Tetrahedron 64 (2008) 4511-4574

Advances in the Baylis-Hillman Reaction-assisted Synthesis of Cyclic Frameworks

Vijay Singh and Sanjay Batra*

Medicinal and Process Chemistry Division, Central Drug Research Institute, PO Box 173, Lucknow 226001, India

Dedication- This article is dedicated to Prof. D. Basavaiah for his seminal contributions toward development of this reaction.

Contents

Tetrahedron 64 (2008) 4511-4574

1. Introduction

Acquiring the capability to access structurally complex and diverse molecules through simple starting substrates has been one of the underlying principles of chemical research. These diverse compounds are desired in order to serve mankind in a variety of ways. They might find use in pharmaceutical, agriculture, dyes, materials, electronics and so forth. With the objective of generating an enormously complex skeletal diversity, chemists are always on the lookout for efficient complexity-generating reactions, also referred to as tandem reactions.[1] These reactions may directly lead to a complex product from small and simple building blocks in a single operation or may lead to a product that is multifunctional and becomes a substrate for another complexity-generating reaction. Some of the examples of this class of reactions include the Ugi reaction, Passerini reaction, Diels-Alder reaction, ring-closing metathesis and the Baylis-Hillman reaction.

The Baylis-Hillman reaction, a carbon-carbon bond-forming reaction, which basically involves a reaction between an aldehyde (**1**) and an activated alkene (**2**) in the presence of a tertiary base, affords a highly functionalized product (**3**) (Figure 1). As described by Basavaiah *et al*. in their recent review, it is a three-step reaction involving successive Michael, Aldol and elimination reaction in one pot.[2] The cheap and easy availability of starting materials, ease of performance (since it can be executed in water), atom economy, formation of chemospecific functional groups in the product, provision of an avenue for the introduction of asymmetry, suitability for simulation on the solid phase as a prelude for combinatorial synthesis represent some of the reasons which have led to an exponential increase in the synthetic utility of this reaction.

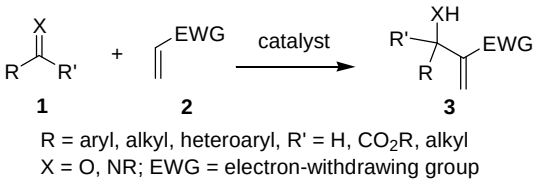


Figure 1. General representation of the Baylis-Hillman reaction

The reaction came into existence in 1968, when H. Morita disclosed that the reaction of an aldehyde with an activated alkene in the presence of tricyclohexylphosphine (PCy_3) affords a densely functionalized product (Figure 2). Subsequently, he published a series of patents detailing the utility of his strategy.[3] This reaction, however earned its name from Baylis and Hillman, who reported that the reaction of aldehydes with activated alkenes including esters, amides, nitriles and ketones in the presence of tertiary bicyclic amines furnished multifunctional products (Figure 2).[4] The synthetic appreciation of this reaction in organic

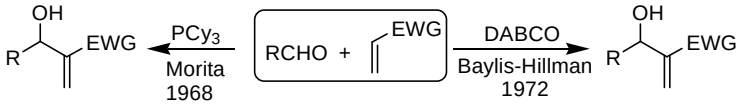


Figure 2. Reactons embodied in patents by Morita and Baylis-Hillman

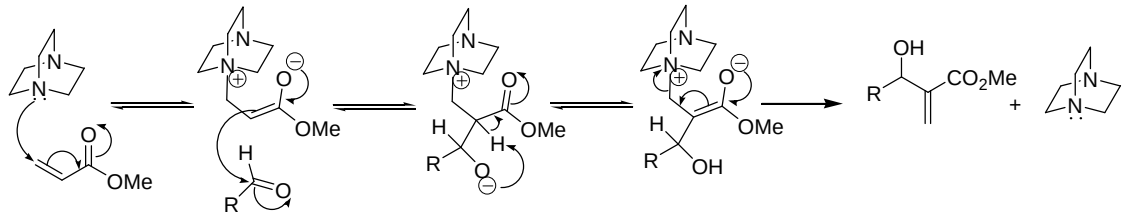
chemistry was at a low ebb during the initial phase. When the utility of the Baylis-Hillman reaction for the synthesis of integerrinecic acid and mikanecic acid was, however demonstrated by Drewes and Emslie[5] in 1982 and Hoffmann and Rabe[6] in 1983, respectively, various chemists became interested in it and started investigating its utility. This led to the publication of the first review in 1988 by Drewes and Roos.[7] Since then, investigations into different aspects of the Baylis-Hillman reaction have gained pace and the second review on the subject, by Basavaiah *et al*., appeared in 1996, covering approximately 200 references.[8] Simultaneously, Ciganek in 1997 authored a chapter in Organic Reactions which discussed the Morita-Baylis-Hillman reaction in great detail.[9] These articles fueled an explosive growth in the scope and applications of this reaction over

the next five years, which was evident by the inclusion of almost 500 references in the review published by Basavaiah *et al*. in 2003.[10] In between these develoments, the progress of the asymmetric Baylis-Hillman reaction was separately reviewed by Langer[11] in 2000, while Kim and co-workers have assimilated the literature pertaining to the developments in the synthesis of cyclic compounds employing this reaction in 2002.[12] Since the publication of the review by Basavaiah *et al*. in 2003, more and more research groups have initiated work on different facets of this reaction. This has led to a search for increasing the scope of the substrates, for novel catalysts, for advancing an understanding of the mechanism and for the disclosure of a variety of synthetic applications of the derivatives generated from this reaction. Interestingly, a major portion of the synthetic applications relates to the synthesis of cyclic frameworks including the carbocyclic, heterocyclic and benzannulated systems. Hence, we feel strongly that an assimilation of the literature since 2003 on this topic will be useful to organic chemists. It was a coincidince that, during the process of writing this report, three more reviews have appeared in the literature which clearly reflects the relevance of this reaction at the present time. Besides the review on the Baylis-Hillman reaction by Basavaiah *et al.*, Shi and co-workers[13] have reviewed the aza-Baylis-Hillman reaction, while Zhu *et al.*[14] have compiled the literature on the enantioselective Morita-Baylis-Hillman reaction and its aza counterpart. Because of areas covered by these articles, we will be limiting this review to all references from 2003 which disclose the synthesis of cyclic systems employing the Baylis-Hillman adducts or their corresponding derivatives. References related to the chemistry originating from the Baylis-Hillman reaction of cyclic compounds (e.g. heterocyclic aldehydes and cyclic enones) have also been excluded. The literature covered in this article has been obtained either from a Sci-Finder search using the keyword “Baylis-Hillman” or from other web resources. This review has been categorized

on the basis of the reaction strategies involved in the process of cyclization. A section of miscellaneous reactions accommodates the strategies or isolated reports which could not be classified under any of the mentioned sections. For the sake of greater attention, the applications relating to the generation of the key intermediates for the synthesis of natural products bearing a cyclic framework have been discussed at the end of the review.

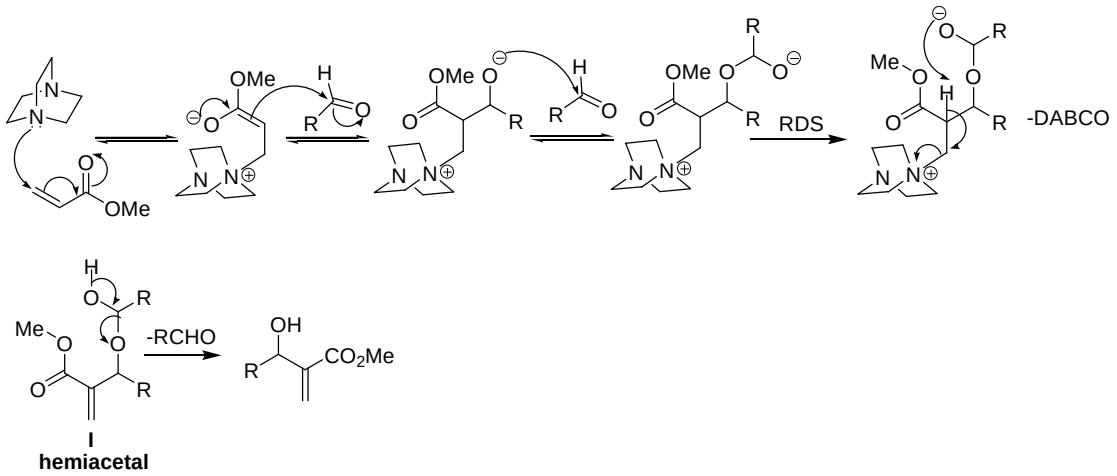
2. Mechanism

The mechanism of the Baylis-Hillman reaction has already been discussed in detail by Basavaiah *et al*.[2,10] and Zhu *et al*.[14] The first acceptable mechanism for the Baylis-Hillman reaction was suggested by Hoffmann and Rabe[15] in 1983, although Morita has reported a mechanism in 1968 related to the phophine-mediated reactions.[3] Later, based on pressure dependence, rate and kinetic isotope effect data, Hill and Isaacs reported a mechanism which was believed to proceed through a Michael-initiated addition-elimination sequence (Scheme 1).[16] This was supported by Bode and Kaye through a rate law and was the most



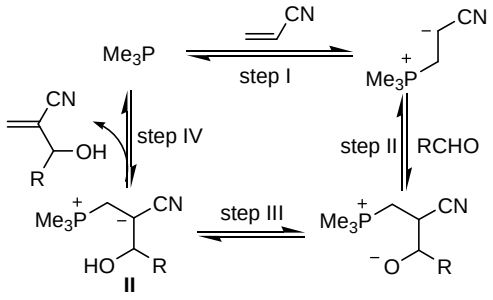
Scheme 1

commonly accepted mechanism.[17] Very recently, however, McQuade and co-workers have proposed a new mechanism involving a hemiacetal intermediate (**I**) (Scheme 2).[18] This mechanism was based on the reaction rate data in aprotic solvents, where they determined that the Baylis-Hillman RDS was second order in aldehyde and first order in DABCO and acrylate. Initially, they carried out studies with 4-nitrobenzaldehyde, but, later, they published their results with other aromatic aldehydes.[19]



Scheme 2

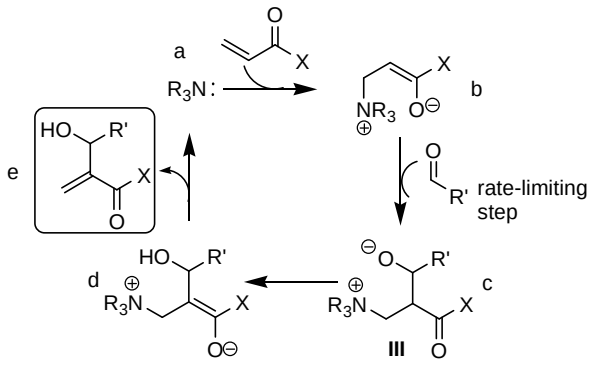
More recently, Xu has carried out density function theory calculations for PMe_3-catalyzed Morita-Baylis-Hillman reactions with the objective of probing the mechanism. He concluded that the catalytic cycle of the Morita-Baylis-Hillman reaction involves four steps.[20] Initially, 1,4-addition of Me_3P to the activated alkene results in a zwitterionic intermediate followed by the zwitterionic phosphonium adduct attacking the ethanal. This is followed by an intramolecular hydrogen transfer and final elimination of the product from the intermediate (**II**) containing the product complexed to PMe_3, as shown in Scheme 3.



Scheme 3

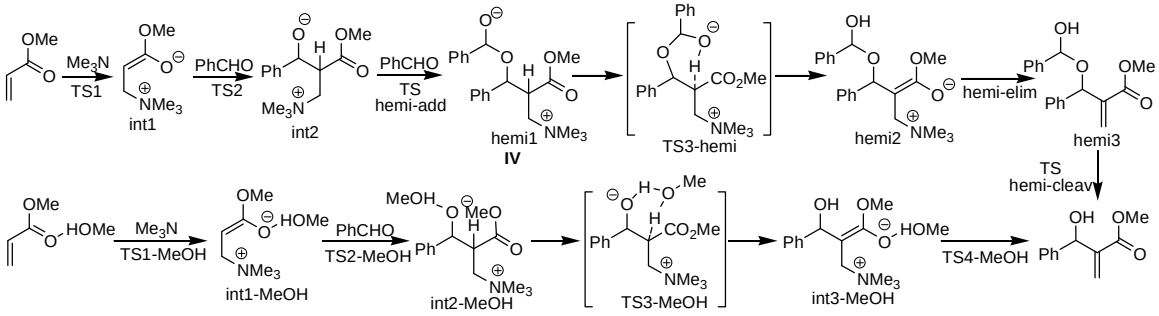
Roy and Sunoj reported the first DFT as well as ab initio investigations on the mechanism of the Morita-Baylis-Hillman reaction between (i) acrolein and formaldehyde catalyzed by trimethylamine (model system) and (ii) methyl vinyl ketone and benzaldehyde catalyzed by

DABCO (real system). They showed that the rate-limiting step involves an intramolecular proton transfer in the zwitterionic intermediate (**III**) afforded by the addition of enolate to electrophiles under polar aprotic conditions (Scheme 4). The activation barrier for the C-C bond-formation was found to be lower than the proton-transfer step for the reaction of methyl vinyl ketone with benzaldehyde in the presence of DABCO.[21]



Scheme 4

Subsequently, Robiette *et al.* carried out a detailed computational investigation for the mechanism of the Morita-Baylis-Hillman reaction. It was mentioned by the authors of this paper that the thorough calibration and mechanistic studies carried out by Roy and Sunoj partly mirror their work. They predicted, that in the absence of a protic solvent, deprotonation of the α–position is the rate-determining step and occurs through a cyclic transition state, with proton transfer to a hemiacetal alkoxide (**IV**) formed by the addition of a second equivalent of aldehyde to the intermediate alkoxide. On the contrary, in the presence of methanol they found a slightly lower energy pathway in which the alcohol serves as a carrier to transfer the proton from carbon to oxygen, as shown in Scheme 5.[22]



Scheme 5

3. Understanding opportunities for the generation of cyclic compounds based on the course of the reaction of the Baylis-Hillman derivatives

Any cyclization process requires the construction of a C-C or C-X bond, where X could be a heteroatom. The intramolecular Baylis-Hillman reaction offers the first opportunity for the synthesis of cyclic compounds. The Baylis-Hillman adducts incorporate three chemospecific groups, viz. a hydroxyl group, a double bond and an EWG. These groups could be appropriately tailored to generate an array of cyclic compounds directly from the Baylis-Hillman adducts. The Baylis-Hillman adduct could be readily transformed into the acetate (**V**) or allyl bromide (**VI**) via acetylation and bromination, respectively (Figure 3). The acetate and allyl bromide undergo a variety of reactions, leading to products which could be efficiently exploited for the generation of cyclic scaffolds. The pictorial depiction of different points of cyclization is delineated in Figure 4.

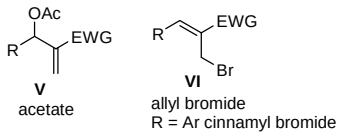


Figure 3. Structures of acetate (III) and allyl bromide (IV) derived from the Baylis-Hillman adduct

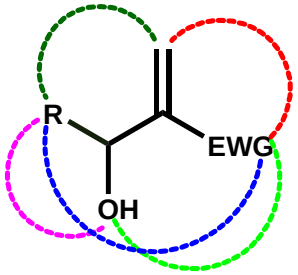


Figure 4. Different colors showing various opportunities for cyclization in the Baylis-Hillman adduct

Since a large number of synthetic manipulations are initiated via the reactions of Baylis-Hillman adducts, and their acetyl or allyl bromide derivatives with nucleophiles, a short discussion on this subject is warranted. The nucleophilic attack on the Baylis-Hillman adducts mainly follows a Michael-type addition, in which the nucleophile adds to the carbon of the methylene group in the molecule, e.g. reaction of a primary amine yields the substituted 3-aminoalkanol **VII** (Figure 5). In contrast, to this situation the nucleophilic

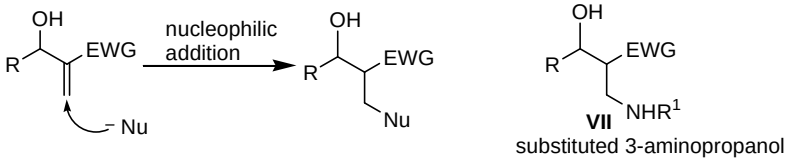


Figure 5. Nucleophilic addition in the Baylis-Hillman adduct, e.g. formation of substituted 3-aminopropanol **VII**

substitution reaction of the Baylis-Hillman acetate depends upon the reaction conditions. If the nucleophile is added in an organic solvent in the presence of a base, an allylic substitution reaction is initiated which proceeds sequentially via addition and elimination processes and is commonly referred as an S_N2'-type reaction, e.g. reaction of a primary amine in an organic solvent furnishes the substituted allyl amine **VIII** (Figure 6). When the

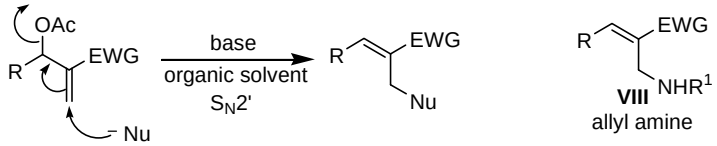


Figure 6. S_N2' reaction of the nucleophile with the Baylis-Hillman acetate, eg. formation of an allyl amine derivative **VIII**

same nucleophile is added to the Baylis-Hillman acetate in the presence of DABCO under aqueous conditions, however, an allylic substitution reaction results involving sequential steps such as addition of DABCO and elimination of acetic acid leading to an intermediate complex (**IX**). This is followed by attack of the nucleophile on the double bond and elimination of the DABCO. This is generally referred as an S_N2-type reaction and the course of the reaction is presented in Figure 7, e.g. S_N2 reaction of a primary amine yielded the substituted allyl amine **X**.

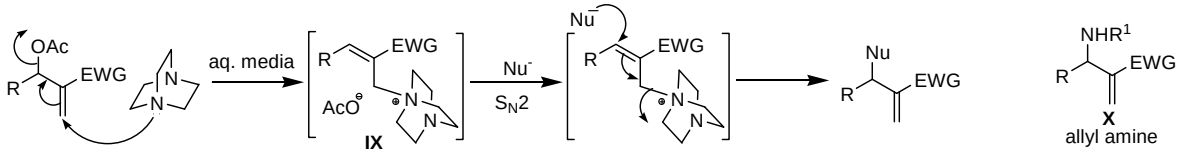
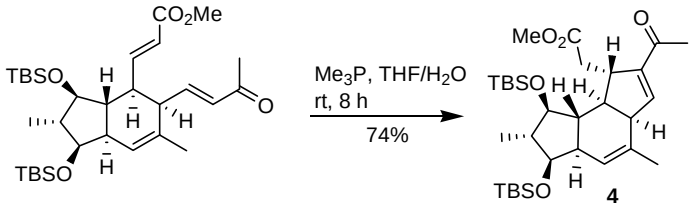


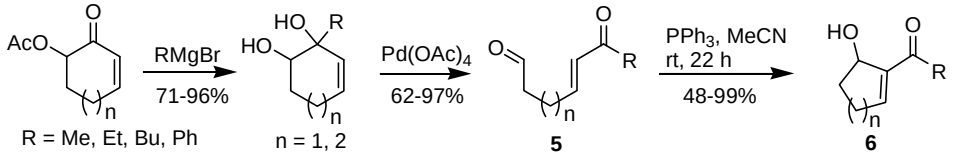
Figure 7. S_N2 reaction of the nucleophile with the Baylis-Hillman acetate in aqueous medium, e.g. formation of substituted allyl amine **X**

4. Intramolecular Baylis-Hillman reaction

The intramolecular Baylis-Hillman reaction which is an excellent strategy for the construction of a cyclic framework has gained significant progress since Murphy *et al*. reported it in 1997.[23] Methot and Roush described the intramolecular vinylogous Morita-Baylis-Hillman reaction to access the central cyclopentane ring (**4**) of FR182877 (Scheme 6).[24] Later, Koo *et al.* developed an efficient synthesis of diverse ω-formyl-α,β-unsaturated carbonyl compounds (**5**), which, under a Ph_3P-mediated intramolecular Baylis-Hillman reaction, yielded several biologically important polycyclic compounds (**6**), as shown in Scheme 7.[25]

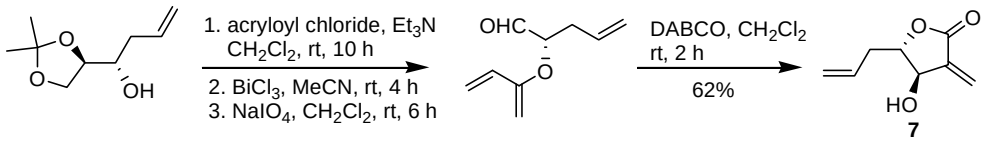


Scheme 6

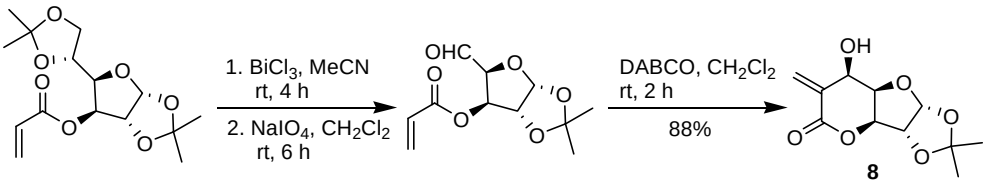


Scheme 7

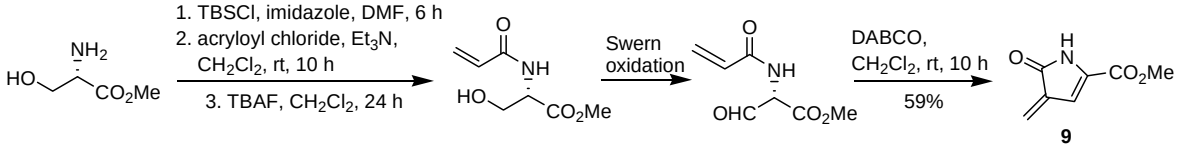
Krishna *et al*. reported the first diastereoselective intramolecular reaction of a chiral substrate in which both aldehyde and activated olefin co-exist as substituents to afford α-methylene-β-hydroxy-γ-butyrolactones (**7**) in good yield (Scheme 8).[26] Further, they demonstrated the synthesis of a single isomer of tetrahydrofurano-2-pyrone (**8**), starting from 1,2-*O*-isopropylidine-3-*O*-acrylate-α-D-*xylo*-pentadialdo-1,4-furanose (Scheme 9). Subsequently, they attempted the synthesis of an α-methylene-*β*-hydroxylactam starting from a chiral acrylamide aldehyde, which, in turn, was derived from L-serine. They isolated the 3-methylene-2-pyrrolone (**9**), however, instead of the expected product, as depicted in Scheme 10.



Scheme 8

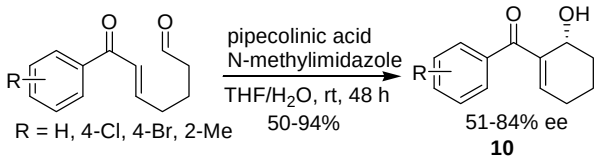


Scheme 9

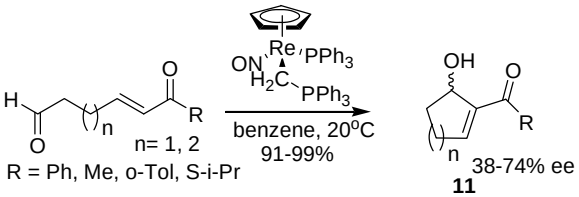


Scheme 10

The intramolecular Morita-Baylis-Hillman reaction with a high level of enantioselectivity was accomplished under the influence of a co-catalyst system involving pipecolinic acid and *N*-methylimidazole by Miller and co-workers.[27] They demonstrated this strategy for the synthesis of cycloalkenes (**10)**. Replacement of pipecolinic acid with proline and its derivatives resulted in a low enantioselectivity (Scheme 11). Recently, Seidel and Gladysz reported that a chiral rhenium-containing phosphine $(\eta^5\text{-}C_5H_5)Re(NO)(Ph_3P)CH_2Ph_3P$-catalyzed intramolecular Morita-Baylis-Hillman reaction in benzene or chlorobenzene afforded carbocycles (**11**) in good yields, but with moderate enantioselectivity (Scheme 12).[28]



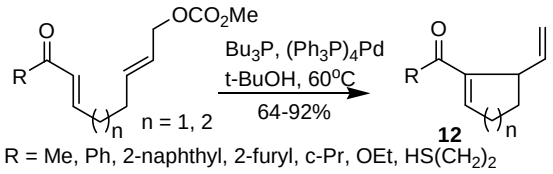
Scheme 11



Scheme 12

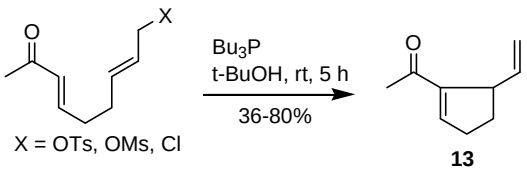
Krische *et al*. demonstrated the feasibility of nucleophilic catalysis as a route to the enolate formation in $Bu_3P/(Ph_3P)_4Pd$-promoted cross coupling, resulting in cycloallylation of the mono-enone mono-allylic acetate to give the cyclic compound **12,** as shown in Scheme 13. The transformation was accomplished by uniting the nucleophilic features of the Morita-

Baylis-Hillman reaction with the electrophilic features of the Trost-Tsuji reaction via the above two-component catalyst systems.[29]

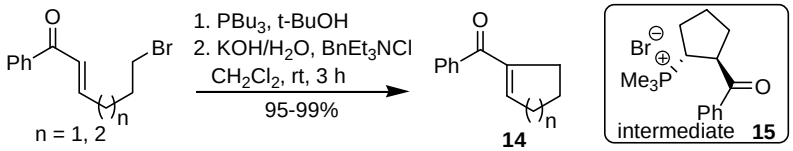


Scheme 13

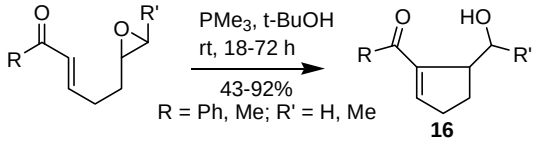
The intramolecular variant of the Morita-Baylis-Hillman reaction encompassing leaving groups on an allylic framework as the electrophilic partner in an organocatalytic process was described by Krafft and Haxell. They observed that the allylic chloride in the presence of Bu_3P provided a better yield of the cyclic enone (**13**) as compared to the allylic mesylate or allylic tosylate. as delineated in Scheme 14.[30] Subsequently, they extended their strategy to the intramolecular α-alkylation of enones using saturated alkyl halides under the influence of Me_3P for the synthesis of cyclic enones **14** (Scheme 15).[31] Later, these workers, with the objective of studying the mechanism, also isolated for the first time a ketophosphonium salt (**15**) which is a Morita-Baylis-Hillman intermediate having *trans* geometry (Scheme 15).[32] They suggested that electrostatic interaction was not the overriding electronic influence for defining the stereochemical outcome of the cyclization. They also demonstrated the success of their methodology in an aqueous medium in the presence of a phase-transfer catalyst.[33] The use of an epoxide as the electrophile in the Morita-Baylis-Hillman chemistry was demonstrated for the first time by these workers for the successful synthesis of various cyclic enones (**16**), as illustrated in Scheme 16.[34]



Scheme 14

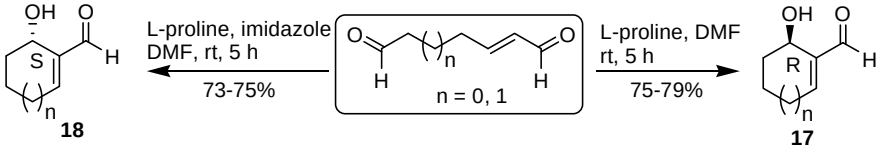


Scheme 15



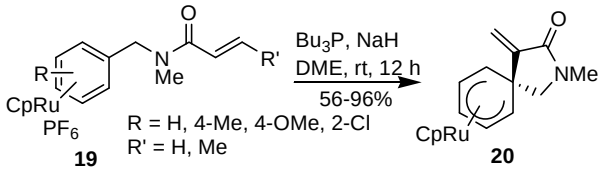
Scheme 16

Hong *et al.* for the first time reported an efficient proline-catalyzed enantioselective intramolecular Baylis–Hillman reaction to obtain cyclohexenol derivatives (**17**). They observed that the addition of imidazole, as a co-catalyst, to the reaction mixture resulted in an inversion of selectivity of the product (**18**), as depicted in Scheme 17.[35]



Scheme 17

More recently, another intramolecular organometallic variation of the Morita–Baylis–Hillman reaction has been reported by Pigge *et al*.[36] It was demonstrated that *N*-benzyl acrylamide–ruthenium complexes **19** were transformed into the spirocyclic derivative (**20**) in the presence of Bu_3P and NaH (Scheme 18). The ruthenium-arene complex served as an electrophile which was capable of trapping enolate generated in the reaction.



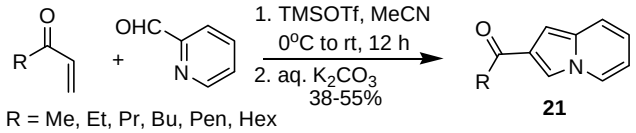
Scheme 18

5. Intramolecular cyclization during the Baylis-Hillman reaction

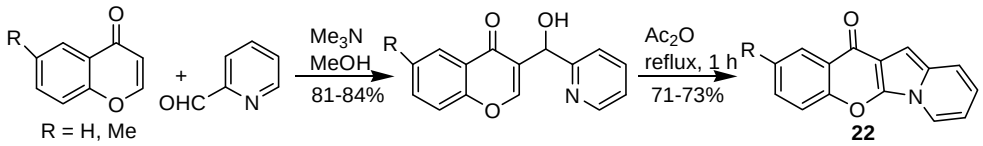
Several nitrogen-, oxygen-, sulfur- and selenium-containing heterocyclic systems have been afforded through intramolecular cyclizations which take place concomitantly after the Baylis-Hillman reaction. Generally, such a property is shown by two structural classes of compounds. In one of these classes, there is a nitrogen atom present adjacent to the carbon bearing the formyl group, which participates in the intramolecular cyclization. In the second structural class, there is a nucleophilic moiety present on the carbon adjacent to the carbon bearing the formyl unit. Once the Baylis-Hillman reaction has been accomplished, there is a tandem intramolecular cyclization via an attack of the nucleophile either on the double bond or on the electron-withdrawing group of the resulting Baylis-Hillman adducts, yielding a cyclic derivative.

5.1 Nitrogen-containing systems

Basavaiah and Rao reported the first example of electrophile induced Baylis-Hillman reaction wherein treatment of pyridine-2-carbaldehyde with alkyl vinyl ketones and cyclic enones under the influence of TMSOTf provided a one-pot synthesis of indolizines (**21**), as shown in Scheme 19.[37] Subsequently, they also demonstrated a facile synthesis of indolizine-fused chromones (**22**) from the reaction between the Baylis-Hillman adducts of pyridine-2-carbaldehyde and 1-benzopyran-4(4*H*)-ones, as presented in Scheme 20.[38]

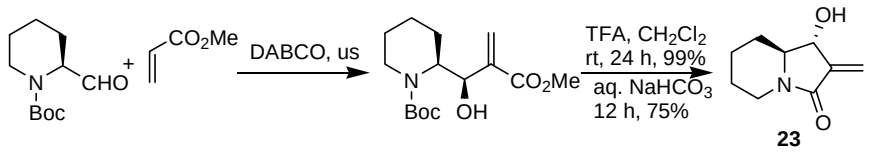


Scheme 19

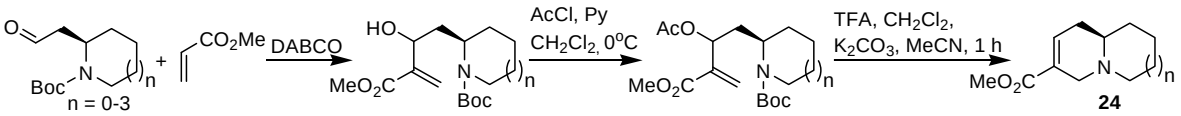


Scheme 20

Almeida and co-workers reported the Baylis-Hillman reaction of chiral α-amino aldehydes under sonication which avoids racemization and described the synthesis of bicyclic lactam (**23**) with an indolizidinic skeleton from the Baylis-Hillman adduct of *N*-Boc-pipecolaldehyde (Scheme 21).[39] Very recently, in an alternate strategy for the generation of *N*-bridgehead heterocyclic systems, Clive and co-workers reported the synthesis of bicyclic amines with nitrogen at a ring-fusion position (**24**) via a sequential Baylis-Hillman reaction between *N*-protected *β*-amino aldehydes and acrylates followed by *O*-acetylation and *N*-deprotection, as shown in Scheme 22.[40] They extended this strategy for the synthesis of (–)-δ-coniceine.

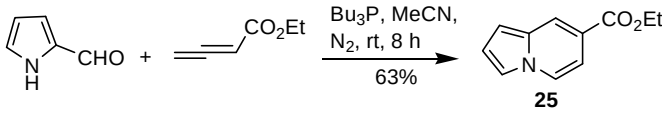


Scheme 21



Scheme 22

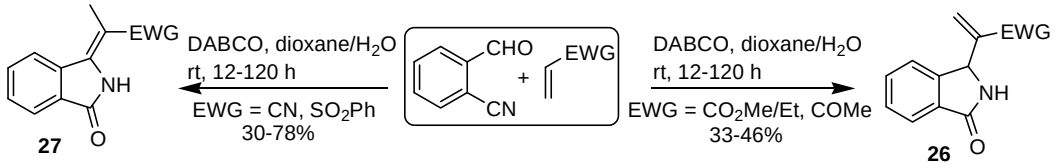
Virieux *et al.* have described the synthesis of indolizine (**25**) using the Baylis-Hillman reaction of pyrrolecarbaldehyde with an electron-deficient allene in the presence of a catalytic amount of Bu_3P (Scheme 23).[41]



Scheme 23

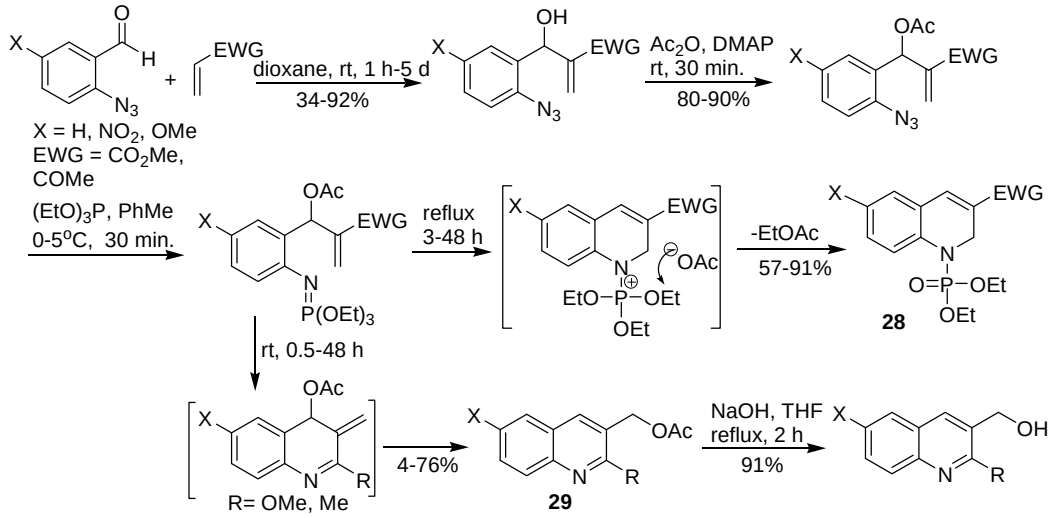
Lee and co-workers demonstrated that the Baylis-Hillman reaction of 2-cyano benzaldehyde with activated alkenes in the presence of DABCO led to the formation of 2-(3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)-acrylates (**26**). When acrylonitrile and phenyl vinyl

sulfone were employed as the alkenes, however the rearranged products (**27**) were obtained, as illustrated in Scheme 24.[42] Later Lee's group successfully accomplished the synthesis

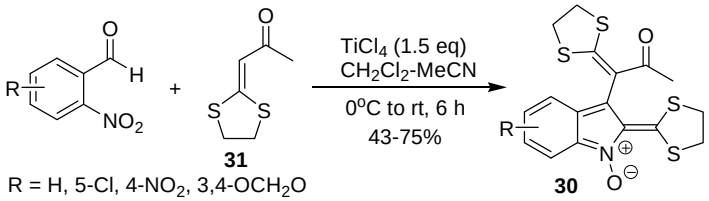


Scheme 24

of several 1,2-dihydroquinoline derivatives (**28**) and 3-acetoxymethyl-quinolines (**29**) in moderate- to -good yields by the reaction between the acetyl derivatives of Baylis-Hillman adducts of 2-azidobenzaldehydes with triethyl phosphite (Scheme 25).[43] Dong and co-workers have described the synthesis of substituted indole *N*-oxides (**30**) via a $TiCl_4$-mediated Baylis-Hillman reaction of α–oxo cyclic ketene-S,S-acetal (**31**) with 2-nitrobenzaldehydes (Scheme 26).[44]



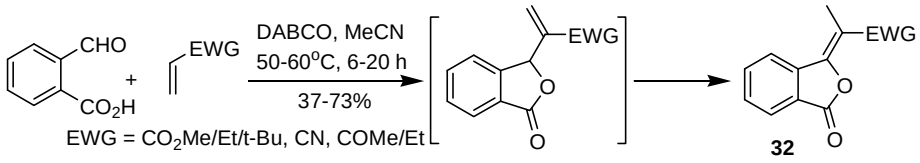
Scheme 25



Scheme 26

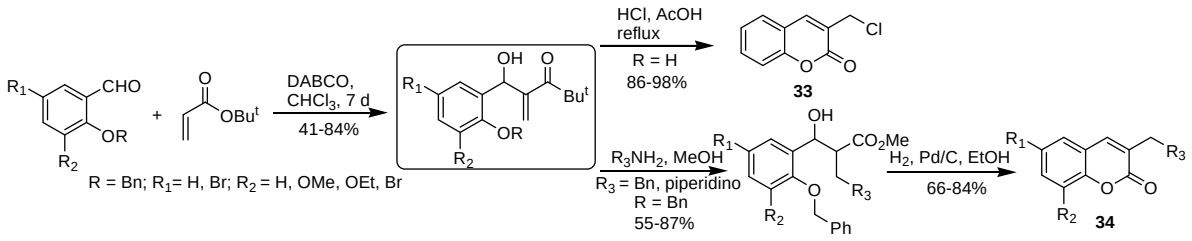
5.2 Oxygen-containing systems

Kim and co-workers demonstrated that the DABCO-catalyzed Baylis-Hillman reaction of 2-carboxybenzaldehyde with activated alkenes gave the enol lactones (**32**) in moderate yields via a sequential Baylis-Hillman reaction, and lactonization followed by a 1,3-hydrogen shift (Scheme 27).[45]



Scheme 27

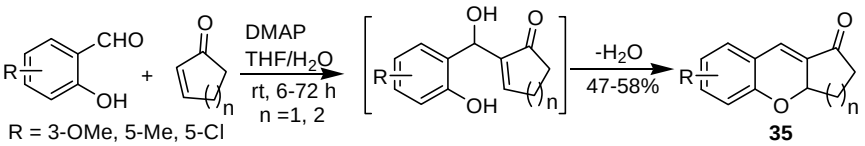
Kaye *et al*. successfully developed a route to access 3-(chloromethyl) coumarin (**33**) via the direct cyclization of unprotected Baylis-Hillman adducts.[46] Subsequently, Kaye and Musa demonstrated a general chemoselective approach to 3-substituted coumarins (**34)** from the Baylis-Hillman adducts of *O*-benzyl-protected salicylaldehydes via Pd-C-mediated hydrogenation, as delineated in Scheme 28.[47]



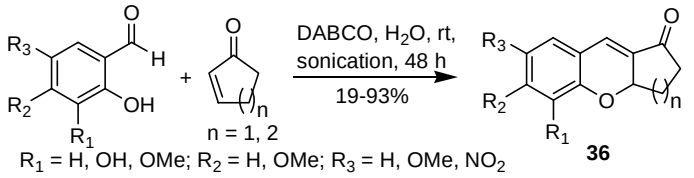
Scheme 28

Kim *et al*. described the synthesis of chromenones (**35**) from the Baylis-Hillman reaction between salicylaldehydes and cycloalkenones under the influence of DMAP. They reported that the use of DABCO gave the products in low yields (Scheme 29).[48] Subsequently, Lesch and Brase successfully achieved the synthesis of tetrahydroxanthenones (**36**) by carrying out the reaction in the presence of DABCO under sonication (Scheme 30).[49] Later, they transformed these tetrahydroxanthenones into highly functionalized

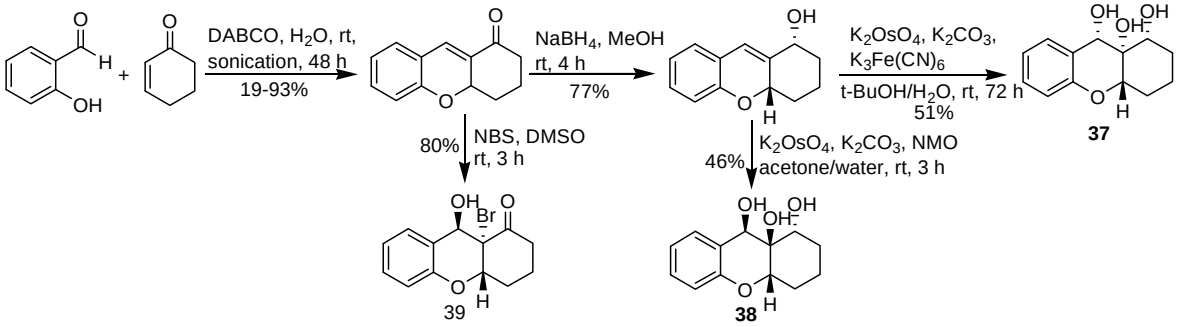
tetrahydroxanthenols (**37**, **38** and **39**) (Scheme 31).[50] In subsequent studies, however, in which they proposed the mechanistic details, they found their reaction to be an oxa-Michael-Aldol condensation, rather than a Baylis-Hillman reaction.[51]



Scheme 29

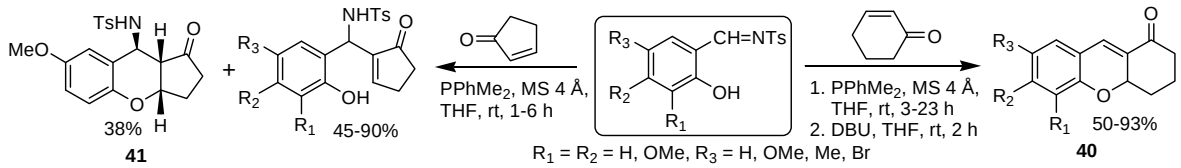


Scheme 30



Scheme 31

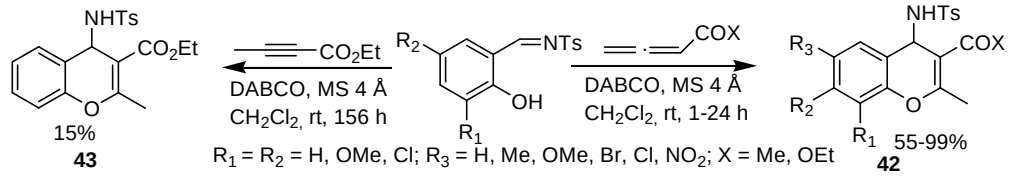
Shi and Shi have also described a successful synthesis of tetrahydroxanthenes (**40**) from the Baylis-Hillman reaction of salicyl *N*-tosylimines with 2-cylohexenone in the presence of $PPhMe_2$ (Scheme 32).[52] They reported a similar reaction with cyclopentenone to afford the cyclized product (**41**) and this was dependent upon the nature of the salicyl *N*-tosylimine.



Scheme 32

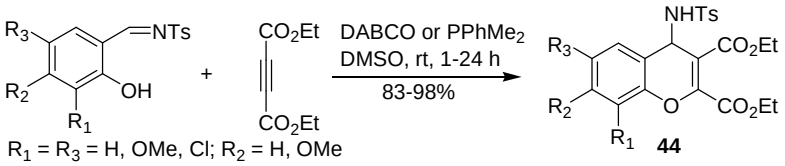
Shi and co-workers reported an efficient approach to highly functionalized chromenes (**42**) via a DABCO-catalyzed reaction of salicyl *N*-tosylimines with ethyl 2-butynoate and penta-

3,4-diene-2-one in dichloromethane.[53] It was observed that the phosphine catalysts were not suitable for this particular reaction as they resulted in [3+2] cycloadducts only. These workers proposed that the formation of chromenes under an amine-catalyzed pathway proceeds via the formation of an unstable zwitterionic intermediate followed by a Michael/Mannich reaction. Based on this rationale they extended their study by reacting ethyl 2-butynoate and salicyl *N*-tosylimine. Unfortunately, the resulting chromene (**43**) was obtained in low yield, possibly due to the steric hindrance in ethyl 2-butynoate towards the nucleophilic attack (Scheme 33).

