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Baylis-Hillman Reaction: Origin and Growth

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Abstract: The Baylis–Hillman reaction is a novel carbon-carbon bond forming reaction which is essentially a three component atom economic reaction involving the coupling at α-position of activated alkene with carbon electrophile under catalytic influence of a tertiary amine, most commonly 1,4-diazabicyclo(2.2.2)octane [DABCO], producing densely functionalized molecules usually referred to as the Baylis-Hillman (B-H) adducts. The Baylis-Hillman reaction originates from a German patent filed in the year 1972 by two American chemists A. B. Baylis and M. E. D. Hillman. They had also U.S patent in the year 1973 on this reaction.

Keywords: Baylis-Hillman Reaction, C-C bond forming reaction, Multifunctional Molecules, Heterocyclic Compounds.

I. INTRODUCTION

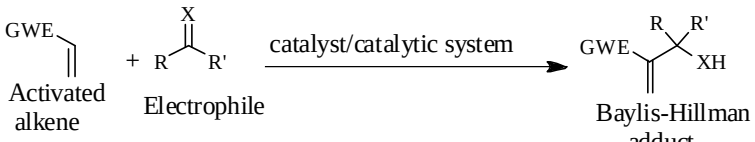
The present day synthetic chemistry demands development of novel carbon-carbon bond forming reactions based on the concept of environmental protection. Synthetic chemists have been working in this direction for the last several years. The Baylis–Hillman reaction[1-5] is a novel carbon-carbon bond forming reaction which is essentially a three component atom economic reaction involving the coupling at α-position of activated alkene with carbon electrophile under catalytic influence of a tertiary amine, most commonly 1,4-diazabicyclo(2.2.2)octane [DABCO], producing densely functionalized molecules usually referred to as the Baylis-Hillman (B-H) adducts (Scheme 1). The Baylis-Hillman reaction originates from a German patent[1] filed in the year 1972 by two American chemists A. B. Baylis and M. E. D. Hillman. They had also U.S patent[2] in the year 1973 on this reaction.

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Scheme 1. Baylis-Hillman (B-H) Reaction



R = alkyl, aryl, hetero-aryl, *etc.*

R' = H, COOR, alkyl, *etc.*

X = O, *N*-Ts, *N*-CO_2R, *N*-$PO(R)_2$, *etc.*

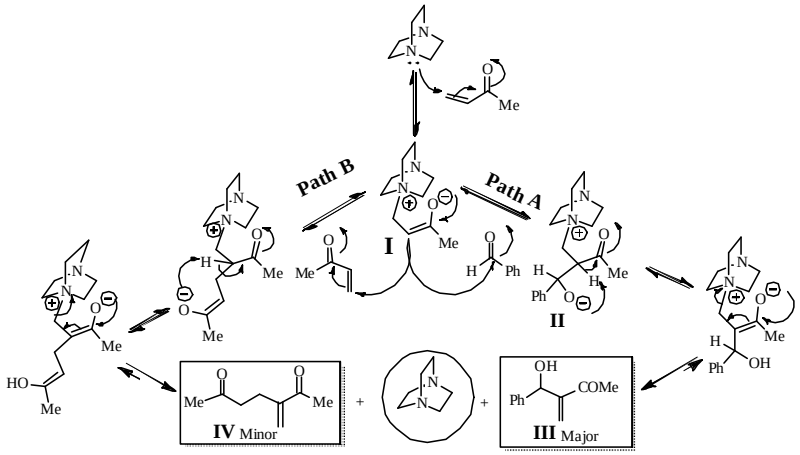
catalyst / catalytic system = *tert*-amines, phosphines, Lewis acids, *etc.*

EWG (Electron Withdrawing Group) = COOR, COR, CHO, CN, $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh, *etc.*

II. MECHANISM

Due to large variations of parameters with respect all three essential components, the exact mechanism is not yet clearly understood. However, a plausible mechanism[4] of the Baylis-Hillman reaction is illustrated in the Scheme 2 taking the reaction between benzaldehyde (as an electrophile) and methyl viny ketone (as an activated olefin) under the catalytic influence of DABCO, as a model case. The first step is believed to involve Michel addition of DABCO to methyl viny ketone leading to the formation of zwitterionic enolate I. This enolate will then react with aldehyde in aldol fashion to generate zwitterionic species II which then releases the catalyst after proton migration to provide the desired multifunctional molecule III (Scheme 2; Path A). In addition to the major product, side product IV is also formed in the case of reactive activated alkenes such as methylvinyl ketone because they themselves act as electrophiles (Scheme 2; Path B).

