INTRODUCTION

The formation of carbon-carbon bond is one of the most fundamental reactions in organic chemistry.\textsuperscript{1,2} Recent developments in organic chemistry demand complete atom-economy in construction of carbon-carbon bonds as such reactions will be environment friendly. Various atom-economy carbon-carbon bond forming reactions, such as aldol reaction,\textsuperscript{3} Diels-Alder reaction\textsuperscript{4} and Michael reaction\textsuperscript{5} have been developed and their applications have been well documented in the literature. The Baylis-Hillman reaction yet another atom economy carbon-carbon bond forming reaction which has become a popular carbon-carbon bond forming reaction in synthetic organic chemistry in recent years.\textsuperscript{6-19}

The Baylis-Hillman Reaction

This is an essentially three component atom-economy carbon-carbon bond forming reaction involving the coupling of \( \alpha \)-position of an activated alkene with carbon electrophile under the influence of a catalyst or catalytic system [commonly tertiary amine and particularly DABCO (1) (1,4-diazabicyclo[2.2.2]octane)], providing an interesting class of highly functionalized molecules (Eq.1).\textsuperscript{6-19}

\[
\begin{align*}
\text{R}^+ & \oplus \text{EWG} \rightarrow \text{R}^+ \text{XH} \rightarrow \text{R}^\prime \text{XH} \rightarrow \text{R}^\prime \text{EWG} \text{XH} \\
\text{EWG} = \text{Electron Withdrawing Group} : \text{COR, CHO, CN, COOR, PO(OEt)\textsubscript{2}, SO\textsubscript{2}Ph, SO\textsubscript{3}Ph, SOPh} \\
\text{R}^+ = \text{alkyl, H, COOR} \\
\text{R} = \text{alkyl, aryl, heteroaryl} \\
\text{X} = \text{O, NCOOR, NTs, NSO\textsubscript{2}Ph} \\
\text{DABCO (1)} \\
\end{align*}
\]

Eq. 1
During the last two decades Baylis-Hillman reaction has grown from almost unknown (patent) level to the stage of high popularity as evidenced by the large number of publications, five major reviews\textsuperscript{8-12} and many mini reviews.\textsuperscript{13-19} In fact Baylis-Hillman reaction has seen tremendous growth in terms of all the three essential components, that is, activated alkenes, electrophiles and catalyst or catalytic systems. There is also considerable progress in the development of asymmetric version of the Baylis-Hillman reaction based on the utility of chiral activated alkenes, chiral electrophiles and chiral catalysts. Significant progress has also been achieved in its intramolecular version. The Baylis-Hillman adducts, which contain a minimum of three functional groups in close proximity have been employed successfully in various organic transformation methodologies and in the synthesis of carbocyclic & heterocyclic molecules of medicinal importance.\textsuperscript{11,12} All these developments have been presented pictorially in Fig. 1.

Since the major part of this thesis deals with the synthetic applications of the Baylis-Hillman adducts, this chapter presents the important developments of Baylis-Hillman reaction with respect to all the three essential components, its asymmetric version and intramolecular version. This chapter will also present the some of the recent and relevant applications of the Baylis-Hillman adducts in organic synthesis. Mechanism of this reaction is presented briefly at the end of this chapter.
ACIVATED ALKENES AND ALKYNES

Several activated alkenes and activated alkynes (see Fig. 2) have been successfully employed for coupling with various electrophiles under the influence of catalysts or catalytic systems to provide multifunctional molecules.

Fig. 2 Activated alkenes and activated alkynes

EWG = Electron withdrawing group
**Earlier work**

A large number of ethylene (alkenes) compounds having electron withdrawing groups such as ketones, nitrile, esters, amide, sulphones, sulphonates, sulphoxides, aldehyde at the α-position, have been employed successfully for Baylis-Hillman coupling with number of electrophiles under the influence of a catalyst or catalytic system to provide the densely functionalized molecules (see Scheme 1). Also allenic esters, crotonic esters and crotononitrile have been used as activated alkenes in the Baylis-Hillman coupling with various electrophiles (Scheme 1).

