INTRODUCTION

The recent developments in organic chemistry, medicinal chemistry and drug discovery demand the continuous evolution of convenient methodologies for atom economical construction of carbon-carbon bonds and functional group transformation strategies involving high levels of stereochemical control thereby leading to the development of operationally simple processes for assembling the carbon structural framework.\textsuperscript{1-10} The Baylis-Hillman reaction\textsuperscript{16} is a novel, three component, atom economical carbon-carbon bond forming reaction, involving the coupling of a-position of activated alkenes with electrophiles under the influence of a catalyst, most commonly a tertiary amine, providing an interesting class of densely functionalized molecules (eq 1).\textsuperscript{12-16}

\begin{equation}
\begin{array}{c}
\text{R}^1 \quad \text{R}^2 \\
\end{array}
+ \quad \begin{array}{c}
\text{EWG} \\
\end{array}
\xrightarrow{\text{tert. amine}} \quad \begin{array}{c}
\text{R}^1 \quad \text{R}^2 \\
\end{array}
\end{equation}

\text{R}^1 = \text{aryl, alkyl, aralkyl, heteroaryl} \\
\text{R}^2 = \text{H, alkyl, COOR} \\
\text{EWG} = \text{COR, CN, CHO, COOR, PO(OEt)}_2, \text{SO}_2\text{Ph, SO}_3\text{Ph, SOPh} \\
\text{X} = O, \text{NCOOR, NTs, NSO}_2\text{Ph}

The most widely accepted mechanism\textsuperscript{12-19} of the Baylis-Hillman reaction is shown in the Scheme 1 taking the reaction between benzaldehyde (as an electrophile) and methyl acrylate (as an activated olefin) under the catalytic influence of DABCO (1), as a model case. The first step of the reaction involves the Michael type nucleophilic addition of the tertiary amine catalyst (DABCO) to the activated alkene (methyl acrylate), leading to the formation of zwitterionic enolate X, which adds on to the electrophile (benzaldehyde) in an aldol fashion, to generate the zwitterionic species Y. The zwitterion Y undergoes
This fascinating reaction in fact originates from a German patent in the year 1972. Although this reaction did not see any growth during 1972-1982, it has experienced a tremendous growth during the last 20-22 years in terms of all the three essential components that is, activated alkenes, electrophiles and catalysts and also applications of the Baylis-Hillman adducts in various organic transformation methodologies have been well documented. This fascinating reaction has now become one of the powerful synthetic tools in organic chemistry as evidenced by four major reviews and large number of publications on various aspects of this reaction. Since the available literature on various aspects of this reaction is very vast, it will not be possible to present all the developments in this section. However, some of the most recent and important
developments dealing with various aspects of Baylis-Hillman reaction are presented in this section.

ACTIVATED ALKENES

A diverse class of activated alkenes such as alkyl (aryl) acrylates, alkyl vinyl ketones, acrylonitrile, acrolen, vinyl sulfones, vinyl sulfonates, vinyl phosphonates, acrylamides, and allenic esters were successfully used for coupling with a number of carbon electrophiles to obtain a wide range of densely functionalized molecules (Scheme 2).

Scheme 2

However, less reactive alkenes such as phenyl vinyl sulfoxide and P-substituted activated alkenes such as crotononitrile and crotonic acid esters require high pressures for coupling with aldehydes (eq 2).
Our research group has recently used 1-benzopyran-4(4H)-one derivatives as activated alkenes in methanolic trimethylamine (3) mediated Baylis-Hillman coupling with heteroaromatic aldehydes, nitrobenzaldehydes and isatin derivatives. Representative examples are presented in Scheme 3.

Scheme 3

Li and co-workers employed 5,6-dihydro-2H-pyran-2-one (2), as an activated alkene for Baylis-Hillman coupling with various aldehydes under the influence of diethylaluminum iodide (eq 3).

Our research group has recently used 1-benzopyran-4(4H)-one derivatives as activated alkenes in methanolic trimethylamine (3) mediated Baylis-Hillman coupling with heteroaromatic aldehydes, nitrobenzaldehydes and isatin derivatives. Representative examples are presented in Scheme 3.

