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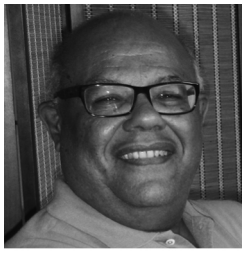
The Morita-Baylis-Hillman Reaction: Advances and Contributions from Brazilian Chemistry

Marilia S. Santos[a], Fernando Coelho[*,a], Cláudio G. Lima-Junior[b] and Mário L. A. A. Vasconcellos[*,b]

M. L. A. A. Vasconcellos

[a]*Department of Organic Chemistry, Institute of Chemistry, University of Campinas, Campinas, São Paulo, Brazil;* [b]*Department of Chemistry, Federal University of Paraíba, João Pessoa, Paraíba, Brazil*

Abstract: The Morita-Baylis-Hillman reaction is an organocatalyzed chemical transformation that allows access to small poly-functionalized molecules and has considerable synthetic potential and promising biological profiles. In this review, we report the efforts made by Brazilian research groups in recent years on the development of Morita-Baylis-Hillman chemistry. The review covers these contributions, with a focus on mechanistic studies, improvement of the experimental conditions, and the use of Morita-Baylis-Hillman adducts as building blocks for the synthesis of heterocycles, natural products and drugs.



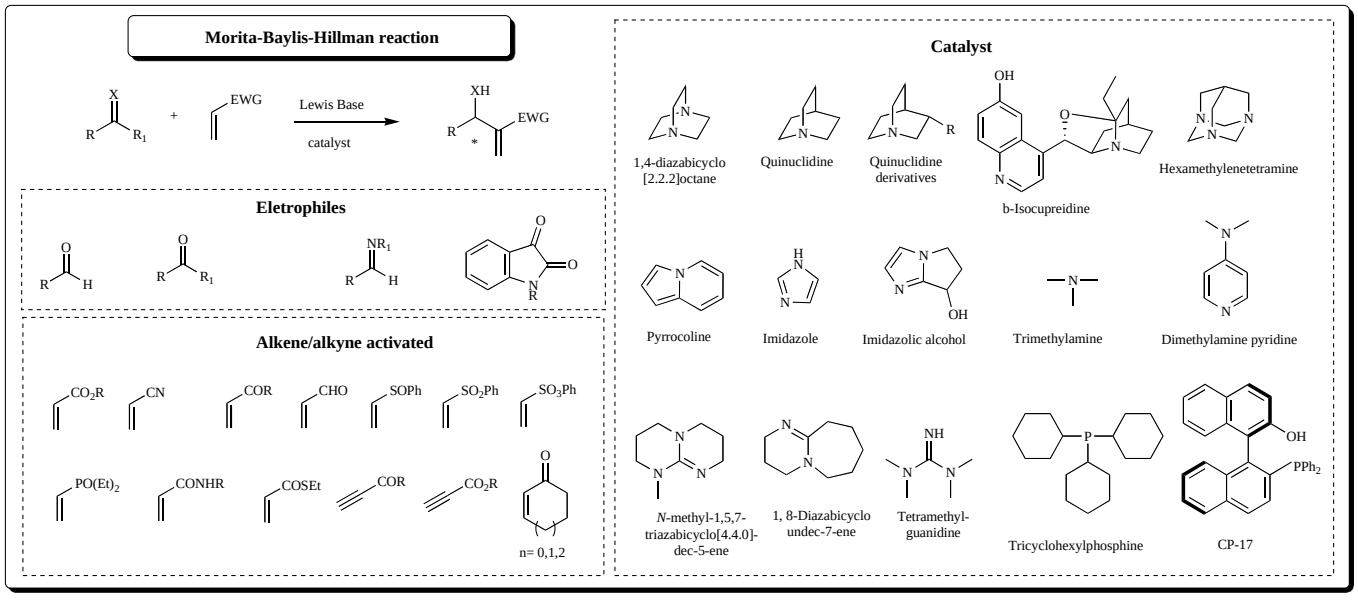
Fernando Coelho

Keywords: Morita-Baylis-Hillman, Heterocycles, Drugs, Acrylates, Mass Spectrometry, Natural Products.

1. INTRODUCTION

In 1968, Ken-ichi Morita reported the discovery of a new vinyl monomer in low yield as a product of a reaction between acrylonitrile or methyl acrylate with aliphatic or aromatic aldehydes catalyzed by tertiary phosphines [1]. Four years later, Anthony B. Baylis and Melville Ernest D. Hillman performed the same transformation; however they used a tertiary amine as the catalyst [2]. This modification provided a meaningful change in the profile of the reaction by increasing its efficiency (conversion and yield) and facilitating access to promising products for organic synthesis.

The Morita-Baylis-Hillman (MBH) reaction can be defined as a chemical transformation between the an α-position of an alkene/alkyne activated by electron withdrawing groups and an electrophile (aldehydes, activated ketones and activated imines) in the presence of an organocatalyst, commonly, a tertiary amine or a phosphine (Scheme **1**). The resulting product, named the MBH adduct, corresponds to a small poly-functionalized molecule with three vicinal functional groups [3].



Scheme 1. Essential components of the Morita-Baylis-Hillman reaction.

The first mechanistic study for the MBH reaction was performed in 1990 by Jonathan S. Hill and Neil S. Isaacs [4]. The kinetic profile demonstrates that the reaction starts by the Michael addition of the catalyst **I** to the β-position of the activated alkene **II** to form the zwitterion enolate **III**, which attacks the carbonyl compound to form the alkoxide **V** (Scheme **2**). Subsequent proton migration and release of the catalyst lead to the final MBH product

*Address correspondence to these authors at the Department of Organic Chemistry, Institute of Chemistry, University of Campinas, P.O. Box: 6154, Campinas – SP, Brazil; Tel/Fax: ++55-19-3521-3085, +55-19-3521-3023; E-mail: coelho@iqm.unicamp.br; and Department of Chemistry, Federal University of Paraiba, PB – Brazil; E-mail: mlaav@quimica.ufb.br

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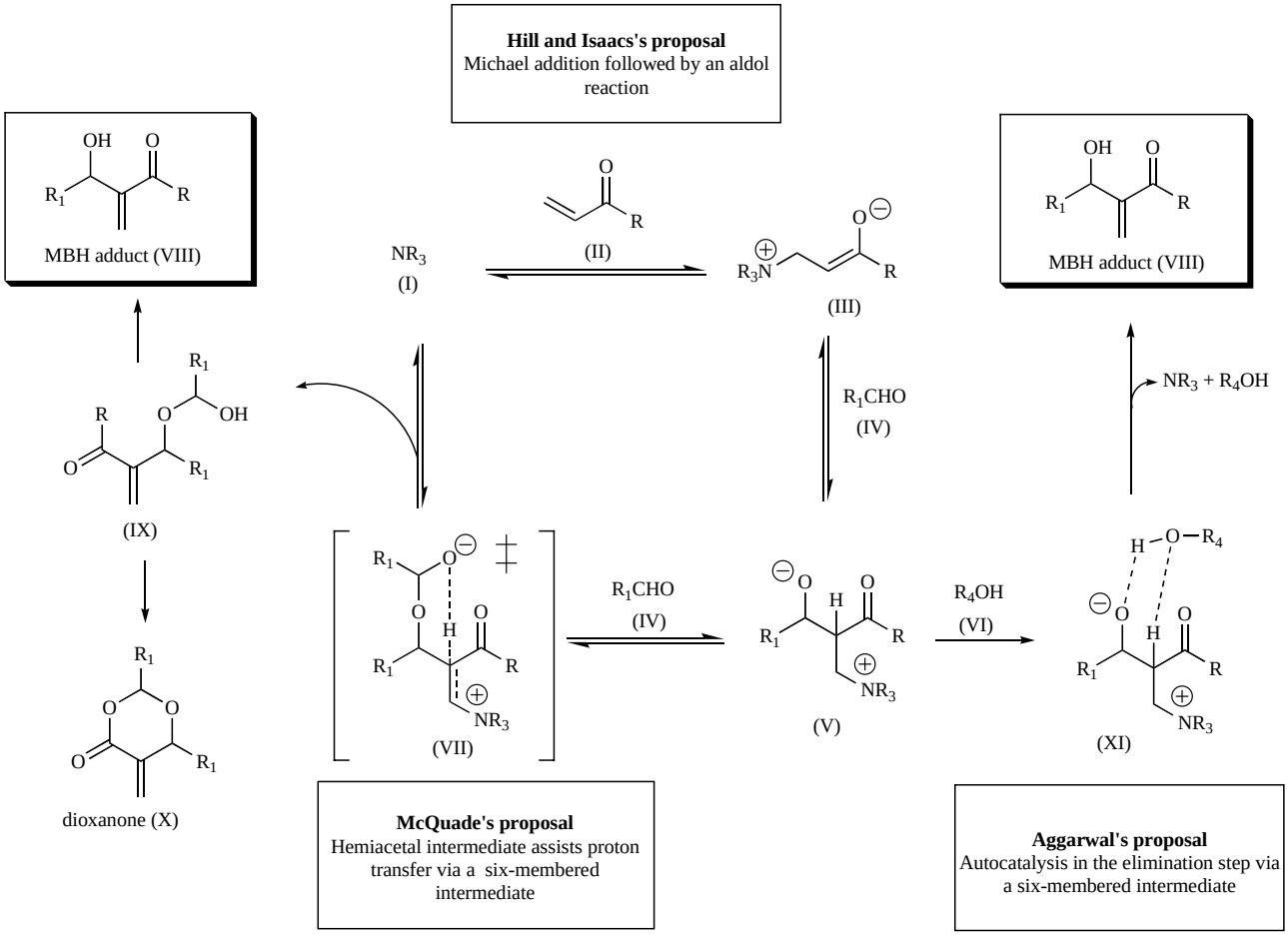


Scheme 2. Mechanistic proposals of the MBH reaction [8].

VIII. The aldolic addition was suggested as the rate-determining step. In 2004, McQuade [5] and Aggarwal [6] independently reported new kinetic and theoretical studies to afford further clarification for understanding the key stages in the MBH mechanism. In both cases, the elimination was considered to be the rate-determining step (RDS). McQuade demonstrated the importance of a second molecule of the aldehyde in the MBH mechanism. According to this proposal, the nucleophilic attack by the alkoxy oxygen atom of **V** on a second molecule of the aldehyde **IV** leads to a hemiacetal anion, which assists the intramolecular proton transfer through a six-membered transition state **VII**, because a 4-centered proton transfer process (alkoxide **V**) would be impossible due to geometrical restrictions. Subsequently, hemiacetal **IX** decomposes generating the final MBH adduct **VIII** (Scheme **2**). This proposal could also explain the observation of dioxanone **X** in previous works about MBH reaction [7]. Furthermore, the achievements made by Aggarwal showed that the reaction initially proceed according to the McQuade proposal and after 20% conversion, the concentration of the adduct is sufficiently high for auto-catalysis. In this case, elimination is mediated by the MBH adduct itself, which simultaneously donates a proton to the alkoxide and removes a proton from the α-position of the carbonyl *via* a six-membered transition state **XI**.

The great potential of this transformation is attributed to its fundamental characteristics such as carbon-carbon bond formation and the creation of a stereogenic center, as well as a high atomic economy, operational simplicity and mild reaction conditions. By virtue of these requirements, the interest in this reaction over the years by the scientific community has grown significantly and great contributions have been made in this area (Fig. **1**) [3]. The studies are focused on developing new catalysts, using alternative solvents, expanding the scope of the reaction, and improving the rate and rationalization of a general asymmetric version. Furthermore, MBH adducts have had a broad applicability as a platform for the synthesis of natural products, heterocycles and complex frameworks.

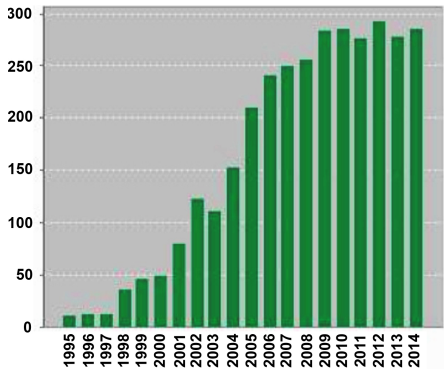


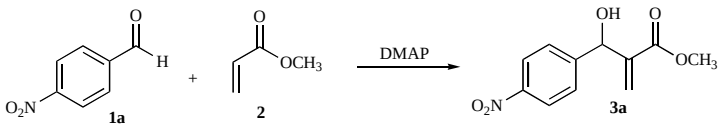
Fig. (1). Items related to the MBH reaction published by year in the last 20 years *via* the Web of Science database (accessed on March 25, 2015).

Following this scenario, the Brazilian chemistry community has made outstanding contributions to MBH chemistry, which is the main focus of this review.

2. PREPARATION OF MBH ADDUCTS

Despite the numerous advantages of the Morita-Baylis-Hillman reaction, some drawbacks of this reaction include its low reaction

Table 1. Influence of the catalyst and temperature.



Entry	Temperature (°C)	Time (h)	Yield (%)
1	25	96	72
2	76	5	>99
3	Microwave	0.25	93
4	-4	5.7	65

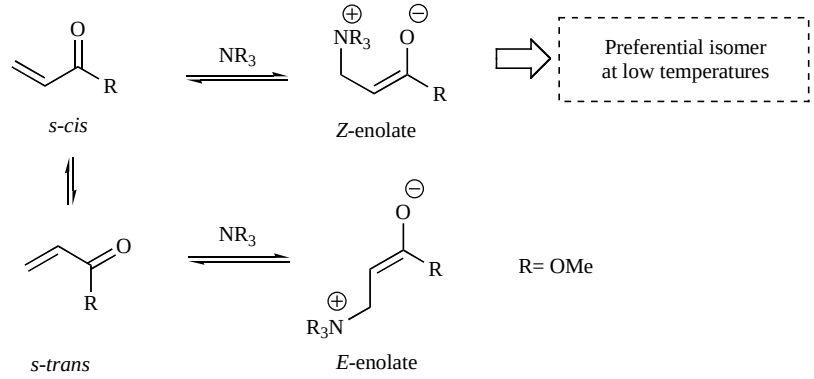


Fig. (2). Enolate configurations.

rate and yields for some cases, which are dependent on the substrates and experimental conditions. The literature has reported efforts directed towards overcoming these limitations, including the use of an ultrasound technique, high pressure, and microwave irradiation as well as the development of new catalysts and co-catalysts [9].

In Brazil, some research groups have dedicated their efforts towards the development of methodologies to improve the yields and rate of the MBH reaction. In 2003, Vasconcellos *et al.* reported the efficient utilization of 4-(*N*,*N*-dimethylamino)pyridine (DMAP), as a catalyst for the Morita-Baylis-Hillman reaction between methyl acrylate and aromatic aldehydes under simple reaction conditions [10]. The adduct **3a** was obtained in a quantitative yield (>99%) at 76 °C in 5 hours (Table **1**, entry 2). When ultrasound was used, the reaction was completed in 15 minutes with a yield of 93%. Surprisingly, good rates were also observed when the reaction was performed at -4°C (Table **1**, entry 4). This unexpected behavior was observed for all of the tested aldehydes.

