Morita-Baylis-Hillman reaction: scope and significance.

Yagyesh Kapoor, Kapil Kumar*

School of Pharmaceutical Sciences, Apeejay Stya University, Sohna-Palwal Road, Sohna, Gurgaon, Haryana, India

Abstract

The MBH (Morita-Baylis-Hillman) reaction has received significant and growing interest since it combines two essential necessities, namely, functional groups generation and atom economy. Indeed, the MBH reaction and its application have seen an exponential growth since last decade. Since 1990s, moreover research group have initiated work on different arena of this reaction, involving novel catalysts (particularly chiral), the scope of the substrates, understanding the mechanism and various synthetic applications of MBH adducts. The Morita-Baylis-Hillman reaction is known to be dominant tool for the construction of densely functionalized alcohols and isatin derivatives which serve as promising electrophile in this reaction.

Keywords: Morita-Baylis-Hillman reaction, Stereochemical control, Organic synthesis, Catalytic cycle.

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Introduction

The C-C bond formation is one amongst the foremost fundamental reactions in organic chemistry. The development of efficient and selective methods for the construction of carbon-carbon bonds continues to be a challenging and exciting endeavour in synthetic chemistry. Various reactions for the formation of C-C bonds have been discovered and exploited. It has been clearly established that, atom selectivity and economy are the two main criteria on which the development of reaction is dependent. Among the C=C forming reactions, the Morita-Baylis-Hillman (MBH) reaction has become one of the most popular and useful routes, with enormous synthetic utility, potential and promise. The reaction uses simple and small building blocks in a single operation and results either in the formation of complex product or a multifunctional product which becomes a substrate for another complexity-generating reaction. This operationally simple and atom-economic Baylis-Hillman reaction has been proved to be an important synthetic method for the preparation of α-methylene-β-hydroxy-carbonyl or α-methylene-β-amino-carbonyl derivatives in one step from carbonyl compounds and electrophilic alkynes by using a tertiary phosphine or tertiary amine as an organic catalyst [1]. A pioneering report presented by Morita (phosphine catalyzed reaction) in 1968 sets an origin for MBH reaction and, subsequently, Baylis-Hillman described a similar amine catalyzed reaction in 1972. Since the mid-1990s, particularly in last decade, this reaction and its applications have received a remarkable growing interest. MBH offers several advantages that have attributed to its rapid growth:

1. Atom-economic nature.
2. Usually involves a nucleophilic organocatalytic system without the heavy-metal pollution.
3. Mild reaction conditions.
4. The starting materials are commercially available, and the reaction is suitable for large-scale production.
5. MBH adducts are flexible and multifunctional.

The three-step reaction which involves the coupling of an electron deficient olefin acting as a Michael acceptor with an electrophile in presence of a strong lewis base (a tertiary amine) creates a new chiral center accompanied with the formation of a new carbon-carbon bond. The Baylis-Hillman reaction is known to be powerful tool for the construction of densely functionalized alcohols and isatins derivatives could serve as promising electrophile in this reaction. The three components Baylis-Hillman reaction has recently came out from a relative insignificance to an importance as a carbon-carbon bond forming reaction that furnishes product from a relative simple starting material of high functional group density. The reaction has undergone significant progress recently in the areas of asymmetric catalysis, mechanistic studies, extending the scope of the substrates and shortening reaction time.

Literature Review

Originating from a German patent [2], the reaction first appeared in 1968, when it was disclosed by H. Morita that the reaction of an aldehyde in the presence of tricyclohexylphophine (PCy3) with an activated alkene affords a densely functionalized product. In simple words, the Baylis-Hillman reaction, originating from a German patent may broadly be defined as "A reaction that results in the formation of a carbon-carbon bond between the α-position of activated alkenes and carbon electrophiles containing electron-deficient sp^2 carbon atom under the influence of a suitable catalyst, particularly a tertiary amine, producing multifunctional molecules". However, this reaction earned its name from Hillman and Baylis, who reported that the reaction of aldehyde with activated alkenes including amides, esters, ketones and nitriles in the presence of tertiary bicyclic amines furnished multifunctional products. The reaction has attracted much attention due to its total atom economy, wide functional group tolerance, mild reaction conditions, ability to generate densely functionalized alkenes of promising synthetic utility and biological activities [3]. However, the drawbacks associated with the reaction are use of expensive catalysts,

difficult handling, low yields, and most significantly slow reaction rates (particularly those involving acrylates). However physical methods like use of microwave irradiation and high pressure, use of highly basic amine, phosphines, hydrogen bonding solvents, ionic salts, lewis salts, enzymatic catalysis, use of polymeric catalysts etc have been tried to accelerate the reaction rates. High speed ball milling (HSBM) was introduced as a novel technique to generate MBH adducts by performing several reactions between methyl acrylates and aryl aldehydes in a reaction time that ranges between 30 mins-1h that uses 1,4-Diazabicyclo [2.2.2] octane (DABCO) as catalyst (Figure 1). The ball-bearing when attains a high speed it generates a force enough to yield an amorphous mixture of reagents that ultimately facilitates the chemical reactions, due to this ability high speed ball milling was employed as an alternative solvent-free method to make such amorphous mixtures. Under neat conditions the technique serves to be as one of the fastest option to produce yields ranging from 28 to 98% when applied to MBH reactions. The Morita-Baylis-Hillman reaction is one of the very few reactions wherein atom economy is perfectly preserved [4] in addition to generating a new carbon-carbon bond between an aldehyde and α-carbon of an electron deficient olefin. Unfortunately, however the applications and the usefulness of reaction in several cases are hampered by low yields, high catalyst loading, slow rates, (sometimes upto a weak for less than 50% conversion) [5], unavailability of a base compatible or a universal solvent system with all activated olefins and electrophiles. Also the reaction is generally inert to enones; α, β-substituted aldehydes and hindered aldehydes.