Scheme 3

Hu et al. have reported acrylamide, as an activated alkene in the Baylis-Hillman coupling with various reactive aromatic and heteroaromatic aldehydes in the presence of stoichiometric amounts of DABCO in dioxane-water medium at room temperature (eq 4).
ELECTROPHILES

Although aldehydes (aliphatic, aromatic and heteroaromatic) are the most widely used electrophiles, various other carbon electrophiles such as aldime derivatives, \(^{41,43}\) \(\alpha\)-keto esters, \(^{44,46}\) non-enolizable 1,2-diketones, \(^{26,28}\) \(N\)-tritylaziridine-2-(S)-carboxaldehyde, \(^{47}\) \(N\)-arylidenediphenylphosphinamides, \(^{48}\) activated alkenes, \(^{49,52}\) isatin derivatives \(^{53}\) and fluoro-ketones \(^{54}\) have been also utilized successfully in this reaction (Scheme 4). Less reactive electrophiles such as propan-2-one and butan-2-one, \(^{27,36}\) which do not undergo Baylis-Hillman reaction under normal conditions, were brought into the scope of this reaction under high pressure conditions (Scheme 4).

Scheme 4
Dialkyl azodicarboxylates have been successfully employed as electrophiles for coupling with activated olefins in the presence of DABCO.\textsuperscript{55,56} One representative example is presented in eq 5.\textsuperscript{56}

\[
\begin{align*}
\text{eq 5} \\
\text{Dialkyl azodicarboxylates have been successfully employed as electrophiles for coupling with activated olefins in the presence of DABCO.} \\
\end{align*}
\]

5-Isoxazolecarboxaldehydes (4) were found to be fast reacting electrophiles in the Baylis-Hillman reaction with various activated olefins by Batra and co-workers (eq 6).\textsuperscript{57} They have also extended this reaction to solid-phase supported aldehydes and polymer supported acrylic acid esters for the generation of isoxazole based combinatorial\textsuperscript{58} libraries and these libraries were further evaluated for their antithrombin activity \textit{in vivo}.\textsuperscript{59}

\[
\begin{align*}
\text{eq 6} \\
\text{Ar = Ph, 4-MePh, 4-(OCH}_2\text{Ph)Ph, 2-ClPh, 3-(NO}_2\text{)Ph} \\
\text{EWG = COMe, COOMe, COOEt, COOBu, COOBu}^1, CN \\
\end{align*}
\]

Our research group,\textsuperscript{60} for the first time employed methyl 3-aryl-2-bromomethylprop-2-enoates, derived from Baylis-Hillman adducts, as electrophiles for coupling with acrylonitrile in the presence of DABCO thus providing a simple methodology for synthesis of functionalized 1,4-pentadienes with substitution at 3-position (eq 7). Subsequently, our research group extended this strategy to alkyl 3-bromomethylprop-2-enoates leading to the development of a simple methodology for one pot synthesis of functionalized 1,4-pentadienes without any substitution at 3-position (Scheme 5).\textsuperscript{61}
Ramachandran et al.\textsuperscript{62-63} have successfully utilized fluorinated aldehydes and aryl trifluoromethyl ketones as electrophiles in a DABCO catalyzed Baylis-Hillman coupling with various activated alkenes (Scheme 6).

Kim and co-workers\textsuperscript{64} have employed 2-carboxybenzaldehyde as an electrophile for the Baylis-Hillman coupling with various activated alkenes (Scheme 7).
Scheme 7

\[
\begin{align*}
\text{CHO} & \quad + \quad \text{EWG} \\
\text{COOH} & \quad \text{DABCO (2 eq.)} \\
\text{CH}_3\text{CN} & \quad 50-60^\circ\text{C} \\
\text{6-20 h} & \quad \rightarrow \quad \text{EWG} \\
\end{align*}
\]

\[\text{EWG} = \text{COOMe, COOEt, COOBu}^\text{t}, \text{CN}; \text{E-only, 61-73%} \]

\[\text{EWG} = \text{COMe, E-39% and Z-27%} \]

\[\text{COEt, E-37% and Z-26%} \]

2,2′-Dithiobenzaldehyde (5) was successfully employed in the Baylis-Hillman coupling with various activated alkenes in the presence of DBU by Kaye and Nocanda to provide a convenient one-pot synthesis of benzothiopyran derivatives (Scheme 8).

