

Intramolecular Baylis-Hillman reaction: synthesis of heterocyclic molecules

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Dedicated to Dr. J. S. Yadav on his 65th birthday

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Abstract

The Baylis-Hillman (BH) [also known as the Morita-Baylis-Hillman (MBH)] reaction is a versatile atom-economic C-C bond forming reaction between the α -position of activated alkenes and electrophiles under the influence of a catalyst and provides interesting classes of densely functionalized molecules. Its intramolecular version is yet another fascinating reaction by itself, producing various carbocyclic and heterocyclic compounds of synthetic and medicinal relevance. Applications of the intramolecular Baylis-Hillman reaction in obtaining heterocyclic molecules of different ring sizes and also to the synthesis of various natural products/bioactive compounds containing heterocyclic frameworks are presented in this brief review.

Keywords: Baylis-Hillman reaction, Rauhut-Currier reaction, activated alkene, electrophile, heterocyclic molecules, natural products

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1. Introduction

Organic synthesis occupies a unique place among all the branches of science because of its extensive applications and direct impact on society.¹⁻⁴ Now it is possible to synthesize any organic compound that is needed. Organic synthesis, in fact, mostly involves C-C bond forming reactions and functional group transformations.⁵⁻⁹ Therefore development of methodologies for construction of C-C bonds that produce molecules containing several functional groups in proximity has become a highly challenging and attractive endeavor in organic chemistry.⁵⁻⁹ The Baylis-Hillman (BH) reaction^{10,11} [also known as the Morita^{12,13}-Baylis-Hillman (MBH) reaction] is one such important C-C bond forming reaction, providing densely functionalized molecules in an atom-economical process (Figure 1). This is a three component reaction and involves C-C bond formation between the α -position of activated alkenes with electrophiles under the influence of a catalyst. One of the interesting and useful aspects of this reaction is that it usually provides molecules having a minimum of three functional groups in proximity, that is, α,α - to each other. Over the past three decades this reaction has grown from obscurity (actually buried in the literature) to a high level of popularity and applicability. It is now a very well-known organic reaction and is widely used as a powerful synthetic tool in organic chemistry.¹⁴⁻³⁰

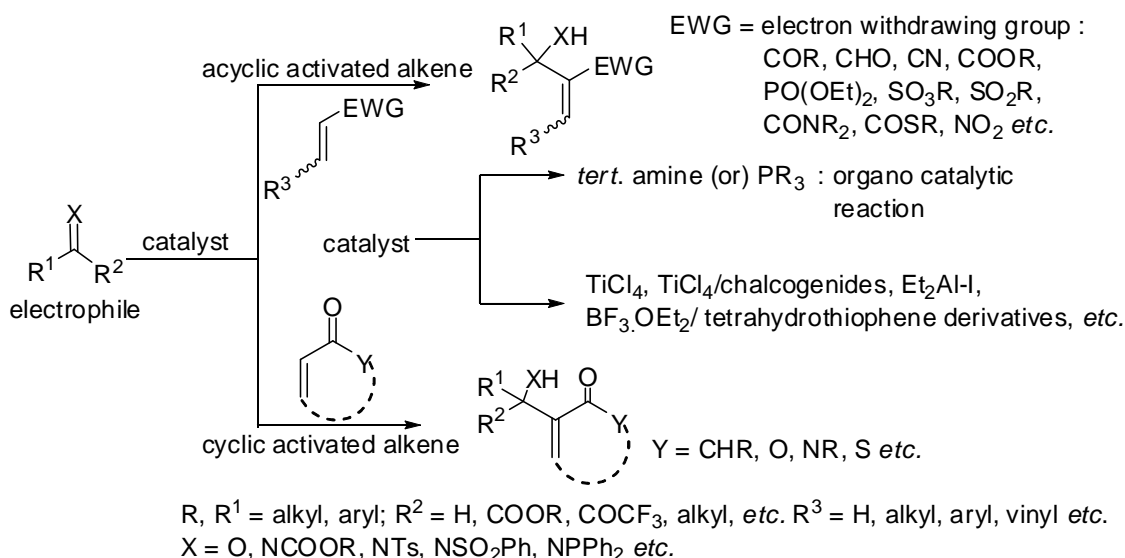
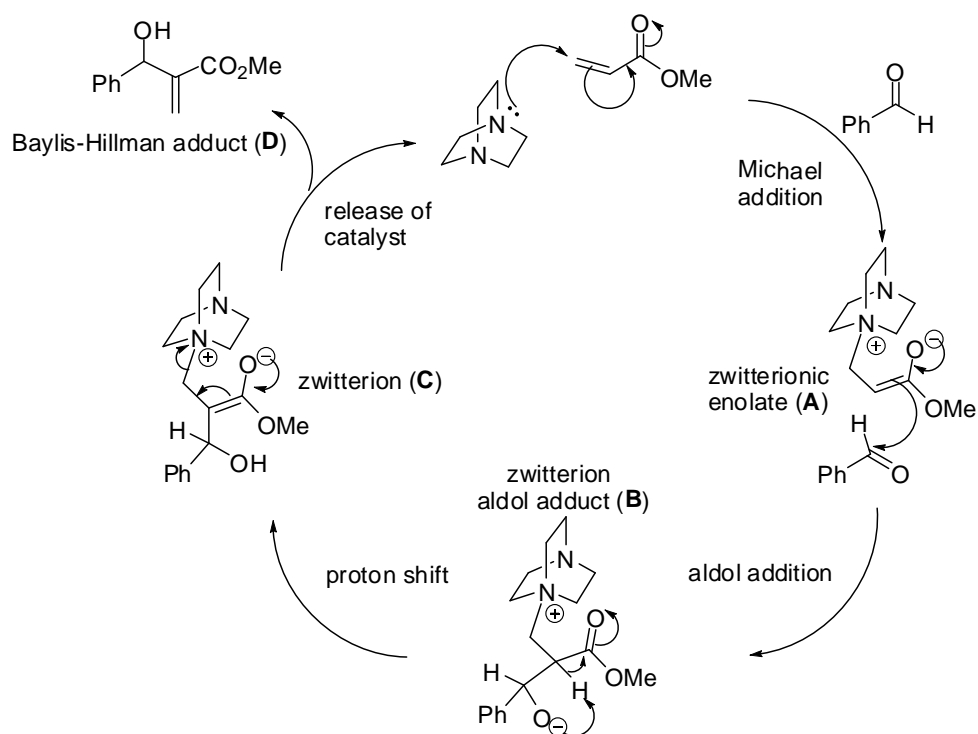


Figure 1. The Baylis-Hillman reaction at a glance.

In the most widely accepted mechanism of this fascinating carbon-carbon bond-forming reaction four steps are believed to be involved. A model case is presented in Scheme 1 by taking as an example the reaction between methyl acrylate and benzaldehyde catalyzed by DABCO. The first-step involves addition of the catalyst to the activated alkene (methyl acrylate) in a Michael fashion to generate *in situ* a zwitterionic enolate (**A**). The second step proceeds by addition of the zwitterionic enolate (**A**) to the electrophile (benzaldehyde) to give a zwitterionic aldol adduct (**B**) which in a third step undergoes a proton shift from the carbon α - to the ester group to oxygen ion to generate a zwitterion (**C**). In the fourth step, the catalyst (DABCO) is released to produce the densely functionalized adduct, which is normally referred to as the Baylis-Hillman adduct (**D**).



Scheme 1. Mechanism of the amine-catalyzed Baylis-Hillman reaction.

The exponential growth of this reaction may be attributed to the five important features: (1) It is an atom-economical C-C bond forming reaction. (2) This is an organo-catalytic reaction because most of the catalysts are organic molecules (tertiary amines and phosphines). (3) It creates a chiral center in the product in the case of prochiral electrophile thus providing opportunities to develop its asymmetric version. (4) If the substrate contains both the activated alkene and electrophilic components in appropriate positions there is a possibility of performing intramolecular BH reaction producing various carbocycles and heterocycles. It, thus, creates opportunities for designing such substrates for intramolecular BH reaction and also offers opportunities to develop its asymmetric version. (5) It produces molecules containing a minimum of three proximal functional groups which are of tremendous potential in synthetic and mechanistic organic chemistry. In fact the wide popularity and applicability of this reaction can be easily understood by publications of a number of major¹⁴⁻²² and mini reviews²³⁻³⁰ and more than 3200 research articles during the past three decades.

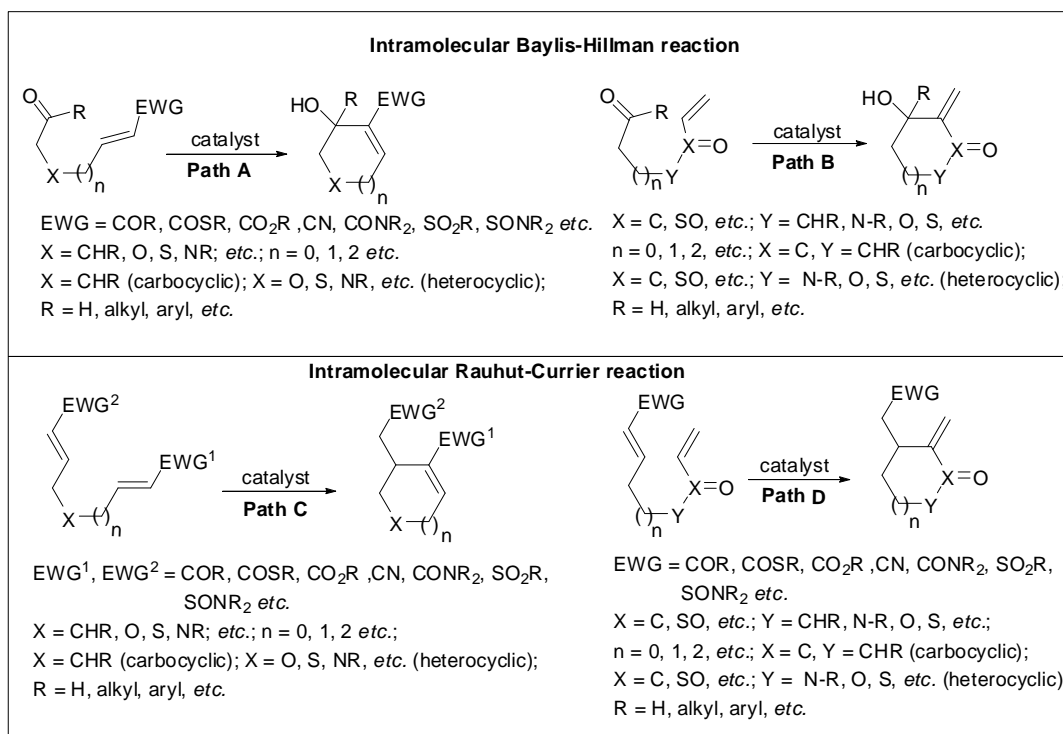
2. Intramolecular Baylis-Hillman (IBH) reactions

As mentioned above, if a substrate is designed so as to have activated alkene and electrophile components in required orientation there is a possibility of performing intramolecular coupling

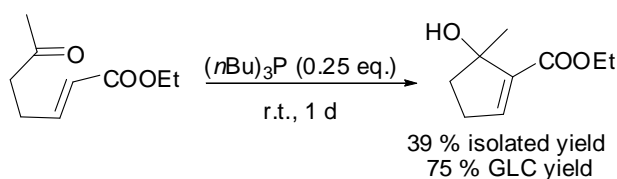
reaction to produce carbocyclic/heterocyclic compounds of synthetic importance. Such an intramolecular version can be, in principle, performed using (1) various activated alkenes (α,β -unsaturated esters / ketones / nitrile / thioesters / sulfonates / amides / sulfonamides / sulfones / sulfoxides *etc.*)- electrophiles (aldehydes / ketones / α -keto-esters / aldimines / epoxides / halides *etc.*) systems (2) activated alkene-activated alkene (Rauhut-Currier reaction)³¹⁻³⁴ system. Substrates for intramolecular BH reaction can in principle be designed so as to have the resulting cyclic compounds with an endocyclic double bond (Scheme 2: Paths A and C) or with exocyclic double bond (Scheme 2: Paths B and D).

