# Baylis-Hillman Reaction: A Novel Opportunity to the Synthetic Organic Chemistry

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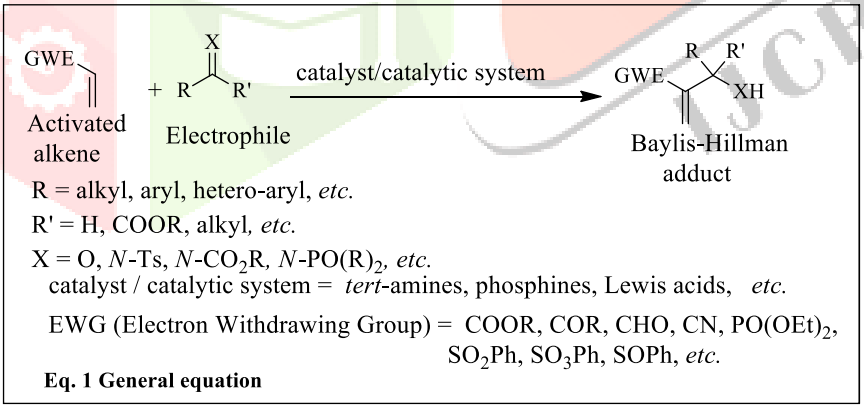
## 1. Introduction

Carbon-carbon bond construction is one of the most fundamental reactions in synthetic organic chemistry.[1] Many carbon-carbon bond forming reactions have been established in the literature.[1-10] Grignard reaction,[2] Diels-Alder reaction,[3] Wittig reaction,[4] aldol reaction,[5] Heck reaction,[6] Friedel-Crafts reaction[7] *etc*. are few such significant reactions are very popular and famous in carbon-carbon bond forming reactions. Applications also have been well known in the past several decades.

The Baylis-Hillman reaction[8-11] is till now another significant carbon-carbon bond forming reaction. This is a fundamentally three component reactions including the coupling at $\alpha$-position of activated alkene with an electrophile in the presence of 3$^o$ amine catalyst. (Eq. 1). The Baylis-Hillman reaction is invented in 1972 by A. B. Baylis & M. E. D. Hillman (German patent[8] in 1972 and US patent[9] in year 1973 by A. B. Baylis & M. E. D. Hillman).




**Eq. 1 General equation**

## 2. Essential components:

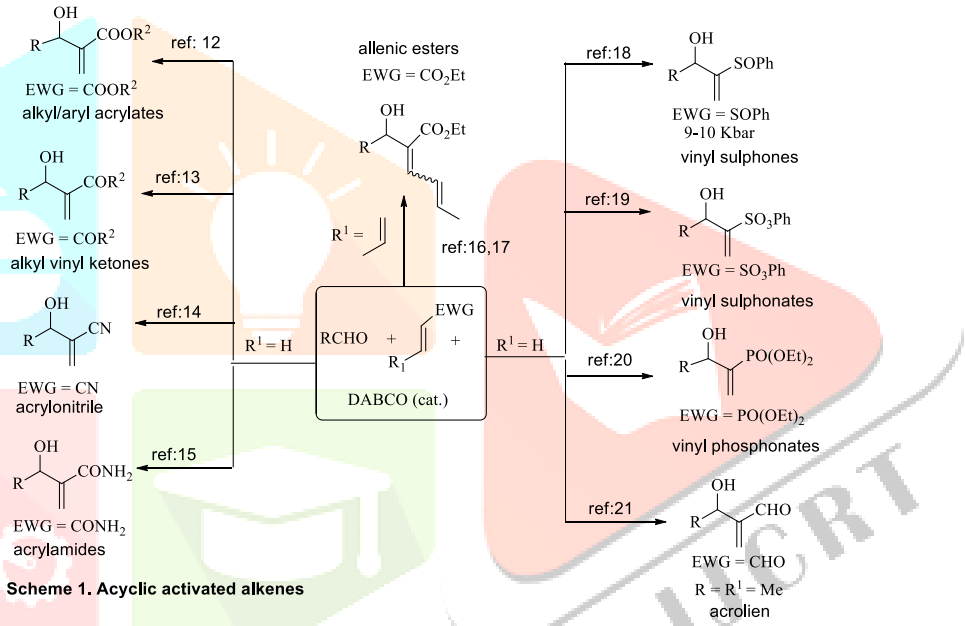
The Baylis–Hillman reaction has amazing development in terms of all the three essential components during last three decades *i.e.*

- Activated alkenes
- Electrophiles
- Catalyst/catalytic system.

