



CHEMISTRY HONOURS EXAMINATION: JUNE 2019

MODULE: REACTION MECHANISMS AND THEORETICAL ASPECTS (CEM 8X01)

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MODERATOR: Dr A.L. Rousseau (University of the Witwatersrand)

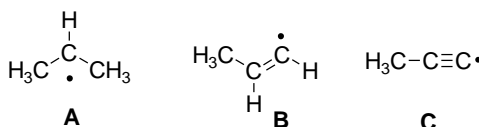
INSTRUCTIONS

- (i) This examination is out of a Total of 100 Marks and you have 3 Hours (180 Minutes) to complete it. No extra time will be allowed for any reason.
- (ii) The Exam comprises 4 Sections. PLEASE ANSWER EACH SECTION IN A SEPARATE BOOK.
- (iii) The use of cell phones and other electronic communication devices is forbidden and they must be switched off. No data/image storing devices, including calculators capable of such, are permitted in this examination.
- (iv) This is a closed book examination. You are NOT allowed to have any book, memorandum, notes, paper, photographs, document or written/printed material other than the question paper and the answer books provided by the examiner/invigilator. If you need paper for rough work, an additional exam answer sheet will be given to you, which must be clearly labelled as **rough work: not for marking**, and handed in together with the question paper and all your answer books.

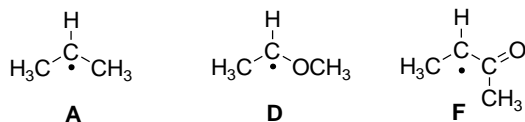
SECTION A: RADICAL REACTIONS (20 MARKS)

QUESTION 1

- 1.1** List the following radicals in order of INCREASING REACTIVITY. Please give an explanation for your answer. (2)



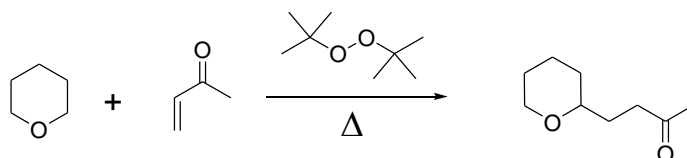
- 1.2** List the following radicals in order of INCREASING ELECTROPHILICITY. Please give an explanation for your answer. (2)



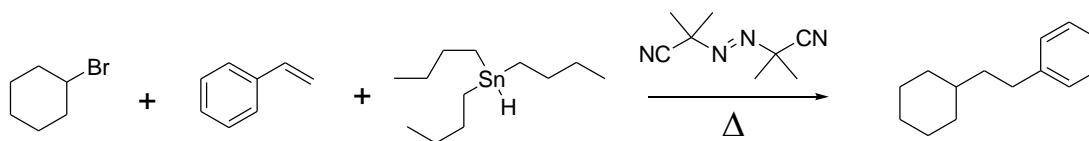
- 1.3** Discuss the statement “Intramolecular radical reactions, in contrast to intermolecular reactions, have become an attractive methodology in Organic Synthesis”. Illustrate your answer with appropriate examples. (4)

QUESTION 2

- 2.1** Do you expect the following radical reaction to provide the product in good or poor yield? Please explain your answer. (3)

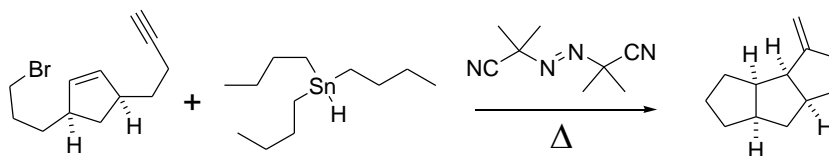


- 2.2** Explain why control of the concentration of Bu_3SnH is critical in ensuring a high yield of product in the following reaction: (3)

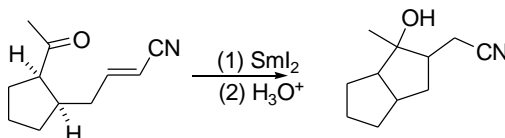


- 2.3** Give reaction mechanisms for the following transformations: (2)

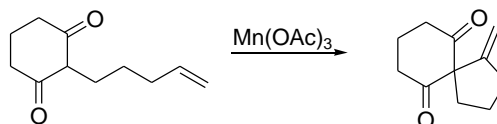
- (i) (2)



- (ii) (2)



- (iii) (2)

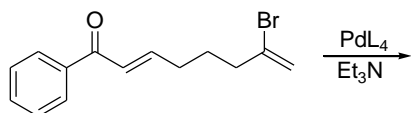


SECTION B: TRANSITION METAL COMPLEXES (30 MARKS)

QUESTION 1

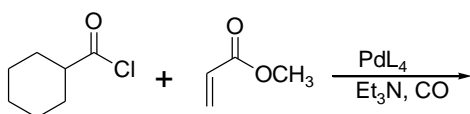
Give the products of each of the following reactions and answer the associated questions ($L = PPh_3$).