**Acyclic activated alkenes**

**Scheme 1**
Activated Alkynes

In addition to the activated alkenes,\textsuperscript{11,12} activated alkynes such as methyl propiolate\textsuperscript{36} methyl 3-trimethylsilylpropionate,\textsuperscript{37} but-3-yn-2-one \textsuperscript{38,39} have also been used for Baylis-Hillman coupling with various electrophiles to provide the $\beta$-substituted Baylis-Hillman adducts (Scheme 2).

\textbf{Scheme 2}
Cyclic activated alkenes

Cyclic activated alkenes such as cyclohex-2-enone,\textsuperscript{40} cyclopentenones,\textsuperscript{41} chromones,\textsuperscript{42} 5,6-dihydro-2\textit{H}-pyran-2-one\textsuperscript{43} etc. have also been used for coupling with aldehydes to provide densely functionalized compounds (Scheme 3).

**Scheme 3**

![Scheme 3](image)

Recent developments

Namboothri and co-workers\textsuperscript{44} have elegantly used β-arylnitroethylenes as activated alkenes for Baylis-Hillman coupling with methyl vinyl ketone and ethyl acrylate as electrophiles
using imidazole / LiCl as catalytic system to provide the resulting adducts in moderate to good yields (Scheme 4).

Scheme 4

Back and co-workers\textsuperscript{45} reported an interesting 3-hydroxyquinuclidine (3-HQD) (6) catalyzed Baylis-Hillman coupling of β-vinylic activated alkene (7), as an activated alkene, with aldimine derivatives to provide the resulting adducts as a mixture of $E/Z$ isomers (Scheme 5).

Scheme 5
1-Benzopyran-4(4H)-one derivatives\textsuperscript{42} have been successfully used as activated alkenes in the Baylis-Hillman coupling with various electrophiles, such as isatins and aldehydes under the influence of methanolic trimethyl amine (4) by our research group to provide the resulting products in good yields (Scheme 6).

\textbf{Scheme 6}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=\textwidth]{Scheme6.png}};
\node at (-2,0) \textit{Electrophiles};
\node at (-2,-2) \textit{Earlier developments};
\end{tikzpicture}
\end{center}

Earlier developments

Although the aldehydes such as aliphatic, aromatic and heteroaromatic constitute a major portion of the electrophiles in Baylis-Hillman coupling with large number of activated alkenes to produce different kinds of densely functionalized molecules, various other electrophiles such as aldimines,\textsuperscript{46-48} \(\alpha\)-keto esters,\textsuperscript{49-51} fluoroketones,\textsuperscript{52} non-enolizable 1,2-diketones,\textsuperscript{53} ninhydrin,\textsuperscript{54,55} and isatin derivatives,\textsuperscript{55,56} have also been successfully employed in this fascinating reaction for coupling with different activated alkenes. Also activated alkenes such as acrylonitrile, alkyl vinyl ketones, aryl vinyl ketones, aryl(alkyl) acrylates have also been employed as electrophiles\textsuperscript{57-60} in the Baylis-Hillman reaction.
Simple ketones\textsuperscript{61} such as 2-butane and acetone, which are usually less reactive, have been employed as electrophiles at high pressure conditions (Scheme 7). Some of the relevant examples are presented in the Scheme 7.

**Scheme 7**

![Scheme 7 diagram](image)

**Recent developments**

Our research group\textsuperscript{62} has successfully employed, for the first time allyl bromides /allyl chlorides, derived from Baylis-Hillman adducts, as electrophiles in the Baylis-Hillman reaction with various activated alkenes. Thus the treatment of the Baylis-Hillman allyl
bromides/chlorides with acrylonitrile under the influence of DABCO provided the 3-substituted 1,4-pentadienes following the reaction sequence as described in Scheme 8. Subsequently our research group has also reported a simple protocol for the synthesis of various 2,4-functionalized 1,4-pentadienes via the Baylis-Hillman coupling of allyl bromides derived from the alkyl 3-hydroxy-2-methylene propanoates, as electrophiles with alkyl acrylates, acrylonitrile, alkyl vinyl ketones and cyclic enones following the reaction sequence as shown in Scheme 9.

