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Advances in the Baylis–Hillman reaction-assisted synthesis of cyclic frameworks☆

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

Keywords: Baylis–Hillman reaction; Cyclic compounds; Heterocycles; Nucleophilic substitution

Contents

Abbreviations: Ac, acetyl; AIBN, 2,20-azobisisobutyronitrile; Aq, aqueous; Ar, aryl; 9BBN, 9-borabicyclo[3.3.1]nonane; BINAP, 2,20-bis(diphenylphosphanyl)-1,10-binaphthyl; $BF_3 \cdot Et_2O$, boron trifluoride etherate; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Bu, butyl; *c*, *cyclo*; CAN, ceric(IV) ammonium nitrate; cat., catalyst; Cp, cyclopentadienyl; DBU, 1,8-dazabicyclo[5.4.0]undec-7-ene; DCE, 1,2-dichloroethane; DDQ, 2,3-dichloro-5,6-dicyanobenzoquinone; de, diastereomeric excess; DIBAL-H, diisobutylaluminum hydride; DIEA, diisopropylethylamine; DMAD, dimethyl acetylenedicarboxylate; DMAP, 4-dimethyl aminopyridine; DME, 1,2-dimethoxyethane; DMF, dimethylformamide; DMSO, dimethylsulfoxide; dppp, 1,3-bis(diphenylphosphino)propane; dr, diastereomeric ratio; DYKAT, dynamic asymmetric kinetic transformation; ee, enantiomeric excess; Et, ethyl; $EtPh_2P$, ethyldiphenylphosphine; EWG, electron-withdrawing group; Hex, hexyl; HFIP, hexafluoro-2-propanol; HFIPA, 1,1,1,3,3,3-hexafluoroisopropyl acrylate; HMDS, bis(trimethylsilyl)amide; HMP, hexamethyl phosphoramide; 3-HQD, 3-hydroxyquinuclidine; HMTA, hexamethylenetetramine; IBX, *o*-iodoxybenzoic acid; β-ICD, β-isocupreidine; LDA, lithium diisopropylamide; *m*-CPBA, *m*-chloroperoxybenzoic acid; Me, methyl; Ms, mesyl; MOM, methoxymethyl; MS, molecular sieves; MVK, methyl vinyl ketone; MW, microwave; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NMO, *N*-methyl morpholine-*N*-oxide; Ns, *p*-nitrobenzenesulfonyl; Nu, Nucleophile; $(o\text{-Tol})_3P$, tri-*ortho*-tolyl-phosphine; PCC, pyridinium chlorochromate; PEG, polyethylene glycol; Pent, pentyl; Ph, phenyl; PMB, *p*-methoxybenzoyl; PMDETA, *N*,*N*,*N*′,*N*′,*N*-pentamethyldiethylinetriamine; Mont., Montmorillonite; PPA, polyphosphoric acid; Pr, propyl; RCM, ring-closing metathesis; RDS, rate-determining step; rt, room temperature; SES, 2-trimethylsilylethylsulfonyl; *t*-Bu, tertiarybutyl; TBAF, tetrabutylammoniumfluoride; TBS or TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TBHP, tetrabutylhydroperoxide; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; TFE, trifluoroethanol; TfOH, triflic acid or trifluoromethanesulfonic acid; THBP, 2,4,5-trihydroxybutyrophenone; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMS, trimethylsilyl; TMSOTf, trimethylsilyl trifluoromethanesulfonate; Tol, toluene; TPAP, tetrapropylammonium perruthenate; Ts, tosyl or 4-toluenesulfonyl; TsOH, *p*-toluenesulfonic acid; TTMSS, tris(trimethylsilyl)silane; us, ultrasound.

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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 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**) (Fig. 1). As described by Basavaiah et al. in their recent review, it is a three-step reaction involving successive Michael, aldol, and elimination reactions 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, and 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.

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 (Fig. 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 (Fig. 2).[4] The synthetic appreciation of this reaction in organic 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

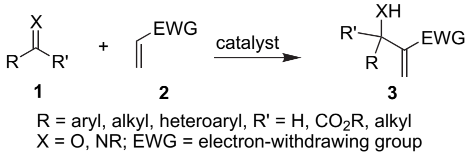


Figure 1. General representation of the Baylis–Hillman reaction.

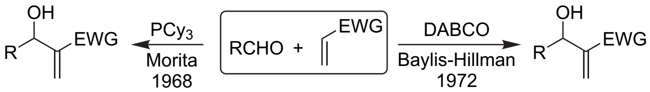
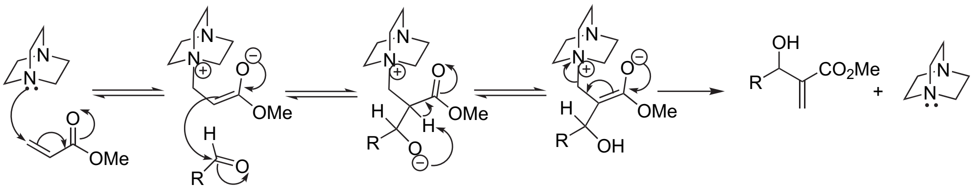


Figure 2. Reactions embodied in patents by Morita and Baylis–Hillman.

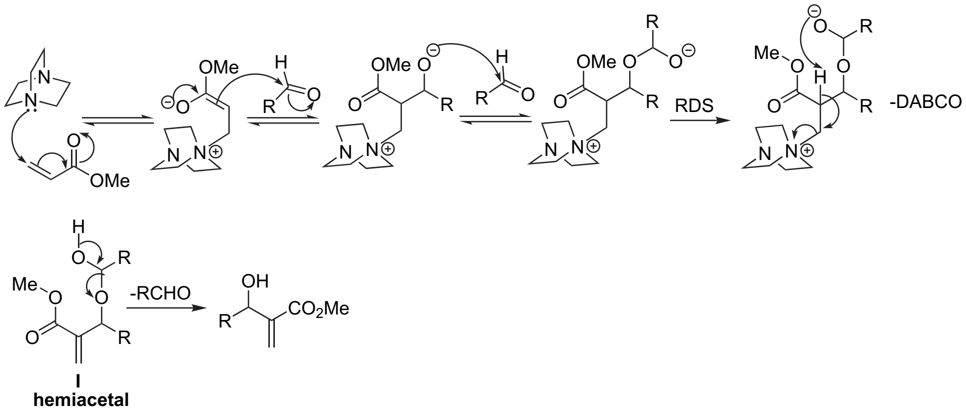
reaction have gained pace and the second review on the subject, by Basavaiah et al., appeared in 1996, covering approximately 200 references.[8] Simultaneously, Ciganek in 1997 authored a chapter on Organic Reactions, which discussed the Morita–Baylis–Hillman reaction in great detail.[9] These articles fueled an explosive growth in the scope and applications of this reaction over the next 5 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 et al. 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 et al.[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 the 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 commonly accepted mechanism.[17] Very recently, however, McQuade et al. 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



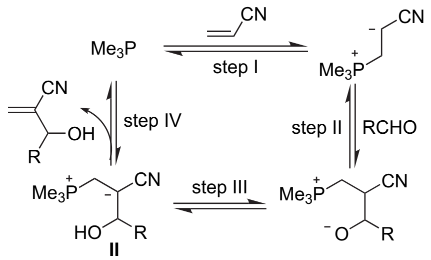
Scheme 1.



Scheme 2.

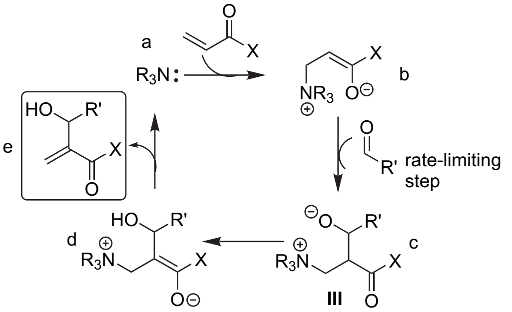
RDS was second order in aldehyde and first order in DABCO and acrylate. Initially, they carried out studies with 4-nitrobenzaldehyde, but, later, they published their results with other aromatic aldehydes.[19]

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).



Scheme 4.

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]

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]

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 (Fig. 3). The acetate and allyl bromide

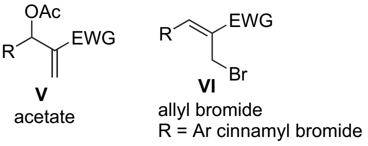
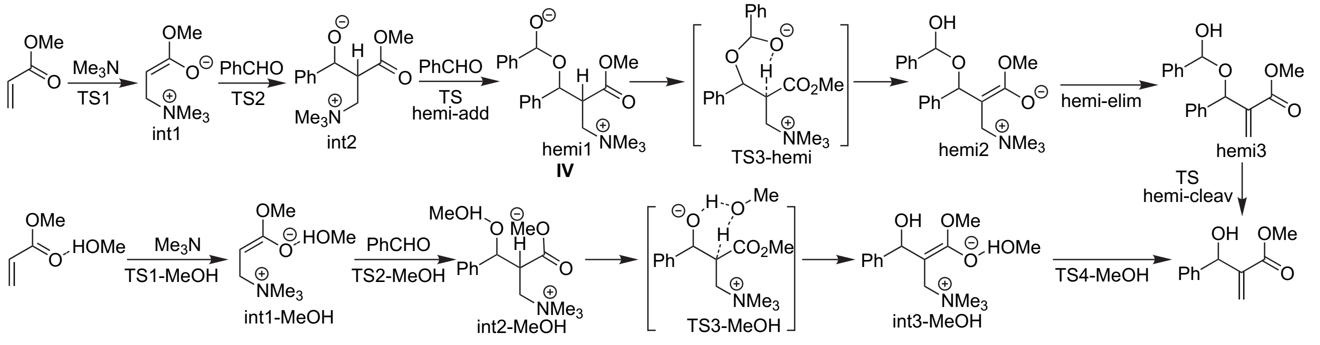


Figure 3. Structures of acetate (**V**) and allyl bromide (**VI**) derived from the Baylis–Hillman adduct.



Scheme 5.

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.

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** (Fig. 5). In contrast, to this situation the nucleophilic 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** (Fig. 6). When the 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**.

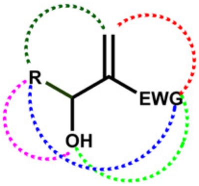


Figure 4. Different colors showing various opportunities for cyclization in the Baylis–Hillman adduct.

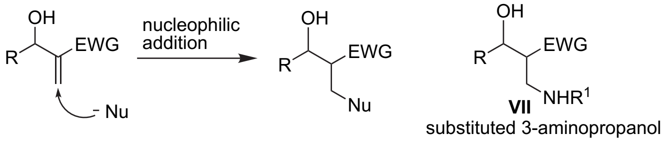


Figure 5. Nucleophilic addition in the Baylis–Hillman adduct, e.g., formation of substituted 3-aminopropanol **VII**.

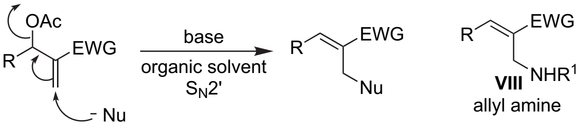
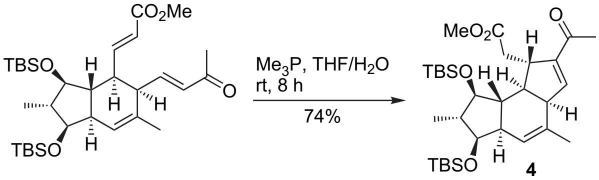


Figure 6. S_N2' reaction of the nucleophile with the Baylis–Hillman acetate, e.g., formation of an allyl amine derivative **VIII**.

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.

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 3-methylene-2-pyrrolone (**9**), however, instead of the expected product, as depicted in 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 et al.[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

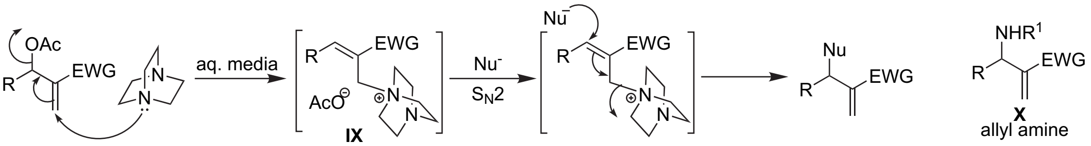
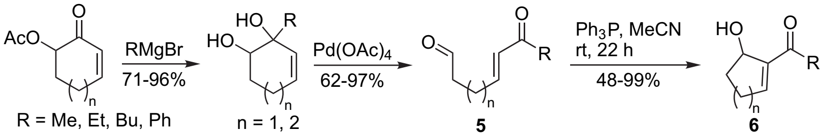
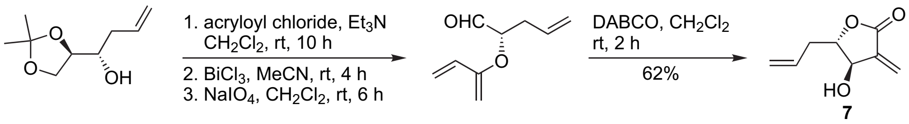


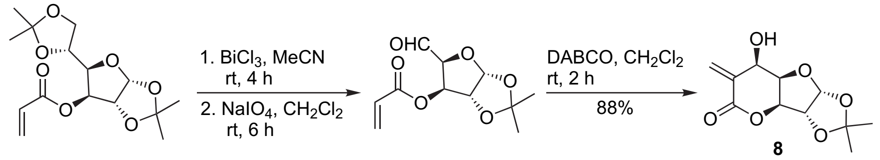
Figure 7. S_N2 reaction of the nucleophile with the Baylis–Hillman acetate in aqueous medium, e.g., formation of substituted allyl amine **X**.



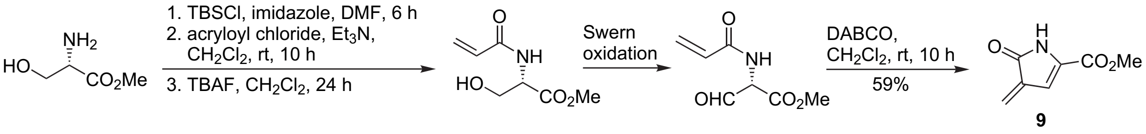
Scheme 7.



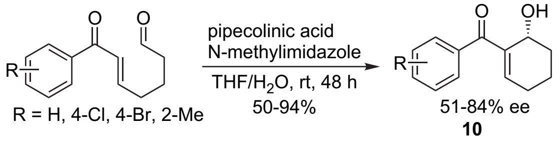
Scheme 8.



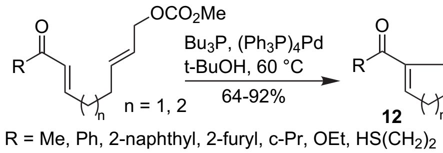
Scheme 9.



Scheme 10.



Scheme 11.

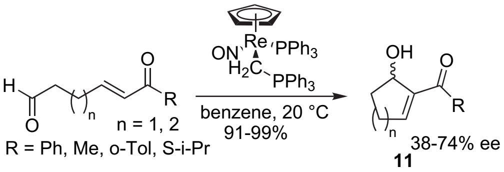


Scheme 13.

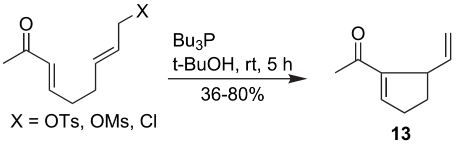
chlorobenzene afforded carbocycles (**11**) in good yields, but with moderate enantioselectivity (Scheme 12).[28]

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]

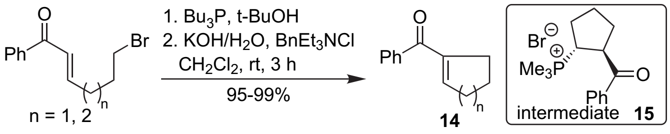
The intramolecular variant of the Morita–Baylis–Hillman reaction encompassing leaving groups on an allylic framework as the electrophilic partner in an organocatalytic process was described by Krafft and Haxell. They observed that the allylic chloride in the presence of Bu_3P provided a better yield 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



Scheme 12.

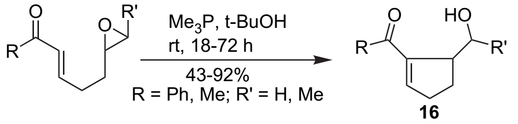


Scheme 14.



Scheme 15.

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]



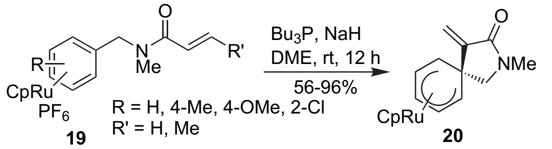
Scheme 16.

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]

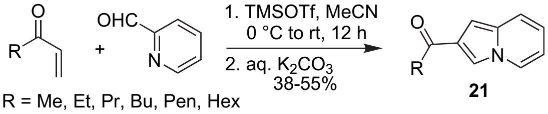
More recently, another intramolecular organometallic variation of the Morita–Baylis–Hillman reaction has been reported by Pigge et al.[36] It was demonstrated that *N*-benzyl acrylamide–ruthenium complexes **19** were transformed into the spirocyclic derivative (**20**) in the presence of Bu_3P and NaH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

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.



Scheme 18.



Scheme 19.

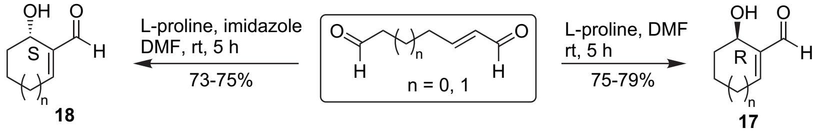
5.1. Nitrogen-containing systems

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]

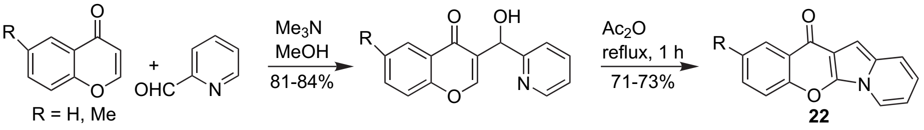
Almeida et al. reported the Baylis–Hillman reaction of chiral α-amino aldehydes under sonication which avoids racemization and described the synthesis of bicyclic lactam (**23**) with an indolizidinic skeleton from the Baylis–Hillman adduct of *N*-Boc-pipecolaldehyde (Scheme 21).[39] Very recently, in an alternate strategy for the generation of *N*-bridgehead heterocyclic systems, Clive et al. 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.

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]

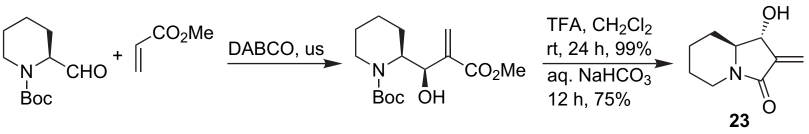
Lee et al. demonstrated that the Baylis–Hillman reaction of 2-cyano benzaldehyde with activated alkenes in the presence of DABCO led to the formation of 2-(3-oxo-2,3-dihydro-1*H*-



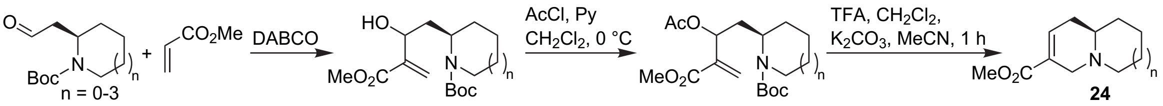
Scheme 17.



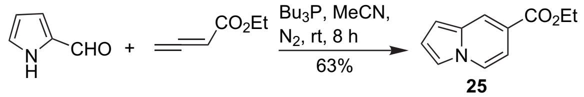
Scheme 20.



Scheme 21.

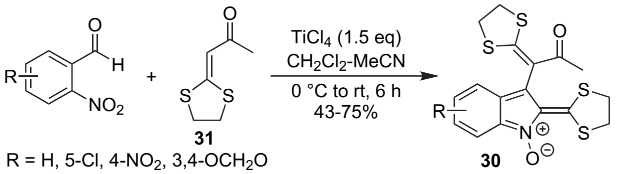


Scheme 22.

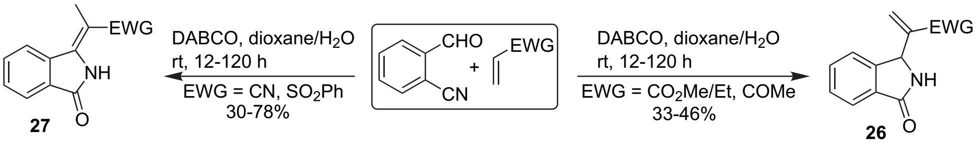


Scheme 23.

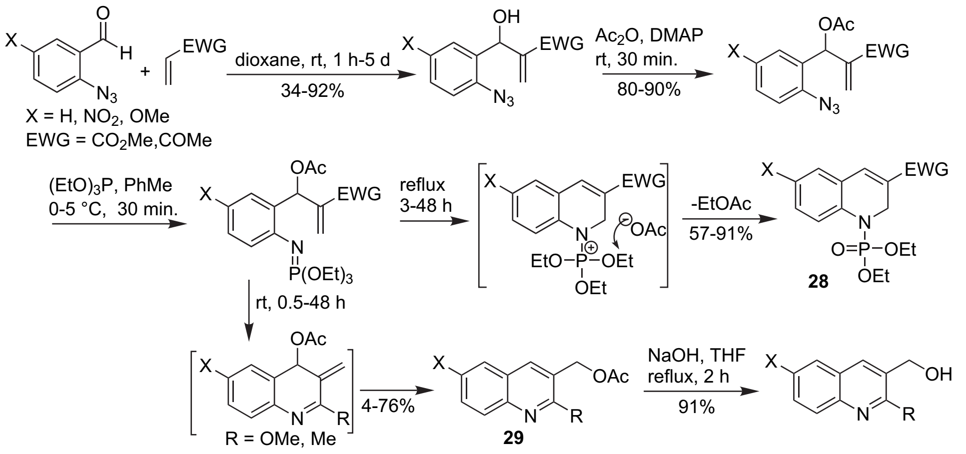
isoindol-1-yl)-acrylates (**26**). When acrylonitrile and phenyl vinyl sulfone were employed as the alkenes, however, the rearranged products (**27**) were obtained, as illustrated in Scheme 24.[42] Later Lee's group successfully accomplished the synthesis of several 1,2-dihydroquinoline derivatives (**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 et al. 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 26.



Scheme 24.



Scheme 25.

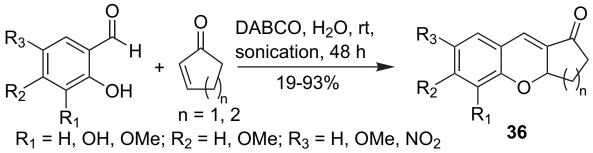
5.2. Oxygen-containing systems

Kim et al. 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]

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]

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]

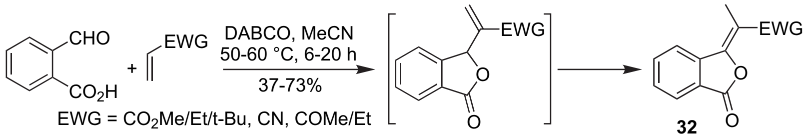
Shi and Shi have also described a successful synthesis of tetrahydroxanthenes (**40**) from the Baylis–Hillman reaction of salicyl *N*-tosylimines with 2-cylohexenone in the presence of $PPhMe_2$ (Scheme 32).[52] They reported a similar reaction with cyclopentenone to afford the cyclized product (**41**)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



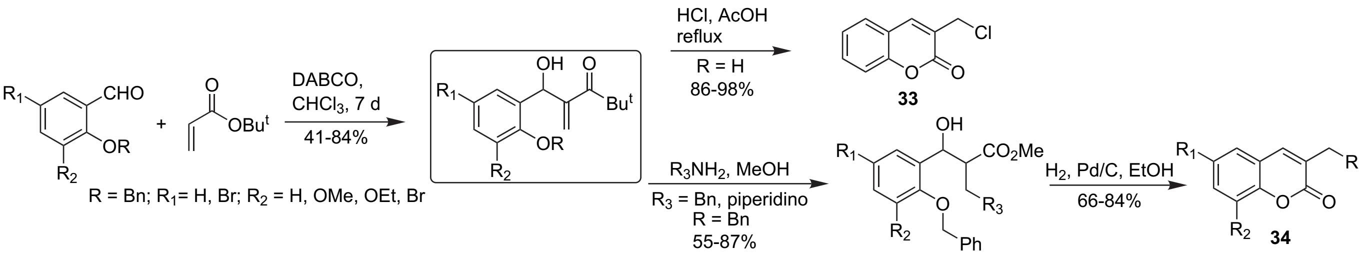
Scheme 30.

Shi et al. 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 toward the nucleophilic attack (Scheme 33).

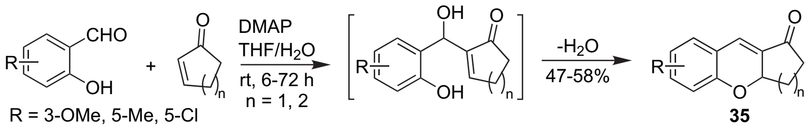
Shi et al. later described that, compared to ethyl 2-butynoate, the reaction between diethyl acetylenedicarboxylate and salicyl *N*-tosylimine in the presence of DABCO or $PPhMe_2$ in DMSO proceeded efficiently to afford the corresponding chromenes (**44**) in excellent yields, as shown in Scheme 34.[54] Subsequently, Shi and Shi prepared substituted



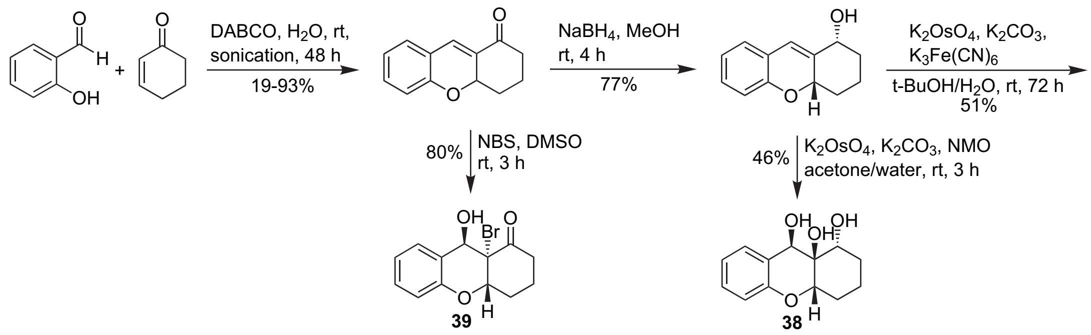
Scheme 27.



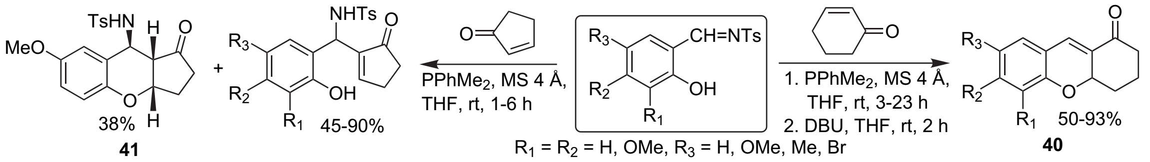
Scheme 28.



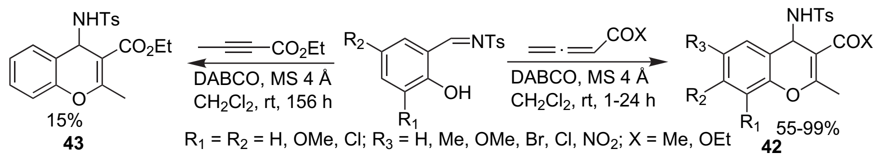
Scheme 29.



