Recent Contributions from the Baylis−Hillman Reaction to Organic Chemistry

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Contents

1. Introduction

1.1. General

Organic synthesis is one of the most successful and useful disciplines of science and mainly involves the construction of carbon−carbon bond(s) and carbon−heteroatom bond(s) and cleavage of these bonds (pictorially represented in Figure 1).[1−5] The strategies regarding how to construct and cleave the above bonds represent the central theme in organic chemistry in which they play unique roles in assembling the diverse and complex carbon frameworks. Therefore, the

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Deevi Basavaiah was born in Valiveru, a village near Tenali, India. He received a Ph.D. degree from the Banaras Hindu University, India, in 1979 working under the supervision of Professor Gurbakhsh Singh. Subsequently he worked as a postdoctoral fellow in the Chemistry Department, Purdue University, in the research group of Professor Herbert C. Brown for three years. In 1984, he joined the University of Hyderabad, Hyderabad, as a faculty member in the School of Chemistry where he is currently Professor. His research group has been working for the last 26 years and continues to work on various aspects of the Baylis−Hillman reaction and its applications with the main objective of developing this reaction into a useful and powerful synthetic tool in organic chemistry. Chiral catalysis is another important area of his research interest.

Bhavanam Sekhara Reddy was born in 1981 in Korisapadu, a village in Prakasam district, Andhra Pradesh, India. After his graduation from the Nagarjuna University, Guntur, he joined as a postgraduate student in 2002 in the School of Chemistry, University of Hyderabad, Hyderabad, and obtained his M.Sc. degree in 2004. Presently he is working for his Ph.D. degree at the University of Hyderabad under the supervision of Professor D. Basavaiah on the development of simple synthetic strategies for carbocyclic and heterocyclic frameworks using Baylis−Hillman chemistry.

development of such strategies has been and continues to represent the forefront of research in organic chemistry. Among these bond-forming and bond-cleavage reactions, the construction of the carbon−carbon bond is the most fundamental reaction due to its unique role in building various classes of carbon frameworks. Because of this fundamental nature, several useful carbon−carbon bond-forming reactions (both named and unnamed) have been developed, and also their applications have been elegantly studied during the last centuries.[1−10] Some of these carbon−carbon bond-forming reactions are well-known for the concept of atom economy.[11] Representative examples of atom-economic and non-atom-economic carbon−carbon bond-forming reactions are given in Figure 2.

Present day synthetic organic chemistry requires and even demands certain regulations and guidelines in developing any

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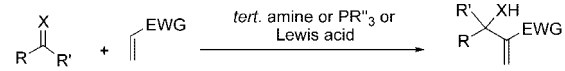
operationally simple, useful and practical carbon−carbon bond-forming reaction keeping the protection of the environment as a major concern. Thus in addition to the concept of atom economy,[11] other aspects such as aqueous reaction media and organocatalysis have also received utmost attention from the synthetic chemists because they play a key role in developing environmentally benign procedures. The Baylis−Hillman reaction[12−45] is one such reaction that is well equipped with these important concepts of atom economy and organocatalysis thus creating a special place for itself in the history of named and unnamed organic reactions.

1.2. The Baylis−Hillman Reaction

The Baylis−Hillman reaction, in the present day version, is an atom-economic carbon−carbon bond-forming reaction between the α-position of the activated alkenes (alkynes) and carbon electrophiles under the influence of a catalyst or catalytic system providing diverse classes of densely functionalized molecules, which are generally referred to as the Baylis−Hillman adducts (eq 1).[19−24] Most of the Baylis−Hillman reactions are catalyzed by organic compounds like tertiary amines and alkyl(aryl) phosphines, and thus these reactions are referred to as the "organocatalysis reactions".



(1)

R = aryl, alkyl, heteroaryl; R' = H, COOR, alkyl; R" = aryl, alkyl
X = O, NCOOR, NTs, NSO_2Ph, $NP(=O)R_2$, $NPPh_2$ etc.

EWG = electron withdrawing group : COR, CHO, CN, COOR, $PO(OEt)_2$, SO_3Ph, SO_2Ph, SOPh, $CONR_2$, COSR etc.

The main features of this reaction are as follows: (1) It is a three-component carbon−carbon bond-forming reaction [activated alkenes (alkynes), electrophiles, and catalysts] providing diversity in selecting substrates. (2) This creates a chiral center in the case of a prochiral electrophile thus offering challenges and opportunities for developing its asymmetric version. (3) Since the Baylis−Hillman adducts are densely functionalized molecules and due to the proximity of functional groups, these adducts are highly useful as

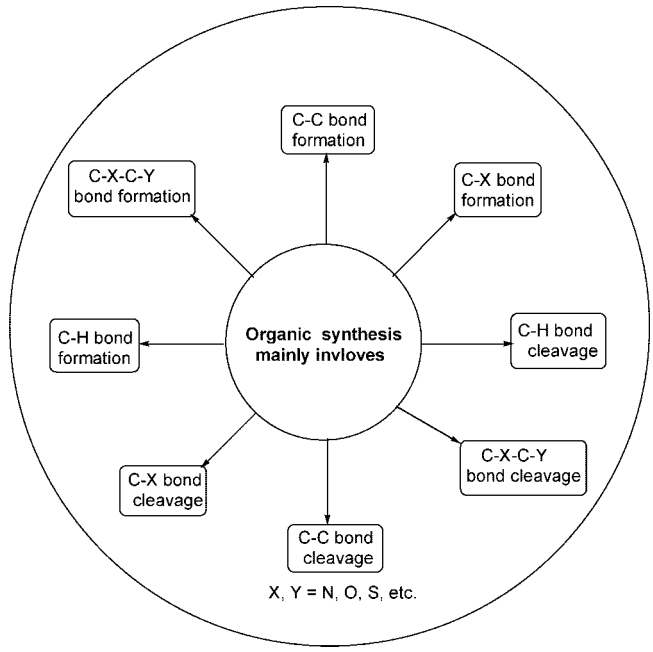


Figure 1.

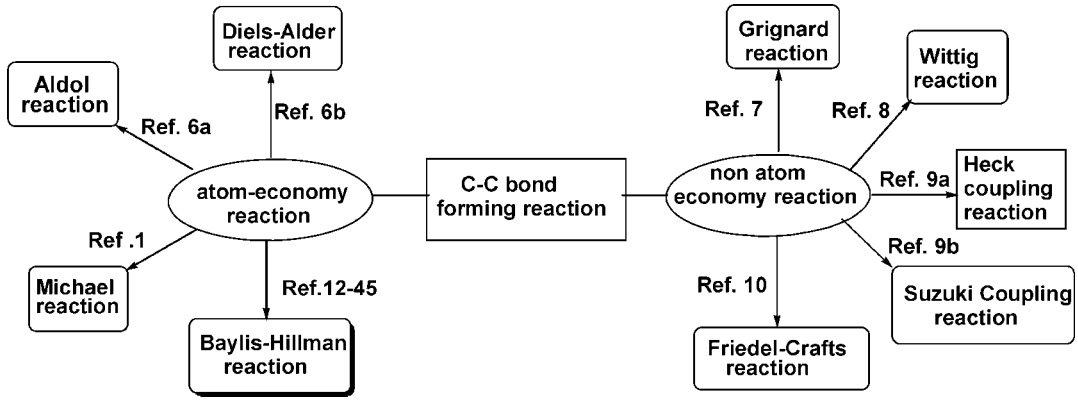


Figure 2.

synthons in a number of synthetic processes and also in synthesis of interesting natural and unnatural products of medicinal relevance. (4) If the substrate contains both the activated alkene and electrophile components in appropriate positions, there is the possibility of developing an intramolecular version of this reaction leading to the synthesis of carbocyclic or heterocyclic compounds, and thus this reaction offers challenges to design and synthesize various substrates that can be transferred into diverse classes of carbocyclic and heterocyclic compounds. (5) Many variations of parameters present in this reaction, in fact, generate a wide spectra of mechanistic pathways, thereby making understanding the mechanism of this reaction an intellectual challenge. All these aspects are pictorially presented in Figure 3.

1.3. Salient Features of the Baylis−Hillman Reaction at a Glance[19−24]

All these fascinating aspects of this reaction have inspired both the synthetic and mechanistic chemists. In fact, several leading chemists all over the world now work on various directions of this reaction. Thus this reaction has grown exponentially and continues to grow further as evidenced by a large number of publications in leading journals in recent years. In fact, there are six major reviews,[19−24] many minireviews,[25−34] and also many key sections in several general reviews[35−45] highlighting the development of the reaction, its applications, and the importance of this reaction in various angles. Since the publication of our major review on this fascinating reaction in *Chemical Reviews* in 2003, there has been a flood of important research publications (more than 700 publications have appeared) highlighting various aspects of this reaction. Therefore, we felt that more comprehensive review covering the recent advances during the last six years (2003−2008), such as (1) the developments of this reaction with respect to all the three essential components, (2) the asymmetric version, (3) the intramolecular version, (4) synthetic applications, (5) mechanistic challenges, and (6) the future prospectus, will be the necessity of the hour and our present review will discuss all these aspects starting from the end of the year 2002 until December 2008, thus providing the readers great detail about the contributions of the Baylis−Hillman reaction to organic chemistry.

2. Essential Components: Earlier Developments

There have been significant developments with respect to all the three essential components, that is, activated alkenes or alkynes, electrophiles, and catalysts or catalytic systems.

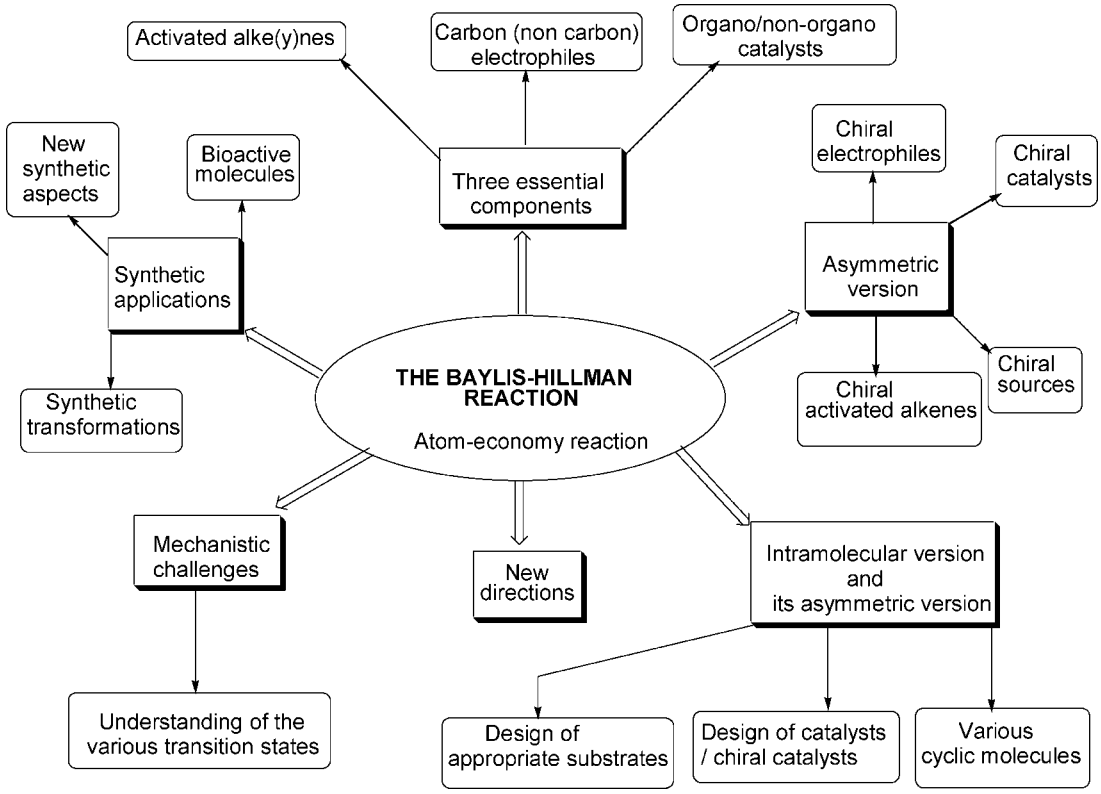


Figure 3.

The lists of various activated alkenes and alkynes, electrophiles, and catalysts and catalytic systems already used successfully in the Baylis−Hillman reaction have been presented in Figures 4−8.

2.1. Activated alkenes/alkynes

2.1.1. Acyclic activated alkenes/ alkynes

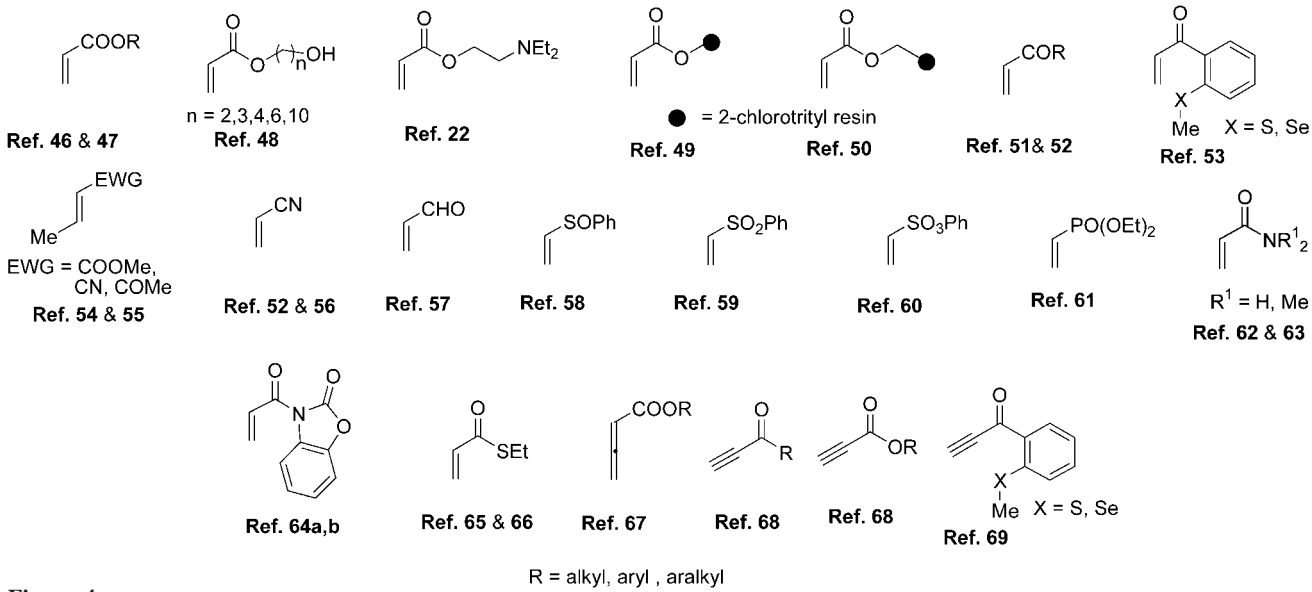


Figure 4.

2.1.2. Cyclic activated alkenes

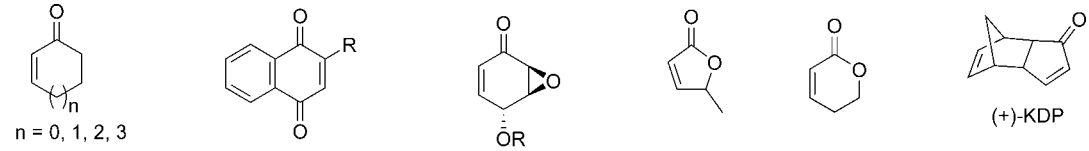


Figure 5.

2.2. Electrophiles[21]

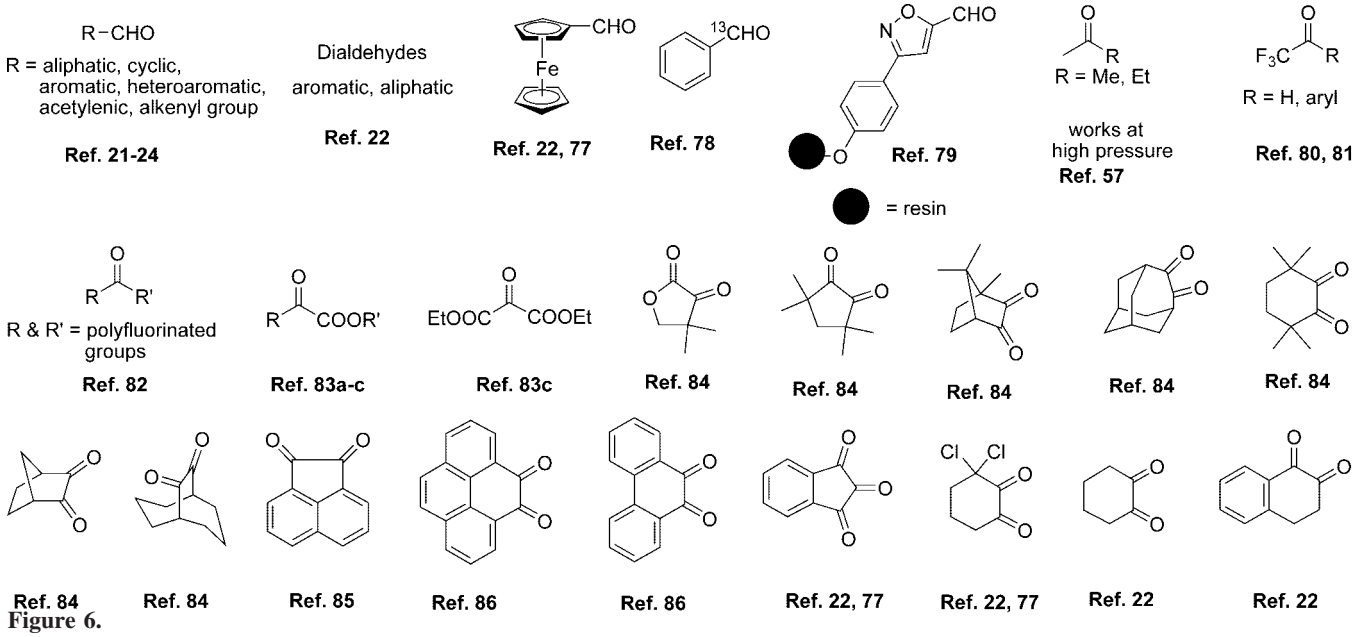


Figure 6.

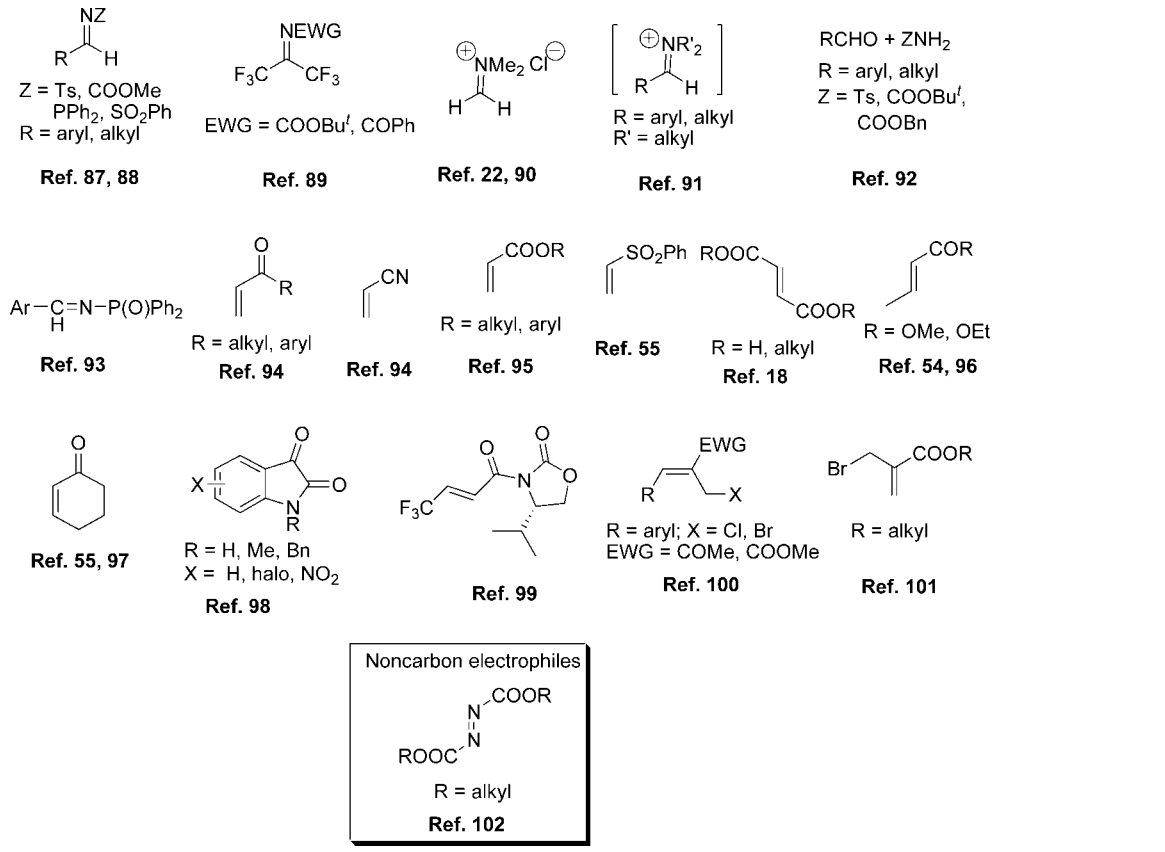


Figure 7.

2.3. Catalysts

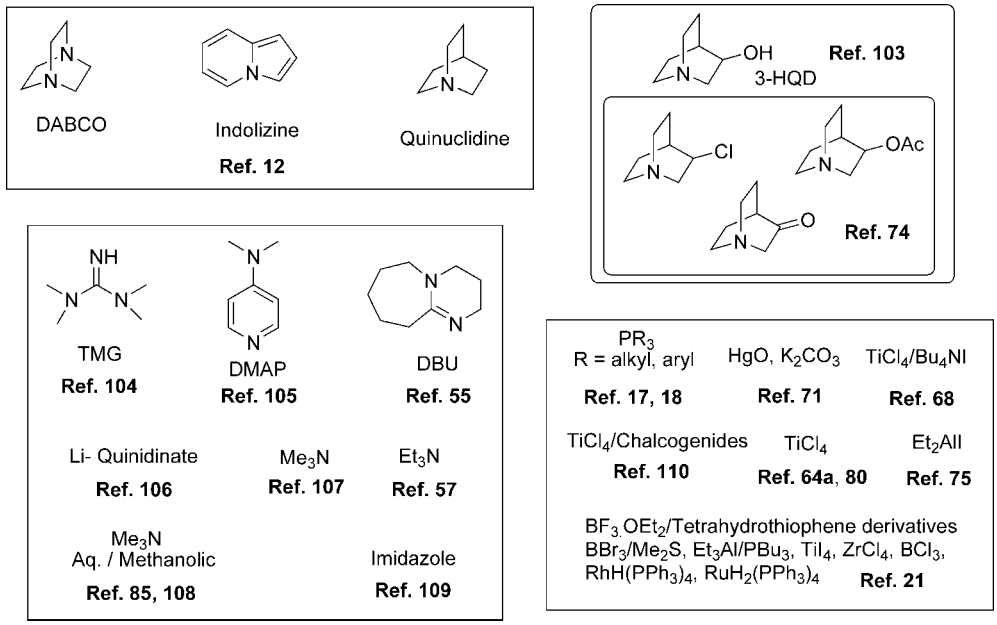


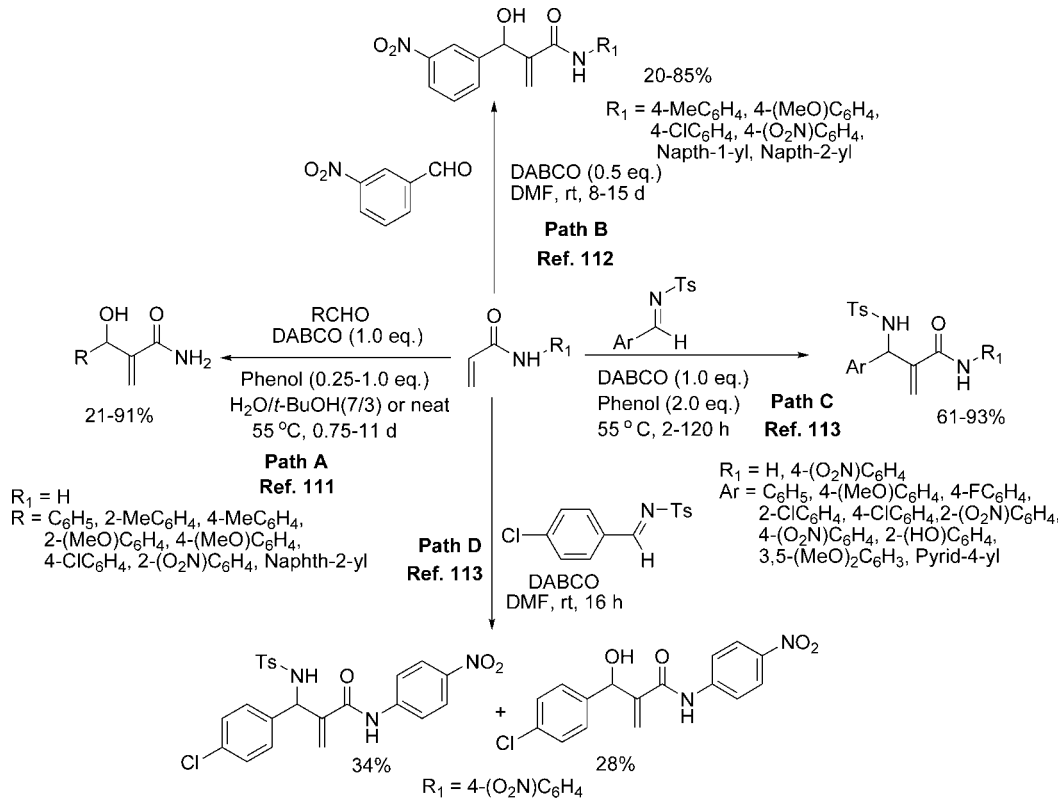
Figure 8.

3. Essential Components: Recent Developments

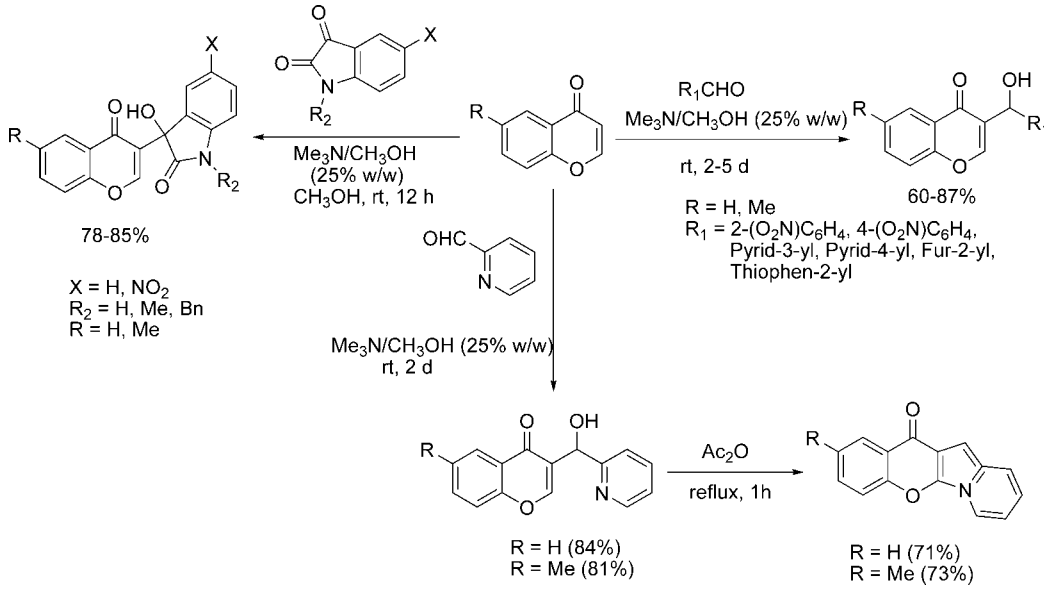
3.1. Activated Alkenes/Alkynes

During the last six years, after publication of a major review article on the Baylis−Hillman reaction in *Chemical Reviews*, several research papers appeared describing applications of various activated alkenes and alkynes for coupling with a number of electrophiles to provide diverse classes of densely functionalized molecules. Connon and co-workers[111] reported a facile coupling of acrylamides with aldehydes in the presence of phenol with a faster reaction rate under the catalytic influence of DABCO (Path A, Scheme 1). Although the actual role of phenol is not understood, the authors[111] proposed that it can act both as a Brønsted acid alkoxide scavenger and a hydrogen-bonding catalyst (Brønsted acid). Later on, Guo and co-workers[112] used various acrylamides as activated alkenes for performing the Baylis−Hillman coupling with aromatic aldehydes under the influence of DABCO as a catalyst in DMF (Path B, Scheme 1). Guo et al.[113] have also employed acrylamide and

Scheme 1

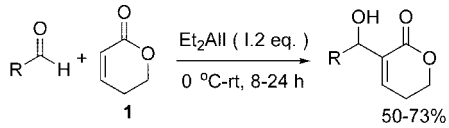


Scheme 2



4-nitrophenylacrylamide as activated alkenes for coupling with various aldimine derivatives to provide the corresponding Baylis−Hillman adducts under the influence of DABCO in the presence of phenol (Path C, Scheme 1). It was interesting to note that in the absence of phenol, aldimines were partly decomposed into aldehydes and Baylis−Hillman adducts corresponding to the aldehydes and aldimines were obtained in low yields (Path D, Scheme 1). Representative examples are shown in Scheme 1.

The coupling of pyrandihydro-5*H*-2-one (**1**) with various aldehydes has been conveniently performed by Li and co-workers in the presence of diethylaluminum iodide to provide the resulting Baylis−Hillman adducts in high yields (eq 2).[75]



(2)

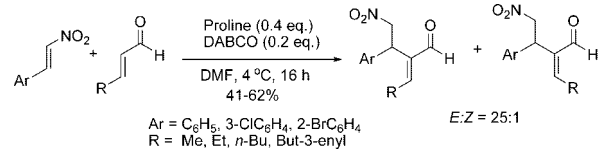
R = C_6H_5, 2-MeC_6H_4, 4-(MeO)C_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$(O_2N)C_6H_4$, Naphth-2-yl

1-Benzopyran-4(4*H*)-one derivatives have been systematically used as novel activated alkenes in the Baylis−Hillman coupling with reactive electrophiles such as heteroaromatic aldehydes, nitrobenzaldehydes, and isatin derivatives by our research group (Scheme 2).[114] The Baylis−Hillman adducts thus derived from pyridine-2-carboxaldehyde as electrophile were converted into the novel tetracyclic indolizine-fused chromone frameworks (Scheme 2).

Parthenin sesquiterpene lactone (**2**), containing a fused five-membered cyclic enone moiety, has been examined by Teneja and co-workers[115] as activated alkene for coupling with various aldehydes. The aliphatic aldehydes such as butanal, pentanal, and heptanal provided the dehydrated Baylis−Hillman products (alkylidene derivatives) where as aromatic aldehydes, formaldehyde, acetaldehyde, and propanal produced unexpected dioxalane derivatives (Scheme 3).

Namboothiri and co-workers[116−120] for the first time have elegantly employed various nitroalkenes as activated alkenes for coupling with a number of electrophiles such as HCHO, activated alkenes (MVK, ethyl acrylate), α-keto esters, azadicarboxylates, and aldimine derivatives (Scheme 4). The Baylis−Hillman derivatives obtained from HCHO were also investigated for their anticancer activity.[121]

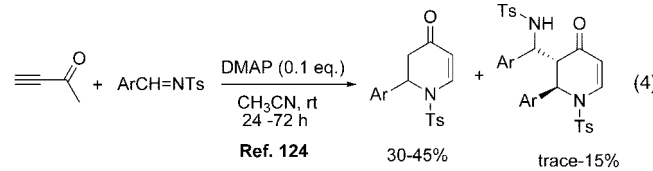
Later on, Cordova and co-workers[122] reported an interesting coupling between nitrostyrene derivatives as electrophiles and α,β-unsaturated aldehydes as activated alkenes under the catalytic influence of DABCO in the presence of proline to provide the corresponding β-substituted Baylis−Hillman adducts (eq 3).



(3)

Ar = C_6H_5, 3-ClC_6H_4, 2-BrC_6H_4
R = Me, Et, *n*-Bu, But-3-enyl

Shi and co-workers[123−126] have systematically examined the application of various allene derivatives such as ethyl 2,3-butadienoate, ethyl penta-2,3-dienoate, and but-3-yn-2-one as activated alkenes for coupling with a number of aldimine derivatives under Baylis−Hillman reaction conditions and obtained nitrogen heterocyclic compounds as described in Scheme 5 and eq 4. When they used methyl propiolate as activated alkene for coupling with aldimine, derived from benzaldehyde, using various Lewis bases, mixture of compounds were obtained in low yields. In the case of penta-3,4-dien-2-one derivatives, DMAP provided 5-substituted adducts when coupled with aldehydes or aldimines while DABCO or PBu_3 afforded heterocyclic compounds (Scheme 6).

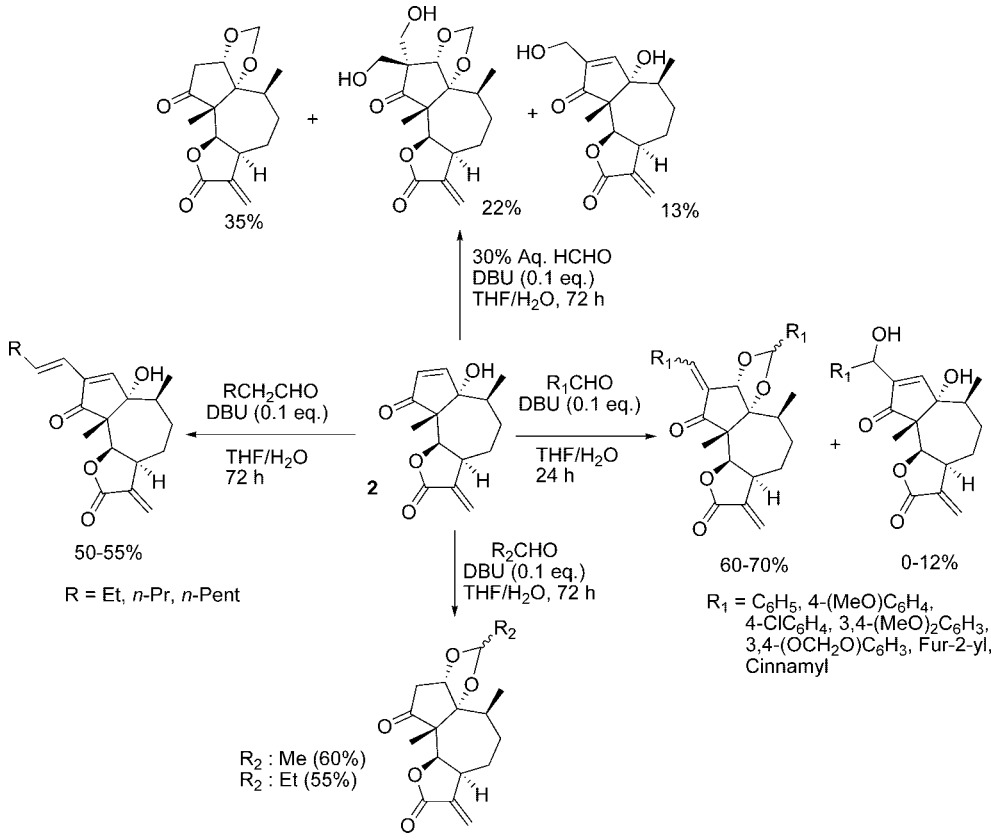


(4)

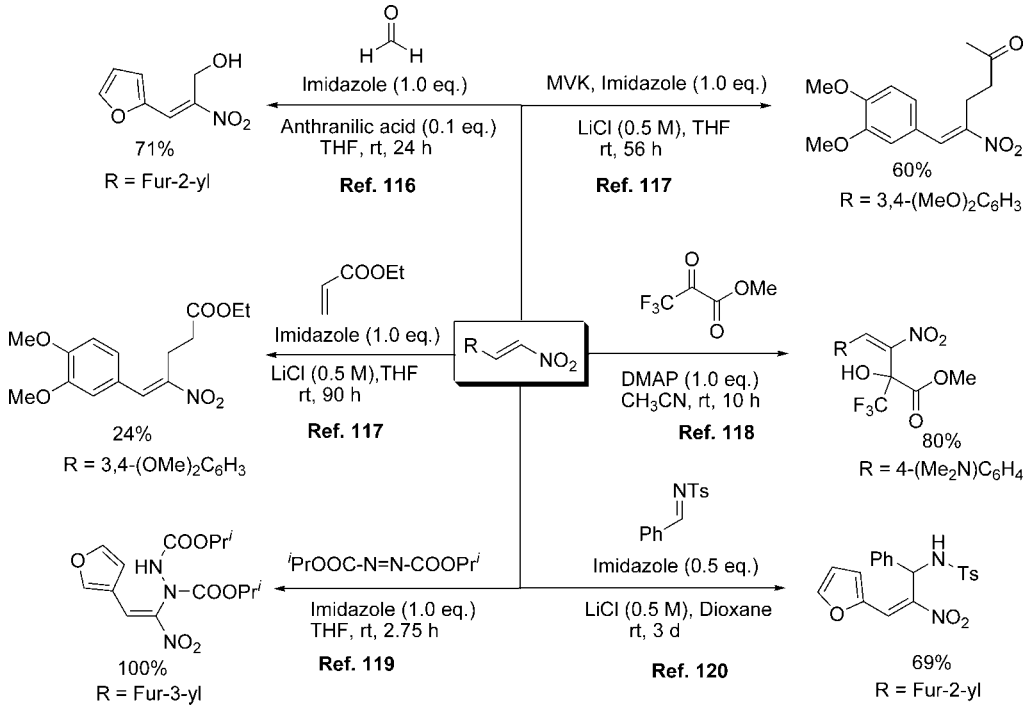
Ar = C_6H_5, 4-MeC_6H_4, 4-EtC_6H_4, 4-(MeO)C_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4

Shi and co-workers[127,128] have also examined β-substituted acrylate derivatives (phenyl crotonate, phenyl thiocrotonate, α-naphthyl crotonate, phenyl (2*E*)-2,4-pentadienoate, crotonaldehyde, (*E*)-propenyl phenyl ketone, and hex-2-enal)

Scheme 3



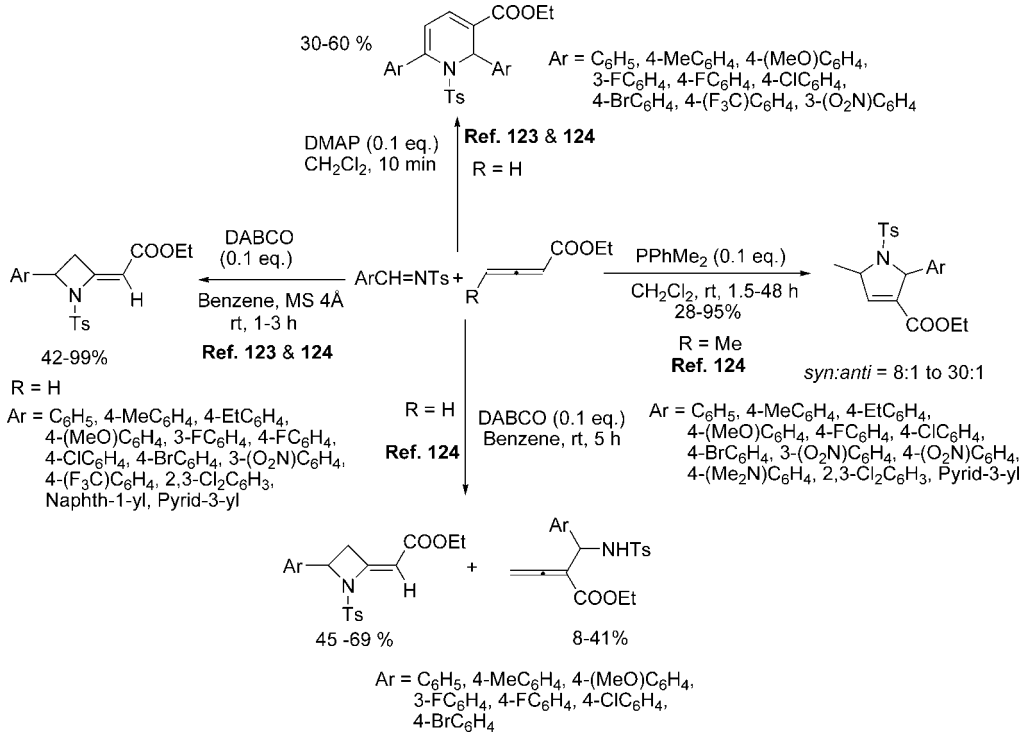
Scheme 4



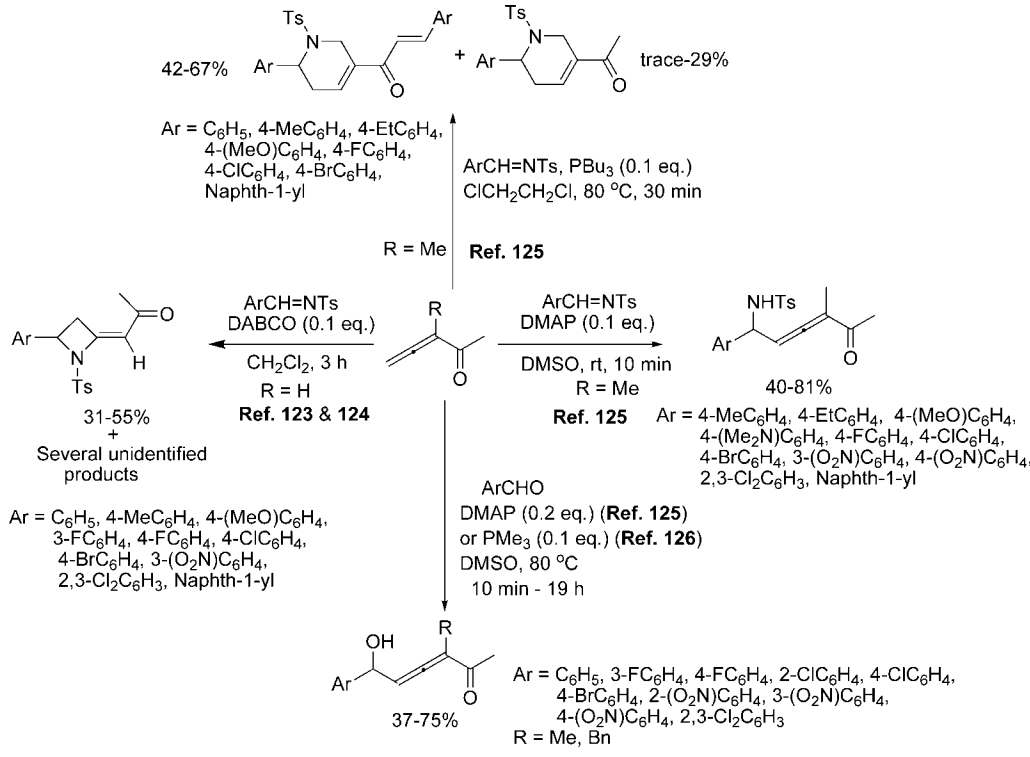
as activated alkenes for coupling with various aldimine derivatives under the influence of catalysts such as PMe_2Ph, $PMePh_2$, and DABCO. The resulting adducts were obtained as a mixture of *E*- and *Z*-isomers except in the case of crotonaldehyde, which provided *E*-adduct with high selectivity (99%). One representative example each is given in Scheme 7.

Back and co-workers[129−131] used 1-(*p*-toluenesulfonyl)-1,3-butadiene, methyl 2,4-pentadienoate, hex-3,5-dien-2-one, 1-phenylpenta-2,4-dien-1-one, and penta-2,4-dienenitrile as activated alkenes for coupling with various aldimine derivatives in the presence of 3-hydroxyquinuclidine (3-HQD) as a catalyst to provide the desired Baylis−Hillman adducts as mixtures of *E*/*Z* isomers. The (*E*)-adducts (separated from

Scheme 5



Scheme 6

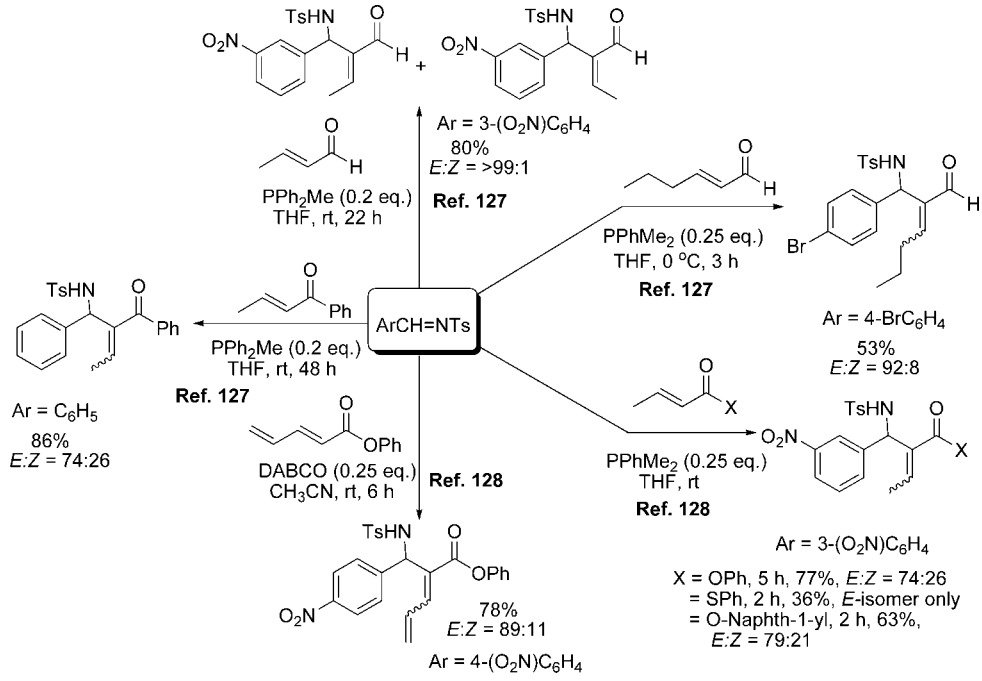


the *E*/*Z* mixture) derived from 1-(*p*-toluenesulfonyl)-1,3-butadiene and methyl 2,4-pentadienoate were further transformed into dihydropyridine derivatives via treatment with K_2CO_3 or DBU (Scheme 8).

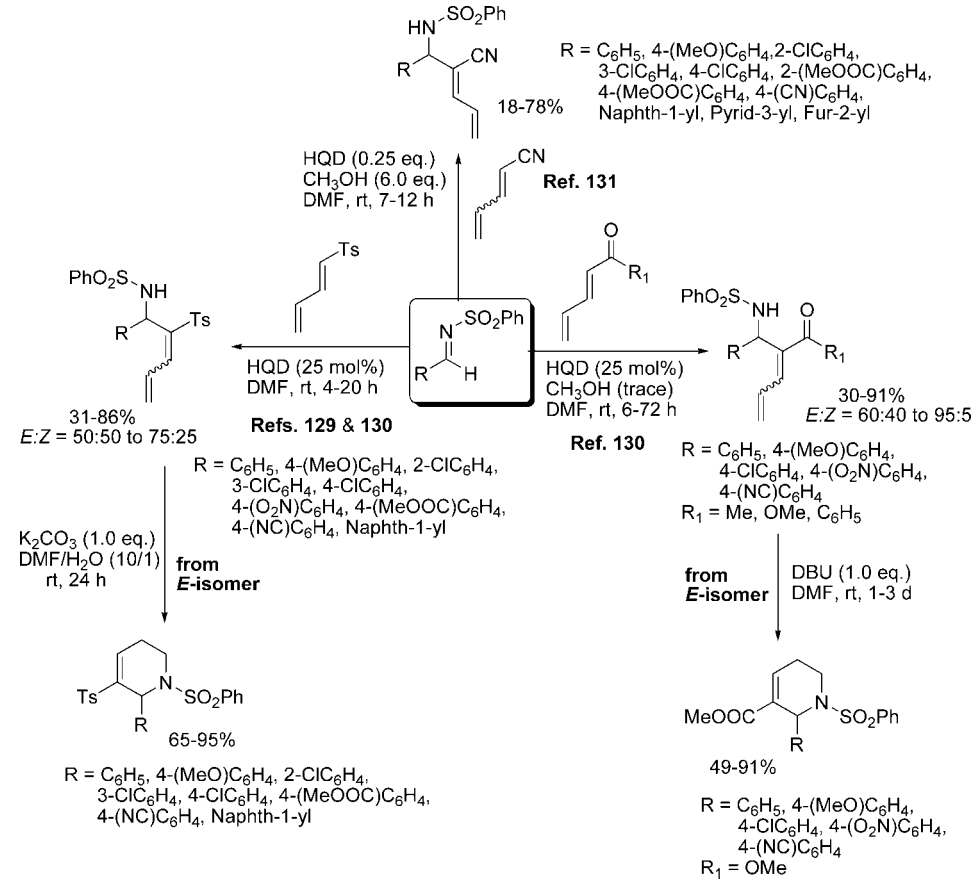
α-Oxaketene-*S*,*S*-acetals have been examined by Liu and co-workers[132−134] as activated alkenes in the Baylis−Hillman reaction with various aldehydes under the influence of $TiCl_4$. Bis adducts were obtained when 4.0 equiv of α-oxaketene-*S*,*S*-acetals was employed.[132] A similar reaction with 2-nitrobenzaldehyde provided bis-adduct, which was immediately converted into indole-*N*-oxide (**3**).[133] With a view to investigate the sequential Baylis−Hillman and Ritter reactions, they have also performed the reaction of α-oxaketene-*S*,*S*-acetals (1.0 equiv) with aldehydes in the presence of $TiCl_4$ (1.2 equiv) in alkyl nitriles as solvents to provide the corresponding amides (**4**).[134] Representative examples (one each) are presented in Scheme 9.

Later on, Zhang and co-workers[135,136] examined reaction between α-cyanoketene-*S*,*S*-acetals with various electrophiles (such as aldehydes, ketones, and cyclic or acyclic enones)

Scheme 7



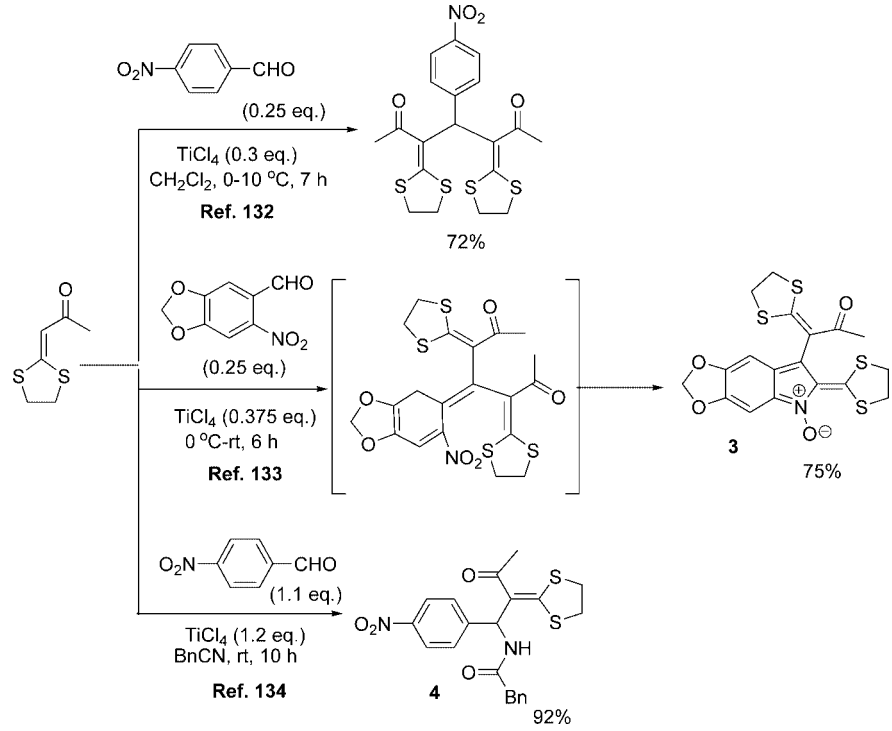
Scheme 8



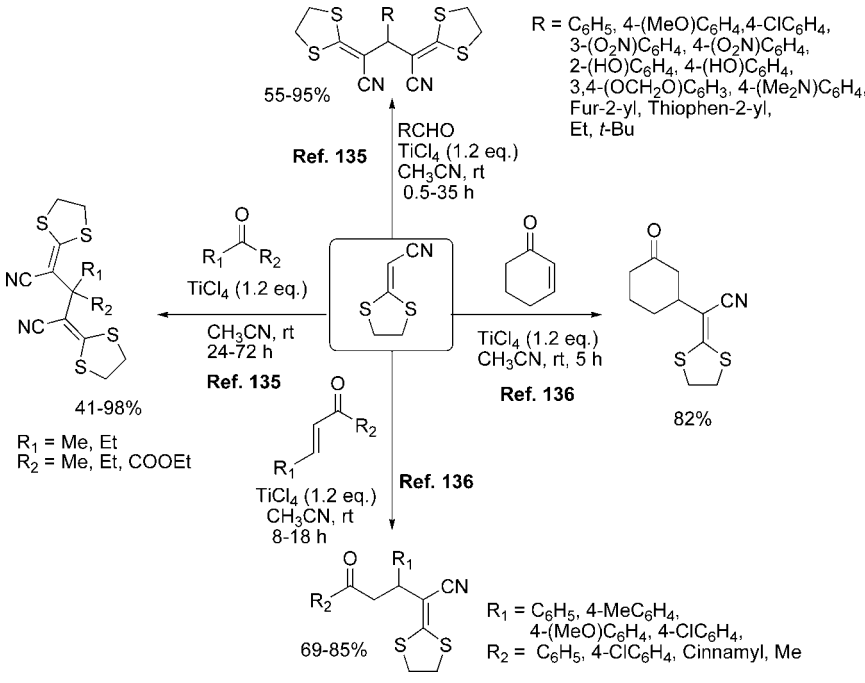
under the influence of $TiCl_4$ (1.2 equiv) using acetonitrile as a solvent. In the case of aldehydes and ketones, as electrophiles, double Baylis−Hillman adducts were obtained,[135] while cyclic and acyclic enones (as electrophiles) afforded the Baylis−Hillman adducts (Michael addition products at α-position)[136] (Scheme 10).

Zhang and co-workers[137] reported that the reaction of α-oxaketene-*S*,*S*-acetals with aryl alkyl carbinols in the presence of $BF_3 \cdot OEt_2$ provided the corresponding α-alkylated products in excellent yields (eq 5). Treatment of α-oxaketene-*S*,*S*-acetals with Baylis−Hillman alcohols, derived from acrylonitrile, provided the corresponding 1,4-pentadiene derivatives (**5**) in high yields. These dienes (**5**) were subsequently transformed into substituted benzene derivatives on treatment with nitroalkanes in the presence of DBU (Scheme 11)[137] and also into pyridine

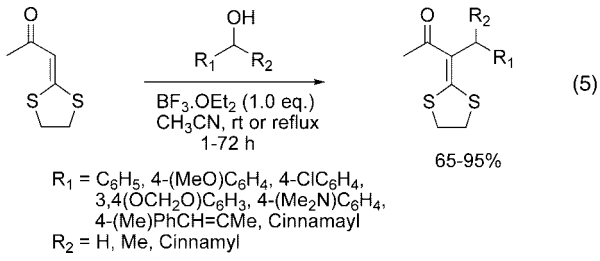
Scheme 9



Scheme 10



derivatives via the treatment with ammonium acetate (Scheme 11).[138]

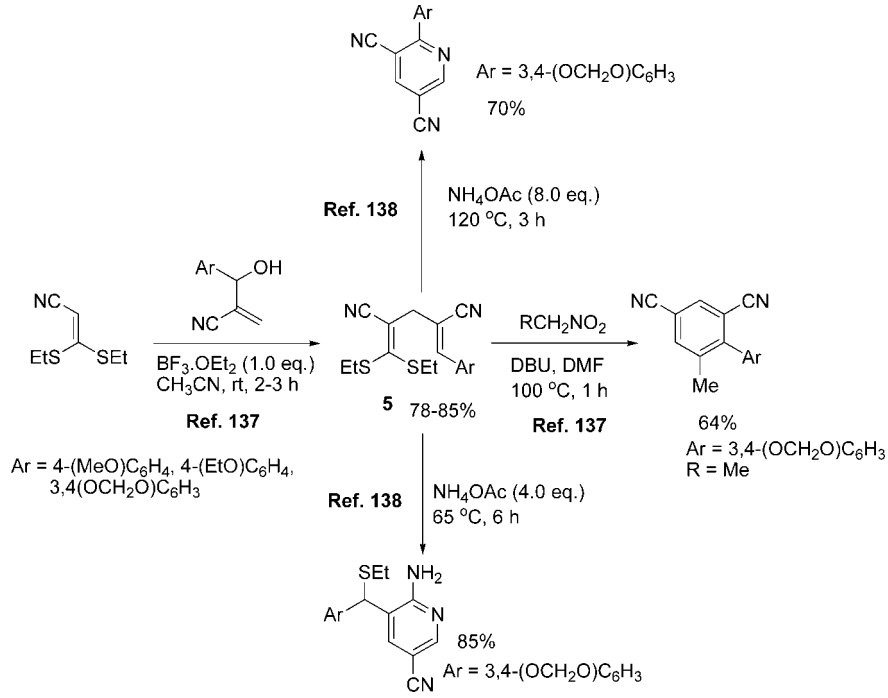


(5)

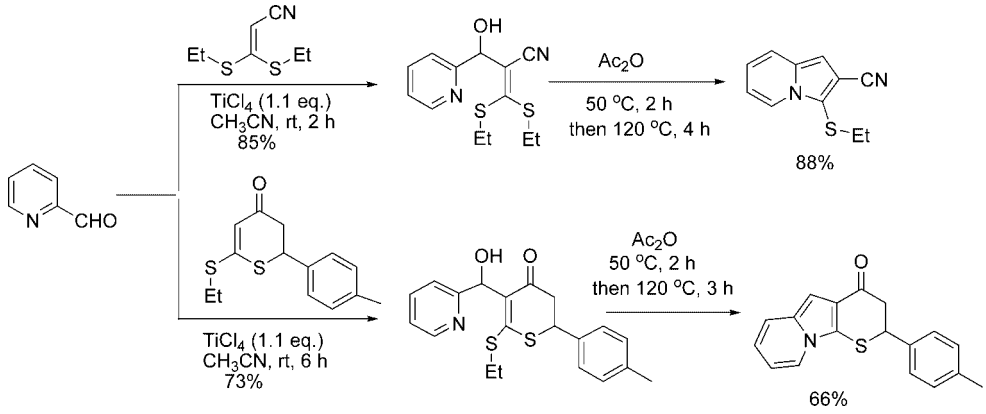
Recently Wang and co-workers[139] have described a facile synthesis of substituted indolizines via a formal [3 + 2] annulation of ketene-*S*,*S*-acetals, containing an electron-withdrawing group, with 2-pyridine-/2-quinolinecarboxaldehydes, under the influence of $TiCl_4$, following the reaction sequence as shown in Schemes 12 and 13. Representative examples are given.

An interesting sila-Baylis−Hillman reaction has been reported by Gevorgyan and co-workers[140] to provide highly functionalized cyclopropene derivatives via the reaction between 1-silyl-substituted cyclopropenes (**6**) and aldehydes or ketones under the catalytic influence of TTMPP [tris(2,4,6-

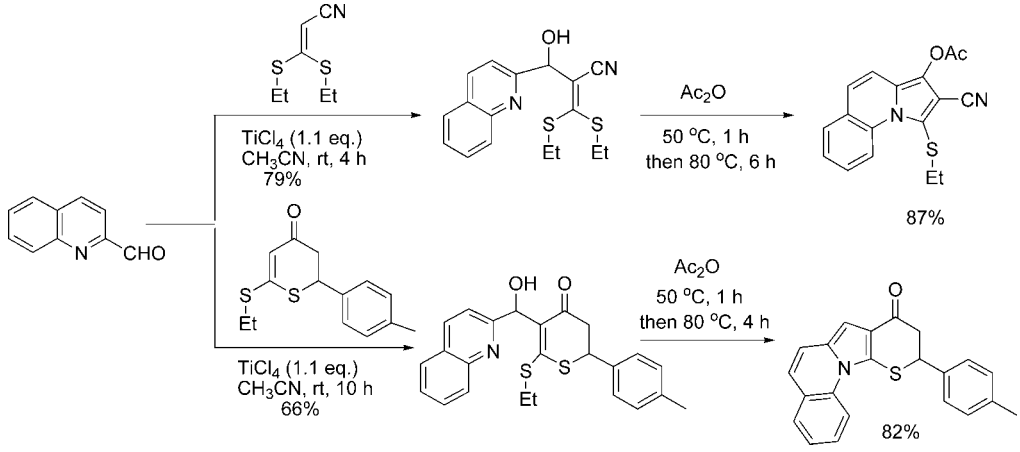
Scheme 11



Scheme 12



Scheme 13

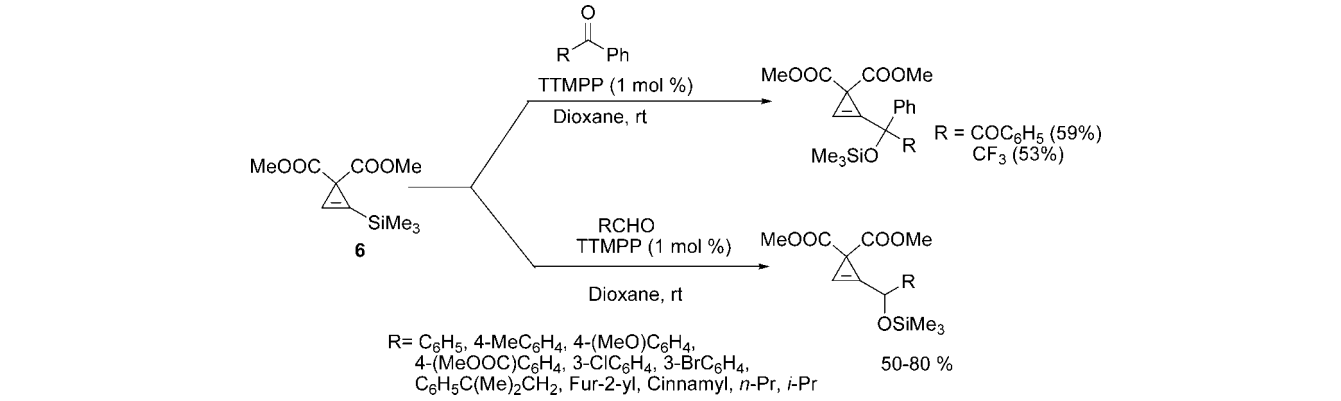


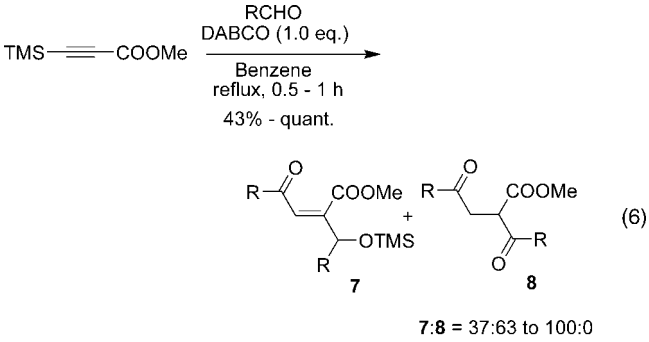
trimethoxyphenyl)phosphine], following the reaction sequence shown in Scheme 14.

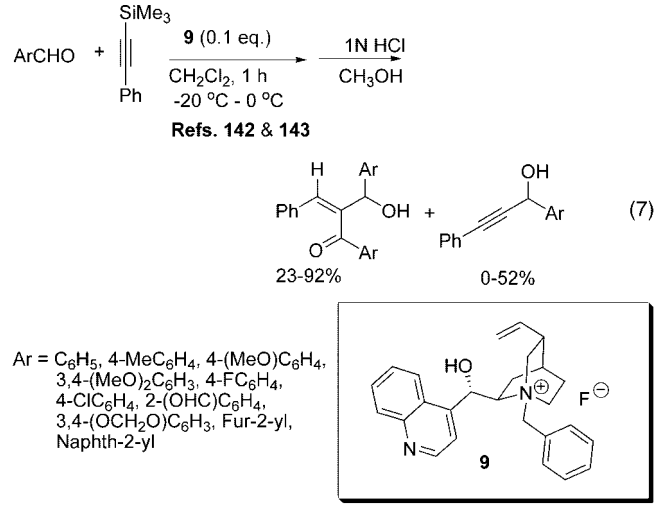
Nemoto and co-workers[141] have used 3-trimethylsilylpropiolate for coupling with aldehydes under the influence of DABCO to provide the Baylis−Hillman-type products **7** along with the diketones **8** (eq 6). It was proposed that the formation of products **8** is probably due to isomerization of the double bond in compounds **7**, followed by hydrolysis.

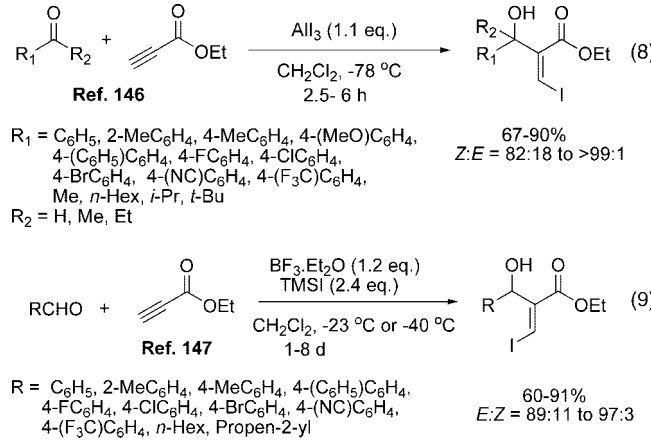
Yoshizawa and Shioiri[142,143] have reported that benzylcinchoninium fluoride (**9**) catalyzed reaction of 1-phenyl-2-(trimethylsilyl)acetylene with aromatic aldehydes to provide β-substituted Baylis−Hillman adducts (eq 7). Subsequently

Scheme 14









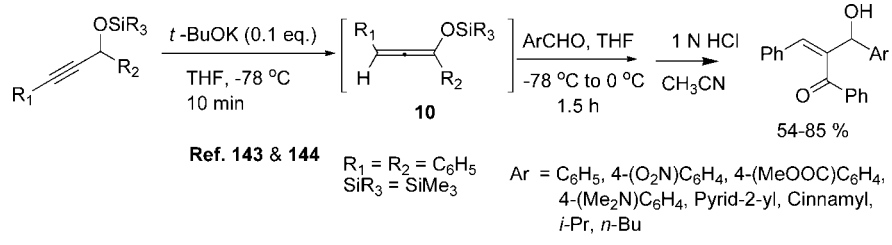
they also described[144] an interesting reaction of 1,3-diphenyl-3-trimethylsilyloxypropyne with aldehydes under the influence of *t*-BuOK to provide the β-substituted Baylis−Hillman adducts. This reaction is believed to proceed via a siloxyallene intermediate (**10**) (Scheme 15).

Subsequently Scheidt and co-workers[145] reported that treatment of silyloxyallenes (**10**) (obtained *in situ* from the acetylenic alcohol) with aldehydes or α-diketones under the catalytic influence of $Sc(OTf)_3$ produced the β-substituted Baylis−Hillman alcohols in high yields (Scheme 16).

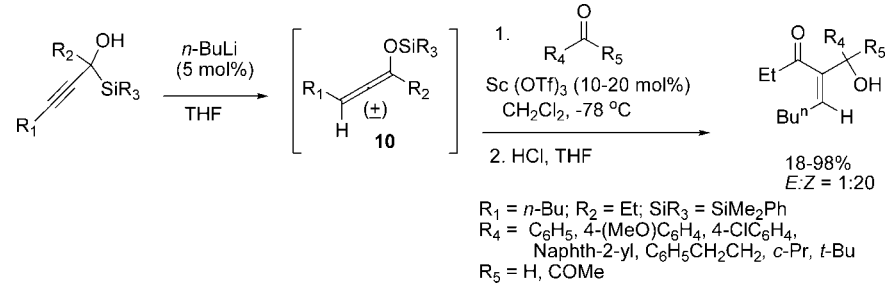
Ryu and co-workers[146] have reported a simple synthesis of β-iodo-Baylis−Hillman alcohols via the reaction between ethyl propiolate and various aldehydes (and ketones) under the influence of AlI_3 (eq 8). Later on, Ryu and co-workers[147] have also reported TMSI-mediated reaction of ethyl propiolate with various aldehydes in the presence of $BF_3 \cdot OEt_2$ to provide the desired β-iodo-Baylis−Hillman alcohols (eq 9). This methodology was subsequently extended to the synthesis of secokotomolide A (**11**), following the reaction sequence described in Scheme 17.

Amri and co-workers[148a] developed an efficient practical methodology for synthesis of hydroxymethyl acrylates via the reaction between aqueous HCHO and alkyl acrylates under the influence of DABCO in the presence of ethereal solvents (DME, THF, 1,4-dioxane) (eq 10). This method offers better yields in comparison with earlier procedures.[21,148b] Recently Acke and Stevens[149] have performed the Baylis−

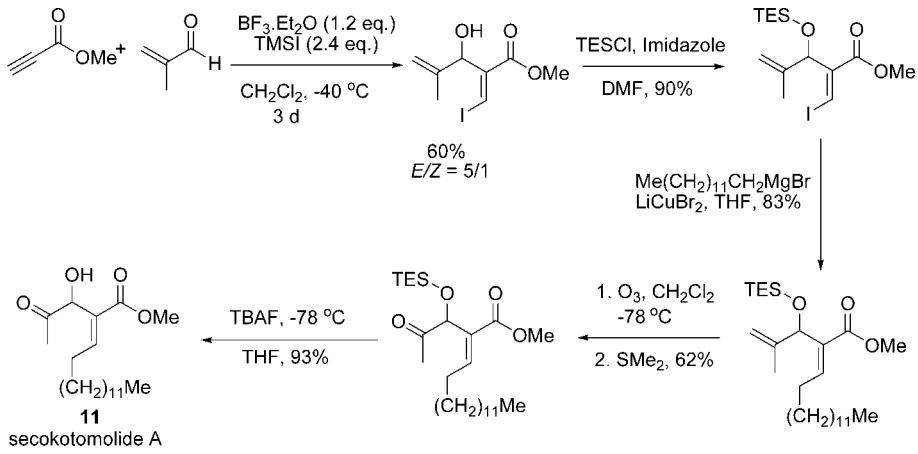
Scheme 15



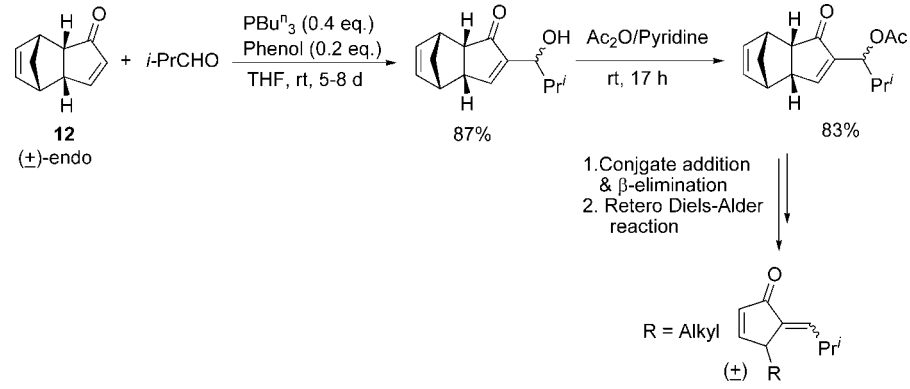
Scheme 16



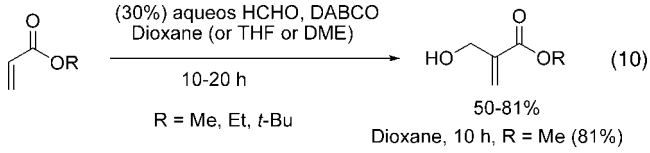
Scheme 17



Scheme 18



Hillman reaction of acrylates with aldehydes under a microreactor using DABCO as catalyst.



(10)

During their work for synthesis of optically pure cross-conjugated cyclopentadienones, Eddolls and co-workers[150] have used **12** as activated alkene for coupling with isobutyraldehyde to provide the Baylis−Hillman adduct, which was subsequently converted into racemic 4-substituted 5-alkylidene-cyclopentenone derivatives, according to Scheme 18. One representative example is presented.

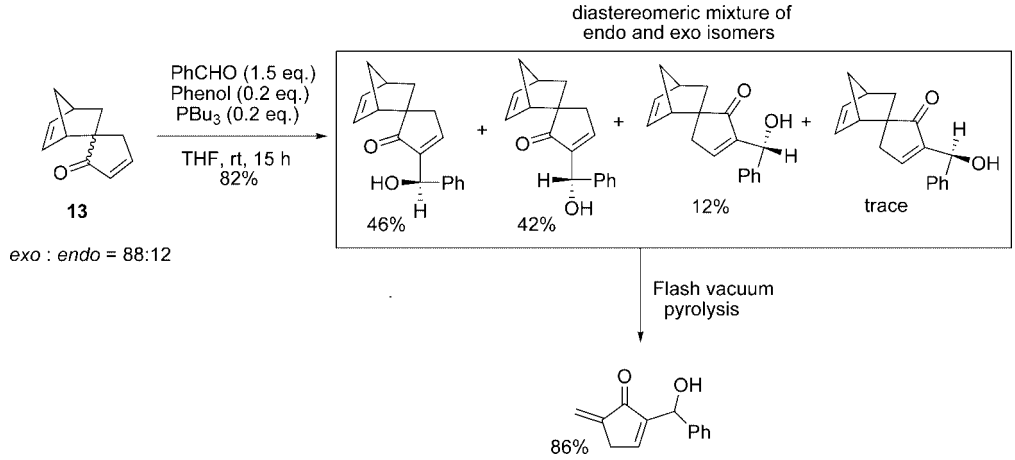
Pohmakotr and co-workers[151] employed 5-spiroalkylidenecyclopent-2-enones (**13**) as activated alkenes for the Baylis−Hillman coupling with aldehydes, under the influence of PPh_3, to provide the resulting Baylis−Hillman alcohols as a mixture of stereoisomers, which on subsequent flash vacuum pyrolysis (FVP) afforded 5-alkylidene-2-(hydroxyalkyl)cyclopent-2-enones, following the reaction sequence shown in Scheme 19. One representative example is presented.

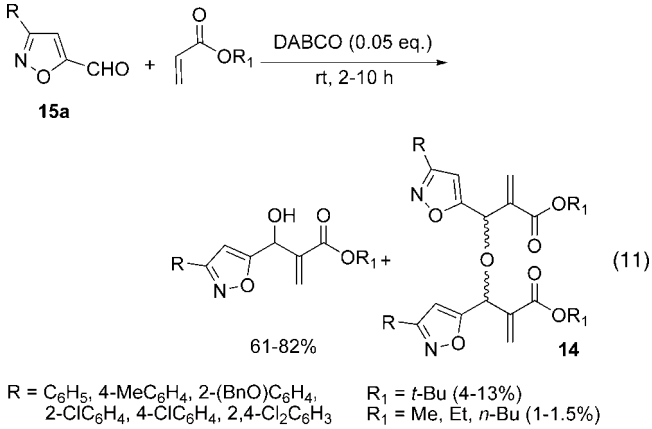
3.2. Electrophiles

During the last six years, various novel electrophiles have been employed for coupling with different activated alkenes leading to the formation of interesting classes of densely functionalized molecules. Batra and co-workers[152] have examined coupling of 5-isoxazolecarboxaldehydes (**15a**) with various alkyl acrylates under the catalytic influence of DABCO in aqueous medium. In these studies, they observed the formation of ethers **14** as minor products. The amount of formation of ethers depends on the nature of acrylate and *tert*-butyl acrylate provided significant amounts of ethers. Representative examples are shown in eq 11.

Batra and co-workers have also examined the Baylis−Hillman reaction of various 5-isoxazolecarboxaldehydes[153] (**15a**),

Scheme 19





4-isoxazolecarboxaldehydes[154] (**15b**), and 3-isoxazolecarboxaldehydes[155] (**15c**) (Figure 9) for coupling with various activated alkenes and observed that 5- and 3-isoxazolecarboxaldehydes react faster than 4-isoxazolecarboxaldehydes (Schemes 20 and 21). They employed polymer-supported acrylate as activated alkene and observed a similar trend with above-mentioned aldehydes (**15a**−**c**) (Scheme 22). Subsequently they[156] also studied the Baylis−Hillman reaction of pyrazole-3-carboxaldehydes (**15d**−**f**) and pyrazole-4-carboxaldehydes (**15g**) (Figure 9) with various activated alkenes and found that pyrazole-3-carboxaldehydes (**15d**−**f**) react faster than pyrazole-4-carboxaldehydes (**15g**). Representative examples are shown in Scheme 23.

Batra and co-workers[157] have used Baylis−Hillman acetates as electrophiles for coupling with various activated alkenes (MVK, methyl acrylate, ethyl acrylate, and acrylonitrile) in the presence of DABCO in aqueous medium providing the corresponding 1,4-pentadiene derivatives. In the case of MVK, they observed the formation of minor amounts of Michael-type dimer along with the usual Baylis−Hillman products (Scheme 24). It is worth mentioning here that earlier our research group[100,101] used Baylis−Hillman bromides as electrophiles for coupling with various activated alkenes under the influence of DABCO to provide 1,4-pentadiene derivatives.

Kim and co-workers[158] have successfully utilized, for the first time, 2-carboxybenzaldehyde as an electrophile in the

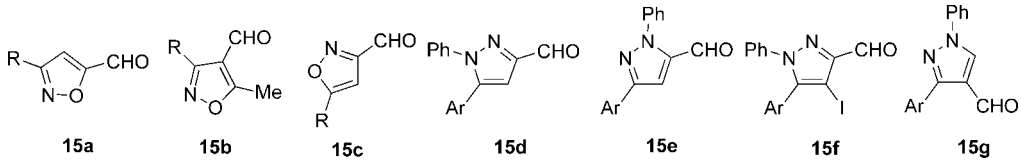
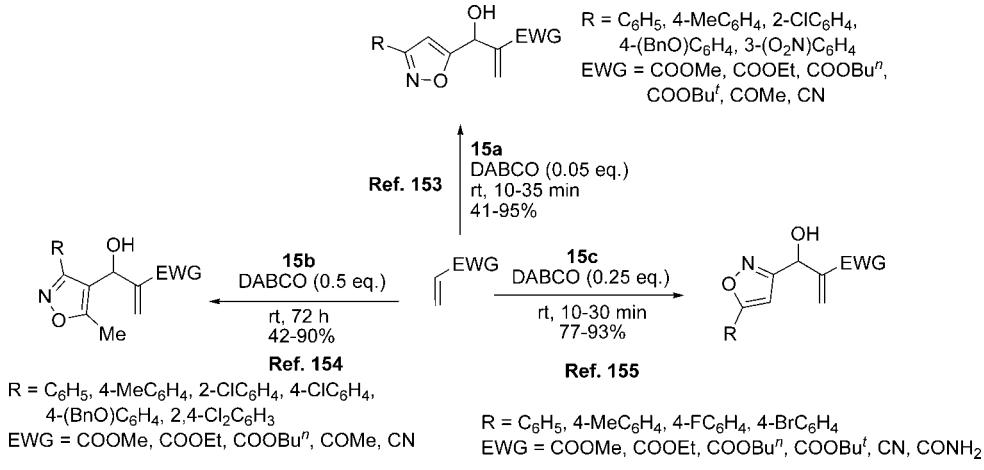
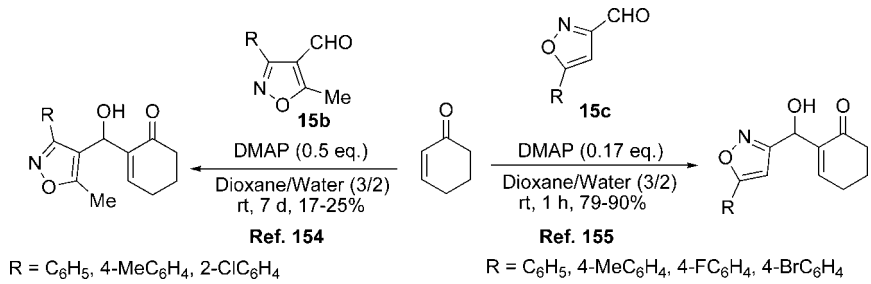


Figure 9.

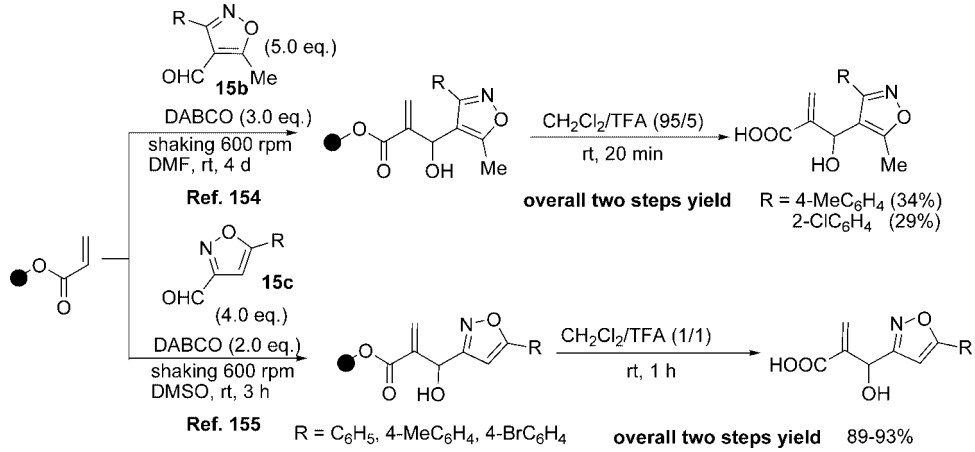
Scheme 20



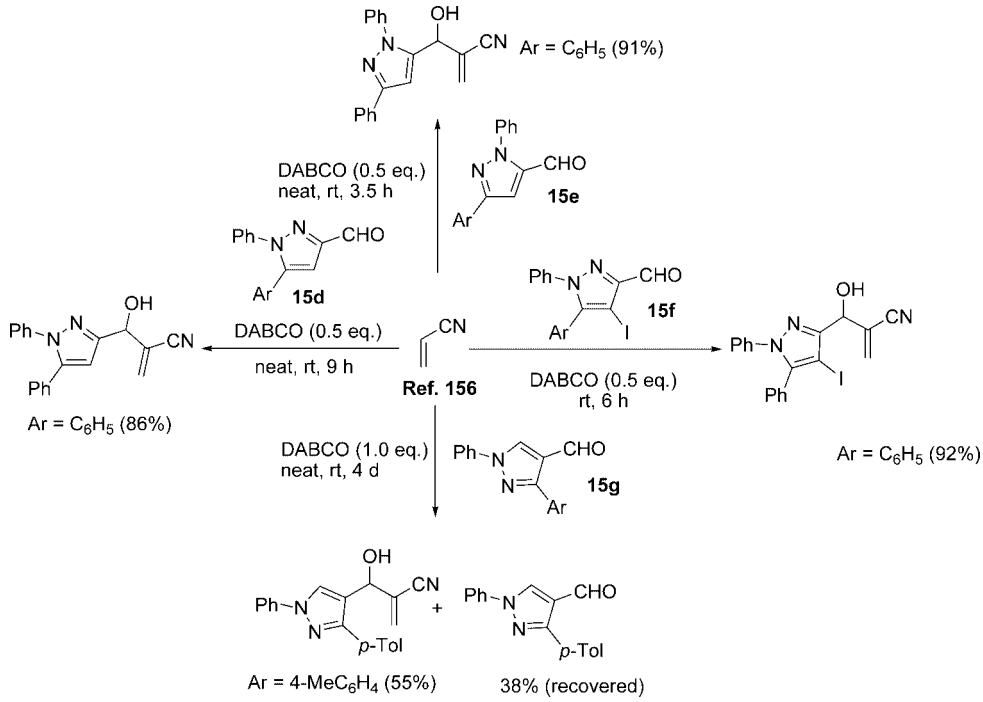
Scheme 21



Scheme 22

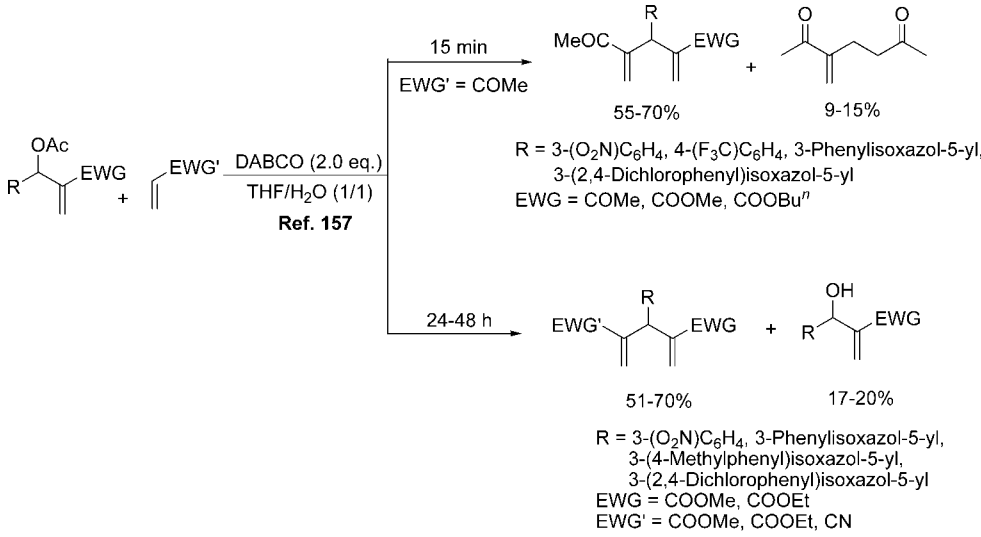


Scheme 23

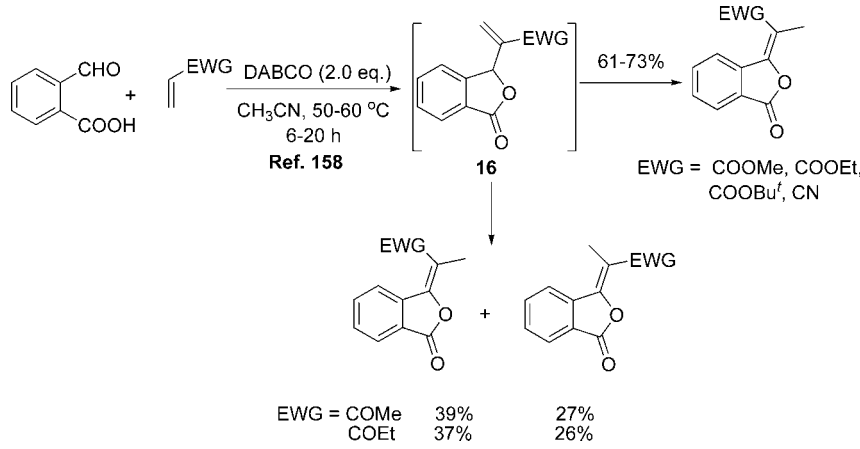


Baylis−Hillman reaction with various activated alkenes under the influence of DABCO in acetonitrile to provide 3-alkylidene-3*H*-isobenzofuranones in good yields. The reaction is believed to proceed through the Baylis−Hillman adducts **16** (Scheme 25). In the case of EVK and MVK, they obtained the products as a mixture of *E*- and *Z*-isomers (in the case of MVK, a minor amount of Michael-type dimer, 3-methylene-2,6-heptanedione, was also obtained). In the case of other activated alkenes, the products were obtained with exclusively *E*-stereoselectivity (in the case of ethyl acrylate, a minor amount of 2-methyl-1,3-dioxoindan-2-carboxylic acid ethyl ester was also obtained). Subsequently Lee and co-workers[159] have used 2-cyanobenzaldehyde as electrophile for coupling with various activated alkenes to provide first Baylis−Hillman adducts, which isomerize to provide isoindole derivatives. In the case of acrylonitrile and phenyl vinyl sulfone as activated alkenes, isoindole derivatives **17** were obtained as a mixture of *E*- and *Z*-isomers while in the case of methyl acrylate, ethyl acrylate, and MVK as activated alkenes, isomeric isoindole derivatives **18** were

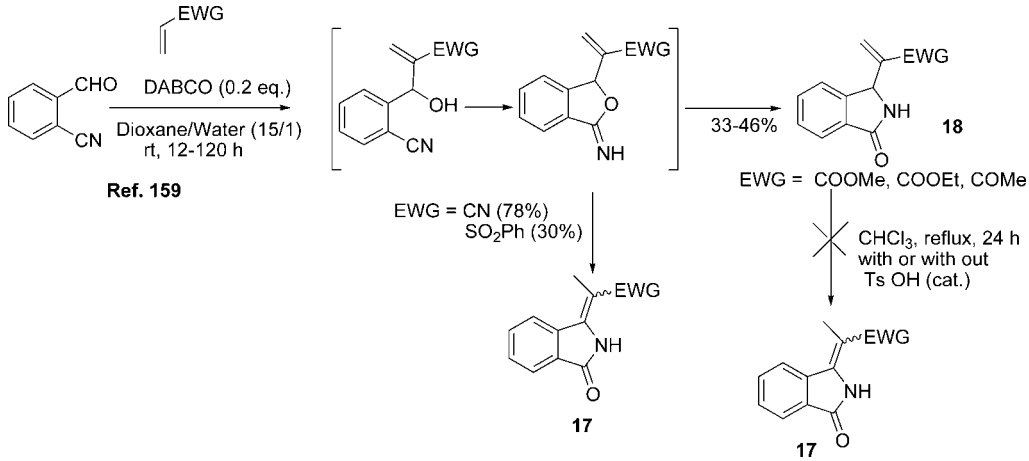
Scheme 24



Scheme 25



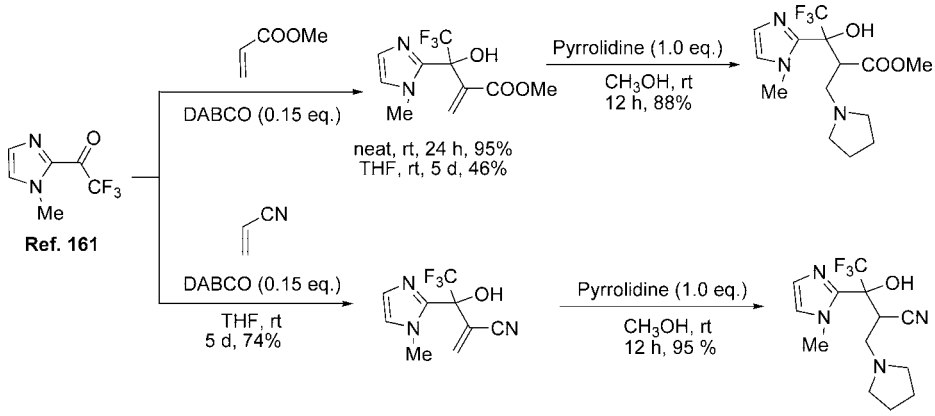
Scheme 26



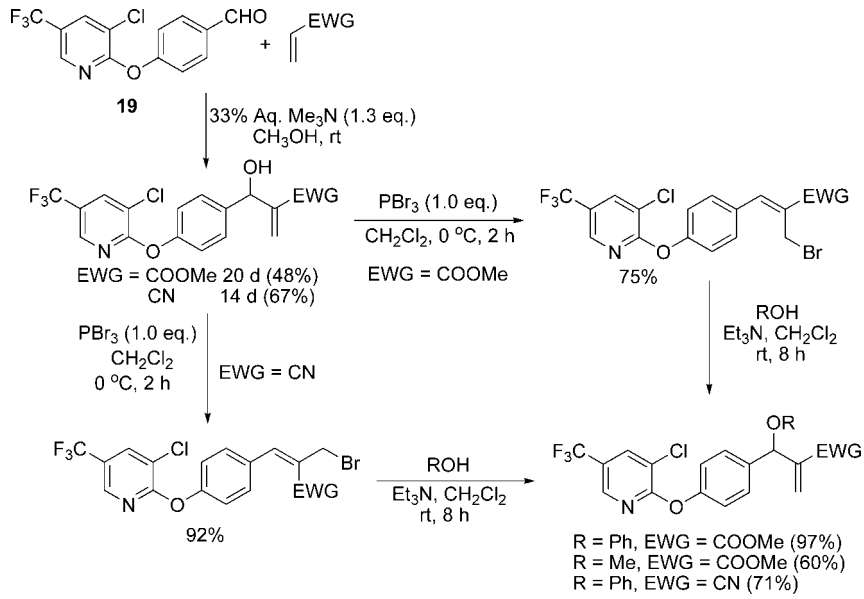
obtained as the products. Attempts to isomerize the *exo*-methylene bond in the isoindoles **18** to afford the isoindoles **17** (EWG = COOMe, COOEt, or COMe) were not successful even using TsOH (Scheme 26).

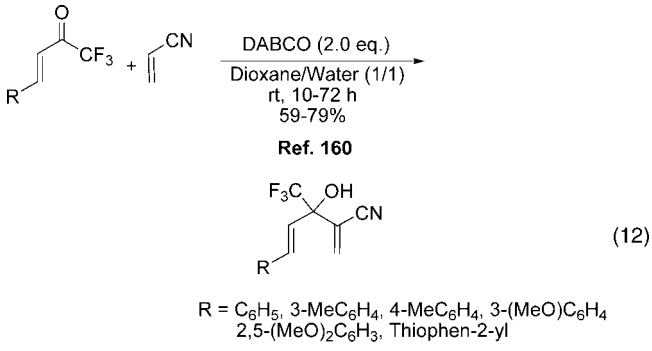
Nenajdenko and co-workers[160] have successfully used α,β-unsaturated trifluoromethyl ketones as electrophiles in the Baylis−Hillman reaction with acrylonitrile under the influence of DABCO in water−dioxane solvent system to provide the corresponding adducts in high yields. Representative examples are shown in eq 12. Other activated alkenes, such as methyl/ethyl acrylate, MVK, acrolein, and phenyl vinyl sulfone, failed to couple with fluoroketones under these conditions. Very recently Volochnyuk and co-workers[161] successfully utilized 2-(trifluoroacetyl)-1,3-azoles as electrophiles in the Baylis−Hillman reaction with methyl acrylate and acrylonitrile under the catalytic influence of DABCO (in these studies, they observed that neat reaction gave better yields than in THF as solvent). These Baylis−Hillman alcohols underwent Michael reaction with reactive amines. Representative examples are shown in Scheme 27.

Scheme 27



Scheme 28





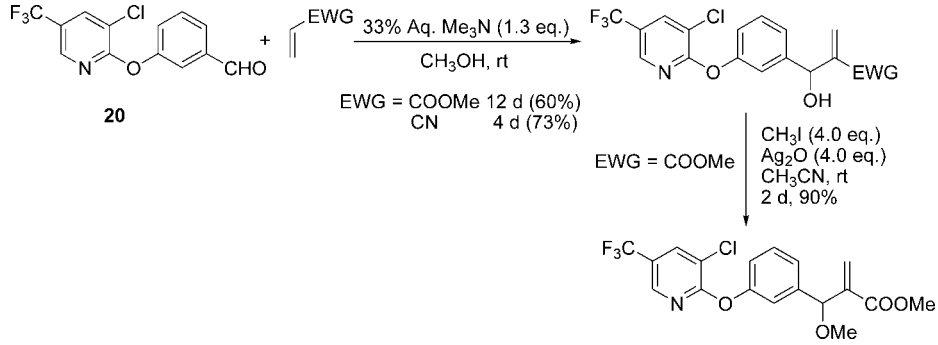
(12)

4-[3-Chloro-5-(trifluoromethyl)pyrid-2-yloxy]benzaldehyde (**19**) (Scheme 28) and 3-[3-chloro-5-(trifluoromethyl)pyrid-2-yloxy]benzaldehyde (**20**) (Scheme 29) were used as electrophiles by Xu and co-workers[162] in the Baylis−Hillman reaction with methyl acrylate and acrylonitrile under the influence of aqueous trimethylamine in methanol to afford the resulting adducts in good yields. They have transformed these Baylis−Hillman adducts into allyl bromides and allyl ethers according to the reaction sequence as shown in Schemes 28 and 29. They have also studied the biological activity of these derivatives.

