TOPIC : Hetero–Diels–Alder reaction with carbonyl functionality using titanium catalysts.

INTRODUCTION

The Diels–Alder (DA) reaction is perhaps the most widely used synthetic method for the construction of six-membered rings.[1,2] The reaction incorporates several interesting features such as regio– and stereo– chemical aspects which have been rationalized on the basis of the orbital symmetry.[3]

The utility of the Diels–Alder reaction has been greatly expanded and the synthesis of heterocycles and complex natural products has been facilitated by the incorporation of hetero atoms both in diene and dienophile. The application of the hetero–Diels–Alder reaction has been recently reviewed.[4]

Carbonyl compounds can undergo hetero–Diels–Alder (HDA) reaction. This class of reaction provides one of the most direct methods for the formation of six–membered oxygen–containing heterocycles and has been studied very intensively because of the importance of the oxygen–heterocycle adducts formed.[5]

A majority of the cycloaddition reactions present in the literature can be classified into two types of ($\pi 2s + \pi 4s$) cycloadditions, the normal and the inverse electron demand HDA reactions, as defined by the relative energies of the frontier molecular orbitals (FMO) of the diene and dienophile.[6] The normal electron demand HDA reaction is a $\mathrm{HOMO_{diene}}$–$\mathrm{LUMO_{dienophile}}$ interaction between an electron-rich diene and electron-deficient dienophile.

The inverse electron demand HDA reaction is primarily controlled by a $\text{LUMO}_{\text{diene}}$–$\text{HOMO}_{\text{dienophile}}$ interaction between an electron-rich dienophile and an electron-deficient diene.

In a typical normal electron demand reaction **(Figure 1)**, the effect of an electron-withdrawing group (EWG) is to lower the energy of the $\text{LUMO}_{\text{dienophile}}$, thereby increasing the orbital mixing with the $\text{HOMO}_{\text{diene}}$. Alternatively, electron-donating groups will increase the energy of the $\text{HOMO}_{\text{diene}}$, once again enhancing the orbital mixing of the $\text{HOMO}_{\text{diene}}$-$\text{LUMO}_{\text{dienophile}}$ pair.[7]

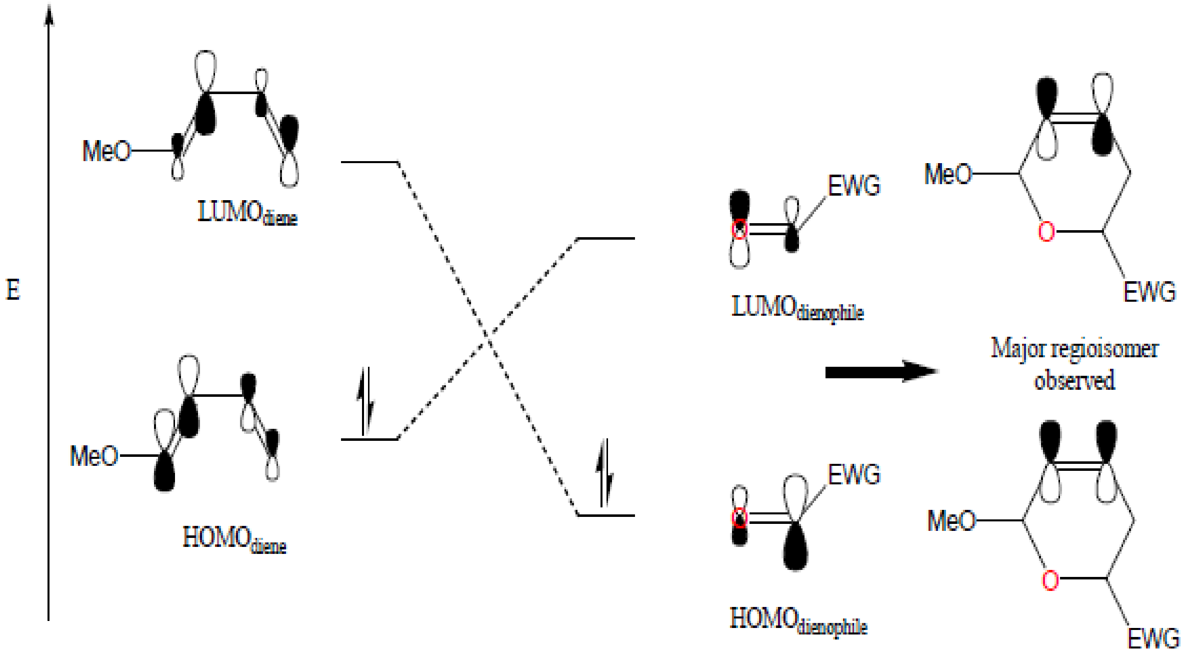


Figure 1. Normal electron-demand controlled hetero-Diels-Alder reactions.