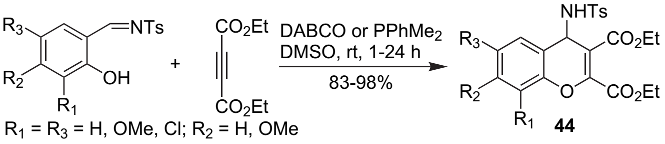
Scheme 31.



Scheme 32.

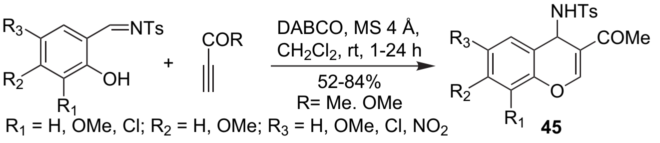


Scheme 33.



Scheme 34.

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).

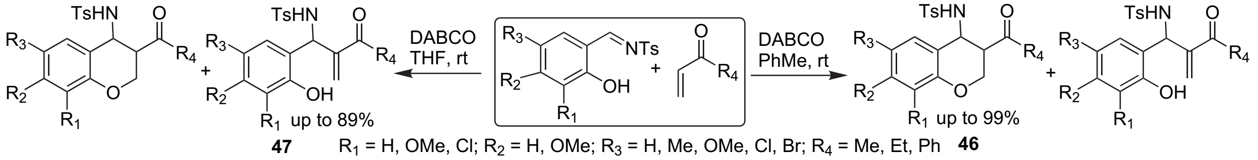


Scheme 35.

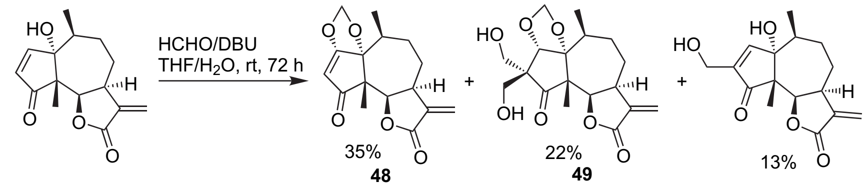
Recently, an interesting reaction describing the formation of 1,3-dioxolanes (**48** and **49**) during the DBU-catalyzed Baylis–Hillman coupling of a sesquiterpene lactone, parthenin, with aromatic and aliphatic aldehydes has been reported by Taneja et al. (Scheme 37).[57] They proposed that the presence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

5.3. Sulfur-containing systems

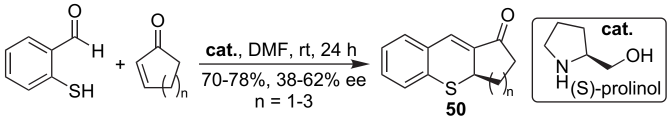
Inspired by the work of Brase et al. on the preparation of tetrahydroxanthenones,[47–49] Cardova et al. transformed 2-mercaptobenzaldehyde in the presence of (*S*)-prolinol, an asymmetric organocatalyst, into tetrahydrothioxanthanes (**50**).[58] The Baylis–Hillman-type product was, in fact, obtained via a domino thia-Michael/aldol reaction (Scheme 38).



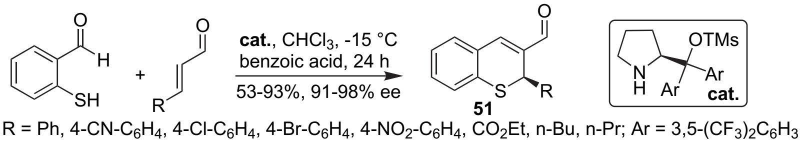
Scheme 36.



Scheme 37.



Scheme 38.

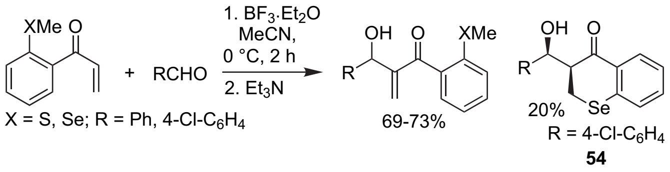


Scheme 39.

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]

5.4. Selenium-containing systems

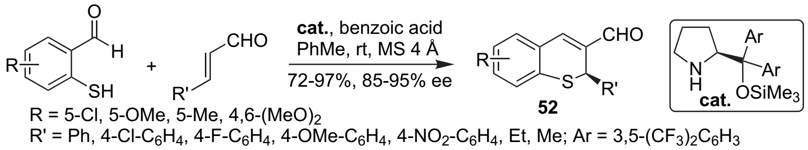
Kataoka et al. have described the Baylis–Hillman reaction of 1-[2-(methylchalcogeno)phenyl]propenones with aldehydes, and found that seleno-substituted chalcogen afforded an unusual product, selenochromanone (**54**), albeit in low yield, along with the usual Baylis–Hillman product (Scheme 42).[61]



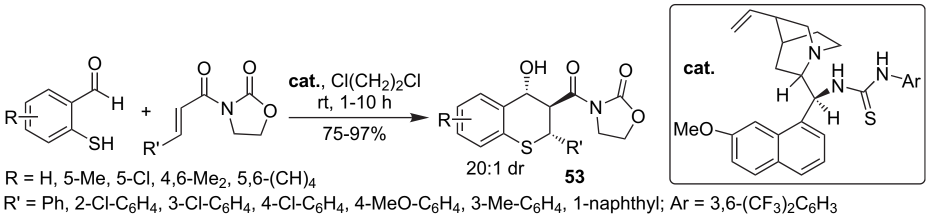
Scheme 42.

6. Nucleophilic aromatic substitution reactions

The nucleophilic aromatic substitution reaction was first introduced by Kim et al. 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



Scheme 40.



Scheme 41.

conjugated ester moiety is crucial to render the S_NAr reaction more facile.

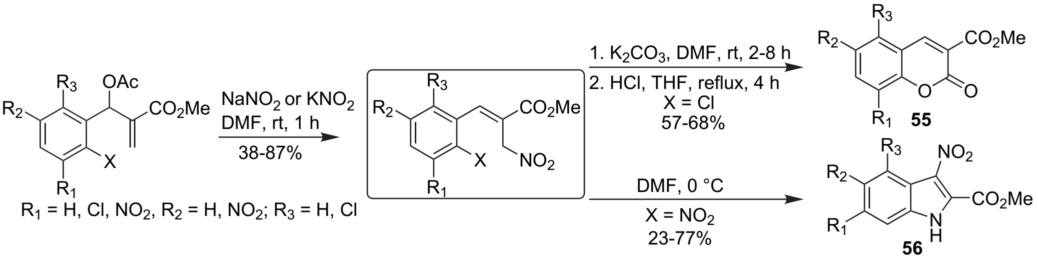
Hong and Lee reported the synthesis of coumarins (**55**) via intramolecular aromatic substitution followed by rearrangement of 3-(2-chloro-phenyl)-2-nitromethyl-acrylic acid methyl esters afforded from the reaction between the Baylis–Hillman acetates and $NaNO_2$ (Scheme 43).[64] Subsequently Horn and 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]

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 et al.[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).

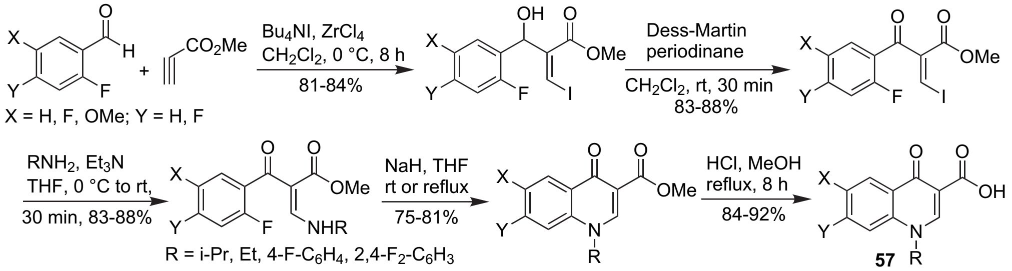
7. Friedel–Crafts reactions

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 methylsulfonic 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 sulfuric 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.

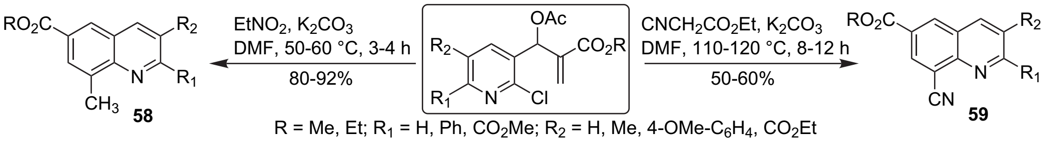
Kim et al. have utilized the Baylis–Hillman acetates for the synthesis of indeno[1,2-*b*]quinolin-10-ones (**63** and **64**).[74] The S_N2' reaction of anilines with Baylis–Hillman acetates afforded the allyl amines, which, upon treatment with PPA, underwent a double Friedel–Crafts reaction to yield 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



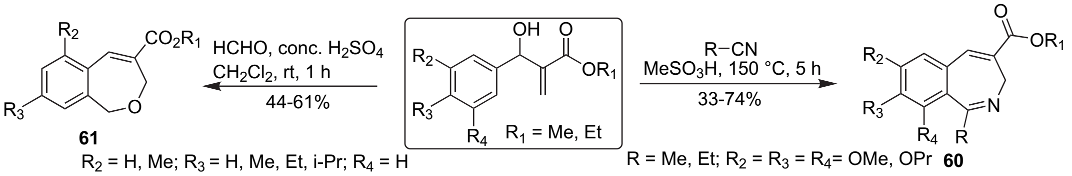
Scheme 43.



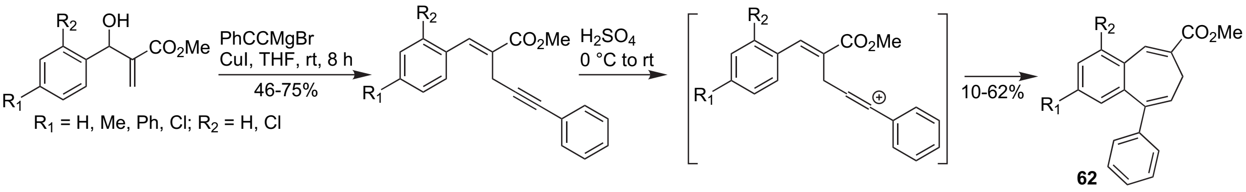
Scheme 44.



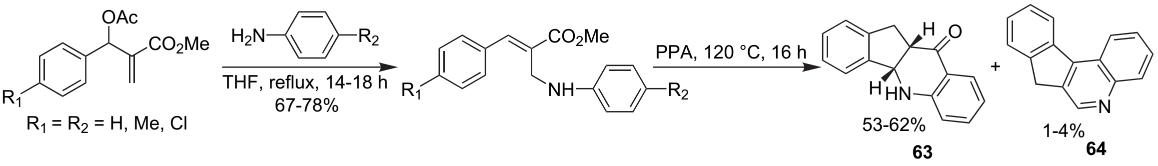
Scheme 45.



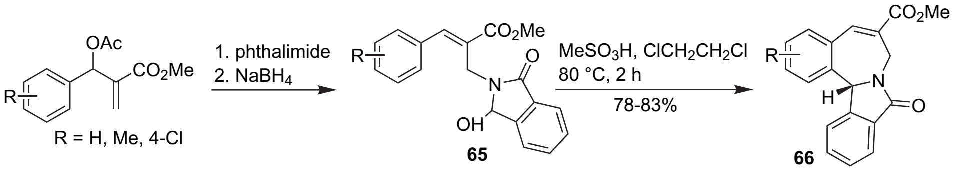
Scheme 46.



Scheme 47.



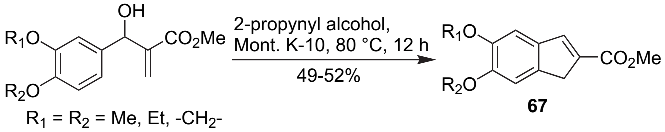
Scheme 48.



Scheme 49.

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

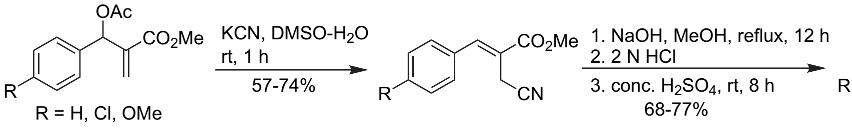
Lee et al. described a simple protocol for the synthesis of 1-hydroxynaphthalenes (**68**) from the allyl cyanides, which, in turn, were obtained from the reaction between the Baylis–Hillman acetates and KCN in the presence of DMSO (Scheme 51).[77] Subsequently, Kim et al. reported a regioselective synthesis 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*-toluenesulfonic acid (Scheme 52).



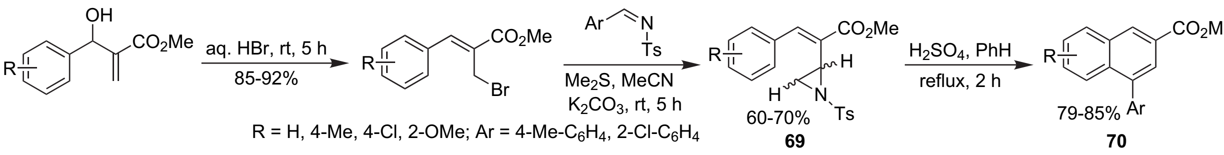
Scheme 50.

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]

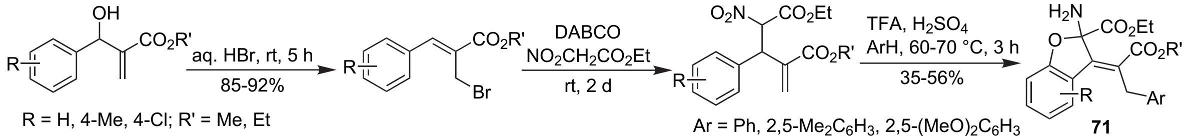
More recently, Lee et al. described the synthesis of 2-(9-fluorenyl)acrylic acid derivatives (**72**) via an intramolecular Friedel–Crafts reaction of the Morita–Baylis–Hillman adducts of 2-biphenylcarbaldehydes, as shown in Scheme 54.[80]



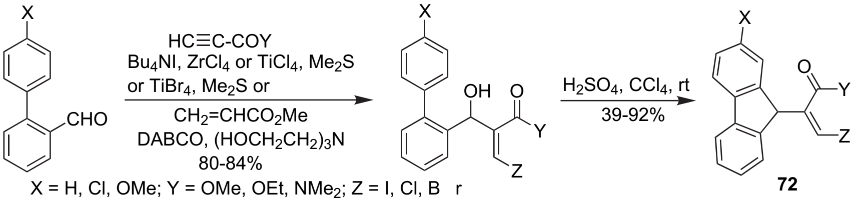
Scheme 51.



Scheme 52.



Scheme 53.



Scheme 54.

Das et al. 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]

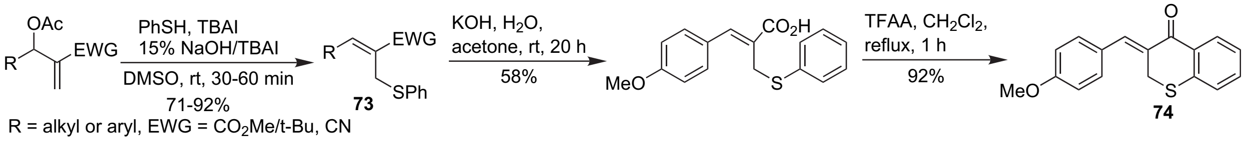
Kanakam et al. demonstrated the preparation of methylene-dinaphthyl bis-chromanones (**75**) via reaction between methylene dinaphthol and allyl bromide followed by saponification and TFA-mediated cyclization. These products showed efficient luminescence in the blue light region and elicited significant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

8. Cycloaddition reactions

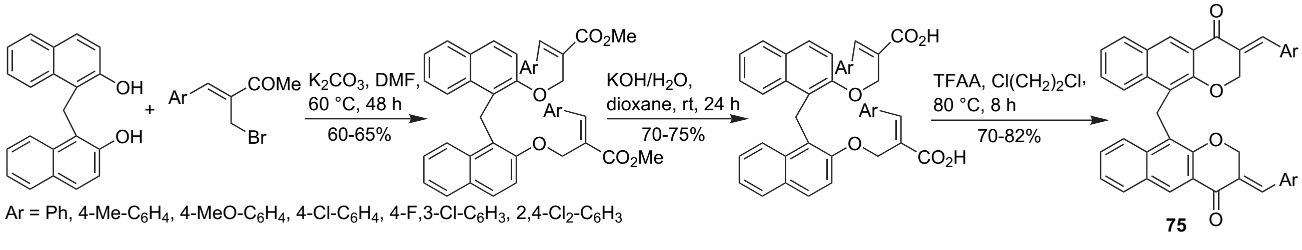
The presence of a double bond in the Baylis–Hillman adduct makes it a suitable substrate for the cycloaddition reactions. Initially, investigations were limited to 1,3-dipolar cycloadditions of nitrile oxides,[83] but, during the last few years, applications of the Baylis–Hillman derivatives for cycloaddition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

8.1. 1,3-Dipolar cycloadditions

Fisera et al. 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



Scheme 55.

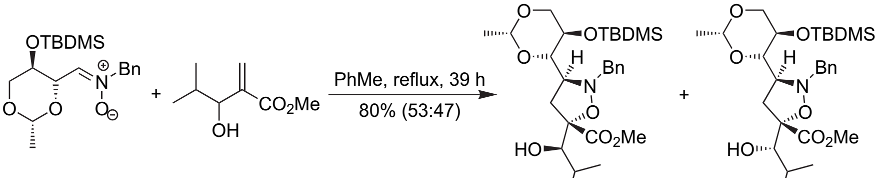


Scheme 56.

(**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]

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 with 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.

Sreedhar et al. 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



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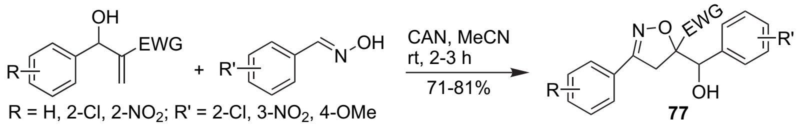
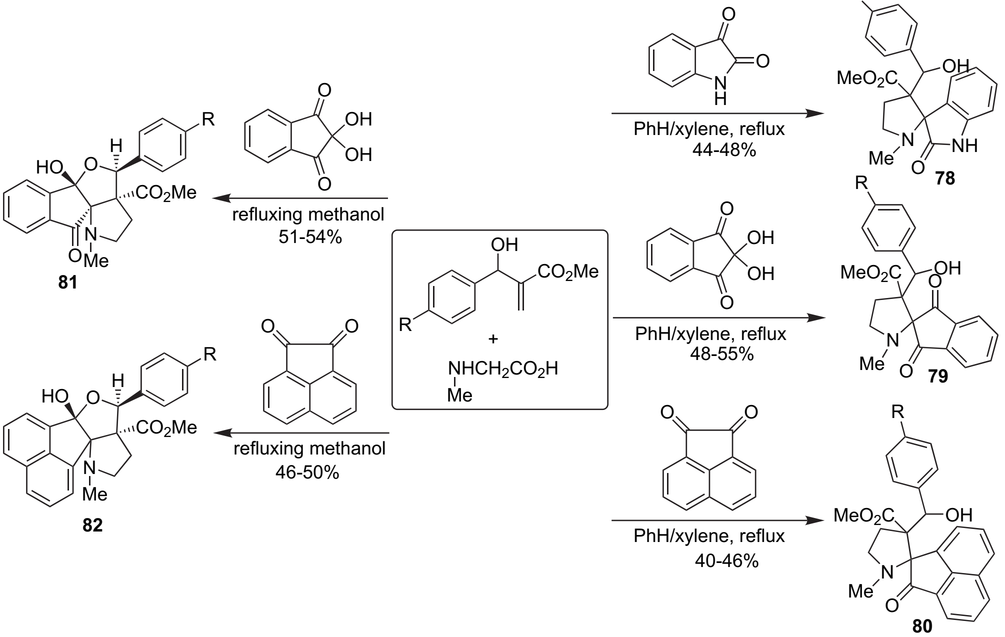
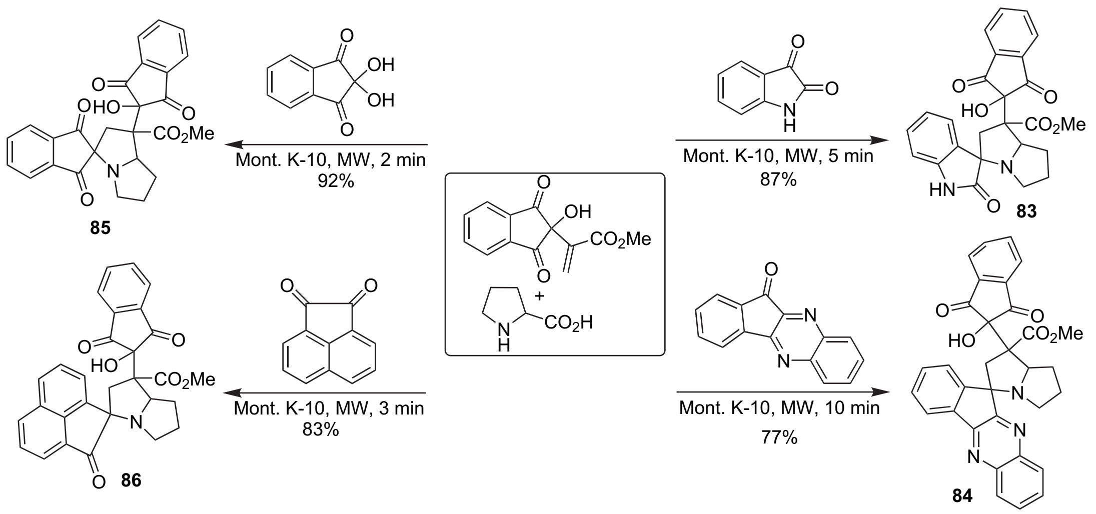
Scheme 57.



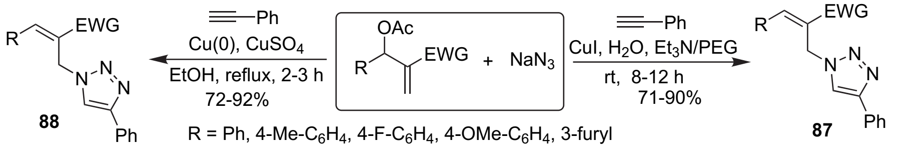
Scheme 58.



Scheme 59.



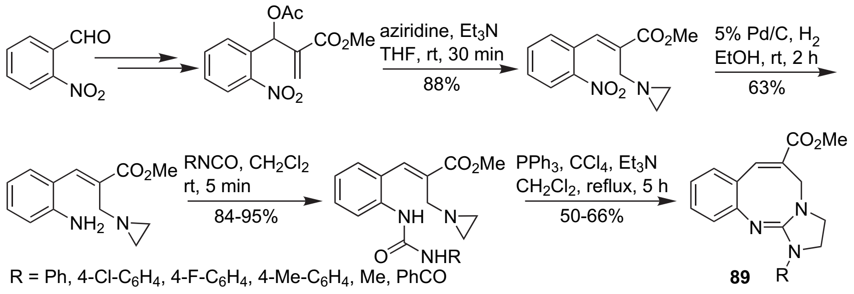
Scheme 60.



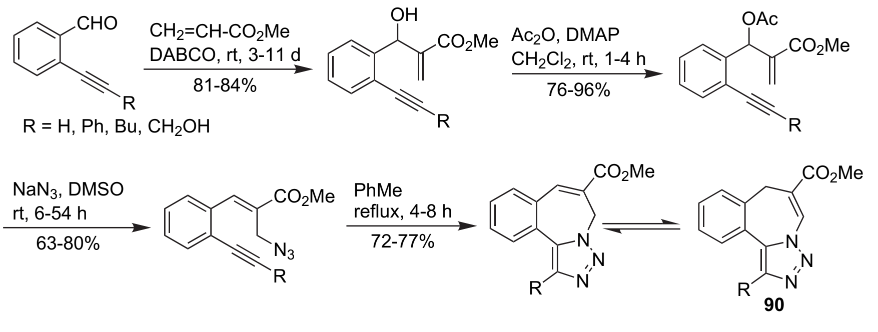
Scheme 61.

triazoles (**88**) by using Cu(0) and $CuSO_4$ in ethanol (Scheme 61).[90]

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 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



Scheme 62.



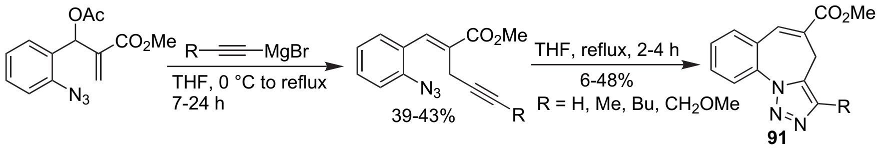
Scheme 63.

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]

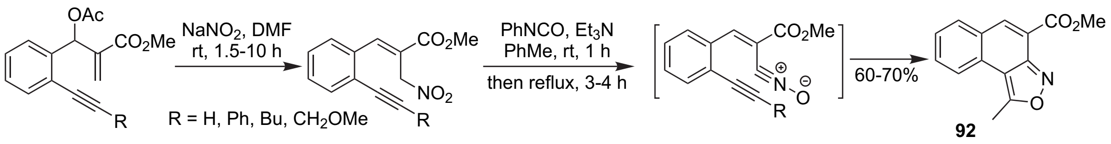
A novel regioselective synthesis of a variety of functionalized 3-spiropyrrolidine oxindoles (**93** and **95**) and 3-spiropyrrolizidines (**96** and **97**) from the Baylis–Hillman adducts of isatin and heteroaldehydes via a [3+2] cycloaddition of azomethine ylides was reported by Shanmugam et al.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

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

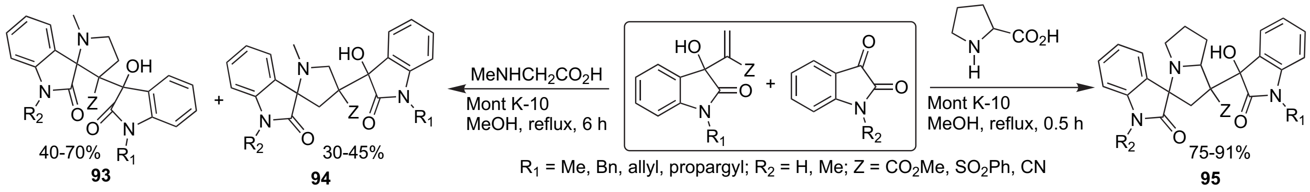
The synthesis of a series of chromene[4,3-*b*]pyrroles (**100**) through an intramolecular 1,3-dipolar cycloaddition reaction of an azomethine ylide with the dipolarophile afforded from



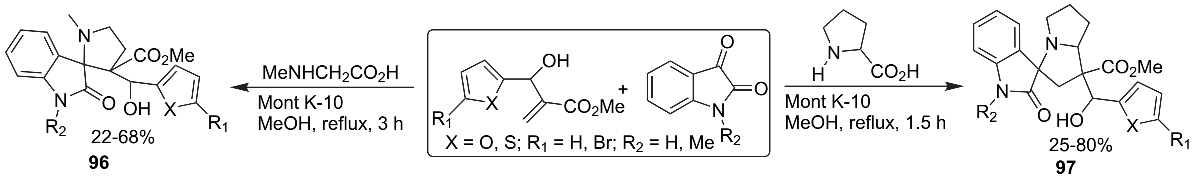
Scheme 64.