Scheme 8

\[
\begin{align*}
\text{CHO} & \quad + \quad \text{EWG} \\
\text{S}_2 & \quad \text{DBU, CHCl}_3 \\
\text{rt, 1-14 days} & \quad \rightarrow \quad \text{EWG} \\
\end{align*}
\]

\[\text{EWG} = \text{COMe, COOEt, CN, COOMe, COOEt, SO}_2\text{Ph, SO}_3\text{Ph} \]

\[\text{40-67%} \]

CATALYSTS/CATALYTIC SYSTEMS

Although DABCO (1) has been the most frequently used catalyst in this fascinating reaction, various other tertiary amine catalysts such as quinuclidine (6), 3-hydroxyquinuclidine (3-HQD) (7), 3-quinuclidinone (8), indolizine (9), DBU (10), DMAP (11), aqueous trimethylamine (12) and Merrifield resin containing 4-aminopyridine units (13) (Figure 1) have been also successfully employed for performing Baylis-Hillman reactions.\textsuperscript{11-16,66-70}
For the first time, Leadbeater et al.\textsuperscript{71,72} have employed tetramethylguanidine (TMG) (14) as a catalyst for the Baylis-Hillman coupling of methyl acrylate with various aldehydes. One representative example is presented in eq 8.

\[ \text{PhCHO} + \text{COOMe} \xrightarrow{12.5 \text{ mol}\% \text{ Me}_3\text{N}} \xrightarrow{67\%} \text{Ph} = \text{Me} \]

Shi and co-workers\textsuperscript{73} have studied (\textit{L}-proline) catalyzed Baylis-Hillman reaction between various aldehydes and MVK in the presence of imidazole as a base. However, the enantioselectivities obtained in these reactions were found to be very low (eq 9).

\[ \text{R = Pr, aryl, heteroaryl, trans-cinnamyl} \]
Later on, Cheng and co-workers & Gatri and El Gaied independently used imidazole as a catalytic source for Baylis-Hillman coupling of cycloalkenones with aldehydes (Scheme 9).

**Scheme 9**

- **NON-AMINE CATALYSTS**

Several non-amine catalysts such as trialkyl phosphines, triaryl phosphines and metal complexes like RhH(PPh₃)₄, RuH₂(PPh₃)₄, have been successfully employed in the coupling of activated alkenes with aldehydes.

Kataoka et al. demonstrated the application of sulfides or selenides (chalcogenides) as catalysts for the Baylis-Hillman coupling of vinyl ketones with various aldehydes in the presence of TiCl₄. They also found 2,6-diphenyl-4H-chalcogenopyran-4-ones (thiones) 15 and 16, to be more efficient catalysts than Me₂S for the Baylis-Hillman reaction. One representative example is presented in the eq 10.
**TiCl₄-mediated** Baylis-Hillman coupling of cyclic enones with various aldehydes in the absence of any Lewis base was reported by Li and co-workers (eq 11).

\[
\begin{align*}
\text{R} & = \text{aryl, alkyl} \\
n & = 1,2
\end{align*}
\]

\[
\text{Aldehyde} + \text{Cyclic Enone} + \text{TiCl}_4 \rightarrow \text{Product} \rightarrow 47-68\%
\]

_α-Keto_ esters and trifluoromethyl phenyl ketone have been employed as electrophiles for the Baylis-Hillman reaction with _alky_ I vinyl ketones under the influence of _TiCl₄_ to provide the desired tertiary alcohol derivatives, by our research group (Scheme 10).

Subsequently, our research group has extended this strategy to _aryl_ 1,2-diones 17, 18. In these cases usual Baylis-Hillman adducts were not obtained, instead an interesting class of functionalized fused furans were obtained (Scheme 11).
Shi and Xu\textsuperscript{89} have successfully used methyl diphenylphosphine as a catalyst for Baylis-Hillman reaction between \textit{N}-tosylated imines and different activated olefins. Representative examples are shown in Scheme 12.

\textbf{Scheme 12}

Verkade and co-workers\textsuperscript{9} have developed a highly active and selective catalyst system 19/TiCl\textsubscript{4} for Baylis-Hillman coupling of activated alkenes such as cyclic enones (including less reactive substituted derivatives), acrylates and acrylonitrile with aldehydes (eq 12). One representative example is shown below.

\textbf{RATE ACCELERATION OF BAYLIS-HILLMAN REACTION}

The normal Baylis-Hillman reaction is a slow reaction and requires a few days to a few weeks for completion depending upon the reactivity of the essential components, that is, electrophile, activated alkene and catalytic source. Several efforts have been made by the organic chemists to surmount this problem. Thus, the use of excess catalyst\textsuperscript{12-14,16} con-
cept of hydrogen bonding (having a hydroxy group either in the catalyst or in the substrate), aqueous medium, microwave irradiation, reactive activated alkenes, reactive electrophiles and high pressures have been examined for accelerating this reaction and considerable success has been achieved in this direction. Some of the recent important and interesting developments are discussed in this section.