The carbon-carbon bond forming MBH reaction is an emerging outcome with all the basic properties that an efficient synthetic method should have i.e., it is selective (chemo, regio, diastereo and enantio), economical in atom and count, requires mild conditions and provides synthetically useful multifunctional molecules. In 1988, this fascinating reaction was reviewed by Roos and Drewes, when the reaction was still in its infancy. Due to its ability to provide versatile molecules with a stereogenic center and minimum of three functional groups (i.e., an electron withdrawing group, hydroxyl and alkene) the Baylis-Hillman reaction has been increasingly drawing the attention of synthetic organic chemists. The Baylis-Hillman adducts may therefore be expected to undergo a variety of organic transformations involving regio and stereochemical control. Several successful examples have already been reported and studies are being directed towards utilizing these fascinating molecules in organic synthesis. Moreover, to examine the enantio- and diastereoselectivites of various methodologies the multifunctionality of these adducts makes them attractive substrates.

Mechanistic Approach

Carbon-carbon bond formation is one of the most fundamental reactions in organic chemistry. The development of efficient and selective methods for the construction of carbon-carbon bonds has been and continues to be a challenging and exciting endeavour in organic synthesis. Due to the ability to generate synthetically useful chiral building blocks (i.e., allylic alcohols) without generating by-products, the Baylis–Hillman reaction has become a superior carbon–carbon bond forming reaction. Extensive studies are being carried out to investigate the mechanistic details of the reaction by isolating the intermediates of the reaction. The mechanism is proposed to be consisting of 3 Steps:

1. Elimination of the catalyst and proton transfer.

2. Michael addition of the nucleophilic trigger catalyst to the activated alkene.

3. Quenching the Zwitterionic adduct with an electrophile.

Invariably, it has been concluded by all the studies that the Baylis-Hillman reaction is the outcome of an addition-elimination sequence involving activated alkene, electrophile and tertiary amine. Initially, the mechanistic details are proposed by Isaacs and Hill, and later based on the kinetic isotope effect (KIE), Pressure dependence and rate data are refined by others. Since the electrophillic quench is RDS, rate enhancement can be achieved by activating the aldehyde or by stabilizing the Zwitterion (Figure 2).

Earlier concept

The mechanism [6] initially proposed by Hillman and Issacs and later refined by others [7], was based on the three factors and involves three steps (Figure 3), which include a sequence of aldol reaction; elimination and Michael addition. The catalytic cycle initiates with the conjugate Michael addition to α, β-unsaturated carbonyl system (2) of a Lewis basic (1) catalyst (STEP 1).

The zwitter ionic intermediate [8] (3) as produced by the reaction has enhanced nucleophilic activity at C-2 due to the nucleophile action. The aldehyde (4) and the generated intermediate (3) then reacts (STEP-2), leading to dipolar intermediate formation (5). After prototropic rearrangement new intermediate (6) forms (STEP- 3) that in the presence of a Lewis base suffers either E_1cb or E_2 elimination to produce the desired Morita-Baylis-Hillman (7) adduct (STEP-4).

Based on a kinetic isotope effect of 1.03 ± 1 for the α-position of acrylonitrile Hill and Isaac concluded that no α-proton cleavage occurred in a series of MBH reactions, thus indicating step II

R = Br, OMe , CL, H , NO_2

Figure 1. *Generation of MBH adducts.*

(addition of enolate to the aldehyde) to be the rate determining step. The proposed [9] key intermediate (6) in step III from the catalytic cycle was isolated and characterized. It can be deduced on the basis of mechanistic proposal, that using protic additives the reaction could be accelerated due to the aldehyde activation.

The Morita-Baylis–Hillman reaction mechanism has recently been re-evaluated [10] and highlighted the significance of proton transfer prior to amine elimination. Unlike the earlier cases where the mechanistic details were more or less based on simply theoretical grounds, now various research groups have been engaged in the isolation and characterization of the reaction intermediates and related kinetic isotopic studies. Such detailed and comprehensive studies have not only helped in the establishment of mechanistic details of the classic reaction but also assisted in discovery of various variants of the reaction. Originally, though pyrrocoline, quinuclidine and DABCO are used as catalysts in Baylis and Hillman reaction, other tertiary amines and phosphines have also been tried. Likewise, the Baylis-Hillman reaction includes a range of aldehydes such as aliphatic, aromatic, hetero aromatic, α, β-unsaturated aldehydes, paraformaldehyde (or formalin) and functionalized aldehydes which have been employed as electrophiles. Thus the reaction promises a vast possibility of substrates, reagents, catalysts and conditions to be exploited [11] various computational studies have been carried out to investigate the mechanistic details of the Baylis-Hillman reaction.

Two theories have come forward in this direction, one is propounded by McQuade et al. and the other one is by Aggarwal et al. The former one discusses the reaction mechanism in absence of the proton donor and the latter in presence of proton donor like alcohol. Hydrogen transfer was considered to be the rate limiting step, and C-C bond forming should not be rate-limiting, except for some imines or aliphatic aldehydes as confirmed by both theoretical studies. These results [12-14] suggested that, in addition to that of the addition to aldehydes the stereocontrol of the proton transfer step is required in the design of asymmetric versions of Morita-Baylis-Hillman reaction.