The uncommon temperature effect on the reaction time was observed again in a later work, wherein the catalytic activities of DMAP, 1,4-diazobicyclo [2.2.2]octane (DABCO) and imidazole were compared [11]. In general, DABCO was considered to be one of the best catalysts for the MBH reaction. However, at lower temperatures, fast conversion was achieved with both DABCO and DMAP, as previously reported by Rafel [12]. This result was attributed to the formation of the preferential and kinetically more reactive, *Z* enolate, which favors the nucleophilic attack on aldehyde (Fig. **2**).

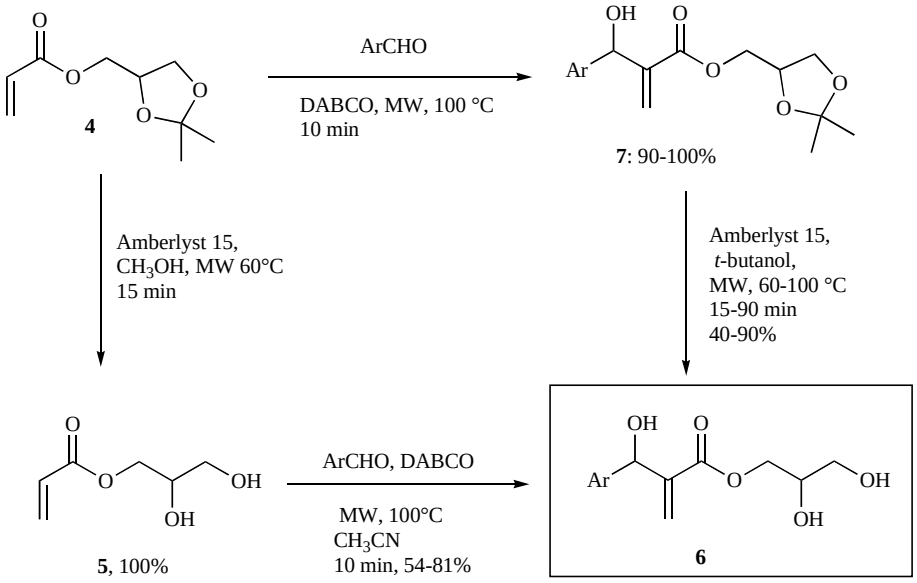
These conclusions were subsequently refuted, when in a new protocol employing an excess of acrylonitrile, the reaction rate was considerably reduced at 0 °C in the presence of DABCO as a catalyst [13]. Since *E* and *Z* geometrical isomerism does not exist for the acrylonitrile zwitterion intermediates, it was concluded that the theory presented previously for the enolates formed from methyl acrylate may not be correct. Authors suggested that due to the volume of activation of the MBH reaction (-70cm^3/mol), which may be one of the highest in terms of absolute value among known reactions, the entropy of activation must be a very important parameter [14].

Therefore, it is a reasonable assumption that the reduction in temperature from room temperature to 0 °C makes the entropic term ($-T\Delta S^{\neq} > 0$) less important, reducing the Gibbs activation energy and thus improving the MBH reaction rate. At high temperatures, ΔH is the dominant term in accelerating the reaction and at lower temperatures (0 °C) ΔS is the dominant term.

A detailed study of the influence of the solvent on the behavior of the MBH reaction between aromatic aldehydes and acrylonitrile or methyl acrylate was described by de Souza *et al.* [9c]. The organic solvent/water system has been demonstrated to be more efficient than with a single solvent. For example, *t*-BuOH: water (6:4) was the solvent mixture of choice, when acrylonitrile is used as nucleophilic component, whereas, for reactions with methyl acrylate, the DMSO: water (6:4) system gave better results.

In 2011, Sousa *et al.* [15] carried out the synthesis of hydrophilic MBH adducts while applying microwave irradiation. Two reaction pathways were followed: first, the acrylate **4** was submitted to diol deprotection affording **5** in a quantitative yield which, after the MBH reaction mediated by microwave irradiation, produced **6** in moderate yields and a short reaction time. In the second reaction, the acrylate **4** was submitted to the MBH reaction in the presence of aromatic aldehydes under microwave irradiation, and intermediate **7** was generated in high yields (90–100%). After diol deprotection, the hydrophilic adducts (**6**) were furnished in yields that ranged from 40% to 90% (Scheme **3**).

In a paper published in the same year, Vasconcellos *et al.* reported a comparative study between two synthetic protocols for the synthesis of MBH adducts (Fig. **3**) [16].



Scheme 3. Reaction pathways employed for the synthesis of a hydrophilic MBH adduct.

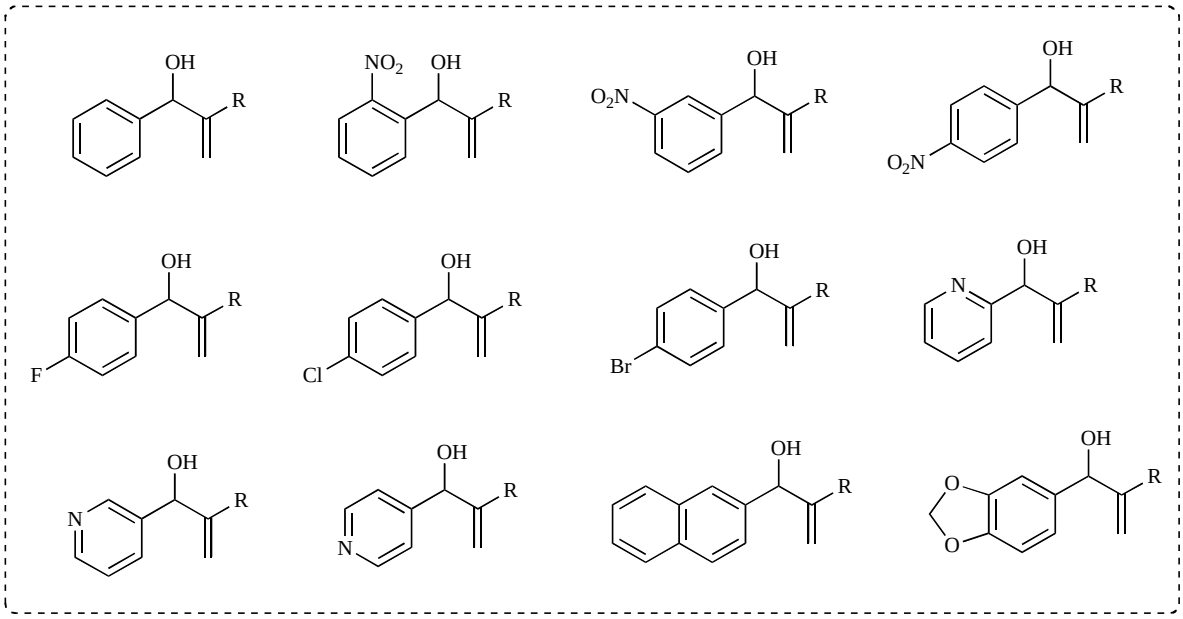


Fig. (3). MBH adducts synthesized by Vasconcellos (R = CN or R = CO_2CH_3).

In this study, it was observed that the successful use of microwave irradiation was dependent on the aldehydes and the Michael acceptor employed. For reactions between aromatic aldehydes and acrylonitrile, the protocol performed at low temperature was more satisfactory, giving adducts in excellent yields (90-99%) and without by-product formation.

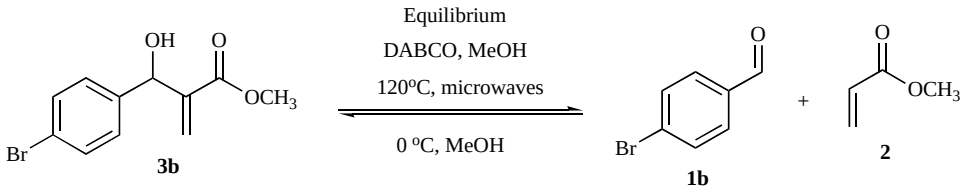
However, with methyl acrylate, only aromatic aldehydes containing a nitro group or pyridine carboxaldehyde gave the MBH adducts in excellent yields and shorter reaction times (5-10 minutes). For less reactive aromatic aldehydes, only the low temperature protocol was able to afford the expected adducts in good to excellent yields (81-99%). For these cases, the use of protic polar solvents is necessary.

All results obtained in this study were rationalized considering the possibility of thermodynamic control in the MBH reaction. In theoretical and experimental results described by Cantillo and Kappe, the MBH reaction between benzaldehyde and methyl acrylate catalyzed by DABCO in methanol proved to be reversible at 120 °C [14].

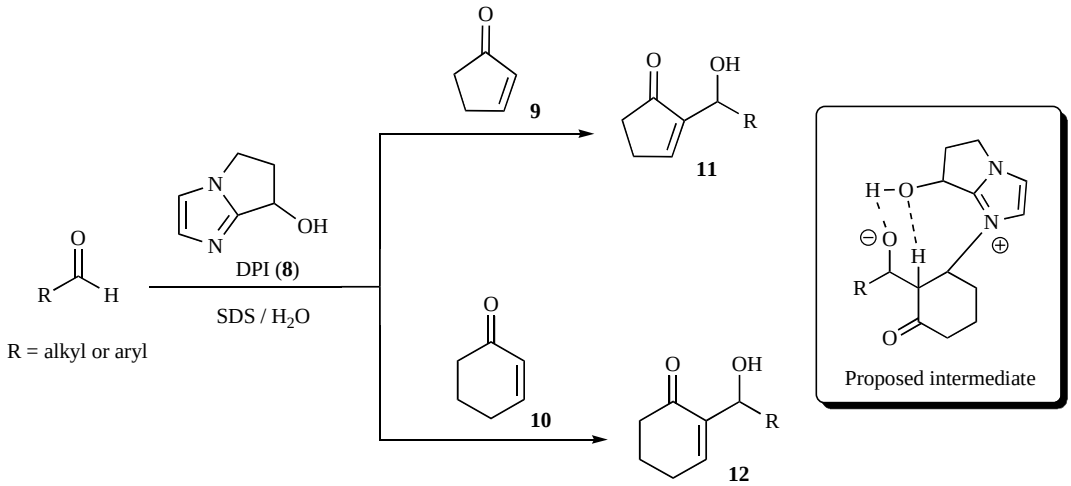
To prove the formation of equilibrium in these reactions, Vasconcellos performed a comparative reaction where a methanol solution of pure methyl 2-[hydroxy(4-bromophenyl) methyl] acrylate adduct (Scheme **4**) containing DABCO (2 equiv.) was heated under microwave irradiation at 120 °C for 2 h.

In this case, the formation of methyl acrylate (**2**) and *p*-bromobenzaldehyde (**1b**) in considerable amounts (ca. 55% by GC-MS) was observed. The reaction temperature was then decreased to 0 °C and the mixture was kept under magnetic stirring for 24 h. The equilibrium shifted once again to the formation of methyl 2-[hydroxy(4-bromophenyl)methyl]acrylate (**3b**) confirming the reversible nature of this sophisticated reaction for some substrates.

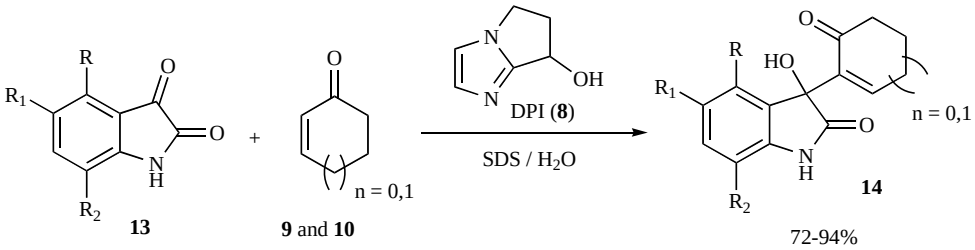
In 2012, Coelho's research group introduced a bicyclic imidazolyl alcohol, 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole (DPI, **8**), as a new catalyst for the MBH reaction between aromatic and aliphatic



Scheme 4. Reversibility of the MBH reaction.



Scheme 5. Bicyclic imidazolyl alcohol as a catalyst for the MBH reaction with cyclic enones.



Scheme 6. Aqueous MBH reaction between isatins and cyclic enones.

aldehydes with cyclic α,β-unsaturated ketones [17]. Cyclic enones present low reactivities in the general experimental protocol employed for the MBH process. However, with the use of DPI (**8**) in the presence of water and a phase transfer catalyst (sodium dodecyl sulfate, SDS), MBH adducts were obtained in good yields (58-98%) and in reasonable reaction times (21-144h). The improvement of yields and rates for this type of system was attributed to possible hydrogen bonding interactions in the structure of the zwitterion intermediate resulting from the Michael addition of Lewis base to a cyclic ketone (Scheme **5**).

The same catalyst was employed in an efficient, simple and environmentally friendly protocol to aqueous MBH reactions between unprotected isatins and cyclic enones [18]. Reactions involving cyclopentenone were generally faster than those performed with cyclohexenone. Apparently, the electron-withdrawing or electron-donating nature of the aromatic moiety in the isatin derivatives does not have relevant effect on the rate of the addition. The methodology provides a variety of 3-substituted 3-hydroxy-2-oxindoles **14** in good yields (Scheme **6**).

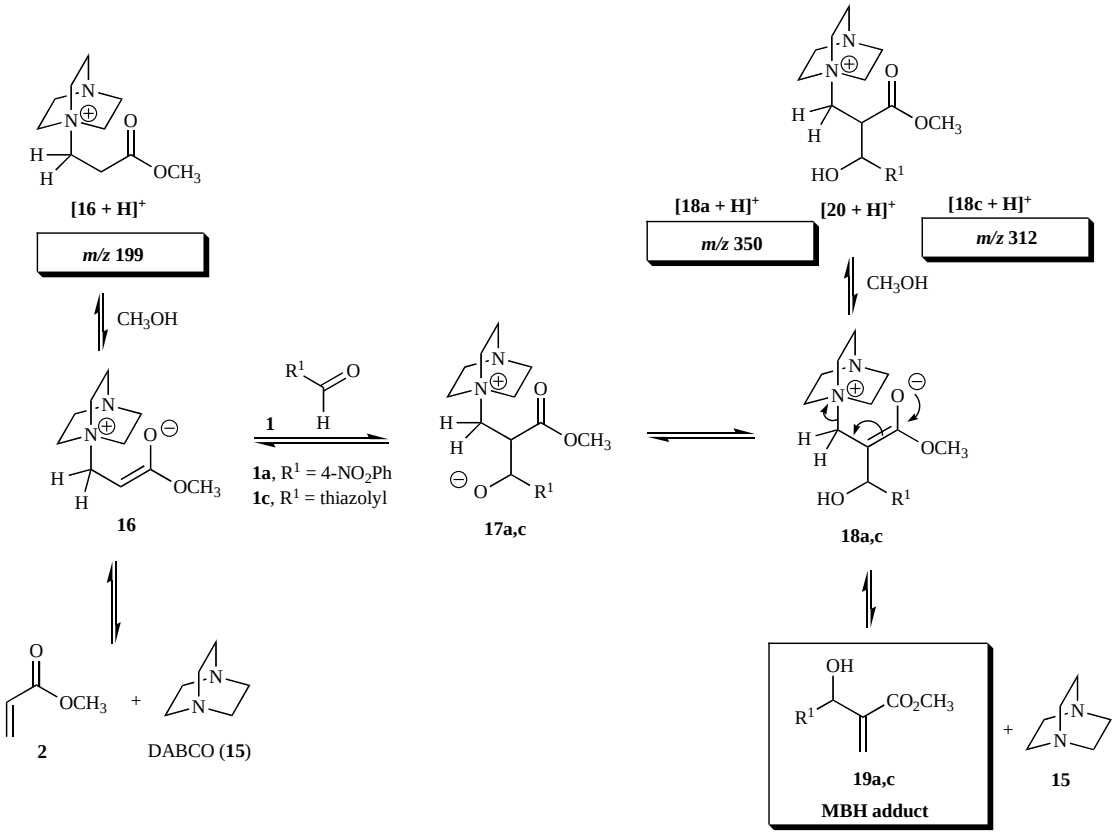
3. MECHANISTIC STUDIES – MASS SPECTROMETRY AS A TOOL

Coelho *et al*. have widely used mass spectrometry with electrospray ionization (ESI-MS) as an efficient tool to screen for intermediates in the reaction solution and hence to provide mechanistic details of the MBH reaction. The main advantage of the ESI process is the transfer of ions from the condensed phase to the gas phase as isolated entities [19].