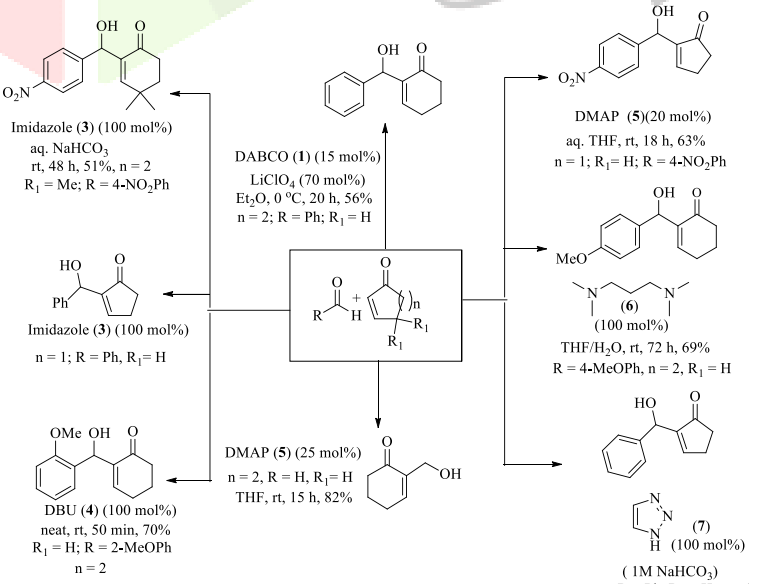
Activated alkenes may acyclic or cyclic, electrophiles may carbon / non-carbon and catalyst/catalytic systems may tert-amine or non-amine

### 2.1 Activated alkenes

Many acyclic activated alkenes[12-21] (alkyl/aryl acrylates, alkyl vinyl ketones, acrylonitrile, acrylamides, allenic esters, vinyl sulphones, vinyl sulphonates, vinyl phosphonates and acrolein) have been effectively working in this reaction with an electrophile to provide the Baylis-Hillman adduct (Scheme 1). Cyclopent-2-enone, cyclohex-2-enone and their derivatives are the most generally used cyclic activated alkenes for the Baylis-Hillman reaction with various electrophiles[22-25] (Scheme 2).