Hemiacetal intermediate

Focusing on the PTS (proton transfer step), MBH mechanism has been re-evaluated using both theoretical studies and kinetics. In the absence of protic solvent relative to aldehyde the MBH reaction as determined by McQuade [15] et al. is second order and first order in acrylates and DABCO showing a significant kinetic isotopic effect (In DMSO, KIE: k_H/k_D=5.2 ± 0.6). Interestingly, the KIE were found to be greater than 2 regardless of the used solvents (THF, DMF, $CHCl_3$, MeCN), indicating the proton abstraction relevance on the rate-determining step (RDS). A new mechanism which involves a hemiacetal intermediate has been proposed (Figure 4).

Six membered intermediate

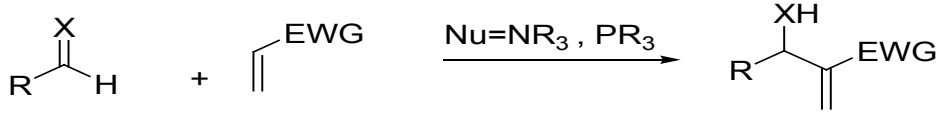
Furthermore, based on kinetic studies Aggarwal [16] proposed that only at the initial (≤ 20% of conversion) stage in relation to the aldehyde, the reaction kinetics is second order afterward becomes autocatalytic. Aggarwal [9] proposed that the MBH adduct may act as a proton donor and therefore assists the elimination step via a six-membered intermediate. Aggarwal et al. [17] suggested that, the proton transfer from carbon to oxygen was influenced by the presence of alcohol in the reaction. Moreover, intramolecular proton transfer transition state was also stabilized (Figure 5).

In these MBH processes, in absence of an added electrophile, the activated alkenes such as vinyl ketones, acrylonitrile, acrylic esters *etc.* they themselves act as electrophiles. It was in fact observed that under the catalytic influence of DABCO vinyl ketones and acrylonitrile undergo Michael type dimerization to provide corresponding dimers (Figure 6).

Dual nature and stereochemistry of MBH reactions

This reaction results in the formation of *α*-methylene *β*-amino carbonyl compound and in particular, of *α*-methylene *β*-amino ester when an acrylate is employed as a Michael acceptor. In the synthesis of various valuable compounds such as amino acid analogues, *β*-lactams, cinnamic acid derivatives, peptides and other nitrogen heterocycles the *α*-methylene *β*-amino esters are highly useful. Thus, the preparation of the starting materials for the synthesis of these compounds considers Morita–Baylis–Hillman reaction as an important method. This successful approach has been used for synthetic design of various natural products and other compounds. The major disadvantages of this important synthetic reaction are long reaction times, difficult handling, expensive catalysts, the slow rate, low yields and stereoselectivity of the reaction. Long reaction time is considered to be the most important as; typically to obtain acceptable product yields it has been shown to take days to weeks. To improve the enantioselectivity, shorten the reaction times and increase the yields the usefulness of this reaction has encouraged researchers to employ different alternatives. Several combinations of the three essential components, within this scenario for MBH reaction, i.e., electrophile, catalyst and activated alkene as well as the cooperative effect of different reaction conditions such as temperature, ultrasound, high pressure and hydrogen bonding additives such as phenols, water, ionic liquids, alcohols and have been investigated.

This fundamental carbon-carbon bond forming reaction incorporates immense flexibility in terms of reaction conditions, use of catalysts, substrates etc. Likewise, the mechanism of the



X= O, NCOR, NSO_2Ph, NTS
EWG= COR, CN, COOR, CHO, SO_2Ph, SO_3Ph
R= alkyl, heteroalkyl, heteroialkyl

