ACS Group Meeting – Problem Session Feb/Mar 2009

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Reactive Intermediates in Organic Synthesis

PART I: CARBENES and NITRENES

Questions for Discussion:

1.1 Properties and Preparation of Carbenes (for Scheme 1):

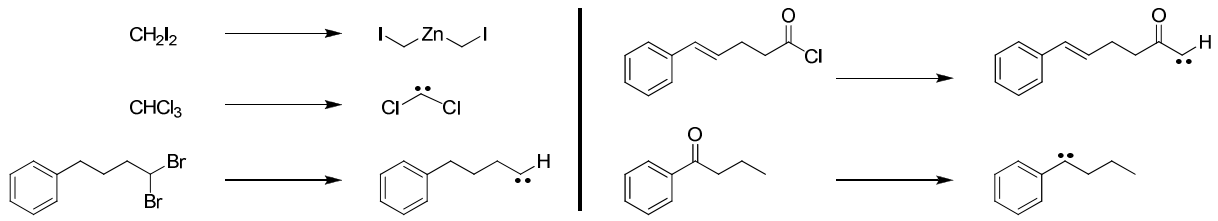
(1) What are Carbenes?

(2) What are Singlet and Triplet Carbenes? What physical method will you use to distinguish singlet and triplet carbenes?

(3) What are Fischer carbenes? Give some examples

(4) What reagents / method will you use to make the following carbenes or carbenoids (Scheme 1)? Discuss appropriate mechanism involved in these reactions.

Scheme 1: Preparation of Carbenes



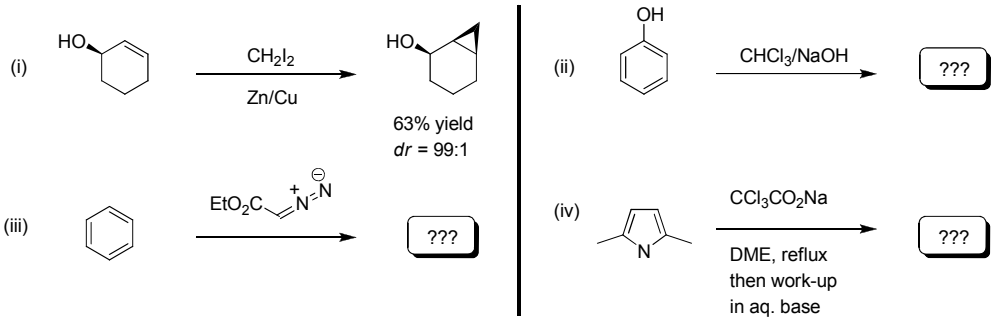
1.2 Reactivities and Application of Carbenes in Synthesis

(5) Account for the origin of the stereoselectivity seen in the following cyclopropanation reaction [Scheme 2(i)]? What is the name of this cyclopropanation reaction?

(6) Predict the product when phenol is reacted with a mixture of $CHCl_3$/NaOH [Scheme 2(ii)]. Name this classic reaction.

(7) Predict the outcome for the reactions (iii) and (iv) with appropriate mechanisms? (Scheme 2)

Scheme 2:



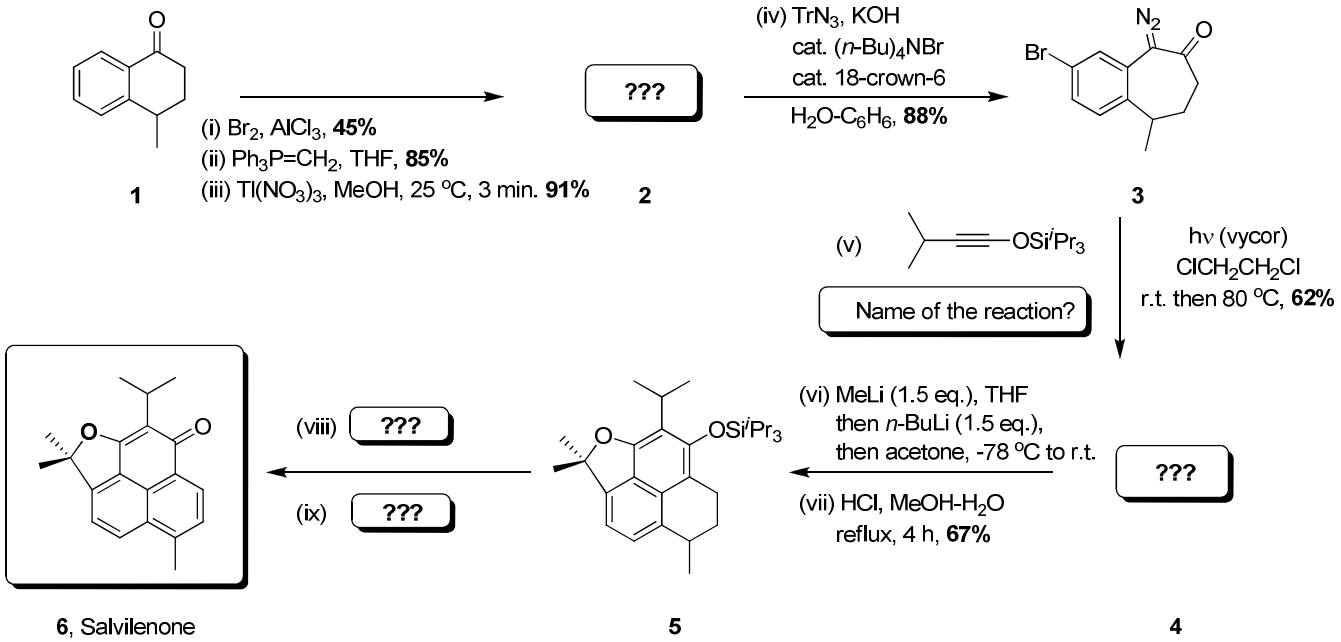
(8) Danheiser reported an elegant and short synthesis of Salvilenone **6** starting from the ketone **1** (Scheme 3). What class of natural product does Salvilenone **6** belong to?

(9) Predict the intermediate **2** based on the reactions (i)-(iii) (Scheme 3).

(10) Explain the mechanism in detail for the conversion of diazoketone **3** to **4**? What is the generic name of the reaction involved in this step (Scheme 3)?

(11) Suggest suitable reagents and conditions in order to convert **5** to the natural product Salvilenone **6** [Steps (viii) and (ix), Scheme 3].

Scheme 3: Total Synthesis of Salvilenone 6

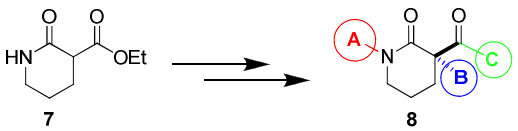


(12) Schreiber reported a diversity-oriented synthesis (DOS) of indole alkaloid-like skeletons using different combination of α-diazo ketocarbonyls and indole groups on different sites of a common scaffold **7** *via* intramolecular rhodium(II) catalysed tandem cyclisation – cyloaddition strategy (Scheme 4). Give an account of the mechanisms involved in these reactions and predict the structure of the products **12**, **13** and **14**.

(13) Schreiber reported the synthesis of the α-diazo ketocarbonyl precursor **11** starting from simple synthons **15-18**. What is the name of this multi-component reaction and give a detailed mechanism that will yield the product **19**?