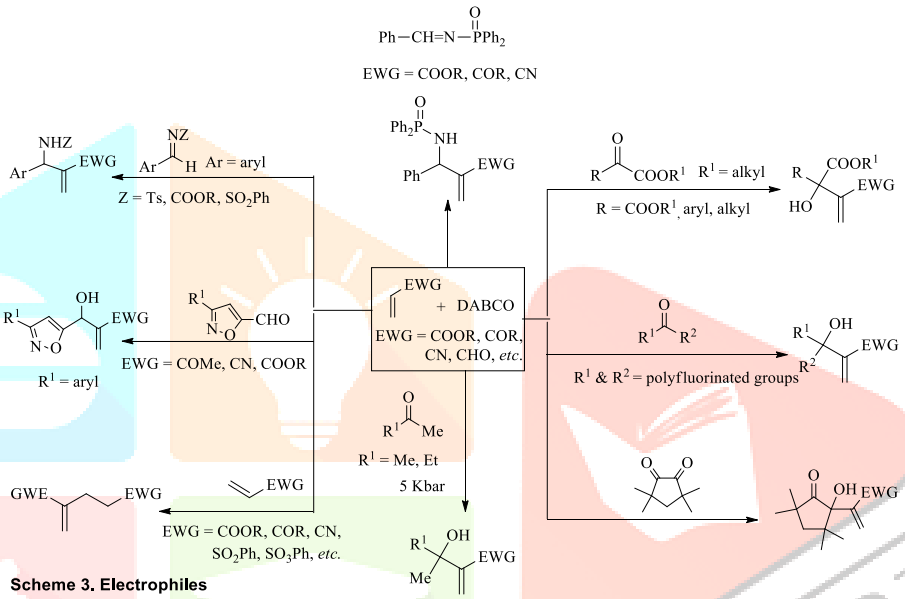

**Scheme 1. Acyclic activated alkenes**



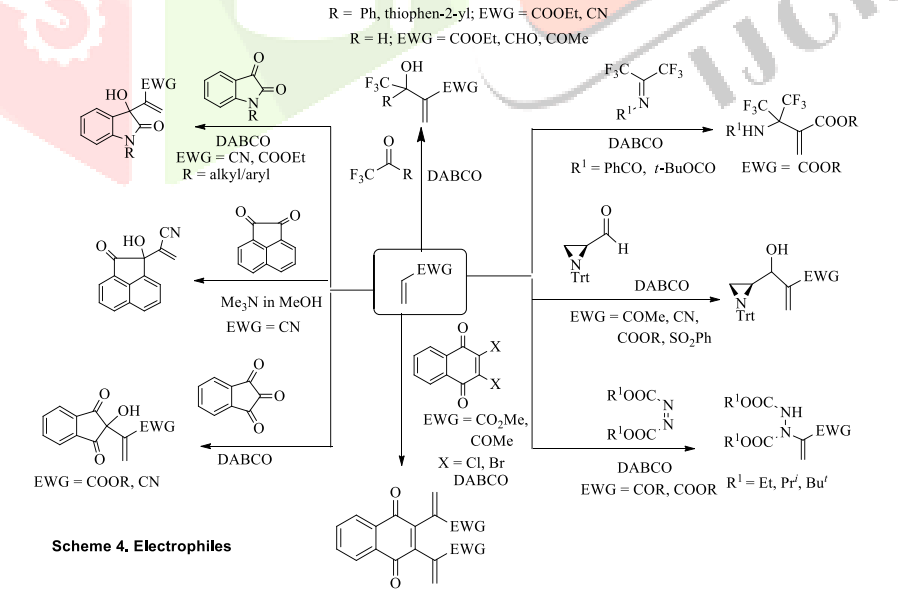

**Scheme 2. Cyclic activated alkenes**

### 2.2 Electrophiles

Aliphatic, aromatic and hetero-aromatic aldehydes are the most normally used electrophiles in the Baylis-Hillman reaction. There are several other electrophiles (α-keto esters,[26] fluoro ketones,[27] aldimine derivatives,[28] non-enolizable 1,2-diketones,[29] *N*-arylidenediphenylphosphinamide[30] and isoxazole-5-carboxaldehydes,[31] fluoro imines,[32] fluorinated aldehydes & ketones,[33] acenaphthenequinone,[34] azodicarboxylates,[35] 2,3-dihalo-1,4-naphthoquinone,[36] isatin derivatives,[37] ninhydrin[38] and *N*-trityl-aziridine-2-(*S*)-carboxaldehyde[39]) been fruitfully active for this reaction. Acetone & 2-butanone are[21] do not react with activated alkenes at normal conditions. But, these were carried into the reaction at high pressure with activated alkenes (Schemes 3 and 4).