Connon and Maher have found that bis-aryl ureas (20) greatly accelerate the DABCO-promoted Baylis-Hillman reaction between a variety of aryl aldehydes and methyl acrylate in the absence of solvent. One representative example is presented in eq 13.

Very recently, Cheng et al. have reported a remarkable rate acceleration of imidazole promoted Baylis-Hillman reaction of cyclic enones with aldehydes in basic (NaHCO₃) water solution. One representative example is shown in eq 14.

Radha Krishna et al. have reported a significant rate acceleration of Baylis-Hillman reaction of various aldehydes with different activated alkenes in sulfolane as solvent. One representative example is shown in eq 15.
A remarkable rate acceleration in silica gel as a solid phase medium in the Baylis-Hillman reaction was observed by our research group.\textsuperscript{101} The less reactive activated alkene, such as tert-butyl acrylate reacts with benzaldehyde to provide the desired adduct in 81\% yield in 36 h under these conditions (eq 16).

Santos and co-workers\textsuperscript{02} have observed some acceleration in the presence of ionic liquids in the Baylis-Hillman coupling between various aldehydes and alkyl acrylates (eq 17). They have also observed further rate acceleration in the presence of lithium perchlorate as an additive.
INTRAMOLECULAR BAYLIS-HILLMAN REACTION

Though the normal Baylis-Hillman reaction is well studied, the intramolecular version of the Baylis-Hillman reaction is not well explored. Some of the recent advances in this aspect are presented in this section.

Very recently, Koo et al.\textsuperscript{10} have reported an efficient method for the preparation of diverse formyl unsaturated carbonyl compounds (21) and successfully employed them in intramolecular Baylis-Hillman reactions. One representative example is shown in Scheme 13.

Scheme 13

Keck and Welch have reported the intramolecular Baylis-Hillman reaction of an unsaturated thiol ester (22) under the influence of DMAP/EtOH or PMe\textsubscript{3}/CH\textsubscript{2}Cl\textsubscript{2}. One representative example is shown in eq 18.

An interesting Bu\textsubscript{3}P catalyzed cycloisomerization of bis-enones (23 & 24) was described by Krische and co-workers. They have examined the effect of electronic (eq 19) and steric factors in these reactions (eq 20).\textsuperscript{105}
Roush and co-workers\textsuperscript{106} reported an intramolecular Baylis-Hillman reaction of diactivated dienes (25) to provide a convenient method for synthesis of functionalized cycloalkene derivatives. A selective example is presented in eq 21.

Our research group has developed a novel synthesis of indolizine derivatives in one-pot operation by an electrophile induced intramolecular Baylis-Hillman reaction via the treatment of alkyl vinyl ketones (including cyclohexenones) with pyridine-2-carboxaldehyde, under the influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (Scheme 14).\textsuperscript{107}
ASYMMETRIC BAYLIS-HILLMAN REACTION

In general, the asymmetric version of the Baylis-Hillman reaction can be performed by selecting appropriate chiral sources in any one (or two or three) of the essential components i.e., activated alkene, electrophile and catalyst. Some of the recent developments in this direction have been described in the following.

i) Chiral activated alkenes:

There are several reports on the asymmetric version of the Baylis-Hillman reaction using chiral activated alkenes\textsuperscript{12,6} such as chiral acrylates\textsuperscript{108-119} and chiral acrylamide derivatives.\textsuperscript{1,0-122} A number of chiral acrylates (26-33) and chiral acrylamides (34, 35) (Figure 2) derived from various chiral auxiliaries have been employed in the Baylis-Hillman reaction, to provide the resulting adducts in low to high diastereoselectivities.\textsuperscript{12,16,108,122}

Figure 2

The influence of high pressure on the diastereoselectivities of chiral auxiliary mediated coupling of activated alkenes with aldehydes was studied by Gilbert and co-workers.\textsuperscript{117}
Thus, the reaction of (-)-menthyl acrylate (26) with benzaldehyde under the catalytic influence of DABCO at higher pressure provided the corresponding Baylis-Hillman adduct with 100% diastereoselectivity, whereas the similar reaction at atmospheric pressure gave the required adduct with 22% diastereoselectivity (eq 22).

