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BAYLIS-HILLMAN BROMIDES IN ORGANIC SYNTHESIS: A BRIEF DESCRIPTION OF OUR CONTRIBUTIONS

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here].

Abstract:

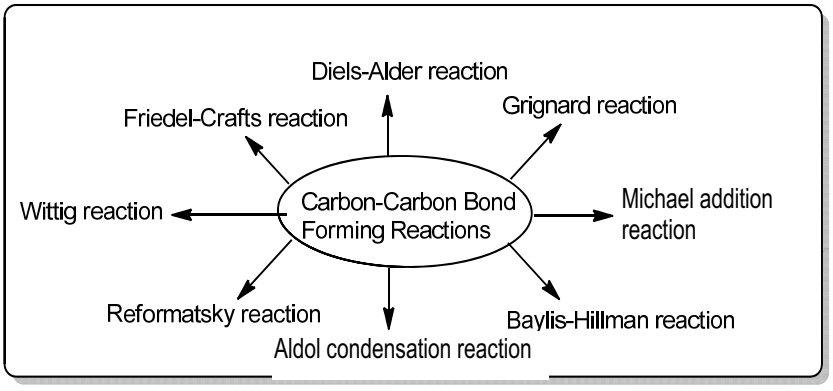
This mini review presents applications of bromides of the Baylis-Hillman adducts in organic synthesis with an emphasis on our own research contributions. This review will also highlight very briefly the importance of the Baylis-Hillman reaction and its potential to grow further.

1. Introduction

The Baylis-Hillman reaction

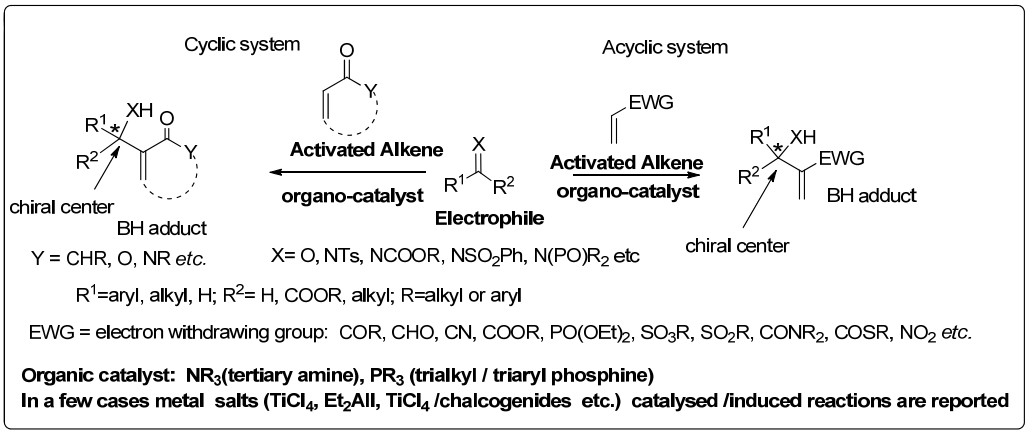
Construction of carbon-carbon bond(s) is not only the most fundamental reaction in organic chemistry but also is one of the most essential requirements in synthesis of almost all the natural products/bioactive molecules.[1-4] Therefore development of atom economical C-C bond forming reactions represents one of the challenging and attractive endeavours in synthetic chemistry. Over the years several C-C bond forming reactions have been discovered, designed and developed; and their applications in many aspects of organic synthesis have been systematically and elegantly demonstrated.[1-4] Some of the important C-C bond forming reactions have been listed in Figure 1.[1-4]

Figure 1. Representative C-C-bond forming reactions [1-4]



Baylis-Hillman reaction[5] (also known as the Morita-Baylis-Hillman reaction)[6,7] is one such atom-economical C-C bond forming reaction uncovered from a little known patent and has grown to the level of popular name reaction.[5-22] This reaction provides molecules containing a minimum of three proximal functional groups *via* C-H functionalization process involving the coupling of α-position of activated alkene with an electrophile in the presence of a catalyst (Scheme 1).[5-22] This reaction is usually catalysed by an organic molecule (tertiary amine or trialkyl/triaryl phosphine) and that is why this reaction represents an important example for organo-catalytic reactions.[16,20] However, some examples of metal catalysed/induced coupling reactions between activated alkenes and electrophiles have also been reported.[16,20]

Scheme 1. The Baylis-Hillman reaction at a glance[16,20]



During the past three-four decades the Baylis-Hillman reaction has grown with respect to all the three reaction components (activated alkene, electrophile and catalyst). Thus, a number of activated alkenes, electrophiles and catalysts have been systematically employed in this reaction producing interesting classes of densely functionalized molecules having very high potential as key synthons in organic synthesis.[16,20]