Scheme 3. Electrophiles




Scheme 4. Electrophiles

### 2.3 Catalysts

Tertiary amines are the most commonly used catalysts for the Baylis-Hillman reaction. Numerous non-amine catalytical systems have also been used to used to this reaction. DABCO,[69,99] is the most successful catalyst among the pool of tertiary amine based catalysts. However several other amines such as 3-hydroxyquinuclidinem,[69,99] imidazole,[63,100,101] DBU,[64] DMAP ,[65,66] TMPDA,[67] quinuclidine,[69] 3-acetoxyquinuclidine,[69,99] methanolic-$Me_3N$,[71,89,102] indolizine,[11] 3-chloroquinuclidine,[69] 3-quinuclidinone,[69] HMT,[103,104] NMM,[104] TMG,[105] TMEDA ,[106] $Et_3N$[48] and aqueous-$Me_3N$[107] have been successfully employed in various and specific Baylis-Hillman reactions. Recently, a variety of polymer supported DMAP derivatives, such as, PAP [polymer-bound 4-(*N*-benzyl-*N*-methylamino)pyridine],[108] DMAP-MSN [mesoporous silica nanosphere],[109] and dendritic DMAP {*N*,*N*-di[3',4',5'-tri(*n*-dec-1-yloxy)benzyl]-4-aminopyridine}[110] have also been successfully employed as catalysts for the Baylis-Hillman reaction of various activated alkenes with electrophiles. Various non-amine catalysts / catalytic systems, such as, trialkyl/triaryl phosphines,[114-117] and metal complexes like $RhH(PPh_3)_4$,[118,119] $RuH_2(PPh_3)_4$,[119,120] have also been successfully employed to promote the Baylis-Hillman reaction. Several Lewis acid based catalysts such as $TiCl_4$,[121,122] $R_2S$-$TiCl_4$,[16,123-126] $TiCl_4$-$R_3N$[127], $TiCl_4$-$R_4NX$ (X = halide),[16,128,129] $R_2X$-$BF_3$ (X = O, S),[130-132] and $Et_2AlI$[133,134] have been found to promote Baylis-Hillman (type) coupling reactions.

## 3. Asymmetric Baylis-Hillman reaction

Asymmetric version of the Baylis-Hillman coupling can be accomplished by choosing appropriate chiral sources of any essential components *i.e.*,

- Chiral activated alkene
- Chiral electrophile
- Chiral catalyst.

It is also possible to perform asymmetric Baylis-Hillman reaction using appropriate chiral additives in the reaction media. Already efforts have been made in this direction and some relevant and recent developments have been described in this section.

### 3.1 Chiral activated alkenes

Many chiral acrylates[61] and chiral acrylamides[62,63] (Fig. 1) obtained from several chiral auxiliaries were successfully employed for stereoselective Baylis-Hillman reaction.

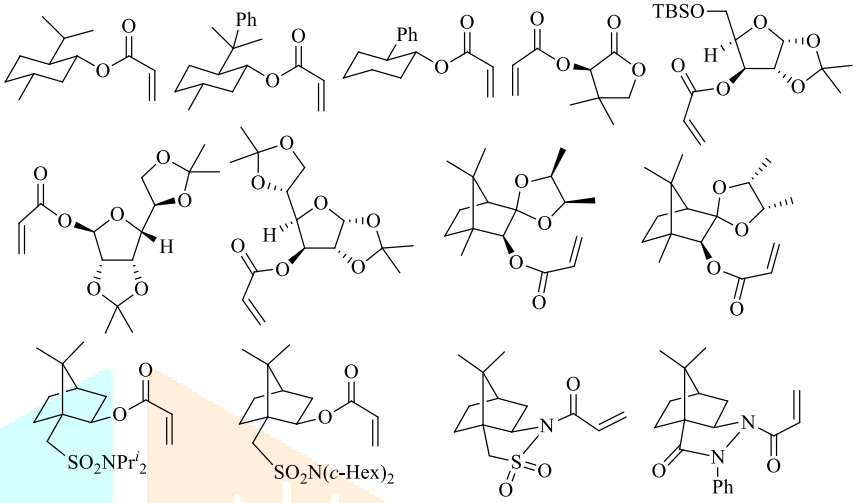



**Fig.1. Chiral activated alkenes**

### 3.2 Chiral electrophiles

Chiral electrophiles such as (*S*)-*O*-(methoxymethyl)lactaldehyde,[64] (*S*)-3-benzyloxybutyraldehyde,[65] α-dialkylamino and, α-(*N*-acylamino)aldehydes,[66] isopropylidene (*R*)-glyceraldehyde,[67] 1-alkenyl- or alkynyl 4-oxoazetidine-2-carbaldehydes,[68] 3-oxo-2-azetidinones,[69] (*R*)-myrtenal,[67] 2(*S*)-*N*-(4-nitrobenzoyl)pyrrolidine-2-carboxaldehyde,[70] chiral *o*-substituted benzaldehyde tricarbonyl-chromium complex[71] and sugar derived aldehydes,[72] *etc.* (Fig. 2) have been used successfully towards the asymmetric Baylis-Hillman reaction in low to high diastereoselectivities**.**