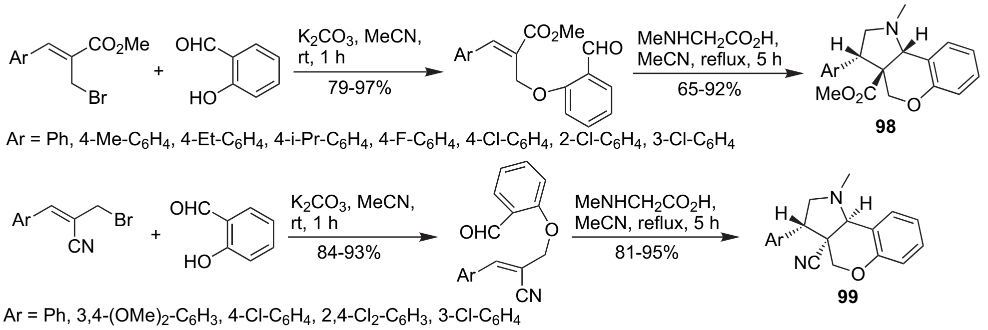
Scheme 65.



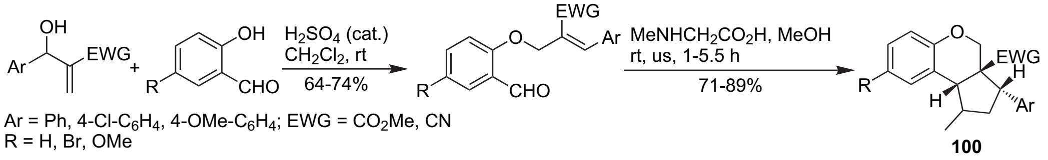
Scheme 66.



Scheme 67.



Scheme 68.



Scheme 69.

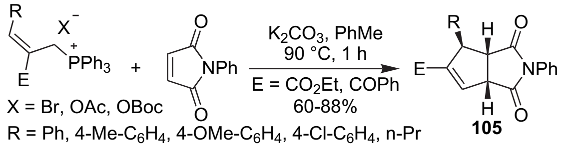
the Baylis–Hillman adducts, as described in Scheme 69, was accomplished by Ramesh and Raghunathan.[97] They observed that the use of ultrasonic radiation for this particular reaction increases the efficiency and the products were generated in better yields.

8.2. Diels–Alder reactions

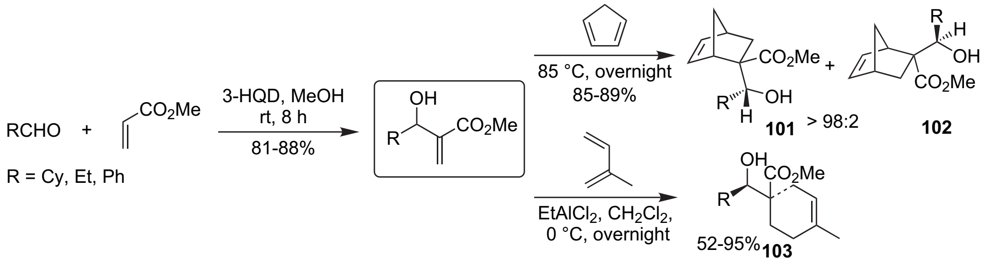
The Diels–Alder reaction of the Baylis–Hillman adducts with cyclopentadiene was first reported by Aggarwal et al.[98] They observed that the thermal conditions favored the *exo* isomer (**101**) over the *endo* isomer (**102**) and the ratio was controlled by a balance of steric and electronic factors. 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-isomer, 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).

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).

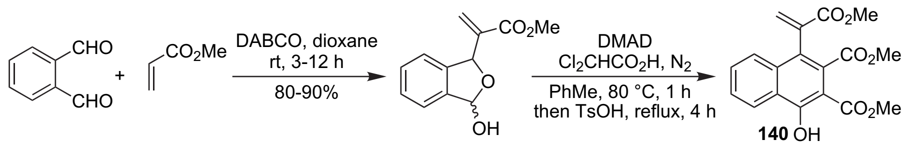
Lu et al. have reported novel approaches involving the cycloaddition of electron-deficient olefins with electron-deficient allylic compound as the three-carbon unit via a phosphorus ylide. Initially, they observed that the phosphonium bromide salt derived from the allyl bromide generated from the Baylis–Hillman 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 et al. 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$_3$P and K$_2$CO$_3$ 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



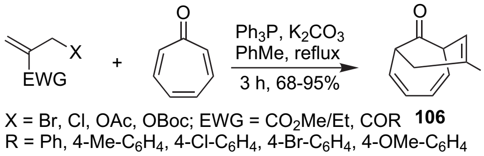
Scheme 72.



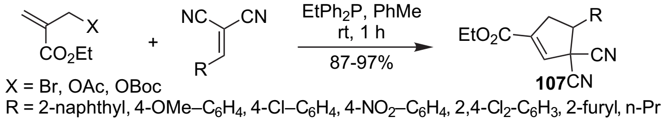
Scheme 70.



Scheme 71.



Scheme 73.



Scheme 74.

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

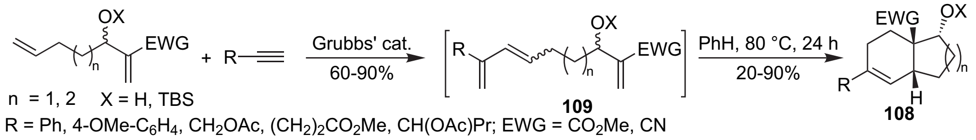
Blechert et al. described the synthesis of cis-fused carbobicyclic compounds (**108**) via an intramolecular (4+2) cycloaddition reaction of compounds **109**, which were, in turn, obtained from the corresponding Baylis–Hillman derivatives via enyne cross-metathesis with terminal alkynes, as outlined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

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]

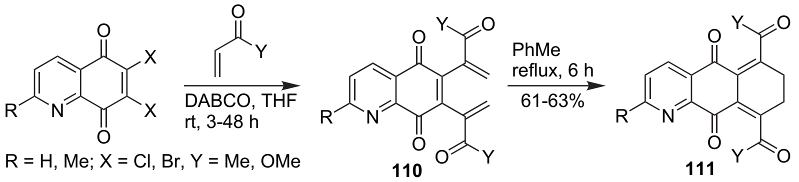
Jorgensen et al. demonstrated the utility of the allyl amine (**112**) for the Diels–Alder reaction with 2,3-dimethyl butadiene for the synthesis of cyclohexene derivative (**113**) with high diastereoselectivity (Scheme 77).[105]

8.3. (n+n) Annulations

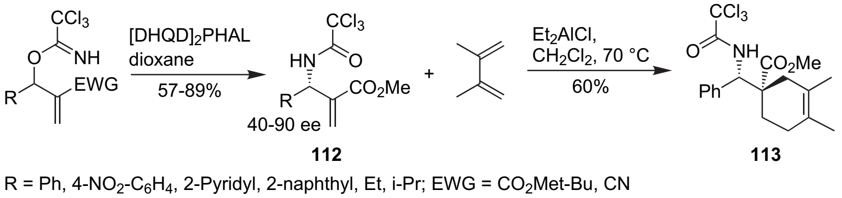
A one-pot, regioselective synthesis of polysubstituted phenols (**114**) from the acetates of the Baylis–Hillman adducts and dimethyl 1,3-acetonedicarboxylate was described by Kim et al. via a formal [3+3] annulation strategy (Scheme 78).[106] Substituted phenol derivatives such as (**115**) were also 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



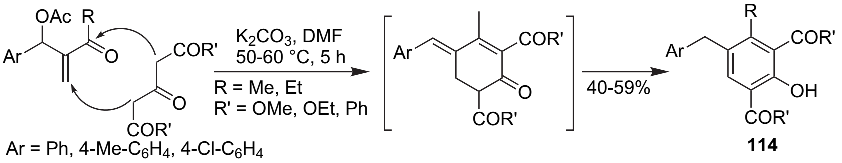
Scheme 75.



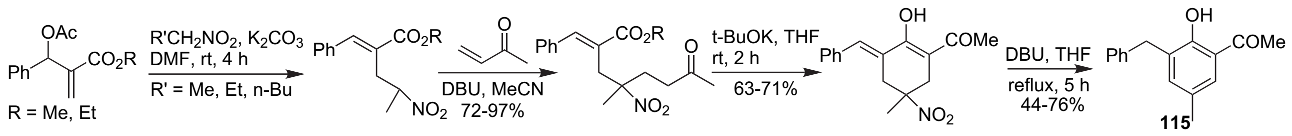
Scheme 76.



Scheme 77.



Scheme 78.



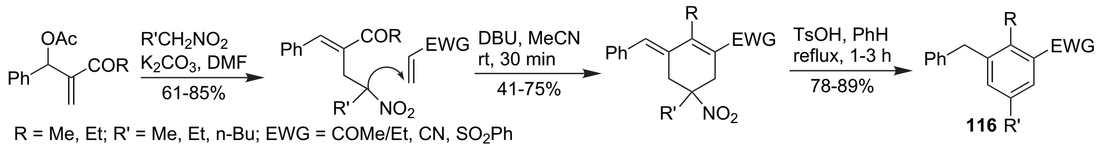
Scheme 79.

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 et al. 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.

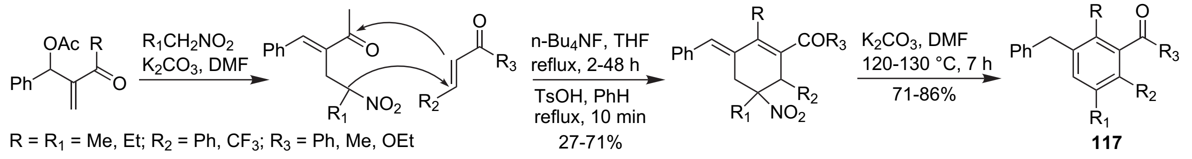
Shi et al. reported an abnormal aza-Baylis–Hillman reaction between *N*-tosylimines and allenes. They observed that the DABCO-catalyzed Baylis–Hillman reaction of ethyl 2,3-butadienoate with *N*-tosylimines yielded the azetidine derivatives (**119**) through a [2+2] cycloaddition process. On changing 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-arylpiperidines (**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.

The aza-Baylis–Hillman reaction between *N*-tosylaldimine 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-tetrahydropyridines (**124** and **125**), as shown in Scheme 86.

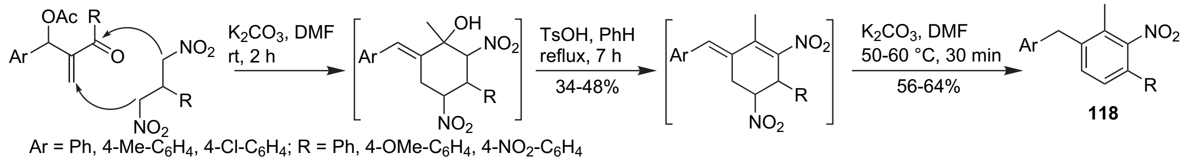
Kim et al. reported a two-step synthesis of polysubstituted benzenes in moderate yields starting from the Baylis–Hillman derivatives (**126**) obtained via an S_N2' reaction of ethyl cyanoacetate. The first step involved the base-promoted reaction of methyl/ethyl vinyl ketone to obtain a cyclohexene derivative (**127**), which, upon treatment with DBU in DMF, yielded



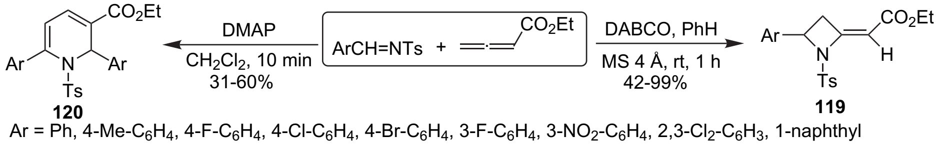
Scheme 80.



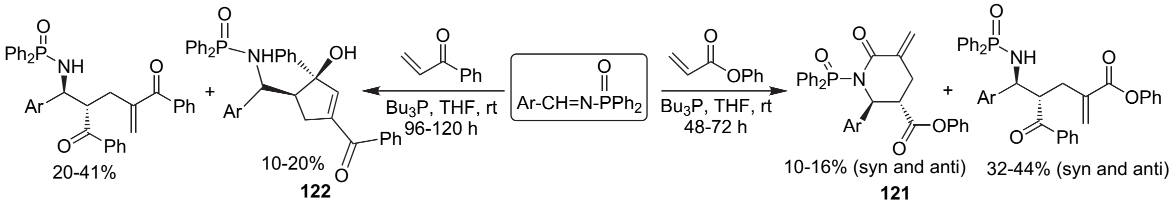
Scheme 81.



Scheme 82.

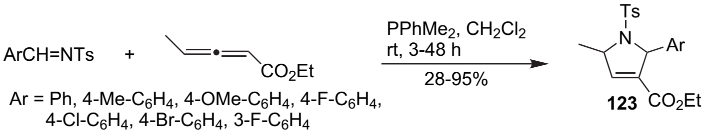


Scheme 83.



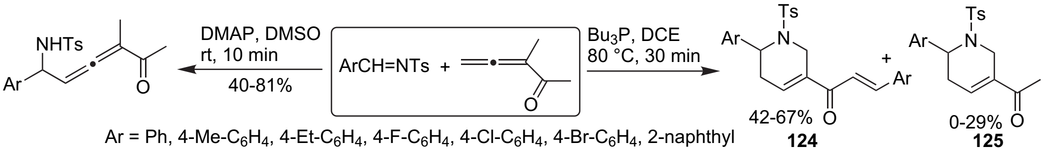
Ar = 4-Et-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-NO_2-C_6H_4, PhCH=CH

Scheme 84.



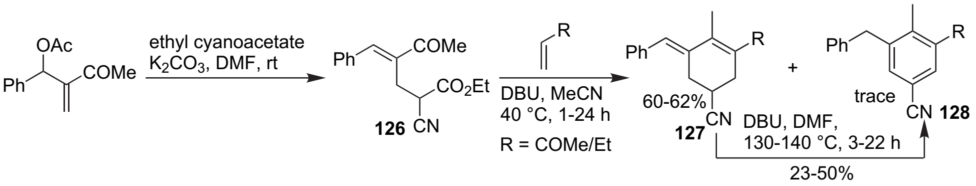
Ar = Ph, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 3-F-C_6H_4

Scheme 85.



Ar = Ph, 4-Me-C_6H_4, 4-Et-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 2-naphthyl

Scheme 86.



Scheme 87.

the highly substituted benzene (**128**), as shown in Scheme 87.[115]

9. Radical cyclizations

The radical cyclization has been extensively applied to the Baylis–Hillman chemistry for the generation of heterocyclic or carbocyclic derivatives. Shanmugam et al. 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 (Fig. 8).[116] Radical 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 *exo*-methylene-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]

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 *exo*-methylene-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

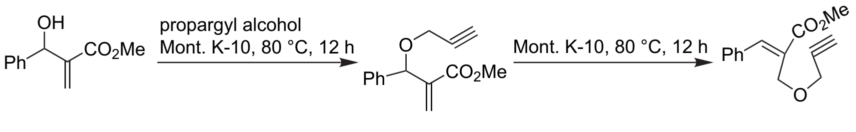
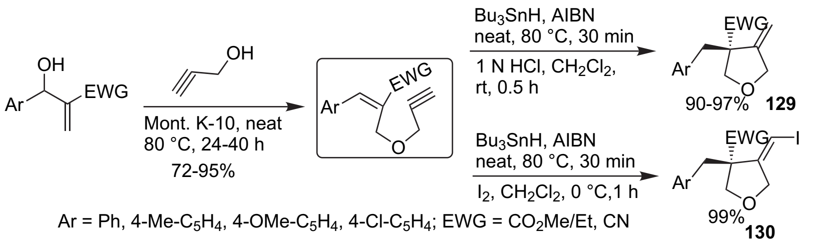
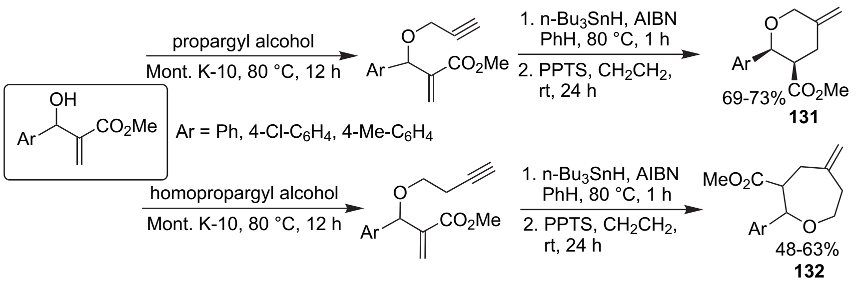


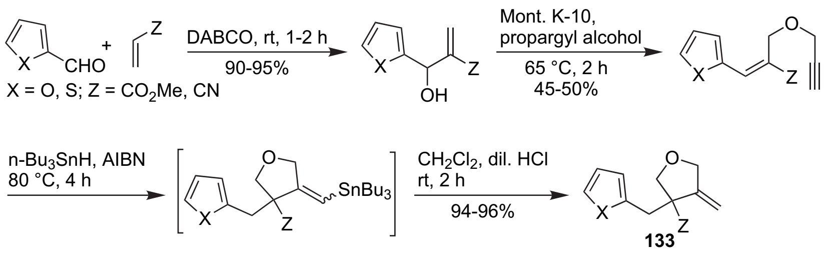
Figure 8. Isomerization of propargyl derivatives at higher temperatures.



Scheme 88.



Scheme 89.

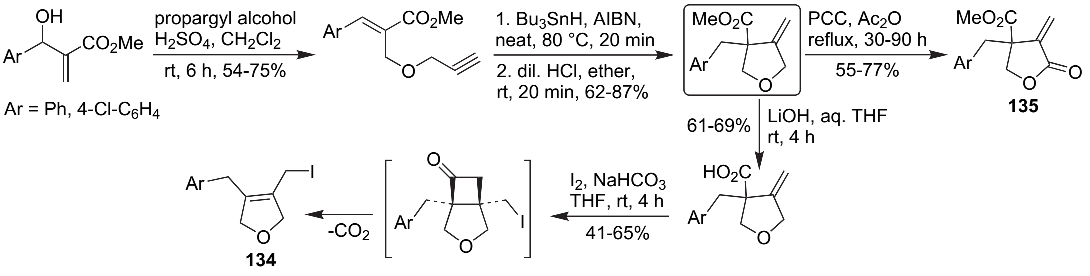


Scheme 90.

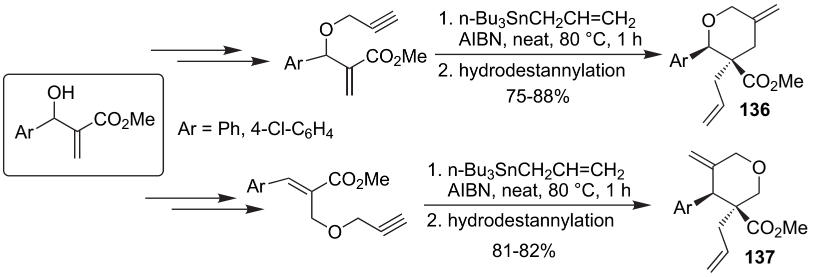
oxidation, as depicted in Scheme 91.[120] They have also disclosed the regioisomeric synthesis of two types of methylene-tetrahydropyrans (**136** and **137**) in high yields by reacting propargyl derivatives and allyltributylstannane followed by the strategy of vinyl radical cyclization, as shown in the reaction sequence in Scheme 92.[121]

In an alternative strategy to afford propargyl derivatives for the radical cyclization reaction, Kim et al. 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 *exo*-methylene-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 Scheme 94. Their attempt to carry out the cyclization in the presence of *n*-Bu_3SnH was unsuccessful.[123]

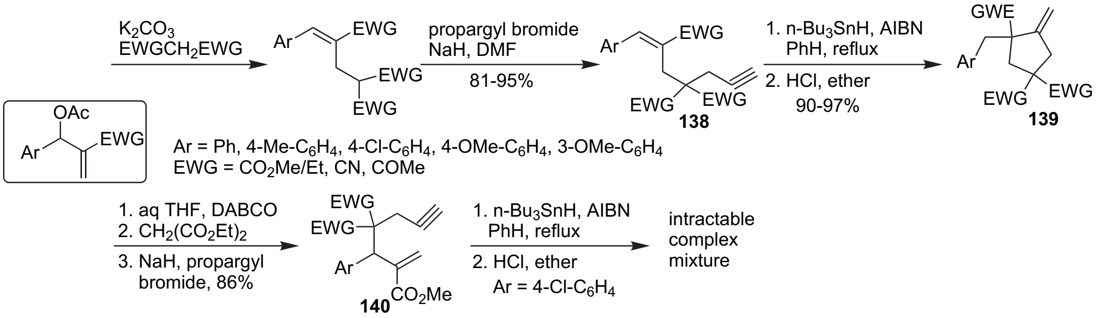
In another variation of the strategy, Kim et al. have successfully transformed the 2-bromophenol-substituted Baylis–Hillman derivatives into 3,3-disubstituted-2,3-dihydrobenzofurans (**143**) in good yield (Scheme 95).[124] Later, they reported an interesting synthesis of hexahydrofuro[2,3-*b*]furans (**144**) and



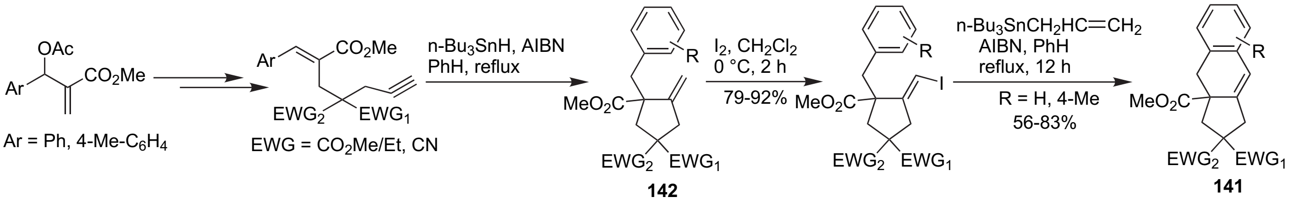
Scheme 91.



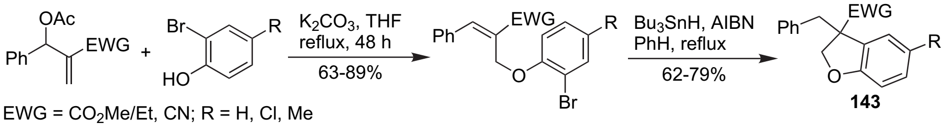
Scheme 92.



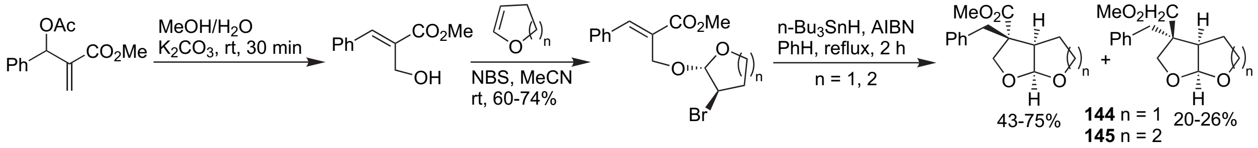
Scheme 93.



Scheme 94.



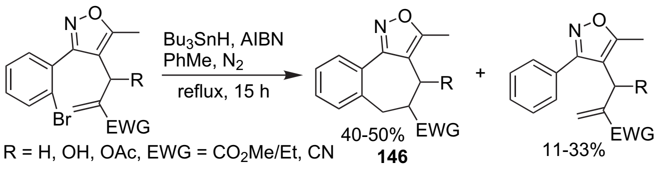
Scheme 95.



Scheme 96.

hexahydrofuro[2,3-*b*]pyrans (**145**) from the bromoacetals in the presence of *n*-Bu_3SnH via the Ueno–Stork reaction (Scheme 96).[125]

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 et al., 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 analogs into noraldehydes, which, upon Baylis–Hillman reaction, followed by successful radical



Scheme 97.

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]

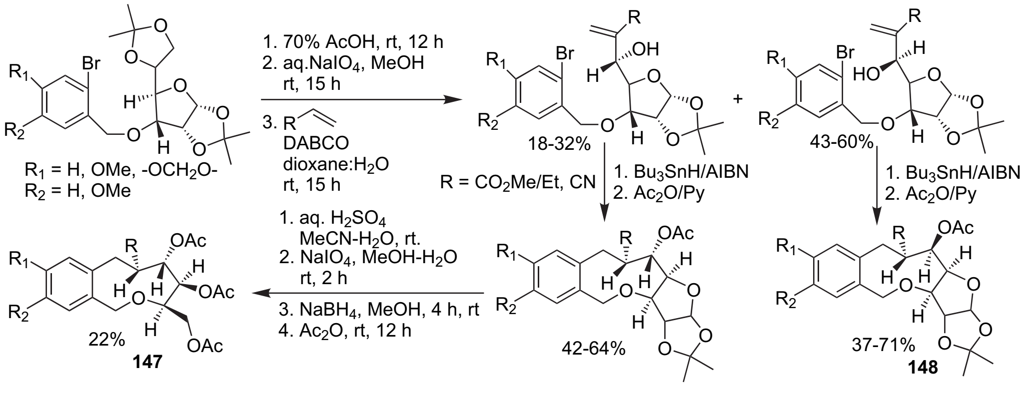
Atom-transfer radical polymerization was employed in the cyclopolymerizaton of a symmetrical dimethacrylate (**150**) under the influence of CuBr/PMDETA by Acar et al. (Scheme 100).[129]

The radical cyclization has been utilized for the generation of isochroman (**152**) and tetrahydroisoquinoline derivatives (**154**) from the Baylis–Hillman acetates by Kim et al. 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]

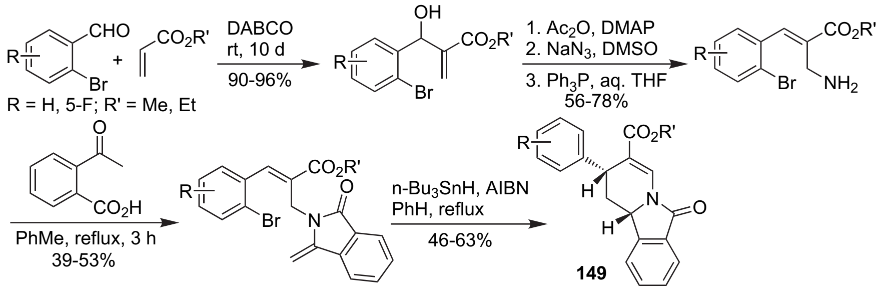
In another strategy, the derivatives afforded via the S_N2' reaction of tosylamine with the Baylis–Hillman acetates followed by alkylation with 1,4-dibromo-2-butane were cyclized in the presence of *n*-Bu_3SnH to afford the *N*-tosyl-3,3,4-trisubstituted-pyrrolidines (**155**) by this group (Scheme 102). 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]

10. Heck coupling reactions

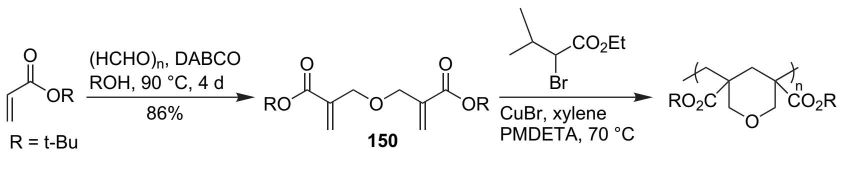
The Heck coupling reaction, another carbon–carbon bond-forming strategy, involving the coupling of halo-substituted arenes with alkenes or alkynes has been successfully applied for the generation of cyclic systems from the Baylis–Hillman derivatives.[132] Lee et al. described the synthesis of indanones (**157** and **158**) from the Baylis–Hillman adducts of 2-iodo-



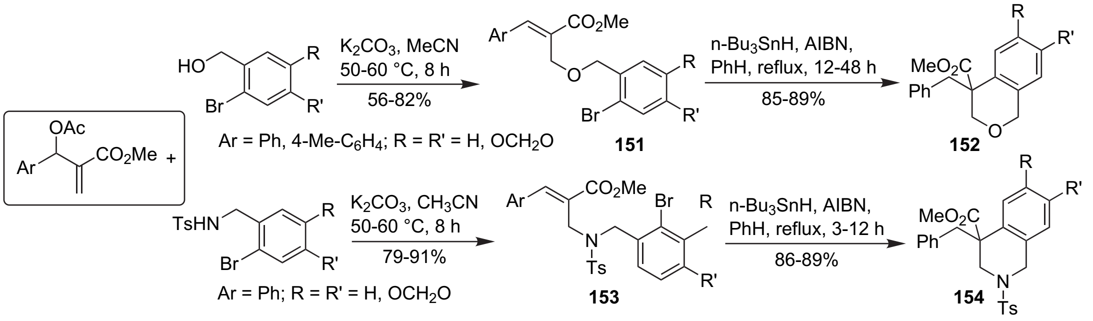
Scheme 98.