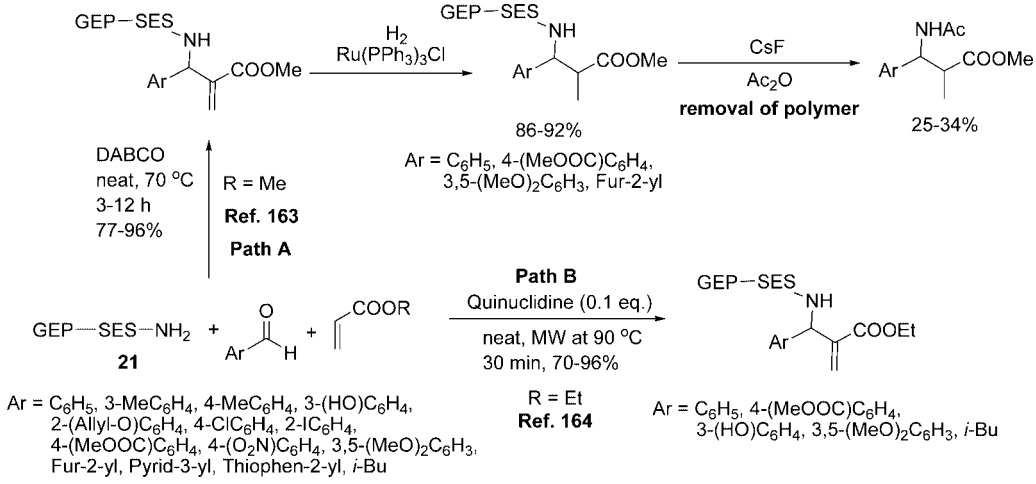
Lamaty and co-workers[163] have reported an interesting three-component Baylis−Hillman reaction between N-anchor polymer-supported sulfonamide (**21**), aldehyde, and methyl acrylate under the influence of DABCO under solvent free conditions at 70 °C to provide the Baylis−Hillman adducts in excellent yields. Advantages of this method are that (1) the polymer melts under reaction conditions and thus acts as solvent and (2) isolation of the product is easy due to the polymer tag. These N-supported β-amino esters were further subjected to hydrogenation in the presence of Wilkinson's catalyst to yield the corresponding alkanes in excellent yields. Representative examples are shown in Path A, Scheme 30. Removal of the polymer support provided 2-methyl-3-amino-3-arylpropionates in low yields. Subsequently these authors[164] also observed that Baylis−Hillman reaction was faster under microwave conditions using quinuclidine as a catalyst. Representative examples are shown in Path B, Scheme 30.

Shi and co-workers[165] have reexamined the Baylis−Hillman reaction of MVK with various aldehydes under the influence of different catalysts. They observed that the coupling of MVK with aryl aldehydes in the presence of DMAP provided only normal Baylis−Hillman adducts, while a similar reaction in the presence of DABCO gave double Baylis−Hillman adducts as minor products along with major usual Baylis−Hillman adducts. It was also noticed that increasing the amounts of MVK provided double Baylis−Hillman adducts as major products. Representative examples are given in Scheme 31. Under these reaction conditions, other activated alkenes such as EVK, methyl acrylate, and acrylonitrile

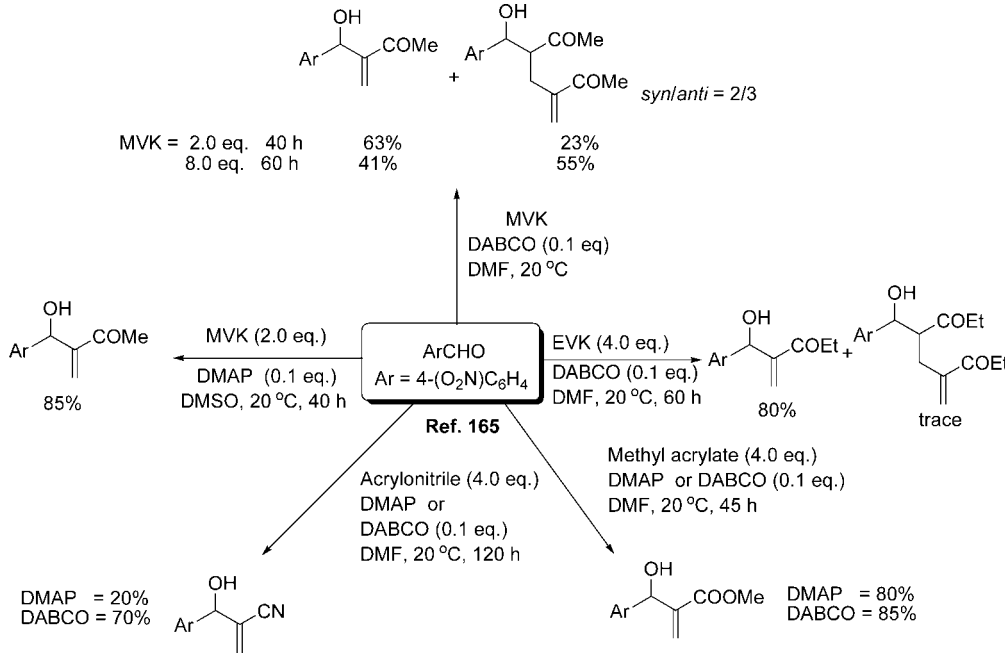
Scheme 29



Scheme 30



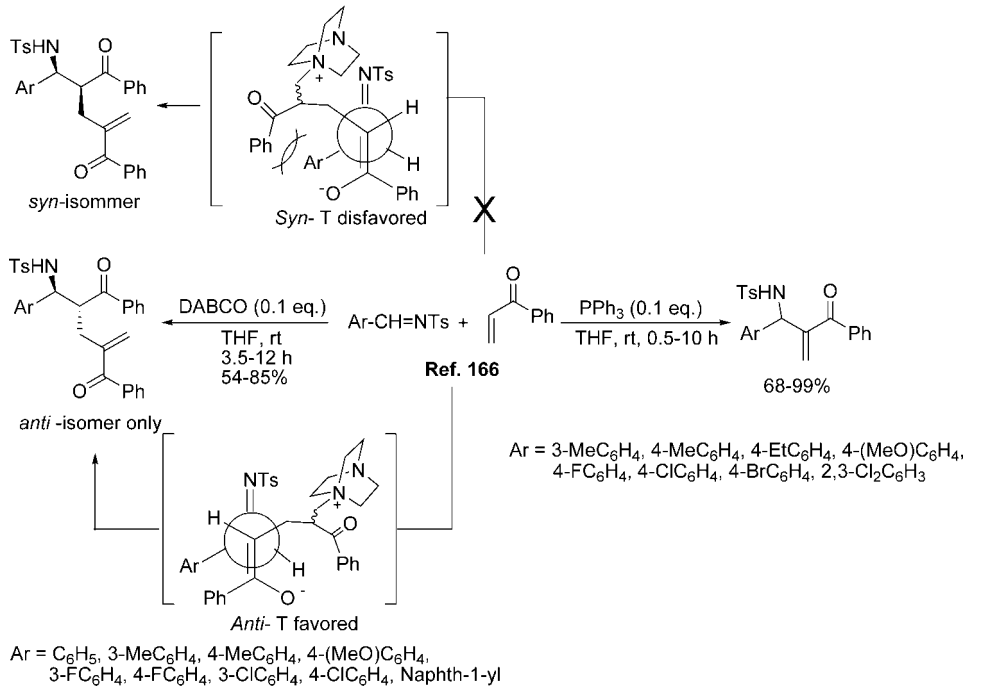
Scheme 31



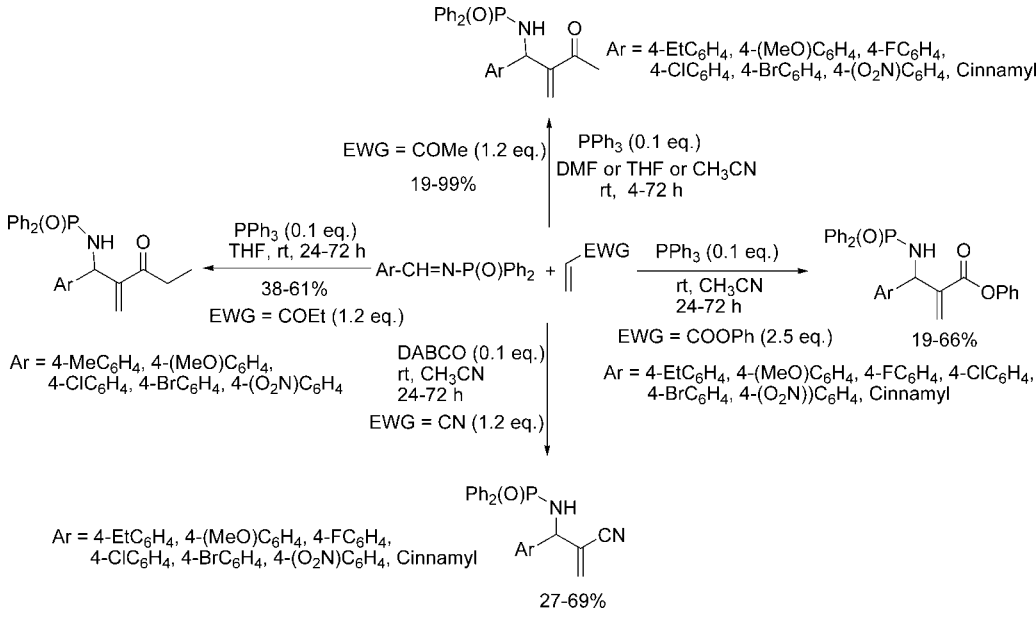
provided usual Baylis−Hillman adducts. Subsequently, Shi and Xu[166] examined the Baylis−Hillman reaction of PVK with N-sulfonated imines under the influence of different Lewis bases. It was observed that DABCO provided double Baylis−Hillman adducts [with *anti* configuration; see transition states, *anti*-T (favorable) and *syn*-T (disfavored)], while PPh_3 gave usual Baylis−Hillman adducts. Representative examples are given in Scheme 32.

Shi and Zhao[167] have examined the Baylis−Hillman reaction of *N*-(arylmethylene)diphenylphosphinamides as electrophiles with various activated alkenes under the influence of different Lewis bases. They found that PPh_3 offered better results for coupling of EVK, MVK, and phenyl acrylate with phosphinamides, while DABCO provided better results for coupling of acrylonitrile with phosphinamides (Scheme 33). They also observed that PPh_2Me provided better results for

Scheme 32



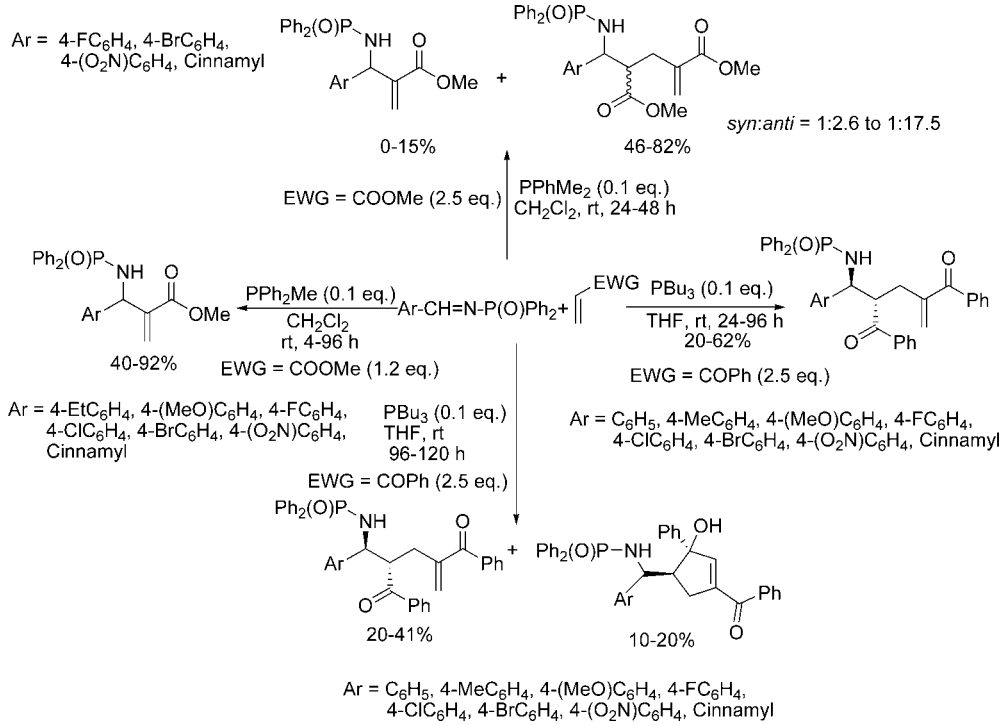
Scheme 33



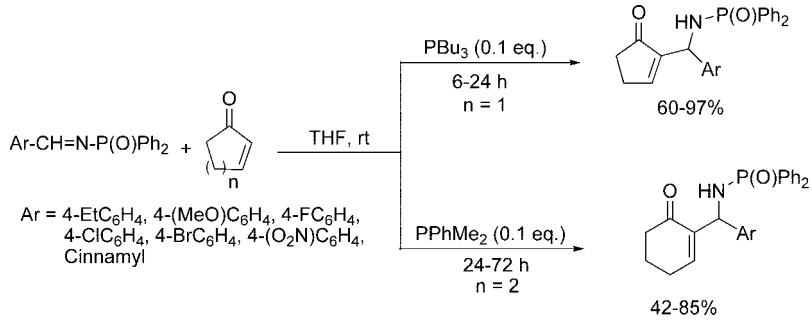
coupling of methyl acrylate with phosphinamides (Scheme 34). It was also noticed that PPh_2Me-catalyzed coupling of excess methyl acrylate (2.5 equiv) with various phosphinamides provided double Baylis−Hillman adducts as major products along with minor usual Baylis−Hillman adducts (Scheme 34). The reaction between PVK and phosphinamides under the influence of PBu_3 provided double Baylis−Hillman adducts. It was also observed that longer reaction time produced cyclopentene derivatives in significant amounts (Scheme 34). The coupling of phenyl acrylate with phosphinamides under the influence of PBu_3 gave the bis-Baylis−Hillman adducts along with piperidine derivatives (eq 13). They also observed that the coupling of cyclic enones with phosphinamides under the influence of $PBu_3/PPhMe_2$ provided the normal Baylis−Hillman adducts (Scheme 35).

Subsequently Zhu and co-workers[168] reported an interesting Baylis−Hillman reaction of polyfluorophenyl aromatic aldimines as electrophiles with methyl vinyl ketone under the catalytic influence of DABCO and PPh_3. They observed that triphenylphosphine as a Lewis base provided the normal Baylis−Hillman adducts **22** along with the double Baylis−Hillman adducts **23** as minor products, while a similar coupling using DABCO afforded only the double Baylis−Hillman adducts **23** (Scheme 36). The resulting double Baylis−Hillman adducts **23** were converted into the corresponding carbocyclic compounds (as a mixture) via intramolecular aldol reaction. Subsequently these authors[169] also examined the application of these polyfluorophenyl aromatic aldimines as electrophiles for coupling with methyl acrylate and acrylonitrile as activated alkenes to provide the corresponding Baylis−Hillman

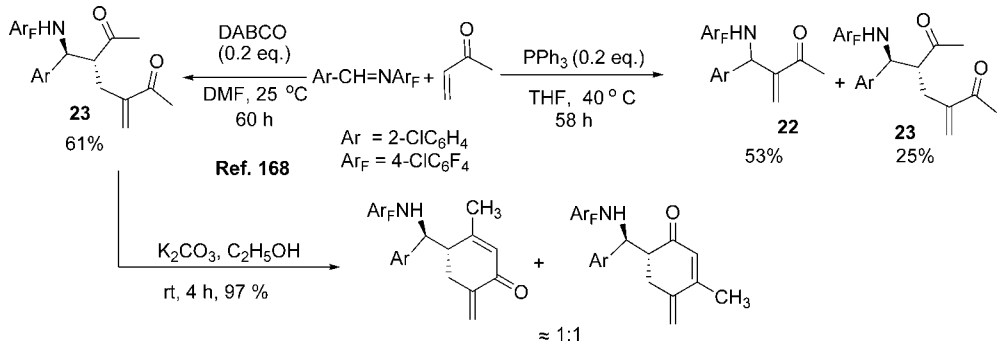
Scheme 34



Scheme 35



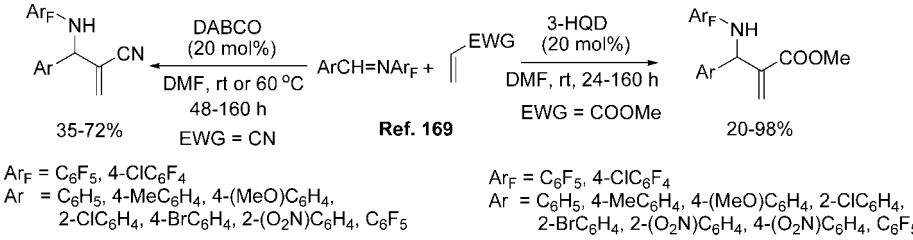
Scheme 36



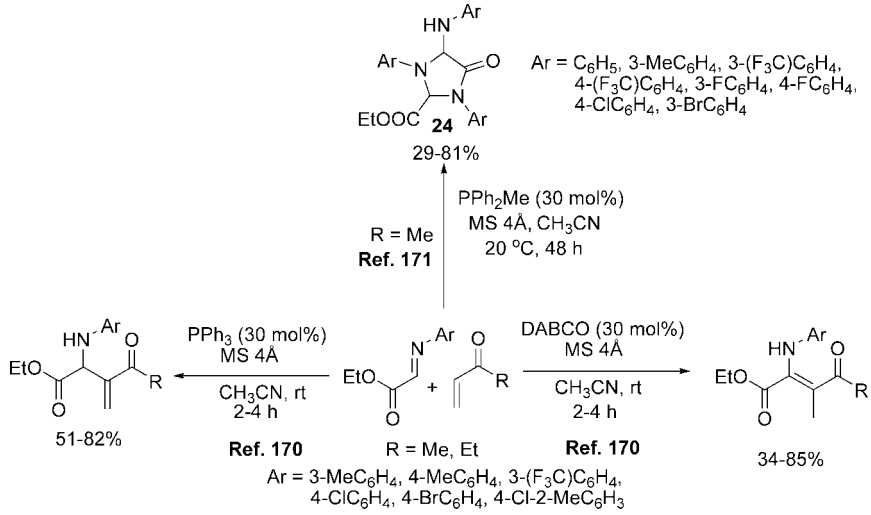
adducts (Scheme 37). It is interesting to note that this is the first report using the simple imine derivatives as electrophiles in the Baylis−Hillman reaction.

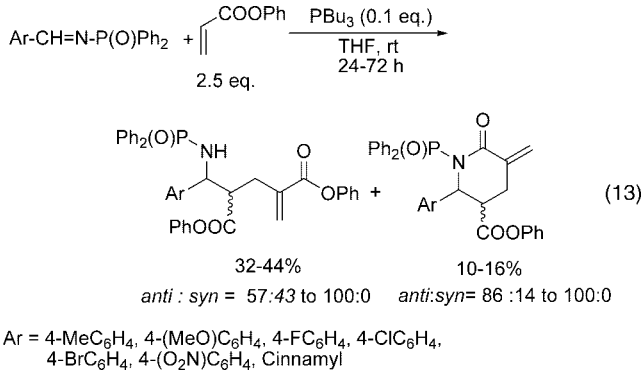
Later on, Shi and co-workers[170] reported Baylis−Hillman reaction of ethyl (arylimino)acetates as electrophiles for coupling with methyl vinyl ketone and ethyl vinyl ketone in the presence of PPh_3 and DABCO. They noticed that PPh_3 provided the corresponding Baylis−Hillman adducts in moderate to good yields, while DABCO afforded the corresponding enamine derivatives (Scheme 38). Subsequently, they[171] also reported an unexpected annulation of ethyl (arylimino)acetates to provide poly-substituted oxoimidazolidine derivatives (**24**) in moderate to good yields under the catalytic influence of PPh_2Me (a more nucleophilic catalyst than PPh_3) in the presence of MVK. It was also noticed that when Ar (in aryl imino acetate) is 3-FC_6H_4 or 3-$(F_3C)C_6H_4$, the products were contaminated with a trace amount of MVK dimer, 3-methylene-2,6-heptanedione, while in the case of Ar is 4-MeC_6H_4, there was formation of Baylis−Hillman adduct (25%) with some unidentified products. Representative examples are given in Scheme 38.

Scheme 37



Scheme 38

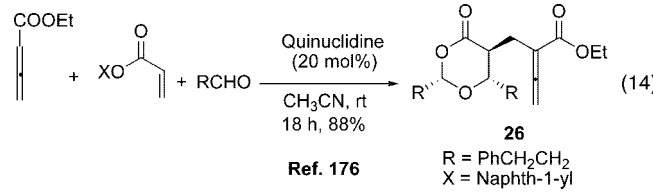




Katritzky and co-workers have used, for the first time, aminomethylbenzotriazoles (**25**) as electrophiles for coupling with various activated alkenes under the influence of $TiCl_4$ to provide the addition products, which on treatment with NaH provided the Baylis−Hillman adducts.[172] One example is given in Scheme 39.

An interesting reaction between 2-halo- or 2,3-dihalo-1,4-naphthoquinones and different activated alkenes (such as methyl acrylate, acrolein, and methyl vinyl ketone) under the influence of DABCO providing the corresponding mono- and bis-adducts via an addition−elimination sequence was reported by Lee and co-workers.[173,174] Bis-adducts were transformed into tricyclic compounds by heating. Representative examples (with methyl acrylate as activated alkene) are presented in Scheme 40. Unhalogenated simple naphthoquinones were found to be ineffective for coupling with MVK or acrylates under these conditions (Scheme 41). When this strategy was extended to haloquinoline-5,8-diones[175] as electrophiles, mixtures of products are obtained, and one such example is shown in Scheme 41.

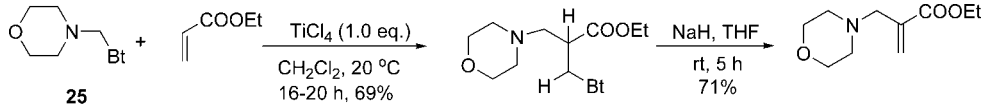
An elegant coupling of allenic esters with α,β-unsaturated ketones (acyclic and cyclic) under the catalytic influence of quinuclidine leading to the formation of α-alkylated allenic esters in high yields was reported by Miller and co-workers.[176,177] Subsequently these compounds were transformed into bicyclic heterocyclic molecules following the reaction sequence as shown in Scheme 42. They have also performed the reaction between allenic ester, α-naphthyl acrylate, and aldehydes under the influence of quinuclidine, which provided an interesting class of 1,3-dioxane derivatives (**26**) via sequential formation of two C−C bonds and two C−O bonds as shown in eq 14.



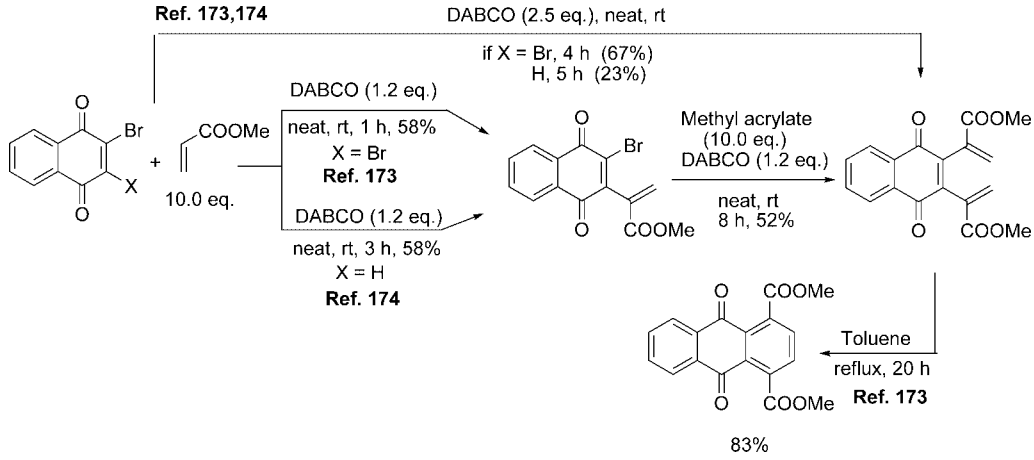
Krishna and co-workers[178] have examined the diastereoselective Baylis−Hillman reaction of chiral 2,3-epoxy aldehydes with alkyl acrylates and acrylonitrile in the presence of DABCO and obtained moderate diastereoselectivity (Scheme 43). Rao and co-workers[179,180] used 2-chloronicotinaldehydes as electrophiles (one example is shown) for coupling with various activated alkenes such as acrylonitrile, methyl acrylate, and cyclic enones in the presence of DABCO (or imidazole) to provide Baylis−Hillman adducts. The adducts derived from acrylonitrile and methyl acrylate were examined for their biological activity (Scheme 44).

The Baylis−Hillman reaction between 2-(*tert*-butyldimethylsilyloxy)ethanal and MVK was reported by Doutheau and co-workers.[181] The resulting products on desilylation, followed by reductive ozonolysis provided, racemic 4,5-dihydroxy-2,3-pentanedione (**27**) (DPD) (Scheme 45).

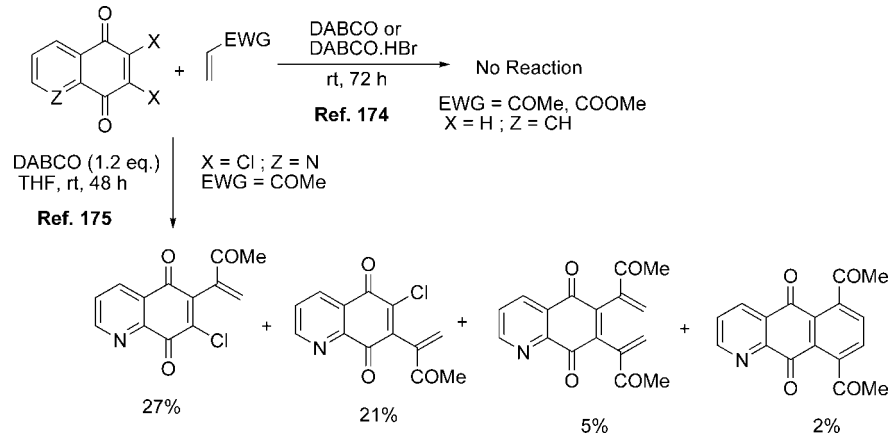
Scheme 39



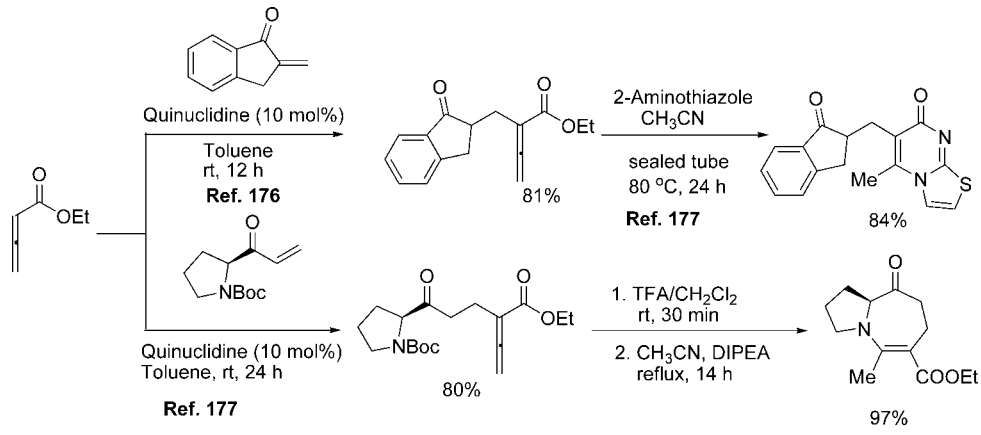
Scheme 40



Scheme 41



Scheme 42

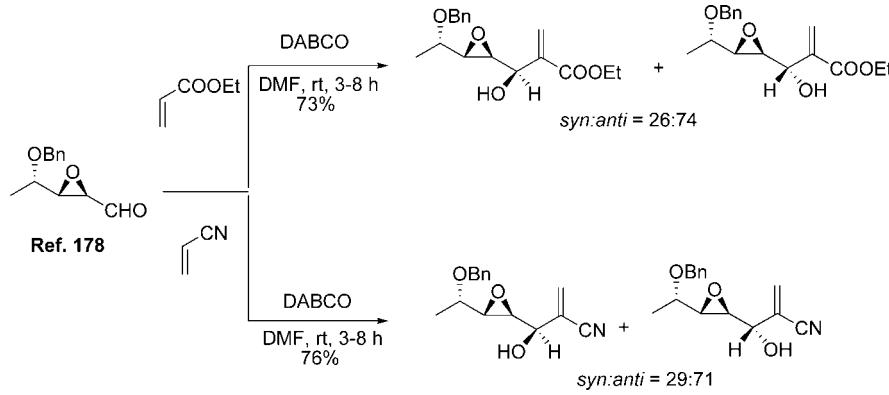


3-Acetyl-1-formyl-1,3-butadiene, generated *in situ* from the aldehyde (**28**), was employed as electrophile in the Baylis−Hillman reaction with alkyl vinyl ketones and acrylates to afford the resulting trienols in good yields (Scheme 46).[182]

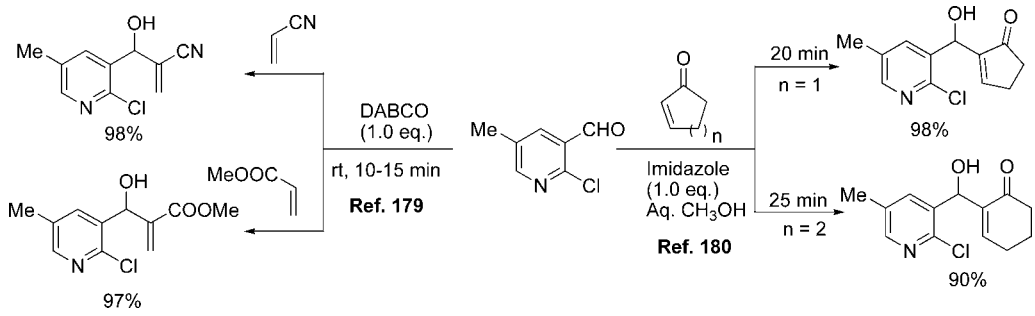
Carborane aldehydes[183] (**29**) have been used as electrophiles for coupling with various activated alkenes to provide the corresponding alcohols, which were further converted into trisubstituted alkenes following the reaction sequence shown in Scheme 47 (one example is presented).

Shi and Zhao[184] examined the reaction of diethyl azodicarboxylate and diisopropyl azodicarboxylate with various alkyl and aryl acrylates and acrylonitrile to provide representative Baylis−Hillman adducts. In this study, they observed that aryl acrylates react faster than methyl acrylate

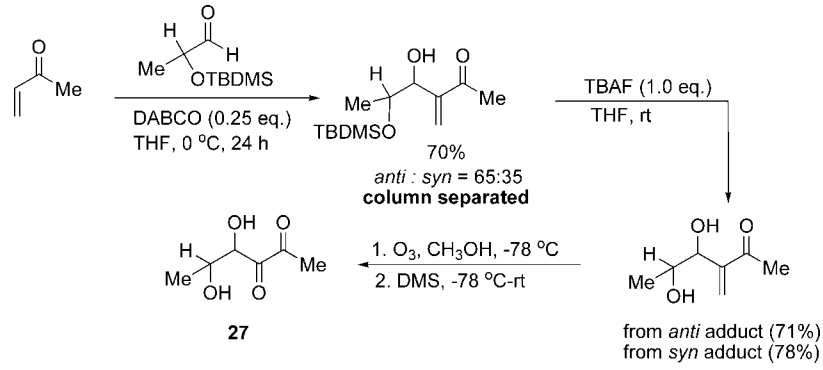
Scheme 43



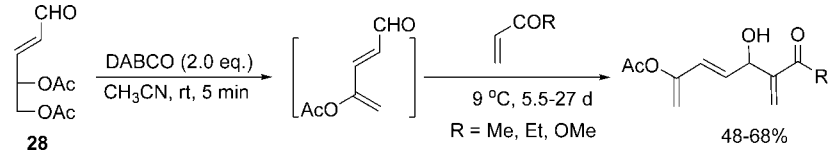
Scheme 44

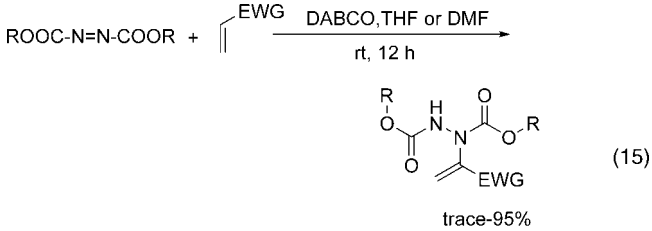


Scheme 45



Scheme 46

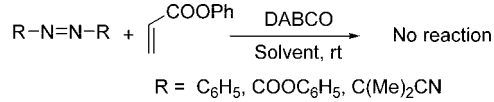




(15)

R = Et, *i*-Pr
EWG = COOMe, COOPh, COO(4-ClC$_6$H$_4$), COO(4-[O$_2$N]C$_6$H$_4$), COO(4-MeC$_6$H$_4$), CN

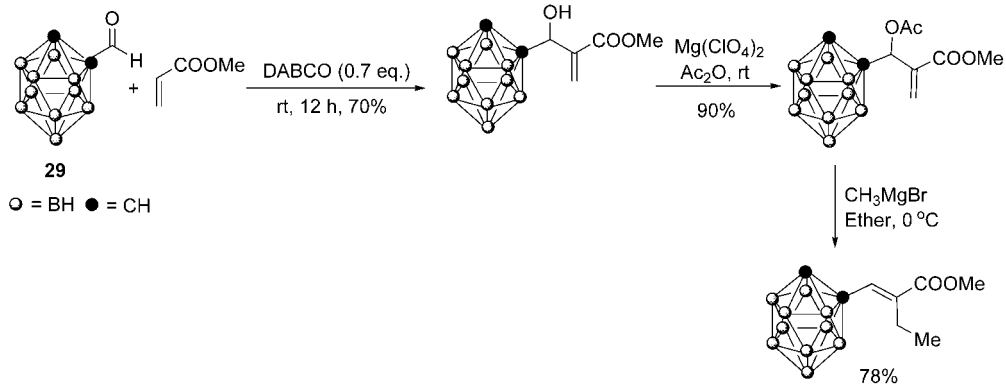
and acrylonitrile (eq 15). They have also noticed that diphenyl azodicarboxylate, 2,2′-azobisisobutyronitrile, and azobenzene failed to react with phenyl acrylate under similar reaction conditions (eq 16).



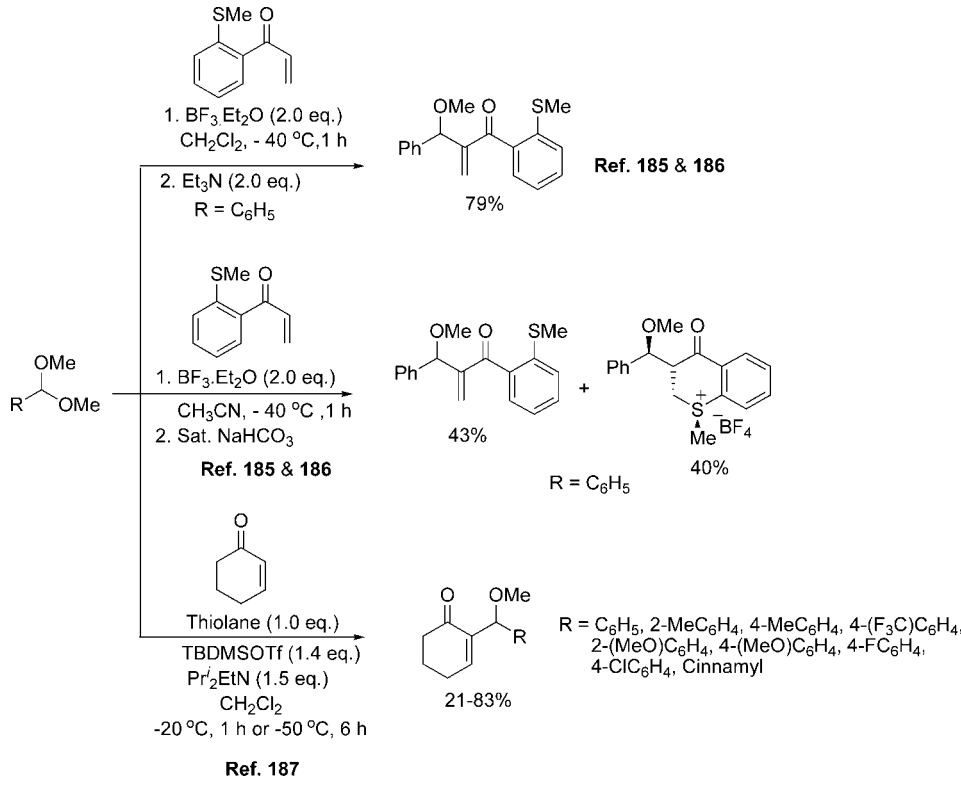
(16)

Kataoka and co-workers[185,186] reported intramolecular chalcogeno-Baylis−Hillman coupling of 2-thiomethylphenyl vinyl ketones with dimethyl acetals of aryl aldehydes to obtain the corresponding methyl ethers of Baylis−Hillman adducts. It was also noticed that the work up with $NaHCO_3$ provided thiopyran salts (sulfonium salts) along with normal Baylis−Hillman products. Very recently Metzner and co-

Scheme 47



Scheme 48



workers[187] have reported an interesting thiolane-mediated coupling of cyclohex-2-enone with aromatic aldehyde dimethoxy acetals under the influence of TBDMSOTf to provide methyl ethers of Baylis−Hillman alcohols as shown in Scheme 48.

Nair and Abhilash[188] have employed *ortho*-phthaldehyde as an electrophile for the Baylis−Hillman reaction with activated alkenes to produce the cyclic (lactol) derivatives, which were converted into carbocyclic derivatives via the reaction with various electron-deficient dienophiles, such as dimethyl acetylenedicarboxylate (DMAD), *N*-phenylmaleimide, or methyl acrylate. Representative examples are presented in Scheme 49.

Awadi and co-workers[189] have used arylhydrazonals as electrophiles for coupling with acrylonitrile or methyl vinyl ketone to provide directly dihydropyridazine derivatives, presumably through Baylis−Hillman adducts (Scheme 50).

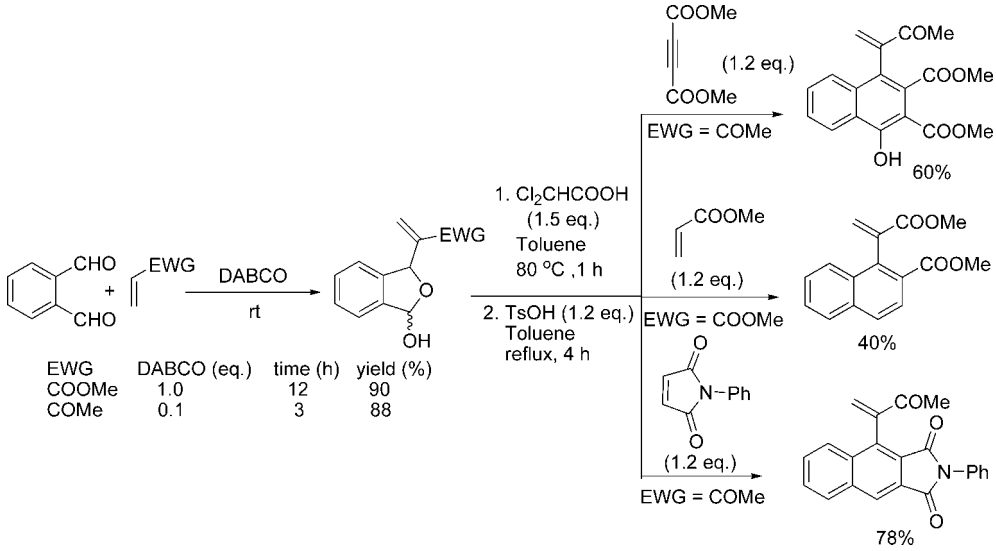
Vasudevan and co-workers[190] have described an interesting reaction between 2-haloarylaldehydes, methyl acrylate, and tosyl amines to provide the corresponding Baylis−Hillman adducts (following the Balan and Adolfsson procedure).[191] The resulting products were transformed into the corresponding indene derivatives via the intramolecular Heck coupling reaction. One example is shown in Scheme 51.

Corey and Wu[192] several years ago, during their work on the total synthesis of miroestrol (**30**), an important natural product, reported an elegant reaction between 4-methoxysalicylaldehyde and acrylonitrile to provide the chromene acid (Scheme 52).

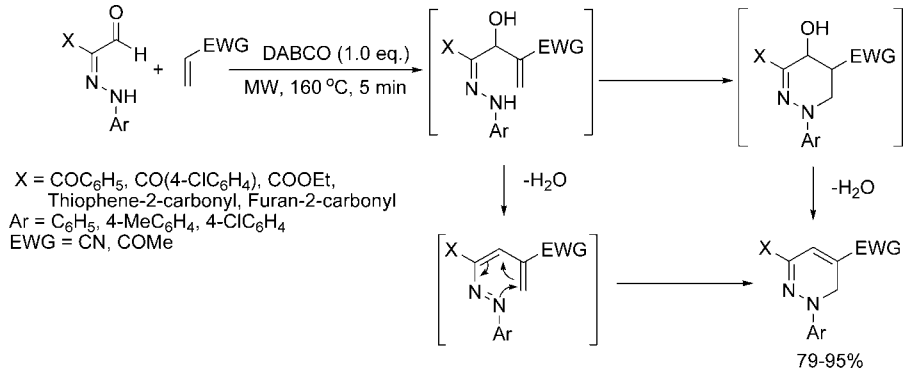
Later, Kaye and co-workers[193,194] reported reactions between 2-benzyloxyarylaldehydes and alkyl acrylates in the presence of DABCO to provide the corresponding Baylis−Hillman adducts (**31**), which were subsequently transformed into various coumarin derivatives following the reaction shown in Path A, Scheme 53. They[195] also noticed that the reaction between unprotected salicylaldehydes and *tert*-butyl acrylate provided the expected Baylis−Hillman adducts, which on treatment with HCl gave the coumarin derivatives (Path B, Scheme 53). Kaye and co-workers also reported mechanistic studies for these transformations.[196]

Later on, Kim[197] and Brase[198] independently reported the facile synthesis of tetra- and hexahydroxanthene derivatives

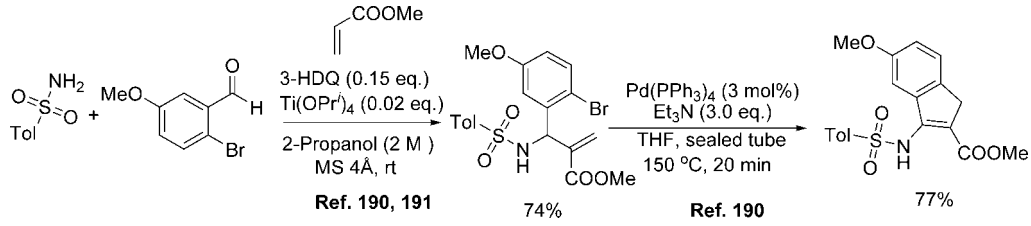
Scheme 49



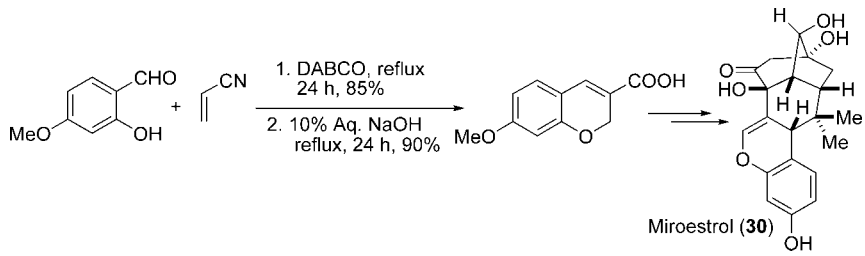
Scheme 50



Scheme 51

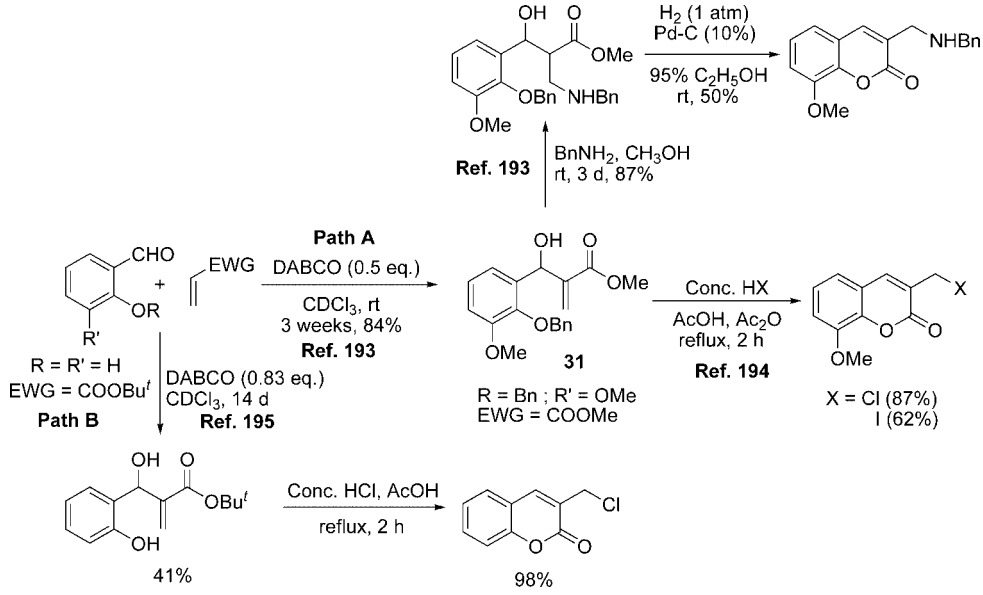


Scheme 52

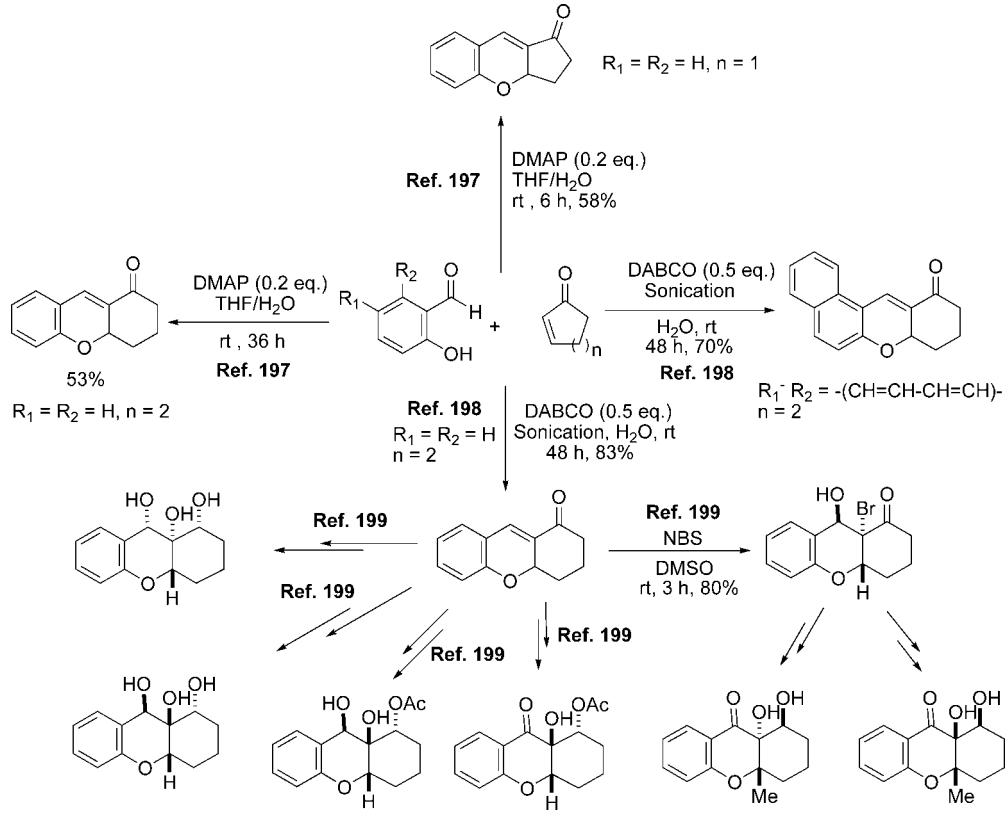


via the Baylis−Hillman reaction between salicylaldehyde and cyclopent-2-enone (or cyclohex-2-enone) in the presence of organobase (DABCO, DMAP). Brase and co-workers[199] have also transformed these hexahydroxanthene derivatives into highly functionalized tetrahydroxanthenols. Representative examples are shown in Scheme 54. Subsequently Brase and co-workers[200] have examined the reaction of salicylaldehyde derivatives with α,β-unsaturated aldehyde (senecialdehyde) and obtained the resulting condensation products, 2,2-dimethyl-2*H*-chromene-3-carboxaldehydes (**32**) along with tricyclic hemiacetal compounds (**33**). The ratio of these products depends on the nature of base used (one example is shown in Scheme 55). They have also performed the reaction of various salicylaldehyde derivatives and representative cyclohex-2-enones.[201] During these studies, they found that 3-substituted cyclohex-2-enone did not provide any product. The reactivity of cyclohex-2-enone derivatives having substitution at C-4 is dependent on the size of the

Scheme 53



Scheme 54



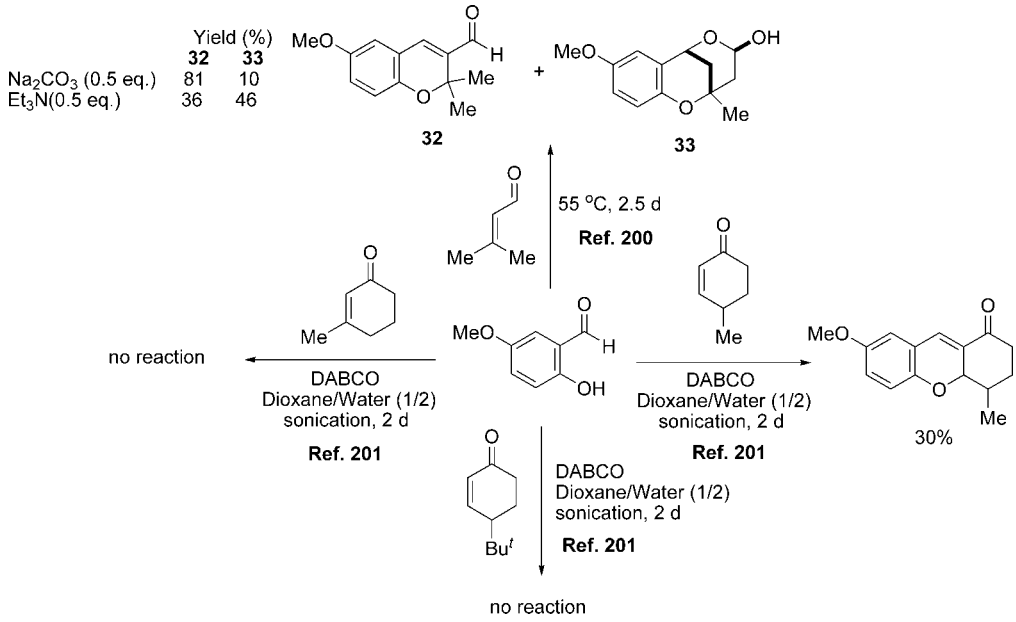
substituent; thus, methyl substitution provided the tricyclic compound in 30% yield, while *tert*-butyl substitution did not yield any product (Scheme 55).

Subsequently Shi and co-workers[202−206] successfully utilized salicyl *N*-tosylimines or salicylaldehydes as electrophiles in Baylis−Hillman coupling with allenic esters, allenic ketones, cyclopent-2-enone, cyclohex-2-enone, 3-methylpenta-3,4-dien-2-one, 3-benzylpenta-3,4-dien-2-one, 2-methylbuta-2,3-dienoate, but-3-yn-2-one, methyl propiolate, and diethyl acetylene dicarboxylate to provide the corresponding polycyclic and oxocyclic aromatic compounds (Schemes 56−58). In the case of MVK, EVK, and PVK, the product formation depends on the nature of solvent. Thus normal Baylis−Hillman adducts were obtained in THF, while in toluene, chromanes were obtained as major products (eq 17).[207]

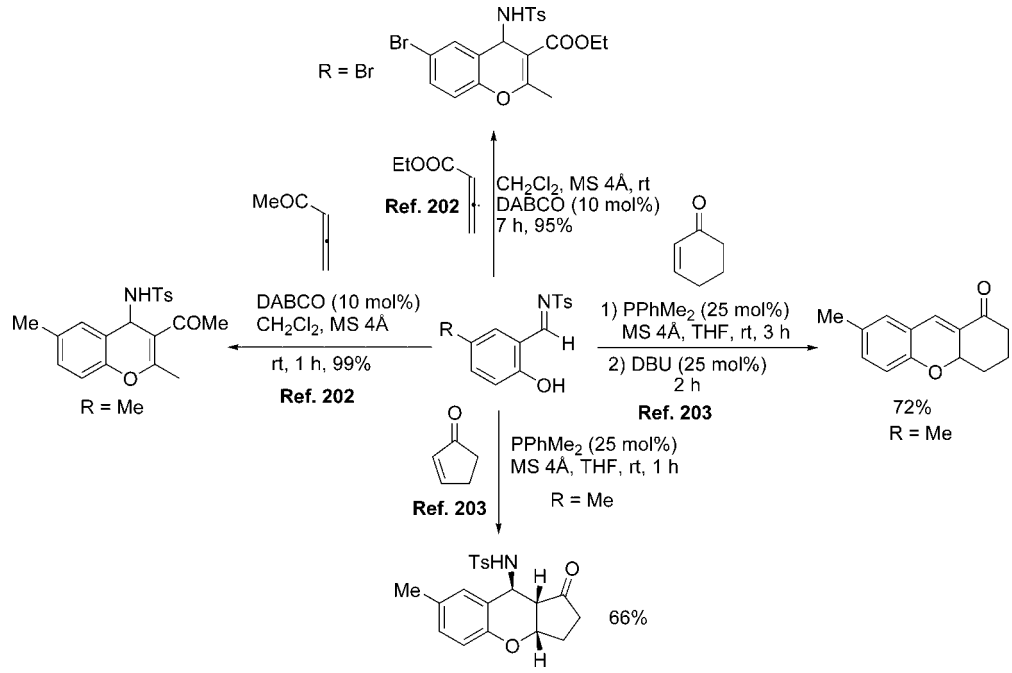
Sosnovskikh and co-workers[208] reported an interesting reaction of polyhaloalkyl-substituted chromones, γ-pyrones, and β-furanones (as activated alkenes) with salicylaldehydes (as electrophiles) leading to the formation of polycyclic oxygen heterocyclic compounds under the influence of organocatalyst. Representative examples are shown in Scheme 59.

Reddy and co-workers[209] successfully utilized 7-hydroxy-2-oxo-2*H*-chromen-8-carboxaldehydes as electrophiles for performing Baylis−Hillman reaction with MVK and acrolein

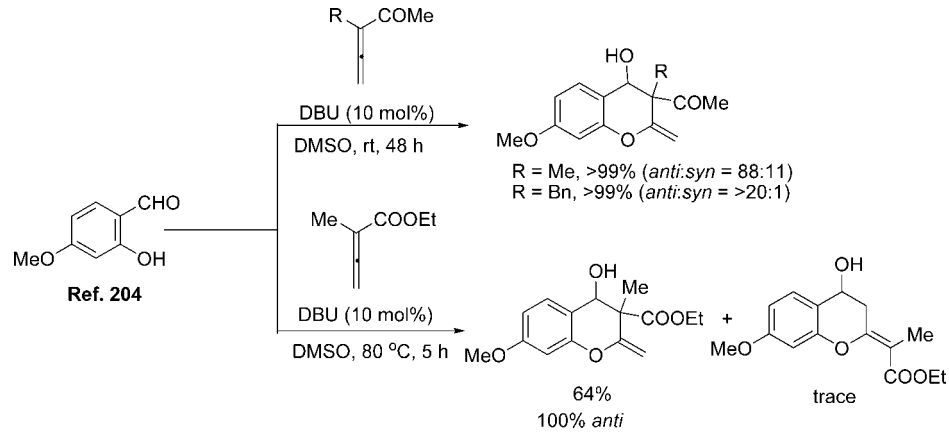
Scheme 55



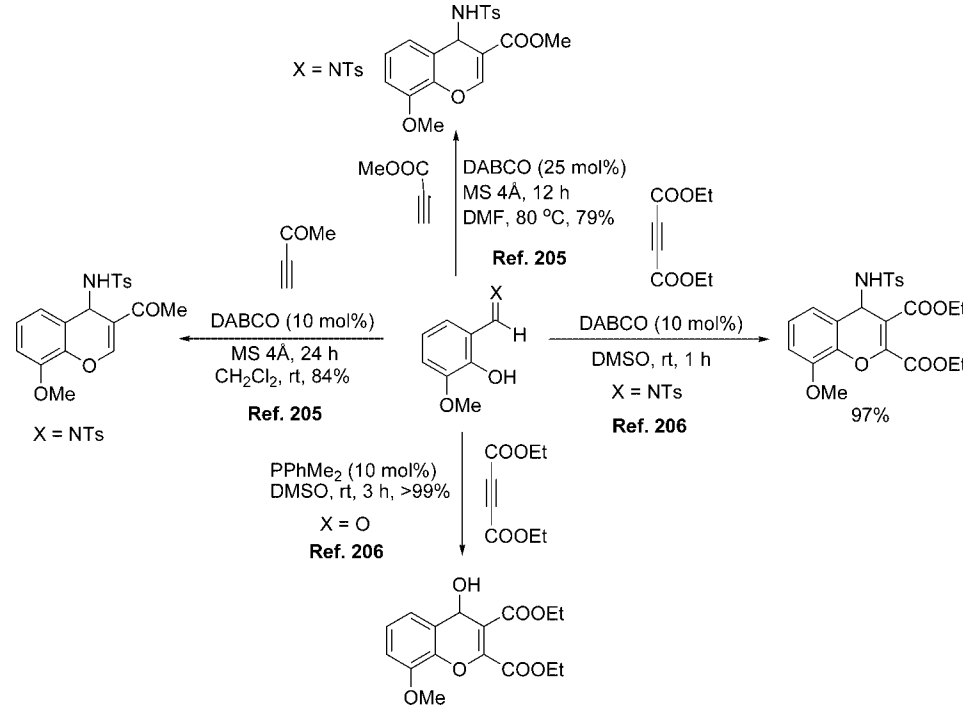
Scheme 56



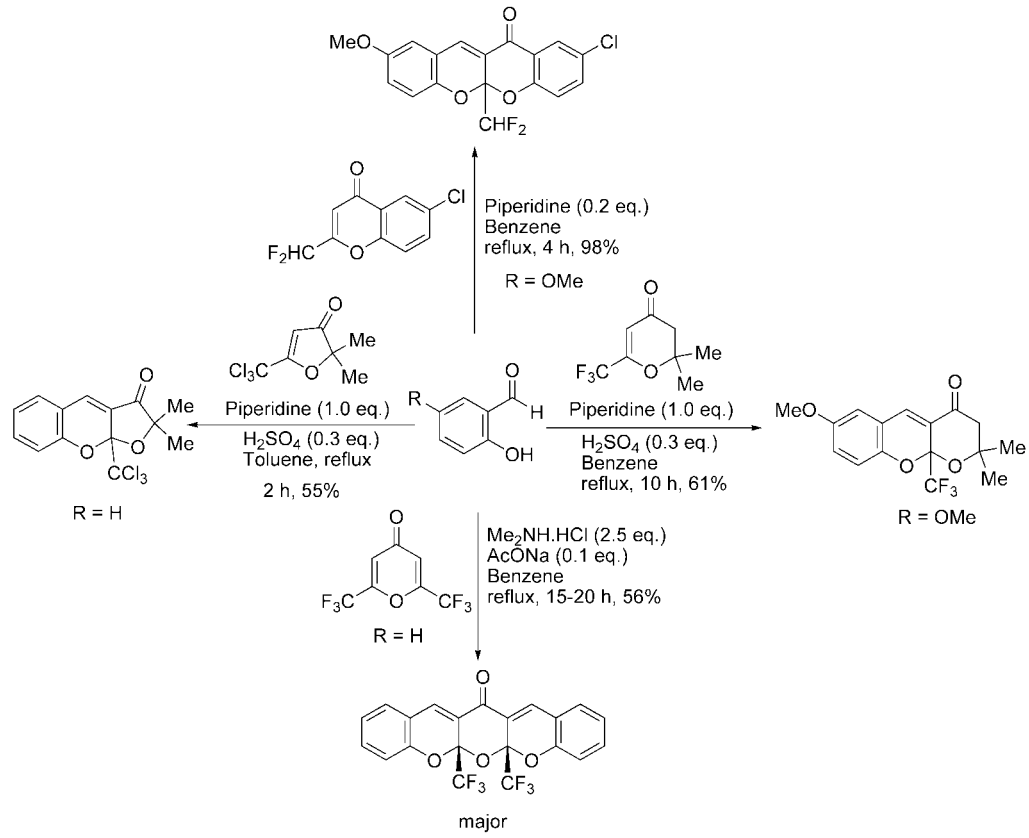
Scheme 57



Scheme 58



Scheme 59

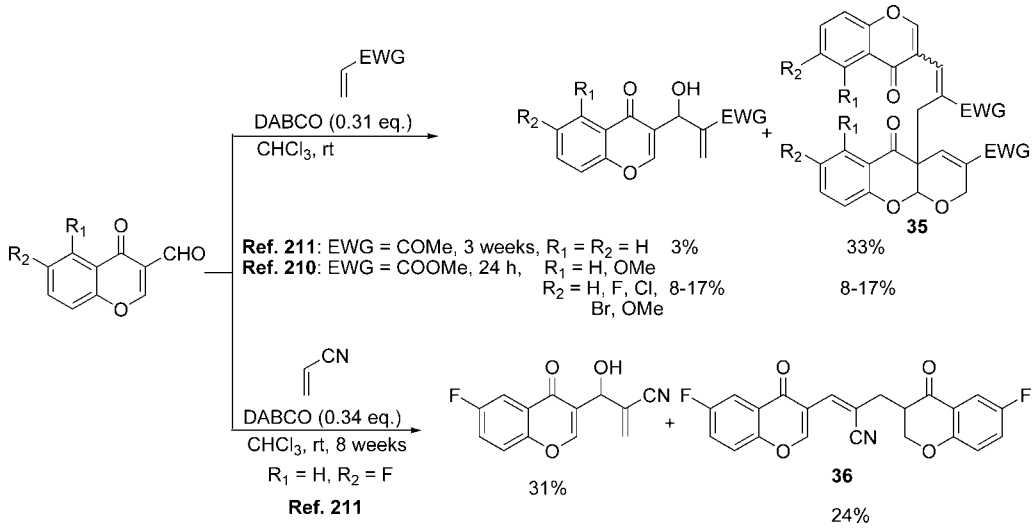


in the presence of DABCO to afford a tricyclic framework (**34**). Representative examples are shown in eq 18.

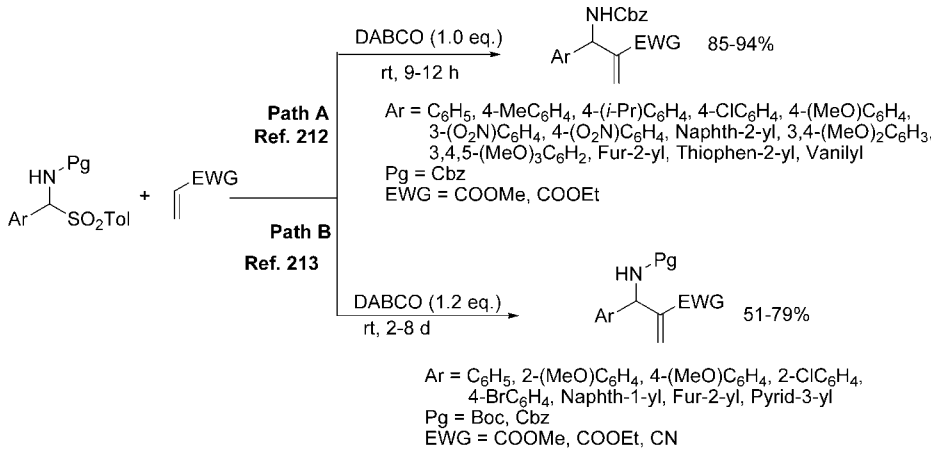
Kaye and co-workers[210,211] have performed Baylis−Hillman reaction of methyl acrylate, acrylonitrile, and MVK (as activated alkenes) with chromone-3-carboxaldehydes (as electrophiles) under the influence of DABCO to produce unusual products (**35**, **36**) along with the usual Baylis−Hillman adducts. Representative examples are shown in Scheme 60.

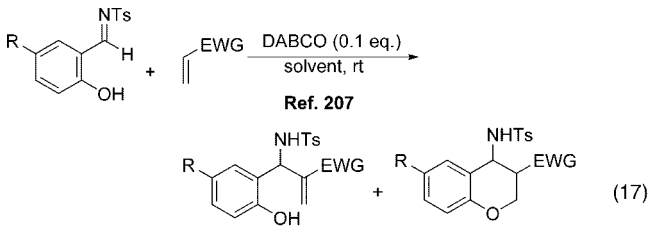
Recently Das and co-workers[212] have demonstrated α-aminosulfones, which were prepared from aromatic and heteroaromatic aldehydes, as new electrophiles for Baylis−Hillman reaction with methyl and ethyl acrylates in the presence of DABCO at room temperature under solvent-free conditions (Path A, Scheme 61). Subsequently Gajda and Gajda[213] also reported the same reaction under solvent-free

Scheme 60

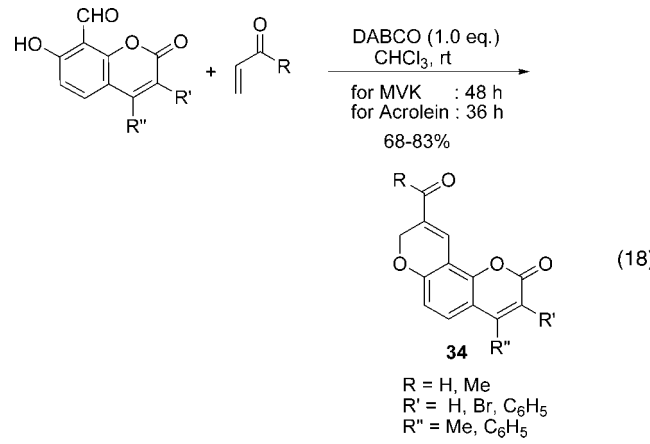


Scheme 61





R	EWG	solvent	time (h)	yield (%)	yield (%) *(anti/syn)*
Me	COMe	THF	12	84	4 (2/1)
		Toluene	12	trace	69 (3/1)
OMe	COEt	THF	20	56	trace
		Toluene	20	trace	62 (2/1)
H	COPh	THF	48	63	0
		Toluene	48	0	67 (8/3)



conditions (Path B, Scheme 61) and observed that neat reaction was faster than reactions in solvent THF.

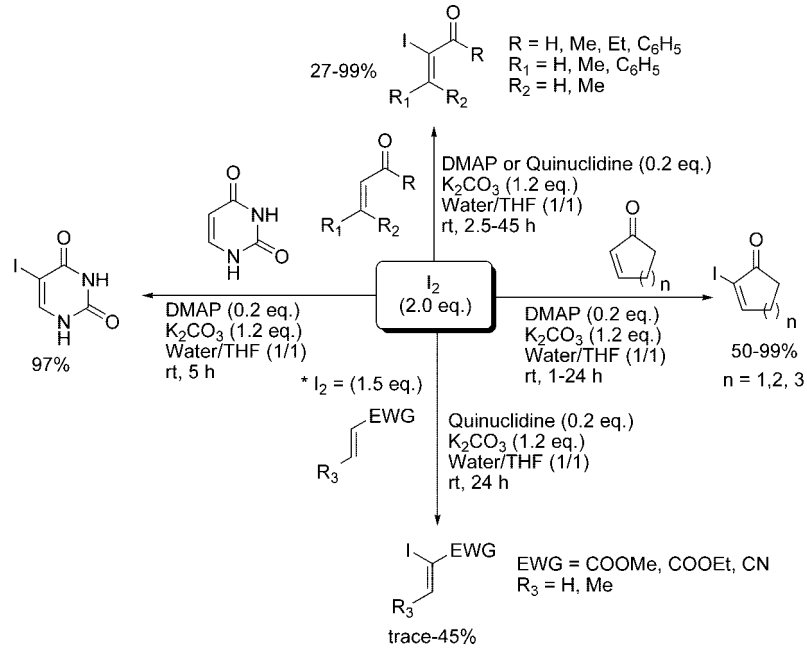
α-Iodination of cyclic and acyclic enones via the reaction with I_2 in the presence of appropriate base was reported by Krafft and Cran.[214] Similar reaction worked equally well with uracil to provide the corresponding α-iodinated product (Scheme 62).

Li and co-workers,[215] for the first time, successfully utilized aryl-oxiranes as electrophiles for the Baylis−Hillman coupling with 3-iodoallenoates (generated *in situ* from methyl propiolate by treating with MgI_2) providing the corresponding homoallylic alcohols stereoselectively (eq 19).

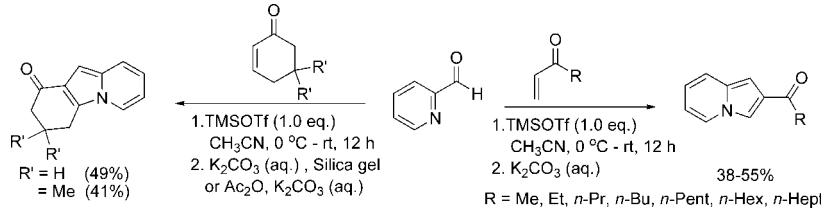
An interesting Baylis−Hillman dimerization of cyclohex-2-enone under the catalytic influence of pyrrolidine and 2-(pyrrolidin-1-yl)pyrrolidine (**37**) was reported by Ramachary and Mondal (eq 20).[216] Similar dimerization using aq. Me_3N was reported by our research group a few years ago.[108]

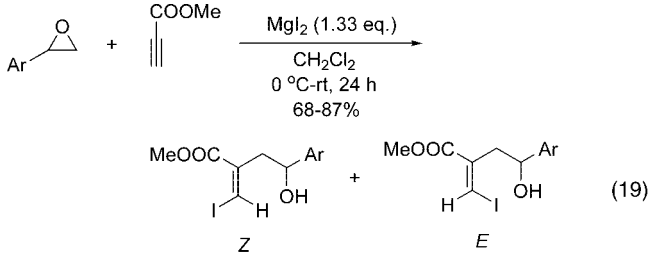
Our research group[217] reported, for the first time, an electrophile-induced Baylis−Hillman reaction via the treatment of pyridine-2-carboxaldehyde with activated alkenes such as alkyl vinyl ketones and cyclic enones in the presence

Scheme 62



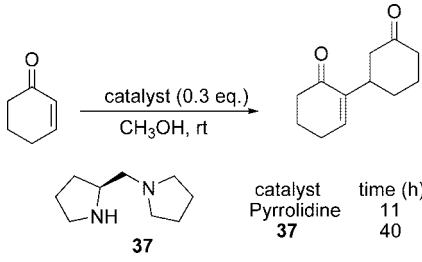
Scheme 63





Ar = C_6H_5, 2-MeC_6H_4, 4-MeC_6H_4, 2-$(MeO)C_6H_4$, 3-$(MeO)C_6H_4$, 4-$(MeO)C_6H_4$, 4-FC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, Thiophen-2-yl

of trimethylsilyl trifluoromethanesulfonate (TMSOTf) thus providing a facile methodology for one-pot synthesis of indolizine derivatives. Representative examples and the reaction pathway are shown in Schemes 63 and 64, respectively.

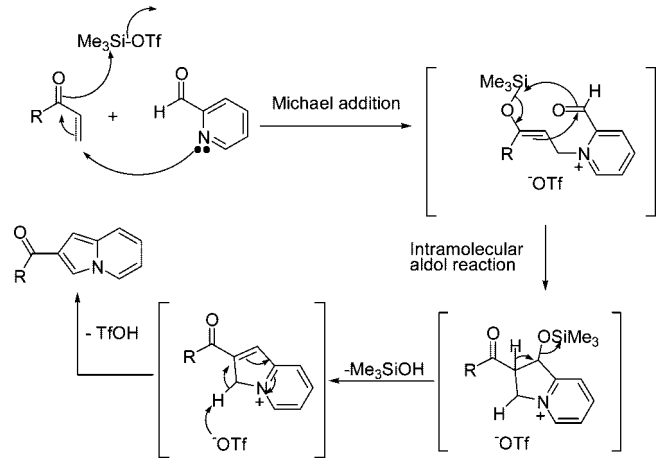


catalyst	time (h)	yield (%)	*ee* (%)
Pyrrolidine	11	50	-
37	40	77	11

3.3. Catalysts

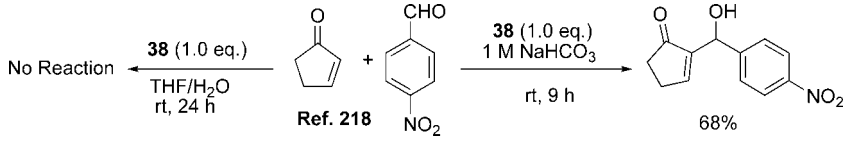
Various organic catalysts such as tertiary amines and phosphines have been successfully employed for the

Scheme 64

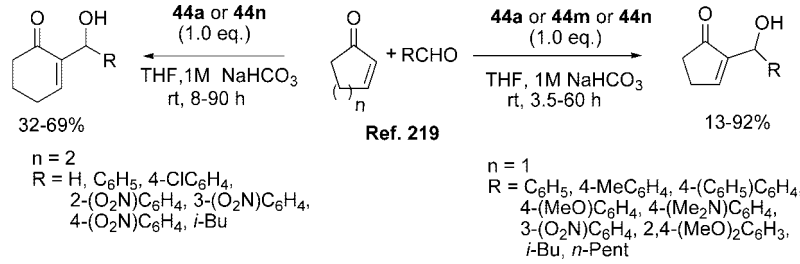


Baylis−Hillman coupling of activated alkenes with electrophiles. Also several acids, such as $TiCl_4$, chalcogeno-$TiCl_4$, Et_2AlI, BX_3, have been used as catalysts/catalytic systems for promoting the Baylis−Hillman reaction.[21] Significant developments have been reported during recent years in the case of catalysts and catalytic systems for performing various kinds of Baylis−Hillman reactions between different electrophiles and a number of activated alkenes. Cheng and co-workers[218] have reported a remarkable rate acceleration of imidazole-promoted Baylis−Hillman reaction of aryl aldehydes with cyclic activated alkenes in the presence of aqueous sodium bicarbonate solution. The rate acceleration is attributed to the enhanced basicity of imidazole under these conditions (in the absence of $NaHCO_3$,

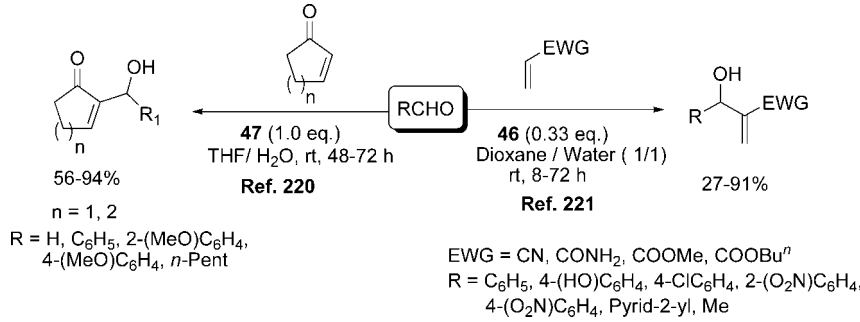
Scheme 65



Scheme 66



Scheme 67



no reaction occurred). One example is presented in Scheme 65. Subsequently they also found various azoles (**38**−**44**) (Figure 10) to be effective catalysts for promoting the Baylis−Hillman reaction between cyclic activated alkenes and aldehydes in aqueous basic solution.[219] Selected examples are given in Scheme 66.

Kim and co-workers[220] examined the application of various tertiary amines/diamines (**45**−**49**) (Figure 11) as catalysts

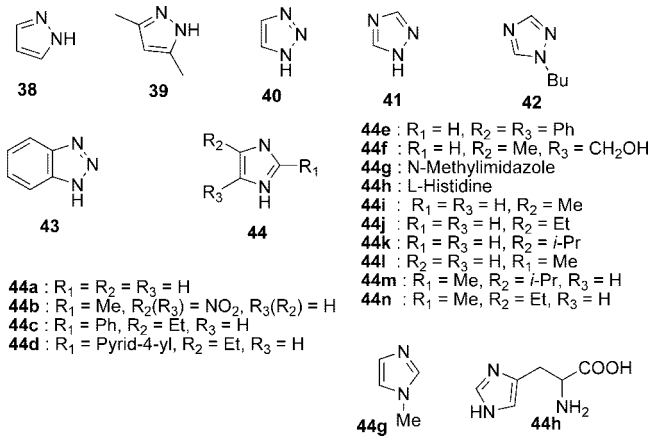


Figure 10.

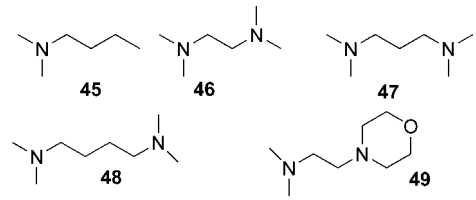


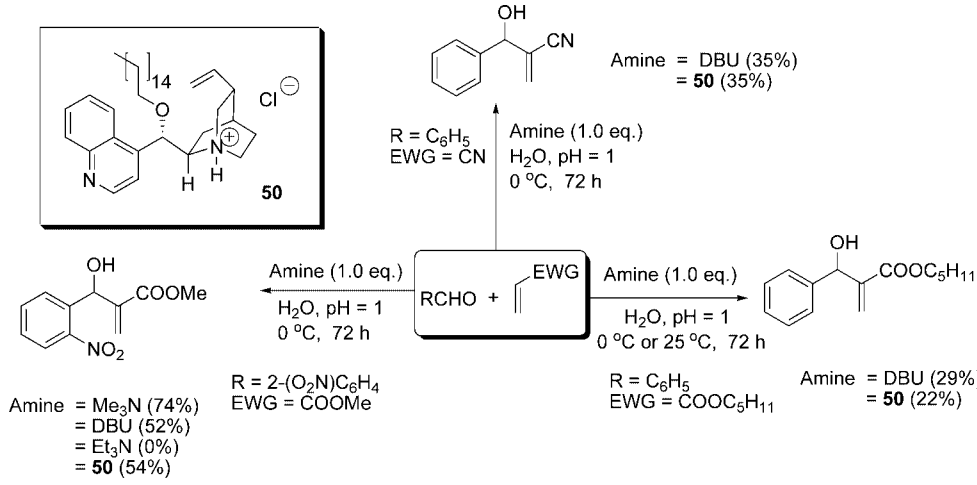
Figure 11.

and found that TMPDA (*N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine) (**47**) was more effective for performing Baylis−Hillman reaction between cyclic activated alkenes and aldehydes (Scheme 67). Subsequently Zhao and Chen[221] have examined the application of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) (**46**) as a catalyst for Baylis−Hillman coupling between aldehydes and acyclic activated alkenes (Scheme 67).

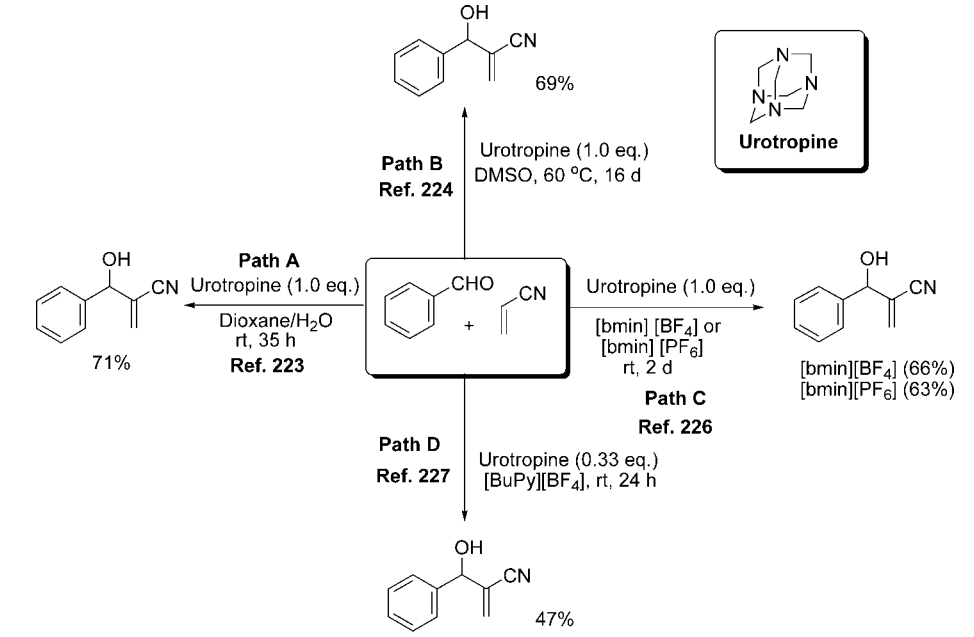
Caumul and Hailes[222] have examined the Baylis−Hillman reaction between activated alkenes and aldehydes under the influence of various amines (DBU, DABCO, Me_3N, Et_3N, and **50**) in the presence of acid with a view to compare their abilities to perform as catalysts (Scheme 68). Very small enantioselectivities (4−8%) (with *R*-configuration) were observed when the chiral catalyst **50** was used.

Later on, Krishna and co-workers[223] (Path A, Scheme 69) and Vasconcellos and co-workers[224] (Path B, Scheme 69) about the same time reported application of urotropine (HMTA) for performing the Baylis−Hillman reaction between activated alkenes and aldehydes. It should be mentioned here that urotropine was used for the first time as a catalyst for performing Baylis−Hillman reaction a few years ago by Tang and co-workers[225] (only one example was reported). Later Vasconcellos and co-workers[226] also used ionic liquids as solvents to perform the urotropine-catalyzed Baylis−Hillman reactions with rate acceleration (Path C, Scheme 69). Chen and co-workers[227] reported the Baylis−Hillman reaction of aldehydes with activated alkenes under the influence of urotropine (HMTA) in the presence of [BuPy][BF_4] and also observed rate acceleration (Path D, Scheme 69). Representative examples are given in Scheme 69.

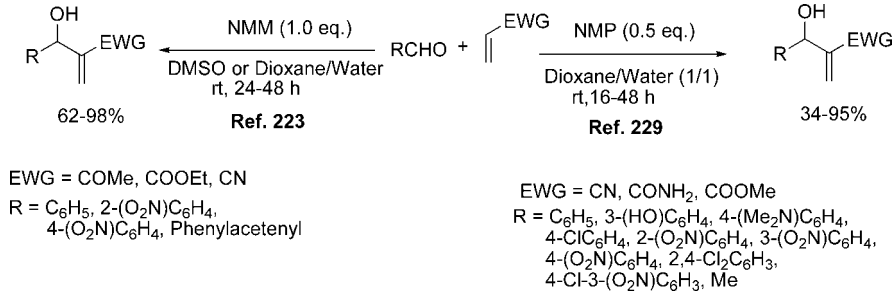
Scheme 68



Scheme 69



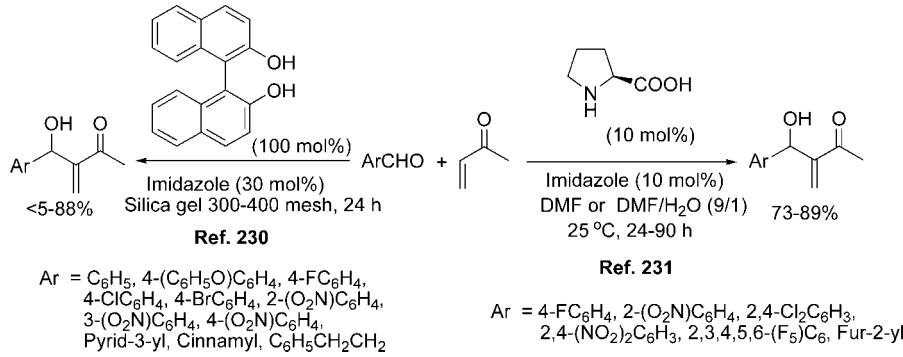
Scheme 70



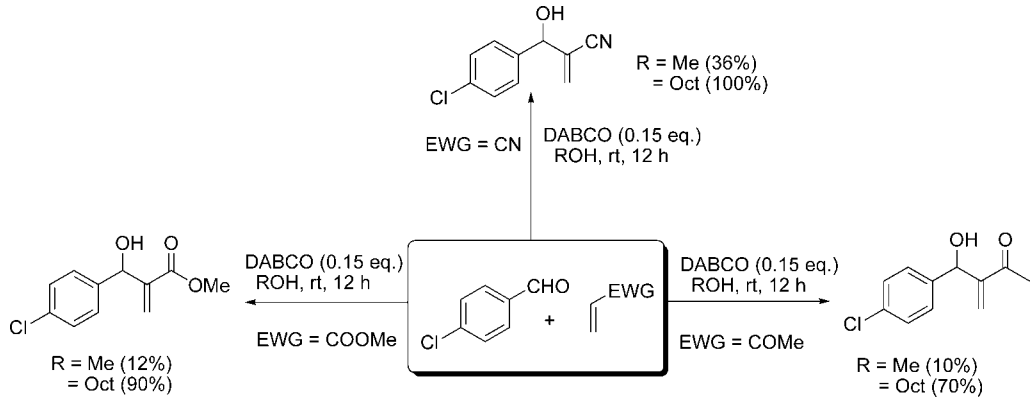
Subsequently *N*-methylmorpholine (NMM) was used as a catalyst for the Baylis−Hillman coupling of various activated alkenes with electrophiles by Krishna and coworkers.[223] Representative examples are given in Scheme 70. Krishna et al. have also reported application of aprotic polar solvents for facile Baylis−Hillman reaction using DABCO as catalyst.[228] Later on, Zhao and Chen[229] also employed *N*-methylpiperidine (NMP) as a catalyst for coupling of acyclic activated alkenes with aldehydes in aqueous media to provide the Baylis−Hillman alcohols in moderate to high yields (Scheme 70).

Recently Shi and Jiang[230] investigated the Baylis−Hillman reaction under the influence of imidazole and BINOL in silica gel media and noticed the key role of silica gel in accelerating the reaction (Scheme 71). Later on, Tomkinson and coworkers[231] examined Baylis−Hillman reaction under the influence of proline and imidazole in aqueous media with a view to understanding the role of water in accelerating the

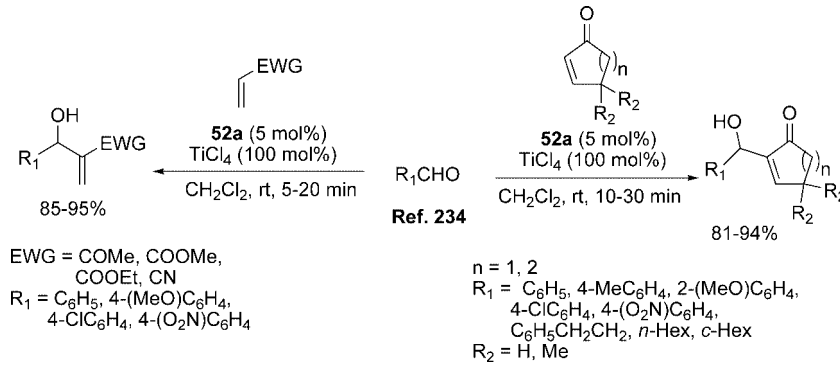
Scheme 71



Scheme 72



Scheme 73



reaction (Scheme 71). These results are inconsistent with the earlier work of Shi and co-workers.[109]

Chong and co-workers[232] have studied the effect of various hydroxy solvents (i.e., water, methanol, ethanol, isopropyl alcohol, butanol, pentanol, octanol, dodecanol, cyclohexanol, phenol) for the rate acceleration of Baylis−Hillman reaction under the influence of DABCO as catalyst and found that octanol provided the best results. A comparison between methanol and octanol as solvents with representative examples is shown in Scheme 72. It is interesting to note that aliphatic alcohols provided encouraging results, while phenol or water did not provide the desired Baylis−Hillman adducts.

The phosphine catalysts, proazaphosphatranes (**51**), were successfully employed some time ago by Verkade and co-workers[233] to obtain the β-substituted Baylis−Hillman adducts via the reaction between allyl cyanide and aldehydes. Recently Verkade and co-workers[234] found that sulfide catalyst **52a** not only provided high yields of Baylis−Hillman adducts but also performed the reaction with rate acceleration in the presence of $TiCl_4$. They have also prepared several catalysts, **52**−**56** (Figure 12), with a view to examining their potential for catalyzing the Baylis−Hillman reaction and noticed that the catalyst **52a** provided the best results. Representative examples are given in Scheme 73.

He and co-workers[235,236] have used 1,3,5-triaza-7-phosphaadamantane (PTA) (**57**) as an efficient organocatalyst for

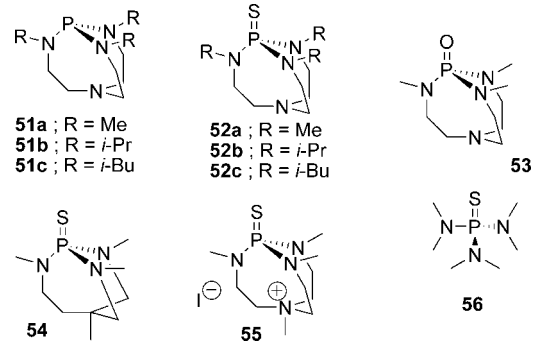
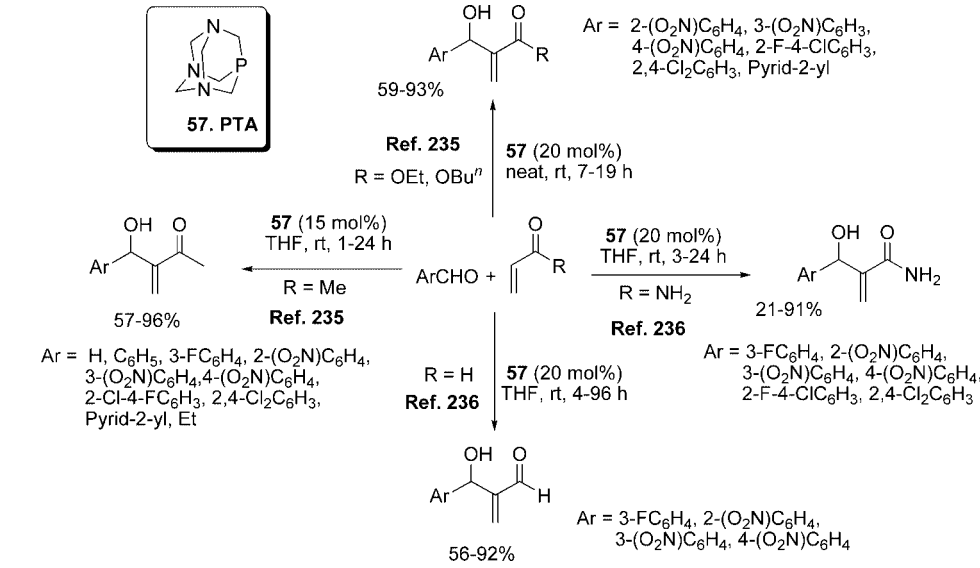
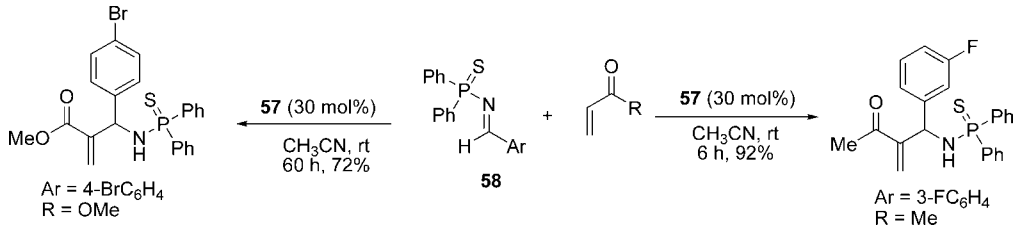


Figure 12.

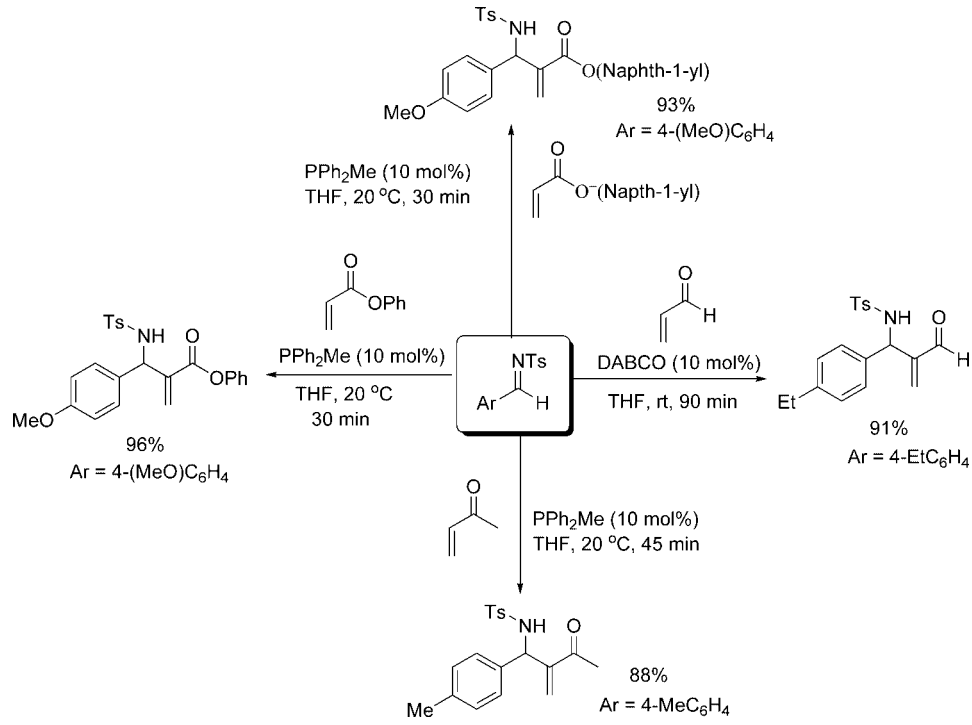
Scheme 74



Scheme 75



Scheme 76

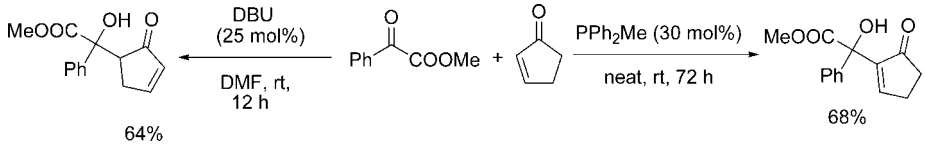


the Baylis−Hillman reaction to provide the resulting adducts in good yields. Selected examples are presented in Scheme 74. Subsequently the application of this catalyst was extended for coupling of various electrophiles such as *N*-diphenylthiophosphinoylimines (**58**) with selected activated alkenes by He and co-workers.[237] Representative examples are presented in Scheme 75.

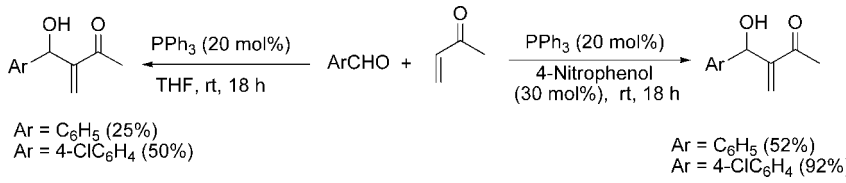
Shi and Xu[238] have systematically investigated the Baylis−Hillman reaction of *N*-tosylated imines with MVK, acrolein, and phenyl and naphthyl acrylates under the influence of PPh_2Me (phosphine catalyst) and DABCO. Selected examples are presented in Scheme 76.

Later on, Ito and co-workers[239] successfully performed the Baylis−Hillman reaction between cyclic activated alkenes

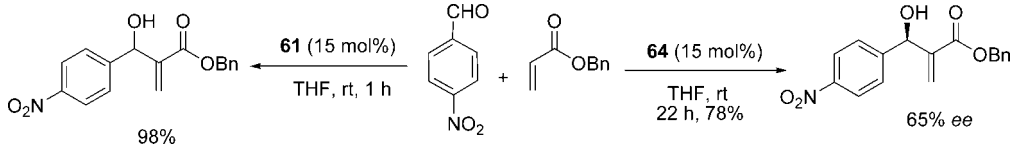
Scheme 77



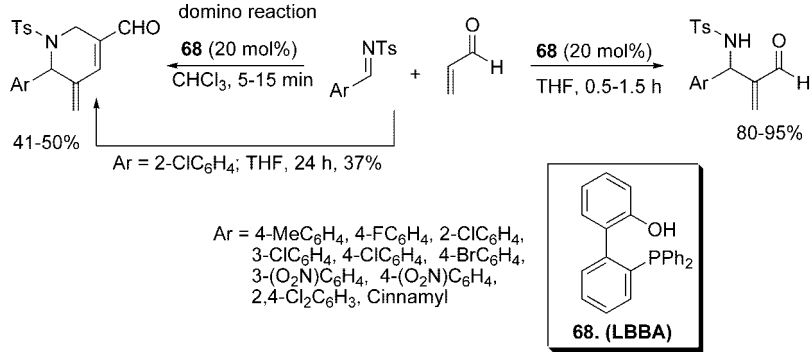
Scheme 78



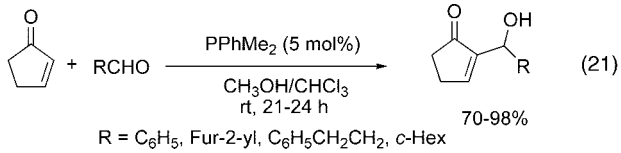
Scheme 79



Scheme 80



and aldehydes under the influence of $PPhMe_2$ to provide the resulting Baylis−Hillman adducts in high yields (eq 21).