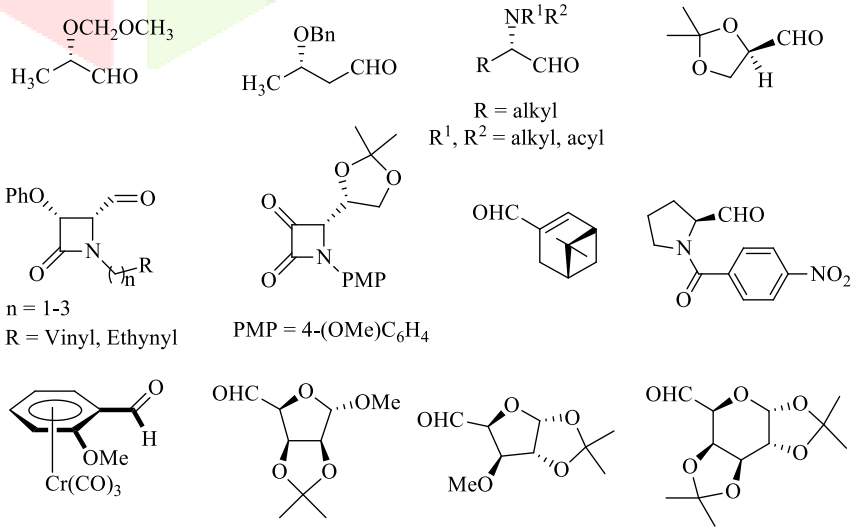



**Fig. 2. Chiral electrophiles**

### 3.3 Chiral catalysts

Noteworthy progresses have been made in the scheming of new chiral catalysts for achieving asymmetric version of Baylis-Hillman reaction. Chiral DABCO,[162,163] (*S*)- enantiopure pyrrolizidine,[73] chiral bicyclic azetidine,[74] quinidine derivatives,[166-170] and proline derivatives,[75] have been applied as chiral catalysts in moderate to good enantioselectivities. Variety of bifunctional catalysts, derived from BINOL,[76,77] have been effectively working in the Baylis-Hillman reaction (Fig. 3).

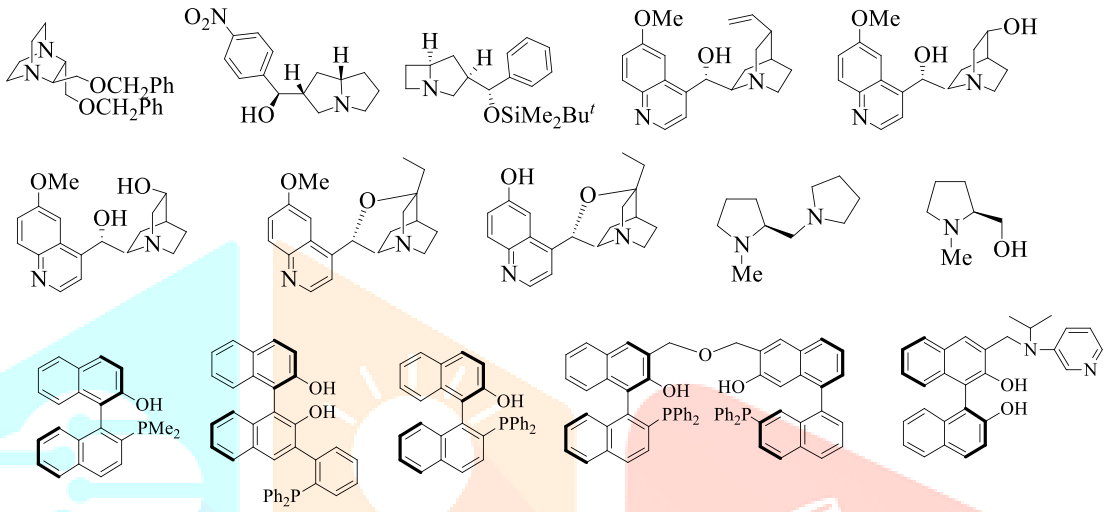


Fig. 3. Chiral catalysts

### 4. Intramolecular of the Baylis-Hillman reaction

Intramolecular version of the Baylis-Hillman reaction is up till now challenging aspect. Literature survey tells that in recent years chemists have focused their attention in significant growth.[78-80]

