Synthetic organic chemistry is one of the most rapidly developing, expanding and successful branches of science. Construction of carbon-carbon bonds and carbon-hetero atom bonds is one of the most fundamental reactions in synthetic organic chemistry and hence represents a forefront of research in organic chemistry. More recently, the concepts of atom economy, selective (both stereo- and regio-) transformations and catalytic processes have become primary requirements for the development of synthetic organic chemistry to be one of the leading scientific disciplines. During the last fifteen years, synthetic organic chemistry has seen enormous growth, not only in terms of development of new methodologies for construction of carbon-carbon and carbon-hetero atom bonds but also in terms of development of new reagents, catalysts, strategies, transformations and technologies often involving the concepts of atom economy and selectivity. Though the arsenal of synthetic organic chemistry is now very rich in the sense that there are methods available to synthesize any molecule which was once thought to be difficult to prepare, the continuing sophistication in and ever changing scenario of synthetic organic chemistry requires and even demands the continuous evolution of synthetic methods that meet the requirements of atom
economy and very high levels of selectivity. The Baylis-Hillman reaction is one such atom economy reaction, which has been nowadays recognized, as an useful and emerging reaction having enormous synthetic potential as a source for various stereoselective processes.

This thesis deals with our efforts to expand the scope of the Baylis-Hillman reaction as an attractive source for organic transformations and consists of three chapters, i.e. 1) Introduction, 2) Objectives, Results and Discussion and 3) Experimental. The first chapter, introduction, describes briefly the literature reports on recent developments and applications of the Baylis-Hillman reaction.

The second chapter deals with the objectives, results and discussion. The Baylis-Hillman reaction is a catalytic process, essentially involving three components, leading to the construction of carbon-carbon bond between the a-position of activated alkene and carbon electrophile under the catalytic influence of a tertiary amine particularly DABCO, thus producing synthetically useful multifunctional molecules. During the last fifteen years, our research group has been actively involved in the development of this fascinating reaction as an useful synthetic tool in organic chemistry and has in fact contributed significantly in this direction.

With a view to further expand the scope of Baylis-Hillman chemistry in organic
synthesis, we have undertaken this research program with the following objectives.

1. Development of simple and convenient methodology for stereoselective synthesis of \((E)\)-\(\alpha\)-cyanocinnamyl alcohols and \((E)\)-\(\alpha\)-cyanocinnamic aldehydes from \(3\text{-}aryl\text{-}3\text{-}hydroxy\text{-}2\text{-}methylenepropanenitriles\), the Baylis-Hillman adducts derived from acrylonitrile, in aqueous media.

2. Development of simple methodology for synthesis of \(2\text{-}methylenealkanoates\) and alkanenitriles \textit{via} the regioselective nucleophilic \((\text{SN}2')\) addition of hydride ion from \(\text{NaBH}_4\) to \((2Z)\)-2-(bromomethyl)alk-2-enoates and 2-(bromomethyl)-alk-2-ene-nitriles, the allyl halides derived from Baylis-Hillman adducts, respectively in the presence of DABCO in environment friendly aqueous media.

3. Application of this methodology (objective 2) for the synthesis of methyl \(2\text{-}tetradecyloxirane\text{-}2\text{-}carboxylate\) (methyl palmoxirate) and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane\text{-}2\text{-}carboxylate (Etomoxir), the important hypoglycemic agents.

4. Application of methyl \((2Z)\)-2-(bromomethyl)alk-2-enoates and \((3Z)\)-3-(chloromethyl)alk-3-en-2-ones as electrophiles in the Baylis-Hillman reaction with
acrylonitrile in the presence of DABCO leading to synthesis of functionalized 1,4-pentadienes.

5. Synthesis of methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates and methyl 3-aryl-2-methylene-3-phenoxypropanoates via the nucleophilic addition (SN2’) of prop-2-yn-1-ol (propargyl alcohol) and phenol respectively to methyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates in the presence of triethylamine.

6. Enantioselective synthesis of (-)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates via chiral leaving group strategy.

Stereoselective synthesis of (E)-α-cyanocinnamyl alcohols and (E)-α-cyanocinnamic aldehydes

Development of simple and convenient methodology for stereoselective synthesis of (E)-α-cyanocinnamyl alcohols and (E)-α-cyanocinnamic aldehydes has been an important endeavor in synthetic organic chemistry because these molecules constitute an important class of synthons for synthesis of various biologically active and heterocyclic molecules. In continuation of our studies on the development of the Baylis-Hillman reaction as a novel source for stereoselective processes, we have developed an aqueous sulfuric acid (20%) mediated
**isomerization** of the Baylis-Hillman adducts, *i.e.* 3-aryl-3-hydroxy-2-methylene-propanenitriles (48a-g) derived from an activated alkene, acrylonitrile, thus providing simple and efficient methodology for synthesis of (E)-α-cyanocinnamyl alcohols (49a-g) in good yields (eq. 29 & 30). Subsequent oxidation of these (E)-α-cyanocinnamyl alcohols (49a-g) with *pyridinium* chlorochromate (PCC) provided the desired **stereochemically pure** (E)-α-cyanocinnamic aldehydes (50a-g) (eq. 33 & 34). This methodology represents an efficient alternative route to Knoevenagel condensation reaction.