**Scheme 8**
Katritzky and co-workers,\textsuperscript{64} successfully used substituted aminomethylbenzotriazoles as a electrophiles in coupling with ethyl acrylate under the influence of TiCl\(_4\), to provide addition products (8), which on treatment with NaH provided the desired Baylis-Hillman products. One representative example is presented in Scheme 10.

N-Protected \(\alpha\)-amino sulphones, have been, for the first time, used by Das and co-workers\textsuperscript{65} as a electrophiles for coupling with alkyl acrylates under catalytical influence of
DABCO to afford Baylis-Hillman adducts (Scheme 11). Subsequently, Gajda et al. performed similar reaction strategy to obtain Morita-Baylis-Hillman adducts (Scheme 11).

Scheme 11

Reddy and co-workers have successfully used carborane aldehyde (9) as electrophile in the Baylis-Hillman reaction with various activated alkenes to provide the corresponding alcohols in good to excellent yields (Scheme 12). These Baylis-Hillman adducts (10) have been transformed into various trisubstituted alkenes. Representative examples are shown in Scheme 12.

Scheme 12
Catalysts

Earlier developments

Several tert-amines such as DABCO (1), DBU (2), imidazole (3), methanolic-Me₃N (4), 3-HQD (6), 3-chloroquinoxalineidene (11), 3-acetoxyquinoxalineidene (12), quinoxalineidene (13), DMAP (14), indolizine (15), NMM (16), HMT (17), TMEDA (18), TMPDA (19), TMG (20), Et₃N (21), benzotriazole (22) have been successfully employed in various Baylis-Hillman reactions. Very recently, [bdmin][PF₆] ionic liquid (23) has also been successfully employed as a catalyst for Baylis-Hillman reaction (Fig. 3).

Recent developments

Cheng and co-workers introduced hydroxy ionic liquid (HIL) (24) built on quinoxalineidene framework, as a novel catalyst for the Baylis-Hillman reaction as shown in Scheme 13. It is interesting to note that this catalyst (24) is recoverable and reusable.
Gruttadauria and co-workers\textsuperscript{84} used an interesting polystyrene-supported proline (25) as a recyclable catalyst for Baylis-Hillman reaction of various aldehydes with alkyl vinyl ketones (Scheme 14).

Ye and co-workers\textsuperscript{85} for the first time employed N-heterocyclic carbenes (NHCs) (26) as efficient catalysts for Baylis-Hillman coupling between cyclic enones and N-tosylarylimines to provide the resulting adducts in good yields. Representative examples are presented in Scheme 15.
Verkade and co-workers\textsuperscript{86} used aza-phosphine catalyst (27) for Baylis-Hillman coupling of various aldehydes with cyclic and acyclic activated alkenes under the influence of TiCl\(_4\) to provide the resulting Baylis-Hillman adducts in excellent yields at faster reaction rates (Scheme 16).
NON-AMINE CATALYZED/MEDIATED BAYLIS-HILLMAN REACTIONS

Literature survey reveals that several catalysts such as alkyl (aryl) phosphines and also metal complexes, RhH(PPh₃)₄, RuH₂(PPh₃)₄ have been successfully employed for the coupling of activated alkenes with electrophiles. Combination of Lewis acids with bases, such as R₂S-TiCl₄, R₂X-BF₃ (X = O, S), TiCl₄-NR₃, TiCl₄-R₄NX have also been successfully employed for obtaining the Baylis-Hillman adducts. Lewis acids such as TiCl₄, Et₂AlI, MgBr₂, MgI₂ have also been used for performing the Baylis-Hillman reactions.

Kataoka and co-workers reported the synthesis of β-halo-Baylis-Hillman adducts via the reaction between aldehydes and activated alkynes under the catalytic influence of dimethyl sulphide in presence of titanium halides (TiX₄) see Eq. 2.