Activation of the carbonyl group is achieved by co-ordination of a Lewis-acid to the carbonyl oxygen atom; in this process, energy of the carbonyl LUMO is lowered and thus a more favorable interaction with the diene HOMO is possible.[8,9]

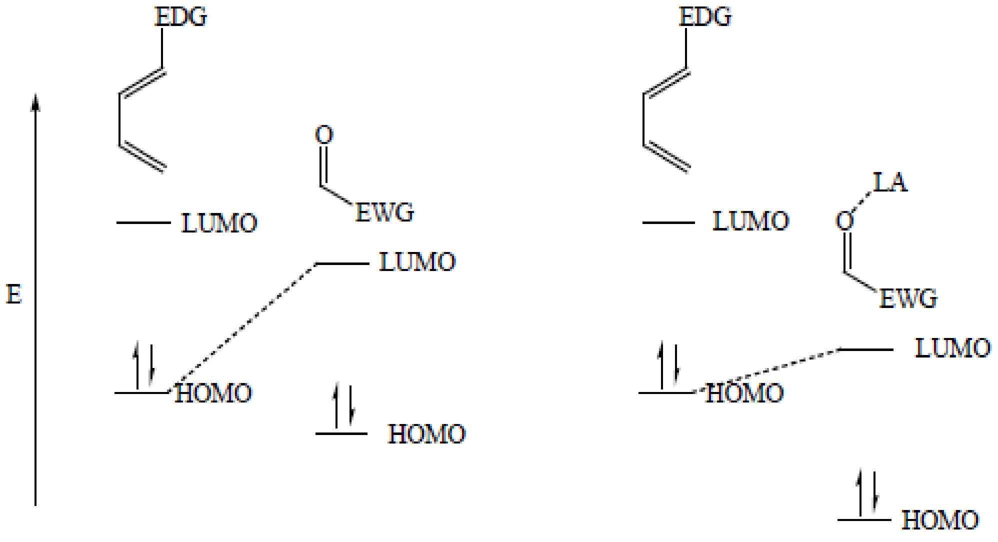


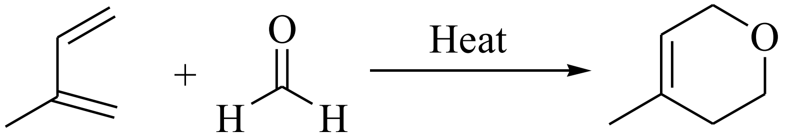
Figure 2. Effect of a Lewis-acid (LA) activation on the relative HOMO-LUMO energies in the normal electron demand cycloadddition.[10]

REVIEW OF LITERATURE

International Status

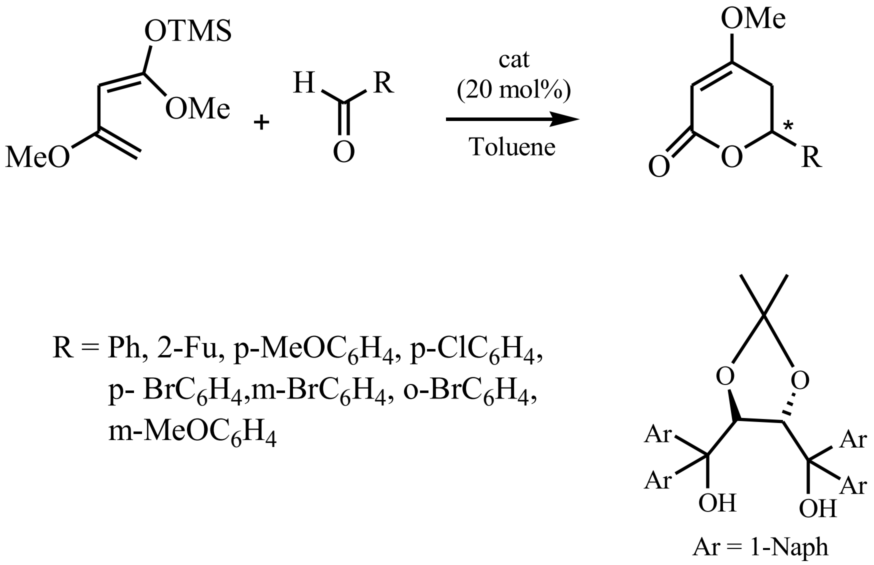
At the **international level,** mostly electron-rich dienes such as Danishefsky's diene,[11-13] and Brassard's diene[14] etc. have been used for the hetero–Diels–Alder reaction of the carbonyl compounds. It is surprising that normal dienes like dimethyl-1,3–butadiene, isoprene, cyclopentadiene, etc. have not been used for the HDA reaction of the normal carbonyl compounds.