Scheme 4: Diversity-Oriented Synthesis (DOS) of Indole Alkaloid – Type Compounds

Multiple modes of cycloaddition using versatile scaffold 7



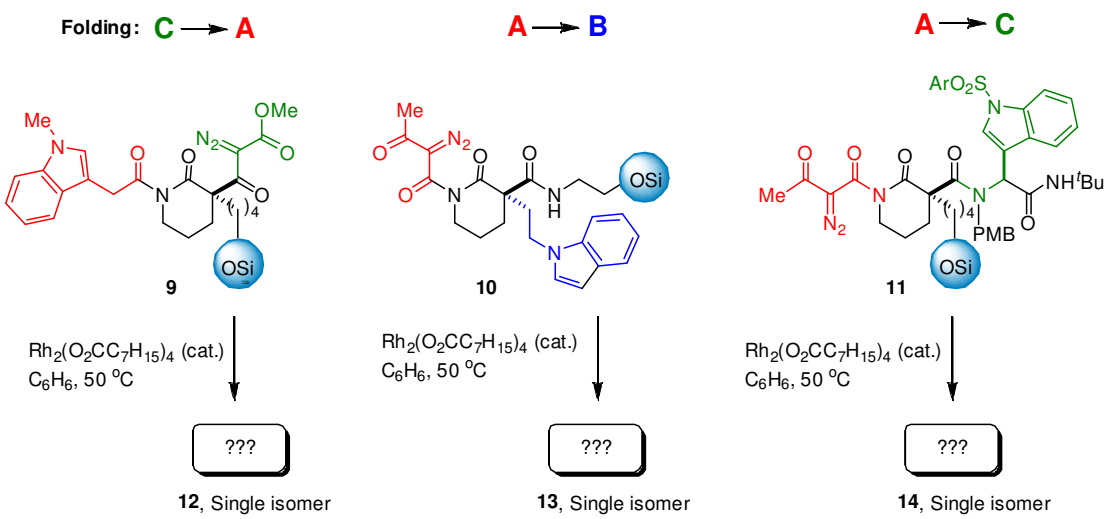
Modes of Cycloaddition

A → B, B → A, C → A

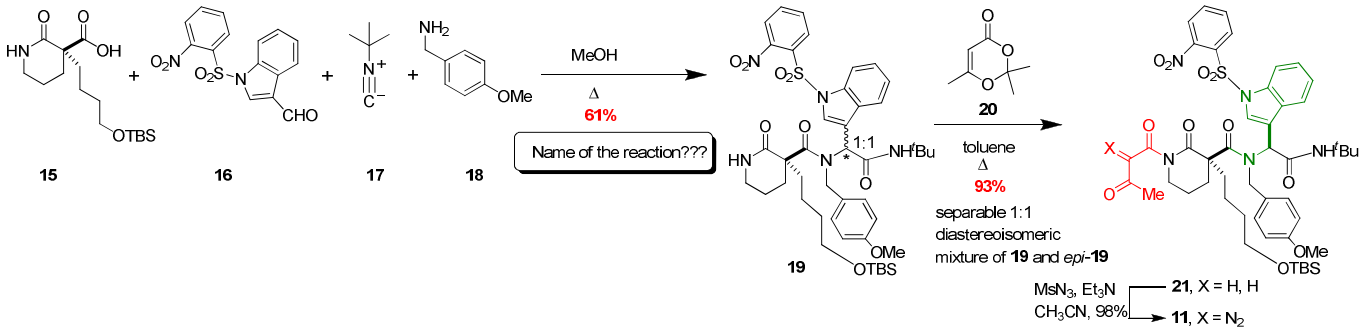
A → C, B → C, C → B

Notation, *e.g.* A → B, is short for: carbonyl ylide on site A reacts with dipolarophile on site B

Scheme 4 (Contd.): Diversity-Oriented Synthesis (DOS) of Indole Alkaloid – Type Compounds



Synthesis of the Precursor 11



1.3 *N*-Heterocyclic Carbenes (NHCs) – Preparation, Properties, Application in Synthesis:

(14) Which of the following NHC precursor salts indicated in Scheme 5(i) is the easiest and the hardest to deprotonate to afford the corresponding NHCs? Suggest few bases that you will generally use to induce deprotonation of the NHC precursors shown in Scheme 5(i).

(15) What is the order of stability of carbenes shown in Scheme 5(ii)? Rationalise your answer.

(16) Predict the order of nucleophilicity for the carbenes shown in Scheme 5(iii).

(17) Give a suitable mechanism for the asymmetric transformation of benzaldehyde to benzoin (*S*)-**23**. What is the name of this reaction [Scheme 5(iv)]?

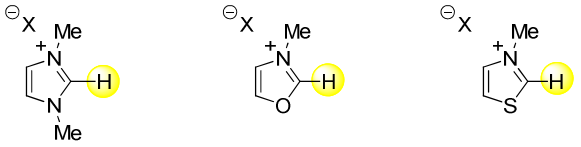
(18) Suggest a synthetic route to synthesise the NHC precursor salt (*S*)-**22** [Scheme 5(iv)]?

(19) In 2006, Fu et al. reported umpolung reactivity of Michael acceptors to make 5 or 6 membered ring systems catalysed by Ender's NHC **26** [Scheme 5(v)]. Speculate the mechanism for this reaction.

