisomer is favoured.
- 2) when R^1 is large (tBu is especially good) then $Me \leftrightarrow R^1 \gg H \leftrightarrow R^1$ and this overrides the $Me \leftrightarrow R^2$ interaction favouring the formation of the *cis*-stereoisomer.

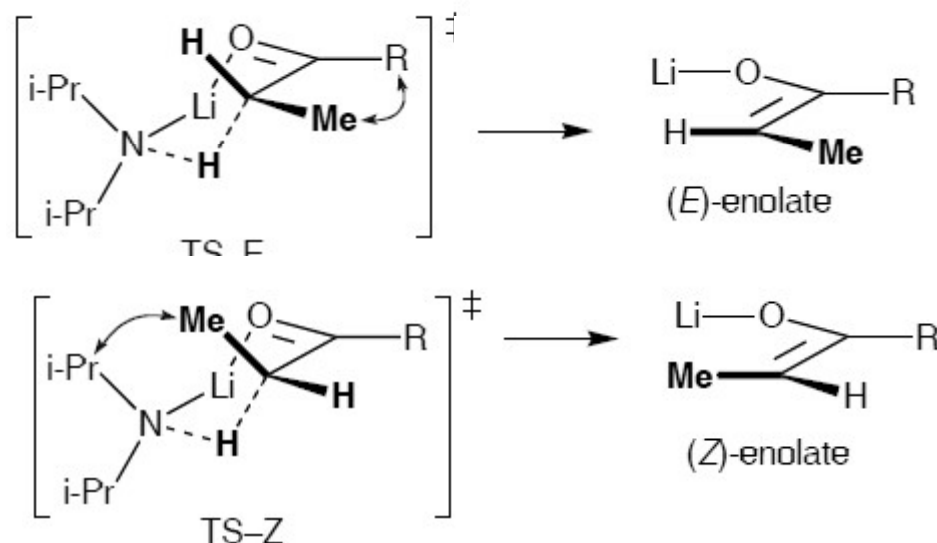


Rationalisation: the Ireland model

As the size of R increases, the preference for (Z) increases



R	Z : E
Et	1:3
i-Pr	3:2
t-Bu	98:2
Ph	98:2



1. When R is small, the i-Pr/Me interaction in TS-Z dominates forcing the reaction to proceed via TS-E.

2. When R is large, the R/Me interaction in TS-E dominates forcing the reaction to proceed via TS-Z.

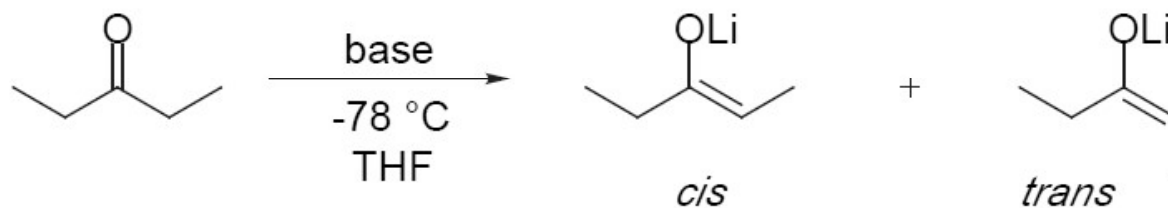
Many additional factors determine Z:E including

1. solvent
2. temperature
3. metal cation (Li, Na, K)
4. size of groups on the nitrogen base
5. additives (e.g. dipolar aprotic solvents)