(21)

Shi and Zhang[240] noticed that PPh_2Me catalyzed the Baylis−Hillman reaction between α-keto esters and cyclopent-2-enone while a similar reaction with DBU led to aldol reaction. Representative examples are presented in Scheme 77. They also noticed that other phosphines such as PBu_3 and PPh_3 were less effective for performing the Baylis−Hillman reaction.

Shi and Liu[241] have reported that the Baylis−Hillman reaction of aldehydes with methyl vinyl ketone (MVK) under the influence of PPh_3 can be accelerated in the presence of 4-nitrophenol. Representative examples are shown in Scheme 78.

Ferrocenyldialkylphosphines (**59**−**61**) (Figure 13) have been used by Carretero and co-workers as catalysts for the coupling between aldehydes and acrylates to provide the resulting adducts in high yields at faster reaction rate.[242] The phosphine **61** was found to be a superior catalyst. They have also examined the application of various chiral catalysts (**62**−**67**) (Figure 13) and observed that catalyst **64** provided highest enantioselectivity of 65% for the coupling between 4-nitrobenzaldehyde and benzyl acrylate. Representative examples are shown in Scheme 79.

Chen and co-workers[243] have developed an interesting bifunctional catalyst, LBBA (Lewis base−Brønsted acid) (**68**), for performing Baylis−Hillman reaction between acrolein and N-tosylated imines (Scheme 80) in THF. It was noticed that longer reaction times in THF with excess acrolein provided domino reaction leading to the formation of pyridine derivatives. They have also found that the same domino reaction was faster in the less polar solvent $CHCl_3$. A possible mechanism for this domino reaction is given in Scheme 81.

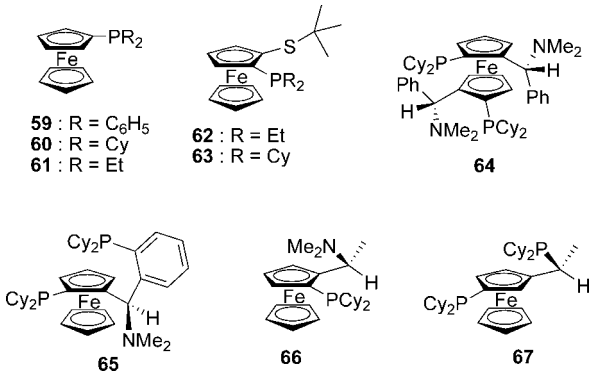
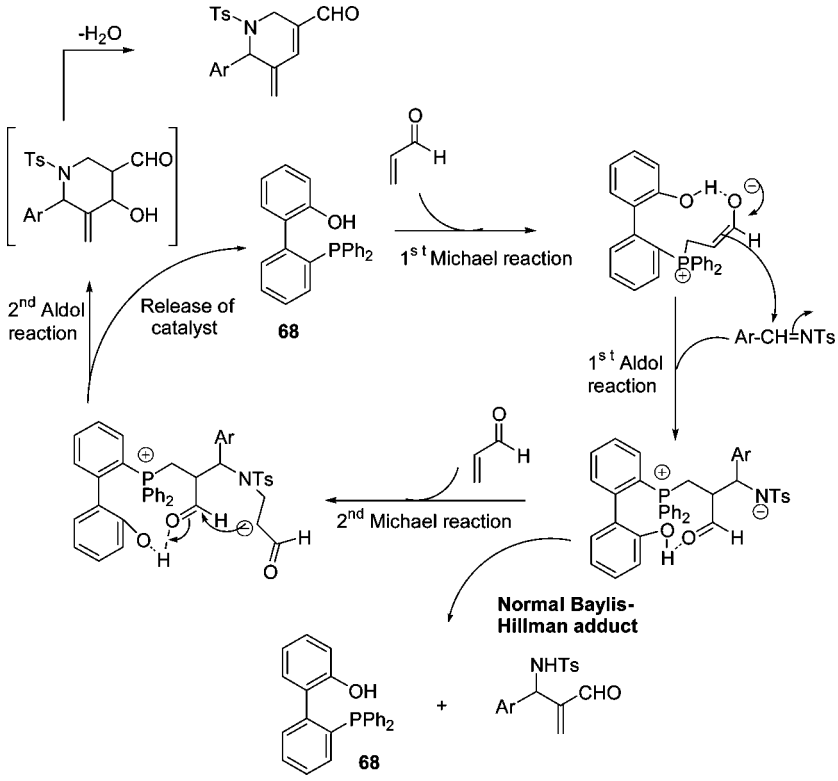
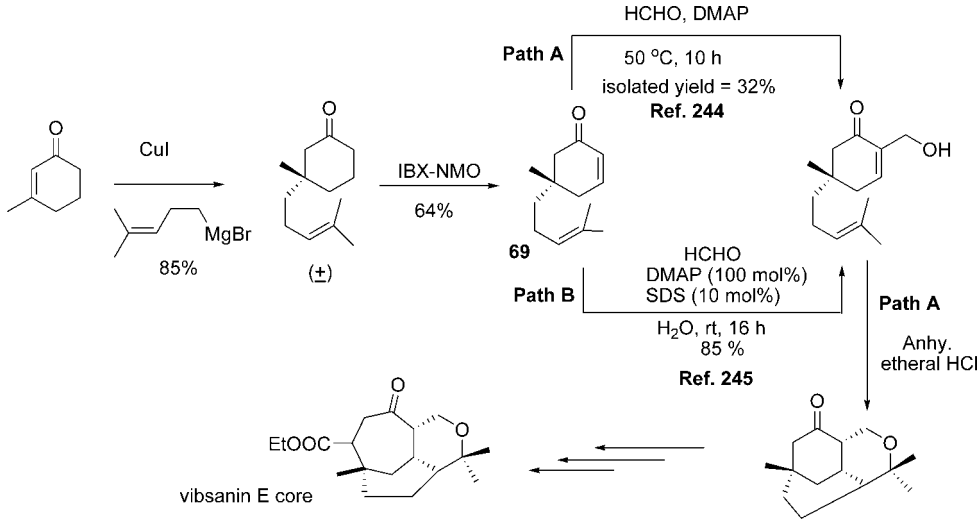


Figure 13.

Scheme 81

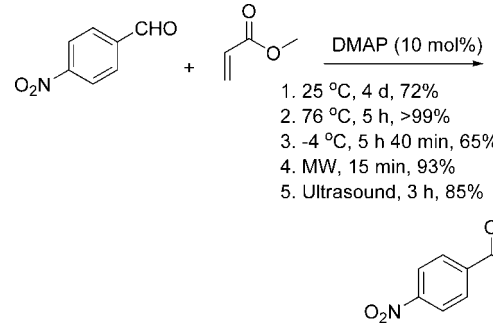


Scheme 82



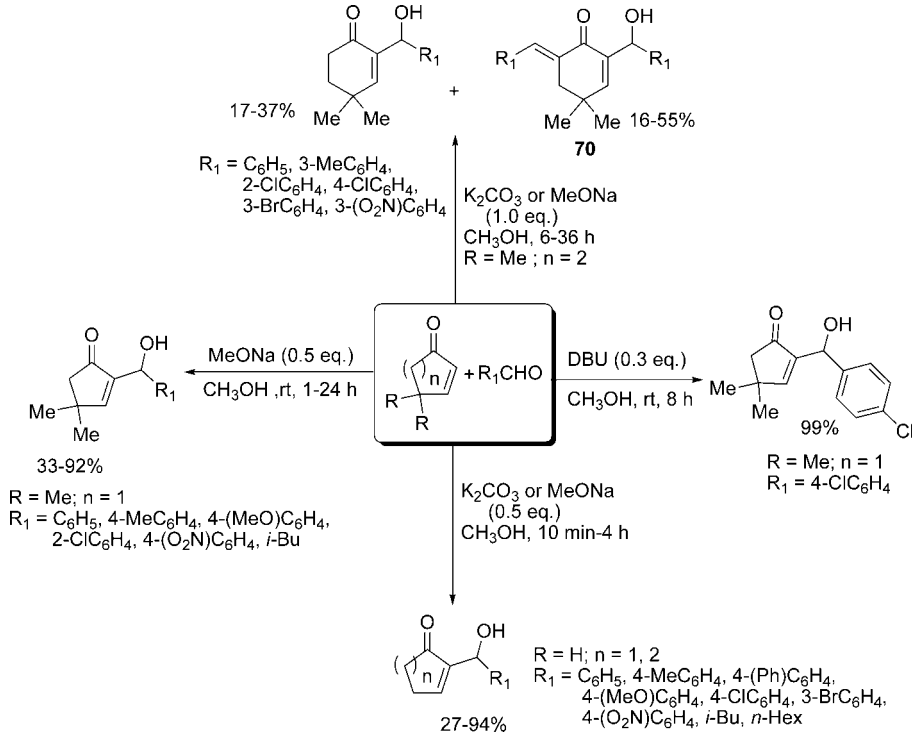
Williams and co-workers[244] have used Baylis−Hillman reaction between **69** and HCHO as the key step for the synthesis of the vibsanin E core (Path A, Scheme 82). Since the yield was less in this reaction, they[245] have also examined the influence of various surfactants, such as SDS (sodium dodecyl sulfate), CTAB (cetyltrimethylammonium bromide), and Oct-Glc (α-octyl-glucoside), with a view to improving the yield and obtained 85% yield using SDS as an additive (Path B, Scheme 82).

Vasconcellos and co-workers[246] have studied the effect of temperature on DMAP-catalyzed Baylis−Hillman reaction of methyl acrylate with aldehydes and observed that the reactions provided better results at high (76 °C) and low temperature (−4 °C) than at room temperature. They also studied the microwave-assisted Baylis−Hillman reaction and observed remarkable rate acceleration with increased yields. One example is shown in eq 22.

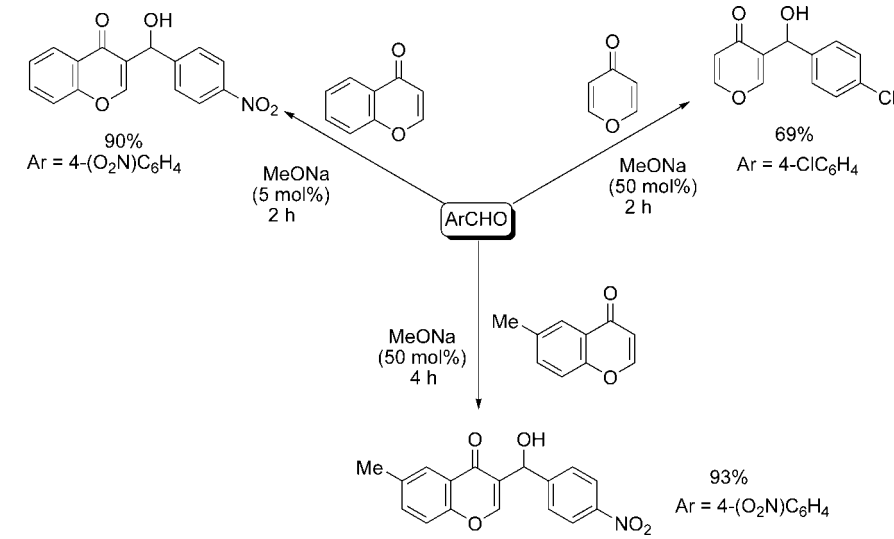


Cheng and co-workers[247] have reported that the Baylis−Hillman reaction between cyclic activated alkenes and various electrophiles can be conveniently performed under the influence of sodium methoxide or DBU in methanol or K_2CO_3 in methanol. In case of 4,4-dimethylcyclohex-2-

Scheme 83



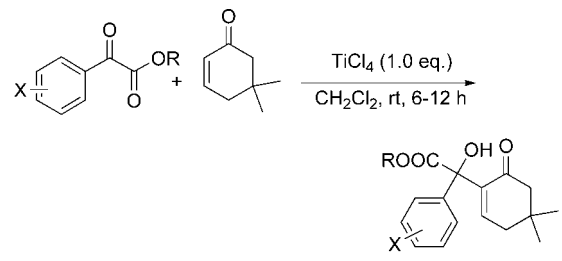
Scheme 84



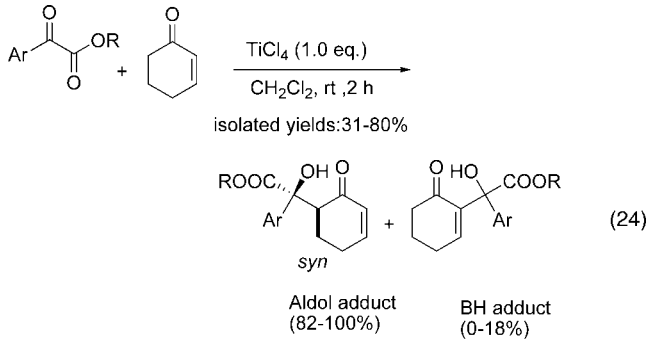
enone, the products **70** (formed through both Baylis−Hillman and aldol reaction) were also obtained. Representative examples are described in Schemes 83 and 84.

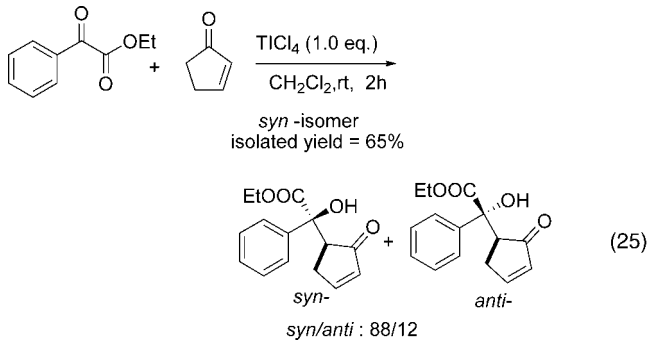
Our research group[248] reported that titanium tetrachloride-mediated reaction of α-keto esters with 5,5-dimethylcyclohex-2-enone provided the corresponding Baylis−Hillman adducts exclusively, whereas a similar reaction of α-keto esters with cylclohex-2-enone furnished the corresponding aldol adducts (with high *syn*-diastereoselectivity) as the major product (along with the Baylis−Hillman adducts as the minor product), thus clearly demonstrating the role of steric factors in directing the reaction pathway (eqs 23−25). The possible transition states for these aldol and Baylis−Hillman reactions are shown in Figure 14.

Medvedeva and co-workers[249] have described an elegant reaction of alk-2-yn-1-one with alk-2-ynals under the influence of $TiCl_4$ in the presence of SMe_2 to provide β-substituted Baylis−Hillman products (eq 26). It is worth mentioning here that Li and co-workers have already reported synthesis of β-chloro Baylis−Hillman adduct via $TiCl_4$-mediated reaction between acetylenic ketones and aldehydes.[250a,b]



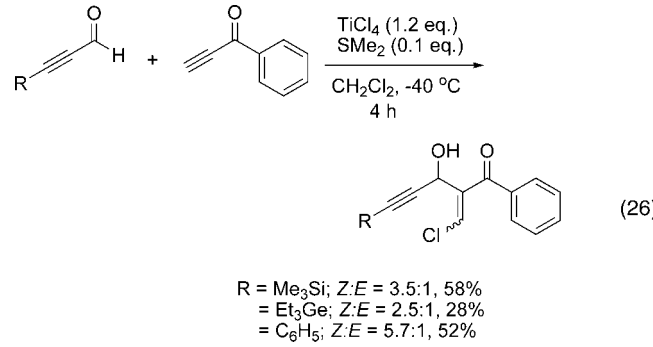
(23)





Xue and co-workers[251,252] have reported a simple synthesis of β-substituted Baylis−Hillman adducts via the reaction of alk-2-yn-1-one with aldehydes under the influence of CF_3CO_2ZnR or diarylzinc following the reaction sequence shown in Scheme 85.

The reaction between alk-2-yn-1-one and various aldehydes has been also examined by various research groups[253−258] under the influence of various reagents such as MgI_2, MgI_2/TMSI, $MgBr_2$, $CeCl_3 \cdot 7H_2O$/NaI, and GaI_3 to provide the β-substituted Baylis−Hillman adducts. Selected examples are given in Scheme 86. In the case of MgI_2, the complex (**B1**) between aldehyde and MgI_2 was the key intermediate for the reaction (Path A),[253,254] while in the case of TMSI, it is believed that the reaction proceeds through intermediate **B2** (Path B).[255]



Li and co-workers[259] have also reported an interesting reaction between acetylenic ketones and N-sulfonated imines under the influence of MgI_2 to provide the β-substituted Baylis−Hillman adducts in high *Z*-selectivity (Scheme 87). Later on, Li and co-workers[260] used simple imines for coupling with acetylenic ketones under the influence of TMSI and $ZrCl_4$ to provide the β-substituted Baylis−Hillman adducts (Scheme 87).

Subsequently, Shi and Wang[261] examined application of $TiBr_4$ for performing the reaction between alk-2-yn-1-one and aldehydes to provide the corresponding β-bromo-Baylis−Hillman alcohols or dibromo products (**71**) depending on the reaction conditions (Scheme 88).

Nanocrystalline MgO (NAP−MgO) was used as catalyst for performing Baylis−Hillman reaction between cyclic enones and aldehydes and aldimine derivatives by Kantam and co-workers.[262] It was found that aldimine derivatives

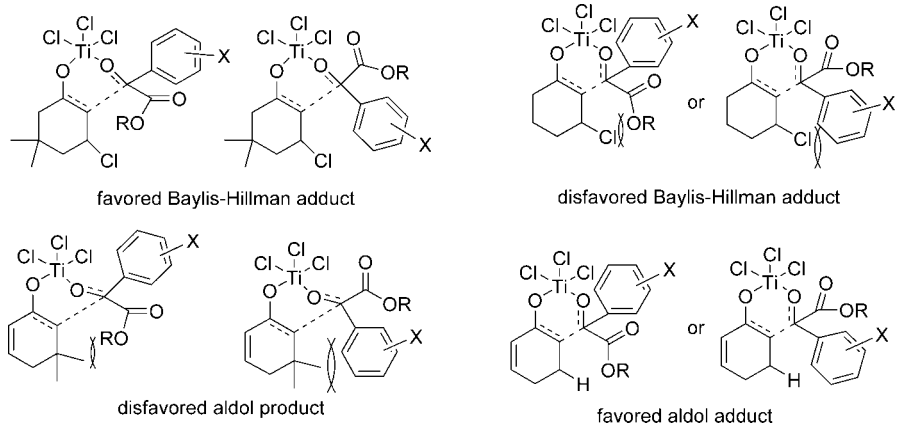
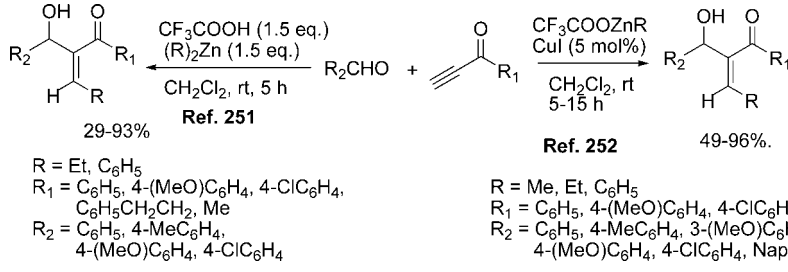
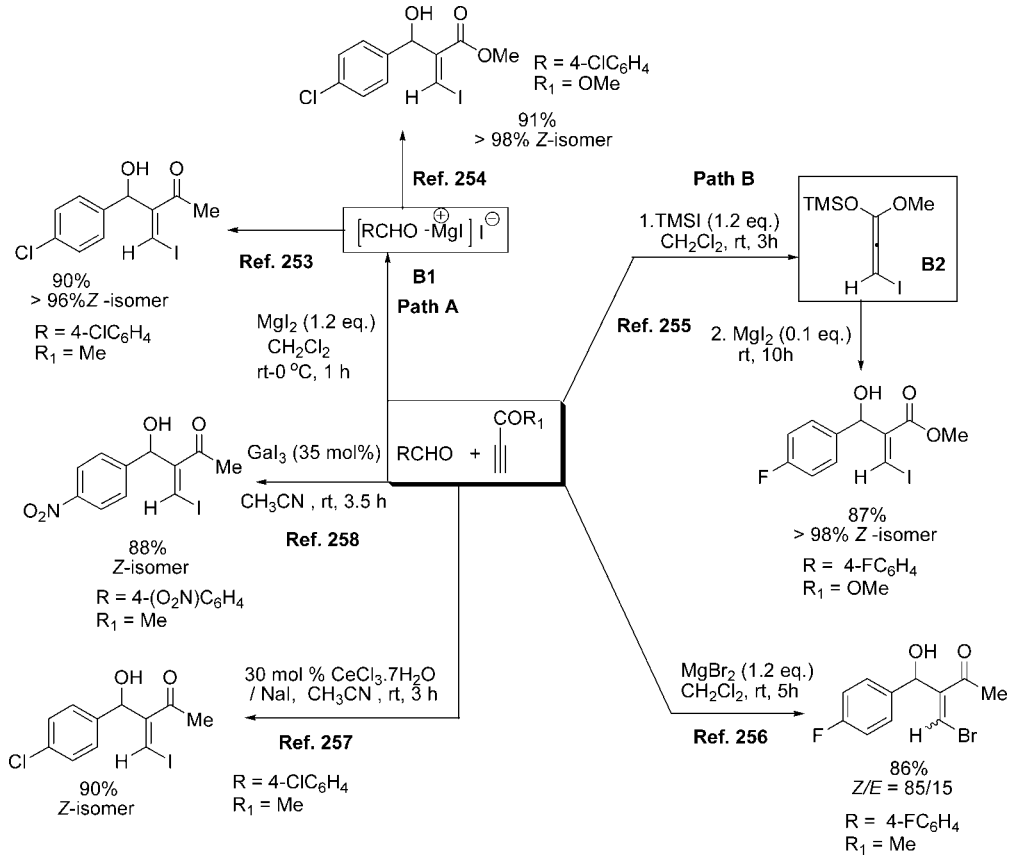


Figure 14.

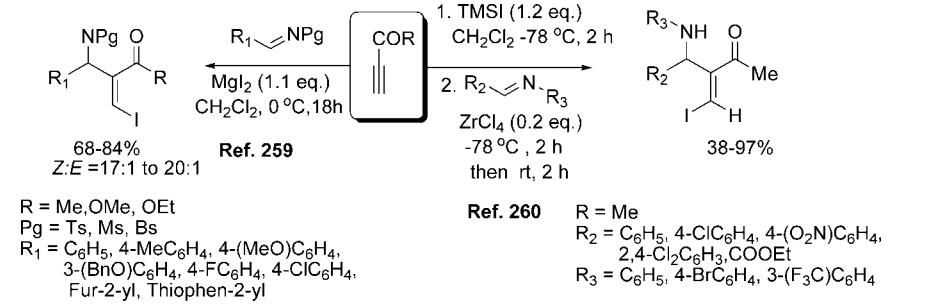
Scheme 85



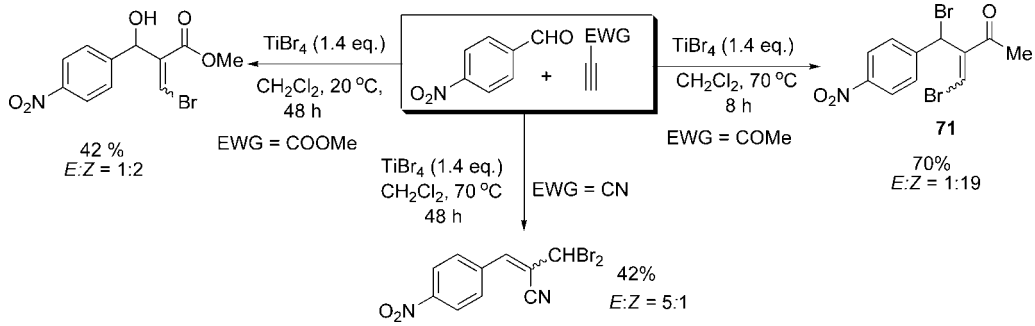
Scheme 86



Scheme 87



Scheme 88

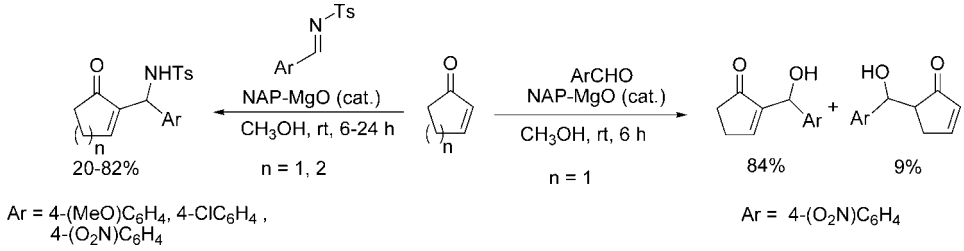


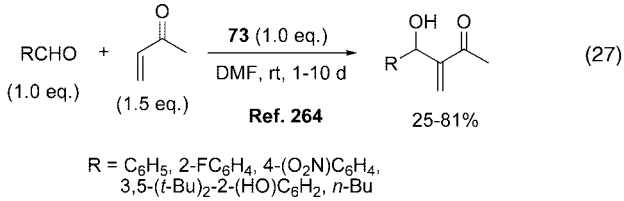
provide exclusively Baylis−Hillman adducts while aldehydes provide Baylis−Hillman adducts along with a minor amount of aldol products. Representative examples are given in Scheme 89.

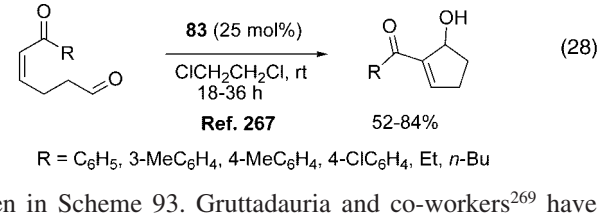
Huang and Shi[263] used polymer-supported Lewis base catalysts [PEG_{4600}−$(PPh_2)_2$ (**72**) and poly(DMAP)(PAP (**73**))] (Figure 15) for performing Baylis−Hillman reaction between *N*-tosylimines and aldehydes with various activated alkenes (Scheme 90). About the same time, Corma and co-workers[264] also employed polystyrene-bound 4-(*N*-benzyl-*N*-methylamino)pyridine (PAP (**73**)) as a catalyst for promoting the Baylis−Hillman reaction. Representative examples are shown in eq 27.

Later on, Shi and co-workers[265−267] also prepared various polystyrene-supported triphenyl phosphines (**74**−**85**) (Figure 16) and polystyrene-supported 4-dimethylaminopyridines

Scheme 89







(**86**−**91**) (Figure 16) and examined their potential as catalysts for performing the Baylis−Hillman reaction between various aldehydes and activated alkenes. It was found that the catalysts **74**, **79**, **83**, and **88** provided the best results. Representative examples are given in eq 28 and Schemes 91 and 92.

A new nucleophilic catalytic system containing dialkylaminopyridine-functionalized mesoporous silica nanospheres (DMAP-MSN, **92**) (Figure 17) has been synthesized and used by Lin and co-workers as a heterogeneous catalyst for the Baylis−Hillman reaction.[268] Representative examples are given in Scheme 93. Gruttadauria and co-workers[269] have used polystyrene-supported proline (**93**) (Figure 17) as a catalyst along with imidazole for Baylis−Hillman coupling between alkyl vinyl ketones and aldehydes. Representative examples are presented in Scheme 93.

Yang and co-workers[270] have reported a new thermomorphic dendritic derivative catalytic system containing a 4-(*N*,*N*-dimethylamino)pyridine framework (**94**) for performing the Baylis−Hillman reaction of aryl aldehydes with MVK and acrylonitrile (Scheme 94). The recyclability of this catalyst has been also demonstrated in the binary solvent system DMF/cyclohexane (1/1, v/v).[271]

Hawker and co-workers[272] have prepared star polymers **95** and **96** (Figure 18) with core-confined catalyst [acidic (PTSA), basic (DMAP)] and used them in one-pot cascade reactions involving acid-catalyzed hydrolysis of acetals to provide *in situ* aldehydes using star polymer **95**, followed by amine-catalyzed Baylis−Hillman reaction using star polymer **96** to provide the required adducts. One example is shown in Scheme 95.

With a view to examining the influence of ionic liquids on the rate of the Baylis−Hillman reaction between various

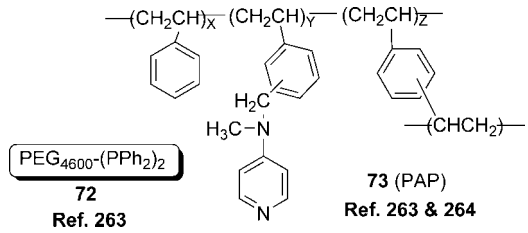
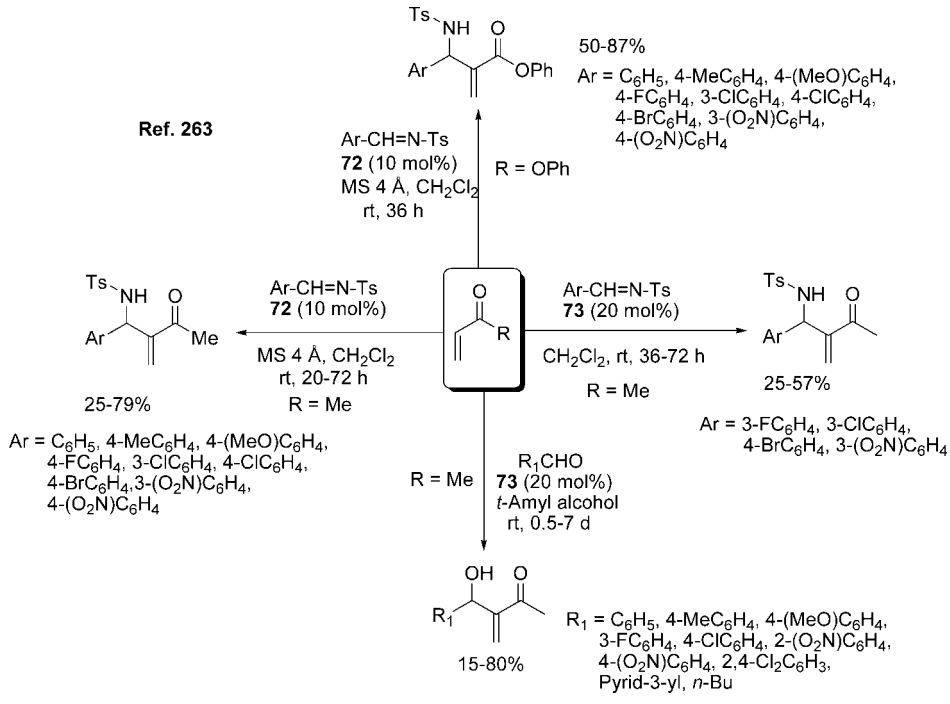


Figure 15.

Scheme 90



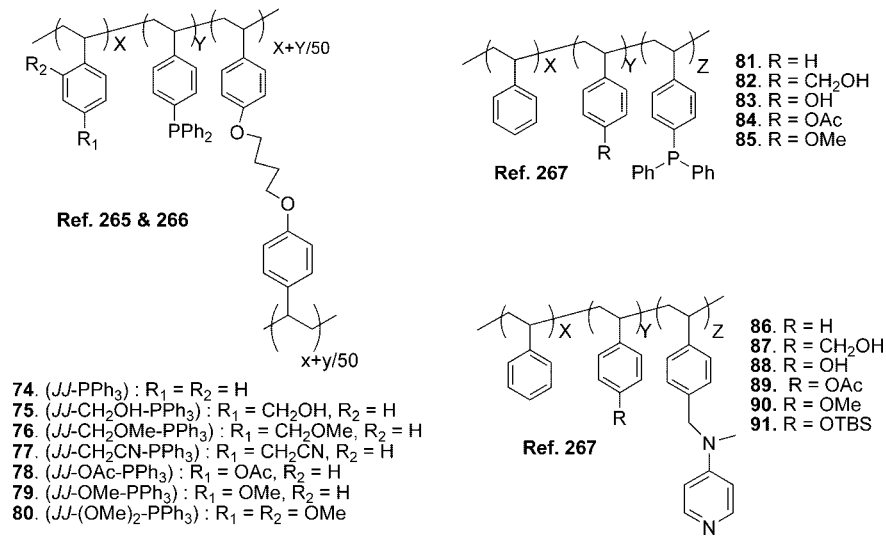
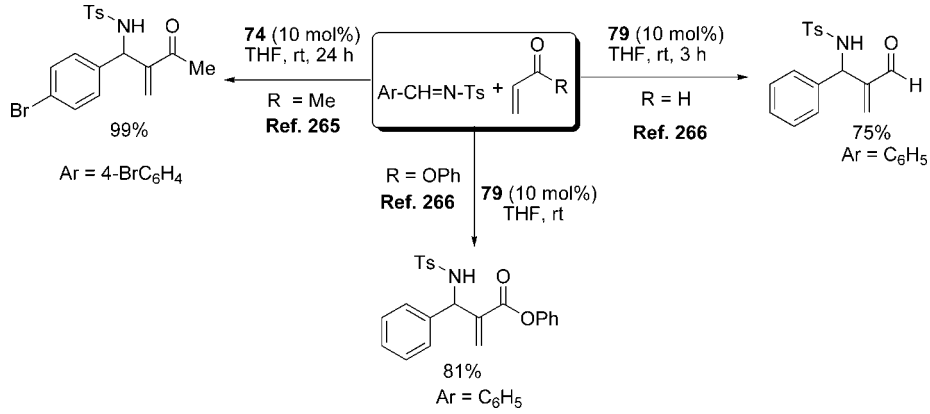
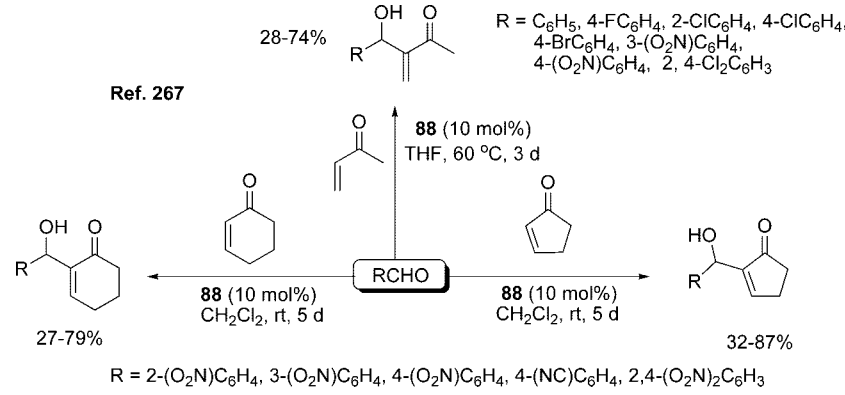


Figure 16.

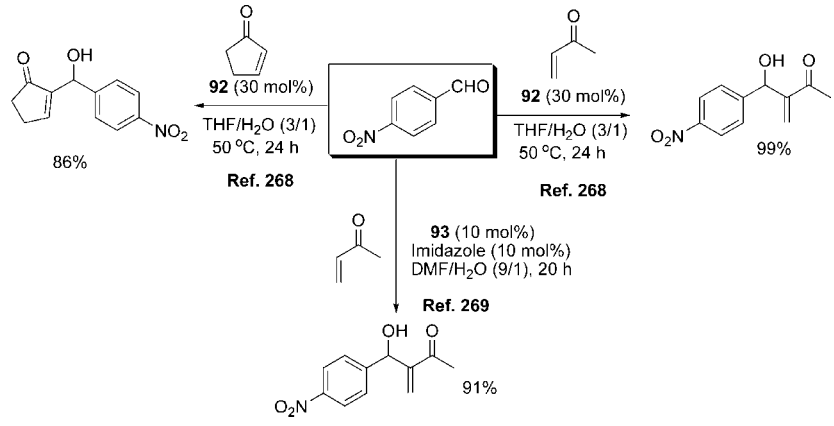
Scheme 91



Scheme 92



Scheme 93



activated alkenes and electrophiles, several ionic liquids (**97**−**105**) (Figure 19) have been prepared and used as solvents in the presence of appropriate catalysts by various research groups.[273−280] It was observed that the reactions are reasonably faster in ionic liquids. Representative examples are shown in Schemes 96 and 97.

Kumar and Pawar[281] have observed that DABCO-catalyzed Baylis−Hillman reactions are faster in $AlCl_3$ at room temperature in ionic liquids **106** and **107**. The authors mentioned that these ionic liquids can be recovered. Representative examples are given in Scheme 98.

Cheng and co-workers[282,283] have prepared several ionic liquids containing the quinuclidine framework (**108**−**116**, Figure 20) and studied systematically their applications in performing Baylis−Hillman reaction. Ionic liquids **108** and **111** offered better results. Some representative examples are given in eq 29 and Scheme 99.

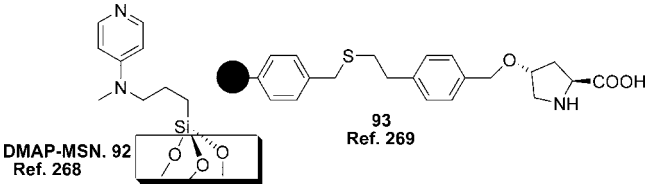
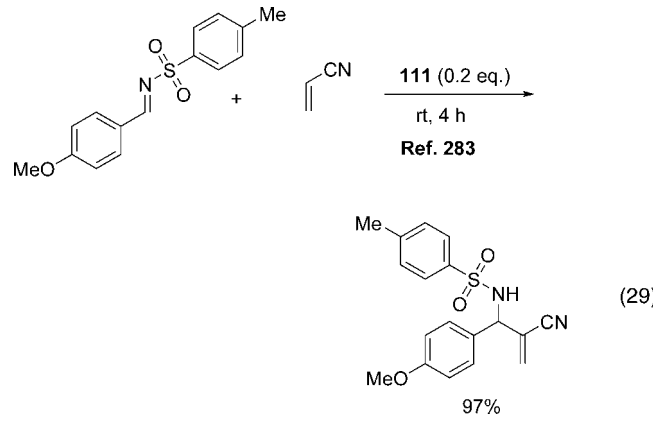


Figure 17.



Liu and co-workers[284] have introduced a novel DABCO-based ionic liquid catalyst **117** (Figure 21) for the Baylis−Hillman coupling of ethyl acrylate with various aldehydes (Path A, Scheme 100). Later on, Zhao and co-workers[285] prepared

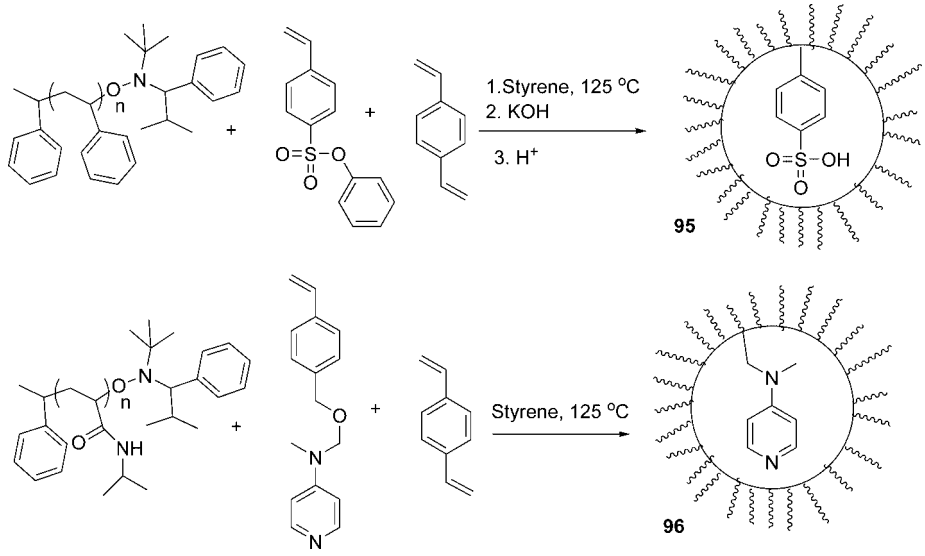
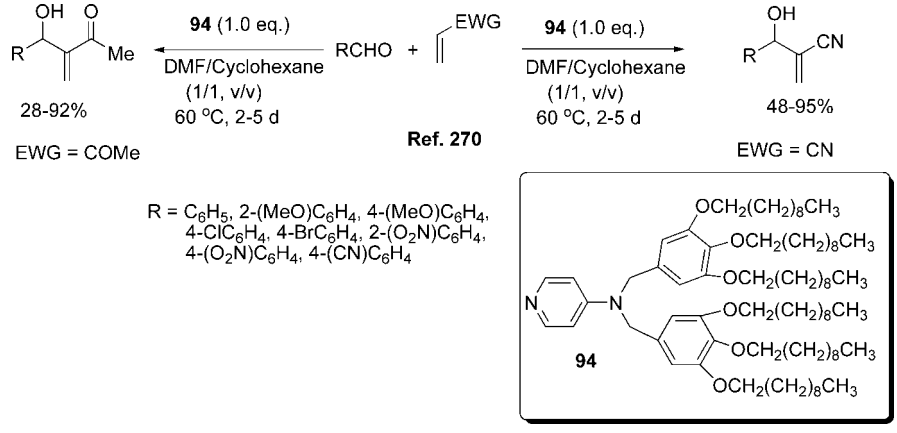
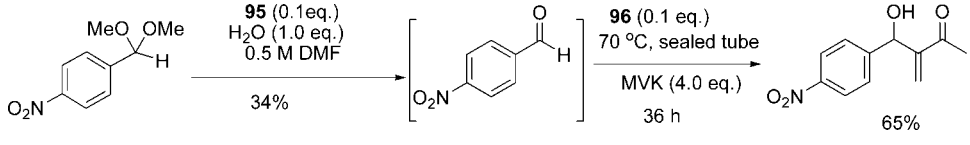


Figure 18.

Scheme 94



Scheme 95



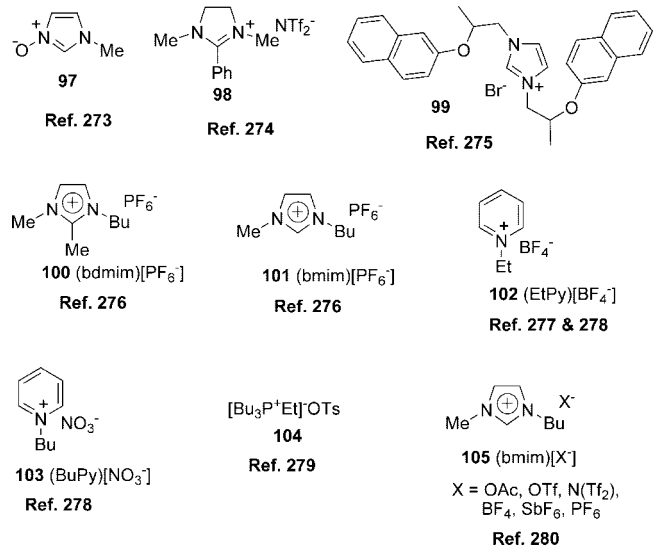
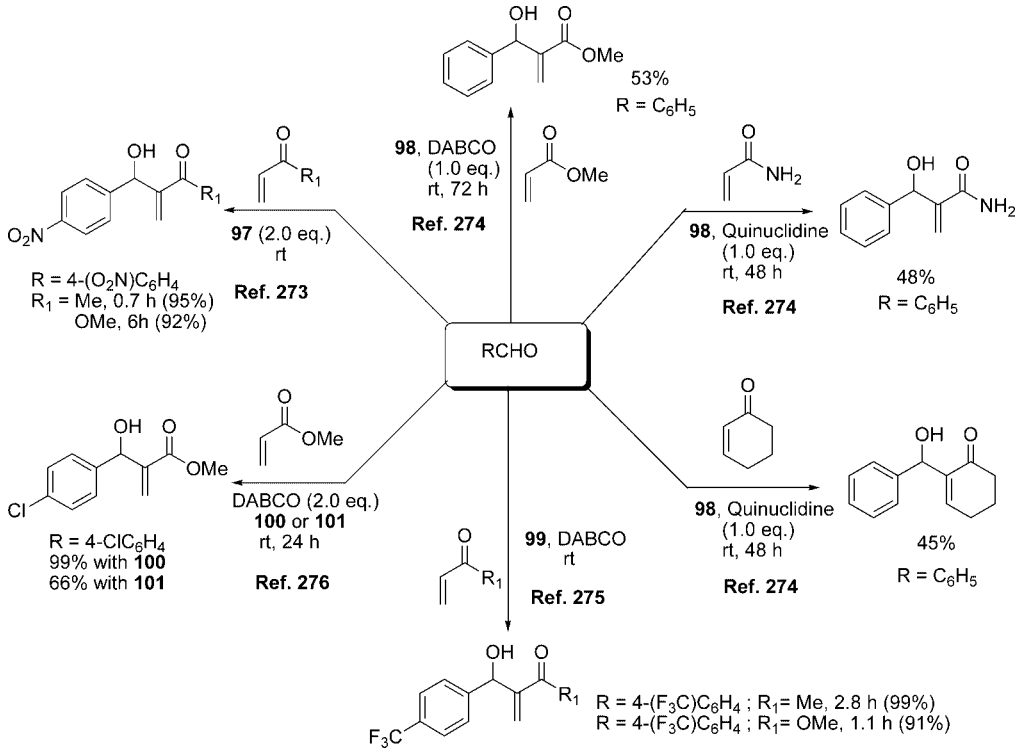


Figure 19.

Scheme 96



pyridinium ionic liquids **118** and **119** (Figure 21) and used them for the Baylis−Hillman coupling between various activated alkenes and aldehydes under the influence of DABCO as catalyst (Paths B and C, Scheme 100).

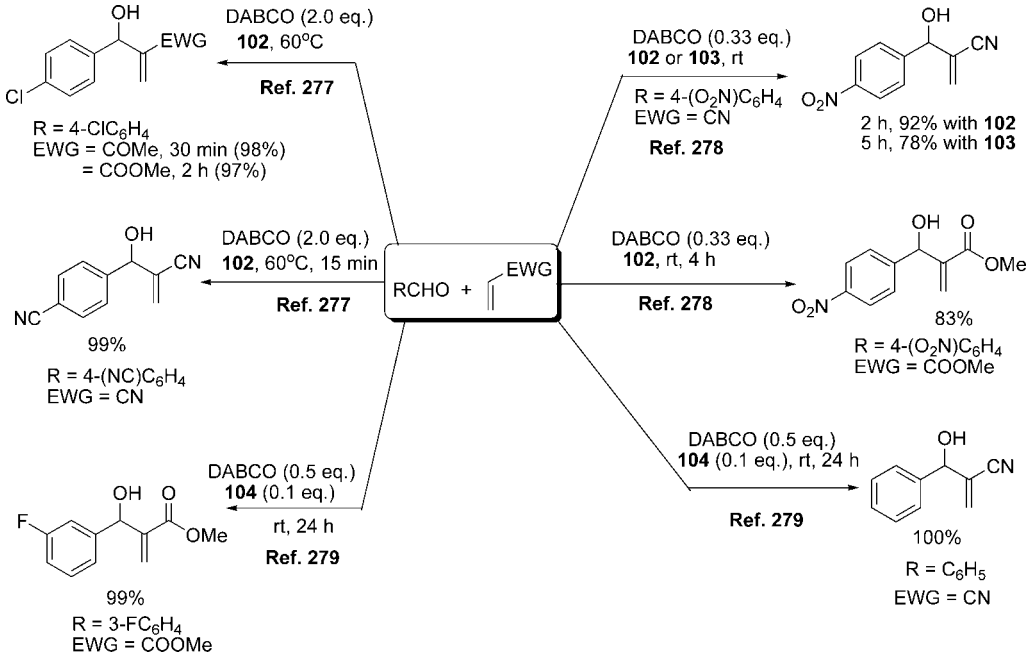
Sulfolane (**120**)[286] and poly(ethylene glycol) (PEG)[287] have been found to accelerate the DABCO-catalyzed Baylis−Hillman reactions. Representative examples are given in Scheme 101.

Connon and co-workers[288] studied applications of a number of catalysts (**121**, **122**) (Figure 22) containing urea and thiourea frameworks for the Baylis−Hillman reaction. They reported, for the first time, applicability of *H*-bonding organocatalysts for accelerating DABCO-catalyzed Baylis−Hillman reaction under solvent-free conditions. It was found that the compound **121c** provided the best results. Representative examples are shown in Scheme 102. Very recently, Philp and co-workers[289] predicted on the basis of theoretical calculations that the thioureas **123** and **124** (Figure 22) might provide superior rate acceleration.

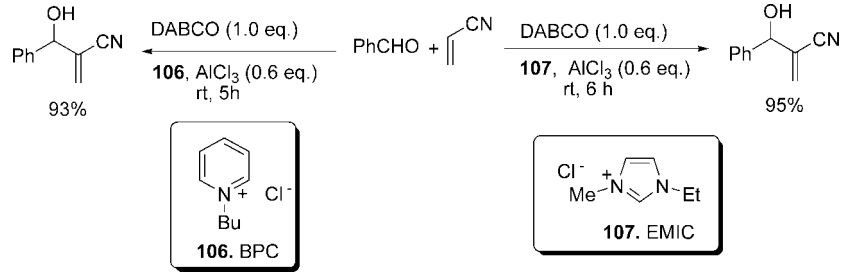
Yi and co-workers[290] have examined the applications of various ytterbium/perfluoroalkylated-pyridine catalysts (**125**−**127**) (Figure 23) in a fluorous biphasic system (FBS) for performing Baylis−Hillman reaction between aldehydes and activated alkenes and found that the catalyst **126** provided encouraging results. Representative examples are given in eq 30.

Ye and co-workers,[291] for the first time, studied the application of *N*-heterocyclic carbenes (NHCs) (**128**−**133**) (Figure 24) as catalysts for performing Baylis−Hillman reaction. The catalyst **128** was found to be an effective catalyst for the Baylis−Hillman reaction between cyclic activated alkenes and N-tosylated imines. Representative

Scheme 97

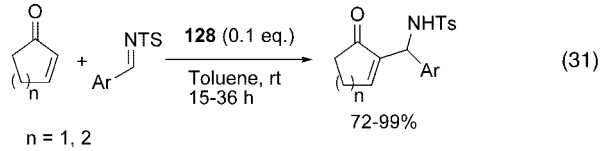


Scheme 98



R = C_6H_5, 4-MeC_6H_4, 4-(MeO)C_6H_4, 4-ClC_6H_4, 4-$(O_2N)C_6H_4$, Naphth-2-yl, Fur-2-yl, Et, *i*-Pr, *n*-Pent
R_1 = Me, OMe, OBu^t

examples are given in eq 31. An appropriate mechanism is represented in Scheme 103.



n = 1, 2

Ar = C_6H_5, 4-MeC_6H_4, 2-(MeO)C_6H_4, 3-(MeO)C_6H_4, 4-(MeO)C_6H_4, 4-FC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-$(O_2N)C_6H_4$, Fur-2-yl

Subsequently, Scheidt and co-workers[292] also used the heterocyclic carbene **128** as a catalyst for the synthesis of

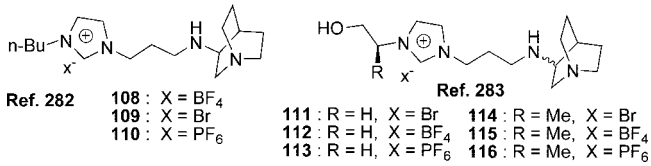
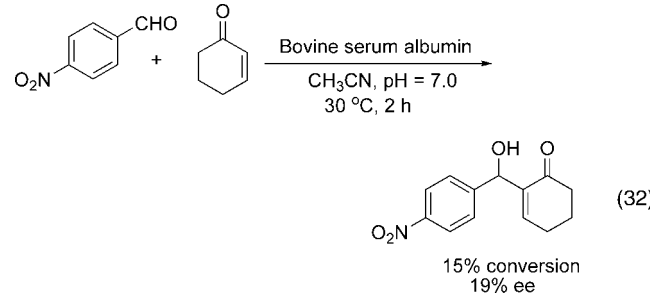


Figure 20.

β-substituted Baylis−Hillman alcohols via the reaction between silyloxyallenes (**10**) (obtained *in situ* from the acetylenic alcohol) with aldehydes. Representative examples are shown in Scheme 104.

Reetz and co-workers[293] have examined the Baylis−Hillman reaction between cyclohex-2-enone and *p*-nitrobenzaldehyde under the influence of various proteins and enzymes and reported that bovine serum albumin (BSA) provided promising results with 19% ee and 15% conversion (eq 32). It needs to be mentioned here that this is the first report of performing Baylis−Hillman reaction using enzymes. Although the yields and enantioselectivities are not high, this report provides the encouragement to plan a suitable biotransformation strategy to develop efficient asymmetric Baylis−Hillman reactions.



Very recently, de Souza and co-workers[294] studied the application of two different reaction media, *t*-BuOH/water

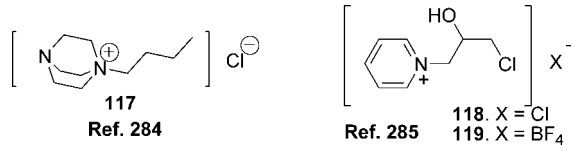
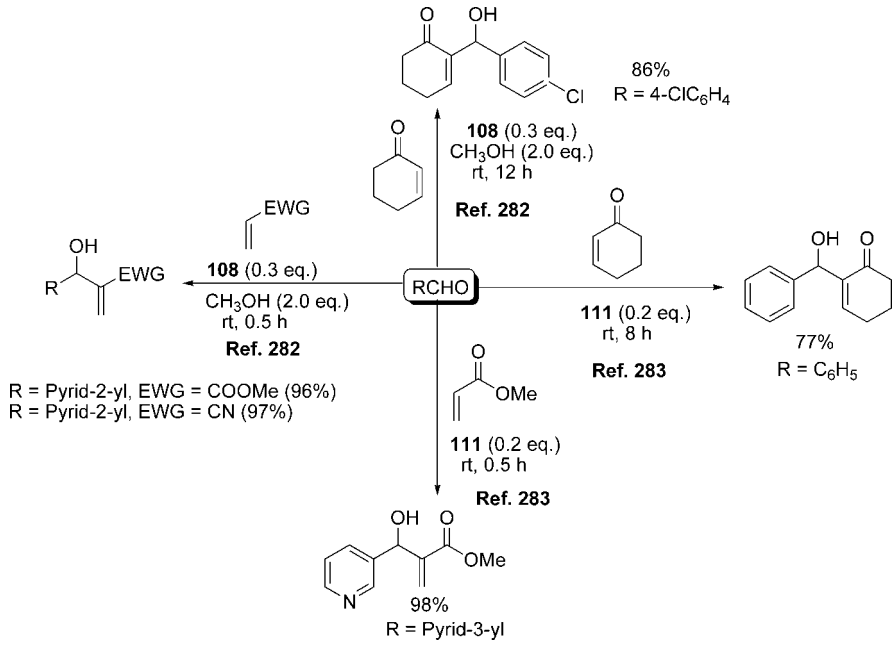
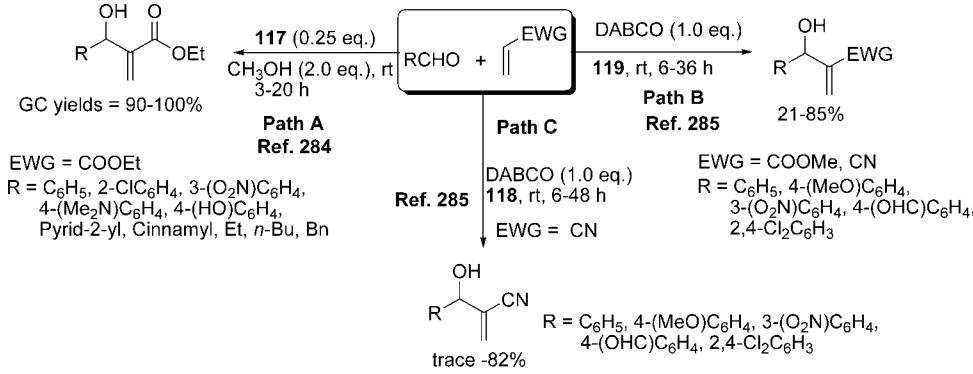


Figure 21.

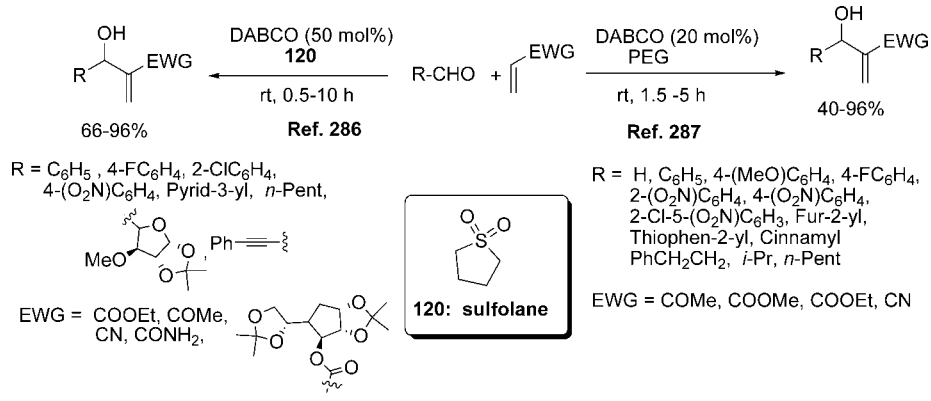
Scheme 99



Scheme 100



Scheme 101



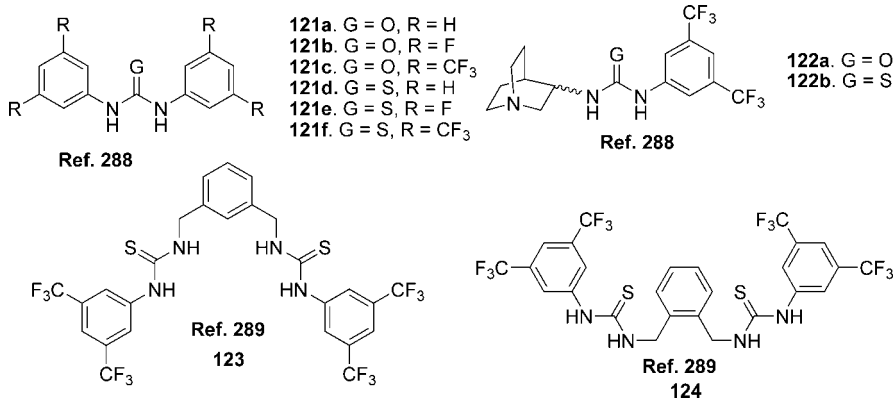
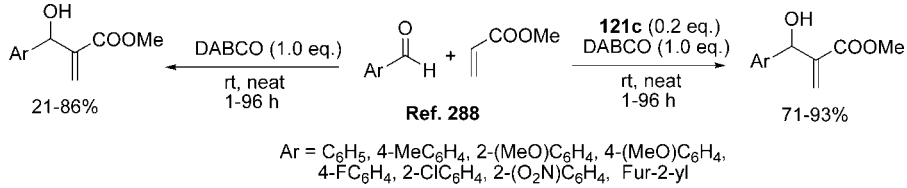


Figure 22.

Scheme 102



(60/40) and DMSO/water (60/40), for performing the Baylis−Hillman reaction. They observed that *t*-BuOH/water (60/40) provided the best results for the coupling of acrylonitrile with aldehydes while DMSO/water (60/40) offered the best results for coupling of acrylates with aldehydes. They also examined various catalysts (DABCO, DBU, DMAP, HMT, Et_3N, and imidazole), and they observed that DABCO provided encouraging results under these reaction conditions. Representative examples are given in Scheme 105. Mack and Shumba[295] reported an interesting rate enhancement of Baylis−Hillman reaction through a mechanochemistry of high-speed ball milling. One example is presented in Scheme 105.

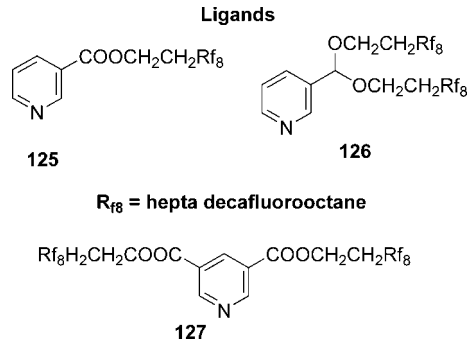


Figure 23.

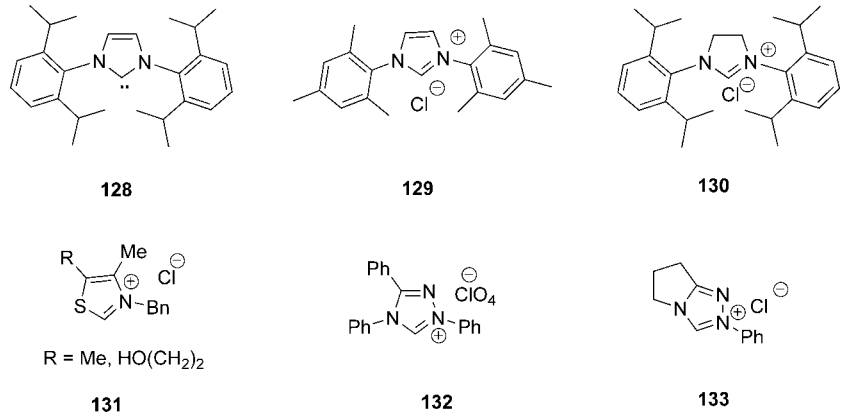
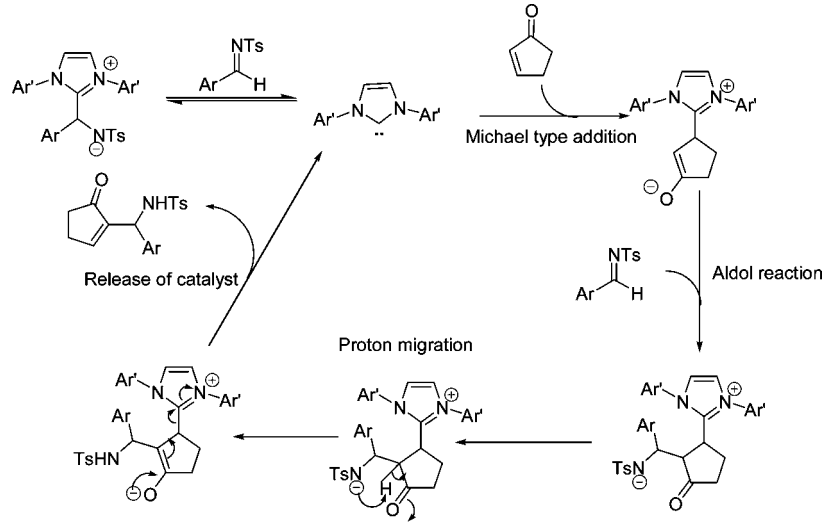
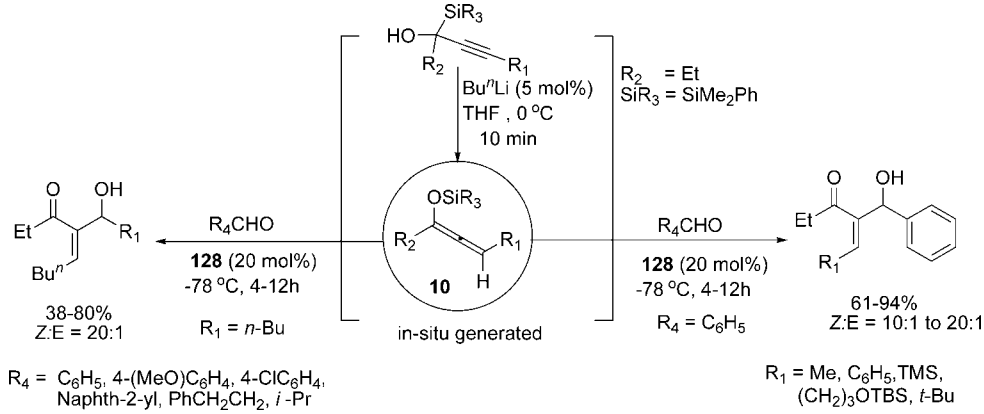


Figure 24.

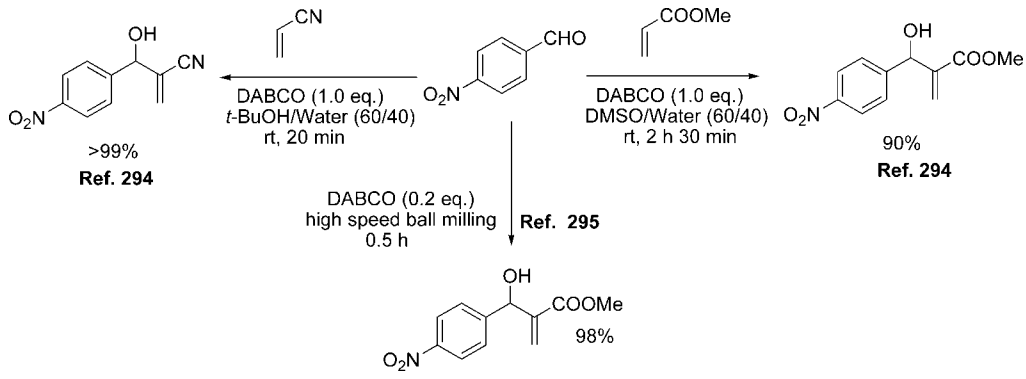
Scheme 103. A Plausible Mechanism for Carbene-Catalyzed Baylis−Hillman Reaction



Scheme 104



Scheme 105



4. Asymmetric Baylis−Hillman Reaction: Earlier Developments

If the electrophile is prochiral, there exists a possibility of asymmetric induction in Baylis−Hillman coupling with an appropriate activated alkene under a suitable chiral environment leading to the formation of enantiopure or enantioenriched multifunctional molecules. This can be, in principle, achieved with enantiomerically pure or enantiomerically enriched activated alkenes, electrophiles, catalysts, additives, or medium or combinations of some or all of these. Attempts have been made in all these directions during last several years, and considerable progress has been achieved in all four aspects.[21] During the last 5−6 years, several interesting publications appeared dealing with asymmetric Baylis−Hillman reaction. It is, in fact, interesting to note here that there has been much emphasis in this period on the development of chiral catalysts for performing various kinds of Baylis−Hillman reactions with high enantioselectivities. All these developments are described in this section. To have better understanding and continuity, earlier work on the asymmetric Baylis−Hillman reaction with respect to all the three essential components is pictorially presented in Figures 25 and 26 (chiral activated alkenes), Figure 27 (chiral electrophiles), and Figures 28 and 29 (chiral catalysts).

4.1. Chiral Activated Alkenes and Alkynes

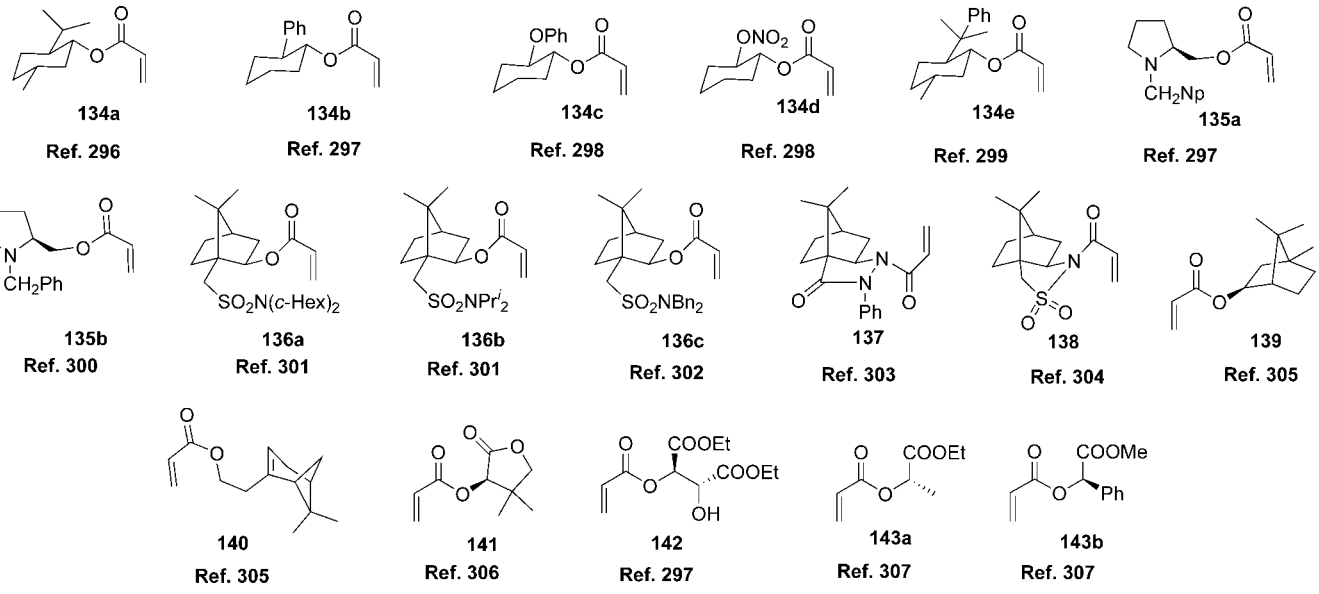


Figure 25.

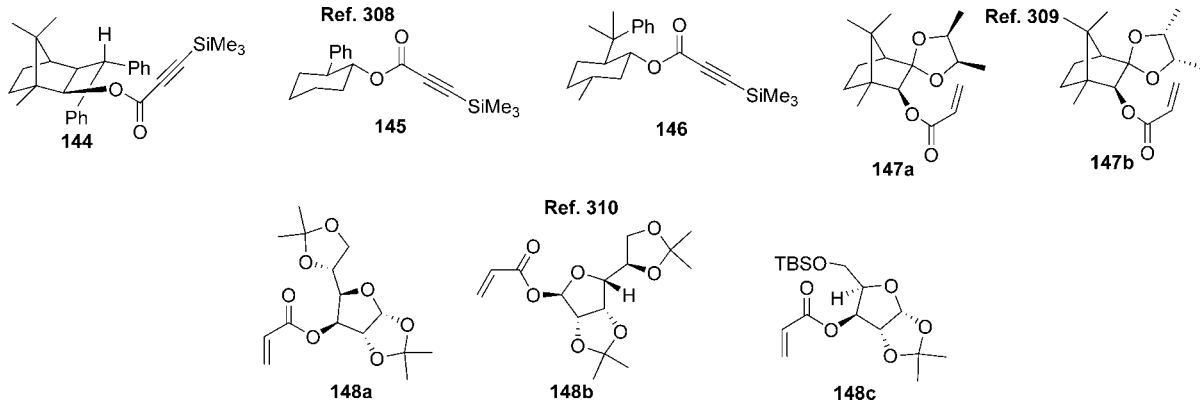


Figure 26.

4.2. Chiral Electrophiles

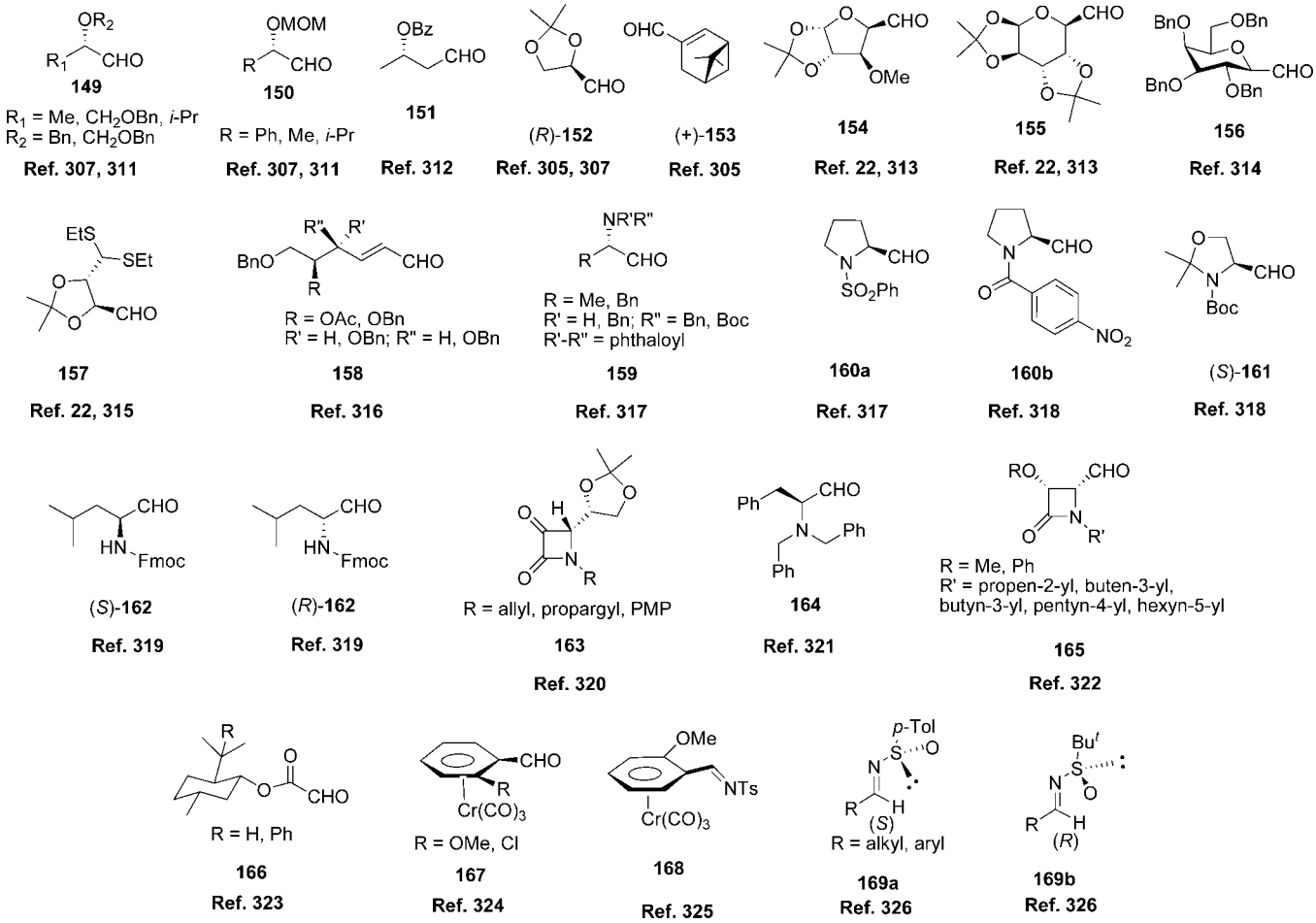


Figure 27.

4.3. Chiral Catalysts

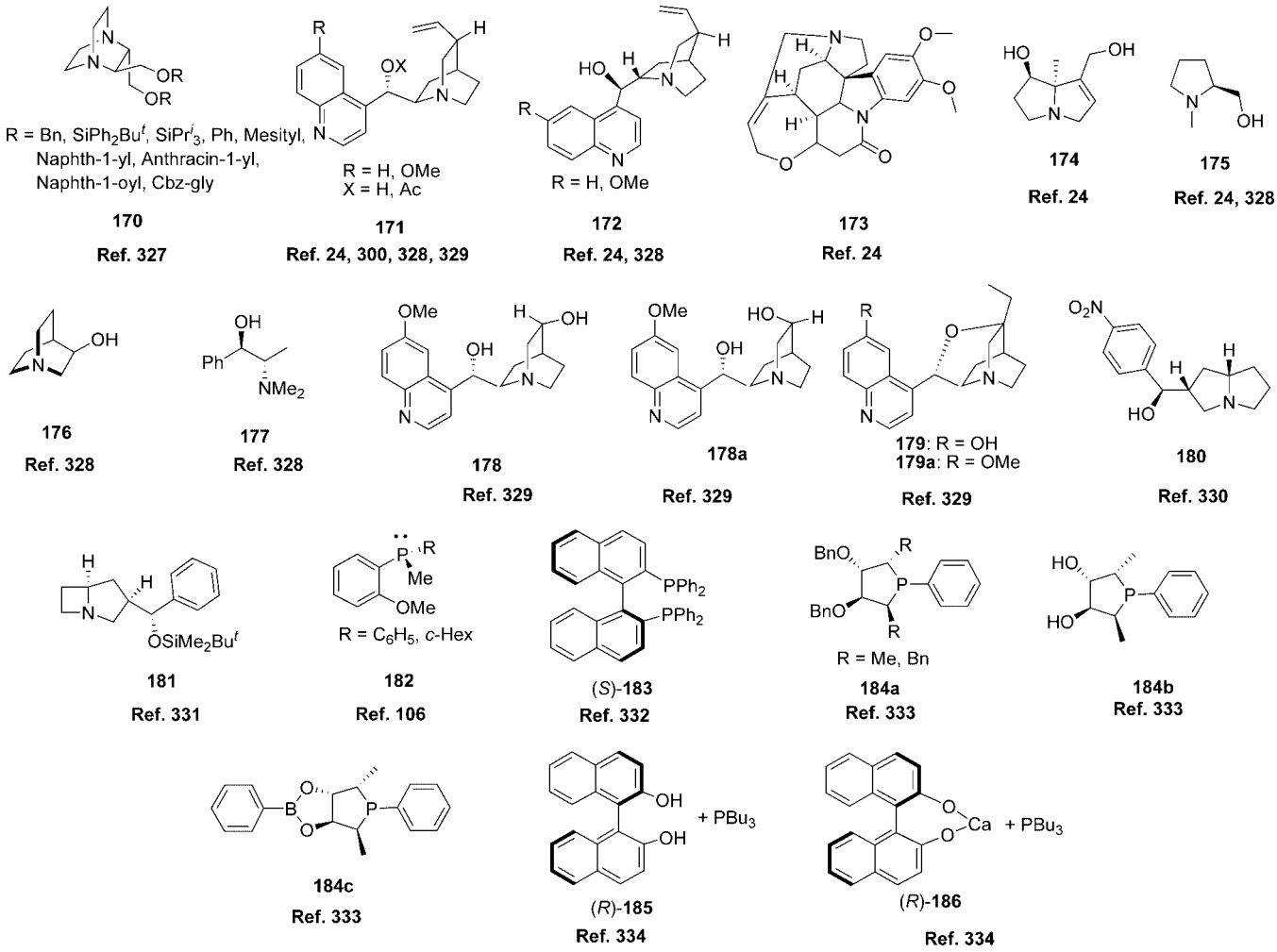


Figure 28.

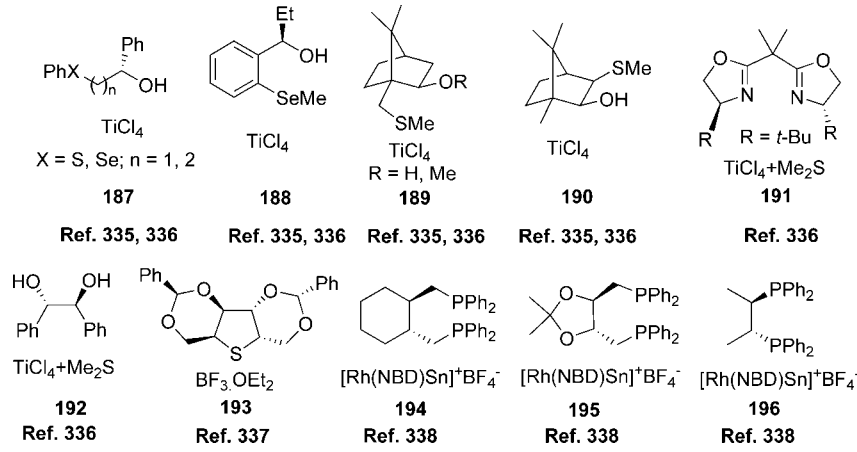


Figure 29.

5. Asymmetric Baylis−Hillman Reaction: Recent Developments

5.1. Chiral Activated Alkenes and Alkynes

Krishna and co-workers[339,340] have used chiral acrylate, 1,2:5,6-di-*O*-isopropylidene-3-*O*-acrylate-D-glucopentoaldo-1,4-furanose (**148a**) as activated alkene in the Baylis−Hillman reaction with various acetylenic aldehydes to provide the resulting adducts in moderate diastereoselectivities (eq 33). This chiral acrylate provided moderate to high diastereoselectivity when chiral aldehydes **149**, (*R*)-**152**, **154a**, (*R*)-**161**, **197**, and **198** (Figure 30) were used as electrophiles in Baylis−Hillman reaction under the influence of DABCO in DMSO. Representative examples are shown in eq 34.

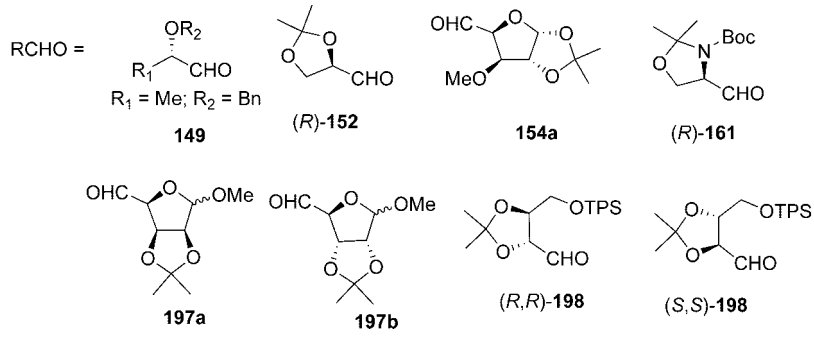
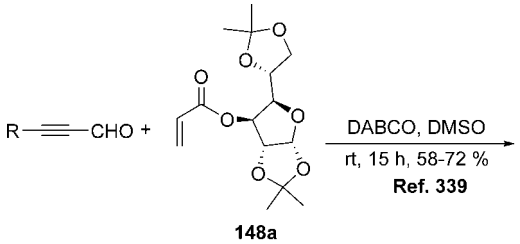
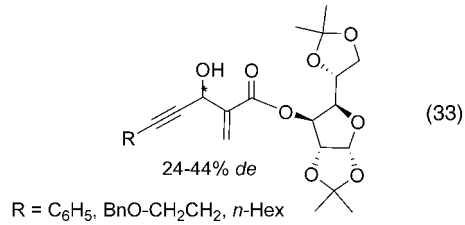
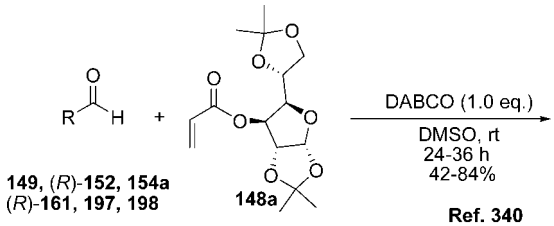


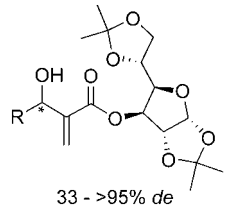
Figure 30.





(33)



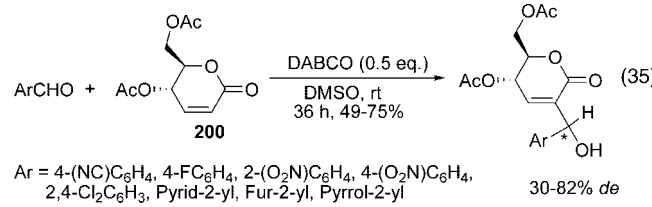


(34)

Shaw and co-workers[341,342] have used *C*-6-acyl-protected enuloside (**199**) as activated alkene for coupling with various aldehydes under the influence of $TiCl_4$/TBAI. Resulting adducts were obtained in high diastereoselectivity. Some of these adducts were reduced with $NaBH_4/CeCl_3 \cdot 7H_2O$ to provide the corresponding alcohols in high diastereoselectivity. Representative examples are shown in Scheme 106. They have also reported studies toward evaluation of these derivatives for antitubercular activity.[342]

Subsequently Krishna and co-workers[343] used chiral lactone **200** as activated alkene for the Baylis−Hillman coupling with various aromatic and heteroaromatic aldehydes, which provided resulting adducts in 30−82% diastereoselectivities. Representative examples are shown in eq 35. They have also presented theoretical calculations for the transition state models in this reaction.

Calmes and co-workers[344] have prepared chiral acrylate **201** and polymer bound chiral acrylate **202** and examined

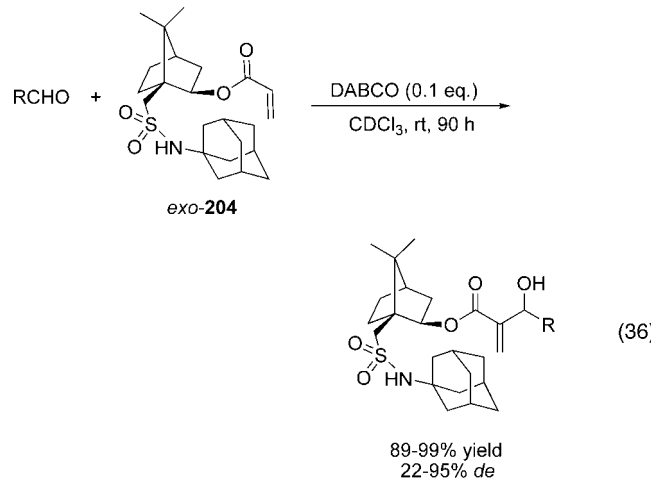


(35)

their applicability as chiral activated alkenes in Baylis−Hillman reaction with various aromatic aldehydes. The resulting adducts were obtained in high yields and moderate selectivity. Representative examples are shown in Scheme 107.

Recently Zhou and co-workers[345,346] have successfully demonstrated the applicability of chiral acrylates, L-menthyl acrylate (**134a**) and α-phenylethyl acrylamide (**203**), derived from L-menthol and α-phenylethylamine, respectively, as chiral activated alkenes for the Baylis−Hillman reaction with various aromatic aldehydes under the influence of trimethyl amine. The resulting Baylis−Hillman adducts were obtained in high diastereoselectivities. Representative examples are shown in Scheme 108.

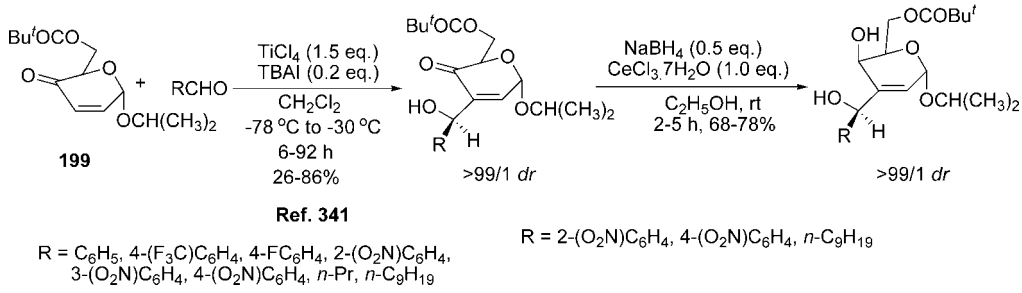
Duggan and Kaye[347] prepared 2-*endo*- and 2-*exo*-acryloyloxy-*N*-(1-adamantyl)bornane-10-sulfonamide diastereomers (*exo*-**204** and *endo*-**204**) (Figure 31) and used *exo*-**204** as activated alkene for coupling with various aldehydes. Resulting adducts were obtained in moderate to excellent diastereoselectivities (eq 36).



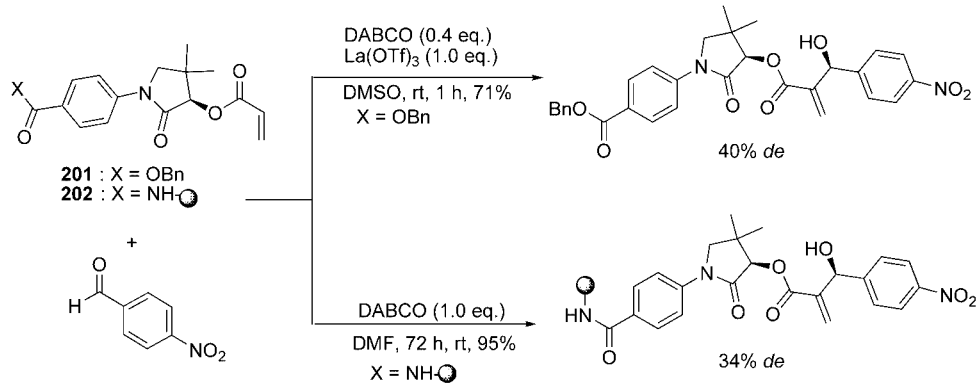
(36)

Casiraghi and co-workers[348] have used **205** [which was prepared from (*R*)-**152**] as a chiral activated alkene for coupling with the aldehyde (*R*)-**152** to provide the corresponding adducts **206a** (major) and **206b** (minor), which

Scheme 106



Scheme 107



Scheme 108

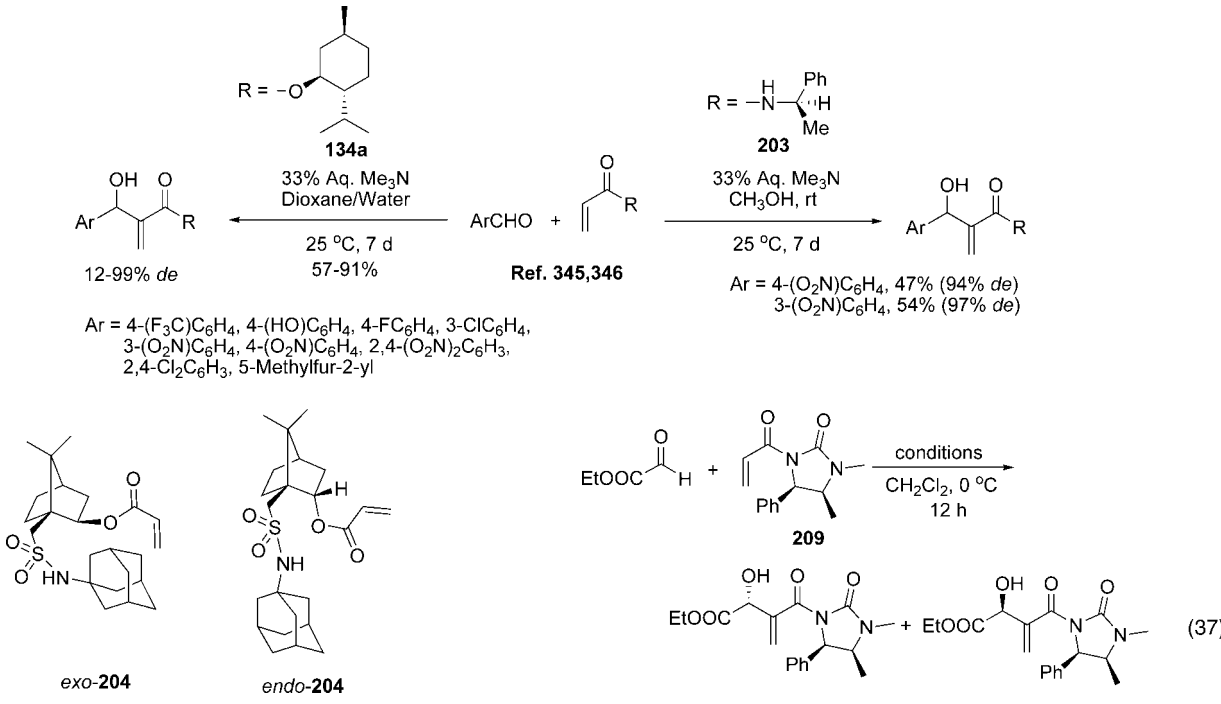


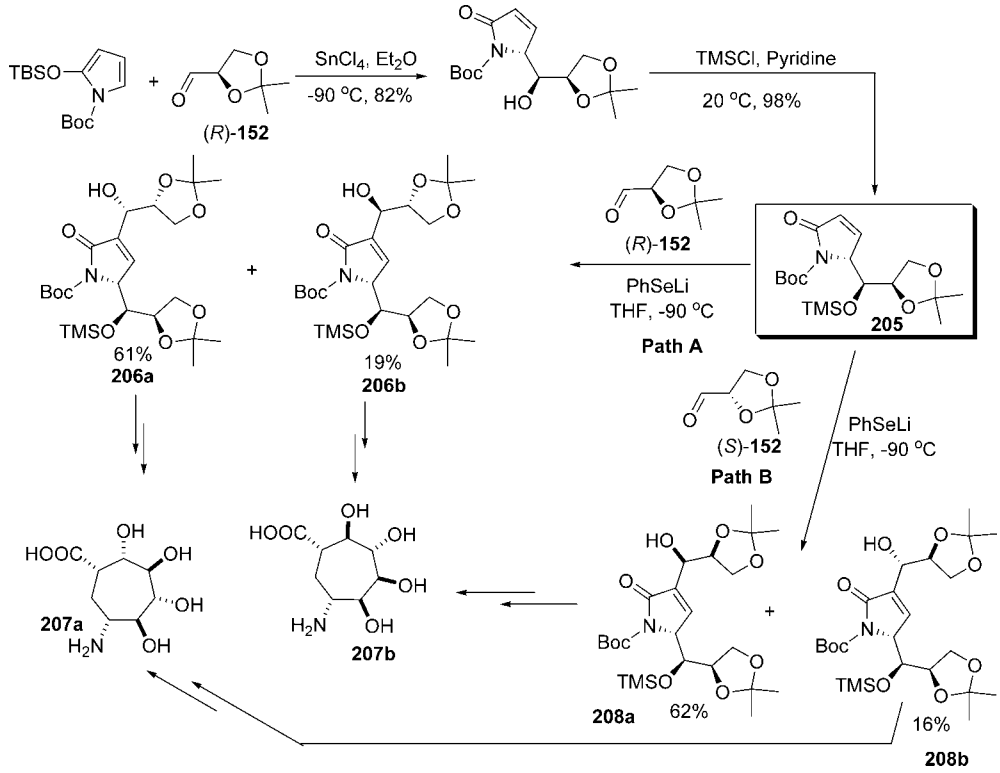
Figure 31.

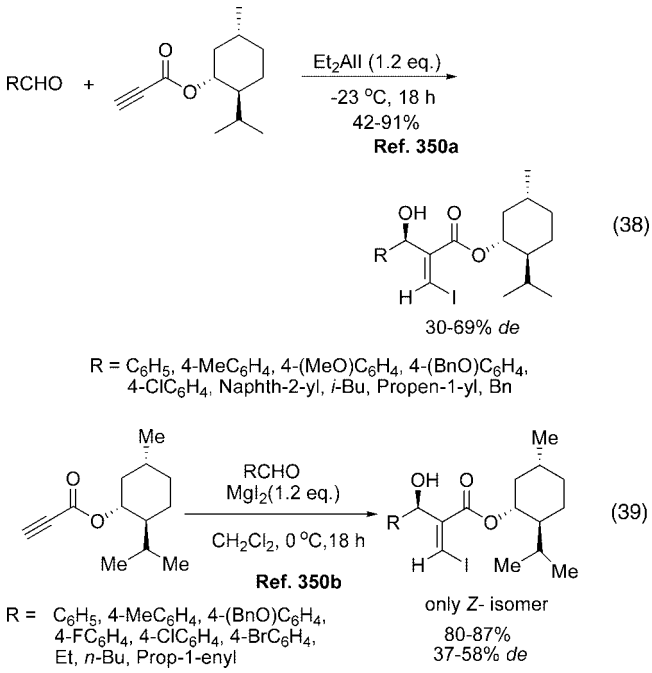
were further converted into polyols **207a** and **207b**, respectively (Path A, Scheme 109). Similarly they also performed the coupling between chiral activated alkene **205** and aldehyde (*S*)-**152** to provide **208a** (major) and **208b** (minor), which were subsequently transformed into polyols **207b** and **207a**, respectively (Path B, Scheme 109).

Orena and co-workers[349] reported an interesting chelation-controlled stereochemical reversal in Baylis−Hillman reaction between the chiral acrylimide **209** and ethyl glyoxalate. One example is shown in eq 37.

Li and co-workers[350a] used L-menthyl propiolate as activated alkyne for coupling with various aromatic and aliphatic aldehydes under the influence of diethylaluminum iodide to provide the resulting adducts in 30−69% diastereomeric purities. Representative examples are shown in eq 38. Subsequently Li, Pare, and co-workers[350b] examined the Baylis−Hillman reaction between menthyl propiolate and aldehydes under the influence of MgI_2 to afford the β-iodo-Baylis−Hillman adducts in moderate diastereoselectivities (eq 39).