Figure 2. *General representation of Morita-Baylis-Hillman reaction.*

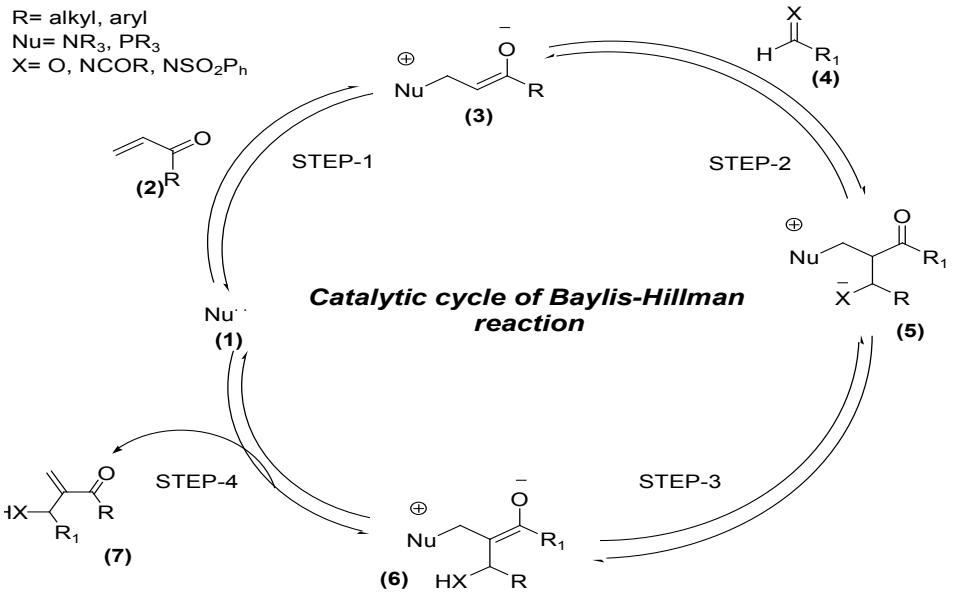


Figure 3. *General representation of Baylis-Hillman catalytic cycle.*

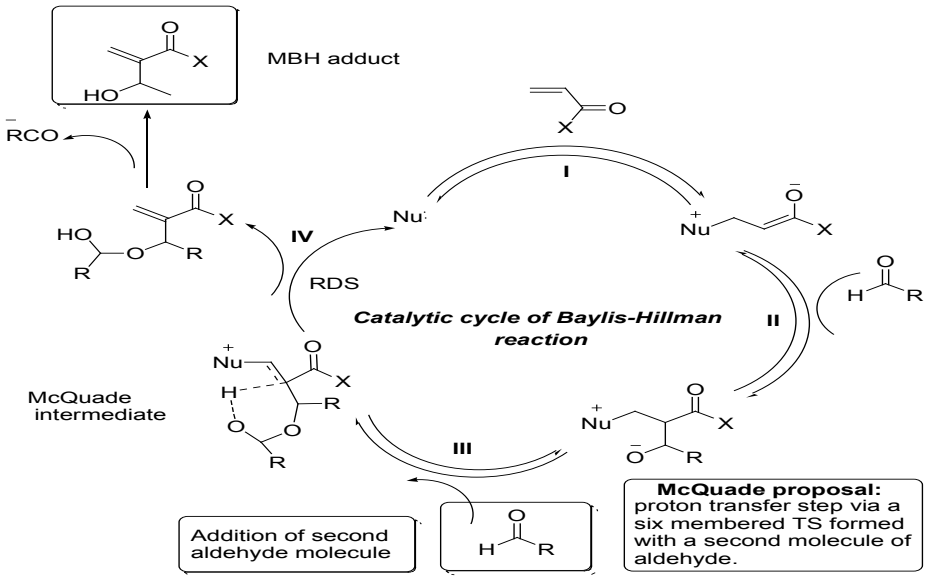


Figure 4. *Hemiacetal intermediate mechanism as proposed by McQuade.*

reaction has been studied numerous times by different research groups to further explore the reaction. Unlike previous attempts, now various analytical techniques are being employed for the uncovering of the details associated with the mechanistic aspects of this classical carbon-carbon bond forming reaction. Accurate computational studies on MBH reaction between benzaldehyde and methyl acrylate, catalyzed by tertiary amine, have revealed that relative to reactants energy for the addition transition state of the amine-acrylate betaine adduct to the aldehyde is much lower, so C−C bond formation should not be rate-limiting, except perhaps for some imines or aliphatic aldehydes.

For the dualist nature [18] of the elimination step of the MBH reaction mechanism investigations are being carried out. Theoretical studies on the MBH reaction mechanism has been stimulated by new kinetic evidence. These studies suggested that step IV can occur via two pathways:

- As proposed by McQuade in the absence of a proton source, second molecule of aldehyde assists elimination.
- As proposed by Aggarwal in presence of a proton source such as alcohol, a new intermediate assists elimination. Aggarwal's proposal agrees the characterization and interception of a proton source participation in the elimination step by assisting the removal of the base. The complex equilibrations occurring during MBH reactions get exemplifies by the "fishing" and structural characterization of these key intermediates (Figures 7 and 8).

Great discrepancies could result in the yields of the MBH reactions due to the differences in the accessibility to the β-position of the Michael acceptors. The stereochemistry effect of Michael acceptors involved in intramolecular MBH reactions catalyzed as reaction substrates by using isomerically pure *E* and *Z* ω-formyl α, β-unsaturated carbonyl compounds and PPh_3 has been studied. The same product was obtained in all studied cases using both isomers. However, 2–8 times higher yield of the (*Z*)-alkene afforded than the *E* isomer. The results were rationalized on the basis of steric hindrance [19].

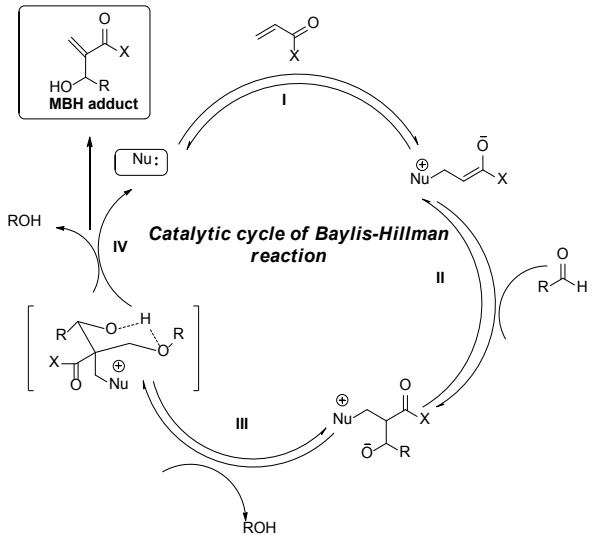


Figure 5. *Mechanism of Baylis-Hillman catalytic cycle involving a six membered intermediate.*