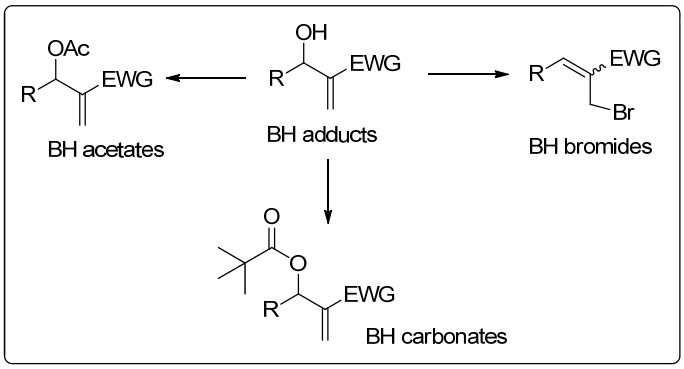
If the electrophile used in this reaction is a prochiral molecule then there is a possibility of developing its asymmetric version and obtaining enantiomerically pure/enriched adducts by using appropriate chiral source or environment. Thus asymmetric version of Baylis-Hillman reaction has been developed using chiral source either in activated alkenes (chiral activated alkenes), in electrophiles (chiral electrophiles), in catalysts (chiral catalysts) (any one of the reaction components) or in two/all of the three reaction components.[16,20] Although significant efforts were directed towards kinetic resolution using enzymes or by chemical methods; this strategy has not been explored/pursued systematically.[16,20] It needs to be mentioned here that even though asymmetric Baylis-Hillman reaction has grown to a considerable

extent, it did not reach the levels of successful asymmetric BH reaction. Therefore there are several challenges and opportunities to reach that level.

Application of Baylis-Hillman bromide

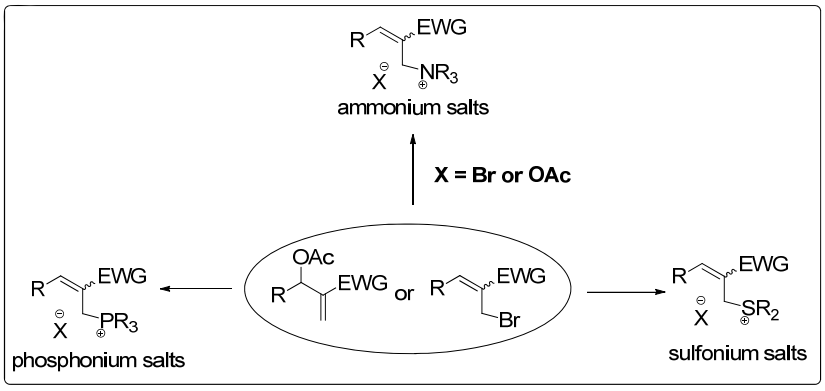
The Baylis-Hillman adducts have been employed extensively in a number of organic transformation strategies due to the proximity of three functional groups present in them.[16,20] Baylis-Hillman alcohols (adducts) have been very conveniently converted into the corresponding acetates, bromides, and carbonates (Scheme 2) which have been also systematically and meticulously employed in a number of ways in synthetic chemistry.[16,20]

Scheme 2. Baylis-Hillman adducts and derivatives[16, 20]



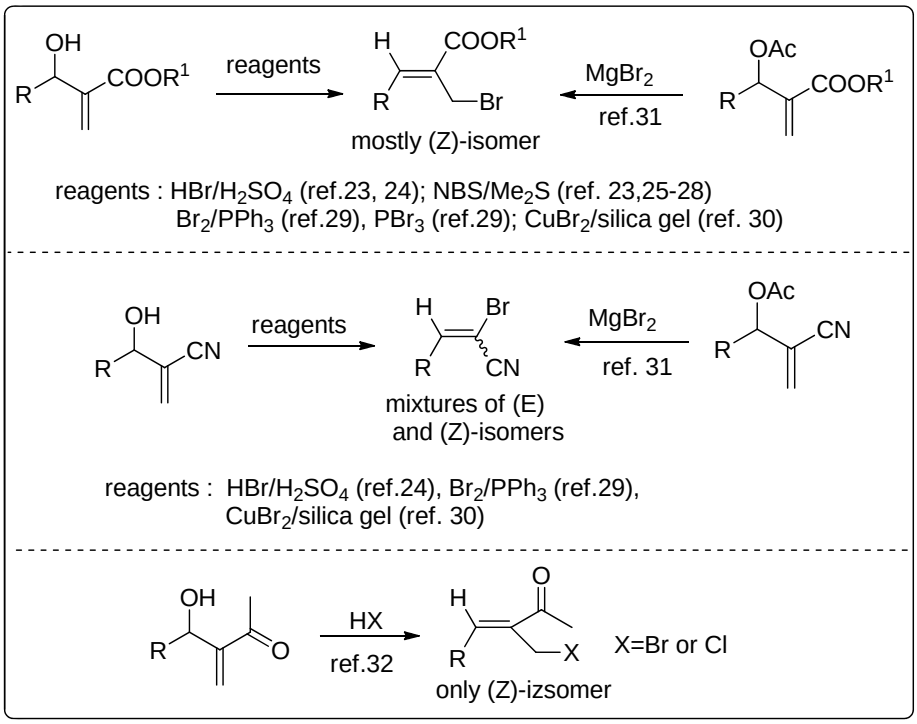
The Baylis-Hillman acetates and bromides can be easily converted into reactive intermediates, *i.e.*,sulfonium, ammonium and phosphonium salts which have been elegantly used in many transformation methodologies and synthetic processes (Scheme 3).[9,16,20]