### 5. 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 of the Baylis-Hillman reaction is illustrated in the Scheme 1 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 **A**. This enolate will then react with aldehyde in aldol fashion to generate zwitterionic species **B** which then releases the catalyst after proton migration to provide the desired multifunctional molecule (**C**) (Fig. 4**;** Path I). In addition to the major product, side product (**D**) is also formed in the case of reactive activated alkenes such as methylvinyl ketone because they themselves act as electrophiles (Fig. 4; Path II).

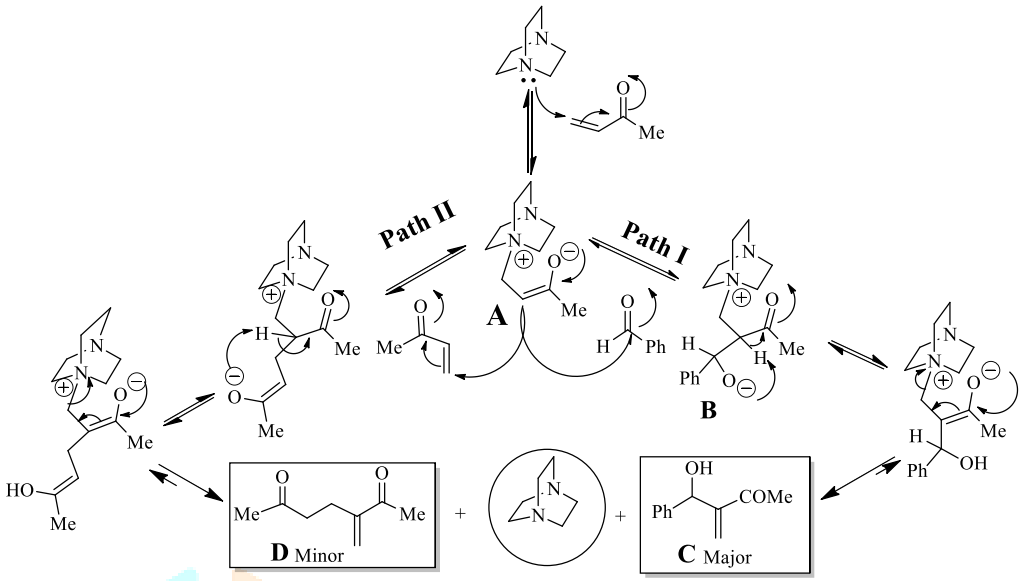
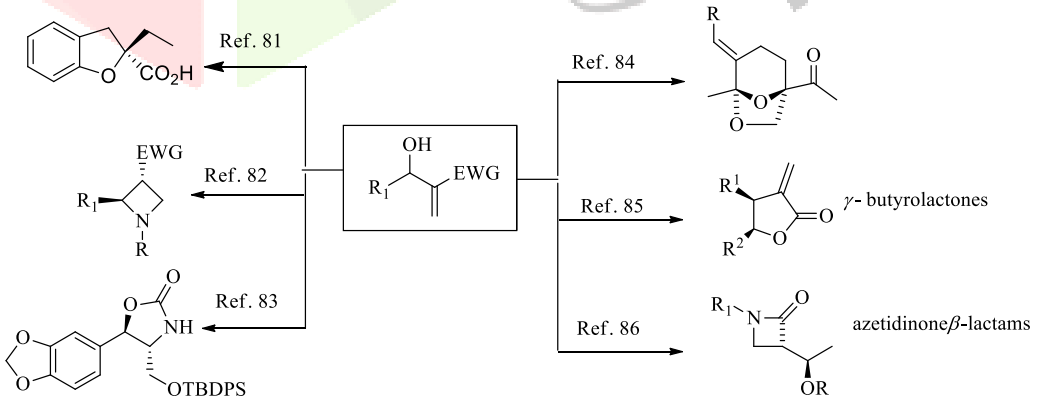