The first intramolecular Baylis-Hillman reaction was reported as early as 1992 by Frater and co-workers.³⁵ In fact, this is a landmark publication in the sense that ketones are used as electrophile components (Equation 1). They have also reported intramolecular BH reaction of the ene-ester (α,β -unsaturated ester)-ketone substrate under the influence of chiral catalysts, (-)-CAMP and Li-quinidinate (Equations 2 and 3).³⁵ Even though the yields and enantioselectivities are not that high, this strategy paved the way for intramolecular BH-reaction, its asymmetric version and also demonstrated the possible application of ketones as electrophiles in the BH-reaction.³⁵

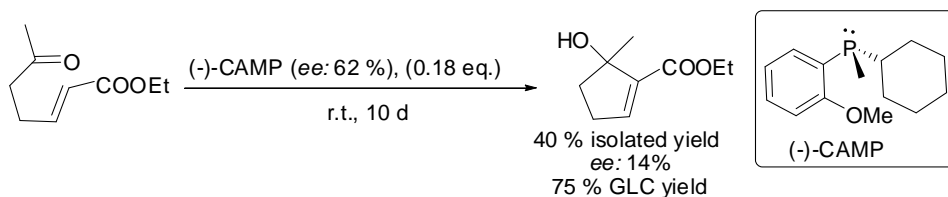
Subsequently various substrates and strategies were designed for intramolecular BH-reaction. This mini review presents the literature on the intramolecular Baylis-Hillman reaction and its asymmetric version with an emphasis on the synthesis of heterocycles and application to the synthesis of natural products / bioactive compounds containing heterocyclic frameworks.



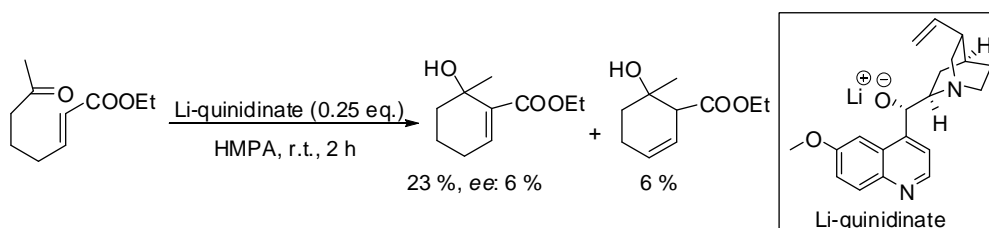
Scheme 2. Different modes of intramolecular Baylis-Hillman reaction.



Equation 1. Intramolecular BH (IBH) reaction of α,β -unsaturated ester-ketone.



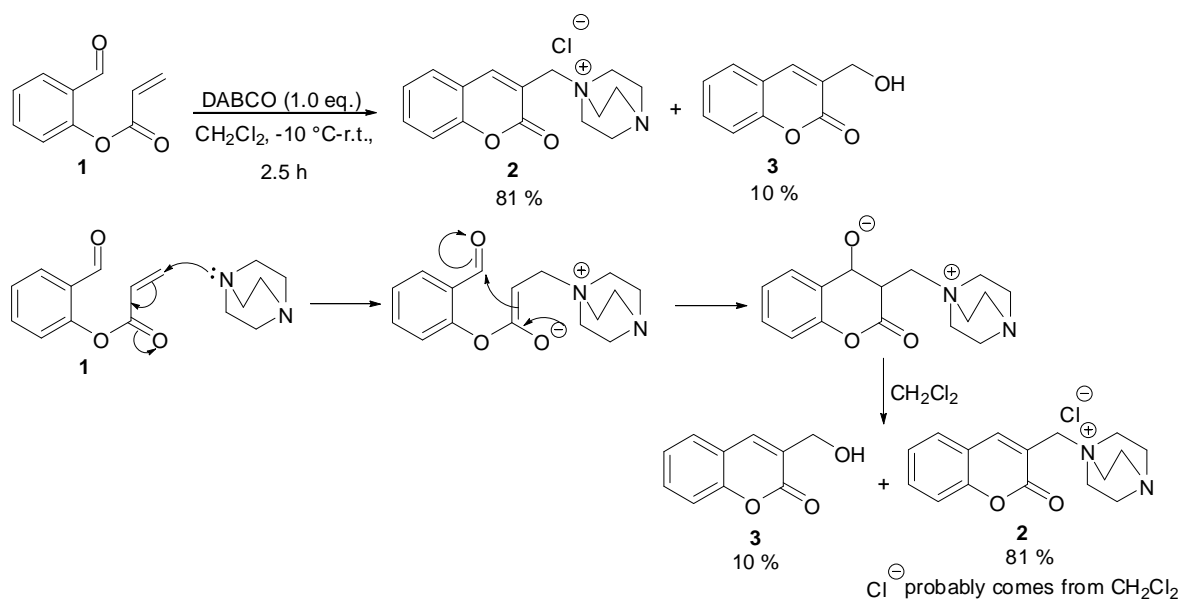
Equation 2. Asymmetric IBH reaction of α,β -unsaturated ester-ketone using (-)-CAMP as catalyst.



Equation 3. Li-quinidinate catalyzed asymmetric IBH reaction of α,β -unsaturated ester-ketone.

2.1. IBH reactions: activated alkene (α,β -unsaturated ester)-aldehyde system

Drewes and co-workers reported an interesting intramolecular Baylis-Hillman reaction of acrylate-aldehyde **1** (obtained via the treatment of salicylaldehyde with acryloyl chloride) in presence of DABCO which provided the coumarin salt **2** as a major product and the rearranged B-H-alcohol **3** as a minor product (Scheme 3).³⁶ It is believed that initially the Baylis-Hillman adduct was formed which was subsequently converted into coumarin-chloride salt on reaction with CH_2Cl_2 and DABCO (Scheme 3).³⁶

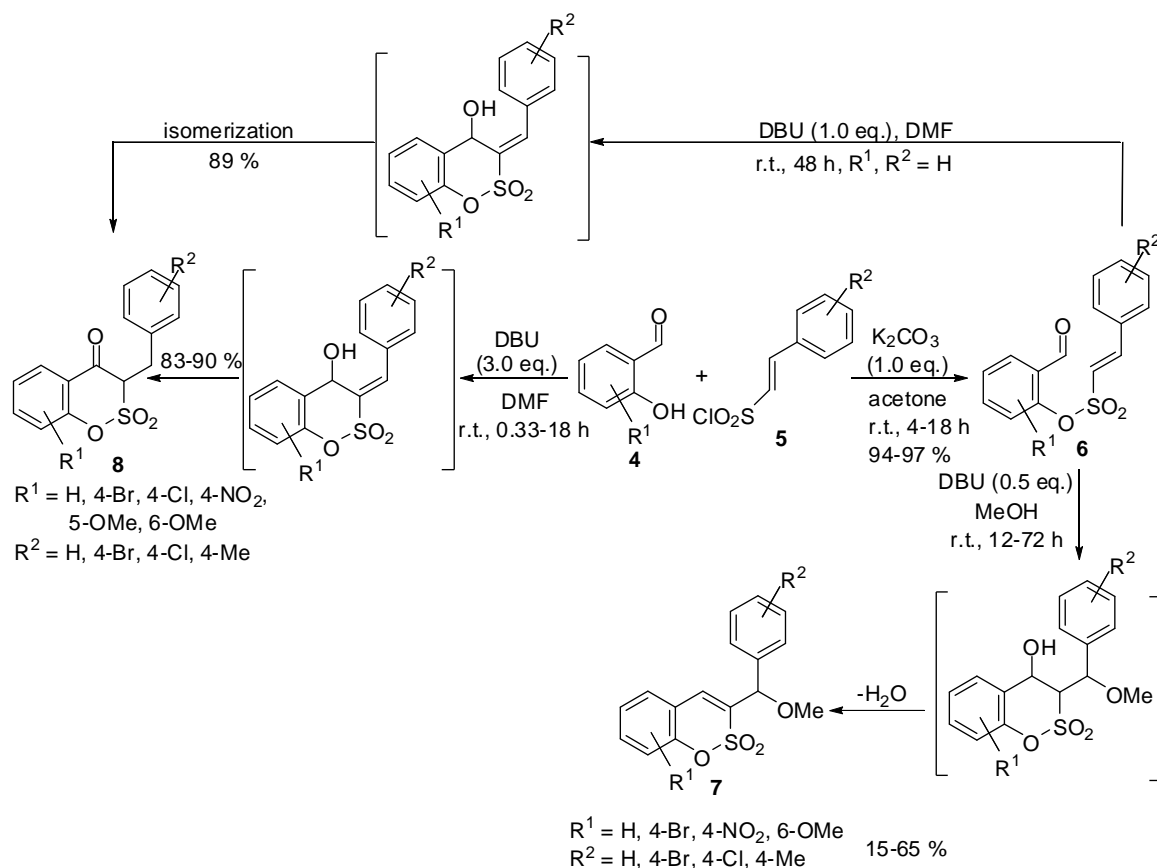


Scheme 3. IBH reaction of α,β -unsaturated ester-aldehyde: synthesis of coumarin salt.

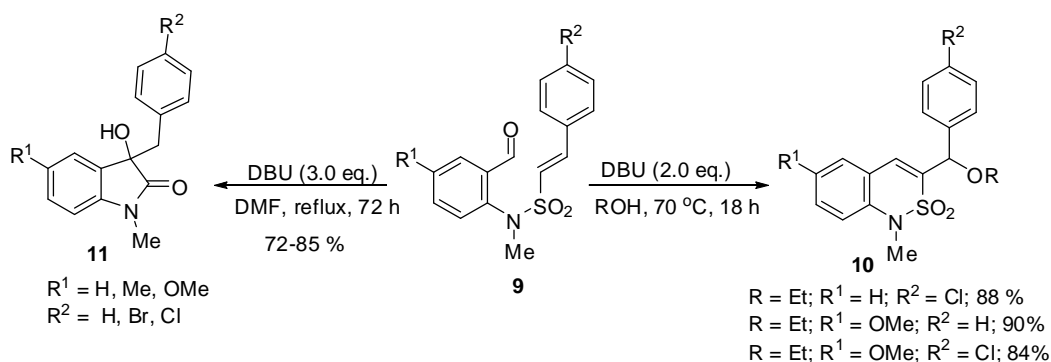
2.2. IBH reactions: activated alkenes (α,β -unsaturated sulfonates or α,β -unsaturated sulfonamides)-aldehyde system

In 2011 Ghandi and co-workers reported³⁷ an interesting solvent-dependant intramolecular BH reaction of 2-formylaryl-(*E*)-2-arylethanesulfonates **6** which were obtained via the reaction between 2-hydroxyarylaldehydes **4** and (*E*)-2-arylethanesulfonyl chlorides **5**. Reaction of **6** with DBU (cat.) in DMF as a solvent provided β -keto- δ -sultone derivative ($R^1 = R^2 = \text{H}$) **8** while same reaction with DBU (cat.) in MeOH gave the ene-sultone **7** (Scheme 4). It is believed that β -keto- δ -sultone **8** was obtained from the BH adduct after isomerization involving 1,3-proton shift while the ene-sultone **7** was derived from the IBH adduct after dehydration (Scheme 4). They also observed that the reaction between 2-hydroxyarylaldehydes and (*E*)-2-arylethanesulfonyl chlorides under the influence of DBU (cat.) in DMF directly gave the β -keto- δ -sultones **8** (Scheme 4).³⁷

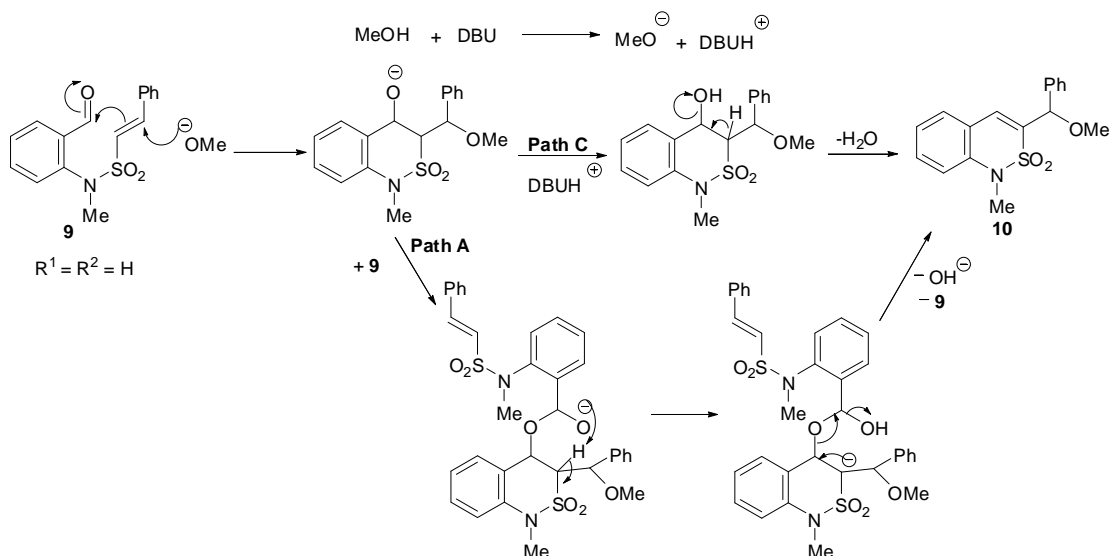
Three years later Ghandi and co-workers also reported intramolecular BH reaction of vinyl (styryl)-sulfonamide-aldehyde system **9** using DBU as a catalyst. When this reaction was performed in alcoholic solvents benzo- δ -sultams **10** were obtained. The same reaction in DMF as solvent provided 3-benzyl-3-hydroxyoxindoles **11** (Scheme 5).³⁸ The authors presented reasonable mechanisms for these transformations [for benzo- δ -sultams **10**, see Scheme 6 (Path A) and indole derivatives **11**, see Scheme 7 (Path B)].³⁸ It seems to us that alternative Path C (Scheme 6) and Path D (Scheme 7) are also possible.