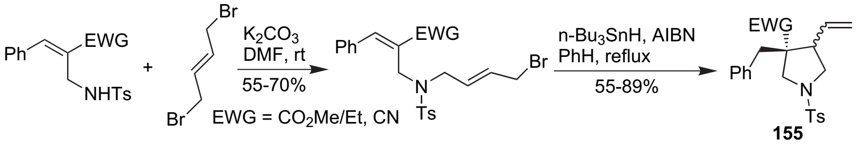
Scheme 99.



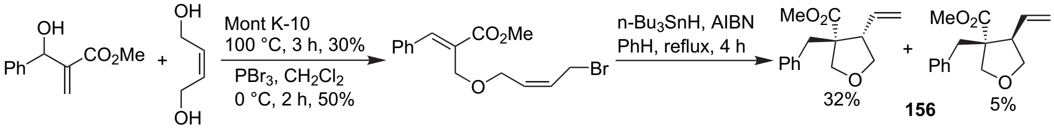
Scheme 100.



Scheme 101.

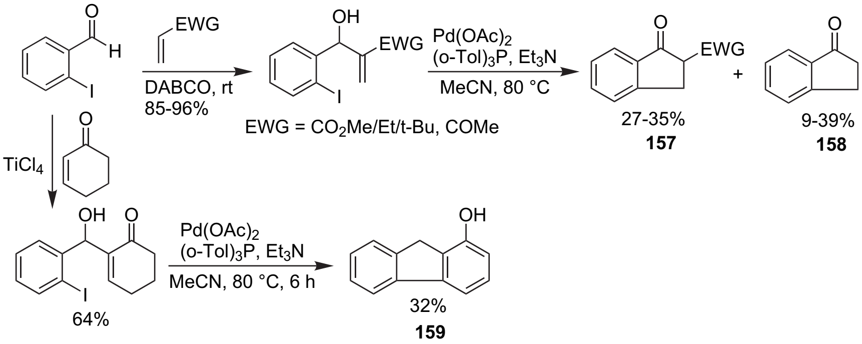


Scheme 102.

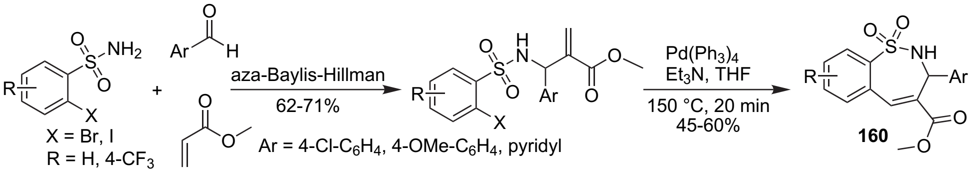


Scheme 103.

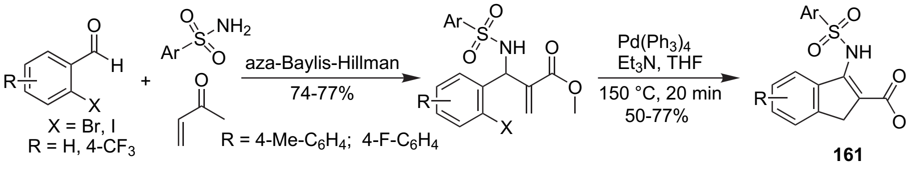
benzaldehydes via intramolecular Heck cyclization in the presence of $Pd(OAc)_2$ and (*o*-Tol)$_3$P, whereas, under similar reaction conditions the Baylis–Hillman adducts of 2-cyclohexen-1-ones afforded the 1-hydroxyfluorenes (**159**) (Scheme 104).[133] The successful transformation of aza-Baylis–Hillman 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 et al. via a sequential intramolecular Heck reaction followed by an aerial



Scheme 104.



Scheme 105.

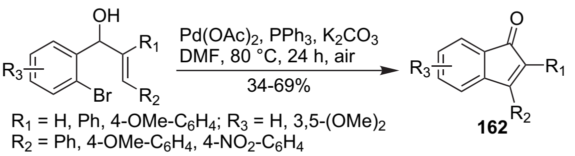


Scheme 106.

oxidation of allylic alcohols of Baylis–Hillman adducts of 2-halo-benzaldehydes, as shown in Scheme 107.[135]

Kim et al. 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]

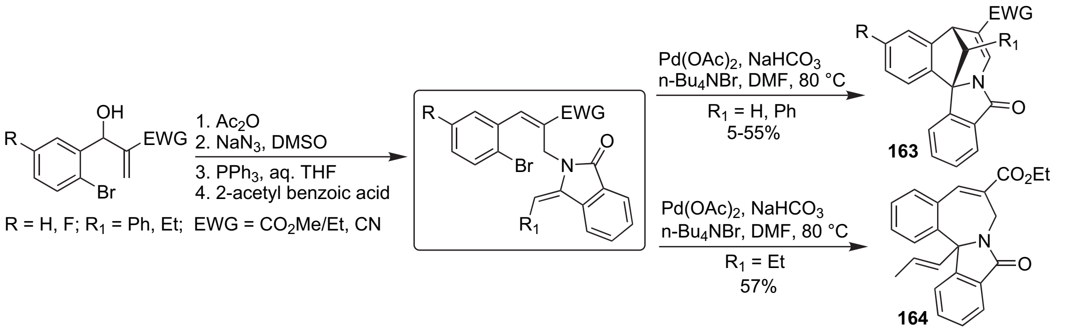
Very recently, these workers have also reported the synthesis of 2-arylquinolines **166** via a Pd-mediated sequential Heck-type cyclization and concomitant aerobic oxidation from the S_N2 reaction product **165** provided by the reaction between the Baylis–Hillman acetates and 2-bromoanilines, as shown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



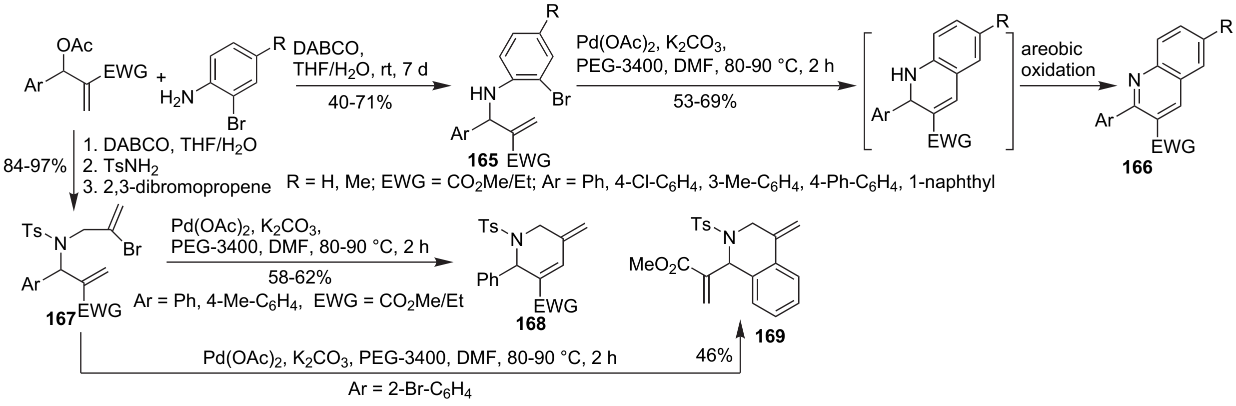
Scheme 107.

11. Ring-closing metathesis reactions

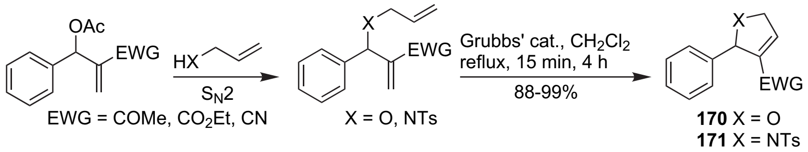
Ring-closing metathesis in Baylis–Hillman chemistry was introduced by Paquette and Mendez-Andino for the synthesis of α-methylene-γ-lactones fused to medium and large rings.[138] Kim et al. have published a series of papers on the application of RCM on a variety of Baylis–Hillman derivatives to generate several heterocyclic scaffolds. Initially, they subjected the *O*- and *N*-allylic derivatives to RCM in the presence of Grubbs' second-generation catalyst to synthesize



Scheme 108.



Scheme 109.

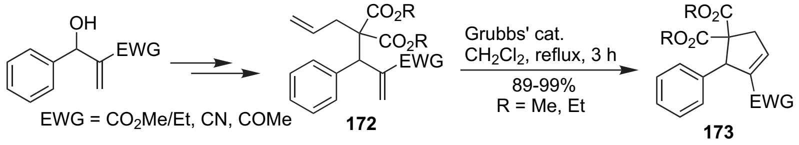


Scheme 110.

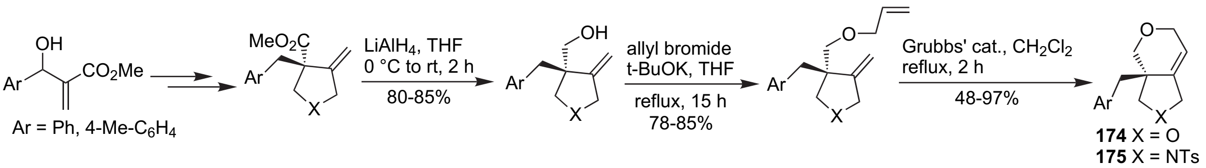
dihydrofurans (**170**) or dihydropyrroles (**171**) (Scheme 110).[139] Further, they generated other allyl derivatives (**172**), which served as useful synthons for the RCM reaction to yield cyclopentenes (**173**) in excellent yields (Scheme 111).[140] Recently, the same workers have demonstrated 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]

Balan and Adolfsson 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*-tosyldihydropyrrole (**177**) (Scheme 113).[142] Subsequently, Lamaty et al. 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]

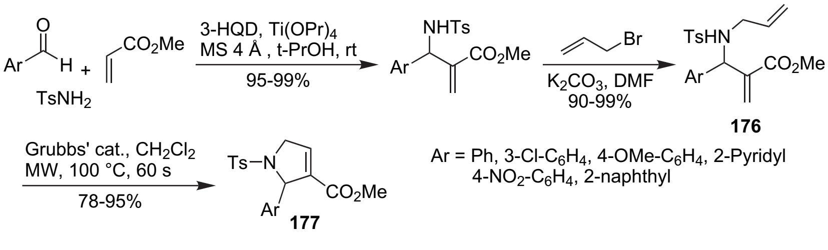
Krafft et al. described a new and efficient approach to functionalized hetero- and carbocyclic alkenoles, which are also afforded via an intramolecular Baylis–Hillman reaction. They generated the required synthon via a quinuclidine-promoted



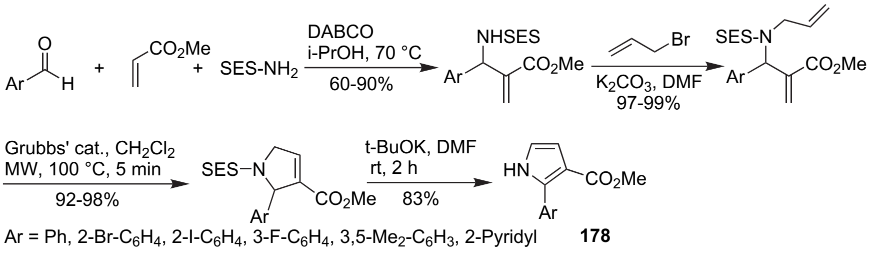
Scheme 111.



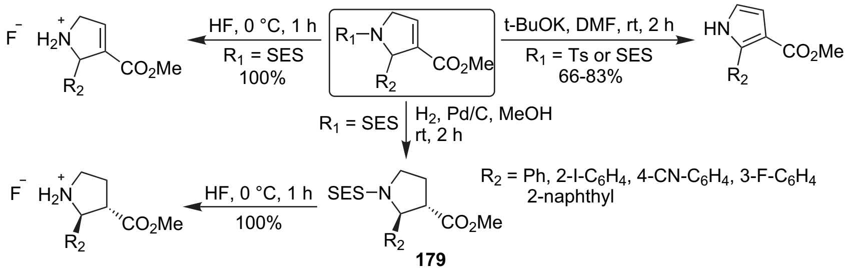
Scheme 112.



Scheme 113.



Scheme 114.



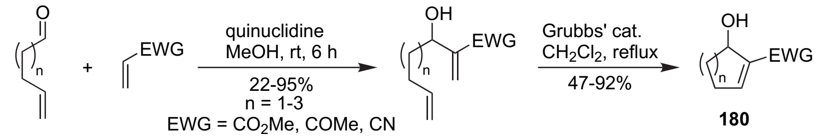
Scheme 115.

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 et al. 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]

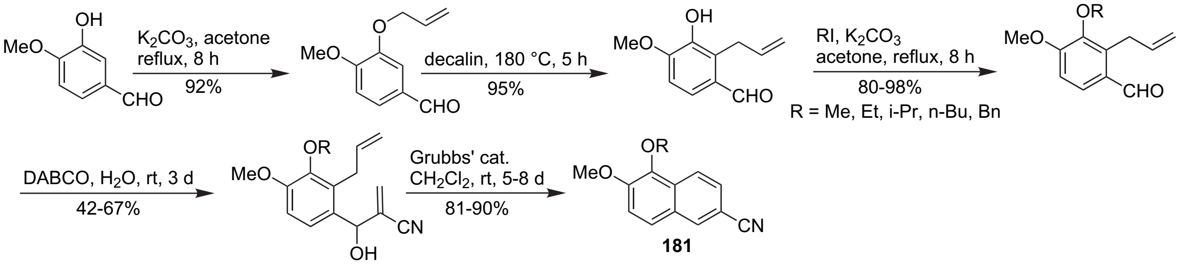
The sugar-based Baylis–Hillman adducts were efficiently utilized to prepare a library of diverse α,β-unsaturated λ-lactones (**182**) by Krishna and Narsingam using the RCM reaction (Scheme 118).[147]

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]

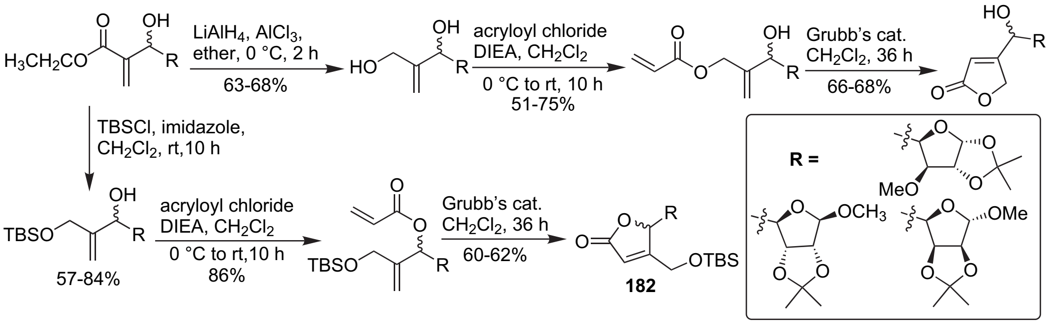
Recently, Kim et al. disclosed an expeditious route for the synthesis of pyrrolidines and tetrahydrofurans (**185** and **186**), starting from the suitably modified Baylis–Hillman adducts involving RCM followed by hydrogenation or radical cyclization and subsequent hydrogenation protocols, as shown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



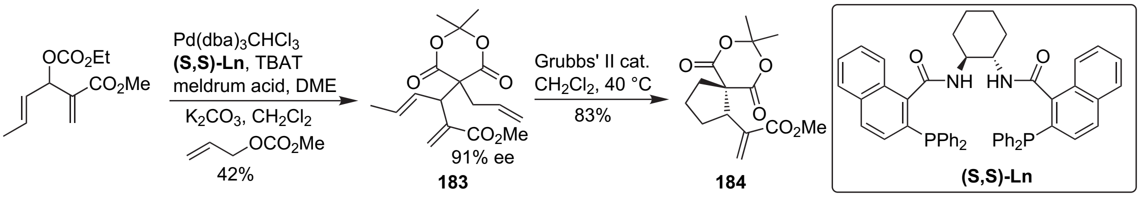
Scheme 116.



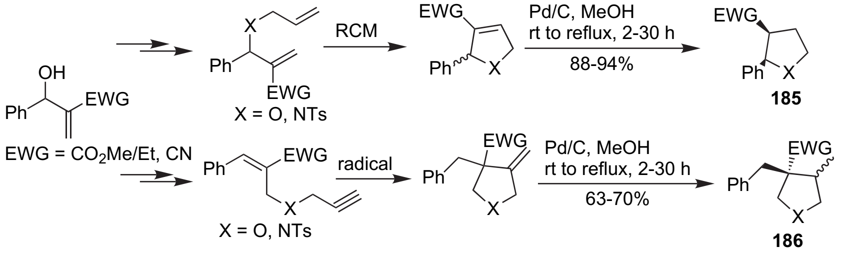
Scheme 117.



Scheme 118.

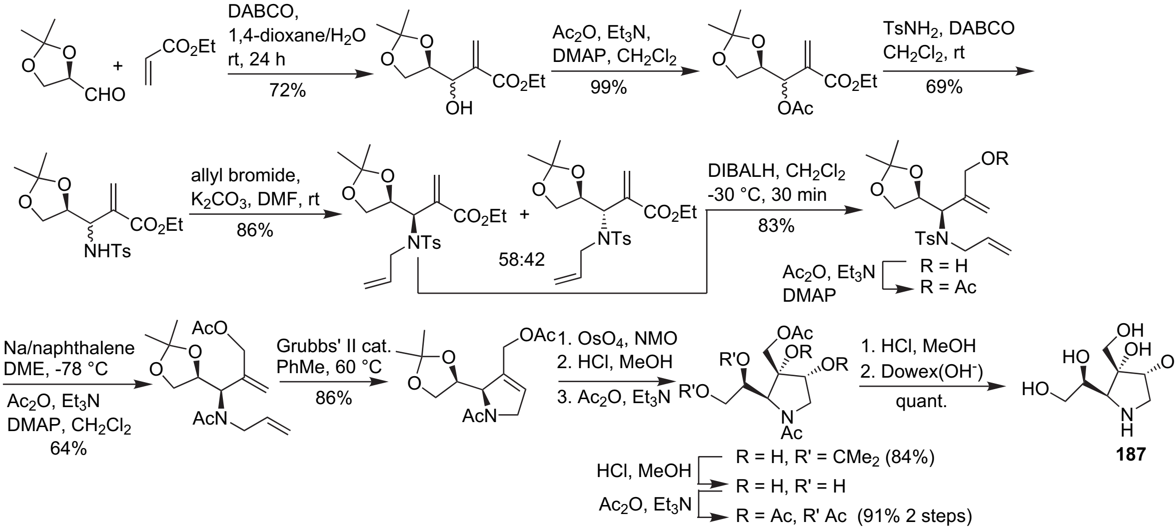


Scheme 119.

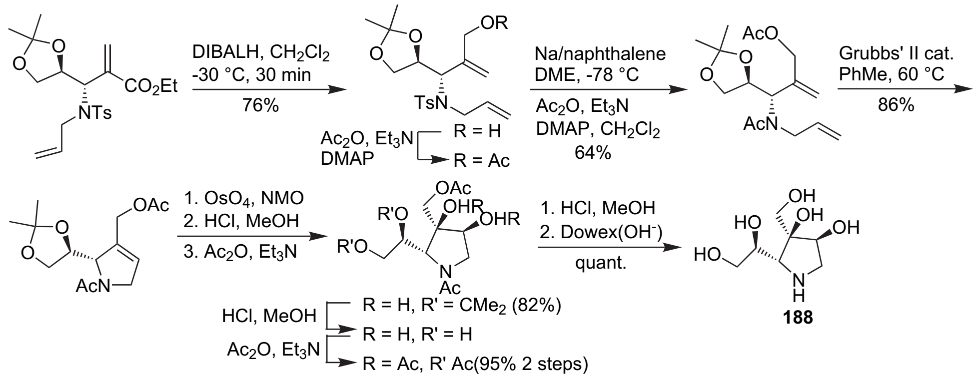


Scheme 120.

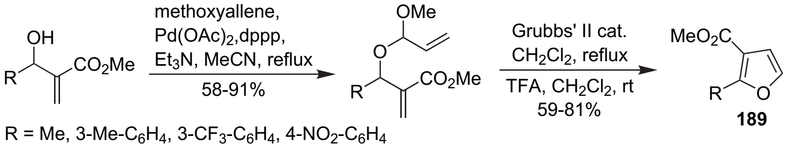
Doddi and Vankar described efficient syntheses of two pyrrolidine-based imino sugars (**187** and **188**) initiating from the Baylis–Hillman adduct of (*R*)-2,3-*O*-isopropylidene-glyceraldehydes. The key steps included the regiospecific amination (via an S_N2 reaction), RCM and diastereospecific dihydroxylations,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



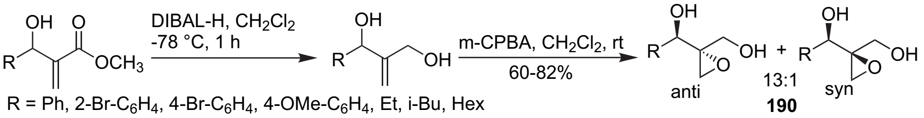
Scheme 121.



Scheme 122.



Scheme 123.



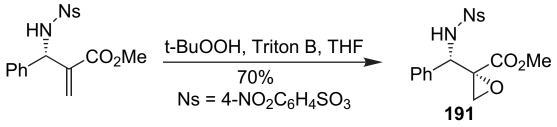
Scheme 124.

Donohoe et al. 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]

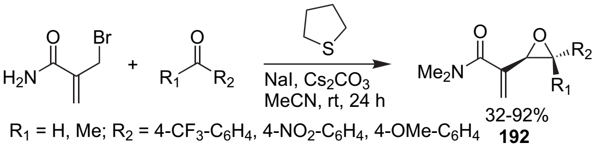
Several other research groups have also employed the RCM strategy for the synthesis of a variety of natural products from the Baylis–Hillman derivatives. Theses approaches are discussed in Section 21.

12. Epoxide formation

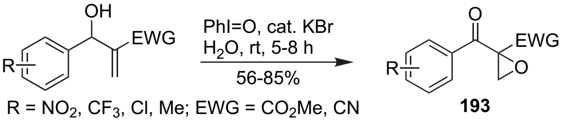
Baylis–Hillman derivatives have been successfully exploited for the generation of several substituted oxirane compounds. A highly diastereoselective epoxidation of allylic diols to provide the *trans*-epoxides (**190**) from the Baylis–Hillman adducts was reported by Coelho et al. The high *anti*-diastereoselectivity 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]



Scheme 125.



Scheme 126.



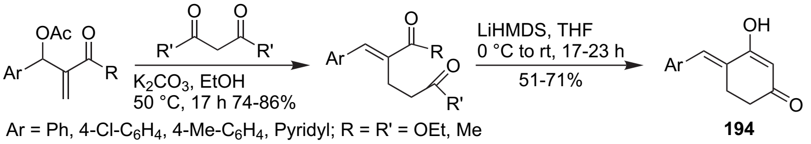
Scheme 127.

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]

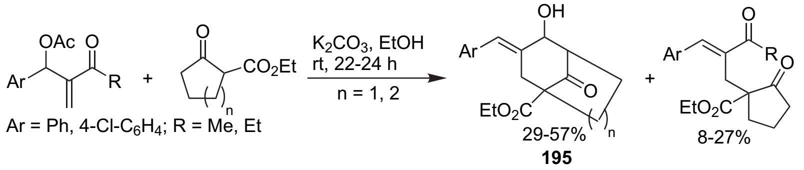
Das et al. described the synthesis of acyloxiranes (**193**) from the Baylis–Hillman adducts in the presence of iodosobenzene, which was utilized as an oxidizing agent for the two-fold oxidation of a secondary alcohol followed by epoxidation of the generated enone (Scheme 127).[155] A catalytic amount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

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 et al. 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'



Scheme 128.



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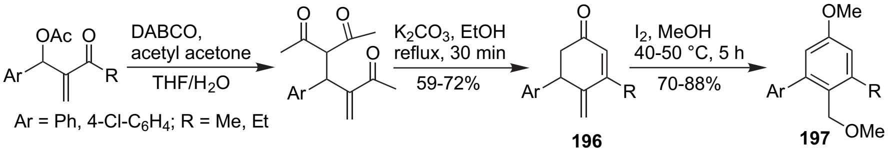
Scheme 129.



196

197

Scheme 130.

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]

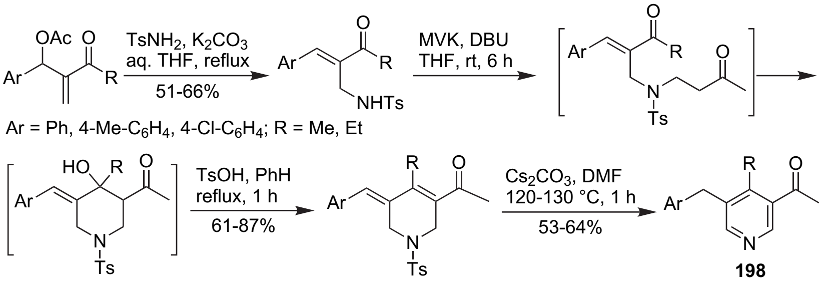
Subsequently, Kim et al. demonstrated that the S_N2 reaction of Baylis–Hillman acetates of alkyl vinyl ketones with acetylacetone in the presence of DABCO led to a synthon, which, on refluxing with K_2CO_3 in ethanol, gave 4-methylene-2-cyclohexenones (**196**) (Scheme 130).[159] Further treatment of 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]

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]

Recently, Kim et al. 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]

14. Claisen rearrangement

Basavaiah's group demonstrated the synthesis of alkylidine dialkanoates from the reaction between Baylis–Hillman



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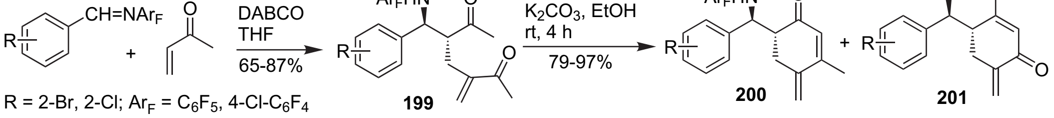
Scheme 131.

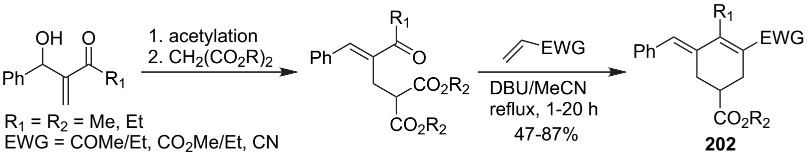


199

200

201

Scheme 132.