![Eq. 2](image)

Later our research group developed Lewis acid (TiCl₄) catalyzed Baylis-Hillman coupling of electrophiles such as α-keto esters, and aldehydes with alkyl vinyl ketones to provide the desired product and allyl halides respectively in moderate to good yields (Scheme 17).
Scheme 17

He and co-workers\textsuperscript{106} used 1, 3, 5-triaza-7-phosphaadamantane (PTA) (28) as an efficient catalyst to promote the Baylis-Hillman reaction of alkyl acrylates and alkyl vinyl ketones with various aldehydes. Representative examples are described in Scheme 18.

Scheme 18

Shi and co-workers\textsuperscript{107} successfully used PPh\textsubscript{2}Me (29) as a catalyst for Baylis-Hillman coupling between cyclopentenone and \(\alpha\)-keto esters providing the desired adducts. One representative example is presented in Eq. 3.
Asymmetric Baylis-Hillman reaction

Asymmetric version of the Baylis-Hillman reaction in the case of prochiral electrophiles in principle can be performed using chiral activated alkenes or chiral electrophiles or chiral catalysts or chiral additives or combination of some of these components in chiral form. Efforts have been directed in all these possibilities and considerable progress has been achieved in certain aspects.\textsuperscript{11,13}

CHIRAL ACTIVATED ALKENES

Chiral activated alkenes most generally, chiral acrylates and chiral amides have been employed for coupling with various electrophiles. A number of chiral acrylates, derived from various chiral auxiliaries such as cyclohexnol derivatives (30, 31,\textsuperscript{108,109} $(R)$\textsuperscript{\textdagger}-(+)-pentolactone (32),\textsuperscript{110-112} camphor derivatives (33-35),\textsuperscript{113-115} and sugar derivatives (36-38)\textsuperscript{116,117} (see Fig. 4) are successfully used in the Baylis-Hillman reaction with various electrophiles, to provide the resulting products in low to moderate diastereoselectivities.
Gillbert\textsuperscript{118} and co-workers described interesting effect of pressure on the enantioselectivity of the Baylis-Hillman reaction of benzaldehyde with (-)-menthyl acrylate (30) under the influence of DABCO. Thus high pressure (7.5 Kbar) provided 100\% diastereoselectivity while normal pressure provided 22\% diastereoselectivity only (Scheme 19).

**Scheme 19**

Leahy and coworkers\textsuperscript{119} successfully used chiral acrylamide (39) as an activated alkene in the Baylis Hillman reaction with aldehydes to provide the resulting Baylis-Hillman adducts in excellent diastereoselectivities (Scheme 20).
In the year 2000, Chen and co-workers\textsuperscript{120}, developed highly diastereoselective Baylis-Hillman reaction using chiral acryloylhydrazide (40) as a activated alkene for coupling with carbon electrophiles. They also found an interesting reversal of diastereoselectivity by changing the solvent from THF/H\textsubscript{2}O to DMSO. One representative example is presented in Eq. 4.

CHIRAL ELECTROPHILES

Several enantiopure aldehydes such as (S)-3-benzyloxybutyraldehyde (41),\textsuperscript{121} enantio pure ortho substituted benzaldehyde tricarbonylchromium complex (42),\textsuperscript{122} N-phenylsulfonyl-
(L)-prolin (43)\textsuperscript{123}, (-)-8-phenylmenthylglyoxylate (44)\textsuperscript{124} enantiopure 1-alkenyl(alkynyl)-4-oxoazetidine-2-carbaldehydes (45)\textsuperscript{125} (see Fig. 5) were used as chiral electrophiles for coupling with activated alkenes to provide the resulting adducts in moderate to good diastereoselectives.