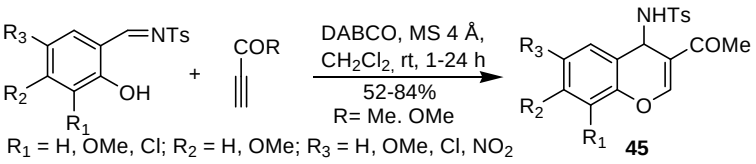


Scheme 33

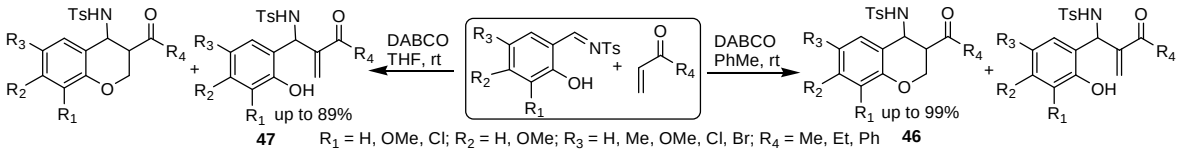
Shi and co-workers later described that, compared to ethyl 2-butynoate, the reaction between diethyl acetylenedicarboxylate and salicyl *N*-tosylimine in the presence of DABCO or $PPhMe_2$ in DMSO proceeded efficiently to afford the corresponding chromenes (**44**) in excellent yields, as shown in Scheme 34.[54] Subsequently, Shi and Shi prepared substituted chromenes (**45**) by the reaction of but-3-yn-2-one and methyl propiolate with salicyl *N*-tosylimines (Scheme 35).[55] On the basis of their proton NMR observations, the reaction mechanism for this transformation was also delineated. Very recently, Qi and Shi reported the DABCO-catalyzed aza-Baylis-Hillman reaction of salicyl *N*-tosylimines with methyl vinyl ketone, ethyl vinyl ketone or phenyl vinyl ketone.[56] They found that performing the reaction in toluene afforded chromans (**46**) as the major products, whereas a similar reaction in THF led to the formation of the aza-Baylis-Hillman adducts (**47**) as the major products (Scheme 36).



Scheme 34

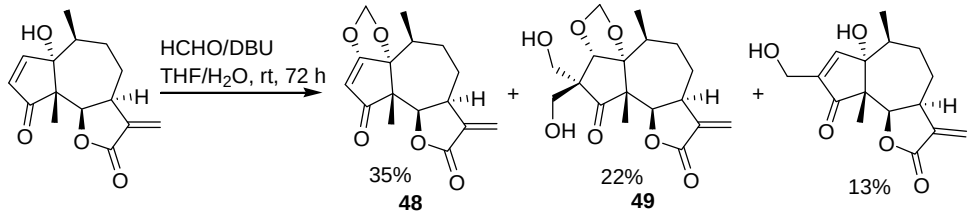


Scheme 35



Scheme 36

Recently, an interesting reaction describing the formation of 1,3-dioxolanes (**48** and **49**) during the DBU-catalyzed Baylis-Hillman coupling of a sesquiterpene lactone, parthenin, with aromatic and aliphatic aldehydes has been reported by Taneja and coworkers (Scheme 37).[57] They proposed that the presence of a tertiary homoallylic hydroxyl group at the C-1 position may be responsible for the 1,3-dioxolane formation.

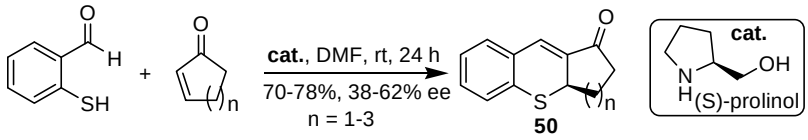


Scheme 37

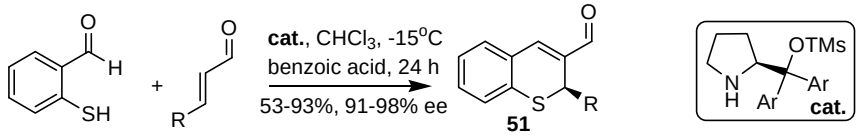
5.3 Sulfur-containing systems

Inspired by the work of Brase *et al.* on the preparation of tetrahydroxanthenones,[47-49] Cardova *et al.* transformed 2-mercaptobenzaldehyde in the presence of (S)-prolinol, an

asymmetric organocatalyst, into tetrahydrothioxanthanes (**50**).[58] The Baylis-Hillman-type product was, in fact, obtained via a domino thia-Michael/Aldol reaction (Scheme 38). Subsequently, these also generated thiobenzopyrans (**51**) in the presence of a chiral diarylprolinol, as delineated in Scheme 39.[59] Wang *et al*. independently studied other organocatalysts such as diarylprolinol silyl ethers and cinchona alkaloid-derived thioureas for the reaction of 2-mercaptoaldehydes, resulting in similar products **52** and **53** with good- to -excellent yields and enantioselectivities, as shown in Schemes 40 and 41, respectively.[60]

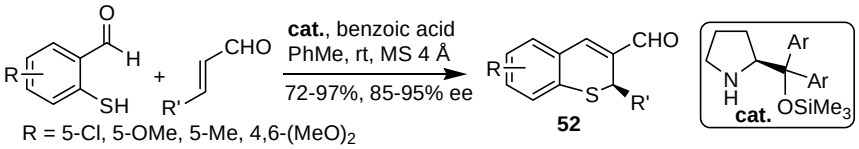


Scheme 38



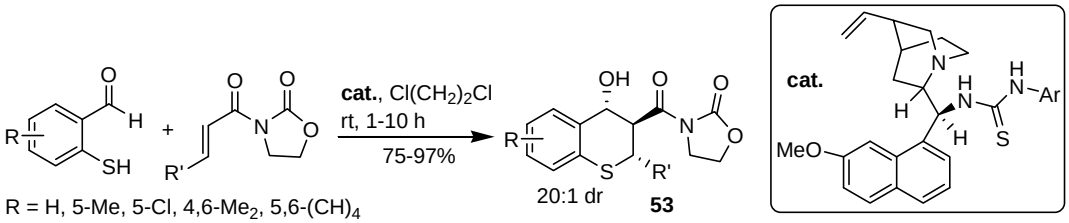
R = Ph, 4-CN-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-NO_2-C_6H_4, CO_2Et, n-Bu, n-Pr; Ar = 3,5-$(CF_3)_2C_6H_3$

Scheme 39



R = 5-Cl, 5-OMe, 5-Me, 4,6-$(MeO)_2$
R' = Ph, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-OMe-C_6H_4, 4-NO_2-C_6H_4, Et, Me; Ar = 3,5-$(CF_3)_2C_6H_3$

Scheme 40



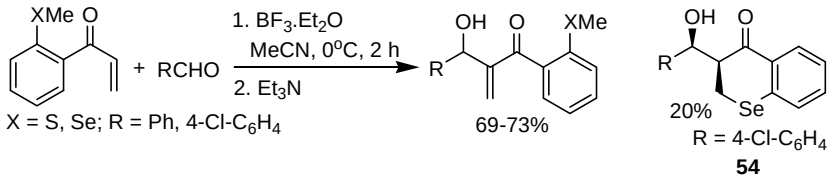
R = H, 5-Me, 5-Cl, 4,6-Me_2, 5,6-$(CH)_4$
R' = Ph, 2-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Cl-C_6H_4, 4-MeO-C_6H_4, 3-Me-C_6H_4, 1-naphthyl; Ar = 3,6-$(CF_3)_2C_6H_3$

Scheme 41

5.4 Selenium-containing systems

Kataoka and co-workers have described the Baylis-Hillman reaction of 1-[2-(methylchalcogeno)phenyl]propenones with aldehydes, and found that seleno-substituted

chalcogen afforded an unusual product, selenochromanone (**54**), albeit in low yield, along with the usual Baylis-Hillman product (Scheme 42).[61]

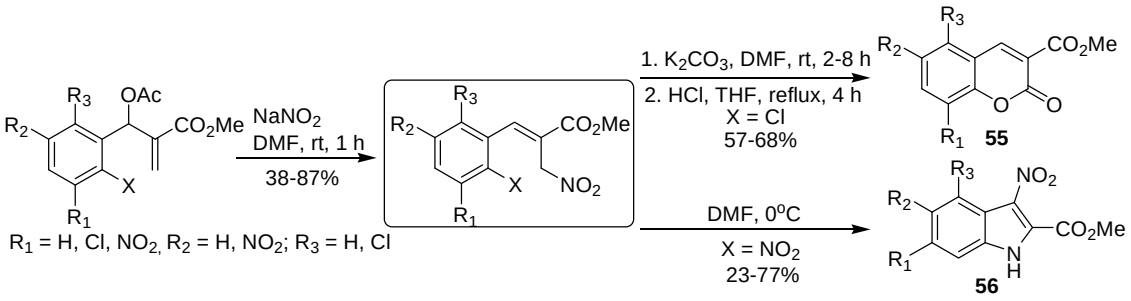


Scheme 42

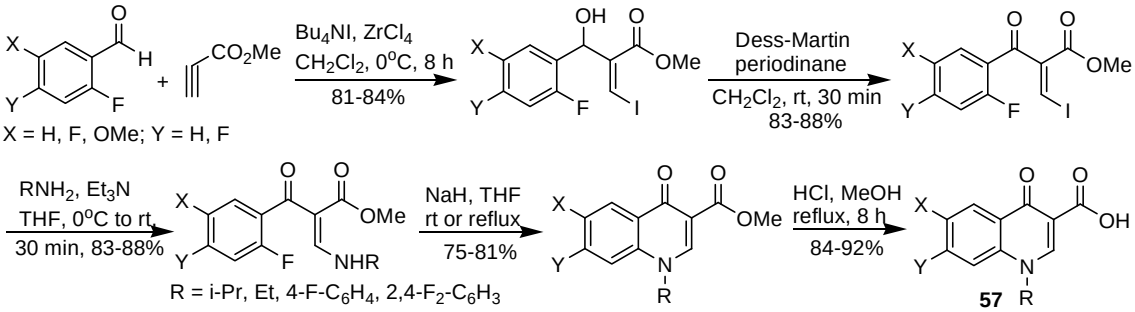
6. Nucleophilic aromatic substitution reactions

The nucleophilic aromatic substitution reaction was first introduced by Kim and co-workers for the synthesis of quinolines.[62] Later, this group extended their strategy to the synthesis of *N*-substituted 1,4-dihydroquinolines and 2-substituted naphthalenes.[63] They observed that the electron-withdrawing conjugated ester moiety is crucial to render the S_NAr reaction more facile.

Hong and Lee reported the synthesis of coumarins (**55**) via intramolecular aromatic substitution followed by rearrangement of 3-(2-chloro-phenyl)-2-nitromethyl-acrylic acid methyl esters afforded from the reaction between the Baylis-Hillman acetates and $NaNO_2$ (Scheme 43).[64] Subsequently Horn and Perez disclosed the formation of 3-nitroindole derivatives (**56**) from the reaction between the Baylis-Hillman acetates and KNO_2.[65] It was presumed that the 2-nitromethyl-3-(2-nitro-phenyl)-acrylic acid methyl esters, initially generated, cyclized via nucleophilic aromatic substitution to yield the indole derivatives, as shown in Scheme 43. Recently, Hong and Lee have demonstrated that the treatment of methyl propiolate with substituted 2-fluorobenzaldehydes in the presence of $ZrCl_4/Bu_4NI$ offers the β-iodo-α-(hydroxyalkyl)acrylates, which, upon reaction with primary amines, lead to quinolones (**57**), according to the reaction sequence shown in Scheme 44.[66]

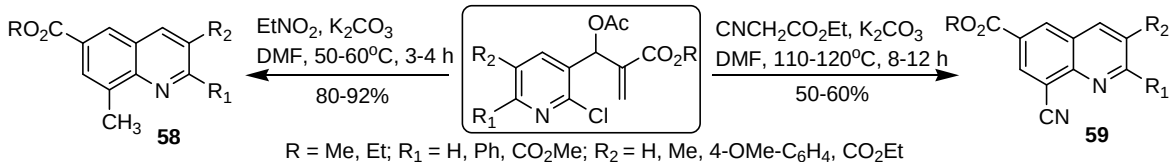


Scheme 43



Scheme 44

The acetyl derivatives of Baylis-Hillman adducts, derived from 2-chloronicotinaldehydes, were successfully utilized for the development of a convenient protocol for the general synthesis of 8-methyl- and 8-cyano-quinolines (**58** and **59**) by Rao and coworkers.[67] The Baylis-Hillman acetates by undergoing an S_N2' reaction with nitroethane or ethyl cyanoacetate via a successful S_N2-S_NAr elimination led to these quinolines (**58** and **59**), which exhibited substantial antibacterial and antifungal activities (Scheme 45).

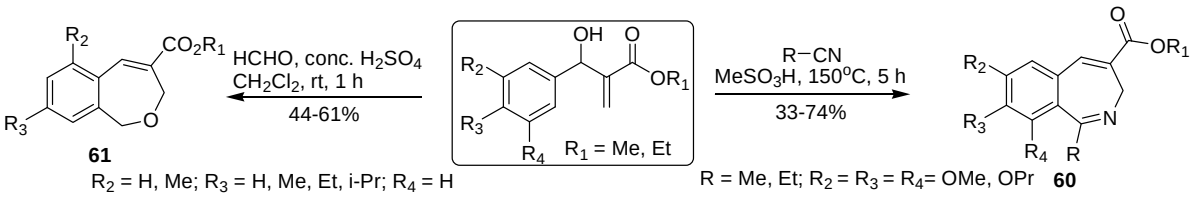


Scheme 45

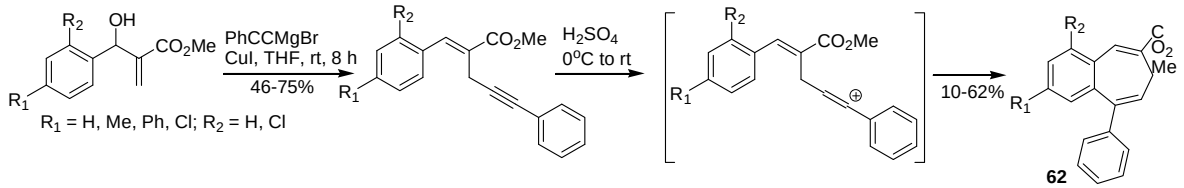
7. Friedel-Crafts reactions

The use of the Friedel-Crafts reaction in the Baylis-Hillman chemistry was initially introduced by Basavaiah during a stereoselective synthesis of trisubstituted alkenes[68] and

was later described by several research groups.[69]Basavaiah *et al.* described the synthesis of 2-benzazepines (**60**) via C-N bond formation between the Baylis-Hillman adducts and nitriles in the presence of methylsulphonic acid.[70] Subsequently, they also reported the synthesis of 2-benzoxepines (**61**) via C-O bond formation between the Baylis-Hillman adducts and HCHO in the presence of sulphuric acid (Scheme 46).[71] Recently, Das *et al.* demonstrated the synthesis of similar 2-benzoxepines using the same substrates in the presence of silica-supported hypochlorite.[72] Interestingly, Kim *et al*. developed the synthesis of 7*H*-benzocycloheptene derivatives (**62**), which are carbon surrogates of 2-benzazepines.[73] Their preparation involved an intramolecular Friedel-Crafts alkenylation reaction with an electron-deficient arene unit, as shown in Scheme 47.



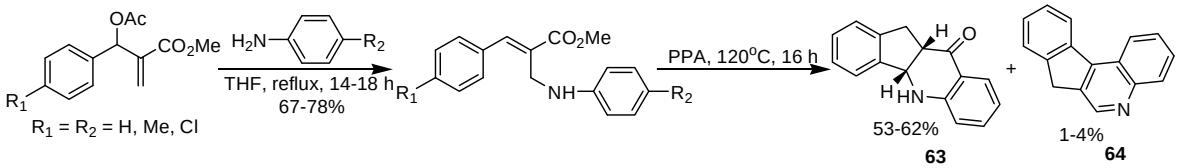
Scheme 46



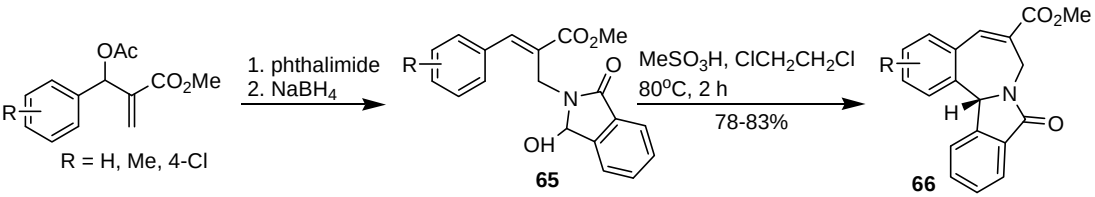
Scheme 47

Kim *et al*. have utilized the Baylis-Hillman acetates for the synthesis of indeno[1,2-b]quinolin-10-ones (**63** and **64**).[74] The S_N2' reaction of anilines with Baylis-Hillman acetates afforded the allyl amines, which, upon treatment with PPA, underwent a double Friedel-Crafts reaction to yield the tetrahydro-indeno[1,2-b]quinolones (**63**) as the major products along with minor yields of the 7*H*-indeno[2,1-c]quinolines (**64**) (Scheme 48). Later, the same workers showed that phthalimide-substituted Baylis-Hillman derivatives

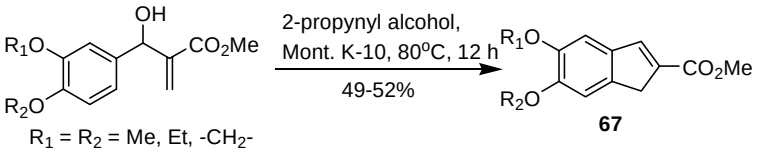
(**65**), on treatment with methylsulphonic acid in dichloroethane, afforded the benzo[3,4]azepino[2,1-a]isoindoles (**66**) in excellent yields (Scheme 49).[75] Shanmugam and co-workers developed an efficient and eco-friendly protocol for the synthesis of indene derivatives (**67**) from the Baylis-Hillman adducts via a Montmorillonite K-10 (Mont. K-10)-mediated intramolecular Friedel-Crafts reaction (Scheme 50).[76]



Scheme 48

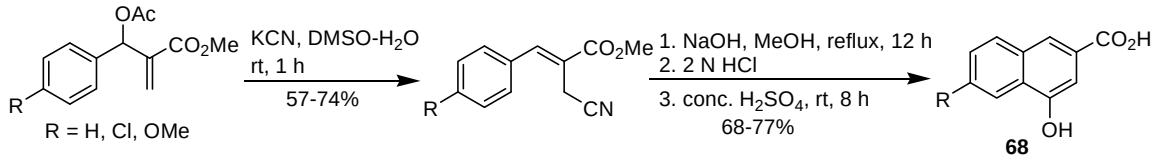


Scheme 49

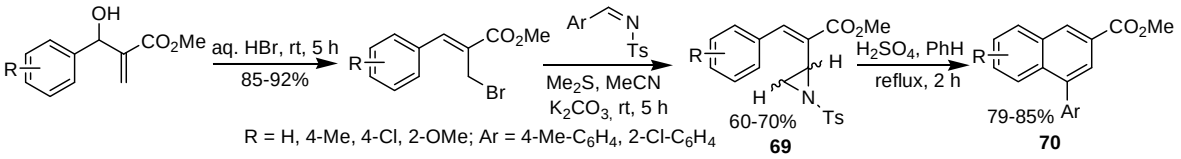


Scheme 50

Lee and co-workers described a simple protocol for the synthesis of 1-hydroxynaphthalenes (**68**) from the allyl cyanides, which, in turn, were obtained from the reaction between the Baylis-Hillman acetates and KCN in the presence of DMSO (Scheme 51).[77] Subsequently, Kim *et al*. reported a regioselective synthesis of 1-arylnaphthalene derivatives (**70**) from *N*-tosylaziridines (**69**), which, in turn, were obtained by reacting the appropriate *N*-tosylimine with cinnamyl bromides obtained from the Baylis-Hillman adducts.[78] The pathway for the final product (**70**) was mediated via aziridine ring opening followed by a Friedel-Crafts-type reaction and elimination of p-toluenesulphonic acid (Scheme 52).

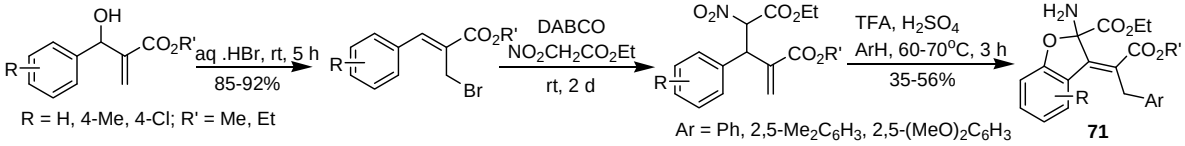


Scheme 51



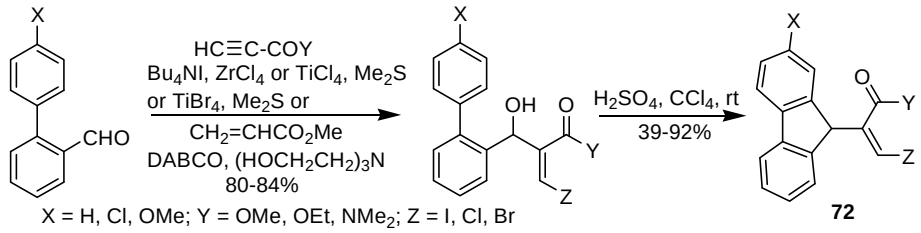
Scheme 52

An unusual formation of 2-amino-2,3-dihydrobenzofurans (**71**) from an appropriate substrate has been reported by Kim *et al*. (Scheme 53). The required substrate was prepared by reacting ethyl nitroacetate with the appropriate allyl bromide and in the presence of DABCO via an acid-promoted (TFA and H_2SO_4 mix) oxygen-atom-transfer process.[79]



Scheme 53

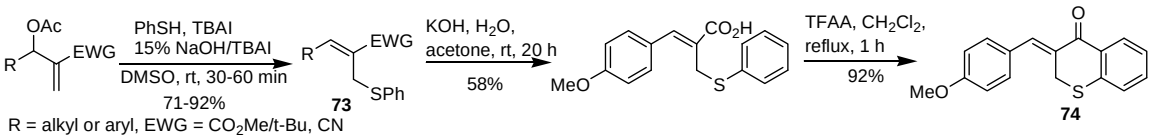
More recently, Lee and co-workers described the synthesis of 2-(9-fluorenyl)acrylic acid derivatives (**72**) via an intramolecular Friedel-Crafts reaction of the Morita-Baylis-Hillman adducts of 2-biphenylcarbaldehydes, as shown in Scheme 54.[80]



Scheme 54

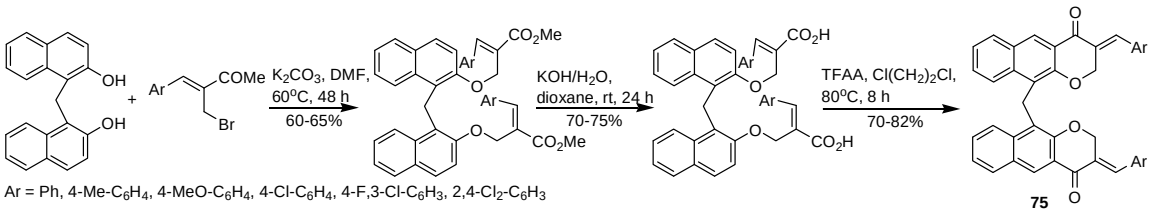
Das and his group reported a one-pot synthesis of allyl sulfides (**73**) from the acetates of the Baylis-Hillman adducts by treatment with benzenethiol in the presence of a catalytic amount of 15% NaOH and TBAI in DMSO. The base-mediated hydrolysis of the ester

group followed by TFAA-promoted cyclization yielded (*Z*)-3-(4-methoxybenzylidene)thiochroman-4-one (**74**). Compound **74** was found to display promising antifungal activity (Scheme 55).[81]



Scheme 55

Kanakam and his group demonstrated the preparation of methylene-dinaphthyl bis-chromanones (**75**) via reaction between methylene dinaphthol and allyl bromide followed by saponification and TFA-mediated cyclization. These products showed efficient luminescence in the blue light region and elicited significant activity against *Staphylococcus aureus* and *Streptococcus faecalis* (Scheme 56).[82]



Scheme 56

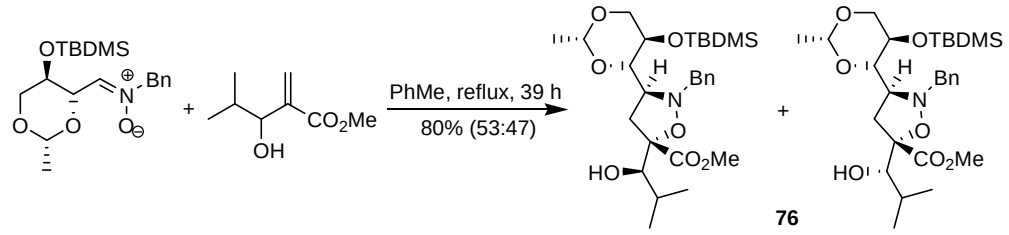
8. Cycloaddition reactions

The presence of a double bond in the Baylis-Hillman adduct makes it a suitable substrate for the cycloaddition reactions. Initially, investigations were limited to 1,3-dipolar cycloadditions of nitrile oxides,[83] but, during the last few years, applications of the Baylis-Hillman derivatives for cycloaddition reactions have grown tremendously.

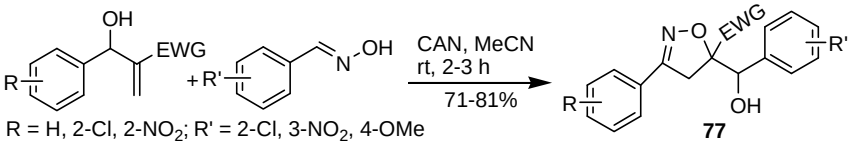
8.1 1,3-Dipolar cycloadditions

Fisera and co-workers reported that the 1,3-dipolar cycloaddition of a *C*-phenyl-*N*-methyl nitrone to the Baylis-Hillman adducts proceeded with complete regioselectivity to afford

the corresponding diastereomeric 3,5,5-trisubstituted isoxazolidines (**76**) in good yields (Scheme 57).[84] They observed that the use of microwave irradiation helped in increasing the rate of the reaction.[85] Later, Das *et al*. successfully synthesized the isoxazolines (**77**) in high yields via the reaction of the Baylis-Hillman adducts with aldoximes in the presence of CAN (Scheme 58).[86]



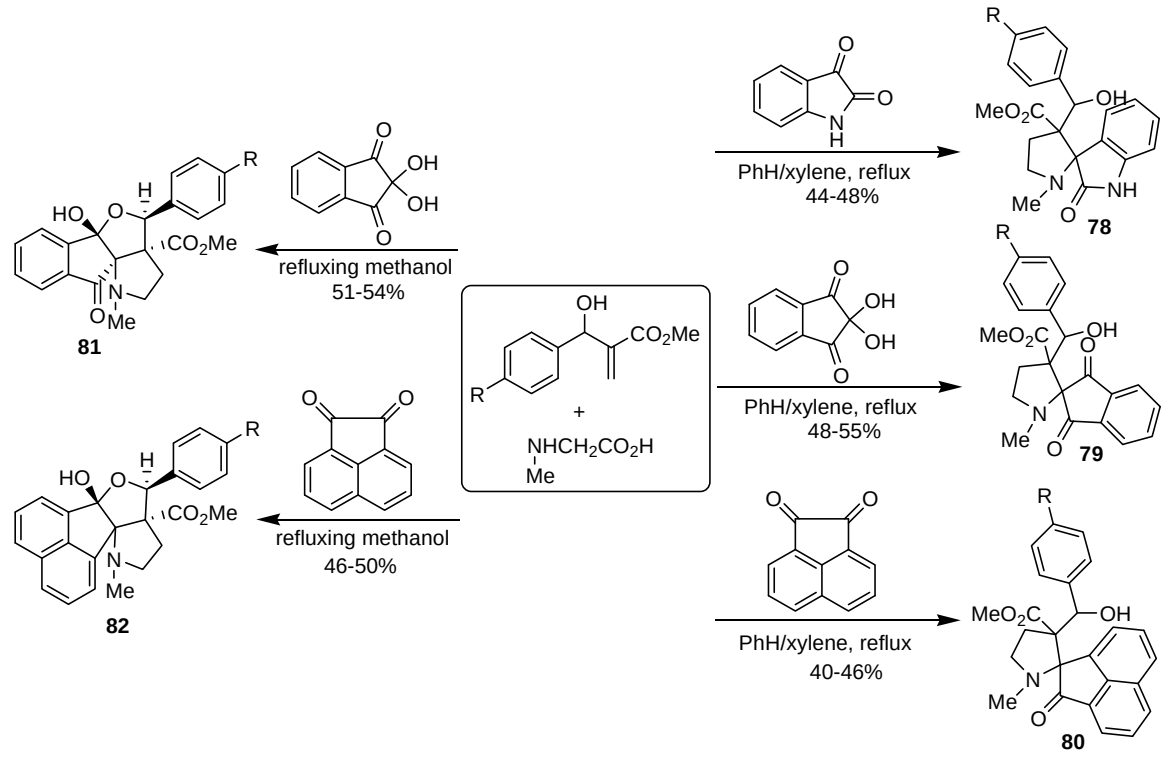
Scheme 57



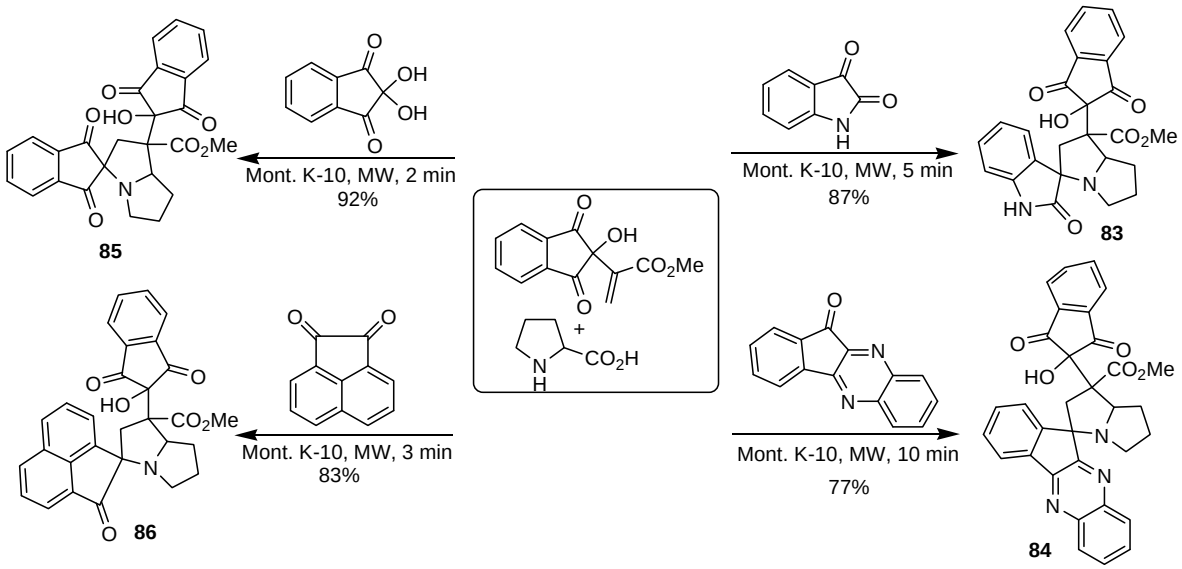
Scheme 58

Raghunathan *et al*. have reported the synthesis of novel spiroheterocycles (**78, 79** and **80**) via a 1,3-dipolar cycloaddition reaction of nonstabilized azomethine ylides generated by the decarboxylative condensation of di- and tri- ketones with sarcosine and the Baylis-Hillman adducts. The reaction sequence, which is described in Scheme 59, was performed in refluxing toluene and proceeded with high regioselectivity and stereoselectivity. Interestingly, when the same reaction was performed in refluxing methanol, an unusual nucleophilic attack of the hydroxy group on a ketone carbonyl occurred, resulting in the products **81** and **82** (Scheme 60).[87] Very recently, the same workers have reported the results of similar studies conducted with the Baylis-Hillman adducts of ninhydrin and sarcosine and proline. Since the yields were low in the conventional method of refluxing in methanol, they investigated the use of microwave conditions. They have reported that the time of the reaction can be drastically reduced by performing the reaction on Mont. K-10

with a significant improvement in yields and with high regioselectivity.[88] The synthesis of a number of spiropyrrolidine/pyrrolizidine derivatives (**83-86**) developed by these workers is shown in Scheme 60.

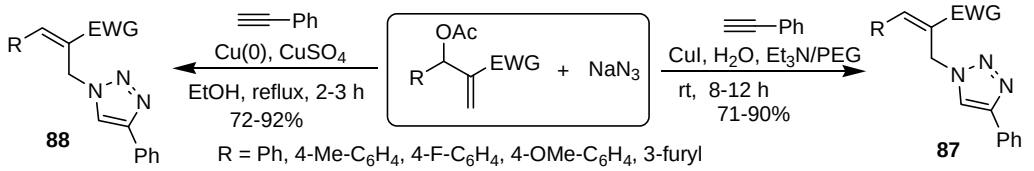


Scheme 59



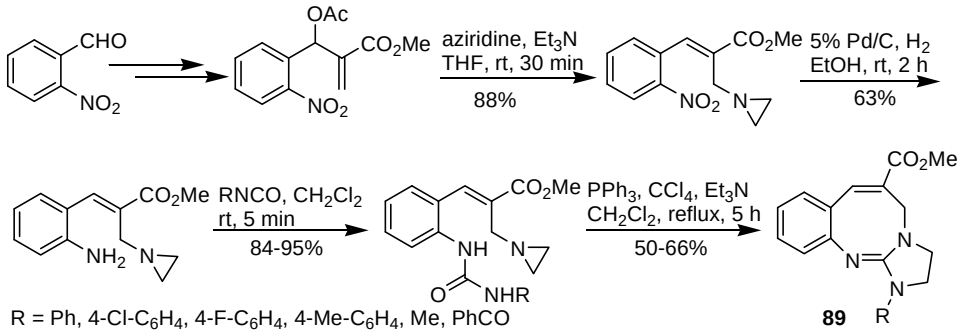
Scheme 60

Sreedhar and co-workers have reported a Cu(I)-catalyzed one-pot regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles (**87**) in high yields.[89] Their methodology involved nucleophilic displacement of the acetyl group in the Baylis-Hillman acetate with sodium azide followed by 1,3-dipolar cycloaddition of terminal alkynes in PEG (Scheme 61). Simultaneously, Chandrasekhar *et al*. demonstrated the synthesis of similar triazoles (**88)** by using Cu(0) and $CuSO_4$ in ethanol (Scheme 61).[90]



Scheme 61

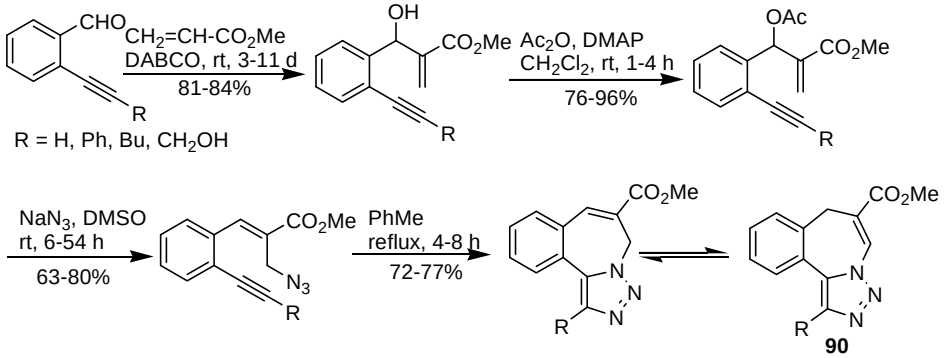
Lee *et al*. have elegantly utilized the Baylis-Hillman derivatives for performing intramolecular 1,3-dipolar cycloadditions.[91] They have successfully synthesized 6-carbomethoxy-1,2,3,5-tetrahydroimidazo[2,3-b][1,3]benzodiazocines (**89**) in good yields by the intramolecular 1,3-dipolar cycloaddition of 2-(1-aziridinylmethyl)-3-(2-ureidophenyl) acrylic acid methyl ester, as delineated in Scheme 62. Simultaneously, they accomplished



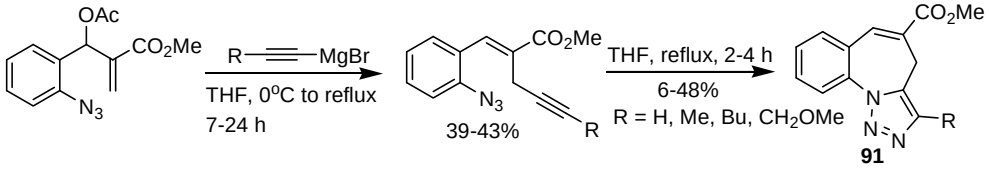
Scheme 62

the synthesis of 5*H*-1,2,3-triazolo[4,3-a][2]benzazepines (**90**) in good yields via an intramolecular 1,3-dipolar cycloaddition of the allylic azido group with the alkyne group present on the aromatic ring (Scheme 63).[92] Alternatively, they generated the alkyne moiety at the allylic position from the Baylis-Hillman acetates via a Grignard reaction and utilized

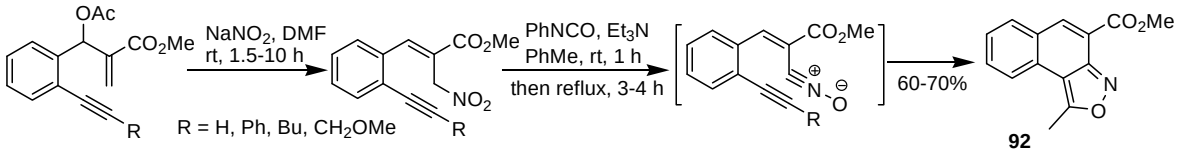
it for intramolecular cyclization with the azido group which was present on the phenyl ring, leading to the generation of 5-carbomethoxy-4*H*-1,2,3-triazolo[1,5-a][1]benzazepines (**91**) in low yields, as shown in Scheme 64.[93] In a continuation of their studies, they have recently reported the synthesis of 4-carbomethoxy-naphtho[2,1-c]isoxazoles (**92**) via an intramolecular 1,3-dipolar cycloaddition of 2-alkynylphenylallyl nitrones (Scheme 65).[94]



Scheme 63

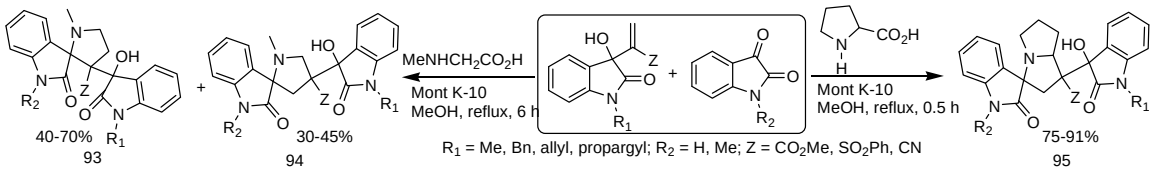


Scheme 64

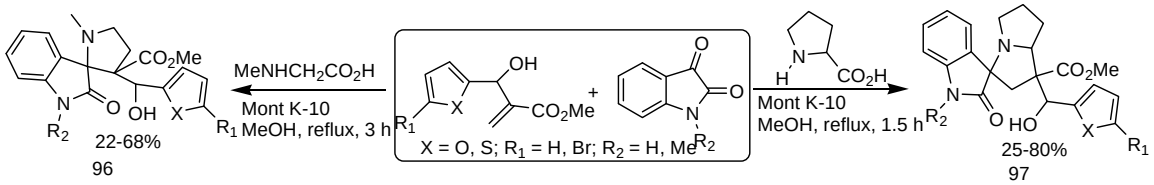


Scheme 65

A novel regioselective synthesis of a variety of functionalized 3-spiropyrrolidine oxindoles (**93 and 95**) and 3-spiropyrrolizidines (**96 and 97**) from the Baylis-Hillman adducts of isatin and heteroaldehydes via a [3+2] cycloaddition of azomethine ylides was reported by Shanmugam *et al.* (Schemes 66 and 67).[95]

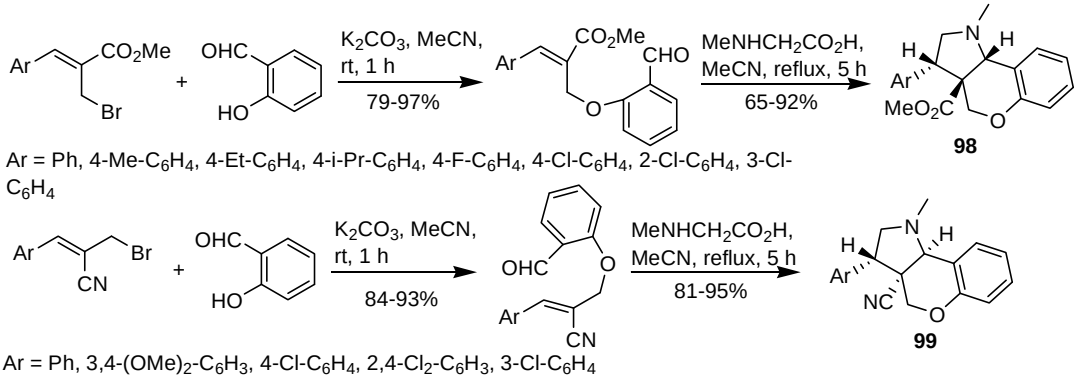


Scheme 66



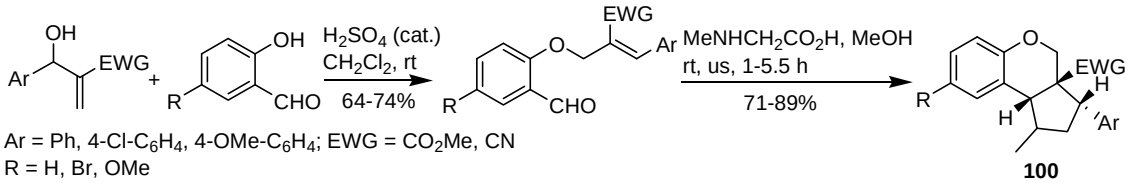
Scheme 67

Bakthadoss and co-workers utilized the allyl bromides afforded from the Baylis-Hillman adducts for a highly regio- and stereo-selective synthesis of tricyclic chromeno[4,3-*b*]pyrrolidines (**98** and **99**) frameworks via a substitution reaction followed by the *in situ* formation of an imine, decarboxylation and a [3+2] cycloaddition sequence, as outlined in Scheme 68.[96]



Scheme 68

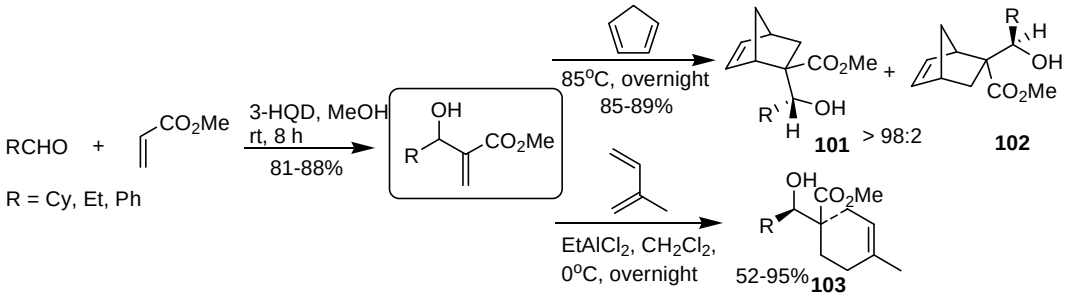
The synthesis of a series of chromene[4,3-*b*]pyrroles (**100**) through an intramolecular 1,3-dipolar cycloaddition reaction of an azomethine ylide with the dipolarophile afforded from the Baylis-Hillman adducts, as described in Scheme 69, was accomplished by Ramesh and Raghunathan.[97] They observed that the use of ultrasonic radiation for this particular reaction increases the efficiency and the products were generated in better yields.