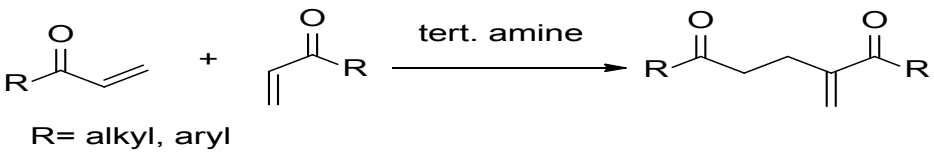


Figure 6. *Dimerization in vinyl ketones.*

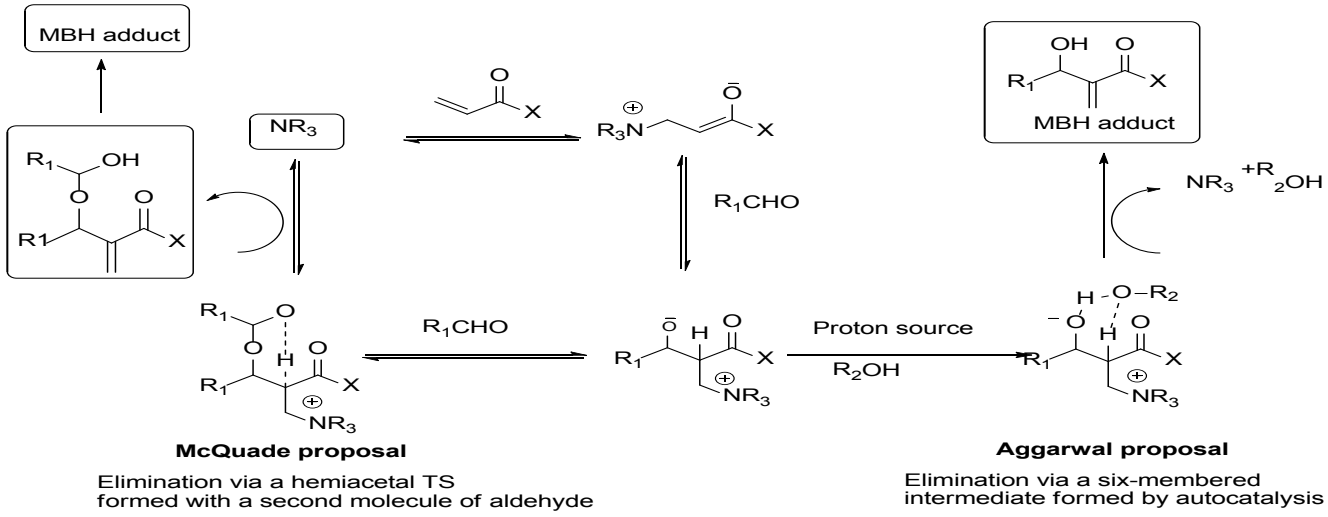


Figure 7. *Dual nature of Baylis-Hillman reaction.*

Scope and Limitations

MBH reaction tolerates a wide range of activated alkenes, electrophiles and catalysts as well. For the generation of heterocycles and other cyclic frameworks the MBH adducts and their derivatives have been extensively utilized. To alkyl halides the reaction is also found to extend as an electrophillic reagent under special reaction conditions. Amine nucleophiles are unsuitable in this variation and trialkyl phosphines are used instead. These phosphines do not react directly with the alkyl halide under the given reaction conditions. In the second step of this reaction he added base promotes the elimination reaction to the enones. The electrophile in the aza-MBH reaction is an imine. Various conjugated nitroalkenes, aromatic, heteroaromatic, have been used as MBH substrates and various activated carbonyl compounds like pyruvic aldehyde, ethylglyoxylate, diethylketomalonate, trifluoromethyl pyruvate as electrophiles. Generally, the Baylis-Hillman coupling of activated alkenes with electrophiles catalyzed by DABC0 [β-hydroxyalkylation of acrylate esters can take several weeks to evolve fully] when carried out at atmospheric pressure and room temperature under neat conditions is a very slow process. For any synthetic process, to be accomplished rapidly and with high yields from both practical and economic point of view, to circumvent this undesirable nature of the Baylis-Hillman

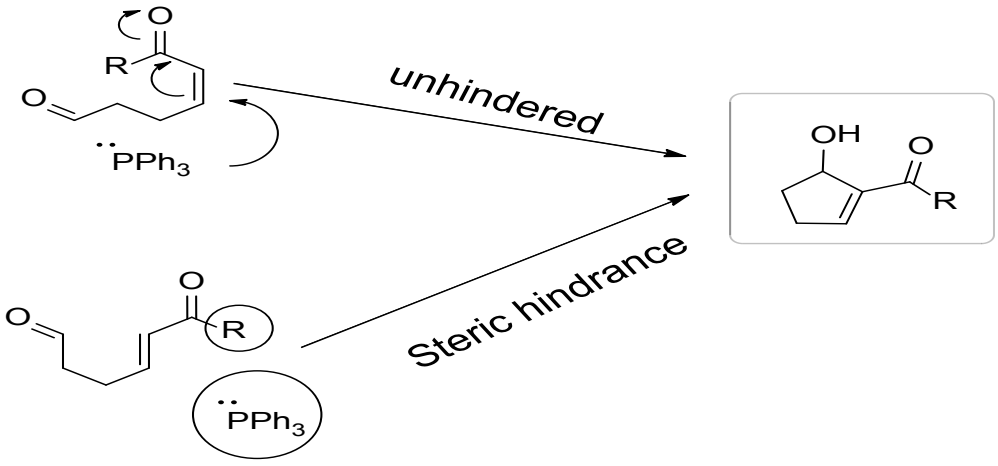


Figure 8. *MBH reaction as influenced by the stereochemistry of the Michael acceptor.*

reaction efforts have been made. Using higher proportions of catalyst has been tried as the first and obvious option on many an occasion. Other drawbacks associated with the reaction are use of expensive catalysts, difficult handling, low yields, and most significantly slow reaction rates (particularly those involving acrylates). However physical methods like use of microwave irradiation and high pressure(the crotonic derivatives; methyl crotonate, crotononitrile; and vinyl sulfoxides that do not undergo Baylis-Hillman reaction at atmospheric pressure, were brought into the scope of the reaction at elevated pressures) [20], use of highly basic amines, phosphines, novel solvent media such as supercritical CO_2, hydrogen bonding solvents, ionic solvents, Lewis salts, enzymatic catalysis [21] (lipases and Serum albumins), use of polymeric catalysts(containing 4-dimethylaminopyridine with phenol groups or alkyl alcohol and soluble polystyrene-supported triphenylphosphane) [22] etc. have been tried to accelerate the reaction rates. Also, high speed ball milling (HSBM) was introduced as a novel technique to generate MBH adducts by performing several reactions between methyl acrylates and aryl aldehydes in a reaction time that ranges between 30 mins to 1h. HSBM was employed as an alternative solvent-free method, and consisted of a ball bearing that was placed inside a vessel and shaken at high speeds. Under neat conditions the technique serves to be as one of the fastest option to produce yields ranging from 28 to 98% when applied to MBH reactions. As no solvents are required, the technique is furthermore an example of green chemistry [23] (Figures 9-12).