General observations

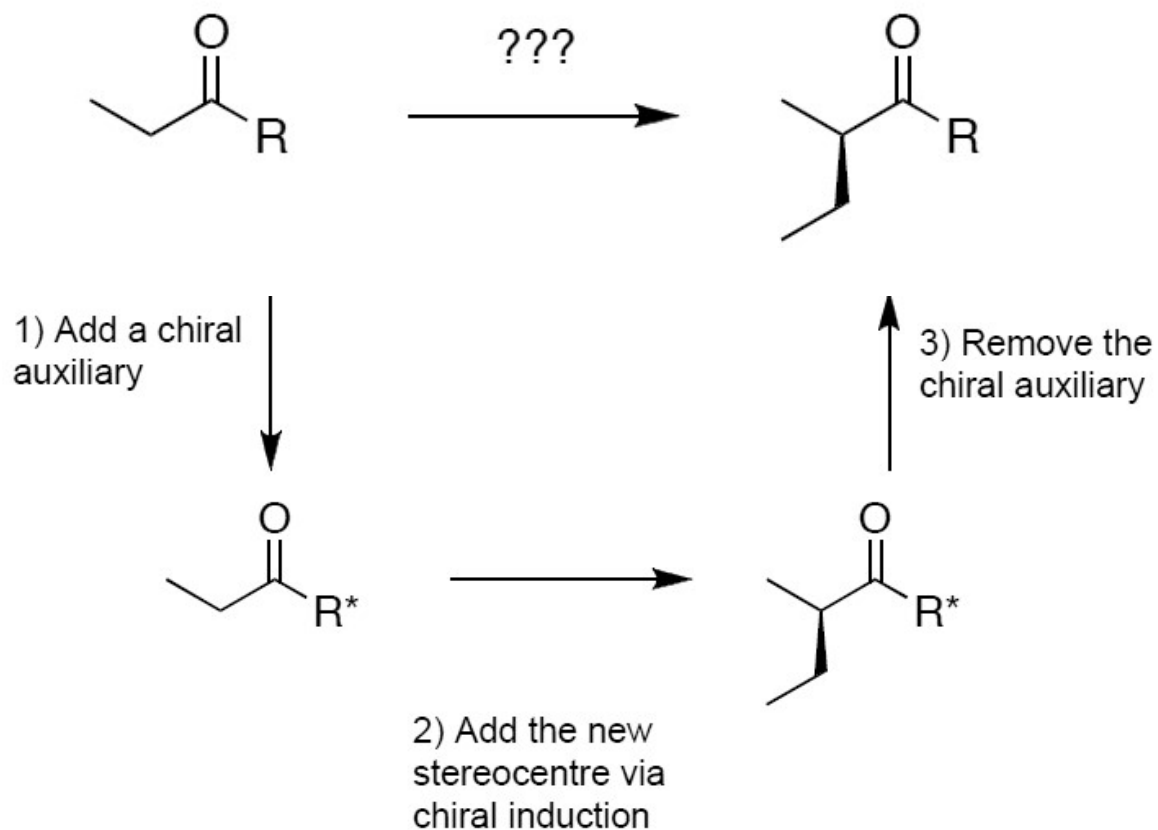
- 1) LHMDS generally provides the *cis*-enolate as the major product
- 2) LTMP (very bulky) affords the *trans*-enolate as the major product
- 3) LDA gives intermediate results.
- 4) use of HMPA as a strongly Lewis basic donor-co-solvent can reverse selectivity.



LTMP	14	86
LTMP / HMPA	92	8
LDA	33	67
LHMDS	66	34



Asymmetric Alkylation of Enolates



Asymmetric Synthesis

Chiral Auxiliaries

Chiral Reagents

Chiral Catalysts

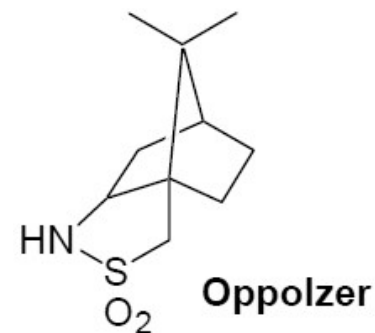
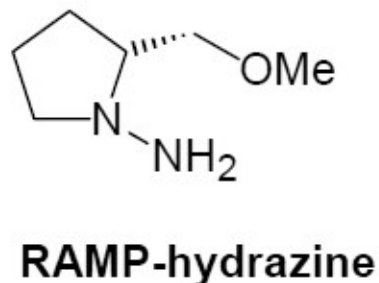
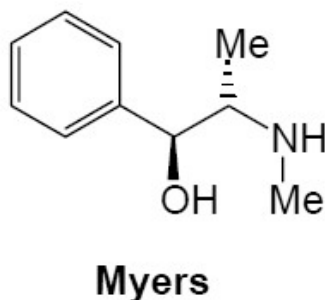
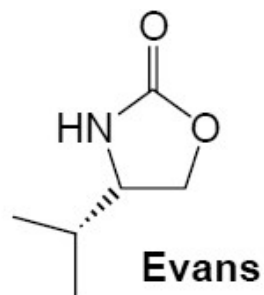
chiral induction

chiral pool



Asymmetric Alkylation of Enolates

Chiral Auxiliary: A chiral control element temporarily incorporated into the structure of the substrate in order to direct the stereochemistry at new stereogenic centre(s) formed in a reaction. The auxiliary is removed (either immediately during work up or in a separate subsequent step) and may be recovered for re-use. Some examples are given below.





Racemic alkylation – no chiral auxiliary present.