Scheme 69

8.2 Diels-Alder reactions

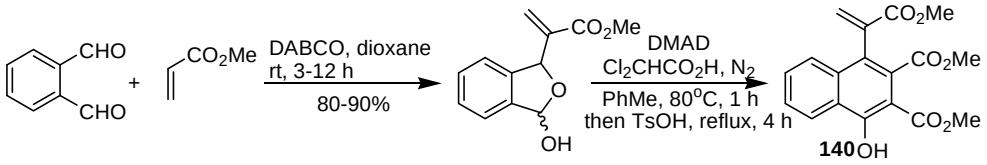
The Diels-Alder reaction of the Baylis-Hillman adducts with cyclopentadiene was first reported by Aggarwal and co-workers.[98] They observed that the thermal conditions favored the exo isomer (**101**) over the endo isomer (**102**) and the ratio was controlled by a balance of steric and electronic factors. The use of a Lewis acid had no effect on this ratio, although, in the presence of $EtAlCl_2$, the ratio of the exo to the endo form was reversed. Interestingly, they reported that the Diels-Alder reaction of the Baylis-Hillman adducts with isoprene under thermal conditions gave a mixture of stereo- and regio-isomers, whereas the use of $EtAlCl_2$ furnished essentially a single diastereoisomer and regioisomer (**103**) in all cases. Initially, as compared to ethyl and cyclohexyl, the yield of **103** bearing phenyl substitution was moderate, but the use of 2,6-di-*tert*-butylpyridine in the reaction as base effectively increased the yield to quantitative (Scheme 70).



Scheme 70

Later, Nair and Abhilash reported the synthesis of polycyclic aromatic hydrocarbons from the hemiacetal derived from the Baylis-Hillman reaction of o-phthaldehyde.[99] Strategically, the synthesis of the naphthalene (**104**) was achieved by DMAD-catalyzed dehydration of

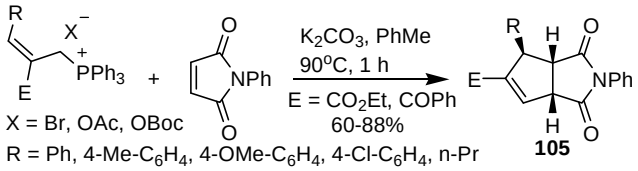
the hemiacetal leading to the isobenzofurans, which were trapped with several electron deficient-dienophiles (Scheme 71).



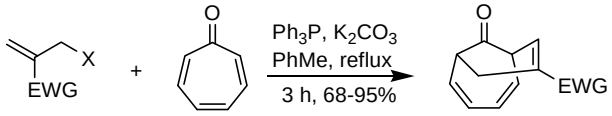
Scheme 71

Lu *et al*. have reported novel approaches involving the cycloaddition of electron-deficient olefins with electron-deficient allylic compound as the three-carbon unit via a phosphorus ylide. Initially, they observed that the phosphonium bromide salt derived from the allyl bromide generated from the Baylis-Hillman adducts of formaldehyde reacts with *N*-phenylsuccinimide to yield the annulated cyclopentene (**105**) via (3+2) a cycloaddition (Scheme 72).[100] Consequently, they demonstrated their strategy to be successful with several substrates. A variety of allyl bromides, acetates, and *O*-Boc-protected derivatives of Baylis-Hillman adducts were treated with different electron-deficient alkenes to yield several cyclopentenes including the spiro derivatives. Subsequently, Lu and co-workers extended the scope of their methodology to the convenient construction of bridged nine-membered carbacycles (**106**).[101] The synthesis of the (3+6) cycloadducts was achieved by the reaction of allylic compounds with tropone in the presence of Ph_3P and K_2CO_3 as additives (Scheme 73). More recently, the reactions of the same allylic compounds with 2-substituted-1,1-dicyanoalkenes for the synthesis of highly substituted cyclopentenes (**107**) have also been reported by these workers (Scheme 74).[102] They found that their strategy was successful only with dicyanoalkenes, since replacement of the cyano group led to unsatisfactory results. Additionally, although regioselective and stereoselective formation

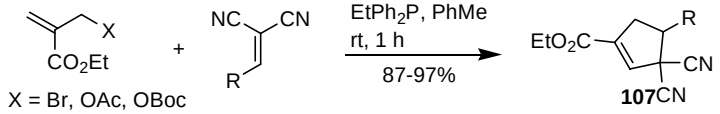
of cyclopentene was successful with Ph_3P, better yields and regioselectivity were achieved by using $EtPh_2P$.



Scheme 72

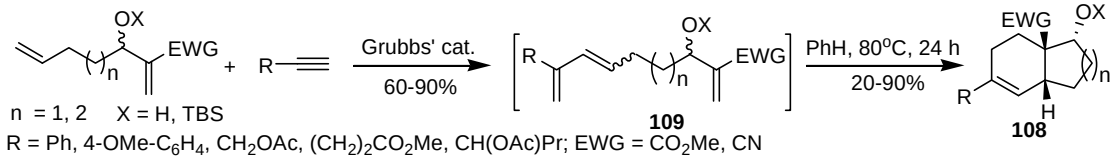


Scheme 73



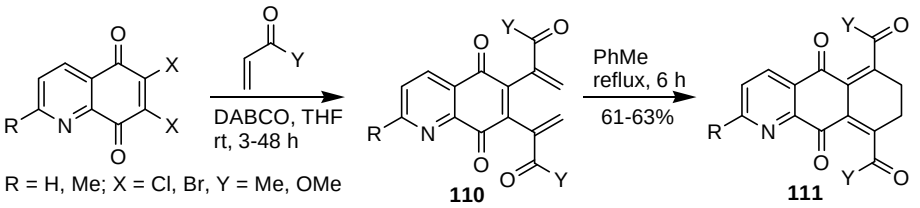
Scheme 74

Blechert *et al*. described the synthesis of *cis*-fused carbobicyclic compounds (**108**) via an intramolecular (4+2) cyloaddition reaction of the compounds **109**, which were, in turn, obtained from the corresponding Baylis-Hillman derivatives via enyne cross-metathesis with terminal alkynes, as outlined in Scheme 75.[103]



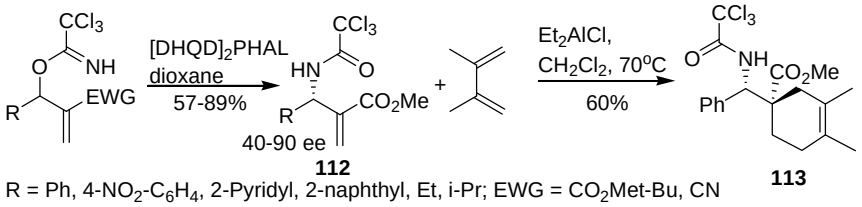
Scheme 75

Lee *et al*. described the synthesis of divinylquinolinediones (**110**) by subjecting dihaloquinolinediones to a Baylis-Hillman-type reaction. They demonstrated that these divinylquinolinediones (**110**) undergo a thermal 6π electrocyclization to yield the benzo[g]quinolines (**111**) (Scheme 76).[104]



Scheme 76

Jorgensen *et al.* demonstrated the utility of the allyl amine (**112**) for the Diels-Alder reaction with 2,3-dimethyl butadiene for the synthesis of cyclohexene derivative (**113**) with high diastereoselectivity (Scheme 77).[105]

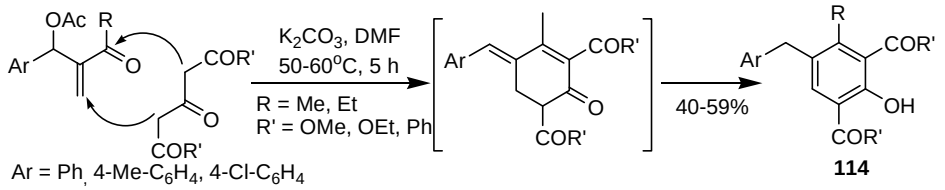


Scheme 77

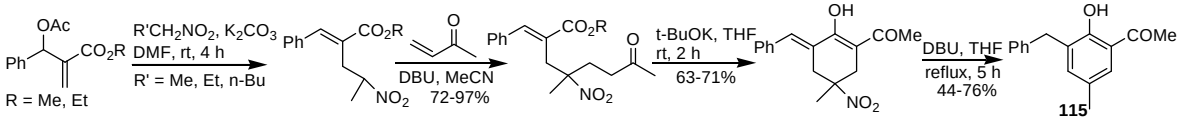
8.3 (n+n) Annulations

A one-pot, regioselective synthesis of polysubstituted phenols (**114**) from the acetates of the Baylis-Hillman adducts and dimethyl 1,3-acetonedicarboxylate was described by Kim and co-workers via a formal [3+3] annulation strategy (Scheme 78).[106] Substituted phenol derivatives such as (**115**) were also synthesized from nitroalkane-substituted Baylis-Hillman derivatives of acrylates via a [4+2] annulation strategy, in which the nitroalkane derivative served as the four-carbon unit and the Michael acceptor (alkyl vinyl ketone or alkyl acrylate) as a two-carbon unit (Scheme 79).[107] The nitroethane-substituted Baylis-Hillman derivatives of methyl vinyl ketone or ethyl vinyl ketone were demonstrated to be excellent precursors for the regioselective synthesis of polysubstituted benzenes (**116** and **117**), as shown in Schemes 80 and 81, respectively.[108,109] Recently, Kim and co-workers have successfully synthesized polysubstituted nitrobenzene derivatives (**118**) from the Baylis-Hillman acetates via a [3+3] annulation strategy,[110] in which 1,3-dinitroalkanes

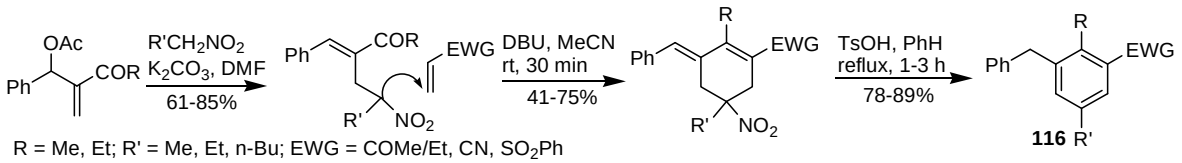
served as the 1,3-dinucleophilic component, while the Baylis–Hillman acetates featured as the 1,3-dielectrophilic unit, as shown in Scheme 82.



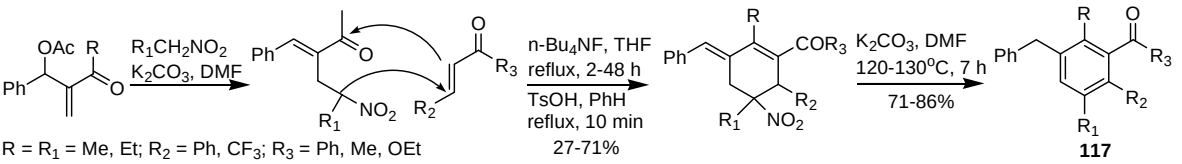
Scheme 78



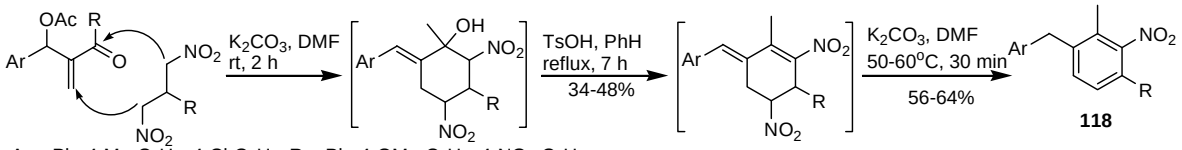
Scheme 79



Scheme 80



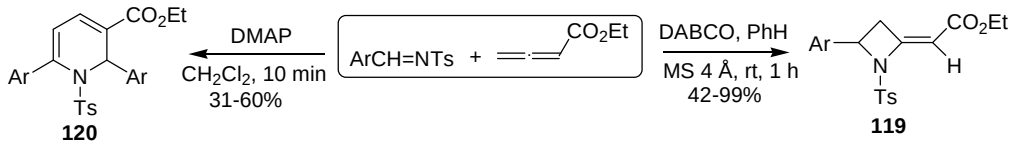
Scheme 81



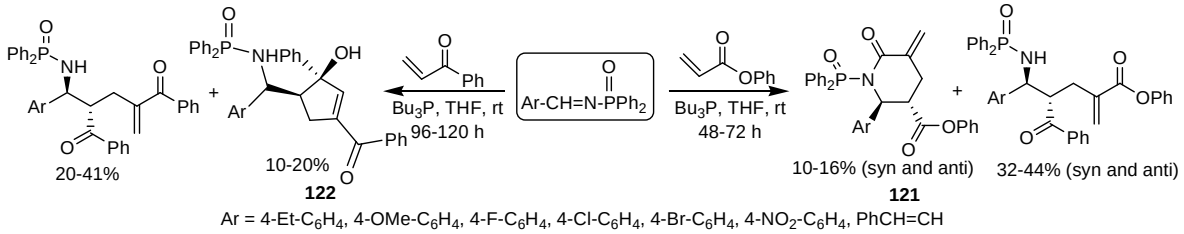
Scheme 82

Shi and co-workers reported an abnormal aza-Baylis-Hillman reaction between *N*-tosylimines and allenes. They observed that the DABCO-catalyzed Baylis-Hillman reaction of ethyl 2,3-butadienoate with *N*-tosylimines yielded the azetidine derivatives (**119**) through a [2+2] cycloaddition process. On changing the base to DMAP, however, the reaction proceeded quickly to furnish dihydropyridines (**120)** via a [4+2] cycloaddition reaction (Scheme 83).[111] Later, Shi and Zhao studied the aza-Baylis-Hillman reaction of *N*-

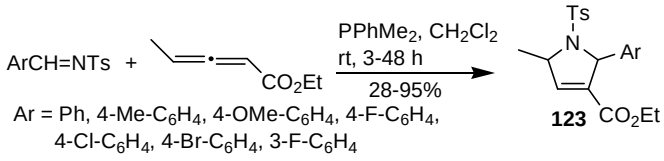
(arylmethylene)-diphenylphosphinamides with various activated alkenes and observed that the Bu_3P-promoted Baylis-Hillman reaction with phenyl acrylate furnished 5-methylene-6-oxo-2-aryl-piperidines (**121**) along with normal Baylis-Hillman adducts, whereas a similar reaction with phenyl vinyl ketone yielded highly substituted cyclopentenes (**122**), as shown in Scheme 84.[112] Subsequently, a detailed study of the aza-Baylis-Hillman reactions of *N*-tosylated aldimines with activated allenes and alkynes in the presence of various Lewis base promoters was carried out by these workers.[113] The $PPhMe_2$-mediated aza-Baylis-Hillman reaction afforded 2,5-dihydro-1*H*-pyrroles (**123**), as delineated in Scheme 85.



Scheme 83

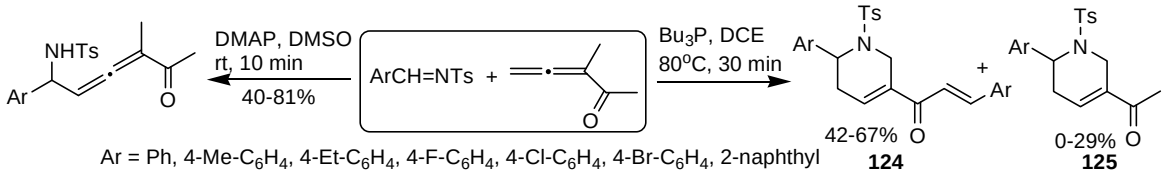


Scheme 84



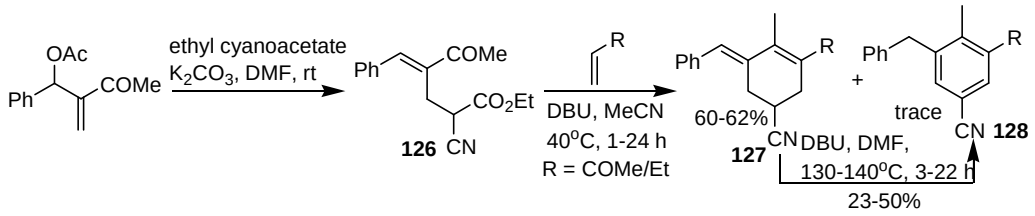
Scheme 85

The aza-Baylis-Hillman reaction between *N*-tosyl aldimine and 3-methylpenta-3,4-dien-2-one was also described by Shi and Zhao.[114] Interestingly, although the DMAP-catalyzed reaction afforded normal Baylis-Hillman adducts, the Bu_3P-mediated Baylis-Hillman reaction yielded 1,2,3,6-tetrahydro-pyridines (**124** and **125**), as shown in Scheme 86.



Scheme 86

Kim *et al.* reported a two-step syntheses of polysubstituted benzenes in moderate yields starting from the Baylis-Hillman derivatives (**126**) obtained via an S_N2' reaction of ethyl cyanoacetate. The first step involved the base-promoted reaction of methyl/ethyl vinyl ketone to obtain a cyclohexene derivative (**127**), which, upon treatment with DBU in DMF, yielded the highly substituted benzene (**128**), as shown in Scheme 87.[115]



Scheme 87

9. Radical cyclizations

The radical cyclization has been extensively applied to the Baylis-Hillman chemistry for the generation of heterocyclic or carbocyclic derivatives. Shanmugam and co-workers have demonstrated the use of radical cyclization for the synthesis of several oxygen-containing heterocycles. Most of these syntheses have been accomplished from the suitable propargyl derivatives obtained by the reaction of propargyl alcohol with the Baylis-Hillman adduct on Mont. K-10. Interestingly, they reported the isomerization of the propargyl compounds if the reaction on Mont. K-10 was pursued for longer periods (Figure 8).[116] Radical

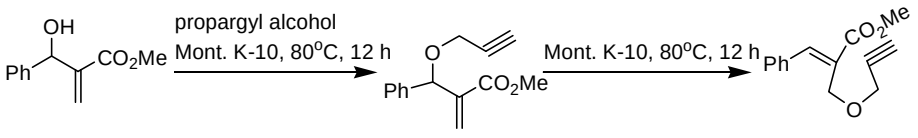
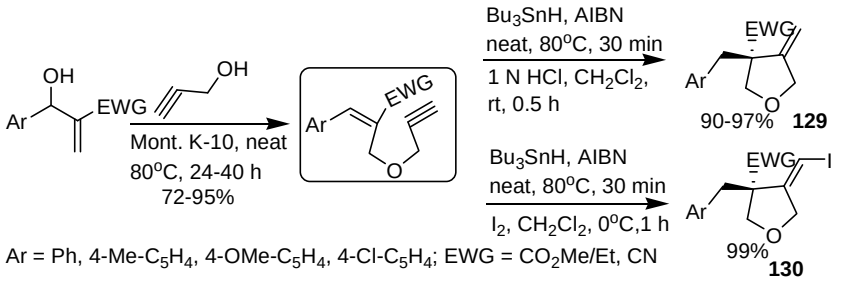
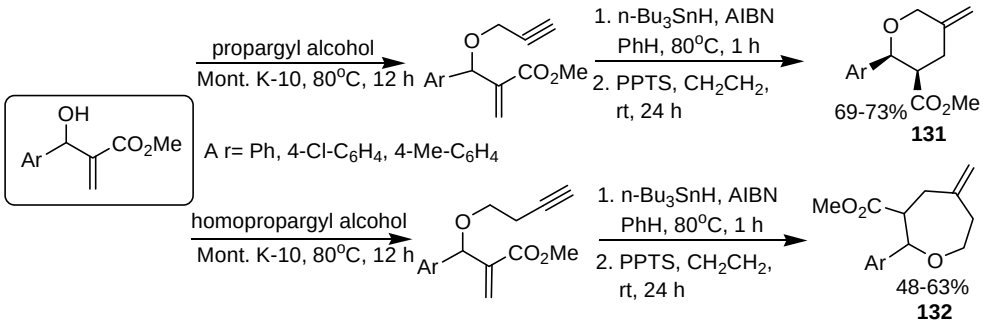


Figure 8. Isomerization of propargyl derivatives at higher temperatures

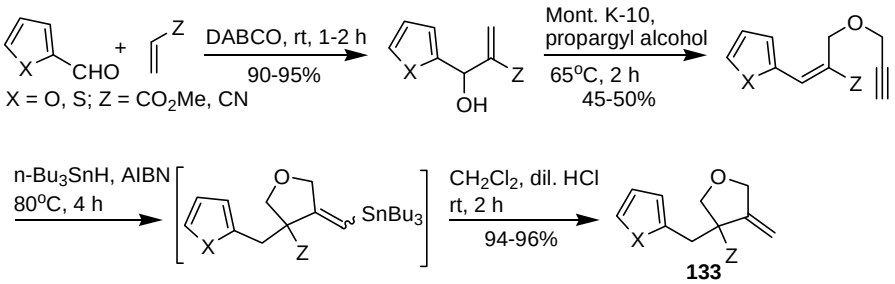
cyclization of the alkenyl propargyl ether with freshly distilled n-Bu_3SnH in the presence of AIBN yielded the vinylstannane through 5 exo-trig cyclization. The vinylstannane on protiodestannylation in the presence of 1 N HCl afforded the exomethylene-tetrahydrofurans (**129** and **130**) (Scheme 88).[116] They extended this strategy for the synthesis of pyrans (**131**) and oxepenes (**132**), as shown in Scheme 89.[117,118] Very recently they have demonstrated the scope of this strategy for the synthesis of 3-heteroarylmethyl-substituted tetrahydrofurans **133** (Scheme 90).[119]



Scheme 88

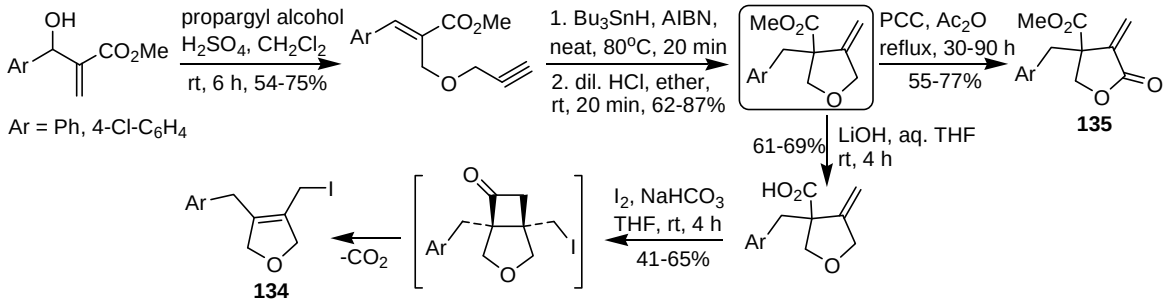


Scheme 89

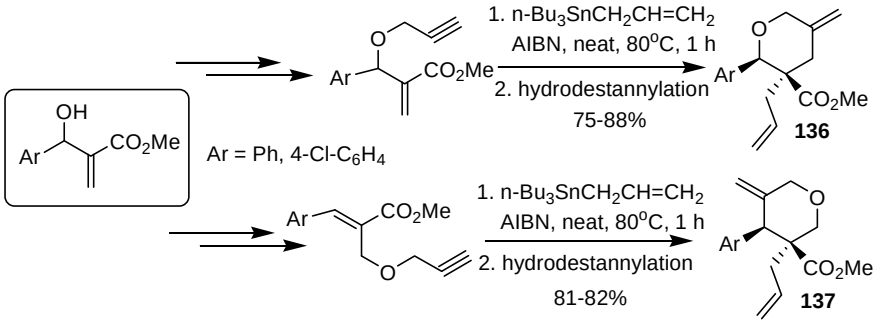


Scheme 90

Subsequently, in a slight modification of this strategy in which the same propargyl derivatives were obtained via a reaction in the presence of catalytic H_2SO_4 in place of Mont. K-10, Kim *et al*. described the synthesis of similar exomethylene-tetrahydrofurans. Further, they utilized these compounds to accomplish the synthesis of 3,4-disubstituted 2,5-dihydrofurans (**134**) via saponification, and halolactonization followed by final spontaneous decarboxylation and β,β-disubstituted-α-methylene-γ-butyrolactones (**135**) via PCC/Ac_2O-mediated oxidation, as depicted in Scheme 91.[120] They have also disclosed the regioisomeric synthesis of two types of methylene-tetrahydropyrans (**136** and **137**) in high yields by reacting propargyl derivatives and allyltributylstannane followed by the strategy of vinyl radical cyclization, as shown in the reaction sequence in Scheme 92.[121]



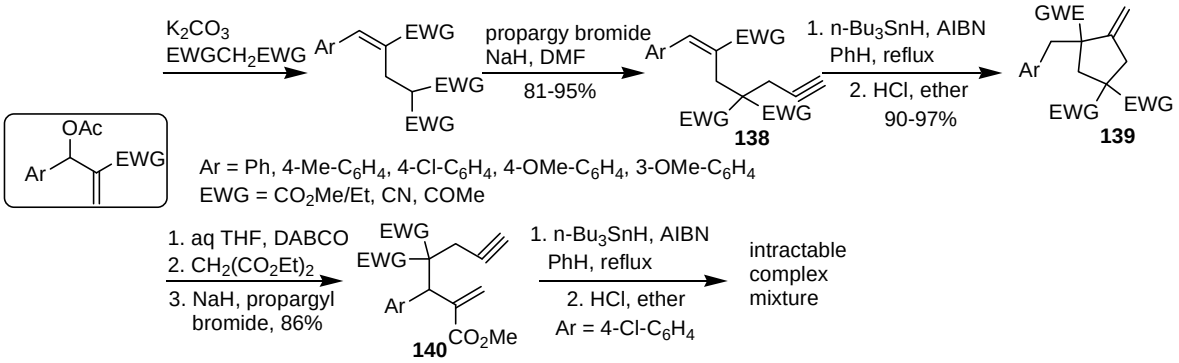
Scheme 91



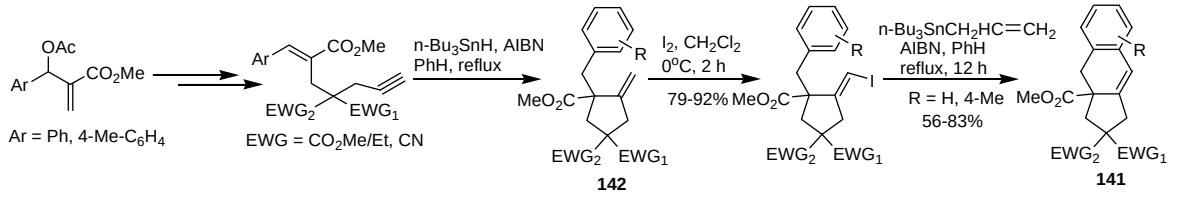
Scheme 92

In an alternative strategy to afford propargyl derivatives for the radical cyclization reaction, Kim and co-workers treated the S_N2' reaction products with propargyl bromide in the presence of NaH. These propargyl derivatives (**138**) in the presence of n-Bu_3SnH

underwent radical cyclization to furnish the exomethylene-cyclopentanes (**139**). They also attempted a similar reaction with propargyl derivatives (**140**) generated from the S_N2 reaction products, but this failed to yield the desired compounds (Scheme 93).[122] Recently, they have reported a successful synthesis of dihydronaphthalene (**141**) scaffolds using these cyclopentanes (**142**) as the starting substrates. Treating **142** with I_2 or NBS leads to the addition of halogen on the methylene group, which, on radical cyclization in the presence of allyltributylstannane yielded the dihydronaphthalenes (**141**), as shown in the Scheme 94. Their attempt to carry out the cyclization in the presence of n-Bu_3SnH was unsuccessful.[123]

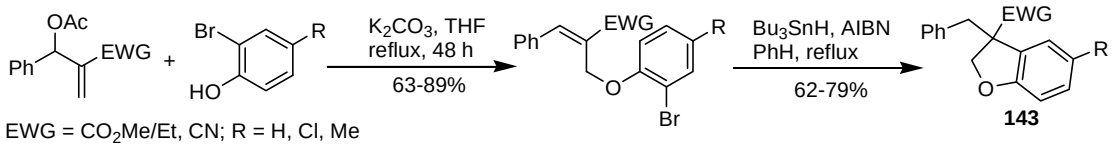


Scheme 93

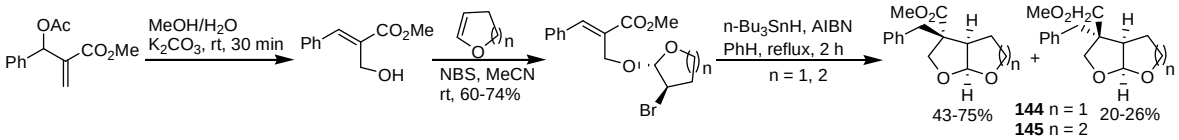


Scheme 94

In another variation of the strategy, Kim and co-workers have successfully transformed the 2-bromophenol-substituted Baylis-Hillman derivatives into 3,3-disubstituted-2,3-dihydrobenzofurans (**143**) in good yield (Scheme 95).[124] Later, they reported an interesting synthesis of hexahydrofuro[2,3,b]furans (**144**) and hexahydrofuro[2,3,b]pyrans (**145**) from the bromoacetals in the presence of n-Bu_3SnH via the Ueno-Stork reaction (Scheme 96).[125]

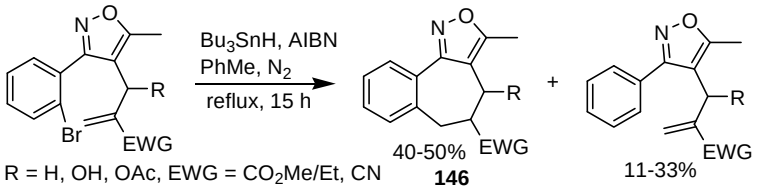


Scheme 95

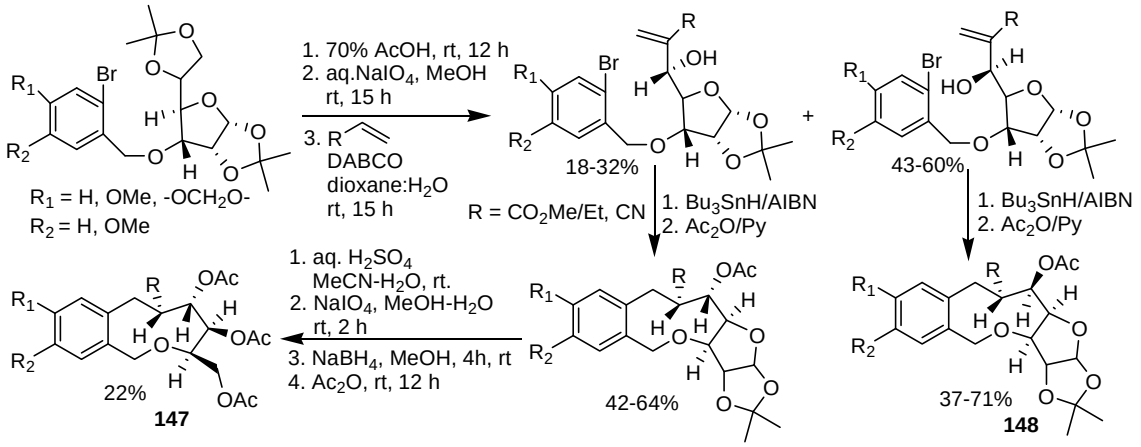


Scheme 96

Our research group was the first to report the radical cyclization involving the halide of the aromatic ring and the methylene group of the Baylis-Hillman adducts during the successful synthesis of a new isoxazolo-benzazulene system (**146**) from the derivatives of 3-(2-bromophenyl)-4-isoxazolecarbaldehydes (Scheme 97).[126] We found that this reaction did not take place with the corresponding chloro derivatives. Later, Chattopadhyay and co-workers, using a similar strategy, reported the synthesis of enantiopure benzo-fused nine-membered oxacycles (**147** and **148**). Initially, they transformed the *O*-2-bromobenzylated-1,2:5,6-di-*O*-isopropylidene glucofuranoside and its analogues into noraldehydes, which, upon Baylis-Hillman reaction, followed by successful radical cyclization, yielded the macrocycles (Scheme 98).[127] Very recently, they reported n-Bu_3SnH-mediated transformation of the enamides generated from the Baylis–Hillman adducts of 2-bromobenzaldehydes into dihydropyrido[2,1-a]isoindolones (**149**), as shown in Scheme 99.[128]

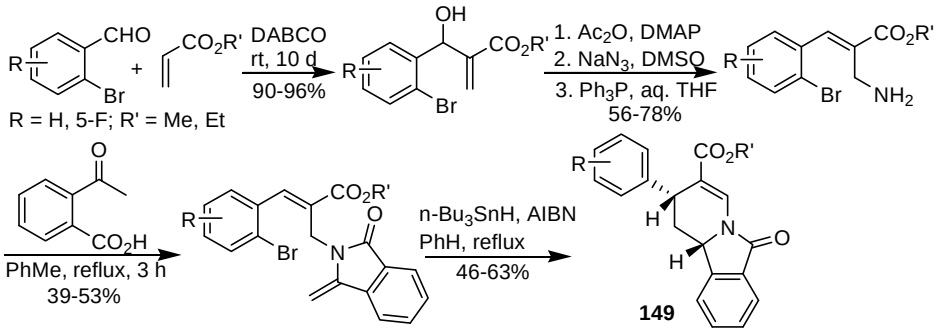


Scheme 97

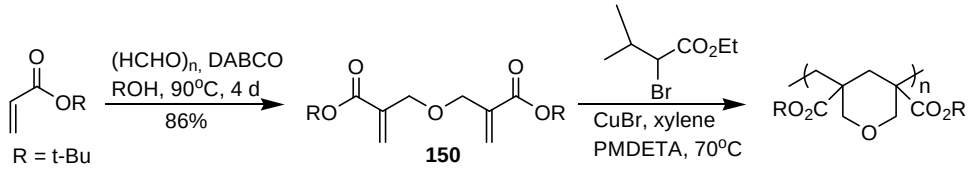


Scheme 98

Atom-transfer radical polymerization was employed in the cyclopolymerizaton of a symmetrical dimethacrylate (**150**) under the influence of CuBr/PMDETA by Acar *et al*. (Scheme 100).[129]



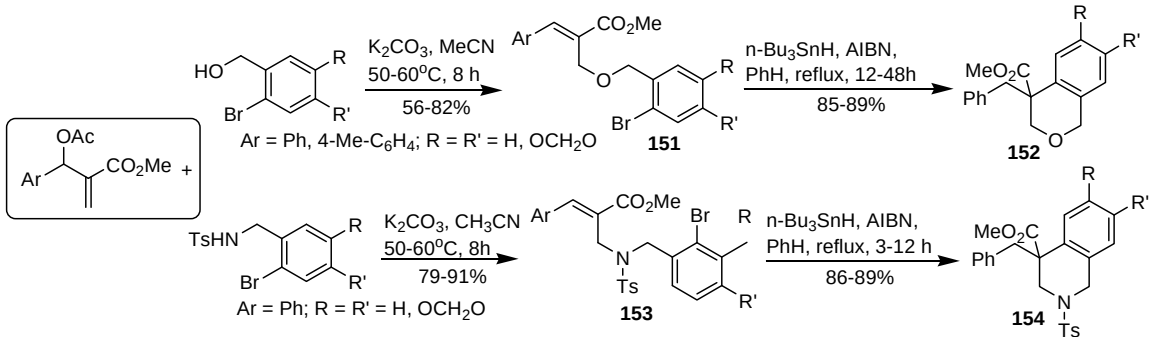
Scheme 99



Scheme 100

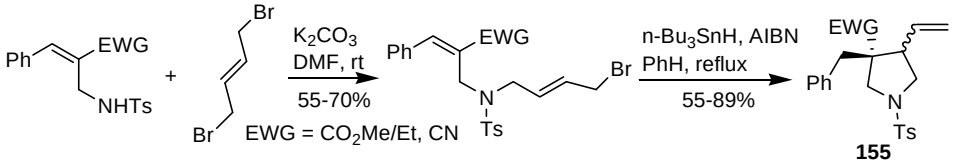
The radical cyclization has been utilized for the generation of isochroman (**152**) and tetrahydroisoquinoline derivatives (**154**) from the Baylis-Hillman acetates by Kim and his group. The S_N2' reaction of 2-bromobenzyl alcohols with the acetates yielded **151,** which were transformed into the isochroman (**152**) in the presence of n-Bu_3SnH, as shown in

Scheme 101. A similar reaction sequence with 2-bromobenzyl tosylamides (**153**) resulted in the formation of the tetrahydroisoquinolines (**154**) in good yields.[130]

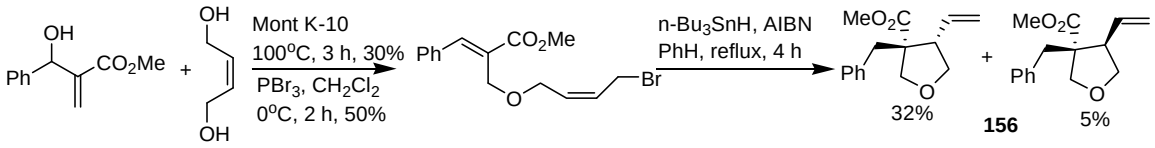


Scheme 101

In another strategy, the derivatives afforded via the S_N2' reaction of tosylamine with the Baylis-Hillman acetates followed by alkylation with 1,4-dibromo-2-butane were cyclized in the presence of n-Bu_3SnH to afford the *N*-tosyl-3,3,4-trisubstituted-pyrrolidines (**155**) by this group (Scheme 102). Furthermore, they also employed a similar protocol for the generation of tetrahydrofuran systems (**156**). Accordingly, the Baylis Hillman adducts were reacted with cis-1,4-butanediol followed by bromination and radical cyclization resulting in **156,** albeit in low yields (Scheme 103).[131]



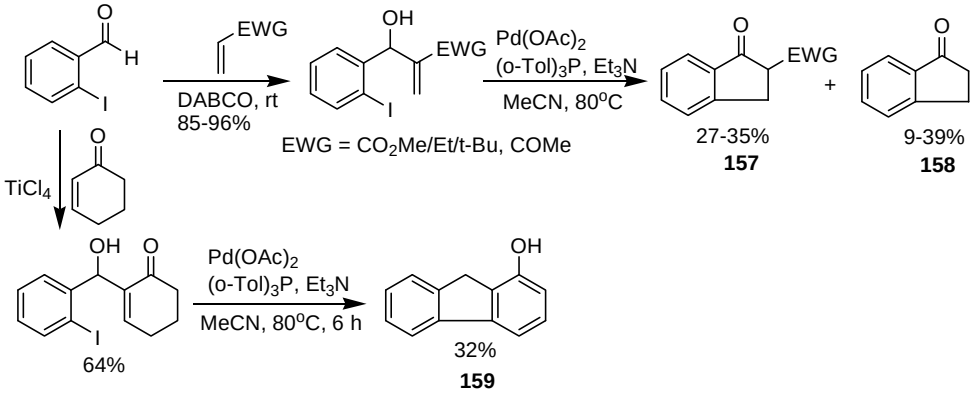
Scheme 102



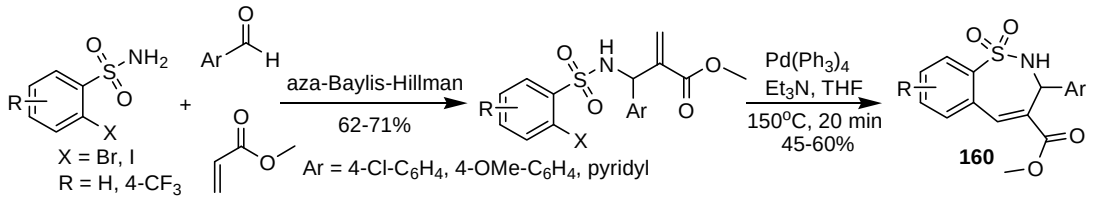
Scheme 103

10. Heck coupling reactions

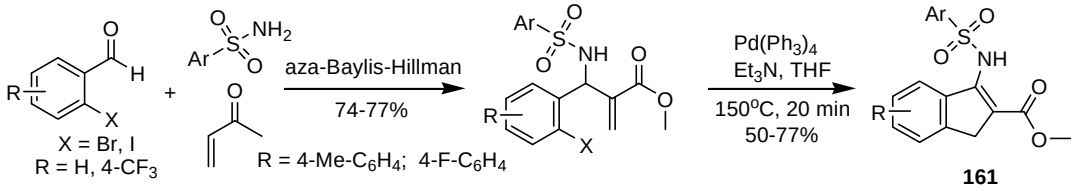
The Heck coupling reaction, another carbon-carbon bond-forming strategy, involving the coupling of halo-substituted arenes with alkenes or alkynes has been successfully applied for the generation of cyclic systems from the Baylis-Hillman derivatives.[132] Lee and co-workers described the synthesis of indanones (**157** and **158**) from the Baylis-Hillman adducts of 2-iodo-benzaldehydes via intramolecular Heck cyclization in the presence of $Pd(OAc)_2$ and $(o\text{-}Tol)_3P$, whereas, under similar reaction conditions the Baylis-Hillman adducts of 2-cyclohexen-1-ones afforded the 1-hydroxyfluorenes (**159**) (Scheme 104).[133] The successful transformation of aza-Baylis-Hillman adducts of 2-halosulfonamides into highly constrained bicyclic 6,7-dihydro-5-thia-6-aza-benzocycloheptene 5,5-dioxides (**160**) via the intramolecular Heck reaction was reported by Vasudevan *et al.* (Scheme 105). Alternatively, these workers utilized similar products originating from 2-halo-benzaldehydes to synthesize substituted indenes (**161**) in moderate- to -good yields (Scheme 106).[134] The construction of 1*H*-inden-1-ones (**162**) was also successfully described by She and co-workers via a sequential intramolecular Heck reaction followed by an aerial oxidation of allylic alcohols of Baylis-Hillman adducts of 2-halo-benzaldehydes, as shown in Scheme 107.[135]



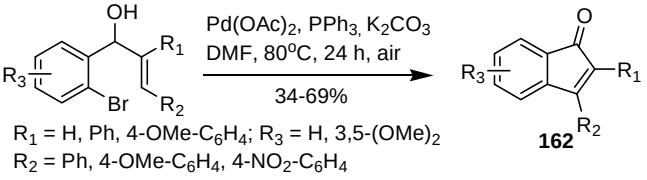
Scheme 104



Scheme 105

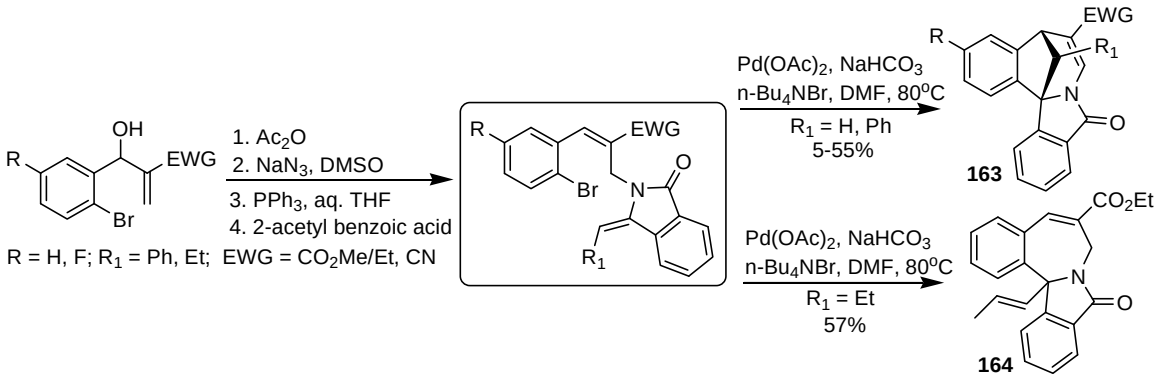


Scheme 106



Scheme 107

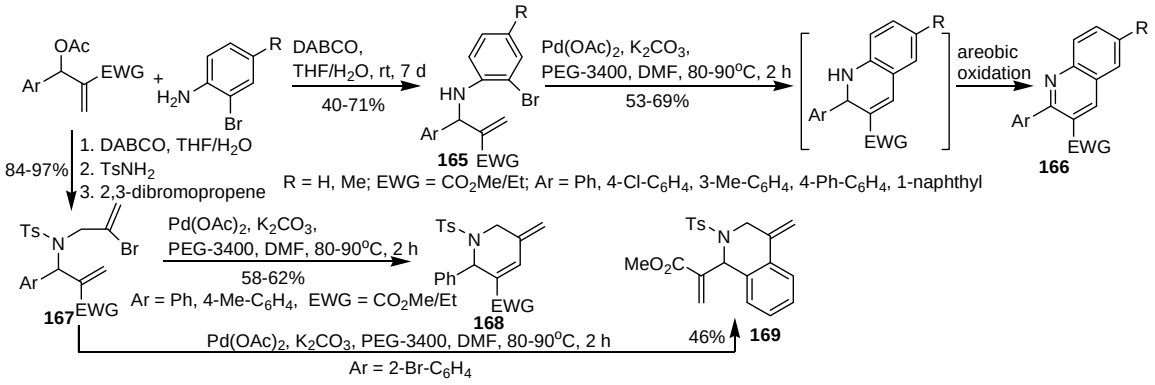
Kim and co-workers have earlier described the synthesis of **149** from the enamides.[128] In an extension of this work, they have reported a successful transformation of these enamides into novel pentacyclic benzoazepino[2,1-*a*]isoindole derivatives (**163** and **164**) via a double carbopalladation using Heck-type cyclization conditions, as shown in Scheme 108.[136]



Scheme 108

Very recently, these workers have also reported the synthesis of 2-arylquinolines **166** via a Pd-mediated sequential Heck-type cyclization and concomitant aerobic oxidation from the S_N2 reaction product **165** provided by the reaction between the Baylis-Hillman acetates and

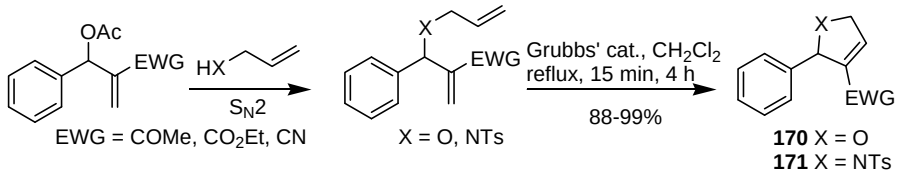
2-bromoanilines, as shown in Scheme 109.[137] With the aim of the extending the scope of their strategy, they also demonstrated the synthesis of tetrahydropyridines (**168**) following a similar reaction sequence. The amides (**167**) afforded by the reaction of the Baylis-Hillman acetates with tosylamide followed by alkylation with 2,3-dibromopropene or allyl bromide and subsequent Pd-catalyzed cyclization resulted in tetrahdropyridines (**168** and **169**) in moderate yields.