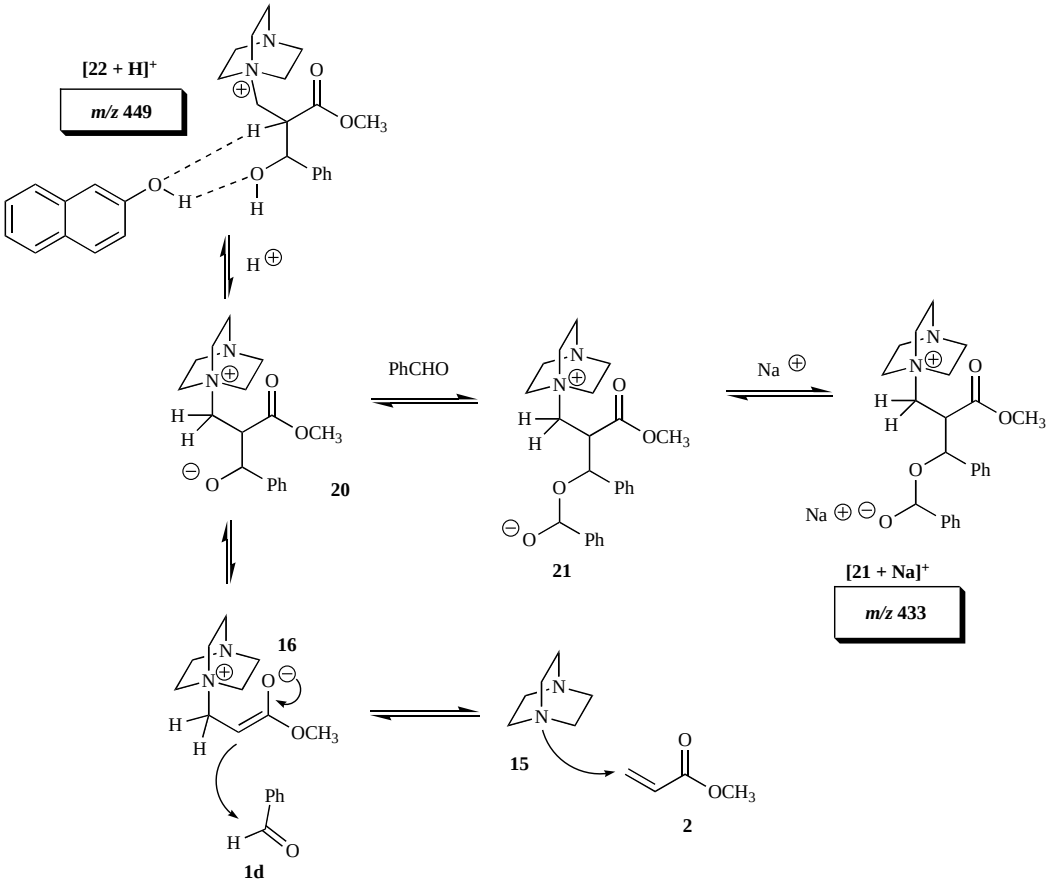
The first mechanistic study of the MBH reaction, employing mass spectrometry, detected and characterized the zwitterion intermediates proposed by Hill and Isaacs [4]. Monitoring reactions between methyl acrylate (**2**) and activated aldehydes, catalyzed by DABCO, intercepted and successfully structurally characterized the intermediates from the Michael addition $[\mathbf{16}+H]^+$ *m/z* 199, aldolic addition $[\mathbf{18a}+H]^+$ *m/z* 350 and $[\mathbf{18c}+H]^+$*m/z* 312. (Scheme **7**) [20].

Later, a new mechanistic study of the MBH reaction using ESI-MS (/MS) was performed, motivated by the discoveries introduced by McQuade [5] and Aggarwal [6] regarding the proton transfer step [22]. The target of this study was to intercept and characterize the new intermediates proposed (Scheme **8**).

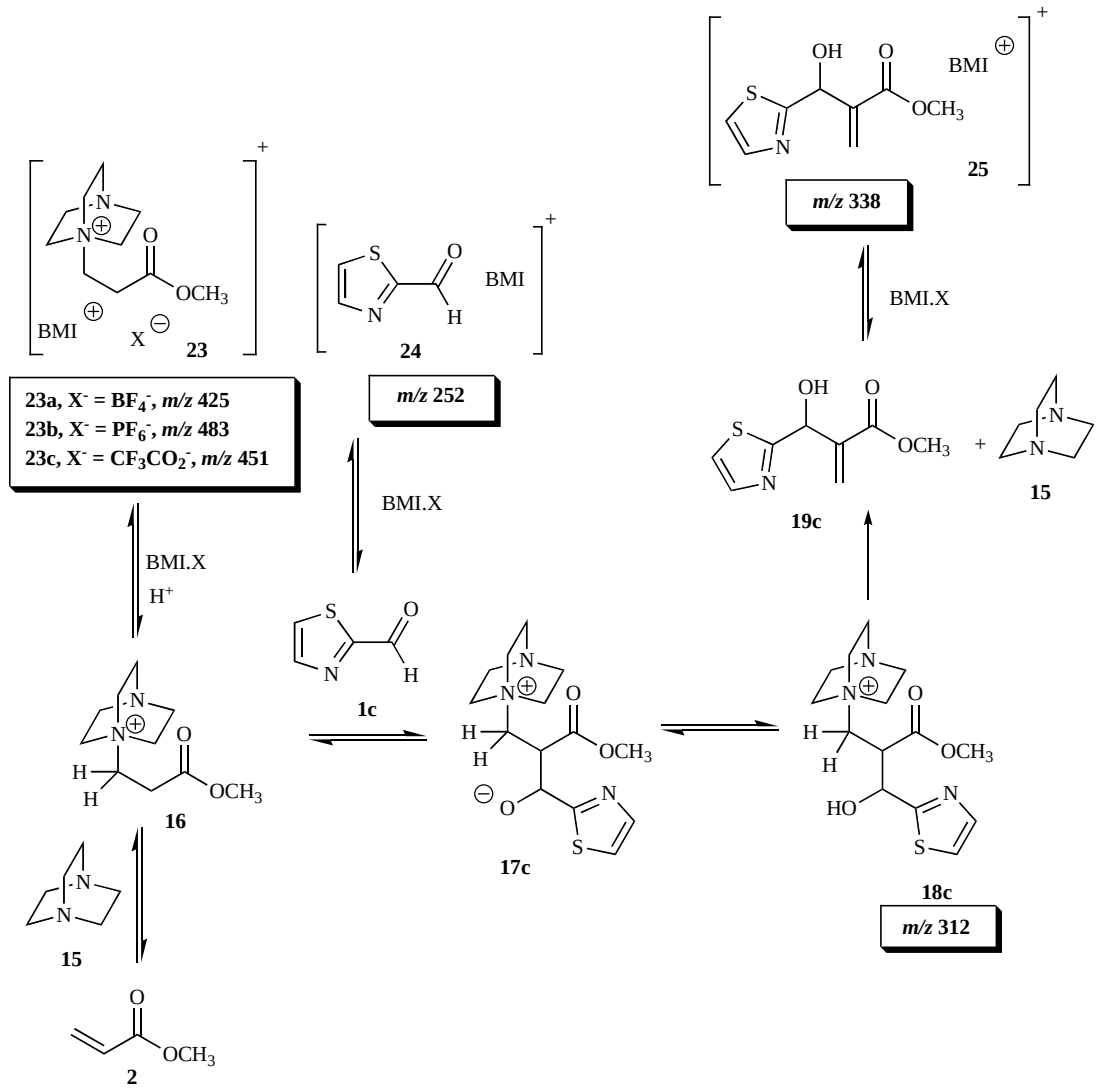
The intermediate proposed by McQuade **21** in its sodiated form $[\mathbf{21} + Na]^+$ of *m/z* 433 was able to be intercepted. It is resulting from the nucleophilic attack of the alkoxide **20** on the aldehyde **1d**. In addition, the Aggarwal's proposal was investigated employing β-naphthol as an external proton source. The new specie $[\mathbf{22} + H]^+$ of *m/z* 449 was intercepted and properly characterized, confirming that a proton source participates in the proton transfer step *via* a six-membered ring intermediate and assists the elimination of the catalyst.



Scheme 7. Mechanism and characterization of intermediates from the first MBH proposal [21].



Scheme 8. Capture and characterization of intermediates proposed for the the RDS step.



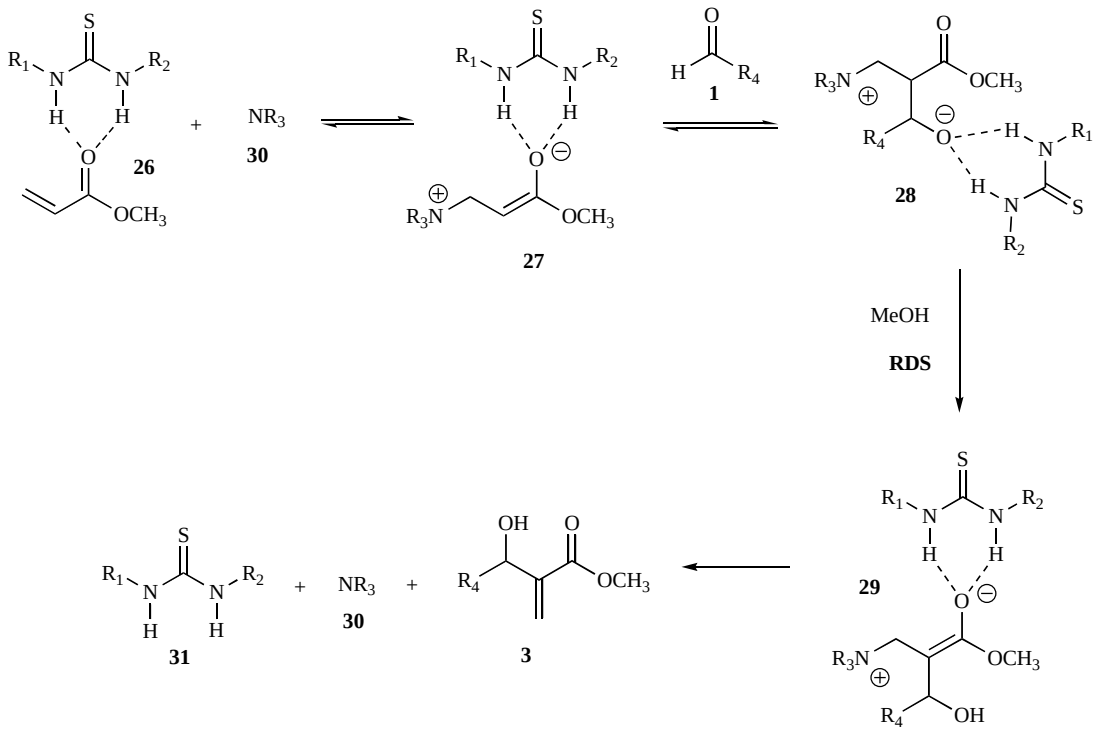
Scheme 9. Monitoring the MBH reaction co-catalyzed by ionic liquids BMI.X (X=BF_4, PF_6, CF_3CO_2).

One of drawbacks of the MBH reaction is the low reaction rate, which has stimulated the search for more efficient catalysts and optimal experimental conditions. In this aspect, ionic liquids (ILs) and *N,N'*-diarylthiourea have been reported as efficient promoters to increase MBH reaction rates. The catalytic effect from IL has been attributed to the stabilization of the zwitterion intermediates through different types of H-bonded supramolecular ion pairs (Scheme **9**) [23].

In this study, ionic liquids based on the cation 1-*N*-butyl-3-methylimidazolium (BMI^+) were employed as co-catalysts in the MBH reaction between 2-thiazolecarboxaldehyde (**1c**) and methyl acrylate (**2**) catalyzed by DABCO (**15**). Reaction monitoring online by ESI-MS both in the positive and negative ion modes allowed for the interception and characterization of supra-molecular species resulting IL coordination with reactants and products [24]. Despite the fact that IL was associated with almost all of the molecules intercepted, its role in the increase of the reaction rate was attributed to: aldehyde activation, with it acting as a Lewis acid such as $[\mathbf{24}]^+$*m/z* 252; stabilizing effects on the intermediate **23**; and shifting the equilibrium of the reaction towards the formation of the MBH adduct due to complex IL-adduct $[\mathbf{25}]^+$*m/z* 338.

The behavior of thiourea as a co-catalyst in the MBH reaction was investigated through theoretical optimizations with 3LYP/6-31+G(d) and ESI-MS(/MS) experiments. The theoretical study showed that in rate-determining transition state (TS), thiourea, in protic media, acts as a Brønsted acid and stabilizes the basic oxygen center through bidentate hydrogen bonding. In the ESI-MS(/MS) experiment, the MBH reaction co-catalyzed by thiourea showed intermediates bound to the thiourea. They were intercepted and characterized [25]. The results allowed the following proposal: thiourea facilitates the Michael addition of DABCO (**26**) during the first step of the MBH reaction, acts in stabilizing the zwitterion intermediates resulting from both the Michael addition and aldol addition (**27** and **28**) and decreases the activation barrier of the RDS (proton transfer step) due to bidentate hydrogen bonds with oxygen (**28**) (Scheme **10**).

To obtain additional evidence about the MBH mechanism, a charge-tagged acrylate derivative (Fig. **4**) was used as the substrate in a MBH reaction monitored by ESI-MS. An imidazolium ion was used as the charge-tag because its ionic nature facilitates ESI transfer of the intermediate to the gas phase allowing it to be used in neutral reactions. The results associated with theoretical studies were in accordance with the mechanistic views from McQuade and Aggarwal. DFT calculations provided information about the IL effect, which formed an electrostatic intermediate complex that led to a transition state with a lower energy barrier promoting the ongo-



Scheme 10. Proposed mechanism for the MBH reaction co-catalyzed by di-substituted thiourea in the presence of methanol.

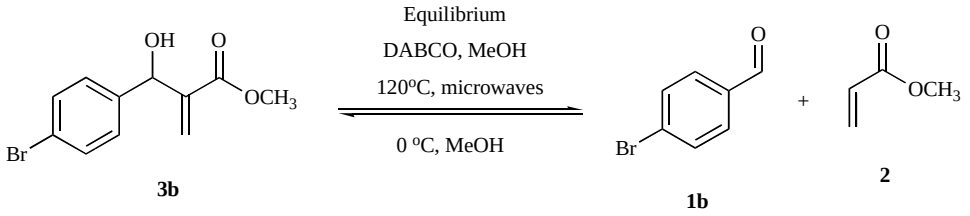


Fig. (4). Charge-tagged acrylate.

ing reaction. Additionally, stabilization occurs through ion-pairing and supra-molecular aggregates [26].