Scheme 109





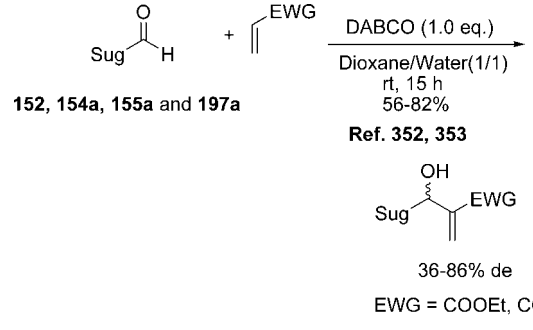
(38)

(39)

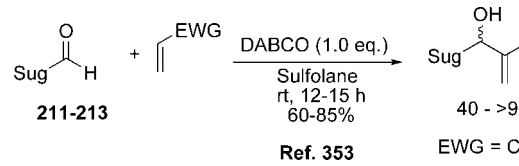
Later on, menthyl propiolate was also employed by Shi and Wang[351] under the influence of $TiBr_4$ for coupling with aldehydes to provide the resulting Baylis−Hillman adducts as a mixture of *E*- and *Z*-isomers in moderate diastereoselectivities (Path A, Scheme 110). This methodology was subsequently extended to (1*S*,5*R*,7*R*)-1-(10,10-dimethyl-3,3-dioxo-3-thia-4-aza-tricyclo[5.2.1.$0^{1,5}$]decan-4-yl)-2-propyn-1-one (**210**) as activated alkyne, which gave the corresponding adducts as a mixture of *E*- and *Z*-isomers. It is interesting to note that the *E*-isomer was obtained in high diastereomeric excess, though in low yields (Path B, Scheme 110, representative examples are given).

5.2. Chiral Electrophiles

During the last 5−6 years, some interesting publications have appeared on the application of chiral electrophiles in Baylis−Hillman reaction with activated alkenes. Krishna and co-workers[352] have described the Baylis−Hillman reaction of representative chiral aldehydes, **154a**, **155a**, and **197a** (Figure 32) derived from sugars, as chiral electrophiles with activated alkenes under the influence of DABCO to provide the resulting adducts in 36−86% diastereoselectivities. Subsequently, Krishna and Kannan[353] have extended this strategy for a number of chiral aldehydes (**152**, **211**−**213**) (Figure 32), derived from different sugars. In these reactions, they observed that sulfolane as solvent provided slightly better yields than the dioxane/water system. Representative examples that gave higher diastereoselectivities are presented in eqs 40 and 41.



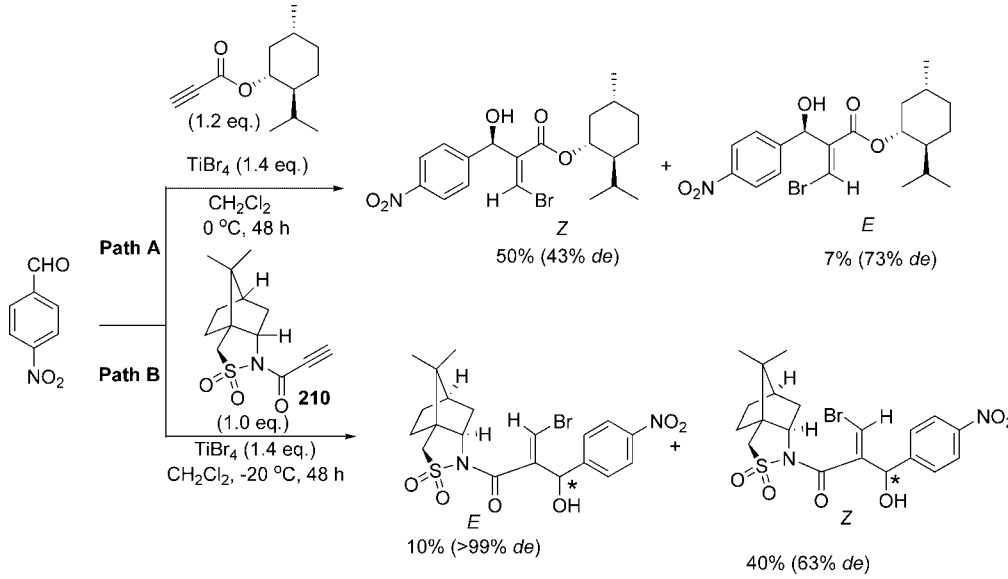
(40)



(41)

Alcaide and Almendros[354] have prepared various enantiopure azetidine-2,3-diones **163** and used them as chiral

Scheme 110



electrophiles in the Baylis−Hillman reaction with various activated alkenes or alkynes in the presence of DABCO to afford the corresponding Baylis−Hillman adducts with high diastereoselectivities and in high yields. They have also noticed that when but-3-yn-2-one was used as activated alkene, the resulting adduct was obtained in low yield. Representative examples are shown in Scheme 111.

Pan and Chen[355] have successfully used *N*-glyoxyloylcamphorpyrazolidinone **214** as electrophile in Baylis−Hillman reaction with various activated alkenes in the presence of DABCO in the DMSO/H_2O system to provide the resulting adducts in high diastereoselectivities. These adducts were further transformed into *N*-phthalimidoaziridine derivatives via treatment with *N*-aminophthalimide in the presence of lead tetraacetate. Representative examples are shown in Scheme 112.

Coelho and co-workers[356] successfully utilized chiral amino aldehydes as electrophiles in the asymmetric Baylis−Hillman reaction with methyl acrylate under the influence of ultrasound radiation (eq 42). Under these conditions, it was observed that there was no racemization. The adduct obtained from (*S*)-1-*tert*-butoxycarbonylpiperidine-2-carboxaldehyde was successfully used as an intermediate for the preparation of a bicyclic indolizidine framework (Scheme 113).

Very recently Zhou and co-workers[237,357] used chiral thiophosphorylimines, derived from (*S*)-binaphthol, as chiral electrophiles in Baylis−Hillman reaction with MVK under the influence of PTA (**57**) as a catalyst. The resulting Baylis−Hillman adducts were obtained in moderate to excellent diastereoselectivities (up to 99%). Representative examples are shown in eq 43.

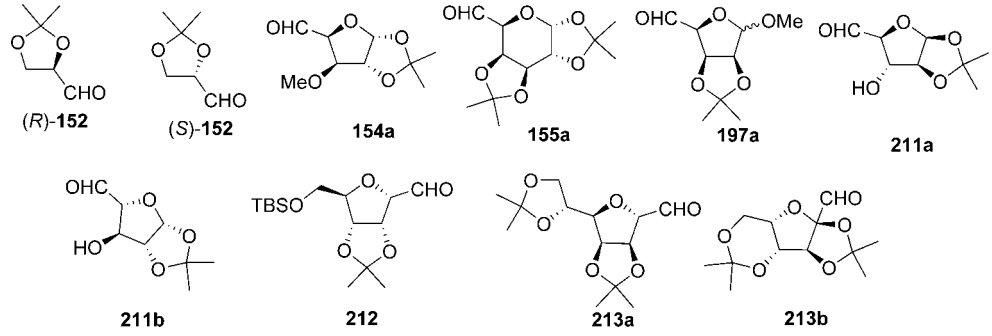
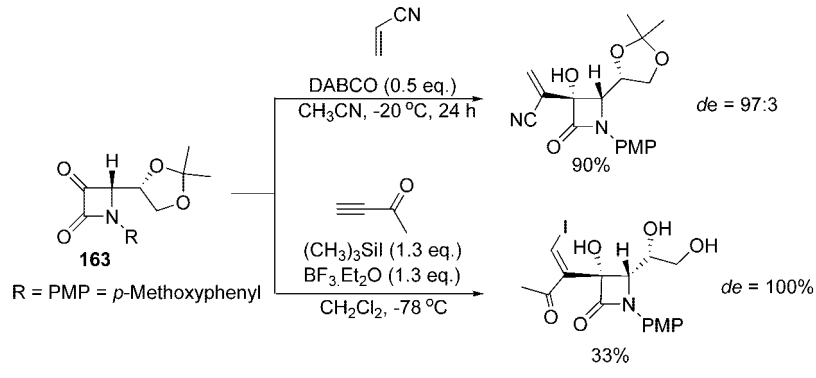
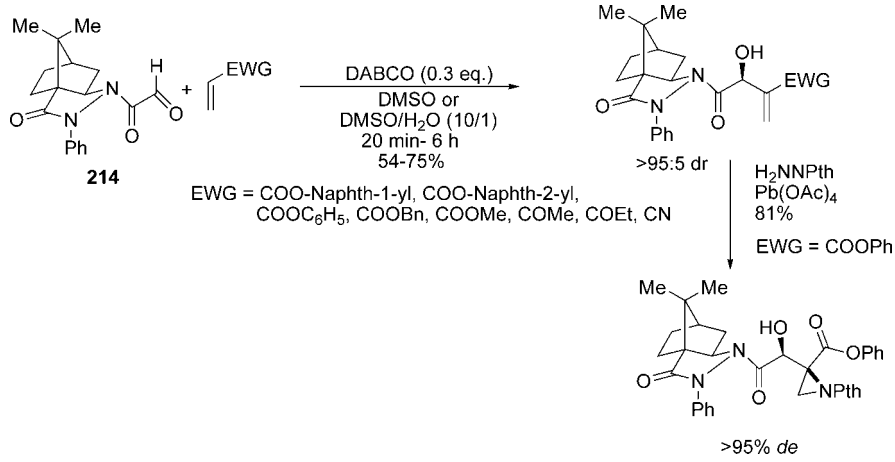


Figure 32.

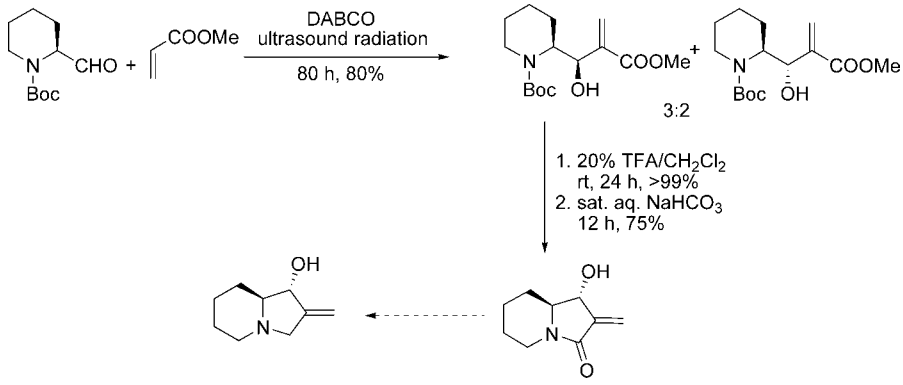
Scheme 111

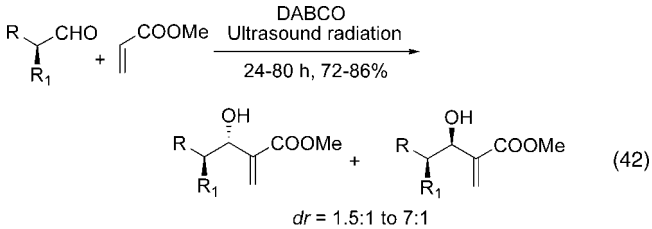


Scheme 112

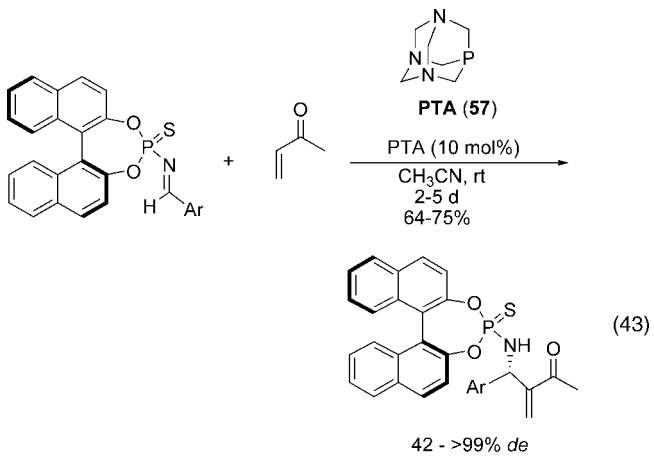


Scheme 113





Aldehyde = *N*-Boc-*L*-phenylalaninal, *N*-Boc-*L*-alaninal, *N*-Boc-*L*-leucinal, *N*-Boc-*L*-serinal, *N*-Boc-*L*-prolinal, *N*-Boc-pipecolaldehyde



Ar = C_6H_5, 4-MeC_6H_4, 4-$(MeO)C_6H_4$, 4-$(F_3C)C_6H_4$, 2-ClC_6H_4, 4-BrC_6H_4

5.3. Chiral Catalysts

During the last six years, development of appropriate catalysts for asymmetric Baylis−Hillman reaction has become a major objective and central theme of the research in many world leading research laboratories. Hatakeyama and co-workers[329] examined various chiral catalysts, **171**, **178**, and **179** (Figure 33), based on the quinidine framework as catalysts for asymmetric Baylis−Hillman reaction between 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) and aldehydes. The catalyst β-isocupreidine (β-ICD) (**179**) provided better selectivities (Path A, Scheme 114). Subsequently, they[358] have also extended this strategy to aldimine derivatives as electrophiles and observed a remarkable reversal of stereoselectivity from aldehydes to aldimine derivatives (Paths B and C, Scheme 114). These products were transformed into the corresponding β-lactams. Representative examples are given in Scheme 114.

Subsequently Hatakeyama and co-workers[359] showed that the azeotropically dried β-ICD (**179**) has remarkable catalytic activity, in particular, for aromatic aldehydes in the asymmetric Baylis−Hillman reaction with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (HFIPA) (eq 44). They[360] have used azeotropically dried β-ICD for coupling of chiral *N*-Boc-α-amino aldehydes with HFIPA. It is interesting to note that *N*-Boc-α-acyclic amino aldehydes and *N*-Boc-α-cyclic amino aldehydes showed different reactivities and selectivities, depending on the chirality. Thus in the case of *N*-Boc-α-acyclic amino aldehydes, L-substrates show excellent *syn* selectivity and high reactivity (in contrast to D-substrates), while in the case of *N*-Boc-α-cyclic amino aldehydes,

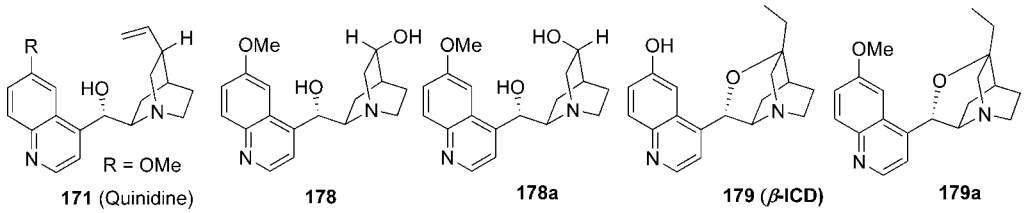
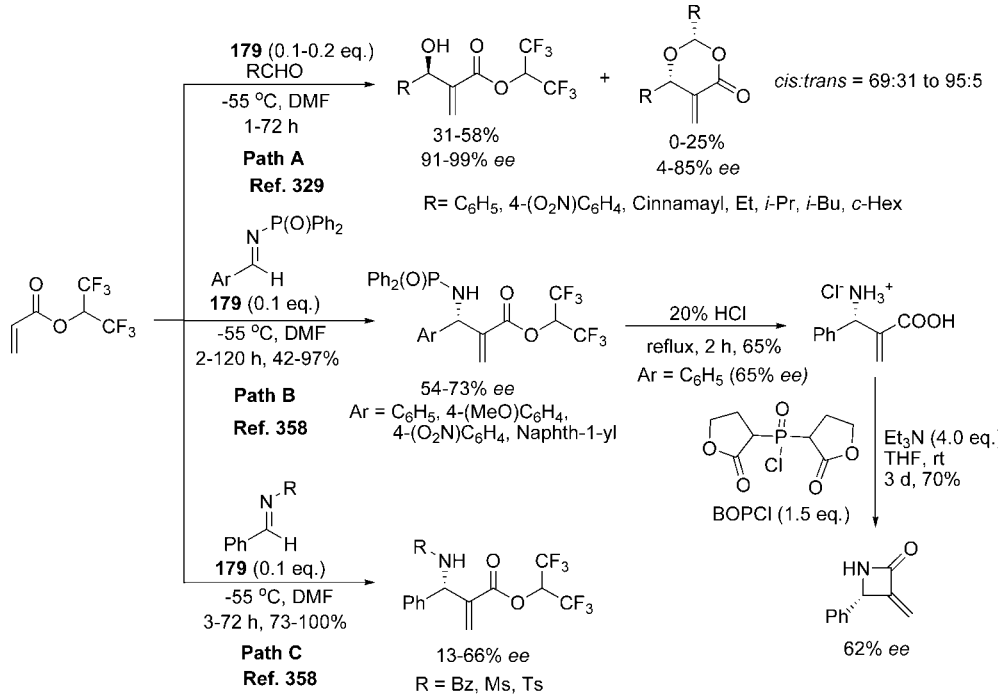
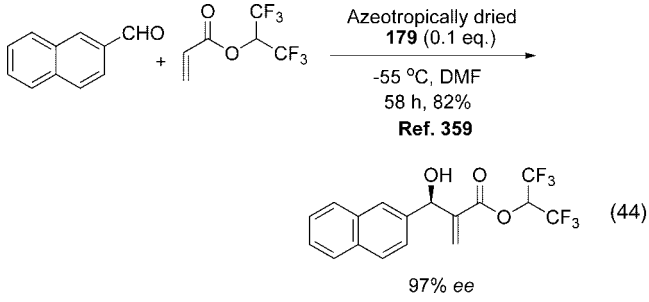


Figure 33.

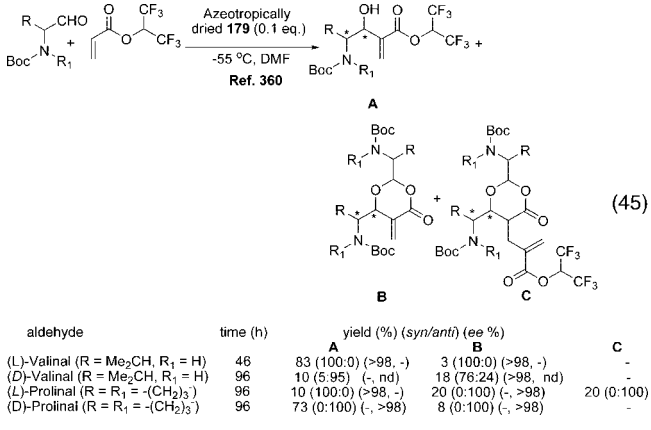
Scheme 114



D-substrates exhibited excellent *anti* selectivity and high reactivity (eq 45).



(44)



(45)

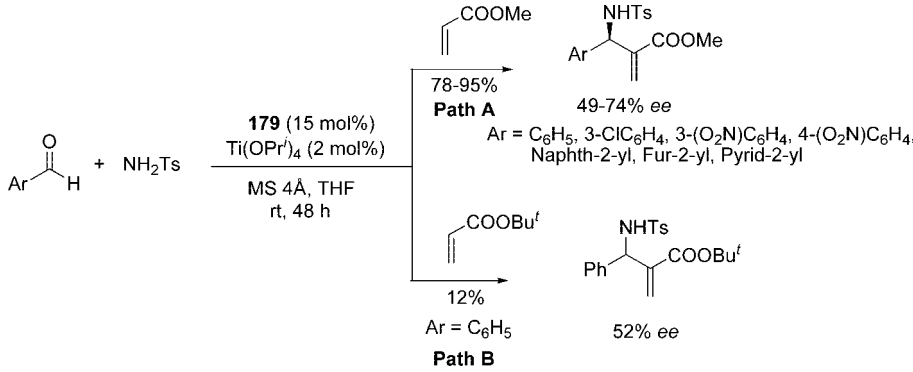
aldehyde	time (h)	yield (%) (*syn/anti*) (*ee* %) A	B	C
(L)-Valinal (R = Me_2CH, R_1 = H)	46	83 (100:0) (>98, -)	3 (100:0) (>98, -)	-
(*D*)-Valinal (R = Me_2CH, R_1 = H)	96	10 (5.95) (-, nd)	18 (76:24) (>98, nd)	-
(*L*)-Prolinal (R = R_1 = $-(CH_2)_3-$)	96	10 (100:0) (>98, -)	20 (0:100) (-, >98)	20 (0:100)
(D)-Prolinal (R = R_1 = $-(CH_2)_3-$)	96	73 (0:100) (-, >98)	8 (0:100) (-, >98)	-

Subsequently Balan and Adolfsson[361] studied the catalytic potential of chiral amines (**172**, **215**−**218**, Figure 34) for asymmetric Baylis−Hillman coupling between benzaldehyde, tosylamine, and methyl acrylate to provide the resulting adducts in 49−74% enantiomeric purities. However they noticed that β-ICD (**179**) provided better results. Representative examples are shown in Path A, Scheme 115. When *tert*-butyl acrylate was used as activated alkene for coupling with benzaldehyde and tosylamine under the catalytic influence of **179**, the resulting adduct was obtained in 52% ee and 12% yield (Path B, Scheme 115).

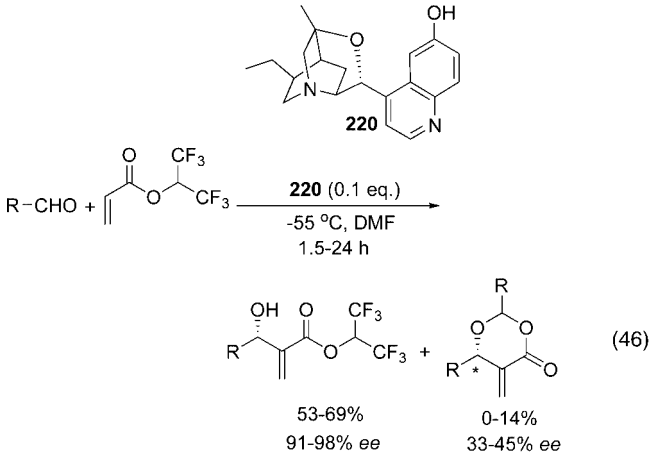
Warriner and co-workers[362] have studied the applicability of various Sharpless ligands, $(DHQD)_2PHAL$ (**219a**), $(DHQD)_2AQN$ (**219b**), and $(DHQD)_2PYR$ (**219c**) (Figure 35), as bifunctional catalysts for the asymmetric Baylis−Hillman coupling between various aromatic aldehydes and methyl acrylate and observed that $(DHQD)_2AQN$ (**219b**) provided better selectivity than other ligands in the presence of carboxylic acid (cat.) but with low yields. Representative examples are given in Scheme 116.

Recently Shi and co-workers[363] examined the application of Hatakeyama catalyst β-isocupreidine (**179**) in the asymmetric Baylis−Hillman coupling of aldimines (*N*-tosylimine derivatives) with various activated olefins such as MVK, EVK, acrolein, methyl acrylate, phenyl acrylate, acrylonitrile, and α-naphthyl acrylate to provide the resulting adducts in high ee (Scheme 117). It is interesting to note that this method provided better selectivity than that of Balan and Adolfsson as shown in Scheme 115. Another interesting finding is that the absolute configuration of these adducts derived via the asymmetric Baylis−Hillman reaction of N-sulfonated imines with MVK or EVK were opposite that of adducts obtained

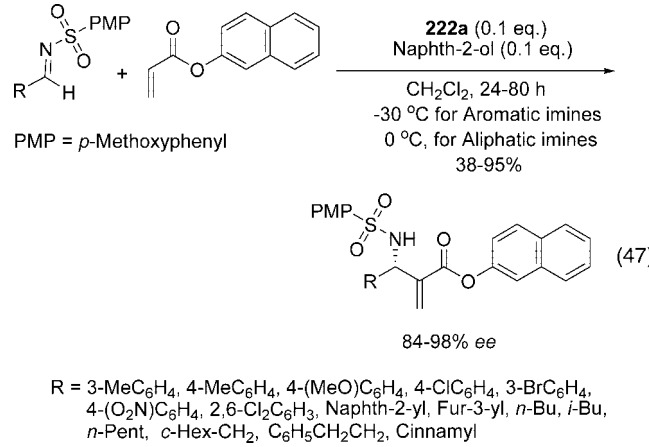
Scheme 115



via the coupling with acrolein, methyl acrylate, phenyl acrylate, acrylonitrile, and α-naphthyl acrylate in the presence of β-ICD (**179**) under similar reaction conditions. Subsequently, these authors[364] also observed that the reaction between *N*-tosyl salicylaldehyde imines and MVK/EVK under the influence of β-ICD (**179**) provided the resulting adducts with opposite stereoselectivity to that obtained from simple *N*-tosyl aldimine derivatives (in the absence of the 2-hydroxy group in the aromatic ring) (Scheme 117). This reaction clearly indicates the key role of the hydroxyl group in the stereochemical outcome of the reaction. Representative examples are presented in Scheme 117.



Hatakeyama and co-workers[365] synthesized a pseudoenantiomer (**220**) of β-isocupreidine (**179**) from quinine and used it as a catalyst for asymmetric Baylis−Hillman reaction between HFIPA and aldehydes. The resulting Baylis−Hillman adducts were obtained in high ee with opposite configuration to that of β-isocupreidine obtained from quinidine (see Path A, Scheme 114) indicating the enantio-complementary nature of the catalyst **220** to that of **179** (eq 46).



Zhu and co-workers[366] have modified the Hatakeyama catalyst and prepared a number of β-isocupreidine derivatives (**221** and **222**, Figure 36) and examined their catalytic potential in asymmetric Baylis−Hillman reaction of aromatic and aliphatic imines with β-naphthyl acrylate. The catalyst **222a** provided better selectivity even for aliphatic aldehydes (eq 47).

Sasai and co-workers[367,368] examined the applicability of a number of bifunctional organocatalysts (**223a**−**l**) (Figure 37) based on a binaphthol structure containing an amino pyridine skeleton or aniline moiety (**224**) for the asymmetric Baylis−Hillman reactions between acrolein, MVK, or EVK

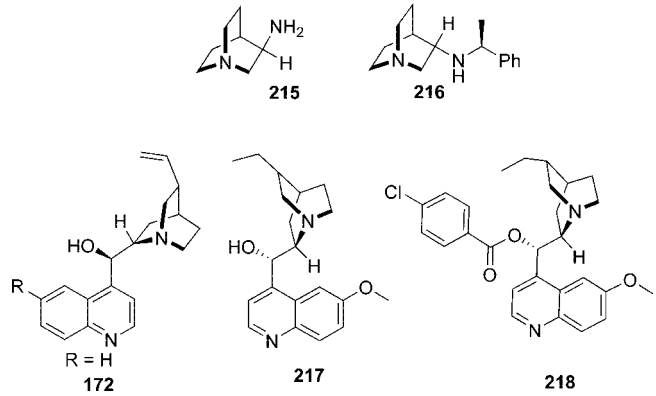
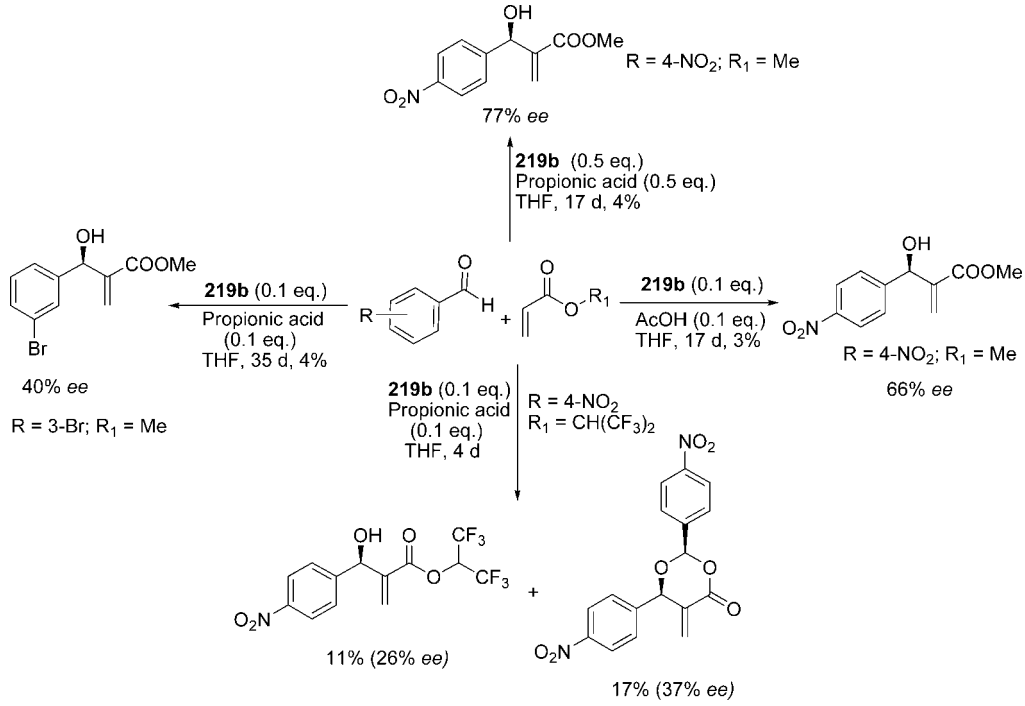
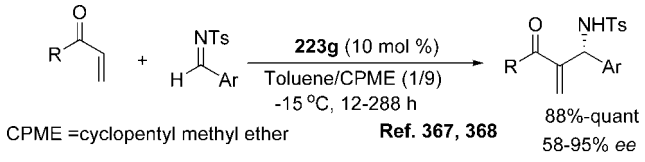


Figure 34.

Scheme 116

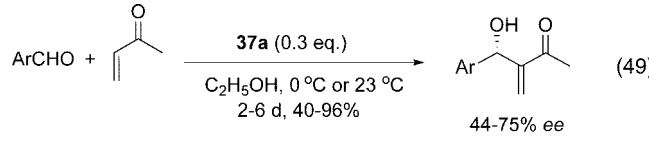


and aldimine derivatives. Among these catalysts, **223g** provided superior selectivities. Representative examples are presented in eq 48.



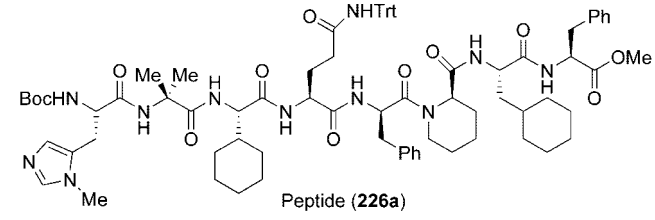
Ar = C_6H_5, 4-MeC_6H_4, 4-EtC_6H_4, 4-$(NC)C_6H_4$, 4-$(MeO)C_6H_4$, 4-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3-$(O_2N)C_6H_4$, 4-$(O_2N)C_6H_4$, Naphth-1-yl, Naphth-2-yl, Fur-2-yl
R = H, Me, Et, C_6H_5 (48)

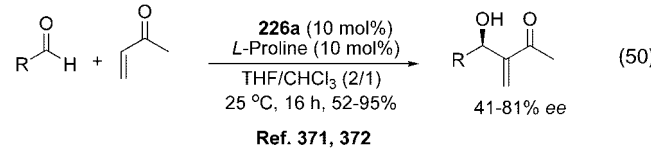
Krishna and co-workers[369] have used *N*-methylprolinol (**175**) as a chiral catalyst for Baylis−Hillman reaction between aromatic aldehydes and MVK or ethyl acrylate in a dioxane/water solvent system (Scheme 118) to provide the resulting adducts in 15−78% enantioselectivities. However aliphatic aldehydes such as hexanecarboxaldehyde and heptanecarboxaldehyde failed to undergo Baylis−Hillman reaction under these conditions. They have also observed that diphenyl(1-methylpyrrolidin-2-yl)methanol (**225**) was ineffective for Baylis−Hillman reaction with aromatic carboxaldehydes.



(49)

Ar = C_6H_5, 4-$(NC)C_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2-$(O_2N)C_6H_4$, 4-$(O_2N)C_6H_4$, 2,4-$Cl_2C_6H_3$, Fur-2-yl





(50)

R = C_6H_5, 2-$(F_3C)C_6H_4$, 2-FC_6H_4, 2-$(O_2N)C_6H_4$, 3-$(O_2N)C_6H_4$, 4-$(O_2N)C_6H_4$, 2,4-$(O_2N)_2C_6H_3$, 3-(MeO)-2-$(O_2N)C_6H_3$, 1-(O_2N)-Naphth-2-yl, Fur-2-yl

About the same time, Hayashi and co-workers[370] examined the potential of various chiral diamines (**37**, **37a**−**e**) (Figure 38) prepared from (*S*)-proline as catalysts for asymmetric Baylis−Hillman reaction between methyl vinyl ketone and aromatic aldehydes. Among these catalysts, the catalyst **37a** was found to be the best for coupling between MVK and various aromatic aldehydes (eq 49).

Miller and co-workers[371,372] observed an interesting dual catalyst control in the amino acid−peptide-catalyzed Baylis−Hillman reaction between aromatic aldehydes and MVK.

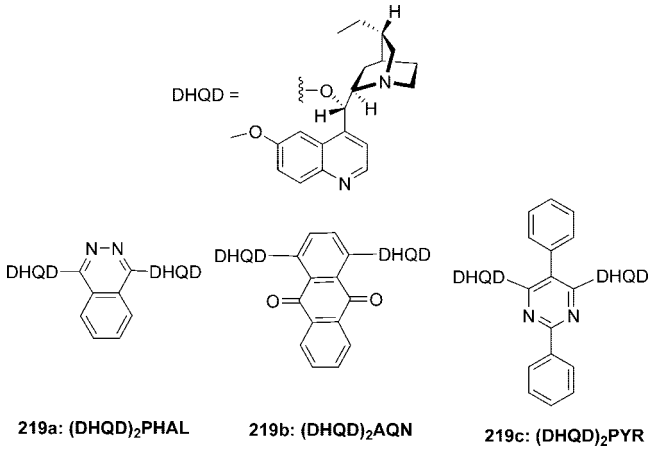
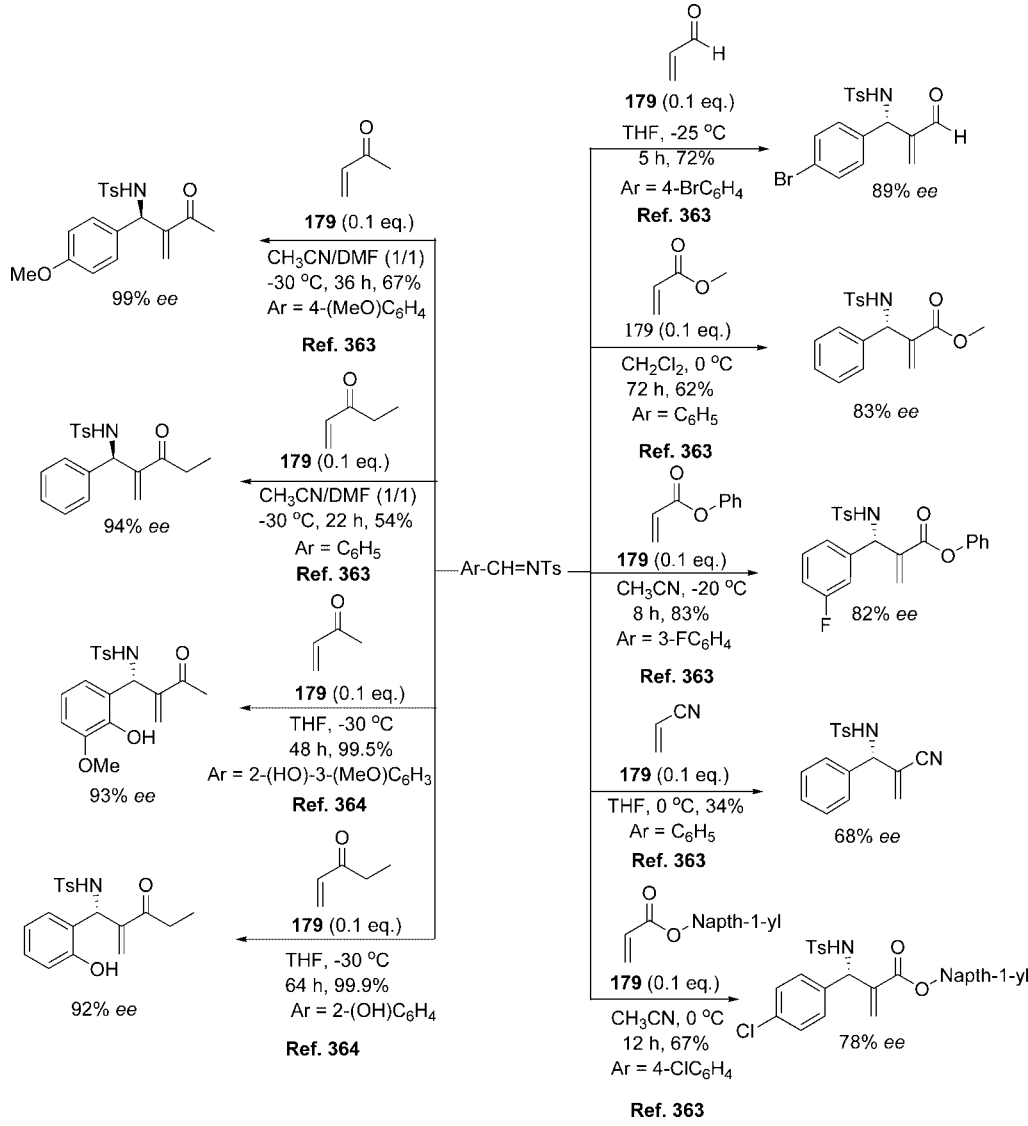


Figure 35.

Scheme 117



They also examined the applicability of various amino acid−peptides and concluded that the peptide **226a** and proline combination provided better selectivity up to 81% ee in the coupling between various aromatic aldehydes and MVK (eq 50).

Subsequently Zhao and Zhou[373−375] synthesized various chiral diamines and amino alcohols (**227**−**230**) (Figure 39) and studied their applicability in combination with L-proline as cocatalyst for performing Baylis−Hillman reaction between representative aromatic aldehydes and MVK. The resulting Baylis−Hillman alcohols were obtained in 31−83% enantiomeric purities. Selected examples are presented in Scheme 119.

Tan and co-workers[376] prepared various chiral imidazole catalysts (**231a**−**j**) (Figure 40) for asymmetric Baylis−Hillman reaction and found that the catalyst **231i** provided better enantioselectivities for the coupling of aromatic aldehydes with acrylates and alkyl vinyl ketones (Scheme 120).

Shi and co-workers[377,378] have, for the first time, developed an elegant bifunctional chiral catalyst, (*R*)-**232**, built on a chiral binaphthyl skeleton, for performing asymmetric Baylis−Hillman reaction between aldimine derivatives and MVK. The resulting Baylis−Hillman adducts were obtained in high enantiomeric purities. In this study, they observed that the presence of molecular sieves 4 Å resulted in improvement of yields (Path A, Scheme 121). Subsequently

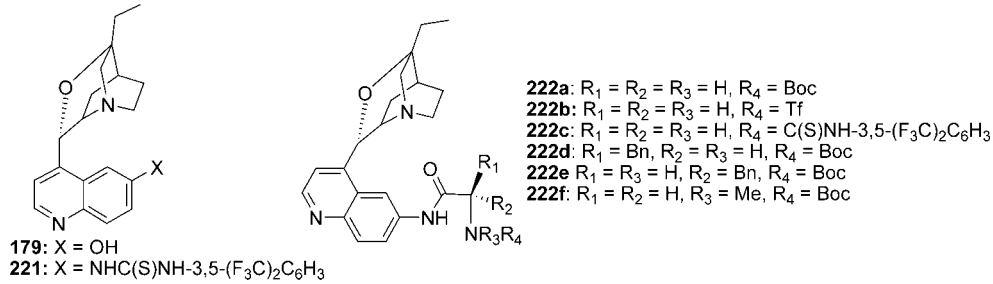


Figure 36.

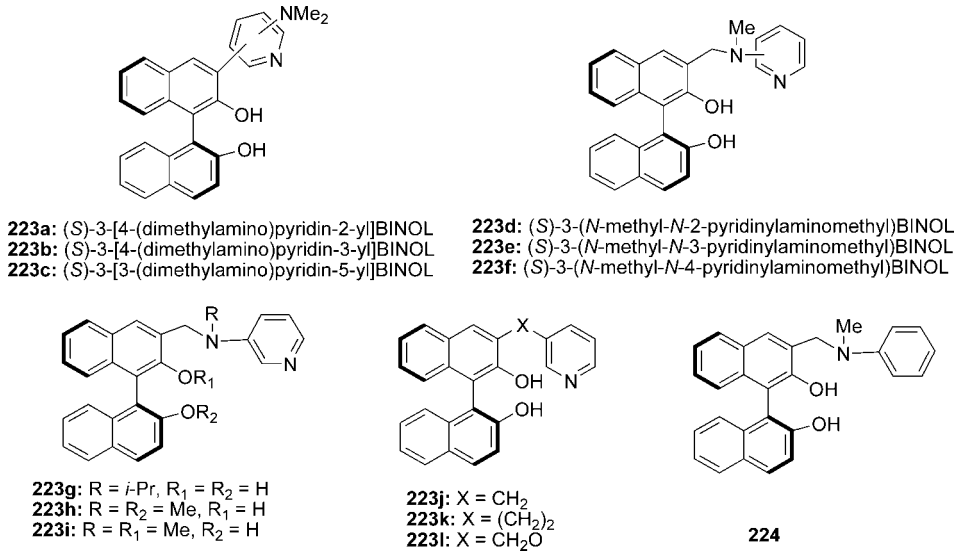
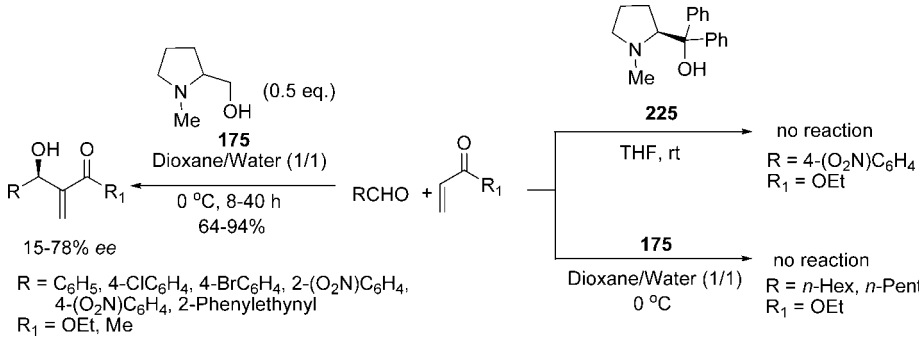
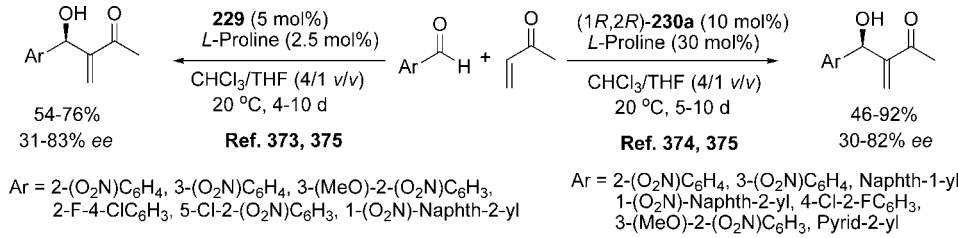


Figure 37.

Scheme 118



Scheme 119



the same strategy (presence of molecular sieves 4 Å) was extended to EVK (Path B, Scheme 121). They have also examined the application of this catalyst to phenyl acrylate and acrolein, as activated alkenes, which gave reasonably high enantioselectivities (Paths A and B, Scheme 122). When they extended the same strategy to methyl acrylate, the resulting products were obtained with low enantioselectivities (Path C, Scheme 122). Similar reactions with cyclopent-2-enone and cyclohex-2-enone using the catalyst (*R*)-**232** were not successful.[378,379] They noticed that the catalyst (*R*)-**233** provided high selectivity in the reaction between cyclopent-2-enone and N-sulfonated imines (Path A, Scheme 123) while in the case of cyclohex-2-enone the selectivities were low (Path B, Scheme 123).

Subsequently Shi and co-workers[380−390] have designed and synthesized a large number of chiral phosphine catalysts (**234**−**257**, Figures 41−43) built on a binaphthyl framework [(*R*)-**183**, **234**−**250**, and **253**−**257**] and also on cyclobutane (**251**) and ferrocenyl (**252a** and **252b**) skeletons. All these catalysts were examined for asymmetric Baylis−Hillman reaction between representative activated alkenes and electrophiles. The catalysts **238**, **244a**, **246c**, **249c**, and **250e** were found to offer better results. Representative examples are given in Scheme 124. From these studies, it is well established that in the absence of a second functional group (NH or OH) [(*R*)-**183**, **253**−**257**] enantioselectivities were very low (Scheme 125). When aldehydes were used as electrophiles, enantioselectivities were found to be inferior

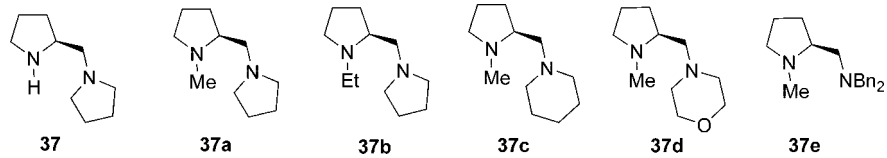


Figure 38.

to those of aldimine derivatives, and the best enantioselectivity of 56% was observed in the case of reaction between MVK and 3-phenylpropanal using the catalyst **241c**. Selected examples are presented in Scheme 126.

Sasai and co-workers[391] have successfully examined chiral phosphines **258**−**262** (Figure 44) as catalysts for asymmetric Baylis−Hillman reactions. The catalyst **258a** was found to be the best (Path A, Scheme 127). Ito and co-workers[392] synthesized and studied bisphenol-based bifunctional organocatalysts (**262a**−**d**) (Figure 44) for the asymmetric Baylis−Hillman reaction between aldimines and MVK. Catalyst **262c** provided high selectivity even with 1.0 mol %. Representative examples are given in Path B, Scheme 127.

Schaus and co-workers[393,394] have examined the applications of various chiral binaphthol derivatives (**185**, **263**−**266**) (Figure 45) as catalysts in the asymmetric Baylis−Hillman reaction of cyclohex-2-enone with aldehydes under the influence of PEt_3. From these studies, they observed that catalysts **264e** and **264f** provided high enantioselectivities in the case of aliphatic aldehydes while aromatic aldehydes provided inferior selectivities. Representative examples are shown in Scheme 128.

Sasai and co-workers[395] prepared heterobimetallic catalysts (**267a**−**d**) (Figure 46) for performing Baylis−Hillman reaction between cycloalkenones and aldehydes in the presence of tributylphosphine as cocatalyst and observed that aliphatic aldehydes provided better enantioselectivities while benzal-

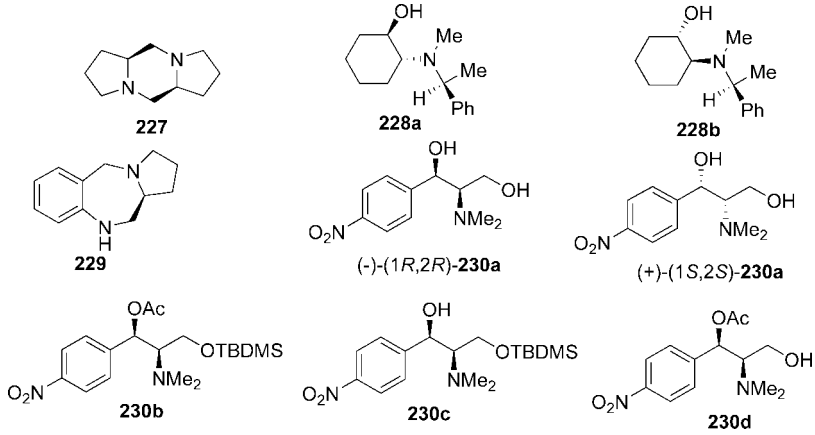


Figure 39.

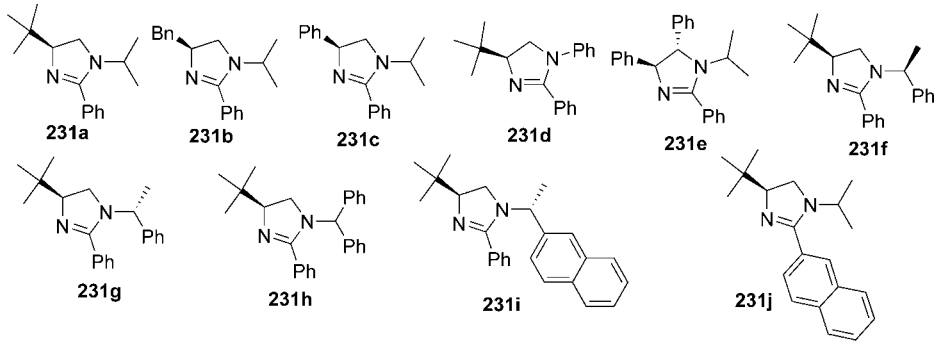
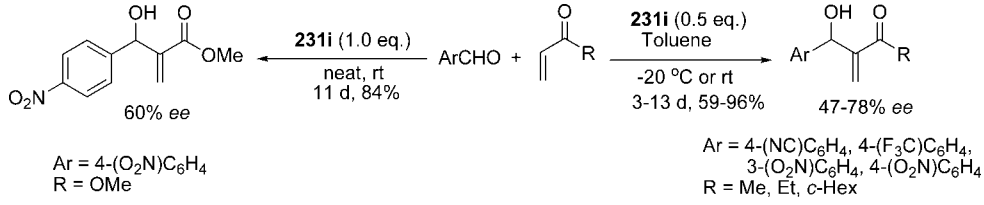
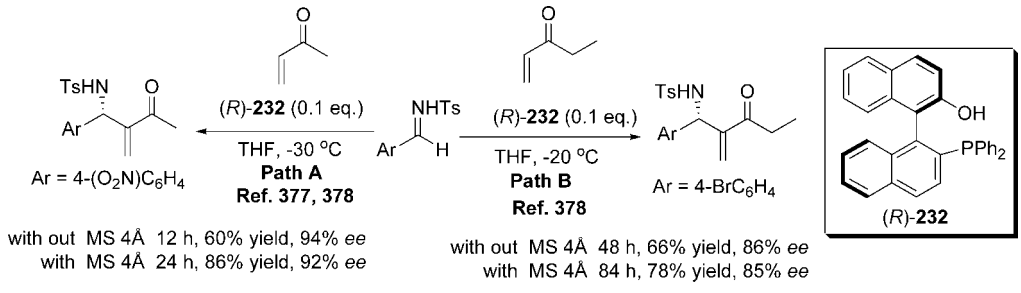


Figure 40.

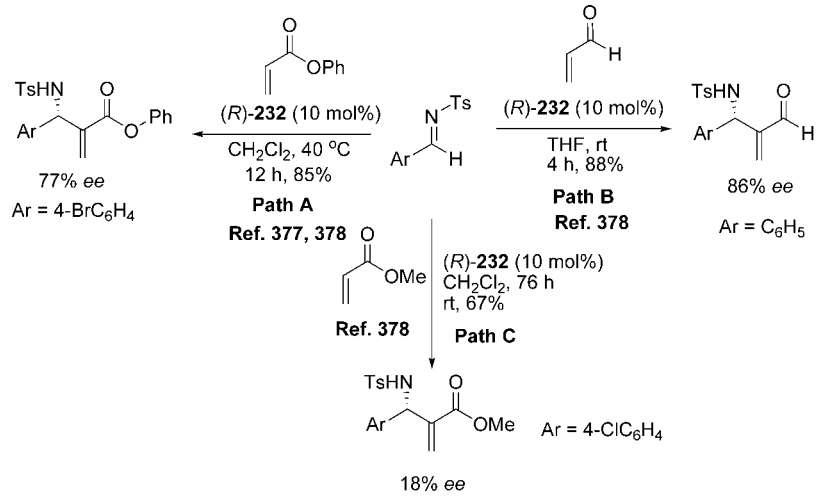
Scheme 120



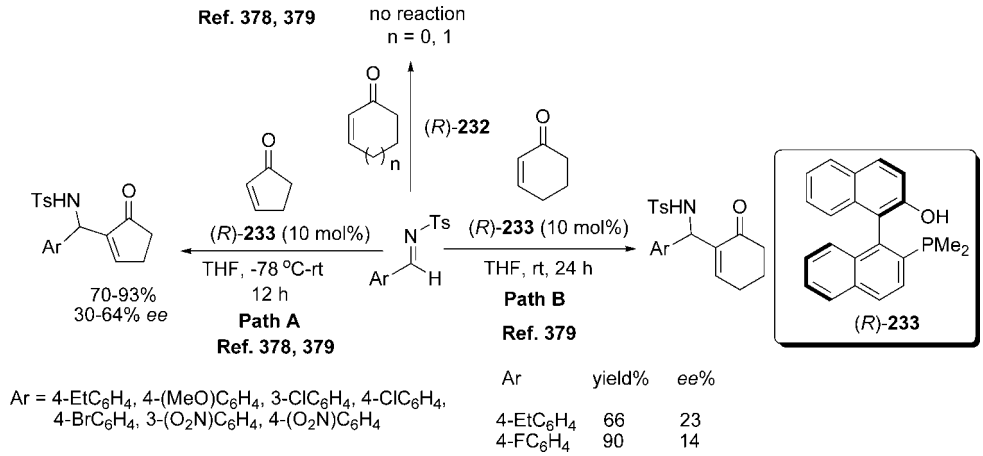
Scheme 121



Scheme 122



Scheme 123



dehyde gave low selectivity (Scheme 129). The highest selectivity in these studies was in the case of catalyst **267c**

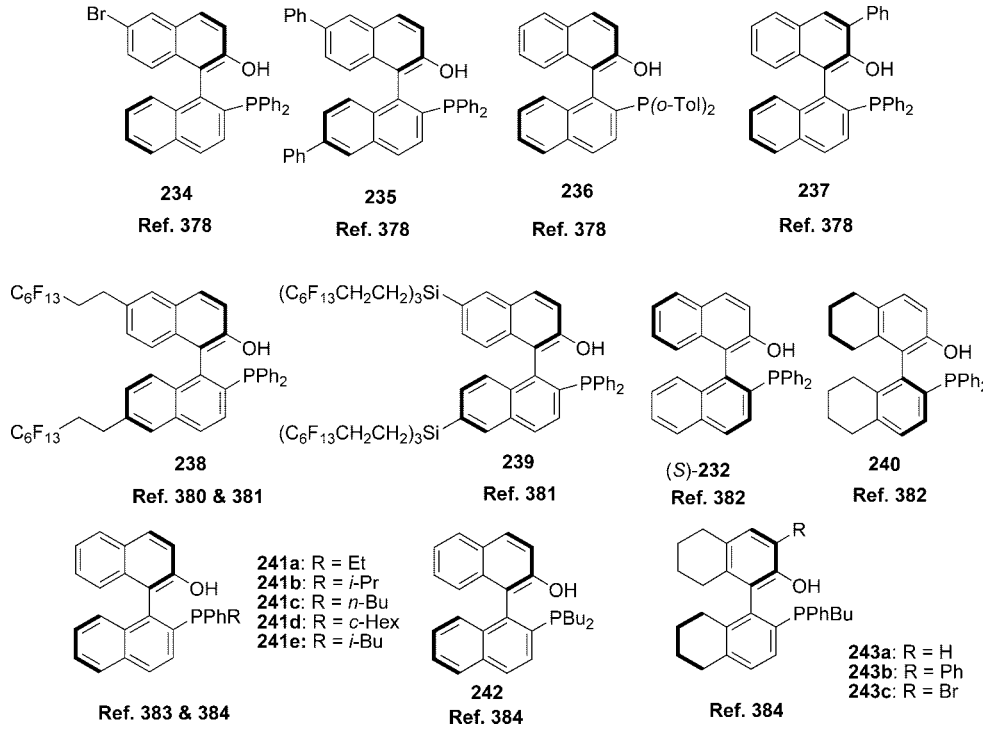


Figure 41.

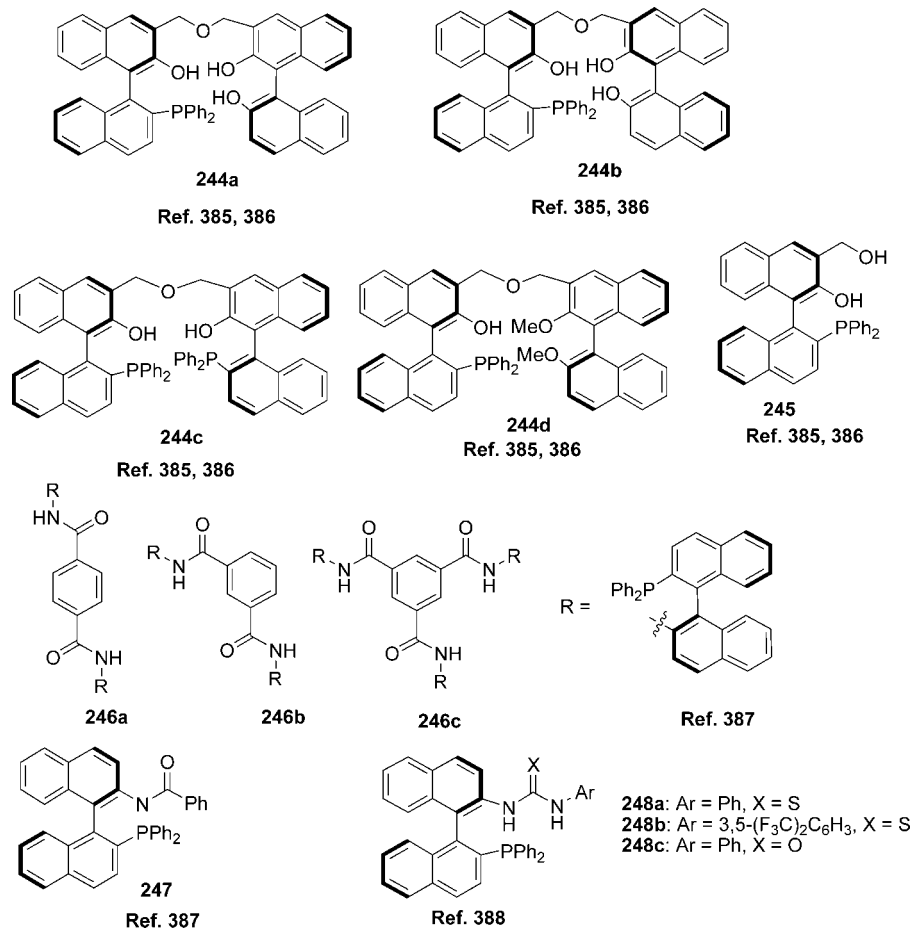


Figure 42.

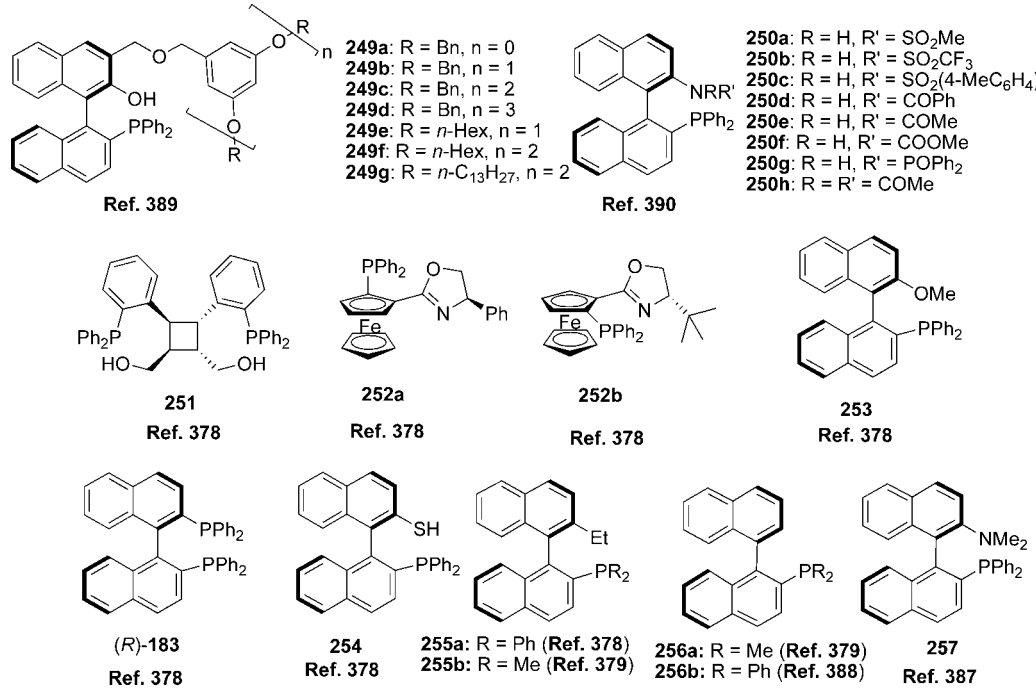
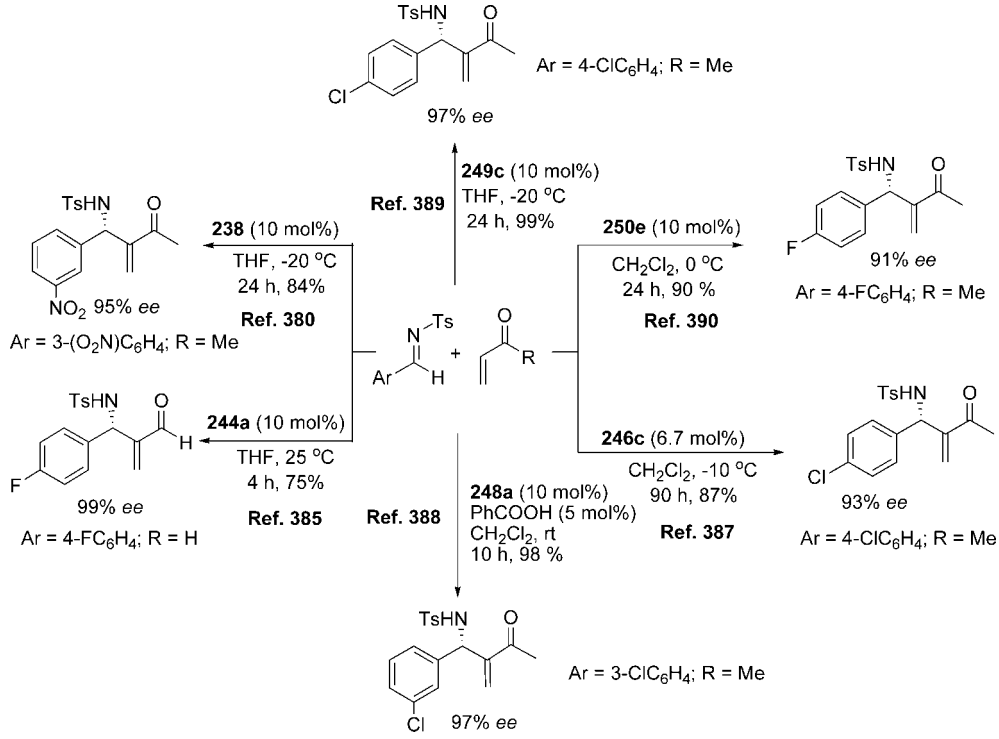


Figure 43.

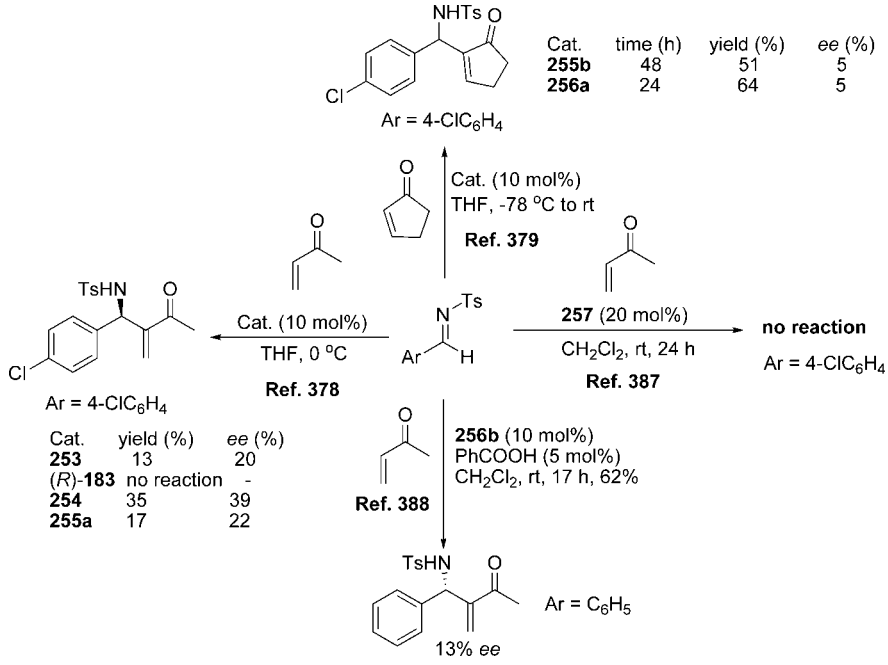
for the reaction between cyclohex-2-enone and 2-methylpropionaldehyde (R = *i*-Pr) providing the resulting adduct in 99% ee.

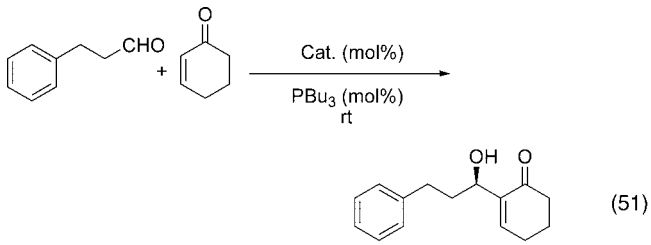
Gao and co-workers[396] have synthesized a series of new chiral triethoxysilane derivatives (**268a**−**f**) (Figure 47) based on a binaphthyl framework and immobilized them on mesoporous silica SBA-15 and amorphous silica gel (as a comparison) and examined their potential as chiral catalysts in the presence of tributylphosphine in the Baylis−Hillman reaction of 3-phenylpropanal with cyclohex-2-enone to provide the corresponding derivatives in good yield and poor enantioselectivities. It should be mentioned here that (*S*)-

Scheme 124



Scheme 125





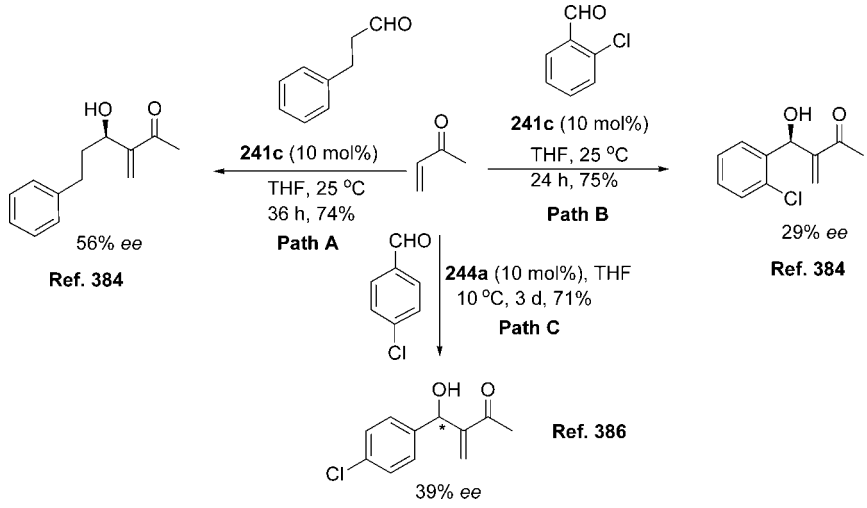
(51)

Cat.	Cat. (mol%)	PBu_3 (mol%)	time (h)	yield (%)	*ee* (%)
268a	10	20	72	88	23
(*S*)-**186**	16	10	48	89	32

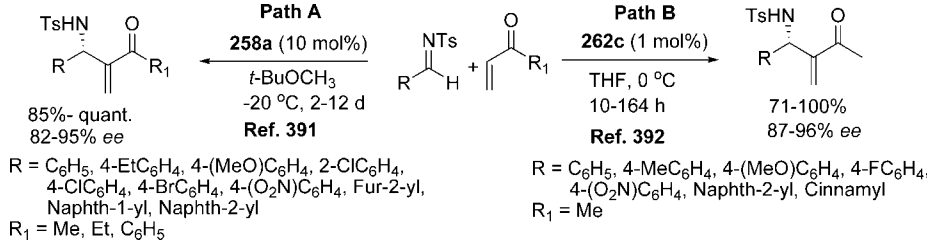
BINOL-Ca (**186**) provided better enantioselectivities than the catalyst **268a** in a coupling between cyclohex-2-enone and hydrocinnamaldehyde providing the resulting adduct in 32% ee (eq 51).

Vo-Thanh and co-workers[397] have reported, for the first time, the application of various chiral ionic liquids (**269a**−**c**), prepared from ephedrine (Figure 48), as a chiral medium for performing Baylis−Hillman reaction between aromatic aldehydes and methyl acrylate in the presence of DABCO. They have also examined the application of (−)-*N*-methylephedrine (**270**) as a chiral medium for asymmetric Baylis−Hillman reaction. Ionic liquid **269a** gave better selectivities (up to 44% ee) in Baylis−Hillman reaction

Scheme 126



Scheme 127



between benzaldehyde and methyl acrylate (Path A, Scheme 130). Subsequently, Leitner and co-workers[398] prepared ionic liquids (**271a**−**c**, Figure 48) from L-malic acid and used them as a chiral medium in asymmetric Baylis−Hillman reaction between aldimines and MVK in the presence of nucleophilic phosphine (PPh_3). The ionic liquid **271a** provided high enantioselectivity of 84% in the reaction between MVK and N-tosylated 4-bromophenylaldimine (Path B, Scheme 130). Very recently, Headley and co-workers[399] prepared three bistereogenic chiral ionic liquids (**272a**−**c**) and **273** (with

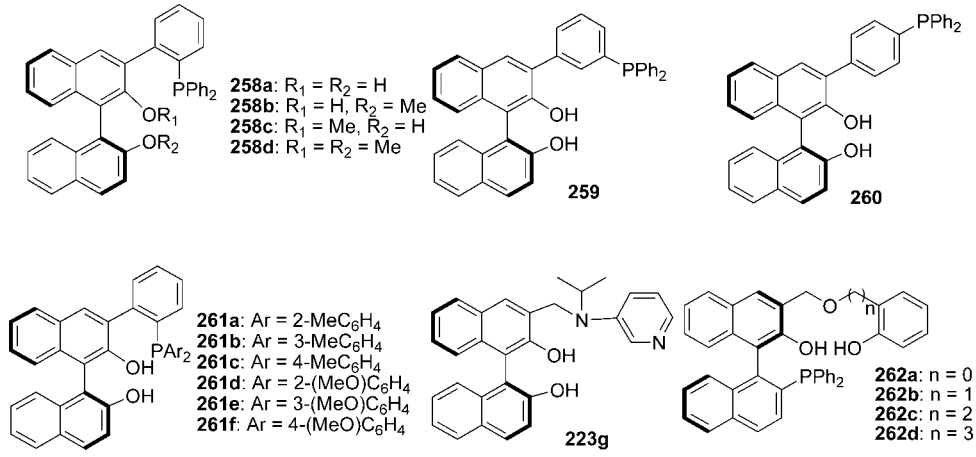


Figure 44.

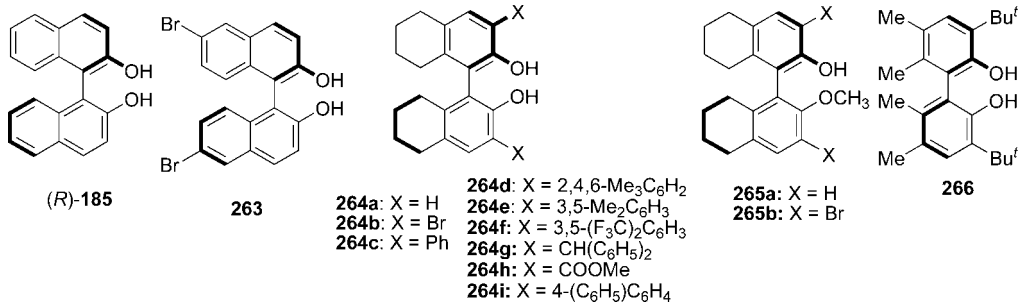
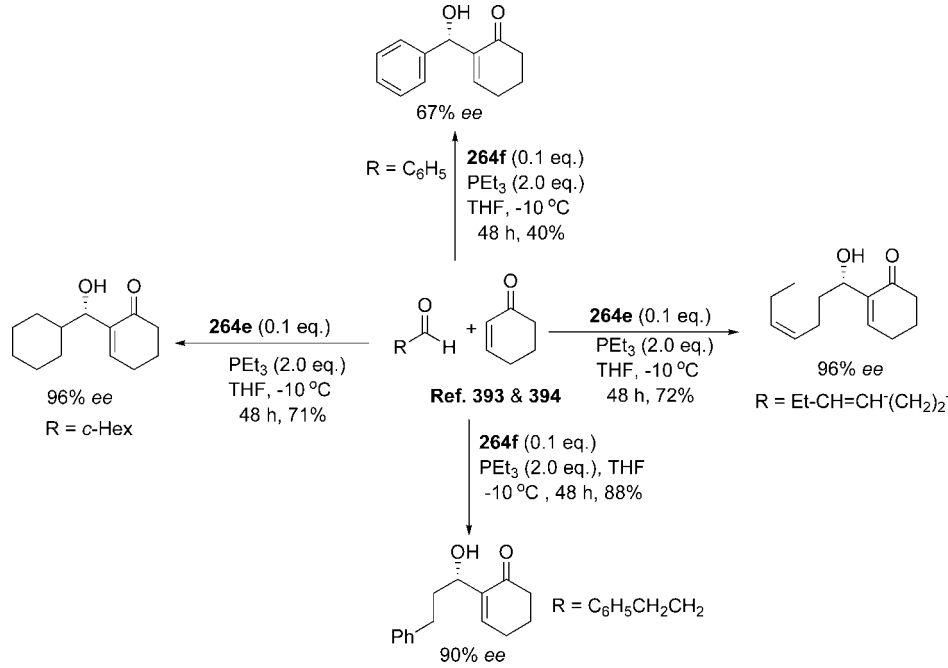


Figure 45.

Scheme 128



one chiral center) (Figure 48) and used them as chiral media for performing Baylis−Hillman reaction between aromatic aldehyde and acrylates under the influence of DABCO as a catalyst. However the resulting adducts were obtained in low enantioselectivities (Path C, Scheme 130).

Ye and co-workers[400] have prepared a series of chiral bifunctional *N*-heterocyclic carbene (NHCs) precursors (**274a**−**g**, Figure 49) containing a proximal hydroxyl group from pyroglutamic acid and used these carbene precursors as chiral catalysts for performing asymmetric Baylis−Hillman reaction between cyclopent-2-enone and phenyl-*N*-tosylamine in the presence of Cs_2CO_3 as a base. The highest selectivity of 44% ee was obtained using **274e** as ionic liquid for the coupling of cyclohex-2-enone with phenyl-*N*-tosylamine in the presence of Cs_2CO_3 (eq 52).

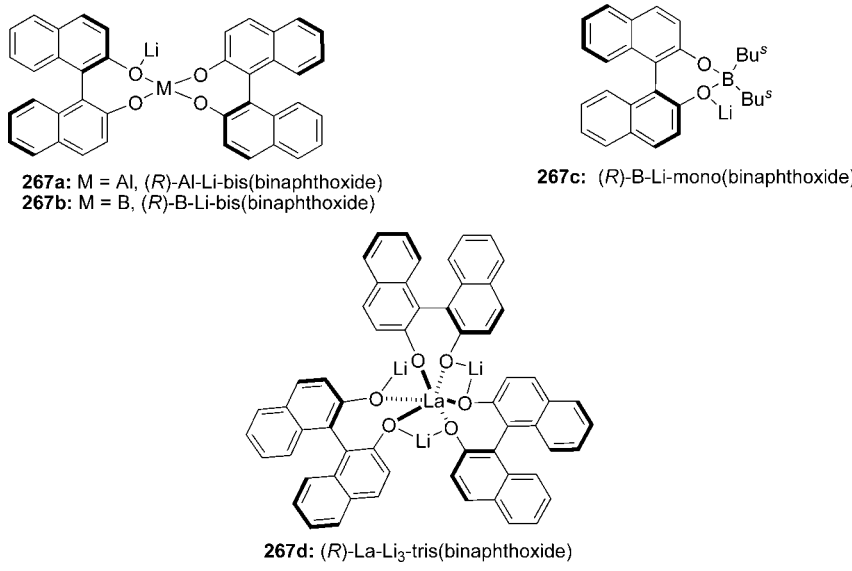
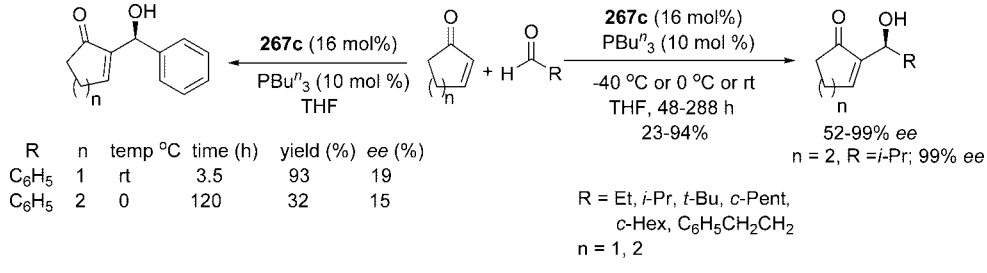


Figure 46.

Scheme 129



R	n	temp °C	time (h)	yield (%)	*ee* (%)
C_6H_5	1	rt	3.5	93	19
C_6H_5	2	0	120	32	15

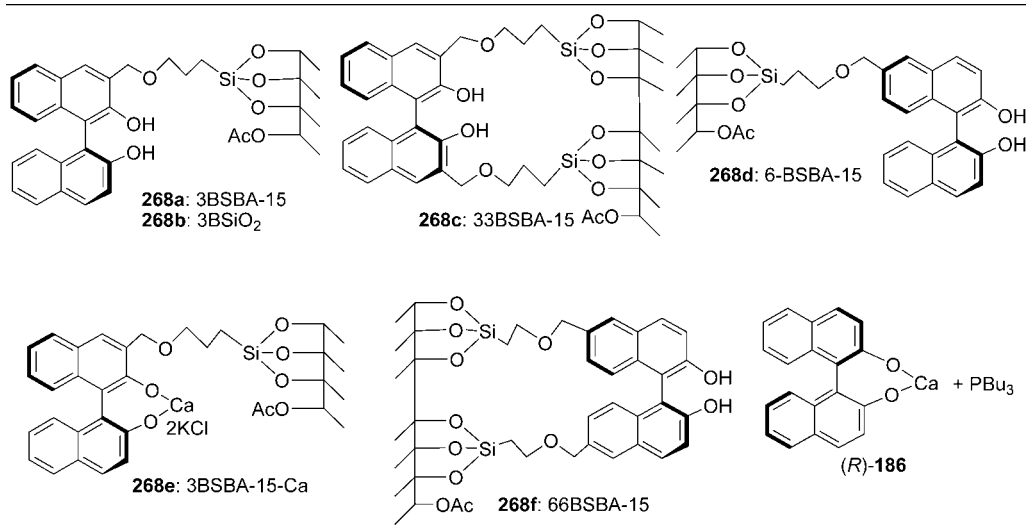


Figure 47.

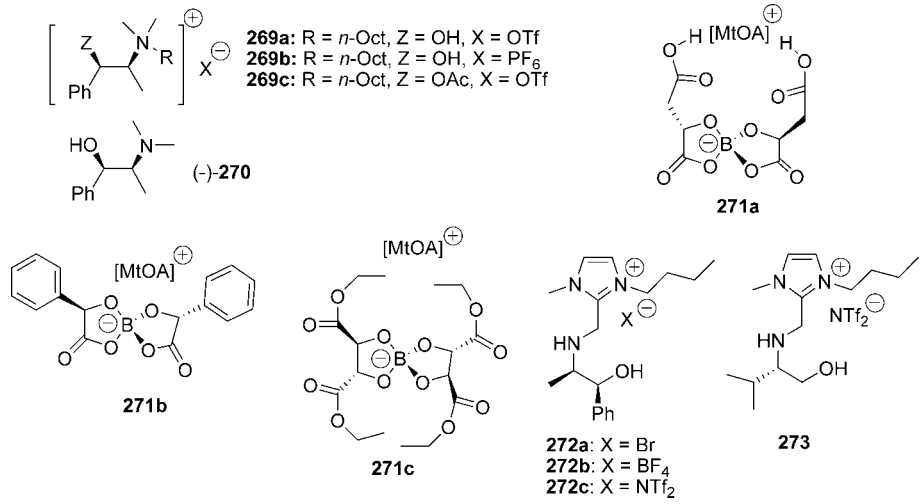


Figure 48.

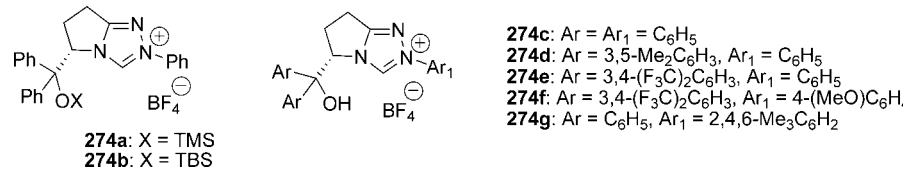
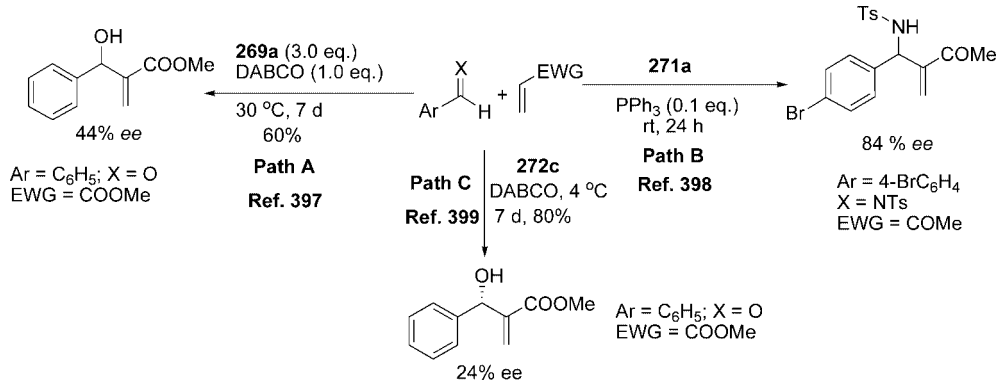


Figure 49.

Chen and co-workers[401] demonstrated the applicability of camphor-derived dimeric ligands (**275a**−**d**) (Figure 50) in association with Lewis acids for performing asymmetric Baylis−Hillman reaction between aldehydes and acrylates under the influence of DABCO. Selected examples are shown

Scheme 130



Chen and co-workers[401] demonstrated the applicability of camphor-derived dimeric ligands (**275a**−**d**) (Figure 50) in association with Lewis acids for performing asymmetric Baylis−Hillman reaction between aldehydes and acrylates under the influence of DABCO. Selected examples are shown

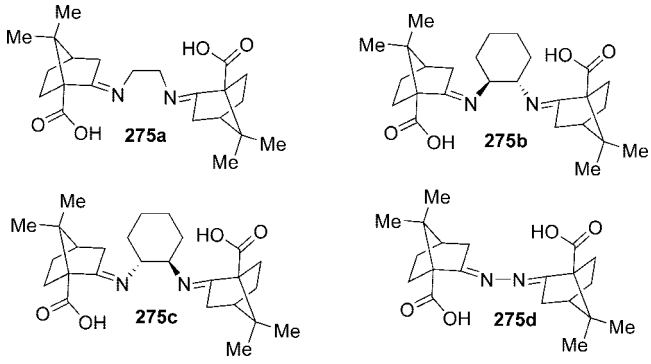
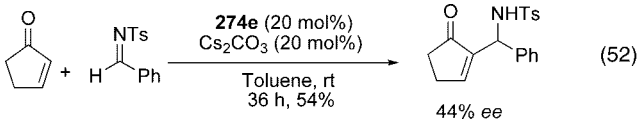


Figure 50.



in Scheme 131. A proposed transition state model for the enantioselective Baylis−Hillman reaction is shown in Figure 51.

After the elegant report on the remarkable rate acceleration of Baylis−Hillman reaction using the thiourea derivatives (**121** and **122**, Figure 22) along with DABCO by Connon and co-workers,[288,402] there has been increasing interest in developing an asymmetric version of the Baylis−Hillman reaction via the application of chiral thiourea derivatives in the presence of appropriate catalysts. Nagasawa and co-workers[403,404] have prepared representative chiral thiourea compounds (**276a**−**c**, Figure 52), examined their application in asymmetric Baylis−Hillman reaction, and found that the compound **276a** provided better selectivities. Thus, the coupling of cyclohex-2-enone with cyclohexanecarboxaldehyde under the influence of **276a** in the presence of DMAP provided the required Baylis−Hillman adduct in 90% enantiomeric purity. However, a similar reaction of cyclohex-2-enone with benzaldehyde provided the required product in low selectivities (Scheme 132).

Subsequently, Jacobsen and Raheem[405] systematically studied the applicability of a number of thiourea derivatives (**277**−**279**) (Figure 53) in asymmetric Baylis−Hillman reaction between aldimine derivatives and activated alkenes. The catalyst **279** was found to provide better selectivities. They have also transformed these enantiomerically enriched Baylis−Hillman adducts into β-amino acid derivatives, and one such example is shown in Scheme 133.

Wang and co-workers[406] have recently designed and synthesized representative binaphthyl-based chiral thiourea derivatives (**280a**−**c** and **281**) (Figure 54) with a view to examining their potential as catalysts for asymmetric

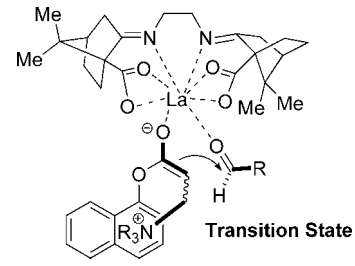


Figure 51.

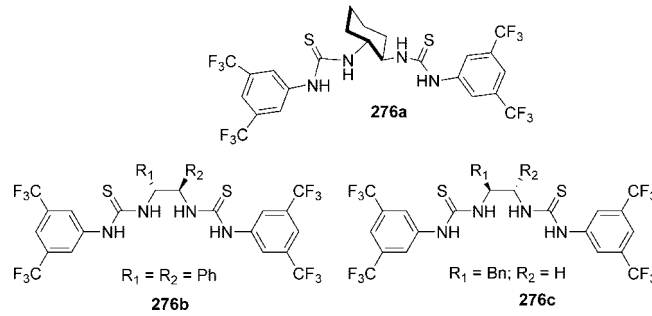
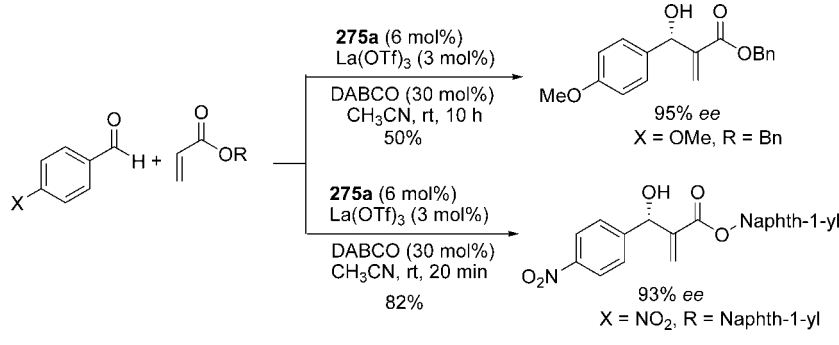


Figure 52.

Baylis−Hillman reaction. The catalyst **280c** provided encouraging selectivities, and one example is shown in Scheme 134. Very recently, isophoronediamine-derived bisthioureas (**282a**−**f**) (Figure 54) were conveniently used as catalysts for asymmetric Baylis−Hillman reaction of various aromatic and aliphatic carboxaldehydes with enones and acrylates (**282d** provided best results) by Berkessel and co-workers.[407] Amino alcohol derived thioureas (**283a**−**h**) (Figure 54) were also successfully utilized as catalysts for asymmetric Baylis−Hillman reaction of cyclohex-2-enone and aldehydes in the presence of triethylamine under solvent-free conditions by Lattanzi (**283f** was found to be a superior catalyst).[408] During these studies, the necessity and importance of the hydroxyl group in the catalytic moiety (**283a**−**g**) to provide high selectivities, rather than using external alcohol as hydrogen-bonding donor, was also demonstrated. Representative examples are presented in Scheme 134.

Very recently Shi and Liu[409] synthesized novel bis(thio urea) catalysts (**284a**−**c** and **285a**−**h**, Figure 55) based on (*R*)-1,1′-binaphthyl-2,2′-diamine and (*R*)-(−)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (H_8-BINAM) frameworks, for performing asymmetric Baylis−Hillman reaction of cyclohex-2-enone or cyclopent-2enone with a wide range of aromatic aldehydes to provide the resulting adducts in high selectivities. One representative example is shown in eq 53. Recently Wu and co-workers[410] reported synthesis and applicability of various chiral phosphinothiourea organocatalysts (**286a**−**f**) (Figure 55) for the asymmetric

Scheme 131



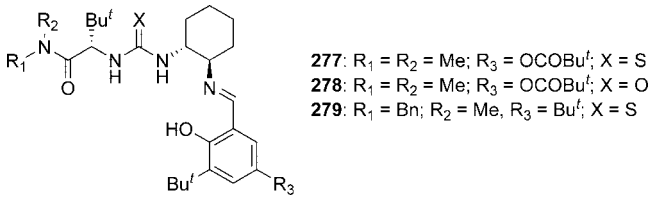
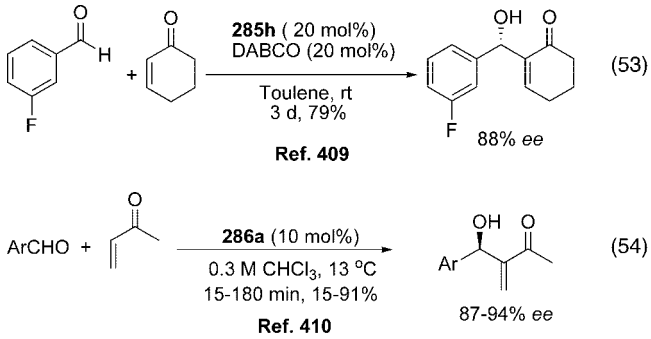


Figure 53.

Baylis−Hillman reaction between various aromatic aldehydes and MVK under very mild conditions at faster reaction rates in good yields with high enantioselectivities up to 94% ee (eq 54).



Cordova and co-workers[411] have reported a simple methodology for obtaining β-substituted Baylis−Hillman adducts via the reaction between β-mono- or disubstituted acrolein and aldimine derivatives under the influence of proline and DABCO. The corresponding adducts were obtained as a mixture of *E*- and *Z*-isomers in high enantiomeric purities. Representative examples are shown in eq 55.

Wang and co-workers[412] (for the first time) synthesized enantiomerically enriched thiochromenes from 2-mercaptobenzaldehydes by treating with α,β-unsaturated aldehydes under the catalytic influence of proline derivatives (proline, **37**, **287**−**289a**−**c**) (Figure 56) and observed that the catalyst **289b** gave better enantioselectivities (Path A). Subsequently, the research group of Wang[413] also extended this strategy to α,β-unsaturated oxazolidinones (**294**) for obtaining synthetically useful and medicinally important chiral thiochromanes under the catalytic influence of thiourea derivatives (**280c**, **281**, **292**, or **293**) and quinidine (**171**) (Figure 57) and found that the thiourea **293** provided better enantioselectivites (Path B). About the same time Cordova and co-workers also developed an interesting methodology for synthesis of 2*H*-1-benzothiopyrans[414] (Path C) and tetrahydrothioxanthenones[415] (Path D) following a similar strategy employing proline-based catalysts (proline, prolinol, **37**, **289a**,**b**,**d**,**e**, **290**, and **291**, Figure 56). Representative examples are shown in Scheme 135.

Aggarwal and co-workers[416] have reported *in situ* generated iminium ions as electrophiles for Baylis−Hillman coupling with various activated alkenes under the influence of TMSOTf and dimethyl sulfide to provide α-alkylated cyclic enones. They have also developed asymmetric version using chiral sulfide (**295**) to provide the resulting adducts up to 98% ee (Scheme 136).

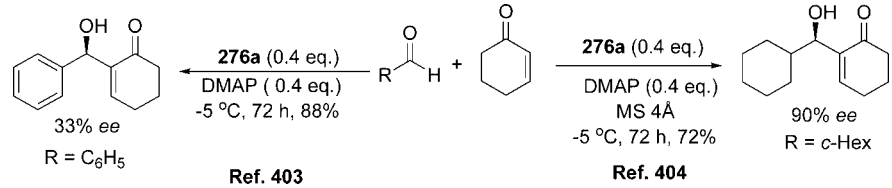
Li and co-workers[417a] have examined the application of chiral ligands (**185**, **191a**, **296**−**298a**, Figure 58) for performing the coupling of ethyl propiolate with various aromatic and aliphatic aldehydes under the influence of diethylaluminum iodide. The ligand **297** was found to offer better results thus providing the β-iodo substituted Baylis−Hillman adducts in up to 76% ee. Representative examples are shown in Scheme 137. Subsequently, the same research group[417b] also slightly modified this strategy for obtaining the same products via the reaction between ethyl propiolate with aldehyde under the influence of TMSI and lithium iodide in the presence of chiral catalysts (**186a**,**b**, **298b**, and **299**). In this case, it was found that **299e** provided better results (Scheme 137).

Ryu and co-workers[418a] very recently reported highly enantioselective synthesis of (*Z*)-β-iodo-Baylis−Hillman adducts by the treatment of aldehydes with ethyl propiolate in the presence of TMSI under the catalytical influence of chiral oxazaborolidinium catalysts (**300a**−**d**). Subsequently, these adducts were further converted into (*Z*)-β-branched derivatives. Representative examples are presented in Scheme 138. It is worth mentioning here that Li et al. have previously reported synthesis of β-iodo-Baylis−Hillman adducts via treatment of allenolates with aldehydes using chiral oxazaborolidine catalyst.[418b]

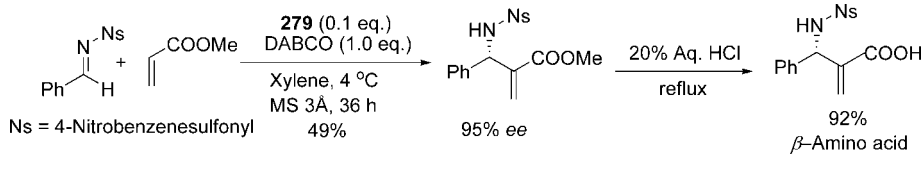
6. Kinetic Resolutions

The enantiomerically pure and enriched Baylis−Hillman alcohols were obtained via the kinetic resolution of the Baylis−Hillman alcohols via (1) a hydrogenation process using chiral catalysts, (2) biotransformations through transesterification or hydrolysis of the Baylis−Hillman adducts or derivatives, and (3) oxidation using horseradish peroxidase (HRP) (Scheme 139). Brown and Cutting[419] for the first time examined the kinetic resolution of the Baylis−Hillman alcohols via asymmetric hydrogenation

Scheme 132



Scheme 133



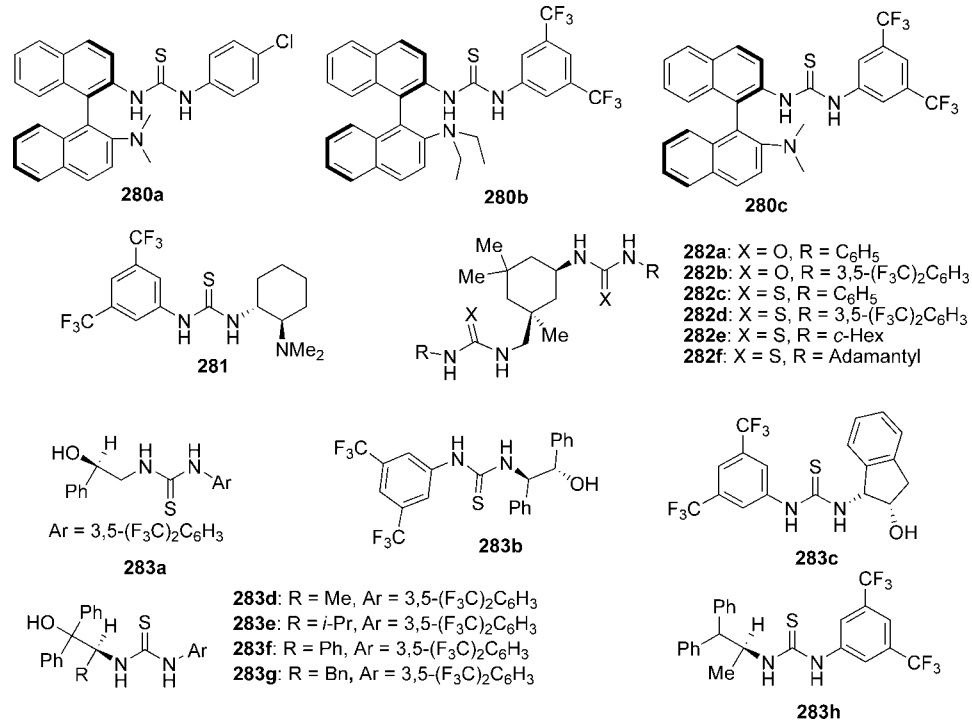
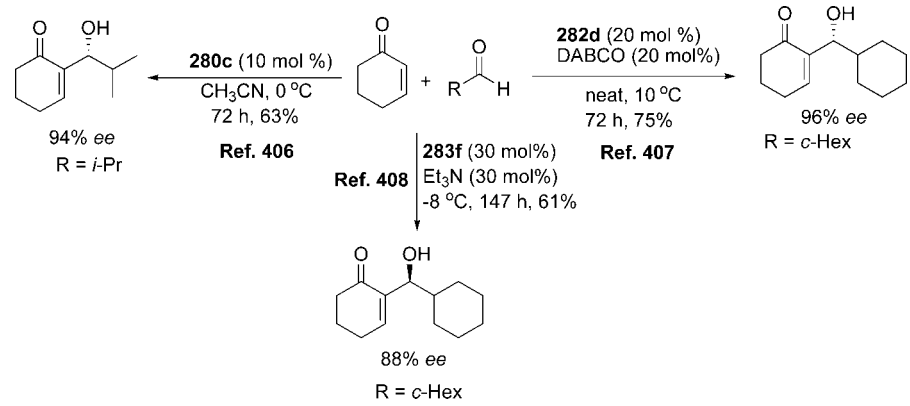


Figure 54.