**Fig. 5**

Alcaide and co-workers\textsuperscript{126} successfully used chiral azetidine (46) as a chiral electrophile in the Baylis-Hillman reaction with acrylonitrile to provide the resulting Baylis-Hillman adducts in high diastereoselectivity. One representative example is presented in (Eq. 5).

\[ \text{Eq. 5} \]

Chen and Pan have\textsuperscript{127} used enantio pure N-glyoxyloyl camphorpyrazolidinone (47), as a chiral electrophile in the Baylis-Hillman reaction with various activated alkenes in presence of DABCO as a catalyst which provided the resulting adducts in high diastereoselectivity. One representative example is presented in Eq. 6.
Recently, Zhou and co-workers\textsuperscript{128} used chiral N-thiophosphorylimines containing (S)-binapthalene scaffold (48), as an electrophile for coupling with methyl vinyl ketone to afford the resulting Baylis-Hillman adducts in good yields and in moderate to excellent diastereoselectivities (Eq. 7).

**CHIRAL CATALYSTS**

Development of appropriate chiral catalysts for various Baylis-Hillman reactions to provide the resulting adducts in high enantiomeric purities has been and continues to be a challenging endeavor in asymmetric Baylis-Hillman reaction. Various catalysts have been developed for this purpose (Fig. 6).\textsuperscript{129-134}
Hatakayema and co-workers\textsuperscript{129} have been used the catalyst (49) for coupling of various electrophiles with 1,1,1,3,3,3-hexafluoroisopropyl acrylate to provide the resulting adducts in high enantiomeric purity up to 99\% see Eq. 8.

\[
\text{RCHO + } \text{Cat.} 49 (10 \text{ mol\%}) \xrightarrow{\text{DMF, -55 °C}} \text{yield } 4-25 \% \\
\text{ee } 4-85 \% \\
\text{R = Ph, 4-(NO}_2\text{)Ph, trans-cinnamyl, Et, Pr\text{'}, Bu\text{'}, c-HeX}
\]

Recently, Chen and co-workers\textsuperscript{130} used a novel, camphor derived bidentate ligands (50) as additives for asymmetric Baylis-Hillman reaction between acrylates and various aldehydes under the catalytic influence of DABCO to obtain the resulting Baylis-Hillman adducts in 6-95\% enantiomeric purities (Eq. 9).
Schaus and Mcdougal\textsuperscript{131} reported highly enantioselective Baylis-Hillman reaction of 2,2-dimethyl-1,3-dioxane-5-carbaldehyde with various cyclic enones under the catalytic influence of Et\textsubscript{3}P in presence of catalytic amount of chiral tetrahydro-BINOL (51). One representative example is presented in Eq. 10.

Aggarwal and co-workers\textsuperscript{132} have used chiral sulphide (52) as an efficient catalyst for asymmetric Baylis-Hillman reaction, between in situ generated iminium ions as electrophiles and cyclic enones (as activated alkenes) to provide the resulting adducts in high enantioselectivities. One representative example is presented in Eq. 11.
Very recently, Wu and co-workers\textsuperscript{133} reported a highly enantioselective Baylis-Hillman reaction of methyl vinyl ketone with various aromatic aldehydes under the influence of chiral phosphinothiourea catalyst (\textsuperscript{53}), derived from trans-2-amino-1-(diphenylphosphino)cyclohexane, to provide the resulting adducts in good to excellent enantiomeric purities (Eq.12).

Very recently, Miller and co-workers\textsuperscript{134} reported an asymmetric Baylis-Hillman reaction between N-acyl imines as electrophiles and allenoates as activated alkenes using
pyridylalanine (Pal)-peptide (54), as a catalyst. One representative example is presented in Eq. 13.

\[
\text{COOBn} \quad \text{NO} \quad \text{Ph} \quad \text{HN} \quad \text{O} \quad \text{Ph} \\
\text{COOBn} + (10 \text{~mol~}) \quad 23 \text{~}^{0}\text{C}, \text{Toluene} \quad 16 \text{~h}, 82\% \\
\text{Eq. 13}
\]

INTRAMOLECULAR BAYLIS-HILLMAN REACTION

In recent years intramolecular Baylis-Hillman reaction has received considerable attention from synthetic chemists.\(^{11}\) Kraft and co-workers,\(^{135}\) have described an interesting intramolecular Baylis-Hillman reaction of enone-allylic alcoholic system (55) under the catalytic influence of trimethylphosphine to provide carbocyclic framework in good yields. One representative example is mentioned in Eq. 14.

\[
\text{Eq. 14}
\]
Very recently, Miller and Aroyan developed\textsuperscript{136} an interesting, highly enantioselective intramolecular Baylis-Hillman reaction of enone-enoe framework (56), under the influence of 57 as shown in Eq. 15.