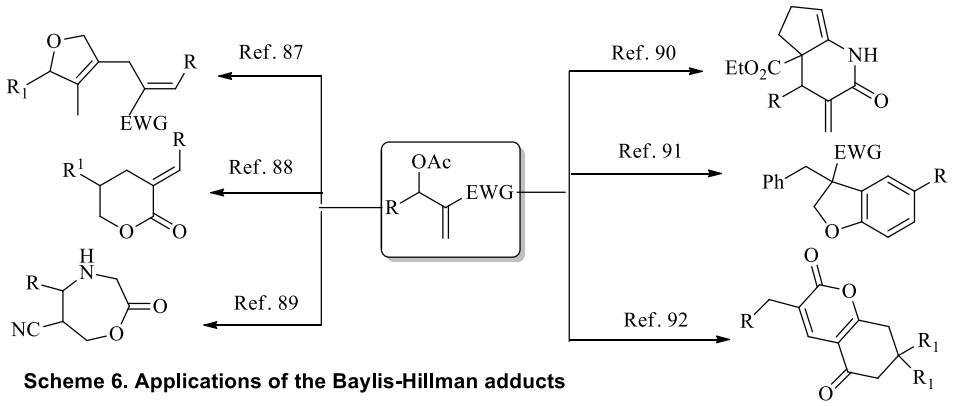

**Fig. 4 A plausible mechanism**

## 6. Applications of Baylis-Hillman adducts

Applications of the Baylis-Hillman adducts in various approaches have also been well documented. Three functional groups Baylis-Hillman adducts are handy and thus offer chances to the organic chemists to develop various organic transformation methodologies through appropriate alteration of these groups. These adducts have effectively been showing to various organic reactions such as Friedel-Crafts reaction, Diels-Alder reaction, Heck reaction and Claisen rearrangements *etc* and formed many organic compounds. The Baylis-Hillman adducts have also been employed as useful synthons in the synthesis of several important carbocylic, heterocyclic, biologically active molecules and natural products (Scheme 5-7, Fig.4).




**Scheme 5. Applications of the Baylis-Hillman adducts**




**Scheme 6. Applications of the Baylis-Hillman adducts**

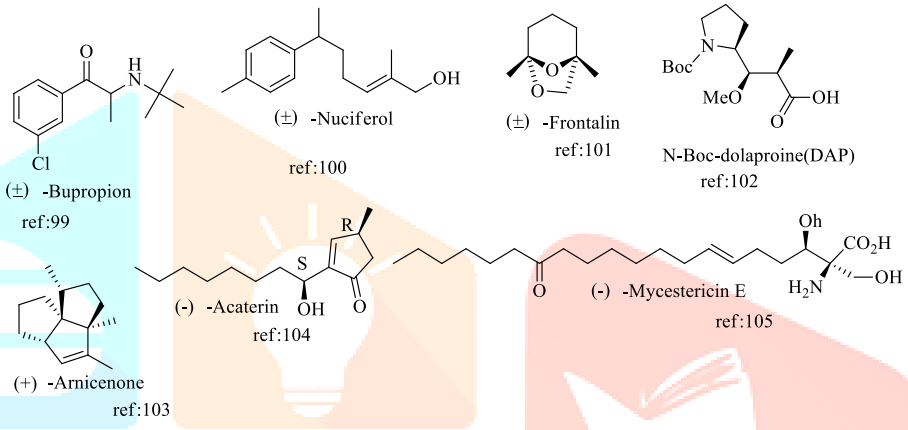



**Fig 4. Applications of the Baylis-Hillman adducts**


## 7. Acknowledgements

We express our gratitude to our colleagues and friends for their suggestions and helpful discussions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