The *aza*-MBH reaction is a variation of the reaction in which imines are used as electrophiles. The mechanism of the *aza*-reaction has received less attention compared to the classical MBH, because of their supposed similarities. Recently, a mechanistic investigation was performed through monitoring the reaction between tosylamide and methyl acrylate catalyzed by DABCO [27]. The expected intermediates intercepted (**33** and **35**) gave additional information about the reaction pathways. The unknown intermediate detected [**34**+H]$^+$ would be result of the nucleophilic attack of **33** on tosylimine **32** and the loss of a molecule of DABCO would then lead to intermediate [**35**+H]$^+$. Additionally, the pyrimidone **37** (equivalent to dioxanone observed in previous works) was not detected in this study. These findings show differences in the proton transfer step compared with the traditional MBH and they can help to explain the good progress in the development of enantioselective versions of the *aza*-MBH (Scheme **11**).

4. APPLICATIONS OF MORITA-BAYLIS-HILLMAN ADDUCTS

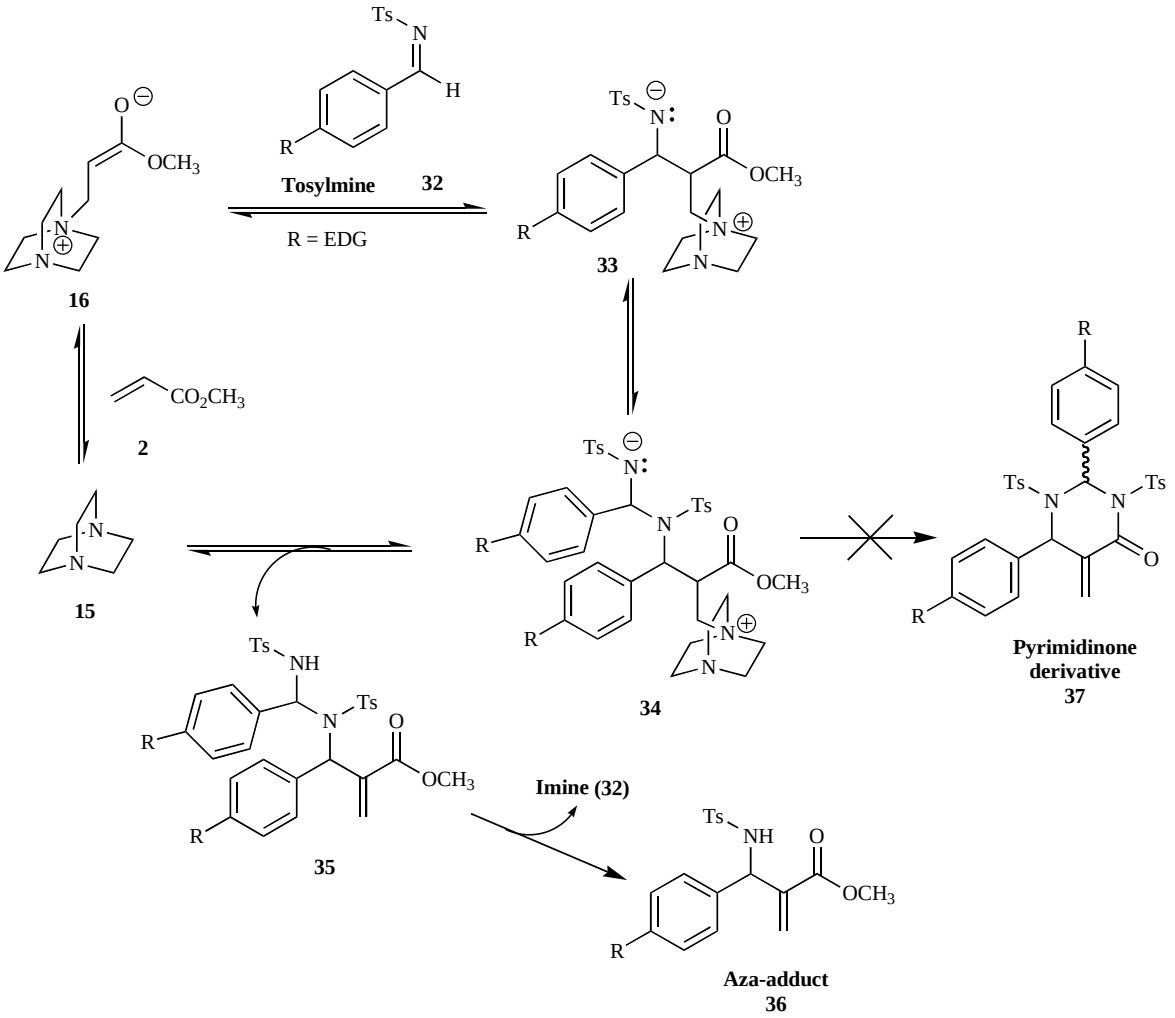
4.1. Synthesis of Derivatives

MBH derivatives have been reported as important intermediates in the synthesis of different frameworks, representing a valuable class of substrates for synthetic purposes.

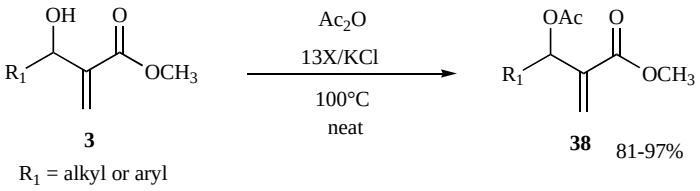
In 2007, Sá *et al*. [28] introduced an alternative protocol for the synthesis of acetate derivatives from MBH adducts using recyclable solid catalysts and high temperature under solvent-free conditions. Several Morita-Baylis-Hillman adducts were acetylated with Ac_2O and potassium exchange molecular sieves (13X/KCl) in high yields with regioselectivity (Scheme **12**). The heterogeneous base-like catalyst 13X/KCl was important in the progress of the reaction and in the distribution of the possible products formed; moreover, it can be reused several times while maintaining its original activity.

Allyl bromides were employed as precursors in the preparation of (*E*)-2-methylacrylates *via* reduction promoted by zinc and acetic acid [29]. (*Z*)-2-(bromomethyl)alk-2-enoates were obtained with high stereoselectivity, by the treatment of the MBH adducts with HBr and H_2SO_4. Bromo-methylacrylates **39**, then, undergo reduction to the corresponding olefins by means of zinc in acidic medium, providing (*E*)-2-methyl-3-substituted acrylates **40** in very good yields (Scheme **13**).

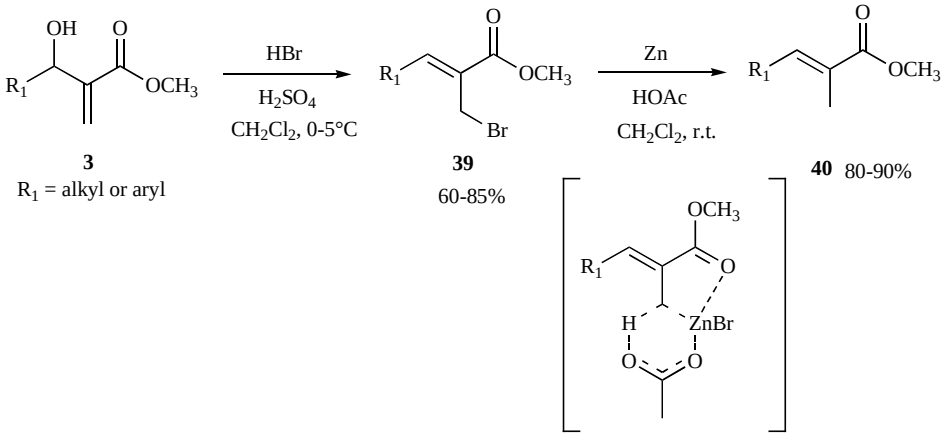
The success of the reduction process depends on the solvent, the amount of zinc and the order in which the reactants are added. It was proposed that the reduction occurred *via* a 6-membered transition state involving acetic acid, zinc and the terminal carbon of the allylic framework. The observed *E*-stereochemistry was confirmed by X-ray crystallography. The synthetic applicability of this method was demonstrated in the synthesis of pheromone (*E*)-2,4-



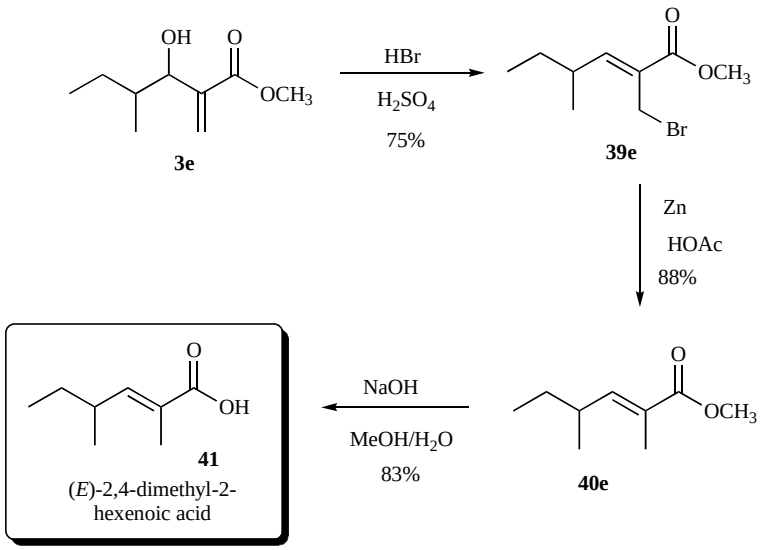
Scheme 11. Mechanistic proposal for the *aza*-MBH reaction based on the interception of the bis-sulfonamide intermediate **34**.



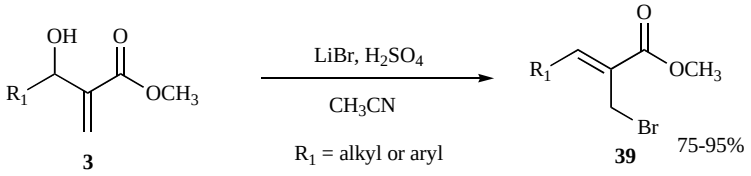
Scheme 12. Acetate derivatives by heterogeneous catalysis.



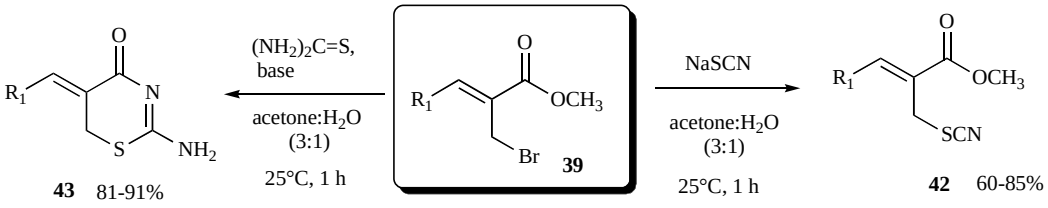
Scheme 13. 2-methylalk-2-enoates by the zinc-promoted reduction of allylic bromides.



Scheme 14. Synthesis of pheromone (*E*)-2,4- dimethyl-2-hexenoic acid **41**.



Scheme 15. (*Z*)-allylic bromides from MBH adducts.



Scheme 16. Synthesis of tiocyanates and thiazinones.

dimethyl-2-hexenoic acid (**41**), an active substance found in gland secretions of male ants of the genus *Camponotus* (Scheme **14**).

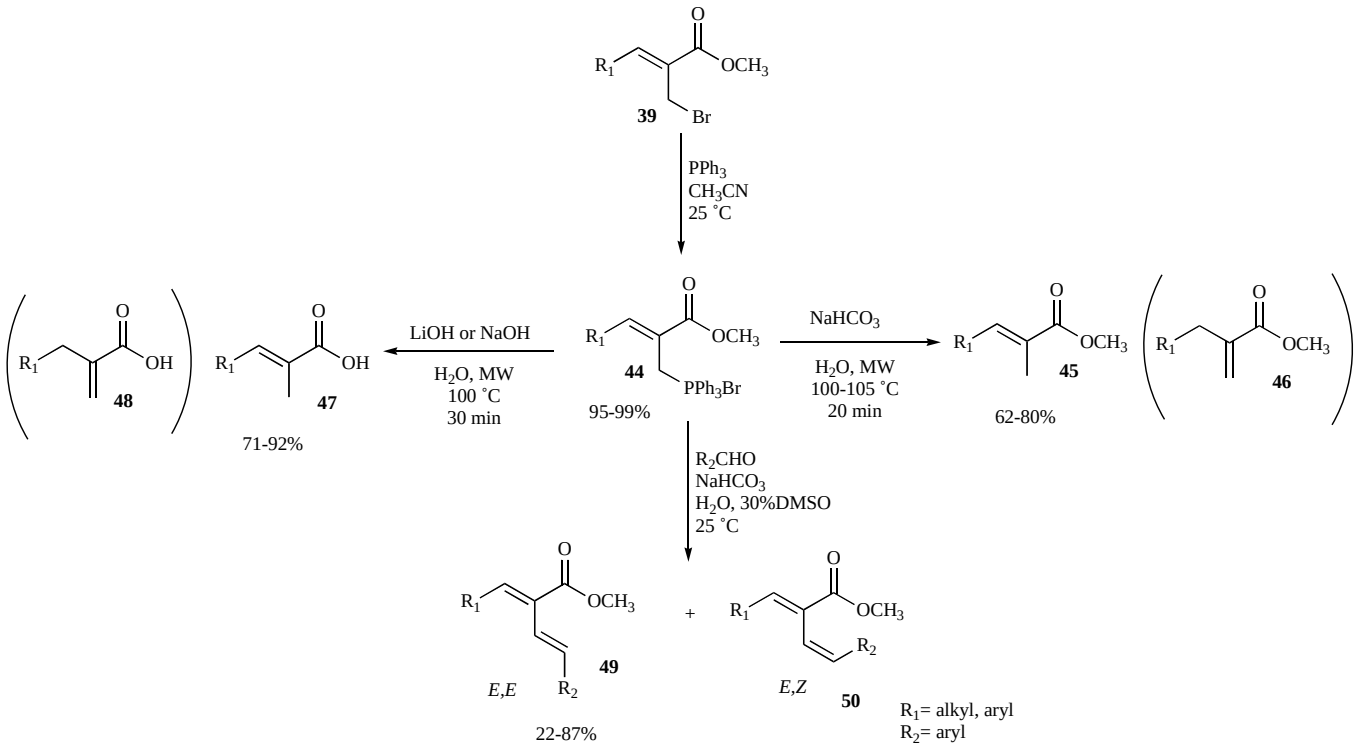
Improvements in the preparation of (*Z*)-allylic bromide were achieved when the MBH adduct was subjected to a mixture of $LiBr/H_2SO_4$ in acetonitrile (Scheme **15**) [30]. Although some adjustments in the amounts of the reagents for chloro- and nitro-substituted adducts are necessary, the generality of the method was clearly demonstrated.