Scheme 2. Plausible Mechanism



III. ESSENTIAL COMPOUBDS

During the last several years this reaction has grown exponentially with respect to all the three essential compounds i.e.

a. Activated alkenes

b. Electrophiles

c. Catalysts or catalytic systems.

Several activated alkenes[6-22] (acyclic and cyclic) have been successfully employed for coupling with various electrophiles to provide diverse classes of multifunctional molecules. Representative examples are given in Fig 1 and 2.

Fig. 1 Acyclic Activated Alkenes

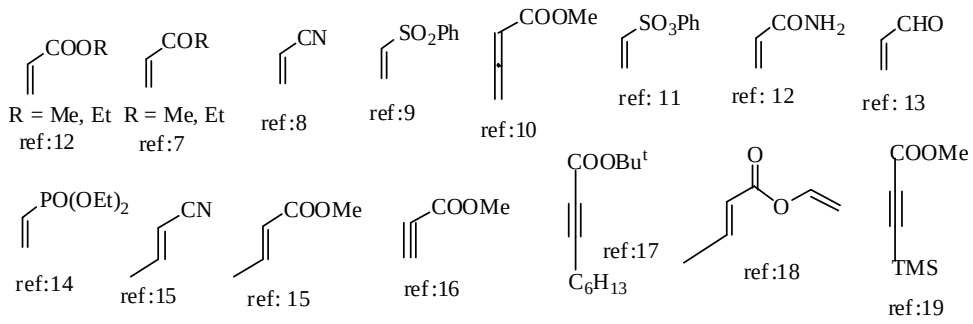
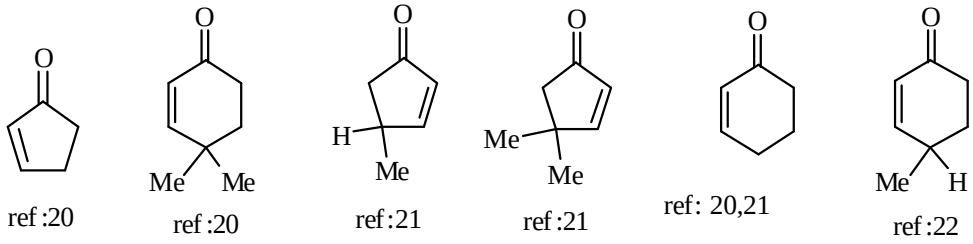


Fig. 2 Cyclic Activated Alkenes

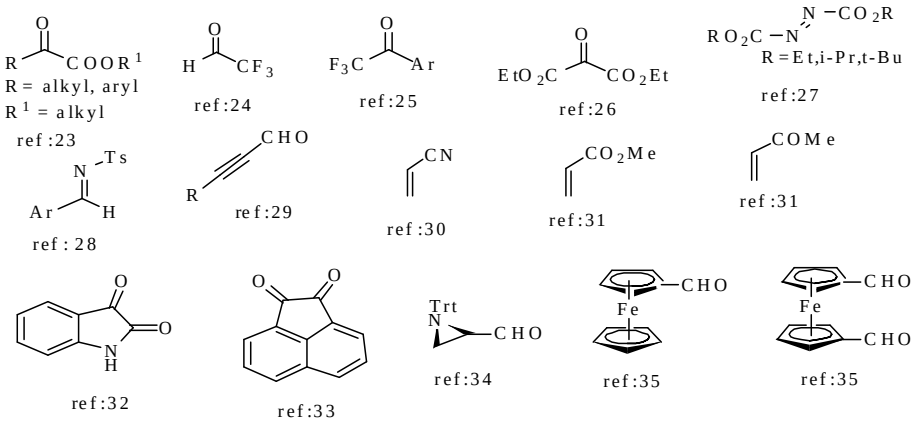


A verity of electrophiles[23-35] (Fig 3), in addition to aldehydes, have been employed for coupling with activated alkenes providing different classes of multifunctional molecules.