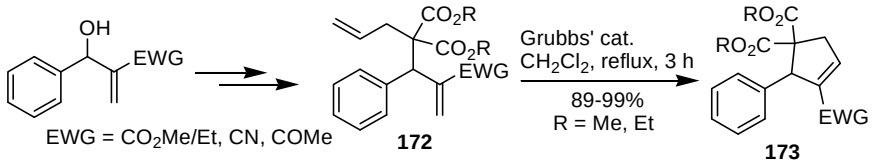
Scheme 109

11. Ring-closing metathesis reactions

Ring-closing metathesis in Baylis-Hillman chemistry was introduced by Paquette for the synthesis of α–methylene-γ-lactones fused to medium and large rings.[138] Kim and co-workers have published a series of papers on the application of RCM on a variety of Baylis-Hillman derivatives to generate several heterocyclic scaffolds. Initially, they subjected the O- and N-allylic derivatives to RCM in the presence of Grubbs' second-generation catalyst to synthesize dihydrofurans (**170**) or dihydropyrroles (**171**) (Scheme 110).[139] Further, they generated other allyl derivatives (**172)** which served as useful synthons for the RCM reaction to yield cyclopentenes (**173**) in excellent yields (Scheme 111).[140]

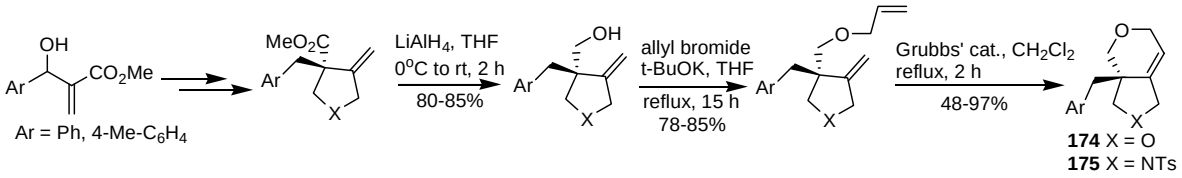


Scheme 110

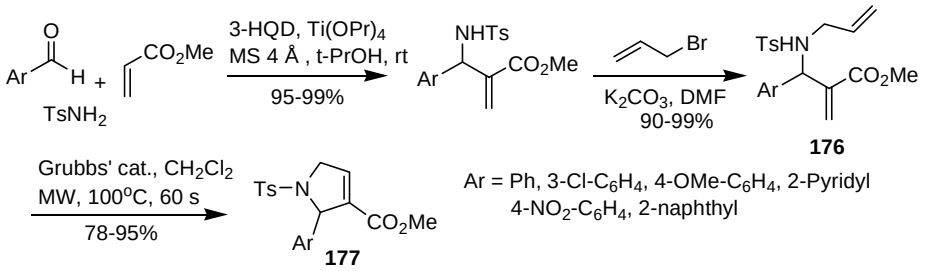


Scheme 111

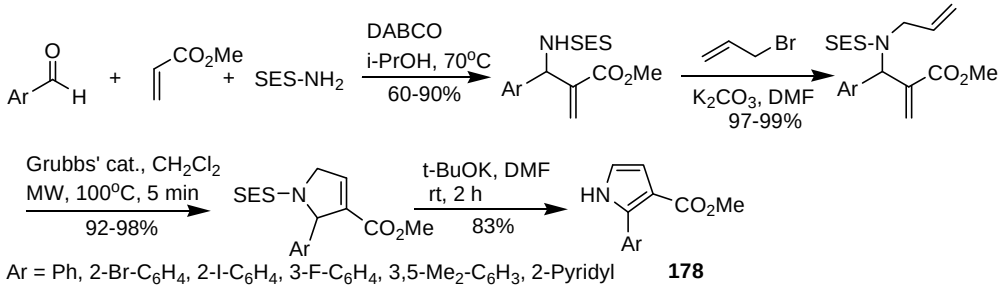
Recently, the same workers have demonstrated the utility of RCM for the generation of furo[3,4-c]pyran (**174**) and pyrano[3,4-c]pyrrole (**175**) rings, as shown in Scheme 112.[141] Simultaneous to the work of Kim *et al*. on the synthesis of dihydropyrroles, Balan and Adolfsson also reported the RCM of allyl amino derivatives (**176**) originating from the aza-Baylis-Hillman products via Grubbs' second-generation catalyst under microwave conditions to afford *N*-tosyl dihydropyrrole (**177**) (Scheme 113).[142] Subsequently, Lamaty and co-workers demonstrated the synthesis of similar products, but these contained a 2-SES group instead of a tosyl moiety. They showed that, in the presence of t-BuOK, these dihydropyrroles can be easily deprotected and aromatized to generate pyrroles (**178**) (Scheme 114).[143] Later, in another report, they compared the SES group with a tosyl group for the preparation of nitrogen-containing five-membered rings obtained by the aza-Baylis-Hillman/alkylation/RCM route. They observed that deprotection of tosyl-protected pyrrolines gave only pyrroles, whereas deprotection of similar SES-protected derivatives furnished either pyrroles or pyrrolines depending on the deprotecting conditions. Indeed, they also hydrogenated the SES-protected pyrrolines to yield pyrrolidines (**179**) with excellent diastereoselectivity (Scheme 115).[144]



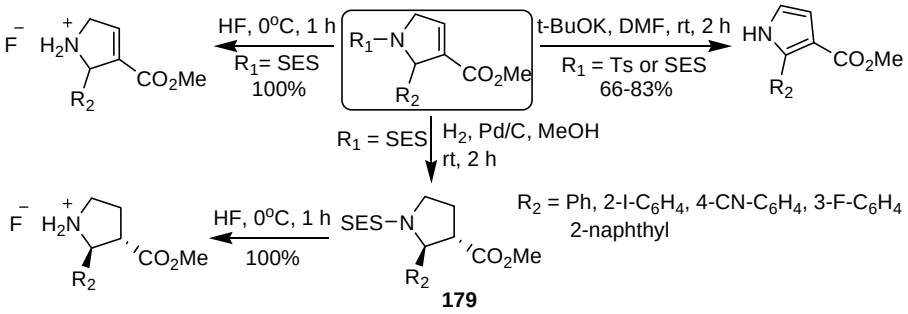
Scheme 112



Scheme 113



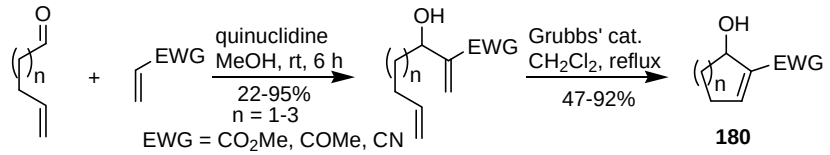
Scheme 114



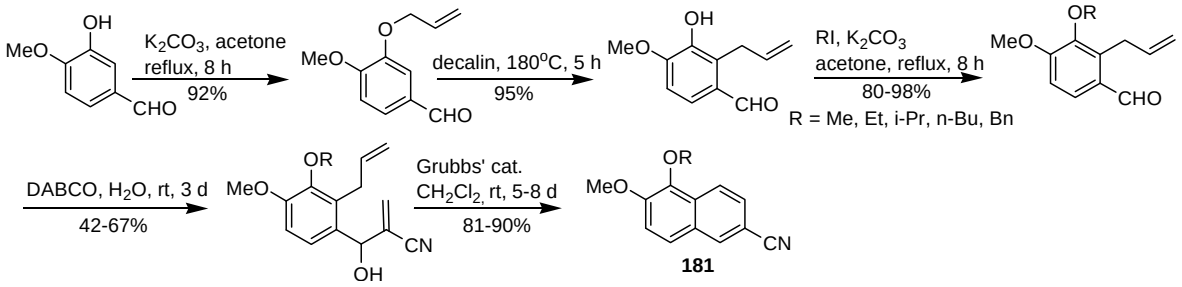
Scheme 115

Kraft *et al*. described a new and efficient approach to functionalized hetero- and carbocyclic alkenoles which are also afforded via an intramolecular Baylis-Hillman reaction. They generated the required synthon via a quinuclidine-promoted Morita-Baylis-Hillman reaction of alkenyl aldehydes which, on RCM reaction under the influence of Grubbs' second-generation catalyst, yielded the cycloalkenoles (**180**) in excellent yields (Scheme 116).[145] They reported that their methodology was successful for the generation of

eight- or nine-membered rings. More recently, Wang and co-workers have reported a novel, simple, and eco-friendly method to provide cyanonaphthalenes (**181**) via a sequential Claisen rearrangement, Baylis–Hillman reaction and RCM in the presence of Grubbs' second-generation catalyst (Scheme 117).[146]

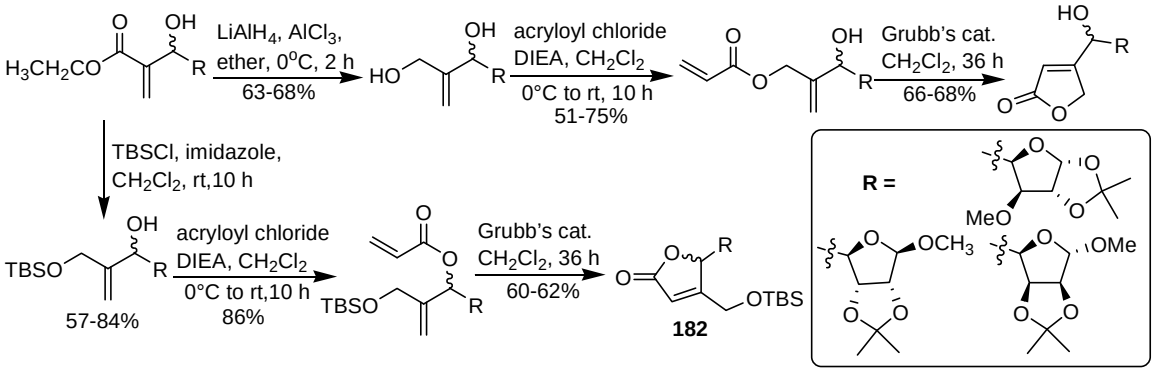


Scheme 116



Scheme 117

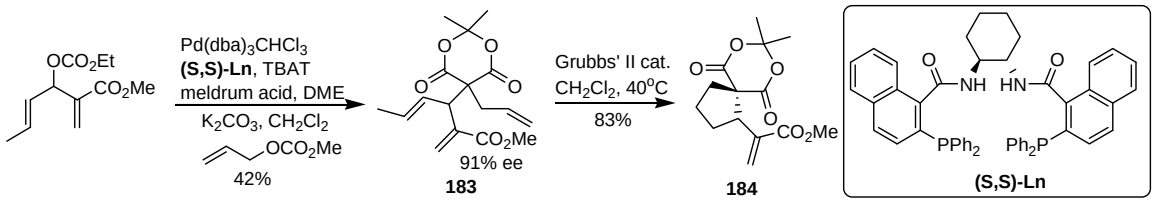
The sugar-based Baylis-Hillman adducts were efficiently utilized to prepare a library of diverse α,β-unsaturated λ-lactones (**182**) by Krishna and Narsingam (Scheme 118).[147]



Scheme 118

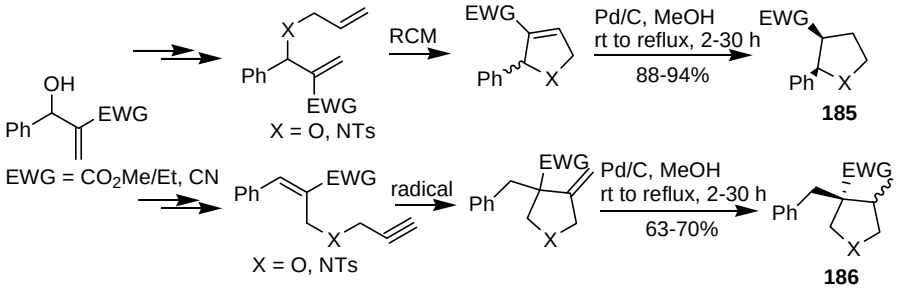
Trost and Brennan successfully employed the dienes generated for the Morita-Baylis-Hillman adducts in a Pd-catalyzed asymmetric alkylation with Meldrum acid to generate a product, which, on further alkylation, furnished a bisalkylated derivative **183** in moderate

yields over two steps, as shown in Scheme 119. The product **183** upon treatment with a second-generation Grubbs' catalyst afforded the 1,2-disubstituted alkene **184**.[148]



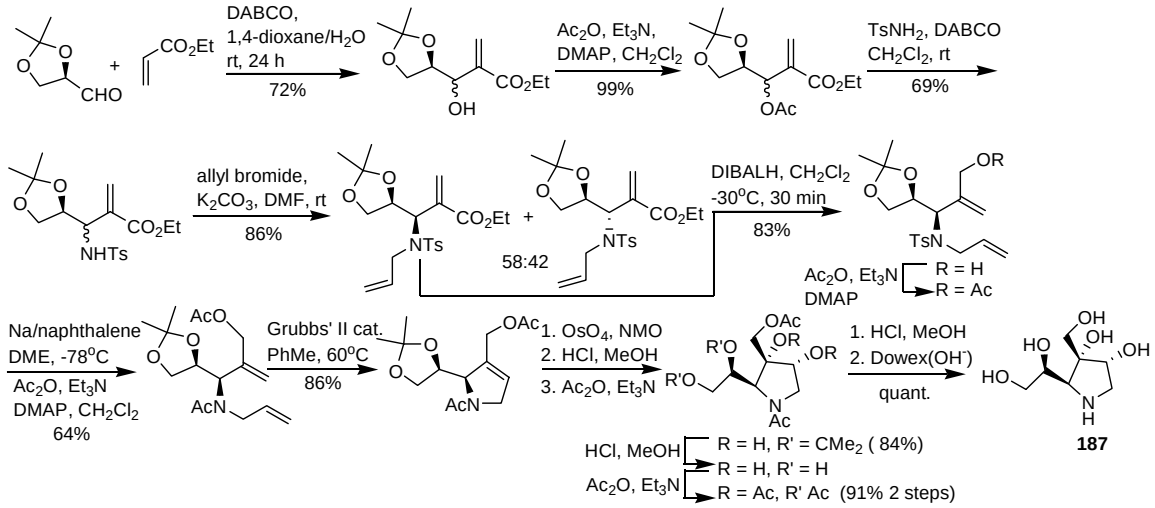
Scheme 119

Recently, Kim and co-workers disclosed an expeditious route for the synthesis of pyrrolidines and tetrahydrofurans (**185** and **186**), starting from the suitably modified Baylis-Hillman adducts involving RCM followed by hydrogenation or radical cyclization and subsequent hydrogenation protocols, as shown in Scheme 120.[149]

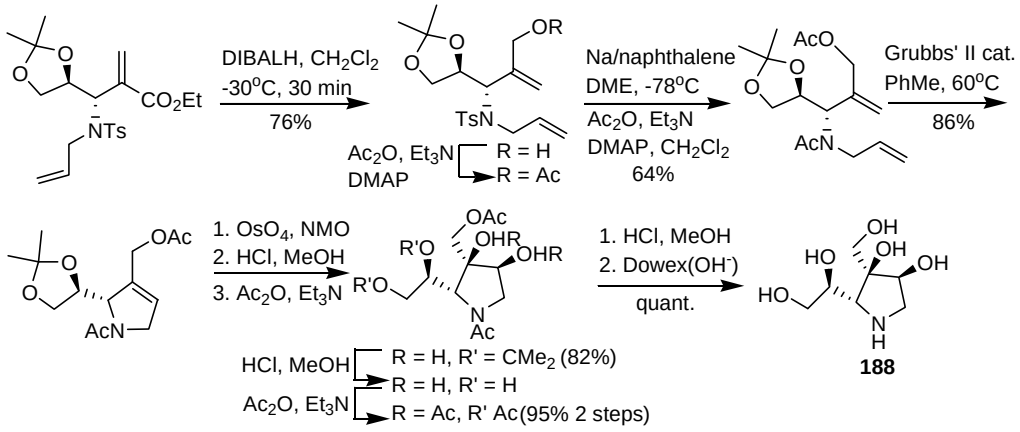


Scheme 120

Doddi and Vankar described efficient syntheses of two pyrrolidine-based imino sugars (**187** and **188**) initiating from the Baylis-Hillman adduct of (*R*)-2,3-*O*-isopropylidene-glyceraldehydes. The key steps included the regiospecific amination (via an S_N2 reaction), RCM and diastereospecific dihydroxylations, as delineated in Schemes 121 and 122. These azasugars were reported to be moderate inhibitors of glycosidase.[150]

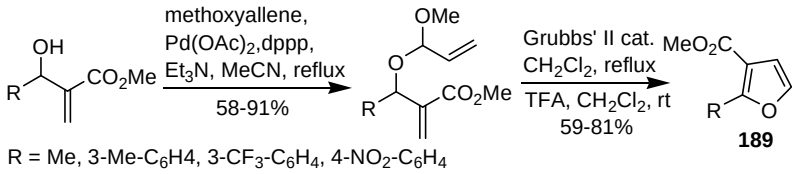


Scheme 121



Scheme 122

Donohoe and co-workers reported the transformation of the Baylis-Hillman adducts into mixed acetates, which, upon RCM reaction followed by aromatization, furnished the 2,3-substituted furans (**189**) in excellent yields, as shown in Scheme 123.[151]



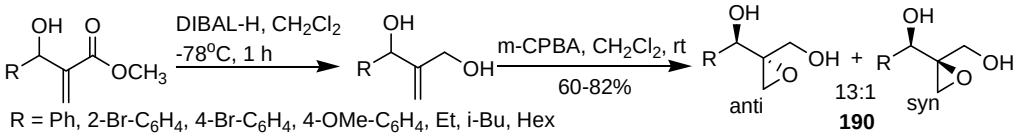
Scheme 123

Several other research groups have also employed the RCM strategy for the synthesis of a variety of natural products from the Baylis-Hillman derivatives. Theses approaches are discussed in Section 21.

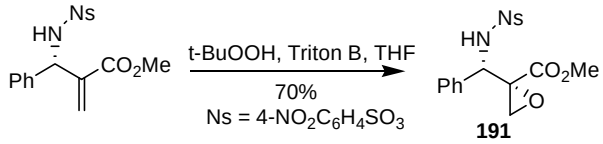
12. Epoxide formation

Baylis-Hillman derivatives have been successfully exploited for the generation of several substituted oxirane compounds. A highly diastereoselective epoxidation of allylic diols to provides the trans-epoxides (**190**) from the Baylis-Hillman adducts was reported by Coelho and co-workers. The high *anti*-diastereoselectivity was attributed to the formation of an intramolecular hydrogen bond (Scheme 124).[152] Raheem and Jacobson described the formation of a syn-epoxide (**191**) from the aza-Baylis-Hillman adduct under the influence of t-BuOOH and Triton B, as shown in Scheme 125.[153]

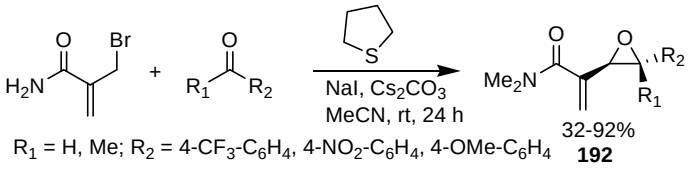
Metzner *et al*. developed a highly diastereoselective organocatalytic synthesis of functionalized vinyl epoxides (**192**), displaying a Morita-Baylis-Hillman backbone by means of sulfonium ylide epoxidation of aldehydes from the easily available α-(bromomethyl)acrylamide derivatives (Scheme 126).[154]



Scheme 124

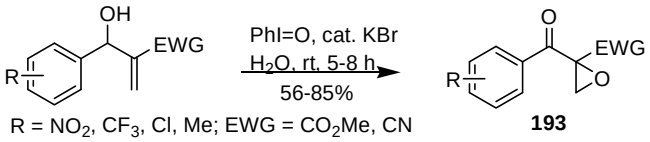


Scheme 125



Scheme 126

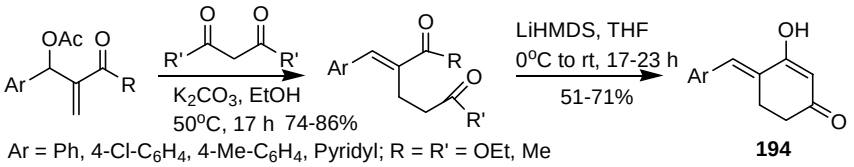
Das *et al.* described the synthesis of acyloxiranes (**193**) from the Baylis–Hillman adducts in the presence of iodosobenzene, which was utilized as an oxidizing agent for the two-fold oxidation of a secondary alcohol followed by epoxidation of the generated enone (Scheme 127).[155] A catalytic amount of KBr was required for the success of this reaction, since iodosobenzene alone did not give products.



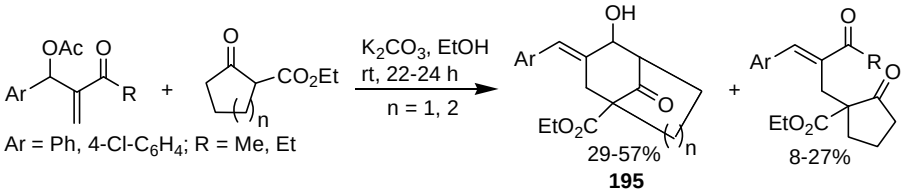
Scheme 127

13. Aldol condensation

The products originating from the S_N2 or S_N2' reaction of activated methylene compounds with the Baylis-Hillman acetates have been successfully employed for the aldol condensation to afford the cyclic scaffolds. Amri *et al.* reported the first aldol condensation reaction in the Baylis-Hillman chemistry to provide an easy access to 4-alkylidene-2-cyclohexen-1-ones.[156] Kim and co-workers also reported that the S_N2' reaction of the Baylis-Hillman acetates of acrylates with 2,4-pentanedione yielded a product, which, under the influence of LiHDMS, furnished the 4-arylidenecyclohexane-1,3-diones (**194**) (Scheme 128).[157] Alternatively the products afforded from the S_N2' reaction between the Baylis-Hillman acetates of methyl vinyl ketone and diethyl malonate were transformed into the same products via a similar protocol. Changing the nucleophile to ethyl cycloalkanone-2-carboxylate in the S_N2' reaction of Baylis-Hillman acetates of alkyl vinyl ketones yielded 3-alkylidenebicyclo[3.2.1]octan-8-ones (**195**) albeit in slightly lower yields and longer reaction times (Scheme 129).[158]

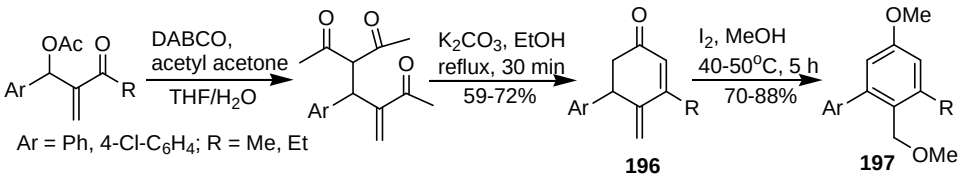


Scheme 128

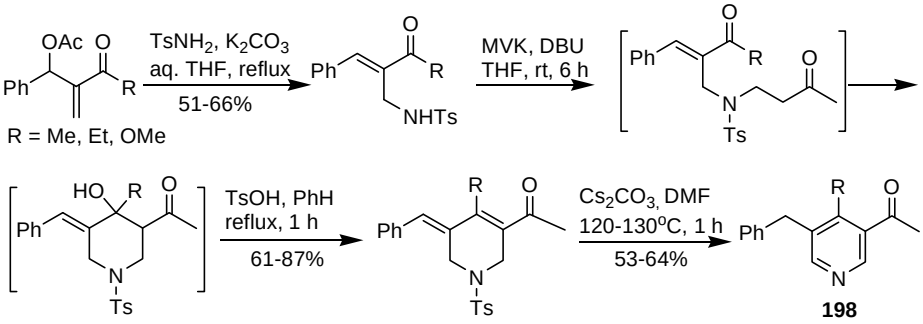


Scheme 129

Subsequently, Kim *et al*. demonstrated that the S_N2 reaction of Baylis-Hillman acetates of alkyl vinyl ketones with acetyl acetone in the presence of DABCO led to a synthon, which, on refluxing with K_2CO_3 in ethanol, gave 4-methylene-2-cyclohexenones (**196**) (Scheme 130).[159] Further treatment of these products with I_2 in methanol led to the formation of the benzene derivatives (**197**). Recently, these workers have developed the synthesis of 3,4,5-trisubstituted pyridines (**198**) from the Baylis-Hillman acetates involving an aldol reaction as the key step (Scheme 131).[160]

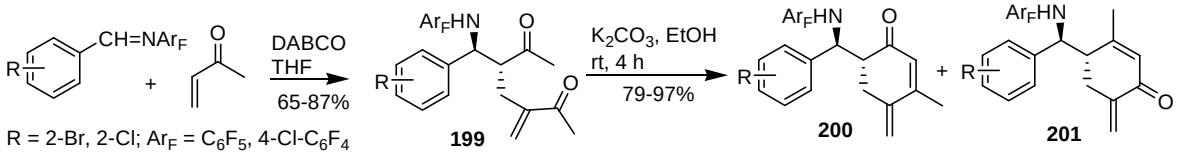


Scheme 130



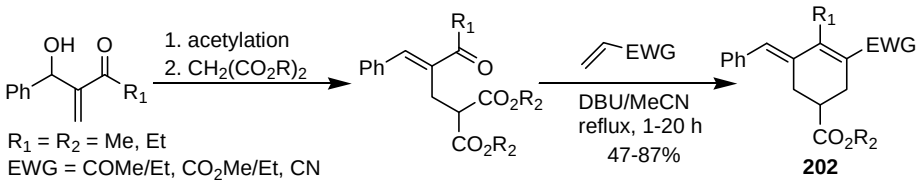
Scheme 131

Zhu *et al.* reported a double aza Baylis-Hillman reaction between per- (or poly-) fluorophenyl aromatic aldimines with methyl vinyl ketone and found that the double aza-Baylis-Hillman adduct (**199**) was a viable precursor for the construction of fluorine-containing 4-alkylidene-2-cyclohexen-1-ones (**200** and **201**) under mild conditions and with good yields (Scheme 132).[161]



Scheme 132

Recently, Kim and co-workers have demonstrated the synthesis of 3-benzylidene-cyclohexenes (**202**) from the Baylis-Hillman derivatives via a Michael addition of the appropriately substituted Baylis-Hillman derivatives to the activated alkenes followed by a DBU-promoted intramolecular aldol reaction (Scheme 133).[162]

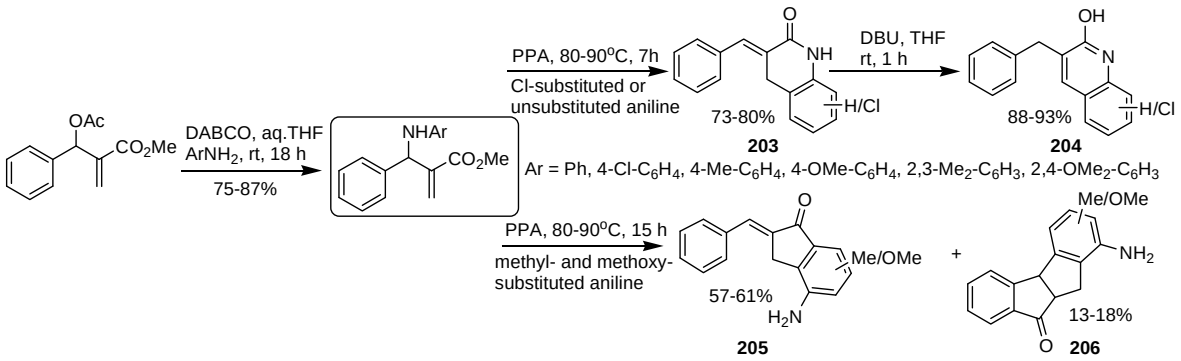


Scheme 133

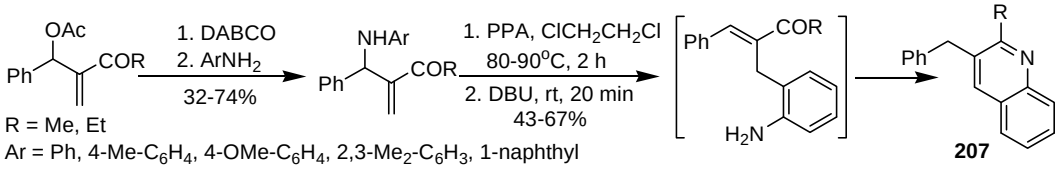
14. Claisen rearrangement

Basavaiah's group demonstrated the synthesis of alkylidine dialkanoates from the reaction between Baylis-Hillman adduct and triethyl orthoacetate as the first example of a Claisen rearrangement in the Baylis-Hillman chemistry.[163] Recently, Kim and co-workers reported a PPA-promoted Claisen rearrangement for the synthesis of 3-benzylidene-3,4-dihydro-1*H*-quinolin-2-one (**203**), 3-benzylquinolin-2-ol (**204**), 4-amino-2-benzylidene-indan-1-one (**205**), and 1-amino-9a,10-dihydro-4b*H*-indeno[1,2-a]inden-9-one (**206**) skeletons from the Baylis-Hillman derivatives of acrylates.[164] They observed that a slight difference in the

electron density of the aniline moiety causes strikingly different reaction pathways, as methyl- or methoxy- substituted anilines favor a Friedel-Crafts reaction, whereas chlorine-substituted or unsubstituted anilines cyclize via an intramolecular cyclization between the amino and the ester group (Scheme 134). Subsequently, the same workers reported a synthesis of quinolines (**207**) from the Baylis-Hillman derivatives of methyl or ethyl vinyl ketone via a sequential aza-Claisen rearrangement, intramolecular cyclization and DBU-promoted isomerization (Scheme 135).[165]



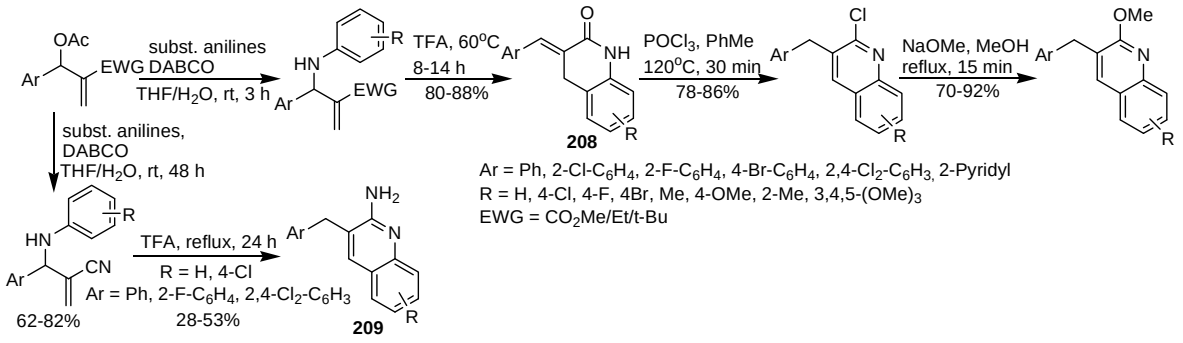
Scheme 134



Scheme 135

With an objective of our research group being to develop an easy and scaleable approach to the starting material for the anti-tubercular compound R207910, we have also developed a strategy to obtain 3-arylidene-2-quinolones (**208**). In our effort to replace PPA (difficult to handle on a large scale), we discovered that TFA is a better choice to effect the Claisen reaction. In contrast to the PPA-promoted reaction, the TFA-mediated cyclization was not affected by the change in the substituent-dependent electron density of the phenyl ring (Scheme 136).[166] This led to the development of a high-yielding and column

chromatography-free synthesis of 2-methoxy-3-arylquinolines. Interestingly, a similar synthetic protocol with the Baylis-Hillman derivatives of acrylonitrile provided the 3-aryl-2-amino quinolines (**209**) via a tandem Claisen rearrangement, intramolecular cyclization and subsequent isomerization.



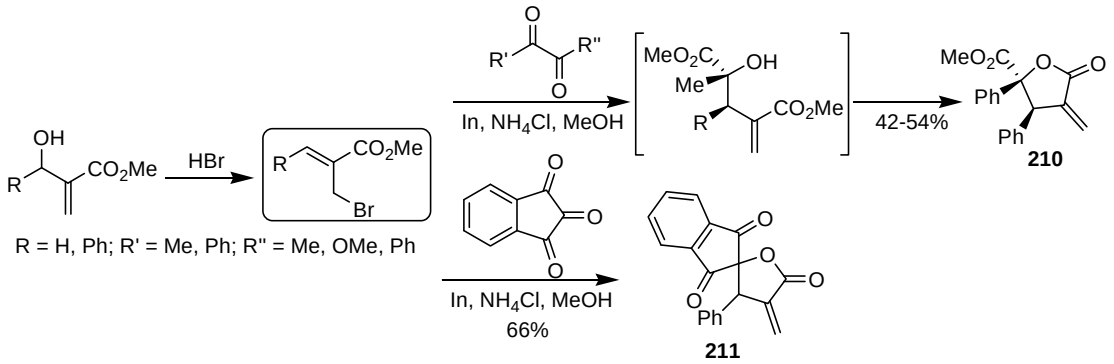
Scheme 136

15.0 Lactonization reaction

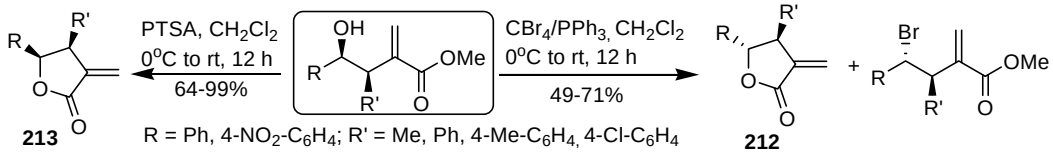
Over the years, several Baylis-Hillman derivatives have been utilized elegantly for the generation of the α-methylene-γ-butyrolactone, ring, which is ubiquitously present in several alkaloids and terpenoids.[167] Kim and co-workers have successfully developed the synthesis of α-methylene-γ-butyrolactones (**210**) via the reaction between allyl bromides and a variety of reactive carbonyl compounds under the influence of In and NH_4Cl, as shown in Scheme 137.[168] Indeed, with ninhydrin or *N*-benzylisatin, they demonstrated the formation of spiro analogs (**211**).

Subsequently, Kabalka and co-workers utilized the *syn*-homoallylic alcohols, prepared via a one-pot, cross-coupling/allylboration reaction on the Baylis-Hillman acetates, for the synthesis of *cis*- and *trans*-α-methylene-γ-lactones. Interestingly using CBr_4/Ph_3P as the ring-closing agent stereoselectively furnished the *trans*-isomer (**212**), while the use of TsOH as the lactonization agent gave the *cis*-isomer (**213**) (Scheme 138).[169]

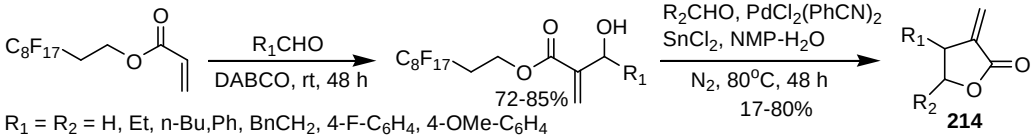
A library of mono- or disubstituted α-methylene-γ-lactones (**214**) was generated via a straightforward two-step reaction by Gouault and coworkers (Scheme 139).[170] Their fluorous-phase synthetic strategy employed flourous acrylates as the starting materials and removal of fluorous alcohol via cycloelimination in the final step.



Scheme 137



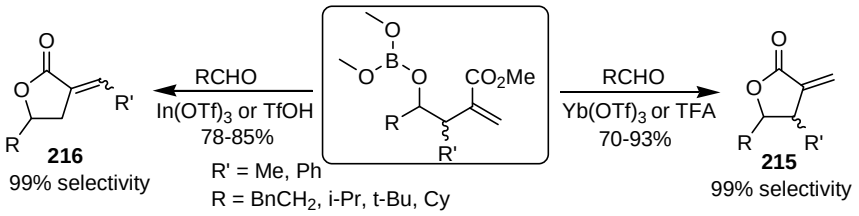
Scheme 138



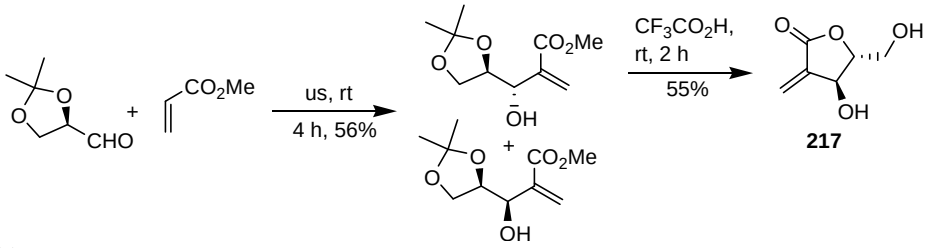
Scheme 139

Very recently, another innovative strategy for the synthesis of α-methylene-γ-lactones with 99% selectivity has been accomplished by Ramachandran and Pratihar.[171] The treatment of (*E*)-methyl or aryl 2-boramethyl-2-butenoate afforded from the Baylis-Hillman adduct of cyclohexane-carbaldehyde under the influence of $Yb(OTf)_3$ or TFA gave the cis-β,γ-disubstituted-α-methylene-γ-butyrolactones (**215**), as shown in Scheme 140. A similar reaction in the presence of $In(OTf)_3$ or triflic acid furnished the γ–substituted-α-*E*-alkylidene-α-methylene-γ-butyrolactones (**216**). Porto and Coelho described a simple and straightforward approach for the synthesis of an α-methylene-γ-butyrolactone (**217**) from

the Baylis-Hillman adduct of 2,3-isopropylidine-D-glyceraldehyde, as depicted in Scheme 141.[172]

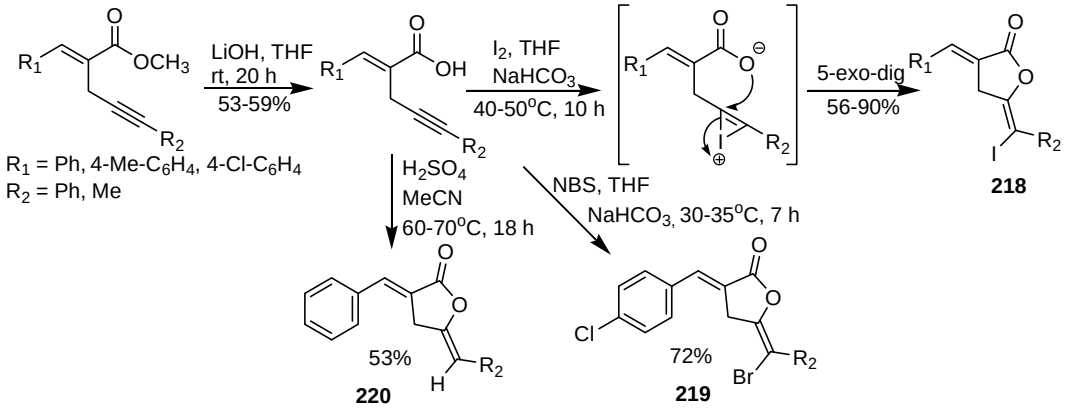


Scheme 140



Scheme 141

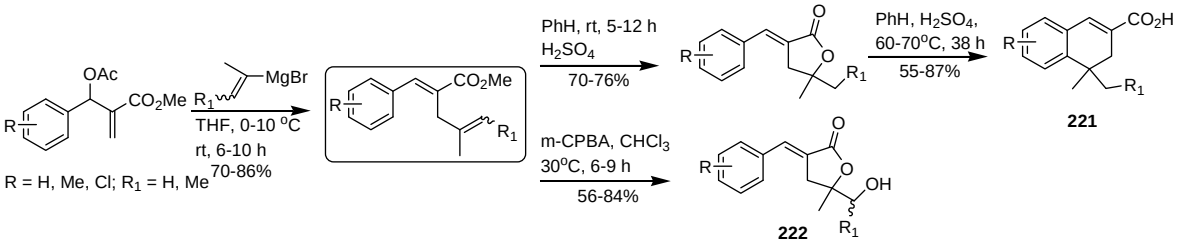
Indeed, several other workers have also described excellent syntheses of arylidene-butyrolactones. The transformation of triple-bond tethered methyl cinnamates to arylidene lactones (**218**) under the influence of iodine via iodolactonization was reported by Kim and co-workers (Scheme 142).[173] They also demonstrated the success of their strategy with



Scheme 142

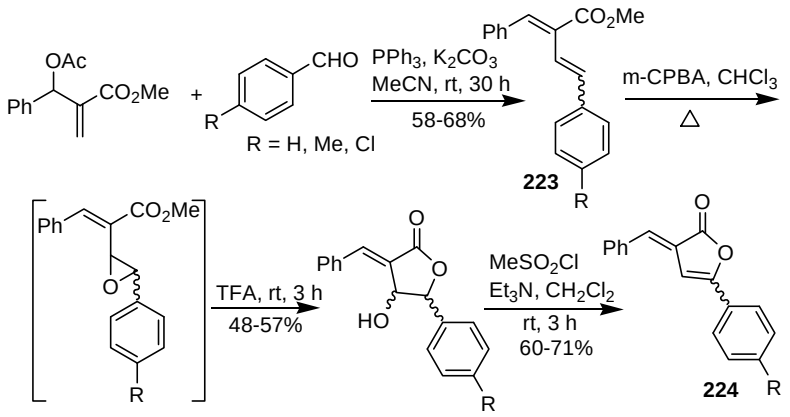
NBS and sulphuric acid as electrophiles to provide bromo- or proton-substituted enol lactones (**219** and **220**). Simultaneously, by sequential introduction of an appropriate vinyl moiety on the Baylis-Hillman acetates by Grignard reaction and treatment with benzene in

the presence of H_2SO_4, these workers demonstrated the synthesis of dihydronaphthalenes (**221**) via the lactonization process, as delineated in Scheme 143.[174] In order to provide evidence for the route of the reaction, they transformed the starting vinyl derivatives into the lactones (**222**) via an epoxy intermediate using m-CPBA.