Allylic bromides were also explored in the synthesis of allylic thiocyanates, which in turn were employed in the preparation of sulphur-containing heterocycles [31]. Allylic bromides were exposed to NaSCN in aqueous acetone in the absence of an external base, affording aromatic-substituted allylic thiocyanates. An equilibrated mixture of allylic thiocyanates and isothiocyanates was observed when aliphatic-substituted allylic bromides where subjected to the same conditions. The nucleophilic ambident character of thioureas was explored; they reacted with allyl bromide and after subsequent transformations, afforded a series of 2-amino-1,3-thiazin-4-ones in good yields (Scheme **16**).

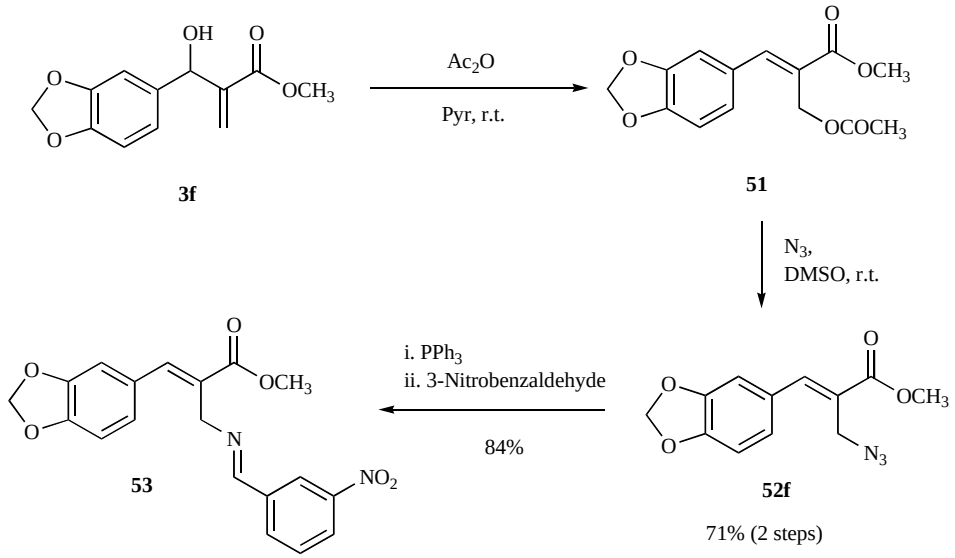
Later, the reaction of allylic bromides **39**, with PPh_3 in acetonitrile gave allylic phosphonium salts, which were employed as precursors in the synthesis of α-methyl alkenoic acids **47** and esters **45** [32] as well as in the preparation of functionalized dienes **49** and **50** [33] (Scheme **17**). Phosphonium salts reacted in the presence of sodium bicarbonate and water at room temperature to give α-methyl alkenoic esters **45**. The reaction time was incredibly reduced when the reaction was carried out under microwaves heating. The electronic nature of groups in the aromatic ring (R_1) had effects on the distribution of products. Although there was exclusive formation of the desired product for compounds with electron-donating R groups on the aromatic ring, the compounds with electron-withdrawing R_1 groups on the aromatic ring led to the generation of the rearranged isomer **46**. When $NaHCO_3$ was replaced by NaOH or LiOH, the redox process also worked with additional ester saponification to give α-methyl alkenoic acids **47**.

Functionalized 1,3-dienes **49** and **50** were synthesized with high stereoselectivity (*E*,*E*):(*E*,*Z*) through a Wittig reaction with an allylic phosphonium salt, an aldehyde, $NaHCO_3$ as the base and a combination of H_2O/DMSO (7:3). The electronic nature of the substituents on the aromatic ring of the aldehyde influenced the progress of the reaction and the presence of an electron withdrawing group in *ortho*-position of the aldehyde aromatic ring favored selectivity towards the (*E*,*E*)-diene.

Inspired by the potential use of azide frameworks as substrates for building heterocycles and nitrogen-compounds having biological and pharmacological activities. Sá *et al.* [34] have described a protocol for the synthesis of allyl azides from MBH bromides. In previous studies, β-substituted-α-(azidomethyl)acrylates were obtained from acetylation of MBH adducts followed by treatment of



Scheme 17. Allylic phosphonium as a precursor of α-methylalkenoic esters, α-methyl alkenoic acids and functionalized dienes.



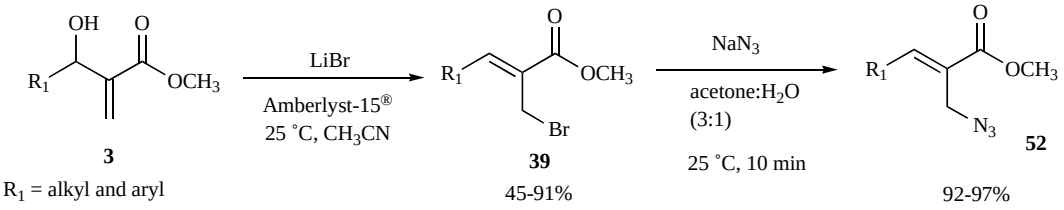
Scheme 18. Allylic azides from MBH acetates.

the MBH acetates with sodium azide [35]. In the presence of triphenylphosphine and an aldehyde, the allyl azides reacted *via* a Staudinger/*aza*-Wittig reaction, furnishing the *N*-allylic imines in good yields (Scheme **18**).

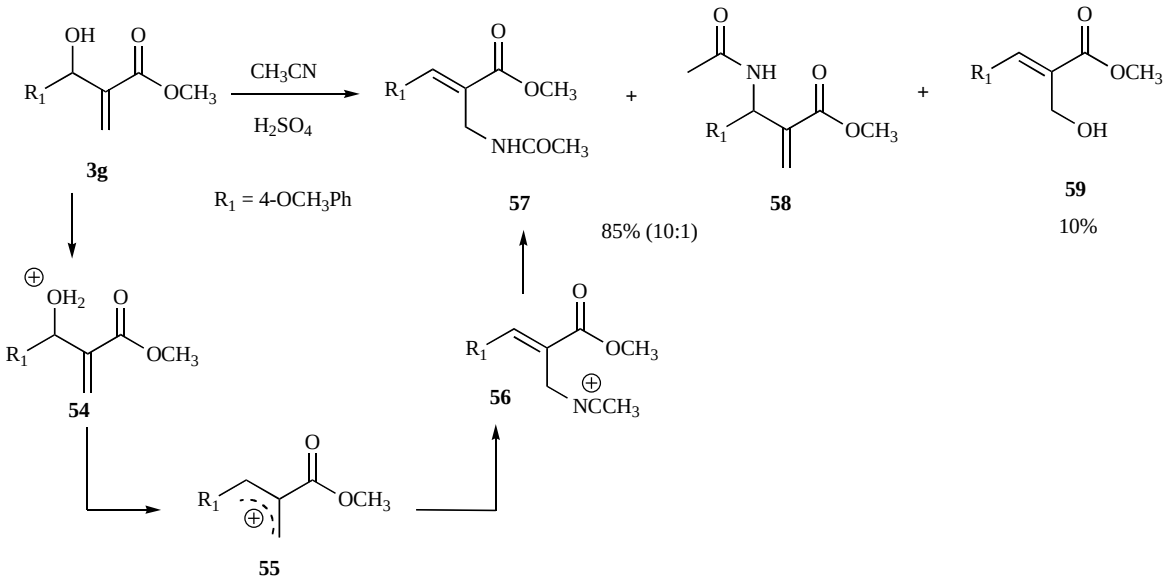
To circumvent some drawbacks of the method (long reaction times and the use of DMSO as a solvent), the authors proposed the use of allylic bromides, readily obtained by the direct bromination of MBH adducts, as substrates for the incorporation of azide. This bromination could be efficiently performed with amberlyst-15®/LiBr (or NaBr) couple in mild reaction conditions. This method is an alternative for substrates incompatible with the previous strongly acidic conditions. The preparation of allylic azides from bromides was performed in a combination of acetone/water, which had an important role in the success of the reaction (Scheme **19**).

The allyl component in the structure of the MBH adduct is responsible to the high susceptibility to nucleophilic substitution reactions, which allows several chemical transformations. The behavior of the allylic alcohol was investigated through studies of a Ritter-type reaction (Scheme **20**) [36]. Kinetic and theoretical studies suggested that the formation of acetamide **57** occurs *via* a stepwise S_N1 type mechanism and that the product distribution is governed by kinetic contol.

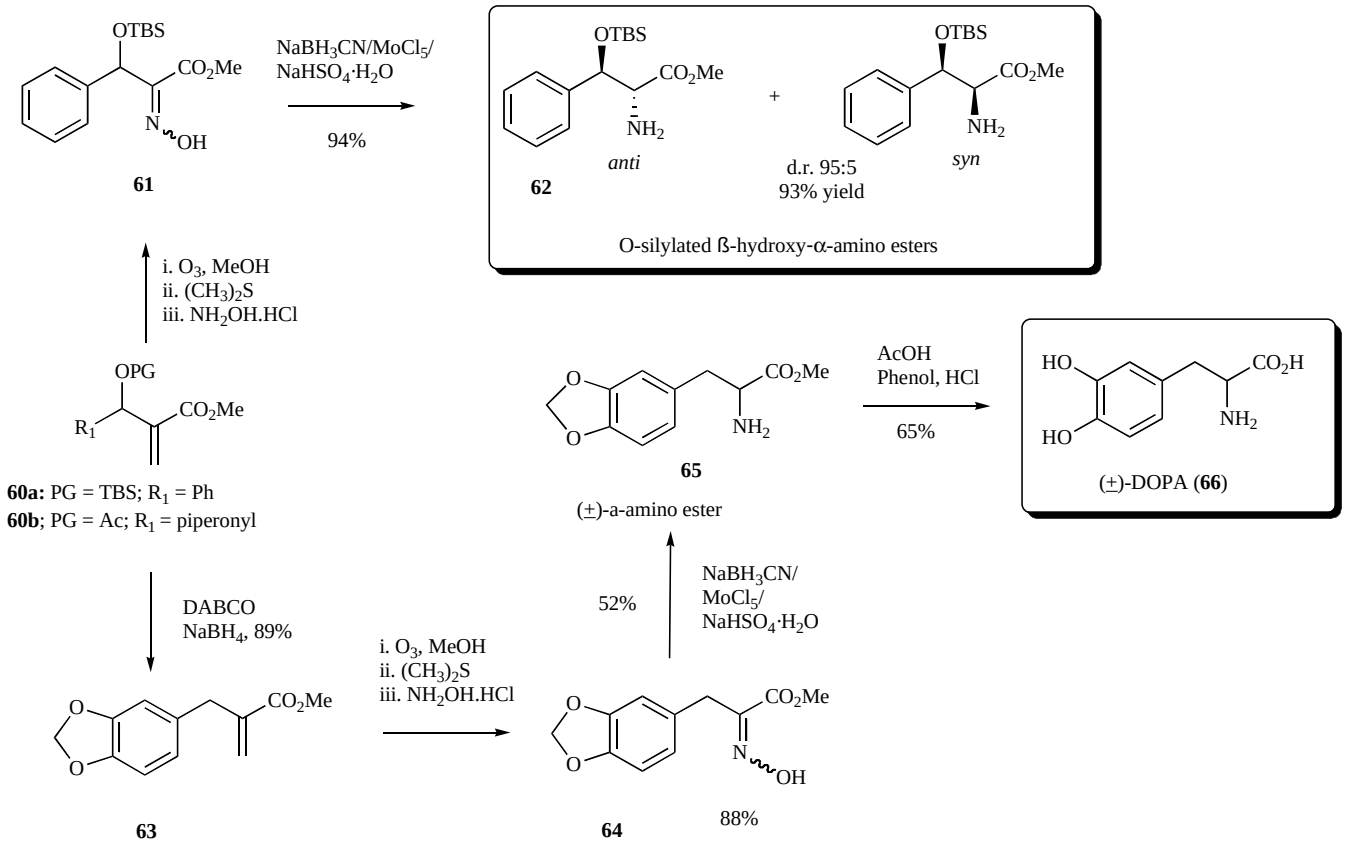
A protocol for the synthesis of noncoded β-hydroxy-α-amino esters and α-amino esters/acids was designed based on one-pot ozonolysis and oximation of MBH derivatives. The silylated adducts **60a** were exposed to oxidative cleavage conditions followed by condensation with hydroxylamine. The corresponding oxime was then reduced by a mixture of $NaBH_3CN/MoCl_5/NaHSO_4{\cdot}H_2O$



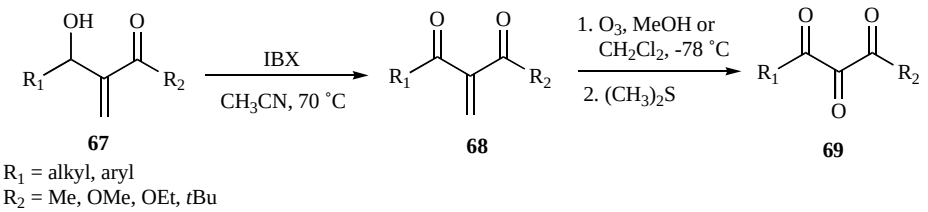
Scheme 19. Synthesis of (*E*)-allyl azides **52** from the corresponding allyl bromides.



Scheme 20. Acid-mediated Ritter-type reactions *via* a S_N1'mechanism for the synthesis of the preferential acetamide.



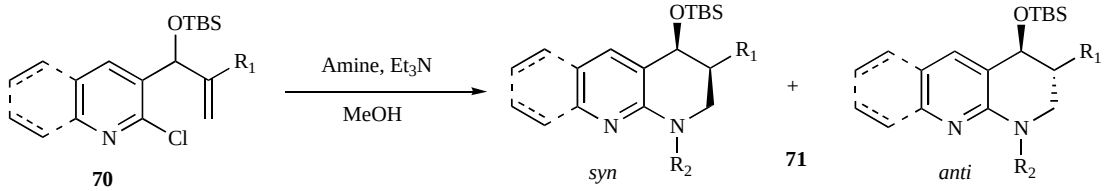
Scheme 21. Noncoded β-hydroxy-α-amino ester and α-amino ester/acid oxime reduction.



67 **68** **69**

R_1 = alkyl, aryl
R_2 = Me, OMe, OEt, *t*Bu

Scheme 22. Synthesis of vicinal tricarbonyl compounds from MBH adducts.