The oxo-DA reaction was first reported in 1949 using a methylpentadiene and formaldehyde as reactants.[15]



Scheme 1.

In 2004, the same TADDOL, derivative was employed by Ding et al. to induce the HAD reactions of aldehydes with Brassard's diene, affording the corresponding δ-lactone derivatives highly enantioselectively.[16]

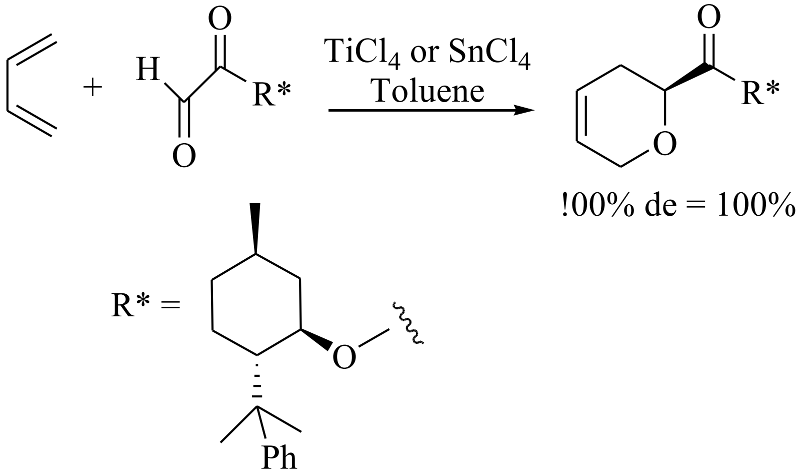


R = Ph, 2-Fu, p-MeOC$_6$H$_4$, p-ClC$_6$H$_4$,
p- BrC$_6$H$_4$,m-BrC$_6$H$_4$, o-BrC$_6$H$_4$,
m-MeOC$_6$H$_4$

Ar = 1-Naph

Scheme 2. Organocatalytic HAD reactions of Brassard's diene.

In 2004, Jurczak et al. developed the HDA reaction of (R)-8-phenylmenthyl glyoxylate with 1,3-butadiene in the presence of a Lewis-acid, such as SnCl$_4$ or TiCl$_4$, which provided the corresponding cycloadduct as a single diastereoisomer and in quantitative yield.[17]



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Scheme 3. HDA reaction of (R)-*-phenylmenthyl glyoxylate with 1,3-butadiene.

- **National Status**

To the best of our knowledge, no other research group at the national level is working on catalyzing HDA reaction of carbonyl compound.

JUSTIFICATION AND RELEVANCE

- The results will be interesting both experimentally and theoretically. It may lead to the synthesis of new heterocyclic compounds that may be bioactive or useful as synthons.
- Theoretical investigations will help to determine the mechanism, concerted or stepwise, of the reaction and how it is affected by the nature of the substituent groups.