Scheme 134



using chiral rhodium catalysts. Noyori and co-workers[420] have reported kinetic resolution of the Baylis−Hillman alcohols via asymmetric hydrogenation using (*S*)-BINAP-Ru diacetate complex. Burgess and Jennings[421] have described an interesting synthesis of Baylis−Hillman alcohols in high ee via transesterification using *Pseudomonas* AK. Our research group[422] has used crude enzyme PLAP for enantioselective hydrolysis of Baylis−Hillman acetates. Adam and co-workers[423] have successfully employed horseradish peroxidase (HRP) for enantioselective oxidation of Baylis−Hillman alcohols. Representative examples are given in Scheme 139.

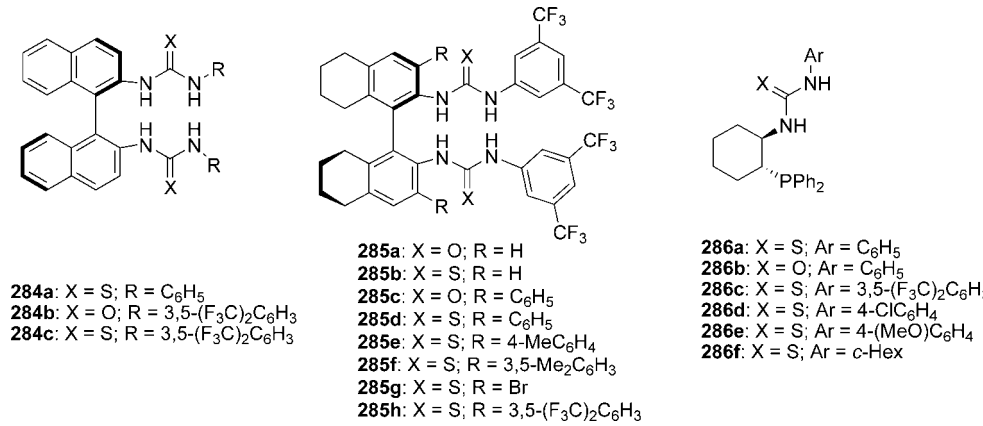


Figure 55.

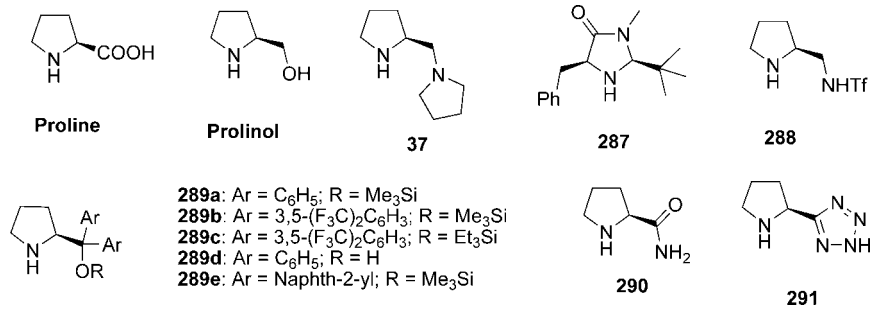


Figure 56.

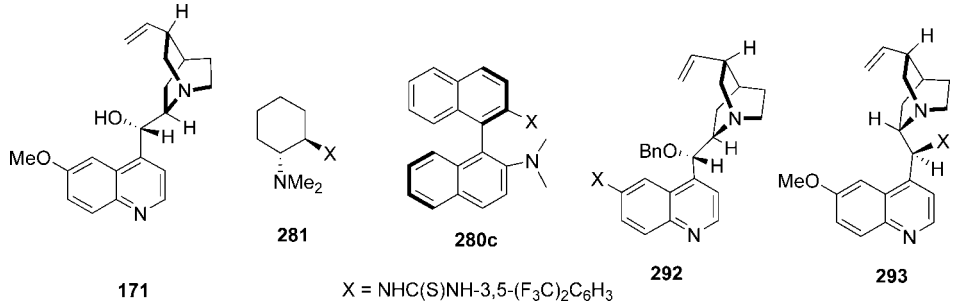
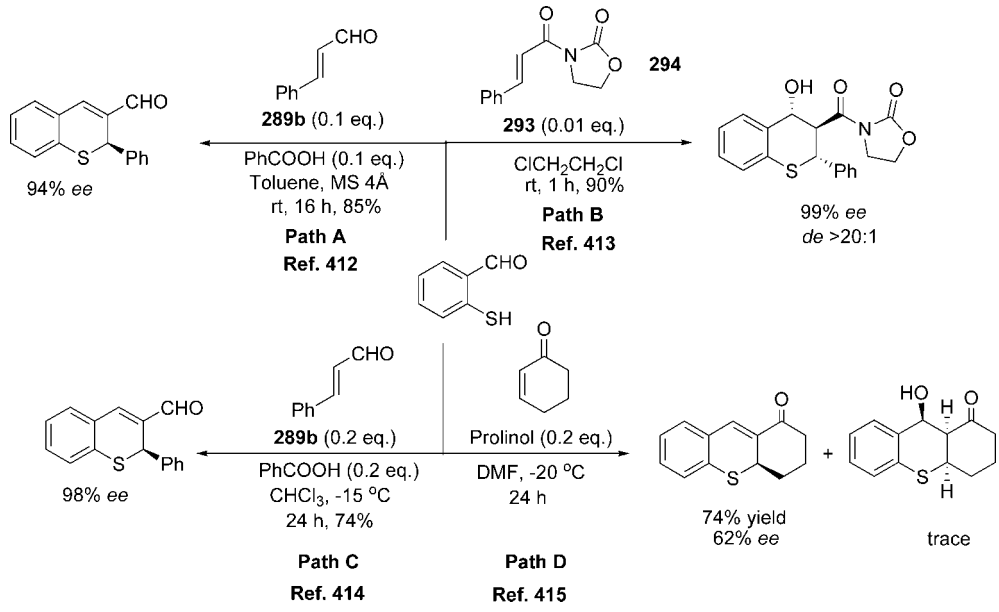
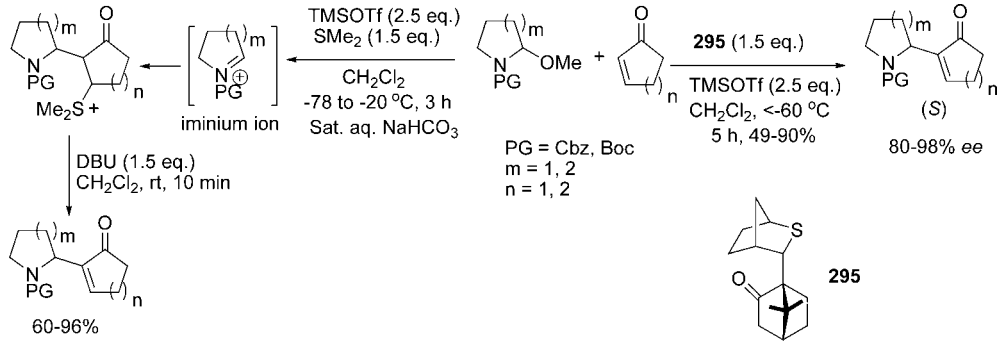


Figure 57.

Scheme 135



Scheme 136



Wang and Wu[424] successfully used nitrile hydratase/amidatase-containing *Rhodococcus* sp AJ270 cells for the hydrolysis of Baylis−Hillman adducts derived from acrylonitrile. They found that nitrile hydratase involved in the

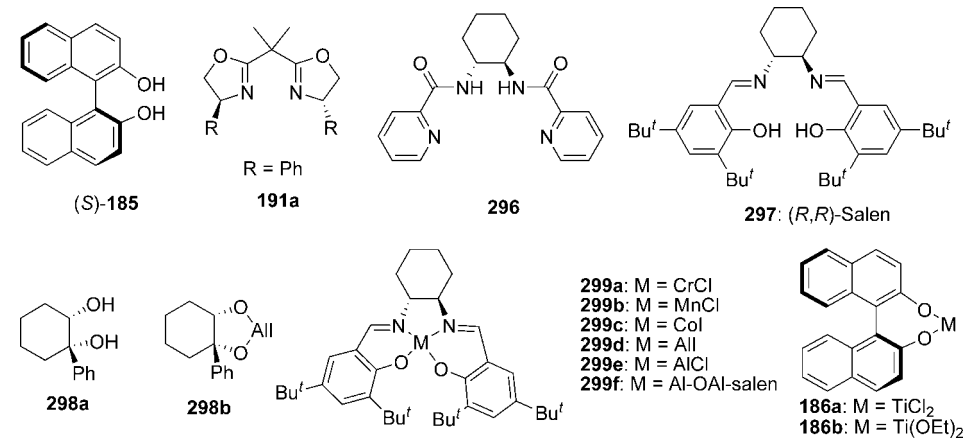
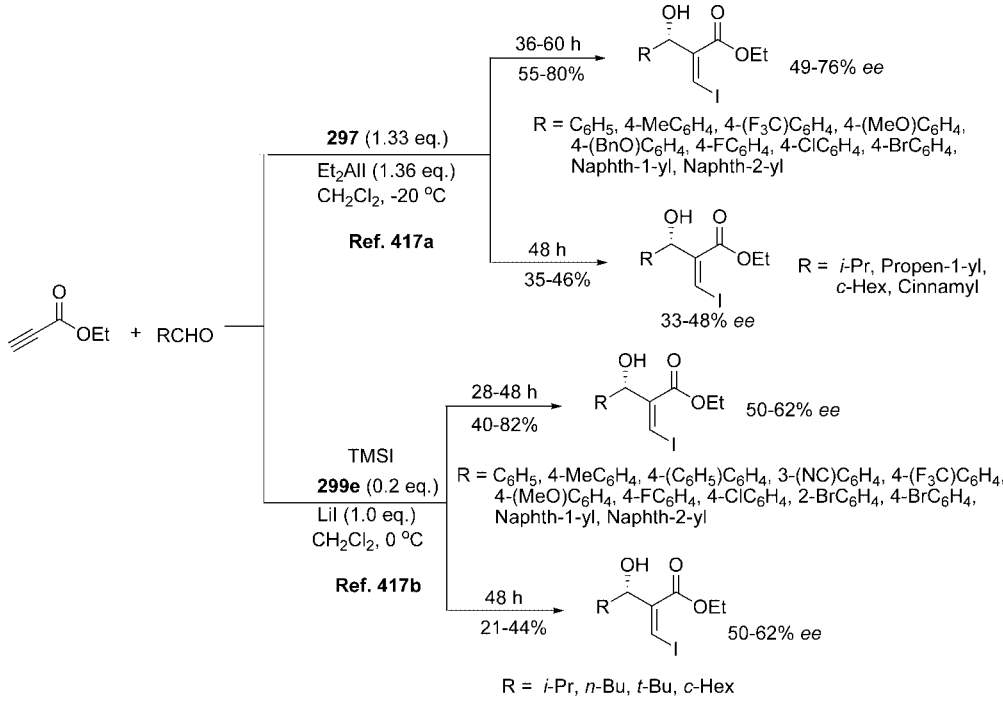
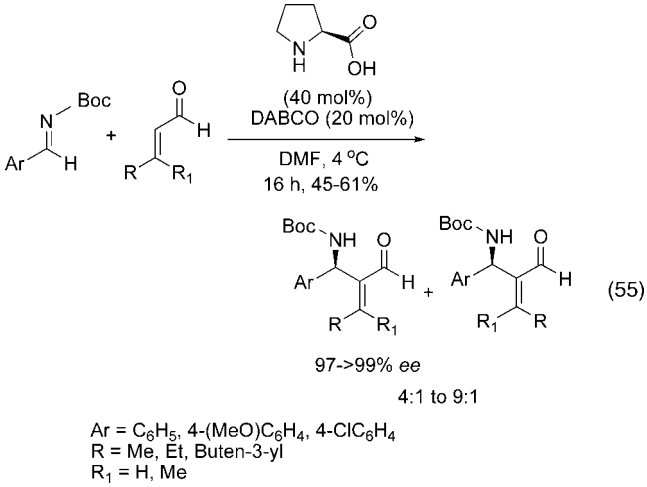


Figure 58.

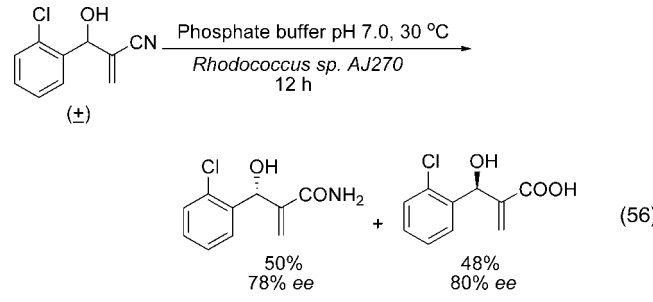
Scheme 137





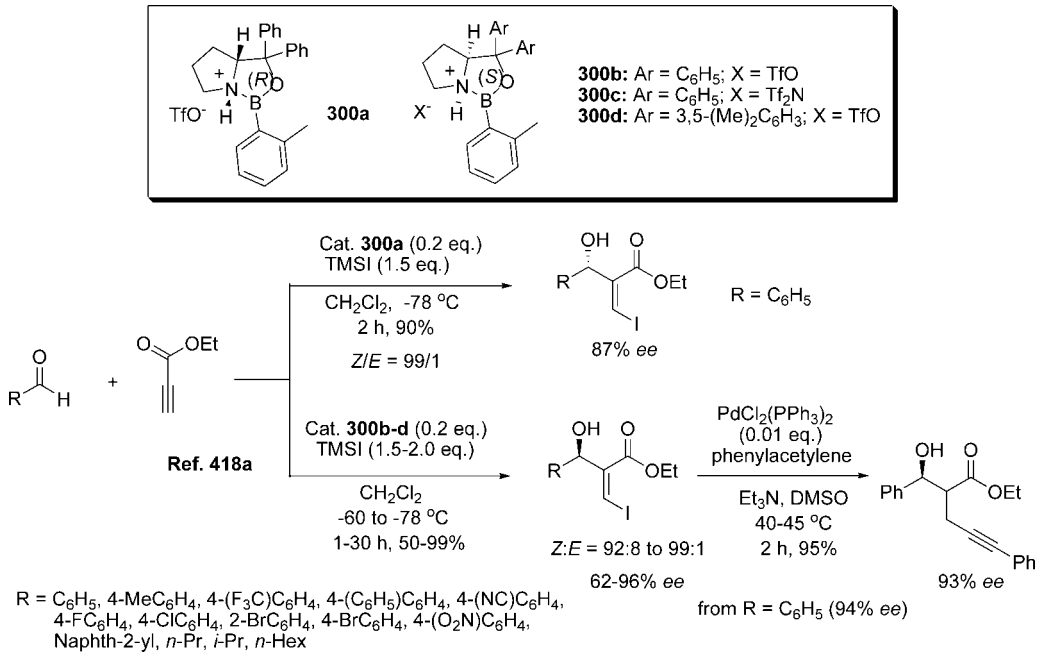
microbial cells showed almost no enantioselectivity against nitrile, while the amidatase exhibits *R*-enantioselection toward amide; a representative example is shown in eq 56.

Bhuniya and co-workers[425] used porcine liver esterase (PLE) for kinetic resolution of Baylis−Hillman adducts. They examined the effect of organic cosolvents and found that DMSO gave better results. Shorter times for hydrolysis provided the resulting acids in up to 75% ee (eq 57), while longer reaction time resulted in the production of Baylis−Hillman adducts in high enantiomeric purities.

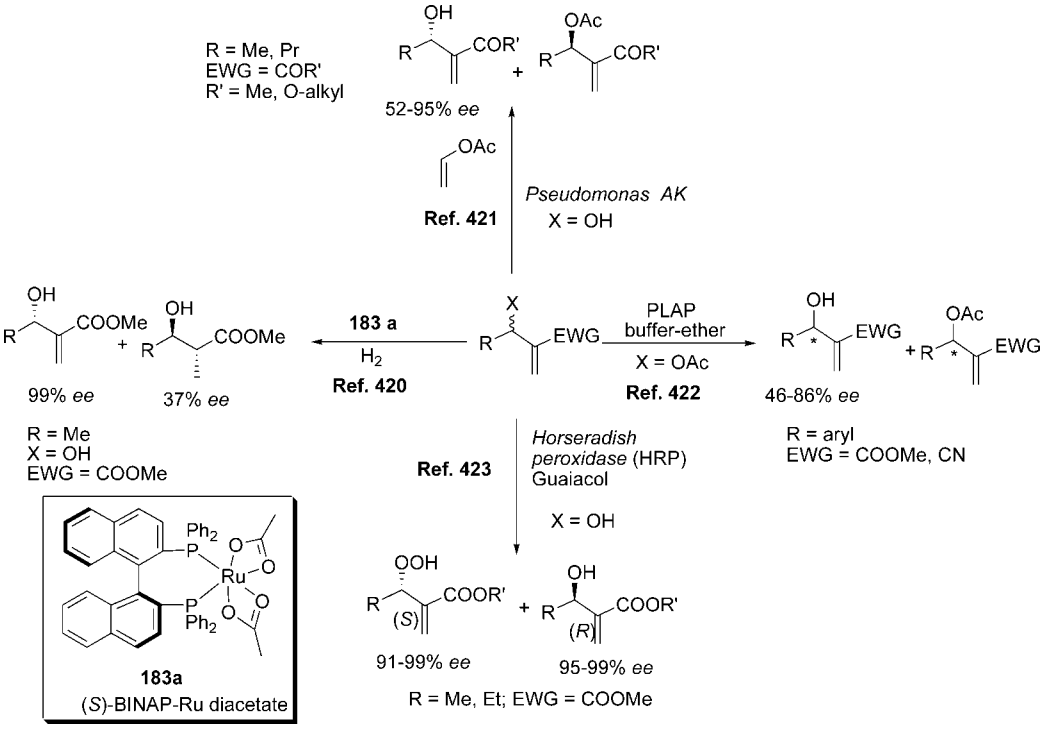


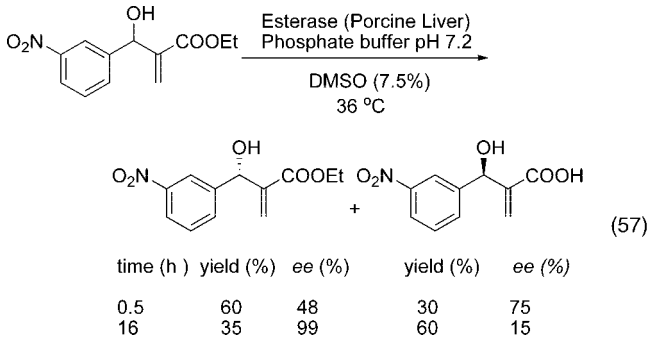
Nascimento and co-workers[426] used immobilized poly(ethylene oxide) *Pseudomonas* sp. lipase (PSL/PEO) for enzymatic enantioselective transesterification of Baylis−Hillman adducts to provide the resulting alcohols with up to 99% enantiomeric purities. The main advantage of this

Scheme 138



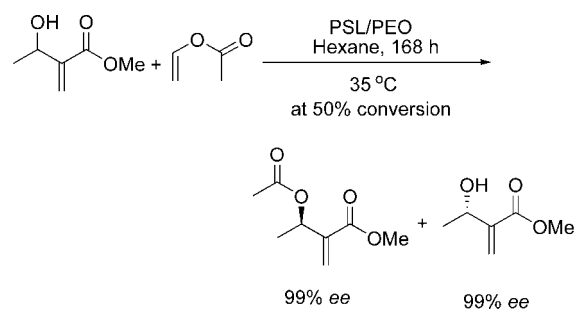
Scheme 139





(57)

process is recoverability and reusability of lipase PSL/PEO. One such example is shown in eq 58.



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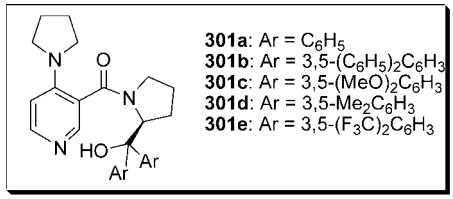
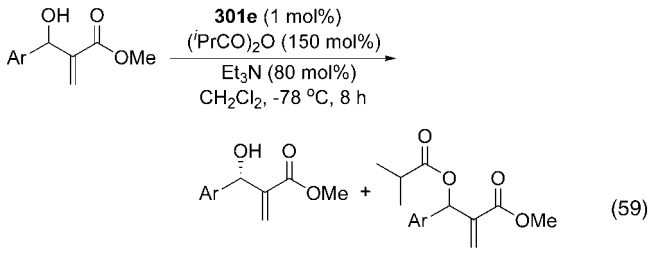
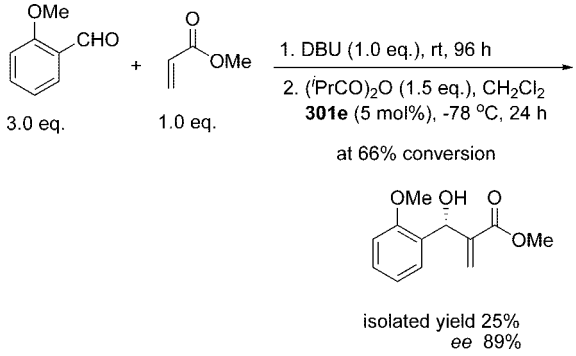




(59)

	conversion (%)	isolated alcohol yield (%)	*ee* (%)
Ar = C_6H_5	83	16	95
Ar = 2-(MeO)C_6H_4	64	35	97

Connon and Ó Dálaigh[427] synthesized organo-catalysts (**301a**−**e**) based on a chiral pyridine framework and used them for nonenzymatic acylative kinetic resolution of Baylis−Hillman alcohols. The catalyst **301e** provided encouraging results, and the unacetylated Baylis−Hillman adducts were obtained in high enantiomeric purities. Representative examples are shown in eq 59. They have also reported one-pot synthesis and kinetic resolution of the Baylis−Hillman adducts by acylation (eq 60).



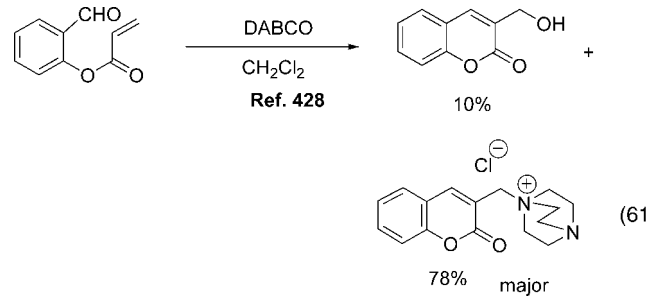
(60)

isolated yield 25%
ee 89%

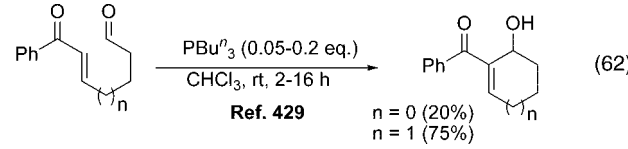
7. Intramolecular Baylis−Hillman Reactions

7.1. Cyclization of Activated Alkene−Aldehyde (Ketone, Imine, or Arene Complex) Systems

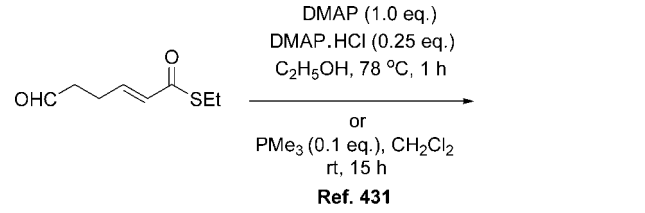
When a substrate contains an activated alkene component and an electrophile component at appropriate positions, there exists the possibility of performing an intramolecular Baylis−Hillman reaction. Such reactions in principle can provide carbocyclic or heterocyclic compounds in different ring sizes with functionality. Organic chemists, in fact, directed efforts toward this goal and examined various combinations of activated alkene (enal, enone, enoate, enamide, and vinyl sulfone) and electrophiles (mostly aldehydes) with a view to understanding the scope of intramolecular Baylis−Hillman reaction. Earlier developments[106,428−432] (before the year 2002) are pictorially presented in Schemes 140 and 141 and eqs 61−64. During the past few years, there has been increasing interest in this area of Baylis−Hillman reaction, and these developments are presented in this section.

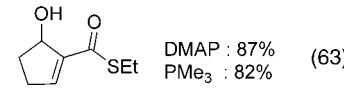


(61)

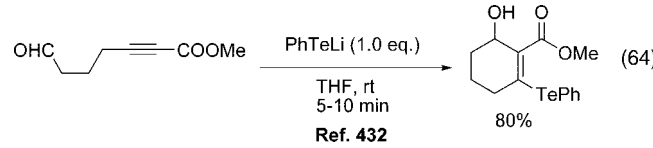


(62)





(63)



(64)

Koo and co-workers[433] described an interesting strategy for synthesis of ω-formyl-α,β-unsaturated carbonyl compounds and conveniently transformed them into a carbocyclic framework via intramolecular Baylis−Hillman reaction using PPh_3 as a promoter following the reaction sequence shown in Schemes 142 and 143.

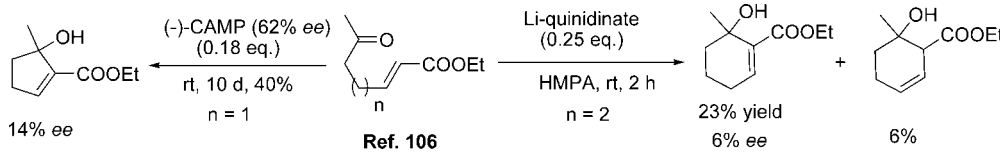
Krishna and co-workers[434] reported the diastereoselective intramolecular Baylis−Hillman reaction of chiral substrates (derived from sugar and amino acids) containing both the aldehyde and activated alkene components to afford α-methylene-β-hydroxylactones (Schemes 144 and 145).

Shi and co-workers[435] have studied systematically the influence of stereochemistry of the substrate (enone−aldehyde) for intramolecular Baylis−Hillman reaction using the catalyst **74** and found that the *Z*-isomer provided superior results (2.5−8.5 times higher yields) than the corresponding *E*-isomer. This remarkable reactivity difference is attributed to the steric factor, that is, addition of phosphine to the *cis*-isomer is more facile than to the corresponding *trans*-isomer (Scheme 146).

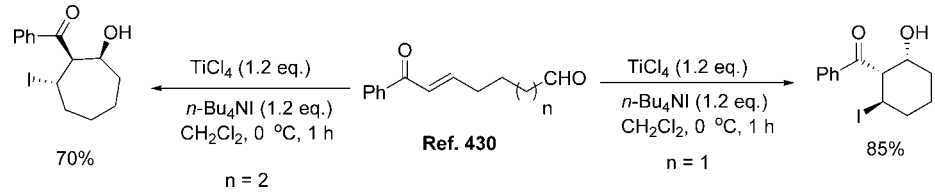
An elegant novel intramolecular Baylis−Hillman reaction leading to formation of new 1′,2′-dihydro-2,3′-biquinolines from quinolines was described by Trifonov and co-workers[436] following the reaction sequence shown in Scheme 147.

Pigge and co-workers[437] have successfully demonstrated the organometallic intramolecular Baylis−Hillman reaction. In this reaction, a ruthenium−arene complex is employed as an electrophile to provide the resulting spiro adducts with 100% diastereoselectivity (eq 65).

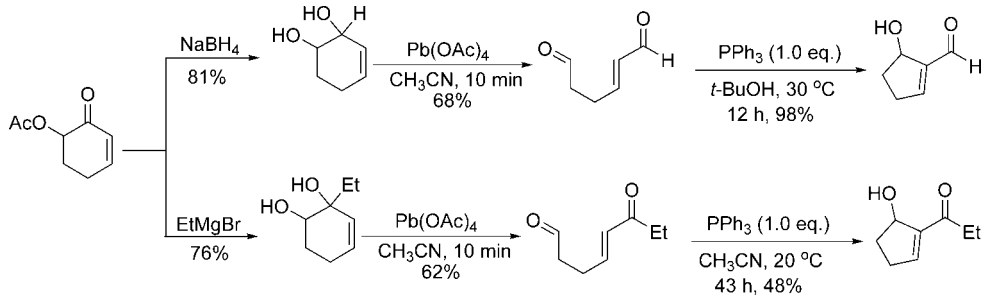
Scheme 140



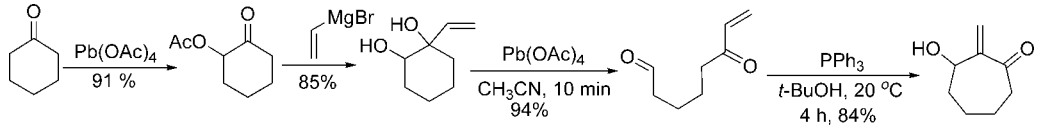
Scheme 141



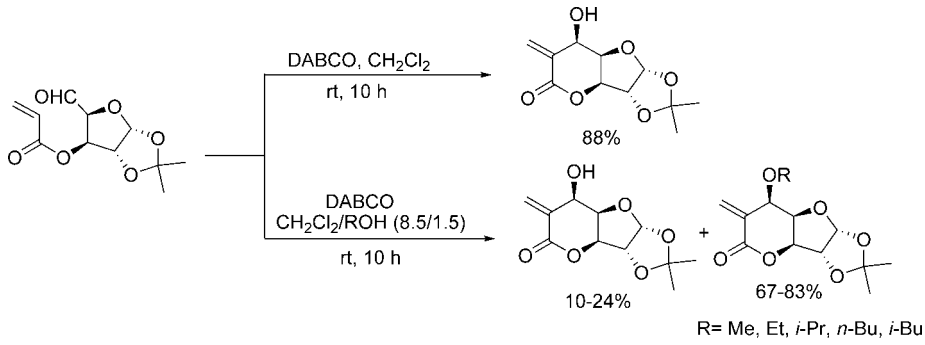
Scheme 142



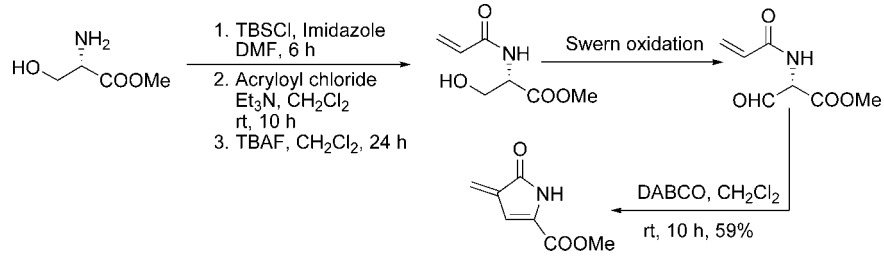
Scheme 143



Scheme 144



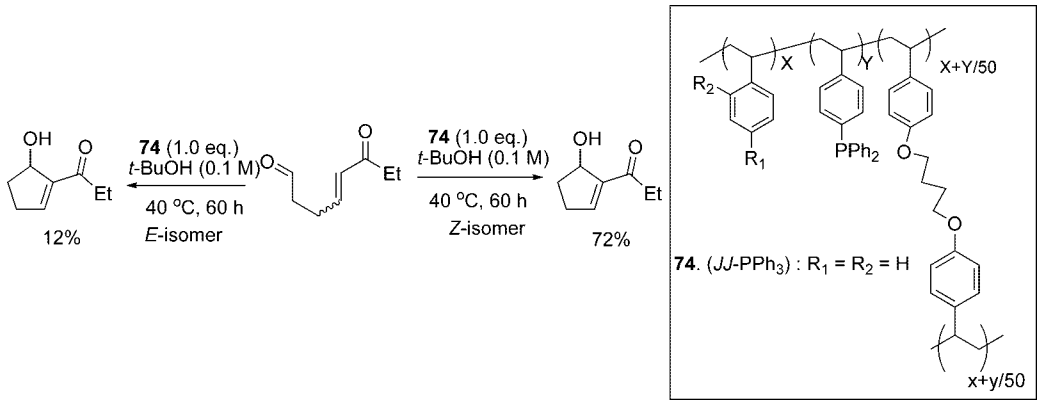
Scheme 145



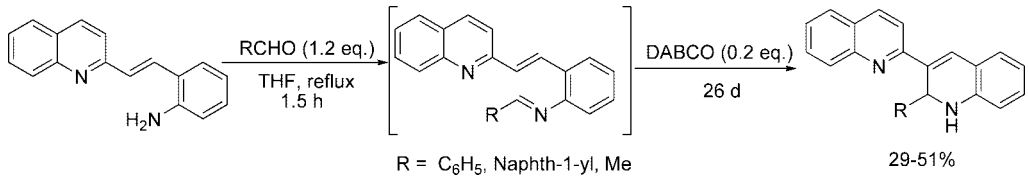
During the total synthesis of salinosporamide A (**302a**) and its biologically active analogue (**302b**), Corey and co-workers[438,439] have used intramolecular Baylis−Hillman reaction to obtain the required intermediate (**303**). They have also reported that the diastereomeric ratio of the products depends on the reaction conditions (Scheme 148).

Zhou and Hanson[440] reported intramolecular Baylis−Hillman reactions of *in situ* prepared vinyl sulfonamide−aldehydes of suitably protected amino alcohols to provide cyclic sulfones with good to excellent diastereoselectivity using DABCO as a catalyst (eq 66).

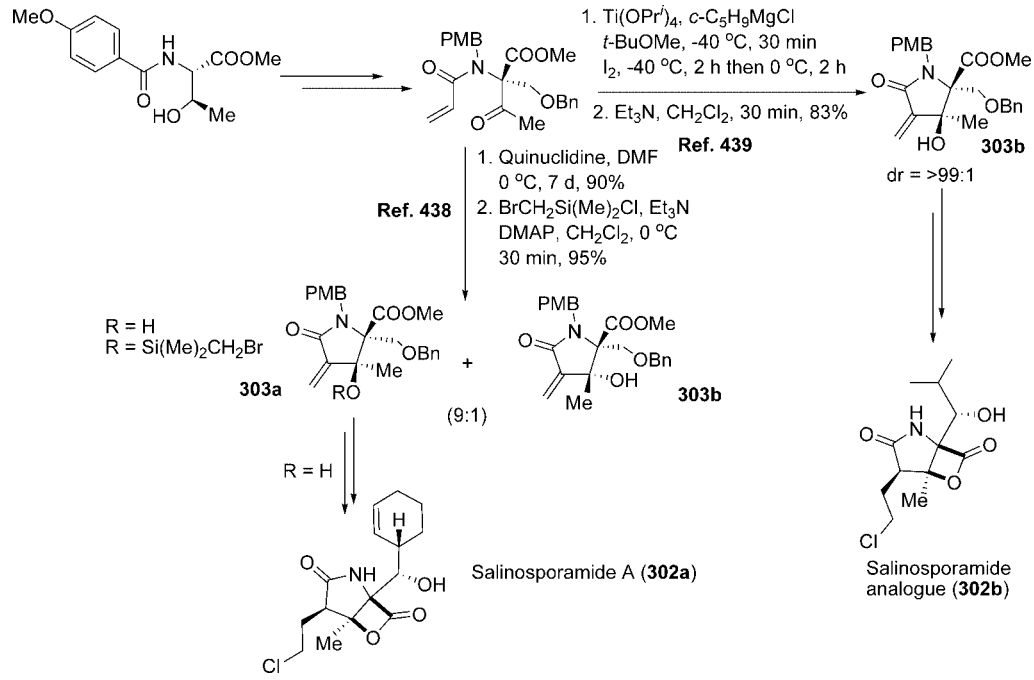
Scheme 146

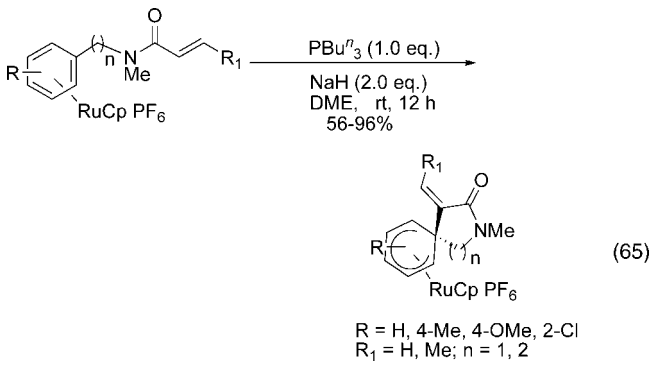


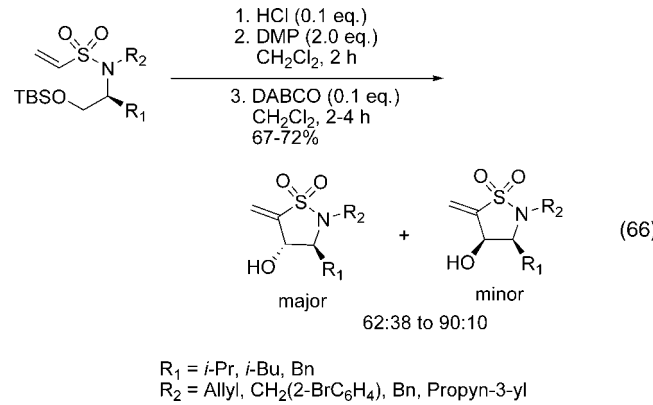
Scheme 147



Scheme 148

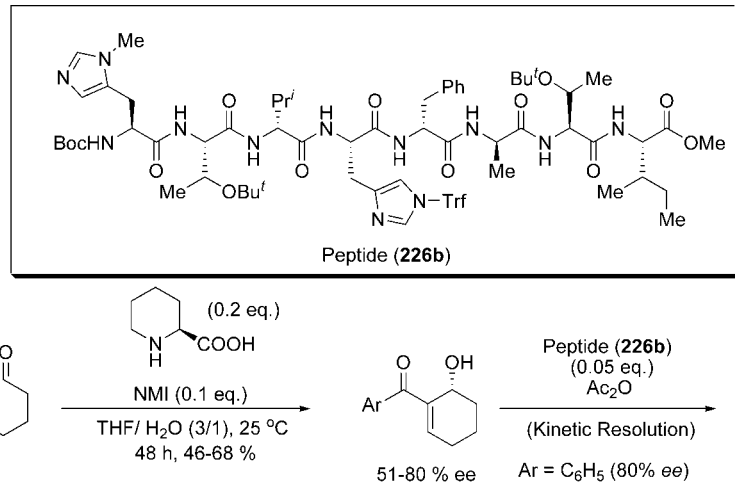




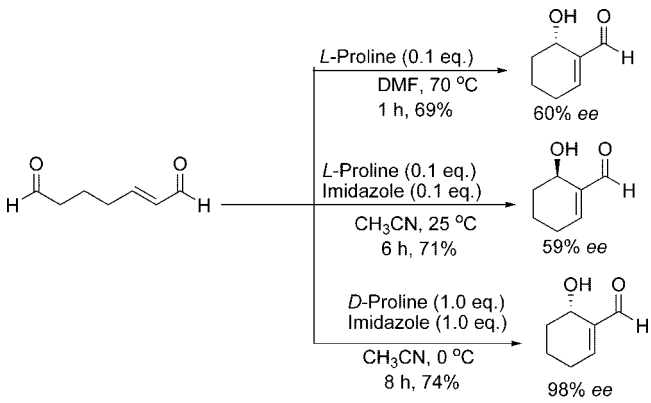


Seidel and Gladysz[441] have reported an interesting intramolecular Baylis−Hillman reaction using fluorous phosphine P[(CH$_2$)$_2$R$_{f8}$]$_3$ (**304**) as catalyst. It is important to note

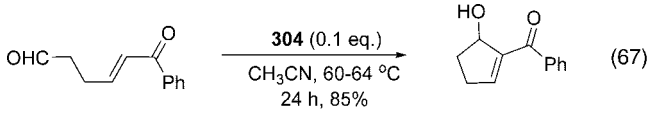
Scheme 149



Scheme 150



that fluorous phosphines were easily recovered. One example is shown in eq 67.



Miller and co-workers[442] reported an elegant asymmetric intramolecular Baylis−Hillman reaction of an enone−aldehyde system using a combination of (*S*)-pipecolonic acid and *N*-methylimidazole (NMI). In fact, they have also studied the combination of various amino acids and cocatalysts and found that pipecolonic acid−*N*-methylimidazole combination

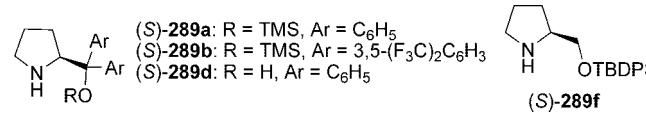


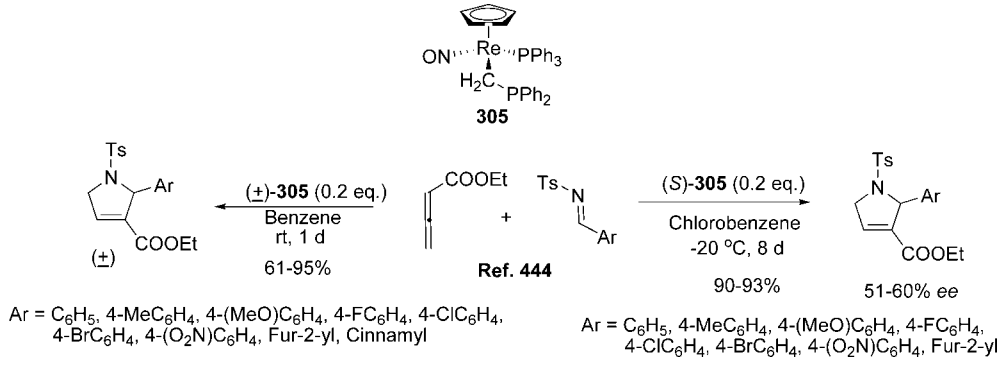
Figure 59.

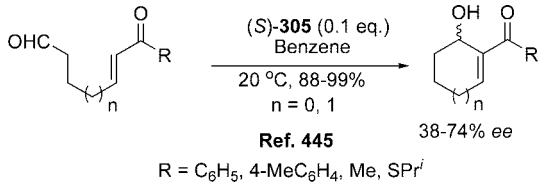
provided the best results (Scheme 149). They have also enhanced the enantiomeric purity of the resulting Baylis−Hillman alcohol (when Ar = Ph) via kinetic resolution using peptide **226b** with acetic anhydride (as acetylating agent) to provide the corresponding alcohol in 98% ee.

Subsequently Hong and co-workers[443] have reported proline-catalyzed intramolecular asymmetric Baylis−Hillman reaction of enal−aldehyde to provide the corresponding cyclic derivatives in 60−98% ee in moderate to high yields. Surprisingly, it was found that in the presence of imidazole, the stereoselectivity was reversed. Representative examples are given in Scheme 150.

Scherer and Gladysz[444] have used racemic and chiral rhenium-containing phosphines (**305**) as catalysts for performing reaction between *N*-tosylimine and allene esters to provide 2-aryl-3-ethoxycarbonyl-3-pyrrolines in racemic and enantioenriched forms, respectively, as shown in Scheme 151. Subsequently, Seidel and Gladysz[445] also successfully used (*S*)-rhenium-containing phosphine [(*S*)-**305**] as chiral catalyst for performing intramolecular Baylis−Hillman reactions of enone−aldehydes to provide the resulting carbocyclic compounds in moderate to good enantiomeric purities. Representative examples are shown in eq 68.

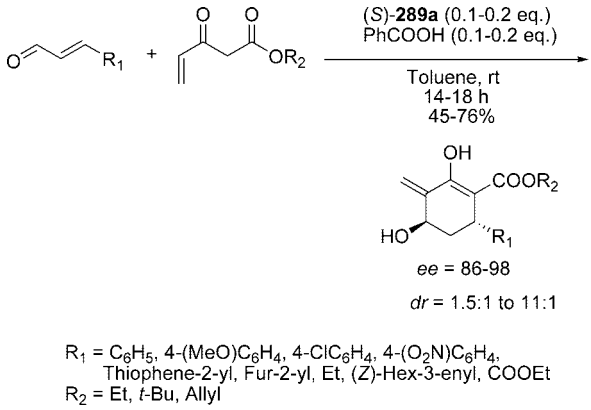
Scheme 151



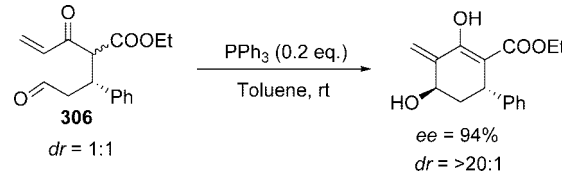


(68)

Jorgensen and co-workers[446] have developed a one-pot procedure for preparation of optically active cyclohexenol derivatives via the reaction of enones with 3-oxo-pent-4-enoates under the influence of catalysts (**289a**, **289b**, **289d**, and **289f**, Figure 59) involving Michael addition and intramolecular Baylis−Hillman reaction as the key steps (eq 69). A plausible mechanism is described in Scheme 152. In fact, they isolated the Michael intermediate **306** and performed the intramolecular Baylis−Hillman reaction using Lewis base (PPh_3) as a catalyst to provide functionalized cyclohexenol derivatives (eq 70).



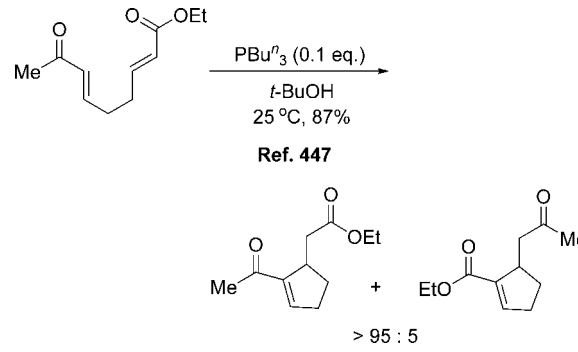
(69)



(70)

7.2. Cyclization of Activated Alkene−Activated Alkene (Allyl Halide, Allyl Carbonate, or Epoxide) Frameworks

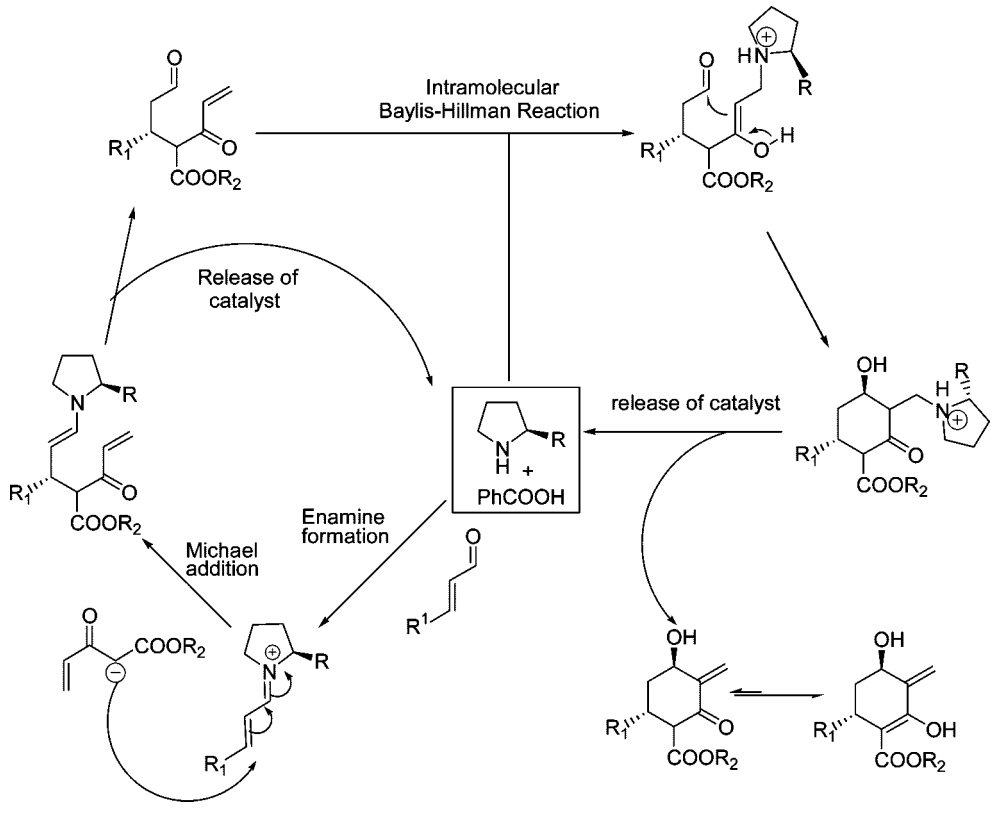
In addition to the above-mentioned strategies, various efforts have also been directed toward synthesis of various carbocylic or heterocyclic molecules via the intramolecular Baylis−Hillman cyclization of a number of substrates with several combinations such as enone−allyl carbonate, enone−vinyl sulfone, thioenolate−vinyl sulfone, enone−enone, enone−allyl halide, enone−halide, and enone−epoxide systems. Interesting developments made earlier[447−449] in this direction are described in Scheme 153 and eqs 71−74, and recent developments are also presented in this section.



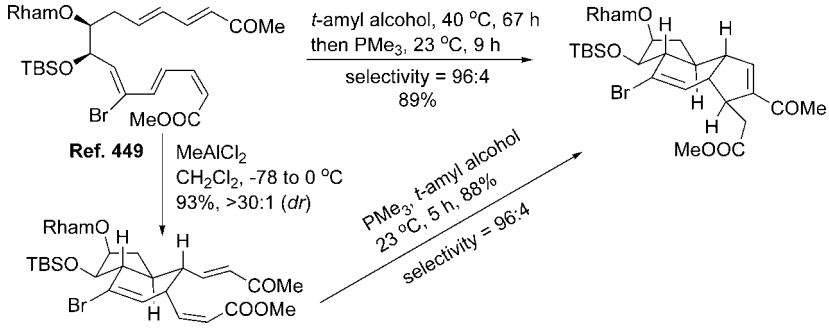
(71)

Murphy and co-workers[450,451] have reported intramolecular cyclization of bis-enones under the catalytic influence of

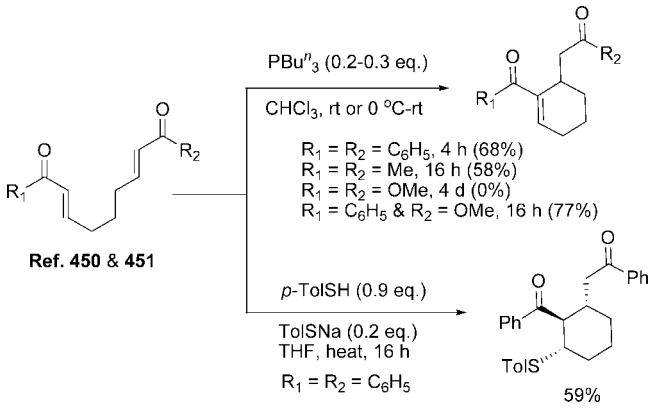
Scheme 152



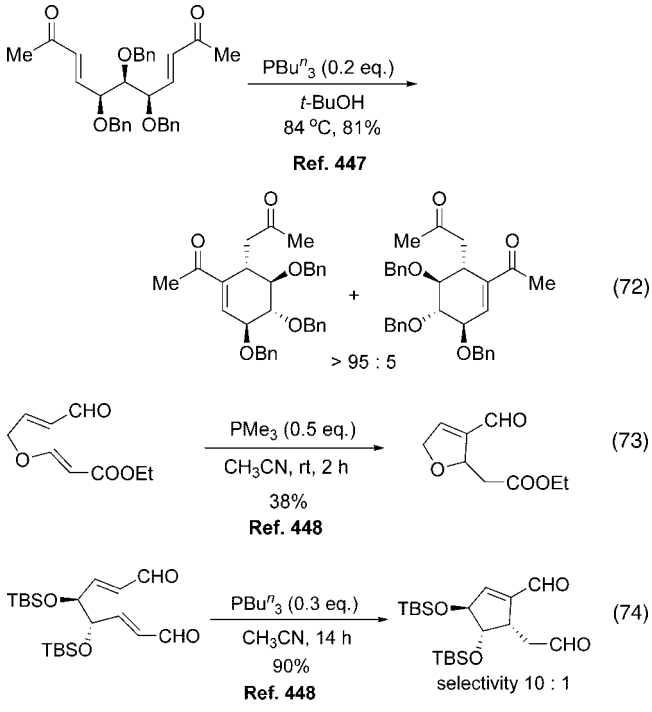
Scheme 153



Scheme 154

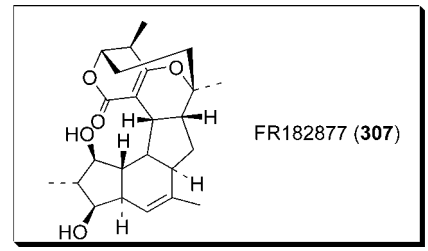


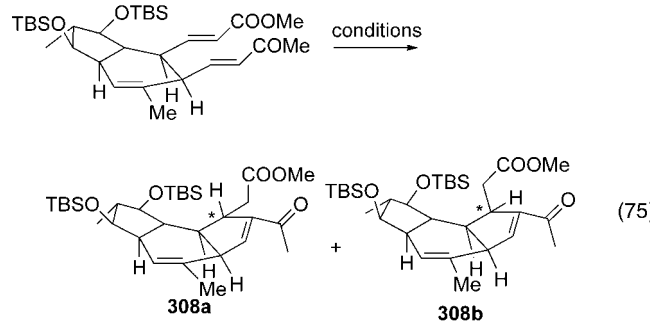
PBu_3 to provide cyclopentenes and cyclohexenes in good yields. They also observed that the bis-enoates failed to undergo cyclization where as enone−enoates provided expected products under similar conditions. Addition of *p*-TolSH instead of PBu_3 along with *p*-TolSNa provided Michael/Michael cyclization products. Representative examples are presented in Scheme 154.



Krische and co-workers[452] reported an intramolecular cycloallylation of enone−allyl acetates under the influence of PBu_3 (100 mol %) and $Pd(PPh_3)_4$ (1.0 mol %) as nucleophilic and electrophilic activators, respectively (Scheme 155). Subsequently, Luis and Krische[453] extended this strategy to the substrate containing an enone−vinyl sulfone (thioenoate) moiety using tributylphosphine as a catalyst (which acts as both nucleophilic and electrophilic activator) (Scheme 156).

During the synthesis of FR182877 (**307**), Methot and Roush[454] have used intramolecular Baylis−Hillman reaction as the key step for obtaining the required tricyclic framework (**308a** and **308b**). They have observed remarkable solvent effect in this reaction (eq 75). Subsequently, Roush and co-workers[455,456] extended this strategy to the total synthesis of (−)-spinosyn A, which involves an intramolecular Baylis−Hillman (Rauhut−Currier) reaction as one of the key steps, following the reaction sequence shown in Scheme 157.



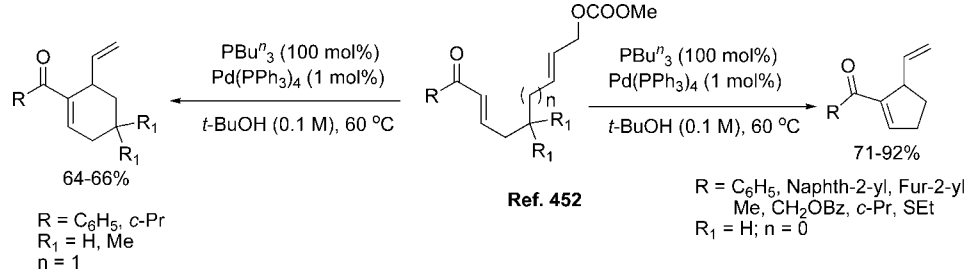


solvent	PMe_3 (eq.)	time (h)	yield % (**308a : 308b**)
0.03 M *t*-amylalcohol	10	20	56 (6:1)
0.03 M THF/H_2O (3/1)	4	12	84 (6:1)
0.03 M CF_3CH_2OH	10	12	62 (4:1)

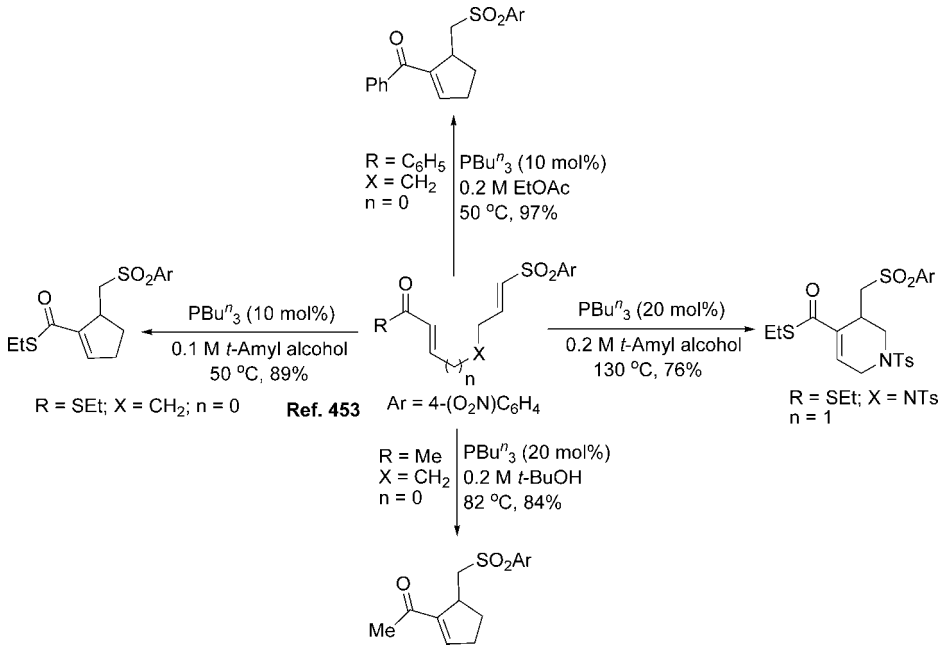
Agapiou and Krische[457] have reported an interesting synthesis of (±)-ricciocarpin A from a monothioenoate−monofuryl enone framework involving the intramolecular Baylis−Hillman reaction as the key step (Scheme 158).

Sorensen and co-workers[458] have successfully used intramolecular cyclization of bis-enone (**312**) under mild reaction conditions, using DABCO as a catalyst, to provide (+)-harziphilone, a naturally occurring inhibitor of the binding interaction between the HIV-1 Rev protein and the Rev-responsive element (RRE) of viral mRNA (Scheme 159).

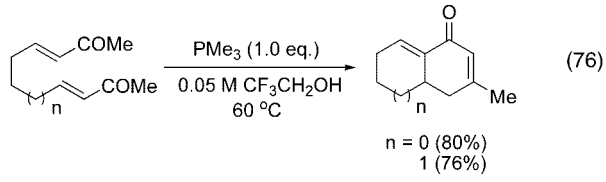
Scheme 155

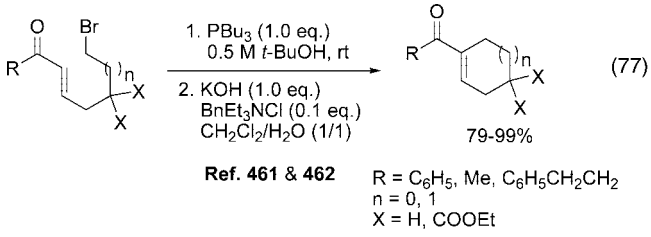


Scheme 156



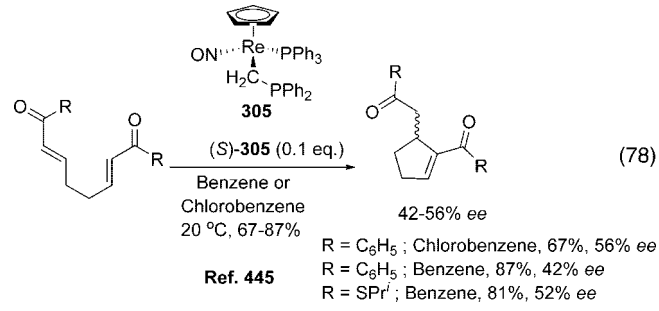
Later on, Thalji and Roush[459] described a facile synthesis of a bicyclic framework (eq 76) via the strategy involving intramolecular Baylis−Hillman and aldol reactions, respectively. Representative examples are presented.





Kraft and co-workers[460−462] have developed an interesting intramolecular Baylis−Hillman cyclization process using enone−allyl chloride and enone−alkyl bromide systems as substrates in the presence of PBu_3 as a catalyst; selected examples are shown in Scheme 160 and eq 77. Recently Kraft and Wright,[463] for the first time, used an enone−epoxide framework for intramolecular Baylis−Hillman cyclization to provide functionalized carbocyclic systems. Two examples are given in Scheme 161.

Seidel and Gladysz[445] have successfully used (*S*)-rhenium-containing phosphine [(*S*)-**305**] as a chiral catalyst for performing intramolecular Baylis−Hillman reactions of dienones to provide the resulting carbocyclic compounds in moderate to good enantiomeric purities. Representative examples are shown in eq 78.

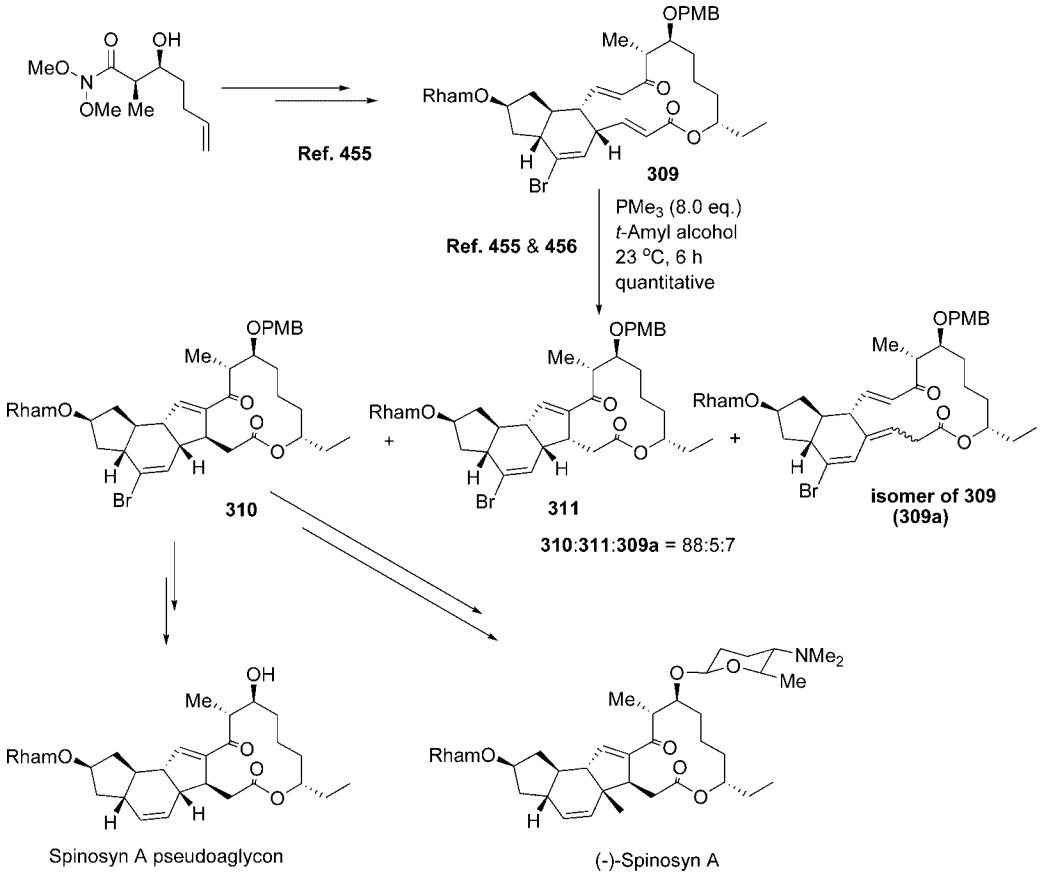


Later on, Aroyan and Miller[464] reported that methyl *N*-acetylcystine ester in the presence of excess *t*-BuOK was an effective promoter for intramolecular Baylis−Hillman reaction of an enone−enone system to provide a carbocyclic framework in up to 95% ee (eq 79).

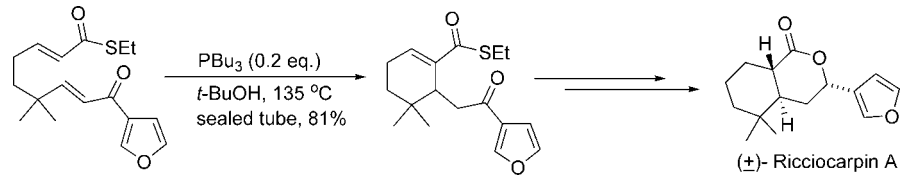
8. Baylis−Hillman-Type Reactions

Hoppe and co-workers[465] have reported an interesting methodology for obtaining β-substituted Baylis−Hillman adducts with high stereoselectivities via the reaction of

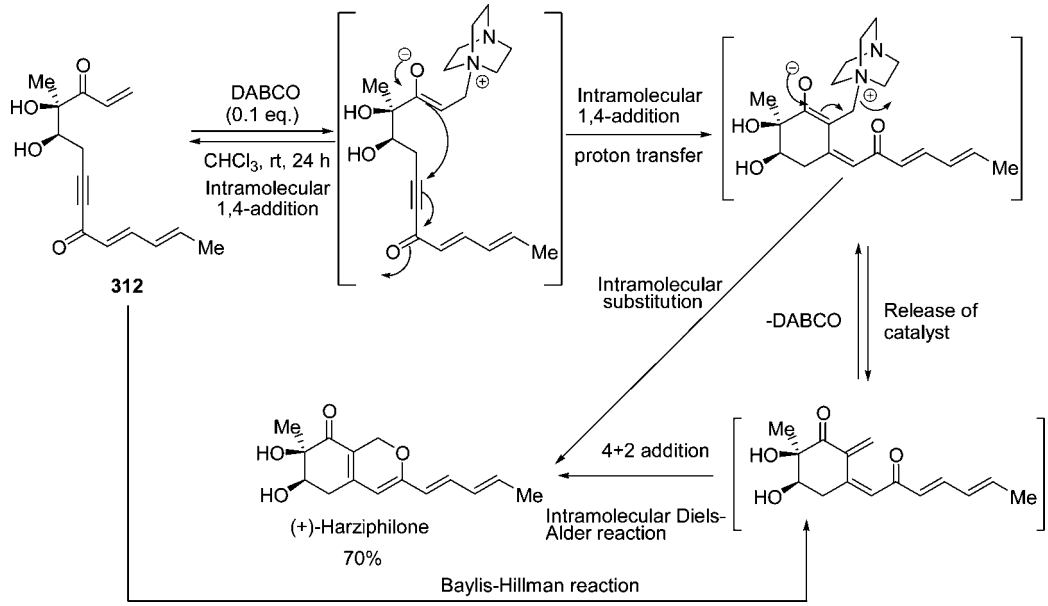
Scheme 157



Scheme 158

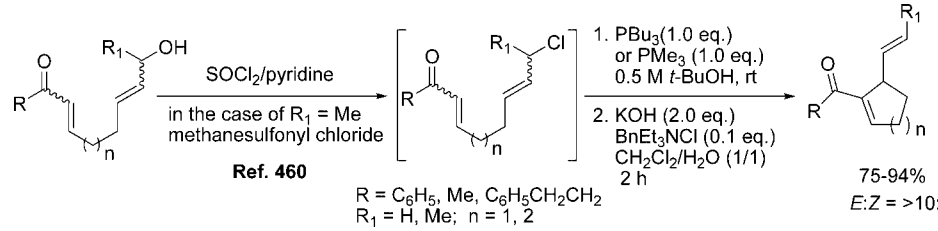


Scheme 159

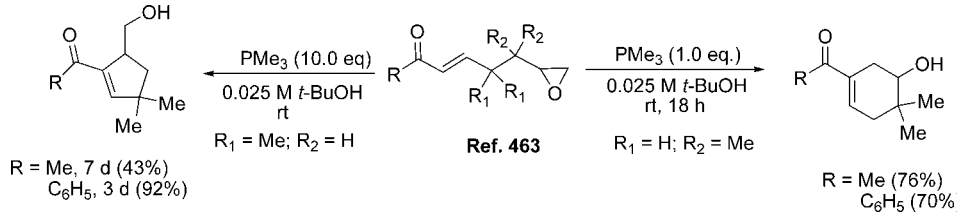


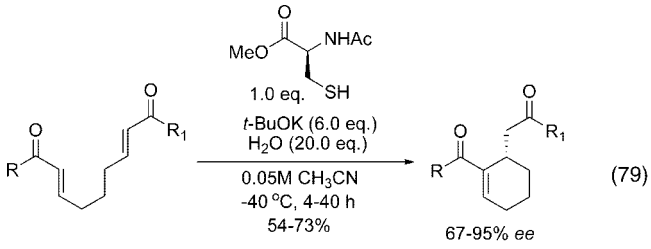
lithium allenolate (generated *in situ* by the treatment of allenyl carbamate with *n*-BuLi) with aldehydes. In these studies, they have carried out investigations with two allenyl carbamate derivatives (R = *t*-Bu and R = Me). In the case

Scheme 160



Scheme 161

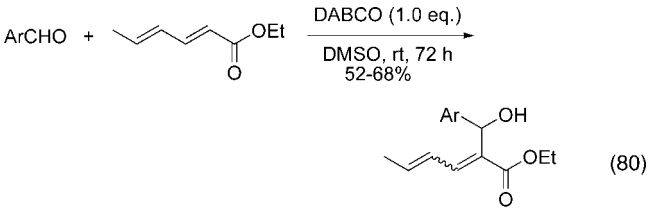




R = C_6H_5, 4-(MeO)C_6H_4, 4-BrC_6H_4, 4-$(O_2N)C_6H_4$, Fur-2-yl, Me
R_1 = C_6H_5, 4-(MeO)C_6H_4, 4-BrC_6H_4, 4-$(O_2N)C_6H_4$, Fur-2-yl, Me, OEt

of allenyl carbamate **313** when R = *t*-Bu, the geometry of the double bond in the final products depends on the temperature of the reaction (except for 2-furyl substitution, which gave only *Z*-isomer whatever the conditions might be), while the compound **313** when R = Me provided the products with *Z*-stereochemistry (Scheme 162).

β-Propen-1-yl-substituted Baylis−Hillman adducts were prepared by Krishna and co-workers[466] via the reaction of ethyl sorbate with aryl aldehydes under the influence of DABCO. The resulting products were obtained as *E*/*Z* mixtures (eq 80).



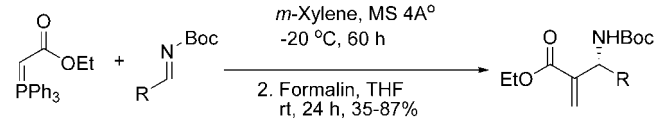
E,*E*/*E*,*Z* = 65/35 to 70/30

Ar = C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 2-$(O_2N)C_6H_4$, 4-$(O_2N)C_6H_4$, 4-$(C_6H_5)C_6H_4$, 4-$(NC)C_6H_4$, 2,4-$Cl_2C_6H_3$

Kamimura and co-workers[467a] reported a simple synthesis of Baylis−Hillman adducts in high diastereoselectivities via the reaction of magnesium thiolate with *t*-butyl acrylate followed by treatment with chiral *N*-sulfinimines, and then the reaction of the resulting thioester with *m*-CPBA according to the reaction sequence shown in Path A, Scheme 163. Davis and co-workers[467b] very recently reported a facile synthesis of *β*-substituted Baylis−Hillman adducts via the reaction of chiral *N*-sulfinimine with vinylaluminum reagent (**314**), which was prepared from the propargylic ester according to Path B, Scheme 163 (one example is presented). It is worth mentioning here that Li and co-workers[468] have earlier used chiral *N*-sulfinimines for the synthesis of Baylis−Hillman-type products.

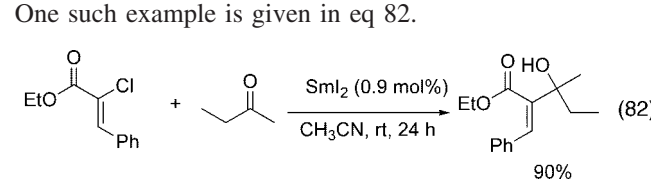
A new protocol for obtaining the Baylis−Hillman adducts (**316**) was reported by Gajda and Gajda,[469] following the reaction sequence as described in Scheme 164. This strategy involves first the formation of 1,1-bisphosphonate (**315**), from tetraethylmethylenebisphosphonate via the reaction with α-tosyl amine, which was subsequently transformed into Baylis−Hillman adducts via the reaction with formaldehyde.

Organocatalytic Mannich-type reaction of phosphorus ylides with aldimine derivatives producing the Baylis−Hillman adducts in high enantiomeric purities have been developed by Chen and co-workers.[470] Various chiral organocatalysts (**276b**,**d**,**e**, **281**, **317**−**318**, Figure 60) were examined for this purpose, and the chiral catalyst **276d** was found to provide the best results (eq 81).



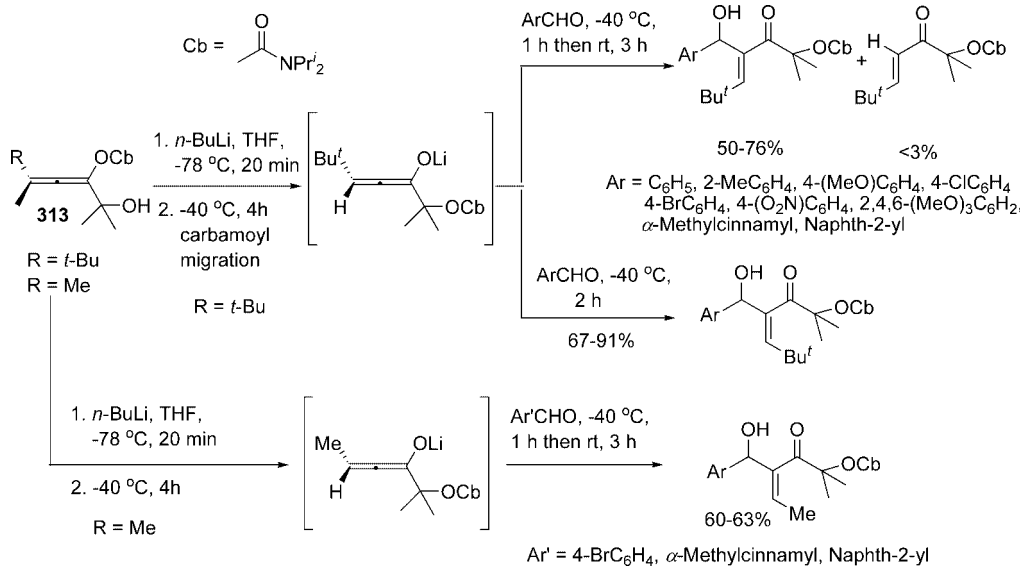
R = C_6H_5, 3-MeC_6H_4, 4-MeC_6H_4, 4-(MeO)C_6H_4, 4-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, Thien-2-yl, *n*-Pr, *i*-Pr, *c*-Hex

An efficient methodology for obtaining *β*-substituted Baylis−Hillman adducts was developed by Concellon and Huerta[471] via the reaction between *β*-halocinnamates with various ketones under the influence of samarium diiodide. One such example is given in eq 82.

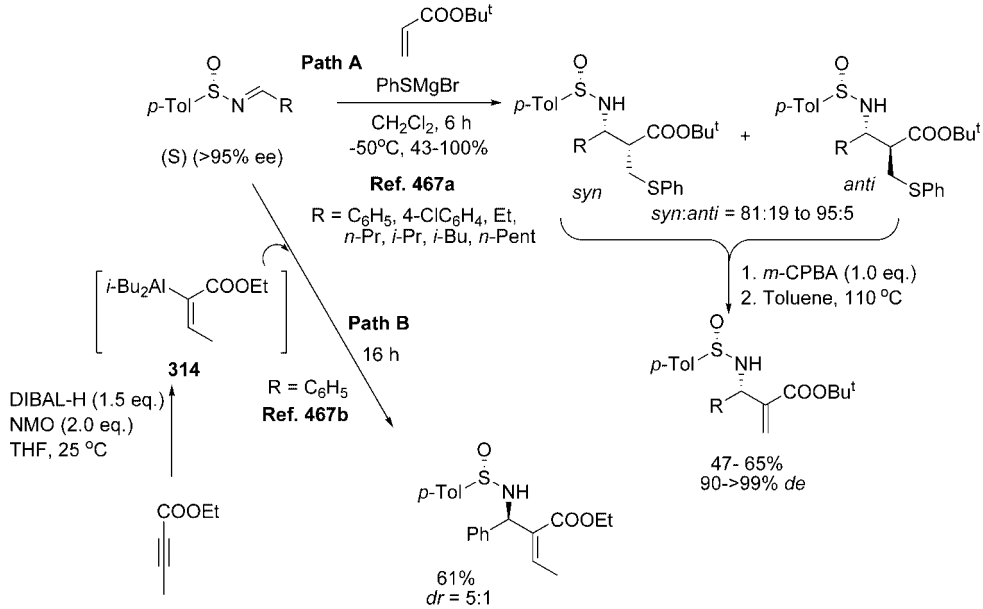


Mamaghani and co-workers[472] have used a similar strategy for the transformation of (*R*)-3-(2-bromo-3-phenylprop-2-enoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (prepared from the corresponding chiral oxazolone as shown in Scheme 165) into chiral *β*-substituted Baylis−Hillman adducts via the reaction with aldehydes under the influence of SmI_2 (Scheme 165).

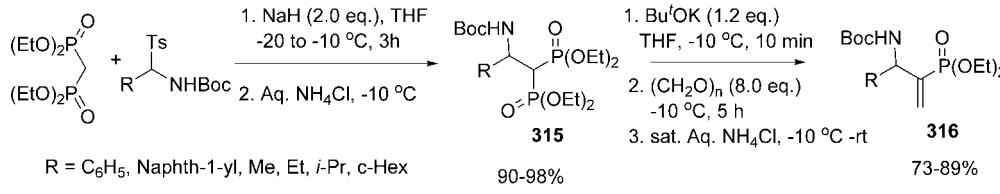
Scheme 162



Scheme 163



Scheme 164



During our attempts to perform the Baylis−Hillman reaction between pyridine-4-carboxaldehyde and phenyl vinyl sulfoxide under the influence of TMG and water, the expected Baylis−Hillman adduct was not obtained (Scheme 166).[473] These results indicate that pyridine-4-carboxaldehyde underwent Cannizzarro reaction in the presence of TMG.

Coltart and co-workers[474] reported a facile methodology for the synthesis of α-alkenyl-β-hydroxy thioesters via the direct aldol cascade sequence of acryloyl/crotonoyl chloride, aldehydes, and PhSLi in the presence of $MgBr_2 \cdot OEt_2$ (which generates *in situ* thioester alcohols), followed by oxidative elimination, according to the reaction sequence shown in Scheme 167. This methodology provides an alternative route to the Baylis−Hillman adducts.

Tanaka, Barbas, and co-workers[475] have reported an interesting methodology for the synthesis of highly enantiomerically enriched Baylis−Hillman-type products via the Mannich type reaction of various enolizable aldehydes with imines under the influence of (*S*)-proline and imidazole, followed by isomerization of double bond (eq 83).

A facile methodology for the synthesis of optically active α-methylene-β-hydroxy esters via the asymmetric aldol reaction of tetra-substituted ketene silyl acetal, containing

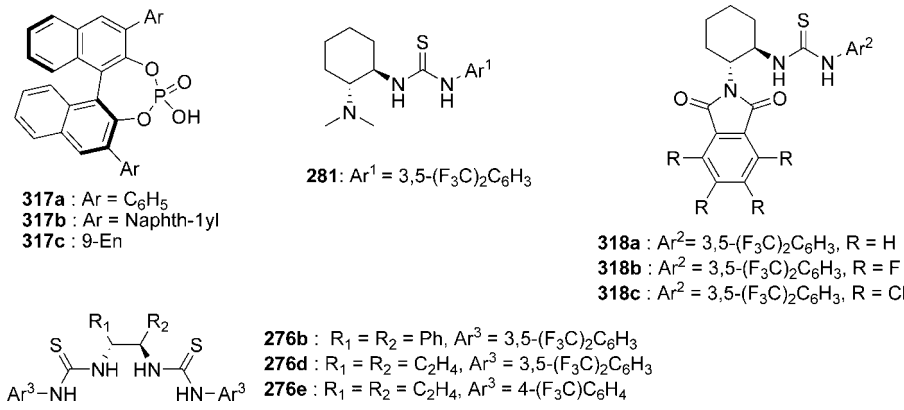
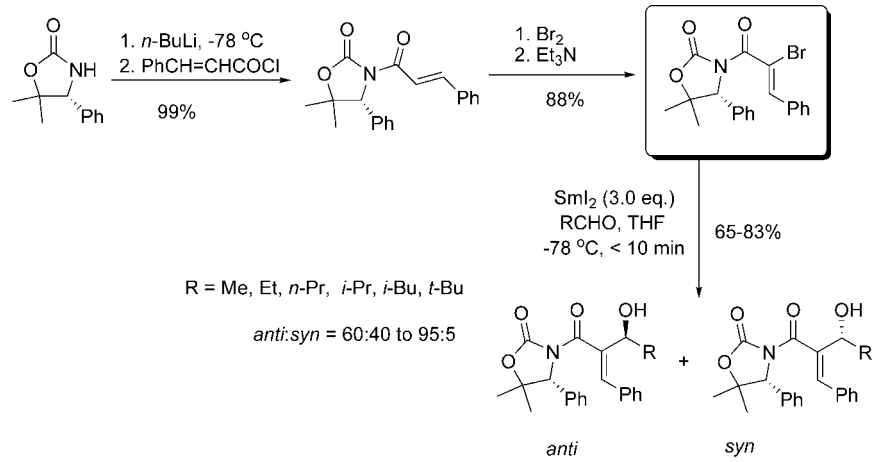
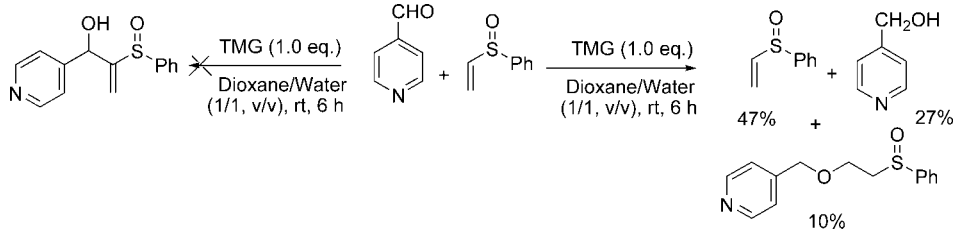


Figure 60.

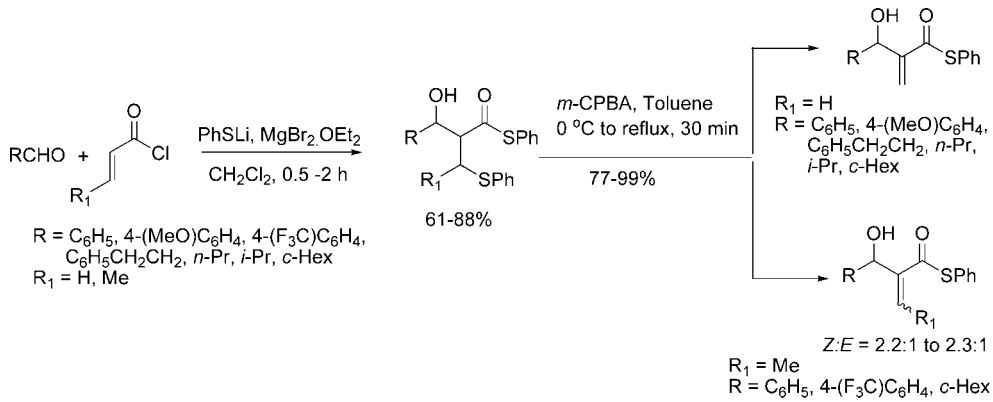
Scheme 165



Scheme 166



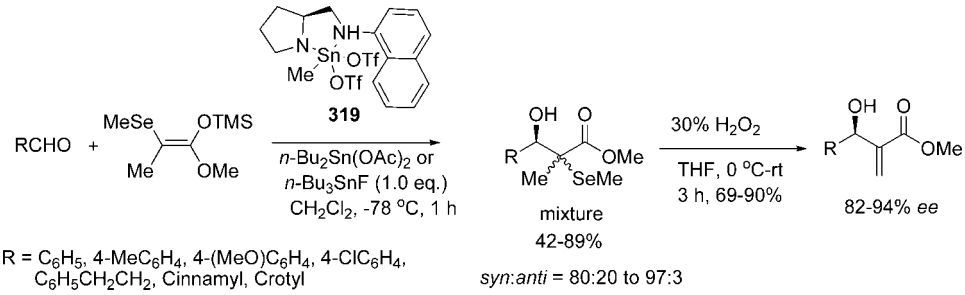
Scheme 167



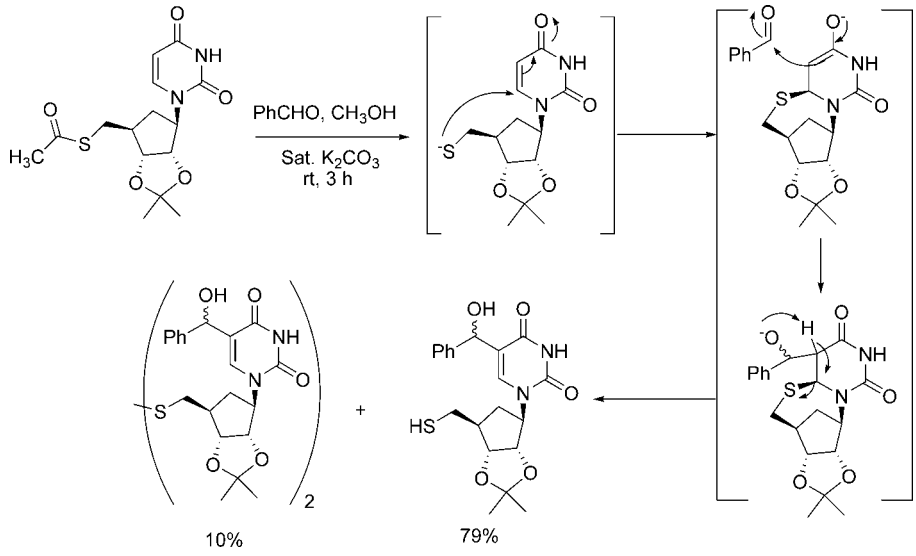
an alkylseleno group, with aldehydes under the influence of chiral triflate **319** followed by oxidative deselenization was reported by Shiina and co-workers (Scheme 168).[476] This protocol provides an alternative way for producing chiral Baylis−Hillman adducts with high enantiomeric purities.

Clivio and co-workers[477] have reported a thiolate-triggered tandem Michael/aldol reaction of pyrimidine nucleobase, which provided Baylis−Hillman adducts, following the reaction sequence shown in Scheme 169.

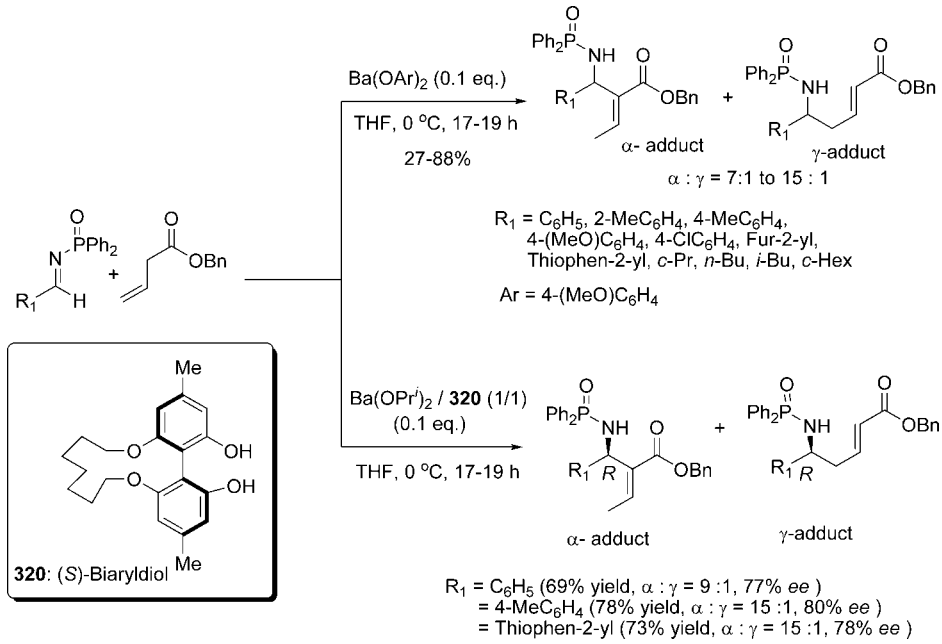
Scheme 168



Scheme 169



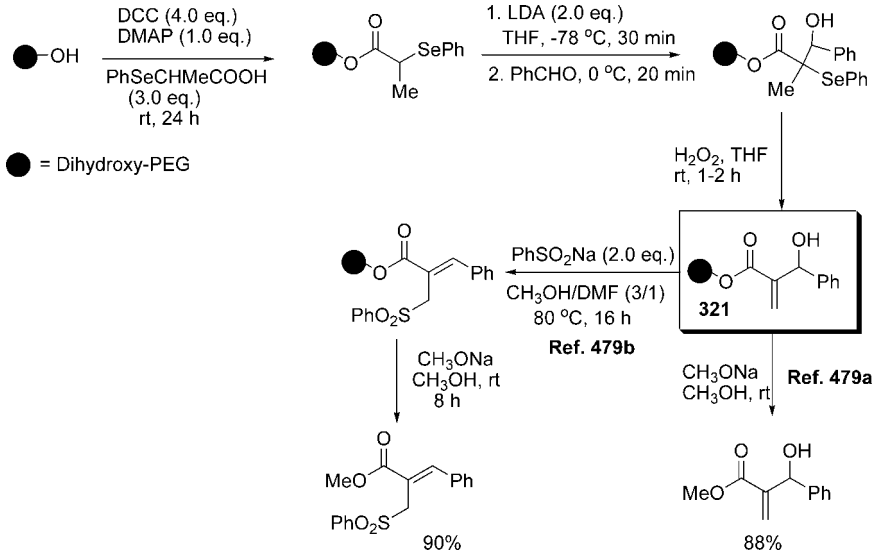
Scheme 170



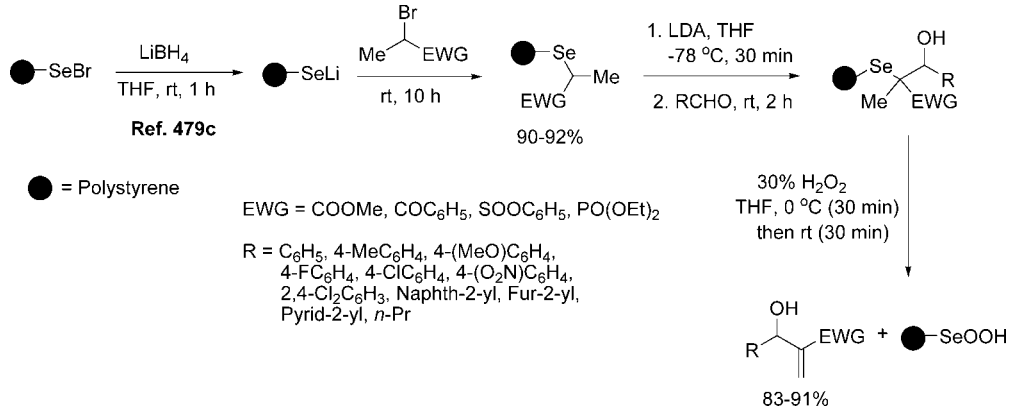
Shibasaki and co-workers[478] have developed a Ba-catalyzed direct Mannich-type reaction/isomerization sequence of β,γ-unsaturated ester to give β-methyl Baylis−Hillman adducts. They have also reported the asymmetric version of this reaction (up to 80% enantioselectivity) using biaryldiol (**320**) as a catalyst along with Ba catalyst (Scheme 170).

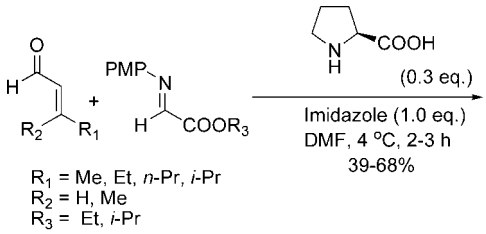
Sheng and co-workers have developed an interesting liquid phase synthesis of Baylis−Hillman adducts (with polymer tag) **321** using PEG-supported α-phenylselenopropionate as the starting material following the reaction sequence shown in Scheme 171.[479a] PEG polymer tag was removed via the treatment with NaOMe. The adduct (**321**) was also transformed into methyl (2*Z*)-2-phenylsulfonylmethyl-2-propionate via the reaction with $PhSO_2Na$ (Scheme 171).[479b] They have also used polymeric selenium reagent to obtain

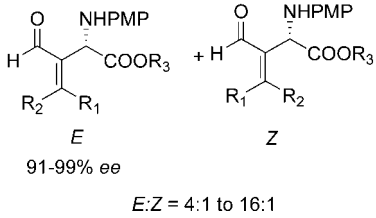
Scheme 171



Scheme 172





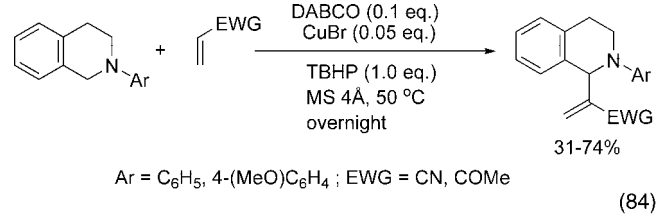


(83)

Baylis−Hillman adducts according to a similar reaction sequence described in Scheme 172.[479c]

Koech and Krische[480] have reported an interesting α-arylation of enones and enals using triarylbismuthdichloride as electrophile under the catalytical influence of PBu_3 (Scheme 173).

Bohle and co-workers[481] reported a useful C−C bond formation between the benzylic carbon α to nitrogen in tetrahydroisoquinolines and the α-position of activated alkenes (MVK and acrylonitrile) under the catalytic influence of CuBr (5 mol %) in the presence of DABCO (10 mol %) to provide the resulting Baylis−Hillman-type products in moderate to good yields (eq 84).