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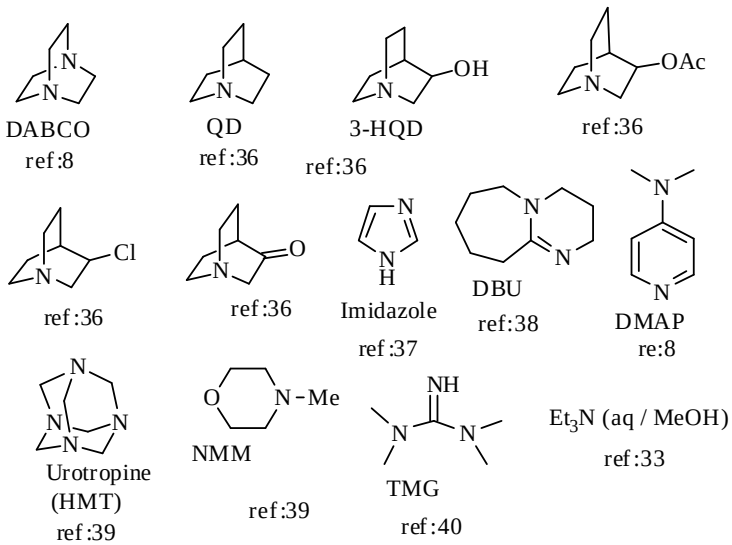
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Fig. 3 Electrophiles



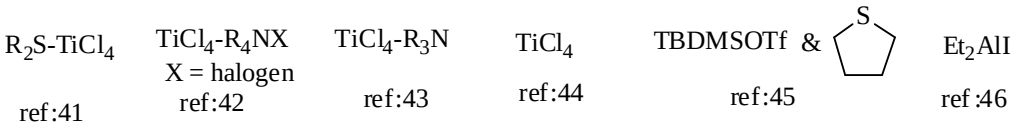
In addition to DABCO several tertiary amine catalysts / catalytic systems[8,36-40] (Fig 4) and non-amine catalysts/catalytic systems[41-46] (Fig. 7) have been successfully employed for catalyzing or promoting the Baylis-Hillman coupling between various activated alkenes and elecrophiles providing a verity of multifunctional molecules. Due to its high versatility DABCO has been the most commonly used catalyst for the Baylis-Hillman reaction. Also, significant developments have been made in asymmetric version and intramolecular version. This review briefly presents the developments and applications of the Baylis-Hillman reaction.

Fig. 4 Amine Catalysts



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Fig. 5 Non-amine Catalysts



IV. ASYMMETRIC VERSION OF BAYLIS-HILLMAN REACTION

If electrophile is prochiral, there is a possibility of achieving chiral induction in the Baylis-Hillman reaction. Asymmetric version can be performed, in principle, in four different ways Chiral chemists have been working for last several years and in fact, made significant progress in all these aspects i.e.

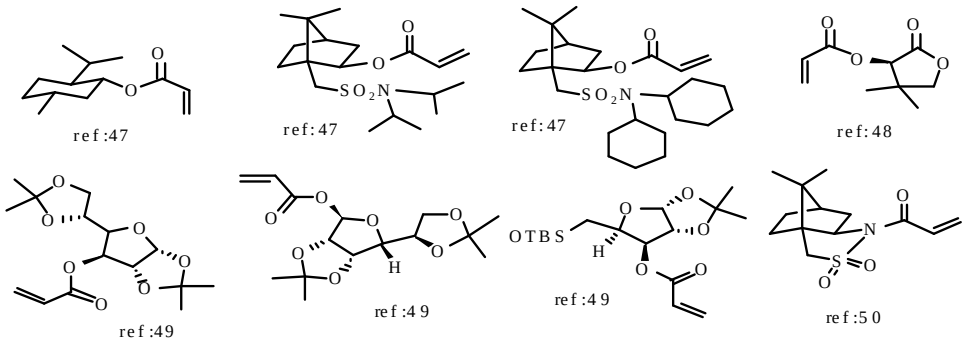
a. *Chiral Activated Alkenes*

b. *Chiral Electrophiles*

c. *Chiral catalysts/catalytic systems*

Various chiral acrylates and acrylamides[47-50] (Fig 6) have been designed, prepared and employed for coupling with electrophiles to provide the resulting the adducts in low to high diastereoselectivities.