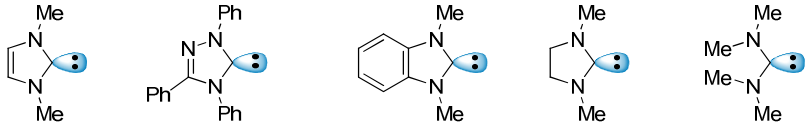
(20) Propose a suitable synthetic route to each of the chiral NHC precursor salts **27-29, 31-33** starting from commercially available starting materials [Scheme 5(vi)].

Scheme 5: *N*-Heterocyclic Carbenes

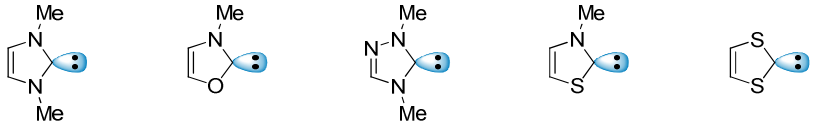
(i) pK_a ?:



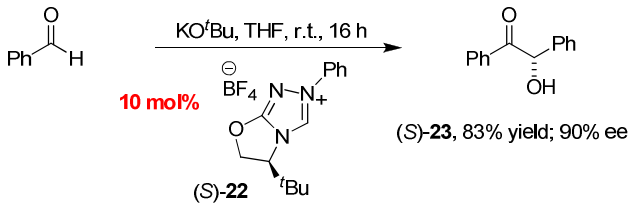
(ii) Stability ?:



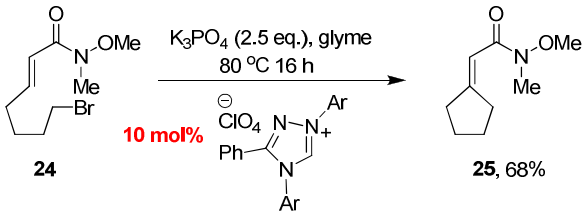
(iii) Nucleophilicity? :



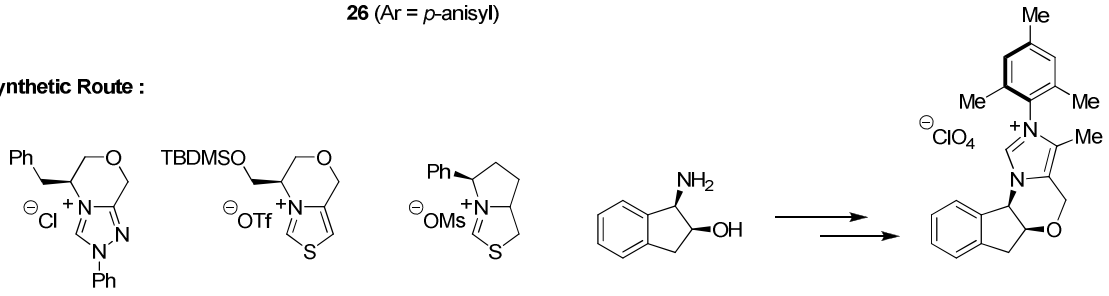
(iv) Mechanism? :

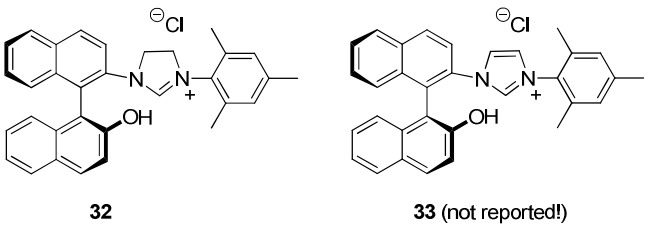


(v) Mechanism? :