202

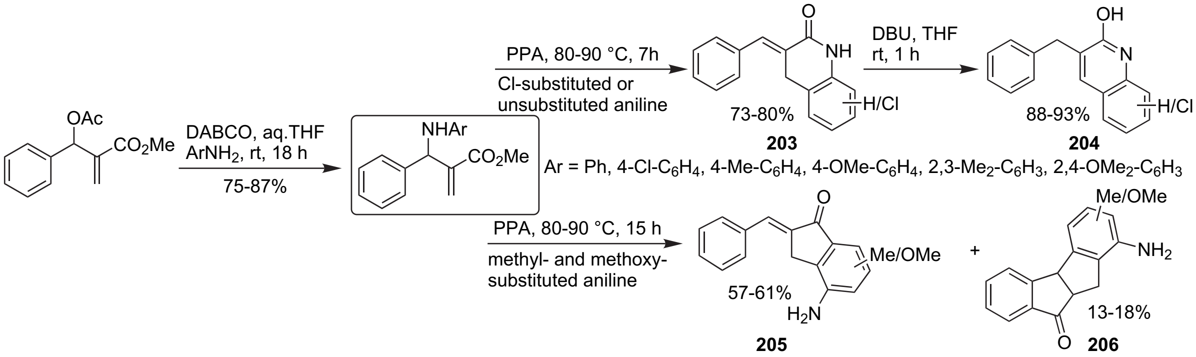
Scheme 133.

adduct and triethyl orthoacetate as the first example of a Claisen rearrangement in the Baylis–Hillman chemistry.[163] Recently, Kim et al. 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]

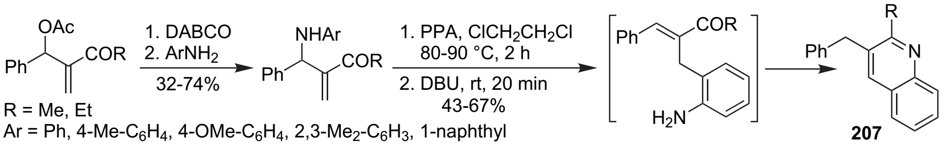
With an objective of our research group being to develop an easy and scaleable approach to the starting material for the anti-tubercular compound R207910, we have also developed a strategy to obtain 3-arylidene-2-quinolones (**208**). In our effort to replace PPA (difficult to handle on a large scale), 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.

15. Lactonization reaction

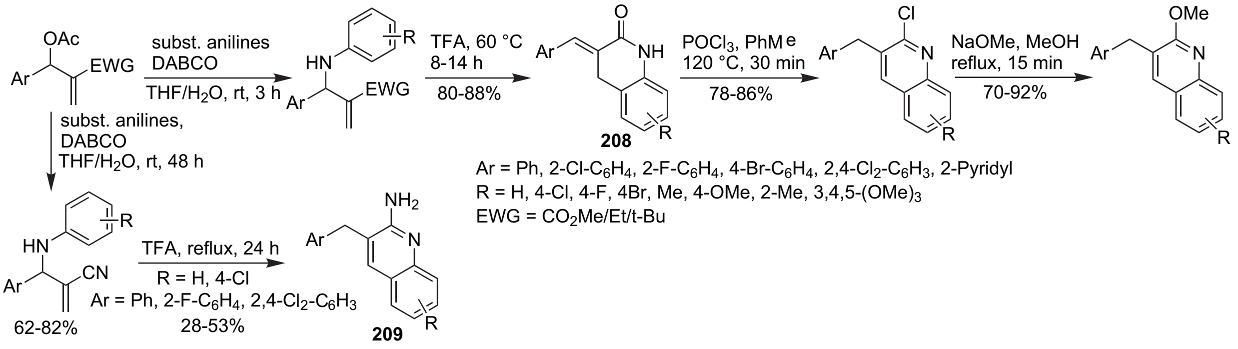
Over the years, several Baylis–Hillman derivatives have been utilized elegantly for the generation of the α-methylene-γ-butyrolactone, ring, which is ubiquitously present in several alkaloids and terpenoids.[167] Kim et al. have successfully developed the synthesis of α-methylene-γ-butyrolactones



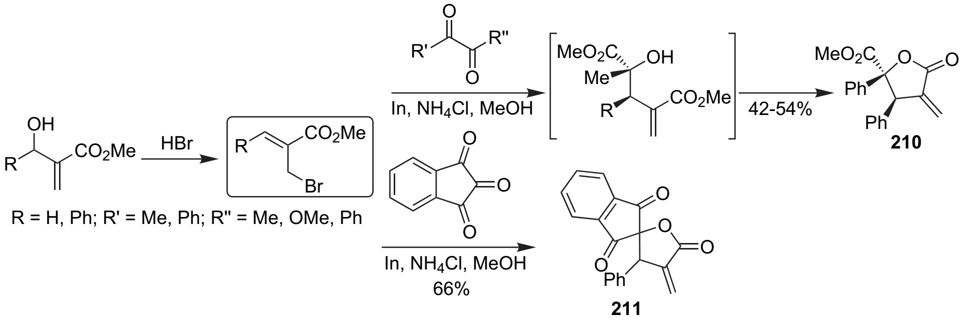
Scheme 134.



Scheme 135.



Scheme 136.



Scheme 137.

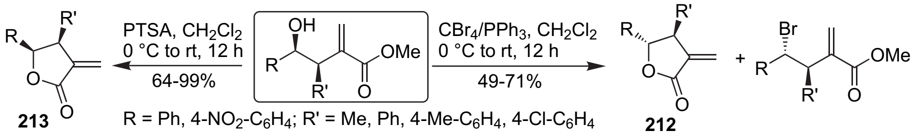
(**210**) via the reaction between allyl bromides and a variety of reactive carbonyl compounds under the influence of In and NH_4Cl, as shown in Scheme 137.[168] Indeed, with ninhydrin or *N*-benzylisatin, they demonstrated the formation of spiro analogs (**211**).

Subsequently, Kabalka et al. 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]

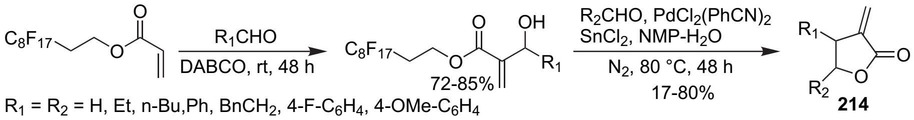
A library of mono- or disubstituted α-methylene-γ-lactones (**214**) was generated via a straightforward two-step reaction by Gouault et al. (Scheme 139).[170] Their fluorous-phase synthetic strategy employed flourous acrylates as the starting materials and removal of fluorous alcohol via cycloelimination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

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 TfOH 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]

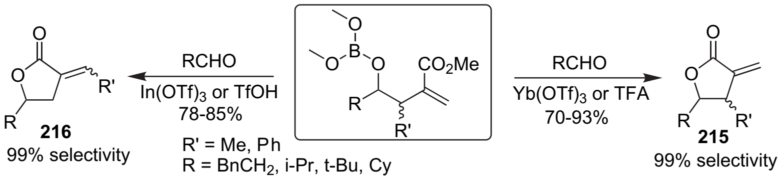
Indeed, several other workers have also described excellent syntheses of arylidene-butyrolactones. The transformation of triple-bond tethered methyl cinnamates to arylidene lactones (**218**) under the influence of iodine via iodolactonization was reported by Kim et al. (Scheme 142).[173] They also demonstrated the success of their strategy with NBS and H_2SO_4 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



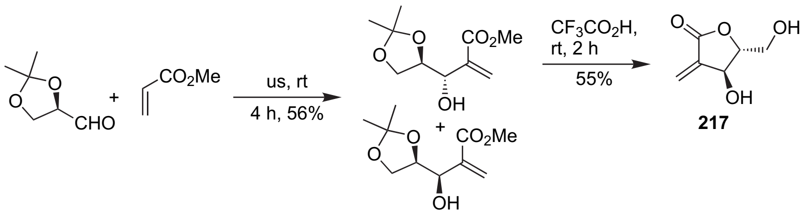
Scheme 138.



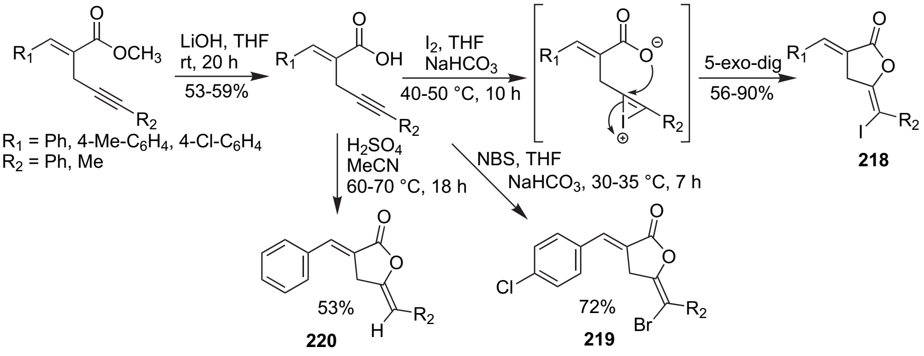
Scheme 139.



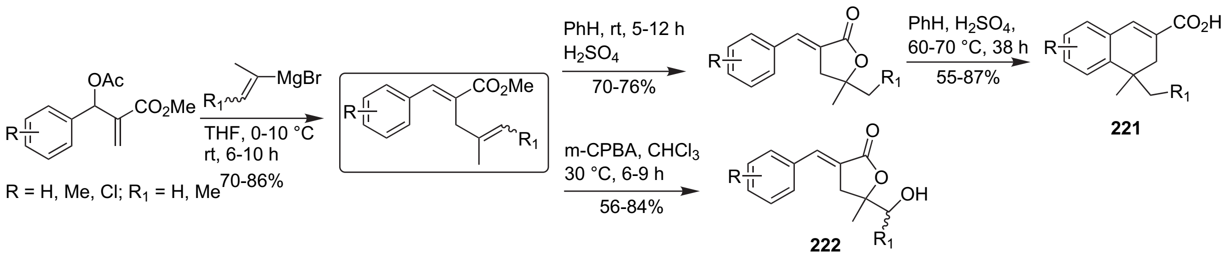
Scheme 140.



Scheme 141.



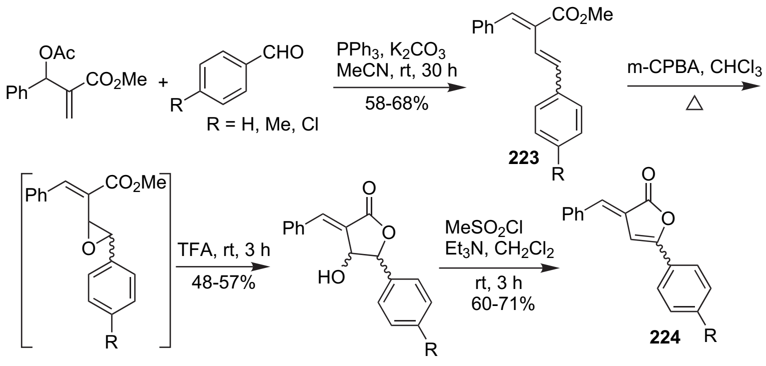
Scheme 142.



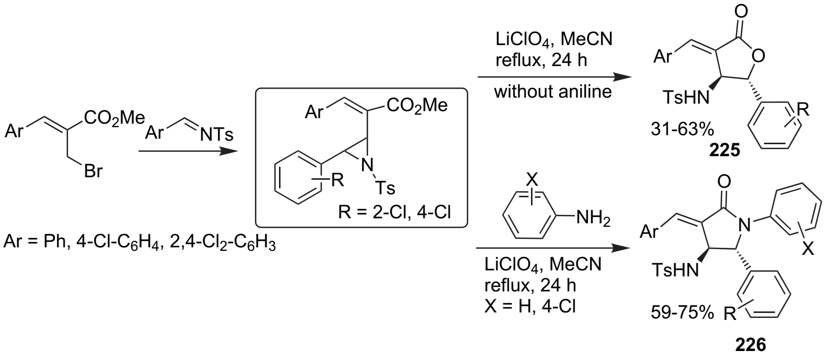
Scheme 143.

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.

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*-tosylaziridines originating from the reaction between the allyl bromide and *N*-tosylamine (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*-tosylaziridine 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



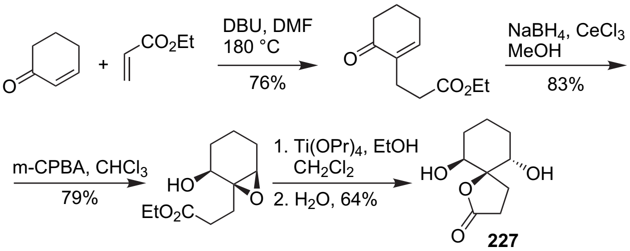
Scheme 144.



225

226

Scheme 145.

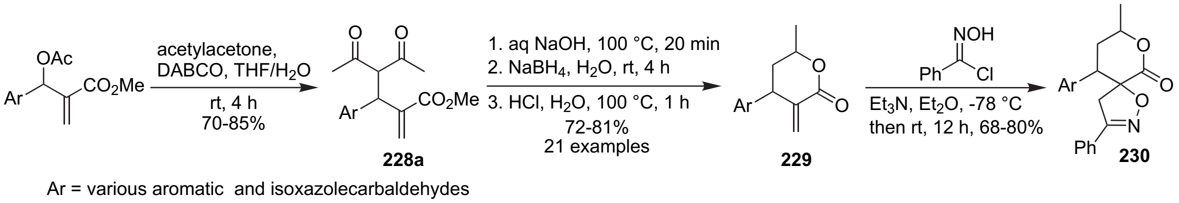


227

Scheme 146.

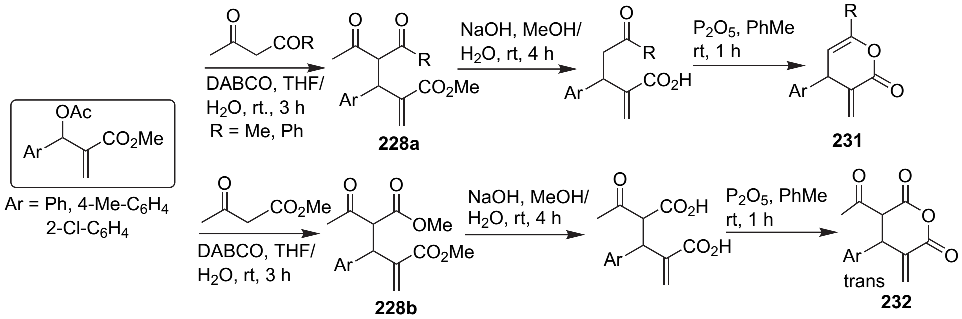
a chelation-controlled epoxide-opening strategy under the influence of Ti(O*i*-Pr)$_4$ (Scheme 146).[177]

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 et al. 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



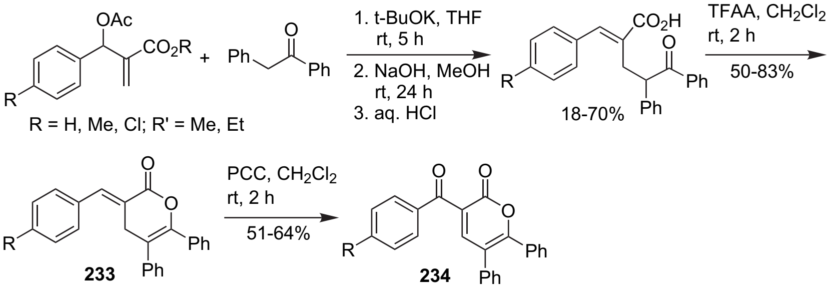
228a **229** **230**

Scheme 147.



228a **231** **228b** **232**

Scheme 148.



Scheme 149.

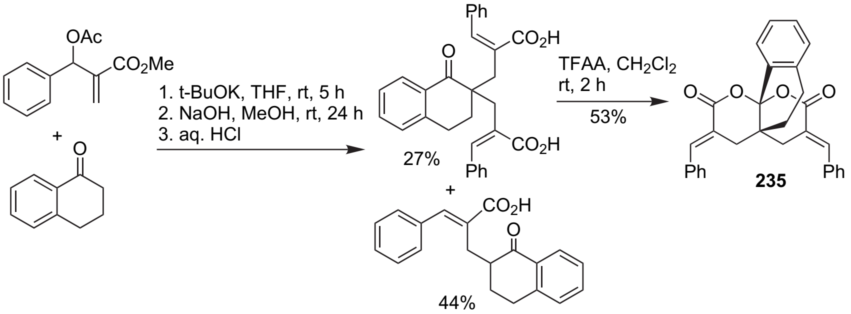
delineated in Scheme 149.[181] These pyranones were oxidized in the presence of PCC to yield 3-aryl-α-pyrones (**234**). A similar protocol with α-tetralone led to the mono- and bis-products (Scheme 150). The bis-product was lactonized to yield the same lactone (**235**), which has been reported earlier 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]

16. Reductive cyclization

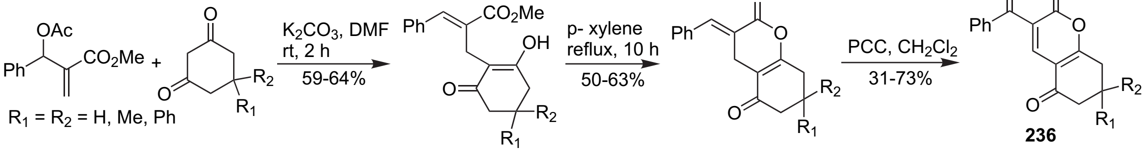
The strategy of reductive cyclization has found extensive applications in the Baylis–Hillman chemistry with respect to the synthesis of a variety of nitrogen- and oxygen-containing heterocyclic systems. The syntheses of several nitrogen-containing heterocycles have been achieved by reduction of the nitro 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

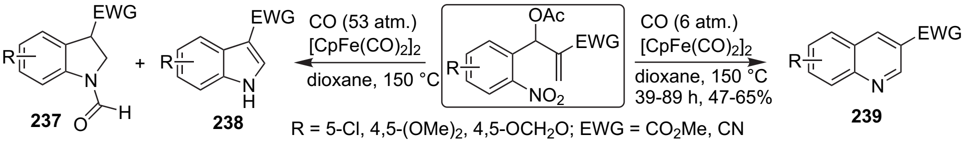
The reductive cyclization involving an aromatic nitro group in the Baylis–Hillman chemistry has evolved extensively. O'Dell and Nicholas reported the formation of a mixture of *N*-formyl indolines (**237**) and indoles (**238**) via reduction of the nitro group by using 53 atm of CO and $[CpFe(CO)_2]_2$ (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]



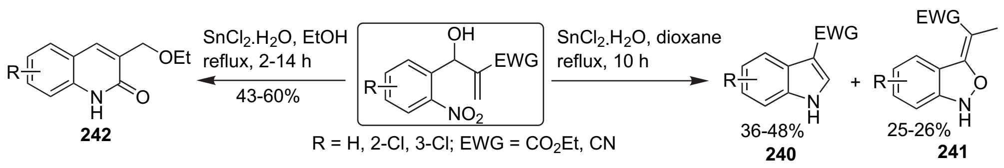
Scheme 150.



Scheme 151.



Scheme 152.



Scheme 153.

Very recently, Kim et al. 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]

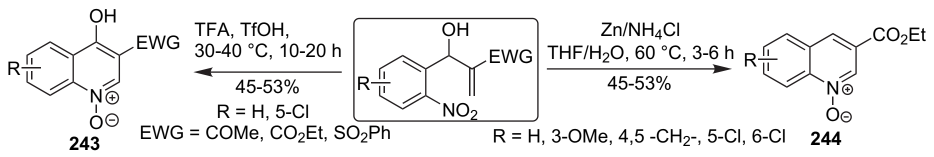
Basavaiah et al. were the first to demonstrate that the Baylis–Hillman derivatives produced from 2-nitrobenzaldehyde are excellent precursors to functionalized 2-quinolones and quinolines.[188] Subsequently, Kim et al. reported the formation of 3-substituted-4-hydroxyquinoline *N*-oxides (**243**) from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

Basavaiah et al. 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]

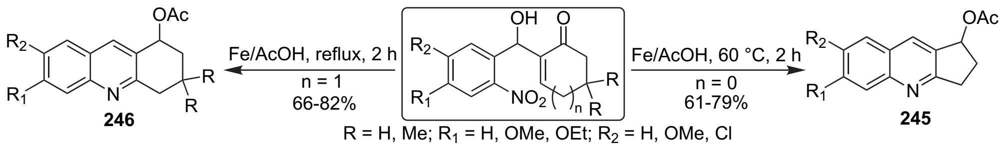
Recently, Liu et al. have described a mild and efficient direct nucleophilic substitution of the Baylis–Hillman acetates derived from cyclic enones with indoles in the presence of AgOTf as a catalyst. The reaction provided highly α-regioselective indole derivatives (**248**). The reaction products of 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]

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]

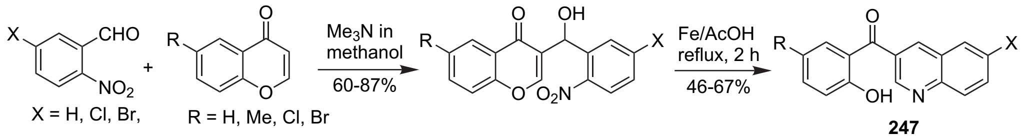
We have recently reported an alternative route to quinolines (**251** and **252**) from the S_N2 reaction products of Baylis–Hillman acetates of substituted 2-nitrobenzaldehydes and carbonyl-group-containing nucleophiles, as shown in Scheme 159.[196] We have observed that treatment of these products 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.



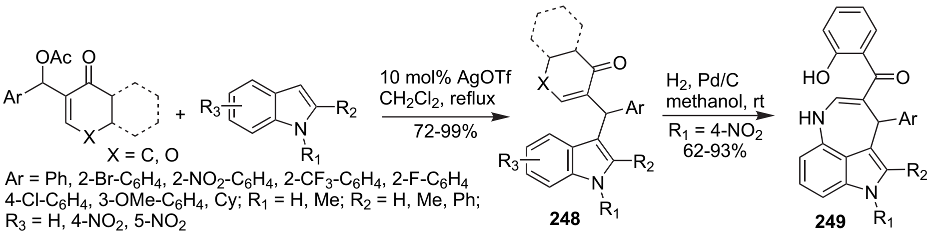
Scheme 154.



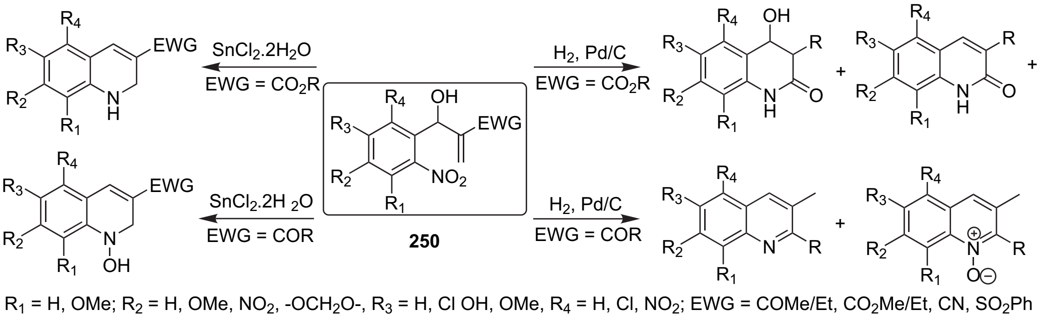
Scheme 155.



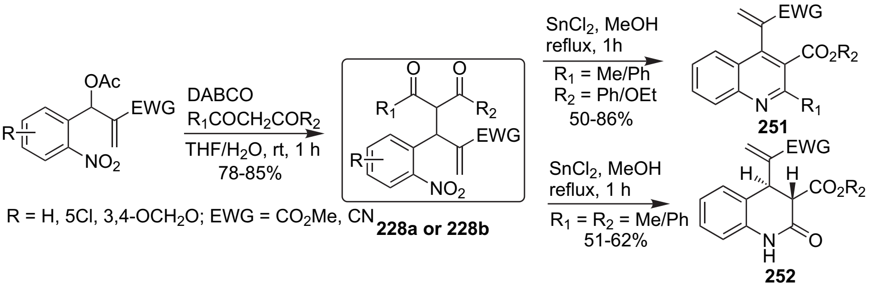
Scheme 156.



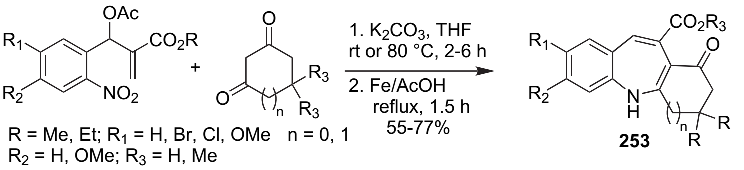
Scheme 157.



Scheme 158.



Scheme 159.



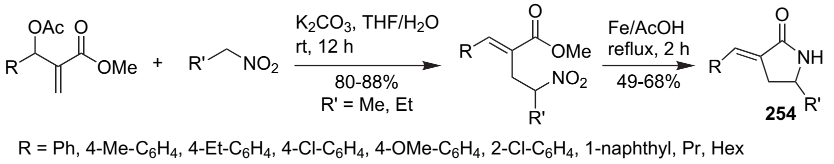
Scheme 160.

Very recently, Basavaiah et al. 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]

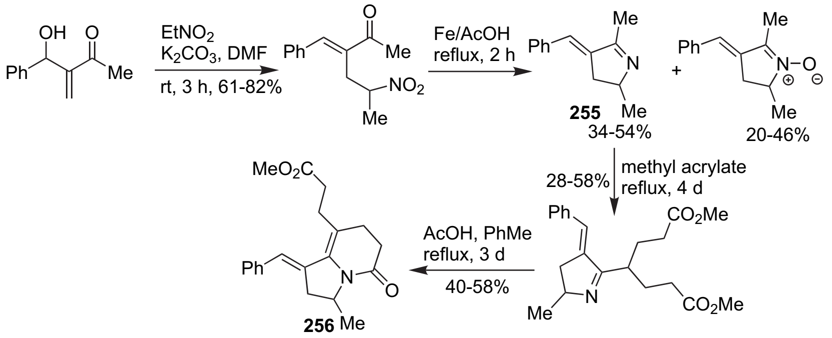
16.2. Reduction of aliphatic nitro groups

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.

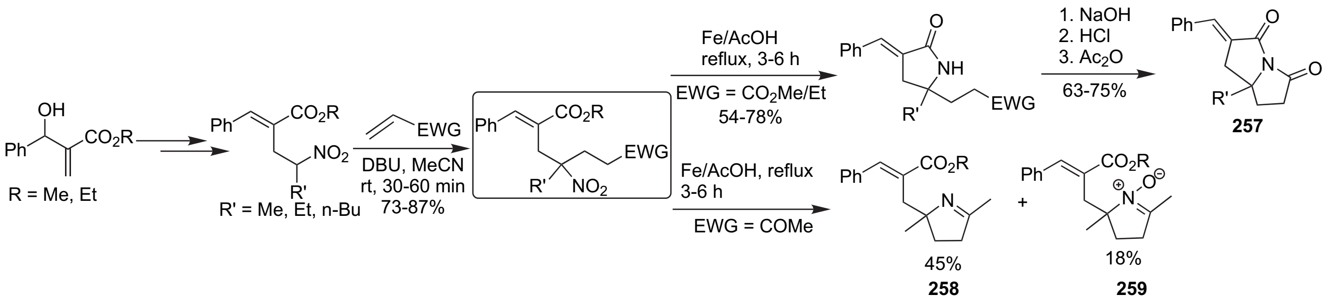
Subsequently, analogous to this strategy, Kim et al. used similar substrates afforded by the Baylis–Hillman adducts of methyl vinyl ketone for the synthesis of 4-benzylidene-2,5-dimethyl-3,4-dihydro-2*H*-pyrroles (**255**), as shown in Scheme 162.[199] Further, they transformed these pyrroles (**255**) 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 methyl vinyl



Scheme 161.