Leahy et al.\textsuperscript{120,121} have employed chiral acrylamide (34), derived from Oppolzer's camphor sultam, as an activated alkene in the Baylis-Hillman reaction to provide the desired adducts in high enantioselectivities. This methodology has been successfully employed for the synthesis of biologically important natural product (-)-tulipalin B (36) (Scheme 15).\textsuperscript{120}

Scheme 15

Yang and Chen have reported a highly diastereoselective Baylis-Hillman reaction of aldehydes with enantiopure acryloylhydrazide (35) as chiral activated alkene. They have
observed reversal of diastereoselectivity by changing the solvent from DMSO to THF/H$_2$O in this reaction. One representative example is presented in the eq 23.\textsuperscript{122}

\[ \text{eq 23} \]

\[ \begin{align*}
\text{R} = \text{Me}_2\text{CHCH}_2 & \quad \text{DMSO, 2 days, 75% : 97 : 3} \\
\text{THF/H}_2\text{O, 3 days, 81% : 1 : 99} 
\end{align*} \]

ii) Chiral electrophiles:

Several efforts have been made towards the asymmetric Baylis-Hillman reaction using chiral electrophiles. Thus, various chiral electrophiles such as (S)-O-(methoxymethyl)lactaldehyde (37),\textsuperscript{123} (S)-3-benzylxobutyraldehyde (38),\textsuperscript{124} (R)-myrtenal (39),\textsuperscript{117} isopropylidene (R)-glyceraldehyde (40),\textsuperscript{117} $\alpha$-dialkylamino and $\alpha$-(N-acylamino)aldehydes (41),\textsuperscript{125,126} N-phenylsulfonyl-(L)-prolinal (42),\textsuperscript{126} enantiopure $\alpha$-substituted benzaldehyde tricarbonylchromium complex (43)\textsuperscript{127,128} and sugar derived aldehydes (44-46)$^{129}$ etc., (Figure 3), have been employed in this reaction to afford the resulting adducts with poor to high diastereoselectivities.

Figure 3
Alcaide and co-workers\textsuperscript{130} have successfully employed enantiopure 3-oxo-2-azetidinones (47) for asymmetric Baylis-Hillman coupling with activated alkenes to provide 3-substituted-3-hydroxy $\beta$-lactam derivatives in high diastereoselectivities (eq 24).

\[
\begin{align*}
\text{eq 24} \\
\text{R = allyl, propargyl, 4-(OMe)Ph} \\
\text{EWG = CN;} \\
\text{EWG = COMe, COOMe; } dr = 97:3 \\
\text{dr = 100:0}
\end{align*}
\]

Enantiomerically pure N-sulfinimines (48) were used as chiral electrophiles for coupling with methyl acrylate in the presence of 3-hydroxyquinuclidine (3-HQD) (7) and In(OTf)$_3$ to provide the corresponding Baylis-Hillman adducts, $\beta$-amino-$\alpha$-methylene esters in moderate to good yields and good diastereoselectivities.\textsuperscript{131} One representative example is presented in eq 25.

\[
\begin{align*}
\text{eq 25} \\
\text{dr = 87:13}
\end{align*}
\]

iii) Chiral catalysts:

Considerable attention has been paid towards developing asymmetric version of Baylis-Hillman reaction using various chiral catalysts.\textsuperscript{12-16,12109} Thus, quinidine (49),\textsuperscript{12109} chiral DABCO (50),\textsuperscript{132,133} (S)-BINAP (51),\textsuperscript{134} calcium salt of (R)-BINOL (52),\textsuperscript{135} enantiopure pyrrolizidine (53),\textsuperscript{136} chiral bicyclic azetidine (54),\textsuperscript{137} $\beta$-isocupreidine (55)\textsuperscript{138,142} and 10-methylthioisoborneol (56)\textsuperscript{143,144} (Figure 4) have been employed as chiral catalysts in this
reaction to obtain the Baylis-Hillman adducts in moderate to high selectivities (up to 99% ee).

Hatakeyama and co-workers\textsuperscript{138,139} have developed an elegant asymmetric Baylis-Hillman reaction using \( \beta \)-isocupreidine (55), as a catalyst for the coupling between various aldehydes and 1,1,1,3,3,3-hexafluoroisopropyl acrylate (57) (as activated alkene) to provide the desired adducts up to 99% enantiomeric purities (Scheme 16). Subsequently, they also successfully employed \( \beta \)-isocupreidine (55) as a catalyst for Baylis-Hillman reaction of aromatic imines with acrylate (57). In contrast to the aldehydes which afforded adducts with (\( R \))-selectivity, the resulting compounds in this reaction (with aromatic imines) were formed with (\( S \))-selectivity, (Scheme 16).\textsuperscript{140}

Scheme 16
Chen and co-workers have used a novel bidendate ligand (58) derived from camphor as a catalyst in the presence of Lewis acid, La(OTf)₃, for performing the asymmetric version of the Baylis-Hillman reaction between various aldehydes and acrylates under the influence of DABCO to provide the corresponding adducts in 6-95% enantioselectivities (eq 26).