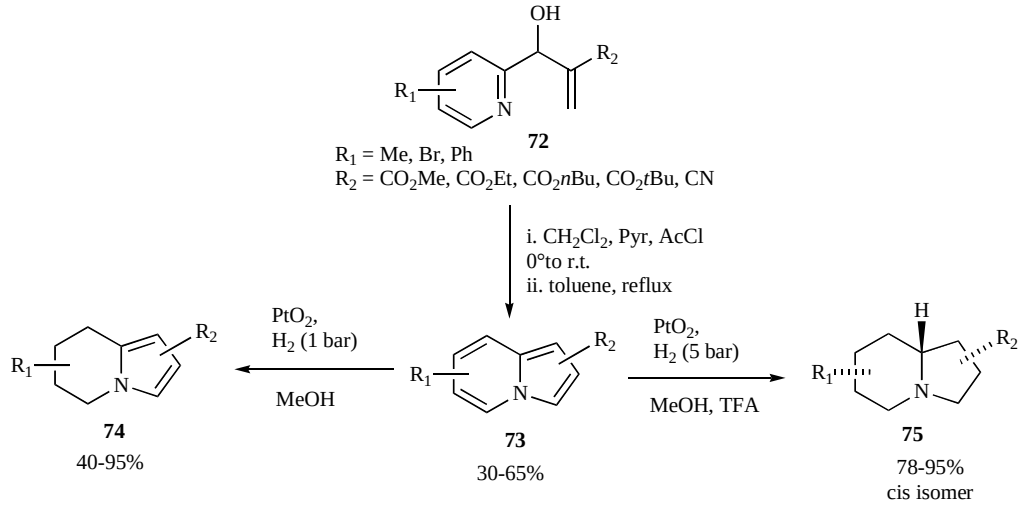


70

R_1 = CO_2Me, CN
R_2 = $(CH_2)_2$Indoyl

R_1	Yield %	*syn*/*anti* ratio
CO_2Me	63	26:1
CN	23	1:22

Scheme 23. Synthesis of 1,2,3,4-tetrahydro-1,8-naphthyridine framework.



Scheme 24. Synthesis of tetrahydroindolizidines and indolizidines by catalyzed hydrogenation.

to give the β-hydroxy-α-amino ester derivatives **62** with high *anti*-diastereoselectivity. This selectivity, resulting from steric hindrance caused by the silyl group, was supported by theoretical calculations. The acetylated derivatives **60b**, after initial allylic acetate reduction, afforded α-amino esters/acids such as the neurotransmitter DOPA (**66**) through a similar reactions sequence (Scheme **21**) [37].

Vicinal tricarbonyl compounds (VTC) could be easily accessed from MBH adducts *via* two sequential oxidation steps [38]. Therefore, 2-iodoxybenzoic acid (IBX) was chosen as the first oxidizing agent to afford α-methylene-β-keto carbonyl compounds in excellent yields and with high purities. The methylene moiety was then exposed to oxidative cleavage conditions (ozonolysis) to provide the tricarbonyl frameworks **69** (Scheme **22**).

4.2. Synthesis of Heterocycles

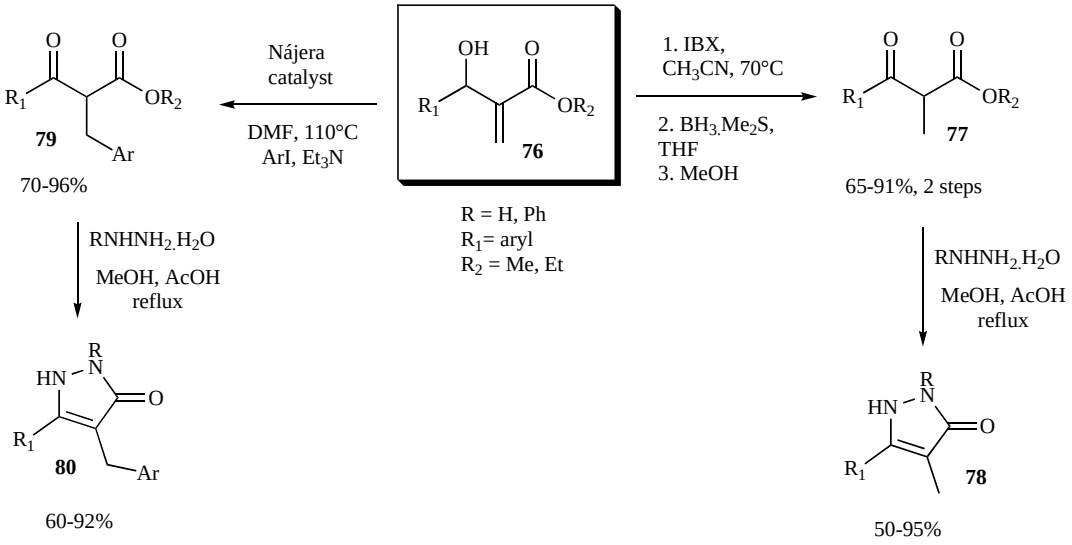
Heterocycles are compounds of great interest for chemists, because they are present in the structure of many biologically active molecules and drugs. They also have been applied as ligand and catalysts in some reactions as well used to modify the polarity of the molecules. The high functionality of MBH adduct has stimulated their use as building block for the preparation of a wide diversity of heterocyclic systems.

1,2,3,4-tetrahydro-1,8-naphthyridine derivatives are of great pharmaceutical importance, because several drugs possess this backbone. In 2010, Coelho *et al.* [39] reported an approach for the synthesis of 1,8-naphthyridine using a silylated MBH adduct as the substrate for a sequence of Michael addition and S_NAr reactions (Scheme **23**).

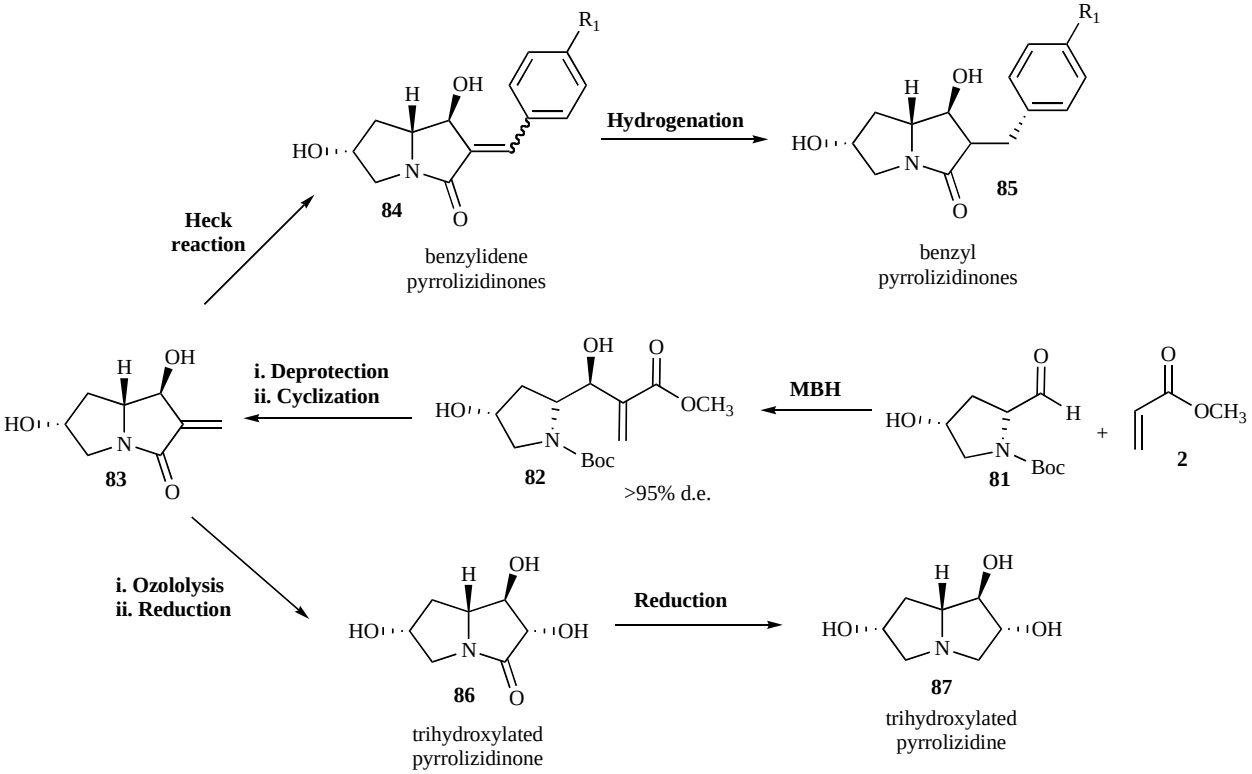
The relative stereochemistry was controlled in the cyclization step affording 1,8-naphthydirines with good diastereoselectivity. The selectivity was attributed to the sterically bulky silyl group in cases where esters are the substituent (diastereoisomer *syn*); however, an inversion on the relative stereochemistry was observed (diastereoisomer *anti*) when R_1 was replaced by a cyano group.

Tetrahydroindolizines and indolizidines were obtained by the partial or total catalytic hydrogenation of indolizines derived from MBH adducts (Scheme **24**).

The indolizines were prepared by a sequence of acetylation and intramolecular cyclization promoted by heating. The catalyst se-



Scheme 25. Synthesis of 4-substituted pyrazolones.



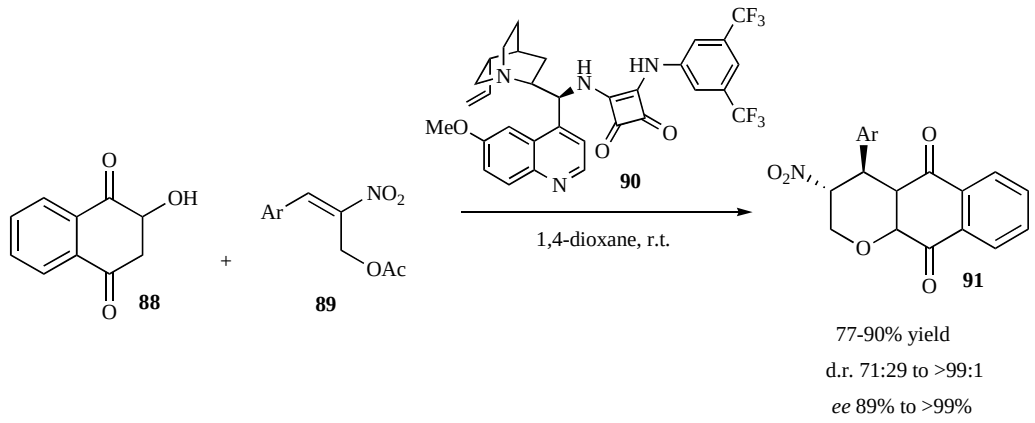
Scheme 26. Synthesis of highly substituted pyrrolizidinones and pyrrolizidines.

lected for the hydrogenation step was PtO_2, which afforded 5,6,7,8-tetrahydroindolizines and indolizidines. The partial and complete hydrogenation reaction was dependent on the hydrogen pressure and the pH of the reaction mixture. Higher pressure and strong acid conditions was necessary to obtain indolizidines, which were synthesized with high diastereoselectivity [40].

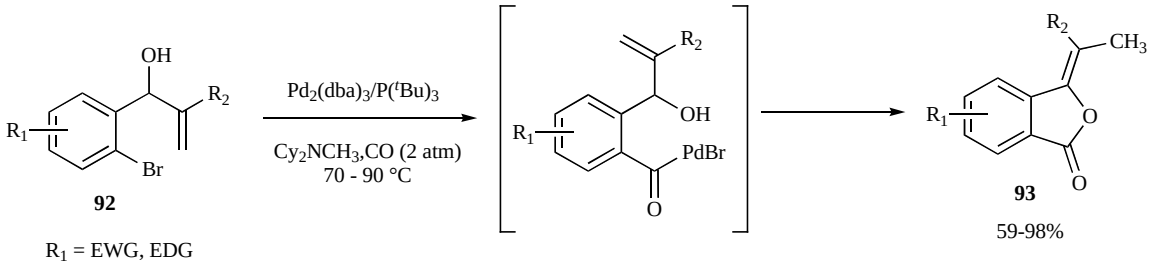
The pyrazolone nucleus has been present in the structures of several drugs such as dipyrone and phenazone. These compounds are currently used in medicine, due to their analgesic, antipyretic and anti-inflammatory activities [41].

4-Substituted pyrazolones were synthesized by the treatment of a β-ketoesters with hydrazine. The β-ketoesters required for this transformation were, in turn, synthesized using two possible approaches. In the first, the secondary hydroxyl group of the MBH adduct was oxidized and the double bond was selectively reduced by treatment with borane dimethyl sulfide to afford α-methyl substituted β-ketoesters. Alternatively, β-ketoesters having different substituents at α-position were synthesized from MBH adducts using the Heck reaction. These methods to synthesize β-ketoesters afforded pyrazolones with different level of functionalization with moderate to good yields (Scheme **25**) [42].

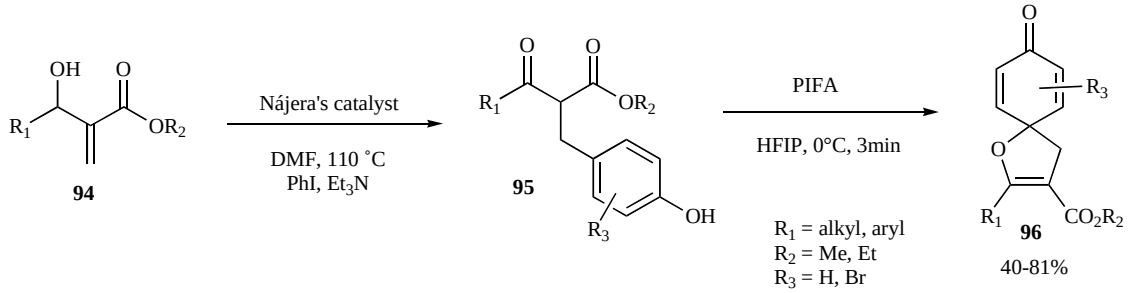
An asymmetric approach for the synthesis of pyrrolizidinone and pyrrolizidine skeletons has been reported in two steps. Firstly the MBH reaction between *N*-Boc-4-hydroxyprolinal **81** and methyl acrylate followed by nitrogen deprotection and cyclization (Scheme **26**) [43]. The correct functional groups on the structures of the



Scheme 27. Synthesis of pyranones and pyranonaphthoquinones *via* a cascade reaction.



Scheme 28. Synthesis of 3-alkenyl phthalides from MBH adducts.



Scheme 29. Synthesis of spiro-hexadienones.

MBH adducts have allowed an intramolecular cyclization to afford the synthesis of highly functionalized pyrrolizidinones and pyrrolizidines. The high stereochemical control of the entire process was mediated directly by an intramolecular hydrogen bond between the hydroxyl and the aldehyde groups present in the structure of **81** (Scheme **26**).

Oxygenated heterocycles such as pyranones and pyranonaphthoquinones were obtained by cascade reactions of 1,3-dicarbonyls **88** with MBH acetates of nitroalkenes **89** [44]. The asymmetric synthesis is result of a reaction sequence beginning with an enantioselective Michael addition of 1,3-dicarbonyls to MBH acetate (and elimination of the acetate, which correspond to a formal S_N2' reaction), followed by a diastereoselective intramolecular oxa-Michael addition. Both reactions were catalyzed by a bifunctional quinine-squaramide catalyst **90** which was responsible for the deprotonation of the dicarbonyl compound by the tertiary amine of the quinuclidine moiety and activation of the nitro group by two H-bond with the squaramide moiety (Scheme **27**).