Scheme 3. Reactive intermediates from Baylis-Hillman acetates and bromides[9,16,20]



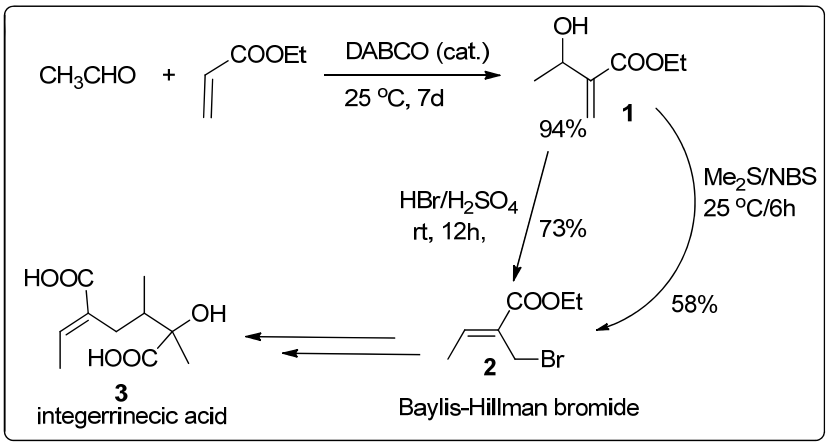
Since the main aim of writing this review is to highlight the applications of the Baylis-Hillman bromides with an emphasis on our own research contributions, it is not possible to describe the applications of the BH adducts and other derivatives in organic synthesis in this review. The Baylis-Hillman bromides can be easily synthesized from the BH adducts or from the corresponding acetates (representative strategies are presented in Scheme 4).[16,20,23-32]

Scheme 4. Synthesis of Baylis-Hillman bromides[16,20,23-32]

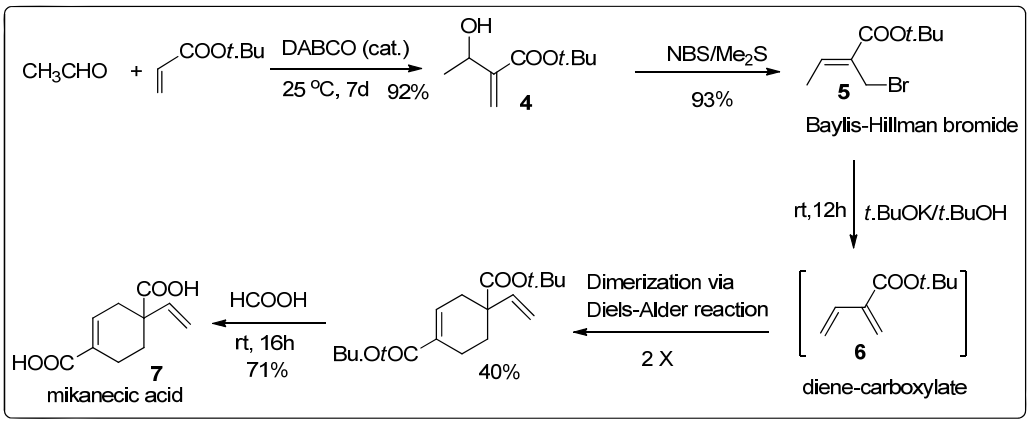


It is appropriate to describe the first application of Baylis-Hillman bromide (**2**) reported by Drewes and Emslie as early as in 1982 (Scheme 5).[23] They prepared bromide **2** of Baylis-Hillman adduct (**1**) (which was obtained from acetaldehyde and ethyl acrylate) and ingeniously transformed into integerrinecic acid (**3)** (Scheme 5).[23] Hoffmann and Rabe have reported brilliant application of the BH bromide (**5**) synthesized from BH alcohol (**4**) (which was in turn obtained from *tert*.butyl acrylate and acetaldehyde) for synthesis of mikanecic acid (**7**), an importantterpene molecule, following the reaction sequence shown in Scheme 6.[26,28] The key step in this strategy is the spontaneous Diels-Alder dimerization of the *in situ* generated diene carboxylate (**6**) which was obtained on treatment of the bromide **5** with *t*.BuOK/*t*.BuOH.

Scheme 5. Conversion of BH bromide (2) into integerrinecic acid (Drewes and Emslie)[23]



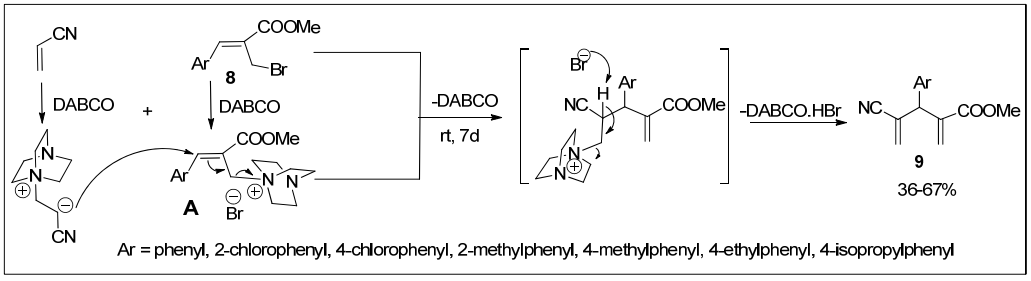
Scheme 6. Conversion of BH bromide 5 into mikanecicacid (7) (Hoffmann and Rabe)[26,28]