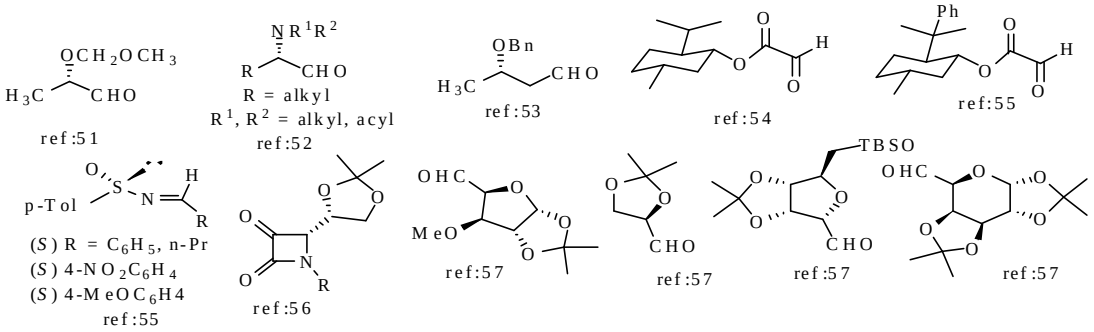
Fig. 6 Chiral Activated Alkenes



Several efforts have been made to use a number of chiral electrophiles[51-57] (Fig 7) for reaction with activated alkenes under the influence of representative catalytic systems to provide the resulting multifunctional Baylis-Hillman adducts in poor to high diastereoselectivities.

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Fig. 7 Chiral Electrophiles



The real challenge in achieving asymmetric version of Baylis-Hillman reaction lies in the development of appropriate chiral catalysts. Efforts have been made by various research groups throughout the world and in fact considerable progress have been achieved in this direction. Representative chiral amine catalysts[58-62] examples are presented in Fig 8. Phosphines and thiourea catalysts[63-71] have been prepared and their applications have been systematically studied, Fig 9. Some of the Baylis-Hillman adducts prepared in this way have been used as synthons for the synthesis of biologically active and natural products.

Fig. 8 Chiral Amine Catalysts

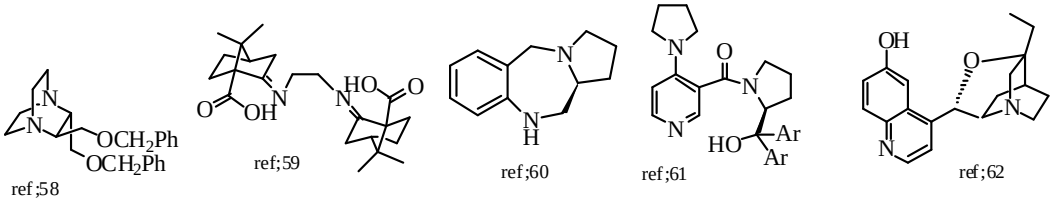
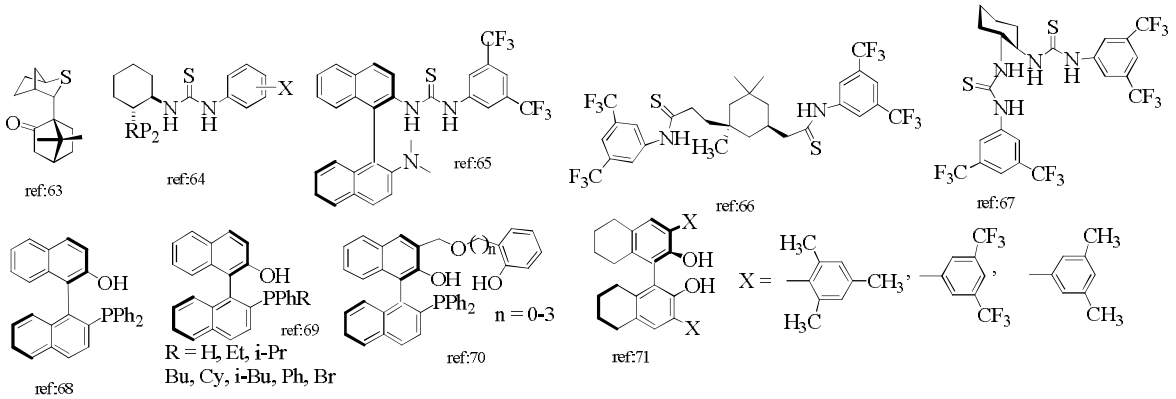