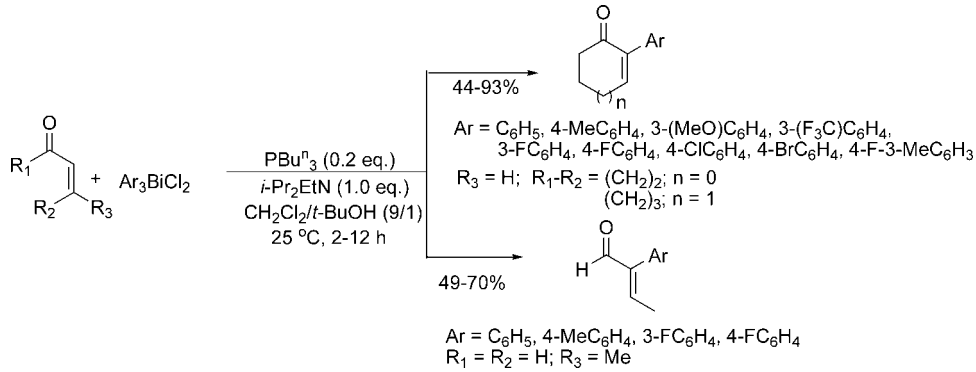


(84)

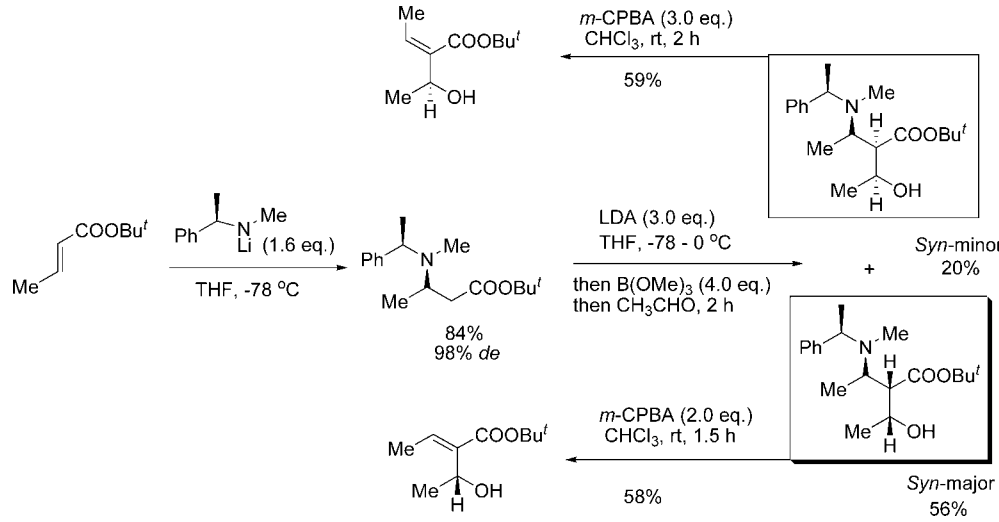
Enantiomerically enriched β-substituted Baylis−Hillman alcohols were obtained from (*E*)-*t*-butyl crotonate via Michael reaction with chiral lithium amide, followed by aldol reaction and elimination according to the reaction sequence shown in Scheme 174.[482]

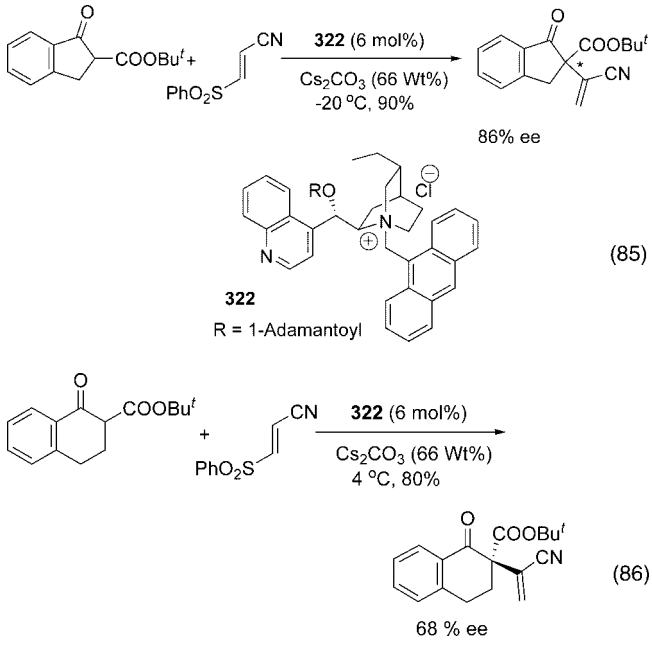
α-Alkylated acrylonitriles were obtained in high enantiomeric purities via the reaction of 1-phenylsulfonyl-2-cyanoethylene with β-keto esters in the presence of chiral phase-transfer catalyst (**322**). Representative examples are shown in eqs 85 and 86. In fact, several catalysts were examined by Jorgensen and co-workers,[483] and the catalyst **322** provided the best results.

Scheme 173



Scheme 174



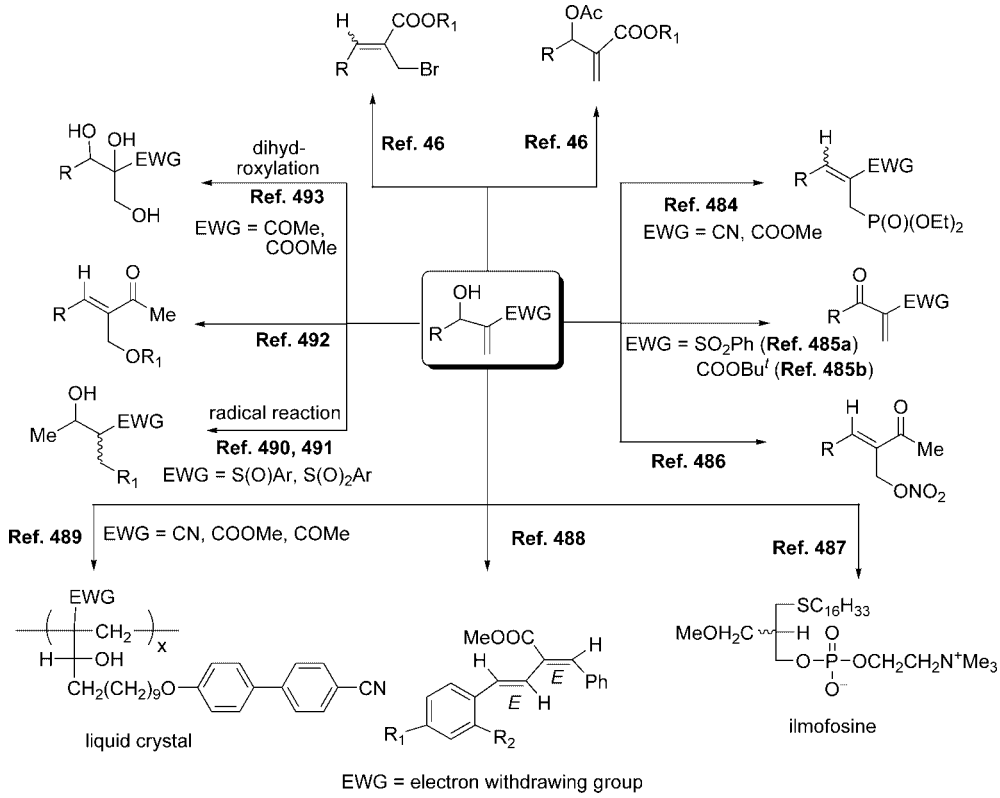


9. Applications of Baylis−Hillman Adducts and Their Derivatives: Earlier Developments

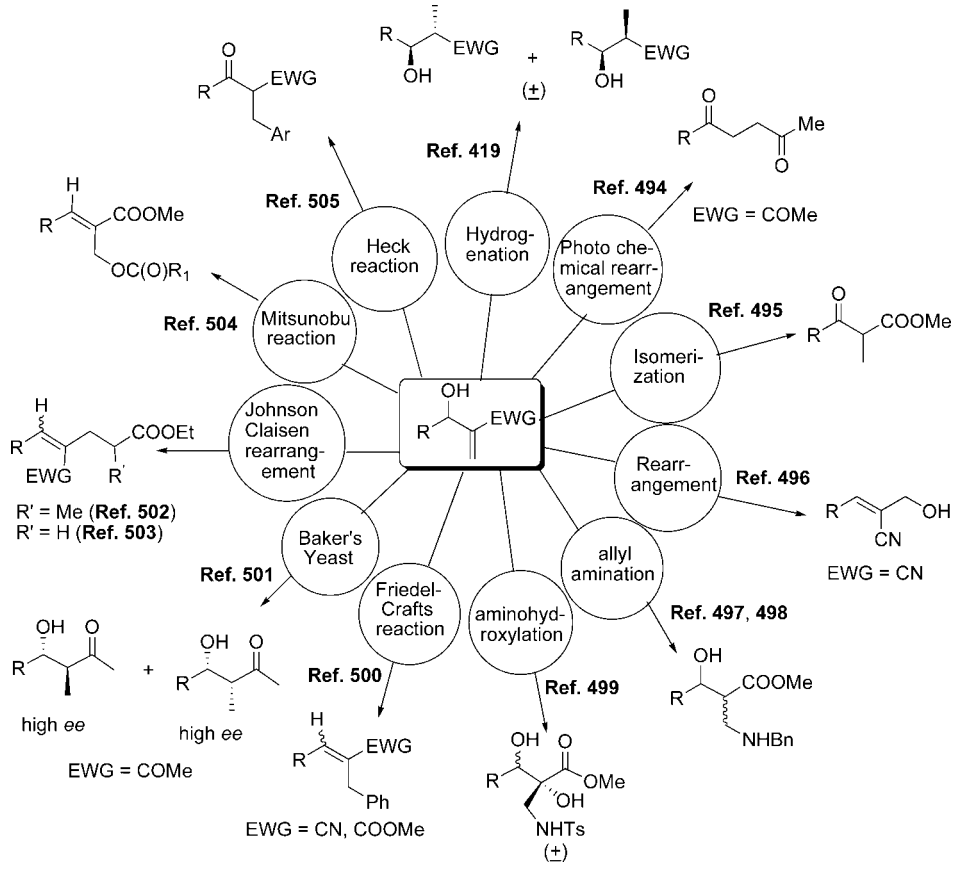
The importance and growth of the Baylis−Hillman reaction, to a large extent, can also be attributed to the enormous applications of the Baylis−Hillman adducts in synthetic chemistry. The Baylis−Hillman adducts containing a minimum of three functional groups in close proximity are valuable substrates for various organic reactions and transformations. Thus the Baylis−Hillman adducts[21] have been successfully employed as substrates in a number of named and unnamed reactions, such as, Friedel−Crafts reaction, Johnson−Claisen rearrangement, hydrogenation reaction, nucleophilic reactions, and hydroxylation. The Baylis−Hillman adducts have also been systematically used as valuable synthons or starting materials for synthesis of representative natural products, unnatural products, and bioactive molecules. Also efforts have been successfully made for the transformation of the Baylis−Hillman adducts and their derivatives into various trisubstituted alkenes with defined stereochemistry and heterocyclic and carbocyclic molecules of biological importance. Earlier developments in these directions are pictorially presented in the Schemes 175−185. During the last 5−6 years, a large number of publications appeared describing the various applications of the Baylis−Hillman adducts, acetates, and halides in a variety of organic transformation methodologies and also in the synthesis of several bioactive molecules. These developments are systematically presented in this section.

9.1. Synthetic Transformations of Baylis−Hillman Alcohols

Scheme 175

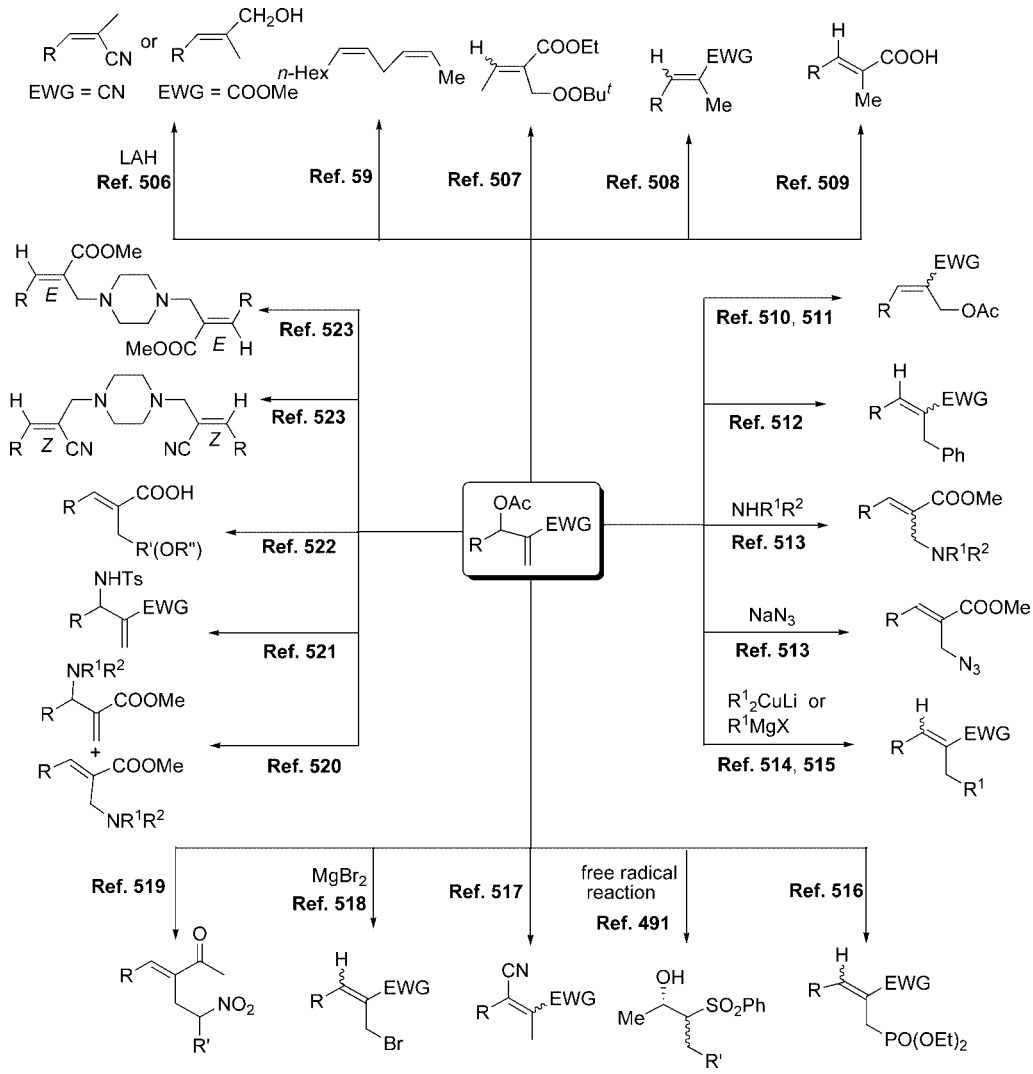


Scheme 176



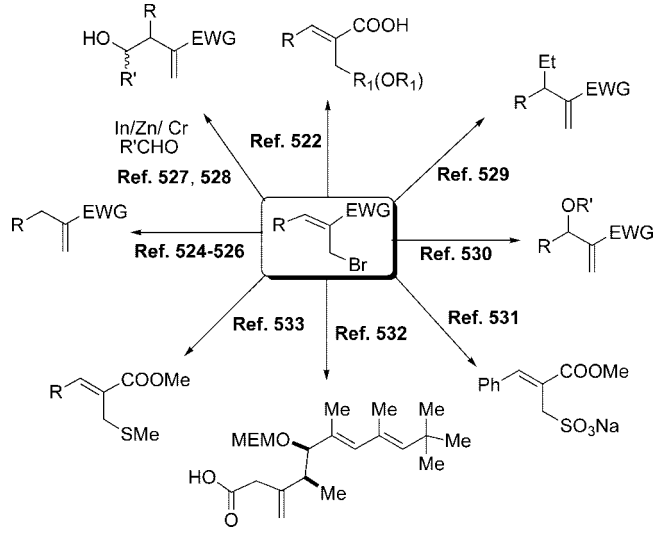
9.2. Synthetic Transformations of Baylis−Hillman Acetates

Scheme 177



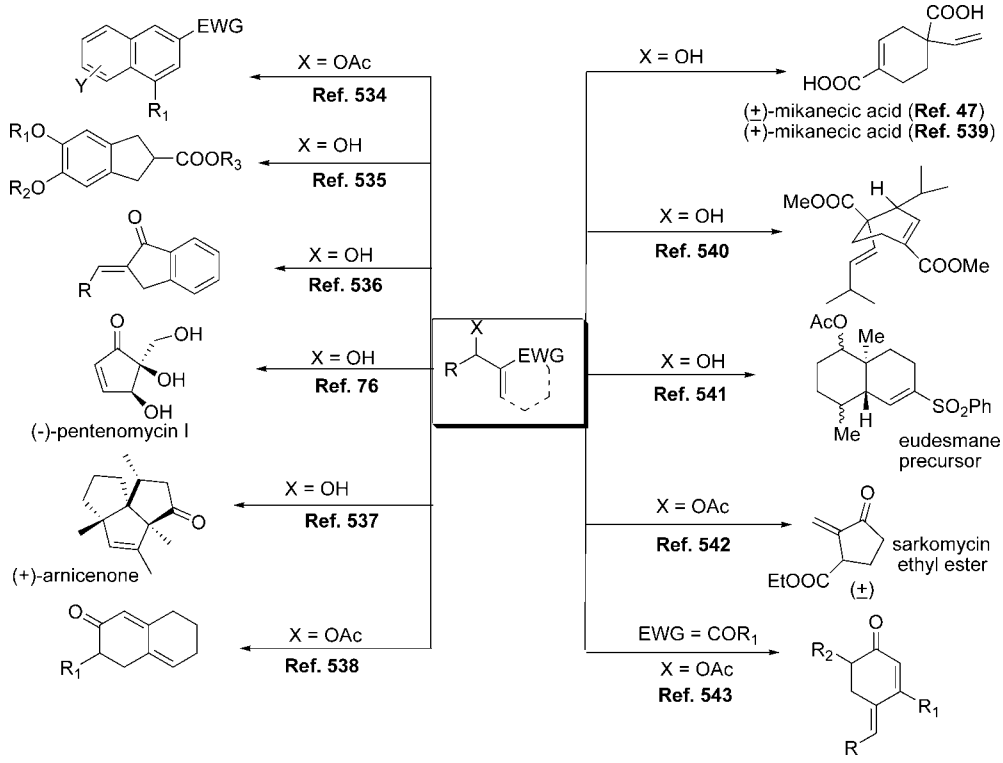
9.3. Synthetic Transformations of Baylis−Hillman Bromides

Scheme 178



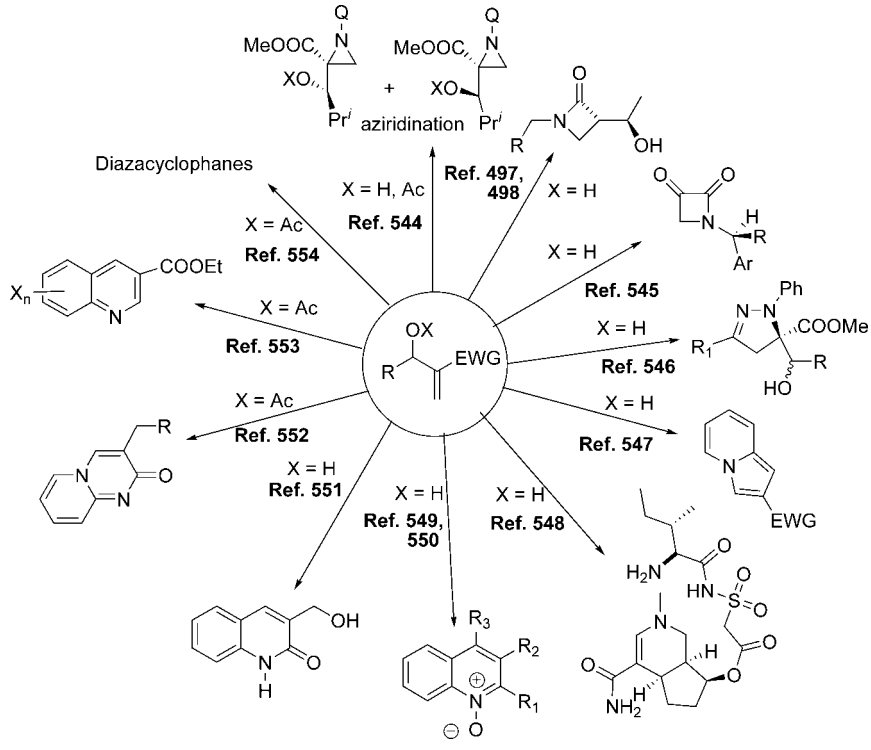
9.4. Synthesis of Carbocyclic Compounds Using Baylis−Hillman Alcohols or Acetates

Scheme 179



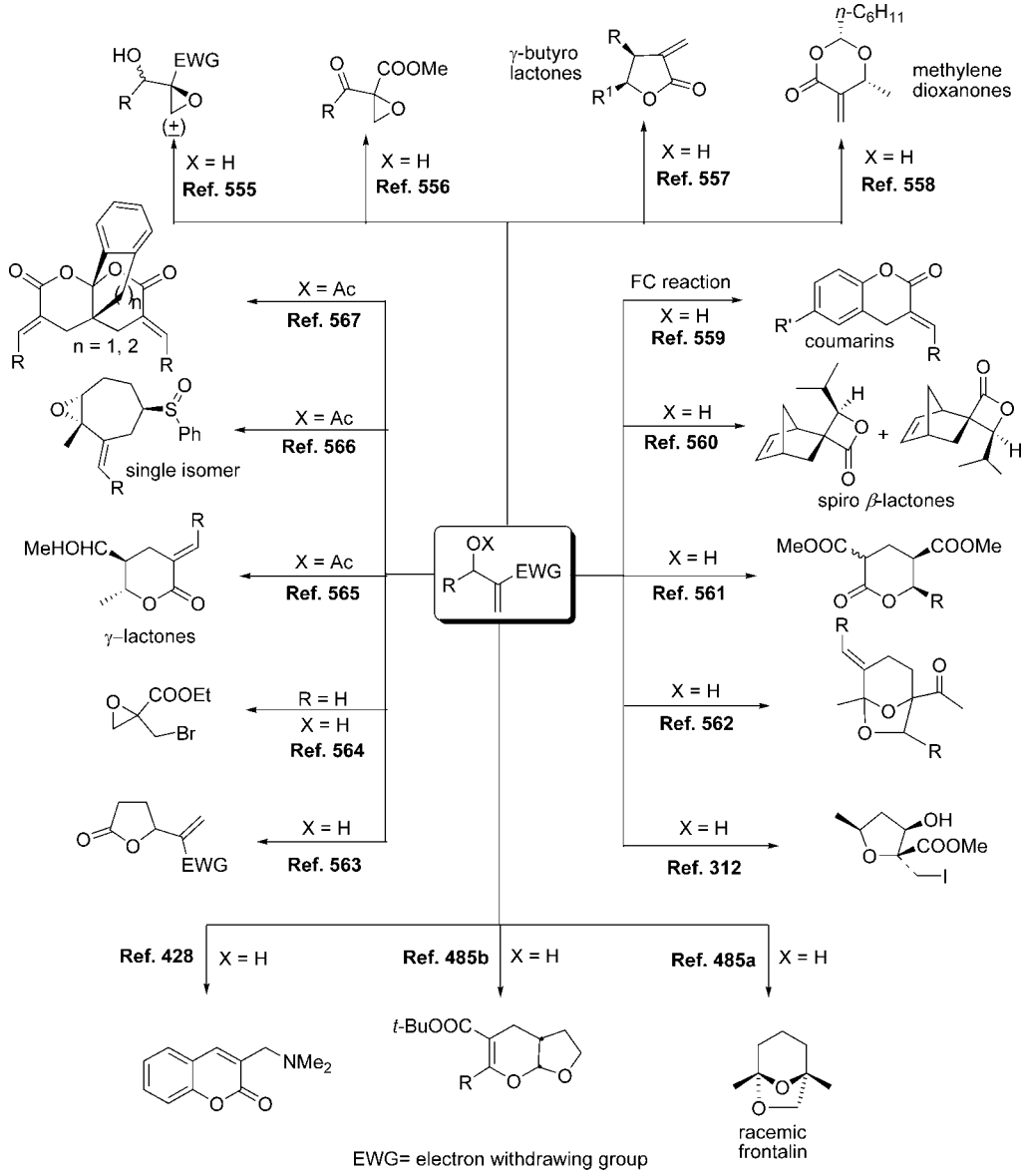
9.5. Synthesis of Nitrogen Heterocyclic Compounds Using Baylis−Hillman Alcohols or Acetates

Scheme 180



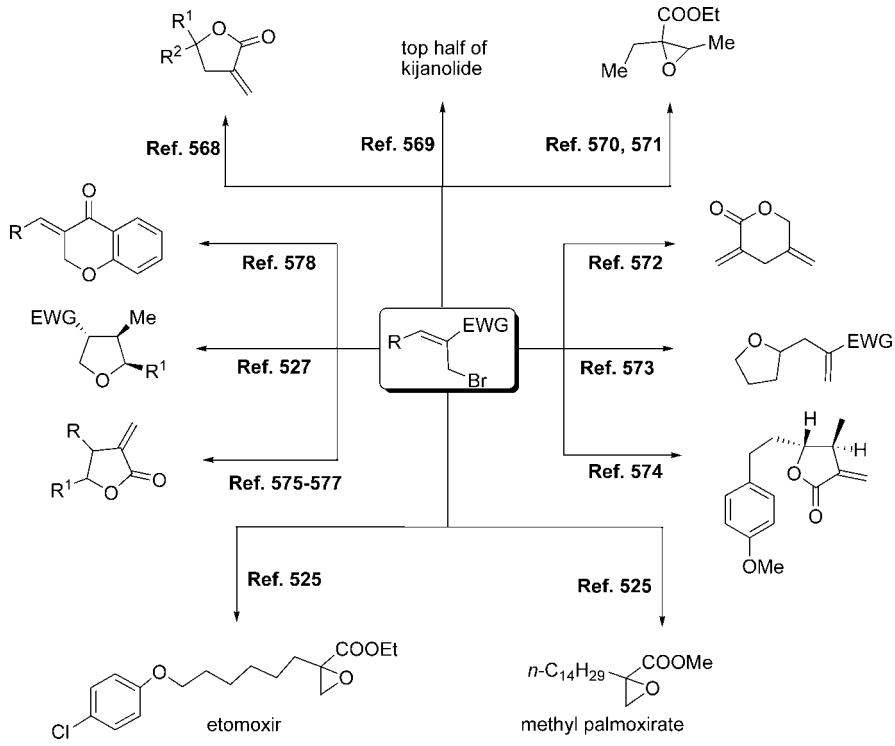
9.6. Synthesis of Oxygen Heterocyclic Compounds Using Baylis−Hillman Alcohols or Acetates

Scheme 181



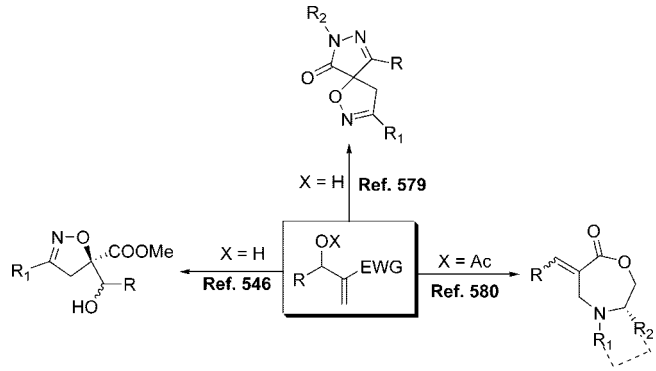
9.7. Synthesis of Oxygen Heterocyclic Compounds Using Baylis−Hillman Bromides

Scheme 182



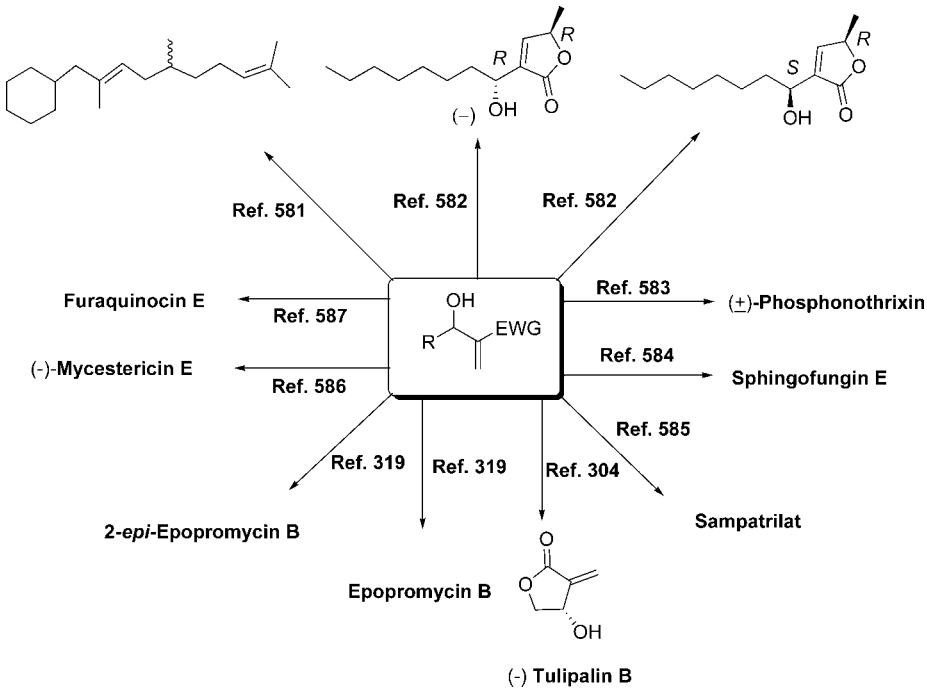
9.8. Synthesis of Heterocyclic Compounds Containing Two or More Hetero Atoms Using Baylis−Hillman Alcohols or Acetates

Scheme 183

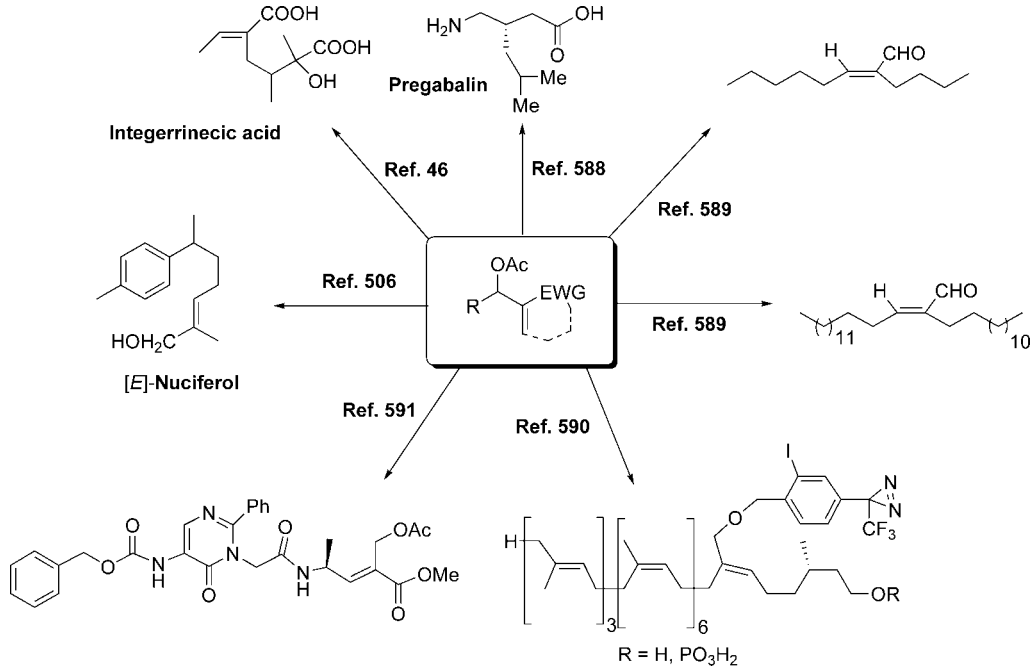


9.9. Synthesis of Natural Products, Synthons, and Bioactive Molecules

Scheme 184



Scheme 185

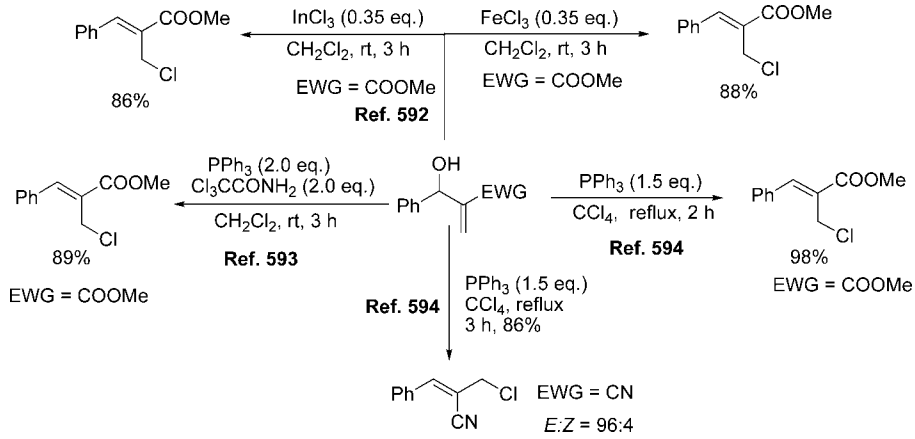


10. Applications of Baylis−Hillman Adducts and Their Derivatives: Recent Developments

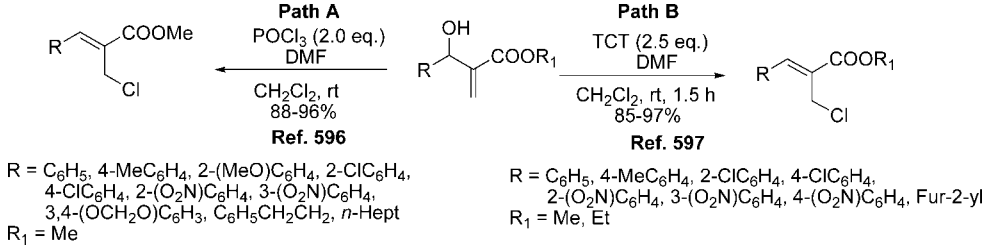
10.1. Organic Transformations of the Baylis−Hillman Adducts, Acetates, and Halides

Due to the importance of Baylis−Hillman acetates and halides as efficient synthons in organic synthesis, organic chemists have continued their efforts to develop easier methods for synthesis of these derivatives. The recent developments are described in this section. Das and co-workers[592] have prepared allyl chlorides from corresponding Baylis−Hillman alcohols, 3-hydroxy-2-methylene-alkanoates, via treatment with $FeCl_3$ or $InCl_3$ in dichloromethane. The resulting allyl chlorides were obtained with *Z* configuration (≤5% *E*). Subsequently Das and co-workers[593,594] have used PPh_3/Cl_3CCONH_2 and PPh_3/CCl_4 as reagents for conversion of Baylis−Hillman alcohols into the corresponding (*Z*)-allyl

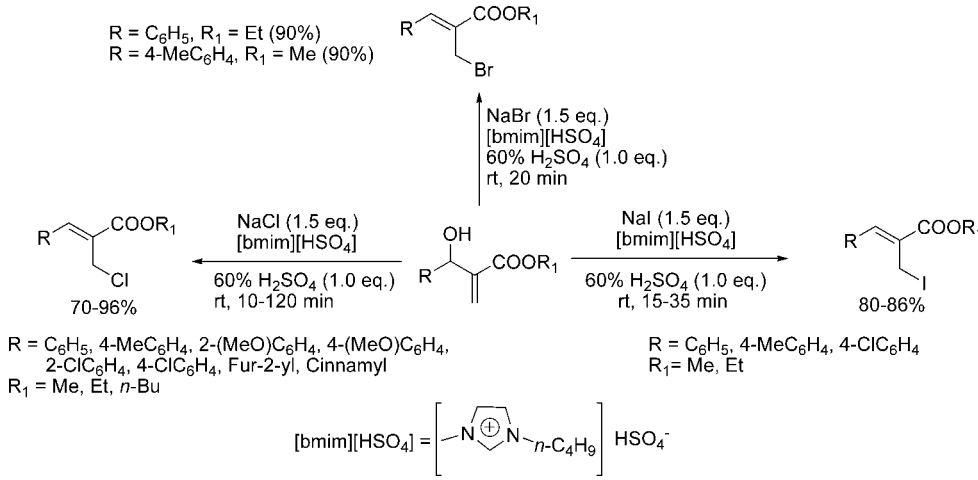
Scheme 186



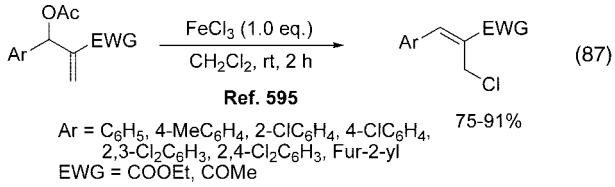
Scheme 187



Scheme 188



chlorides (in the case of EWG = COOR) and (*E*)-allyl chlorides (in the case of EWG = CN). Representative examples are given in Scheme 186. Later on, $FeCl_3$ was also employed as a reagent for conversion of Baylis−Hillman acetates into the corresponding (*Z*)-allyl chlorides by Krishna and co-workers[595] (eq 87).



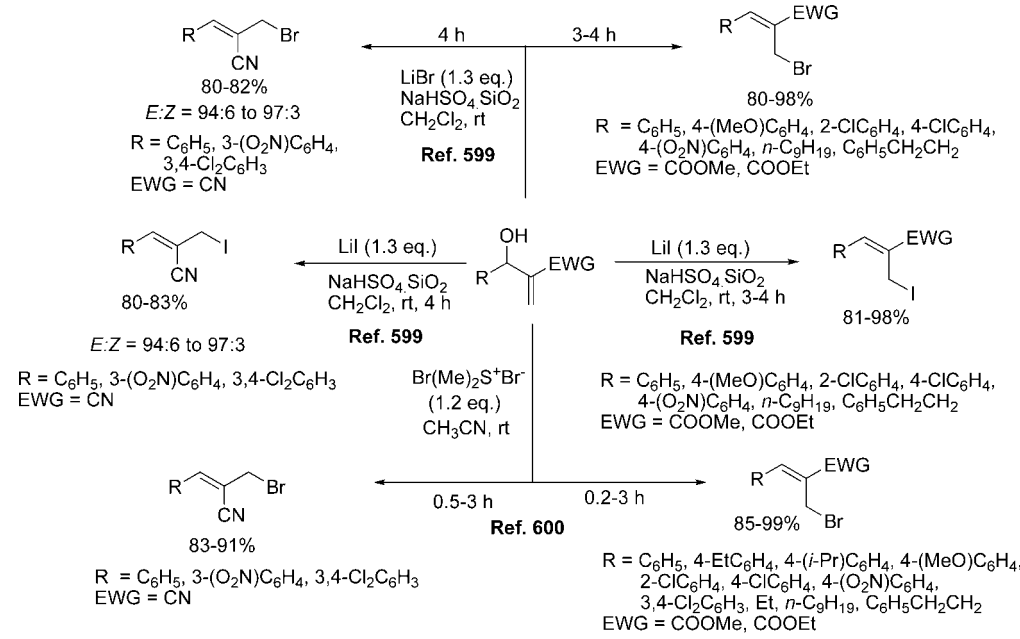
Xu and co-workers[596] reported an efficient and (*Z*)-stereoselective chlorination of Baylis−Hillman adducts using Vilsmeier−Haack reagent in dichloromethane at room temperature (Path A, Scheme 187). Very recently, Li and co-workers[597] found a trichlorotriazine (TCT)/DMF system as an efficient reagent for transformation of the Baylis−Hillman alcohols into (*Z*)-allyl chlorides (Path B, Scheme 187).

Bao and co-workers[598] have found that NaCl, NaBr, and NaI immobilized in 1-butyl-3-methylimidazolinium hydrogen sulfate ([bmim][HSO_4]) ionic liquid are efficient reagents for the conversion of Baylis−Hillman adducts into the corresponding (*Z*)-allyl chlorides, bromides, and iodides, respectively, in high yields (Scheme 188).

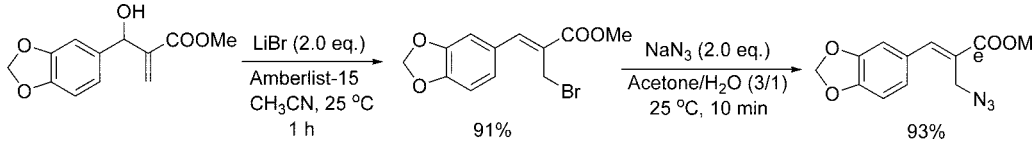
Subsequently, LiBr and LiI have been used for conversion of the Baylis−Hillman alcohols into allyl bromides and iodides in the presence of silica-supported $NaHSO_4$ by Das and co-workers.[599] They[600] have also employed bromo(dimethyl)sulfonium bromide for the conversion of Baylis−Hillman alcohols into allyl bromides (Scheme 189).

Sa and co-workers[601] reported synthesis of allyl bromides via the reaction of Baylis−Hillman alcohols with LiBr under the influence of amberlyst-15. These bromides are conveniently transformed into the corresponding (*E*)-allyl azides

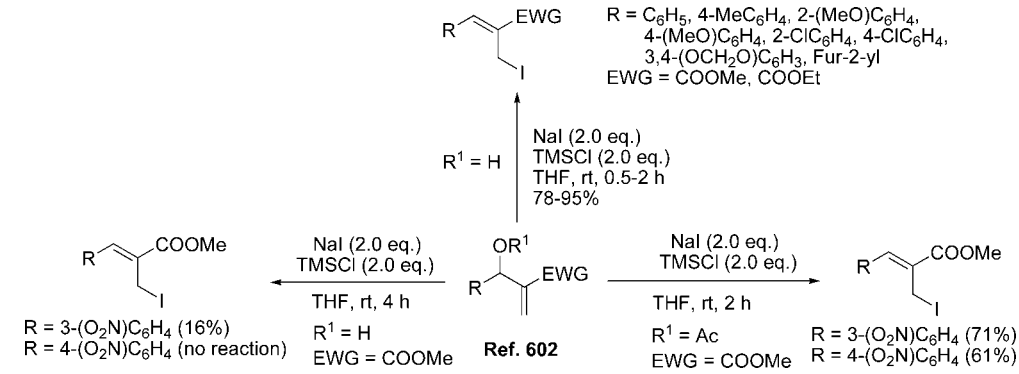
Scheme 189



Scheme 190



Scheme 191



by treating with NaN_3 in an acetone/water system. One example is shown in Scheme 190.

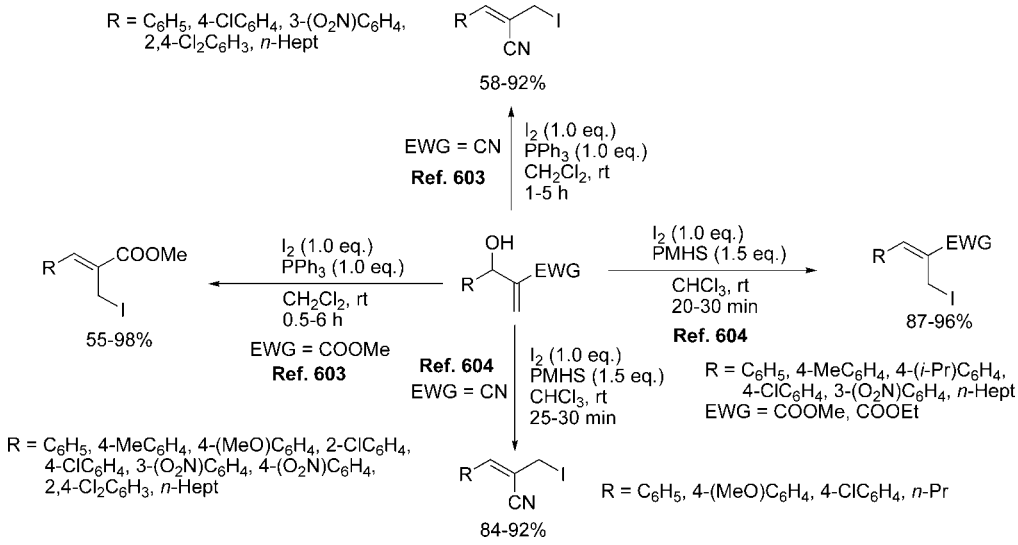
Zhang and co-workers[602] have reported an interesting synthesis of (*Z*)-allyl iodides from Baylis−Hillman alcohols using NaI/TMSCl in THF as a reagent at room temperature. The Baylis−Hillman alcohols derived from 3-nitrobenzaldehyde provided the corresponding allyl iodide in only 16% yield, while the Baylis−Hillman alcohols derived from 4-nitrobenzaldehyde did not undergo any reaction. However their corresponding acetates provided high yields of allyl iodides under similar reaction conditions (Scheme 191). Later on, Das and co-workers[603,604] have employed I_2/PPh_3 and I_2/PMHS as reagents for conversion of the Baylis−Hillman alcohols into the corresponding (*Z*)-allyl iodides (Scheme 192).

Das and Thirupathi[605] have transformed Baylis−Hillman alcohols to the corresponding acetates using acetic anhydride in the presence of $NaHSO_4 \cdot SiO_2$ as a heterogeneous catalyst with high regioselectivity (Path A, Scheme 193). Subsequently, Sa and co-workers[606] have used potassium chloride-exchanged molecular sieves (13X/KCl) as a recyclable catalyst for the conversion of Baylis−Hillman alcohols into the corresponding Baylis−Hillman acetates using acetic anhydride as acetylating agent (Path B, Scheme 193). One example each is presented.

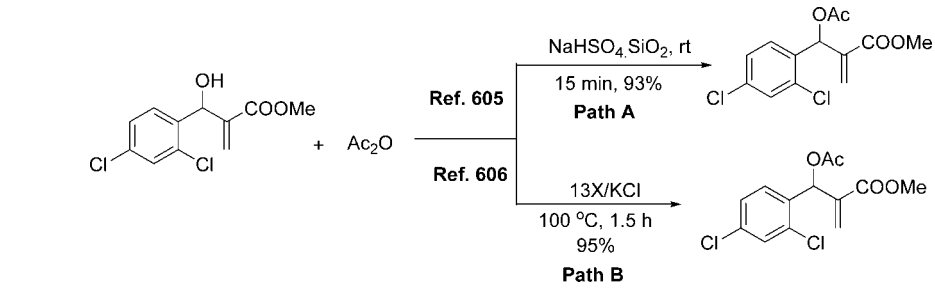
Mamaghani and Badrian have reported the conversion of Baylis−Hillman alcohols into the corresponding trimethylsilyl and *tert*-butyldimethylsilyl ethers via the treatment with hexamethyldisilazane (HMDS)[607] (in the presence of iodine) and *tert*-butyldimethylsilyl chloride (TBDMSCl)[608] (in the presence of lithium sulfide), respectively (Scheme 194).

Transformation of the secondary Baylis−Hillman alcohols or acetates into isomeric primary allylic alcohols or acetates with high stereoselectivity has been and continues to be an attractive and challenging endeavor in organic synthesis.[496,511,609,610] Kim and co-workers[611] have transformed Baylis−Hillman alcohols into the corresponding primary alcohols with (*E*)-configuration in a two-step protocol, that is, via (1) treatment with acetic anhydride in the presence of H_2SO_4 to form acetate and (2) subsequent

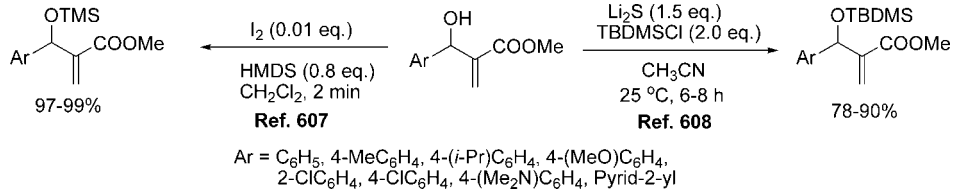
Scheme 192



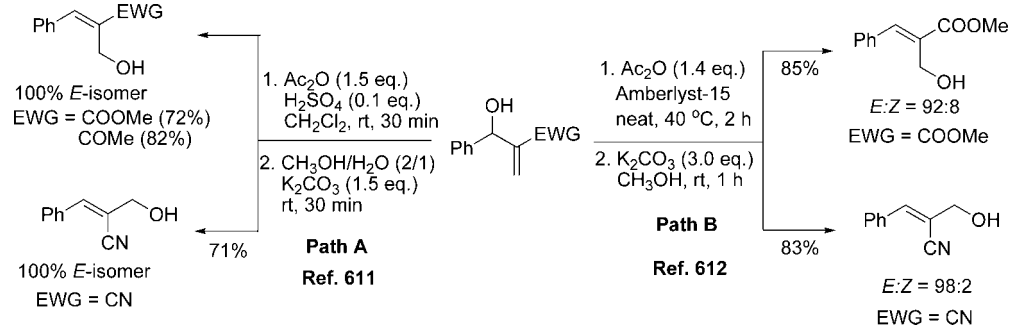
Scheme 193



Scheme 194



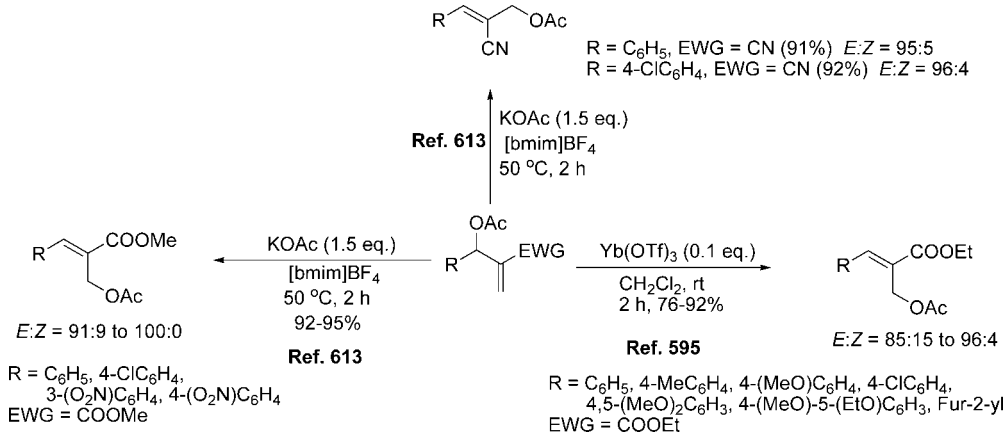
Scheme 195



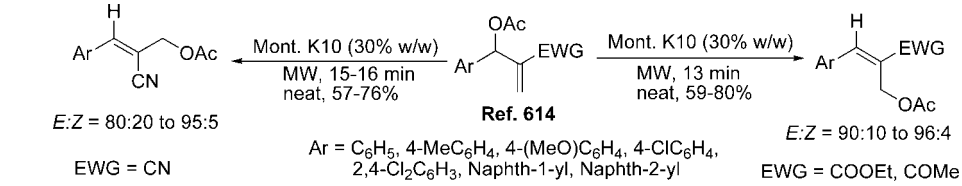
isomerization and hydrolysis using K_2CO_3 in a MeOH/H_2O system as shown in Path A, Scheme 195. Later on, Das and co-workers[612] reported a similar two-step protocol according to Path B, Scheme 195, for such isomerization. It is worth mentioning here that our research group[496] reported isomerization of the Baylis−Hillman alcohols 3-aryl-3-hydroxy-2-methylenepropanenitriles (obtained via the coupling of aromatic aldehydes and acrylonitrile) using 20% aq. H_2SO_4. We[609] earlier reported a one-pot two-step protocol for the conversion of methyl 3-aryl-3-hydroxy-2-methylenepropanoates into methyl (2*E*)-3-aryl-2-hydroxymethylprop-2-enoates via an acetylation, isomerization, and hydrolysis protocol.

Kabalka and co-workers[613] have reported an efficient rearrangement of Baylis−Hillman acetates into primary acetates by treating with KOAc in ionic liquid [bmim]BF_4. Representative examples are shown in Scheme 196. Krishna and co-workers[595] have reported similar rearrangement of Baylis−Hillman acetates under the influence of Yb$(OTf)_3$ in dichloromethane at room temperature (Scheme 196).

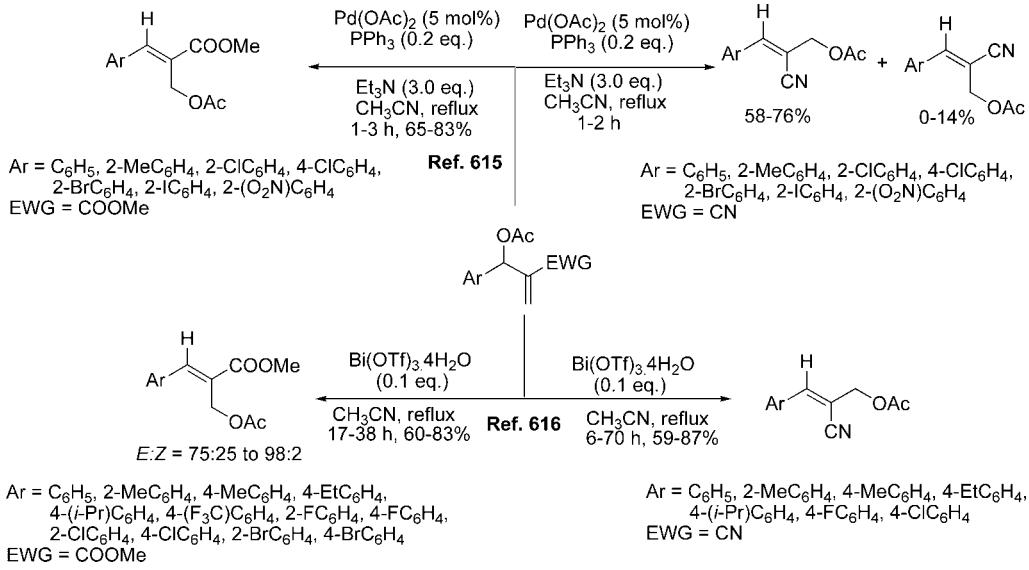
Scheme 196



Scheme 197

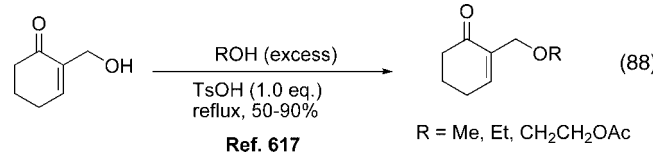


Scheme 198



The isomerization of the Baylis−Hillman acetates with a montmorillonite K10 clay−microwave combination to produce *E*-trisubstituted alkenes in high yields under solvent-free conditions was reported by Shanmugam and Rajasingh (Scheme 197).[614] In this study, they observed that Baylis−Hillman alcohols failed to give rearranged alcohols. Lee and co-workers[615] have used $Pd(OAc)_2$ as a catalyst for isomerization of acetates of Baylis−Hillman adducts at reflux temperature in acetonitrile. Very recently Ollevier and Mwene-Mbeja[616] have reported $Bi(OTf)_3$-catalyzed rearrangement of Baylis−Hillman acetates into the corresponding primary acetates. Representative examples are shown in Scheme 198.

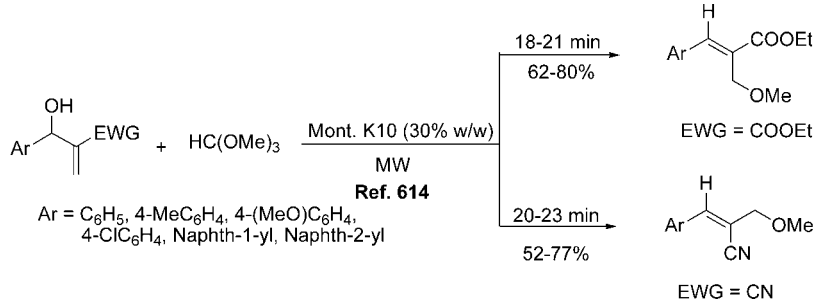
Transformation of the Baylis−Hillman alcohols into the corresponding ethers/rearranged ethers is an interesting endeavor. El Gaied and co-workers[617] have reported regioselective synthesis of ethers of Baylis−Hillman adduct (2-hydroxymethylcyclohex-2-enone) via the reaction with alcohols under the influence of TsOH at reflux temperature in moderate to good yields (eq 88). Subsequently, Jia and co-workers[618] reported the conversion of Baylis−Hillman adducts into ethers via the reaction with alcohols under the catalytic influence of $BiCl_3$ at reflux temperature. In this study, they[619] observed a remarkable solvent effect. Subsequently they found that $FeCl_3$ was also effective for this transformation. Representative examples are shown in eq 89.



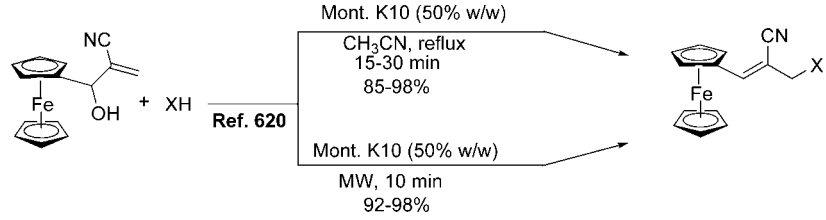
(88)

Shanmugam and Rajasingh[614] have reported a facile conversion of the Baylis−Hillman alcohols into trisubstituted alkenes via treatment with trimethyl orthoformate under solvent-free conditions using a montmorillonite K10 clay−

Scheme 199

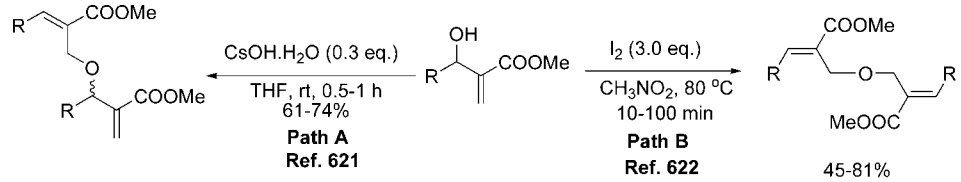


Scheme 200



XH = But-2-yne-1,4-diol, Propargyl alcohol, Allyl alcohol, Trimethyl orthoformate, Homopropargyl alcohol, Benzyl alcohol, Propane-1,3-diol, 4-Methylthiophenol, Benzylamine

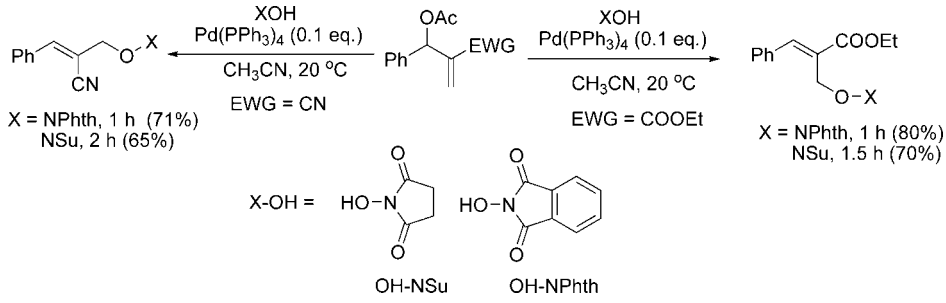
Scheme 201

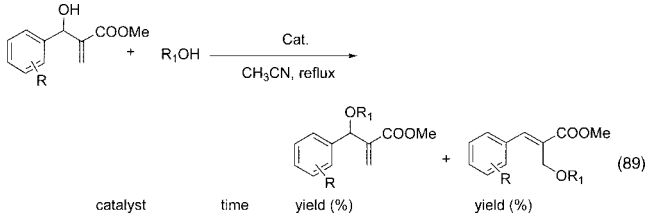


R = C_6H_5, 4-MeC_6H_4, 2-$(MeO)C_6H_4$, 4-$(MeO)C_6H_4$, 2-ClC_6H_4, 4-ClC_6H_4, 2-$(O_2N)C_6H_4$, 3-$(O_2N)C_6H_4$, 3,4-$(OCH_2O)C_6H_3$, Fur-2-yl

R = C_6H_5, 4-MeC_6H_4, 4-(*t*-Bu)C_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4

Scheme 202





R = H, 4-Me, 4-(*t*-Bu), 3-OMe, 4-OMe, 4-Cl
R_1 = Me, Et, *i*-Pr, *n*-Bu, *t*-Bu, CH_2CH_2Cl, Bn

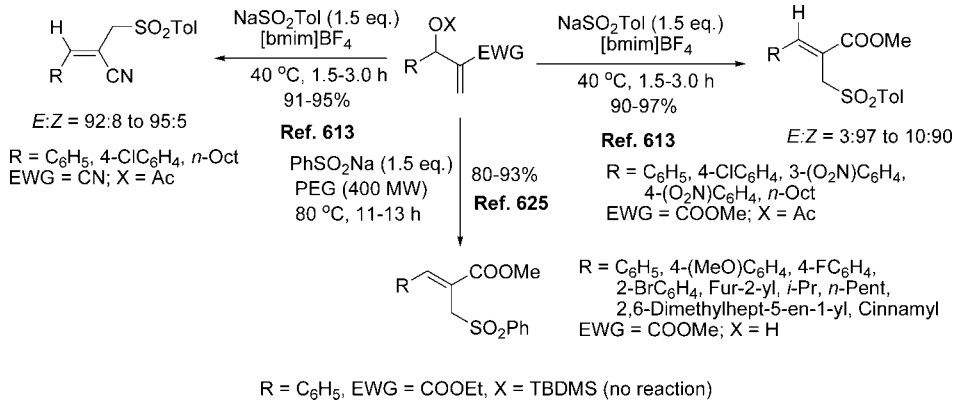
microwave combination (Scheme 199). Subsequently, Shanmugam and co-workers also extended this strategy for the Baylis−Hillman alcohols derived from ferrocenecarboxaldehyde.[620] Representative examples are shown in Scheme 200.

Zhang and co-workers[621] reported a facile methodology for preparation of unsymmetrical bis-allyl ethers via treatment of Baylis−Hillman alcohols with cesium hydroxide (cat.) in THF at room temperature. Later on, Jia and co-workers[622] used iodine in nitromethane as a reagent for the conversion of Baylis−Hillman alcohols into symmetrical allyl ethers. Representative examples are shown in Scheme 201.

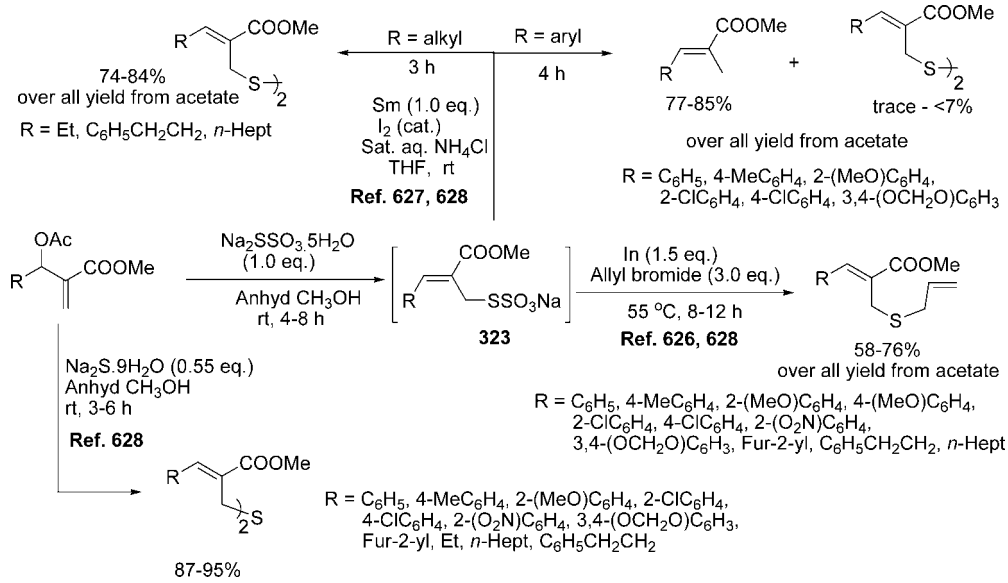
Bhuniya and co-workers[623] have reported Michael addition of oxygen-centered nucleophile oximes on Baylis−Hillman adducts under the catalytic influence of PPh_3 to provide the resulting adducts in good yields (eq 90). Deprotection of oximes with hydrogen (1.0 atm) in the presence of 10% Pd/C (cat.) gave functionalized 1,3-diols (eq 91).

Very recently, Reddy and co-workers[624] used hydroxylamide derivatives as the aminoxy-equivalent nucleophiles in palladium-catalyzed addition to Baylis−Hillman acetates in acetonitrile to produce the required products in good yields

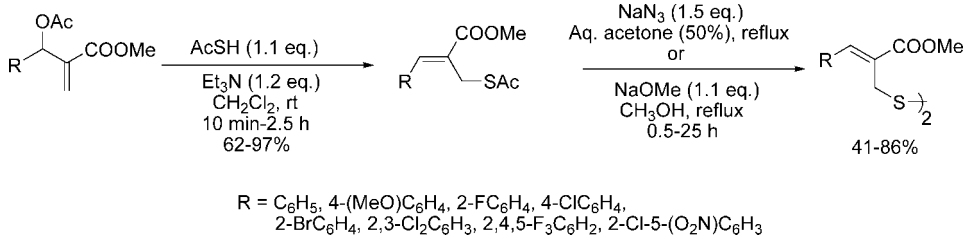
Scheme 203

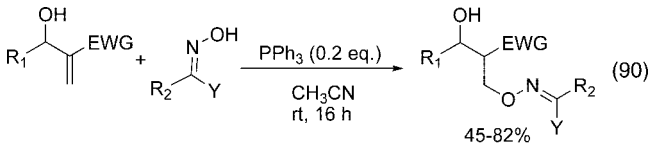


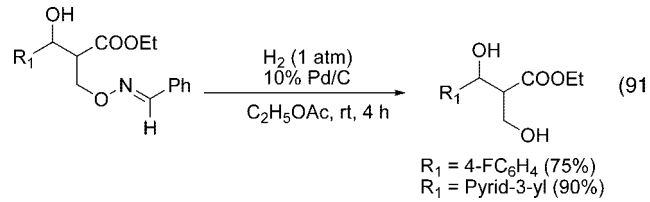
Scheme 204



Scheme 205





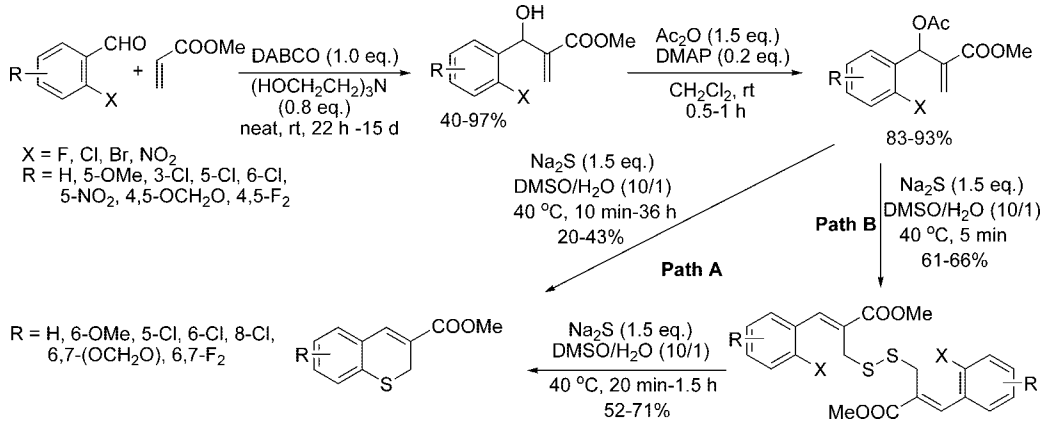


with (*E*)-selectivity. Representative examples are shown in Scheme 202.

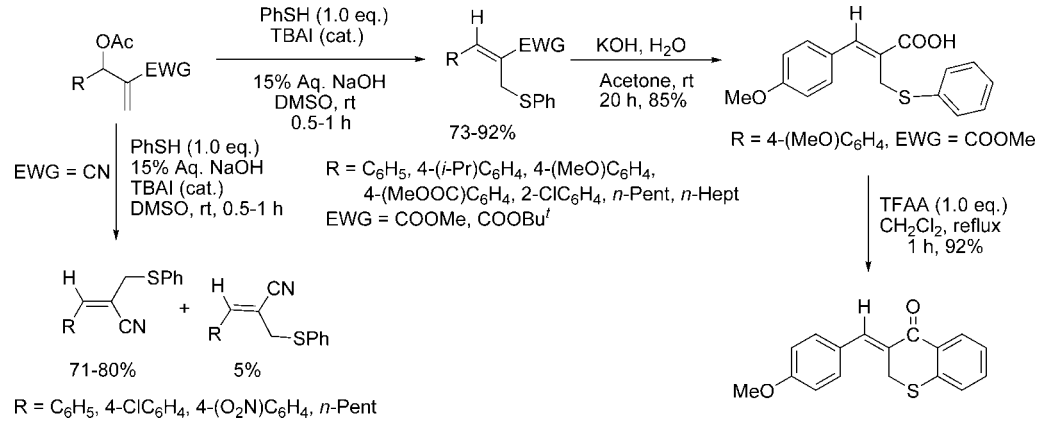
Kabalka and co-workers[613] have reported preparation of sulfones from Baylis−Hillman acetates in ionic liquids via treatment with sodium *p*-toluenesulfinate. Representative examples are shown in Scheme 203. Subsequently Chandrasekhar and co-workers[625] have reported nucleophilic addition of sodium phenylsulfinate in PEG (400 MW) onto Baylis−Hillman adducts (Scheme 203). In this study, they observed that *O-tert*-butyldimethylsilyl ether of Baylis−Hillman adducts failed to undergo a similar transformation.

Zhang and co-workers[626−628] have transformed acetates of Baylis−Hillman adducts into sodium (*Z*)-allylthiosulfates (**323**) in high isolated yields via the treatment with sodium thiosulfate in methanol (eq 92). These allyl thiosulfates generated *in situ* were transformed into unsymmetrical diallylsulfides via the treatment with allyl bromide in the

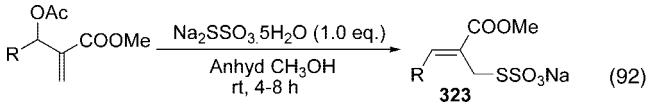
Scheme 206



Scheme 207



presence of indium. These allylthiosulfates, when R was alkyl, provided symmetrical diallylsulfides on treatment with samarium in the presence of iodine, while similar treatment of allylthiosulfates, when R was aryl, gave (2*E*)-α-methylcinnamates. They also converted the Baylis−Hillman acetates into symmetrical (*Z*)-diallylsulfides via treatment with sodium sulfide (Scheme 204).



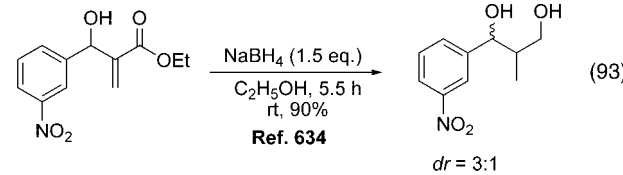
Later on, Lee and co-workers[629] reported synthesis of symmetric diallyl disulfides from the Baylis−Hillman acetates via treatment with thioacetic acid followed by the reaction of the resulting allylthio acetates with sodium azide or sodium methoxide (Scheme 205).

Lee and co-workers[630] have transformed the acetates of Baylis−Hillman alcohols derived from 2-halo or nitro benzaldehydes into 3-methoxycarbonyl-2*H*-thiochromenes following the reaction described in Path A, Scheme 206. They have also performed this transformation in two steps, that is, through isolation of intermediate disulfide followed by treatment with Na_2S (Path B, Scheme 206).

Later on, Das and co-workers[631] reported facile stereoselective synthesis of (*Z*)- (when EWG = COOR) and (*E*)- (when EWG = CN) allyl sulfides from Baylis−Hillman acetates via treatment with benzenethiol in the presence of catalytic amounts of 15% aqueous NaOH and TBAI in DMSO at room temperature (Scheme 207). (*Z*)-Allyl sulfide, [(*Z*)-3-(4-methoxyphenyl)-2-phenylthiomethylpropanoate], prepared in this way was transformed into (*Z*)-3-(4-methoxybenzylidene)thiochroman-4-one, a potent antifungal agent.

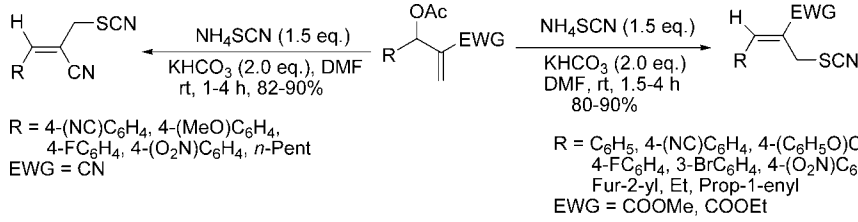
Srihari and co-workers[632] have reported a facile nucleophilic displacement of Baylis−Hillman acetates with ammonium thiocyanate at room temperature under mild basic conditions to provide allyl thiocyanate derivatives (Scheme 208).

(*E*)-3-(2-Isoxazolyl)-2-methylpropionamide derivatives have been synthesized from the Baylis−Hillman acetates via the reaction with $NaBH_4$, followed by hydrolysis and amide formation following the reaction sequence shown in Scheme 209 by Batra and co-workers.[633] These acrylamides have been investigated for biological activity. These authors have also transformed Baylis−Hillman alcohols into diols via treatment with $NaBH_4$.[634] One representative example is shown in eq 93.

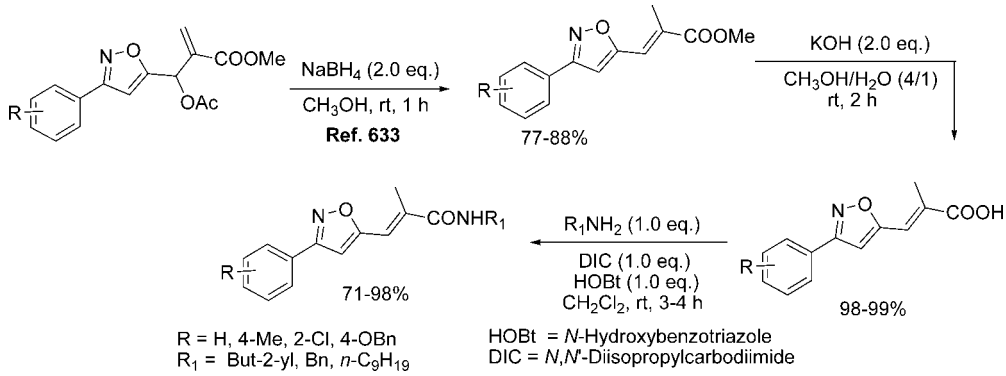


Zhang and co-workers[635] have examined the application of Sm/AcOH/EtOH as a reagent for reduction of Baylis−Hillman acetates. In these studies, they have demonstrated that these transformations were dependent on the quantity of samarium. Thus the Baylis−Hillman acetate on treatment with 1.5 equiv

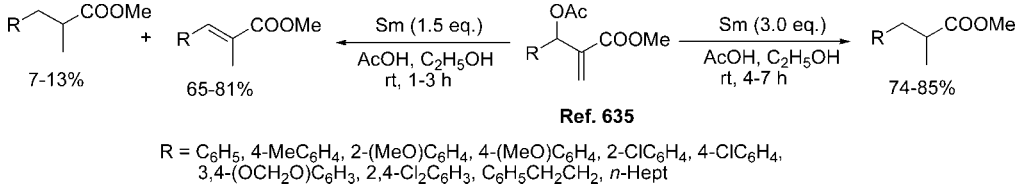
Scheme 208



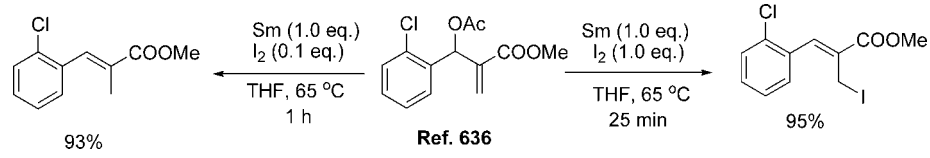
Scheme 209



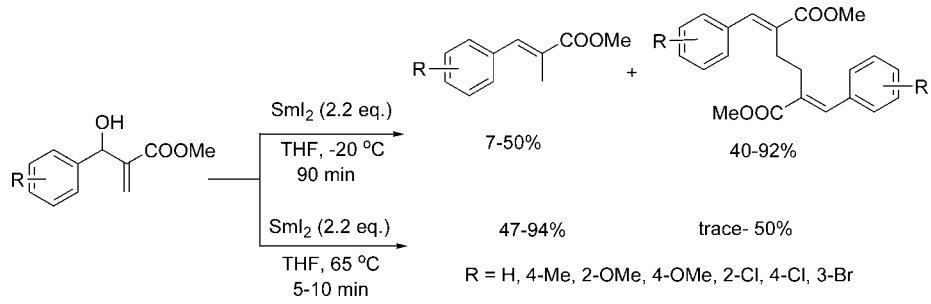
Scheme 210



Scheme 211



Scheme 212



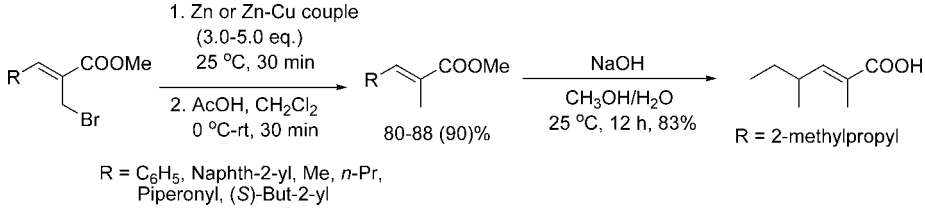
of samarium provided (2*E*)-2-methylalk-2-enoates as the major product, while treatment with 3.0 equiv of samarium resulted in exclusive formation of 2-methylalkanoates (Scheme 210). Subsequently Zhang and co-workers[636] used Sm (1.0 equiv) and I_2 (cat.) as a reagent for the reduction of Baylis−Hillman acetates, which provided the corresponding 2-methylalk-2-enoates. When they used Sm (1.0 equiv) and I_2 (1.0 equiv) the corresponding 2-iodomethylalk-2-enoates were obtained in high yields (Scheme 211).

Very recently, Jia and co-workers[637] developed samarium-promoted C-acetylation of Baylis−Hillman adducts in the presence of $FeCl_3$ and I_2. In this reaction, 2-methylalkenoates were also obtained in minor amounts (eq 94).

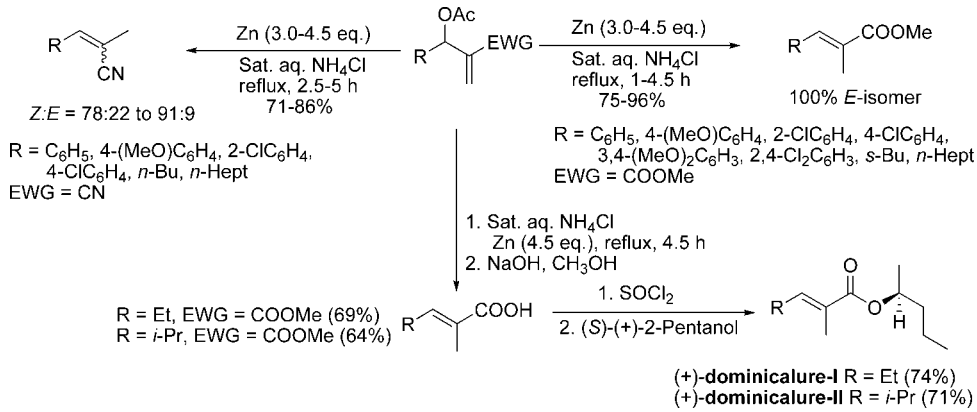
Samarium diiodide induced conversion of the Baylis−Hillman adducts to provide trisubstituted alkenes and 1,5-diene derivatives following the reaction sequence shown in Scheme 212 was described by Zhang and co-workers.[638] These reactions are found to be temperature dependent.

The Baylis−Hillman bromides have been conveniently transformed into 2-methylalk-2-enoates with (*E*)-configuration via treatment with zinc or zinc−copper couple in acetic acid by Sa and co-workers.[639] This methodology has been extended to the synthesis of racemic male ant pheromone, (*E*)-2,4-dimethyl-2-hexenoic acid (Scheme 213). Attempts at asymmetric synthesis of this pheromone starting from (*S*)-2-methylbutyraldehyde were not successful because the

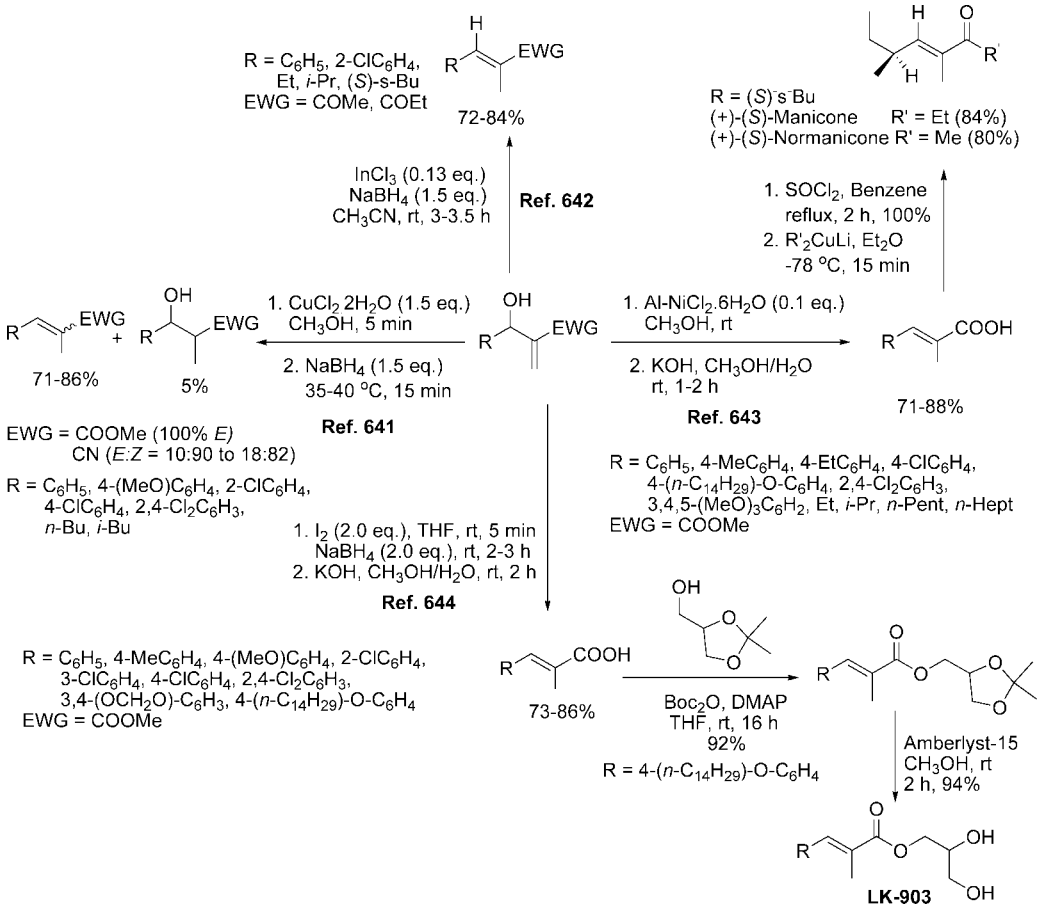
Scheme 213



Scheme 214



Scheme 215

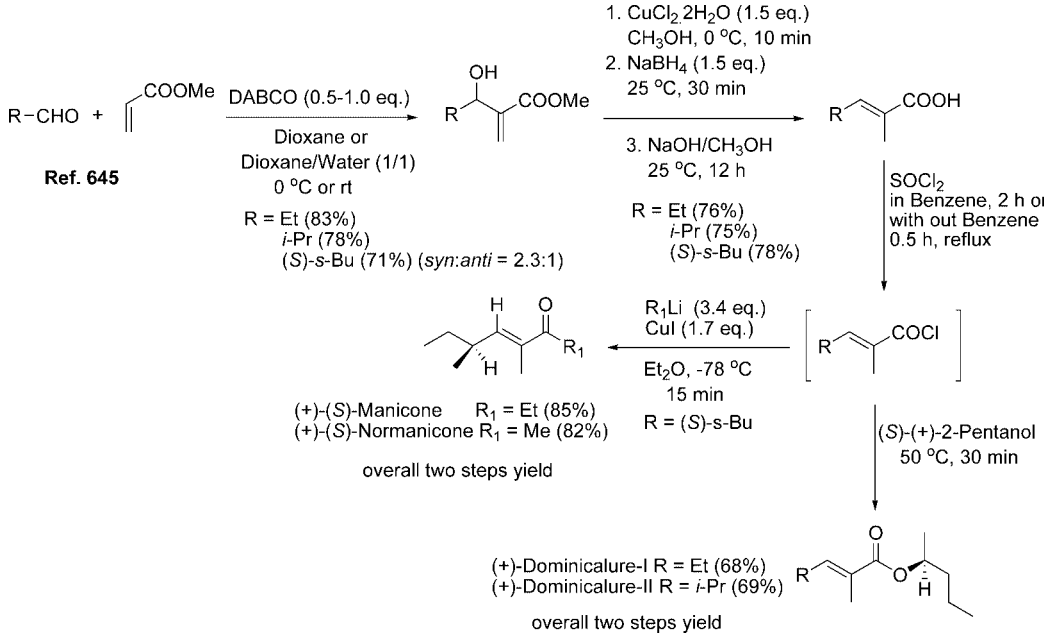


required pheromone was obtained in low enantiomeric purities (25% ee).

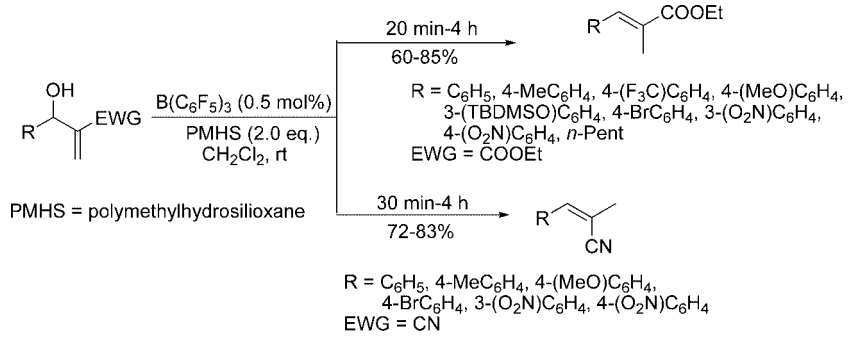
Zinc-induced transformation of acetates of Baylis−Hillman alcohols into trisubstituted olefins with high stereoselectivity was reported by Das and co-workers.[640] By this strategy, two insect pheromones, dominicalure-I and dominicalure-II, of the lesser grain borer *Rhyzopertha dominica* (F) have been synthesized in an enantioselective manner (Scheme 214).

Subsequently, Das and co-workers[641−645] have transformed the Baylis−Hillman alcohols into trisubstituted alkenes using (1) $CuCl_2 \cdot 2H_2O/NaBH_4$, (2) $InCl_3/NaBH_4$, (3) $Al-NiCl_2 \cdot 6H_2O$, and (4) $I_2/NaBH_4$ (Scheme 215). These

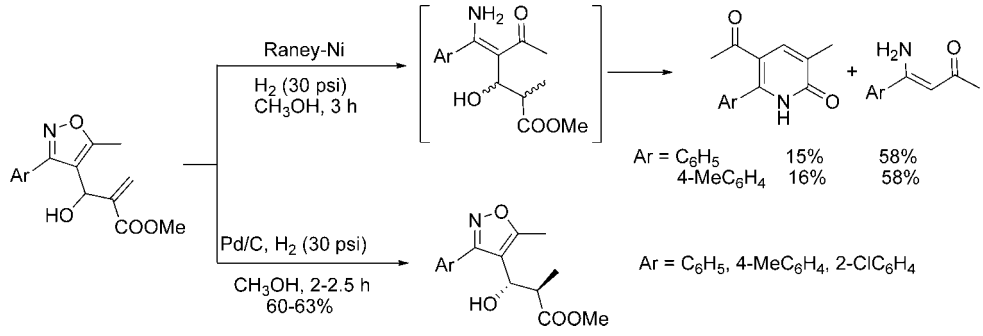
Scheme 216



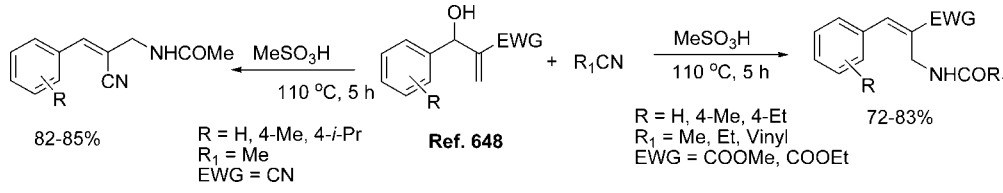
Scheme 217



Scheme 218

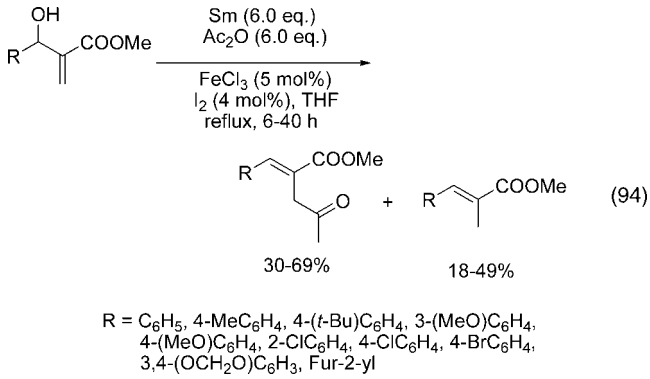


Scheme 219

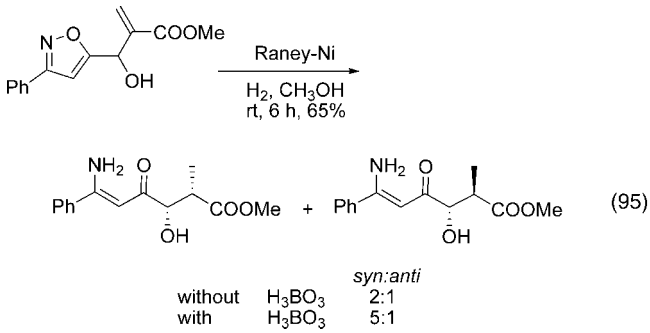


methodologies have been successfully employed for synthesis of pheromones and biologically active molecules, (1) (*E*)-2,4-dimethyl-2-hexenoic acid, (2) (+)-(*S*)-manicone, (3) (+)-(*S*)-normanicone, (4) dominicalure-I, (5) dominicalure-II, and (6) LK-903 (Schemes 215 and 216).

Chandrasekhar and co-workers[646] have used polymethylhydrosiloxane (PMHS) in the presence of $B(C_6F_5)_3$ for transformation of the Baylis−Hillman adducts into 2-methylalkanoates/alkanenitriles (Scheme 217).



Batra and co-workers[647] have examined Raney-Ni- and Pd/C-catalyzed hydrogenation of various Baylis−Hillman adducts derived from isoxazole-5-carboxaldehydes and activated alkenes. During their study, they found that hydrogenation of Baylis−Hillman adducts with Raney-Ni provided *syn* enaminones (via the opening of the isoxazole ring) as a major product. The presence of boric acid in the reaction provided better *syn* selectivity (eq 95). Similar hydrogenation of Baylis−Hillman adducts derived from isoxazole-4-carboxaldehyde derivatives using Pd−C gave *anti* isomer, without the cleavage of the isoxazole ring, while hydrogenation with Raney-Ni provided the decomposed products along with formation of the corresponding pyridine derivatives as minor products. Selected examples are shown in Scheme 218.



Our research group[648] during investigation to develop a facile synthesis of 2-benzazepine from Baylis−Hillman alcohols, has reported a simple conversion of the Baylis−Hillman alcohols into the corresponding (*Z*)-allyl amides (EWG = CN) and (*E*)-allyl amides (EWG = COOMe) under Ritter reaction conditions (Scheme 219). Das and co-workers[649] have subsequently transformed the Baylis−Hillman adducts into the corresponding allyl amides under the catalytic influence of Amberlyst-15 in acetonitrile at reflux temperature under heterogeneous conditions. In the absence of catalyst Amberlyst-15, allyl amides were not formed. Representative examples are shown in Scheme 220.

Li, Headley, and co-workers[650a] have reported an efficient nucleophilic substitution reaction of Baylis−Hillman halides in ionic liquid, [bmim][BF_4], at faster rates than reaction in organic solvents (Scheme 221). An interesting transformation of Baylis−Hillman bromides into 3-carbonylamino (or 3-phosphorylamino)-2-methylenealkanoates via the treatment with ethyl carbamate, diethyl phosphoramidate, diacetamide, and acrylamide in the presence of DABCO has been reported by Kim and co-workers.[650b] They have also used 2-amino-4-methoxy-6-methylpyrimidine as a nucleophile to produce the desired product **324** in 58% yield (Scheme 221).

The Baylis−Hillman adducts derived via the coupling of 3-aryl-5-isoxazolcarboxaldehydes (**15a**, R = Ph) as electrophiles with various activated alkenes were converted into 3-amino alcohols via treatment with various amines by Batra and co-workers.[651] The corrosponding Baylis−Hillman acetates were also converted into the trisubstituted alkenes and the amine derivatives **325**, following the reaction sequence shown in Scheme 222 (one example is presented). Some of these compounds were found to be antithrombotic agents.

Yadav and co-workers[652] have converted the Baylis−Hillman acetates into the corresponding (*E*)-ethyl 2-azidomethylpropenoates (EWG = COOEt) and (*Z*)-2-azidomethyl-3-arylpropenenitriles (EWG = CN) in excellent yields via treatment with sodium azide. Representative examples are shown in Scheme 223. Similarly, treatment of Baylis−Hillman acetates (EWG = CN) with NaCN provided the corresponding dicyano compounds in high yields with (*Z*)-selectivity.

Das and co-workers[653] reported stereoselective synthesis of allylamines from Baylis−Hillman acetates via the treatment with ammonium acetate in anhydrous methanol at room temperature in one-step (Scheme 224). Subsequently, Batra and co-workers[654] reexamined the same reaction and found the formation of tertiary and secondary allyl amines instead of primary allyl amines based on chemical and spectroscopic methods (Scheme 224). Later on, they[655] also reported a facile synthesis of allylamines from Baylis−Hillman acetates using methanolic ammonia.

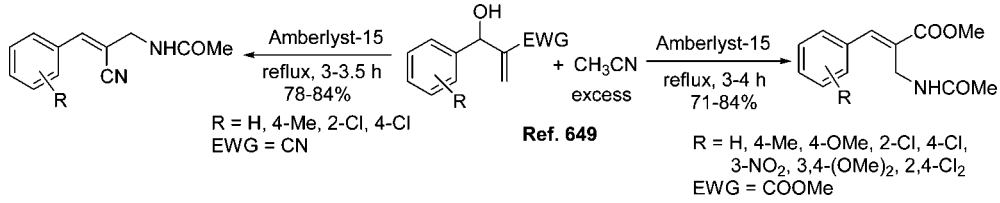
The Baylis−Hillman acetates were transformed into (*E*)-allyl amines (EWG = COOMe) and (*Z*)-allyl amines (EWG = CN) via treatment with primary amines, secondary amines, potassium phthalimide, and *p*-toluenesulfonylamide by Yoon and co-workers.[656] Allyl amine obtained from 3-(2-bromophenyl)-3-acetyl-2-methylenepropionate was converted into a quinoline derivative under Heck reaction conditions (Scheme 225).

Roy and co-workers[657] have reported synthesis of allyl amines from the acetates of Baylis−Hillman adducts via treatment with amines in the presence of a catalytic amount of ceric ammonium nitrate (CAN) (Scheme 226). Later on, Jia and co-workers[658] transformed the Baylis−Hillman acetates into allyl amines via reaction with alkyl or aryl amines under neat conditions.

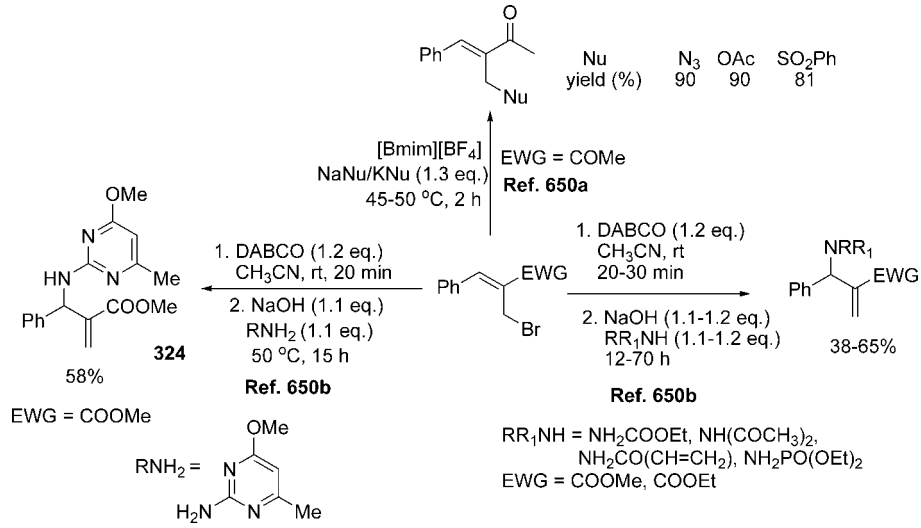
Krische and co-workers[659] have reported an interesting regiospecific allylic amination of Baylis−Hillman acetates under the catalytic influence of PPh_3 with nitrogen nucleophiles through a tandem $SN_2'-SN_2'$ substitution mechanism (Scheme 227). Subsequently, they developed the corresponding asymmetric version using chiral phosphine catalyst (*R*)-Cl-MeO-BIPHEP (**326**) to provide the resulting allyl amines in up to 56% ee. Subsequently, this strategy was extended to the acetates of Baylis−Hillman alcohols derived from vinyl diethylphosphonate to provide the desired allyl amines.[660] Representative examples are shown in Scheme 228.