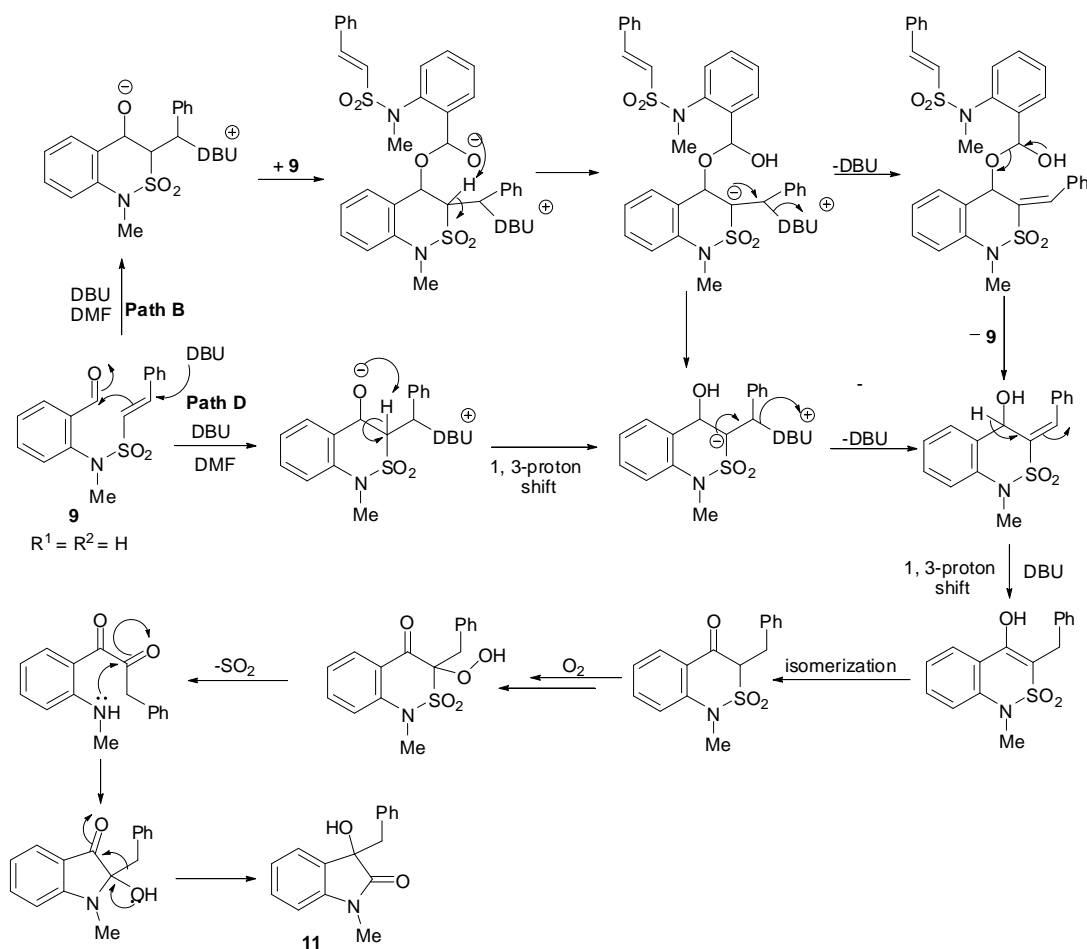
Scheme 4. IBH reaction of α,β -unsaturated sulfonate-aldehyde system.



Scheme 5. Intramolecular BH-reaction of vinyl (styryl)-sulfonamide-aldehyde system.



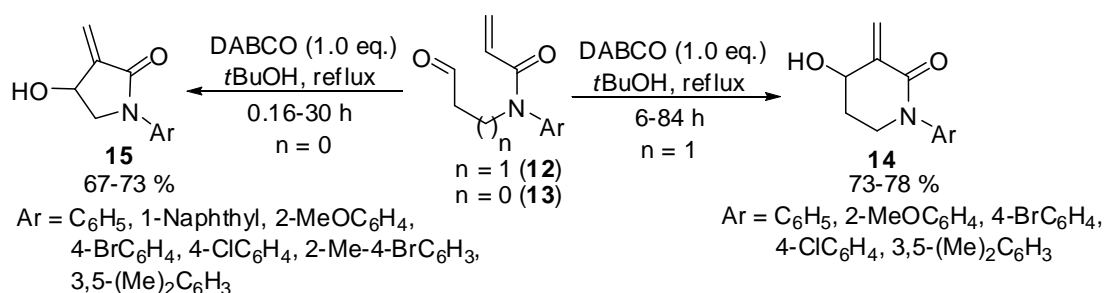
Scheme 6. Plausible mechanisms for the formation of benzo- δ -sultams **10**.



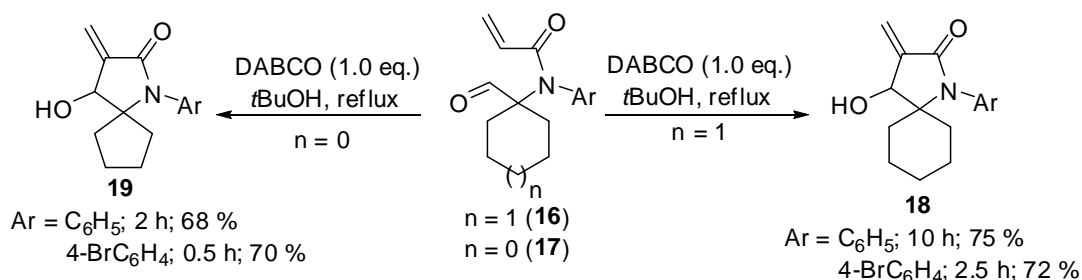
Scheme 7. Plausible mechanisms for the formation of 3-benzyl-3-hydroxyoxindoles **11**.

2.3. IBH reactions: activated alkene (α,β -unsaturated amide)-aldehyde system

Recently our research group has developed a facile intramolecular Baylis-Hillman reaction of the substrates **12**, **13**, **16** and **17** containing less reactive acrylamides as activated alkenes and aldehydes as electrophiles. This strategy provides a convenient and useful protocol for obtaining α -methylene- δ -lactam **14**, α -methylene- γ -lactam **15**, and spiro lactam **18** and **19** frameworks (Schemes 8 and 9).³⁹ It is interesting to note that the reactions are faster in the case of **13** ($n = 0$) to provide α -methylene- γ -lactam derivatives **15** in good yields, in comparison to that of **12** for obtaining **14**.



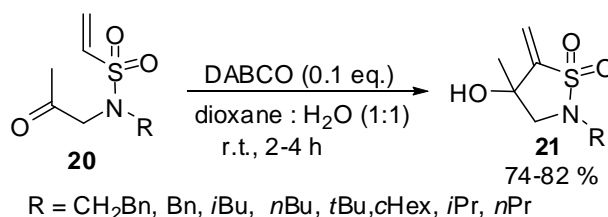
Scheme 8. IBH reaction: Synthesis of α -methylene- δ - and γ -lactams.



Scheme 9. IBH reaction: Synthesis of spiro lactam frameworks.

2.4. IBH reactions: activated alkene (α,β -unsaturated sulfonamide)-ketone system

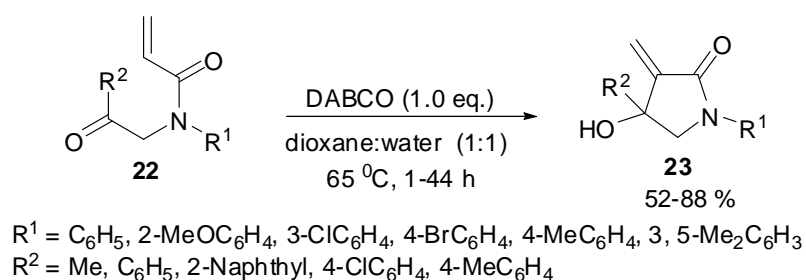
A few years ago Zhou and co-workers described an elegant intramolecular BH reaction of substrates (**20**) having a less reactive ketone as the electrophile component and an ethenylsulfonamide as the activated alkene unit, thus providing a facile synthetic strategy for obtaining five-membered ring sultams **21** according to the reaction shown in Equation 4.⁴⁰



Equation 4. IBH reaction: Synthesis of α -methylene- γ -sultams.

2.5. IBH reactions: activated alkene (α,β -unsaturated amide)-ketone system

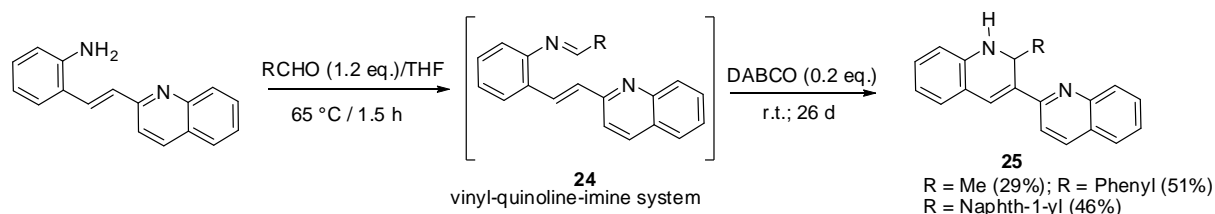
Since the intramolecular BH reactions are faster in the case of acrylamide-aldehyde system **13** for obtaining α -methylene- γ -lactam derivatives **15** (Scheme 8) it occurred to us that this strategy might be extended to acrylamide-ketone system **22**. We were pleased to observe that these reactions were successful and provided a simple protocol for obtaining α -methylene- γ -lactam derivatives **23** containing a tertiary alcoholic functionality in good yields (Equation 5).⁴¹ This study demonstrates the applicability of ketones as electrophiles in BH reactions if substrates are designed appropriately.



Equation 5. IBH reaction: Synthesis of α -methylene- γ -lactams having tertiary alcohol group.

2.6. IBH reactions: activated alkene (vinylquinoline)-imine system

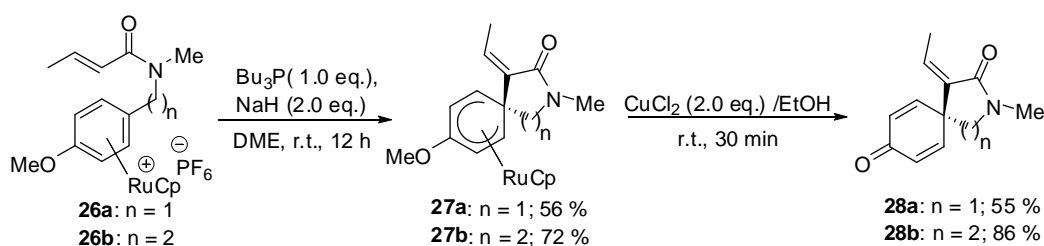
An elegant substrate, the *in situ* generated vinylquinoline-imine system **24**, was used as a substrate for an intramolecular BH reaction by Trifonov and co-workers. This strategy provides a simple protocol for obtaining 1',2'-dihydro-2,3'-biquinoline framework **25** (Scheme 10).⁴²



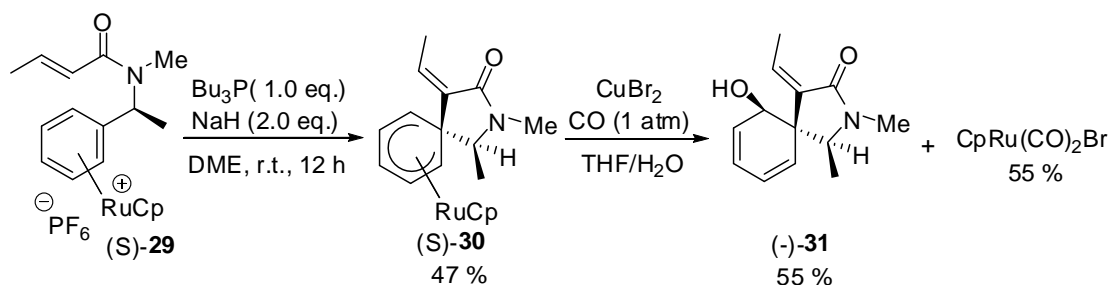
Scheme 10. IBH reaction: Synthesis of 1',2'-dihydro-2,3'-biquinoline framework.