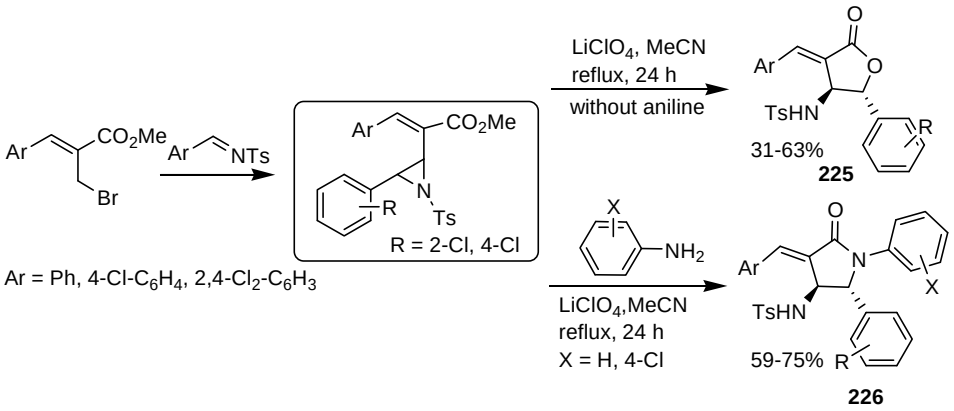


Scheme 143

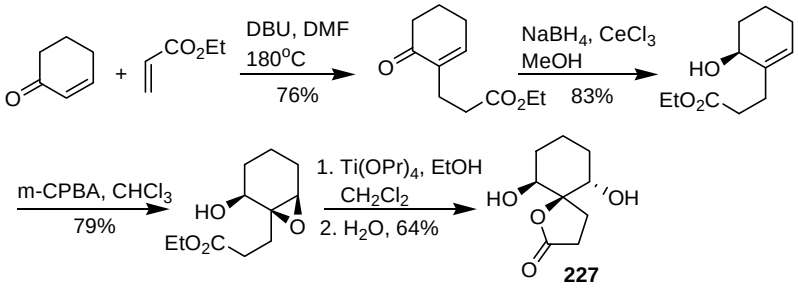
More recently, Kim *et al*. described the transformation of a diene (**223)** afforded from Baylis-Hillman acetates into arylidene lactones (**224**) via an epoxy intermediate, as shown in Scheme 144.[175] Moreover, these workers have also successfully achieved the synthesis of arylidene lactones (**225**) from the *N*-tosyl aziridines originating from the reaction between the allyl bromide and *N*-tosyl amine (Scheme 145).[176] This transformation was accomplished under the influence of $LiClO_4$ in acetonitrile. Interestingly, they reported that, if a similar reaction was performed in the presence of aniline, the *N*-tosyl aziridine was transformed into the 3-arylidene-4,5-disubstituted-γ-butyrolactam derivatives (**226**) in excellent yields. Earlier, Maier *et al.* reported the synthesis of a spirolactone (**227**) from the vinylogous Baylis-Hillman product via a chelation-controlled epoxide-opening strategy under the influence of $Ti(Oi\text{-}Pr)_4$ (Scheme 146).[177]



Scheme 144



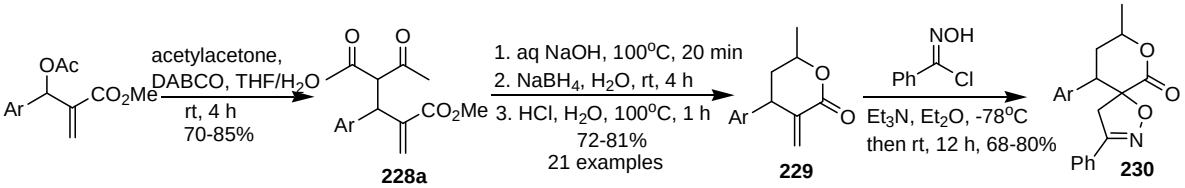
Scheme-145



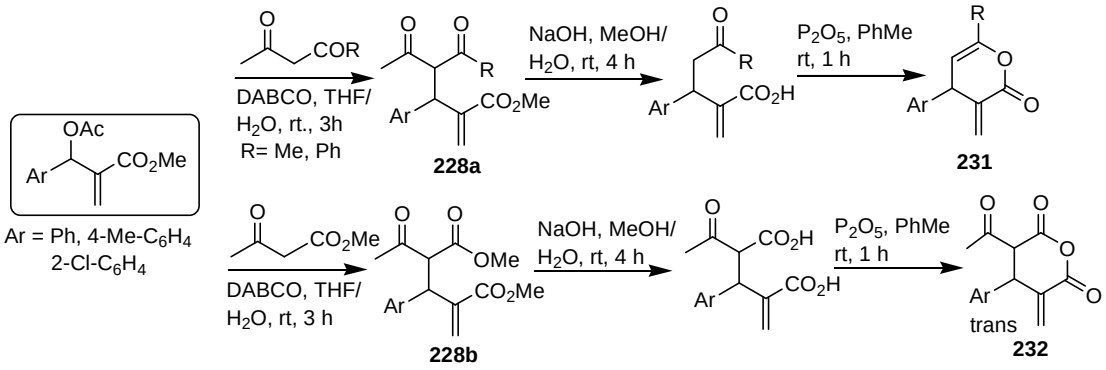
Scheme 146

Similar to five-membered lactones, there are various reports describing the synthesis of six-membered lactones. We have reported a mild and convenient synthesis of substituted α-methylene δ-valerolactones (**229)** from the substrates **(228)** originating by an S_N2 reaction of acetylacetone with the Baylis-Hillman acetates.[178] These products undergo one-pot saponification of the ester, and reduction of the keto group followed by intramolecular ring closure in an aqueous medium, as outlined in Scheme 147. These lactones are viable

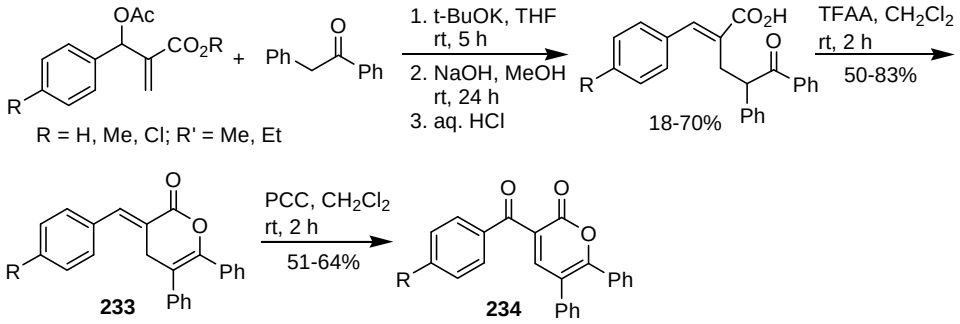
precursors for generating spiro-isoxazolines (**230**) via 1,3 dipolar cycloaddition of nitrile oxides on the double bond.[179] We have successfully employed the diketo derivatives (**228a**) also for the synthesis of 3-methylene-3,4-dihydropyran-2-ones (**231**) via P_2O_5-mediated cyclization (Scheme 148).[180] Conversely, similar products (**228b**) obtained from methyl acetoacetate via a similar reaction sequence stereoselectively yielded *trans* 5-methylene-dihydropyran-2,6-diones (**232**). Kim and co-workers reported the successful lactonization of the S_N2' products of Baylis-Hillman acetates and deoxybenzoins to generate 3-arylidene-5,6-disubstituted-3,4-dihydropyran-2-ones (**233**), as delineated in Scheme 149.[181] These pyranones were oxidized in the presence of PCC to yield 3-aryl-α-pyrones (**234**). A similar protocol with α-tetralone led to the mono- and bis-products (Scheme 150). The bis-product was lactonized to yield the same lactone (**235**) which has been reported earlier by Basavaiah *et al*.[182] Simultaneous to this work, Kim *et al*. reported the formation of 7,8-dihydro-6*H*-chromene derivatives (**236**), starting from the dimedone as nucleophile, according to the reaction sequence shown in Scheme 151.[183]



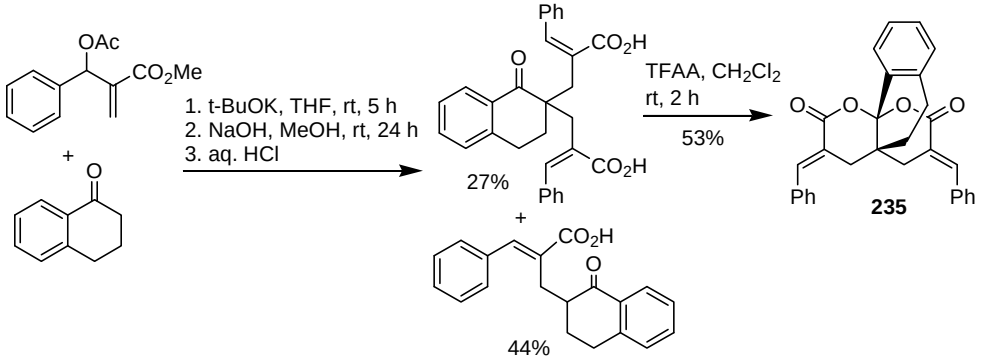
Scheme 147



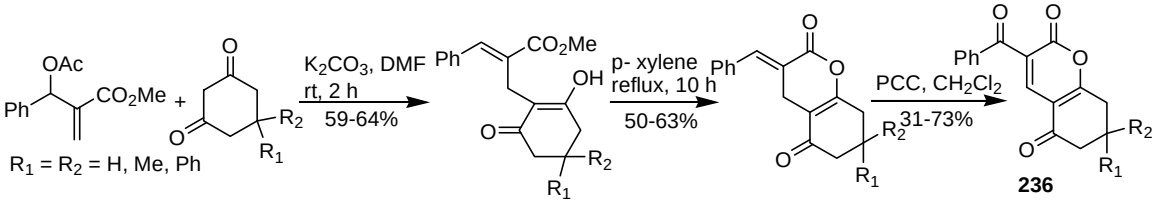
Scheme 148



Scheme 149



Scheme 150



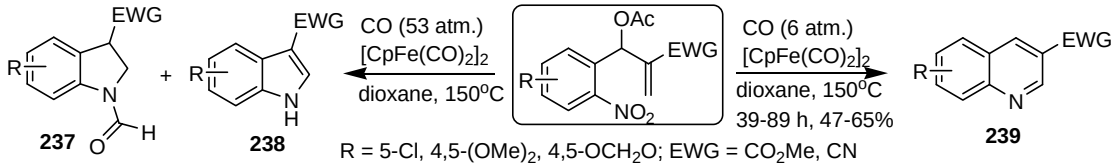
Scheme 151

16. Reductive cyclization

The strategy of reductive cyclization has found extensive applications in the Baylis-Hillman chemistry with respect to the synthesis of a variety of nitrogen- and oxygen-containing heterocyclic systems. The syntheses of several nitrogen-containing heterocycles have been achieved by reduction of the nitro group followed by cyclization with an appropriate functional group. This nitro group can be present either on the aromatic moiety generally at the ortho position to the formyl function on which the Baylis-Hillman reaction has been performed or on the side chain as a part of the nucleophile which has been attached through an S_N2 or S_N2' reaction.

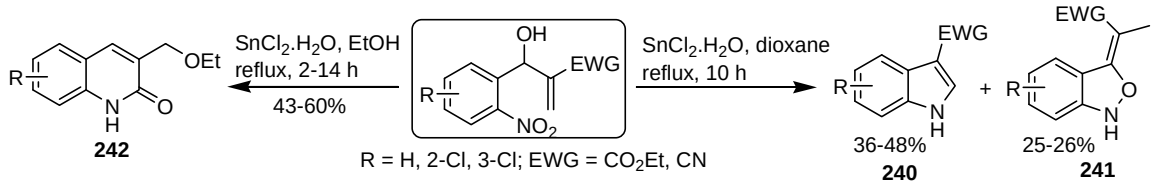
16.1 Reduction of aromatic nitro groups

The reductive cyclization involving an aromatic nitro group in the Baylis-Hillman chemistry has evolved extensively. O'Dell and Nicholas reported the formation of a mixture of *N*-formyl indolines (**237**) and indoles (**238**) via reduction of the nitro group by using 53 atm. of CO and $[CpFe(CO)_2]_2$ (Fp_2) as the catalyst.[184] Later, however, these workers achieved the synthesis of 3-substituted quinolines (**239**) in good yields via chemoselective reduction of the nitro group followed by cyclization by employing 6 atm. of CO and 10 mol% of Fp_2 (Scheme 152).[185]



Scheme 152

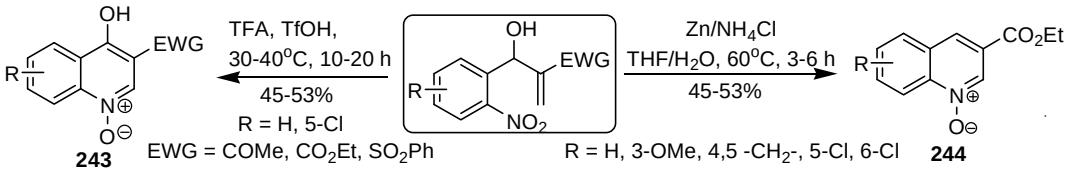
Very recently, Kim and co-workers have reported that the Baylis-Hillman adducts of 2-nitrobenzaldehydes on treatment with $SnCl_2$ in 1,4-dioxane lead to a mixture of indoles (**240**) and benzisoxazolines (**241**) (Scheme 153).[186] Earlier, they have reported that 2-quinolones (**242**) were formed when the same reaction was performed in alcohol.[187]



Scheme 153

Basavaiah *et al*. were the first to demonstrate that the Baylis-Hillman derivatives produced from 2-nitrobenzaldehyde are excellent precursors to functionalized 2-quinolones and quinolines.[188] Subsequently, Kim and co-workers reported the formation of 3-substituted-4-hydroxyquinoline *N*-oxides (**243**) from similar substrates.[189] Unlike Basavaiah *et al*., who have employed Fe-AcOH as reducing agents, these workers used TFA in the presence of

triflic acid for this purpose (Scheme 154). Later, they reported that, in the presence of Zn-NH_4Cl, 3-substituted-quinoline *N*-oxides (**244**) were generated from these substrates in moderate yields (Scheme 154).[190] Recently, Coelho and co-workers have reported their studies on the mechanistic details of the TFA/TfOH-mediated synthesis of quinoline *N*-oxides (**243**) by ESI-(+)-MS(/MS) monitoring.[191]

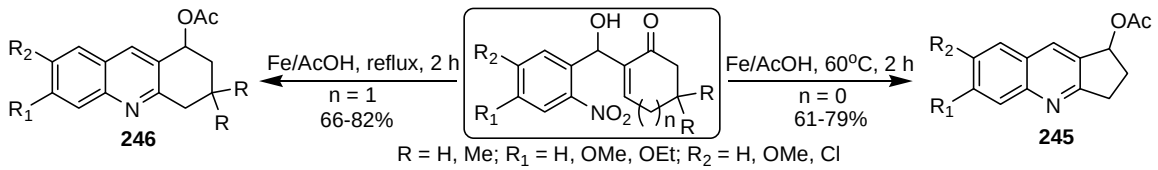


243 EWG = COMe, CO_2Et, SO_2Ph R = H, 3-OMe, 4,5 -CH_2-, 5-Cl, 6-Cl **244**

Scheme 154

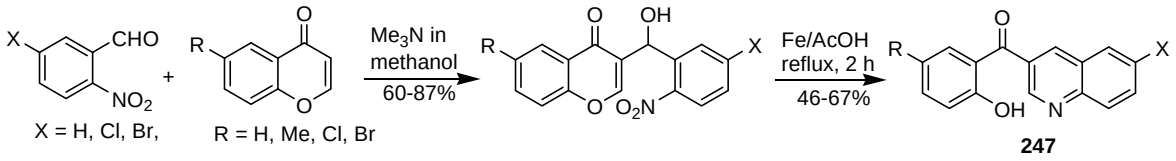
Basavaiah and co-workers demonstrated that the Baylis-Hillman adducts obtained from the reaction of 2-nitrobenzaldehyde with cycloalkenones could be easily transformed into different annulated quinoline systems (**245** and **246**) via reduction of the nitro group with Fe/AcOH (Scheme 155).[192] They extended the scope of this strategy further by developing the synthesis of 3-benzoylquinoline derivatives (**247**) from the Baylis-Hillman adducts of chromenones and 2-nitrobenzaldehyde, as shown in Scheme 156.[193]

Recently, Liu *et al.* have described a mild and efficient direct nucleophilic substitution of the Baylis-Hillman acetates derived from cyclic enones with indoles in the presence of AgOTf as a catalyst. The reaction provided highly α-regioselective indole derivatives (**248**). The reaction products of the 4-nitro-substituted indole derivatives were utilized for the synthesis of novel azepino[4,3,2-*cd*]indoles (**249**) via a one-pot nitro-group reduction followed by an *in situ* aza-Michael addition reaction, as delineated in Scheme 157.[194]

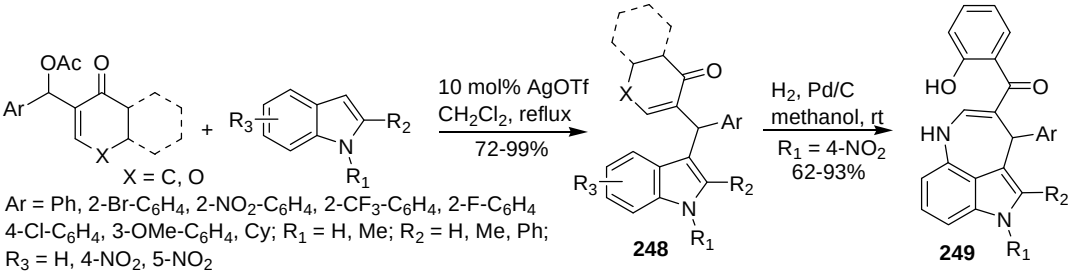


246 R = H, Me; R_1 = H, OMe, OEt; R_2 = H, OMe, Cl **245**

Scheme 155

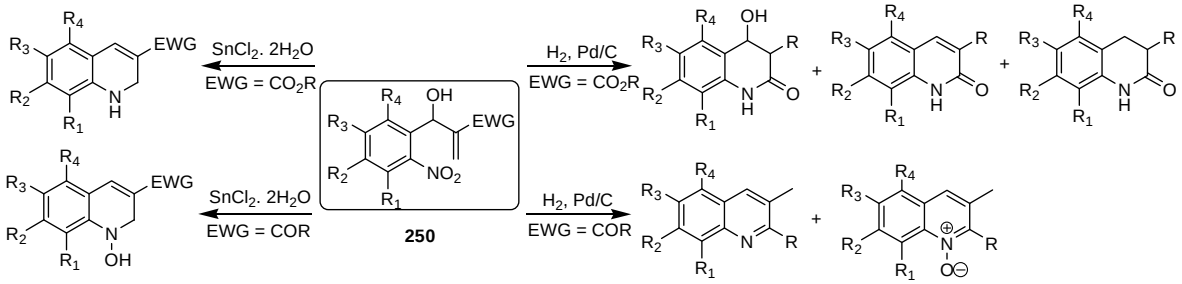


Scheme 156



Scheme 157

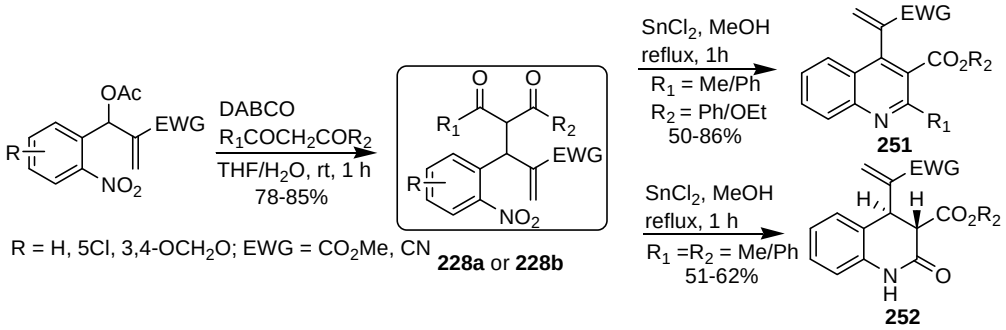
More recently, Kaye *et al* have also reported, the Pd/C-mediated reductive cyclization of Baylis-Hillman adducts of 2-nitrobenzaldehyde (**250**). They observed that the chemo- and regioselectivity of the cyclization is influenced by the choice of both the substrate and the reagent systems (Scheme 158).[195]



Scheme 158

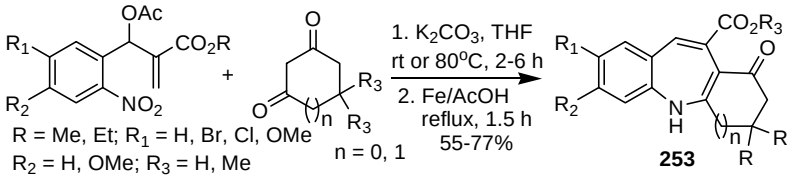
We have recently reported an alternative route to quinolines (**251** and **252**) from the S_N2 reaction products of Baylis-Hillman acetates of substituted 2-nitrobenzaldehydes and carbonyl-group-containing nucleophiles, as shown in Scheme 159.[196] We have observed that treatment of these products with $SnCl_2$ triggers a tandem reaction, in which the reduction of the nitro group is followed by a regioselective intramolecular cyclization and subsequent dehydration. Interestingly, this study indicated that the generated amino group

has preference for the activated carbonyl for cyclization in the order: R = Me > Ph > O-alkyl.



Scheme 159

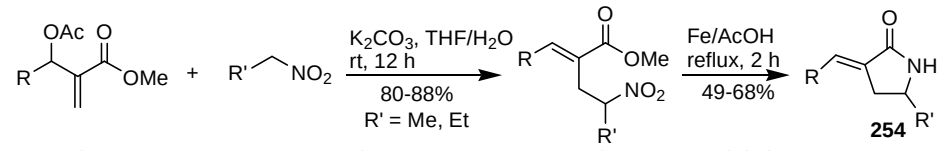
Very recently, Basavaiah and co-workers have demonstrated an elegant synthesis of an azocine moiety via a one-pot, multi-step protocol. Initially, an S_N2' reaction between 1,3-cycloalkanediones and Baylis-Hillman adducts of 2-nitrobenzaldehyde, followed by reduction with Fe-AcOH and subsequent cyclization, yielded the azocine derivatives (**253**) in good yields (Scheme 160).[197]



Scheme 160

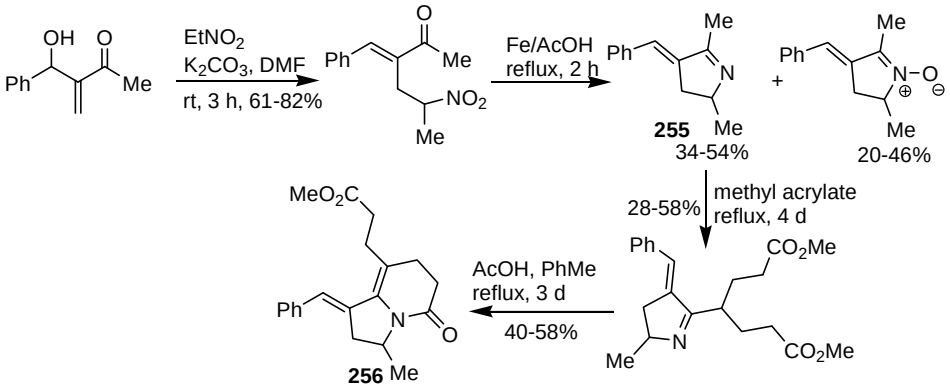
16.2 Reduction of aliphatic nitro groups

Reductive cyclization with aliphatic nitro groups in the Baylis-Hillman derivatives has also been exemplified in variety of procedures. Basavaiah and Rao first reported a one-pot facile synthesis of γ-lactams (**254**) from the product obtained via an S_N2' reaction of Baylis-Hillman acetates and nitroalkanes.[198] The Fe/AcOH-mediated intramolecular reductive cyclization was accomplished by involving the amine generated from the nitro group and the ester of the side chain, as depicted in Scheme 161.

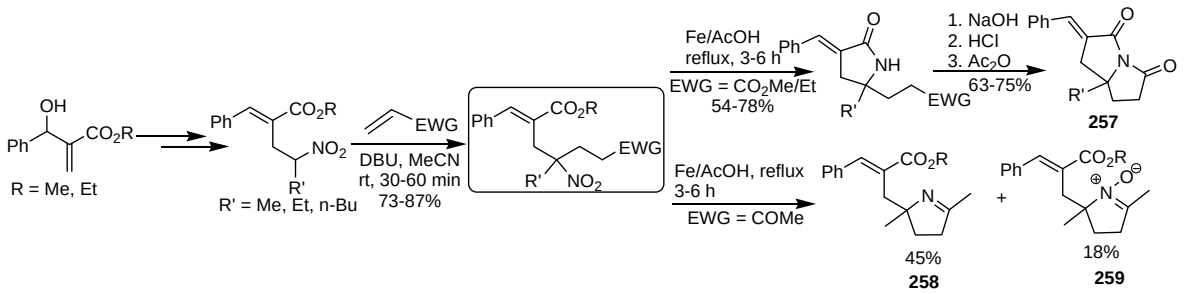


Scheme 161

Subsequently, analogous to this strategy, Kim *et al*. used similar substrates afforded by the Baylis-Hillman adducts of methyl vinyl ketone for the synthesis of 4-benzylidene-2,5-dimethyl-3,4-dihydro-2*H*-pyrroles (**255**), as shown in Scheme 162.[199] Further, they transformed these pyrroles (**255**) into bicylic lactams (**256**) in moderate yields. Later, they extended this strategy and successfully synthesized 2-benzylidene-7a-alkyl-tetrahydropyrrolizine-3,5-dione derivatives (**257**) from the Michael adduct afforded by the reaction between nitroalkanoate and acrylate. However the similar analog obtained via reaction of nitroalkanoate with methylvinyl ketone upon reduction of the nitro group to amine furnished the dihydropyrrole (**258**) and its *N*-oxide derivative (**259**) (Scheme 163).[200]

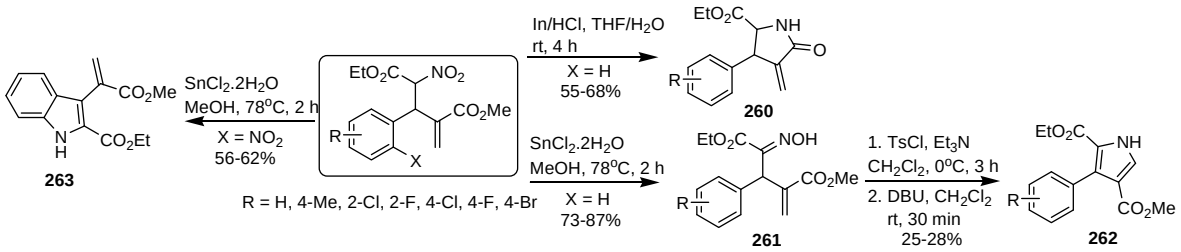


Scheme 162



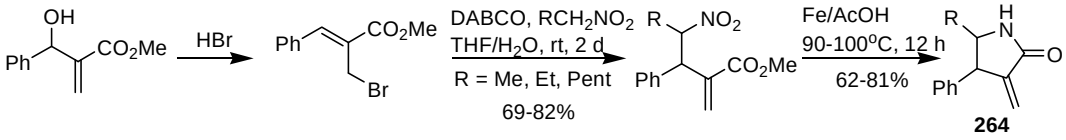
Scheme 163

We have recently reported a facile synthesis of 3-exomethylene pyrrolidinones (**260**) via In/HCl-mediated reductive cyclization of Baylis-Hillman derivatives afforded from the S_N2 reaction of Baylis-Hillman acetates with ethyl nitroacetate, as shown in Scheme 164.[201] We discovered that, in these substrates, the secondary nitro group undergoes a partial reduction to the oximes (**261**) in the presence of $SnCl_2.2H_2O$. These oximes were transformed into pyrrole derivatives (**262**) in low yields. Interestingly, similar nitro derivatives originating from the Baylis-Hillman acetates of substituted 2-nitrobenzaldehydes led to the formation of 3-vinylindoles (**263**) under the influence of $SnCl_2.2H_2O$, due to chemoselective reduction of the aromatic nitro group to amine and the aliphatic nitro group to oxime.



Scheme 164

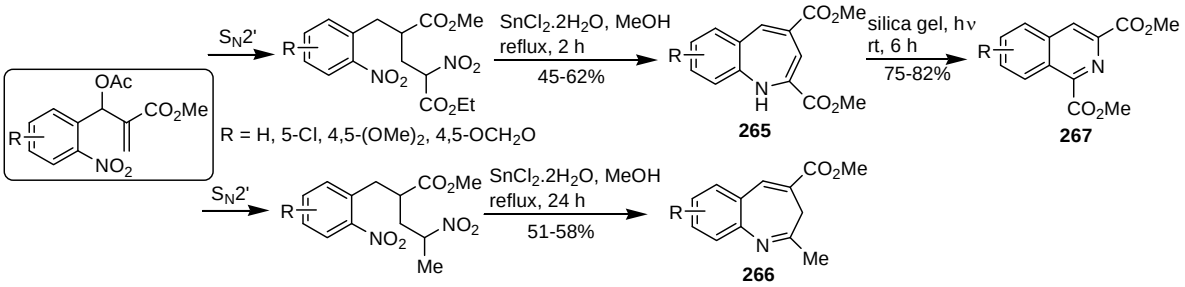
More recently, Kim *et al*. have also transformed the nitro derivatives obtained by an S_N2 reaction between nitroalkanes and allyl bromides into 3-methylene-pyrrolidinones (**264**) via Fe-AcOH-mediated reductive cyclization (Scheme 165).[202]



Scheme 165

In an extension to our work, we have recently reported the synthesis of benzazepines (**265** and **266**) by $SnCl_2.2H_2O$-promoted reductive cyclization of the S_N2' reaction product of ethyl nitroacetate and nitroethane with the Baylis-Hillman acetates of substituted 2-nitrobenzaldehydes, as shown in Scheme 166.[203] We observed that the formation of the 1-

or 3-benzazepines was influenced by the substituent on the phenyl ring in the products obtained as derivatives of ethyl nitroacetate, but such an influence was absent in the products derived from nitroalkanes. Surprisingly, it was observed that the 1*H*-1-benzazepines were unstable in light or on silica gel and rearranged to the isoquinolines (**267**) (Scheme 166). This unusual transformation proceeded by a plausible mechanism, as shown in Figure 9.



Scheme 166

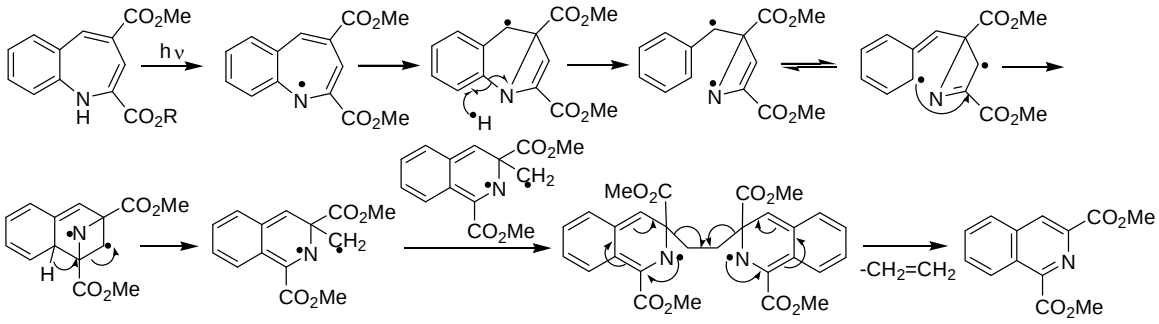
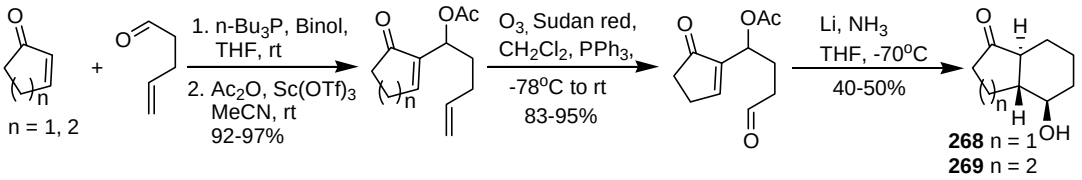


Figure 9

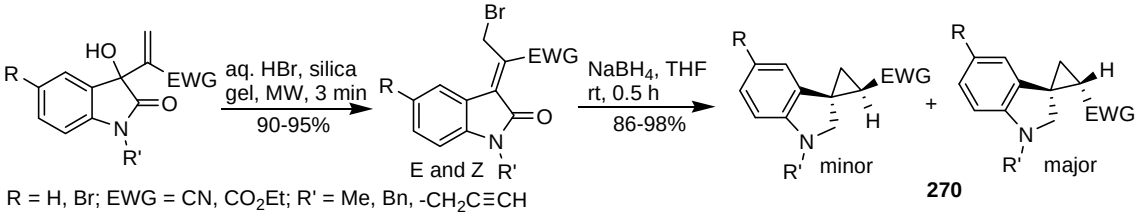
16.3 Reduction of other functional groups

Besides reductive cyclizations involving the nitro group, there are several other reports of generating cyclic systems via this strategy in Baylis-Hillman chemistry. The syntheses of substituted hydrindanones (**268**) and decalones (**269**) via Li/NH_3-promoted intramolecular cyclization of the Baylis-Hillman derivatives, originating from 4-pentenal and cycloalkenones in moderate yields were described by Marko *et al.* (Scheme 167).[204] They proposed that the formation of the products proceeded via a radical reaction.



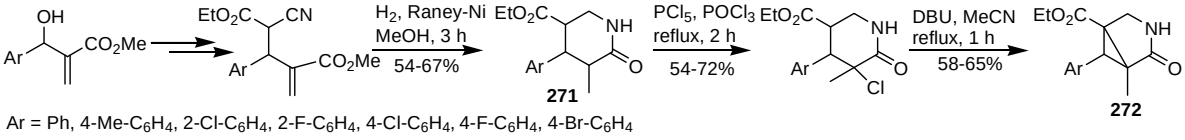
Scheme 167

Shanmugam and co-workers demonstrated the transformation of bromo derivatives of Baylis–Hillman adducts of isatin into functionalized diastereomeric 3-spirocyclopropane-2-indolones (**270**) via $NaBH_4$-mediated reductive cyclization (Scheme 168).[205]



Scheme 168

We have reported a facile synthesis of 6-oxo-4-aryl-piperidine-3-carboxylates (**271**) from the S_N2 products of ethyl cyanoacetate with the Baylis-Hillman acetates under Pd-C-mediated hydrogenation. These substrates were demonstrated to be excellent precursors for the synthesis of a new bicyclic heterocyclic system, namely 5-methyl-4-oxo-6-aryl-3-azabicyclo[3.1.0]hexane-1-carboxylates (**272**) (Scheme 169).[206]

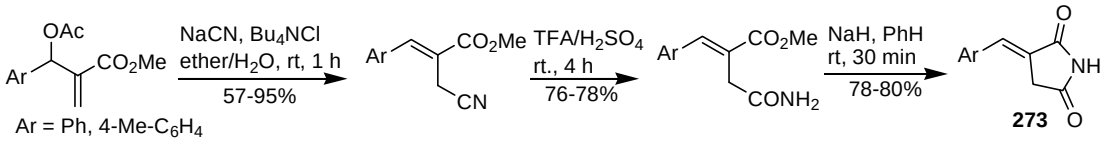


Scheme 169

17. Hydrolysis of nitrile groups

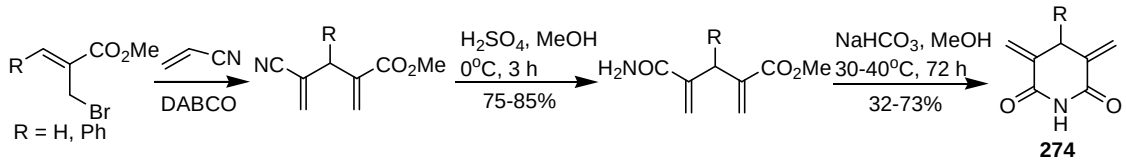
The hydrolysis of the nitrile group, present in the Baylis-Hillman adducts derived from acrylonitrile, or as part of the nucleophile added on to the Baylis-Hillman derivatives, has been utilized in different ways to obtain heterocycles, especially containing an amide linkage.

Kim *et al*. have utilized this strategy for the generation of several heterocycles from the Baylis-Hillman derivatives obtained from the nucleophilic addition of nitrile-containing nucleophiles. The H_2SO_4-mediated hydrolysis of the nitriles of 3-aryl-2-cyano-methyl 1,2-propenoates provided the succinimide derivatives (**273**) via amide formation.[207] Similar succinimides (**273**) were reported by us via TFA/H_2SO_4-promoted hydrolysis followed by cyclization with NaH (Scheme 170).[208]



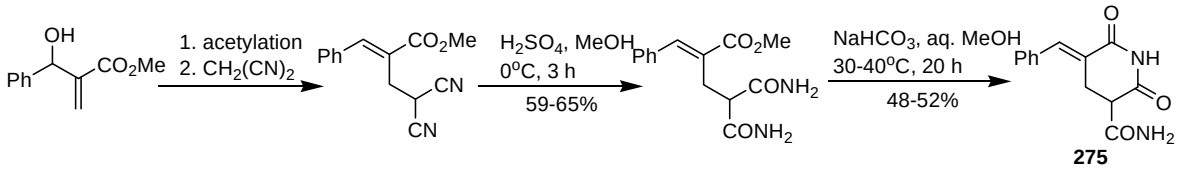
Scheme 170

Kim *et al*. also described the synthesis of glutarimide derivatives (**274**) from the cinnamyl bromides according to the reaction shown in Scheme 171.[207] An S_N2 reaction of malononitrile on the acetate of the Baylis-Hillman adduct of acrylate followed by hydrolysis afforded a diamides which was cyclized by these workers to yield the arylideneglutarimide (**275**) (Scheme 172).

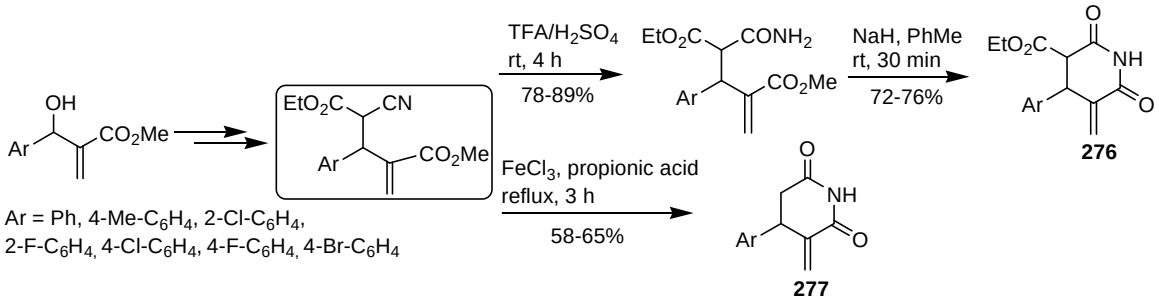


Scheme 171

We have also utilized the hydrolysis of the nitrile group in the Baylis-Hillman derivatives as a strategy for generating glutarimide derivatives.[206] Interestingly, the hydrolysis with TFA/H_2SO_4 yielded 4,5-disubstituted-3-methylene-piperidine-2,6-diones (**276**), while hydrolysis during the $FeCl_3$-promoted reaction provided 4-substituted-3-methylene-piperidine-2,6-diones (**277**) (Scheme 173).

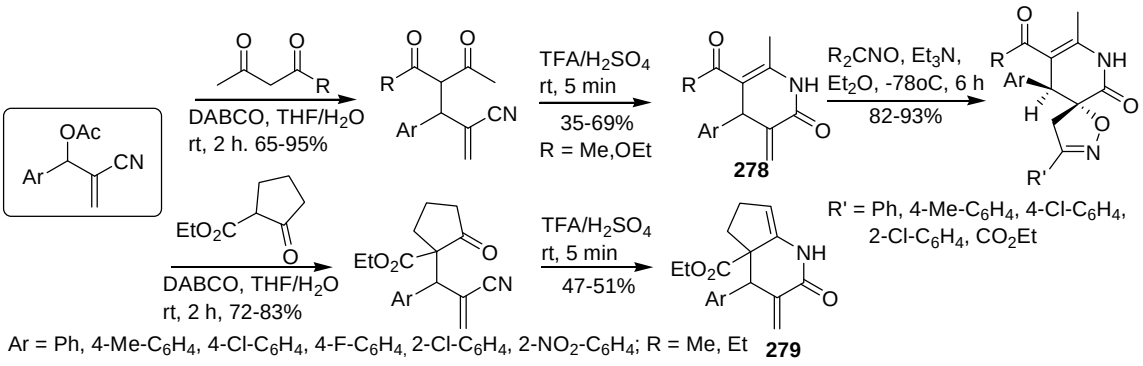


Scheme 172



Scheme 173

More recently, our group has achieved the synthesis of 3-methylene-2-pyridones (**278**) from the S_N2 reaction products of Baylis-Hillman acetates and acetylacetone or methyl acetoacetate via TFA/H_2SO_4-promoted hydrolysis of the nitrile group, as shown in Scheme 174.[209] Replacing the nucleophile with ethyl cyclopentanone-2-carboxylate provided the annulated 2-pyridones (**279**) by the application of the same reaction protocol. These pyridones were demonstrated to be the precursors for synthesizing novel pyrido-spiroisoxazoline derivatives in highly regio- and diastereoselective fashion.

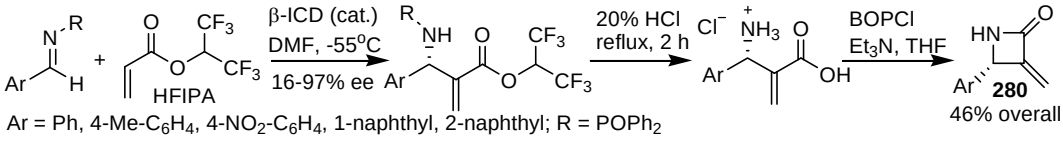


Scheme 174

18. Heterocyclization of substituted 3-aminopropanols and allyl amines

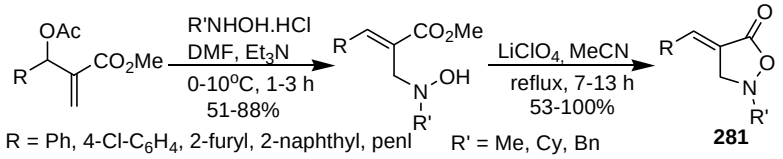
The nucleophilic addition of amines on the Baylis-Hillman adduct results in substituted 3-aminopropanols, while a similar addition on the Baylis-Hillman acetates or allyl bromides afforded substituted allyl amines. Both these substrates have been efficiently utilized for the synthesis of several nitrogen-containing heterocycles.

Hatakeyama *et al*. reported β-ICD-catalyzed asymmetric Baylis-Hillman reactions of aromatic imines with HFIPA and the successful transformation of the products to generate chiral β-lactams (**280**), as outlined in Scheme 175.[210]



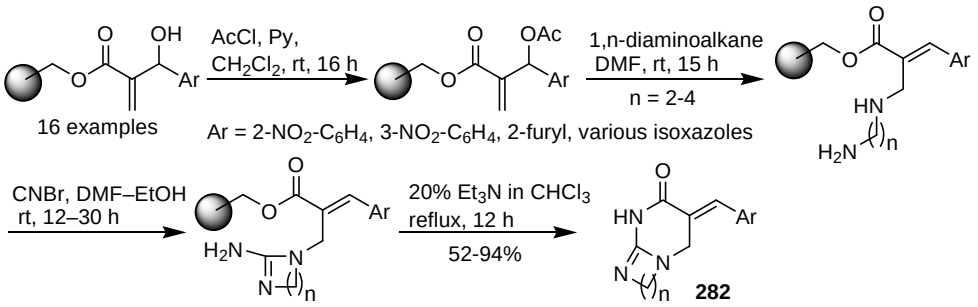
Scheme 175

Kim *et al*. described the synthesis of 4-arylidene-2-substituted-isoxazolidin-5-ones (**281**) from *N*-hydroxy allyl amines via $LiClO_4$-promoted intramolecular cyclization involving hydroxy and ester groups (Scheme 176).[211]



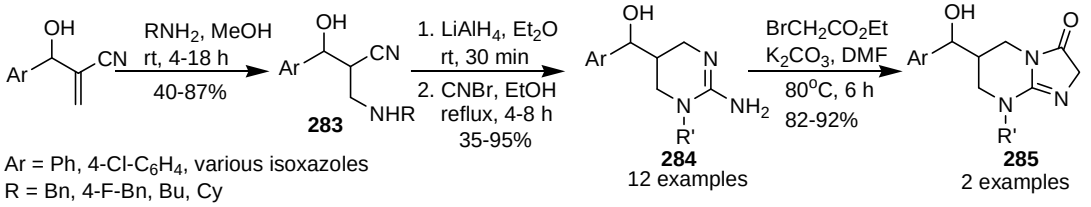
Scheme 176

Our group has described earlier a solid-phase methodology for the facile synthesis of annulated pyrimidinone derivatives (**282**) from the Baylis-Hillman acetate generated on Wang resin via reaction with diamine followed by treatment with cyanogen bromide and subsequent base-promoted cyclative cleavage (Scheme 177).[212] This strategy was simulated on automation and its scope was extended in a series of papers from our group. In this effort, we successfully utilized the Baylis-Hillman adducts (**283, 288**) of acrylonitrile and in most of the cases the different primary amines were added in an S_N2 or S_N2' fashion

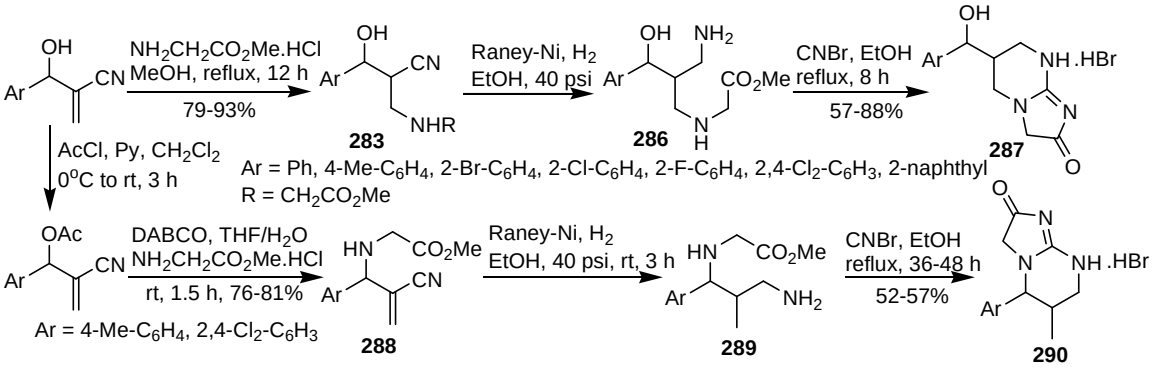


Scheme 177

followed by $LiAlH_4$ or Raney-Ni-mediated reduction of the nitrile group to yield the diamines (such as **286** and **289**), which on subsequent treatment with cyanogen bromide, yielded the tetrahydro-pyrimidines **284**[213] and substituted imidazo[1,2-a]pyrimidin-2-ones (**287** and **290**)[214] according to the reaction sequences depicted in Schemes 178 and 179, respectively. The compounds **284** were easily transformed into the substituted imidazo[1,2-a]pyrimidin-2-ones **285** by treatment with ethylbromoacetate.