OBJECTIVES

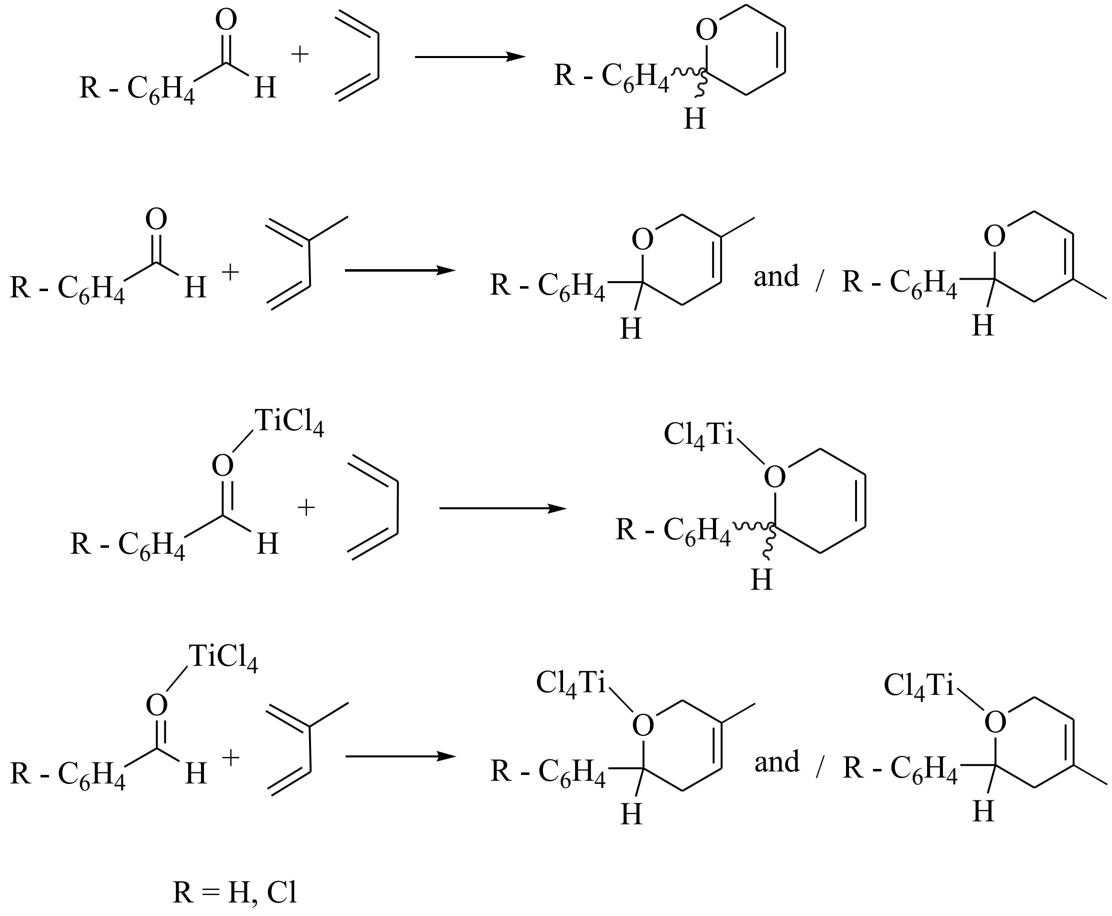
1. To investigate theoretically the hetero–Diels–Alder (HDA) reaction of the carbonyl functionality (>C=O) without and with $TiCl_4$ as catalyst.
2. Based on the theoretical results, to study experimentally the HDA reaction of the carbonyl compounds using $TiCl_4$ and $Ti(OiPr)_2Cl_2$ as catalysts.
3. To study the stereoselectivity and regioselectivity in the HDA reactions and correlate the results with the theoretical results.
4. To study experimentally the asymmetric HDA of the >C=O functionality with a variety of dienes using 1,1’-binaphthoxydichlorotitanium and 1,1’-binaphthoxybis(tert-butoxy)titanium.

HYPOTHESIS

The [4+2] cycloaddition, that is Diels–Alder reaction is symmetry allowed. These reactions are catalysed by Lewis-acids.

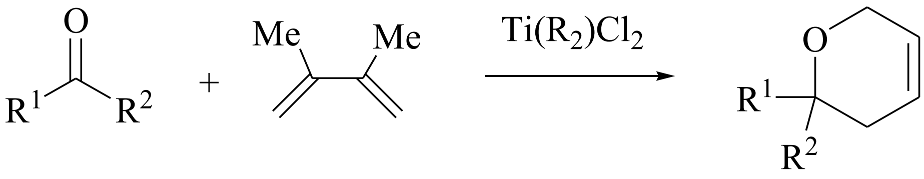
PLAN OF WORK AND METHODOLOY

1) Theoretical investigation of the model HDA reaction with the carbonyl functionality (>C=O) without and with $TiCl_4$ as catalyst.



Scheme 4.

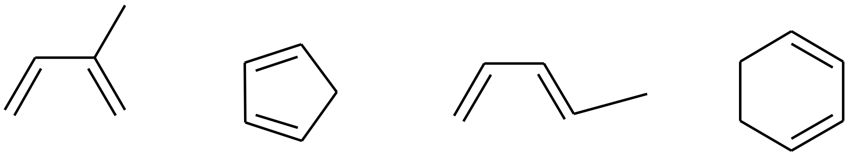
2) Hetero–Diels–Alder reaction of the >C=O functionality with a variety of dienes using $TiCl_4$ and $Ti(O^iPr)_2Cl_2$ as catalysts.