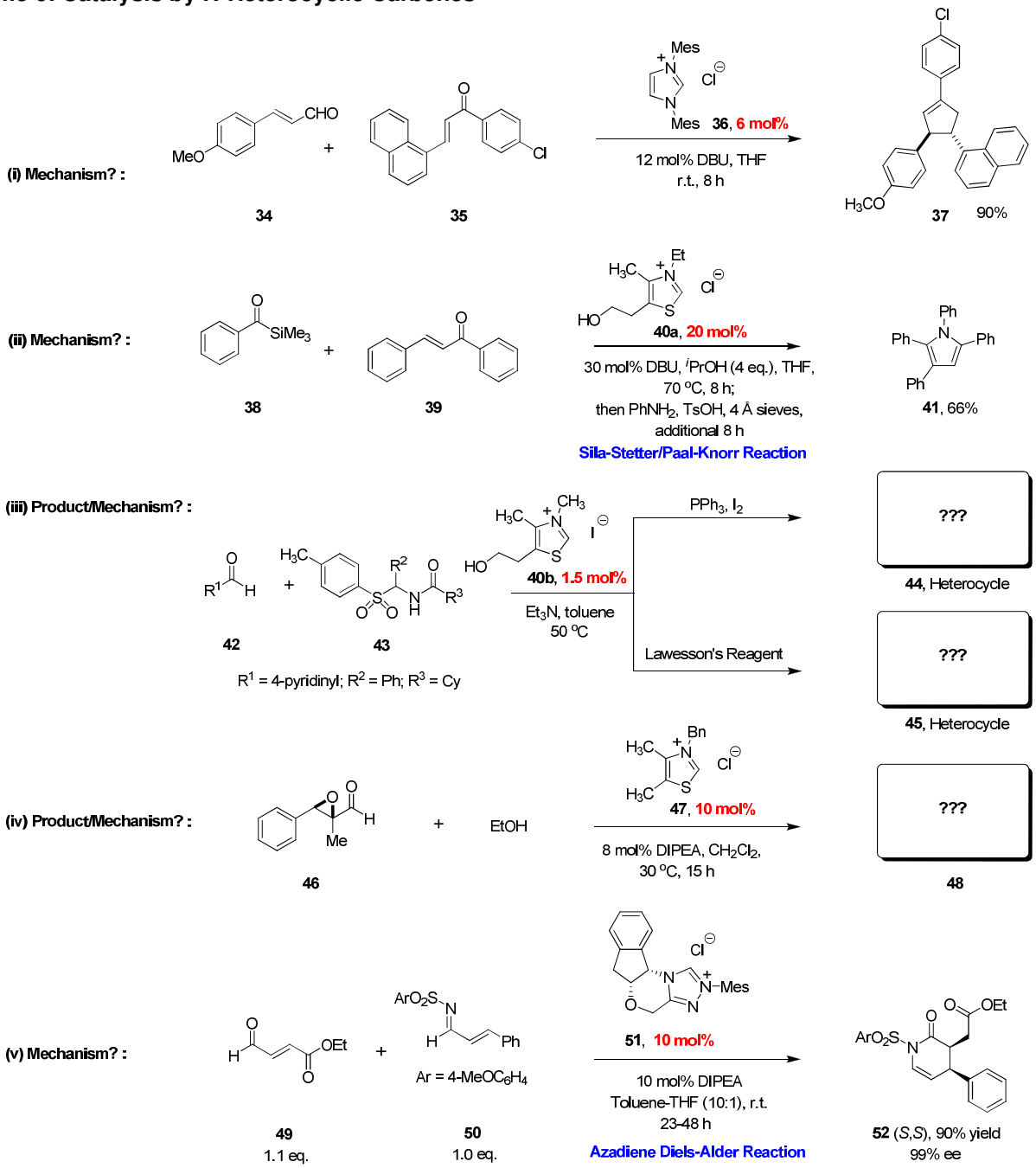


(vi) Synthetic Route :





Scheme 6: Catalysis by *N*-Heterocyclic Carbenes



(21) Nair *et al.* reported an efficient NHC catalysed method of making 1,3,4-trisubstituted cyclopentenes by reacting chalcones and enals [Scheme 6(i)]. Give an account of the mechanism involved in this reaction.

(22) In 2004, Sheidt *et al.* reported multicomponent synthesis of highly substituted pyrroles utilising a one-pot Sila-Stetter/Paal-Knorr Strategy catalysed by NHC derived from salt **36** [Scheme 6(ii)]. Give a plausible mechanism for this multicomponent reaction.

(23) Predict heterocycles **44** and **45** that will be obtained from NHC catalysed reaction of **42** and **43** [Scheme 6(iii)].

(24) What product will be obtained upon treatment of epoxide **46** with ethanol in the presence of NHC derived from thiazolium salt **47**? Predict stereochemistry for the product **48**.

(25) In 2006, Bode *et al.* reported an elegant NHC catalysed azadiene Diels-Alder reaction [Scheme 6(v)]. Draw the transition state of the reaction to account for the enantioselectivity of this process.

----To be continued---Thank you-----