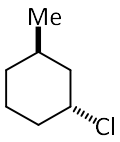
CHM 4002 Asymmetric Synthesis: Substrate and Auxiliary Control

Problems

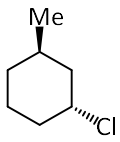
These problems are designed to ensure that you understand the lecture course material as you go. You should look at the problems relating to each lecture before the following one. These are not mock exam questions, and shouldn't be used as such.

Lecture 1 – Introduction to stereoselective synthesis

(i) Explain the difference between the following structures when interpreted according to the Maehr convention.

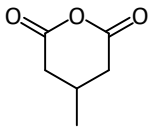


1



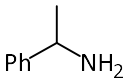
2

(ii) The following molecule is prochiral. What reaction(s) could you carry out to transform it into a chiral (but racemic) product?



3

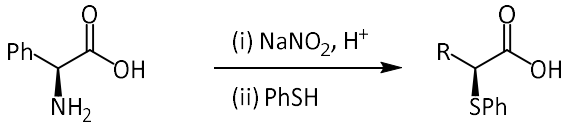
(iii) If molecule **3** were treated with the racemic amine **4**, what would the product be, and how many stereoisomers could be formed?



4

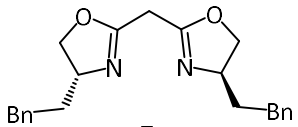
Lecture 2 – The Chiral Pool

(i) Why does the following reaction proceed with *retention* of configuration?



5 **6**

(ii) Bisoxazolines (e.g. **7**) are common ligands in asymmetric synthesis. Which class of chiral pool molecule would be an appropriate starting material for their synthesis?

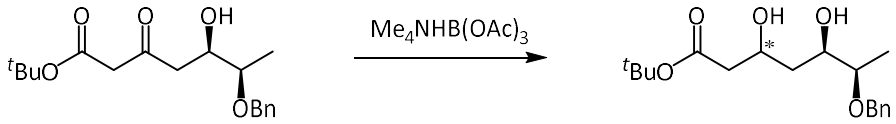


7

Lecture 3 – Substrate controlled stereoselective reactions

(i) What is the Felkin-Anh model for addition to carbonyl compounds?

(ii) What stereochemistry of product would you expect in the following reduction reaction?

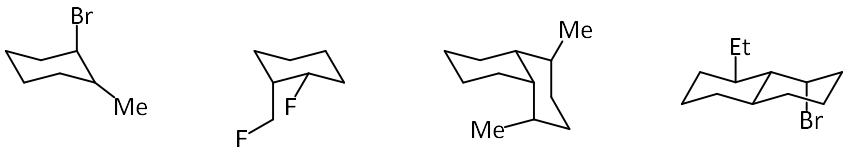


8 **9**

(iii) Which stereochemical model should you consider for addition to alkenes with an adjacent stereocentre?

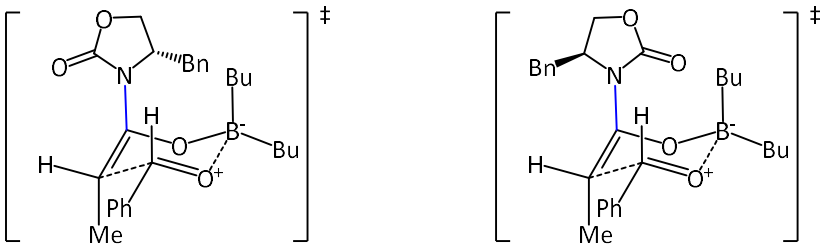
Lecture 4 – Stereoselective aldol reactions under substrate and auxiliary control

(i) The Zimmerman-Traxler model involves a chair transition state. Each structure below has been drawn incorrectly – identify the errors.



10 **11** **12** **13**

(ii) Which interaction causes the Evans auxiliary to prefer conformation **14** to **15**?