The classical Baylis-Hillman reaction usually described as a coupling reaction between α position of an activated alkene and sp^2 electrophillic carbon in a suitable catalyst presence. Including the aza-Morita-Baylis-Hillman reaction, the chalcogenide-mediated Morita-Baylis-Hillman reaction, the $TiCl_4$ mediated version, intramolecular MBH reaction etc. various versions of this reaction have been discovered. For this reaction, recently the asymmetric version and its aza counterpart have also been well exploited. It has been found interestingly [24], that this reaction could also furnish unexpected "abnormal" products such as in double Morita-Baylis-Hillman reaction, sila-Morita-Baylis-Hillman reaction and "abnormal" aza-Morita-Baylis-Hillman reaction and by the conditions to form either the "normal" or the "abnormal" adducts the reaction outcomes can be controlled. Abnormal MBH adducts formation depends on the employed catalytic system and nature of the substrate.

As previously discussed, some serious limitations in carrying out this classical reaction have been faced, e.g., hindered β-substituted derivatives don't react at atmospheric pressures but require higher pressures. Also, at atmospheric pressure ketones are inert. However, activated ketones such as halogenated ketones, α-diketones, α-keto esters and α-keto lactones can generate the corresponding Baylis-Hillman adduct under normal reaction conditions. At atmospheric pressure, vinyl sulfoxides and the crotonic derivatives (crotononitrile and methyl crotonate) and that do not undergo Baylis-Hillman reaction, were brought into the scope of the reaction at elevated pressures. The alkene can also dimerize in the absence of a good electrophile.

Significance of Morita-Baylis-Hillman Reaction

As the Baylis-Hillman reaction provides versatile molecules with a minimum of three functional groups (i.e. hydroxyl, olefin and ester, ketone, nitrile, sulphone or phosphonate, etc.) and a chiral center it has been increasingly drawing the attention of synthetic organic chemists. The Baylis-Hillman adducts may therefore be expected to undergo a variety of organic transformations involving regio, chemo, enantio and stereochemical control. The three component Baylis-Hillman reaction has recently emerged from a relative obscurity to prominence as a carbon-carbon bond forming reaction that furnishes product of high functional group density from relatively simple starting materials. Unfortunately, after it was described in two pioneering reports by Morita (tertiary phosphine catalyzed) and by Baylis, Hillman (tertiary amine catalysed) in 1968 and 1972 respectively it had been ignored for a very long time. For various organic transformations the Baylis-Hillman adducts have become a valuable source and have been transformed into a number of carbocycles and heterocyclic frameworks of medicinal importance. Some of the reasons which have led to an exponential increase in the synthetic utility of this reaction are ease of performance (due to its water execution), the commercial and cheap availability of starting materials, its organocatalytic nature without any heavy metals,