Shi and Chen have reported an interesting chiral phoshine Lewis base (59) catalyzed asymmetric Baylis-Hillman reaction of N-sulfonated imines with methyl vinyl ketone and phenyl acrylate (Scheme 17). Very recently, Schaus and McDougal have reported a highly enantioselective Baylis-Hillman reaction of cyclohexenone with aldehydes using a chiral Bronsted acid (60) as catalyst and triethyl phosphine as the nucleophilic promoter. One representative example is shown in eq 27.
APPLICATIONS OF THE BAYLIS-HILLMAN ADDUCTS

Due to the close proximity of three chemospecific functional groups such as hydroxy group (or amino), olefin and electron withdrawing groups in the Baylis-Hillman adducts, organic chemists have employed these adducts in various stereoselective transformation methodologies by appropriate tuning of the functional groups.\textsuperscript{12-16} These adducts have been successfully utilized as valuable synthons for the synthesis of various trisubstituted olefins, carbocycles, biologically active molecules and natural products.\textsuperscript{12-16} Some of such important and recent developments on applications of Baylis-Hillman adducts have been presented in this section.

Drewes et al.\textsuperscript{20} have reported the synthesis of (+-) integerrineic acid (61) starting from the Baylis-Hillman adduct, ethyl 3-hydroxy-2-methylenebutanoate following the reaction sequence as described in Scheme 18.

\textbf{Scheme 18}
Amri et al. have reported the synthesis of (±)-sarkomycin (62), an antitumor agent from ethyl 2-(hydroxymethyl)prop-2-enoate, the Baylis-Hillman adduct, obtained from ethyl acrylate and formaldehyde, according to Scheme 19.

Scheme 19

Our research group developed a simple stereoselective synthesis of (2E)-2-substituted alk-2-enoates and (2Z)-2-substituted alk-2-enenitriles via the treatment of methyl 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles respectively, with Grignard reagents. This methodology has been successfully applied for the synthesis of (2E)-2-butyloct-2-enal (63), an alarm pheromone component of the African weaver ant, *Oecophylla longinoda* and (2E)-2-tridecylheptadec-2-enal (64) an unusual metabolite from the red alga, *Laurencia* species (Scheme 20).
An interesting one-pot synthesis of alkylidinecyclohex-2-enones (65) via the treatment of acetates of the Baylis-Hillman adducts (obtained from various aldehydes and alkyl vinyl ketones) with aliphatic 1,3-diketones in the presence of K$_2$CO$_3$ in ethanol, was reported by Chamakh and Amri (Scheme 21).

Kim and co-workers$^{151}$ have described an interesting synthesis of 1,3-disubstituted naphthalenes (66) from the acetates of the Baylis-Hillman adducts involving manganese(III) acetate assisted radical cyclization as the key step. Representative examples are presented in Scheme 22.

Kabalka and co-workers$^{152}$ reported an interesting Pd(OAc)$_2$ catalyzed reaction between potassium organofluoroborates and acetates of Baylis-Hillman adducts providing a
simple methodology for stereoselective synthesis of trisubstituted alkenes (Scheme 23 and eq 28).

Scheme 23

Kim et al.\textsuperscript{153} have reported an interesting synthesis of 3-arylidenebicyclo[3.2.1]octan-8-ones (67) via the reaction of Baylis-Hillman acetates with 2-carboethoxycyclopentanone in the presence of K2CO3 in ethanol at room temperature. One representative example is shown in eq 29.

Our research group have developed a simple and convenient synthesis of (E)-\(\alpha\)-methylcinnamic acids via the nucleophilic addition of hydride ion from NaBH\textsubscript{4} to the acetates of the Baylis-Hillman adducts, followed by hydrolysis and crystallization (Scheme 24).\textsuperscript{154} This methodology has successfully applied for synthesis of (E)-p-(myristyloxy)-\(\alpha\)-methylcinnamic acid (68), a hypolipidemic active agent, which is also a
precursor for another active hypolipidemic agent LK-903 (69) and \([E]-p-(\text{carbomethoxy})-\alpha\text{-methylcinnamic}\) acid (70), a valuable synthon for an orally active serine protease inhibitor (71) (Figure 5).\(^{154}\)