Our research group\textsuperscript{137} has developed for the first time electrophile induced Baylis-Hillman reaction between pyridine-2-carboxaldehyde and activated alkenes under the influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), which actually involves intramolecular cyclization (Baylis-Hillman reaction) as the key step, leading to the formation of indolizine frameworks in one-pot operation. Representative examples are mentioned in Scheme 21.

**Scheme 21**
Keck and co-workers\textsuperscript{138} described an intramolecular Baylis-Hillman reaction of $\alpha$, $\beta$-unsaturated ester /thioester aldehyde systems (58) under the influence of DMAP (14), or DMAP.HCl in EtOH as a solvent (Eq. 16).

\begin{equation}
\text{OHC-} \text{SEtOHC} \xrightarrow{\text{DMAP (14) (1 eq) or DMAP-HCl (0.25 eq)}} \text{EtOH, 78\textdegree C, 1 h}} \rightarrow \text{EtOH, 78\textdegree C, 1 h}} \rightarrow \text{88\%} \tag{Eq. 16}
\end{equation}

Stockman and Roe\textsuperscript{139} described the total synthesis of anatoxin & homoanatoxin, \textit{via} interesting intramolecular Baylis-Hillman reaction of the substrate (59) as the key step following the reaction sequence as shown in Scheme 22.

\begin{equation}
\text{Scheme 22}
\end{equation}

\textbf{APPLICATIONS OF THE BAYLIS-HILLMAN ADDUCTS}

The Baylis-Hillman adducts have been employed in various organic transformation methodologies as they contain a minimum of three functional groups in close proximity.
Thus Baylis-Hillman adducts /acetates have been conveniently utilized as substrates for various organic reactions such as Diels-Alder reaction, Heck reaction, Friedel-Crafts reaction, indium mediated reactions, photochemical reactions. Also some of these methodologies have successfully applied for synthesis of various biologically active molecules. Some of the these developments are presented in Scheme 23 and 24.

**Scheme 23**
Hoffman and co-workers\textsuperscript{156} reported an interesting synthesis of functionalized 6,8-dioxabicyclo[3.2.1]octane derivatives (60) (framework present in a number of pheromones) \textit{via} Diels-Alder dimerization of Baylis-Hillman adducts, $\alpha$-methylene-$\beta$-hydroxyalkanones (Scheme 25).

**Scheme 25**

\begin{align*}
\text{R} = \text{H, Me, Et, PhCH}_2\text{CH}_2, \text{tBu}
\end{align*}
Our research group\textsuperscript{114} has reported an interesting synthesis of enantiomerically enriched mikanecic acid (62), a terpene dicarboxylic acid having vinylic quarternary chiral center, from the Baylis-Hillman adduct (61) following the reaction sequence as described in Scheme 26.

\textbf{Scheme 26}

\begin{center}
\begin{tabular}{c}
\includegraphics[width=\textwidth]{scheme26.png}
\end{tabular}
\end{center}

\begin{center}
\textbf{mikanecic acid} 74\% ee
\end{center}

(92\% ee) (hydrolysis after crystalization of the diester)

A simple and convenient methodology for synthesis of (E)-2-arylideneindan-1-ones via inter and intramolecular Friedel-Crafts reactions of the Baylis-Hillman adducts, obtained from tert-butyl acrylate and various aromatic aldehydes, according to Scheme 27 has been reported by our research group\textsuperscript{157}.
Scheme 27

Drewes and co-workers 24 described an efficient synthesis of recemic integerrineic acid (63) from the acetates of the Baylis-Hillman adduct (ethyl 3-acetoxy-2-methylenebutanoate) following the reaction sequence as shown in Scheme 28.