Fig. 9 Phosphines and Thiourea Catalysts



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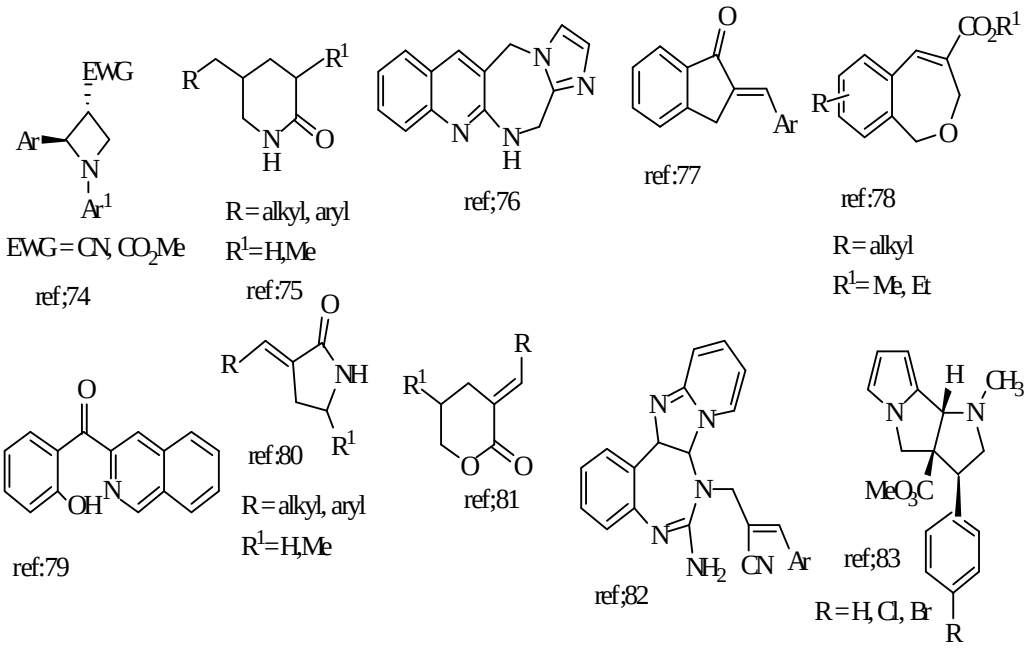
V. INTRAMOLECULAR VERSION OF BAYLIS-HILLMAN REACTION

If the substrates contain both the activated alkene and electrophile components in appropriate position, there is possibility for performing intramolecular version[72-73] of Baylis-Hillman reaction providing cyclic adducts. Although the Baylis-Hillman reaction has grown to high popularity, intramolecular version[72-74] has not grown in that proportion. However, during the last few years this aspect has received considerable attention from synthetic chemists. Some of the recent developments are described in this direction.

VI. APPLICATIONS OF BAYLIS-HILLMAN REACTION

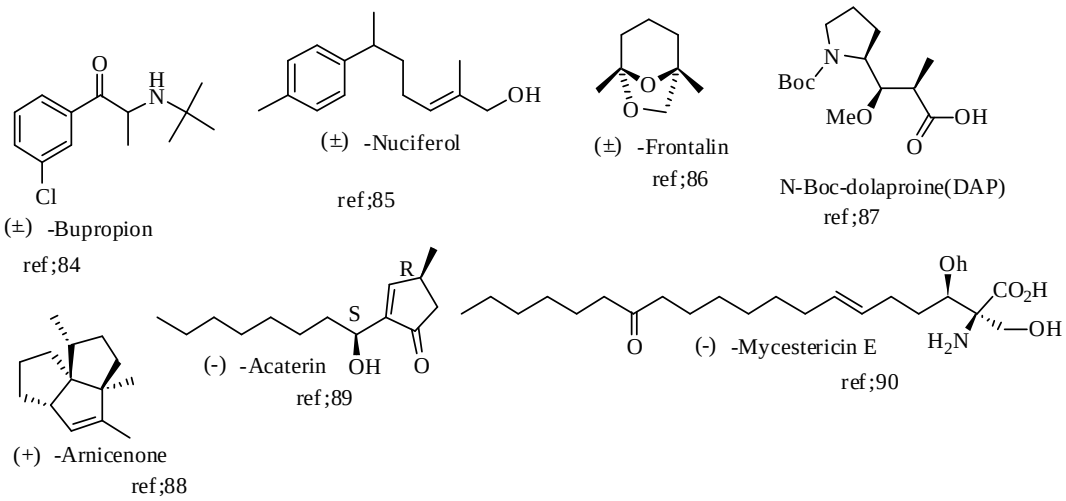
Because of the presence of many fictional groups in proximity the Baylis-Hillman adducts have become important substrates for a number of name and un-named reactions. Thus, these substrates have been used in various organic reactions like Friedel-Crafts reaction, Diels-Alder reaction, Heck reaction, Claisen rearrangements, isomerization, hydrogenation, and photochemical reactions *etc.* These adducts have also been elegantly employed as valuable synthons in the synthesis of important and hetero/carbocycles[75-83] and natural products, biologically active molecules (Fig 10 and 11).[84-90]

Fig. 10 Heterocycles and Carbocycles



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Fig. 11 Natural Products and Biologically Active Molecules



VII. FUTURE AND SCOPE

The Baylis-Hillman reaction has marvelous scope for design with three components. The asymmetric version with chiral catalysts and intramolecular version still infancy.