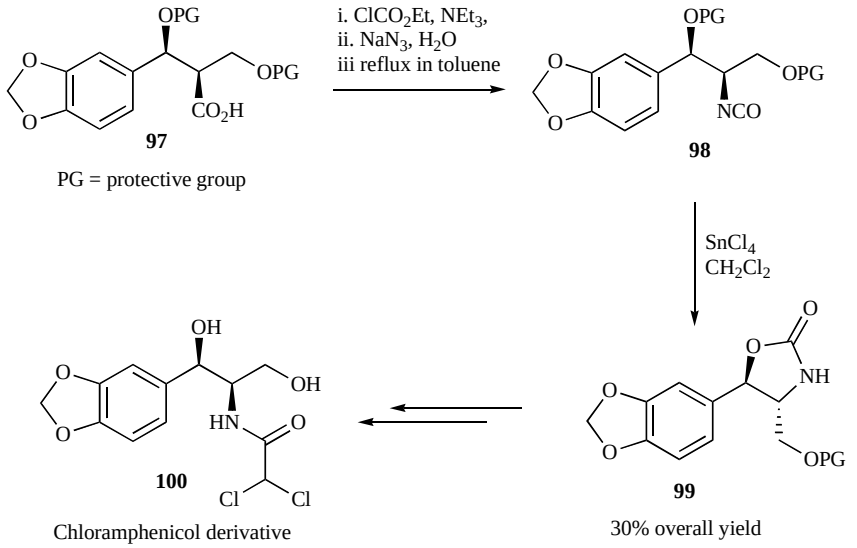
The efficiency of this methodology is noteworthy, because of high yields and high diastereo- and enantioselectivities obtained for several aromatic MBH acetates, even in gram scale. In addition, the presence of a nitro group allowed increased functionalization of the heterocycle after suitable transformations of the amino and azido derivatives.

Phthalides or 3H-isobenzofuran-1-one were synthesized using a palladium-catalyzed carbonylative cyclization of MBH adducts. This approach consists of the utilization of an *o*-brominated aromatic MBH adducts, which, in the presence of CO and $Pd_2(dba)_3/P(^tBu)_3$, give an acyl-palladium intermediate and, after reductive elimination, afforded 3-alkenyl phthalides **93** in good yields and with stereoselectivity in most cases (Scheme **28**) [45].

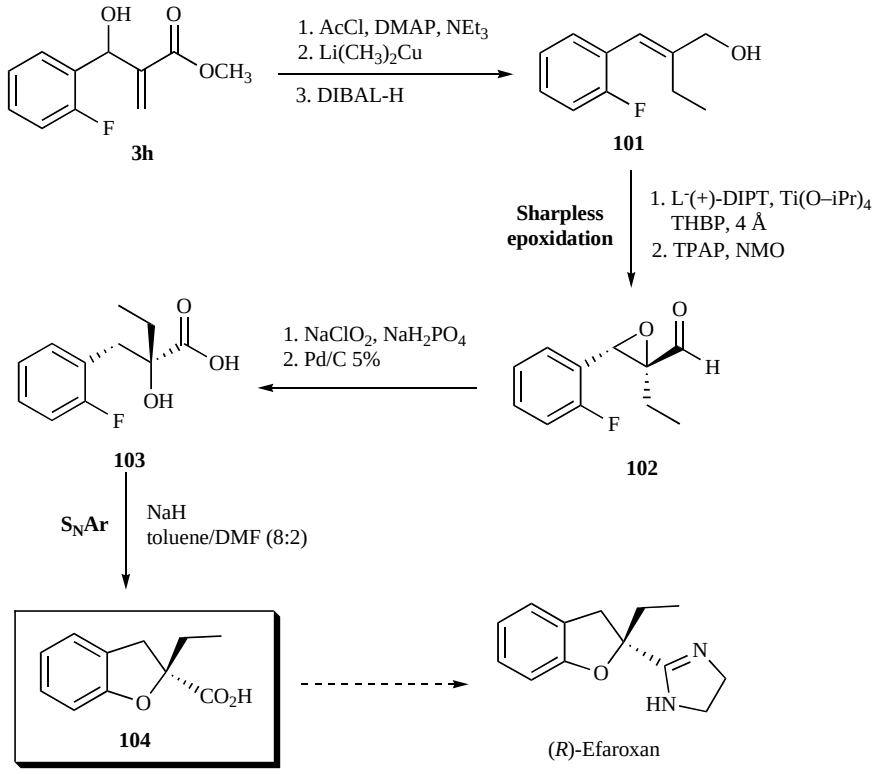
α-Benzyl-β-keto-esters, prepared *via* a Mizoroki-Heck reaction between MBH adducts and iodophenol catalyzed by Nájera palladacyle [46], were used as substrates in the synthesis of spiro-hexadienones like **96**, with diversified structural patterns. The key step in the synthesis of the spiro system was the phenolic oxidation promoted by the hypervalent iodine reagent PIFA [phenyliodine-bis(trifluoroacetate)] which results in an oxidative dearomatization followed by cyclization in a unique step (Scheme **29**) [47].

4.3. Synthesis of Natural Products and Drugs

A formal synthesis of a Chloramphenicol derivative (**100**) was described employing an oxazolidinone as key intermediate, which can also be easily interconverted into aminoalcohols. MBH adducts were modified using a sequence of hydroboration, oxidation and manipulation of the protective groups to afford acid **97** and then to the corresponding isocyanate **98**. Thus, the isocyanate gave the



Scheme 30. Synthesis of a chloramphenicol derivative from 4,5-disubstituted oxazolidin-2-one.



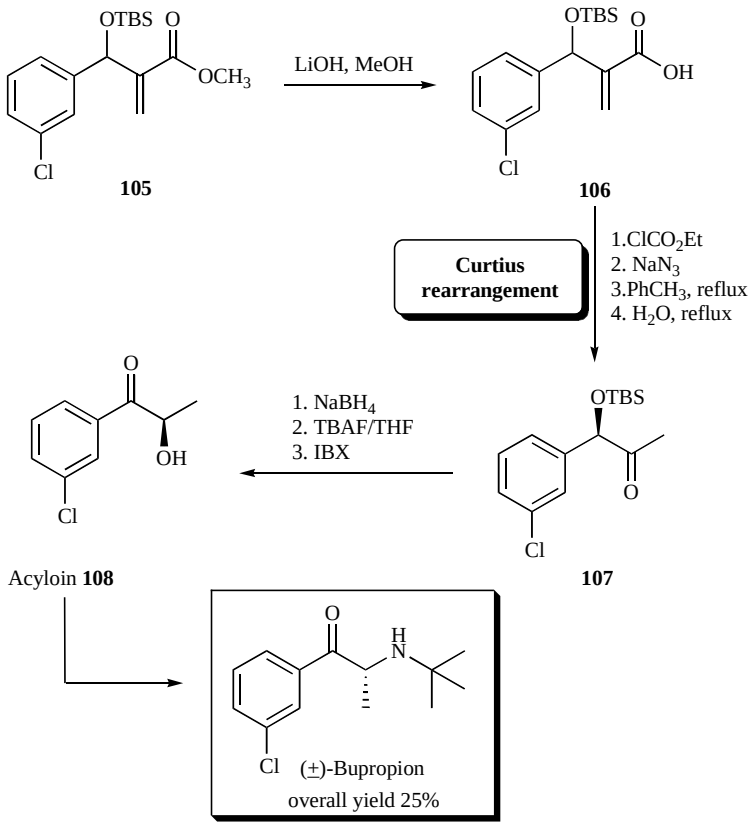
Scheme 31. Enantioselective synthesis of 2-ethyl-2,3-dihydrobenzofuran carboxylic acid.

substitute oxazolidin-2-one **99**, after treatment with $SnCl_4$ (Scheme **30**) [48].

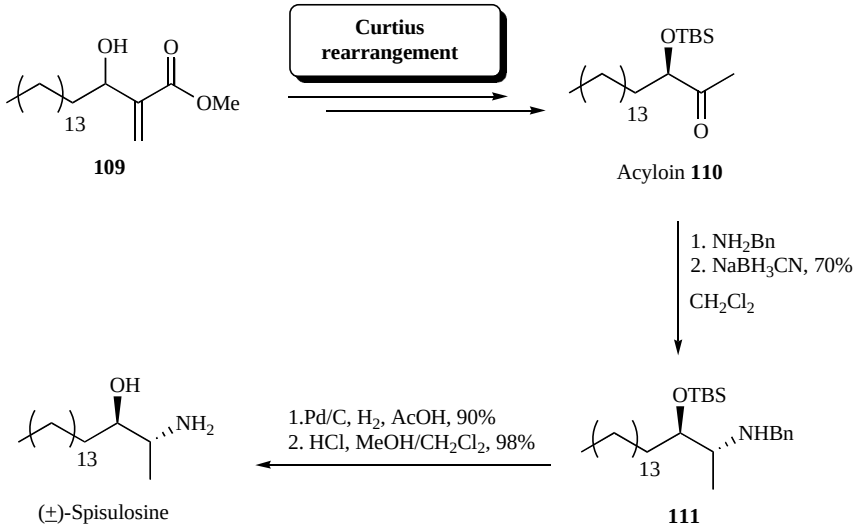
The pharmacological relevance of Efaroxan stimulated the development of an enantioselective strategy for preparation of *R*-(+)-2-ethyl-2,3-dihydrofuran carboxylic acid, a direct precursor of (*R*)-Efaroxan. The MBH adduct **3h** derived from 2-fluorobenzaldehyde and methyl acrylate was used as the starting material. The generation of the stereogenic centers in a controlled fashion was performed by a key Sharpless epoxidation step. After a sequence of oxidations and epoxide ring opening, the diidrobenzofuran ring was obtained *via* a nucleophilic aromatic substitution reaction (S_NAr) (Scheme **31**) [49].

The silylated MBH adducts such as **105** can be transformed to acyloins (α-hydroxyketones) *via* a Curtius rearrangement. This acyloin was used as advanced intermediate in the synthesis of racemic Bupropion. This compound is an antidepressant agent used in the treatment of smoking cessation [50]. The silylated acyloin **107** was then transformed into a respective regioisomer **108** and submitted to nucleophilic substitution conditions to provide Bupropion in 25% overall yield (Scheme **32**) [51].

A similar strategy was designed to synthesize racemic Spisulosine. This marine natural product has a remarkable antitumor activity and was prepared from acyloin **110** obtained from the MBH adduct **109** (Scheme **33**) [52].



Scheme 32. Synthesis of racemic bupropion *via* acyloins obtained from MBH adducts.

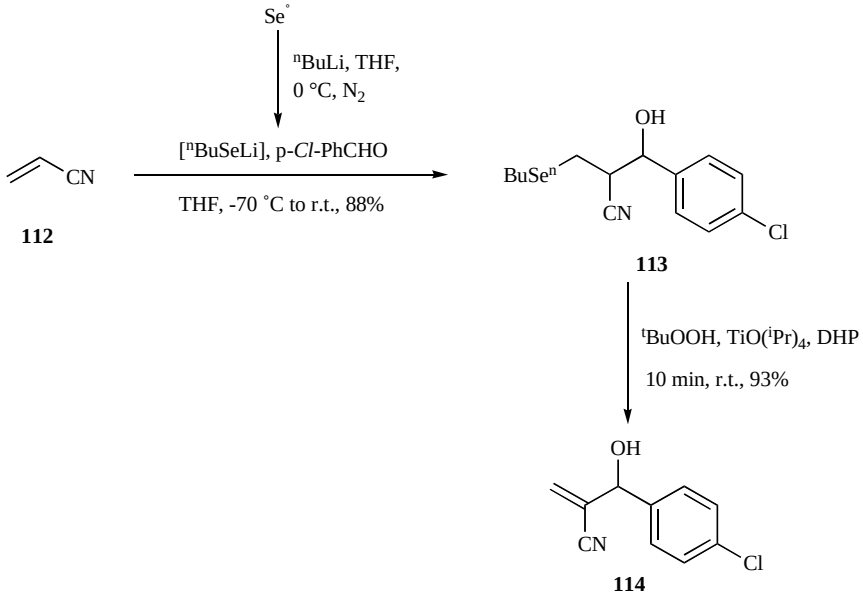


Scheme 33. Synthesis of (±)-spisulosine *via* an acyloin intermediate.

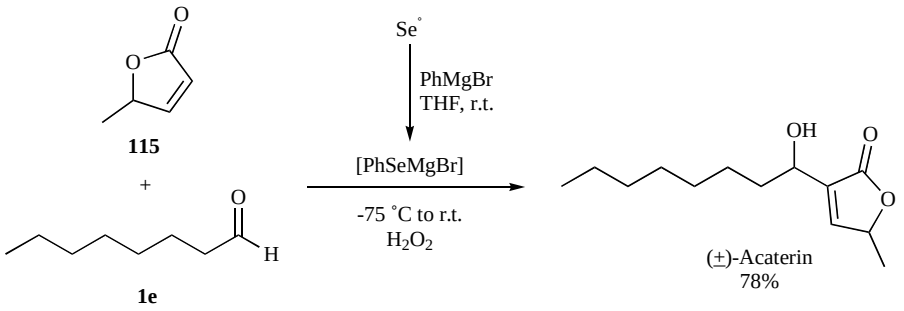
5. ALTERNATIVE APPROACHES FOR THE SYNTHESIS OF MBH ADDUCTS

In 2009, Comasseto *et al.* [53] reported a protocol to prepare organochalcogen employing easily available and environmental friendly precursors. The application of this methodology allowed the preparation of MBH adducts through an electroselenylation followed by oxidation/elimination (Scheme **34**). Lithium *n*-butylselenolates generated *in situ* by reacting the selenium with *n*-butyllithium reacted with acrylonitrile *via* a Michael addition. The resulting enolate intermediate was captured by the *p*-chlorobenzaldehyde to give the corresponding product **113**, which, after the oxidation, triggered the selenoxide elimination to afford the corresponding MBH adduct **114**.

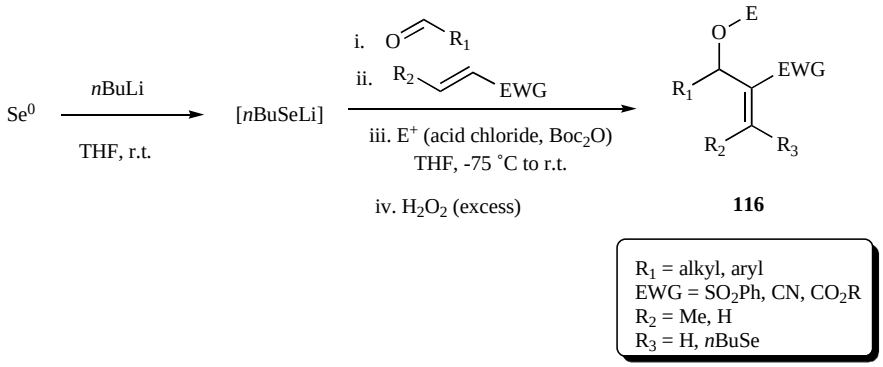
The scope of this method was expanded and the behavior of different chalcogenolates, aldehydes, and Michael acceptors under these conditions was evaluated [54]. The study showed the applicability of sulfides, selenides and tellurides in the aldol reactions and could extend the scope for non-activated aldehydes and to β-substituted Michael acceptors. Furthermore, the reactions were carried out in short reaction times, overcoming a drawback of the traditional MBH reaction. The efficiency of this alternative method



Scheme 34. Morita-Baylis-Hillman adducts from highly functionalized organochalcogenides.



Scheme 35. Application of the synthesis of MBH adducts *via* organochalcogenides for the synthesis of (±)-Acaterin.