Scheme 28

A simple and convenient synthesis of (E)-α-methylcinnamic acid derivatives via the nucleophilic addition of hydride ion from sodium borohydride, to the Baylis-Hillman acetates followed by hydrolysis, and crystallization (Scheme 29) has been developed by our research group.158 This strategy has been extended to the synthesis of the precursors of the hypolipidemic active agent (64).
Hatakeyama and co-workers\textsuperscript{159} synthesized a potent immunosuppressive agent (\textendash\textendash)Mycestericin \textit{E} (66) using the Baylis-Hillman adduct derived via the asymmetric Baylis-Hillman coupling of 1,1,1,3,3,3-hexafluoroisopropyl acrylate as an activated alkene with aldehydes (65) using the chiral catalyst (49) according to Scheme 30.
Very recently, our research group\textsuperscript{160,161} described an expedient facile one-pot synthesis of 2-methylenealkanoates and alkanenitriles from the Baylis–Hillman bromides in aqueous media via the nucleophilic addition of hydride ion from \( \text{NaBH}_4 \) to in situ generated DABCO Baylis-Hillman allyl bromide salt in aqueous media (Scheme 31). This strategy has been extended for synthesis of two hypoglycemic agents methyl palmoxirate (67), and etomoxir (68).

\textbf{Scheme 31}

\[
\begin{align*}
\text{H} & \quad \text{COOR}^1 \quad \text{Br} \\
\text{H} & \quad \text{COOR}^1 \quad \text{Br} \\
\end{align*}
\]

\[
\text{H}_2\text{O}/\text{THF} \ (1/1) \ 	ext{rt, 15 min} \quad \text{NaBH}_4 \ 	ext{rt, 15 min} \quad \text{74-90%}
\]

\[
\begin{align*}
R & = \text{Ph, 4-ClPh, 4-MePh, 2-ClPh, 2-MePh, Pent, tridecy}l \\
R & = \text{Ph, 4-ClPh, 4-MePh, 2-ClPh, 2-MePh, Pent, tridecy}l \\
R^1 & = \text{Me} \\
R & = \text{C}_{13}H_{27} \\
R^1 & = \text{Et} \\
\text{ClCH}_2\text{CH}_2\text{Cl} \ 	ext{reflux} \\
\text{ClCH}_2\text{CH}_2\text{Cl} \ 	ext{reflux} \\
\end{align*}
\]

\text{methyl palmoxirate (67)}

\text{etomoxir (68)}
Our research group\textsuperscript{162} conveniently, transformed the Baylis-Hillman bromides into 3-arylidene(alkylidene)chroman-4-ones following the reaction sequence as described in Scheme 32. This strategy has been conveniently extended to the synthesis of representative natural products such as antifungal agent (69), bonducellin methyl ether (70) (Scheme 32).

**Scheme 32**

\[
\begin{align*}
\text{R} & \quad \text{OMe} \\
& \quad \text{OPh}
\end{align*}
\]

acetone, reflux, 3 h

\[
\begin{align*}
\text{R} & \quad \text{OMe} \\
& \quad \text{OPh}
\end{align*}
\]

KOH, H\textsubscript{2}O, rt, 14 h

\[
\begin{align*}
\text{R} & \quad \text{OH} \\
& \quad \text{OPh}
\end{align*}
\]

K\textsubscript{2}CO\textsubscript{3}

acetone, reflux, 1 h

\[
\begin{align*}
\text{R} & \quad \text{O} \\
& \quad \text{O}
\end{align*}
\]

80-94%

Our research group\textsuperscript{163} developed the simple and convenient synthesis of functionalized [4.4.4] and [4.4.3] propellano-bislactones (71) from the Baylis-Hillman acetates following the reaction sequence as shown in Scheme 33 (involving bisalkylation, hydrolysis and laetonization steps). One example is presented in Scheme 33.
Kim and co-workers have reported a facile synthesis of dihydropyrido[2,1-a]isoindoles 72 and 73 (via Heck reaction and radical cyclization as the key steps respectively) from the Baylis-Hillman acetates following the reaction sequence as shown in Scheme 34.
Recently, Batra and co-workers\textsuperscript{166} reported the synthesis of 1\textit{H}-and 3\textit{H}-1-benzazepine derivatives (74, 75) and quinoline derivatives (76) from the Baylis-Hillman acetates according to Scheme 35.