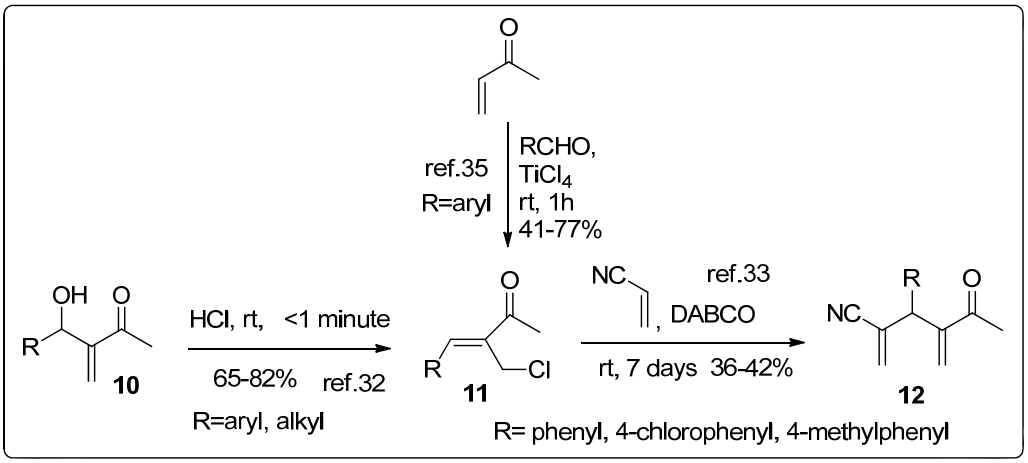
We have successfully used the Baylis-Hillman bromides (**8**) as excellent electrophiles for coupling with acrylonitrile in the presence of DABCO to provide functionalized 1,4-pentadiene molecules (**9**) (Scheme 7).[33] The key step in this transformation is the formation of ammonium salt **A** which is the actual electrophile for BH coupling reaction. The desired allyl bromides **8** were conveniently prepared from the BH adducts (which were obtained from methyl acrylate and aryl aldehydes) *via* the treatment with HBr/H_2SO_4.[23] We have successfully extended this strategy to allyl chlorides (**11**) which provided pentadiene derivatives (**12**) on treatment with acrylonitrile in the presence of DABCO (Scheme 8).[33] The required BH chlorides **11** were obtained from BH adducts (**10**) *via* the reaction with HCl.[32] The desired BH

alcohols **10** were conveniently prepared *via* the coupling of methyl vinyl ketone (MVK) with aldehydes.[34] It is appropriate to mention here that allyl chlorides (**11**) can also be easily obtained *via* the treatment of methyl vinyl ketone (MVK) with aldehydes in the presence of $TiCl_4$.[35]

Scheme 7. BH bromides (derived from methyl acrylate and aldehydes) as excellent electrophiles for coupling with acrylonitrile in the presence of DABCO[33]



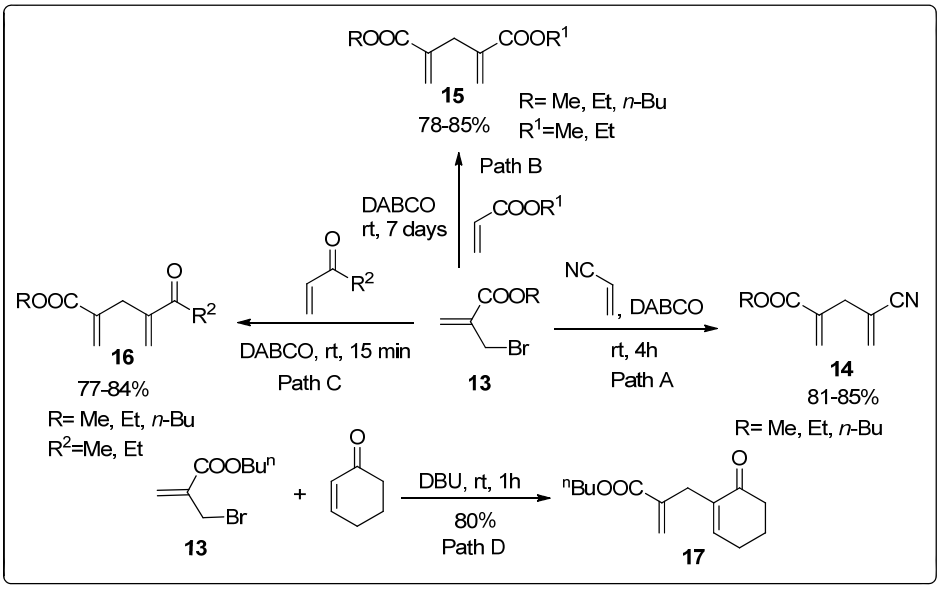
Scheme 8. BH chlorides (derived from methyl vinyl ketone and aryl aldehydes) as excellent electrophiles for coupling with acrylonitrile in the presence of DABCO[33]



We have then employed allyl bromides (**13**) derived from the Baylis-Hillman alcohols (which were in turn prepared *via* the reaction of HCHO with acrylates) as electrophiles for coupling with activated alkenes. Thus the reaction of the allyl bromides **13** with various activated alkenes such as acrylonitrile (Path A), alkyl acrylates (Path B) and alkyl vinyl ketones (Path C), in the presence of DABCO provided the required Baylis-Hillman adducts, 1,4-pentadienes **14**, **15**, and **16** respectively in high yields (Scheme 9).[36] Similarly bromide **13** (R= *n*-Bu) also reacts with cyclohex-2-enone in the presence of DBU to produce the desired BH product **17**

as described in Path D in Scheme 9.[36] In all these Baylis-Hillman reactions the actual electrophile is the ammonium salt **A** (obtained via reaction between BH bromides and DABCO/DBU).