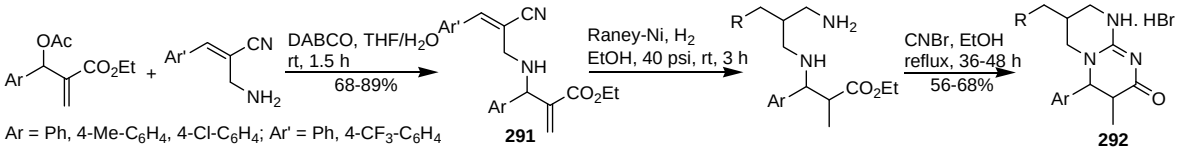
Scheme 178



Scheme 179

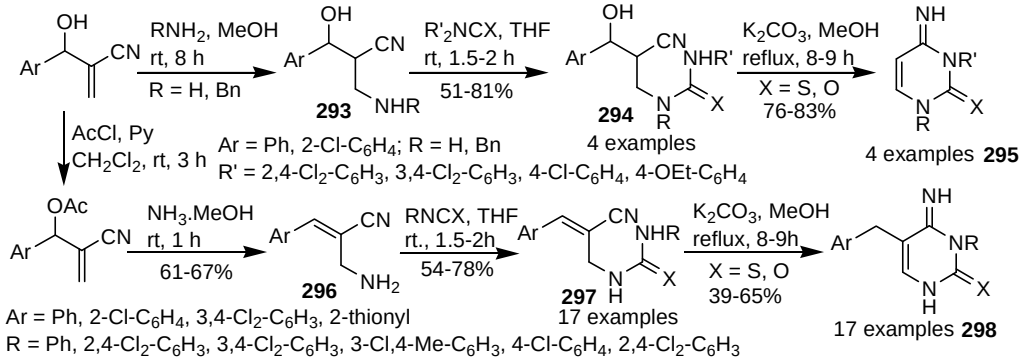
Following a similar reaction protocol, our research group has increased the scope of this strategy by the preparation of hexahydro-pyrimido[1,2-a]pyrimidin-2-ones (**292**) from the products (**291**) originating from the reaction of derivatized primary allyl amines with the

Baylis-Hillman adduct obtained by reacting acrylonitrile and acetyl derivatives of the Baylis-Hillman adducts of acrylates (Scheme 180). These compounds exhibited significant antiparasitic activity.[215]



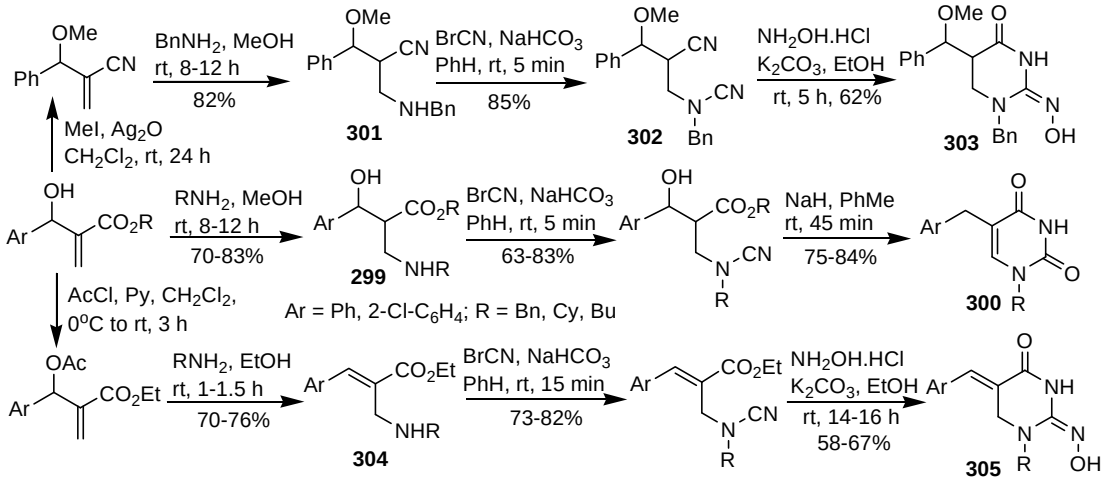
Scheme 180

The substituted 3-aminopropanols **293** derived from the reaction of primary amines with the Baylis-Hillman adduct of acrylonitrile on treatment with isocyanate furnished the urea derivatives **294**. In the presence of a base, compounds **294** cyclized into the pyrimidinones **295,** in which the benzyl moiety was lost during the process of cyclization. This loss was attributed to the presence of the hydroxyl group, since it was prevented on converting the hydroxyl group into a methoxy moiety. On the contrary, the substituted primary allyl amines **296** derived from the Baylis-Hillman acetates were easily transformed into the 4-iminium-pyrimidones **298** via treatment with isocyanate and ring closure of the product (**297**), as shown in Scheme 181.[216] Some of these compounds showed excellent antibacterial activity.



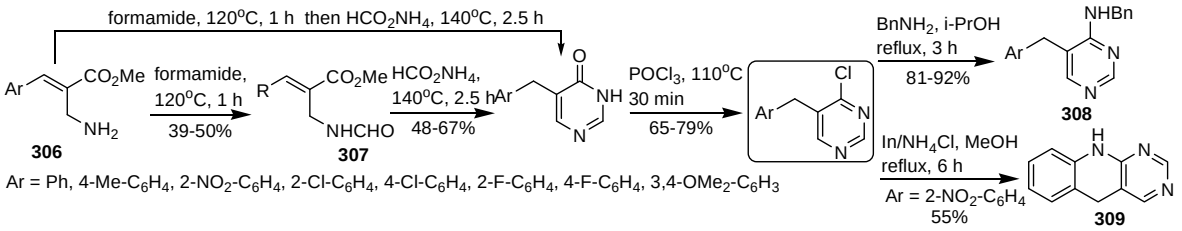
Scheme 181

More recently, substituted 3-aminopropanols **299** have been demonstrated to be excellent precursors for the generation of 5-benzyluracil derivatives **300**.[217] The cyanamides afforded by the compounds **299** undergo a base-promoted cascade reaction in which the nitrile is hydrolyzed due to the migration of hydroxyl group followed by intramolecular cyclization, as shown in Scheme 182. Protecting the hydroxyl group, however, as in compound **301,** provides a stable cyanamide **302** and prevents the cascade cyclization. Treatment of **302** with hydroxylamine hydrochloride furnished the compound **303**. Alternatively, the allyl amine derivatives **304** yielded by the Baylis-Hillman acetates were regioselectively oximated at the 2-position via sequential treatment with cyanogen bromide and hydroxylamine hydrochloride to furnish the uracil derivatives **305**.



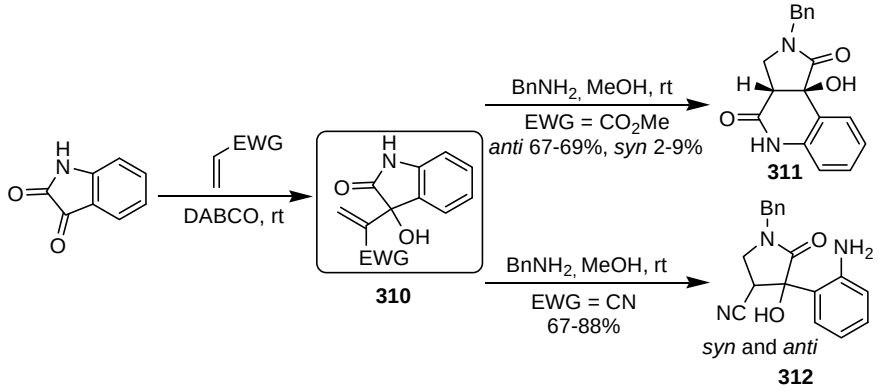
Scheme 182

More recently, we have demonstrated that the primary allyl amines **306** derived from the Baylis-Hillman acetates can be easily formylated with neat formamide to provide the *N*-formamides **307**. This reaction was utilized for the development of a one-pot procedure for the synthesis of 4-amino-5-methylpyrimidines (**308**). Interestingly, the product originating from 2-nitrobenzaldehyde was converted into the pyrimido[4,5-b]quinoline (**309**), as shown in Scheme 183.[218]



Scheme 183

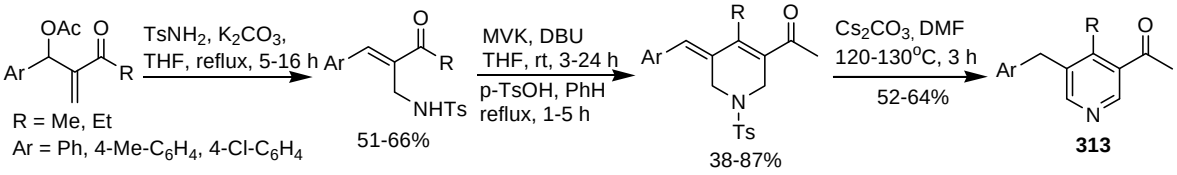
The preparation of 3-aryl-3-hydroxypyrrolidin-2-ones **311** and tricyclic 2-benzyl-9b-hydroxy-3,3a,5,9b-tetrahydro-2*H*-pyrrolo[3,4-c]quinoline-1,4-diones (**312**) starting from the Baylis-Hillman adducts (**310**) of isatin was successfully demonstrated by Kim and co-workers via the sequence shown in Scheme 184.[219]



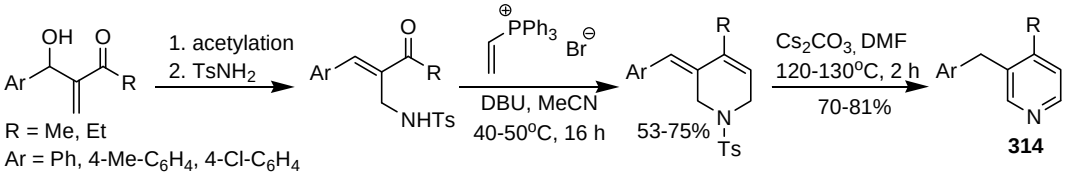
Scheme 184

Kim and co-workers have also developed a facile synthesis of polysubstituted pyridines (**313**) using the Baylis-Hillman adducts of alkyl vinyl ketones via the tosylamine derivatives. Their methodology involved a sequential Michael addition to the appropriate Michael acceptor, an aldol-type cyclization, elimination of p-toluenesulfinic acid and final isomerization by the reaction sequence as shown in Scheme 185.[220] Later, in another variation of this sequence, they successfully developed the synthesis of 3,4-disubstituted pyridines (**314**) from similar starting Baylis-Hillman adducts.[221] A Schweizer reaction of the tosylamine derivatives with vinyltriphenylphosphonium bromide, elimination of tosyl

group and the final 1,3-proton shift yielded the product in very good yields, as shown in Scheme 186.

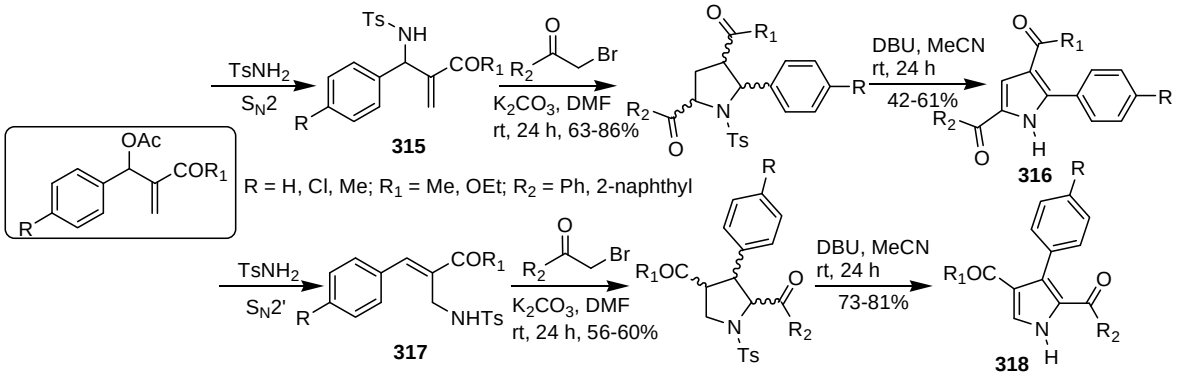


Scheme 185



Scheme 186

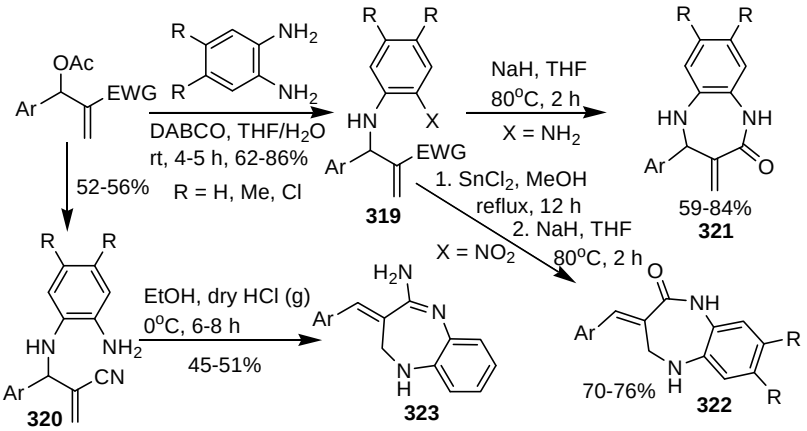
Very recently, these workers have reported a successful synthesis of pyrrole derivatives (**316** and **318**) from the substrates (**315** and **317**) afforded via an S_N2' and S_N2 reaction of the tosylamines with the Baylis-Hillman acetates.[222] The procedure involved *N*-alkylation, Michael addition-elimination of p-toluenesulfonic acid and, finally DBU-mediated oxidative aromatization via the reaction sequence shown in Scheme 187.



Scheme 187

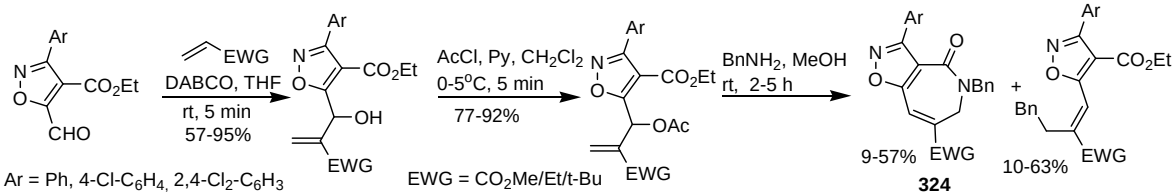
The allyl amine derivative originating from the reaction of 1,2-phenylenediamine with the Baylis-Hillman acetate was utilized by Kim *et al*. to synthesize 3-(benzylidene)-1,5-benzodiazepin-2-one.[223] Our group has also demonstrated the synthetic utility of

derivatized allyl amines (**319** and **320**) from the Baylis-Hillman adducts for the generation of substituted 3-methylenebenzo[b][1,4]di-azepin-2-ones (**321** and **322**) and -benzo[b][1,4]di-azepine-2-ylamines (**323**) in moderate- to -good yields (Scheme 188).[224]



Scheme 188

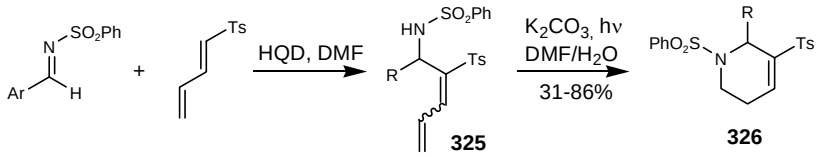
Our research group has earlier reported that primary allyl amines originating from the reaction between Baylis-Hillman acetates of 3-aryl-5-formyl-isoxazole-4-carboxylates and benzylamine undergo an intramolecular cyclization to furnish a novel isoxazole-annulated system (**324**) (Scheme 189).[225] The yield of the annulated system was, however, dependent on the nature of the EWG and was found to be highest with a *tert*-butoxy-carbonyl group.



Scheme 189

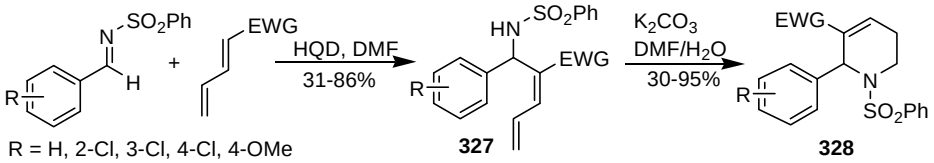
Back and co-workers have described the Morita-Baylis-Hillman reaction of aldimines with 1-(p-toluenesulfonyl)-1,3-butadiene in the presence of 3-hydroxyquinuclidine and found that the *E*-isomers of the products (**325**) cyclize to yield the functionalized piperidines (**326** (Scheme 190).[226] To improve the efficiency of the cyclization, a simultaneous equilibration

of the (*E*)- and (*Z*)-isomers was effected by photo-isomerization. Later, Back *et al*. reported an aza-Morita-Baylis-Hillman reaction between substituted *N*-(phenylsulfonyl)aldimines and conjugated dienes activated by sulfone, ester, or ketone moieties to afford the highly functionalized allylic amine derivatives (**327**) (Scheme 191).[227] Here, too, the *E*-isomer of the product from the dienyl sulfone and the dienoate underwent a facile intramolecular conjugate addition to produce the functionalized piperidines (**328**), whereas the adducts obtained from the dienones failed to cyclize under similar reaction conditions.



Ar = Ph, 4-Cl-C_6H_4, 3-Cl-C_6H_4, 2-Cl-C_6H_4, 4-OMe-C_6H_4, 4-NO_2-C_6H_4, 4-CN-C_6H_4

Scheme 190



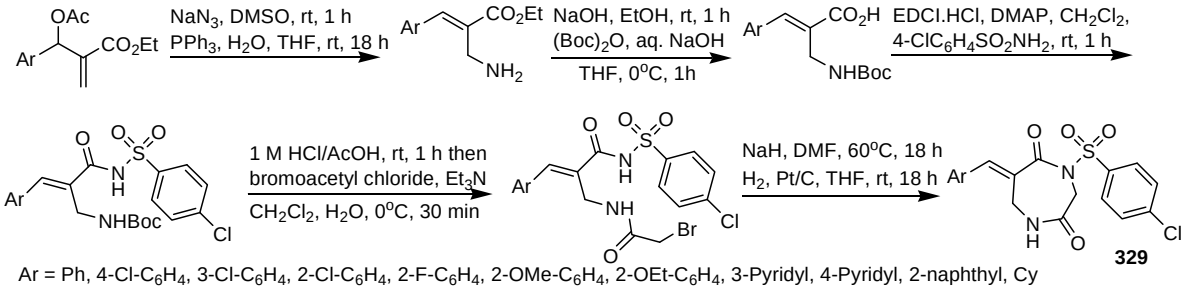
R = H, 2-Cl, 3-Cl, 4-Cl, 4-OMe
4-CO_2Me, 4-NO_2, 4-CN

EWG = Ts, CO_2Me, COMe/Ph

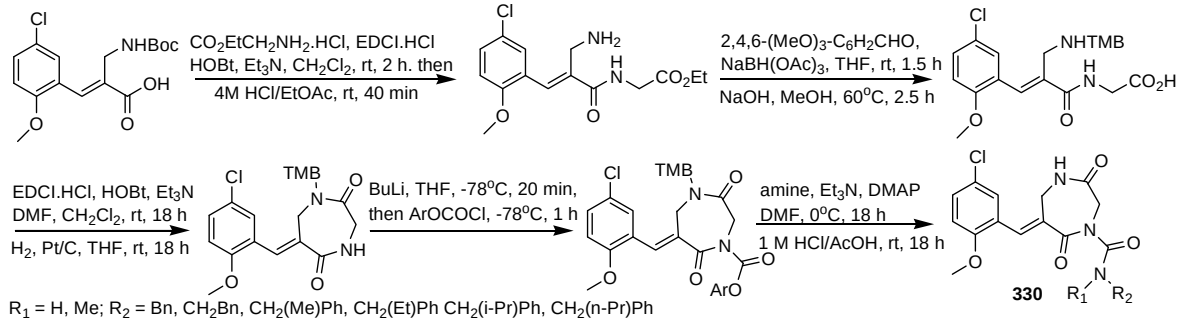
EWG = Ts, CO_2Me

Scheme 191

Muto and co-workers have synthesized a series of 6-substituted-4-sulfonyl-1,4-diazepane-2,5-diones (**329**) starting from the allyl amines, which, in turn, were generated from the corresponding Baylis-Hillman acetates via the introduction of an azide group followed by Ph_3P-mediated reduction (Scheme 192).[228] These compounds exhibit good inhibitory activity against recombinant human chymase. Continuing with this work, Muto *et al*. also reported the synthesis of 4-aminocarbonyl-1,4-diazepane-2,5-diones (**330**), potent human chymase inhibitors, from the *N*-Boc protected allyl amine as shown in Scheme 193.[229]

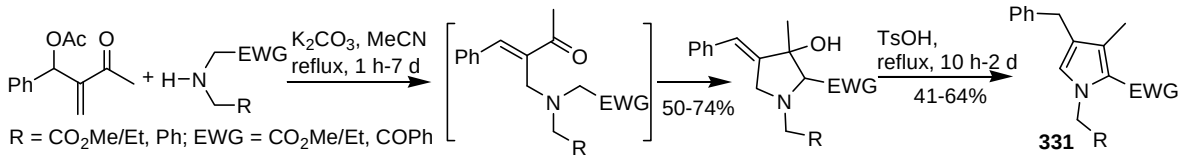


Scheme 192



Scheme 193

Kim and his group reported the facile synthesis of 1,2,3,4-tetrasubstituted pyrroles (**331**) from substituted allyl amines afforded from the acetyl derivatives of Baylis-Hillman adducts via base-mediated cyclization followed by acid-catalyzed dehydration and concomitant double-bond isomerization, as shown in Scheme 194.[230]

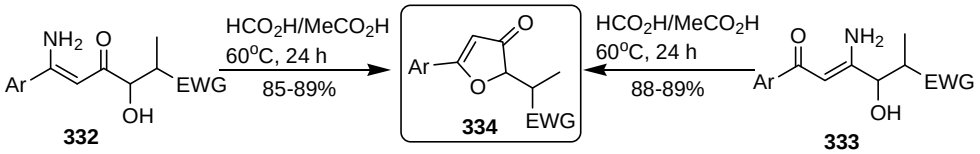


Scheme 194

19. Ring transformations

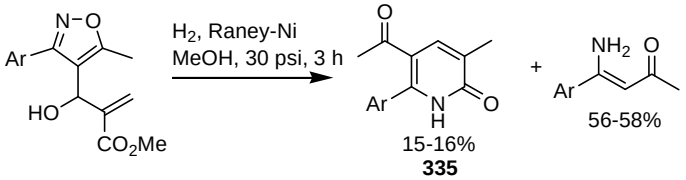
We have reported the ring transformation of several Baylis-Hillman derivatives of substituted isoxazolecarbaldehydes via hydrogenation. Raney-Ni or Pd-C-promoted hydrogenolysis of the Baylis-Hillman adducts of 5- or 3-isoxazolecarbaldehyde leads to the enaminones **332** and **333**, respectively, which were readily cyclized in the presence of a formic and acetic acid mixture to the 2,3-dihydrofurans (**334**) in excellent yields (Scheme

195).[231] In contrast, the hydrogenolysis of the Baylis-Hillman adducts of substituted 4-isoxazolecarbaldehydes provided the substituted 2-pyridinones (**335**), albeit in low yields (Scheme 196).



Ar = Ph, 4-Me-C_6H_4, 4-Cl-C_6H_4; EWG = CO_2Me/Et

Scheme 195

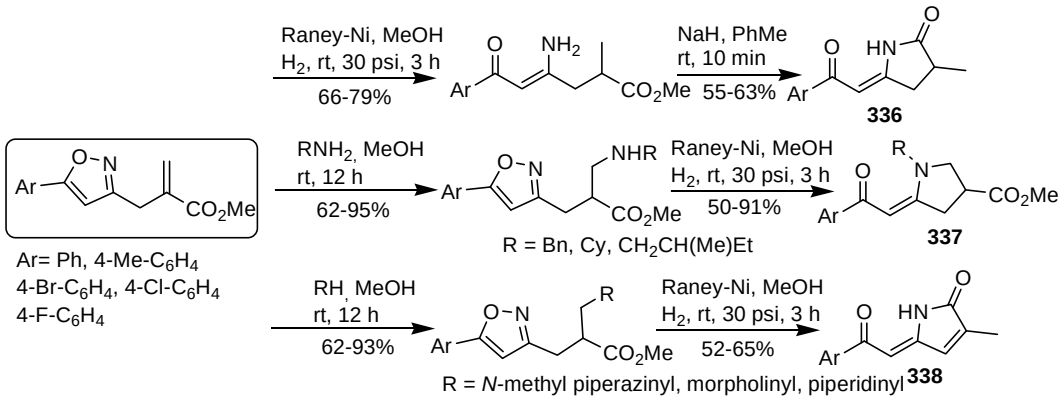


Ar = Ph, 4-Me-C_6H_4, 4-Cl-C_6H_4, 2-Cl-C_6H_4

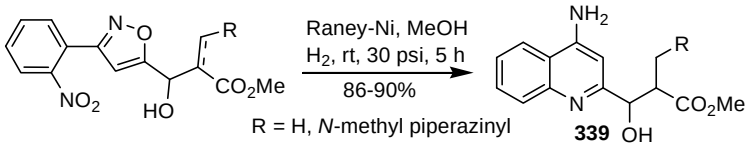
Scheme 196

Subsequently, we were successful in transforming the enaminones afforded from the appropriate Baylis-Hillman derivatives of 3-isoxazolecarbaldehyde into the 2-pyrolidinones (**336**), 2-pyrrolones (**337**) and pyrrolidines (**338**) in good yields, as depicted in Scheme 197.[232] Later, in another study, we have demonstrated the hydrogenolysis of the Baylis-Hillman derivatives of 3-(2-nitrophenyl)-5-isoxazolecarbaldehydes as a facile route for the synthesis of 2-substituted 4-aminoquinolines (**339**) (Scheme 198).[233]

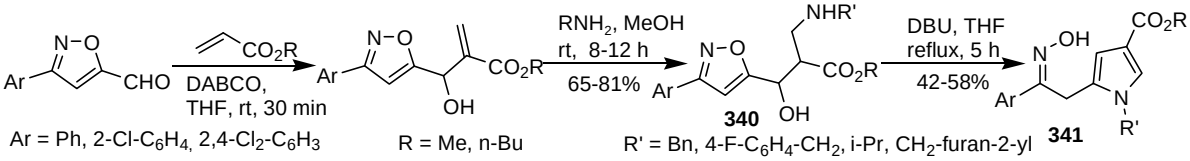
A DBU-promoted ring transformation of substituted 3-aminopropanols (**340**) of Baylis-Hillman adducts of 5-isoxazolecarbaldehydes to the pyrroles (**341**), via neighboring group participation, as shown in Scheme 199, was reported by our group.[234]



Scheme 197

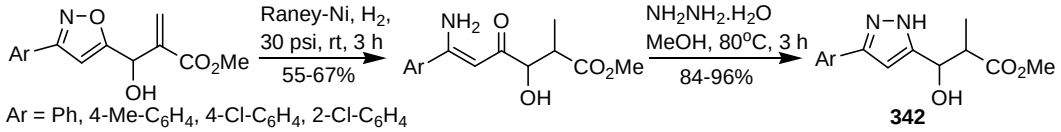


Scheme 198



Scheme 199

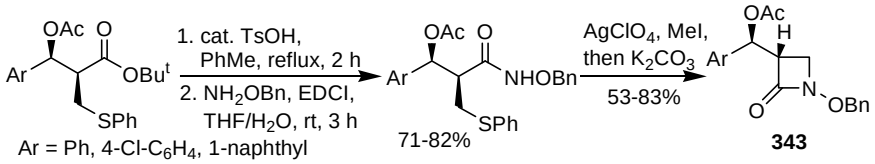
We have reported the transformation of enaminones derived via hydrogenolysis of Baylis-Hillman derivatives of isoxazolecarbaldehydes to the corresponding pyrazoles (**352**) in excellent yields by reacting them with hydrazine hydrate in refluxing conditions (Scheme 200).[235]



Scheme 200

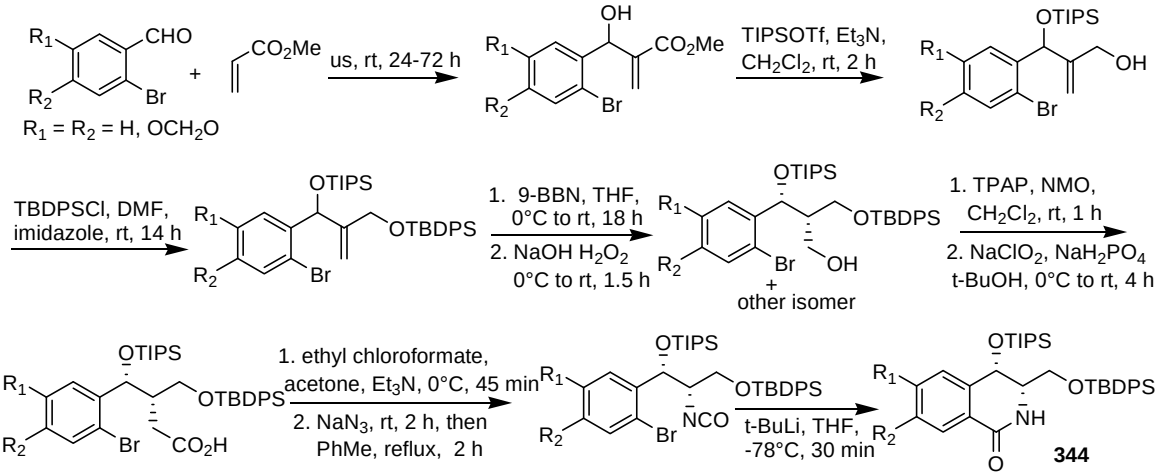
20. Miscellaneous reactions

Kamimura *et al.* described an $AgClO_4$/MeI-mediated elegant stereoselective synthesis of β-lactams (**343**) from thiophenol-substituted Baylis-Hillman derivatives, as shown in Scheme 201.[236]



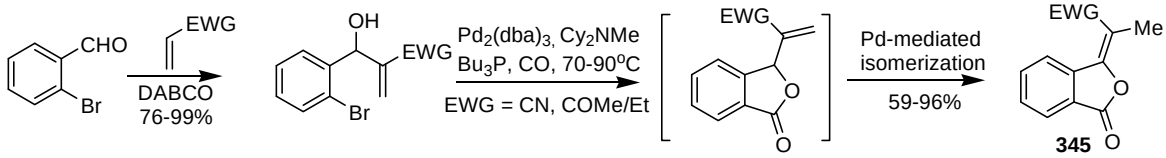
Scheme 201

Coelho and co-workers described an easy and straightforward alternative method of preparation of 3,4-substituted-isoquinolin-1(2*H*)-ones (**344)** from the 2-bromo-substituted Baylis-Hillman derivatives, according to the reaction sequence shown in Scheme 202.[237]



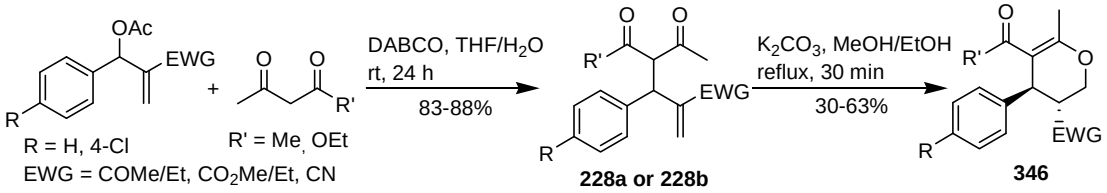
Scheme 202

Later, they described a palladium-mediated carbonylative cyclization reaction for the stereoselective synthesis of 3-alkenylphthalides (**345**) from the Baylis-Hillman adducts of ortho-halo-substituted benzaldehydes (Scheme 203).[238] The quinoline-phthalide derivatives exhibited potent *in vitro* antiproliferative activity against human tumor cell lines.[239]

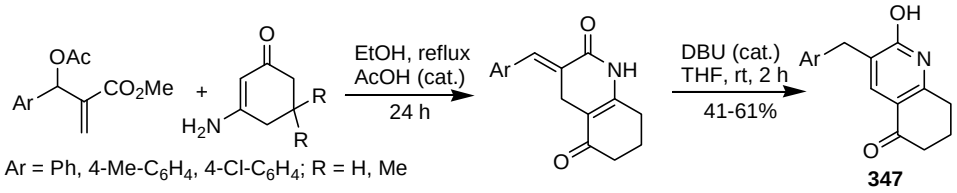


Scheme 203

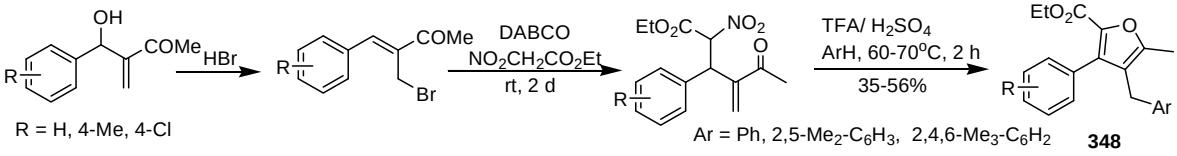
Kim and co-workers demonstrated the synthesis of 3,4,5,6-tetrasubstituted 3,4-dihydro-2*H*-pyrans (**346**) via a K_2CO_3-mediated Michael-type cyclization reaction, as delineated in Scheme 204.[240] Recently, they have synthesized 3-benzyl-2-hydroxy-7,8-dihydro-6*H*-quinolin-5-ones (**347**) via a reaction between the Baylis-Hillman acetates and cyclic enaminones in moderate yields (Scheme 205).[241] Subsequently, they have also described the unusual formation of fully substituted furan derivatives (**348**) from 3-aryl-2-methylene-4-nitroalkanoates under the influence of TFA and H_2SO_4 (Scheme 206).[242]



Scheme 204



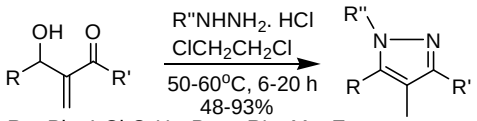
Scheme 205



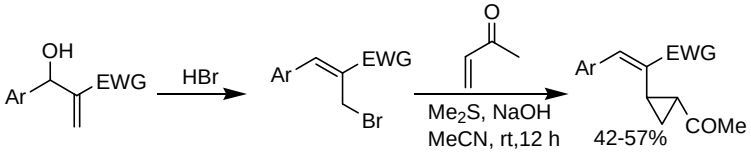
Scheme 206

Kim *et al*. described a regioselective synthesis of tetrasubstituted pyrazole derivatives (**349**) from the reaction of the Baylis-Hillman adducts of methyl vinyl ketone and hydrazine hydrochloride under conventional heating (Scheme 207).[243] Subsequently, Mamaghani and co-workers prepared the same pyrazoles under microwave irradiation.[244]

The transformation of cinnamyl bromides to cyclopropane derivatives (**350**) in moderate yields was reported by Kim and co-workers via a sequential *in situ* generation of the sulfur ylide and reaction with methyl vinyl ketone or 2-chloroacrylonitrile (Scheme 208).[245]

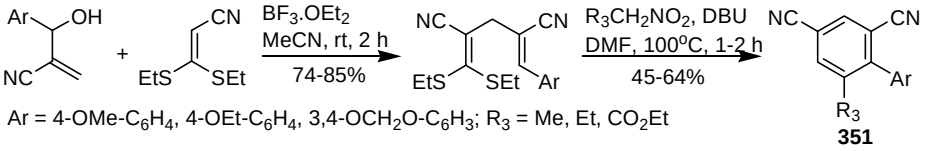


Scheme 207



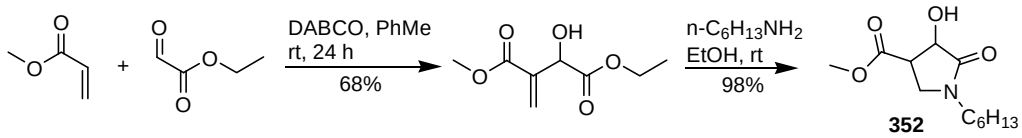
Scheme 208

Liu and co-workers described an efficient $BF_3.OEt_2$-catalyzed C-C coupling reaction between α-EWG ketene-(*S*,*S*)-acetals and various Baylis-Hillman alcohols which led to the synthesis of unsymmetrical biaryls (**351**) from the 1,4-pentadienes by a one-pot annulation-aromatization process (Scheme 209).[246]



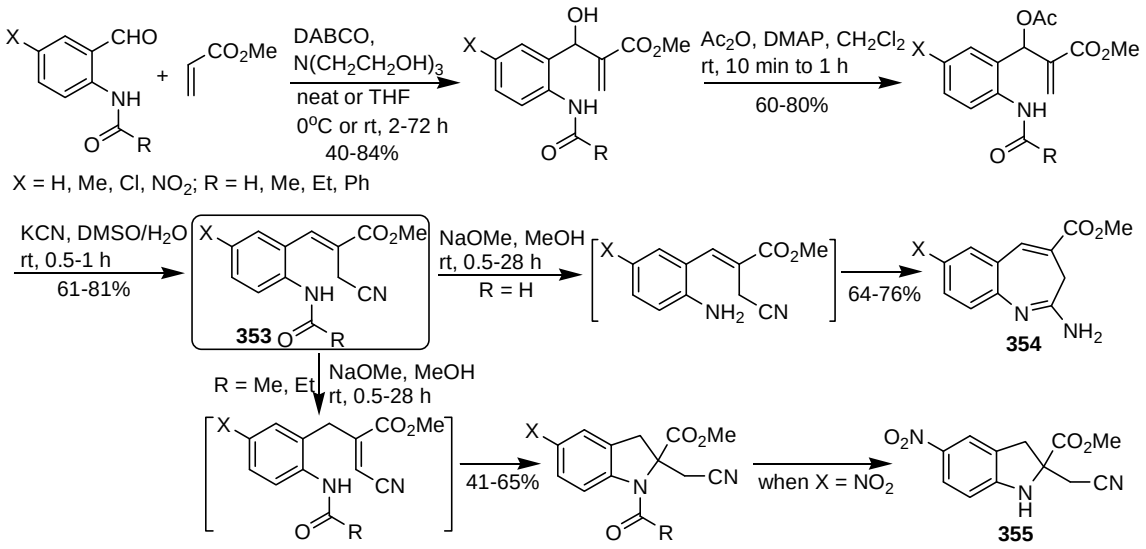
Scheme 209

Very recently, Morizur and Mathias described the synthesis of polyfunctional 2-pyrrolidinones such as (**352**) from methyl 2-(carboethoxyhydroxymethyl)acrylate via a Michael addition/cyclization reaction, as delineated in Scheme 210.[247]



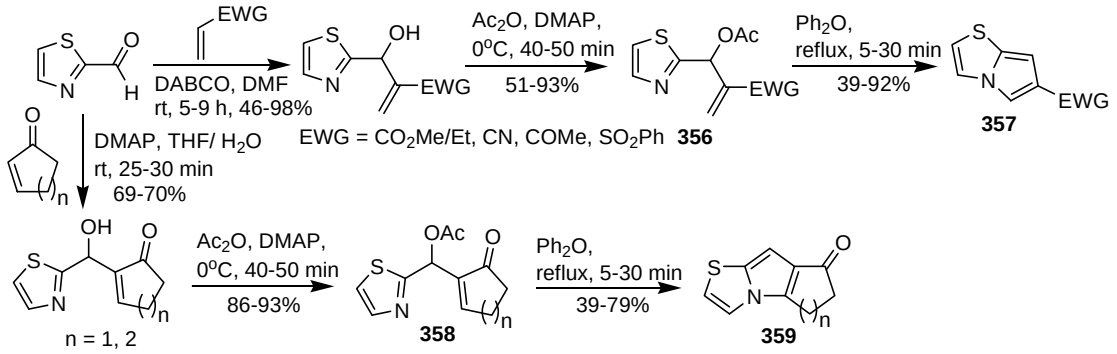
Scheme 210

Lee *et al*. reported the preparation of methyl 2-amino-3*H*-1-benzazepine-4-carboxylates (**354**) or methyl 2-(cyanomethyl)-2,3-dihydro-1*H*-indole-2-carboxylates (**355**) from the reaction of 3-[2-formamido-, 2-acetamido- or 2-(propanoylamino)phenyl]-substituted methyl 2-(cyanomethyl)propenoates (**353**) with sodium methoxide in methanol. The latter substrate was readily synthesized from the Morita–Baylis–Hillman reaction of *N*-protected 2-aminobenzaldehydes with methyl acrylate followed by acetylation and cyanation (Scheme 211).[248]



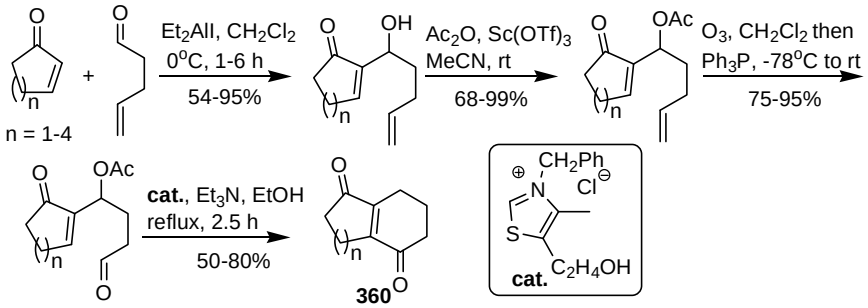
Scheme 211

Song and Lee reported a facile strategy for the synthesis of pyrrolo[2,1-b]thiazoles (**357**) involving the thermal cyclization of several acetyl derivatives of the Baylis-Hillman adducts of thiazole-2-carbaldehydes (**356**). The reaction was also successful with the Morita-Baylis Hillman acetates (**358**) obtained from 2-cyclopentenone and 2-cyclohexenone to yield the corresponding 5,6-dihydro-7*H*-cyclopenta[b]pyrrolo[2,1-b]thiazol-7-one and 6,7-dihydrothiazolo[3,2-a]indol-8(5*H*)-one (**359**), as shown in Scheme 212.[249]



Scheme 212

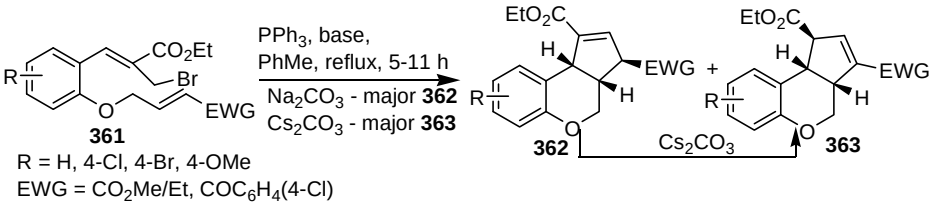
Marko and co-workers demonstrated that bicyclic enediones (**360**) of various sizes can be efficiently assembled by intramolecular Stetter cyclization of the readily available acetyl derivatives of Morita–Baylis–Hillman adducts of cyclic enones and 4-pentenal, as shown in Scheme 213.[250]