2.7. Unusual-intramolecular Baylis-Hillman reaction

An interesting intramolecular organometallic variation of BH reaction of substrates containing ruthenium-arene complexes (**26**) as an electrophile component and less reactive acrylamide as activated alkene component using tributylphosphine/NaH, providing spiroactam-ruthenium frameworks (**27**), was reported by Pigge and co-workers; two examples are given in Scheme 11.⁴³ They have also performed demetallation of these products **27** using CuCl₂ to provide spirocyclohex-2,5-dien-4-one derivatives **28** (Scheme 11).⁴³ Similar treatment of enantiomerically pure acrylamide-ruthenium-arene complex **29** with tributylphosphine/NaH provided the spiro compound **30** which on oxidative demetallation with CuBr₂/CO gave the corresponding oxidized product **31** in enantiomerically pure form in 55% yield (Scheme 12).⁴³

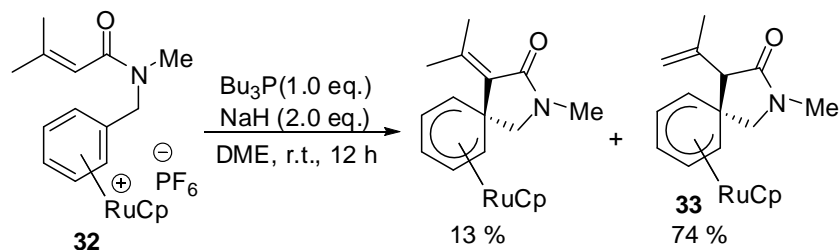


Scheme 11. IBH reaction of acrylamide-ruthenium-arene complexes: Synthesis of spiro compounds **27** and **28**.

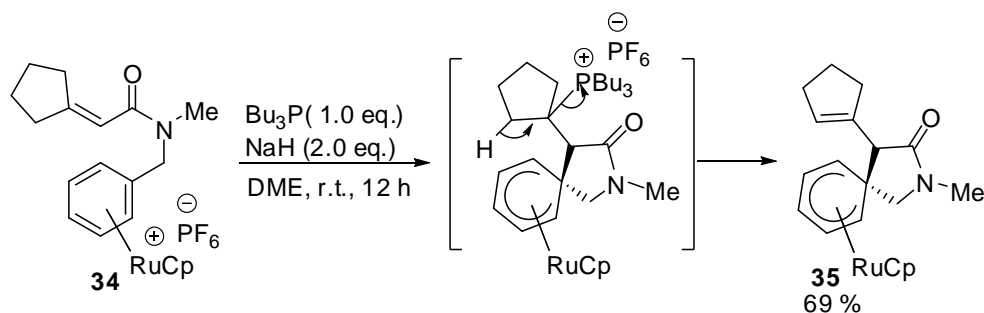


Scheme 12. IBH reaction: Synthesis of enantiomerically pure spiro pyrrolidin-2-one **31**.

When Pigge and co-workers used the β,β -disubstituted acrylamide derivative **32** as a substrate the double bond migrated product **33** was obtained as a major compound (one example is given in Equation 6).⁴³ Similarly in the case of substrate **34**, double bond migrated product **35** was obtained exclusively (Scheme 13).⁴³

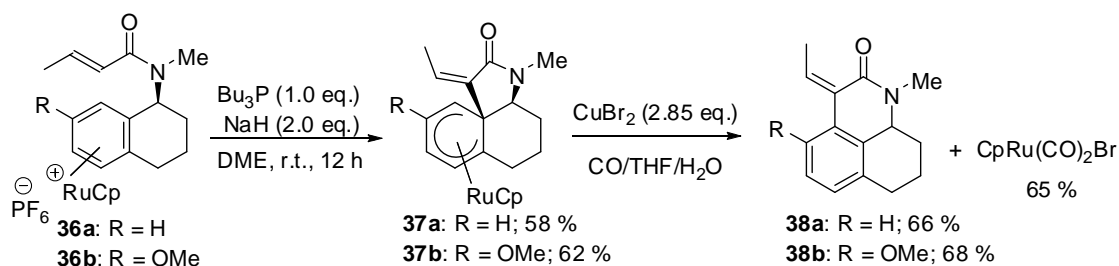


Equation 6. IBH reaction: Synthesis of spiro compound **33**.

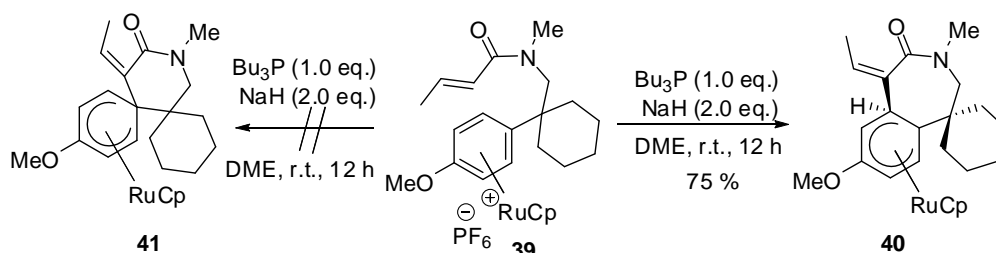


Scheme 13. IBH reaction: Synthesis of spiro compound **35**.

Pigge and co-workers subsequently extended this methodology for polycyclic systems. Two examples are presented in Scheme 14.⁴⁴ Treatment of acrylamide-ruthenium-arene complexes **36a** and **36b** with tributylphosphine/NaH gave tricyclic compounds **37a** and **37b** which on oxidative demetallation with CuBr_2/CO provided rearomatized compounds **38a** and **38b** respectively (Scheme 14). In all these substrates the benzylic carbon contains at least one hydrogen atom. However when they employed the substrate containing a quaternary benzylic carbon (**39**) they did not obtain the expected spiro product **41**; instead the 3-benzazepine derivative **40** was obtained via orthocyclization (Scheme 15).⁴⁴



Scheme 14. IBH reaction: Synthesis of tricyclic compounds.



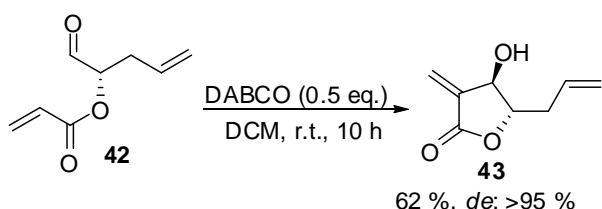
Scheme 15. IBH reaction: Synthesis of spiro compounds having a 3-benzazepine unit.

2.8. Asymmetric intramolecular Baylis-Hillman reactions

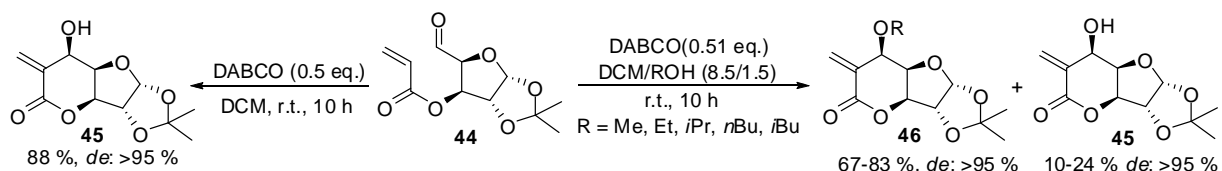
Asymmetric intramolecular B-H reaction can, in principle, be performed: (1) with enantiomerically pure/enriched substrates containing activated alkene and prochiral electrophile components using an appropriate (chiral / achiral) catalyst, and (2) substrates containing activated alkene and prochiral electrophile components using chiral catalyst.

2.8.1. Asymmetric IBH reactions of enantiomerically enriched/pure substrates containing activated alkene and prochiral electrophile components, using achiral catalyst.

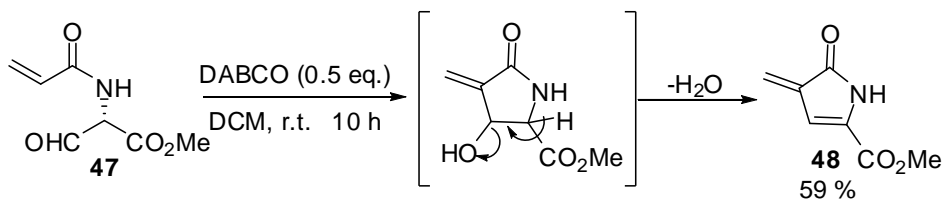
Stereoselective intramolecular BH-reaction of chiral substrate containing acrylate-aldehyde systems **42** and **44** was reported by Krishna and co-workers to provide α -methylene furanone / pyranones (**43**, **45**, **46**) as shown in the Equation 7 and Scheme 16.⁴⁵ They also reported intramolecular BH reaction of chiral substrate having acrylamide-aldehyde unit **47** under the influence of DABCO as a catalyst to provide methyl 4-methylene-5-oxo-4,5-dihydro-1*H*-pyrrole-2-carboxylate **48** (achiral compound) (Scheme 17).⁴⁵



Equation 7. IBH reaction: enantiomerically pure **42** : Synthesis of α -methylene furanone **43**.

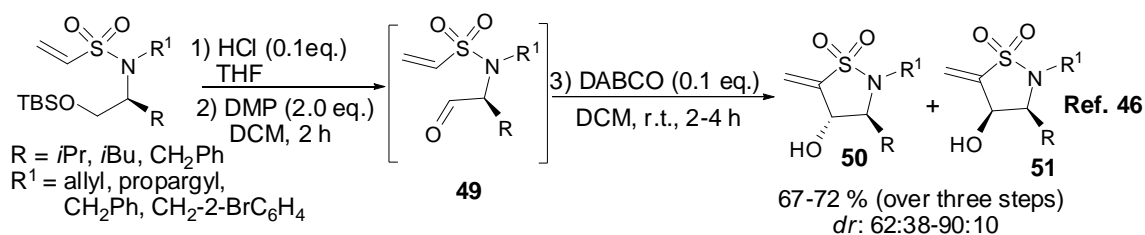


Scheme 16. IBH-reaction: enantiomerically pure **44**; synthesis of α -methylene-pyran-2-ones **45** and **46**.

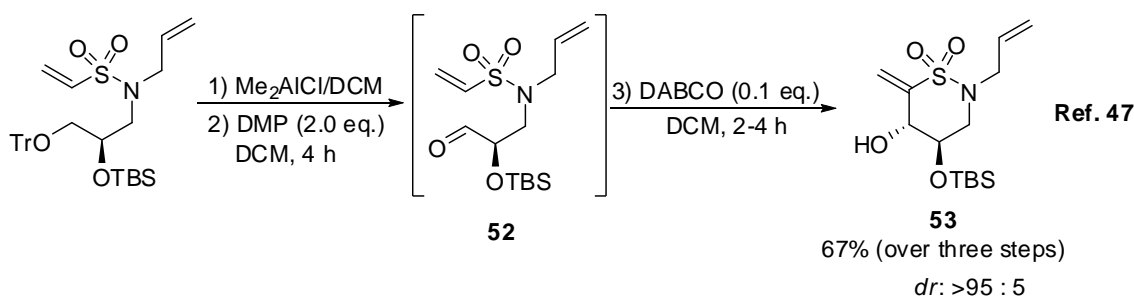


Scheme 17. IBH reaction: Enantiomerically pure acrylamide-aldehyde system **47**: Synthesis of methyl 4-methylene-5-oxo-4,5-dihydro-1*H*-pyrrole-2-carboxylate **48** (achiral compound).