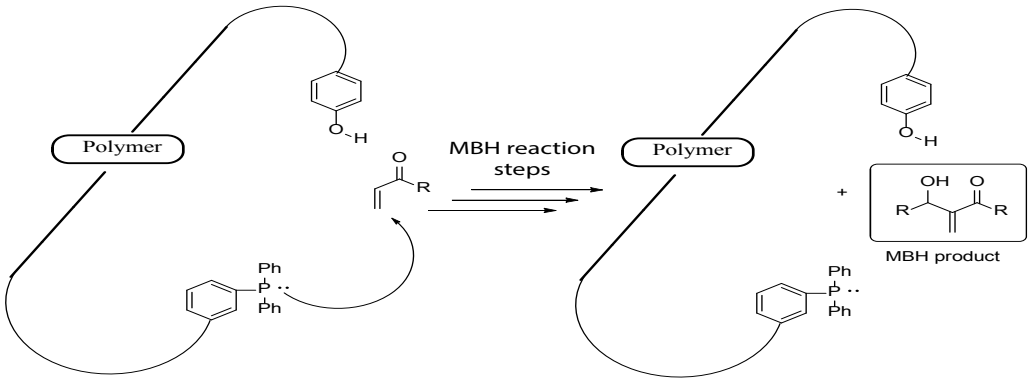


Figure 9. *MBH reaction as catalysed by polymer.*

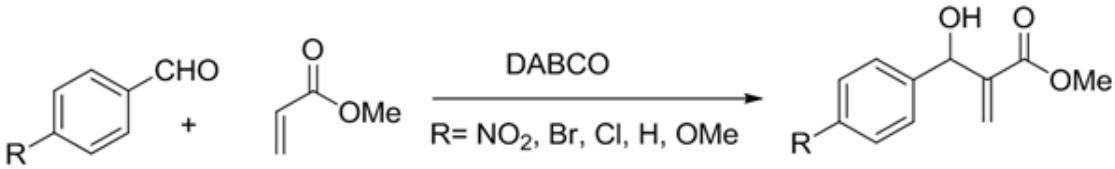


Figure 10. *High speed ball milling assisted MBH reaction.*

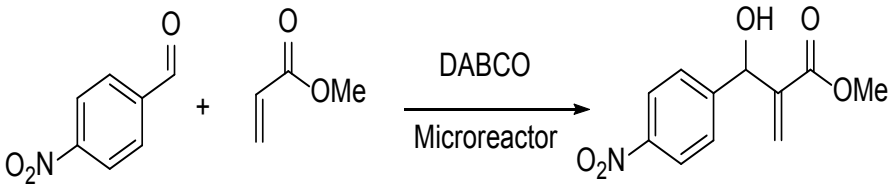


Figure 11. *Microreactor assisted MBH reaction.*

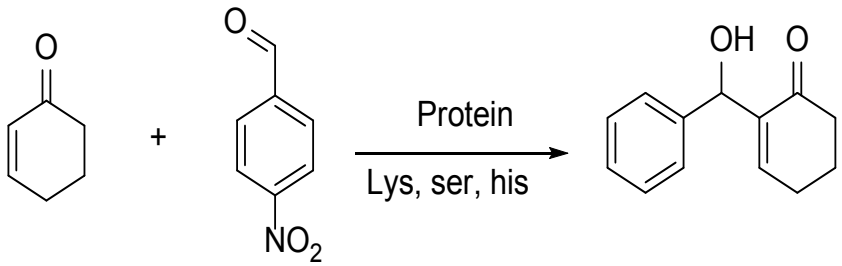


Figure 12. *Enzyme catalysed MBH reaction.*

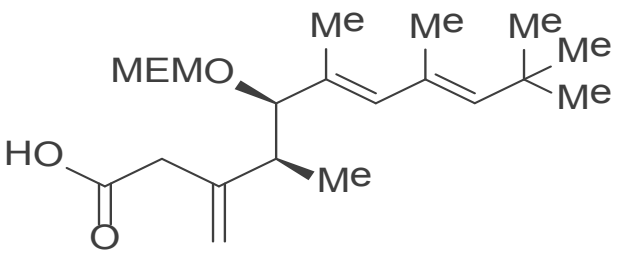


Figure 13. *Structure of antillatoxin.*

use of milder conditions, suitability on large scale, provision of an avenue for the introduction of asymmetry, atom economy, formation of chemospecific functional groups in the product, suitability for simulation on the solid phase as a prelude for combinatorial synthesis and the flexible and multifunctionalised nature of the MBH adducts. The Baylis-Hillman reaction adducts have already been recognized as an excellent source for various stereochemical transformations methodologies. Thus, they have been employed as valuable substrates for various reactions such as Friedal-Crafts reaction, Heck reaction, Diels Alder reaction, radical reactions, cycloaddition reactions, Claisen rearrangement, dihydroxylation, epoxidation etc., thus leading to the discovery of various reactions, pathways and strategies with high level of stereochemical control. In the synthesis of various carbocycles, heterocycles and molecules of various substitution patterns and structural organizations these adduct

have also been used. Using the Baylis-Hillman pathway several biologically active molecules and natural products have also been synthesized. Rauhut–Currier reaction is the lesser known related reaction actually predating the Baylis–Hillman reaction utilising phosphines and not DABCO. As an electrophile if imine is used in the reaction, it is known as the aza-Baylis-Hillman reaction.

The MBH reaction adducts obtained *via* the reaction involving the electrophiles and activated vinylic systems contain a minimum of three chemospecific functional groups that is hydroxyl (or amino), electron withdrawing groups and alkene. Due to the close proximity of these functional groups, they should be in principle useful through appropriate tuning of these groups in various stereoselective transformations. Their derivatives and the functional attributes of the Baylis-Hillman adducts make them appropriate precursors to several complex natural products. Clearly, this reaction has become a standard synthetic methodology in the arsenal of organic chemists as established by the expounding of the synthetic applications of the Baylis-Hillman adducts and their derivatives for the generation of cyclic compounds besides a variety of other products.

For the synthesis of one of the key intermediates of antillatoxin (ATX) a Baylis-Hillman adduct (*Z*)- allyl bromide, that is, methyl-2-(bromomethyl) but-2-enoate, has been used as a starting material, a marine lipopeptide which activates voltage gated sodium channels (Figure 13).

In vitro adducts were shown to have antimalarial activity [25,26] against *P. falciparum* of 3-hydroxy-3-aryl (heteroaryl)-2-methylenepropanenitriles (Baylis-Hillman adducts derived from heteroaryl or aryl aldehydes and acrylonitrile) (Figure 14).

2-Hydroxymethyl-cyclohex-2-enone (Baylis-Hillman adduct obtained from formaldehyde and cyclohex-2-enone) in the preparation of potential antitumor agent has been used, 2- crotonyloxymethyl-2-cyclohexenone (COMC) [27] is an activated prodrug in a process triggered by glutathionyl transferase, the crotonate ester serves as a leaving group. Similarly, asymmetric synthesis of Pregabalin, an adjunct drug with or without secondary generalization in adults for partial seizures, has been developed *via* the Baylis-Hillman methodology and as an anticonvulsant drug used for neuropathic pain (Figure 15).

Synthesis of a stereoselective N-Boc-dolaproine, an amino acid residue of the antineoplastic pentapeptide, dolastatin (complex unit of β-methoxy-γ-amino acid dolaproine) was successfully demonstrated by Almeida and Coelho and is now in Phase II human cancer clinical trials. Its synthesis included a Baylis-Hillman reaction between methyl acrylate and N-Boc-prolinol, followed by hydrolysis of the ester functional group and a diastereoselective double-bond hydrogenation (Figure 16). They subjected the intermediate to cyclization reaction to yield a lactam derivative in order to establish the configuration.

Later, they significantly utilized the adduct (Baylis-Hillman) of methyl acrylate and 2-fluorobenzaldehyde, as a starting material for the straightforward, enantioselective synthesis of (*R*)2-ethyl-2,3-dihydrofuran-2-carboxylic acid, the direct precursor of (*R*)-efaroxan, which is used for the treatment of migraine, neurodegenerative diseases (Alzheimer's or Parkinson's disease) and non-insulin dependent type II diabetes mellitus, T2DM (Figure 17).