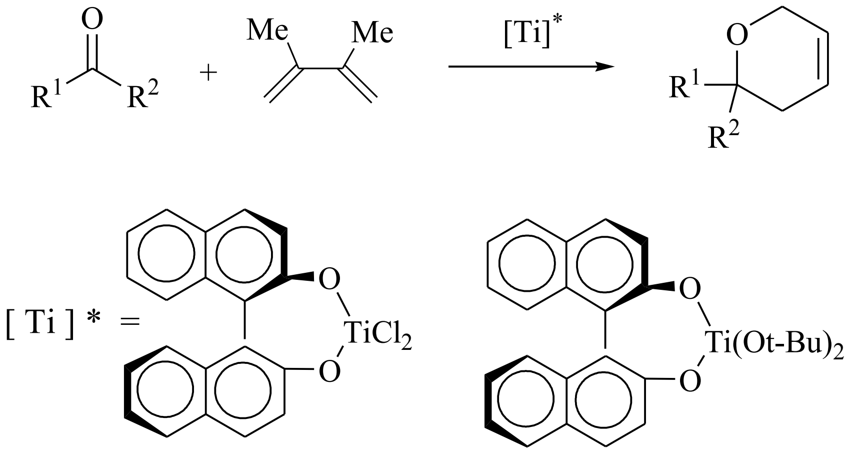
R = O^iPr / Cl
R^1 = C_6H_5, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 3-NO_2-C_6H_4,
2-Cl-C_6H_4, 2-OCH_3-C_6H_4, $2,5^{-}(NO_2)_2$-C_6H_4
R^2 = H

Scheme 5.

Likewise, other dienes shown below will be used:

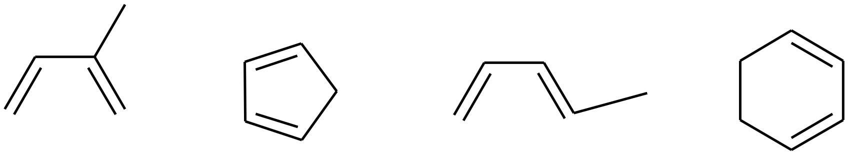


3) Symmetric HDA reaction of carbonyl compounds using Ti(IV) chiral catalysts shown below:



Scheme 6.

Likewise, other dienes shown below will be used:



4) Stereoselectivity and regioselectivity observed in the above reactions will be rationalized on the basis of computational calculations.

YEAR-WISE PLAN OF WORK

♦ **First year** –

a) Theoretical investigation of the model HDA reaction of the carbonyl compounds with and without the use of $TiCl_4$ as catalyst.

b) Experimental investigation of the HDA reaction on the carbonyl functionality using $TiCl_4$ and $Ti(O^iPr)_2Cl_2$ as catalysts.

- **Second year** – Asymmetric HDA reaction of the carbonyl compound using chiral Ti*(IV) catalysts.

- **Third year** – Consolidation, compilation and publication of above results.

PLACE OF WORK AND FACILITIES AVAILABLE

Department of Chemistry, IIS University, Jaipur. A modern well equipped laboratory, with modest instruments is available.

LIMITATION AND ALTERNATIVE PLAN OF STUDY

The non-availability of multinuclear NMR spectrometer is the main limitation. We shall try to take the help of the institutions where this instrument is available.

REFERENCES

1. Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.

2. Woodward, R. B.; Katz, T. J. *Tetrahedron* **1959**, *5*, 70.

3. Fleming, I. *Frontial Orbitals and Organic Chemical Reactions*; Wiley: New York, **1976**.

4. Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: New York, **1987**.

5. Tietze, L. F.; kettschau, G.; *Top. Curr. Chem.* **1997**, *189*, 1 and references there in.

6. Woodward, R. B.; Hoffman, R. *Conservation of Orbital Symmetry*; Verlag Chimie: Weinheim, Bergstr, **1970**.

7. Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558.

8. Carrol, R. A. *Perspectives on Structure and Mechanism in Organic Chemistry*; Brooks/Cole: New York, **1998**; p. 777.

9. Houk, K. N.; Lin, Y.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554.

10. Tarasow, T. M.; Eaton, B. E. *Cell. Mol. Life Sci.* **1999**, *55*, 1463.

11. Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060.

12. Jorgensen K. A. *Eur. J. Org. Chem.* **2004**, 2093.

13. Yang, W. Q.; Shang, D. J.; Liu, Y. L.; Du, Y.; Feng, X. M. *J. Org. Chem.* **2005**, *70*, 8533.

14. Lin, L.; Chen, Z.; Yang, X.; Liu, X.; Feng, X. *Org. lett.* **2008**, *10* (6), 1311.

15. Gresham. T. L.; Steadman T. R. *J. Am. Chem. Soc.* **1949**, *71* (2), 737.

16. Du, H.; Zhao, D.; Ding, K. *Chem. – Eur. J.* **2004**, I, 5964.

17. Kosior, M.; Asztemborska, M.; Jurczak, *J. Synthesis* **2004**, *1*, 87.