VIII. ACKNOWLEDGEMENTS

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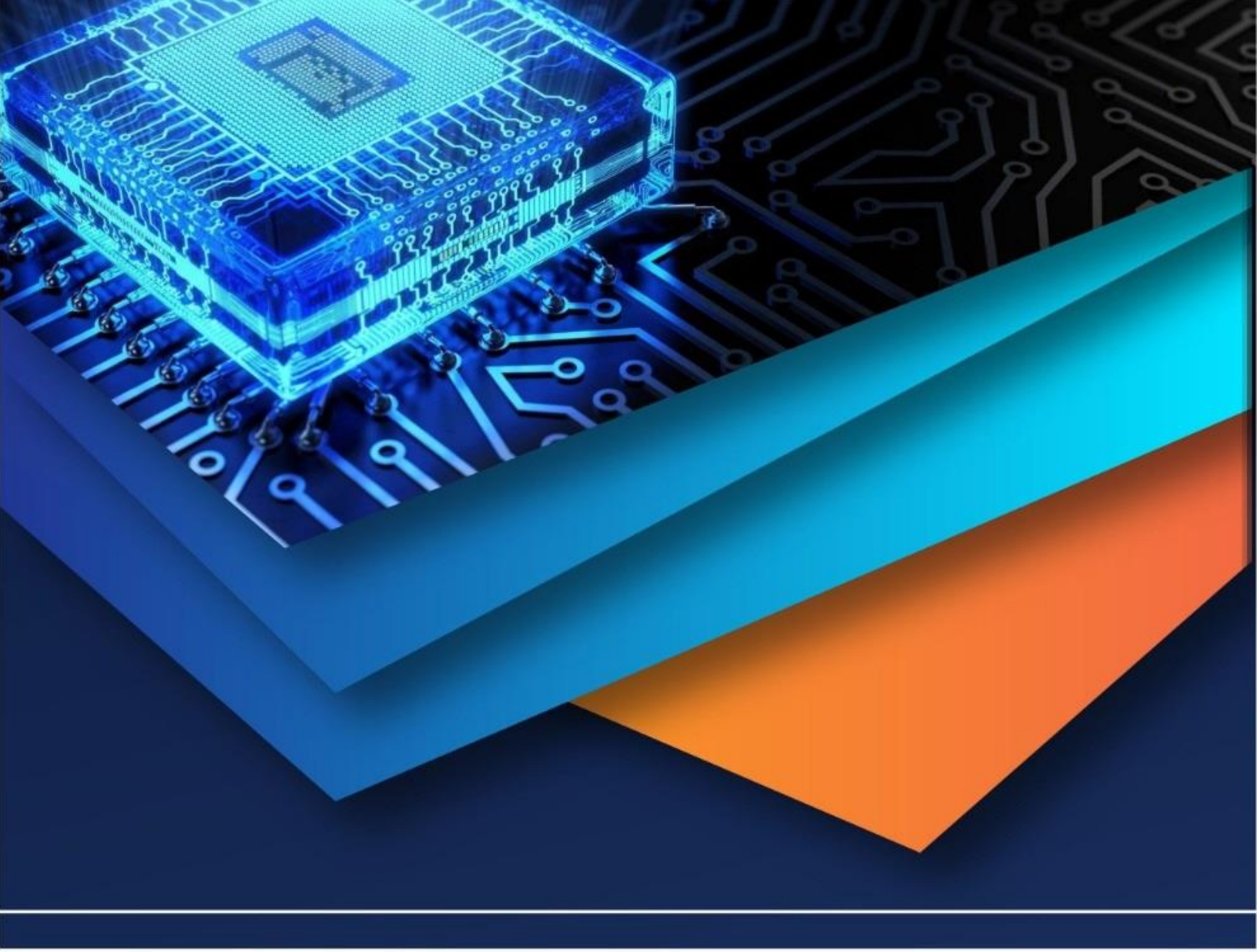
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