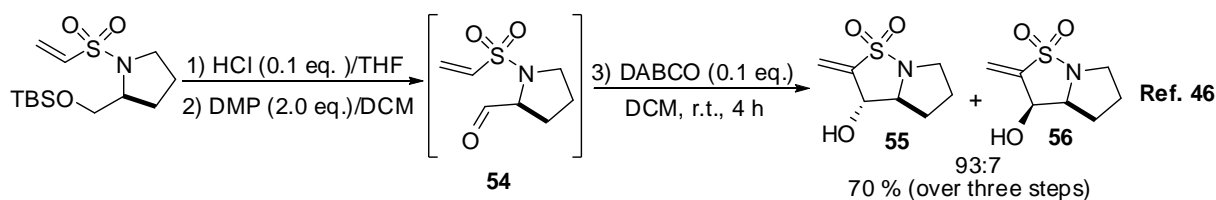
A facile diastereoselective intramolecular BH-reaction of ethenylsulfonamide-carbonyl system [aldehyde (**49**, **52** and **54**)] derived from amino alcohols was reported by Hanson and co-workers to produce five-membered (**50** and **51**) (Scheme 18),⁴⁶ and six-membered (**53**) (Scheme 19)⁴⁷ ring sultams and also [5.5] bicyclic sultams (**55** and **56**) (Scheme 20).⁴⁶ This strategy worked well also with a ketone (**57**) as the electrophile component to provide the [5.6] bicyclic sultam (**58**) (Equation 8).⁴⁶



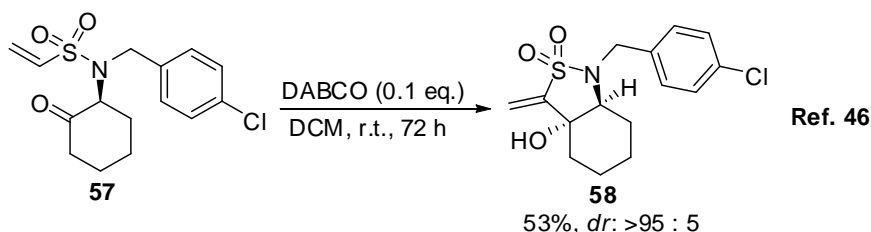
Scheme 18. IBH reaction: Synthesis of α -methylene- γ -sultams.



Scheme 19. IBH reaction: Synthesis of α -methylene- δ -sultam.

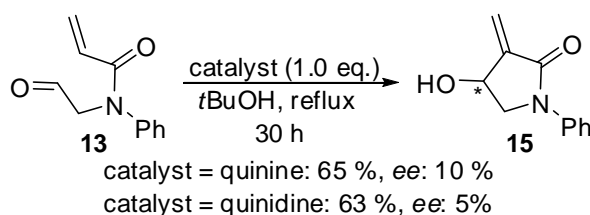


Scheme 20. IBH reaction: Synthesis of [5.5] bicyclic sultams.



Equation 8. IBH reaction: Synthesis of [5.6] bicyclic sultam.

2.8.2. Asymmetric IBH reactions of substrates containing activated alkene and prochiral electrophile components using chiral catalyst. Our research group has examined the possibility of achieving enantioselectivity in intramolecular Baylis-Hillman reaction using quinine and quinidine as catalysts in the case of *N*-formylmethyl-*N*-phenyl acrylamide (**13**, Ar = Phenyl, $n = 0$). Although the resulting *N*-phenyl-3-methylene-4-hydroxy- γ -lactam (**15**, Ar = Phenyl, $n = 0$) was obtained in low (10% and 5%) enantioselectivities (Equation 9), this strategy certainly indicates that there is a possibility of achieving high selectivity by employing an appropriate chiral catalyst.³⁹



Equation 9. Asymmetric IBH reaction using quinine and quinidine as catalysts.

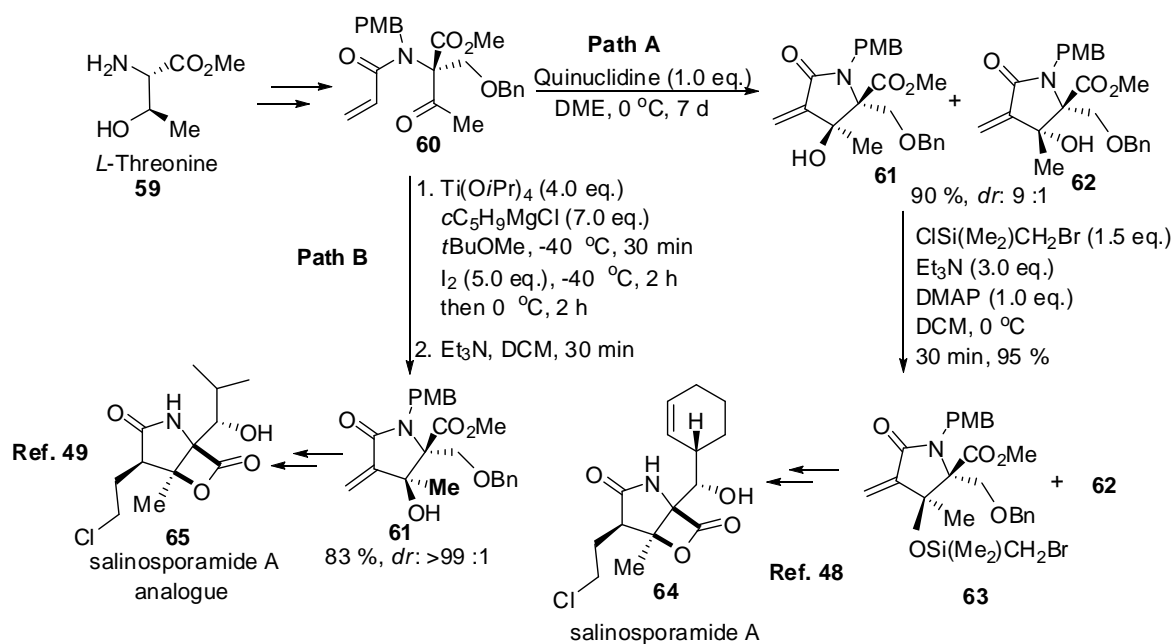
Unfortunately this aspect did not receive adequate attention from chemists. We are sure in the coming years it will receive the attention it deserves from synthetic chemists and grow further.

2.9. Application to biologically active molecules and natural products

Intramolecular asymmetric BH reactions providing heterocyclic compounds have been successfully employed in the synthesis of number of bioactive compounds and natural products. This section describes such applications of intramolecular BH reactions.

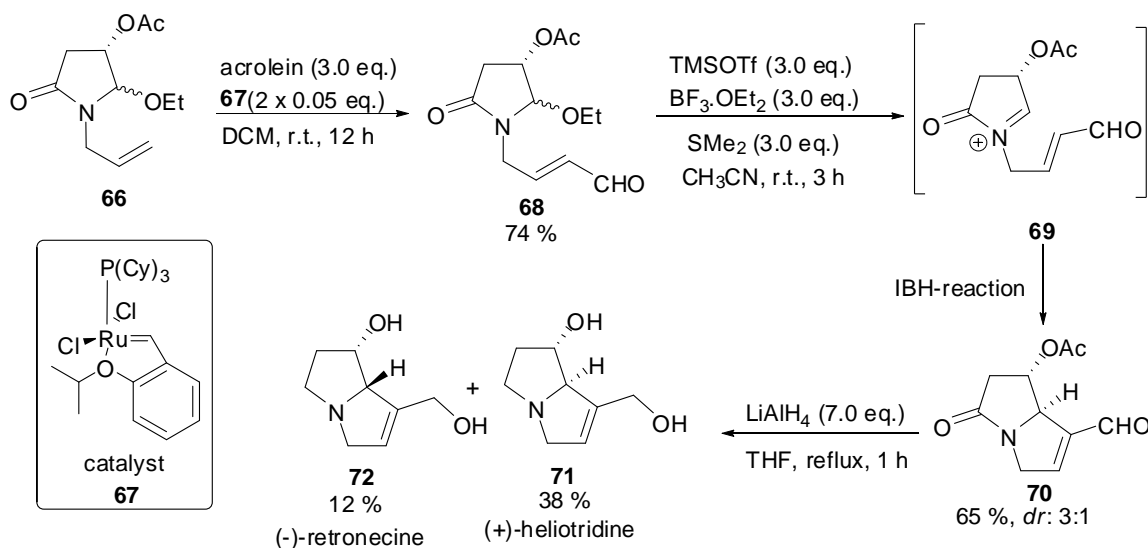
In 2004 Corey and co-workers⁴⁸ reported a meticulous application of the intramolecular BH-reaction as the key step in a total synthesis of the biologically important natural product salinosporamide A (**64**) using L-threonine (**59**) as the starting material (Scheme 21). In this strategy they employed an intramolecular BH reaction of **60** (substrate containing acrylamide as activated alkene component and ketone as electrophile component) in the presence of a catalytic amount of quinuclidine as the key step to provide the resulting adducts **61** and **62** in 9:1

diastereoselectivity in 90% yield. The major compound **61** was selectively alkylated to provide the desired compound **63** (which was subsequently transformed into salinosporamide A **64** (Scheme 21, Path A).⁴⁸ One year later Corey and co-workers came up with improved reaction conditions (Path B: titanium isopropoxide/cyclopentylmagnesium chloride/ and iodine) for performing the intramolecular BH reaction of the substrate **60** to produce the resulting adduct **61** in 99:1 diastereoselectivity (Path B, Scheme 21).⁴⁹ The major compound **61** was subsequently transformed into analogue **65** of salinosporamide A **64** (Scheme 21, Path B).⁴⁹



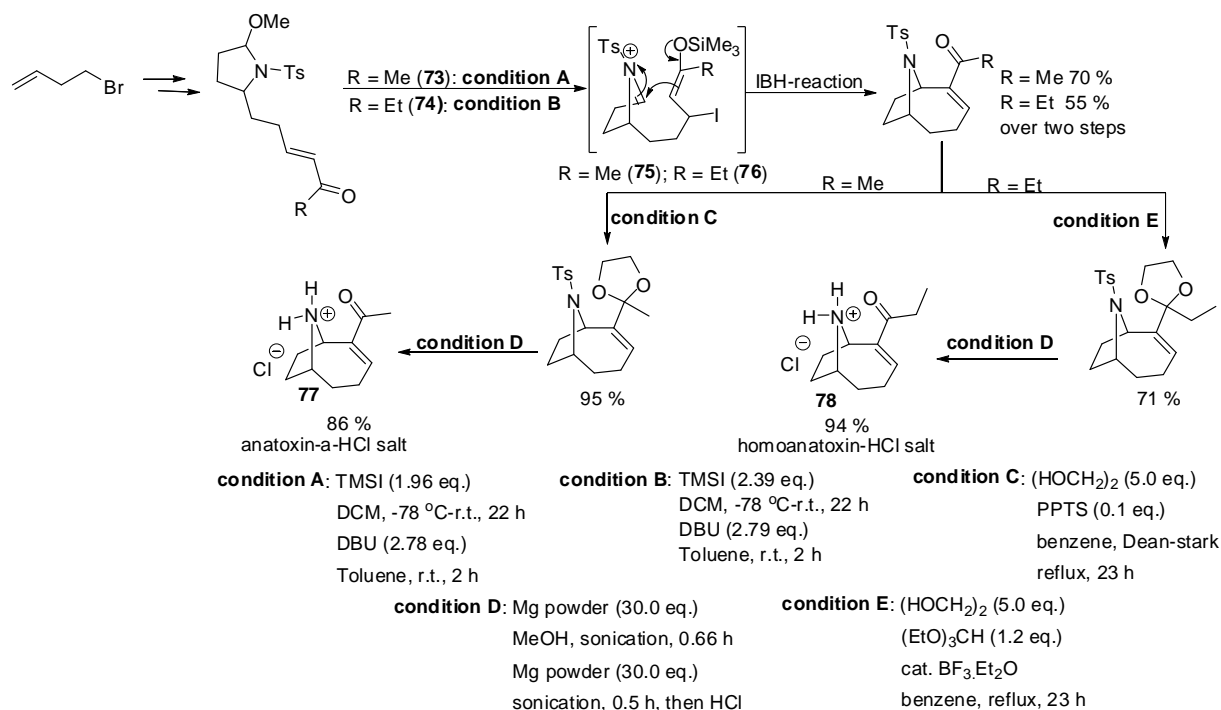
Scheme 21. IBH reaction as a key step in synthesis of salinosporamide A and its analogue.