Later on, Hou and co-workers[661] have used various planar chiral [2.2]paracyclophane monophosphines (**327a−f**) (Figure 61) as chiral catalysts for the asymmetric amination of the Baylis−Hillman acetates. The catalyst **327e** provided the best results thus providing the resulting allyl amine derivatives in up to 71% ee in the case of acetates of the Baylis−Hillman alcohols derived from aryl aldehydes and alkyl acrylates. The acetates of Baylis−Hillman alcohols derived from aliphatic aldehydes and acrylates provided the corresponding products in low yield and also in low

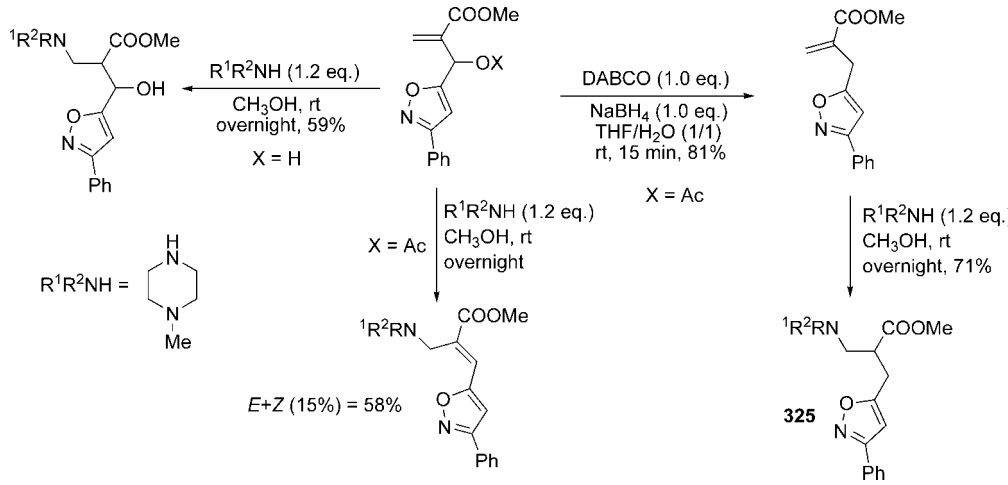
Scheme 220



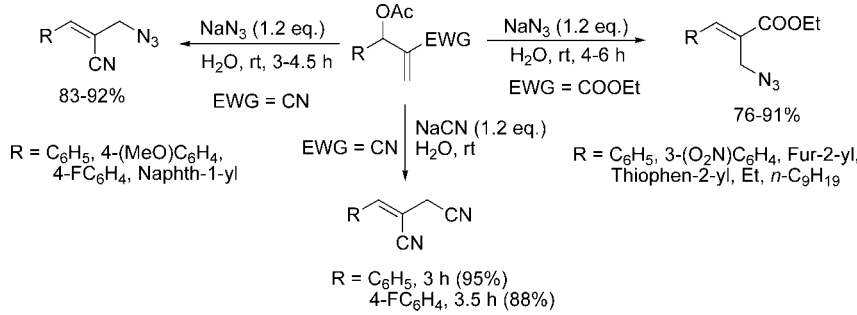
Scheme 221



Scheme 222



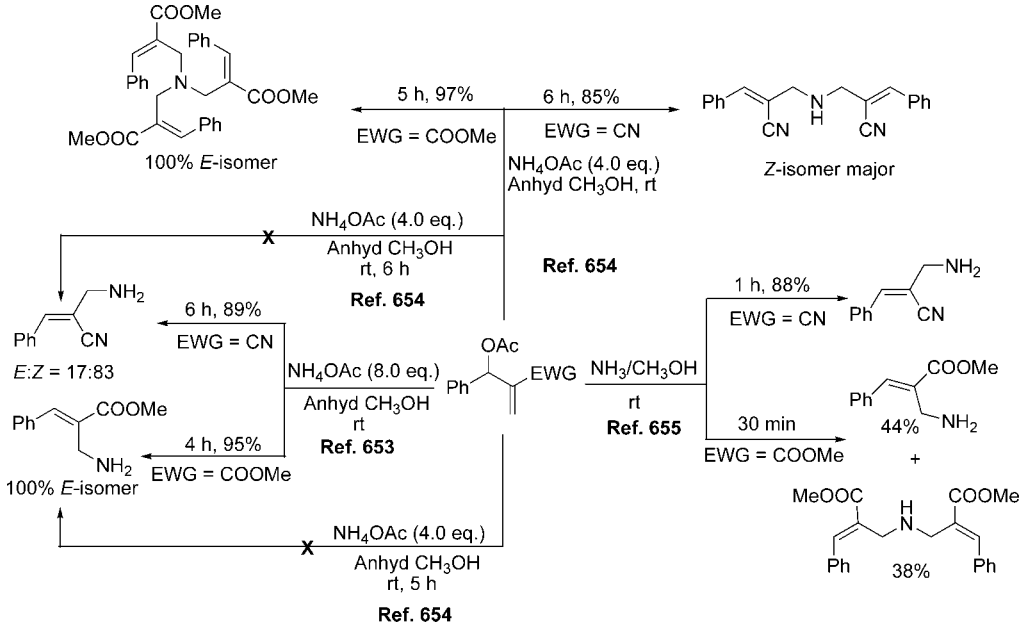
Scheme 223



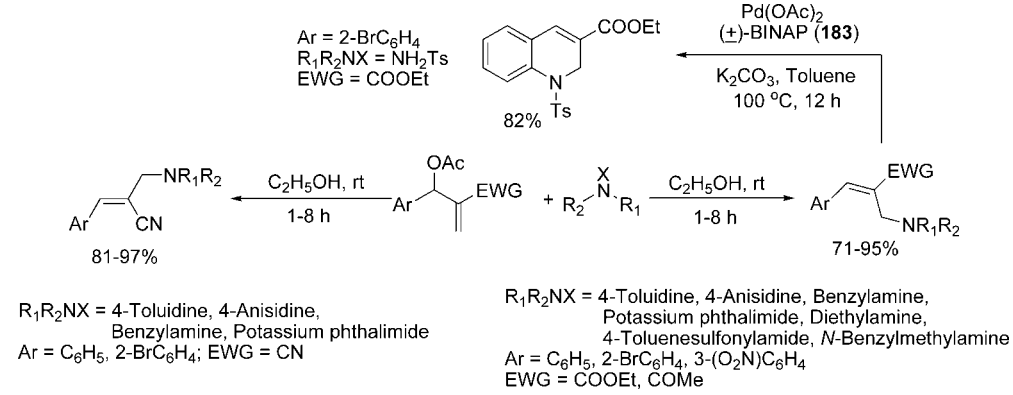
enantioselectivity (Scheme 229). They have also examined the potential of (*S*)-**256b** as a catalyst for this transformation and obtained low selectivity (25% ee). In these reactions, they also observed that acetates of Baylis−Hillman alcohols derived from MVK provided inferior enantioselectivities though the yields are high.

Very recently, Kim and co-workers[662] have disclosed an efficient synthetic approach for *N*-tosyl (or mesyl) allyl

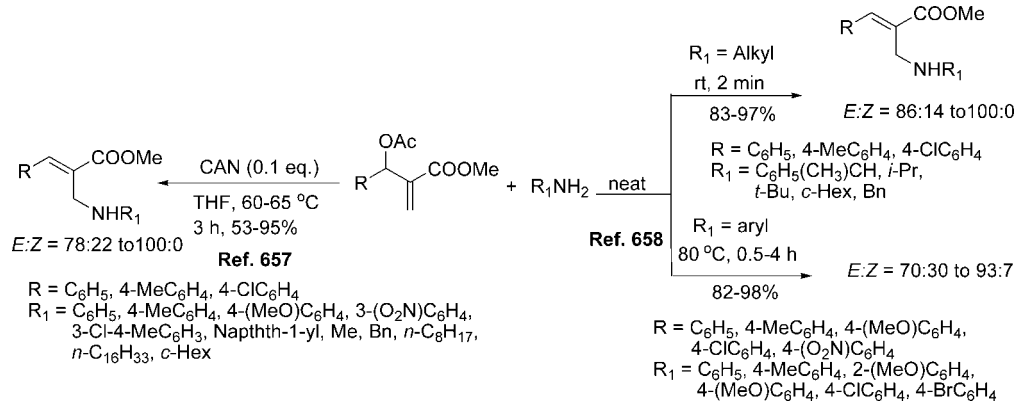
Scheme 224



Scheme 225



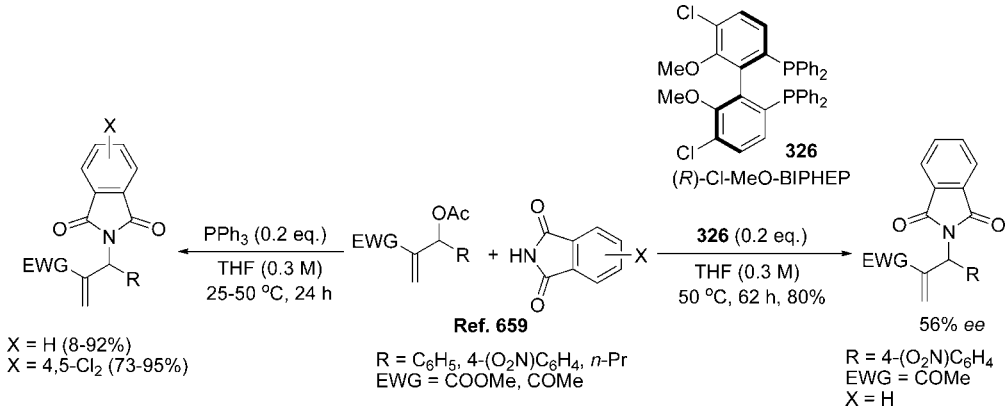
Scheme 226



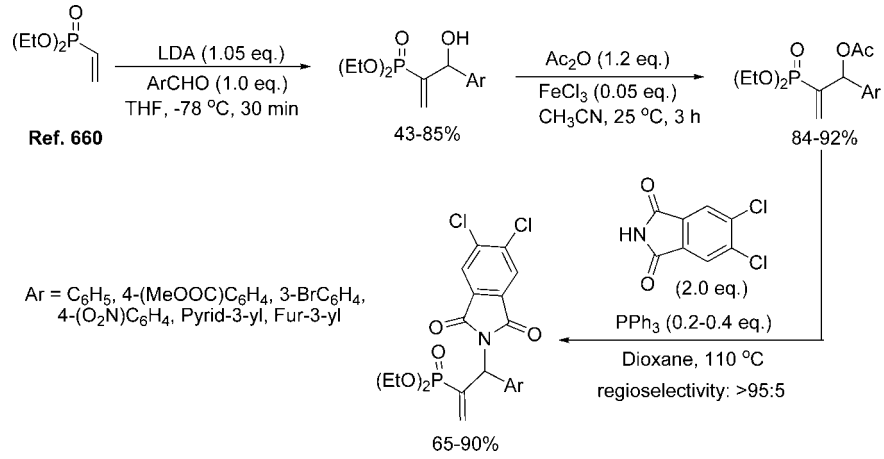
amines via the $FeCl_3$-mediated reaction between the Baylis−Hillman alcohols derived from cyclohex-2-enone or cyclopent-2-enone and tosyl amine (or methyl sulfonamide) (Scheme 230).

Zhang and co-workers[663] have transformed the Baylis−Hillman acetates into trisubstituted alkenes with (*E*)-stereoselectivity via treatment with imidazole and benzimidazole in the presence of water. They have also prepared 3-(imidazol-1-yl)-2-methylenepropionates via the treatment of Baylis−Hillman acetates first with DABCO and then with imidazole in the presence of water. Subsequently Su and co-workers[664] have converted the Baylis−Hillman acetates into (*E*)-1,2,4-triazole-substituted alkenes via the treatment with triazole. Cho and Kwon[665] have transformed the Baylis−Hillman acetates into 3-(pyrrol-1-yl)-2-methylenepropionate derivatives via treatment with 2.0 equiv of pyrrole derivatives. They have also examined the reaction between the acetate of Baylis−Hillman alcohol derived from (−)-8-phenylmenthyl acrylate and 2.0 equiv of pyrrole derivatives to provide the

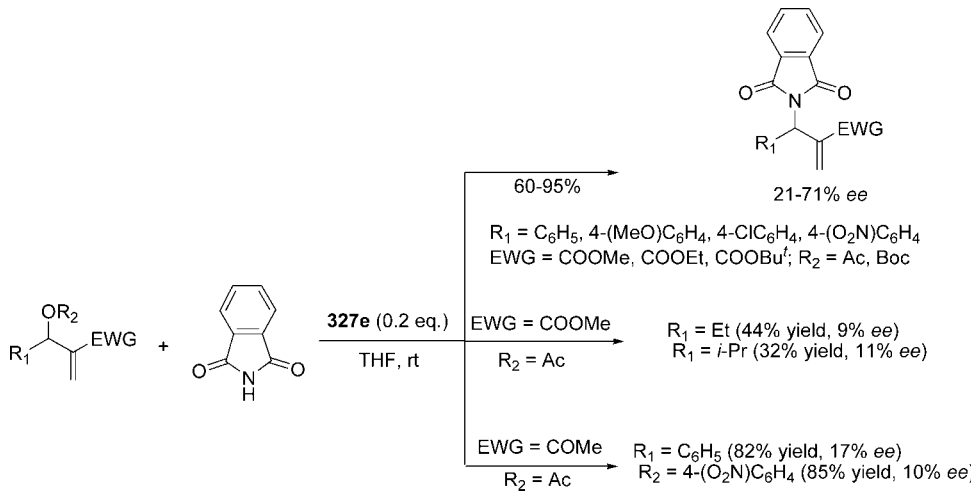
Scheme 227



Scheme 228



Scheme 229



resulting product in up to 7:1 diastereoselectivity. Representative examples are given in Scheme 231.

Ramachandran and co-workers[666] have transformed the Baylis−Hillman acetates into N-protected allyl amines following the reaction sequence shown in Scheme 232. This strategy involves the Overman rearrangement as the key step. Representative examples are given.

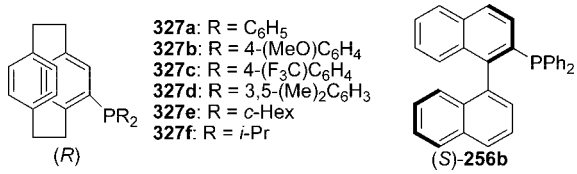
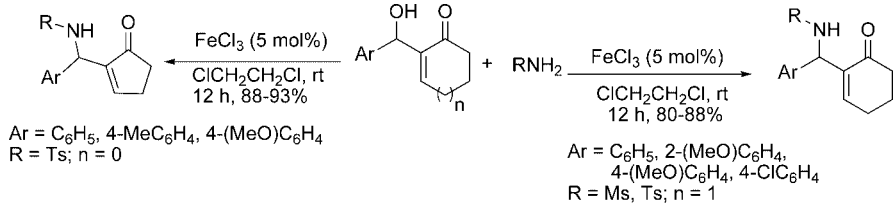


Figure 61.

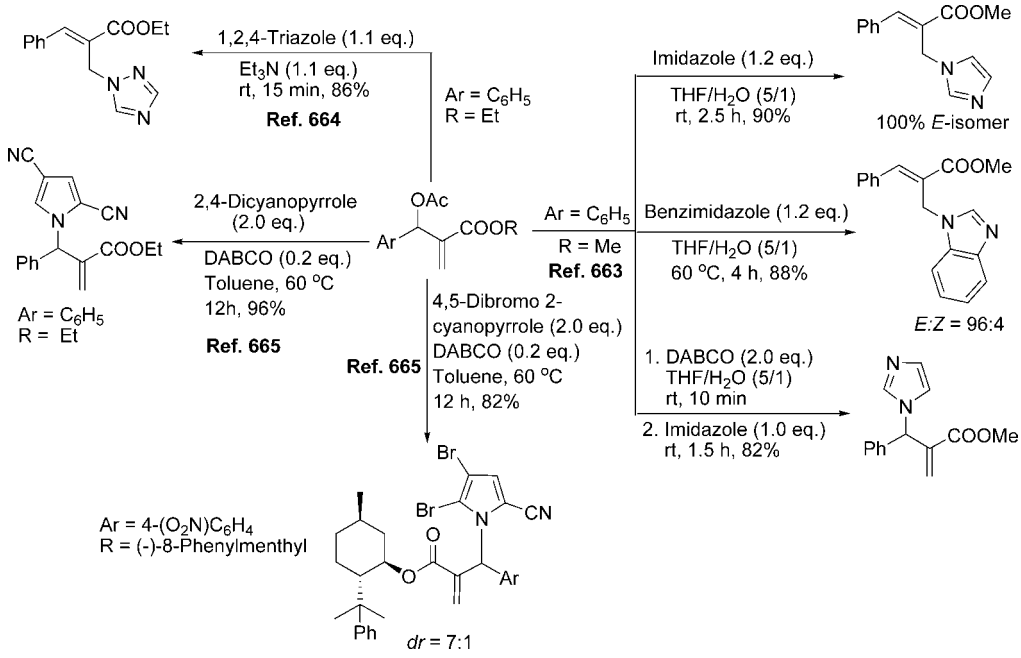
The Baylis−Hillman acetates were converted into β-nitroacrylic acid derivatives and β-nitro alcohols via treatment with $NaNO_2$−ceric ammonium nitrate (CAN).[667] A similar reaction with Baylis−Hillman alcohols provided β-nitro alcohols, which were subsequently transformed into 2-cyano-3-substituted acrylic esters following the reaction sequence shown in Scheme 233.

Mamaghani and Badrian[668] have reported one-pot transformation of Baylis−Hillman adducts into carbamates of

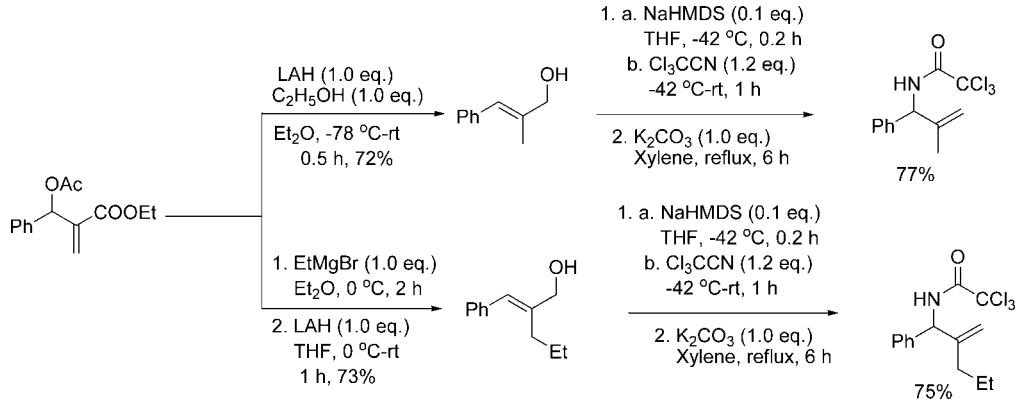
Scheme 230



Scheme 231



Scheme 232

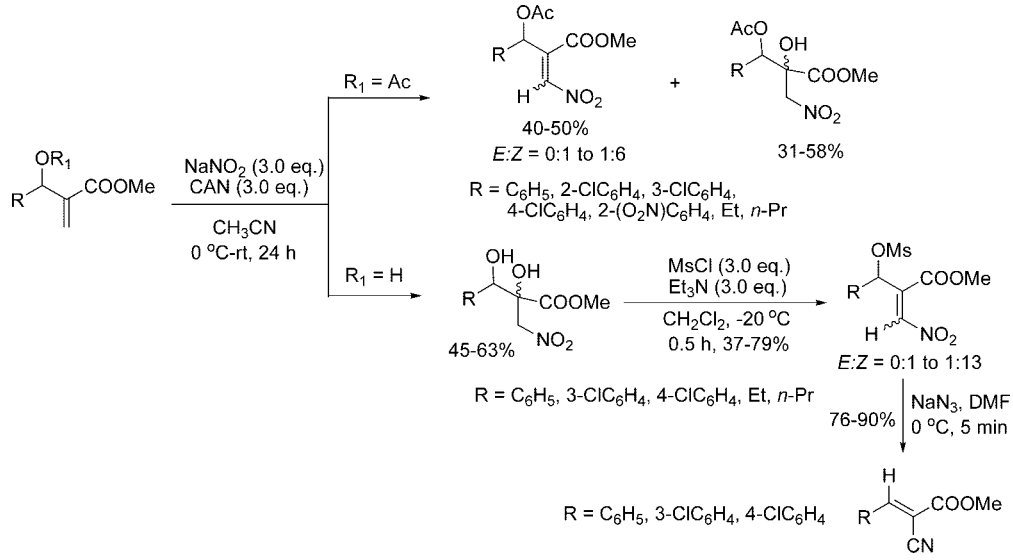


unsaturated β-amino acids using Burgess reagent [methyl *N*-(triethylammoniumsulfonyl) carbamate] under mild conditions. Representative examples are shown in Scheme 234.

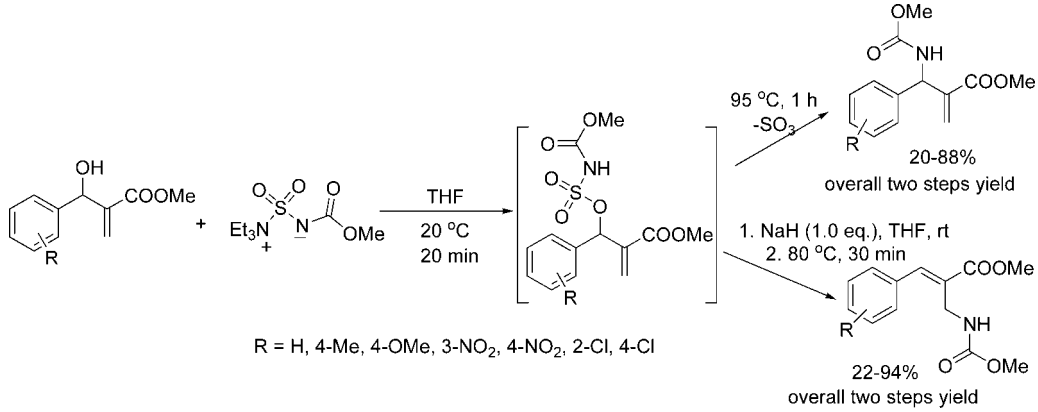
Yadav and co-workers[669] have reported one-pot synthesis of β-thiocyanato- or β -phenylsulfenyl-α-cyanohydrocinnamaldehydes with high diastereoselectivity via the conjugate addition of sulfur-centered nucleophiles, such as ammonium thiocyanate or thiophenol, onto (*Z*)-cyanocinnamaldehydes derived via the oxidation of Baylis−Hillman adducts (obtained from aromatic aldehydes and acrylonitrile) with $NaNO_3$ in the Brønsted acidic ionic liquid [Hmim]HSO_4 (Scheme 235). Subsequently, they[670] also extended this strategy to the Baylis−Hillman adducts derived from methyl acrylate. Representative examples are shown in Scheme 235. The Baylis−Hillman adducts were *in situ* oxidized with IBX in ionic liquid to give 2-methylene-3-oxo derivatives, which on treatment with TMSCN provided 2-cyanomethyl-3-oxo derivatives.[671] Similar oxidation of Baylis−Hillman alcohols with $NaNO_3$ in acidic ionic liquid [Hmim]HSO_4 provided rearranged oxidized product (**328**) *in situ*, which on treatment with TMSCN provided 3-cyano-2-formylalkanoates or alkanenitriles with *syn* selectivity (Scheme 236).

Das and co-workers[672] have developed simple methodology for synthesis of (*E*)- and (*Z*)-trisubstituted alkenes starting from the acetates of Baylis−Hillman adducts via treatment with alkyl iodides in the presence of Zn in saturated aqueous NH_4Cl solution at room temperature (Scheme 237). This methodology has been extended to the synthesis of an alarm pheromone component (**329**) of the African weaver ant, *Oecophylla longinoda*.

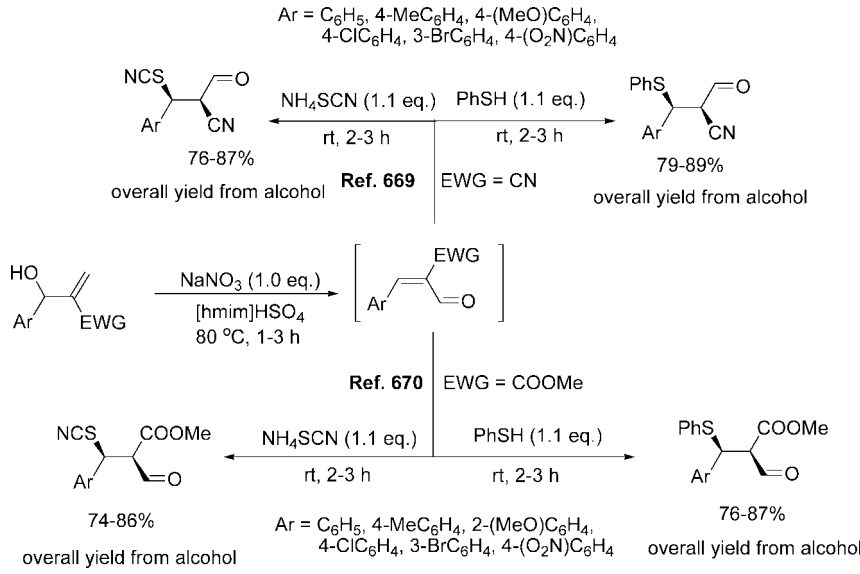
Scheme 233



Scheme 234



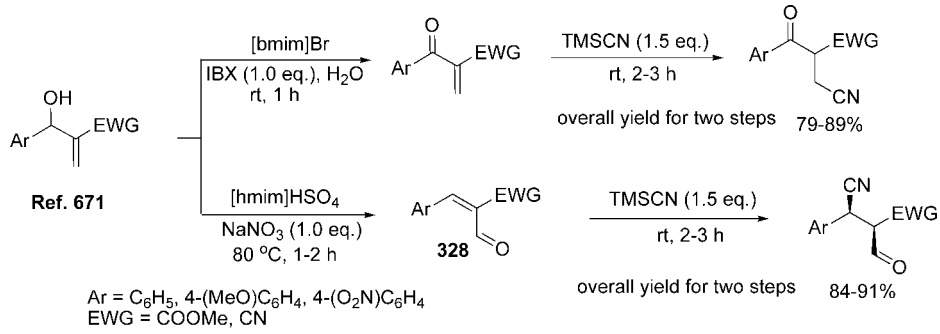
Scheme 235



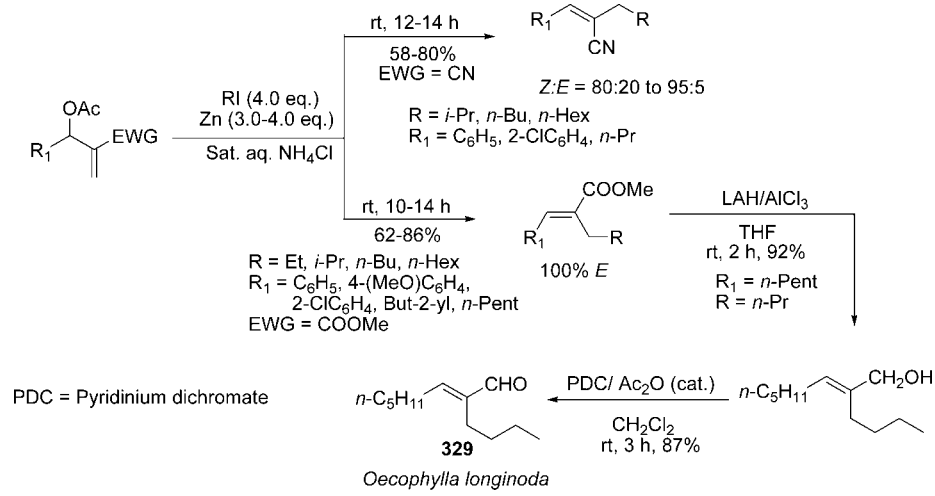
Amri and co-workers[673] transformed the Baylis−Hillman acetates into trisubstituted alkenes (homo allylsilanes) with high (*Z*)-stereoselectivity via treatment with trimethylsilylmethylmagnesium chloride in the presence of $LiCuBr_2$ (cat.) (Path A, Scheme 238). They[674] have extended this strategy to vinylmagnesium chloride as nucleophile leading to an interesting methodology for synthesis of 1,4-dienes with (*E*)-stereoselectivity (Path B, Scheme 238).

Subsequently, Kim and co-workers[675] converted acetates of the Baylis−Hillman adducts into ene−ynamide derivatives via treatment with alkynyl Grignard reagents followed by

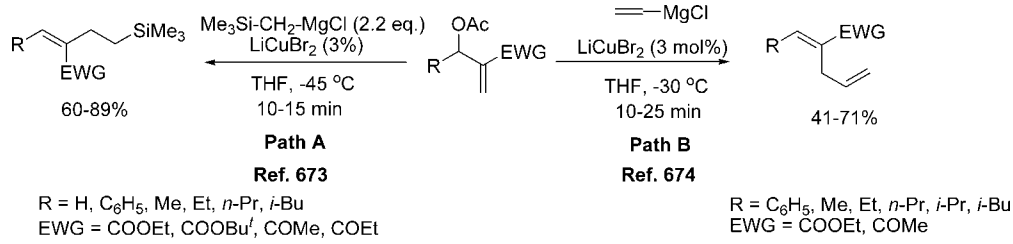
Scheme 236



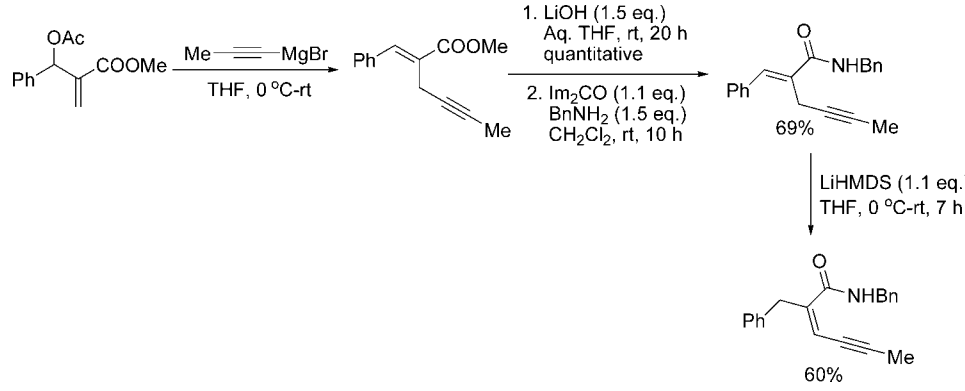
Scheme 237



Scheme 238



Scheme 239

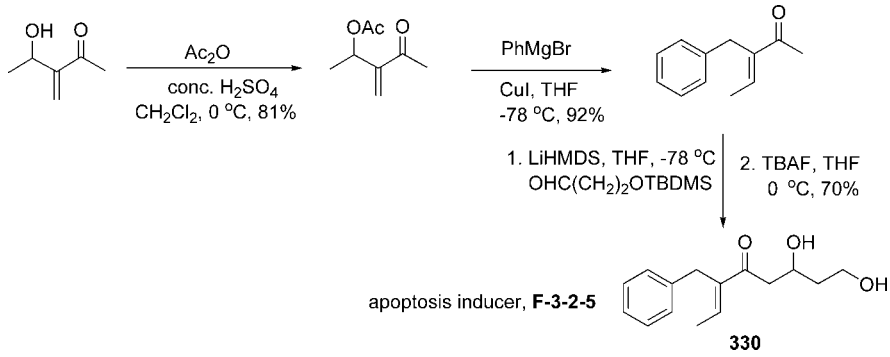


hydrolysis and amide formation, following the reaction sequence shown in Scheme 239 (one example is presented).

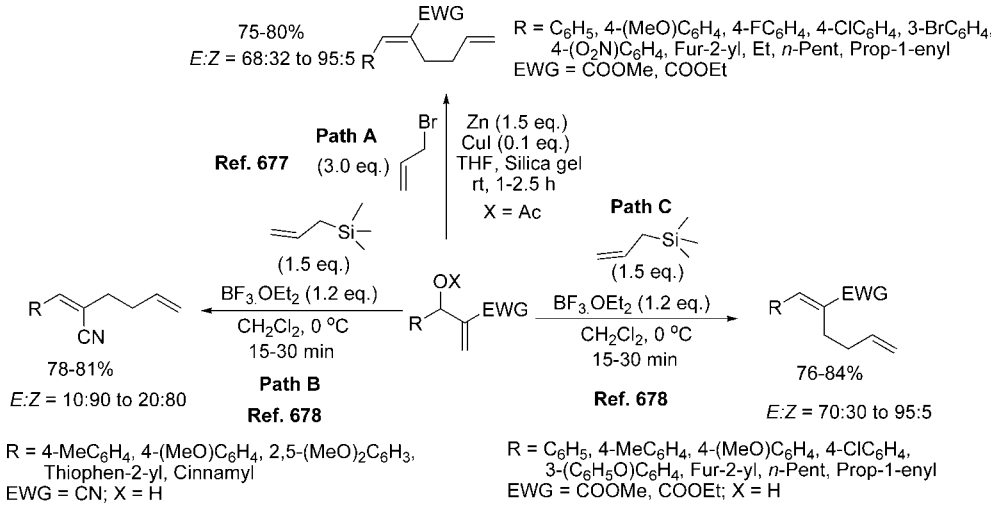
Very recently, Choo and co-workers[676] described an efficient synthesis of a novel apoptosis inducer, F-3-2-5 (**330**), starting from the Baylis−Hillman alcohol obtained via the coupling between MVK and acetaldehyde, following the reaction sequence shown in Scheme 240.

Allylation of the Baylis−Hillman acetates using allyl bromide in the presence of zinc and copper iodide to provide 1,5-dienes was reported by Srihari and co-workers (Path A, Scheme 241).[677] Later on, Yadav and co-workers[678] converted the Baylis−Hillman alcohols into 1,5-dienes via treatment with allyltrimethylsilane in the presence of $BF_3 \cdot OEt_2$ (Path B and C, Scheme 241).

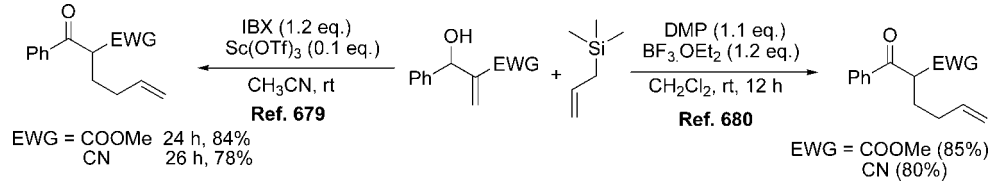
Scheme 240



Scheme 241



Scheme 242



An interesting IBX/$Sc(OTf)_3$-promoted oxidative allylation of Baylis−Hillman adducts with allyltrimethylsilane to provide various homoallylated keto ester derivatives was reported by Yadav and co-workers.[679] Dess−Martin periodinane (DMP)/$BF_3 \cdot OEt_2$ was also found to be effective for performing a similar reaction.[680] One example for each condition is presented in Scheme 242.

Ranu and co-workers[681] have used triarylindium as an efficient reagent for alkylation of Baylis−Hillman acetates in the presence of CuI (Path A, Scheme 243) and $Pd(PPh_3)_4$ (Path B and C, Scheme 243). Xu and Zhang and co-workers have demonstrated CCl_4 as an excellent reagent for alkylation of Baylis−Hillman acetates in the presence of $Al/PbCl_2$ to provide the corresponding trisubstituted alkenes (Path D, Scheme 243).[682]

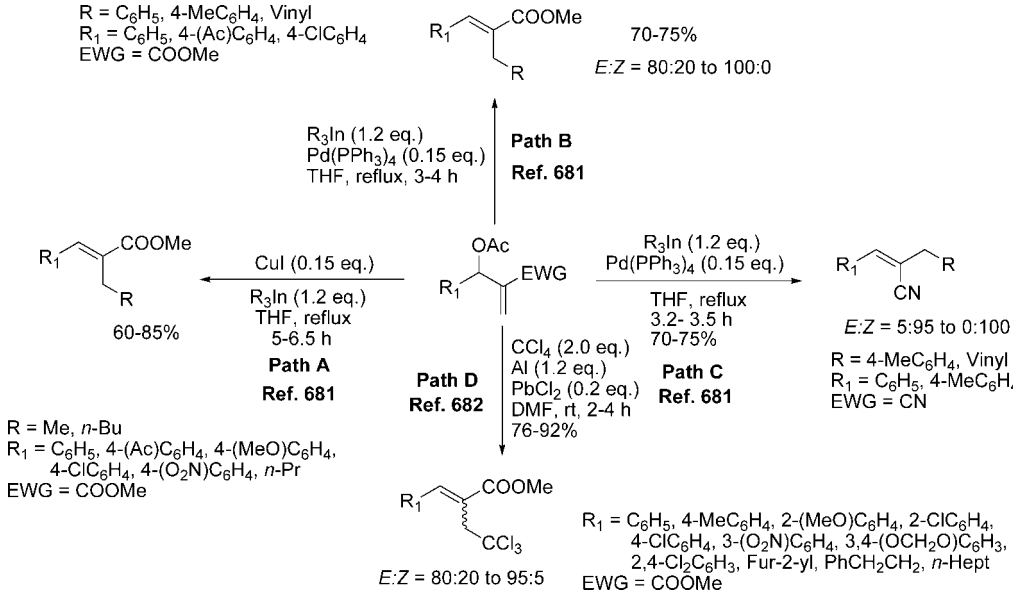
Very recently, Yadav and co-workers[683] have transformed the Baylis−Hillman acetates into 1,4-enynes with (*Z*)-stereoselectivity (EWG = CN) and (*E*)-stereoselectivity (EWG = COOR) via the reaction with iodoalkynes in the presence of indium (2.0 equiv) and $InBr_3$ (Scheme 244). In these reactions, minor amounts of S_N2' products were also obtained.

Acetates of the Baylis−Hillman alcohols derived from formaldehyde were transformed into 2-methylenealkanoates via treatment with benzyl halides in the presence of titanocene(III) chloride (Cp_2TiCl) by Roy and co-workers.[684] Similarly, acetates of the Baylis−Hillman alcohols derived from aromatic aldehydes were converted into trisubstituted alkenes following this strtagey. They have extended the same strategy for epoxides instead of benzyl halides, which provided α-methylene- or arylidene-δ-lactone derivatives. One representative example for each kind is given in Scheme 245.

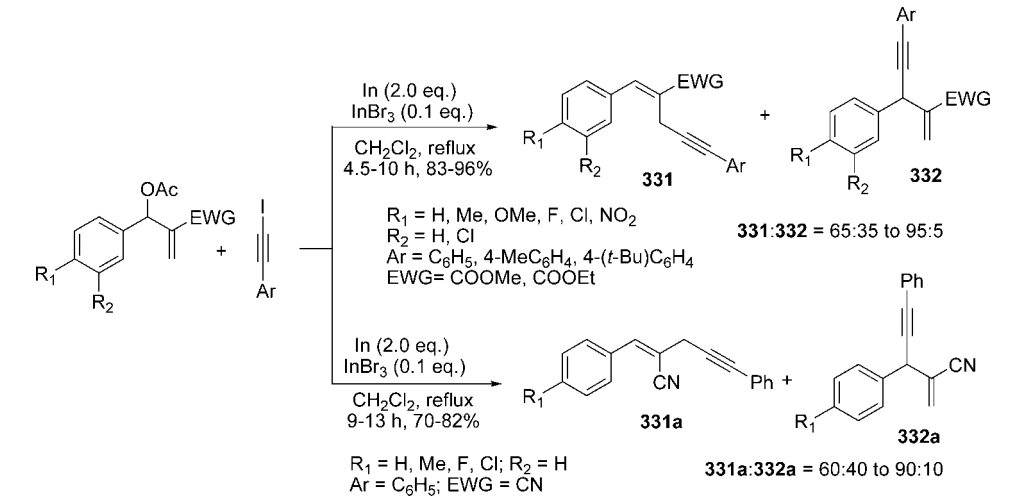
Woodward and co-workers[685] have transformed the Baylis−Hillman bromides and chlorides into β,β-disubstituted α-methylenepropionate derivatives via treatment with dialkyl zinc derivatives in the presence of $[Cu(MeCN)_4]BF_4$ or $CuCN/NBu_4Br$ (Scheme 246).

The Baylis−Hillman acetates and bromides were transformed into the corresponding allyl cyanides via treatment with NaCN under the influence of phase-transfer catalyst in aqueous medium by Batra and co-workers.[686] Subsequently allyl cyanides were transformed into succinimides via the partial hydrolysis of the cyano group followed by cyclization (Scheme 247).

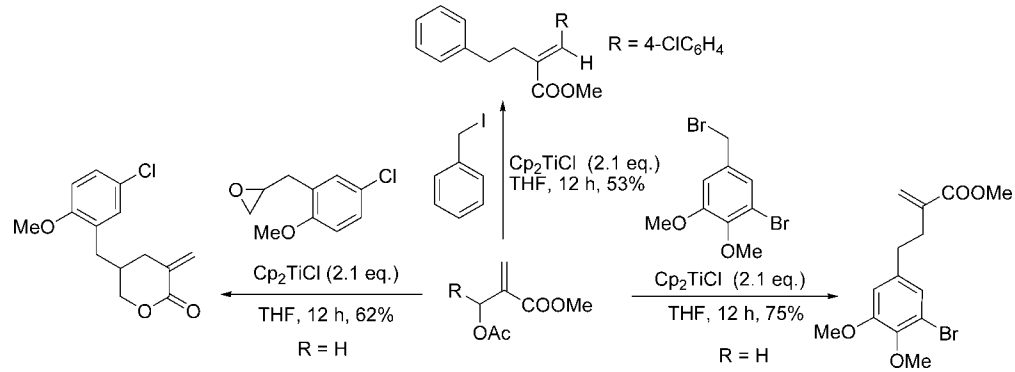
Scheme 243



Scheme 244



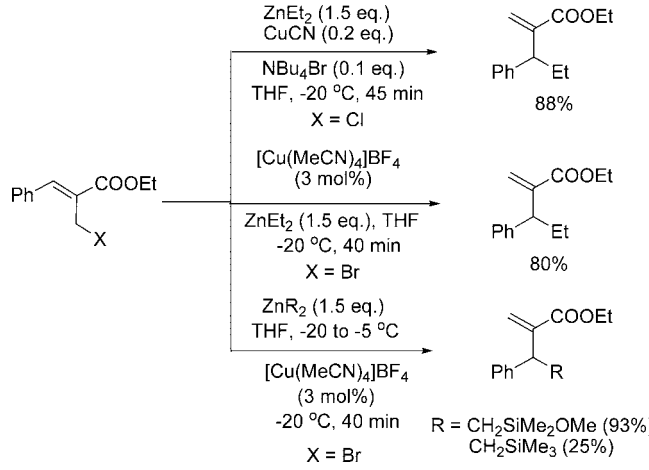
Scheme 245



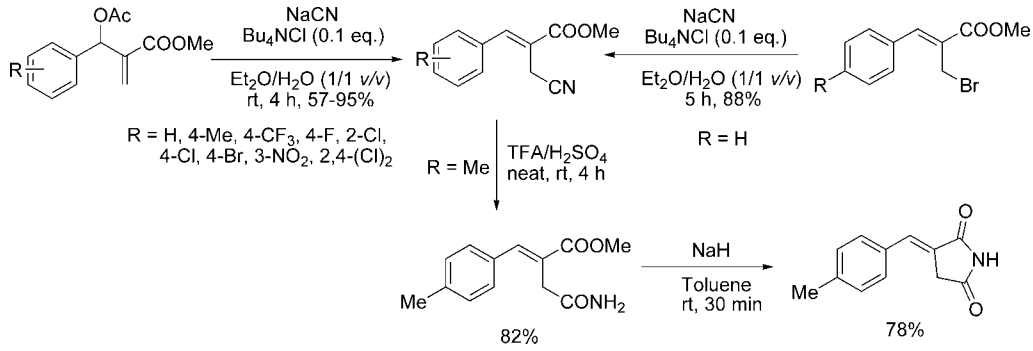
A facile cross-coupling of potassium organotrifluoroborates with acetates of Baylis−Hillman adducts under the catalytic influence of $Pd(OAc)_2$ providing the trisubstituted alkenes with high stereoselectivity was reported by Kabalka and co-workers.[687] When the EWG is COOMe, minor amounts of 2-methylene alkanoates were also obtained (Scheme 248). Later on, they[688] also employed organosilanes for coupling with Baylis−Hillman acetates under the influence of $Pd_2(dba)_3$ using poly(ethylene glycol) (PEG) as a solvent to provide the corresponding trisubstituted alkenes. A similar reaction with acetates of the Baylis−Hillman alcohols derived from cyclohex-2-enone and cyclopent-2-enone provided 2-(α-substituted alkyl)cyclohex-2-enones and 2-(α-substituted alkyl)cyclopent-2-enones (Scheme 249).

Genet and co-workers[689,690] described an interesting rhodium-catalyzed coupling of Baylis−Hillman adducts with arylboronic acids and potassium trifluoro(organo)bo-

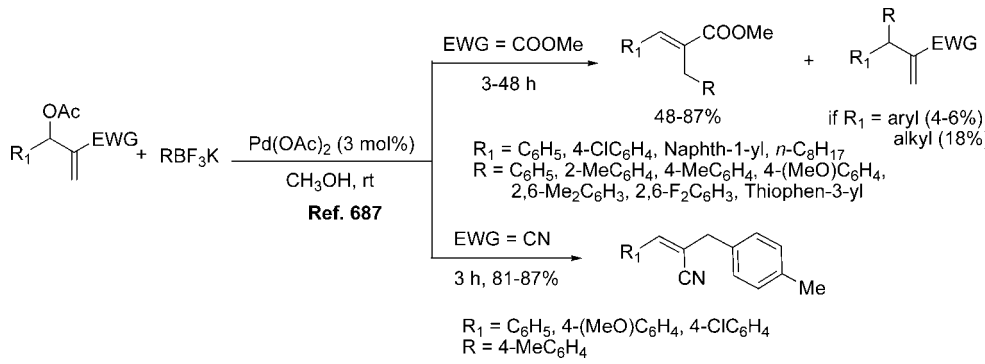
Scheme 246



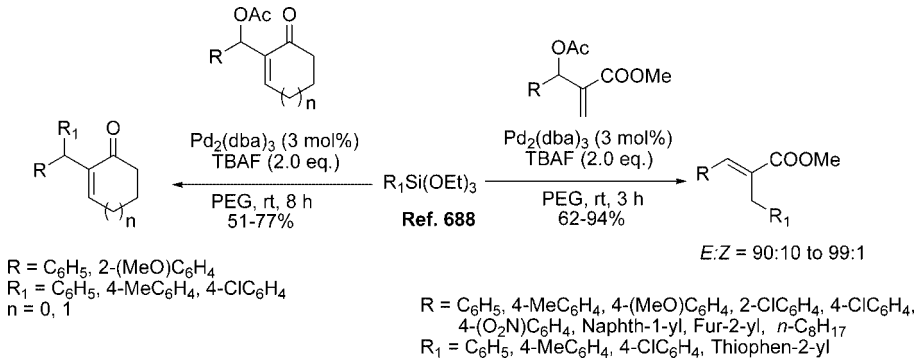
Scheme 247



Scheme 248



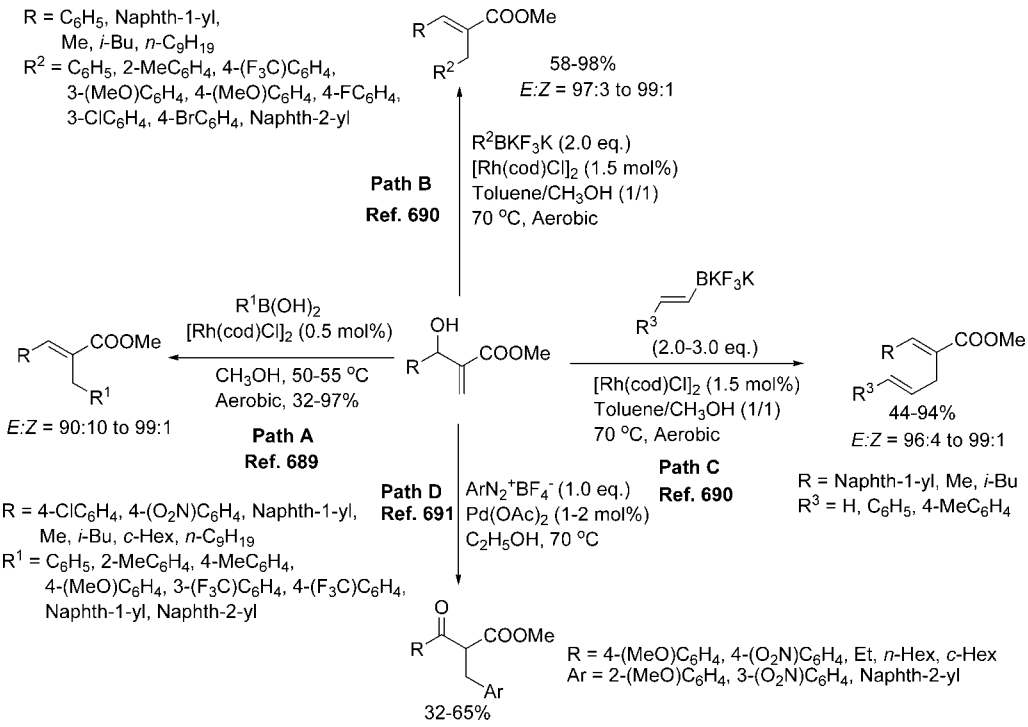
Scheme 249



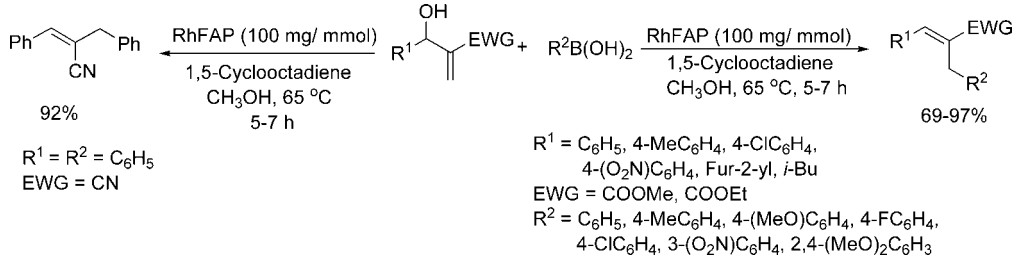
rates to afford trisubstituted alkenes in good yields (Paths A−C, Scheme 250). Subsequently coupling of arenediazonium tetrafluoroborate salts with Baylis−Hillman adducts catalyzed by $Pd(OAc)_2$ to provide α-benzyl-β-keto esters was reported by Antunes and co-workers[691] (Path D, Scheme 250).

Very recently, rhodium-exchanged fluorapatite (RhFAP) was used by Kantam and co-workers as recoverable and

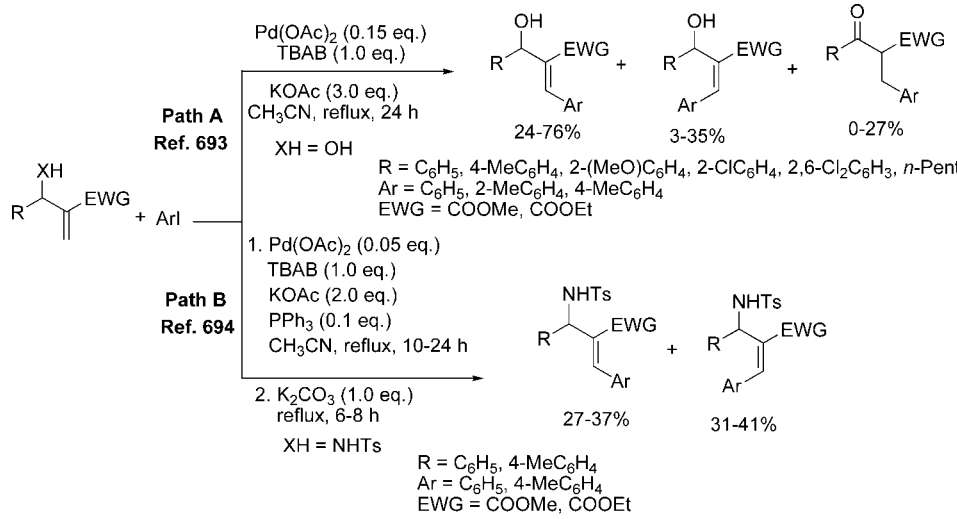
Scheme 250



Scheme 251



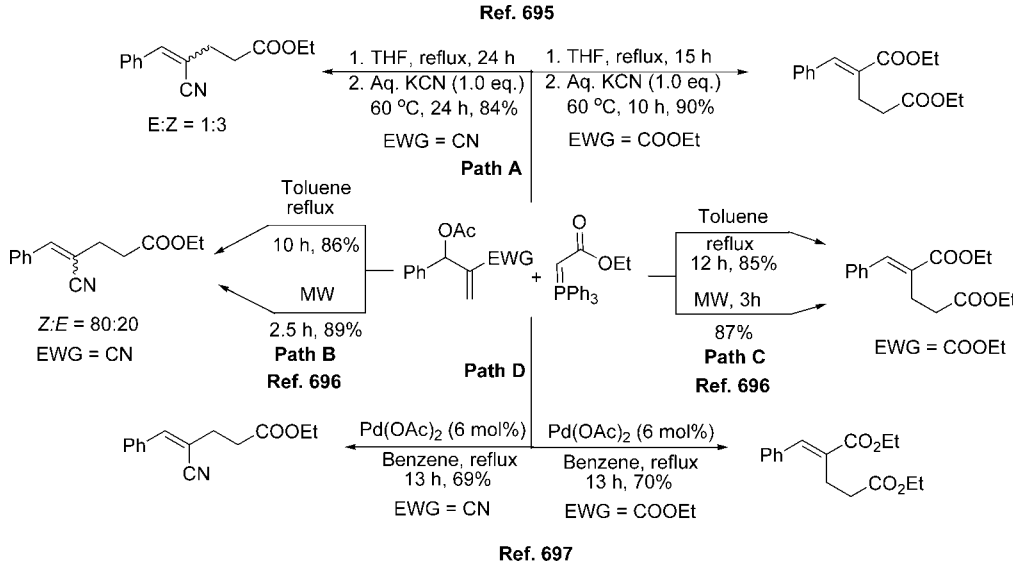
Scheme 252



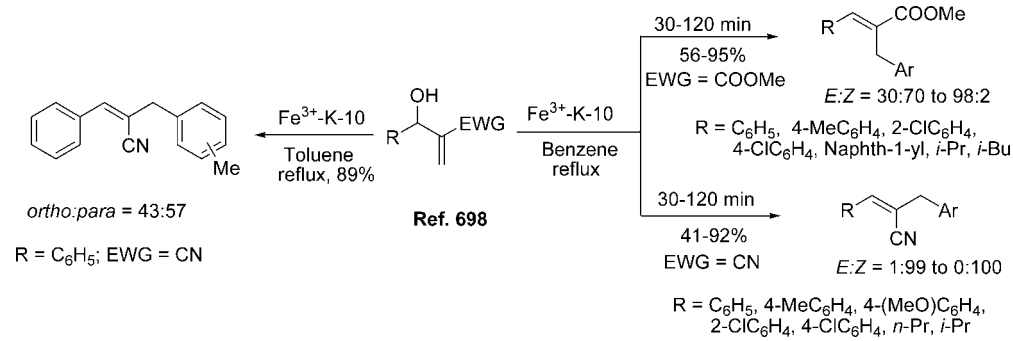
reusable catalyst for the coupling of Baylis−Hillman adducts with arylboronic acids to provide trisubstituted alkenes with high stereoselectivity (Scheme 251).[692]

Transformation of the Baylis−Hillman alcohols into β-substituted Baylis−Hillman alcohols (with *Z*-configuration) via coupling with aryl iodides with $Pd(OAc)_2$/*n*-Bu_4NBr/KOAc was reported by Kim and co-workers,[693] following the reaction sequence shown in Path A, Scheme 252. In these reactions, minor amounts of β-substituted Baylis−Hillman alcohols with (*E*)-configuration and α-substituted β-keto esters were also obtained. Subsequently, they[694] extended this strategy to Baylis−Hillman adducts derived from aldimine derivatives, as electrophiles, to provide the corresponding

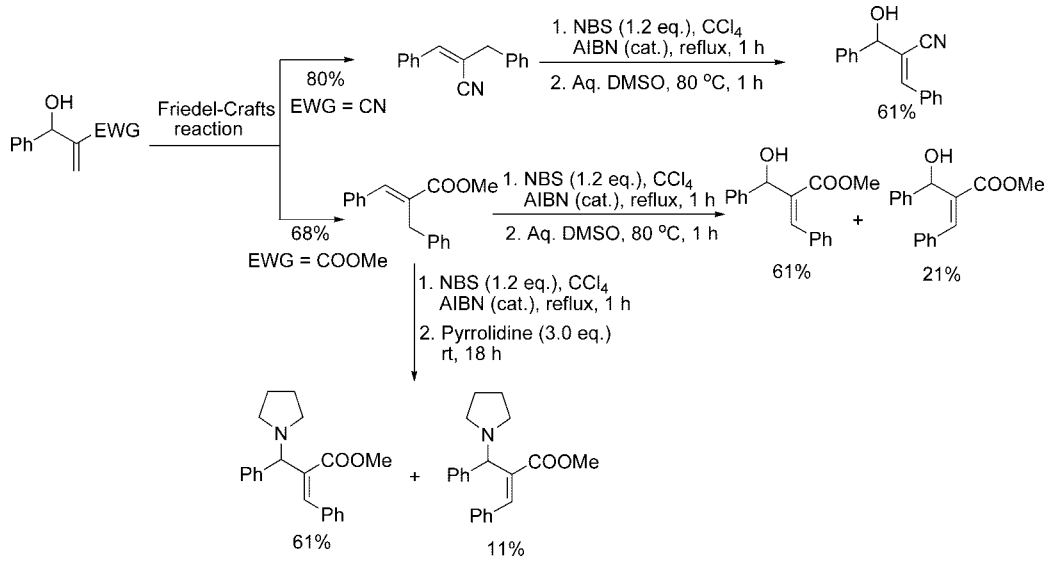
Scheme 253



Scheme 254



Scheme 255

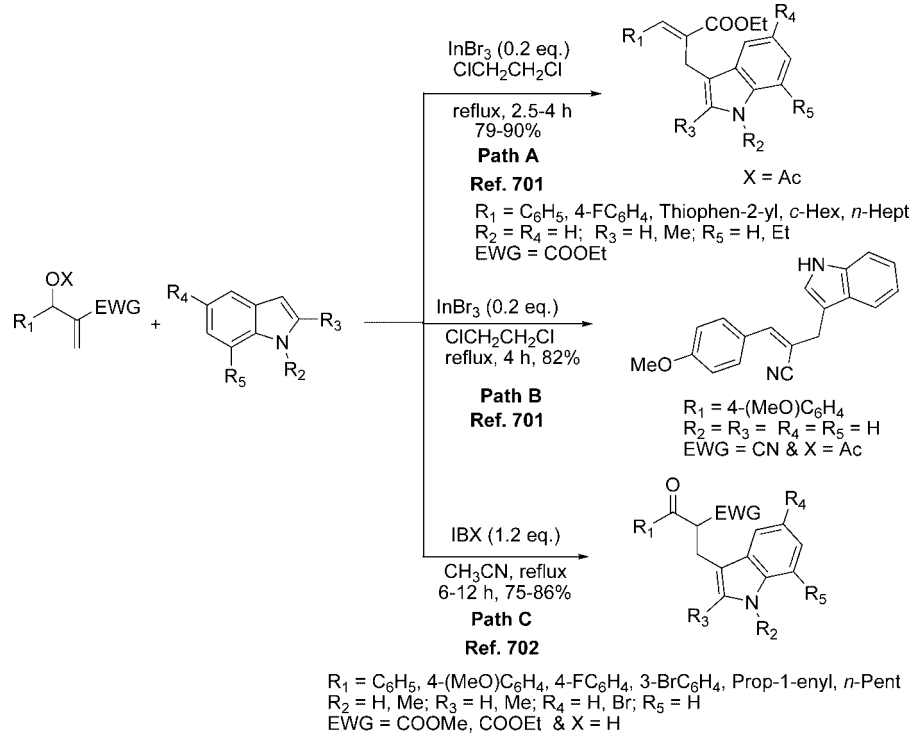


β-substituted Baylis−Hillman adducts as a mixture of *E*- and *Z*-isomers (Path B, Scheme 252).

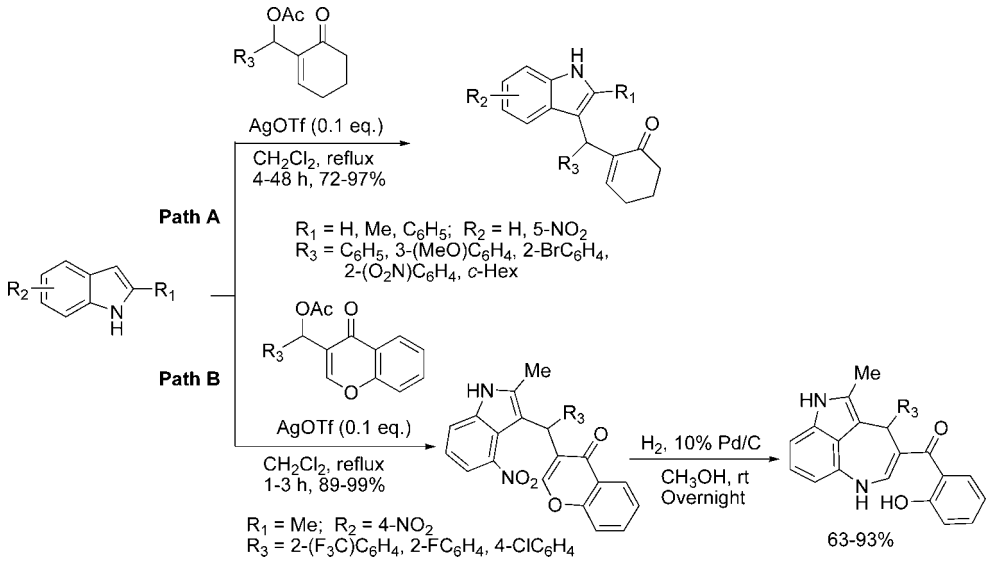
Kim and co-workers[695] have transformed Baylis−Hillman acetates into 5-arylpent-4-enoate derivatives via treatment with ethyl (triphenylphosphoranylidene)acetate (Wittig reagent), following the reaction sequence shown in Path A (Scheme 253). Later on, Yadav and co-workers[696] reported a similar reaction under thermal and microwave irradiation conditions (Paths B and C, Scheme 253), while Chandrasekhar and co-workers[697] found that this reaction can be catalyzed by $Pd(OAc)_2$ as shown in Path D, Scheme 253. One representative example of each class is presented.

The Baylis−Hillman adducts have already been employed successfully as substrates in various Friedel−Crafts reactions.[500,536] Recently Das and co-workers[698] have performed Friedel−Crafts reaction of Baylis−Hillman alcohols with benzene using Fe^{3+}−K-10 montmorillonite clay as a catalyst to provide the resulting products with high

Scheme 256

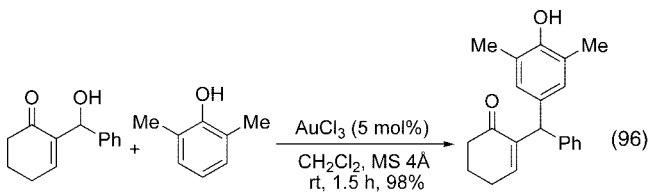


Scheme 257



stereoselectivity (Scheme 254). When toluene was used for Friedel−Crafts reaction in the place of benzene, the resulting products were obtained as a *ortho* and *para* mixtures. One example is presented in Scheme 254.

An interesting gold-catalyzed Friedel−Crafts reaction of the Baylis−Hillman alcohol α-(hydroxyphenylmethyl)cyclohex-2-enone with 2,6-dimethylphenol to provide an arylated Baylis−Hillman adduct was reported by Rao and Chan (eq 96).[699]



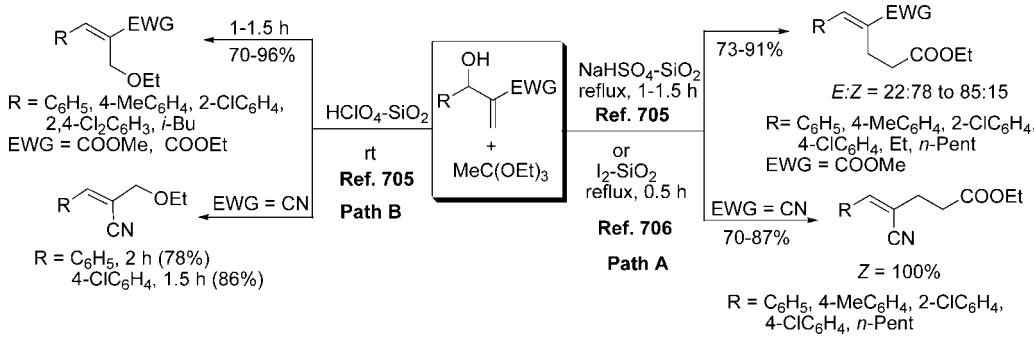
(96)

Kim and co-workers[700] disclosed an efficient synthesis of β-phenyl-substituted Baylis−Hillman adducts via the Friedel−Crafts reaction of the Baylis−Hillman alcohols followed by allylic bromination and nucleophilic substitution reaction (S_N') according to Scheme 255.

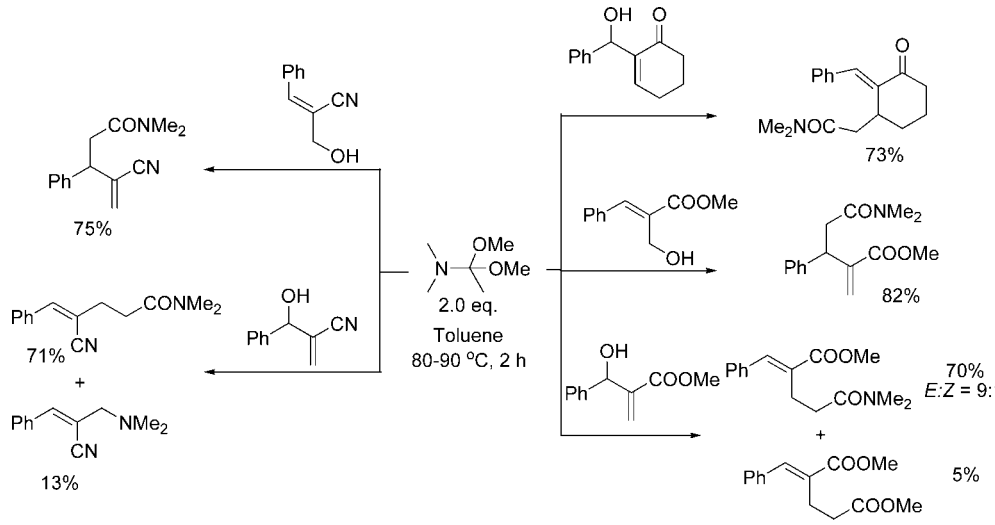
Indium tribromide catalyzed C-alkylation of indole derivatives with Baylis−Hillman acetates was reported by Yadav and co-workers (Paths A and B, Scheme 256).[701] Subsequently, they have also reported one-pot oxidative Michael reaction of indoles with Baylis−Hillman adducts promoted by 2-iodoxybenzoic acid (IBX) (Path C, Scheme 256).[702]

Later on, Chen and co-workers[703] reported an interesting AgOTf-catalyzed reaction between acetates of the Baylis−Hillman alcohols, obtained from chromones (as activated alkenes) and indole derivatives to provide C-alkylated

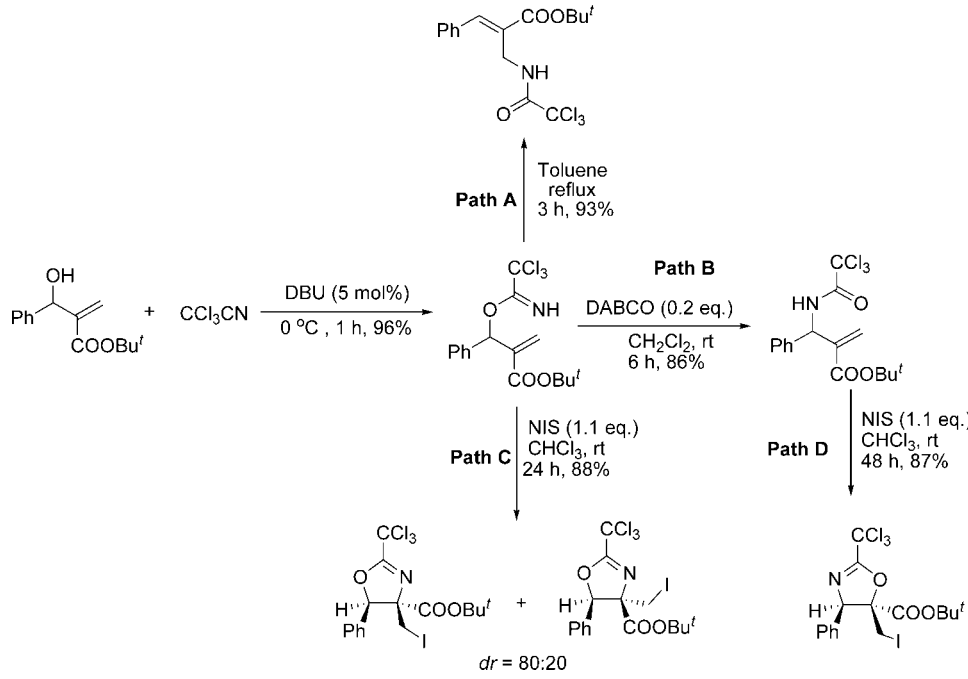
Scheme 258



Scheme 259



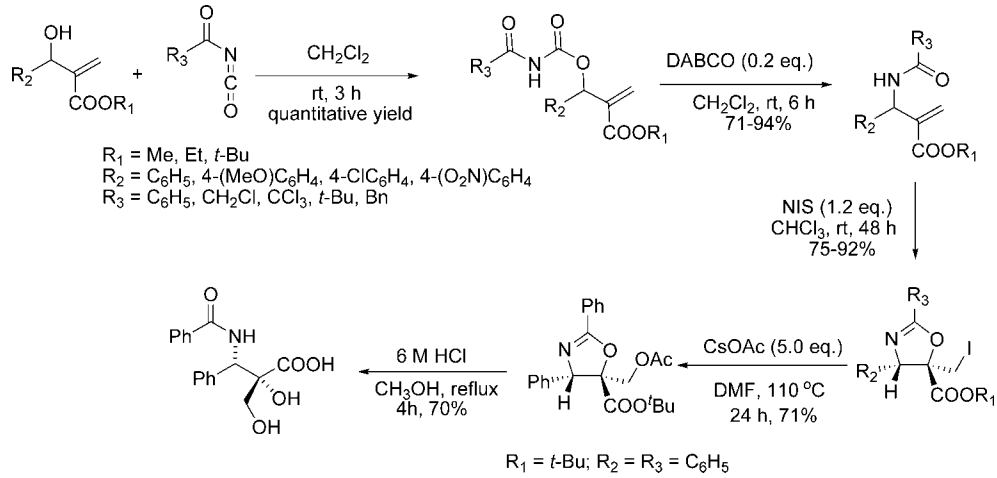
Scheme 260



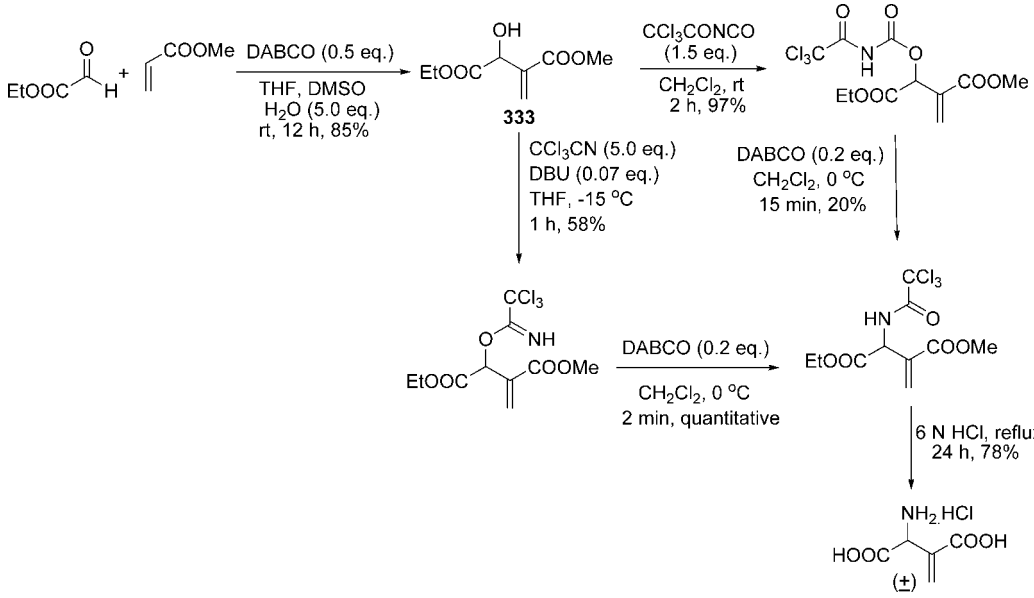
products (Path A, Scheme 257). During these studies, they also transformed C-alkylated indole products obtained from 4-nitroindoles into fused azepinoindole derivatives via reduction of the nitro group, followed by conjugated addition (Path B, Scheme 257).

Application of the Baylis−Hillman adducts as valuable substrates in various kinds of Claisen rearrangement reactions has been well documented in the literature.[502,503,704] Das and co-workers[705] performed the Johnson−Claisen rearrangement of Baylis−Hillman alcohols with triethylortho acetate under

Scheme 261



Scheme 262



the influence of $NaHSO_4-SiO_2$ to provide the corresponding trisubstituted alkenes in high yields. When EWG is CN, the products were obtained with high *Z*-stereoselectivity, while when EWG is COOR, the resulting products were obtained as a mixture of *E* and *Z* isomers. Representative examples are shown in Path A, Scheme 258. Later on, Das and co-workers[706] used I_2-SiO_2 as a heterogeneous catalyst for performing Johnson−Claisen rearrangement of Baylis−Hillman alcohols. They have also found $HClO_4-SiO_2$ to be a useful catalyst for transformation of Baylis−Hillman alcohols into corresponding ethers (of primary allyl alcohols) with high stereoselectivity (Path B, Scheme 258).

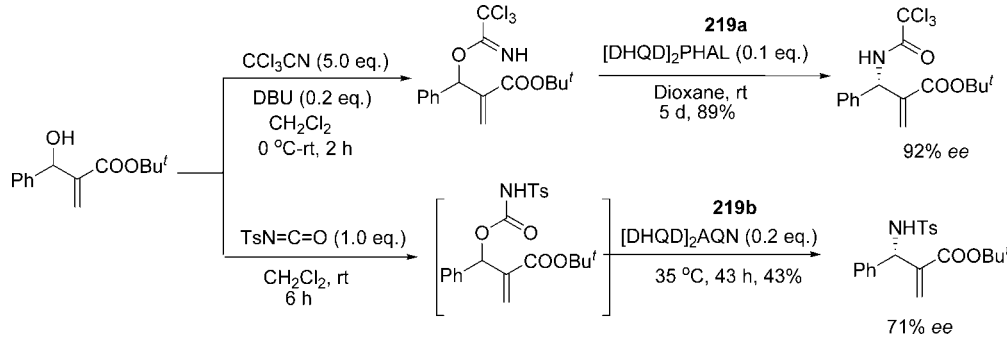
Eschenmoser−Claisen rearrangement of Baylis−Hillman adducts with *N*,*N*-dimethylacetamide−dimethylacetal (DMA-DMA) in toluene to produce the corresponding trisubstituted alkenes in moderate yields was reported by Kim and co-workers.[707] Rearranged Baylis−Hillman alcohols, in a similar rearrangement reaction, provided α-substituted acrylates and acrylonitriles (Scheme 259). Similar rearrangement of the Baylis−Hillman alcohols derived from cyclohex-2-enone provided 2-arylidene-3-substituted cyclohexanone derivatives. Representative examples are given in Scheme 259.

Orena and co-workers[708] have transformed the Baylis−Hillman adducts into trichloroacetimidates via treatment with CCl_3CN in the presence of DBU. These trichloroacetimidate derivatives were converted into (1) (*E*)-2-trichloroacetylaminomethyl-2-propenoates on thermal rearrangement (Path A, Scheme 260) or (2) 2-methylene-3-trichloroacetylamino esters via treatment with DABCO (Path B, Scheme 260). They have also transformed trichloroacetimidates (Path C, Scheme 260) and 2-methylene-3-trichloroacetylamino esters (Path D, Scheme 260) into 1,3-isoxazole derivatives via iodolactonization. Representative examples are given.

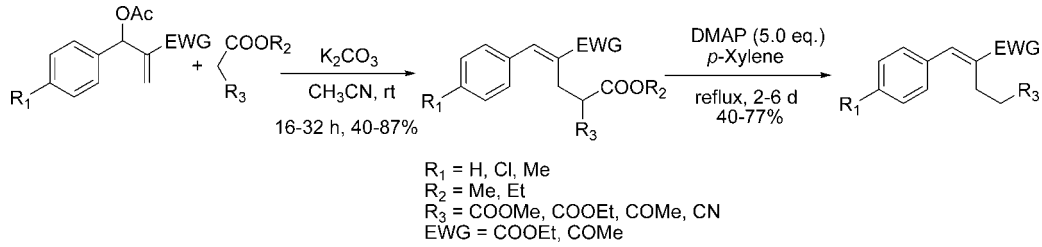
Subsequently Orena and co-workers[709] reported alternative preparation of 3-acylamino-2-methylenealkanoates from the Baylis−Hillman alcohols via the reaction with acylisocyanate followed by the treatment with DABCO. These acylamino derivatives were converted into isoxazole derivatives via iodolactonization (Scheme 261). Subsequently, this strategy was extended to the synthesis of *N*-benzoyl-*syn*-phenylisoserine derivatives. Very recently, they used a similar strategy for synthesis of (±)-β-methyleneaspartic acid,[710] an inhibitor of glutamate−asparate transaminase starting from the Baylis−Hillman alcohol **333**, derived from ethylglyoxlate, following the reaction sequence shown in Scheme 262.

More recently, Jorgensen and co-workers[711] described an interesting asymmetric [1,3]-sigmatropic rearrangement reaction of racemic allylic trichloroacetimidates, derived from

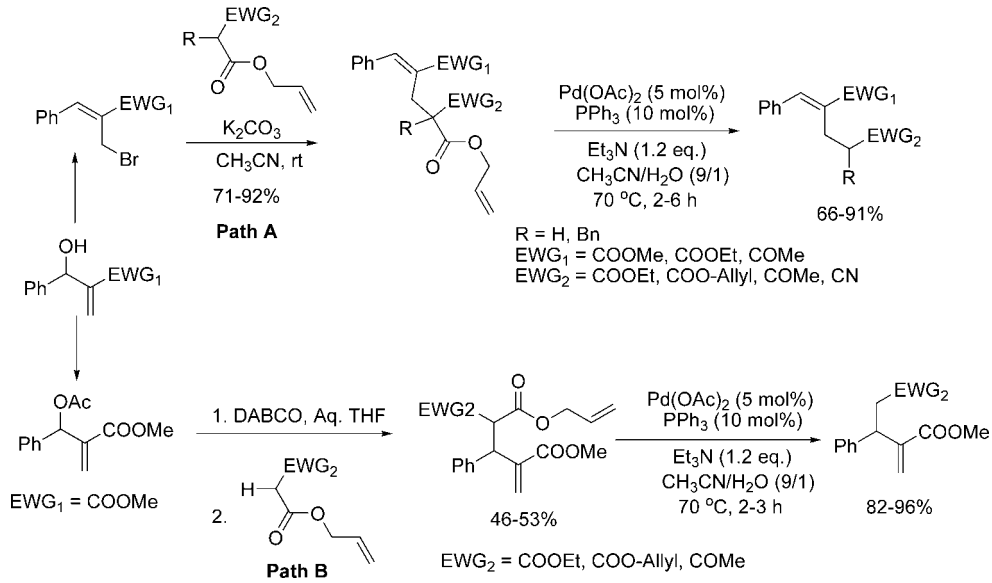
Scheme 263



Scheme 264



Scheme 265



Baylis−Hillman alcohols, into enantiomerically enriched allylic trichloroacetamides under the catalytic influence of cinchona alkaloid derivatives (**219a**−**c**, Figure 35). During these studies, cinchona alkaloid derivatives **219a** and **219b** provided better results (Scheme 263).

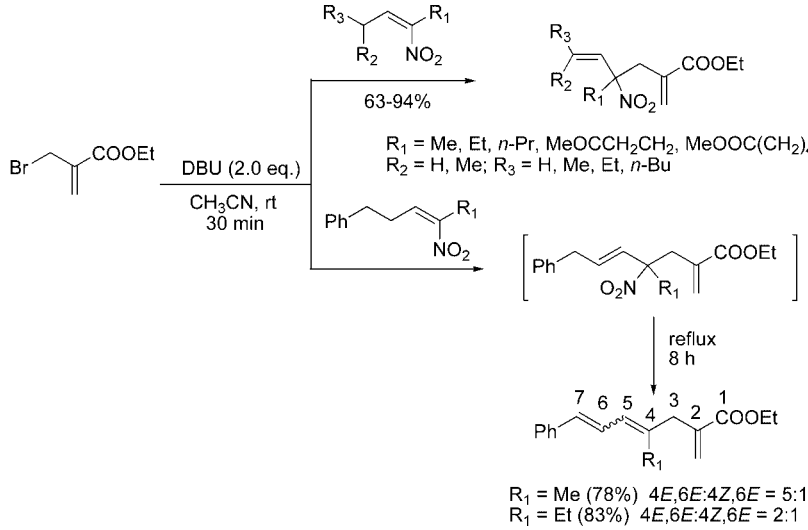
Baylis−Hillman alcohols have been converted into 2-(*E*)-arylidene-1,5-pentanedicarboxylates via the reaction with diethyl malonate followed by decarboxylation according to the reaction sequence shown in Scheme 264, by Kim and co-workers.[712] Similar treatment of Baylis−Hillman acetates with ethyl cyanoacetate and ethyl acetoacetate, followed by decarboxylation, provided 2-(*E*)-arylidene-4-cyanobutanoates and 2-(*E*)-arylidene-5-oxohexanoates. It is worth mention here that this represents an alternative methodology for obtaining Johnson−Claisen rearrangement products of Baylis−Hillman alcohols.

Kim and co-workers[713] reported an alternative procedure for obtaining 2-arylidene-1,5-pentanedicarboxylates via the reaction of Baylis−Hillman bromides with allyl alkylmalonates followed by deallylcarboxylation using $Pd(OAc)_2$ (Path A, Scheme 265). They have also transformed the Baylis−Hillman acetate methyl 3-acetoxy-2-methylene-3-phenylpropanoate into 2-methylene-3-phenylpentane-1,5-dicarboxylates following the reaction sequence shown in Path B, Scheme 265.

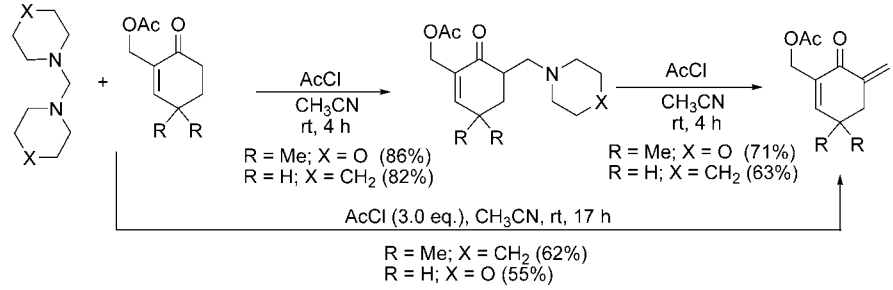
Ballini and co-workers[714] reported reaction between nitroalkenes and ethyl 2-bromomethylacrylates under the influence of DBU to provide nitrodienes in good yields at faster reaction rates (Scheme 266). Some of these derivatives prepared *in situ* were transformed into 2-methyleneheptane-4,6-dienoates under thermal conditions.

Acetates of the Baylis−Hillman alcohols derived from cyclohex-2-enone and formaldehyde were converted into 6-methylene-2-acetoxymethylcyclohexenone derivatives[715] via treatment with di-(*N*-piperidinyl)methane and di-(*N*-morpholinyl)methane followed by elimination of piperidine or morpholine according to the reaction sequence shown in Scheme 267.

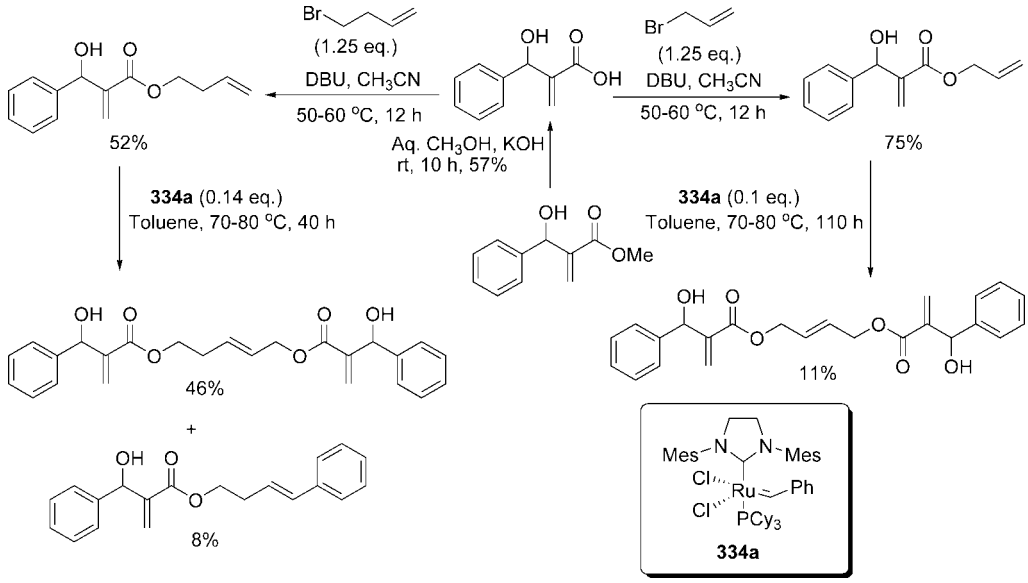
Scheme 266



Scheme 267



Scheme 268

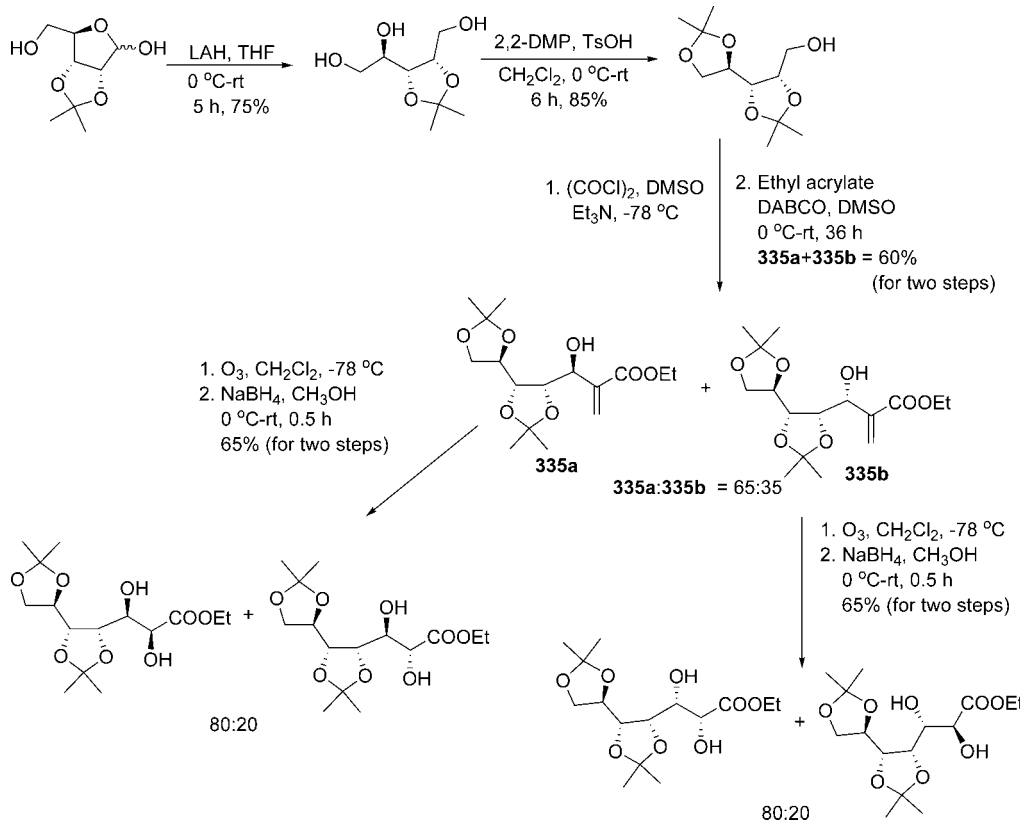


Kim and co-workers[716] examined ring-closing metathesis (RCM) of the dienes obtained via the hydrolysis of the Baylis−Hillman alcohols followed by the esterification with allyl bromide/4-bromobut-1-ene, using Grubbs second-generation catalyst (**334a**). Expected cyclic derivatives were not formed. Instead cross-metathesis (CM) products were obtained (Scheme 268). Authors provided theoretical calculations to support these results.

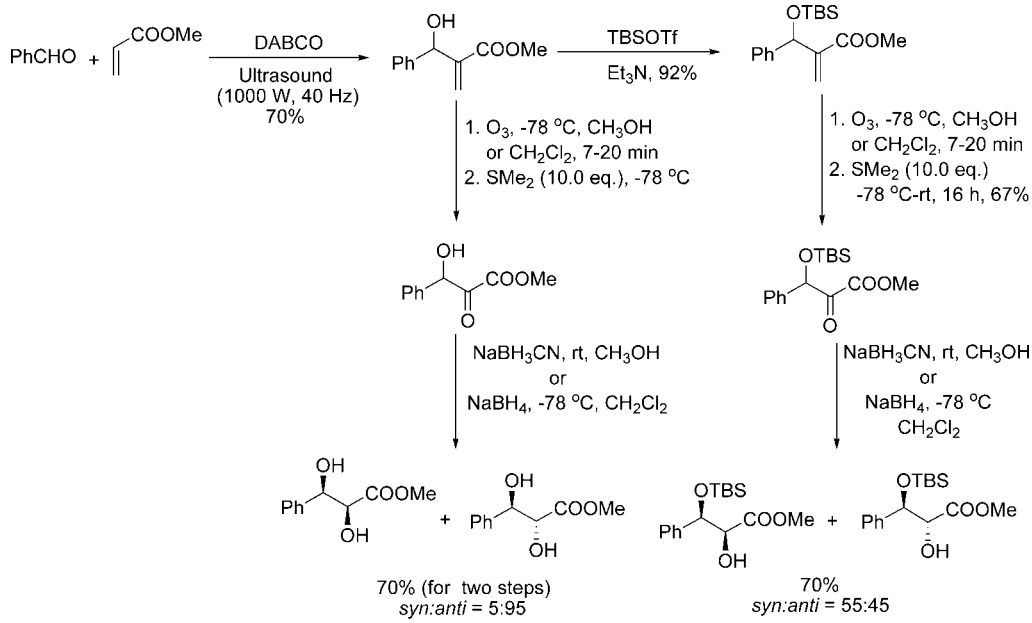
Krishna and co-workers[717] have reported an interesting protocol for synthesis of higher-carbon sugar derivatives involving the Baylis−Hillman reaction as the key step. Thus 2,3-*O*-isopropylidene D-ribose was transformed into higher sugar derivatives according to the reaction sequence shown in Scheme 269.

Coelho and co-workers[718] have transformed via ozonolysis the Baylis−Hillman and TBS-protected Baylis−Hillman alcohols into α-keto carbonyl compounds, which were further reduced with $NaBH_3CN$ into diol derivatives. In the case of unprotected Baylis−Hillman alcohols, *anti* diols were obtained as major products, while protected Baylis−Hillman alcohols did not show any significant selectivity. One representative example is presented in Scheme 270.

Scheme 269



Scheme 270

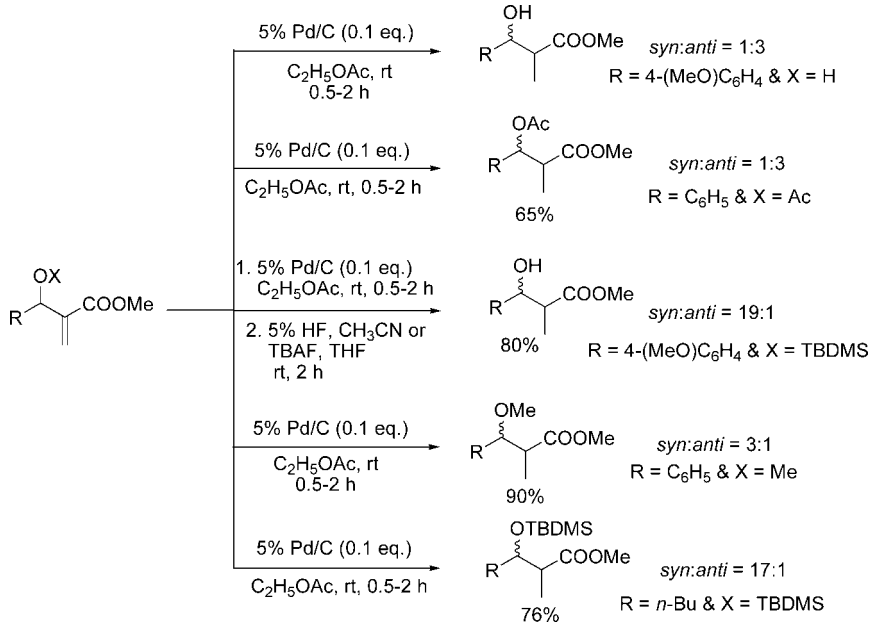


The research group of Coelho[719] has examined the heterogeneous hydrogenation of Baylis−Hillman alcohols (derived from aromatic and aliphatic aldehydes) and protected Baylis−Hillman alcohols. During their studies, they observed that the unprotected and acetylated Baylis−Hillman alcohols provided the corresponding hydrogenated product with moderate *anti* selectivity while silylated Baylis−Hillman adducts provided high *syn* diastereoselectivity. Methyl ethers provided the corresponding hydrogenated product with moderate *syn* selectivity. One representative example for each kind is presented in Scheme 271.

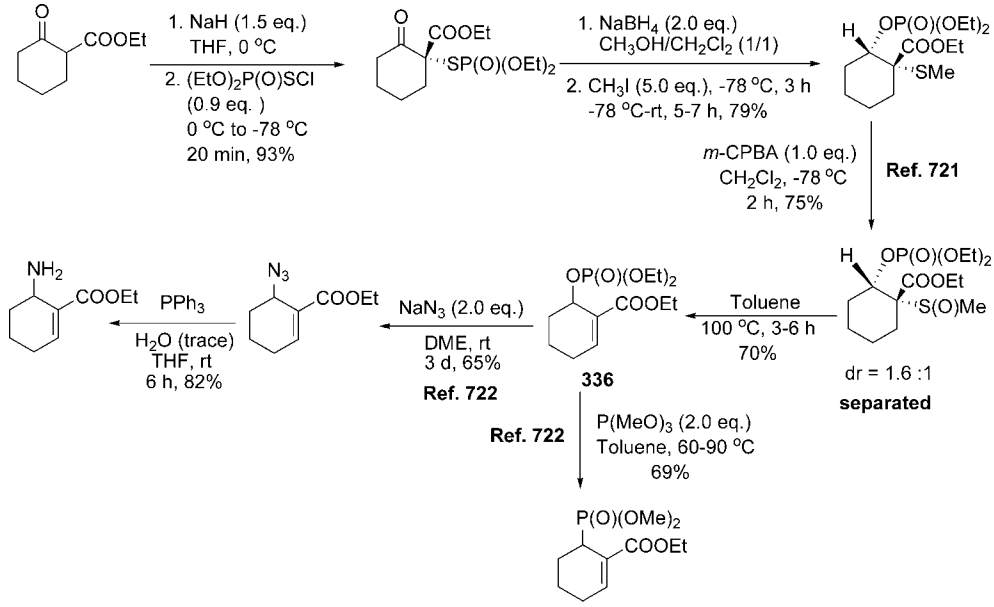
Wang and Yu[720] have reported three-component reaction between aromatic aldehydes, β-unsubstituted acrylates, and nitroalkanes (or dimethyl methylmalonate) to provide highly functionalized molecules under the influence of DBU. The reaction essentially involves sequential Baylis−Hillman and Michael reactions. Representative examples are given in eq 97.

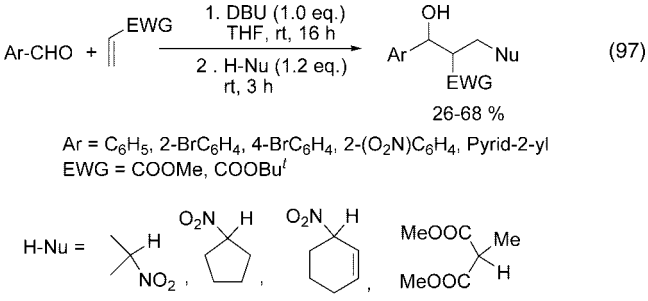
Skowronska and co-workers[721,722] have synthesized Baylis−Hillman-type adducts **336**, from 2-ethoxycarbonylcyclohexanone following the reaction sequence shown in Scheme 272. These adducts were further transformed

Scheme 271



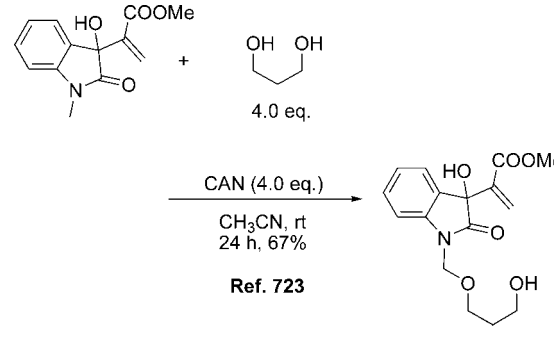
Scheme 272

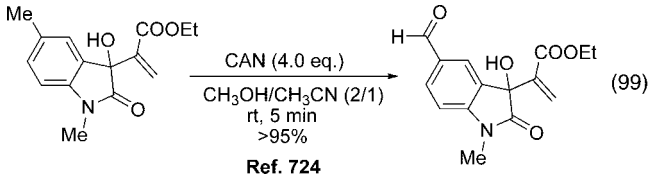




into various allyl amines and phosphonate derivatives following the reaction sequence shown in Scheme 272 (one example is presented).