\textbf{Scheme 35}

![Scheme 35](image)

The Baylis-Hillman acetates were transformed into (\textit{E})-arylidine-tetralone-spiro-glutarimides (77) and di (\textit{E})-arylidine-spiro-bisglutarimides (78) by our research group\textsuperscript{167} according to reaction sequence as shown in Scheme 36.

\textbf{Scheme 36}

![Scheme 36](image)
Recently, Selvakumar and co-workers \(^{168}\) developed a facile methodology for synthesis of butenolides from the Baylis-Hillman adducts involving RCM as the key step using the Grubbs catalyst \((79)\) according to Scheme 37. They have successfully applied this methodology for synthesis of phaseolinic acid \((80)\).

**Scheme 37**

The Baylis-Hillman acetates have been conveniently transformed into tri-/tetracyclic framework containing azocine skeleton following the reaction sequence as described by our research group \(^{169}\) (Scheme 38).

**Scheme 38**
Recently, Shanmugam and co-workers\textsuperscript{170} reported the synthesis of functionalized 3-spiropyrrolizidineoxindoles (81) and 3-spiropyrrolidineoxindoles (82) from the Baylis-Hillman adducts, derived from isatin and heteroaldehydes, involving [3+2] cycloaddition between azomethine ylides and Baylis-Hillman adducts as the key step (Scheme 39).

**Scheme 39**

![Scheme 39](image)

Very recently, our research group\textsuperscript{171} has developed a facile synthesis of functionalized dihydropyrazole derivatives, from the Baylis-Hillman bromides in an operationally simple one-pot procedure via [3+2] annulation strategy, following the reaction sequence as shown in Scheme 40.

**Scheme 40**

![Scheme 40](image)
Recently, Ryu and co-workers\textsuperscript{172} reported an interesting coupling of $\alpha$, $\beta$-acetylinic esters with aldehydes under the influence of BF$_3$.OEt$_2$ and TMS-I to provide $\beta$-iodo Baylis-Hillman adducts and successfully utilized this methodology for synthesis of naturally occurring secokotomolide (83) (Scheme 41).

**Scheme 41**

![Scheme 41 diagram]

Ethyl (2-bromomethyl)acrylate was transformed into bicyclo[3.2.1]nonane derivative via the treatment with 1, 3-dinitroalkanes in the presence of DBU by Ballini and co-workers.\textsuperscript{173} This reaction is believed to proceed through domino process involving double alkylation and double Michael addition reactions (Eq. 17).
MECHANISAM

Although the Baylis-Hillman reaction has seen tremendous progress in terms of its variations and applications its mechanism has been not bee completely understood because of the large number variations involved in all the three essential components. However, the most generally accepted mechanism\textsuperscript{174-176} of this fascinating reaction is presented in the Scheme 42 by taking methyl vinyl ketone (as an activated alkene), and benzaldehyde (as an electrophile), under the catalytical influence of DABCO (as a catalyst) as a model case.

The first step of this Baylis-Hillman reaction is believed to involve the Michael type addition of DABCO, on to the activated alkene (methyl vinyl ketone) to generate zwitterionic enolate \( \text{A} \), which then might add onto electrophile (benzaldehyde), \emph{via} an aldol fashion leading to the formation of zwitterionic enolate \( \text{B} \) (path \( \text{X} \)). This zwitterionic species \( \text{B} \) might undergo proton migration and release the catalyst to provide the desired multi-functional molecules, usually called as the Baylis-Hillman alcohols (adducts). On the other hand if the activated alkene is more reactive such as methyl vinyl ketone, then there is a possibility of itself act as an electrophile leading to the formation of Micheal type dimer (Path \( \text{Y} \)) as a minor product as indicated in Scheme 42.
Scheme 42

Path Y

Path X

Path X

Path Y

minor

major