**Simple synthesis of 2-methylenekanoates and alkanenitriles**

Development of simple and convenient methodology for the synthesis of 2-methylenekanoates and alkanenitriles is an interesting problem in organic synthesis because of their versatile applications as synthons in the synthesis of various biologically active molecules and liquid crystalline polymers. For example, methyl 2-tetradecyloxirane-2-carboxylate (methyl *paloxirate*) (51) and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir) (52) have been found to be potent inhibitors of the fatty acid oxidation and oral **hypoglycemic** agents in mammals including human beings. In connection with our ongoing research program in environment friendly chemistry and sodium borohydride chemistry, we have planned to develop a general and convenient
methodology for the synthesis of pure 2-methylenealkanoates (55a-g) via the regioselective nucleophilic (S_N2') addition of hydride ion from sodium borohydride to methyl (2Z)-2-(bromomethyl)alk-2-enoates (54a-g), the allyl bromides obtained from the corresponding Baylis-Hillman adducts i.e. methyl 3-hydroxy-2-methylenealkanoates (53a-g), in environment friendly aqueous media. Thus, treatment of methyl (2Z)-2-(bromomethyl)alk-2-enoates (54a-g) with DABCO in the presence of H_2O/THF at room temperature followed by the treatment with NaBH_4 at room temperature provided the desired pure 2-methylenealkanoates (55a-g) in high yields (Schemes 42 & 43).

With a view to understanding the generality of this methodology, we have also transformed 2-(bromomethyl)alk-2-enenitriles (57a-c, 58-61), the allyl bromides obtained from the corresponding Baylis-Hillman adducts (48a-c, e, h-j), into 2-methylenealkanenitriles (63a-g) in high yields (Schemes 44 & 45).

**Synthesis of hypoglycemic agents**

To prove the efficacy of this methodology we have undertaken the synthesis of two representative hypoglycemic agents methyl 2-tetradecyloxirane-2-carboxylate (methyl palmoxirate) (51) and ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir) (52).
Synthesis of methyl 2-tetradecyloxirane-2-carboxylate (methyl palmoxirate)

We have synthesized methyl 2-tetradecyloxirane-2-carboxylate (methyl palmoxirate) (51) via the reaction of methyl 2-methylenehexadecanoate (55g) with \textit{m}-CPBA in 1,2-dichloroethane at reflux temperature (eq. 40).

Synthesis of ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir)

We have next synthesized ethyl 2-[6-(4-chlorophenoxy)hexyl]oxirane-2-carboxylate (Etomoxir) (52) starting from 4-chlorophenol via the Baylis-Hillman methodology according to equations 41 & 42 and Schemes 46 & 47.

Application of (2Z)-2-(bromomethyl)alk-2-enoates and (3Z)-3-(chloromethyl)alk-3-en-2-ones as electrophiles in the Baylis-Hillman reaction: A novel synthesis of functionalized 1,4-pentadienes

Though various electrophiles such as aldehydes, aldmines, \textit{\alpha}-keto esters, fluorinated ketones, \textit{non-enolizable} 1,2-diketones, acrylonitrile, \textit{alkyl} vinyl ketones have been successfully employed in the Baylis-Hillman reaction, application of allyl halides as electrophiles has not been studied so far in the literature. We have therefore undertaken this research program of examining the possible application of allyl halides as electrophiles in the Baylis-Hillman reaction. During our efforts in \textbf{this} study, we directed our attention towards the
application of methyl (2Z)-2-(bromomethyl)alk-2-enoates (54a-e, 73, 74) as electrophiles in the Baylis-Hillman reaction. Accordingly, we have developed a simple methodology for the coupling of acrylonitrile with methyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates (54a-e, 73, 74) in the presence of DABCO at room temperature for 7 days, thus leading to the formation of functionalized 1,4-pentadienes (72a-g) (eq. 43 & 44).

With a view to understanding the generality of this reaction, we have also carried out the coupling of acrylonitrile with (3Z)-4-aryl-3-(chloromethyl)but-3-en-2-ones (75a-c) in the presence of DABCO at room temperature to provide the desired 2-acetyl-3-aryl-4-cyanopenta-1,4-dienes (76a-c) (eq. 46 & 47).

**Synthesis of methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates and methyl 3-aryl-2-methylene-3-phenoxypropanoates**

With a view to expand the scope of the allyl bromides, methyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates (54a-e, 73, 74) in organic synthesis, we have used propargyl alcohol as a nucleophile for addition onto these allyl bromides in SN2' fashion under the influence of triethylamine thus providing a simple methodology for the synthesis of 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates (79a-g) in high yields (eq. 53 & 54).
We have next used phenol as a nucleophile for the addition (Sn2') onto methyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates (54a-e, 73, 74) in the presence of triethylamine to provide the desired methyl 3-aryl-2-methylene-3-phenoxypropanoates (80a-g) in good yields (eq. 55 & 56).

**Enantioselective synthesis of (-)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates via chiral leaving group strategy**

On the basis of above successful results, we envisioned that if we use a chiral tertiary amine in place of triethylamine, which subsequently becomes a chiral leaving group, there might be chiral induction. We have therefore directed our studies towards the enantioselective synthesis of methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates (79) via chiral leaving group strategy. We have thus developed a simple method for enantioselective synthesis of (-)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates (79a-g) in 25-40% enantiomeric excess via the nucleophilic addition (Sn2') of prop-2-yn-1-ol to a representative class of methyl (2Z)-3-aryl-2-(bromomethyl)prop-2-enoates (54a-e, 73, 74) in the presence of quinidine (Schemes 59 & 60).

The third chapter deals with the experimental procedures in detail, IR, 1H NMR, 13C NMR, mass spectral data, elemental analyses and physical constants (bp, mp and optical rotations).