Scheme 162.



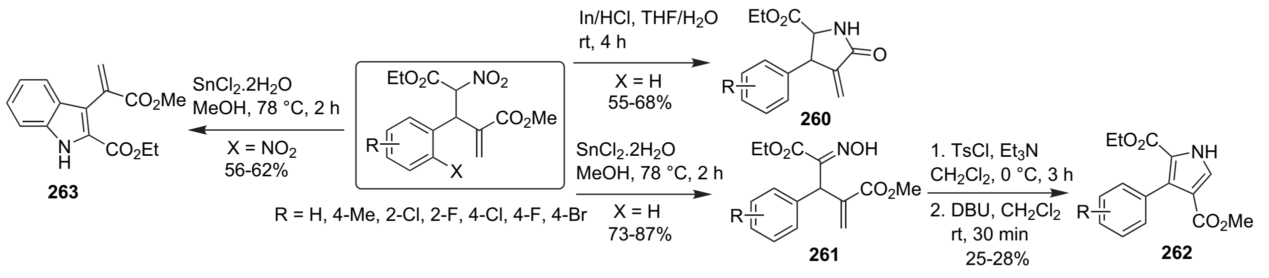
Scheme 163.

ketone upon reduction of the nitro group to amine furnished the dihydropyrrole (**258**) and its *N*-oxide derivative (**259**) (Scheme 163).[200]

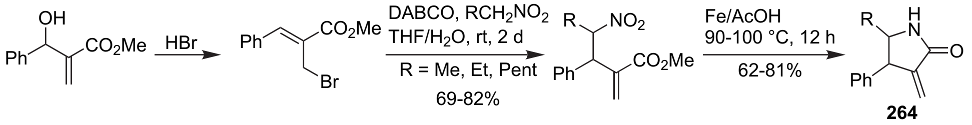
We have recently reported a facile synthesis of 3-*exo*-methylene pyrrolidinones (**260**) via In/HCl-mediated reductive cyclization of Baylis–Hillman derivatives afforded from the S_N2 reaction of Baylis–Hillman acetates with ethyl nitroacetate, as shown in Scheme 164.[201] We discovered that, in these substrates, the secondary nitro group undergoes a partial reduction to the oximes (**261**) in the presence of $SnCl_2 \cdot 2H_2O$. 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 $SnCl_2 \cdot 2H_2O$, due to chemoselective reduction of the aromatic nitro group to amine and the aliphatic nitro group to oxime.

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]

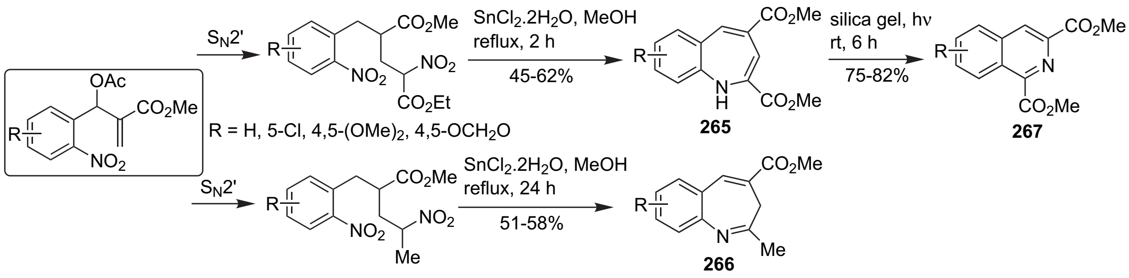
In an extension to our work, we have recently reported the synthesis of benzazepines (**265** and **266**) by $SnCl_2 \cdot 2H_2O$-promoted reductive cyclization of the S_N2' reaction product of ethyl



Scheme 164.



Scheme 165.



Scheme 166.

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.

16.2.1. 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.

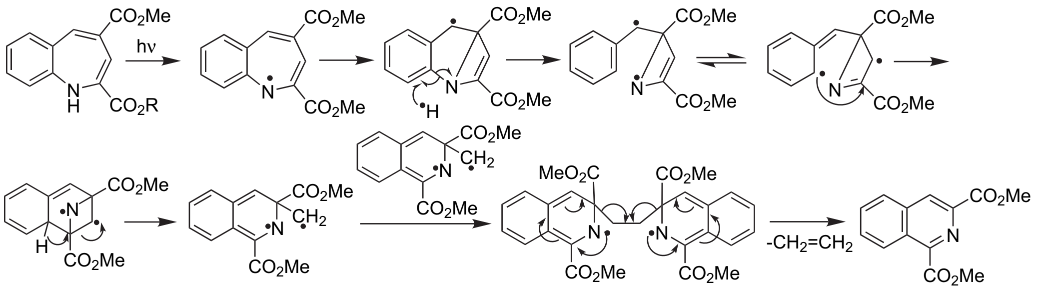
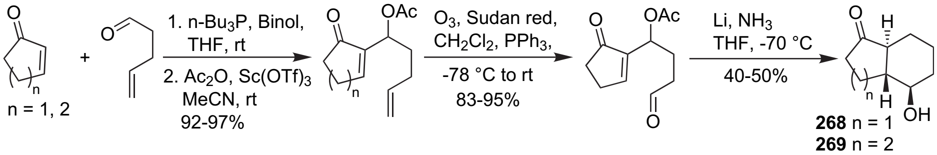
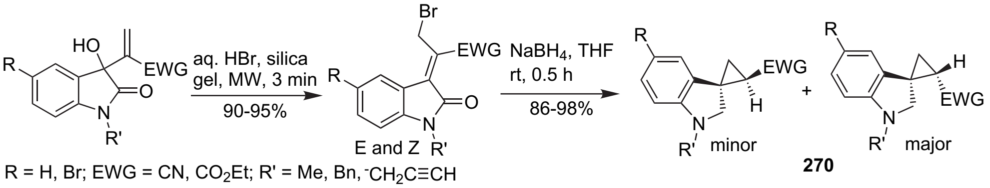


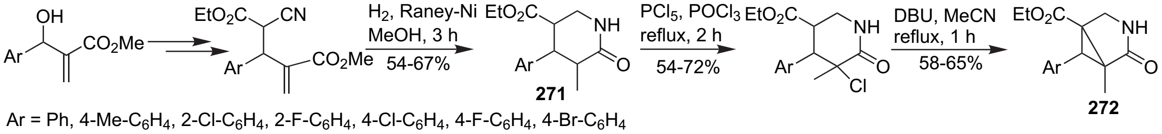
Figure 9.



Scheme 167.



Scheme 168.



Scheme 169.

Shanmugam et al. 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]

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]

17. Hydrolysis of nitrile groups

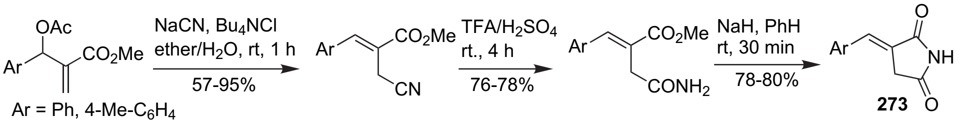
The hydrolysis of the nitrile group, present in the Baylis–Hillman adducts derived from acrylonitrile, or as part of the nucleophile added on to the Baylis–Hillman derivatives, has been utilized in different ways to obtain heterocycles, especially containing an amide linkage.

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]

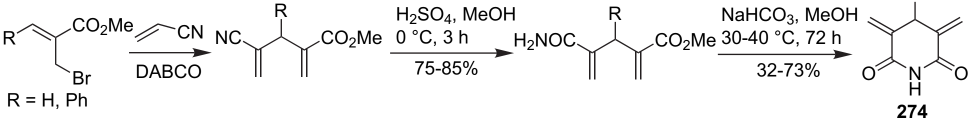
Kim et al. also described the synthesis of glutarimide derivatives (**274**) from the cinnamyl bromides according to the reaction shown in Scheme 171.[207] An S_N2 reaction of malononitrile on the acetate of the Baylis–Hillman adduct of acrylate followed by hydrolysis afforded a diamides, which was cyclized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

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).

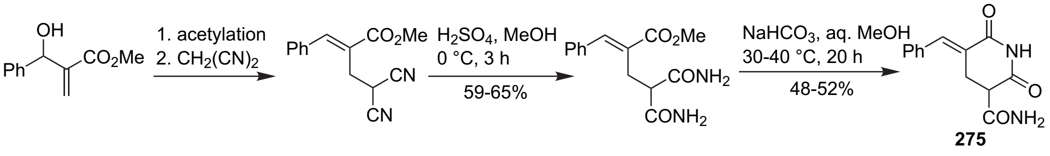
More recently, our group has achieved the synthesis of 3-methylene-2-pyridones (**278**) from the S_N2 reaction products of Baylis–Hillman acetates and acetylacetone or methyl acetoacetate via TFA/H_2SO_4-promoted hydrolysis of the nitrile group, as shown in Scheme 174.[209] Replacing the nucleophile 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 2-pyridone-spiroisoxazoline derivatives in highly regio- and diastereoselective fashion.



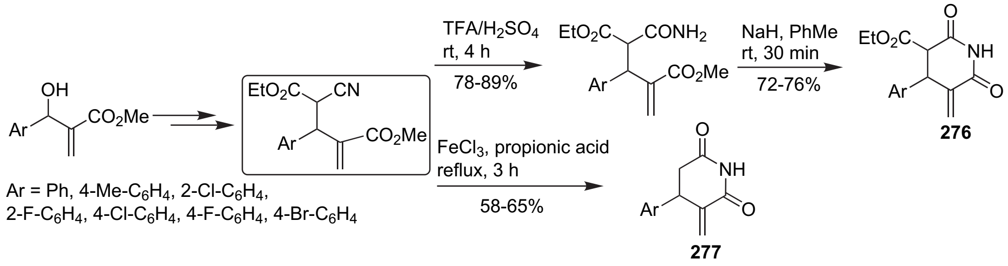
Scheme 170.



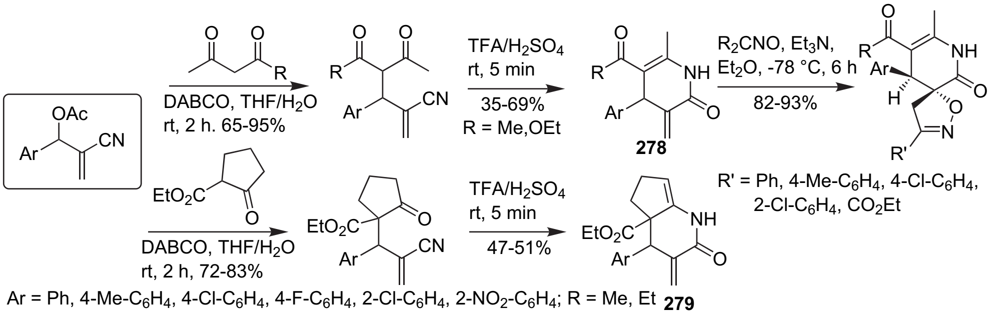
Scheme 171.



Scheme 172.



Scheme 173.



Scheme 174.

18. Heterocyclization of substituted 3-aminopropanols and allyl amines

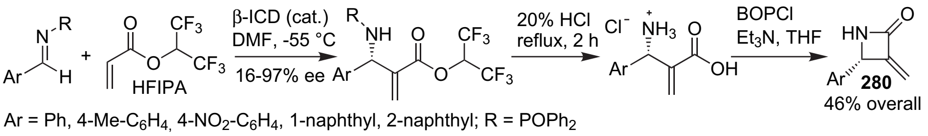
The nucleophilic addition of amines on the Baylis–Hillman adduct results in substituted 3-aminopropanols, while a similar addition on the Baylis–Hillman acetates or allyl bromides afforded substituted allyl amines. Both these substrates have been efficiently utilized for the synthesis of several nitrogen-containing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

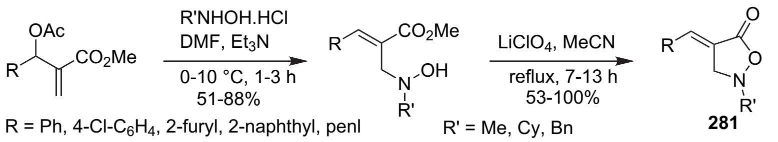
Kim et al. described the synthesis of 4-arylidene-2-substituted-isoxazolidin-5-ones (**281**) from *N*-hydroxyallyl amines via $LiClO_4$-promoted intramolecular cyclization involving hydroxy and ester groups (Scheme 176).[211]

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 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. Compounds **284** were easily transformed into the substituted imidazo[1,2-*a*]pyrimidin-2-ones **285** by treatment with ethylbromoacetate.

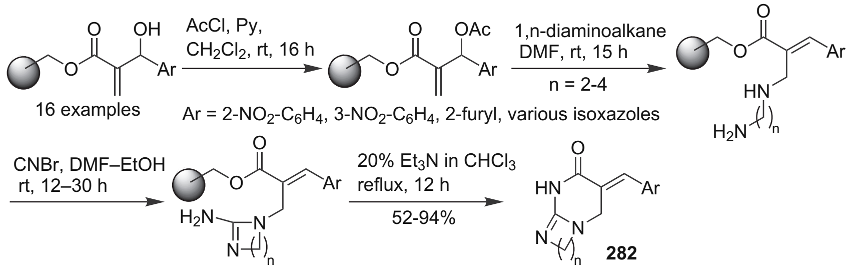
Following a similar reaction protocol, our research group has increased the scope of this strategy by the preparation of



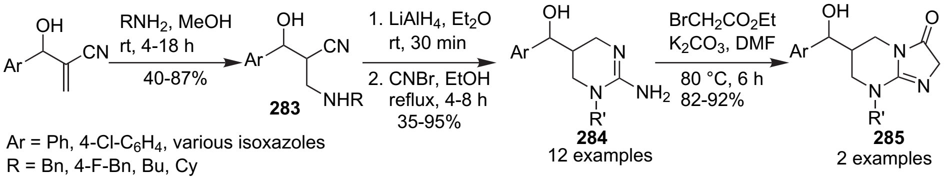
Scheme 175.



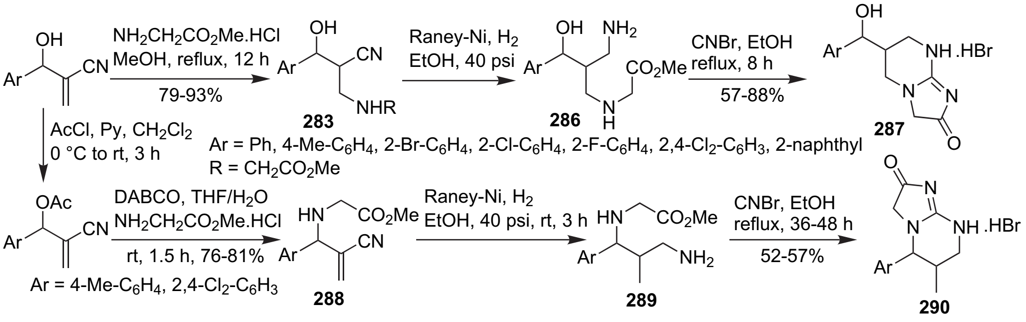
Scheme 176.



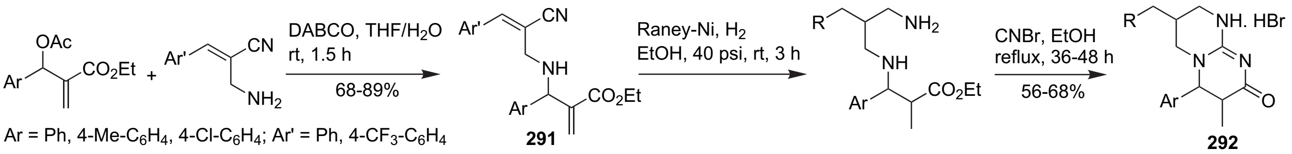
Scheme 177.



Scheme 178.



Scheme 179.

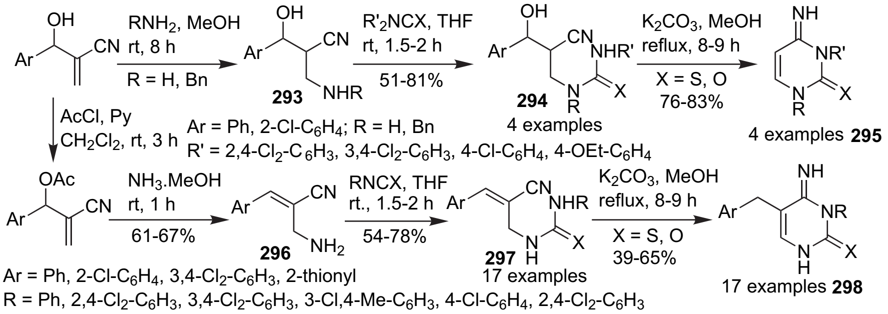


Scheme 180.

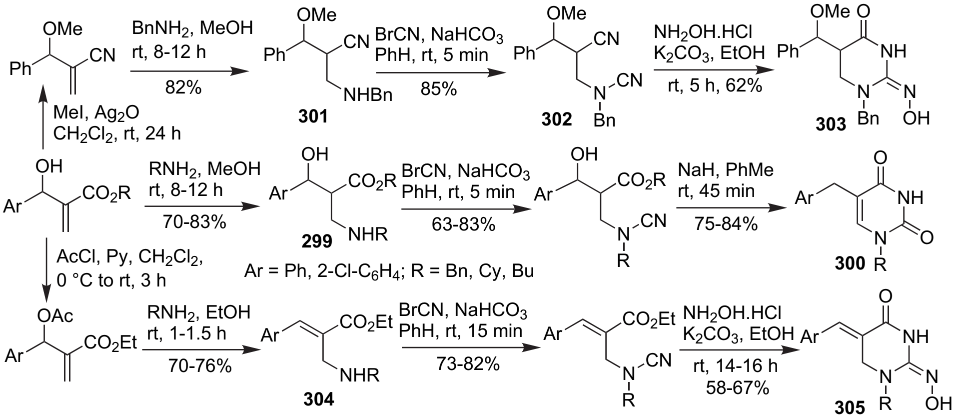
hexahydro-pyrimido[1,2-*a*]pyrimidin-2-ones (**292**) from the products (**291**) originating from the reaction of derivatized primary allyl amines with the Baylis–Hillman adduct obtained by reacting acrylonitrile and acetyl derivatives of the Baylis–Hillman adducts of acrylates (Scheme 180). These compounds exhibited significant antiparasitic activity.[215]

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.

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 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 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**.



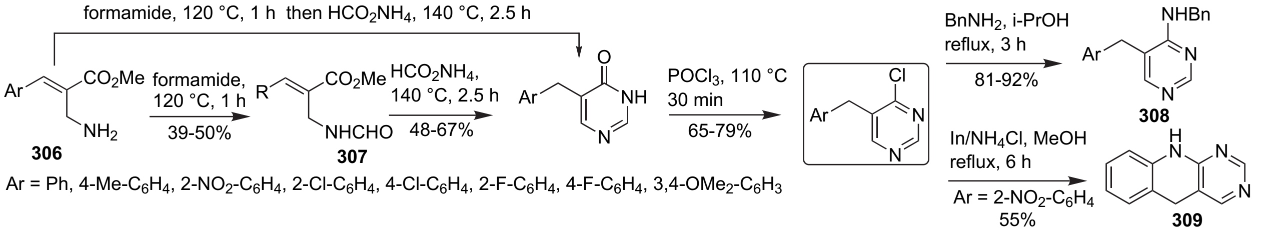
Scheme 181.



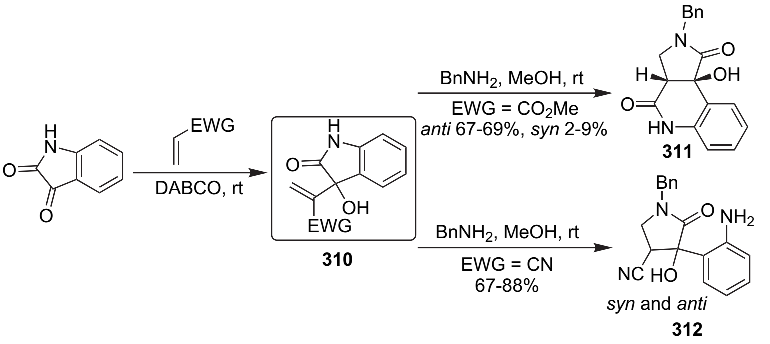
Scheme 182.

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]

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



Scheme 183.



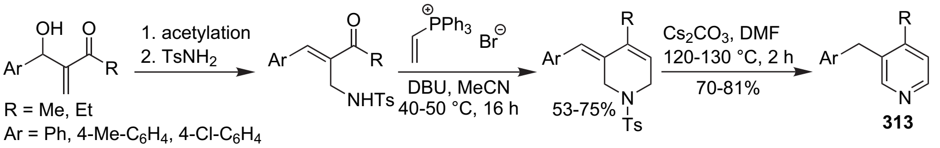
Scheme 184.

demonstrated by Kim et al. via the sequence shown in Scheme 184.[219]

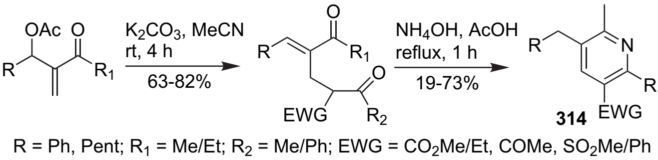
Kim and coworkers successfully developed the synthesis of 3,4-disubstituted pyridines (**313**) from the tosylamides of the Baylis–Hillman adducts of alkyl vinyl ketones.[220] A Schweizer reaction of the tosylamine derivatives with vinyltriphenylphosphonium bromide, elimination of tosyl group and the final 1,3-proton shift yielded the product in very good yields, as shown in Scheme 185. In a more recent report these workers disclosed another synthesis of polysubstituted pyridines (**314**) via a 3+2+1 annulation strategy as delineated in Scheme 186.[221] Although this synthesis did not involved allyl amines as substrate directly, it was an extension of their previously described work (vide infra Scheme 131).

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.

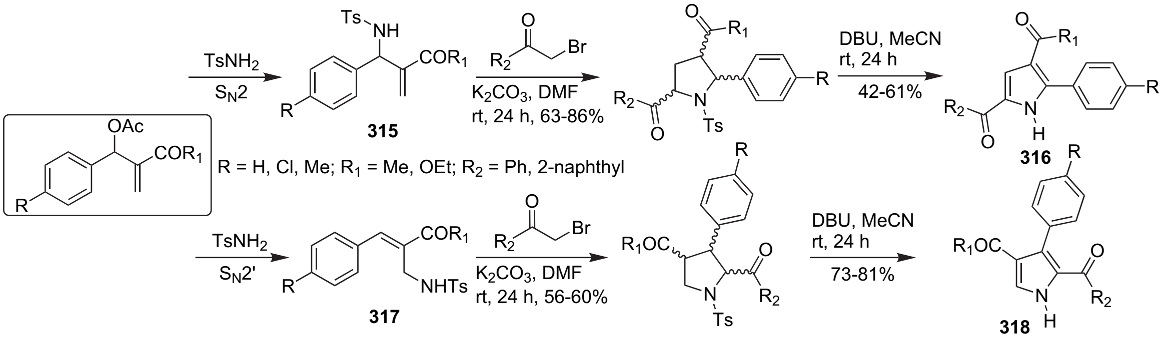
The allyl amine derivative originating from the reaction of 1,2-phenylenediamine with the Baylis–Hillman acetate was utilized by Kim et al. to synthesize 3-(benzylidene)-1,5-benzodiazepin-2-one.[223] Our group has also demonstrated the



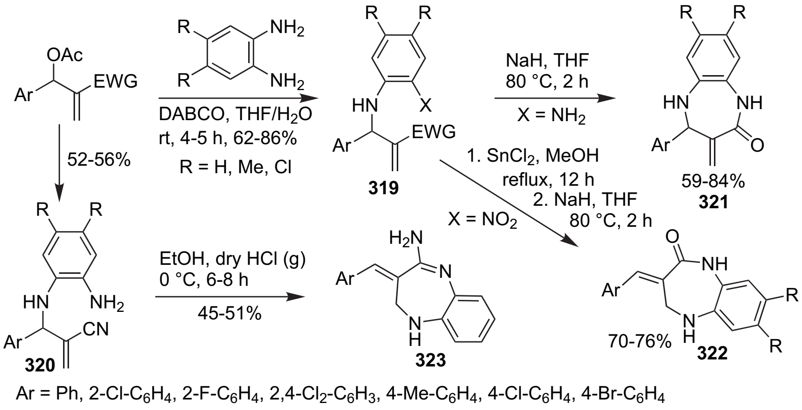
Scheme 185.



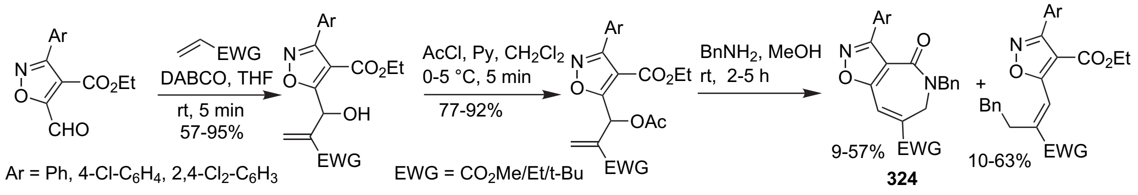
Scheme 186.



Scheme 187.



Scheme 188.

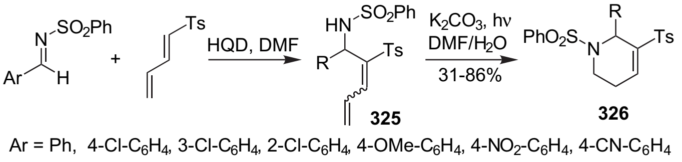


Scheme 189.

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]

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.

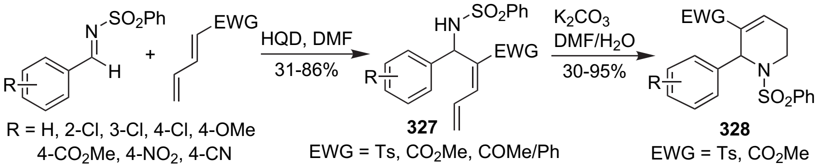
Back et al. have described the Morita–Baylis–Hillman reaction of aldimines with 1-(*p*-toluenesulfonyl)-1,3-butadiene in the presence of 3-hydroxyquinuclidine and found that the *E*-isomers of the products (**325**) cyclize to yield the functionalized piperidines (**326**) (Scheme 190).[226] To improve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



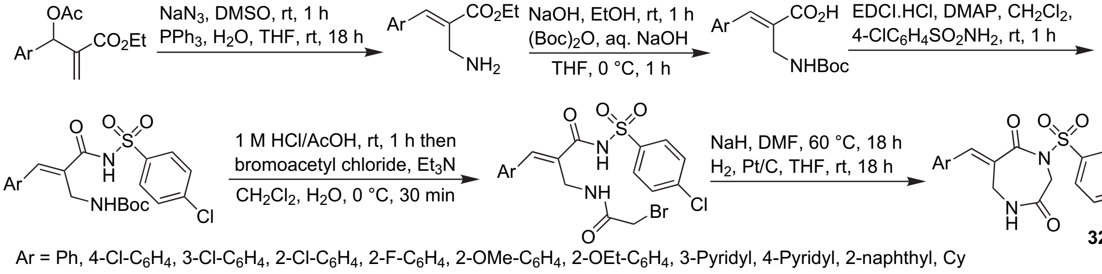
Scheme 190.