Aggarwal and co-workers have elegantly used intramolecular Baylis-Hillman reaction as the key step in the synthesis of the natural product (+)-heliotridine **71** and its unnatural isomer (-)-retronecine **72**. Thus the IBH reaction of the *in situ* generated α,β -unsaturated aldehyde (activated alkene component)-iminium ion (electrophilic component) system **69** using TMSOTf/BF₃·OEt₂/SMe₂ gave the BH adduct **70** which was conveniently transformed into (+)-heliotridine **71** and its unnatural isomer (-)-retronecine **72** via the reaction with LAH following the reaction sequence illustrated in Scheme 22.⁵⁰ The required *in situ* generated α,β -unsaturated aldehyde (activated alkene component)-iminium ion system **69** was easily obtained from the corresponding precursor **68** (which was readily accessible from pyrrolidin-2-one derivative **66** via the treatment with acrolein using Hoveyda-Grubbs catalyst **67**) following the reaction sequence shown in Scheme 22.⁵⁰

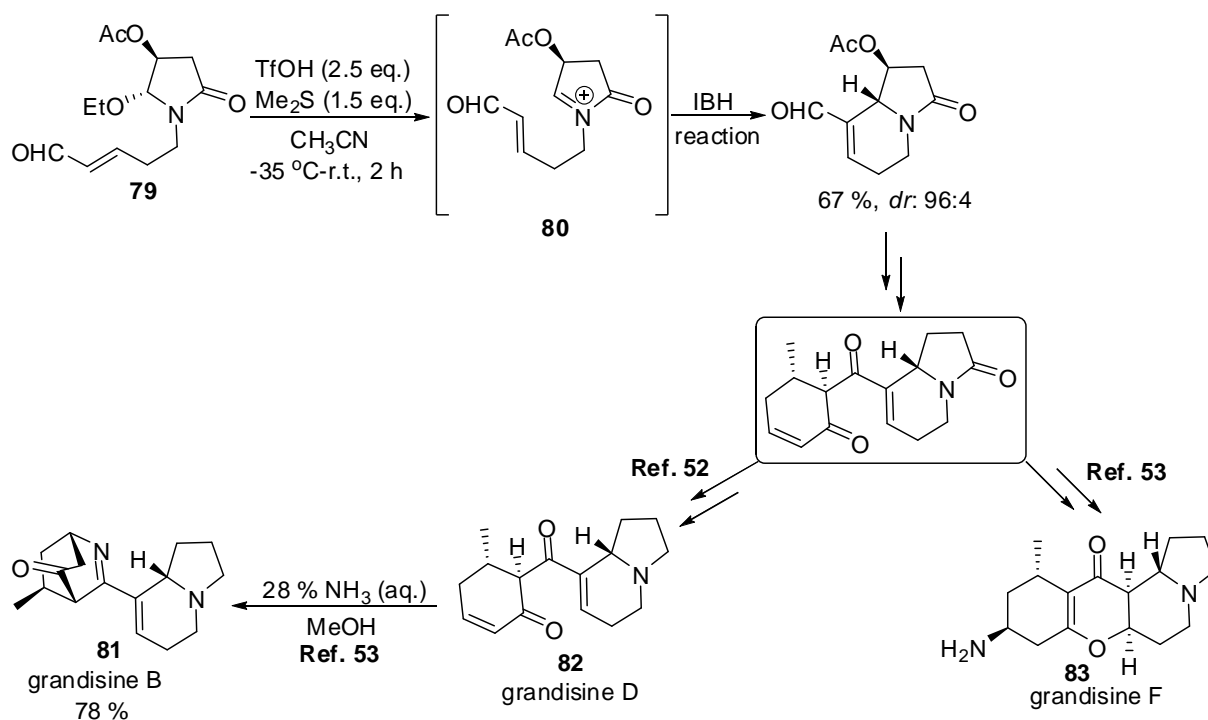


Scheme 22. IBH reaction as a key step in synthesis of (+)-heliotridine and (-)-retronecine.

Subsequently Roe and Stockman reported an intramolecular Baylis-Hillman reaction of substrates **75** and **76** (obtained from **73** and **74**), containing α,β -unsaturated ketone-iminium ion system, as a key step for synthesis of anatoxin-a HCl salt **77** and homoanatoxin-HCl salt **78**, following the strategy shown in Scheme 23.⁵¹



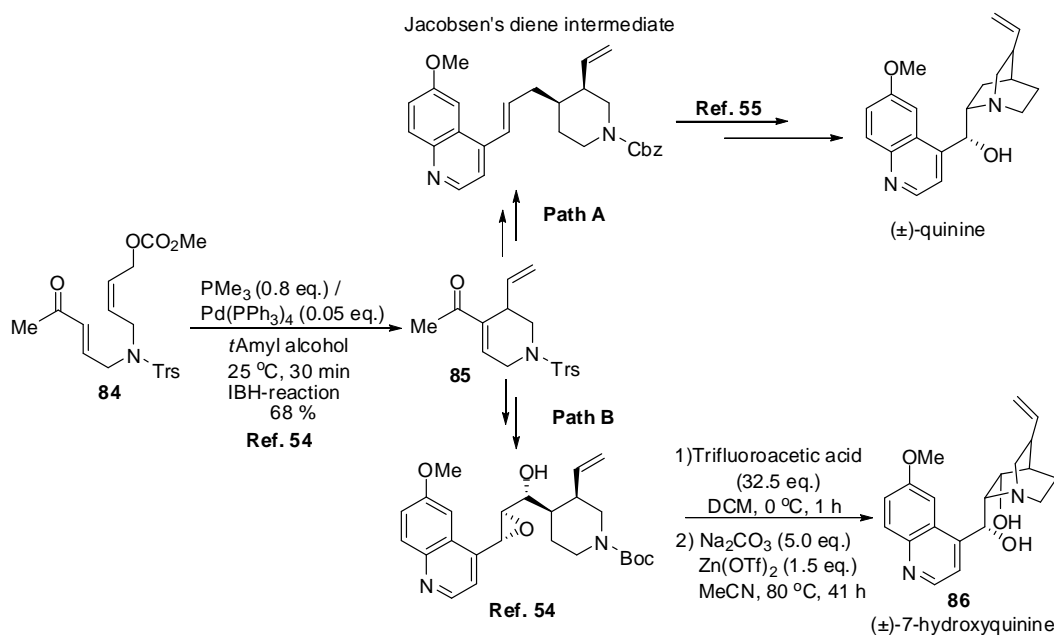
Scheme 23. IBH reaction in the synthesis of anatoxin-a and homoanatoxin hydrochlorides.



Scheme 24. IBH reaction as a key step in the synthesis of grandisines B, D and F.

Intramolecular BH reactions of molecule **80** having an α,β -unsaturated aldehyde-iminium ion system has been employed by Tamura and co-workers for synthesis of the natural products/biologically active molecules grandisines B, D and F (**81**, **82** and **83**) according to the sequence shown in Scheme 24.^{52,53} The required α,β -unsaturated aldehyde-iminium ion system **80** was prepared from easily accessible pyrrolidin-2-one derivative **79** (Scheme 24).

Webber and Krische⁵⁴ have elegantly used intramolecular BH-reaction as the key step in formal synthesis of (\pm)-quinine (Scheme 25 –Path A). Thus IBH reaction of enone (activated alkene component)-allyl carbonate (electrophilic unit) system **84** provided the corresponding product **85** which was conveniently transformed into Jacobsen's diene (the key intermediate for synthesis of quinine).⁵⁵ They have also used the IBH product **85** in the total synthesis of (\pm)-7-hydroxyquinine **86** (Scheme 25-Path B).⁵⁴

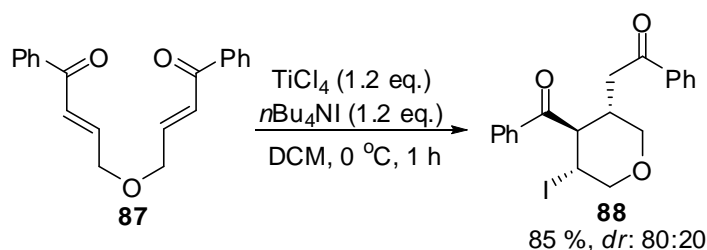


Scheme 25. Formal synthesis of (±)-quinine and total synthesis of (±)-7-hydroxyquinine

3. Intramolecular BH reactions (activated alkene-activated alkene system) [also known as intramolecular Rauhut-Currier (IRC) reaction]

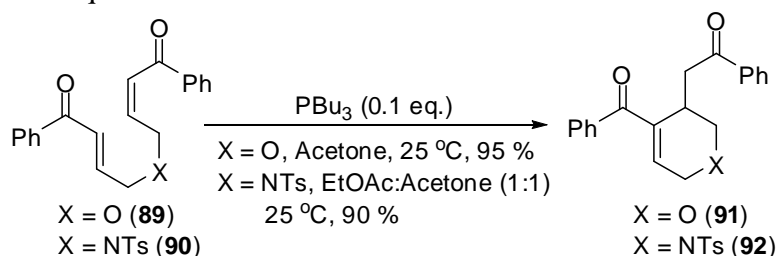
In the BH reaction, if the electrophile is also an activated alkene, then such reactions are known as Rauhut-Currier reactions. Intramolecular Rauhut-Currier reactions are well documented in the literature for obtaining carbocyclic compounds.^{15,18,31-34} However, very few reports have appeared for obtaining heterocyclic compounds. This section presents such examples.

Oshima and co-workers reported a facile protocol for obtaining tetrahydro-2*H*-pyran derivative **88** with high stereoselectivity via intramolecular vinylogous Baylis-Hillman (Rauhut-Currier) reaction of substrate **87** (containing enone-enone system) using TiCl₄ / *n*Bu₄NI as shown in Equation 10.⁵⁶



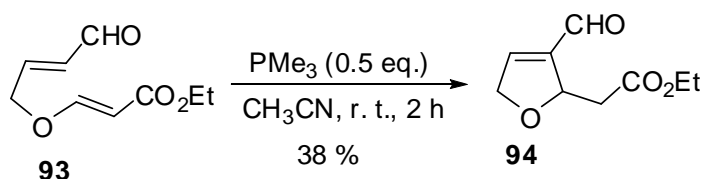
Equation 10. Intramolecular Rauhut-Currier reaction (IRC reaction) of enone-enone system.

Tributylphosphine catalyzed intramolecular Baylis-Hillman (intramolecular Rauhut-Currier) (IRC) reaction of enone-enone systems **89** and **90** was reported by Krische and co-workers to provide tetrahydropyran and piperidine derivatives **91** and **92** respectively following the reaction sequence as shown in Equation 11.⁵⁷



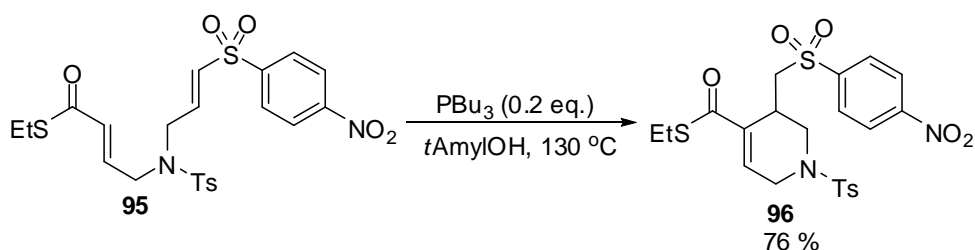
Equation 11. IRC reaction of enone-enone systems.

A highly reactive enal was utilized as the activated alkene component for coupling with en-ester as electrophile component (as shown in compound **93**) in an intramolecular Rauhut-Currier reaction by Roush and co-workers, thus providing an interesting strategy for obtaining the 2,5-dihydrofuran derivative **94** (Equation 12).⁵⁸



Equation 12. IRC reaction of enal-enoate system: synthesis of 2,5-dihydrofuran derivative.