Scheme 9. BH bromides (derived from HCHO and acrylates) as excellent electrophiles for coupling with activated alkenes[36]

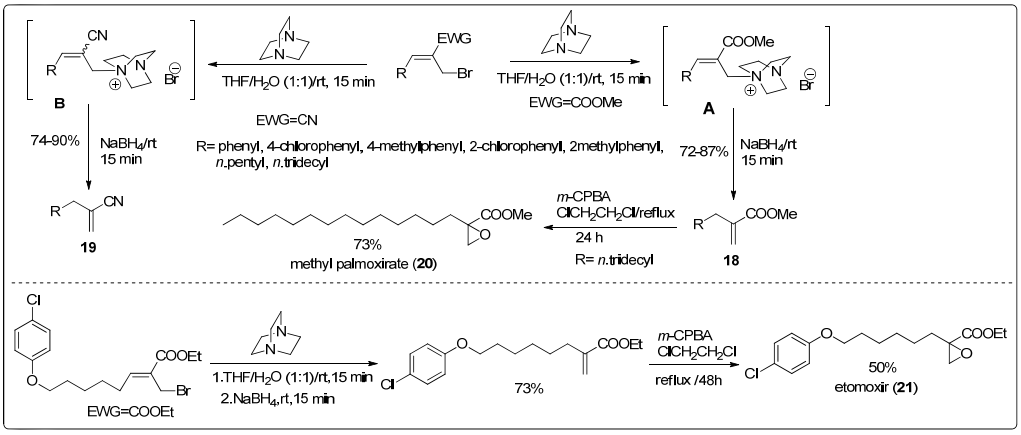


We have then successfully employed the ammonium salts (BH bromide-DABCO salts **A** and **B**) as electrophiles for reaction with $NaBH_4$.Thus, we have developed an interesting strategy for obtaining 2-methylenealkanoates (**18**) and alkanenitriles (**19**) (very important synthons for synthesis of bioactive molecules) from the Baylis-Hillman bromides *via* the reaction with DABCO at room temperature for 15 minutes followed by the treatment of the resulting ammonium salts with $NaBH_4$ for 15 minutes at the room temperature (Scheme 10).[37,38] This strategy has been successfully employed for synthesis of methyl palmoxirate (**20**) and etomoxir (**21**) (important hypoglycemic agents) following the reaction strategy as described in Scheme 10.[37] It is appropriate to mention here the elegant work of Hoffmann and Rabe who reported the conversion of BH bromides (one example was reported) into 2-methylenealkanoates *via* the treatment with super hydride ($LiBEt_3H$) (Scheme 11).[25,27]

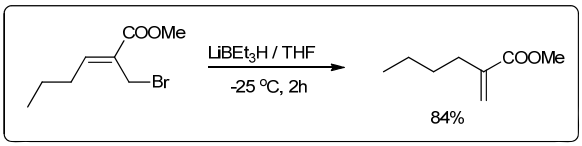
We have also successfully used the *in situ* generated ammonium salts (BH bromide-Et_3N salts) as electrophiles for reaction with phenol and propargylic alcohols in the presence of Et_3N to produce the corresponding phenyl (**22**) and propargylic (**23**) ethers of BH alcohols respectively following the reaction sequence as described in Scheme 12.[39] With a view to understand the applications of chiral ammonium salts, we have used readily available natural product quinidine for generating *in situ* the chiral ammonium salt (**X**) via the reaction with BH bromides.[39] Subsequent treatment of this

in situ generated salt **X** with proargylic alcohol in the presence of quinidine provided the resulting proargylic ethers (**24**) of BH alcohols in 25-40% enantiomeric purities (Scheme 13).[39]

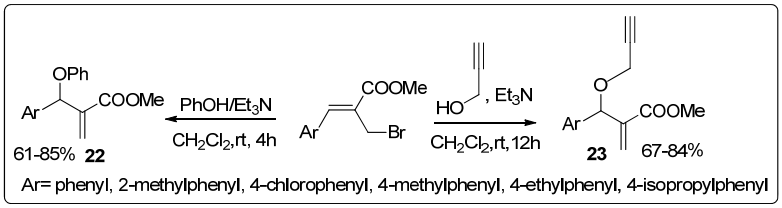
Scheme 10. Synthesis of 2-methylenealkanoates and alkanenitriles[37,38]: Application to synthesis of methyl palmoxirate (20) and etomoxir (21) important hypoglycemic agents[37]