Involving the MBH reaction as one of the key steps total synthesis of a 16-membered macrolide antibiotic i.e., natural (+)-tubelactomicin A comprises of total 54 steps from methyl (*R*)-lactate has been successfully achieved (Figure 18).

For the synthesis of luminacin D (the strongest member of

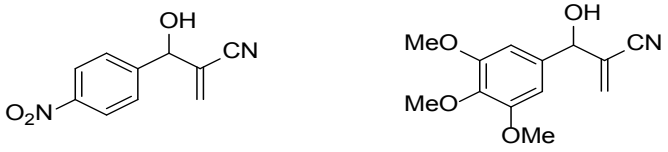


Figure 14. *Structure of MBH adducts with antimalarial activity.*

Figure 15. *Structure of COMC and Pregabalin.*

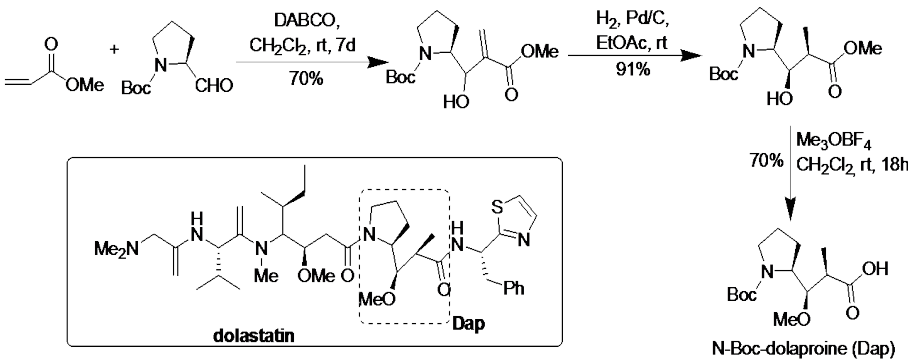


Figure 16. *Chiral MBH reaction.*

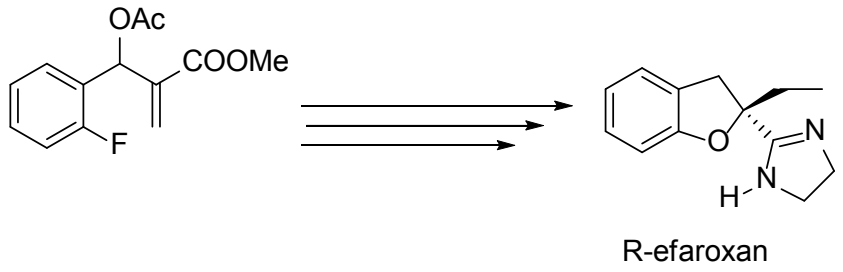


Figure 17. *Structure of R-efaroxan.*

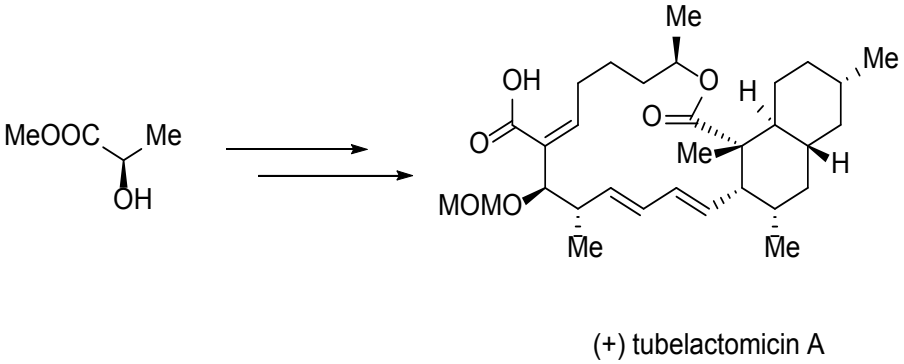


Figure 18. *Structure of tubelactomicin A.*

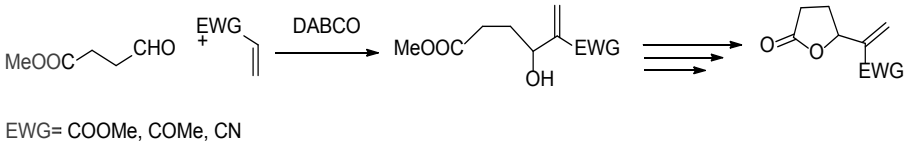


Figure 19. *Synthesis of lactones by the MBH pathway.*

the luminacin family, which inhibits both endothelial cell proliferation and capillary tube formation) a novel route was recently been developed. Followed by trans OH position the starting aldehyde, which was obtained by a simple Baylis-Hillman reaction between methyl acrylate and acetaldehyde, was extended by two highly stereoselective asymmetric aldol reactions. Similarly, using the Baylis-Hillman reaction as the key step for the synthesis of the lactones in two steps has been reported (Figure 19).

Discussion and Conclusion

Apart from the above discussed applicability of the Baylis-Hillman reaction, there are numerous other cases of the reaction synthetic utility. On similar grounds, MBH reaction strategy has been successfully exploited for various synthetic and industrial purposes [28-30]. Our laboratory is actively engaged in heterocyclic synthesis and asymmetric synthesis [31-42].

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***Correspondence to:**

Kapil Kumar
School of Pharmaceutical Sciences
Apeejay Stya University
Sohna-Palwal Road,
Sohna, Gurgaon,
Haryana,
India
Tel: 8872041174
E-mail: kapil.py@gmail.com