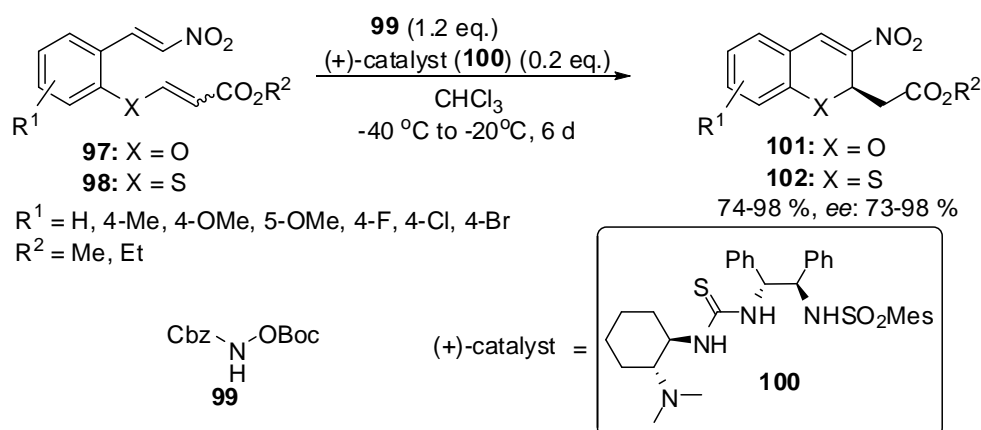
Luis and Krische reported a facile chemoselective intramolecular Rauhut-Currier reaction of vinyl thiolate (as activated alkene component)-vinyl sulfone (as electrophile component) system **95** under the catalytic influence of tributylphosphine for obtaining piperidine derivative **96** as shown (Equation 13).⁵⁹



Equation 13. Chemoselective IRC reaction of vinyl thiolate-vinyl sulfone system **95**.

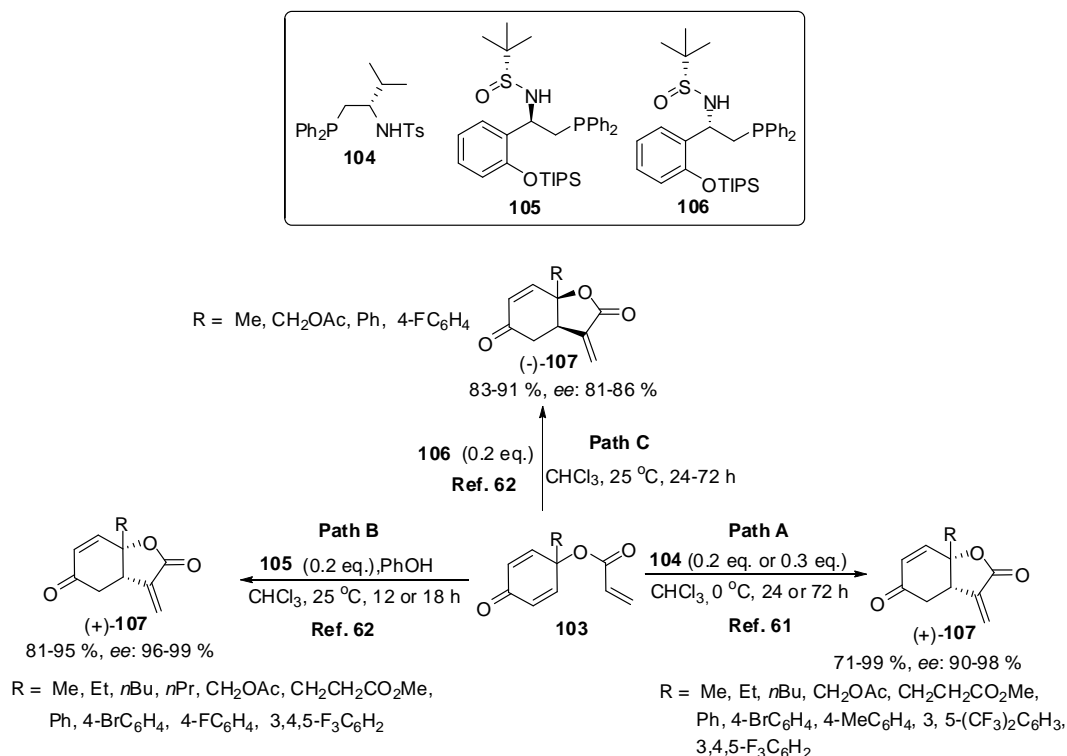
3.1. Asymmetric intramolecular Rauhut-Currier reactions

A convenient procedure for the synthesis of 2-(3-nitro-2*H*-chromen-2-yl)acetate **101** and 2-(3-nitro-2*H*-thiochromen-2-yl)acetate derivatives **102** in high enantioselectivities via asymmetric intramolecular Rauhut-Currier reaction of **97** and **98** respectively using a chiral catalyst **100** (in the presence of **99**) was reported by Xiao and co-workers (Equation 14).⁶⁰

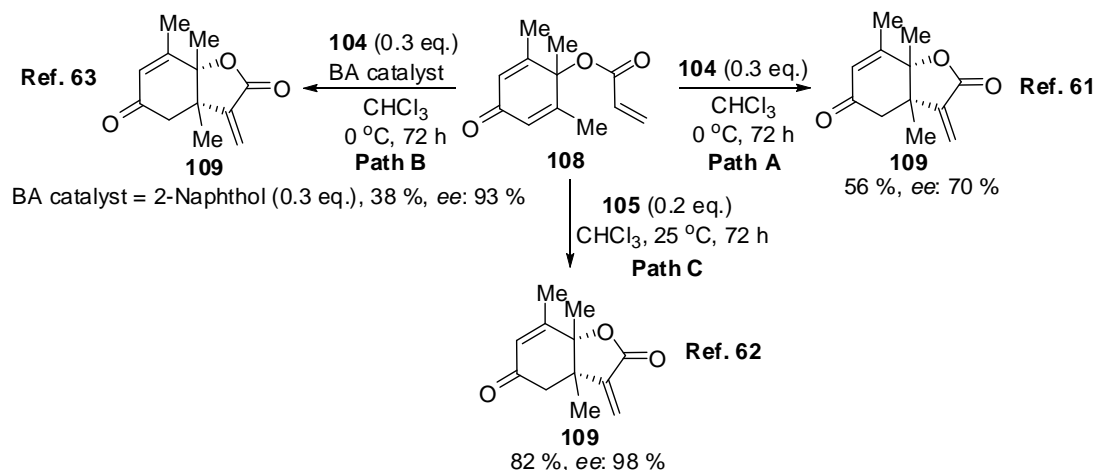


Equation 14. Asymmetric IRC reaction of α,β -unsaturated nitro- α,β -unsaturated esters using chiral thiourea **100** as a catalyst.

Sasai and co-workers have used chiral phosphine catalysts **104** for highly diastereo- and enantio-selective intramolecular Rauhut-Currier reaction of **103** for obtaining α -alkylidene- γ -butyrolactones **107** (Scheme 26, Path A).⁶¹ Subsequently Zhang and coworkers utilized phosphine catalysts **105** and **106** for similar enantioselective Rauhut-Currier reaction (Scheme 26, Paths B and C) of **103** to provide the resulting adducts **107** in high enantioselectivities.⁶² Sasai and coworkers also used trimethylated compound **108** for Rauhut-Currier reaction under similar conditions to provide the resulting α -alkylidene- γ -butyrolactone **109** in 70 % *ee* (Scheme 27, Path A).⁶¹ When the same reaction was performed in the presence of Brønsted acid (BA) (2-naphthol) the resulting bicyclic compound **109** was obtained in 93 % *ee* (but in 38 % yield) (Scheme 27, Path B).⁶³ It is interesting to note that the Zhang's catalyst **105** provided better selectivities for intramolecular Rauhut-Currier reaction of **108** thus producing the resulting adduct **109** in 98 % *ee* and in high yield (89 %) (Scheme 27, Path C).⁶²



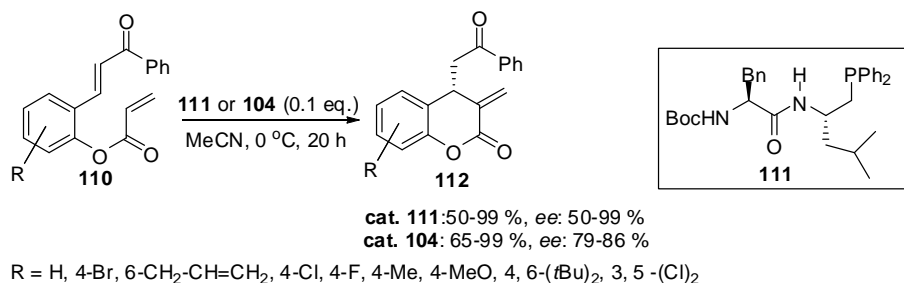
Scheme 26. Asymmetric IRC reaction of acrylate-enones using chiral phosphines **104-106** as catalysts.



Scheme 27. Asymmetric IRC reaction of acrylate-enone **108**.

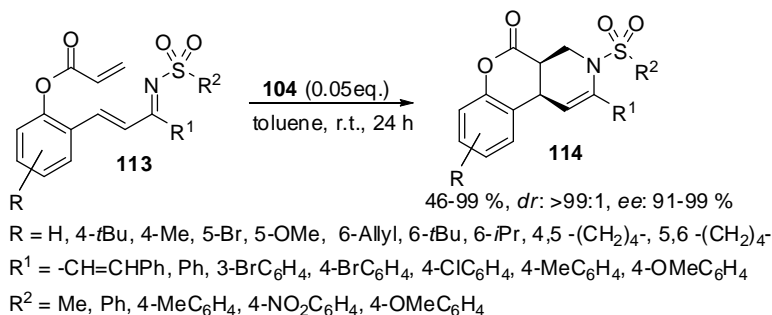
Very recently Spring and co-workers have utilized peptidic phosphine **111** and sulfonamide phosphine **104** as chiral catalysts for asymmetric intramolecular Rauhut-Currier reaction of acrylate-enones **110** for the synthesis of chromanone derivatives **112** in good enantioselectivities

as shown in the Equation 15.⁶⁴ It is interesting to note that when R is 4-nitro group in **110** no reaction occurred in the case of both the catalysts.

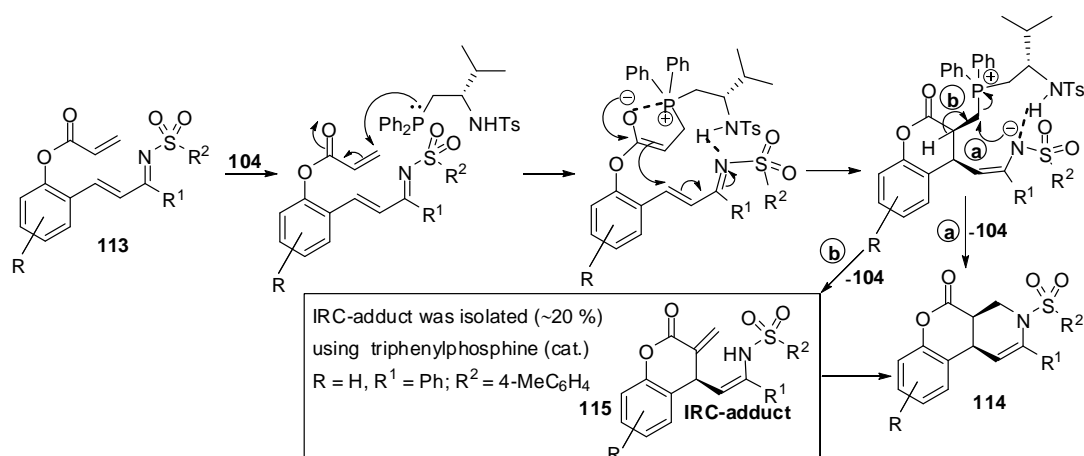


Equation 15. Asymmetric IRC reaction of acrylate-enones **110**.