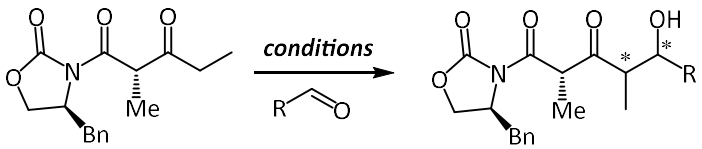


14 **15**

(iii) Which reagents would you use to selectively generate *cis* or *trans* enolates from ketones?

Lecture 5 – Other auxiliary-controlled reactions of enolates

(i) Why is it possible to carry out the following reaction without epimerizing the carbon between the two carbonyl groups?



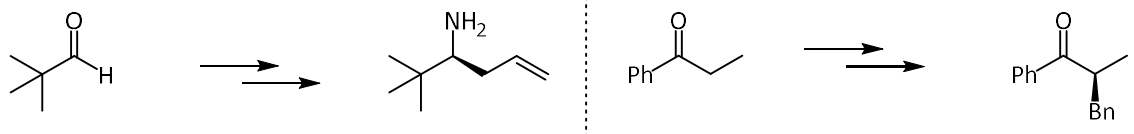
16 17

(ii) If you were designing a new chiral auxiliary, what attributes do you think would be important?

(iii) What is the transition state model for aldol reactions involving Myers' auxiliary?

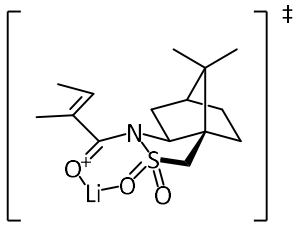
Lecture 6 – Chiral auxiliaries on ketones and aldehydes, and asymmetric 1,4-addition reactions

(i) Which chiral auxiliary strategies would you select for the following overall transformations?



18 19 20 21

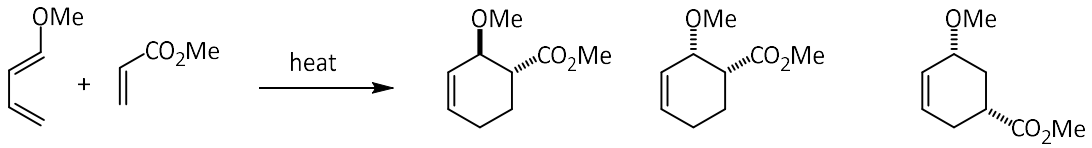
(ii) Which face of the electrophilic alkene in **22** will be attacked by nucleophiles, and what interaction determines this facial selectivity?



22

Lecture 7 – substrate and auxiliary control in pericyclic reactions

(i) Which will be the major product in the following reaction, **23**, **24** or **25**?

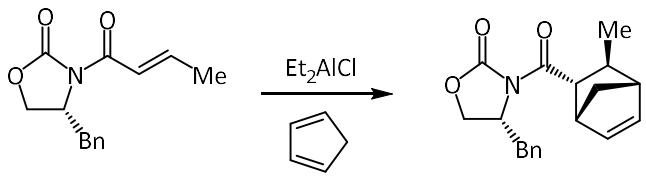


23 24 25

(ii) Despite being stereospecific, why does the reaction above require an auxiliary or catalyst to generate the product as a single enantiomer?

(iii) What do we mean by *conrotatory* and *disrotatory* with reference to electrocyclic reactions, and what determines which reactions are conrotatory and which are disrotatory?

(iv) Give a convincing transition state for the following Diels-Alder reaction. What is the role of the Et_2AlCl?

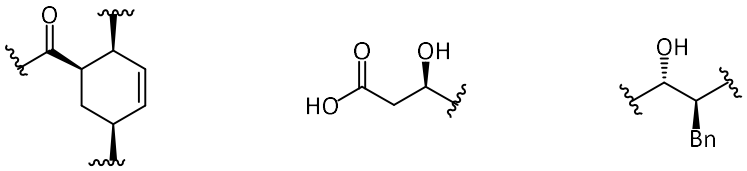


26 **27**

Lecture 8 – stereochemical considerations in retrosynthesis of complex molecules

(i) Why do you think it is a good idea to disconnect molecules at the middle?

(ii) Pattern recognition is important in retrosynthetic analysis. If your target molecules contained the following motifs, what stereoselective reactions would you consider?



28 **29** **30**