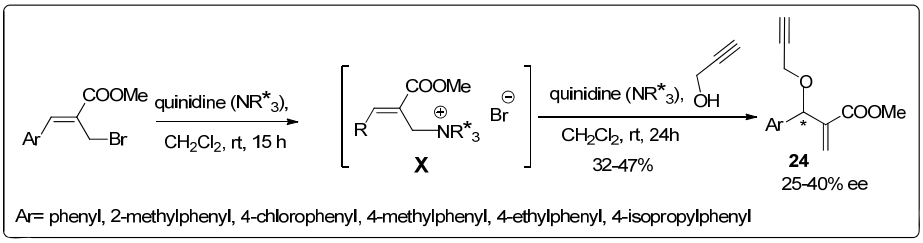
Scheme 11. Synthesis of 2-methylenealkanoates (Hoffmann andRabe)[25,27]



Scheme 12. Applications of BH bromides: Synthesis of phenyl and propargylic ethers[39]

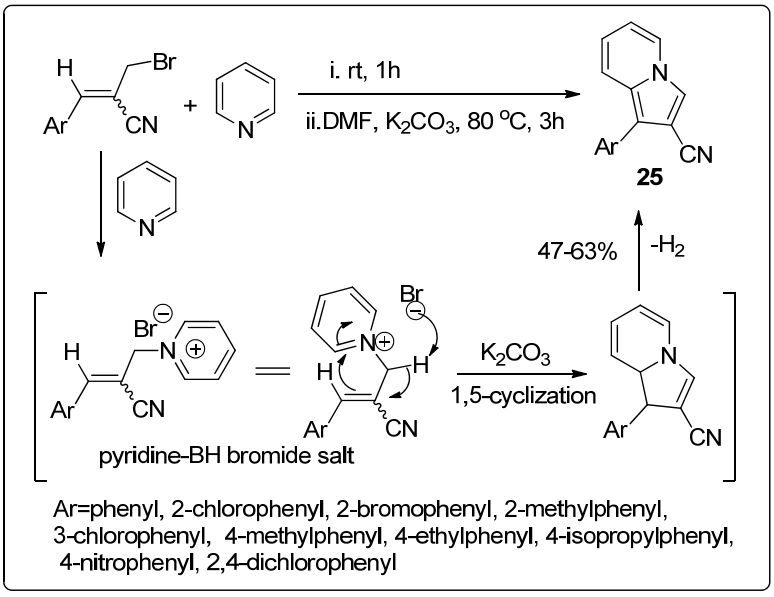


Scheme 13. Applications of BH bromides: Synthesis of enantiomerically enriched propargylic ethers[39]

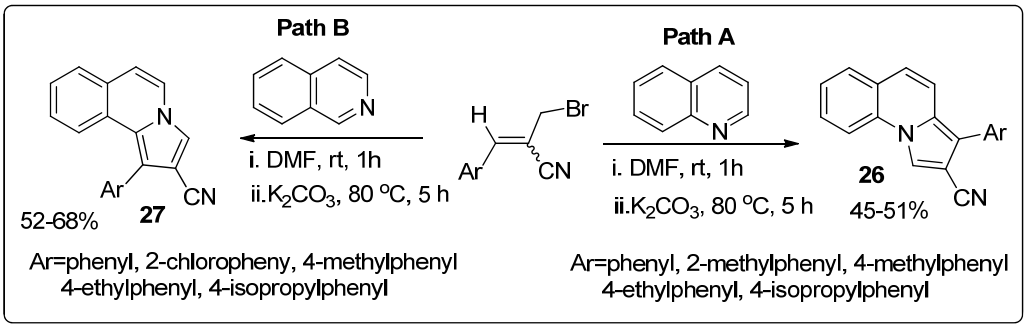


We have successfully employed the bromides of the Baylis-Hillman alcohols, derived from acrylonitrile and aryl aldehydes, for synthesis of indolizines **(25**) (Scheme 14) and benzo-fusedindolizines, (pyrrolo[1,2-*a*]quinolines) (**26)** (Path A in Scheme 15) and pyrrolo[1,2-*a*]isoquinolines (**27**) (Path B in Scheme 15) derivatives *via* the treatment with pyridine, quinoline, isoquinoline, respectively in the presence of K_2CO_3.[40] This strategy involves first the formation of quaternary ammonium salts (BH-bromide-pyridine/quinoline/isoquinoline) followed by 1,5-cyclization as shown in Scheme 14.[40]

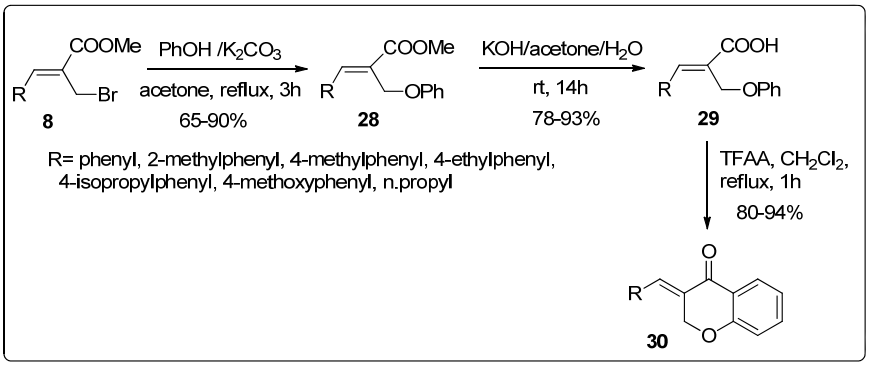
Scheme 14. Applications of BH bromides: Synthesis of indolizines[40]