It is quiet fascinating to note that Chi and co-workers⁶⁵ have proposed an interesting reaction pathway (a plausible mechanism-Scheme 28) involving intramolecular Rauhut-Currier reaction in their work on chiral phosphine (**104**) catalyzed enantioselective intramolecular [2+4] annulation of acrylate- α,β -unsaturated imine systems (**113**), providing tricyclic heterocyclic compounds (**114**) in high diastereo and enantio selectivities (Equation 16). In fact, in order to prove the mechanism proposed, they isolated the intramolecular Rauhut-Currier adduct **115** using triphenylphosphine as a catalyst.⁶⁵



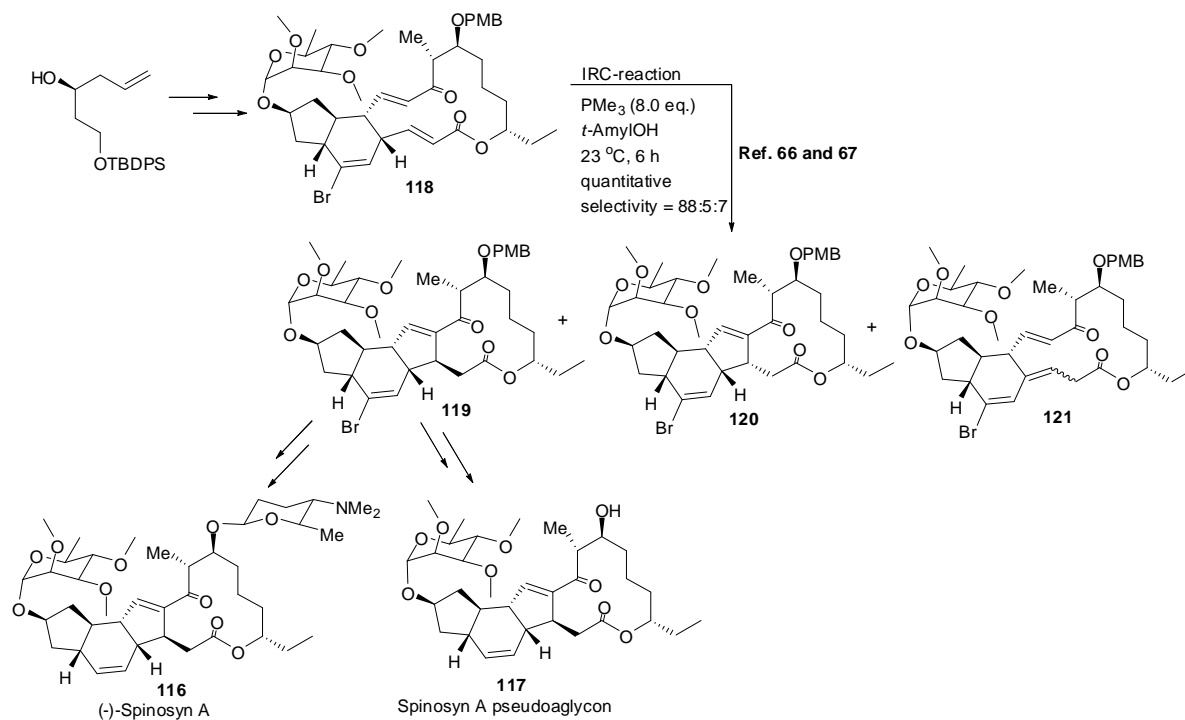
Equation 16. Asymmetric [2+4] annulation of acrylate- α,β -unsaturated imine systems **113**.



Scheme 28. A plausible mechanism involving intramolecular Rauhut-Currier reaction in the synthesis of tricyclic compounds **114**.

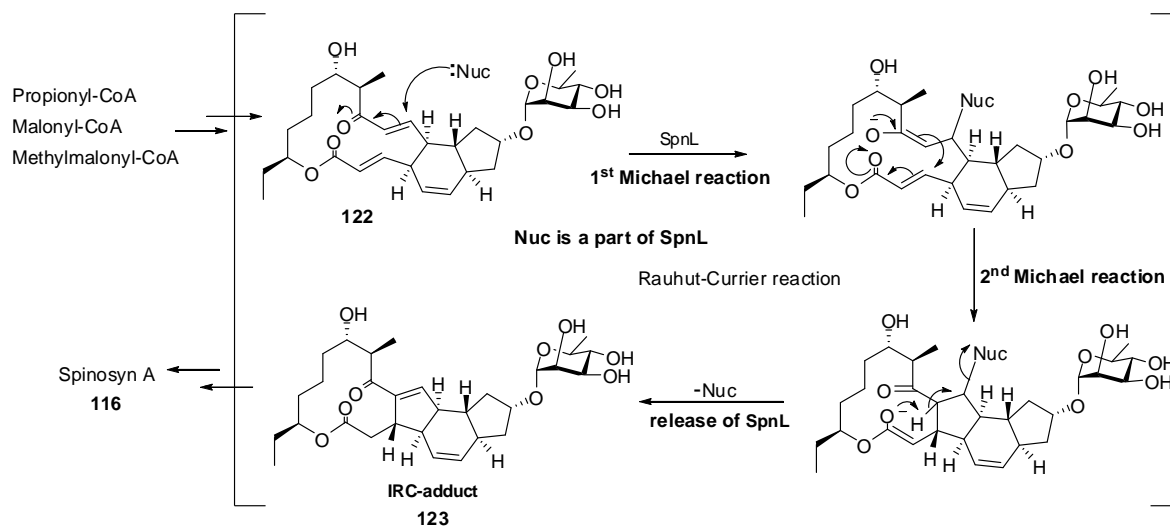
3.2. Applications of intramolecular Rauhut-Currier reactions

Roush and co-workers reported an elegant synthesis of (-)-spinosyn-A **116** and its analogue spinosyn-A pseudoaglycon **117** using intramolecular BH-(intramolecular Rauhut-Currier) reaction as a key step (Scheme 29).^{66, 67} The IRC reaction of **118** provided the corresponding adduct **119** as the major product along with two minor products **120** and **121**. The major product was transformed into (-)-spinosyn-A **116** and its analogue spinosyn-A pseudoaglycon **117** following the reaction strategy as shown in Scheme 29.^{66, 67}



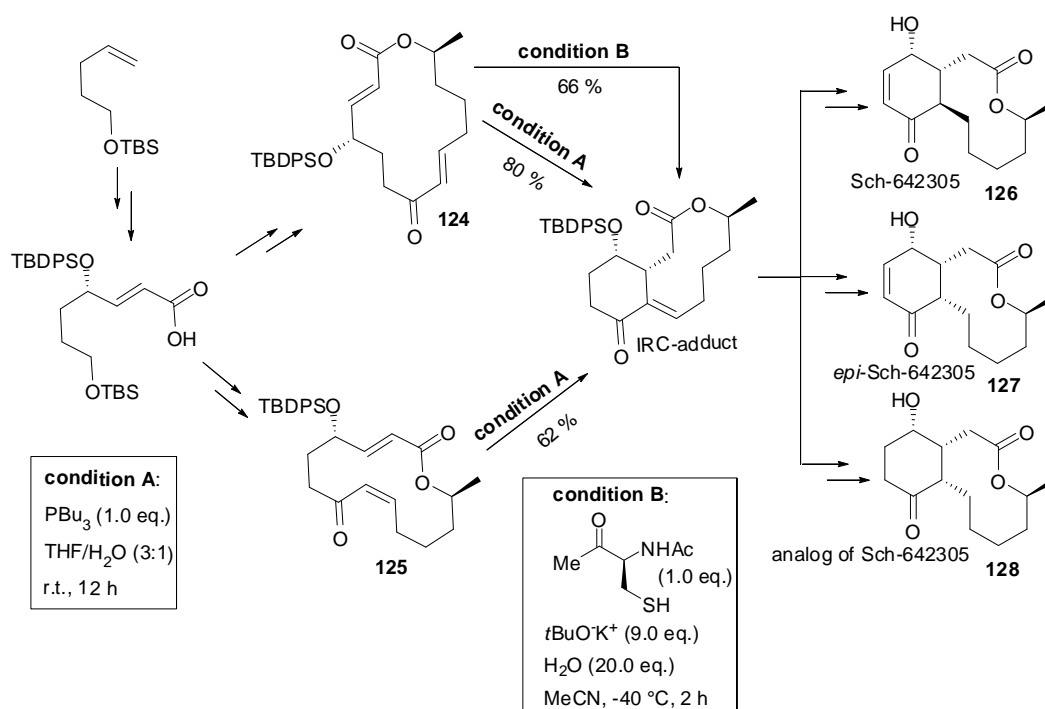
Scheme 29. Synthesis of (-)-spinosyn-A and its analogue spinosyn-A pseudoaglycon.

It is interesting to note the elegant work of Ruszczycky, Choi and co-workers who demonstrated the involvement of Rauhut-Currier reaction as the key step for the formation of tetracyclic core **123** from the tricyclic unit **122** under the influence of coenzyme *SpnL* in biosynthetic pathway of spinosyn-A (**116**) (Scheme 30).⁶⁸



Scheme 30. Biosynthetic pathway of spinosyn-A: IRC-reaction as the key step.

Miller and coworkers have used intramolecular Rauhut-Currier reaction of enone-ene-esters **124** and **125** as the key step for the formation of bicyclic framework during the total synthesis of natural product Sch-642305 (**126**) and related analogs (**127** and **128**). It is fascinating to notice that these workers also examined the application of cysteine based catalyst in the Rauhut-Currier reaction (Scheme 31).⁶⁹

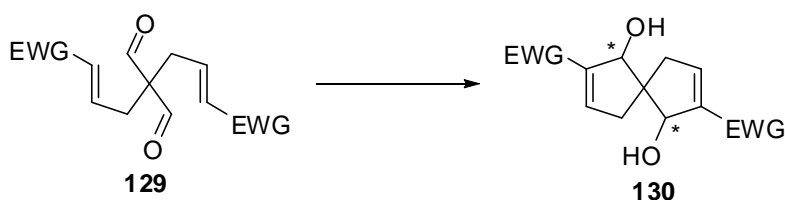


Scheme 31. Total synthesis of natural product Sch-642305 and analogs: IRC-reaction as the key step.

4. Future Challenges and Projections

Although there are not many publications so far on the applications of intramolecular Baylis-Hillman reaction for obtaining heterocyclic compounds, from this brief review it is quite clear that it is an extremely convenient and useful protocol for the synthesis of heterocyclic compounds containing oxygen, nitrogen or sulfur. Literature survey also clearly shows that in comparison to the utility of intramolecular Baylis-Hillman reaction for obtaining carbocyclic systems, such reactions for the synthesis of heterocyclic compounds have not been systematically explored, and only a few synthetic protocols have been reported for 5/6 membered heterocyclic compounds. If substrates are designed appropriately it is possible to synthesize any heterocyclic compounds (including medium and large rings) of medicinal relevance. Thus this strategy offers many opportunities and challenges to the synthetic heterocyclic chemists. The

asymmetric version is yet another challenge. There are a few reports on asymmetric intramolecular BH reactions and several aspects have not been yet explored. This is indeed a present day requirement and challenge. We predict that during the coming ten years this aspect will be followed up and exciting results will be obtained. There is also the possibility to use this strategy (both achiral and chiral versions) for the synthesis of heterocyclic compounds with two or more hetero atoms. This aspect has not so far been considered seriously and it can be expected that it will also receive appropriate attention in the coming years and fascinating results can be predicted. There is unexplored possibility of synthesizing spiro compounds **130** using two intramolecular BH reactions of **129** (Equation 17). This needs to be addressed in the coming years. Thus, the intramolecular BH reaction offers unending opportunities for designing strategies for obtaining heterocyclic compounds.



Equation 17. Two intramolecular BH reactions: synthesis of spiro compounds.

5. Conclusions

From this brief review it is quite clear that although intramolecular Baylis-Hillman reaction provides important classes of useful heterocyclic compounds of medicinal relevance, this aspect has not received much attention from organic and medicinal chemists. The main objective of writing this review is to draw attention to this apparent neglect. We predict that this fascinating area of the Baylis-Hillman reaction will receive considerable attention from synthetic chemists in the coming years and useful and interesting themes will be developed so as to demonstrate its power in synthetic, mechanistic and medicinal chemistry.

6. Abbreviations

Ac	acetyl
BA	Brønsted acid
Bn	benzyl
Boc	<i>t</i> -butoxycarbonyl
Bu	butyl
Cbz	benzyloxycarbonyl

CoA	Coenzyme A
Cp	cyclopentadienyl
DABCO	1,4-diazabicyclo(2.2.2)octane
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
Et	ethyl
EWG	electron withdrawing group
GLC	gas liquid chromatography
HMPA	hexamethyl phosphoramidate
Me	methyl
Mes	mesityl
Nuc	nucleophilic center in <i>S. spinosa</i> (coenzyme)
PMB	<i>p</i> -methoxybenzyl
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl
<i>SpnL</i>	<i>S. spinosa</i> (coenzyme)
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
Tr	trityl
Trs	2,4,6-triisopropylbenzenesulfonyl
Ts	tosyl

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