Muto et al. 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]

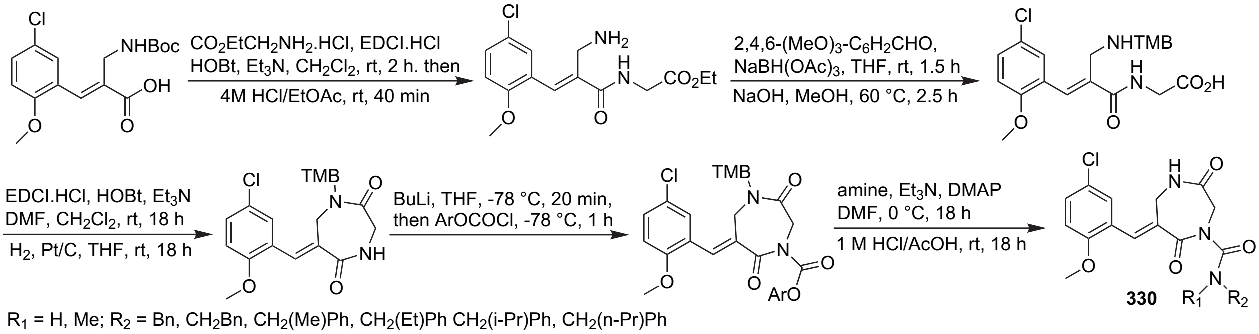
Kim et al. reported the facile synthesis of 1,2,3,4-tetrasubstituted pyrroles (**331**) from substituted allyl amines afforded from the acetyl derivatives of Baylis–Hillman adducts via base-mediated cyclization followed by acid-catalyzed dehydration and concomitant double-bond isomerization, as shown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



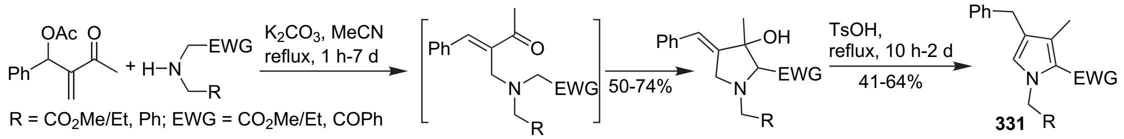
Scheme 191.



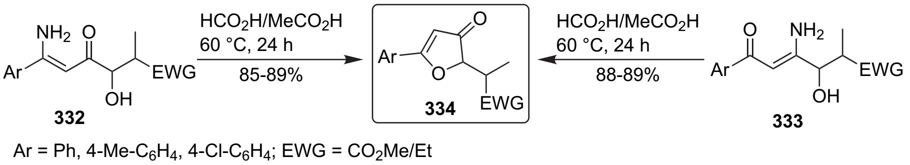
Scheme 192.



Scheme 193.



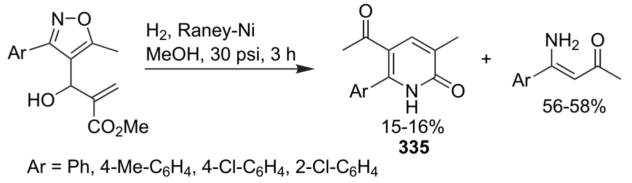
Scheme 194.



Scheme 195.

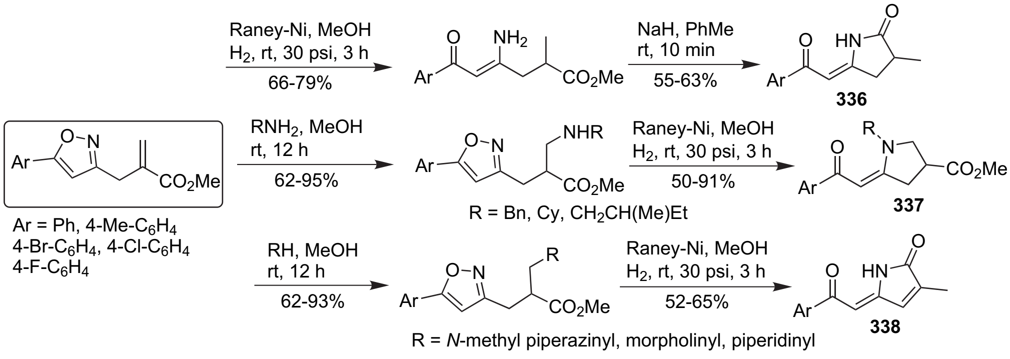
19. Ring transformations

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).

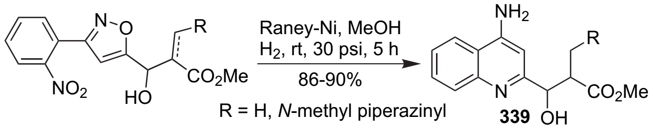


Scheme 196.

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]



Scheme 197.



Scheme 198.

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]

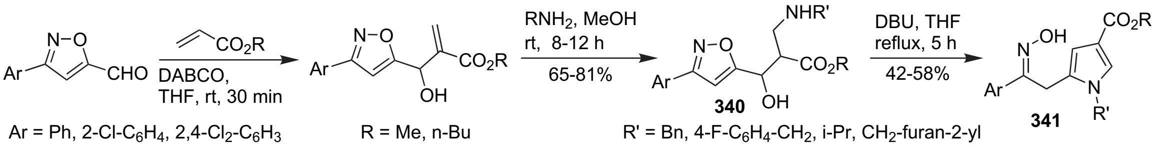
We have reported the transformation of enaminones derived via hydrogenolysis of Baylis–Hillman derivatives of isoxazolecarbaldehydes to the corresponding pyrazoles (**352**) in excellent yields by reacting them with hydrazine hydrate in refluxing conditions (Scheme 200).[235]

20. Miscellaneous reactions

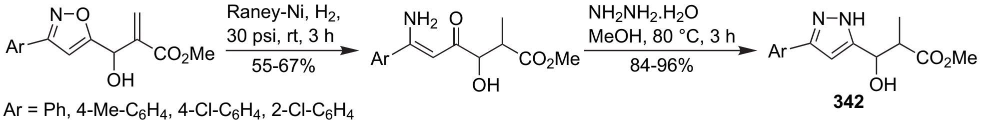
Kamimura et al. described an $AgClO_4$/MeI-mediated elegant stereoselective synthesis of β-lactams (**343**) from thiophenol-substituted Baylis–Hillman derivatives, as shown in Scheme 201.[236]

Coelho et al. 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]

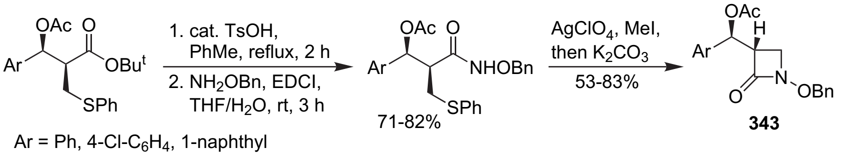
Later, they described a palladium-mediated carbonylative cyclization reaction for the stereoselective synthesis of 3-alkenylphthalides (**345**) from the Baylis–Hillman adducts of *ortho*-halo-substituted benzaldehydes (Scheme 203).[238] The quinoline-phthalide derivatives exhibited potent in vitro antiproliferative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



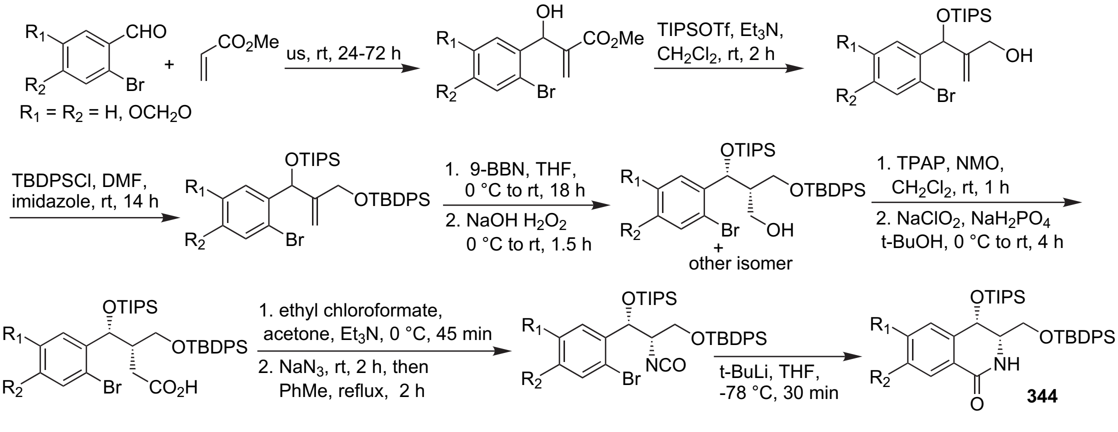
Scheme 199.



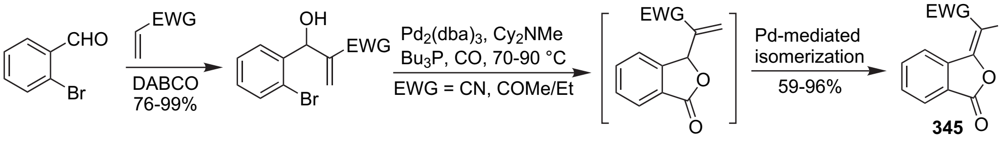
Scheme 200.



Scheme 201.



Scheme 202.



Scheme 203.

Kim et al. 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]

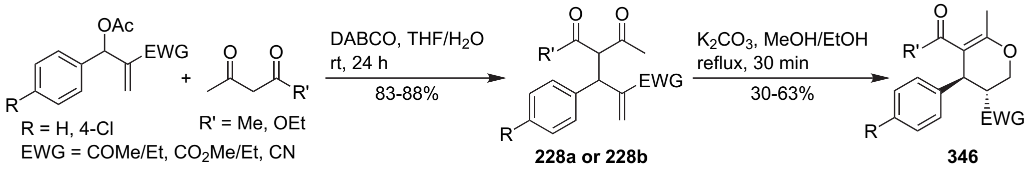
Kim et al. described a regioselective synthesis of tetrasubstituted pyrazole derivatives (**349**) from the reaction of the Baylis–Hillman adducts of methyl vinyl ketone and hydrazine hydrochloride under conventional heating (Scheme 207).[243] Subsequently, Mamaghani et al. prepared the same pyrazoles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

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

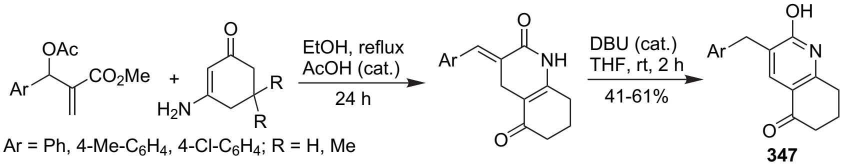
Liu et al. described an efficient $BF_3 \cdot OEt_2$-catalyzed C–C coupling reaction between α-EWG ketene-(*S*,*S*)-acetals and various Baylis–Hillman alcohols, which led to the synthesis of unsymmetrical biaryls (**351**) from the 1,4-pentadienes by a one-pot annulation–aromatization process (Scheme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

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]

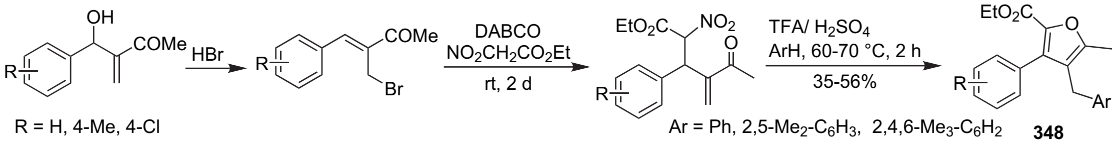
Lee et al. reported the preparation of methyl 2-amino-3*H*-1-benzazepine-4-carboxylates (**354**) or methyl 2-(cyanomethyl)-2,3-dihydro-1*H*-indole-2-carboxylates (**355**) from the reaction of 3-[2-formamido-, 2-acetamido- or 2-(propanoylamino)-phenyl]-substituted methyl 2-(cyanomethyl)propenoates (**353**)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



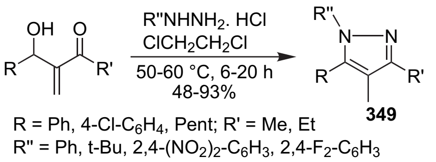
Scheme 204.



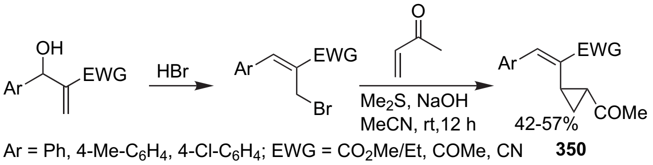
Scheme 205.



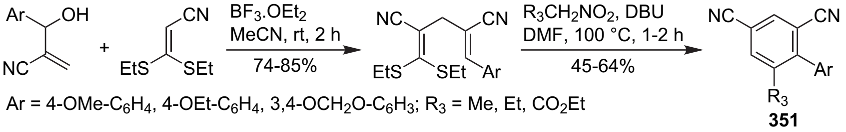
Scheme 206.



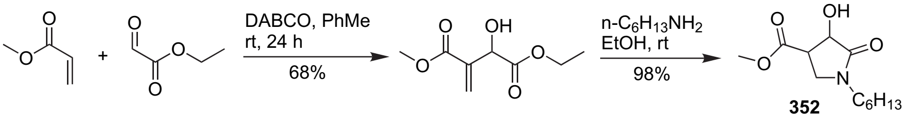
Scheme 207.



Scheme 208.



Scheme 209.



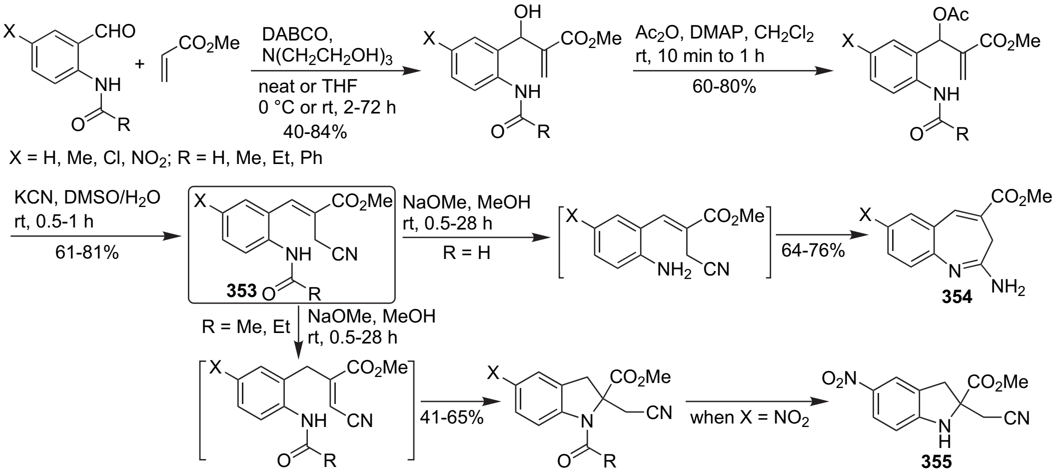
Scheme 210.

of *N*-protected 2-aminobenzaldehydes with methyl acrylate followed by acetylation and cyanation (Scheme 211).[248]

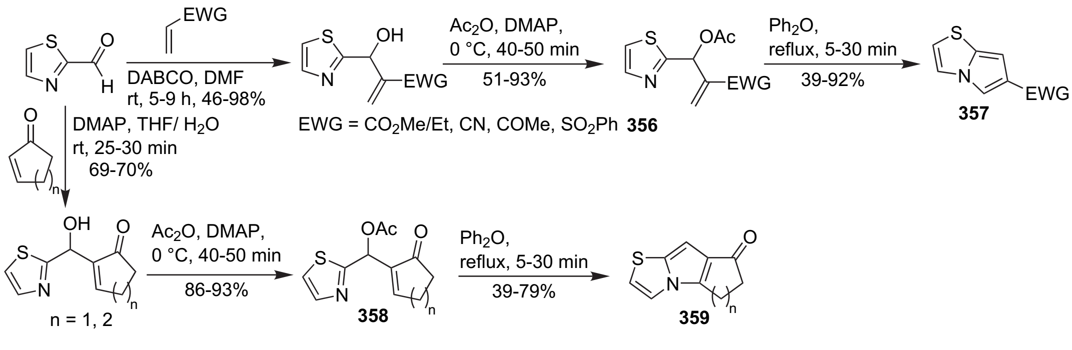
Song and Lee reported a facile strategy for the synthesis of pyrrolo[2,1-*b*]thiazoles (**357**) involving the thermal cyclization of several acetyl derivatives of the Baylis–Hillman adducts of thiazole-2-carbaldehydes (**356**). The reaction was also successful with the Morita–Baylis–Hillman acetates (**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]

Marko et al. 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]

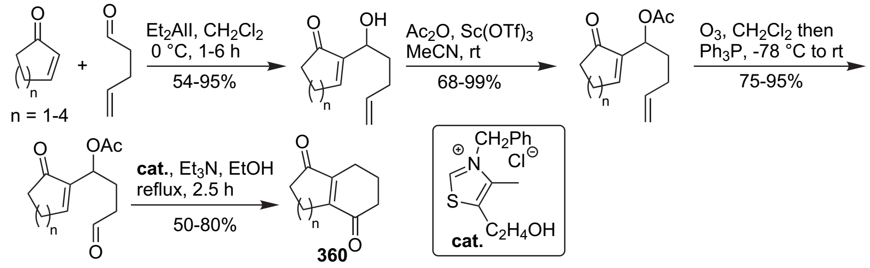
Tang et al. described an exciting Ph_3P-catalyzed intramolecular ylide annulation of an allyl bromide derivative (**361**) for the construction of benzobicyclo[4.3.0] ring systems (**362** and **363**) with three continuous stereogenic centers in a single step. It was demonstrated that the same starting substrates could yield selectively benzobicyclo[4.3.0] products **362** or



Scheme 211.



Scheme 212.



Scheme 213.

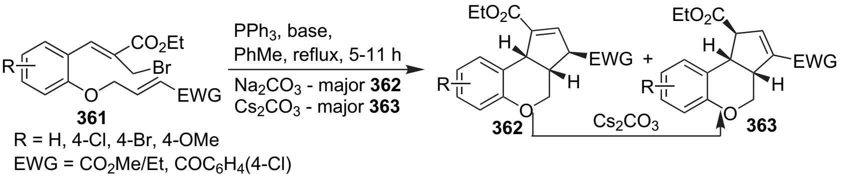
363 by simply changing the base. By the use of Na_2CO_3, compound **362** was obtained as the major product, while Cs_2CO_3 yielded the product **363**. These workers also demonstrated that **362** isomerizes to **363** under the influence of a strong base and studied this transformation via a detailed ^1H 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]

Jorgensen et al. 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]

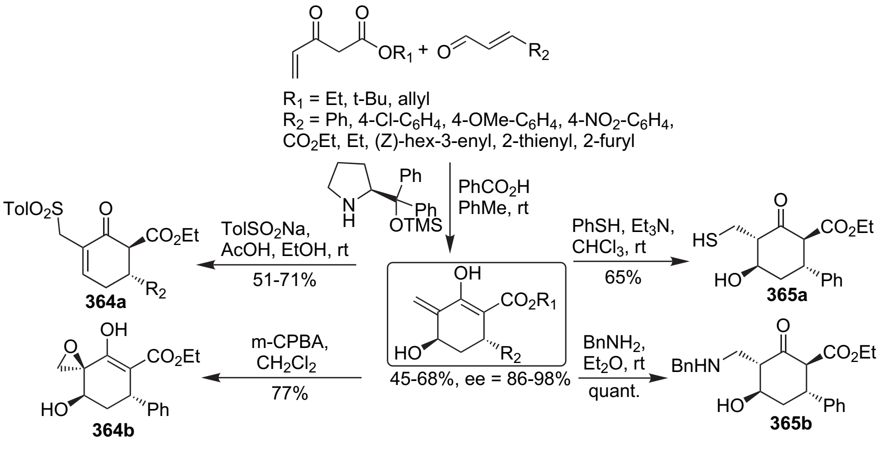
Kim et al. utilized acyloxiranes (**366**) generated from the Baylis–Hillman adducts for the facile synthesis of 1,3,4-trisubstituted pyrazoles (**367**) via a reaction with hydrazine derivatives in dichloromethane, as shown in Scheme 216.[253]

Schiesser et al. 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]

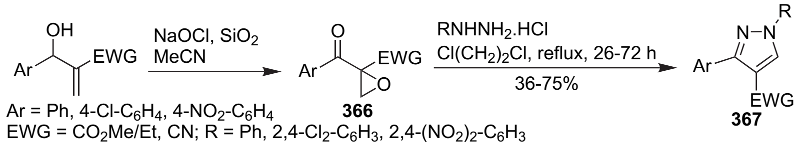
Kim et al. transformed the Baylis–Hillman acetates into 2,4,5-trisubstituted pyrimidines (**369**) by reacting them with



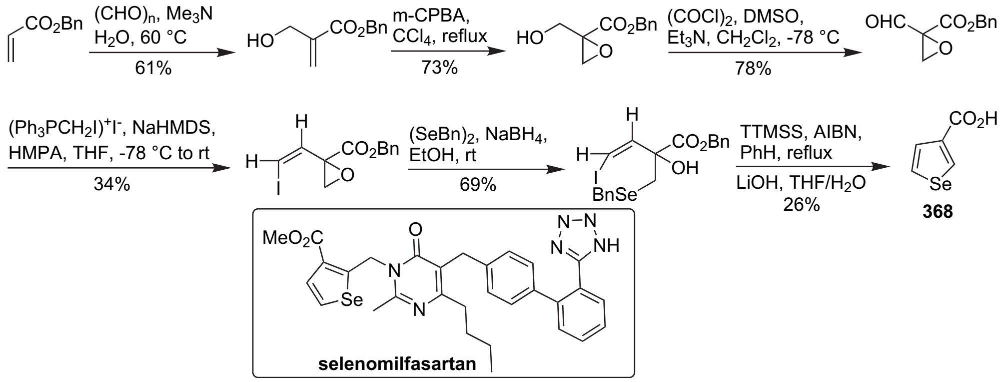
Scheme 214.



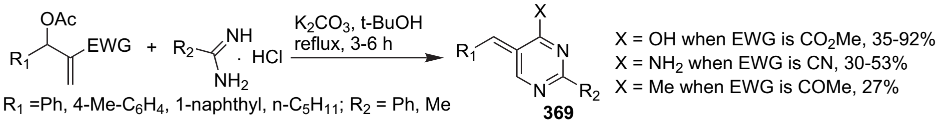
Scheme 215.



Scheme 216.



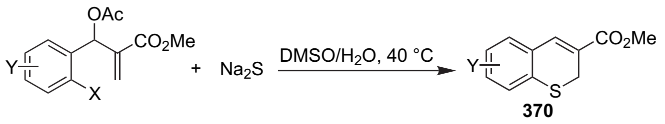
Scheme 217.



Scheme 218.

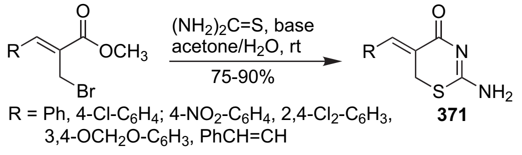
amidines, as delineated in Scheme 218. They reported that the yields of the substituted pyrimidines were better in the case of the derivatives of acrylates, as compared to those afforded by methyl vinyl ketone or acrylonitrile.[255]

Lee et al. 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 et al. 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

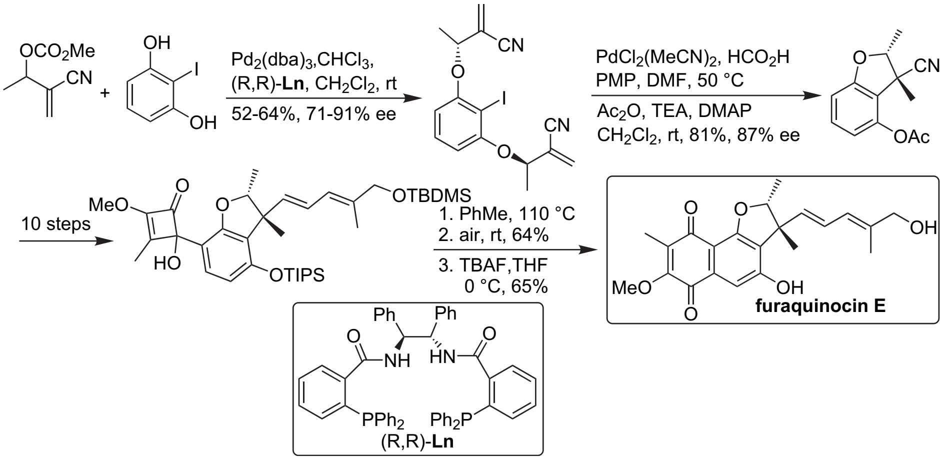
The functional attributes of the Baylis–Hillman adducts and their derivatives make them appropriate precursors to several complex natural products. This has also been elegantly exemplified by several research workers prior to 2003.[258]

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 analogs of furaquinocin E.[260] Their work highlighted the ability to use racemic Baylis–Hillman adducts for asymmetric synthesis (Schemes 221–223). 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]

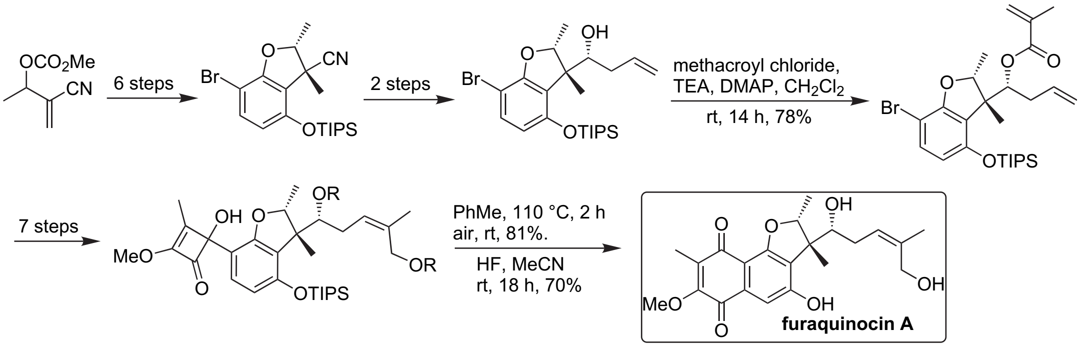
Krishna et al. successfully accomplished the total synthesis of syributins **1** and **2** using the Baylis–Hillman adduct of 2,3-*O*-isopropylidene-*R*-glyceraldehyde (**372**) as the starting material followed by ring-closing metathesis of the acrylate derivative of the resulting diol as the key step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

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 et al. 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]

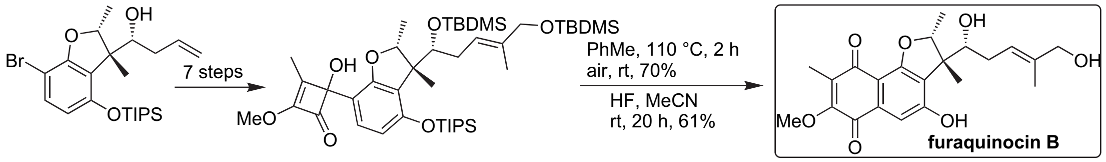
Corey et al. utilized an intramolecular Baylis–Hillman reaction between keto and acrylamide for the cyclization to



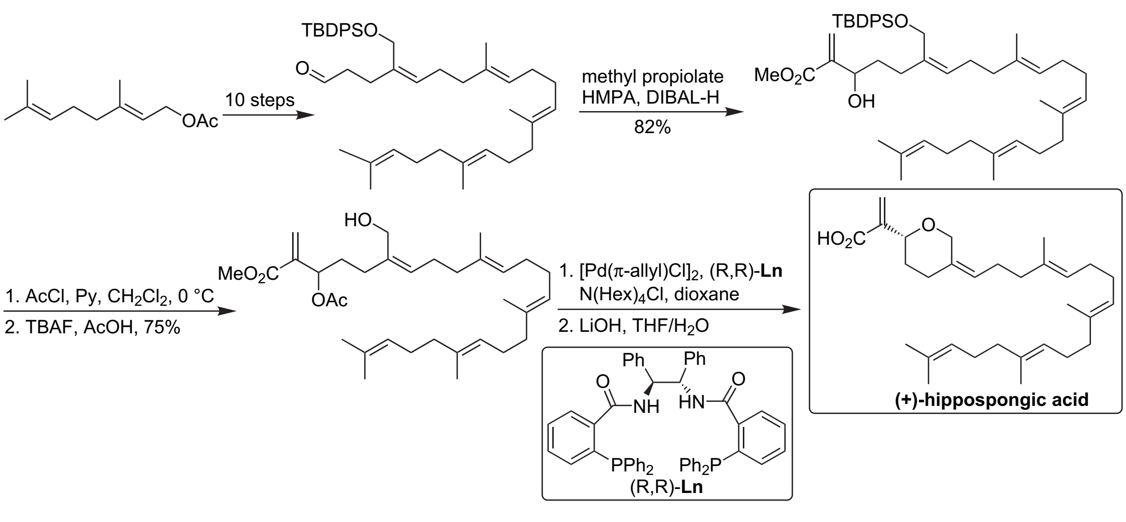
Scheme 221.