(i) (2)



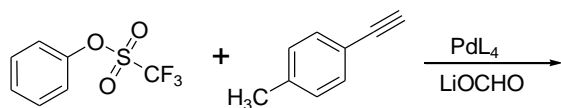
What is the role of Et_3N in the reaction?

(ii) (2)



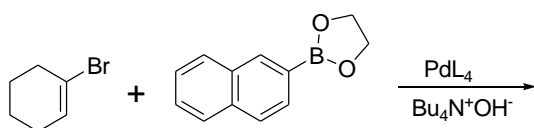
What is the role of CO in the reaction?

(iii) (2)



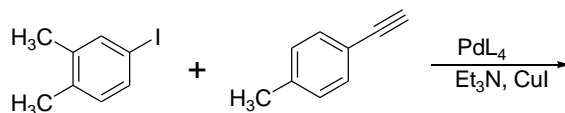
What is the role of lithium formate (LiOCHO) in the reaction?

(iv) (2)



What is the role of Bu_4NOH in the reaction?

(v) (2)

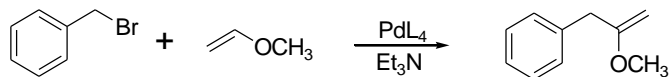


What is the role of CuI in the reaction?

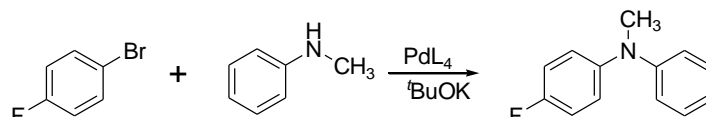
QUESTION 2

2.1 Provide detailed mechanisms for each of the following reactions below. Name each step of the mechanism according to reaction type.

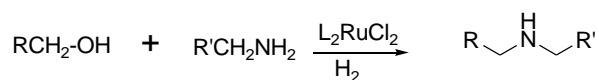
(i) (3)



(ii) (3)



2.2 Explain the mechanistic basis of the following Ru-catalysed direct amination of alcohols. (4)

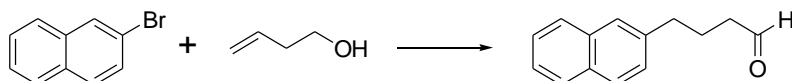


L = a bidentate phosphine

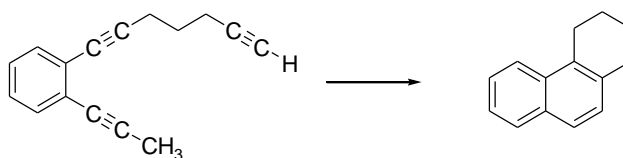
QUESTION 3

Suggest a catalyst for each of the following chemical transformations and propose a reaction mechanism in each case.

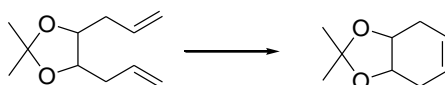
(i) (3)



(ii) (4)

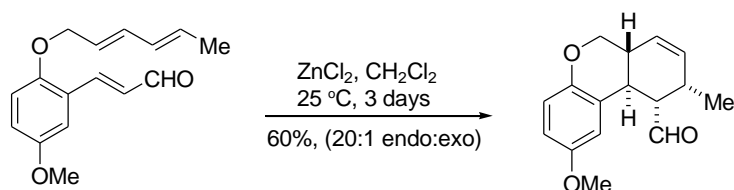


(iii) (3)



SECTION C: FRONTIER MOLECULAR ORBITAL THEORY (25 MARKS)

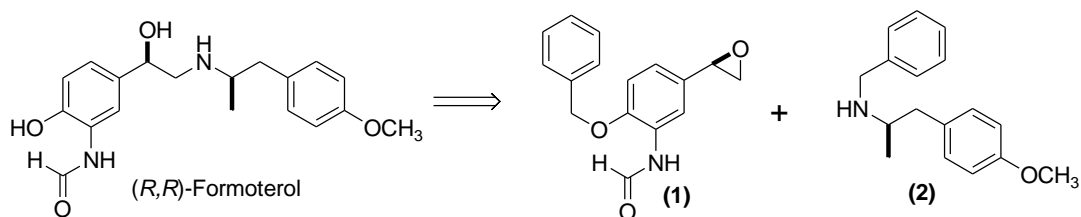
Carefully study the following reaction and answer the questions that follow.