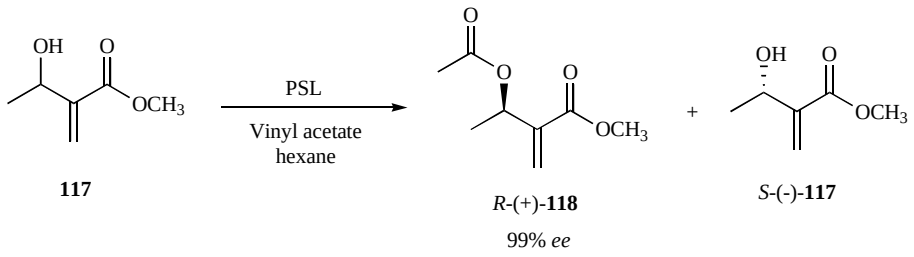
Scheme 36. Synthesis of MBH derivatives *via* organochalcogenides.

was demonstrated in the racemic synthesis of the natural product Acaterin (Scheme **35**).

This methodology works well for aromatic aldehydes having electron-releasing substituents, but it is much less efficient for electron-withdrawing substituted aromatic aldehydes. Thus, this protocol is a valid alternative for affording MBH adducts and is an important complement to the traditional MBH reaction, in which aldehydes having electron-releasing substituents are poor substrates.

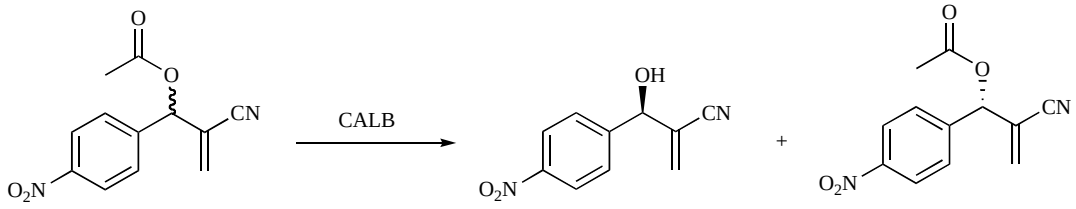
In addition, dos Santos *et al*. [55] reported a fast and high-yielding methodology to synthesize MBH derivatives **116** *via* a one-pot Michael/aldol/*O*-functionalization/selenoxide elimination cascade thus expanding the synthetic utility of this MBH-type reaction (Scheme **36**). Good results were observed including Michael acceptors containing a methyl group at the β position, non-activated alkyl aldehydes and electron-rich aromatic aldehydes. The combination with different acid chlorides and anhydrides as electrophiles led to a broad series of acetates and carbonates derived from MBH adducts.

Another serious drawback of the MBH reaction is the absence of a general asymmetric version. Although much progress in understanding the factors that govern this reaction has been achieved, the complete understanding of it remains lacking, and obtaining a general chiral version of the MBH reaction is still a challenge. However, high enantiomeric purity can be accessed by biocatalysts such



117 *R*-(+)-**118** 99% *ee* *S*-(-)-**117**

Scheme 37. Kinetic resolution of the MBH adduct using PSL.



(±)-**119** *R*-(+)-**120** 37%, >99% *ee* *S*-(-)-**119**

Scheme 38. Kinetic resolution of an acetate MBH derivatives.

as lipases from *Pseudomonas* sp. (PSL) [56] and *Candida antarctica* (CALB) [57] which have been efficiently employed in kinetic resolutions of MBH adducts and their acetate derivatives (Schemes **37** and **38**).

6. BIOLOGICAL ACTIVITIES OF MBH ADDUCTS

6.1. Biological Profiles

Since the pioneering publication reporting the antimalarial activities of some aromatic and hetero aromatic MBH adducts [58], considerable advances have occurred regarding the investigation of the biological profile of these poly-functionalized compounds. Lima-Junior and Vasconcellos highlight the broad spectrum of biological activities from MBH adducts such as antitumor, antibacterial, and antifungal activities as well as uses as herbicides. Moreover, several MBH adducts have been reported as bioactive compounds against neglected diseases such as malaria, leishmaniasis, schistosomiasis and Chagas (Fig. **5**) [59].

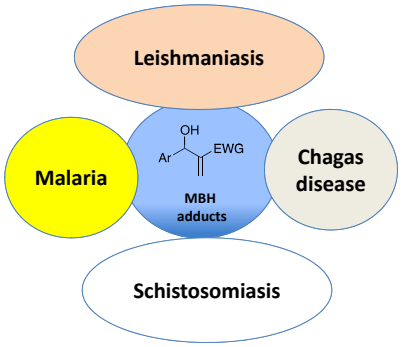


Fig. (5). MBH adducts as promising drugs for neglected parasitic diseases.

Due to its biological profile, the Morita-Baylis-Hillman reaction now appears not only as a source of intermediates for synthetic purposes, but also as a source of infinite classes of potential bioactive compounds. For this reason, research groups have recently published more elaborate works that advance the expansion of the biological profile of MBH adducts. Furthermore, studies related to the rationalization of Quantitative Structure-Activity Relationship (QSAR) and of possible mechanisms of biological action against various diseases have been also published.

Recently, theoretical conformational and QSAR studies involving 32 aromatic MBH adducts were described to rationalize the development of effective compounds against *Leishmania amazonensis* [60]. The preferred conformations for these adducts were controlled by six and/or seven- membered intramolecular hydrogen bonds (Fig. **6**), which are characterized by QTAIM calculations and spectroscopic data. The QSAR study provided a model with good values for parameter validation (R_2 = 0.71, = 0.61 and Q_2ext = 0.92) [60].

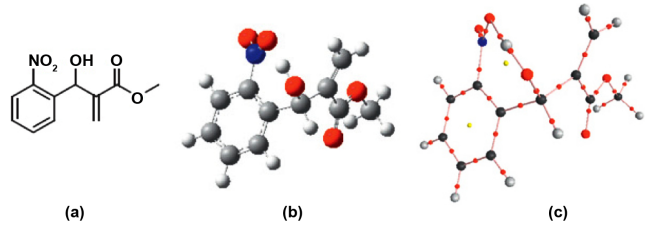
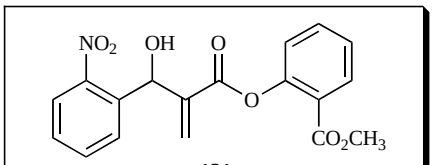


Fig. (6). (a) MBH adduct, (b and c) conformation controlled by intramolecular hydrogen bonds.



121

L. (V.) braziliensis: MHOM/BR/1975/M2903

IC_{50} = 2.73 mg/mL
SI = 5.55

Fig. (7). Hybridized MBH adduct.

A MBH adduct **121** designed by a molecular hybridization strategy between methyl salicylate and MBH adduct derivative from *ortho*-nitrobenzaldehyde (Fig. **7**), presented a potent *in vitro* activity against amastigote and promastigote *Leishmania* (Viana) *braziliensis* [61]. Biological evaluation demonstrated the highest leishmanicide activity thus far (IC_{50} = 2.73μM) and a selectivity index (SI) equal to 5.55 for a reference strain MHOM/BR/1975/

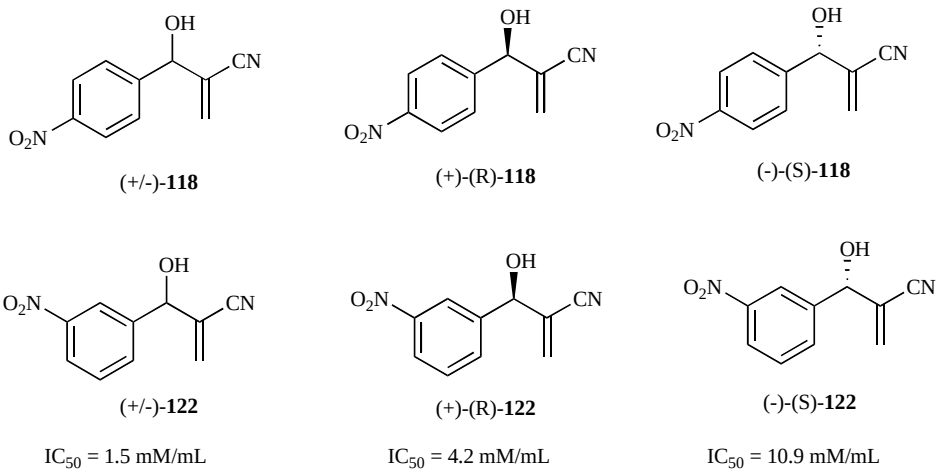


Fig. (8). Racemates and enantiomers obtained by kinetic resolution.

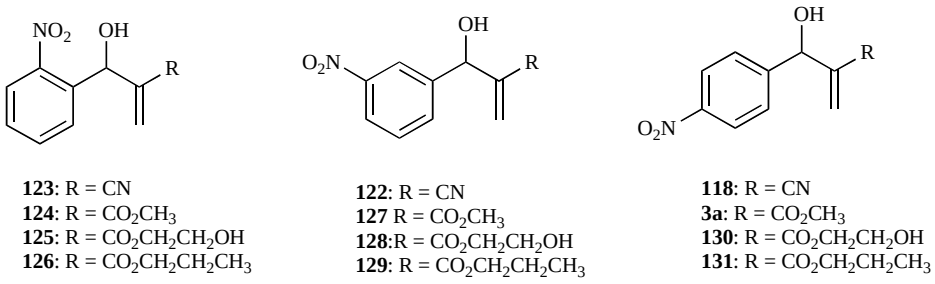


Fig. (9). Twelve MBH adducts electrochemically studied by cyclic voltammetry (CV).

M2903. After investigation of immunomodulatory properties, it was observed that MBH **121** decreased IL-6 and IL-10 production, resulting in a reduction of the infection rate.

In 2014, Sandes *et al*. [62] published a study of the adduct **122** to understand the physiological changes and cell death mechanism induced by *T. cruzi*. Employing confocal microscopy and flow cytometry, it was observed that high concentrations of the adduct induced a series of injuries such as damage to the parasite plasma membrane, loss of mitochondrial membrane potential, DNA fragmentation and cytoplasmic acidification resulting in a cell death by necrosis.

In a pioneering work, Xavier *et al*., [57] made by kinetic resolution of **118** and **122** MBH adducts using *Lipase B Candida antarctica* (Fig, **8**). The MBH adducts were obtained with high optical purities (>99% e.e.) and the absolute configuration was determined using the Mosher methodology [63]. (±)-**118**, (±)-**122**, and its optically active enantiomers (*R*)-(+)-**122** and (*S*)-(-)-**122** were tested against promastigote forms of *Leishmania* (Viannia) *braziliensis* and curiously, it was found that the racemic compound, (±)-**122**, was more potent than either of the isolated enantiomers. Furthermore, peritoneal macrophage cytotoxicity in Swiss mice demonstrated that racemic (±)-**122**, as well as (*R*)-(+)-**122** and (*S*)-(-)-**122** enantiomers were absent of toxicity.

Alencar-Filho *et al*. [64] in a structure-activity relationship from leishmanicidal MBH adducts described a rugged and predictive QSAR model to help the search for new and more powerful MBH adducts as leishmanicide agents. In this study, the authors attributed the presence of the nitro group in the *ortho* position and larger molecular volumes in MBH adducts as important characteristics for biological activity.

Electrochemical methods are useful tools to simulate *in vivo* metabolic processes. The biological activity of nitrocompounds is associated to nitro group reduction that generates different intermediates. In a electrochemical study, carried out in a protic medium, the cyclic voltammetry (CV) on twelve nitro-substituted MBH adducts was evaluated (Fig. **9**) [65]. This study aimed at looking for additional information for a better understanding of the behaviors of these compounds in a biological environment. It was observed a strong correlation between reduction potential and leishmanicidal activity.

The perspectives of MBH adducts applied to drug design can be exponentially expanded, if we consider the derivatives that can be easily prepared from these adducts. For example, in a recent study, thirteen allylthiocyanates (Fig. **10**) obtained from MBH adducts in two steps, showed moderate to high antimicrobial activities [66]. Coupled with the satisfactory activities presented, the authors have highlighted the facile and low cost preparation, of these thiocyanates derived from MBH adducts, making them a promising class of compounds for drug development.

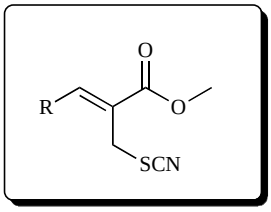
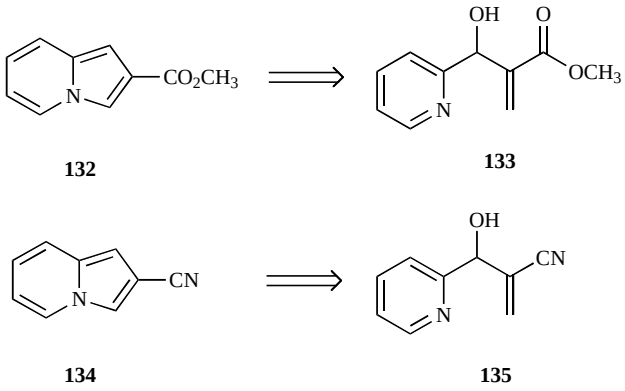


Fig. (10). Allylthiocyanates derived from MBH adduct.

In another example, Cunha *et al.* [67] described the syntheses of 2-substituted aromatic indolizines from MBH adducts. These compounds have high potential activities as ionic channels blockers, according to the *in silico* evaluation performed using the free Molispiration software (Scheme **39**).

The Morita-Baylis-Hillman adducts should not be seen only as building blocks for the synthesis of different compounds but also as

a platform for the development of compounds with interesting biological properties. This broad spectrum of biological activities should be used as a stimulus in the search for more attractive synthetic methodologies, using all possible combinations of electrophiles and Michael acceptors. This open the possibility of accessing to a large collection of new small conjugated molecules having different biological activities.



Scheme 39. 2-Indolizines prepared from MBH adducts.

6.2. Mechanism of Action

As the MBH adducts present an unsaturated α,β-carbonyl portion (Michael acceptor), their behavior as electrophiles in front of biological nucleophiles (receptors and enzymes) is quite obvious. A possible mechanism of action to explain the anti-malarial effect exhibited by the MBH adducts could be the inactivation of falcipain enzyme, through the nucleophilic addition of a thiol group on the adduct conjugated double bond. Concerning the antitumor activity, Vasconcellos *et al.* has suggested that MBH adducts could act as stimulators or inhibitors of GSH synthesis or possibly affect their intracellular concentration. Trying to contribute to the expansion of the biological profile and increase the understanding of the mechanism of biological action of MBH adducts, Bertinaria *et al.* [68] recently published an elegant work in which a library of MBH adducts showed antipyroptotic activities. According to the authors who investigated the chemical reactivity of MBH adducts against glutathione (GSH), a covalent bond occurred between the GSH and the Michael-acceptor which characterizes the MBH adduct as a covalent, irreversible thiol-trapping agents. These results confirm the action of MBH adducts as electrophile in a biological environment, as proposed by Lima-Junior and Vasconcellos [60].

CONCLUSION AND PERSPECTIVES

The Brazilian chemical community has given relevant contributions for the Morita-Baylis-Hillman chemistry, exploring several aspects of this amazing transformation. Thus, studies related to circumvent the drawbacks of this reaction by using different solvents and Lewis bases, mechanistic investigations, development of new synthetic methods and the use of MBH adduct as platform for the synthesis of natural products and drugs. In addition to synthetic targets, MBH adducts have been applied in biological and medicinal chemistry and several studies exploring theirs biological profile have been reported.

The Morita-Baylis-Hillman reaction is a young chemical transformation and there is much more to be explored with these adducts in different area.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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