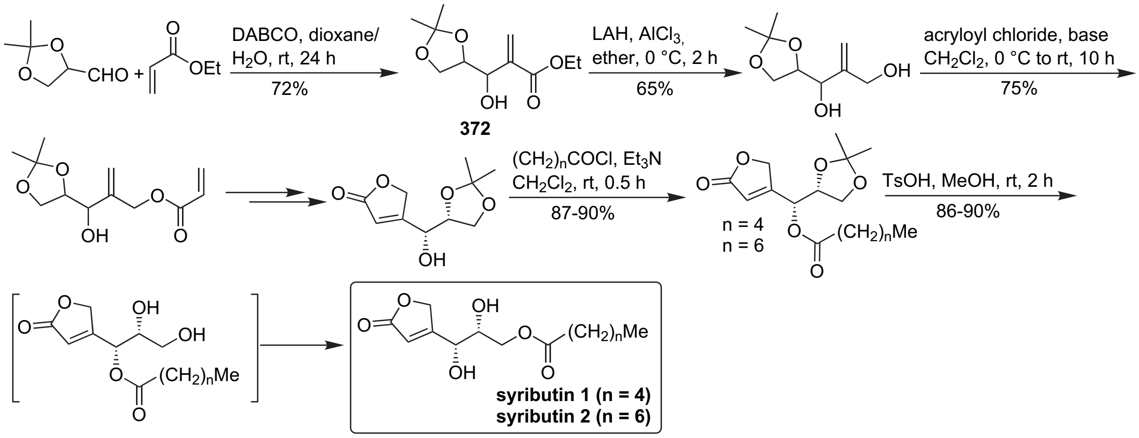
Scheme 222.



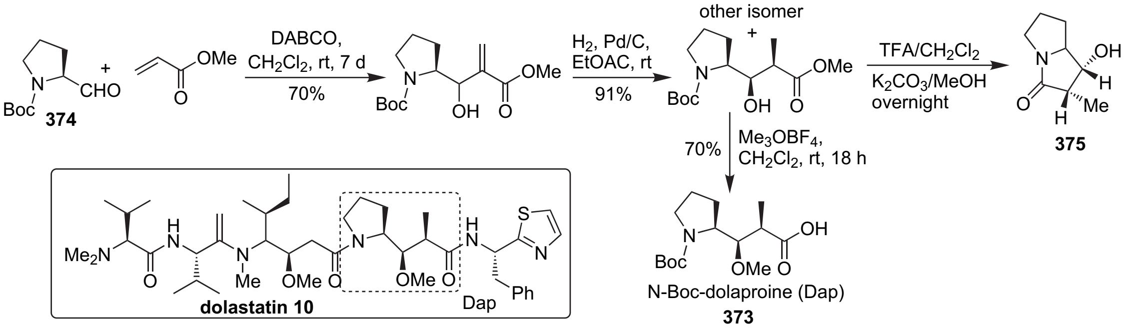
Scheme 223.



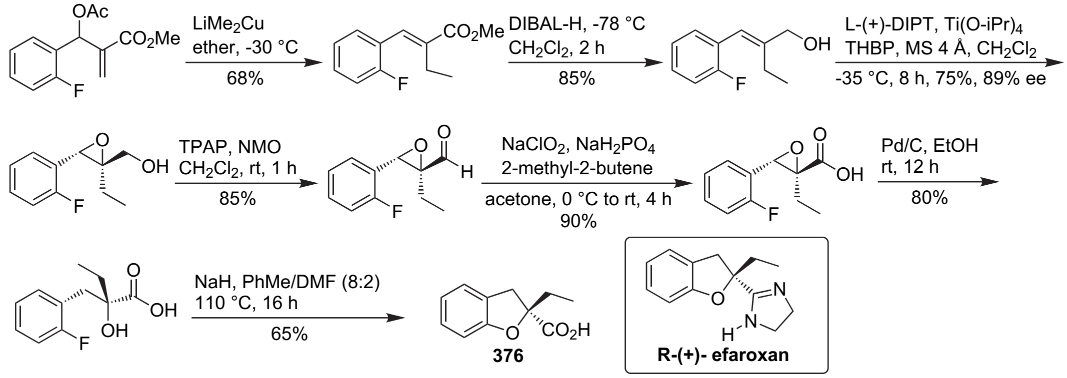
Scheme 224.



Scheme 225.



Scheme 226.



Scheme 227.

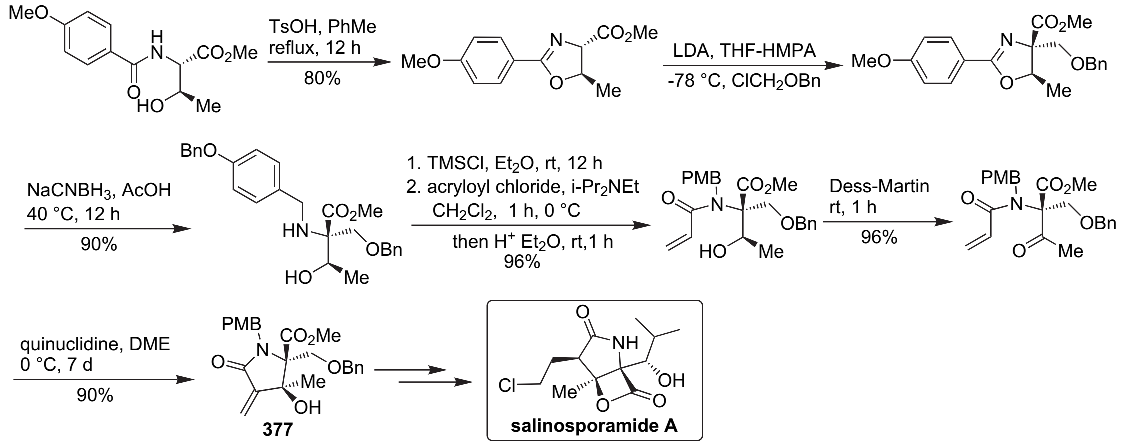
produce a highly substituted 4-methylene-5-oxo-pyrrolidine derivative (**377**), which served as the starting material in the enantioselective total synthesis of salinosporamide A (Scheme 228).[265] As this key step was time consuming, they developed an attractive method using a Kulinkovich reagent followed 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 analog (Scheme 229).

Chang et al. 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]

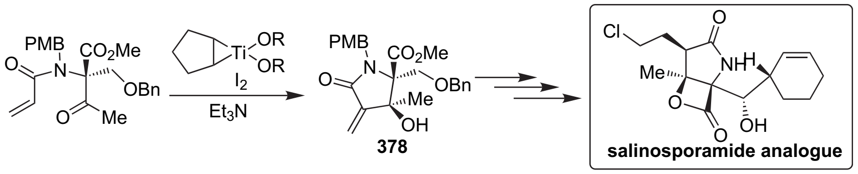
Tadano et al. reported a total synthesis of natural (+)-tubelactomicin A, a 16-membered macrolide antibiotic, which comprised 54 total steps from methyl (*R*)-lactate (**380**) in 6.2% overall yield involving the Baylis–Hillman reaction as one of the key steps (Scheme 231).[268]

Subsequently, Orena et al. described the synthesis of conformationally restricted analogs 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]

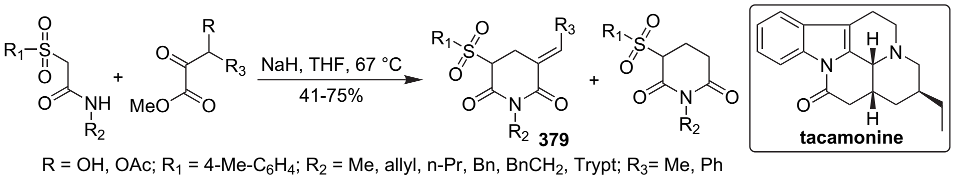
Franck et al. described a convergent, highly stereoselective total synthesis of (−)-spinosyn A, a polyketide natural product



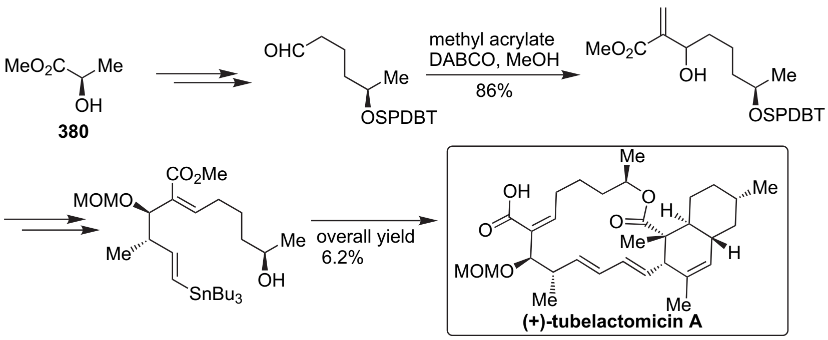
Scheme 228.



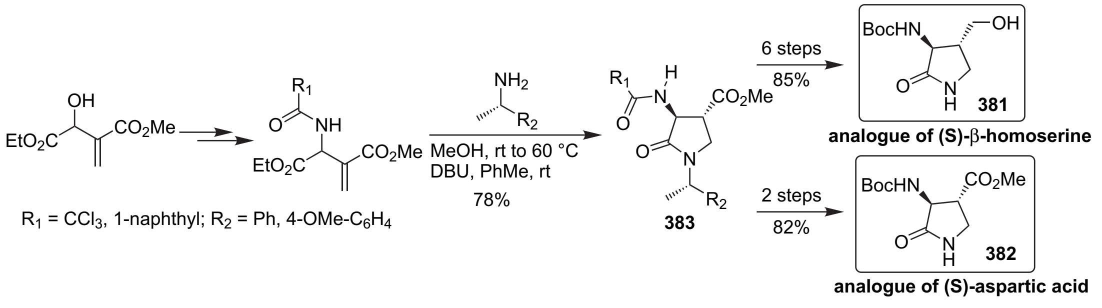
Scheme 229.



Scheme 230.



Scheme 231.

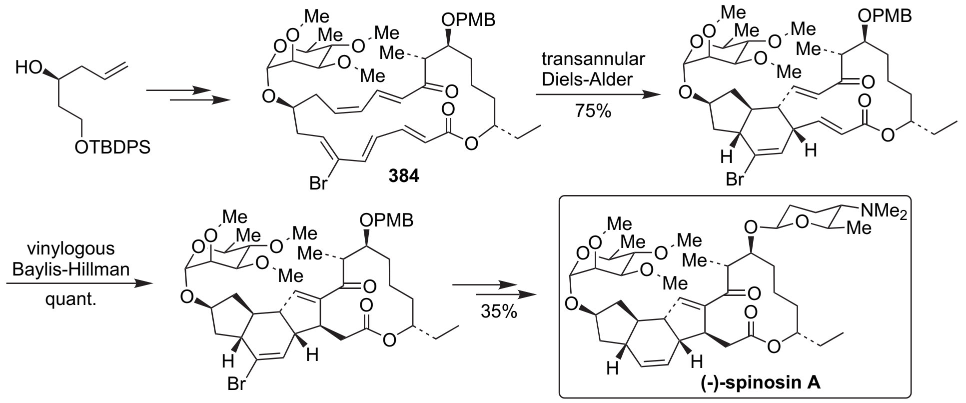


Scheme 232.

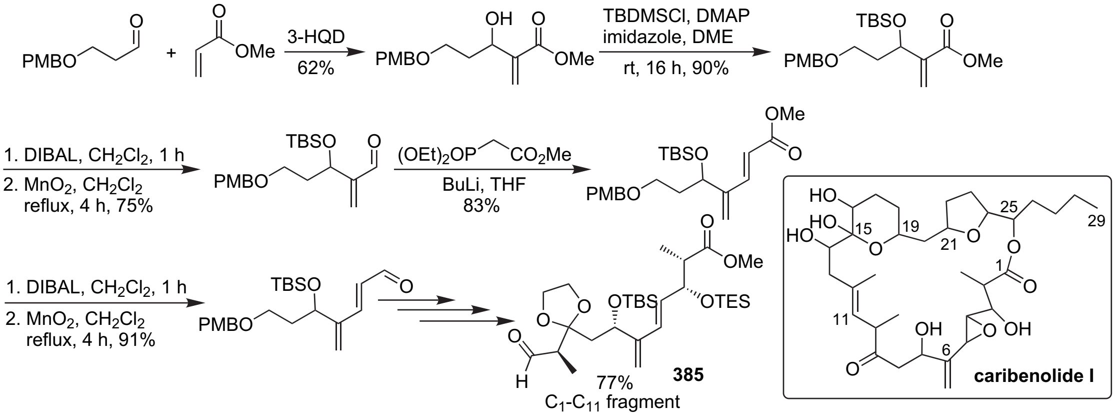
possessing an extraordinary insecticidal activity. The key feature of the synthesis included a transannular Diels–Alder reaction of a macrocyclic pentaene (**384**) and transannular vinylogous Morita–Baylis–Hillman cyclization to yield (−)-spinosin A (Scheme 233).[270] In addition, they successfully 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]

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]

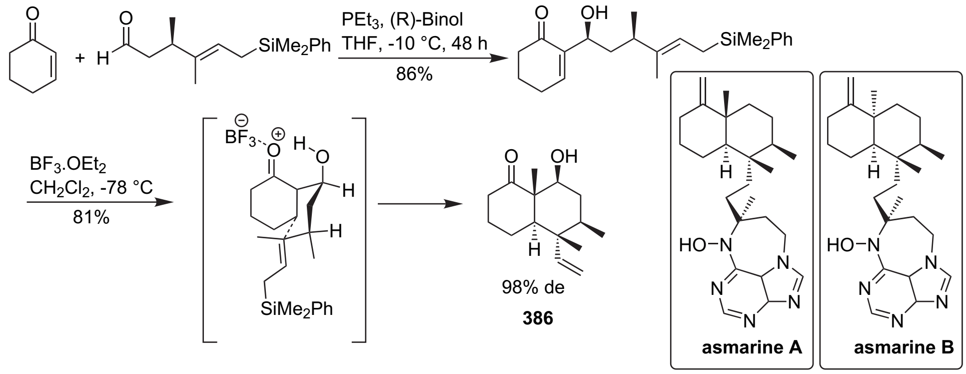
Recently, Jogireddy and Maier have developed a novel route for the synthesis of luminacin D. The starting aldehyde (**387**), which was obtained by a simple Baylis–Hillman reaction between acetaldehyde and methyl acrylate, followed by OH transposition, was extended by two highly stereoselective asymmetric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



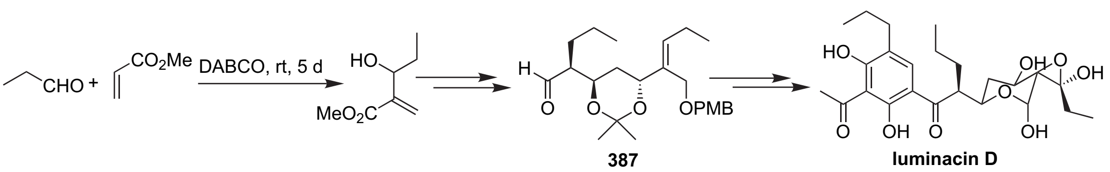
Scheme 233.



Scheme 234.



Scheme 235.



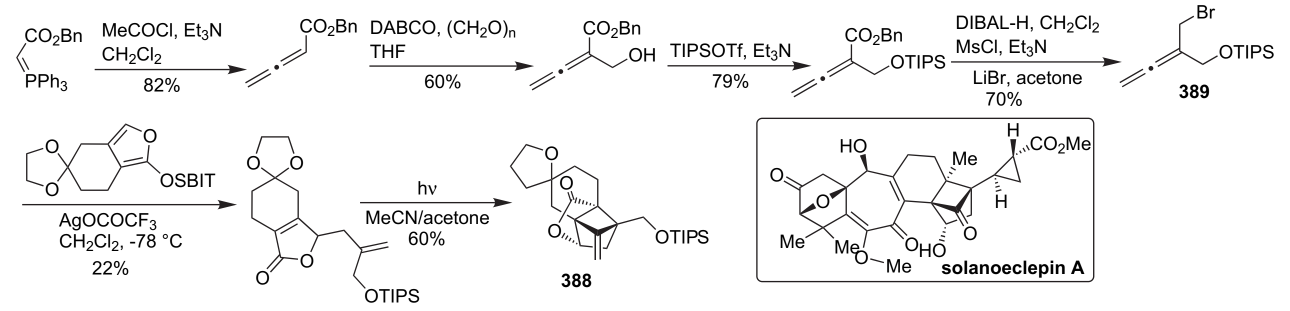
Scheme 236.

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]

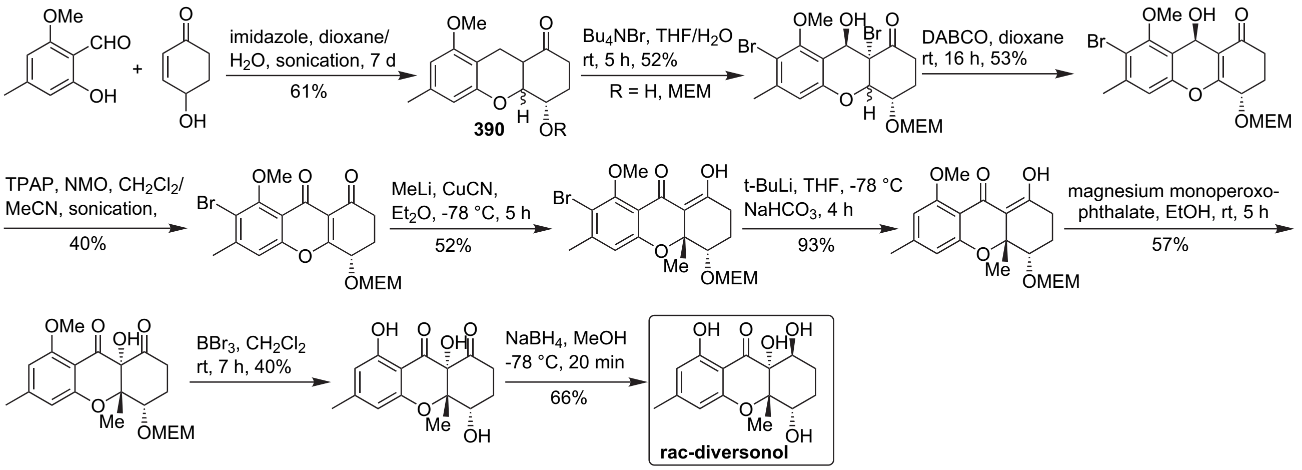
Brase et al. have developed a synthetic route to tetrahydroxanthenone mycotoxins (**390**) via a domino oxa-Michael–aldol condensation. By applying this methodology, they achieved the first total synthesis of the secondary metabolite, diversonol, in a racemic form, as delineated in Scheme 238.[275]

Selvakumar et al. 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]

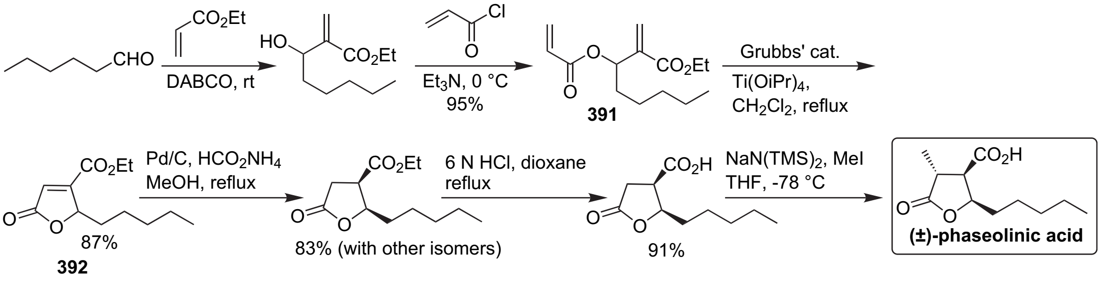
Aggarwal et al. reported a novel methodology in which a broad range of Michael acceptors were allowed to couple



Scheme 237.



Scheme 238.



Scheme 239.

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 $BF_3 \cdot Et_2O$ 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.

Recently, Murphy et al. reported the formation of a side product **397** resulting from a Baylis–Hillman-type cyclization during the preparation of the diene **396** from the *tert*-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]

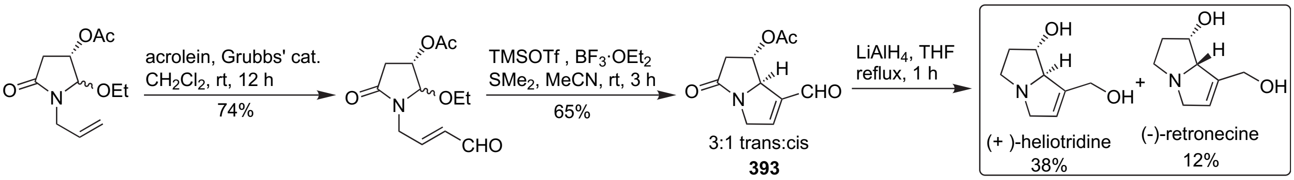
Koert et al. utilized the Baylis–Hillman adduct to generate the molecular framework for the efficient stereoselective synthesis of methyl 7-dihydro-trioxacarcinoside B (**398**). The key steps in the process were biocatalytic resolution of the Baylis–Hillman adduct, RCM reaction, a substrate-controlled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

Ciufolini et al. 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]

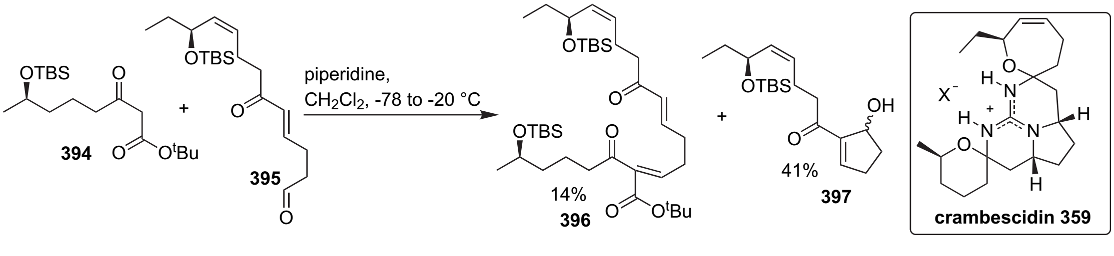
Other natural products having open chain structures have also been synthesized employing Baylis–Hillman chemistry. These include (2*E*)-2-butyloct-2-enal,[281] *cis*-hedione and methyl jasmonate,[282] 4,5-dihydroxy-2,3-pentanedione (DPD),[283] and 5-*O*-acylated derivatives of DPD,[284] sitophilate,[285] (+)-(*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

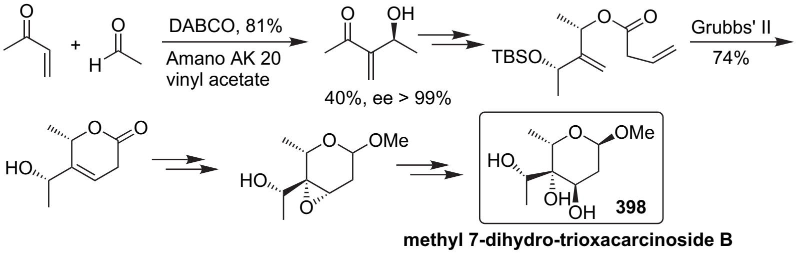
The expounding of the synthetic applications of the Baylis–Hillman adducts and their derivatives for the generation of cyclic compounds, besides a variety of other products, clearly establishes that this reaction has become a standard synthetic methodology in the arsenal of organic chemists. Figure 10 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



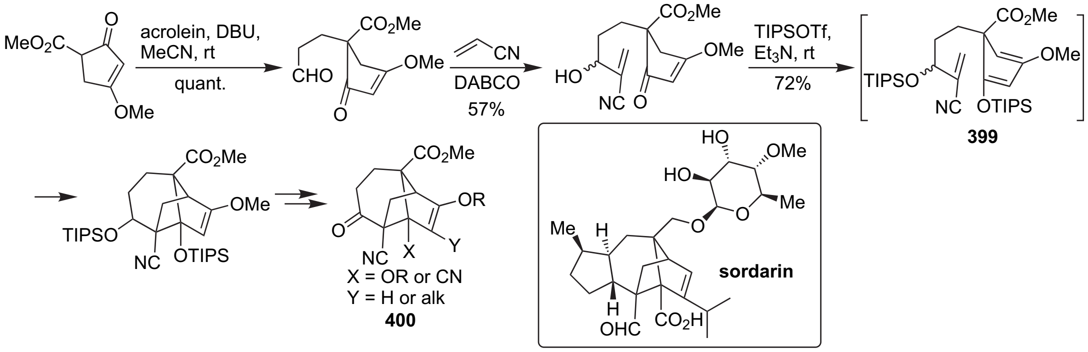
Scheme 240.



Scheme 241.



Scheme 242.



Scheme 243.

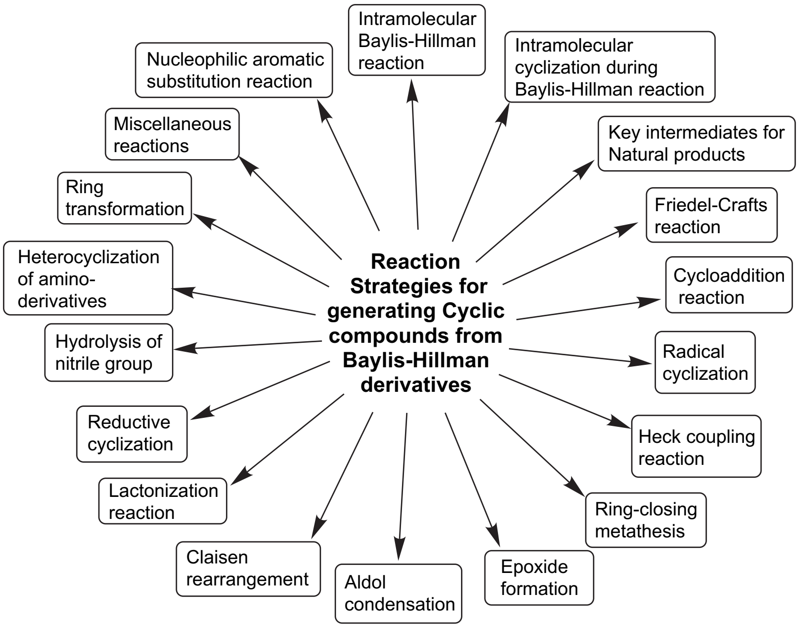


Figure 10. Reaction strategies employed on the Baylis–Hillman derivatives for the generation of the cyclic compounds.

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 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.

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