- (i) Explain in detail, the stereochemistry at all the newly created stereogenic centers. (5)
- (ii) Comment on the observed ratio of the *endo* and *exo* products (1)
- (iii) Using Frontier Molecular Orbital diagrams, show in detail how the product forms and on the basis of the energies of the orbitals, decide which combinations lead to the product and which do not. (12)
- (iv) What is the role of zinc chloride in the reaction? (2)
- (v) List all the virtues of the Diels-Alder reaction, which explain why it is such a landmark reaction in Organic Chemistry. This is why its discoverers were awarded the 1950 Nobel Prize in Chemistry. (5)

SECTION D: RETROSYNTHETIC ANALYSIS (25 MARKS)

(*R,R*)-Formoterol is a long-acting, very potent β_2 -agonist, which is used as a bronchodilator in the therapy of asthma and chronic bronchitis. One published synthesis of (*R,R*)-Formoterol was centered around the following disconnection:

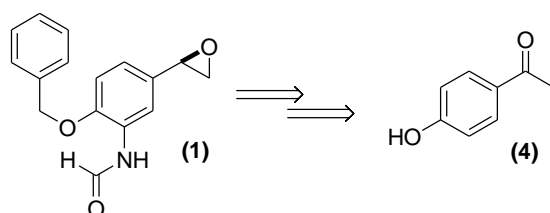


Answer the following questions.

QUESTION 1

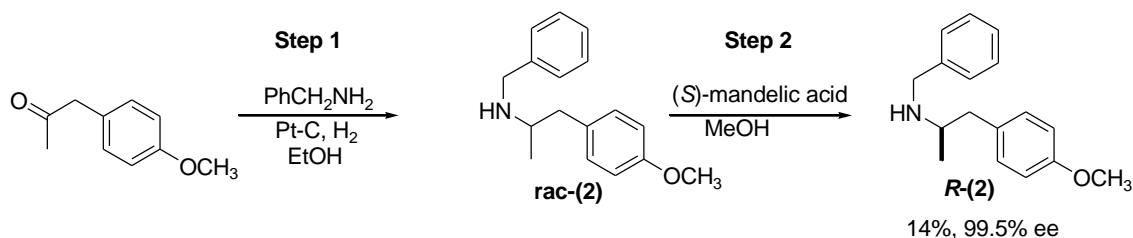
- (i) Please explain why the assembly of (*R,R*)-Formoterol by joining nearly two equal halves as the last step, is a good idea. (2)

- (ii) The synthesis of (*R,R*)-Formoterol (the reverse of the above disconnection) was done by heating the depicted chiral epoxide **(1)** and chiral amine **(2)** to give an intermediate product that was not isolated but immediately subjected to catalytic hydrogenation to give (*R,R*)-Formoterol. Suggest the structure of this intermediate product. Why was catalytic hydrogenation used instead of other possible reagents? (2)
- (iii) Show how you could synthesize the epoxide **(1)** from 4-hydroxyacetophenone **(4)**. Please show a retrosynthetic analysis then give all reagents and reaction conditions for the synthesis, including anticipated product yields. You are allowed to use any reagent, solvent, acid, base and catalyst of your choice. Please suggest how you would go about introducing the epoxide enantioselectively. State potential problems you might encounter in the synthesis and how you could resolve them. (10)



QUESTION 2

The amine **(2)** was prepared in 14% overall yield as follows:



- (i) Explain, in words or with the aid of a reaction mechanism, what happens in Step 1. (3)
- (ii) What is the point of using enantiopure mandelic acid in Step 2? (1)
- (iii) What is the major disadvantage of Step 2 and how can that be remedied? (2)
- (iv) Critically assess this synthesis of (*R,R*)-Formoterol in terms of (i) number of steps, (ii) overall yield of the product, (iii) atom economy, and (iv) environmental benignity. (5)

THE END

TOTAL

100 MARKS