Scheme 15. Applications of BH bromides: Synthesis of benzo fused indolizines[40]

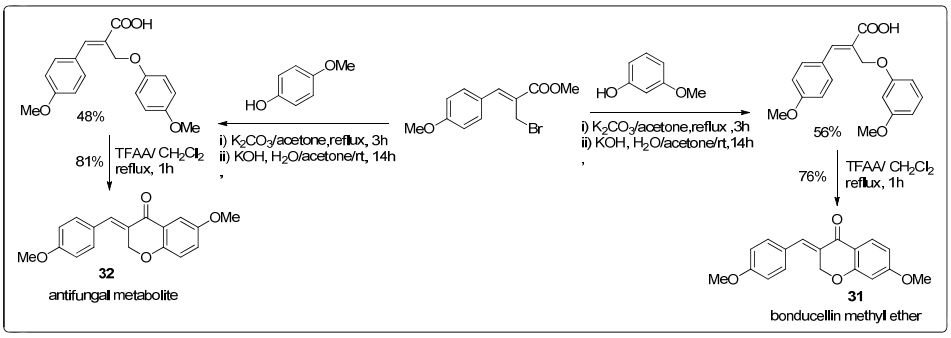


Scheme 16. Applications of BH bromides: Synthesis of 3-arylmethylidenechrom-4-ones [41]



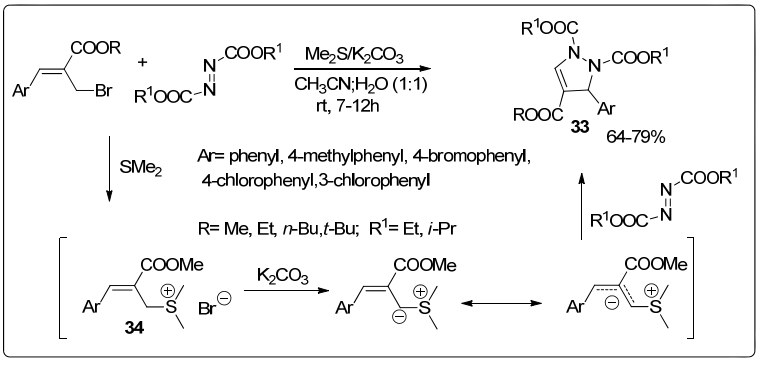
We have also transformed the Baylis-Hillman bromides (**8**) into α-aryloxymethylcinnamic esters (**28**) *via* the reaction with phenols in the presence of a base. Subsequent hydrolysis of these α-aryloxymethylcinnamic esters (**28**) using KOH/acetone provided the resulting cinnamic acids **(29**) which were then conveniently converted into 3-arylmethylidenechrom-4-ones (**30**) *via* the reaction with TFAA (Scheme 16).[41] We have successfully demonstrated the application of this strategy for synthesis of important biologically active molecules, bonducellin methyl ether (**31**) and antifungal metabolite (**32**) (Scheme 17).[41]

Scheme 17. Applications of BH bromides: Synthesis of bonducellin methyl ether and antifungal metabolite[41]