**Scheme 24**

\[
\begin{align*}
\text{OAc} &\quad \text{NaBH}_4 \quad t-\text{BuOH} \\
\text{Ar} &\quad \text{COOMe} \\
\text{15 min, rt} &\quad 93-98\% \text{ (E)} \\
\text{Ar} &\quad \text{COOH} \\
\end{align*}
\]

**Figure 5**

Our research group\(^{155}\) has described a simple one-pot stereoselective transformation of the Baylis-Hillman adducts, obtained from aromatic aldehydes and tert-butyacrylate into \((E)-2\text{-arylideneindan-1-ones}\) (72) via the strategy involving one inter- and intramolecular Friedel-Crafts reactions according to Scheme 25.

**Scheme 25**

\[
\begin{align*}
\text{OH} &\quad \text{COOBu}^+ \\
\text{Ar} \quad \text{H} \quad \text{H} \\
\text{Ar} &\quad \text{COOH} \\
\text{MeOOC} &\quad \text{Me} \\
\text{C}_{14}H_{29}O &\quad \text{Me} \\
\text{H} &\quad \text{H} \\
\text{H} &\quad \text{MeSO}_{3}H \\
\text{N} \quad \text{Me} &\quad \text{O} \\
\text{N} \quad \text{Me} &\quad \text{COOH} \\
\text{C}_{14}H_{29}O &\quad \text{Me} \\
\end{align*}
\]
Isomerization of methyl 3-aryl-3-hydroxy-2-methylene propanoates, the Baylis-Hillman adducts obtained from methyl acrylate and aromatic aldehydes, into methyl 3-aryl-2-methyl-3-oxopropanoates under the catalytic influence of RuCl$_2$(PPh$_3$)$_3$ was reported by our research group (eq 30).$^{156}$

\[
\text{Ar} = \text{Ph, 4-MePh, 4-EtPh, 4-(i-Pr)Ph, 4-(O-Me)Ph, 2-(O-Me)Ph}
\]

Our research group$^{157}$ has reported a simple enantioselective synthesis of mikanecic acid (73), a terpene dicarboxylic acid from the Baylis-Hillman adduct derived from chiral acrylate (31), following the reaction sequence as described in Scheme 26.

Scheme 26

A highly syn-diastereoselective heterogeneous hydrogenation of Baylis-Hillman adducts with palladium on carbon in the presence of MgBr$_2$, producing the corresponding syn-products (syn-aldol derivatives) was reported by Bouzide (eq 31).$^{158}$
A convenient and efficient synthesis of 2-methylenealkanenitriles and alkanoates via the regioselective nucleophilic ($S_{N}2'$) addition of hydride ion from NaBH$_4$ to the in situ generated DABCO-allyl bromides [2-(bromomethyl)alk-2-enenitriles and 2(Z)-2-(bromomethyl)alk-2-enoates] salts in environment friendly aqueous media was developed by our research group (Scheme 27 and Scheme 28). Subsequently, this methodology has been successfully applied for synthesis of two hypoglycemic agents, etomoxir (74) & methyl palmoxirate (75) (Scheme 28).$^{159}$

**Scheme 27**

**Scheme 28**
Ogasawara and co-workers\textsuperscript{160,161} have successfully employed the Baylis-Hillman adducts, derived from chiral bicyclic enones (−)-KDP (76) & (+)-KDP (76) and formalin, in the synthesis of angular triquinane sesquiterpene (+)-arnicenone (77) and cyclopentanoid antibiotic (−)-pentenomycin I (78) according to the Scheme 29.

Scheme 29

Very recently, Fields\textsuperscript{162} has reported a convenient synthesis of phosphonothrixin (79), an important natural product, starting from the Baylis-Hillman adduct, methyl 3-hydroxy-2-methylenebutanoate, following the reaction sequence as shown in the Scheme 30.

Scheme 30
APPLICATIONS OF BAYLIS-HILLMAN ADDUCTS TO HETEROCYCLIC COMPOUNDS

Most of the important natural products, biologically active compounds, drug intermediates are heterocyclic molecules. Considerable progress has been achieved in the synthesis of heterocyclic compounds such as lactones, lactams, coumarines, epoxides, indolizines, 6,8-dioxa bicyclo[3.2.1]octanes, methylenedioxa-nones, aziridines, tetrahydrofurans, pyrazolines and diazacyclopahnes using the Baylis-Hillman adducts (pictorially presented in Schemes 31, 32 & 33). Some of the important and recent developments on the applications of Baylis-Hillman adducts to heterocyclic molecules have been presented in this section.