Scheme 213

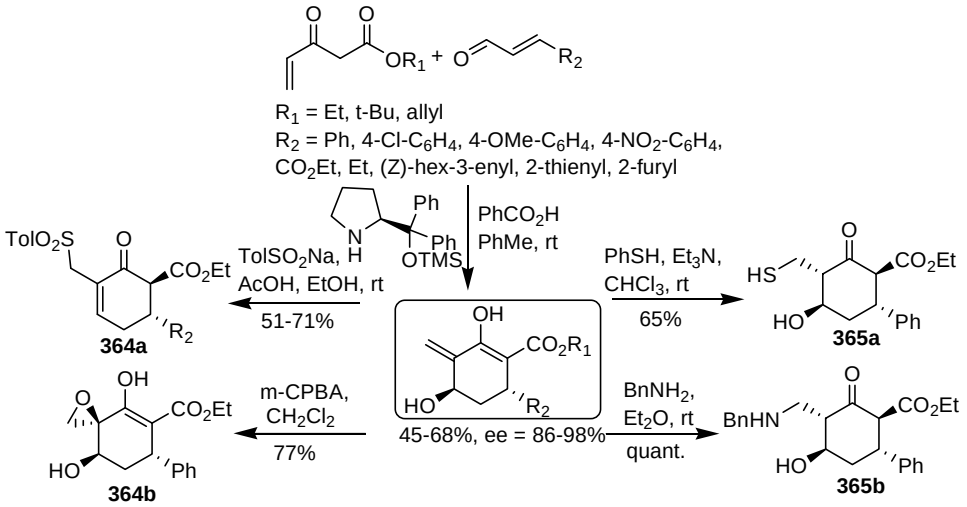
Tang *et al* described an exciting Ph_3P-catalyzed intramolecular ylide annulation of an allyl bromide derivative (**361**) for the construction of benzobicyclo[4.3.0] ring systems (**362** and **363**) with three continuous stereogenic centers in a single step. It was demonstrated that the same starting substrates could yield selectively benzobicyclo[4.3.0] products **362** or **363** by simply changing the base. By the use of Na_2CO_3, compound **362** was obtained as the major product, while Cs_2CO_3 yielded the product **363**. These workers also demonstrated that **362** isomerizes to **363** under the influence of a strong base and studied this transformation via a detailed ^{1}H-NMR experiment (Scheme 214). Mechanistically, it was proposed that Ph_3P

reacts with the bromide **361** to form an intermediate phosphonium salt, which was deprotonated by Cs_2CO_3, leading to the corresponding phosphonium ylide in situ. An intramolecular Michael addition of the ylide, followed by a Michael addition of the phosphonium salt and subsequent β-elimination of Ph_3P, afforded the required product.[251]



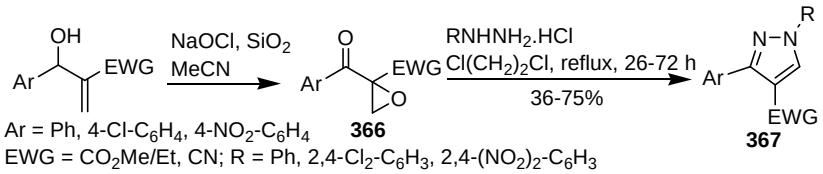
Scheme 214

Jorgensen and co-workers reported an unusual diarylprolinol ether-catalyzed tandem reaction of α,β-unsaturated aldehydes and Nazarov reagent following a Michael/Morita–Baylis–Hillman mechanism for the synthesis of various types of optically active cyclohexenone (**364)** and cyclohexanone (**365**) derivatives with up to four stereocenters (Scheme 215).[252]



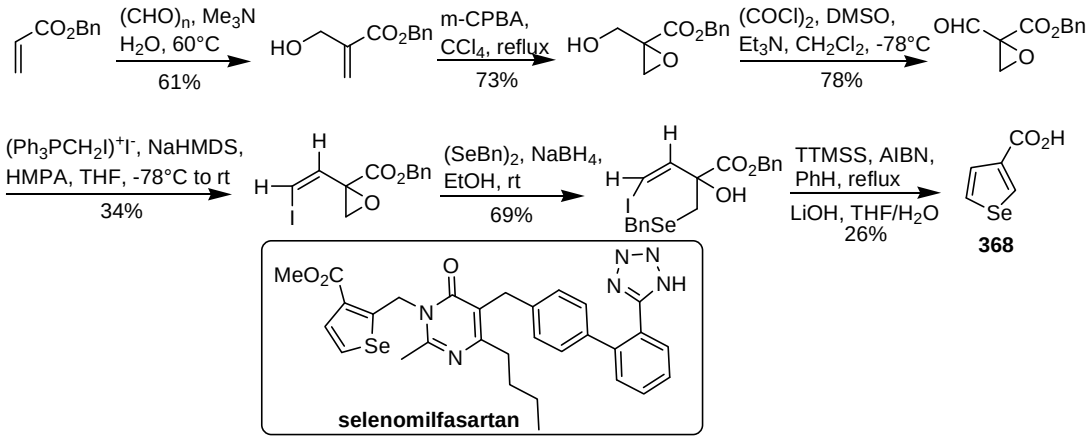
Scheme 215

Kim and his group utilized acyloxiranes (**366**) generated from the Baylis-Hillman adducts for the facile synthesis of 1,3,4-trisubstituted pyrazoles (**367**) via a reaction with hydrazine derivatives in dichloromethane, as shown in Scheme 216.[253]



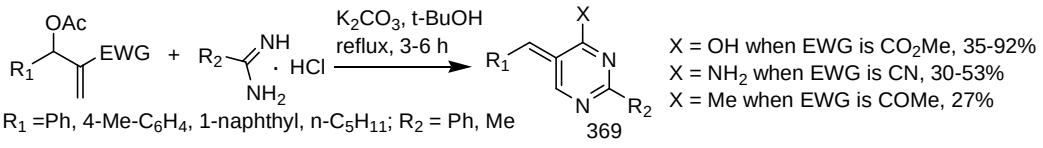
Scheme 216

Schiesser and co-workers also utilized the epoxide afforded by the Baylis-Hillman adducts to develop the synthesis of selenophene-3-carboxylic acid (**368**), as delineated in Scheme 217. This selenophene-3-carboxylic acid was further employed as substrate for obtaining selenomilfasartan, which proved to be a potent AT_1-receptor antagonist.[254]



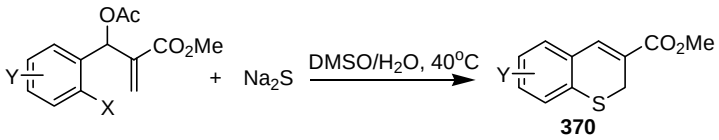
Scheme 217

Kim and co-workers transformed the Baylis-Hillman acetates into 2,4,5-trisubstituted pyrimidines (**369**) by reacting them with amidines, as delineated in Scheme 218. They reported that the yields of the substituted pyrimidines were better in the case of the derivatives of acrylates, as compared to those afforded by methyl vinyl ketone or acrylonitrile.[255]



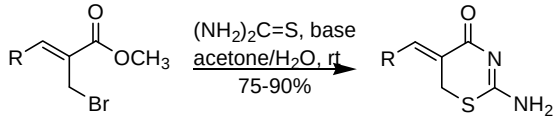
Scheme 218

Lee and co-workers reported synthesis of 3-carbomethoxy-2*H*-thiochromenes (**370**) from the acetyl derivatives of the Baylis Hillman adducts by reacting them with Na_2S in DMSO/H_2O, as shown in Scheme 219.[256]



Scheme 219

Very recently, Sa and co-workers reported a facile synthesis of 1,3-thiazin-4-ones (**371**) in high yields from the allyl bromides via a reaction of thiourea in the presence of a base under an aqueous medium (Scheme 220).[257]



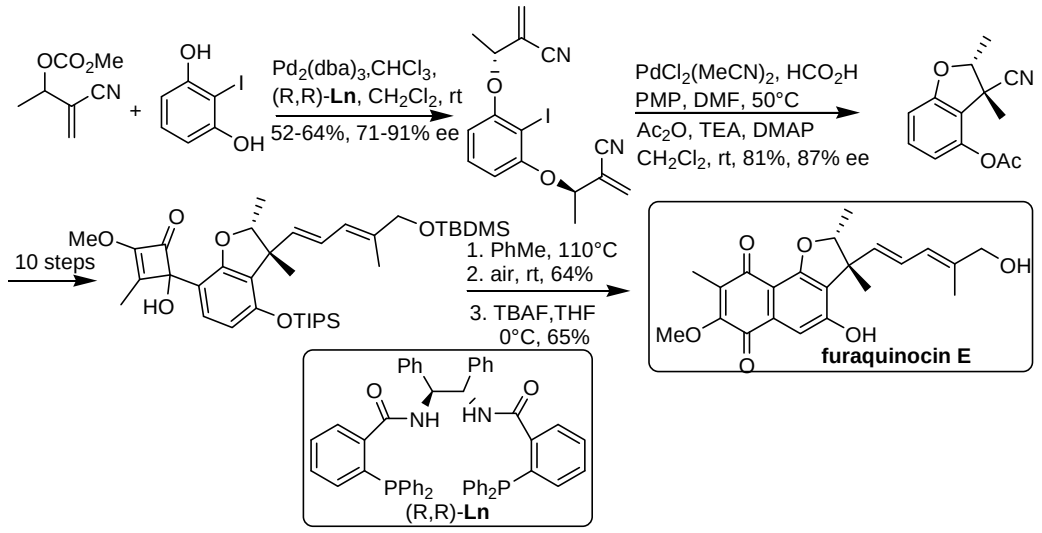
Scheme 220

21. Natural products

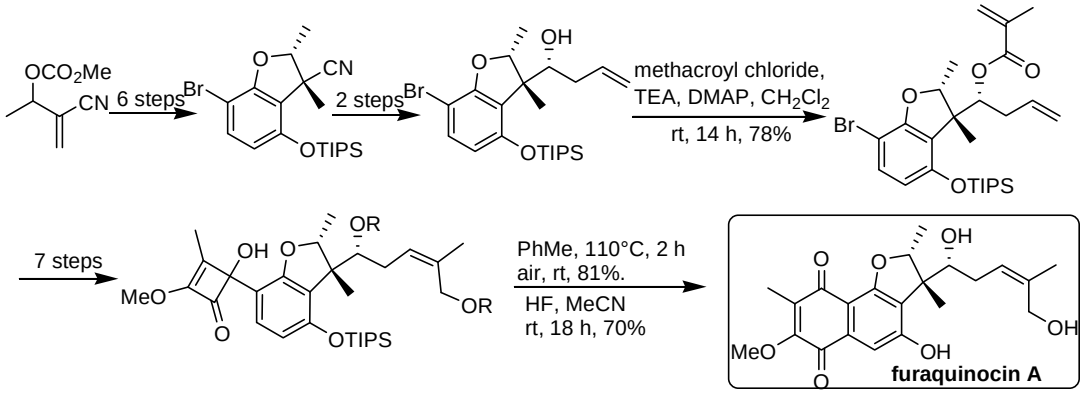
The functional attributes of the Baylis-Hillman adducts and their derivatives make them appropriate precursors to several complex natural products. This has also been elegantly exemplified by several research workers prior to 2003.[258]

Trost *et al*. have reported the DYKAT of Baylis-Hillman derivatives for the total synthesis of furaquinocin E.[259] They elegantly extended the scope of their strategy by developing the synthesis of furaquinocins A and B and three more analogues of furaquinocin E.[260] Their work highlighted the ability to use racemic Baylis-Hillman adducts for asymmetric synthesis (Schemes 221 222 and 223). Later, they successfully employed aliphatic alcohols as competent nucleophiles in the Pd-catalyzed DYKAT reactions, the utility of which was

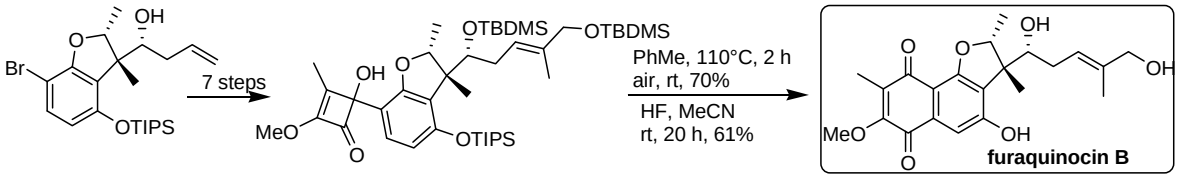
demonstrated via a concise total synthesis of the gastrulation inhibitor, (+)-hippospongic acid A, as shown in Scheme 224.[261]



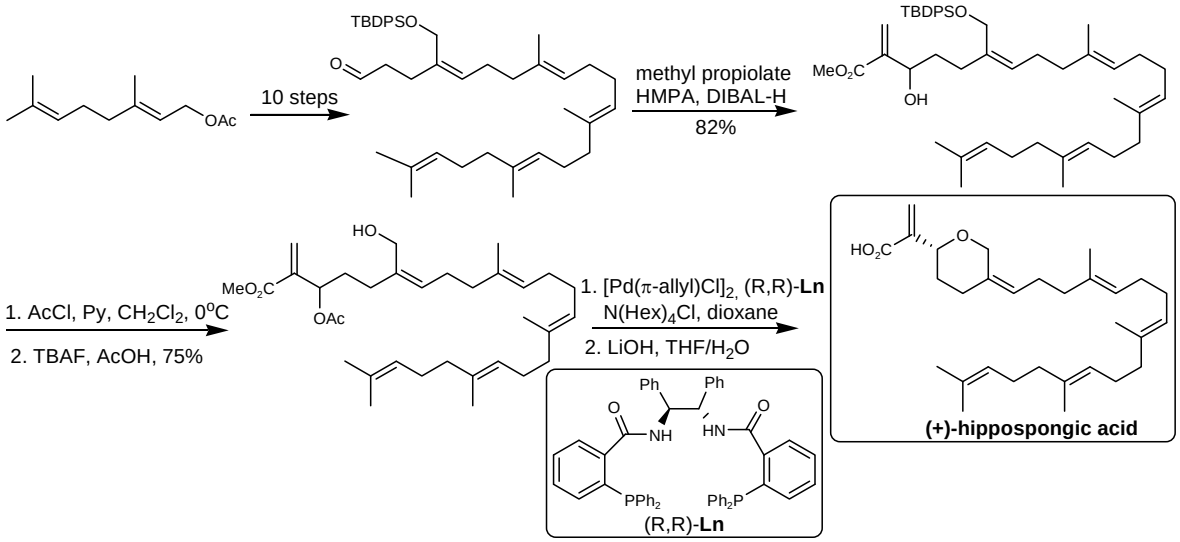
Scheme 221



Scheme 222

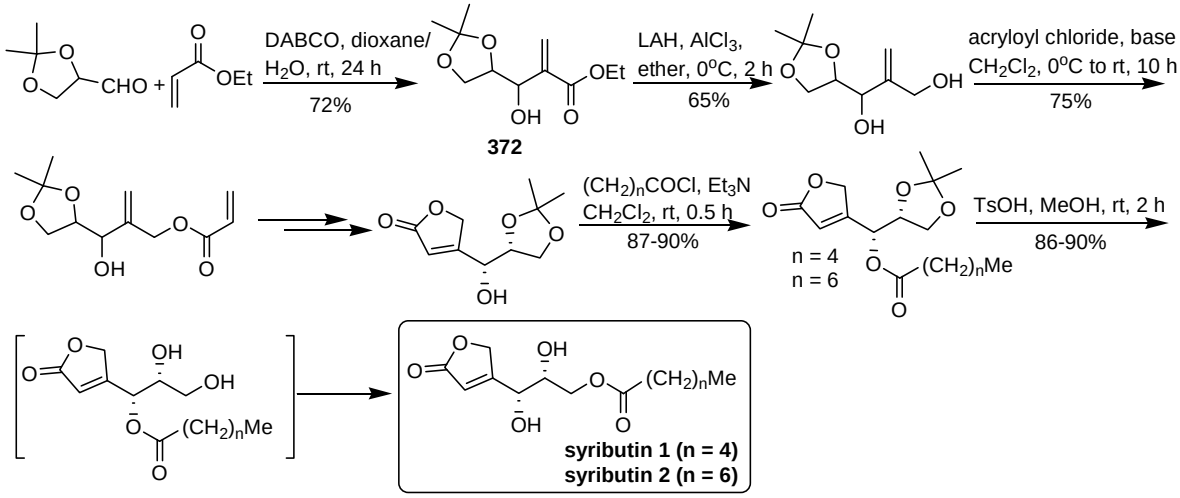


Scheme 223



Scheme 224

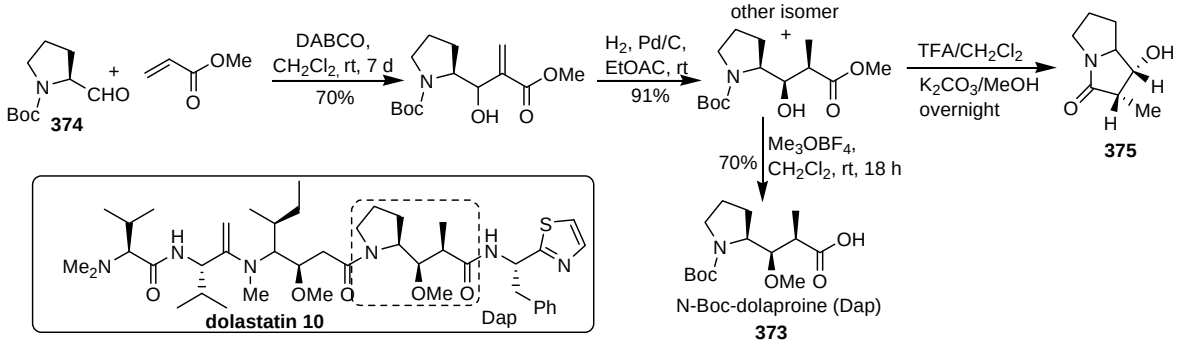
Krishna and co-workers successfully accomplished the total synthesis of syributins 1 and 2 using the Baylis-Hillman adduct of 2,3-O-isopropylidene-R-glyceraldehyde (**372**) as the starting material followed by ring-closing metathesis of the acrylate derivative of the resulting diol as the key step (Scheme 225).[262]



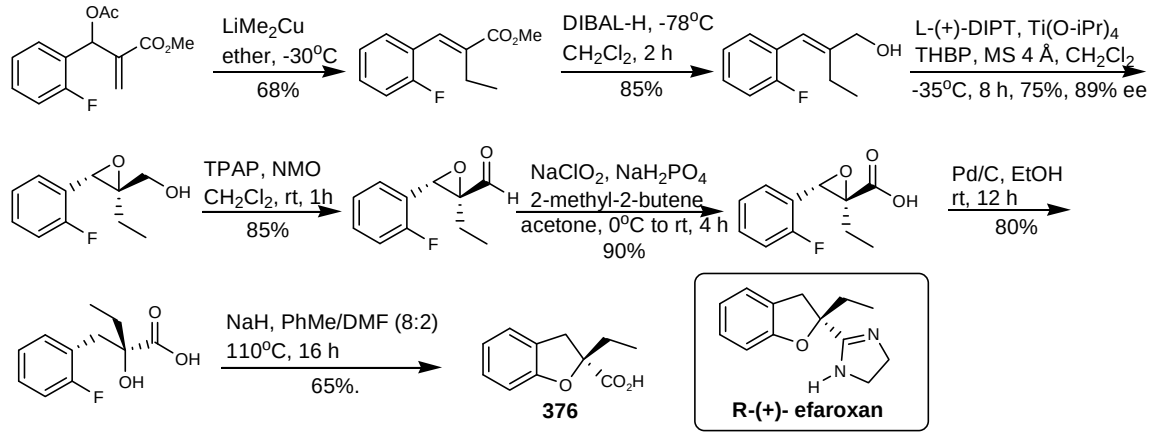
Scheme 225

Almeida and Coelho demonstrated a stereoselective synthesis of *N*-Boc dolaproine (Dap, **373**), an amino acid residue of the antineoplastic pentapeptide, dolastatin 10.[263] Their synthesis included a Baylis-Hillman reaction between *N*-Boc-prolinal (**374**) and methyl

acrylate, followed by a diastereoselective double-bond hydrogenation and hydrolysis of the ester moiety. In order to establish the configuration they subjected the intermediate to cyclization via a sequential TFA and K_2CO_3-mediated reaction to yield a lactam derivative (**375**) (Scheme 226). Later, Coelho and co-workers elegantly utilized the Baylis-Hillman adduct of 2-fluorobenzaldehyde and methyl acrylate, as a starting material for the straightforward, enantioselective synthesis of R-(+)-2-ethyl-2,3-dihydrofuran-2-carboxylic acid (**376**), the direct precursor of R-(+)-efaroxan, which is used for the treatment of neurodegenerative diseases (Alzheimer's or Parkinson's disease), migraine and type II (non-insulin dependent) diabetes (Scheme 227).[264]



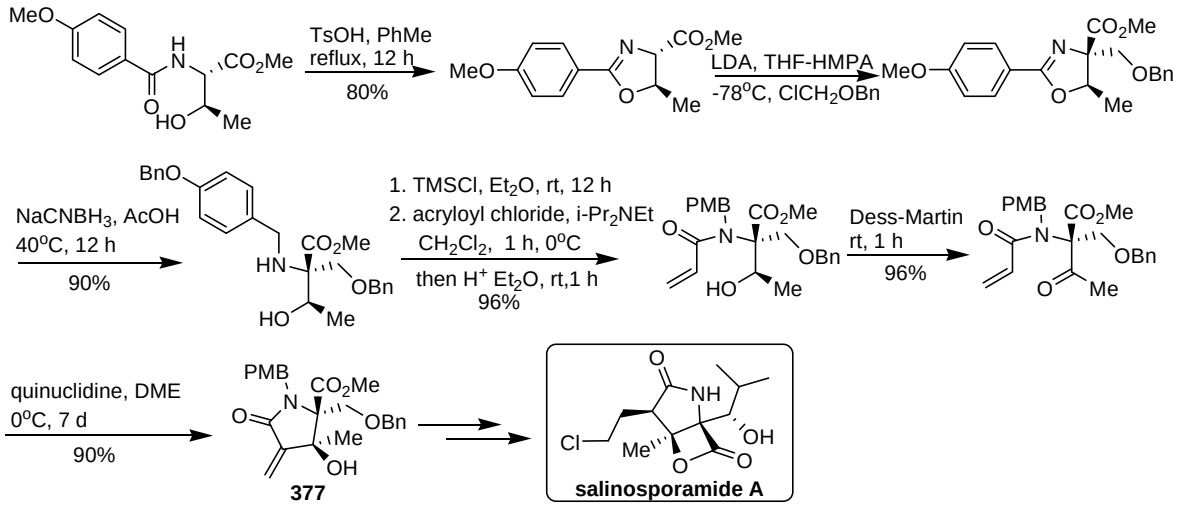
Scheme 226



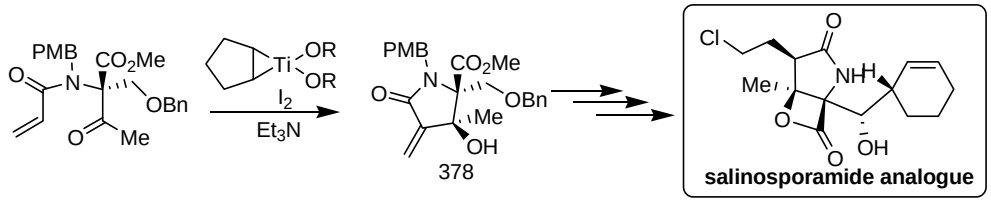
Scheme 227

Corey *et al.* utilized an intramolecular Baylis-Hillman reaction between keto and acrylamide for the cyclization to produce a highly substituted 4-methylene-5-oxo-

pyrrolidine derivative (**377**), which served as the starting material in the enantioselective total synthesis of salinosporamide A (Scheme 228).[265] As this key step was time consuming, they developed an attractive method using a Kulinkovich reagent followed by treatment with I_2 and, later, with Et_3N to yield the diastereomerically pure pyrrolidinone (**378**).[266] This was further utilized for the synthesis of a salinosporamide analogue (Scheme 229).

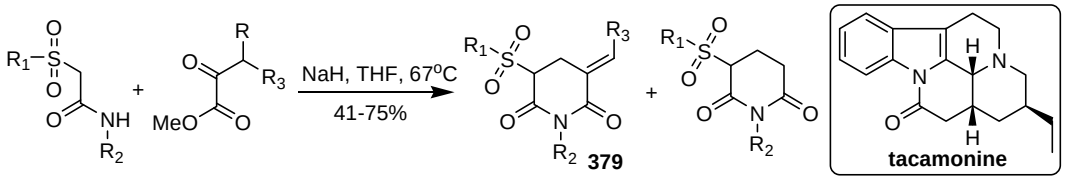


Scheme 228



Scheme 229

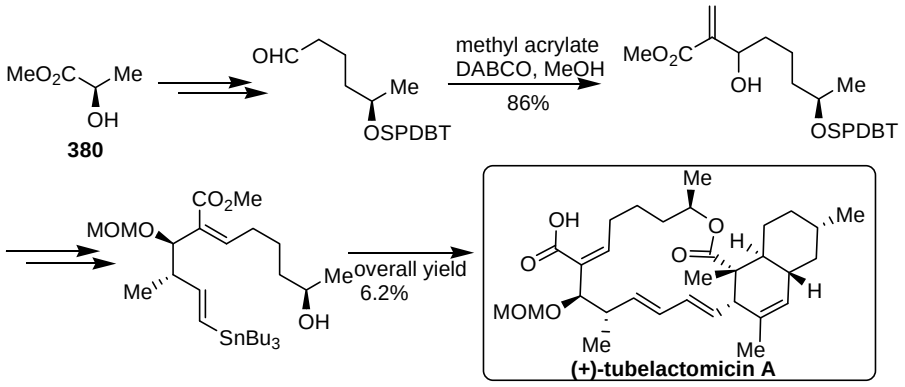
Chang and co-workers reported the synthesis of *N*-alkyl 3-(*E*)-alkylidene-5-substituted sulfonylpiperidine-2,6-diones (**379**) via a [3+3] annulation strategy which was used for a one-pot formal synthesis of tacamonine alkaloid, a vasodilator and hypotensive agent (Scheme 230).[267]



R = OH, OAc; R_1 = 4-Me-C_6H_4; R_2 = Me, allyl, n-Pr, Bn, $BnCH_2$, Trypt; R_3= Me, Ph

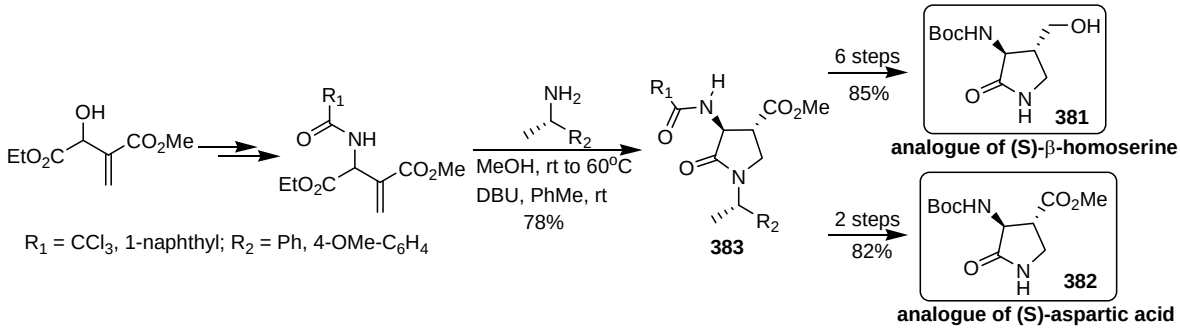
Scheme 230

Tadano and co-workers reported a total synthesis of natural (+)-tubelactomicin A, a 16-membered macrolide antibiotic, which comprised 54 total steps from methyl (*R*)-lactate (**380**) in 6.2% overall yield involving the Baylis-Hillman reaction as one of the key steps (Scheme 231).[268]



Scheme 231

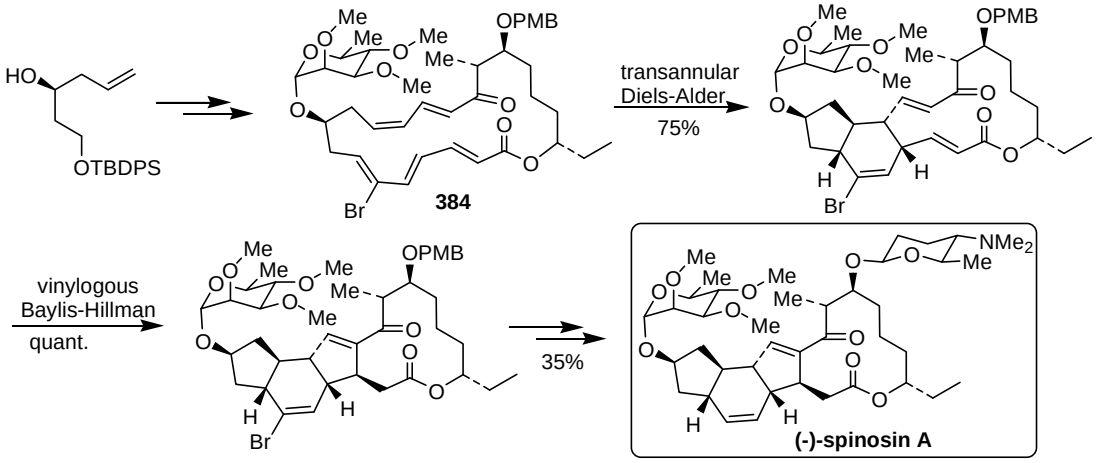
Subsequently, Orena and co-workers described the synthesis of conformationally restricted analogues of (S)-β-homoserine (**381**) and (S)-aspartic acid (**382**) starting from chiral 3,4-trans-disubstituted pyrrolidin-2-ones (**383**), which, in turn, were obtained from the Baylis–Hillman adducts, as shown in Scheme 232.[269]



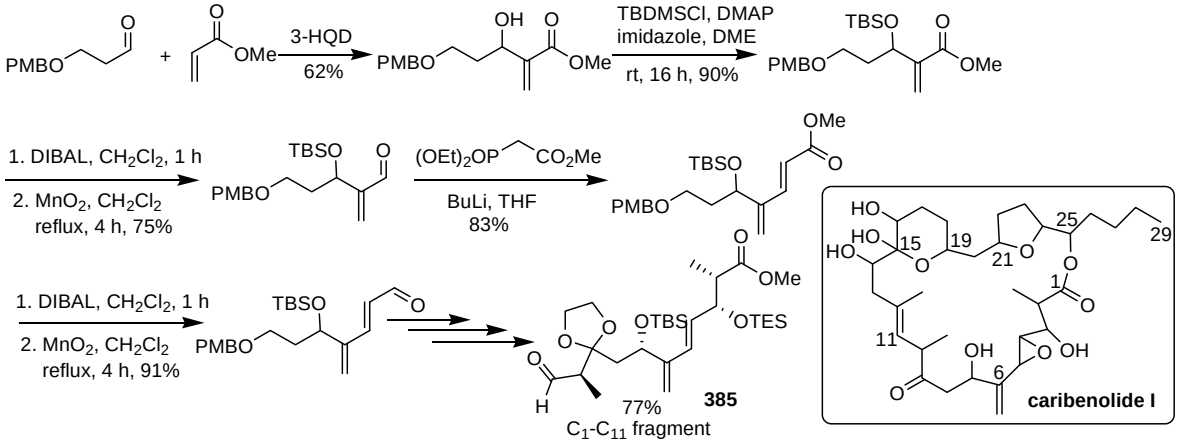
R_1 = CCl_3, 1-naphthyl; R_2 = Ph, 4-OMe-C_6H_4

Scheme 232

Franck *et al*. described a convergent, highly stereoselective total synthesis of (-)-spinosyn A, a polyketide natural product possessing an extraordinary insecticidal activity. The key feature of the synthesis included a transannular Diels-Alder reaction of a macrocyclic pentaene (**384**) and transannular vinylogous Morita-Baylis-Hillman cyclization to yield (-)-spinosin A (Scheme 233).[270] In addition, they successfully synthesized C_1-C_{11} the fragment (**385**) of caribenolide I, a 26-membered macrolactone that possesses *in vitro* cytotoxicity against human colon tumor cells, starting from the Baylis-Hillman reaction between 3-para-methoxybenzyloxypropanal and methyl acrylate in the presence of 3-hydroxyquinuclidine, as illustrated in Scheme 234.[271]



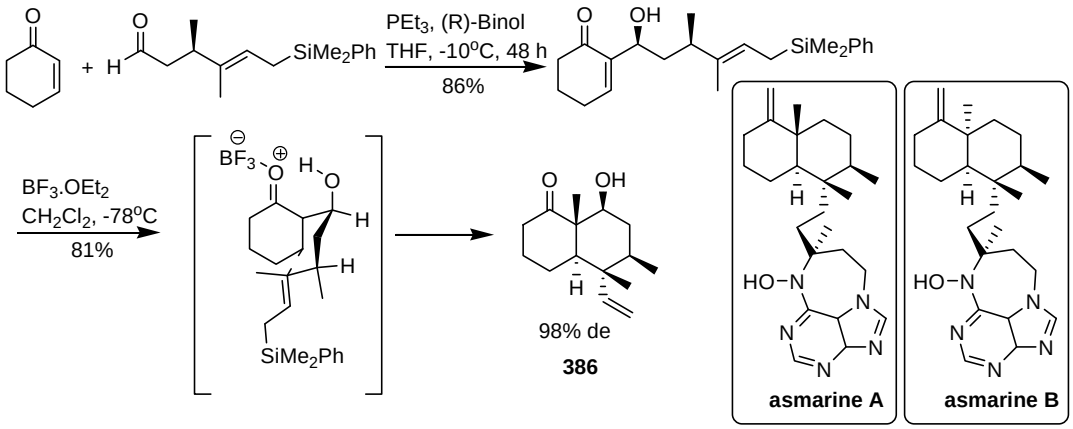
Scheme 233



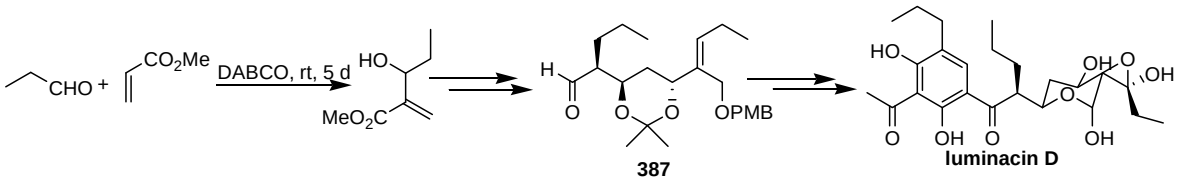
Scheme 234

Rodgen and Schaus reported an efficient route for the construction of the clerodane decalin core (**386**) of asmarines A and B using an asymmetric Baylis-Hillman reaction followed by a Lewis acid-mediated ring-annulation strategy, as shown in Scheme 235.[272]

Recently, Jogireddy and Maier have developed a novel route for the synthesis of luminacin D. The starting aldehyde (**387)** which was obtained by a simple Baylis-Hillman reaction between acetaldehyde and methyl acrylate, followed by OH transposition, was extended by two highly stereoselective asymmetric aldol reactions (Scheme 236).[273]

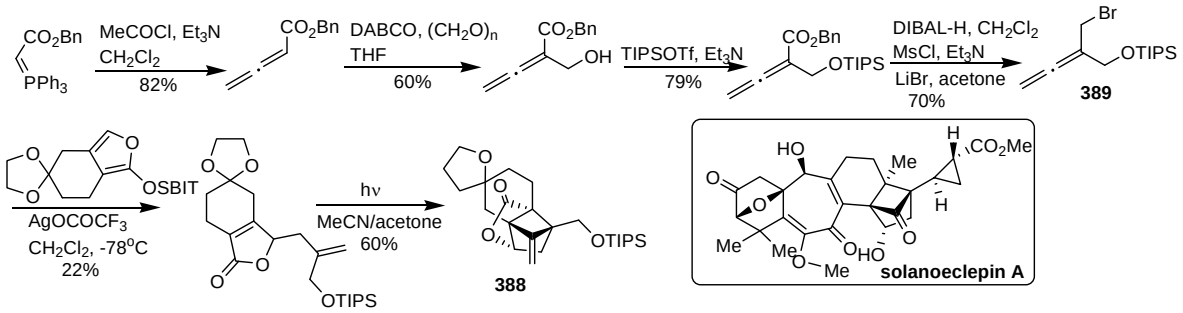


Scheme 235



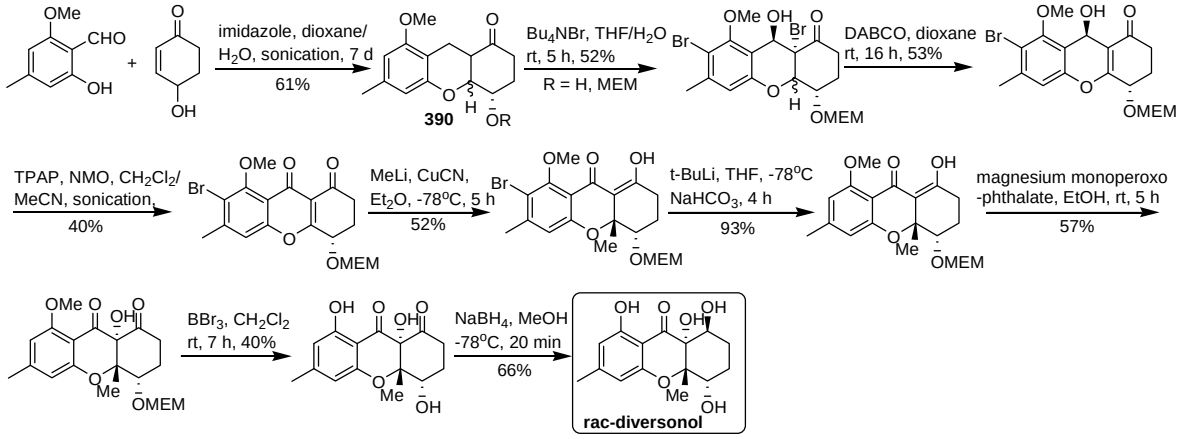
Scheme 236

Hiemstra *et al*. described the synthesis of the compact tricyclic core (**388**) of solanoeclepin A, a hatching agent of potato cyst nematodes. The total synthesis required the allenic bromide (**389**) which was prepared from the Baylis-Hillman adduct of allene (Scheme 237).[274]



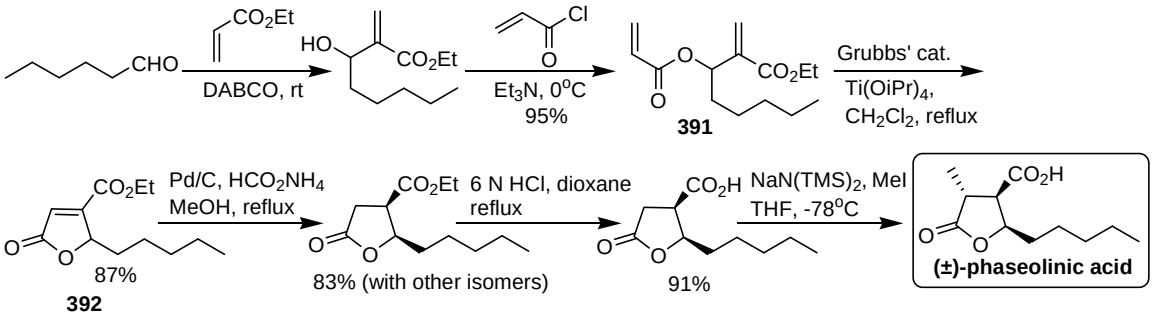
Scheme 237

Brase *et al.* have developed a synthetic route to tetrahydroxanthenone mycotoxins (**390**) via a domino oxa-Michael–aldol condensation. By applying this methodology, they achieved the first total synthesis of the secondary metabolite, diversonol, in a racemic form, as delineated in Scheme 238.[275]



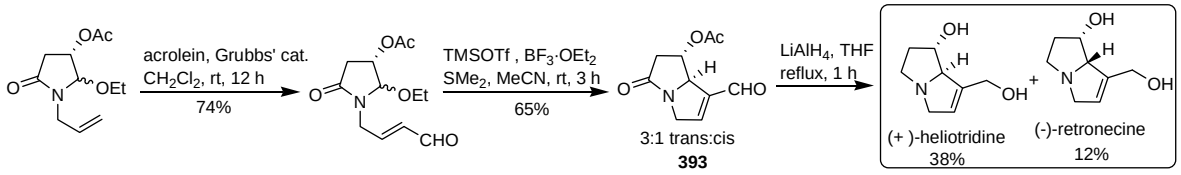
Scheme 238

Selvakumar and co-workers described an RCM reaction of electron-deficient dienes (**391**) for the synthesis of diverse butenolides (**392**) and employed this methodology in the total synthesis of (±)-phaseolinic acid, a natural product of the paraconic acid class (Scheme 239).[276]



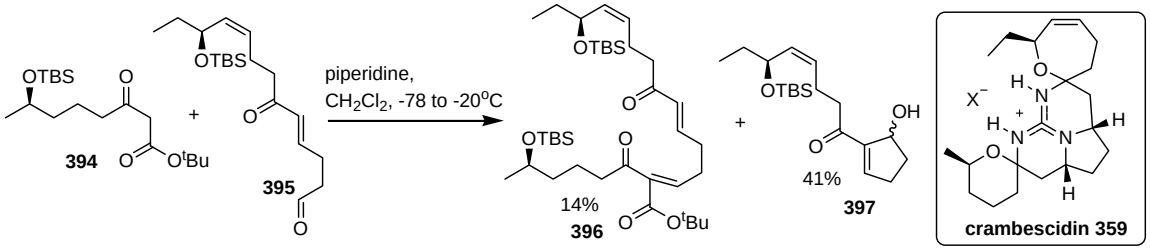
Scheme 239

Aggarwal and co-workers reported a novel methodology in which a broad range of Michael acceptors were allowed to couple with the readily available iminium ion in an inter- and intramolecular Morita-Baylis-Hillman-type reaction to afford densely functionalized heterocycles.[277] The iminium ions generally present as masked N,O-acetals were generated by TMSOTf, while $BF_3.Et_2O$ in the presence of Me_2S was used to accomplish the reaction. More importantly, the process was highly enantioselective for cyclic enones (**393**). By employing this methodology, they reported a short synthesis of (+)-heliotridine, as shown in Scheme 240.



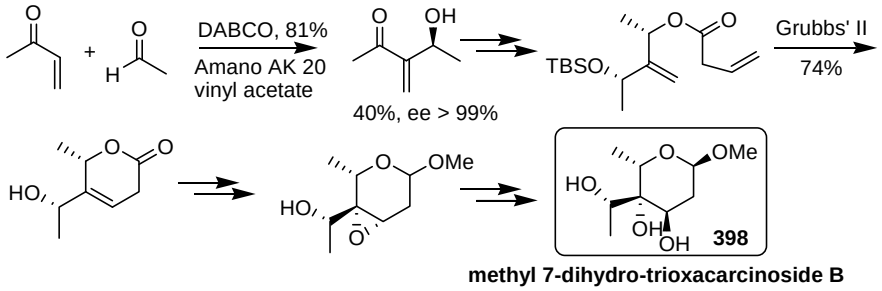
Scheme 240

Recently, Murphy and co-workers reported the formation of a side product **397** resulting from a Baylis-Hillman-type cyclization during the preparation of the diene **396** from the *t*-butyl acetate **394** and the aldehyde **395** in their endeavors to carry out a Knoevenagel condensation between **394** and **395** en route to the total synthesis of crambescidin 359 (Scheme 241).[278]



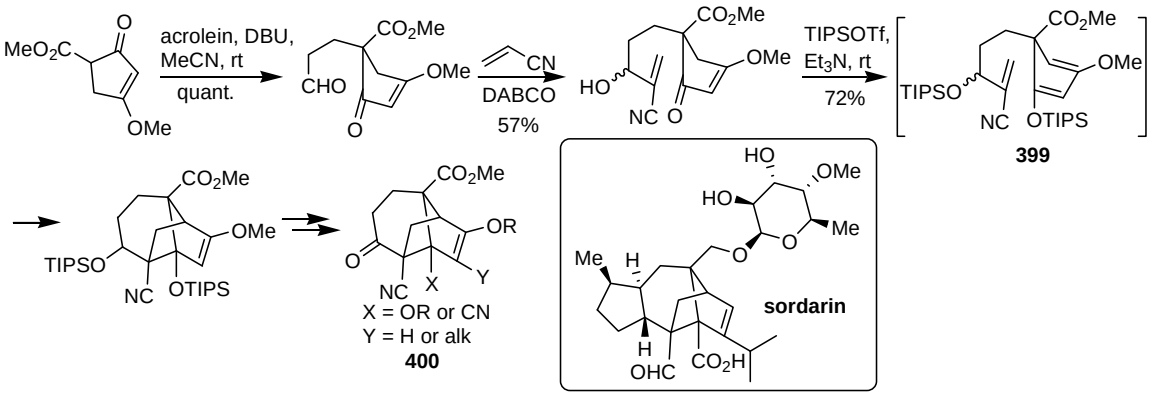
Scheme 241

Koert and his group utilized the Baylis-Hillman adduct to generate the molecular framework for the efficient stereoselective synthesis of methyl 7-dihydro-trioxacarcinoside B (**398**). The key steps in the process were biocatalytic resolution of the Baylis-Hillman adduct, RCM reaction, a substrate-controlled epoxidation, and stereo- and regio-controlled opening of epoxide by allyl alcohol, as shown in Scheme 242.[279]



Scheme 242

Ciufolini and co-workers utilized the Baylis-Hillman adducts to synthesize ketones **400,** via trialkylsilyl triflate/Et_3N-catalyzed cyclization, which served as useful building blocks for the preparation of analogs of the potent antifungal agent, sordarin. It was presumed that the exposure to TIPSOTf induces the formation of the bis-trialkylsilyl derivative **399,** which undergoes a spontaneous Diels-Alder reaction to furnish the expected product as mixture of diastereomers (Scheme 243).[280]



Scheme 243

Other natural products having open chain structures have also been synthesized employing Baylis-Hillman chemistry. These include (2*E*)-2-butyloct-2-enal,[281] cis-hedione and methyl jasmonate,[282] 4,5-dihydroxy-2,3-pentanedione (DPD),[283] and 5-O-acylated derivatives of DPD,[284] sitophilate,[285] (+)-(S)-manicone,[286] (+)-(S)-normanicone,[287] (+)-(S)-dominicalure-I and (+)-(S)-dominicalure-II,[288] 1-[p-(myristyloxy)-α-methylcinnamoyl]glycerol (LK-903),[289] F-3-2-5[290] and umbelactones.[291] These natural products are, however not discussed here in detail, as ther are beyond the scope of this review.