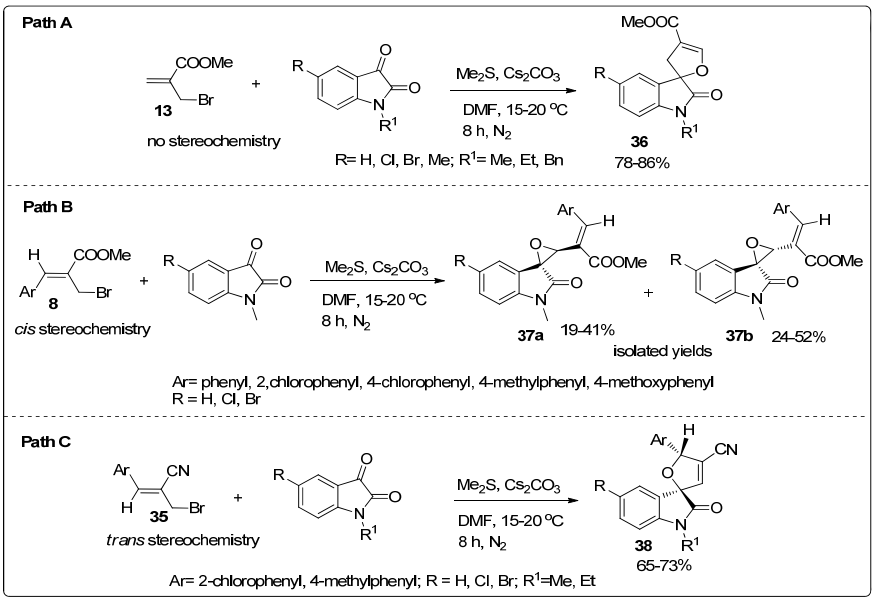


We have then demonstrated the importance of the Baylis-Hillman bromides as interesting and valuable source of 1,3-dipoles for cycloaddition (3+2) reactions with dialkylazodicarboxylates (dipolarophiles) in the presence of dimethyl sulphide and K_2CO_3 (Scheme 18).[42] Resulting functionalized dihydropyrazole derivatives **33** were obtained in high yields.[42] This study also demonstrates the applications of the *in situ* prepared BH bromide-sulfonium salts **34** in organic synthesis. Next we have selected three sterically different Baylis-Hillman bromides (**8, 13, 35**) and examined their applications as 1,3 diploes for cycloaddition reaction with isatin derivatives as dipolarophiles, with a view to understand the role of stereochemistry of BH bromides (**8, 13, 35**) in the product formation.[43] The bromide **13** (having no stereochemistry) provided the dihydrofurans fused with oxindoles (**36**). Interestingly the (*Z*)-allyl bromides (**8**) gave mixtures of *cis/trans* epoxides spirofused with oxindoles (**37a, 37b**) while (*E*)-allyl bromides **35** furnished oxindole-spiro-dihydrofurans (**38**) with high stereoselctivity as shown in Scheme 19.[43]

Scheme 18. Applications of BH bromides: Synthesis of substituted dihydro-pyrazoles[42]

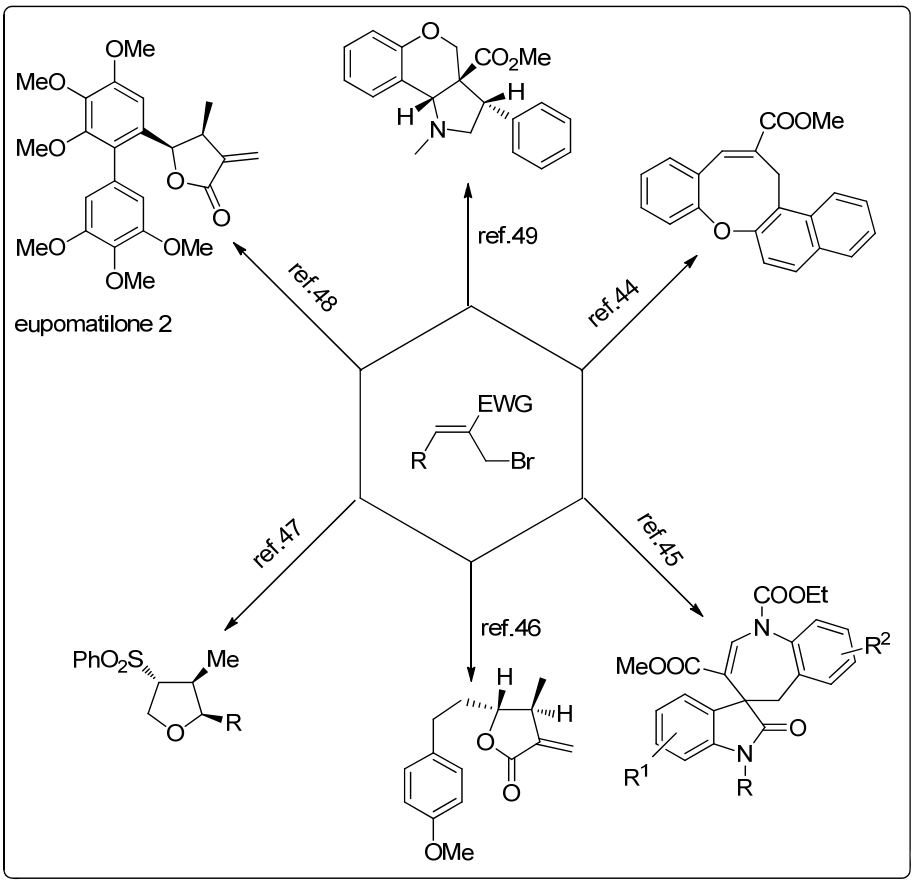


Scheme 19. Applications of BH bromides: Synthesis of spirooxindoles[43]



The Baylis-Hillman bromides have been extensively used for various organic transformation methodologies and also in synthesis of a number of natural products and bioactive compounds by the other research groups.[16,20] Representative examples are presented in the Scheme 20.[44-49]

Scheme 20. Applications of BH bromides: (Representative examples: Literature reports)[44-49]



Conclusions

This mini review describes the applications of the Baylis-Hillman bromides in organic synthesis with an emphasis on the contributions of our own research group. This review also briefly presents the highlights of contributions of other research groups on the applications of BH bromides in synthetic chemistry. From this review it is clear that the Baylis-Hillman bromides containing three functional groups in proximity play an important role in organic transformations and show high potential for further expansion and growth. It is very appropriate to mention here that although the Baylis-Hillman reaction has grown from an unknown patent level to the state of prominent name reaction and many research groups throughout the world are actively working on various aspects of this reaction, there is enormous scope for its continuous growth because of the challenges and opportunities it offers. Therefore this review

extends an invitation to every chemist to work in this area of research so that this reaction will grow further and reach to the greater heights and provide solutions to unsolved problems in synthetic chemistry.

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