Scheme 31
Very recently, Ramachandran et al.\textsuperscript{190} have reported an interesting synthesis of $\beta$-substituted $\alpha$-methylene $\gamma$-butyrolactones (81) via the nucleophilic addition of boronates (80) to the acetates of Baylis-Hillman adducts followed by the treatment of the resulting allyl boronates with aldehydes. One representative example is shown in Scheme 34.

Chang and co-workers\textsuperscript{191} have described a one-pot conversion of Baylis-Hillman adducts into alkyl-$3(E)$-aryl/alkylidene-$5$-substituted sulfonylpiperidine-$2,6$-diones (82). One
representative example is shown in eq 32. This methodology has been successfully applied for synthesis of tacamonine (83), an indole alkaloid according to Scheme 35.

Our research group has developed a simple and convenient three-step synthesis of functionalized [4.4.3] and [4.4.4]propellano-bislactones (84) & (85) from acetates of Baylis-Hillman adducts following the reaction sequence as shown in Scheme 36.\(^{192}\)
A tandem Michael-intramolecular Corey-Chaykovsky reaction of the five membered cyclic oxosulfonium ylide with acetates of the Baylis-Hillman adducts leading to the stereoselective synthesis of cycloheptene oxide derivatives (86) was reported by Fujimoto and co-workers. A similar reaction with six membered oxosulfonium ylide provided cyclooctene oxide derivatives (87) as mixture of stereoisomers in moderate yields. Representative examples are presented in Scheme 37.

Scheme 37

A facile, one-pot synthetic transformation of the acetates of the Baylis-Hillman adducts into fused pyrimidones (88) via the reaction with 2-aminopyridine in an environment-friendly aqueous media, has been developed by our research group (eq 33).

Howell et al. have described an elegant synthesis of 3-alkylidene-2-methyleneoxetanes (89) via the treatment of α-alkylidene-β-lactones (which in turn were prepared from Baylis-Hillman adducts) with dimethyltitanocene. One representative example is shown in Scheme 38.
Recently, our research group reported an interesting one-pot transformation of Baylis-Hillman adducts into 2-benzazepines (90) via novel and tandem construction of C-N and C-C bonds involving simultaneous Ritter and Houben-Hoesch reactions as described in Scheme 39. Subsequently, our research group also reported a novel one-pot synthesis of 2-benzoxepines (91) via the treatment of the Baylis-Hillman adducts with formaldehyde in the presence of $\text{H}_2\text{SO}_4$ involving tandem construction of C-0 and C-C bonds as described in Scheme 40.

Scheme 39
Kim et al. have reported an interesting regioselective synthesis of 1,3,4,5-tetrasubstituted pyrazoles (92) via the reaction of Baylis-Hillman adducts with hydrazine hydrochlorides (eq 34)."

Bermejo and co-workers have described an interesting synthesis of methylene lactone (93), from Baylis-Hillman adduct, methyl 3-hydroxy-2-methylenebutanoate according to Scheme 41. This molecule is found to possess extremely interesting properties with regard to its apoptosis inducing ability in HL-60 cells.
Hoffman and Buchholz have reported an interesting synthesis of \( \beta \)-lactam derivatives (94) via the nucleophilic addition of aliphatic or aromatic primary amines to allyl bromides derived from Baylis-Hillman adducts. One representative example is presented in Scheme 42.

Scheme 42

Our research group has developed a convenient synthesis of 3-arylidene(alkylidene)-chroman-4-ones from Baylis-Hillman bromides following the reaction sequence described in Scheme 43. This methodology has been successfully applied for the synthesis of bonducellin methyl ether (95), an important natural product and 3-(4-methoxybenzylidene)-6-methoxycroman-4-one, an antifungal agent (96) (Figure 6).

Scheme 43

Figure 6
An interesting synthesis of bicyclic lactones (97) from the Baylis-Hillman adducts was reported by Paquette and Mendez-Andino following the reaction sequence as described in Scheme 44.\textsuperscript{203}

\textbf{Scheme 44}

Mikami et al.\textsuperscript{204} have reported an interesting synthesis of substituted furan rings (98) via the photochemical reaction of methyl ethers of Baylis-Hillman adducts followed by \textit{in situ} treatment of the resulting dihydropyran derivatives with TMSOTf/Et$_3$N (Scheme 45).

\textbf{Scheme 45}