22. Conclusions

The expounding of the synthetic applications of the Baylis-Hillman adducts and their derivatives for the generation of cyclic compounds, besides a variety of other products, clearly establishes that this reaction has become a standard synthetic methodology in the arsenal of organic chemists. Figure 10 summarizes the different reaction strategies which have been discussed in this article for generating the cyclic compounds. Although tremendous advances have been achieved in this field, we firmly believe that the applications of the Baylis-Hillman derivatives to accomplish the synthesis of novel prototypes will continue to grow. Such growth will surely rely on discovering intelligent applications of the already reported strategies with little variations. Nevertheless, with a

view to enhance the development with respect to cyclic frameworks, there are still many opportunities which have not been explored explicitly. Some of these have been highlighted

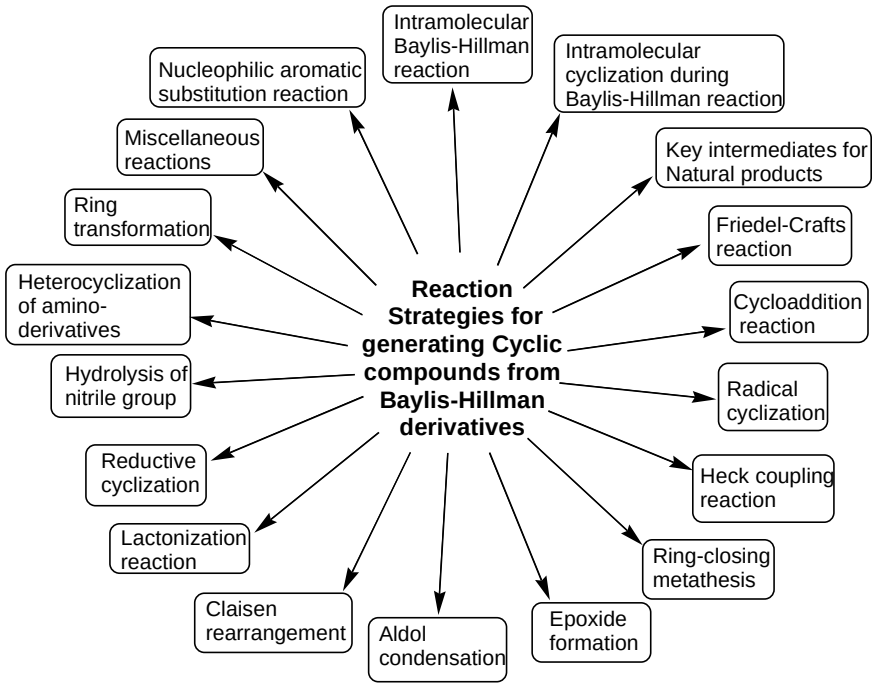


Figure 10. Reaction strategies employed on the Baylis-Hillman derivatives for the generation of the cyclic compounds.

in this report as they might motivate researchers across the boundaries.

The Baylis-Hillman derivatives originating from substituted heterocyclic aldehydes are excellent synthons for the synthesis of hetero-annulated or polycyclic ring systems bearing a resemblance either to natural products or bioactive molecules. Except for a few isolated reports, however, not many efforts have been made to generate cyclic frameworks in this fashion. It is likely that the behavior of the formyl group within the heterocycle for the Baylis-Hillman reaction might be an issue. Intriguingly, the formyl groups present at different positions in a heterocyclic aldehyde show distinctly different rates for this reaction and, to date, no experimental evidence has been provided to establish a reason behind such behavior.

There are still only a limited number of fast-reacting electrophiles discovered for the Baylis-Hillman reaction. On analysis of the publications related to the development of a new catalytic system or medium, it has been noted that most of the reports exemplify the case of substituted nitrobenzaldehydes, which are already known to be fast-reacting substrates for the Baylis-Hillman reaction. Hence, any such exercise would be more fruitful if the investigations are carried out over a range of substrates. The solid-phase methodologies for the Baylis-Hillman reaction are mostly limited to reactions of the acrylate resins with aldehydes. Due to the slow rate of reaction of different electrophiles, the building up of chemical libraries employing this reaction is cumbersome and the products are generally associated with impurities.

The synthetic potential of some of the intermediates which could be efficiently generated through this chemistry needs to be explored further. As an example, the N-formamide derivative generated from the primary allyl amines could be employed for the generation of isocyanides, which may, in turn, undergo different multicomponent reactions. Likewise, the Baylis-Hillman derivatives of sugar-based compounds could be effectively utilized for the generation of several sugar-heterocycle hybrid molecules for development of novel enzyme inhibitors.

To date, there have been more reports of the synthetic applications of the Baylis-Hillman chemistry rather than the utility of the generated products in various spheres of life. Probably due to this reason, it has not been considered essential to investigate the reported synthetic strategies for cyclization at higher scales. Therefore, it would be fruitful to discover the bio-properties in the plethora of compounds which have already been generated in this fashion and also examine the applications of these reaction strategies at higher scales.

Nevertheless, it can be extrapolated from the tremendous advances in the applications of the Baylis-Hillman derivatives that the fruits of such an exercise will ultimately lead to privileged compounds which would be fine tuned to the advantage of mankind.

Acknowledgments- One of the authors (VS) gratefully acknowledges the financial support from the CSIR, New Delhi in the form of a fellowship. We acknowledge the fruitful discussions carried out with Dr. A. P. Bhaduri during compilation of this manuscript. The work on synthesis of cyclic compounds via Baylis-Hillman chemistry in our laboratory is funded by DST, New Delhi.

CDRI Communication No. 7357

References

1. a) Schreiber, S. L. *Science* **2000**, *287*, 1964; b) Burke, M. D.; Berger, E. M.; Schreiber, S. T.; *Science* **2003**, *302*, 613.
2. Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev*. **2007**, *36*, 1581.
3. a) Morita, K. Japan Patent 6803364, 1968; *Chem. Abstr.* **1968**, *69*, 58828s; b) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.
4. Baylis, A. B.; Hillman, M. E. D.; German Patent 2155113, 1972; *Chem. Abstr*. **1972**, *77*, 34174q.
5. Drewes, S. E.; Emslie, N. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2079.
6. Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed.* **1983**, *22*, 795.
7. Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.
8. Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.
9. Ciganek, E., *In Org. React.*; Paquette, L. A., Ed.; John Wiley & Sons: New York, **1997**; Vol. 51, pp 201.
10. Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev*. **2003**, *103*, 811.
11. Langer, P. *Angew. Chem.*, *Int. Ed.* **2000**, *39*, 3049.
12. Kim, J. N.; Lee, K. Y. *Curr. Org. Chem*. **2002**, *6*, 627.

13. a) Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905. b) Shi, Y.-L.; Shi, M. *Org. Biomol. Chem.* **2007**, 5, 1499.
14. Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed*. **2007**, *46*, 4614.
15. Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed.* **1983**, *22*, 795.
16. a) Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett*. **1986**, *27*, 5007; b) Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem*. **1990**, *3*, 285.
17. Bode, M. L.; Kaye, P. T. *Tetrahedron Lett.* **1991**, *32*, 5611.
18. Price, K. E.; Broadwater, S. J.; Jung, H. M.; McQuade, D. T. *Org. Lett*. **2005**, *7*, 147.
19. Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980.
20. Xu, J. *Theochem* **2006**, *767*, 61.
21. Roy, D.; Sunoj, R. B. *Org. Lett*. **2007**, *9*, 4873.
22. Robiette, R.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc*. **2007**, *129*, 15513.
23. a) Black, G. P.; Dinon, F.; Fratucello, S.; Murphy, P. J.; Nielsen, M.; Williams, H. L.; Walshe, N. D. A. *Tetrahedron Lett.* **1997**, *38*, 8561; b) Dinon, F.; Richards, E.; Murphy, P. J.; Hibbs, D. E.; Hursthouse, M. B.; Malic, K. M. A. *Tetrahedron Lett.* **1999**, *40*, 3279. c) Richards, E. L.; Murphy, P. J.; Dinon, F.; Fratucello, S.; Brown, P. M.; Gelbrich, T.; Hursthouse, M. B. *Tetrahedron* **2001**, *57*, 7771.
24. Methot, J. L.; Roush, W. R. *Org. Lett*. **2003**, *5*, 4223
25. Yeo, J. E.; Yang, X.; Kim, H. J.; Koo, S. *Chem. Commun.* **2004**, 236.
26. Krishna, P. R.; Kannan, V.; Sharma, G. V. M. *J. Org. Chem.* **2004**, *69*, 6467.
27. Aroyan, C. E. Vasbinder, M. M.; Miller, S. J. *Org. Lett*. **2005**, *7*, 3849.
28. Seidel, F.; Gladysz, J. A. *Synlett* **2007**, 986
29. Jellerichs, B. G.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc*. **2003**, *125*, 7758.
30. Krafft, M. E.; Haxell, T. F. N. *J. Am. Chem. Soc.* **2005**, *127*, 10168.
31. Krafft, M. E.; Haxell, T. F. N.; Seibert, K. A.; Hirosawa, C. *Chem. Commun.* **2005**, 5772.
32. Krafft, M. E.; Haxell, T. F. N.; Seibert, K. A.; Abboud, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4174.
33. Krafft, M. E.; Seibert, K. A. *Synlett* **2006**, 3334.
34. Krafft, M. E.; Wright, J. A. *Chem. Commun.* **2006**, 2977.
35. Chen, S.-H.; Hong, B.-C.; Sua, C.-F.; Sarshar, S. *Tetrahedron Lett*. **2005**, *46,* 8899.
36. Pigge, F. C.; Dhanya, R.; Hoefgen, E. R. *Angew. Chem. Int. Ed*. **2007**, *46*, 2887.
37. Basavaiah, D.; Rao, A. J. *Chem. Commun.* **2003**, 604.
38. Basavaiah, D.; Rao, A. J. *Tetrahedron Lett*. **2003**, *44*, 4365.

39. Coelho, F.; Diag, G.; Abella, C. A. M.; Almeida, W. P. *Synlett* **2006**, 435.
40. a) Clive, D. L. J.; Yu, M.; Li, Z. *Chem. Commun*. **2005**, 906; b) Clive, D. L. J.; Li, Z.; Yu, M.; *J. Org Chem*. **2007**, *72*, 5608.
41. Virieux, D.; Guillouzic, A.-F.; Cristau H.-J. *Tetrahedron* **2006**, *62*, 3710.
42. Song, Y. S.; Lee, C. H.; Lee, K.-J. *J. Heterocycl. Chem*. **2003**, *40*, 939.
43. Yi, H.-W.; Park, H. W.; Song, Y. S.; Lee, K.-J. *Synthesis* **2006**, 1953.
44. Pan, W.; Dong, D.; Sun, S.; Liu, Q. *Synlett* **2006**, 1090.
45. Lee, K. Y.; Kim, J. M.; Kim, J. N. *Synlett* **2003**, 357.
46. Kaye, P. T.; Musa, M. Y.; Nocanda, X. W. *Synthesis* **2003**, 531.
47. Kaye, P. T.; Musa, M. A. *Synth. Commun.* **2003**, *33*, 1755.
48. Lee, K. Y.; Kim, J. M.; Kim, J. N. *Bull. Korean Chem. Soc*. **2003**, *24*, 17.
49. Lesch, B.; Brase, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 115.
50. Nising, C. F.; Ohhemuller, U. K. Friedrich, A.; Lesch, B.; Steiner, J.; Schnockel, H.; Nieger, M.; Brase, S. *Chem. Eur. J.* **2006**, *12*, 3647.
51. Ohhemuller, U. K.; Nising, C. F.; Nieger, M.; Brase, S. *Eur. J. Org. Chem*. **2006**, 1535.
52. Shi, Y-L.; Shi, M. *Synlett*, **2005**, 2623.
53. Shi, Y.-L.; Shi, M. *Org. Lett*. **2005**, *7*, 3057.
54. Guo,Y.-W.; . Shi, Y.-L.; Li, H.-B.; Shi, M. *Tetrahedron* **2006**, *62*, 5875.
55. Shi, Y.-L.; Shi, M. *Chem. Eur. J*. **2006**, *12*, 3374.
56. Qi, M.-J.; Shi, M. *Tetrahedron* **2007**, *63*, 10415.
57. Shah, B. A.; Taneja, S. C.; Sethi, V. K.; Gupta, P.; Andotra, S. S.; Chimnib, S. S.; Qazi, G. N. *Tetrahedron Lett*. **2007**, *48*, 955.
58. Rios, R.; Sunden, H.; Ibrahem, I.; Zhao, G.-L.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 8679.
59. Rios, R.; Sunden, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 8547.
60. a) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.*, **2006**, *128*, 10354; b) Zu, L.; Wang, J.; Li, H.; Xie, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036.
61. Kinoshita, H.; Kinoshita, S.; Munechika, Y.; Iwamura, T.; Watanabe, S.-i.; Kataoka, T. *Eur. J. Org. Chem*. **2003**, *24*, 4852.
62. a) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Kim, H. S. *Tetrahedron Lett.* **2001**, *42*, 3737; b) Chung, Y. M.; Lee, H. J.; Hwang, S. S.; Kim, J. N. *Bull. Korean Chem. Soc*. **2001**, *22*, 799.

63. a) Kim, J. N.; Kim, H. S.; Gong, J. H.; Chung, Y. M. *Tetrahedron Lett*. **2001**, *42*, 8341; b) Kim, J. N.; Im, Y. J.; Gong, J. H.; Lee, K. Y. *Tetrahedron Lett*. **2001**, *42*, 4195; c) Im, Y. J.; Chung, Y. M.; Gong, J. H.; Kim, J. N. *Bull. Korean Chem. Soc*. **2002**, *23*, 787.
64. Hong, W. P.; Lee, K.-J. *Synthesis* **2005**, 33.
65. Horn, C. R.; Perez, M. *Synlett* **2005**, 1480.
66. Hong, W. P.; Lee, K.-J. *Synthesis* **2006**, 963.
67. Narender, P.; Srinivas, U.; Ravinder, M.; Rao, B. A.; Ramesh, C.; Harakishore, K.; Gangadasu, B. U.; Murthy, S. N.; Rao, V. J. *Bioorg. Med. Chem.* **2006**, *14,* 4600.
68. a) Basavaiah, D.; Pandiaraju, S.; Padmaja, K. *Synlett* **1996**, 393; b) Basavaiah, D.; Krishnamacharyulu, M.; Suguna Hyma, R.; Pandiaraju, S. *Tetrahedron Lett*. **1997**, *38*, 2141.
69. a) Basavaiah, D.; Bakthadoss, M.; Jayapal Reddy, G. *Synthesis* **2001**, 919; b) Basavaiah, D.; Mallikarjuna Reddy, R. *Tetrahedron Lett.* **2001**, *42*, 3025; c) Lee, H. J.; Kim, T. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2001**, *22*, 1063; d) Basavaiah, D.; Bakthadoss, M.; Pandiaraju, S. *Chem. Commun.* **1998**, 1639; e) Roy, O.; Riahi, A.; Henin, F.; Muzart, J. *Tetrahedron* **2000**, *56*, 8133.
70. Basavaiah, D.; Satyanarayana, T. *Chem. Commun.* **2004**, 32.
71. Basavaiah, D.; Sharada, D. S.; Veerendhar, A. *Tetrahedron Lett.* **2004**, *45*, 3081.
72. Das, B.; Majhi, A.; Banerjee, J.; Chowdhury, N.; Holla, H.; Harakishore, K.; Murty, U. S. *Chem. Pharm. Bull*. **2006**, *54*, 403.
73. GowriSankar, S.; Lee, K. Y.; Lee, C. G.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 6141.
74. Lee, C. G.; Lee, K. Y.; GowriSankar, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 7409.
75. Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc*. **2005**, *26*, 1112.
76. Shanmugam, P.; Rajasingh, P. *Chem. Lett*. **2005**, *34*, 1494.
77. Hong, W. P.; Lim, H. N.; Park, H. W.; Lee, K.-J. *Bull. Korean Chem. Soc*. **2005**, *26*, 655.
78. Lee, K. Y.; Kim, S. C.; Kim, J. N. *Tetrahedron Lett*. **2006**, *47*, 977.
79. Lee, K. Y.; Seo, J.; Kim, J. N. *Tetrahedron Lett*. **2006**, *47*, 3913.
80. Lim, H. N.; Ji, S.-H.; Lee, K. J. *Synthesis* **2007**, 2454.
81. Das, B.; Chowdhury, N.; Damodar, K.; Benerjee, J. *Chem. Pharm. Bull.* **2007**, *55*, 1274.
82. Rajan, Y. C.; Kanakam, C. C.; Selvam, S. P.; Murugesan, K. *Tetrahedron Lett*. **2007**, *48*, 8562.
83. a) Kanemasa, S.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2685; b) Micuch, P.; Fisera, L.; Cyranski, M. K.; Krygowski, T. M. *Tetrahedron Lett.* **1999**, *40*, 167; c) Micuch, P.; Fisera, L.; Cyranski, M. K.; Krygowski, T. M.; Krajcik, J. *Tetrahedron* **2000**, *56*, 5465.

84. Dugovic, B.; Fisera, L.; Hametner, C.; Cyranski, M. K.; Pronayova, N. *Monatshefte fur Chemie* **2004**, *135*, 685.
85. Dugovic, B.; Fisera, L; Hametner, C; Pronayova, N *ARKIVOC* **2003**, 162.
86. Das, B.; Mahender, G. Holla, H. Banerjee, J. *ARKIVOC* **2005**, 27.
87. Jayashankaran, J.; Manian, R. D. R. S.; Sivaguru, M.; Raghunathan, R. *Tetrahedron Lett.* **2006**, *47*, 5535.
88. Ramesh, E.; Kathiresan, M.; Raghunathan, R. *Tetrahedron Lett*. **2007**, *48*, 1835.
89. Sreedhar, B.; Reddy, P. S.; Kumar, N. S. *Tetrahedron Lett.* **2006**, *47*, 3055.
90. Chandrasekhar, S.; Basu, D.; Rambabu, C. *Tetrahedron Lett.* **2006**, *47*, 3059.
91. Cho, H. I.; Lee, S. W.; Lee K. J. *J. Heterocycl. Chem*. **2004**, *41*, 799.
92. Ko, S. H.; Lee K. J. *J. Heterocycl. Chem.* **2004**, *41*, 613.
93. Song, Y. S.; Lee, K.-J. *J. Heterocycl. Chem.* **2006**, *43*, 1721.
94. Ji, S. H.; Hong, W. P.; Ko, S.-H.; Lee K. J. *J. Heterocycl. Chem.* **2006**, *43*, 799.
95. Shanmugam, P.; Viswambharan, B.; Madhavan, S. *Org. Lett.* **2007**, *9*, 4095.
96. Bakthadoss, M.; Sivakumar, N.; Sivakumar, G.; Murugan, G. *Tetrahedron Lett.* **2007**, *49*, 820.
97. Ramesh, E.; Raghunathan, R. *Tetrahedron Lett*. **2008**, *49*, 1125.
98. Aggarwal, V. K.; Patin, A.; Tisserand, S. *Org. Lett*. **2005**, *7*, 2555.
99. Nair, V.; Abhilash, K. G. *Synthesis* **2005**, 1967.
100. Du, Y.; Lu, X.; Zhang, C. *Angew. Chem. Int. Ed*. **2003**, *42*, 1035.
101. Du,Y.; Feng, J.; Lu, X. *Org. Lett*. **2005**, *7*. 1987.
102. Feng, J.; Lu, X.; Kong, A.; Han. X. *Tetrahedron*. **2007**, *63*. 6035.
103. Mix, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 2015.
104. Song, H. S.; Song, Y. S.; Lee, K.-J. *J. Heterocycl. Chem*. **2006**, *43*, 1533.
105. Kobbelgaard, S.; Brandes, S.; Jorgensen, K. A. *Chem Eur. J.* **2008**, *14*, 1464.
106. Park, D. Y.; Kim, S. J.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett*. **2006**, *47*, 6315.
107. Kim, S. C.; Lee, H. S.; Lee, Y. J.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47,* 5681.
108. a) Lee, M. J.; Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 1355; b) Lee, M. J.; Lee, K. Y.; Park, D. Y.; Kim, J. N. *Tetrahedron* **2006**, *62*, 3128.
109. Park, D. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 6641.
110. Park, D. Y.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 1633.
111. Zhao, G.-L.; Huang, J.-W.; Shi, M. *Org. Lett*. **2003**, *5*, 4737.
112. Shi, M.; Zhao G.-L. *Adv. Synth. Catal*. **2004**, *346*, 1205.
113. Zhao, G.-L.; Shi, M. *J. Org. Chem.* **2005**, *70*, 9975.

114. Shi, M.; Zhao G.-L *Org. Biomol. Chem*. **2005**, *3*, 3686.
115. Kim, S. C.; Lee, K.Y.; Lee, H. S.; Kim, J. N. *Tetrahedron* **2008**, *64*, 103.
116. Shanmugam, P.; Rajasingh, P. *Tetrahedron* **2004**, *60*, 9283.
117. Shanmugam, P.; Rajasingh, P. *Synlett* **2005**, 939.
118. Shanmugam, P.; Rajasingh, P. *Tetrahedron Lett*. **2005**, *46*, 3369.
119. Shanmugam, P.; Rajasingh, P.; Viswambharan, B.; Vaithiyanathan, V. *Synth. Commun.* **2007**, *37*, 2291.
120. Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett*. **2005**, *46*, 4859; b) Gowrisankar, S.; Kim, S. J.; Kim, J. N. *Tetrahedron Lett*. **2007**, *48*, 289.
121. Gowrisankar, S.; Lee, K. Y.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett*. **2006**, *47*, 5785.
122. Gowrisankar, S.; Lee, H. S.; Kim, J. N. *Bull. Korean Chem. Soc*. **2006**, *27*, 2097.
123. Gowrisankar, S.; Lee H. S.; Kim, J. N. *Tetrahedron Lett*. **2007**, *48*, 3105.
124. Park, D. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1440.
125. Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 929.
126. Singh, V.; Batra, S. *Tetrahedron Lett*. **2006**, *47*, 7043.
127. Majhi, T. P.; Neogi, A.; Ghosh, S.; Mukherjee, A. K.; Chattopadhyay, P. *Tetrahedron* **2006**, *62*, 12003.
128. Gowrisankar, S.; Kim, S. J.; Lee, J.-E.; Kim, J. N. *Tetrahedron Lett*. **2007**, *48*, 4419.
129. Erkoc, S.; Mathias, L. J.; Acar, A. E. *Macromolecules* **2006**, *39,* 8936.
130. Gowrisankar,S.; Lee, H. S.; Kim, J. N. *Bull. Korean Chem. Soc*. **2007**, *28*, 2501.
131. Lee, H.–S., Kim, H.-S., Kim, J.–M., Kim, J.–N. *Tetrahedron* **2008**, *64*, 2397.
132. a) Basavaiah, D.; Muthukumaran, K. *Tetrahedron* **1998**, *54*, 4943; b) Sundar, N.; Bhat, S. V. *Synth. Commun.* **1998**, *28*, 2311; c) Kumareswaran, R.; Vankar, Y. D. *Synth. Commun.* **1998**, *28*, 2291.
133. Park, J. B.; Ko, S. H.; Hong, W. P.; Lee, K. J**.** *Bull. Korean Chem. Soc*. **2004**, *25*, 927.
134. Vasudevan, A.; Tseng, P. S.; Djuric, S. W. *Tetrahedron Lett*. **2006**, *47,* 8591.
135. Chen, B.; Xie, X.; Lu, J.; Wang, Q.; Zhang, J; Tang, S; She, X. *Synlett* **2006**, 259.
136. Gowrisankar, S.; Lee, H. S.; Lee, K. Y.; Lee, J.-E.; Kim, J. N. *Tetrahedron Lett*. **2007**, *48*, 8619.
137. Gowrisankar, S.; Lee, H. S.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett*. **2008**, *49*, 1670.
138. Paquette, L. A.; Mendez-Andino, J. *Tetrahedron Lett*. **1999**, *40*, 4301.
139. Kim, J. M.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron Lett*. **2004**, *45*, 2805.
140. Lee, K. Y.; Na, J. E.; Lee, J. Y.; Kim, J. N. *Bull. Korean. Chem. Soc*. **2004**, *25*, 1280.
141. Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron* **2006**, *62*, 4052.

142. Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2004**, *45*, 3089.

143. Declerck, V.; Ribiere, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372.

144. Declerck, V.; Allouchi, H.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2007**, *72*, 1518.

145. Krafft, M. E.; Song, E.-H.; Davoile, R. J. *Tetrahedron Lett*. **2005**, *46*, 6359.

146. Chen, P.-Y.; Chen, H.-M.; Chen, L.-Y.; Tzeng, J.-Y.; Tsai, J.-C.; Chi, P.-C.; Lic, S.-R. Wang, E.-C. *Tetrahedron* **2007**, *63,* 2824.

147. Krishna, P. R.; Narsingam, M. *J. Comb. Chem.* **2007**, *9*, 62.

148. Trost, B. M. ; Brennan, M. K. *Org. Lett*. **2007**, *9*, 3961.

149. Gowrisankar, S.; Kim, H. S.; Lee, H. S.; Kim, J. N. *Bull. Korean Chem. Soc*. **2007**, *28*, 1844.

150. Doddi, V. R.; Vankar, Y. D. *Eur. J. Org. Chem.* **2007**, 5583.

151. Donohoe, T. J.; Kershaw, N. M.; Orr, A. J.; Wheelhouse (nee Gosby), K. M. P.; Fishlock, L. P.; Lacy, A. R.; Bingham, M.; Procopiou, P. A. *Tetrahedron* **2008,** *64*, 809.

152. Porto, R. S.; Vasconcellos, M. L. A. A.; Ventura, E.; Coelho, F. *Synthesis* **2005**, 2297.

153. Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal*. **2005**, *347*, 1701.

154. Davoust, M.; Briere, Jean-Francois; Metzner, P. *Org. Biomol. Chem*. **2006**, *4*, 3048.

155. Das, B.; Holla, H.; Venkateswarlu, K.; Majhi, A. *Tetrahedron Lett*. **2005**, *46*, 8895.

156. a) Chamakh, A.; Amri, H. *Tetrahedron Lett*. **1998**, *39*, 375; b) Chamakh, A.; M'hirsi, M.; Villieras, J.; Lebreton, J.; Amri, H. *Synthesis* **2000**, 295.

157. Im, Y. J.; Lee, C. G.; Kim, H. R.; Kim, J. N. *Tetrahedron Lett*. **2003**, *44*, 2987.

158. Kim, J. N.; Kim, J. M.; Lee, K. Y. *Synlett* **2003**, 821.

159. Kim, J. M.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc*. **2004**, *25*, 328.

160. Park, D. Y.; Lee, M. J.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett*. **2005**, *46*, 8799.

161. Liu, X.; Zhao, J.; Jin, G.; Zhao, G.; Zhu, S.; Wang, S. *Tetrahedron* **2005**, *61*, 3841.

162. Lee, M. J.; Park, D. Y.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett*. **2006**, *47*, 1833.

163. Basavaiah, D.; Pandiaraju, S.; Krishnamacharyulu, M. *Synlett* **1996**, 747.

164. Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 1493.

165. Kim, S. C.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc*. **2005**, *26*, 1001.

166. Pathak, R.; Madapa, S.; Batra, S. *Tetrahedron* **2007**, *63*, 451.

167. Masuyama, Y.; Nimura, Y.; Kurusu, Y. *Tetrahedron Lett.* **1991**, *32*, 225; b) Choudhury, P. K.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 3581; c) Gonzalez, A. G.; Silva, M. H.; Padron, J. I.; Leon, F.; Reyes, E.; Alvarez-Mon, M.; Pivel, J. P.; Quintana, J.; Estevez, F.; Bermejo, J. *J. Med. Chem.* **2002**, *45*, 2358.

168. Lee, K. Y.; Park, D. Y.; Kim, J. N. *Bull. Korean Chem. Soc*. **2006**, *27*, 1489.

169. Kabalka, G. W.; Venkataiah, B.; Chen, C. *Tetrahedron Lett*. **2006**, *47*, 4187.
170. Lamer, A.-C. L.; Gouault, N.; David, M.; Boustie, J.; Uriac, P. *J. Comb. Chem.* **2006**, *8,* 643.
171. Ramachandran, P. V.; Pratihar, D. *Org. Lett*. **2007**, *9*, 4753.
172. Porto, R. S.; Coelho, F. *Synth. Commun.* **2006**, *34*, 3037.
173. GowriSankar, S.; Lee, M. J.; Lee, S.; Kim, J. N. *Bull. Korean Chem. Soc*. **2004**, *25*, 1963.
174. GowriSankar, S.; Lee, C. G.; Kim, J. N. *Tetrahedron Lett*. **2004**, *45*, 6949.
175. Lee,C. G.; Lee, K. Y.; Kim, S. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2007**, *28*, 719.
176. Lee, K. Y. Lee, H. S. Kim, J. N. *Tetrahedron Lett*. **2007**, *48*, 2007.
177. Eipert, M.; Maichle-Moessmer, C.; Maier, M. E. *Tetrahedron* **2003**, *59*, 7949.
178. Singh, V.; Batra, S. *Synthesis*. **2006**, 63.
179. Singh, V.; Batra, S. unpublished results.
180. Singh, V.; Madapa, S.; Batra, S. *Synth. Commun*. **2007**, accepted.
181. Kim, S. J. Lee, H. S. Kim, J. N. *Tetrahedron Lett*. **2007**, *48*, 1069.
182. Basavaiah, D.; Satyanarayana, T. *Org. Lett*. **2001**, *3*, 3619.
183. Kim, S. C.; Lee, H. S.; Kim, J. N. *Bull. Korean Chem. Soc*. **2007**, *28*, 147.
184. Nicholas, K. M.; O'Dell, D. K. *Tetrahedron* **2003**, *59*, 747.
185. O'Dell, D. K.; Nicholas, K. M. *J. Org. Chem*. **2003**, *68*, 6427.
186. Lee, K. Y.; Lee, H. S.; Kim, J. N. *Bull. Korean Chem. Soc*. **2007**, *28*, 333.
187. Lee, K. Y.; Kim, J. M.; Kim, J. N. *Bull. Korean Chem. Soc*. **2002**, *23*, 1493.
188. Basavaiah, D.;Mallikarjuna Reddy, R. M.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron* **2002**, *58*, 3693.
189. Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron.* **2003**, *59*, 385.
190. Lee, K. Y.; Kim, S. C.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1109.
191. Amarante, G. W.; Benassi, M.; Sabino, A. A.; Esteves, P. M.; Coelho, F.; Eberlinb, M. N. *Tetrahedron. Lett*. **2006**, *47*, 8427.
192. Basavaiah, D.; Rao, J. S.; Reddy, R. J. *J. Org. Chem.* **2004**, *69*, 7379.
193. Basavaiah, D.; Reddy, R. J.; Rao, J. S. *Tetrahedron Lett*. **2006**, *47*, 73.
194. Shafiq, Z.; Liu, L.; Liu, Z.; Wang, D.; Chen Y.-J. *Org. Lett*. **2007**, *9*, 2525.
195. Familoni, O. B.; Klaas, P. J.; Lobb, K. A.; Pakade, V. E.; Kaye, P. T. *Org. Biomol. Chem.*, **2006**, *4*, 3960.
196. Madapa, S.; Singh, V.; Batra, S. *Tetrahedron* **2006**, *62*, 8740.
197. Basavaiah, D.; Aravindu, K. *Org. Lett*. **2007**, *9*, 2453.
198. Basavaiah, D.; Rao, J. S. *Tetrahedron Lett*. **2004**, *45*, 1621.

199. Lee, M. J.; Lee, K. Y.; Park, D. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26,* 1281.
200. Lee, H. S.; Kim, S. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27,* 1063.
201. Singh, V.; Kanojiya, S.; Batra, S. *Tetrahedron* **2006**, *62*, 10100.
202. Lee, K. Y.; Lee, Y. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2007**, *28,* 143.
203. Singh, V.; Batra, S. *Eur. J. Org. Chem.* **2007**, 2970.
204. Wasnaire, P.; Wiaux, M.; Touillaux, R.; Marko, I. E. *Tetrahedron Lett*. **2006**, *47*, 985.
205. Shanmugam, P.; Vaithiyanathan, V.; Viswambharan, B. *Tetrahedron* **2006**, *62*, 4342.
206. Singh, V.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Tetrahedron* **2006**, *62*, 8731.
207. Lee, M. J.; Kim, S. C.; Kim, J. N. *Bull. Korean Chem. Soc*. **2006**, *27*, 140.
208. Singh, V.; Pathak, R.; Batra, S. *Catal. Commun*. **2007**, *8*, 2054.
209. Singh, V.; Yadav, G. P.; Maulik, P. R.; Batra, S. **2008**, doi: 10.1016/j.tet.2008.01.74.
210. Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett*. **2003**, *5*, 3103.
211. Lee, K. Y.; Lee, C. G.; Kim, T. H.; Kim, J. N. *Bull. Korean Chem. Soc*. **2004**, *25*, 33.
212. Pathak, R.; Roy, A. K.; Kanojiya, S.; Batra, S. *Tetrahedron Lett*. **2005**, *46*, 5289.
213. Pathak, R.; Roy, A. K.; Batra, S. *Synlett* **2005**, 848.
214. Pathak, R.; Batra, S. *Tetrahedron* **2007**, *63*, 9448.
215. Pathak, R.; Batra, S.; Singh, N. unpublished results.
216. Nag, S.; Pathak, R.; Kumar, M.; Shukla, P. K.; Batra, S. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 3824.
217. Nag, S.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Synthesis* **2007**, 911.
218. Nag, S.; Madapa, S.; Batra, S. *Synthesis* **2007**, **2008**, 101.
219. Kim, S. C.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 3463.
220. Park, D. Y.; Lee, M. J.; Kim,T. H.; Kim, J. N. *Tetrahedron Lett*. **2005**, *46*, 8799.
221. Lee, M. J.; Kim, S. C.; Kim, J. N. *Bull. Korean Chem. Soc*. **2006**, *27*, 439.
222. Lee, H. S.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett*. **2007**, *48,* 4119.
223. Kim, J. M.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc*. **2002**, *23*, 1055.
224. Pathak, R.; Nag, S.; Batra, S. *Synthesis* **2006**, 4205.
225. Batra, S.; Roy, A. K. *Synthesis* **2004**, 2550.
226. Back, T. G.; Rankic, D. A.; Sorbetti, J. M.; Wulff, J. E. *Org. Lett*. **2005**, *7*, 2377.
227. Sorbetti, J. M.; Clary, K. N.; Rankic, D. A. Wulff, J. E.; Parvez, M.; Back, T. G. *J. Org. Chem.* **2007**, *72*, 3326.
228. Tanaka, T.; Muto, T.; Maruoka, H.; Imajo, S.; Fukami, H.; Tomimori, Y.; Fukuda, Y.; Nakatsuka, T. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 3431.

229. Maruoka, H.; Muto, T.; Tanaka, T.; Imajo, S.; Tomimori, Y.; Fukuda, Y.; Nakatsuka, T. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 3435.

230. Kim, S. J.; Kim, H. S.; Kim, T. H.; Kim, J. N. *Bull. Korean Chem. Soc*. **2007**, *28*, 1605.

231. Saxena, R.; Singh, V.; Batra, S. *Tetrahedron* **2004**, *60*, 10311.

232. Singh, V.; Saxena, R.; Batra, S. *J. Org. Chem.* **2005**, *70*, 353.

233. Singh, V.; Madapa, S.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Synthesis* **2006**, 1995.

234. Roy, A. K.; Pathak, R.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Synthesis* **2006**, 1021.

235. Saxena, R.; Batra, S. Poster at 9th Conference of Society of Chemists and Biologists, 8th-10th Jan, 2005, Rajkot.

236. Kamimura, A.; Morita, R.; Matsuura, K.; Mitsudera, H.; Shirai, M. *Tetrahedron* **2003**, *59*, 9931.

237. Coelho, F.; Veronese, D.; Lopes, E. C. S.; Rossi, R. C. *Tetrahedron Lett*. **2003**, *44*, 5731.

238. Coelho, F.; Veronese, D.; Pavam, C. H.; de Paula, V. I.; Buffon, R. *Tetrahedron* **2006**, *62,* 4563.

239. Kohn, L. K.; Pavam, C. H.; Veronese, D.; Coelho, F.; de Carvalho, J. E.; Almeida, W. P. *Eur. J. Med. Chem.* **2006**, *41,* 738.

240. Kim, J. N.; Kim, J. M.; Lee, K. Y.; Gowrisankar, S. *Bull. Korean Chem. Soc.* **2004**, *25*, 1733.

241. Gowrisankar, S.; Na, J. E.; Lee, M. J.; Kim, J. N. *Bull. Korean Chem Soc* **2005**, *26*, 319.

242. Lee, K. Y.; Gowrisankar, S.; Lee, Y. J.; Kim, J. N. *Tetrahedron* **2006**, *62*, 8798.

243. Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett*. **2003**, *44*, 6737

244. Mamaghani, M.; Tabatabaeian, K.; Mirzaeinejad, M.; Nikpassand, M. *J. Iranian Chem. Soc.* **2006**, *3*, 89.

245. Lee, K. Y.; Kim, S. C.; Kim, J. N. *Bull. Korean Chem. Soc*. **2006**, *27*, 319.

246. Zhang, Q.; Sun, S.; Hu, J.; Liu, Q.; Tan, J. *J. Org. Chem.* **2007**, *72*, 139.

247. Morizur, J.-F.; Mathias, L. J. *Tetrahedron Lett*. **2007**, *48*, 5555.

248. Lim, H. N.; Song, Y. S.; Lee, K.-J. *Synthesis*, **2007**, 3376.

249. Song, Y. S.; Lee, K.-J. *Synthesis* **2007**, 3037.

250. Wasnaire, P.; de Merode, T.; Marko, I. E. *Chem. Commun*. **2007**, 4755.

251. Ye, L.-W., Han, X.; Sun, X.-L.; Tang, Y. *Tetrahedron* **2008**, *64*, 1487.

252. Cabrera, S.; Aleman, J.; Bolze, P.; Bertelsen, S.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 121.

253. Kim, H. S.; Kim, S. H.; Kim, J. N. *Bull. Korean Chem. Soc*. **2007**, *28*, 1841.

254. Grange, R. L.; Ziogas, J.; North, A. J.; Angus, J. A.; Schiesser, C. H. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 1241

255. Kim, J. M.; Kim, S. H.; Kim, J. N. *Bull. Korean Chem. Soc*. **2007**, *28*, 2505.

256. Cha, M. J.; Song, Y. S.; Han, E.-G.; Lee, K.-J. *J. Heterocylic Chem*. **2008**, 235.

257. Sa, M. M.; Fernandes, L.; Ferreira, M.; Bortoluzzi, A. J. *Tetrahedron Lett*. **2008**, *49*, 1228

258. a) Vijaya Anand, R.; Baktharaman, S.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 5393; b) Loh, T.-P.; Cao, G.-Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1457; c) Basavaiah, D.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 1253; d) Grassi, D.; Lippuner, V.; Aebi, M.; Brunner, J.; Vasella, A. *J. Am. Chem. Soc.* **1997**, *119*, 10992; e) Li, S.; Peng, L.; Zhang, T.; Li, Y. *Gaodeng Xuexiao Huaxue Xuebao* **2003**, *24*, 1410.

259. Trost, B. M.; Thiel, O. R.; Tsui, H. C. *J. Am. Chem. Soc*. **2002**, *124*, 11616.

260. Trost, B. M.; Thiel, O. R.; Tsui, H. C. *J. Am. Chem. Soc*. **2003**, *125*, 13155.

261. Trost, B. M.; Machacek, M. R.; Tsui, H. C. *J. Am. Chem. Soc*. **2005**, *127*, 7014.

262. Krishna, P. R.; Narsingam, M.; Kannan, V. *Tetrahedron Lett.* **2004**, *45,* 4773.

263. Almeida, W. P.; Coelho, F. *Tetrahedron Lett*. **2003**, *44*, 937.

264. De, G. P.; Silveira, C.; Coelho, F. *Tetrahedron Lett.* **2005**, *46,* 6477.

265. Reddy, L. R.; Sarvanan, P.; Corey, E. J. *J. Am. Chem. Soc*. **2004**, *126*, 6230.

266. Reddy, L. R.; Fournier, J.-F.; Reddy, B. V. S.; Corey, E. J. *Org. Lett*. **2005**, *7*, 2699.

267. Chen, C.-Y; Chang, M.-Y.; Hsu, R.-T.; Chen, S.-T.; Chang, N.-C. *Tetrahedron Lett.* **2003**, *44*, 8627.

268. Motozaki, T.; Sawamura, K.; Suzuki, A.; Yoshida, K.; Ueki, T.; Ohara, A.; Munakata, R.; Takao, K.-i.; Tadano, K.-i. *Org. Lett*. **2005**, *7*, 2265.

269. Galeazzi, R.; Martelli, G.; Orena, M.; Rinaldia, S.; Sabatino, P. *Tetrahedron* **2005**, *61*, 5465.

270. Mergott, D. J.; Frank, S. A.; Roush, W. R. *Proc. Nat. Acad. Sci. U.S.A*. **2004**, *101*, 11955.

271. Seck, M.; Franck, X.; Seon-Meniel, B.; Hocquemiller, R.; Figadere, B. *Tetrahedron Lett.* **2006**, *47,* 4175.

272. Rodgen, S. A.; Schaus, S. E. *Angew. Chem. Int. Ed*. **2006**, *45,* 929.

273. Jogireddy, R.; Maier, M. E. *J. Org. Chem.* **2006**, *71*, 6999.

274. Buu Hue, B. T.; Dijkink, J.; Kuiper, S.; van Schaik, S.; van Maarseveen, J. H.; Hiemstra, H. *Eur. J. Org. Chem.* **2006**, 127.

275. Nising, C. F.; Ohhemuller, U. K.; Brase, S. *Angew. Chem. Int. Ed.* **2006**, *45*, 307.

276. Selvakumar, N.; Kumar, P. K.; Reddy, K. C. S.; Chary, B. C. *Tetrahedron Lett*. **2007**, *48*, 2021.

277. Myers, E. L.; de Vries, J. G.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2007**, *46*, 1893.

278. Moore, C. G.; Murphy, P. J.; Williams, H. L.; McGown, A. T.; Smith, N. K. *Tetrahedron* **2007**, *63,*11771.

279. Konig, C. M.; Harms, K.; Koert, U. *Org. Lett*. **2007**, *9*, 4777.

280. Liang, H.; Schule, A.; Vors, J.-P.; Ciufolini, M. A. *Org. Lett*. **2007**, *9*, 4119.

281. Das, B.; Banerjee, J.; Mahender, N.; Majhi, A. *Org. Lett.* **2004**, *6*, 3349.

282. Chapuis, C.; Büchi, G. H.; Wüest, H. *Helv. Chim. Acta* **2005**, *88*, 3069.

283. Frezza, M.; Soulere, L.; Queneau, Y.; Doutheau, A. *Tetrahedron Lett*. **2005**, *46,* 6495.

284. Frezza, M.; Balestrino, D.; Soulère, L.; Reverchon, S.; Queneau, Y.; Forestier, C.; Doutheau, A. *Eur. J. Org. Chem.* **2006**, 4731.

285. Coelho, F.; Antonio, S.; Mateus, C. R.; Almeida, W. P. Braz. Pedido 2003003854, 2005; *Chem. Abstr.* **2006**, *145*, 397270.

286. Das, B.; Chowdhury, N.; Banerjee, J.; Majhi, A. *Tetrahedron Lett*. **2006**, *47*, 6615

287. Das, B.; Banerjee, J.; Chowdhury, N.; Majhi, A.; Holla, H. *Synlett* **2006**, 1879.

288. Das, B.; Banerjee, J.; Chowdhury, N.; Majhi, A.; Mahender, G. *Helv. Chim. Acta* **2006**, *89*, 876.

289. Das, B.; Banerjee, J.; Chowdhury, N.; Majhi, A. *Chem. Pharm. Bull.* **2006**, *54*, 1725.

290. Kang, S.-Y.; Park, K.-S.; Kim, J.; Chong, Y.; Choo, H. *Bull. Korean Chem. Soc.* **2007**, *28*, 179.

291. Kamal, A.; Krishnaji, T.; Reddy, P. V. *Tetrahedron Lett*. **2007**, *48*, 7232.