Shanmugam and co-workers[723] have reported an interesting CAN-mediated activation of C−NH bond of Baylis−Hillman adducts derived from *N*-methylisatin and methyl acrylate to provide *N*-alkoxymethylisatin derivatives (eq 98). Subsequently, they also reported an interesting CAN-mediated oxidation[724] of Baylis−Hillman alcohols (derived from 5-methyl-*N*-alkylisatin and ethyl acrylate) to provide 5-formyl-*N*-alkylisatin derivatives (one representative example is given in eq 99).





(99)

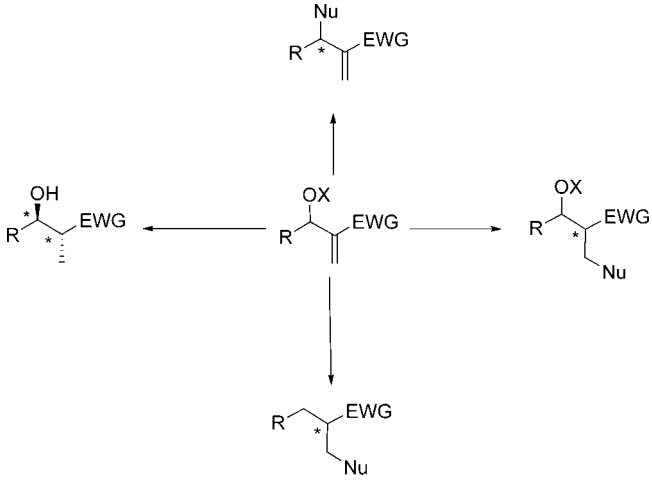
10.2. Asymmetric Transformations of Baylis−Hillman Adducts, Acetates, and Halides

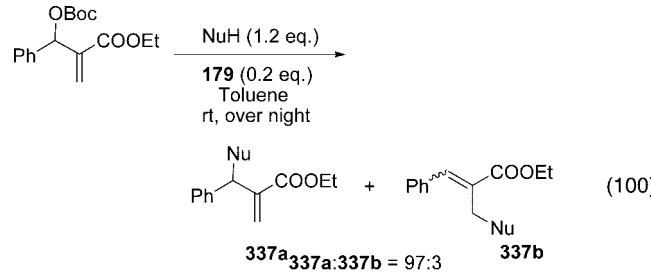
The Baylis−Hillman adducts or derivatives in principle can be transformed into chiral molecules in four different major ways shown in Scheme 273. Organic chemists have contributed in all four of these directions, and recent developments have been described in this section.[21]

Lu and co-workers[725] have examined the application of various alkaloids and their derivatives as catalysts for performing the allylic nucleophilic substitution of *tert*-butyl carbonate of the Baylis−Hillman adducts with representative nitrogen, oxygen, and carbon pronucleophiles. During this study, they found that β-isocupreidine (β-ICD, **179**, Hatakeyama catalyst) provided best results in this asymmetric nucleophilic substitution. They also observed the formation of minor amounts of trisubstituted alkene in these reactions as shown in eq 100.

Very recently, Hiemstra and co-workers[726] have used the same catalyst, β-ICD (**179**), for asymmetric C−C bond formation of *tert*-butyl carbonates of the Baylis−Hillman adducts using various racemic carbon pronucleophiles to provide the resulting products in up to 4:1 diastereoselectivities and 85% enantioselectivities (Scheme 274). In these reactions, they also observed that carbonates of the Baylis−Hillman alcohols derived from acrylonitrile did not provide any enantioselectivities though the yields are high. Representative examples are given.

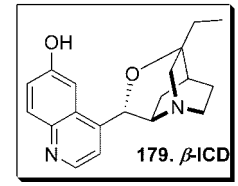
Scheme 273





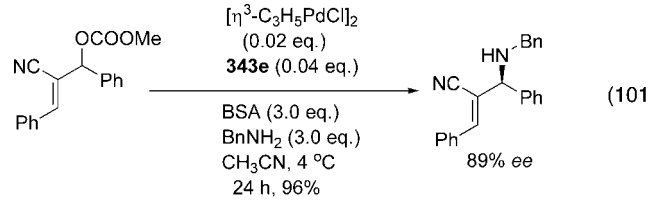
(100)

NuH	yield (%)	*ee* (%) (sign)
$TsNH_2$	84	66 (-)
Phthalimide	96	68 (+)
Phenol	85	61(-)
Naphth-1-ol	93	72 (-)
Naphth-2-ol	84	60 (-)
Dimethyl malonate	90	51(-)



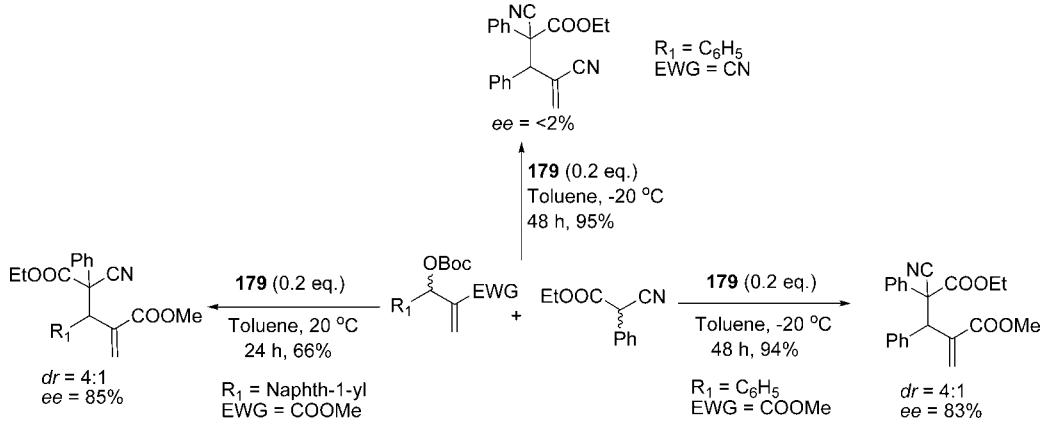
Woodward and co-workers[727] have examined the reaction of $AlMe_3$ on (*Z*)-methyl 2-(chloromethyl)-, (*E*)-2-(acetoxymethyl)-, and (*E*)-2-(methoxymethyl)-3-phenylacrylate (the Baylis−Hillman alcohol derivatives) under the catalytic influence of Ni(II) using various chiral phosphine ligands (*R*-**183**, **338**−**341**) (Figure 62) to provide 2-methylene-3-phenyl-3-methylbutanoate in high ee (up to 94%). Representative examples are presented in Scheme 275.

Subsequently chiral diaminophosphine oxides (DIAPHOXs, **343a**−**g**, Figure 63) were used by Hamada and co-workers[728] as effective catalysts for amination of carbonates of racemic (β-substituted)-Baylis−Hillman adducts using various amines, in the presence of Pd complex, to provide the resulting allyl amines in high yield and enantioselectivities. The best selectivities were obtained when **343e** and **343f** were used as ligands. Representative examples are shown in eqs 101 and 102.



(101)

Scheme 274



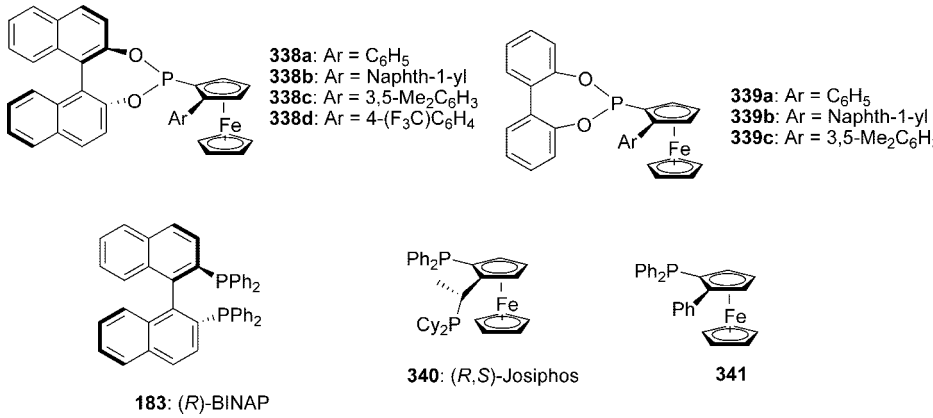
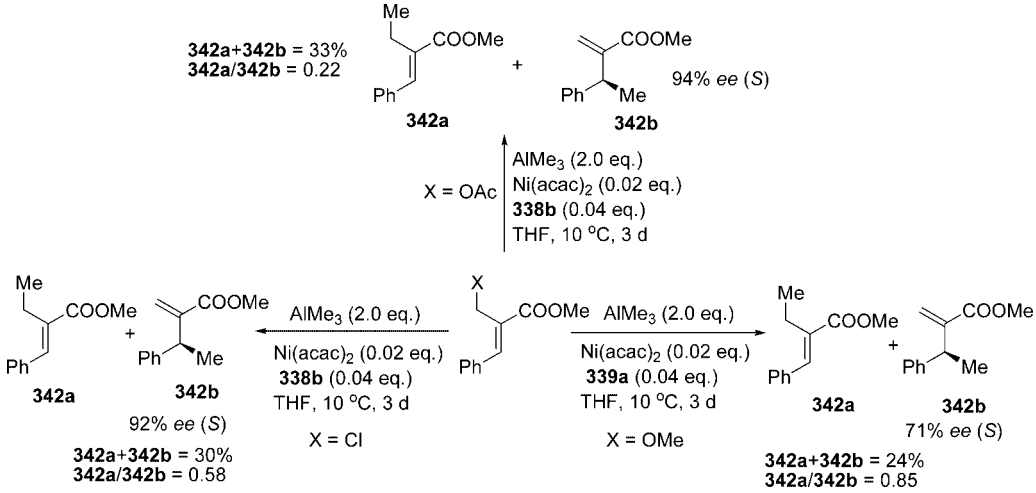
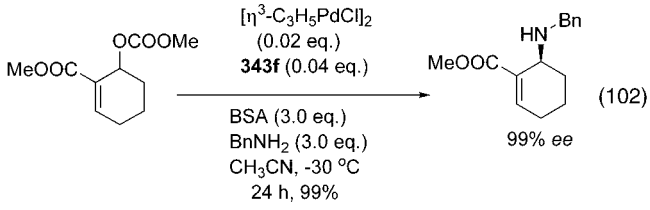


Figure 62.

Scheme 275





Trost and co-workers[729] have also developed an interesting asymmetric synthesis of substituted tetrahydropyran derivatives via the palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) of the Baylis−Hillman acetates containing an aliphatic alcoholic group at the appropriate position using various chiral phosphine ligands (**344a**−**d**, Figure 64). Representative examples are given in Scheme 276. This methodology has been extended for synthesis of (+)-hippospongic acid A (**345**) following the reaction sequence shown in Scheme 277. Subsequently, Trost and Brennan[730] used chiral phosphine ligand (*S*,*S*)-**344c** as an efficient catalyst for palladium-catalyzed regioselective allylic substitution of allyl carbonates of racemic Baylis−Hillman

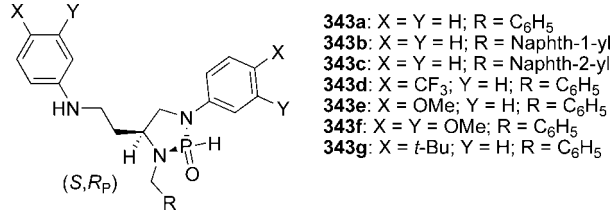


Figure 63.

adducts using various oxygen nucleophiles and also Meldrum's acid as a carbon nucleophile to provide the resulting compounds in high enantioselectivities. One example each is shown in Paths A and B, Scheme 278. They have also extended this strategy to the synthesis of cyclopentene derivatives with high enantioselectivity via the sequential alkylation of carbonates of the Baylis−Hillman alcohols with Meldrum's acid and then allylation (with allyl carbonates) followed by RCM reaction as shown in Path C, Scheme 278.

The Baylis−Hillman acetates were conveniently transformed by Ramachandran and co-workers[731] into 4-alkylideneglutamic acid derivatives in high enantiomeric purities via the conjugate addition of carbanion generated from Schiffs base (obtained from *t*-butyl ester of glycine and benzophenone) in the presence of chiral phase transfer catalyst (PTC) **346a**. They have examined the applications of a number of phase transfer catalysts (PTCs) (**346a**−**e**) and noticed that **346a** provided the most encouraging results. Some of these derivatives were transformed into 4-substituted pyroglutamates via the degeneration of the amine from Schiff base followed by cyclization and hydrogenation as shown in Scheme 279 (one example is presented).

Holz and co-workers[732] have examined the hydrogenation of various Baylis−Hillman adducts derived from formaldehyde and various acrylates using rhodium catalysts in the presence of various chiral phosphine ligands (**347a**−**f**) (Figure 65) to provide the corresponding 3-hydroxy-2-methylpropanoic acid esters in high enantioselectivities. All these ligands provided high enantioselectivities, and it was

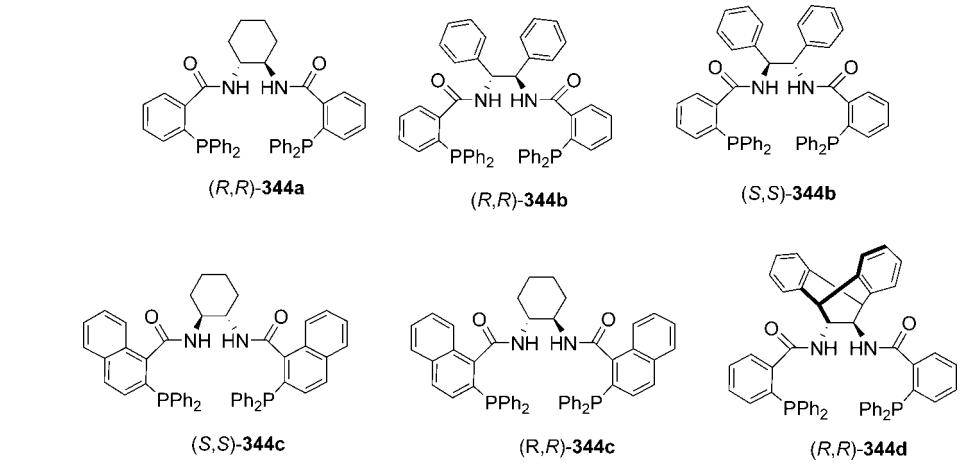
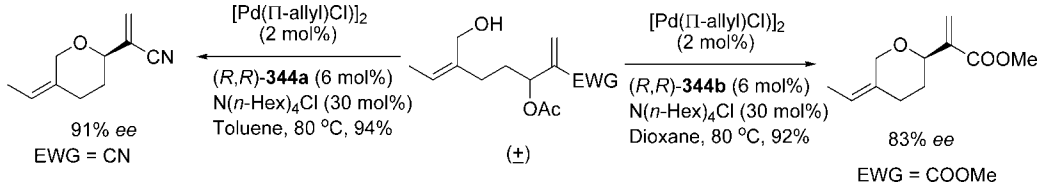
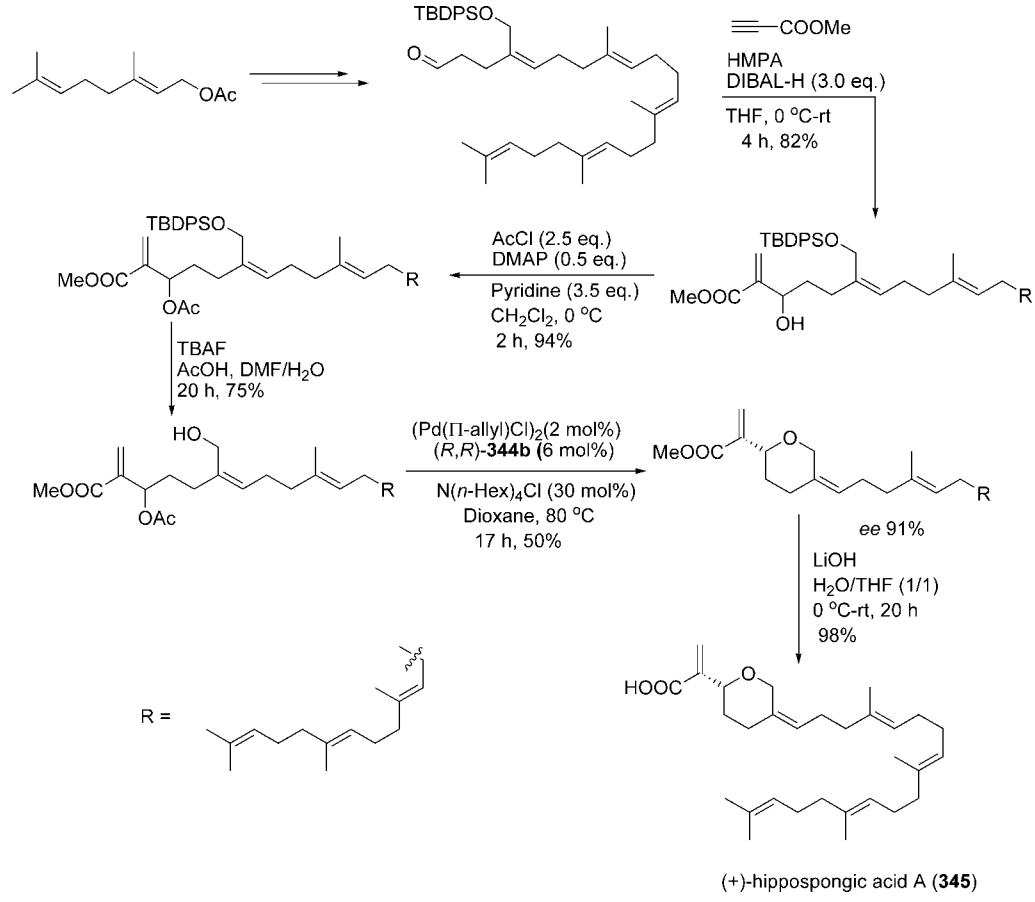


Figure 64.

Scheme 276



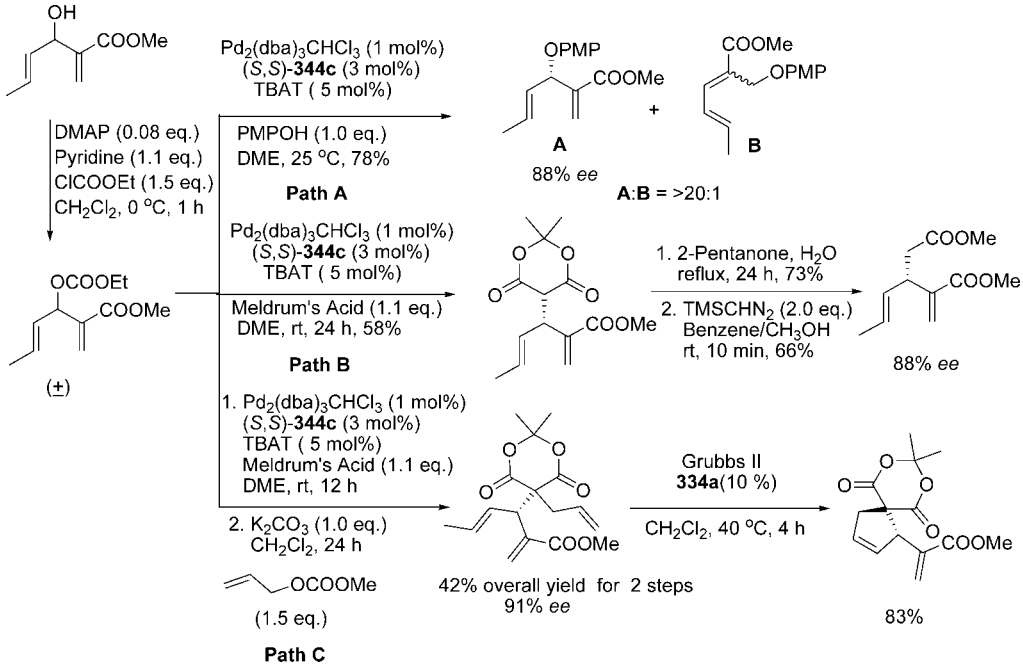
Scheme 277



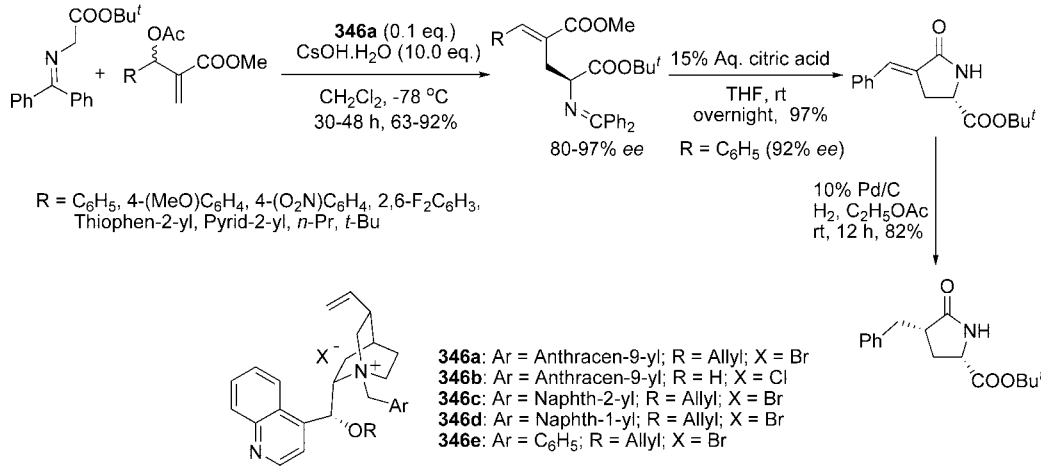
noticed that the ligand **347b** provided superior results. One representative example is shown in Path A, Scheme 280. They have also explored 2-methylene-3-hydroxy-3-arylpropanoates (the Baylis−Hillman adducts derived from acrylates and aryl aldehydes) as substrates for asymmetric hydrogenation using the chiral ligands **347d** (kinetic resolution) and **347f** (diastereoselective hydrogenation) to provide the resulting products in high de and ee (Path B, Scheme 280).

Spilling and co-workers[733] have transformed the Baylis−Hillman acetates into allylphosphonates via treatment with phosphorus nucleophiles. One example is given in Scheme

Scheme 278



Scheme 279



281. They have also examined the asymmetric hydrogenation of allylphosphonates using various chiral phosphine catalysts (**348a**, **348b**) (Figure 66) and obtained a maximum of 42% ee in the case of (Duphos)Rh(COD)BF_4 (**348c**) (Path A, Scheme 281). They have also performed the hydrogenation of the corresponding acid using the chiral catalyst **348b** to provide the resulting product with 91% ee (Path B, Scheme 281).

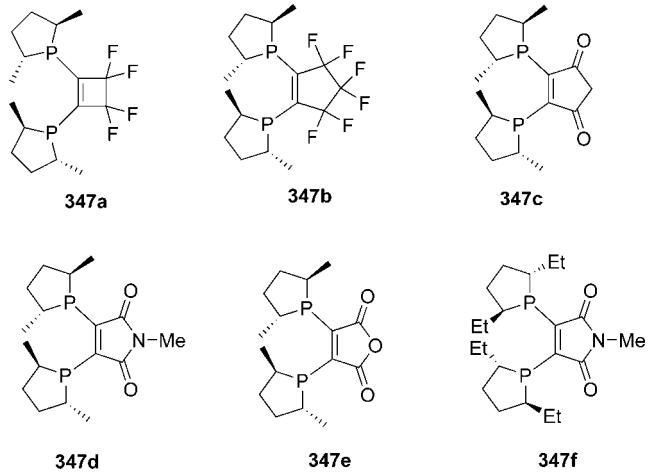


Figure 65.

Qiu and co-workers[734] have reported an interesting rhodium-catalyzed enantioselective hydrogenation of allyl amines, derived from Baylis−Hillman acetates and NH_2OBn, using various chiral phosphine ligands **348c** to provide the resulting β-amino acid derivatives in high ee. One representative example is shown in Scheme 282. During this study, they also found that [Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4 provided promising results.

Sibi and Patil[735] reported an interesting conversion of α-hydroxymethylacrylates into 2-hydroxymethylalkanoates via the nucleophilic addition of radicals generated from allyl iodides in the presence of chiral ligand **349** (Figure 67) using tributyltin hydride as radical initiator. Representative examples are shown in eq 103. Other catalysts, **350** and **299a**,**e**, were also used for this purpose, and it was found that they provided inferior results.

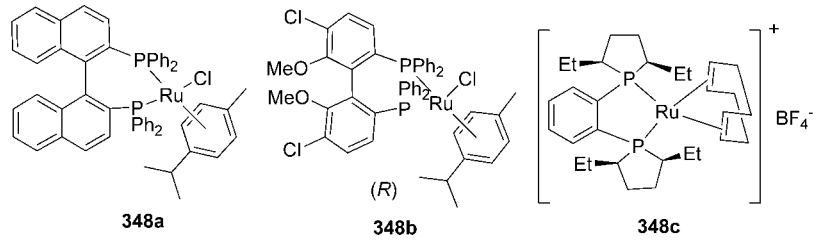
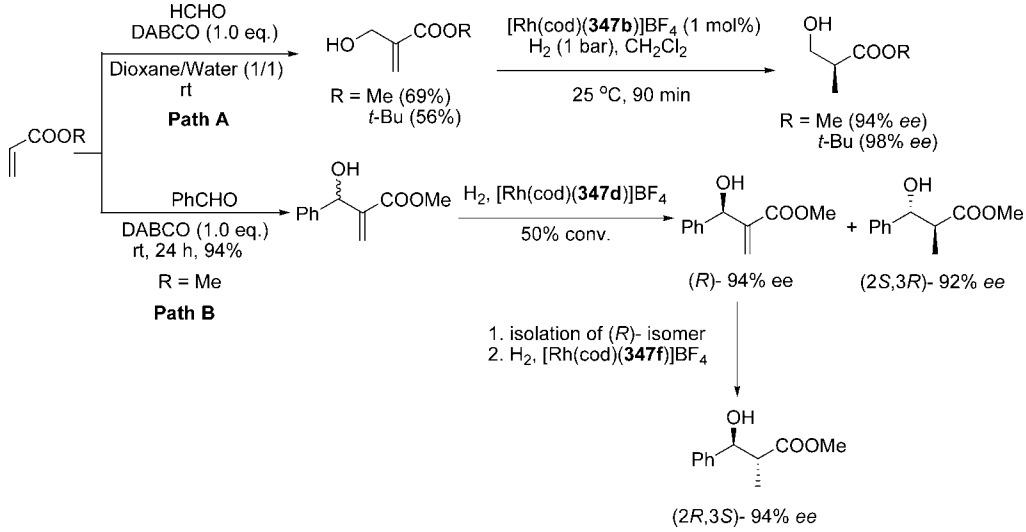
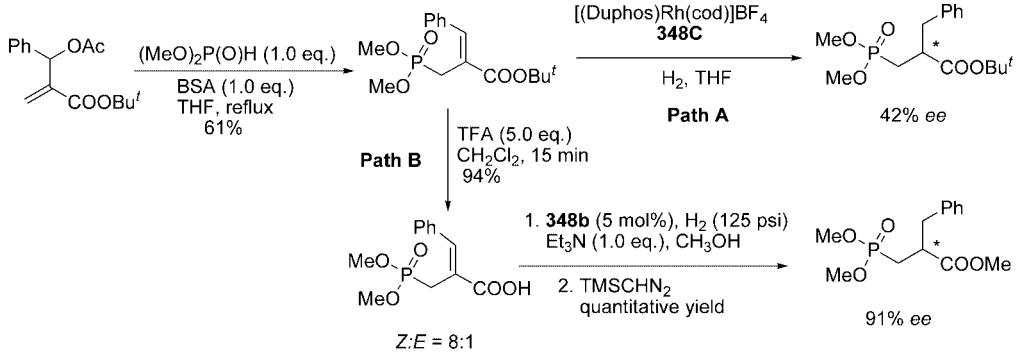


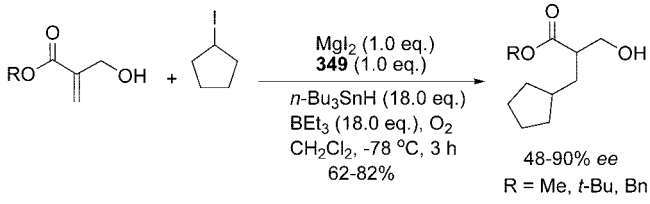
Figure 66.

Scheme 280



Scheme 281





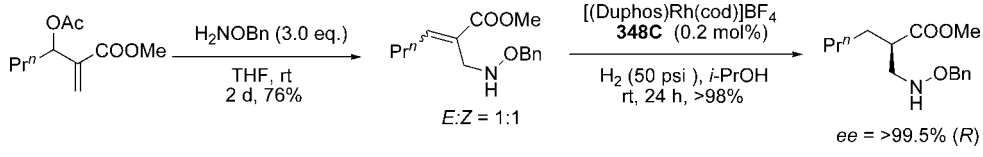
(103)

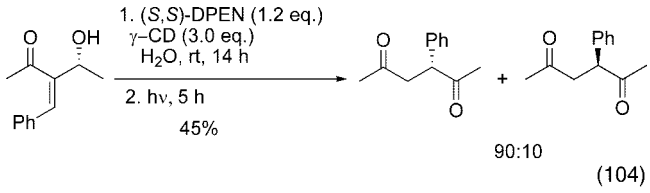
Mikami and co-workers[736] have examined the asymmetric carbon skeleton rearrangement of racemic Baylis−Hillman adducts, 3-benzylidene-4-hydroxypentane-2-one in the presence of various chiral controllers such as γ-cyclodextrin (γ-CD), (*S*,*S*)-diphenylethylenediamine (DPEN), or (*S*,*S*)-diaminocyclohexane. The combination of γ-CD and DPEN provided encouraging results. Thus the photochemical reaction of (*R*)-3-benzylidene-4-hydroxypentane-2-one in the presence of γ-CD and DPEN afforded (*R*)-3-phenyl-2,5-hexanedione in 80% ee. One representative example is presented in eq 104.

10.3. Synthesis of Carbocyclic Compounds

The Baylis−Hillman acetates were converted into 4-arylidenecyclohexane-1,3-dione derivatives by Kim and

Scheme 282





(104)

co-workers[737] via treatment with acetyl acetone, followed by deacetylation and a base-induced cyclization strategy (Scheme 283, one example is presented). Cyclohexane-1,3-dione derivative **351** thus obtained was transformed into potential oxime ether herbicide **352** (Scheme 283).

It is interesting to note that the reaction of the acetate of the Baylis−Hillman alcohols derived from MVK or EVK with 2-ethoxycarbonylcyclopentanone provided a bicyclo[3.2.1]octanone framework at room temperature (kinetic-controlled product) while bicyclo[4.3.0]nonane derivatives were obtained as major products at reflux temperature (thermodynamically controlled condition). Representative examples are given in Scheme 284.[738]

Similar treatment of acetates of Baylis−Hillman alcohols (obtained from MVK or EVK) first with DABCO and then with acetyl acetone provided an alkylated products **353**, which on reaction with base in EtOH provided 4-methylenecyclohex-2-enone derivatives. These cyclohex-2-enone derivatives were subsequently transformed into aromatic compounds via treatment with I_2 and MeOH/EtOH (Scheme 285).[739,740]

Kim and co-workers have reported an interesting protocol for the synthesis of poly-substituted benzene derivatives via the reaction between Baylis−Hillman acetate and nitroalkane followed by sequential Michael addition with activated alkenes and aldol reaction (Path A, Scheme 286),[741,742] or Michael addition to β-substituted activated alkenes and aldol reaction (Path B, Scheme 286),[743] or reaction with vinyltriphenylphosphonium bromide (Path C, Scheme 286)[742] in the presence of DBU. Kim and co-workers[744,745] have also reported an alternative route for the synthesis of poly-substituted benzene derivatives from the acetates of Baylis−Hillman alcohols, first via treatment with dialkylmalonate followed by sequential Michael and cyclization strategies in the presence of DBU, as shown in Path D, Scheme 286.

The acetates of the Baylis−Hillman alcohols derived from alkyl acrylate and aldehydes have been transformed into various poly-substituted phenol derivatives by Kim and co-workers[746] via the alkylation using nitroalkanes, followed by Michael addition, cyclization, and aromatization strategies (Path A, Scheme 287). Also alkylation of the Baylis−Hillman acetates with 1,3,5-tricarbonyl compounds provided poly-substituted phenol derivatives. This reaction strategy also involves first Michael reaction, followed by intramolecular cyclization and then base-induced aromatization (Path B, Scheme 287).[747] A similar strategy using 1,3-dinitroalkanes provided poly-substituted nitrobenzene derivatives. In this reaction sequence, the last step involves the elimination of HNO_2 leading to aromatization (Path C, Scheme 287).[748]

Kim and co-workers[749] have also reported the reaction of the acetate of Baylis−Hillman alcohols derived from MVK first with DABCO and then with 1,3-dinitroalkanes to

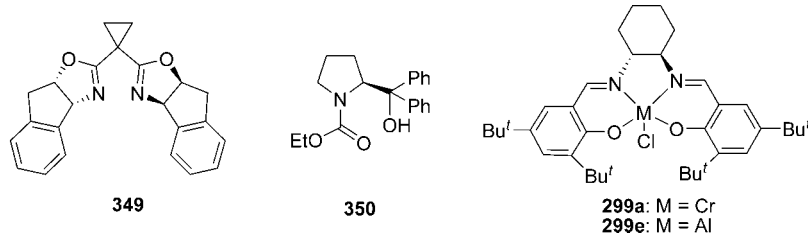
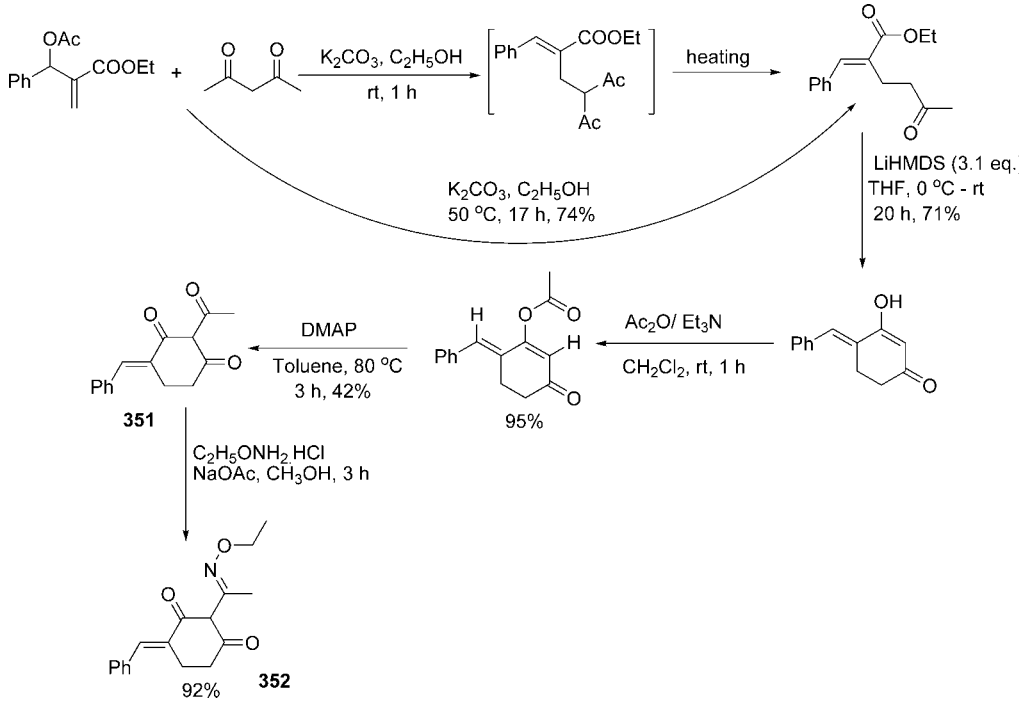
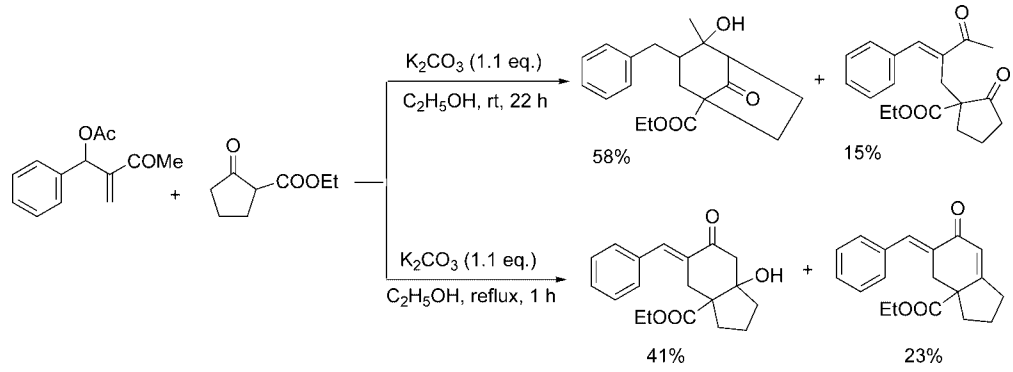


Figure 67.

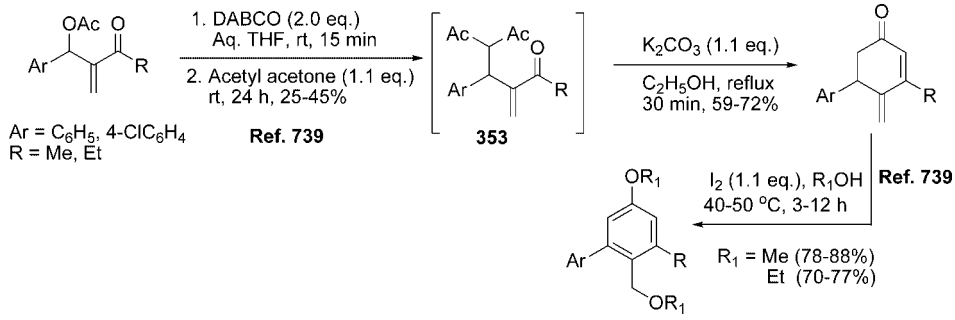
Scheme 283



Scheme 284



Scheme 285



provide substituted cyclohexane derivatives (**354**), which were then transformed into poly-substituted phenol derivatives via treatment with base, as shown in Path A, Scheme 288. One example is presented. An alternative route to poly-substituted phenol derivatives has also been developed by Kim and co-workers via the treatment of acetate of Baylis−Hillman adduct with α-phenylacetophenone in the presence of base (Path B, Scheme 288).[750]

Kim and co-workers[751,752] have reported a facile synthesis of substituted cyclopentane derivatives starting from Baylis−Hillman acetates. This reaction strategy involves the treatment of Baylis−Hillman acetates with active methylene group compounds, followed by alkylation with propargyl bromide to provide key intermediate **355**, which on radical induced cyclization provided the cyclopentane framework (**356**) having a tributyltin group on the exocyclic double bond. Treatment of **356** with conc. HCl provided the desired cyclopentane framework (Path A, Scheme 289).[751] Reaction of **356** with I_2 provided vinyl iodide (**357**), which further underwent radical cyclization to provide the dihydronaphthalene framework (Path B, Scheme 289).[752]

The Baylis−Hillman adducts, which were obtained via the coupling between 3-(2-bromophenyl)-4-isoxazolecarboxaldehydes and activated alkenes were transformed into isoxazolo-benzazulene derivatives by Singh and Batra,[753] under the influence of tributyltin hydride, following the reaction sequence shown in Scheme 290.

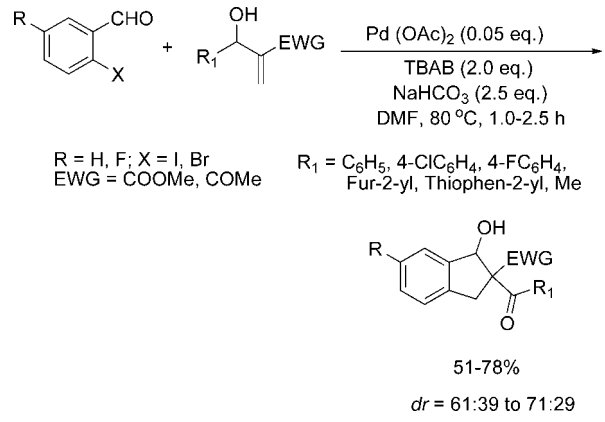
Marko and co-workers[754,755] have developed an interesting synthesis of bicyclic enedione, hydrindanones, and decalone derivatives from the Baylis−Hillman adducts obtained from cycloalkenones and terminal alkenals, following the reaction sequence shown in Schemes 291 and 292.

An interesting stereoselective synthesis of a bicyclic carbon framework has been developed by Handy and co-workers[756] from the Baylis−Hillman adduct derived from 2-formylmethyl-3-methylcyclohex-2-enone (**361**) and methyl acrylate, following the reaction sequence shown in Scheme 293. This strategy involves electrochemical cyclization as the key step. They have also developed stereoselective synthesis of a tricyclic carbon framework using cyclohex-2-enone as activated alkene instead of methyl acrylate (Scheme 293).

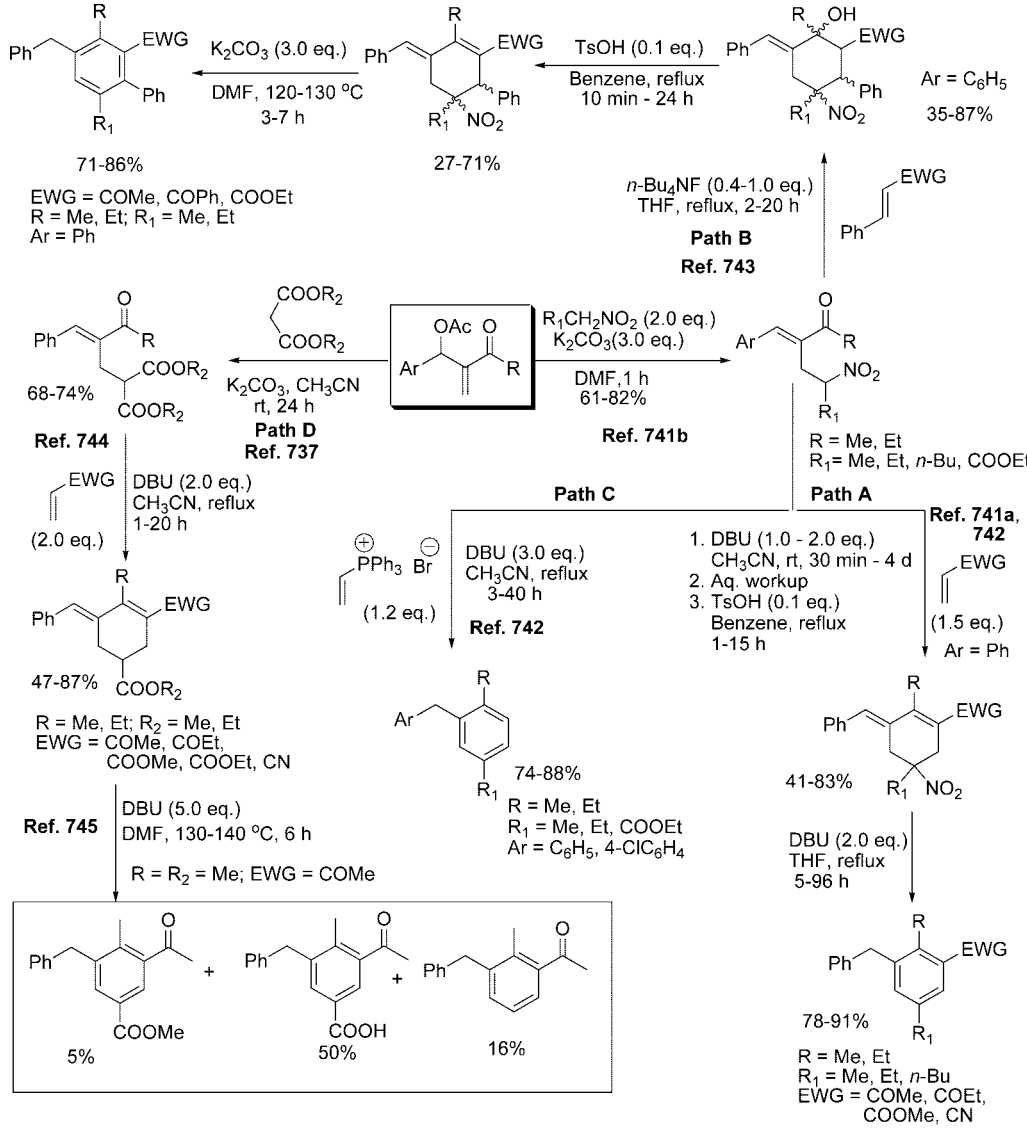
Norton and co-workers[757] have developed an interesting synthesis of substituted cyclopentanone derivatives from the Baylis−Hillman adducts derived from 5,5-diphenylpent-4-enal (**362**) and methyl acrylate. The key step involves the cyclization using $HV(CO)_4$(dppe) as catalyst following the reaction sequence shown in Scheme 294. Similarly, Baylis−Hillman adduct derived from 4-methylhex-4-enal (**363**) was transformed into cyclohexanol derivatives in low yields (Scheme 295).

Lee and co-workers[758] have reported a simple, two-step synthesis of indanone derivatives via the intramolecular Heck cyclization of Baylis−Hillman adducts derived from 2-iodobenzaldehyde (Scheme 296).

Recently Tu and co-workers[759] have developed an interesting synthesis of 2-carbonylalkyl-1-indanols via the intermolecular Heck reaction between 2-haloarylaldehydes and Baylis−Hillman alcohols followed by intramolecular aldol reaction in a one-pot operation (eq 105).



Scheme 286



Later on, Kim and co-workers[760] developed an interesting synthesis of a spiro carbocyclic framework via treatment of acetate of the Baylis−Hillman alcohols derived from 2-bromobenzaldehyde with various 1,3-dicarbonyl compounds or nitroalkanes followed by an intramolecular Heck strategy under the influence of $Pd(OAc)_2$ in a one-pot operation. Representative examples are given in Scheme 297.

Subsequently Kim and co-workers[761] reported the conversion of the acetates of the Baylis−Hillman alcohols obtained via the coupling of cyclohex-2-enone and aldehydes into 2-arylmethylphenols according to Scheme 298.

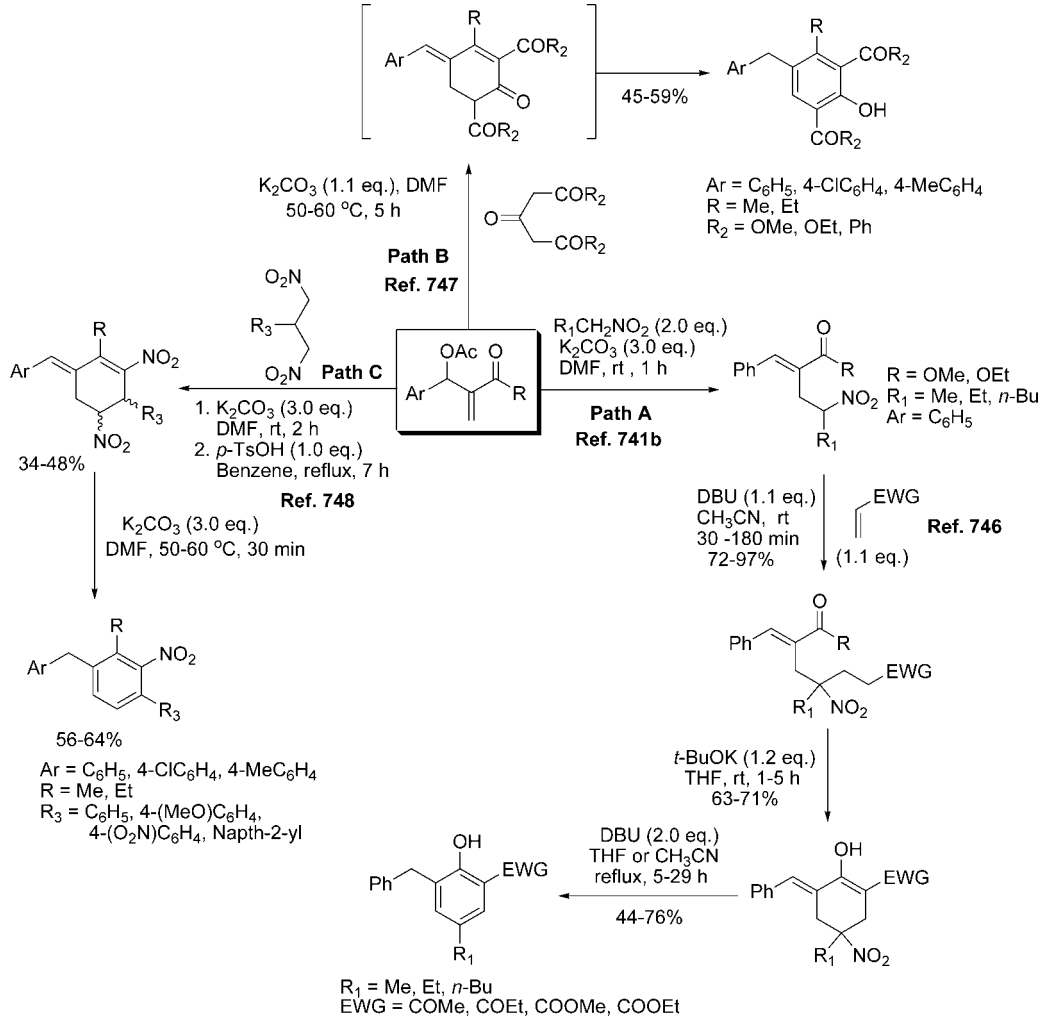
Kim and co-workers[762] have developed a facile synthetic methodology for obtaining 9-phenyl-7*H*-benzocycloheptene derivatives via the intramolecular Friedel−Crafts alkenylation of 2-alkynylmethyl-3-arylprop-2-enoates, prepared via the treatment of acetate of Baylis−Hillman alcohols with alkynyl Grignard reagent, following the reaction sequence shown in Scheme 299.

Shanmugam and Rajasingh[763] have transformed the Baylis−Hillman adduct derived from methyl acrylate and alkoxybenzaldehyde into indene derivatives via treatment with montmorillonite K10 clay in the presence or absence of microwave conditions (Path A, Scheme 300). They have also performed the Friedel−Crafts reaction of Baylis−Hillman alcohols with benzene, which provided trisubstituted alkenes as the major products along with allyl ethers as minor products. The trisubstituted alkene was transformed into a *cis*-cinnamic ester derivative via treatment with NBS and AIBN, followed by the reaction with alcohols. The *cis*-cinnamic ester on treatment with montmorillonite K10 clay under MW conditions provided the indene derivative in 90% yield (Path B, Scheme 300). They have also reported one-pot conversion of Baylis−Hillman alcohol into 3-arylindene derivatives via Friedel−Crafts reaction with benzene followed by successive treatment with (i) NBS, CCl_4, (ii) MeOH, and (iii) montmorillonite K10 clay (Path C, Scheme 300).

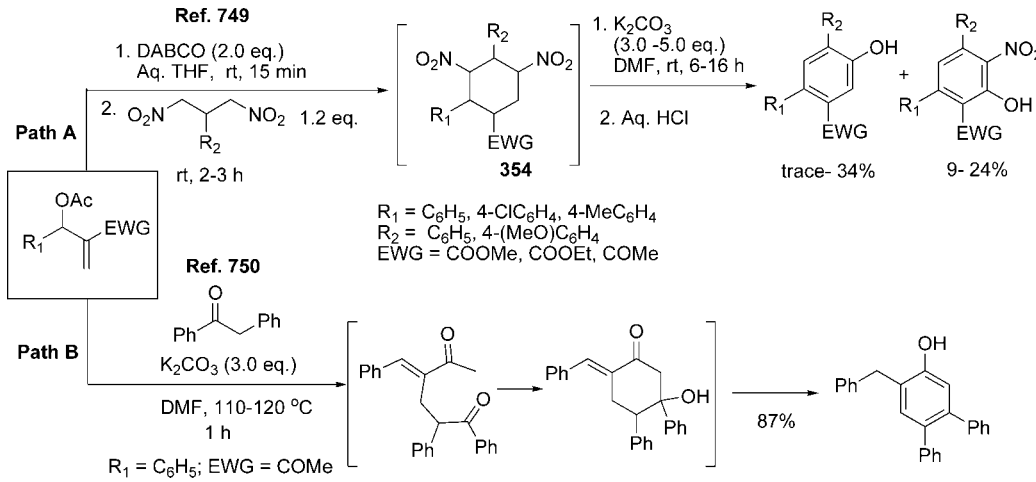
Lee and co-workers[764] have developed an interesting synthesis of 2-(9*H*-fluoren-9-yl)acrylic acid derivatives via intramolecular Friedel−Crafts reaction of Baylis−Hillman adducts obtained from 2-phenylbenzaldehyde derivatives and propiolic acid esters or amides (and methyl acrylate), following the reaction sequence shown in Scheme 301.

Mendez-Andino and Paquette[765] have described an interesting methodology for the synthesis of large rings fused with α-methylene-γ-lactones, starting from the Baylis−Hillman adducts derived from terminal alkenals via the conversion into allyl bromides followed by reaction with alkenals under

Scheme 287



Scheme 288



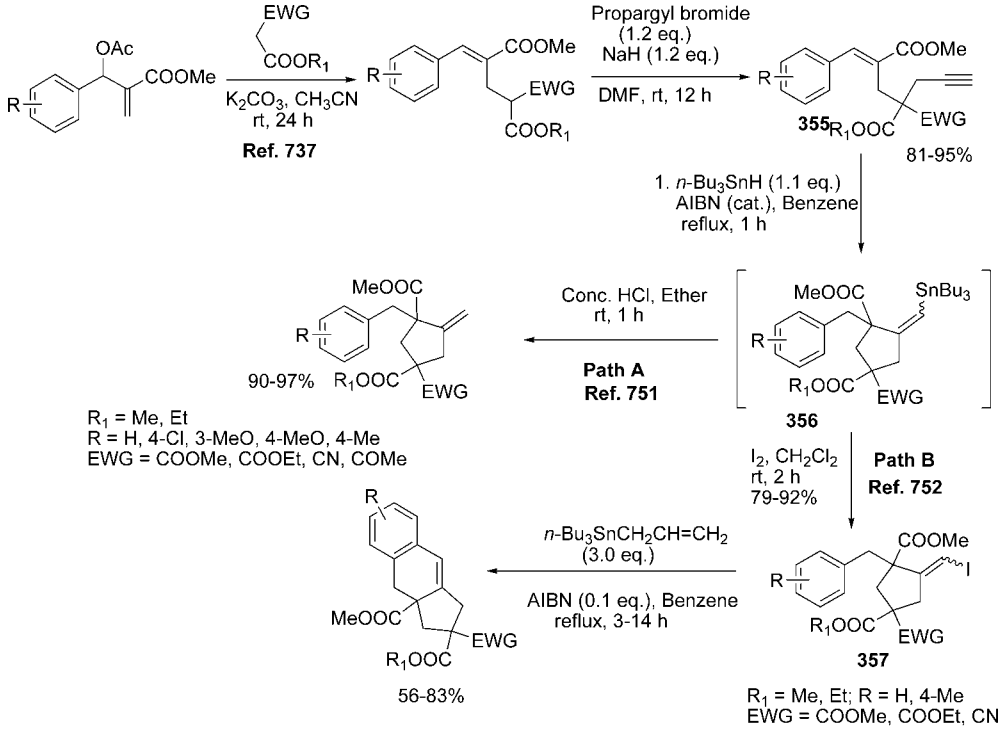
the influence of indium and subsequent ring-closing metathesis (RCM) reaction, following the reaction sequence shown in Scheme 302.

The Baylis−Hillman bromides have been transformed by Kim and co-workers into cyclopentene derivatives via the reaction with dialkylallylmalonates followed by a ring-closing metathesis (RCM) strategy (Scheme 303).[766]

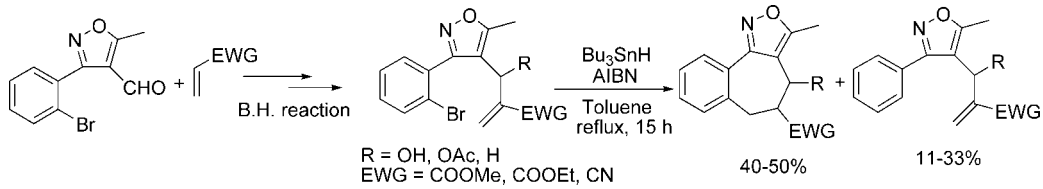
Subsequently Krafft and co-workers[767] have used the ring-closing-metathesis (RCM) strategy for the preparation of carbocyclic and heterocyclic compounds using the Baylis−Hillman adducts derived from terminal alkenals as substrates. Representative examples are shown in Schemes 304−306.

Recently Wang and co-workers[768] have developed a simple synthesis of naphthalene derivatives via the ring-closing metathesis strategy using Baylis−Hillman adducts derived from 2-allylbenzaldehydes as appropriate substrates (Scheme 307).

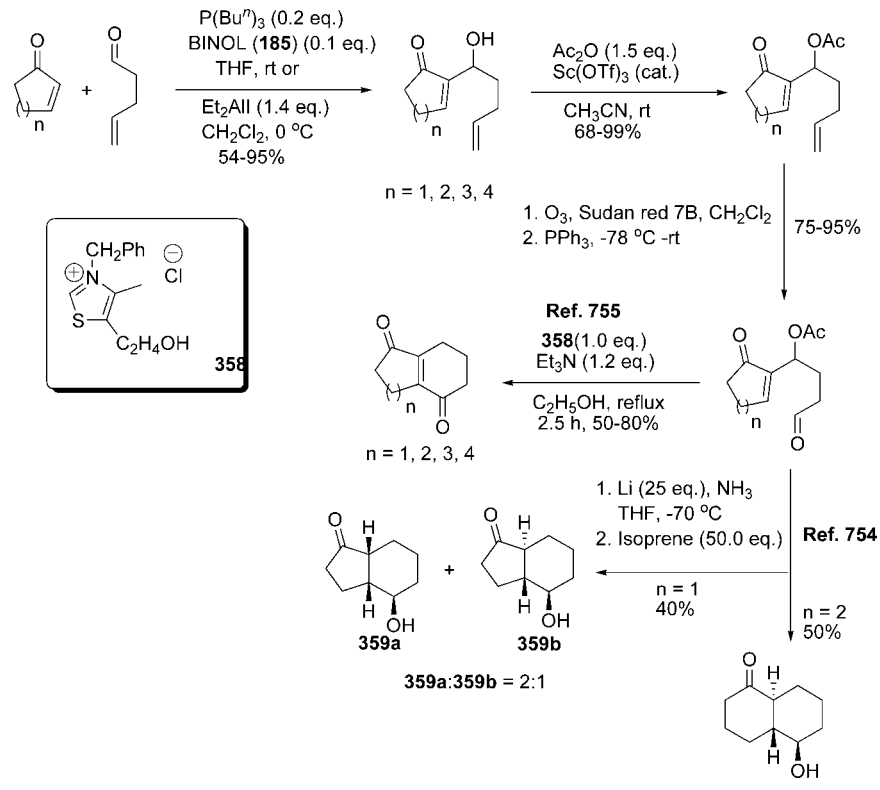
Scheme 289



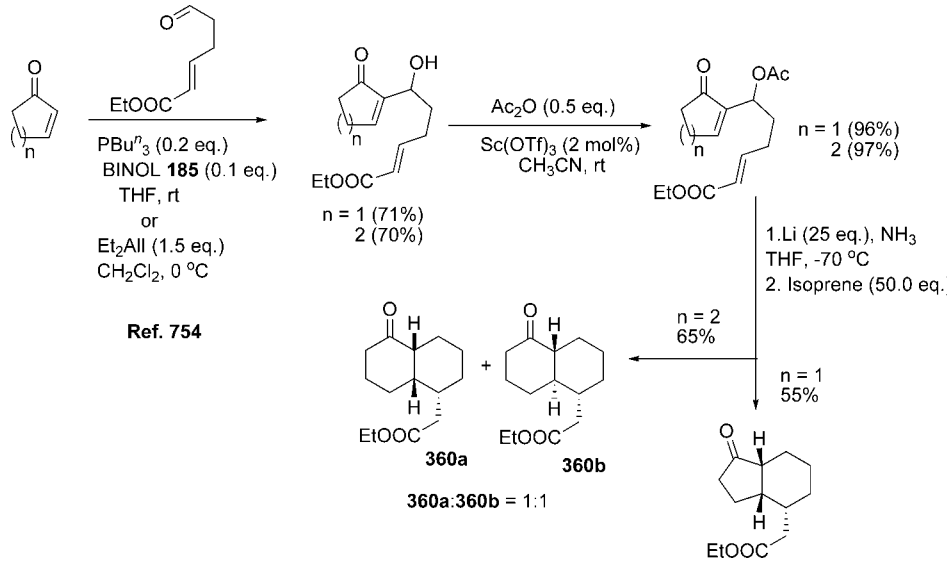
Scheme 290



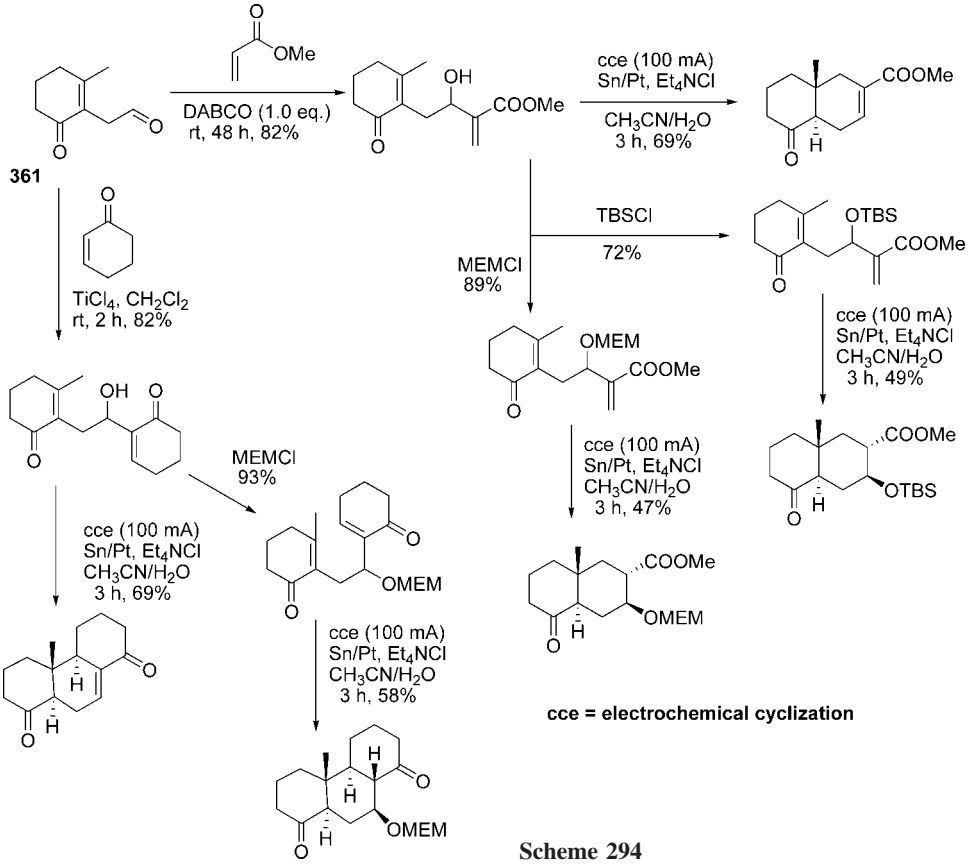
Scheme 291



Scheme 292



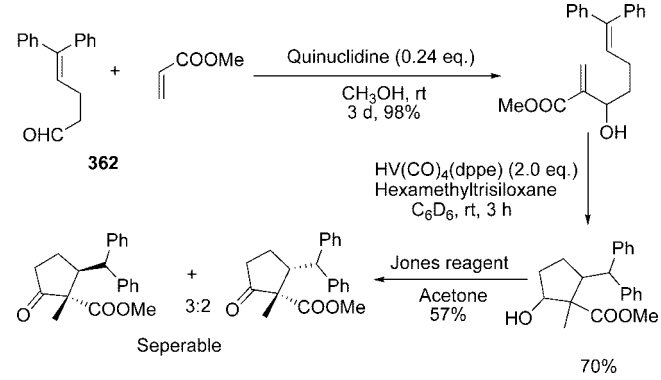
Scheme 293



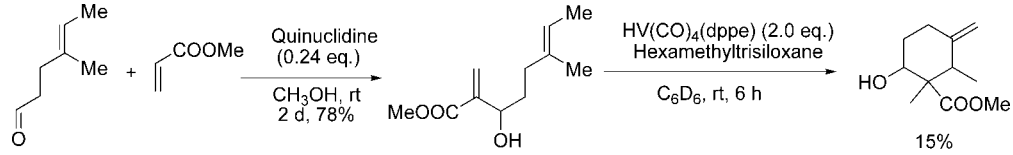
Lu and co-workers[769] have successfully used acetates, bromides, chlorides, or *tert*-butyl carbonates of the Baylis−Hillman adducts derived from formaldehyde for a [3 + 6] annulation strategy in reaction with tropone (**365**) under the catalytic influence of PPh_3 to provide interesting bicyclic compounds having nine-membered carbocycles (Scheme 308). They have also presented a plausible mechanism for this interesting transformation. They[770] have also used these Baylis−Hillman derivatives for synthesis of cyclopentane derivatives via [3 + 2] annulation reaction with arylidene malononitrile derivatives as shown in eq 106.

Kim and co-workers[771] have transformed the sulfonium bromide (**366**, derived from Baylis−Hillman bromide) into

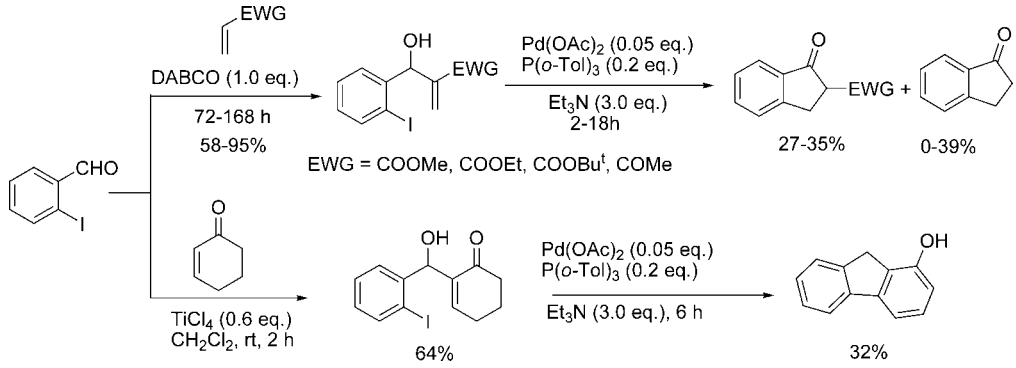
Scheme 294



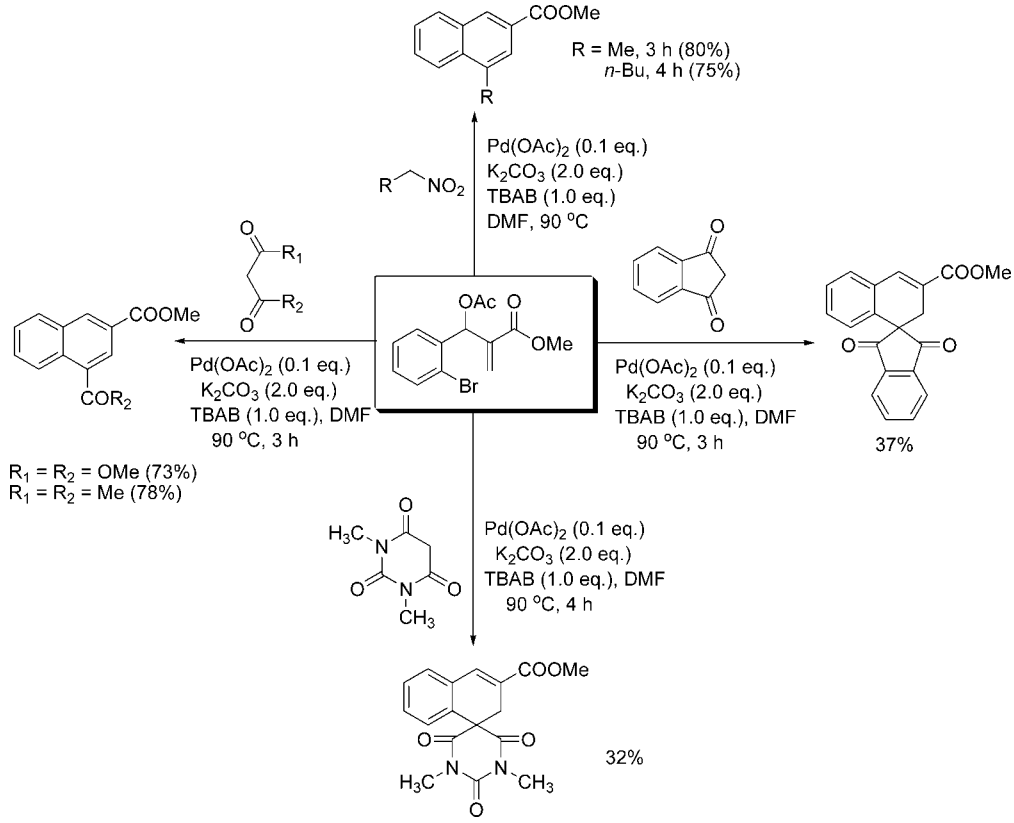
Scheme 295

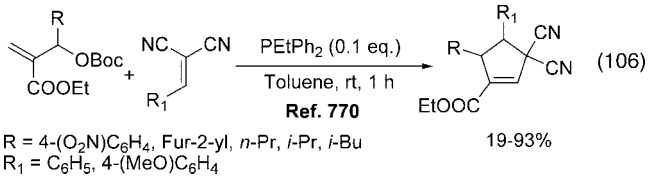


Scheme 296



Scheme 297

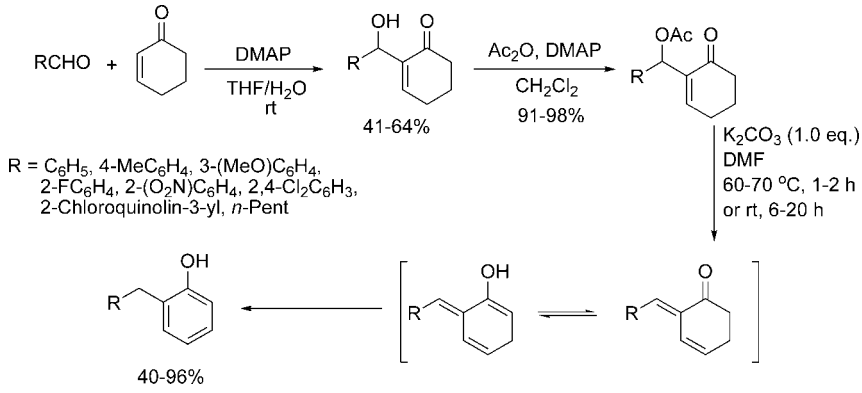




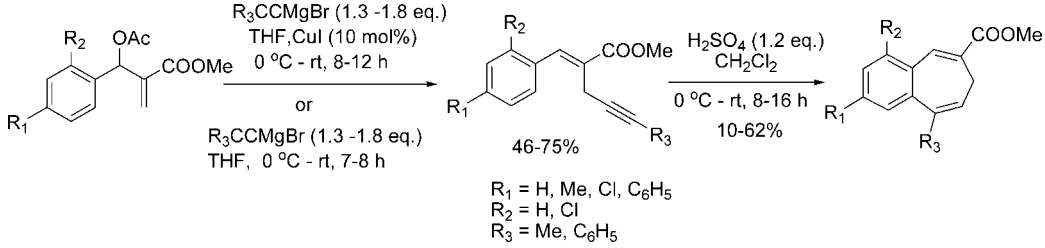
cyclopropane derivatives following the reaction sequence shown in Scheme 309. They[772] have also used sulfonium bromide for synthesis of arylnaphthalene derivatives via the reaction with *N*-tosylamine. This reaction is believed to proceed via an aziridine intermediate (Scheme 309). (One example for each is presented).

The Baylis−Hillman alcohols have been used as dienophiles by Aggarwal and co-workers[773] in (4 + 2) cycloaddition reactions with 2-methylbutadiene under the influence of dichloroethylaluminum in the presence of 2,6-di-*tert*-butylpyridine to provide the resulting adducts with high diastereoselectivity. Similar reaction with cyclopentadiene as diene provided mixture of *exo*−*endo* derivatives in high diastereoselectivity (Scheme 310).

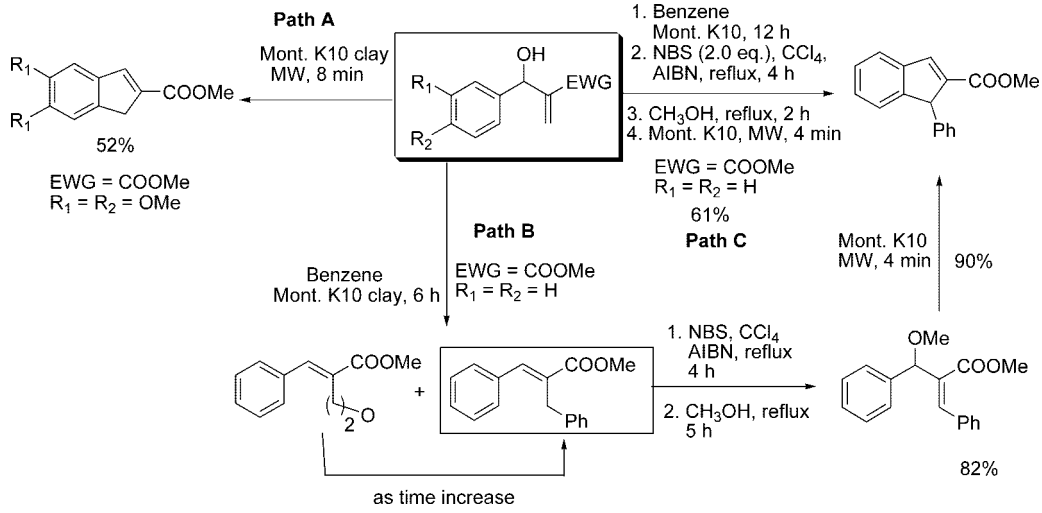
Scheme 298



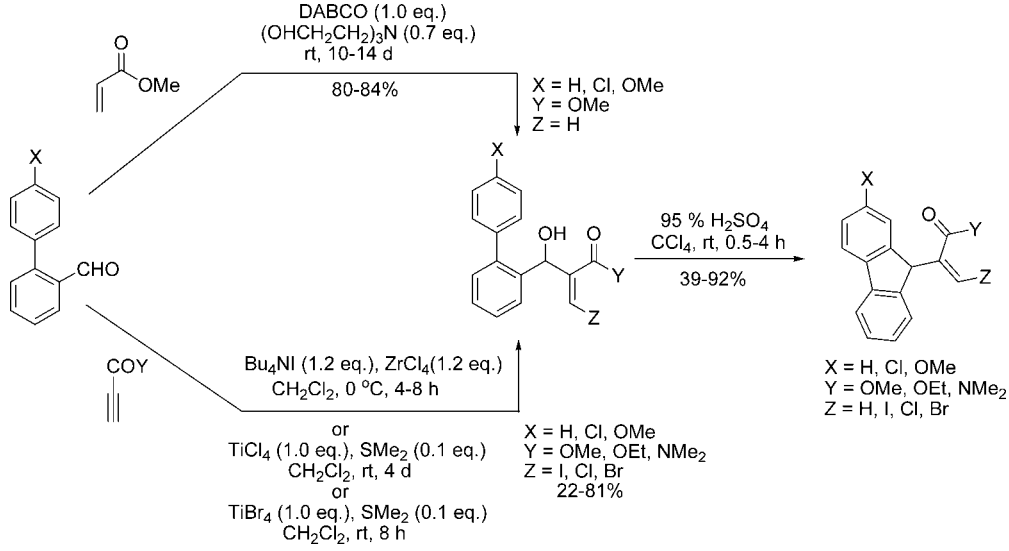
Scheme 299



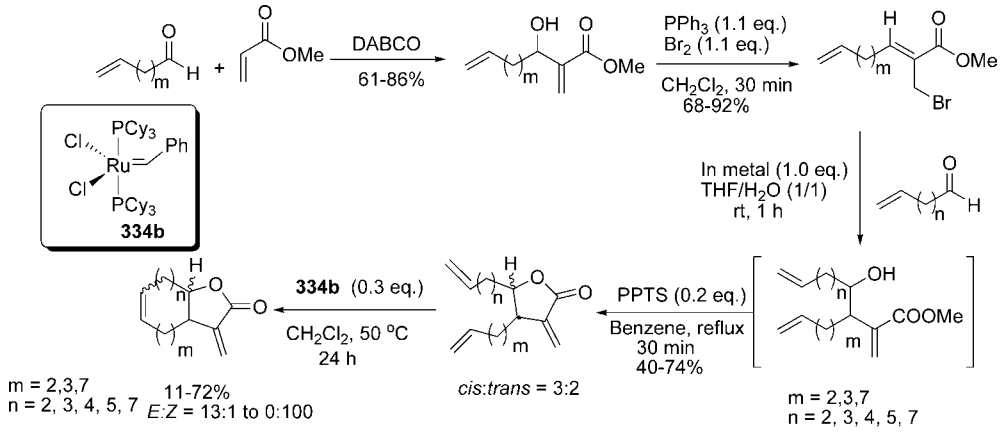
Scheme 300



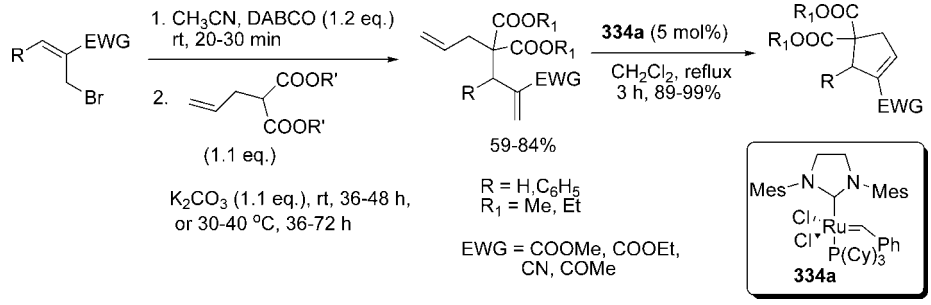
Scheme 301



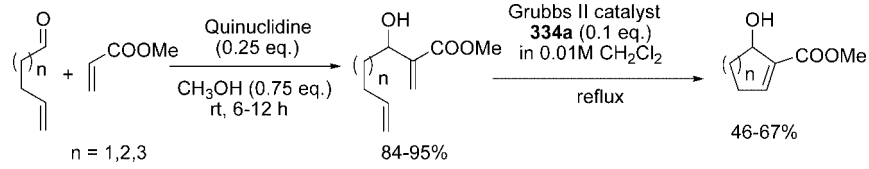
Scheme 302



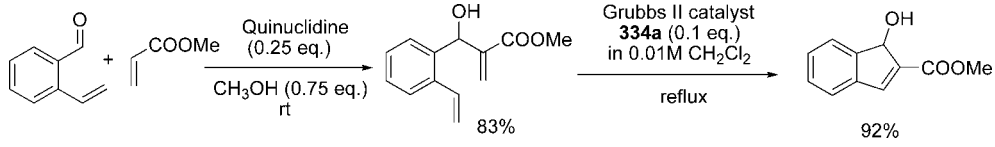
Scheme 303



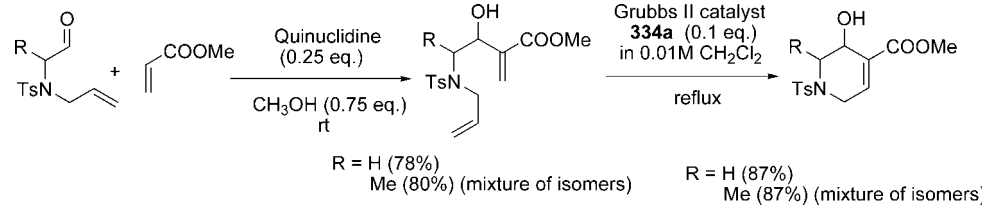
Scheme 304



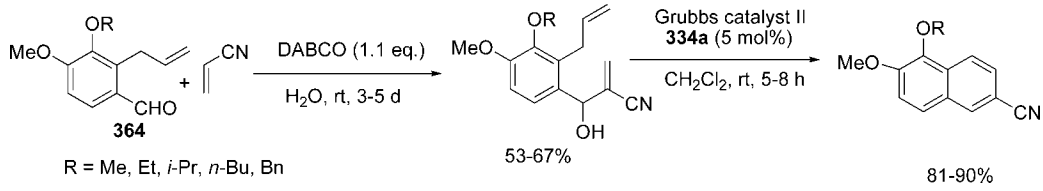
Scheme 305



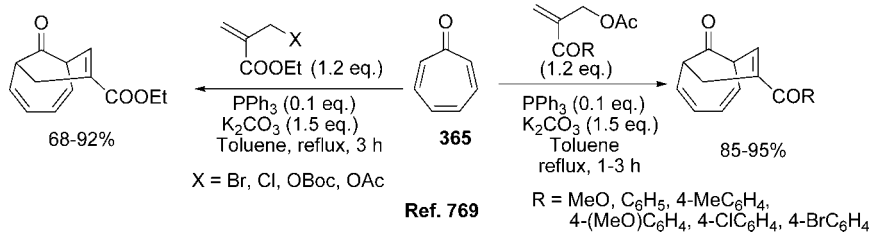
Scheme 306



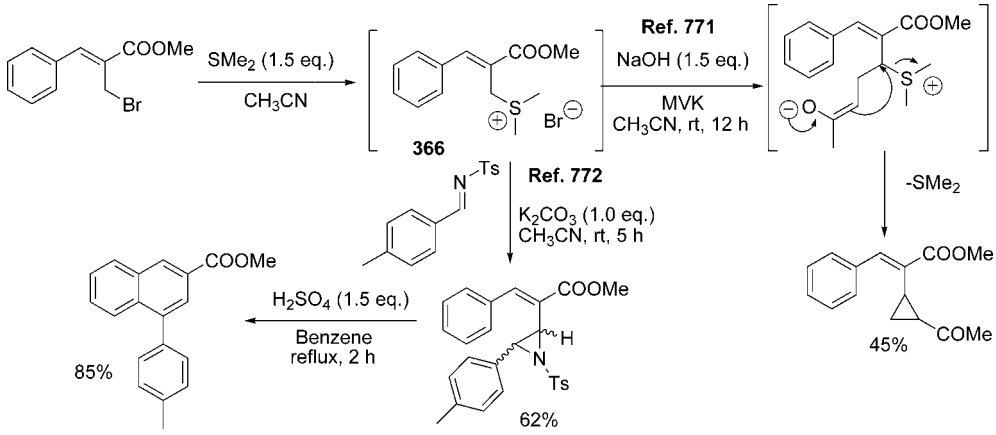
Scheme 307



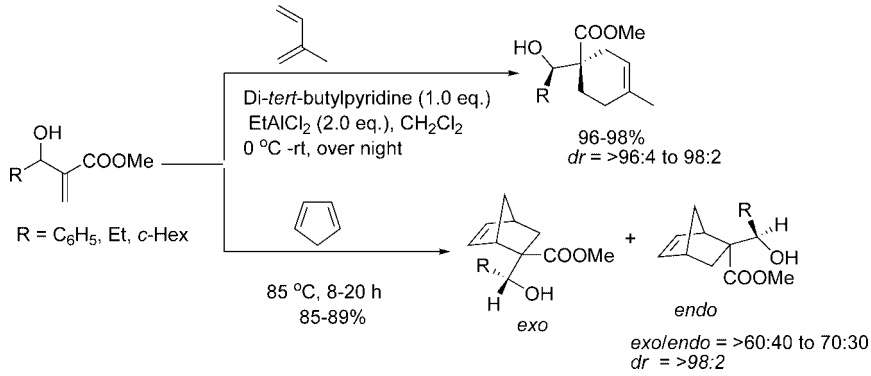
Scheme 308



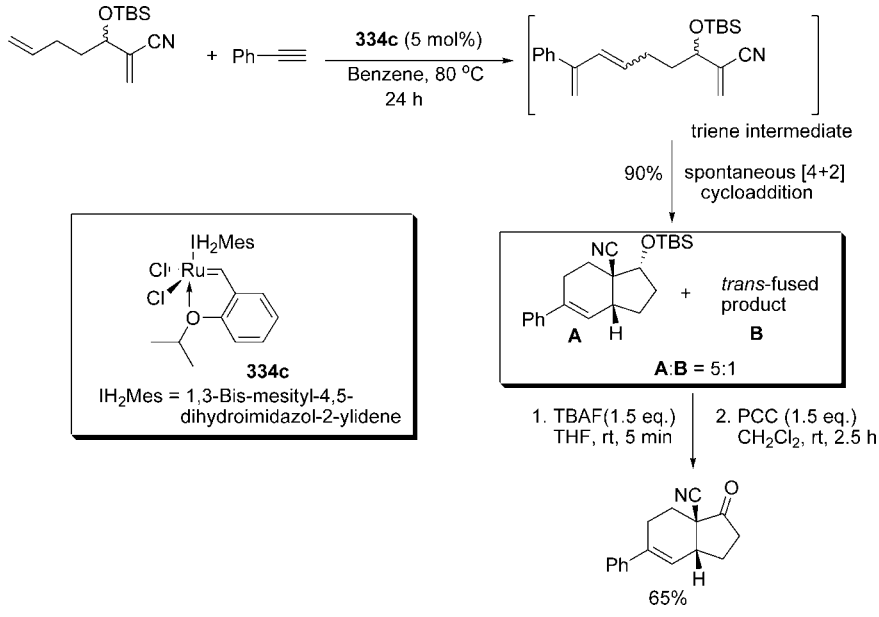
Scheme 309



Scheme 310



Scheme 311



An interesting synthesis of *cis*-fused carbocycles involving successive enyne cross-metathesis and intramolecular Diels−Alder reactions using Baylis−Hillman derivatives and alkynes as effective reaction partners was reported by Mix and Blechert (Scheme 311).[774]

An intramolecular conjugate displacement reaction (Michael addition followed by elimination) on the acetate of Baylis−Hillman adduct derived from appropriate electrophiles (dialdehyde, which can be used as nucleophile at a later stage) providing a carbocyclic framework was reported by Prabhudas and Clive.[775] Representative examples are given in Scheme 312.

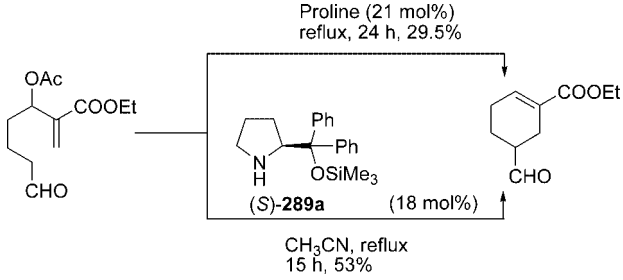
Rodgen and Schaus[776] used the catalyst **364e** for Baylis−Hillman coupling between cyclohex-2-enone and various unsaturated aldehydes to provide the resulting adducts in good yield and high enantioselectivity. They extended this strategy for preparation of clerodane decalin core (**367**), following the reaction sequence shown in Scheme 313.

10.4. Synthesis of Nitrogen Heterocyclic Compounds

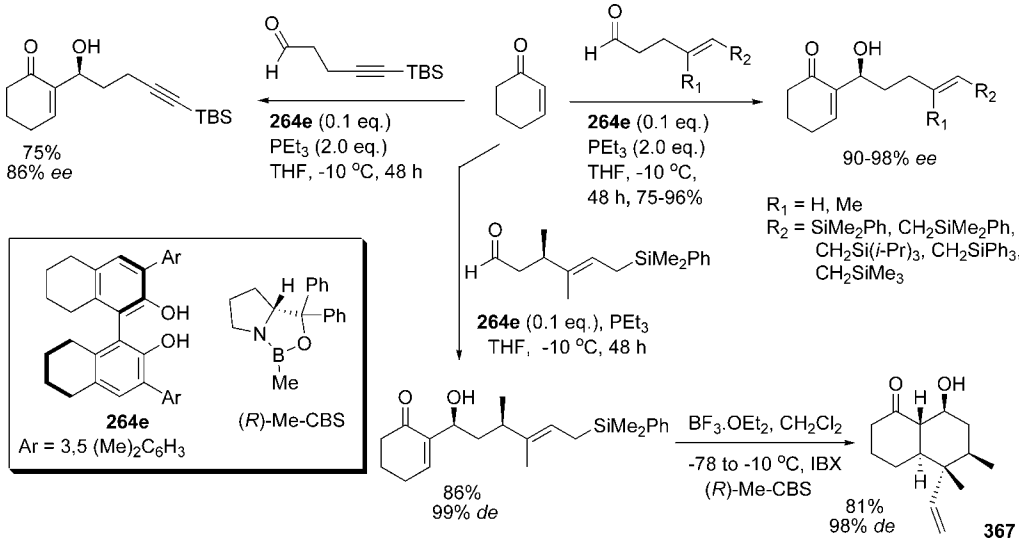
The Baylis−Hillman adducts (**368**) derived from 2-nitrobenzaldehydes and activated alkenes have been transformed into quinoline derivatives via (1) catalytic hydrogenation (Kaye procedure),[549,777] (2) treatment with TFA (Kim procedure),[550,778] and (3) treatment with Fe/AcOH (Basavaiah procedure)[551] (Scheme 314). Coehlo, Eberlin, and coworkers[779] recently monitored the reaction of acetate of Baylis−Hillman adduct **369** derived from 2-nitrobenzaldehyde with TFA (providing quinoline *N*-oxide derivatives) by mass spectroscopy with a view to understanding the mechanism of reaction and proposed methyl 3-(2-nitrophenyl)-3-trifluoroacetoxy-2-methylenepropionate (trifluoroacetyl derivative of Baylis−Hillman adduct, **370**) as a new key intermediate.

Kim and co-workers[780] have transformed the Baylis−Hillman adducts **368** into quinoline derivatives via treatment with Zn/NH_4Cl in aqueous medium (Path A, Scheme 315). Kim also

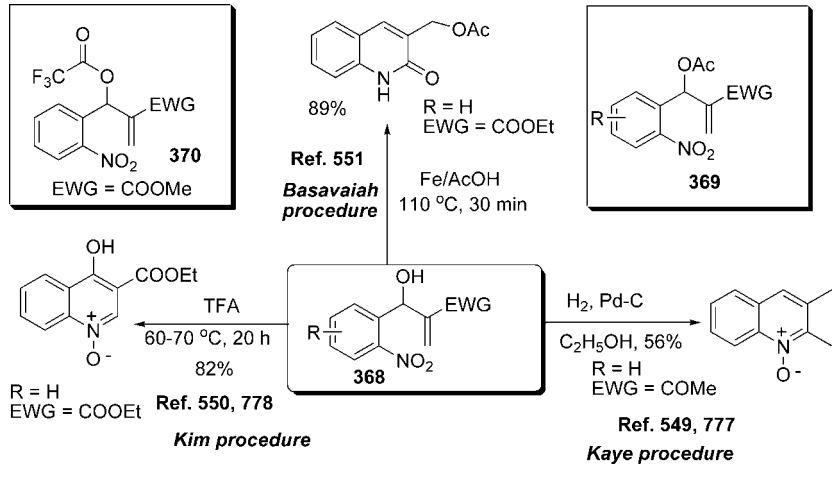
Scheme 312



Scheme 313



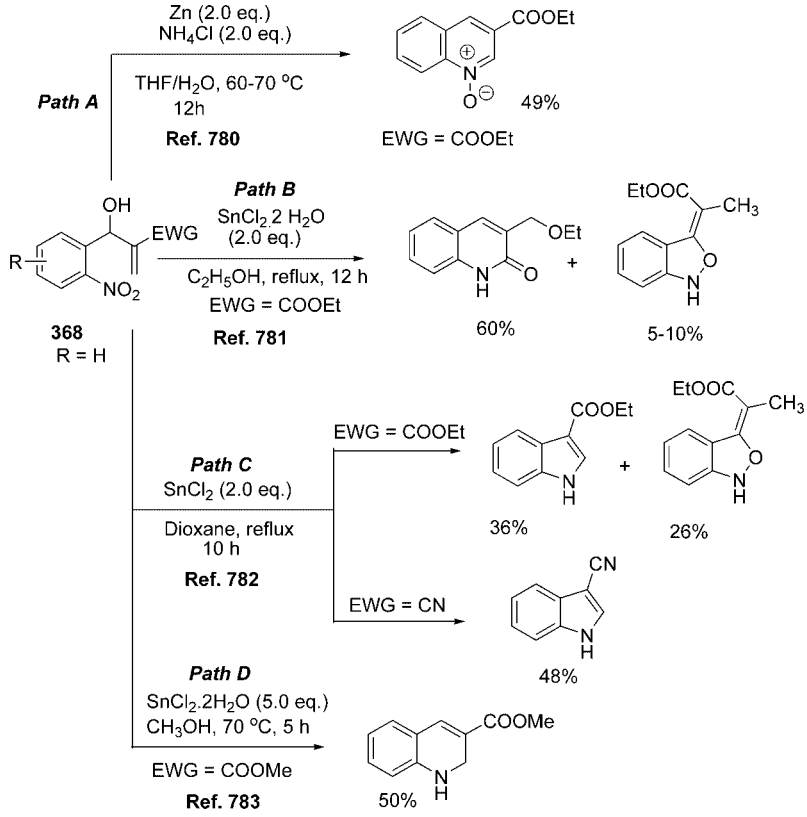
Scheme 314



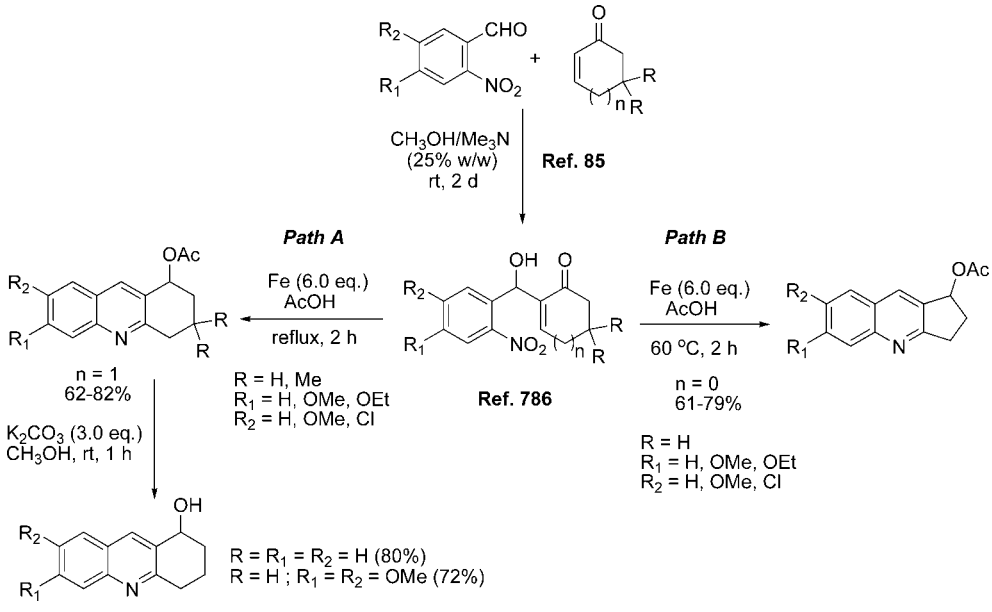
examined $SnCl_2$ as an alternative reagent for conversion of Baylis−Hillman adducts into quinoline derivatives and noticed an interesting solvent effect in the product formation. Thus the treatment of the Baylis−Hillman adducts (**368**) with $SnCl_2/H_2O$/ROH provided quinoline derivatives along with benzisoxazoline derivatives as side product (Path B, Scheme 315),[781] while the same reaction in dioxane provided indole derivatives along with benzisoxazolines as minor products (if EWG = COOEt) and indole derivatives as sole products (if EWG = CN) (Path C, Scheme 315).[782] Later Kaye and co-workers[783] reported the synthesis of quinoline derivatives from the Baylis−Hillman adducts **368** via the reductive cyclization using $SnCl_2/H_2O$ (Path D, Scheme 315). One example for each category is given in Scheme 315.

Nicholas and O'Dell[784] reported an alternative synthesis for quinolinone derivatives from the acetates **369** of the Baylis−Hillman adducts **368** derived from the coupling between 2-nitrobenzaldehydes and activated alkenes via reductive cyclization using carbon monooxide under the influence of $[Cp^*Fe(CO)_2]_2$ (eq 107). However similar reaction with Baylis−Hillman alcohols provided a mixture of compounds (*N*-formylindolines, indoles, and others).[785] One example is given in eq 108.

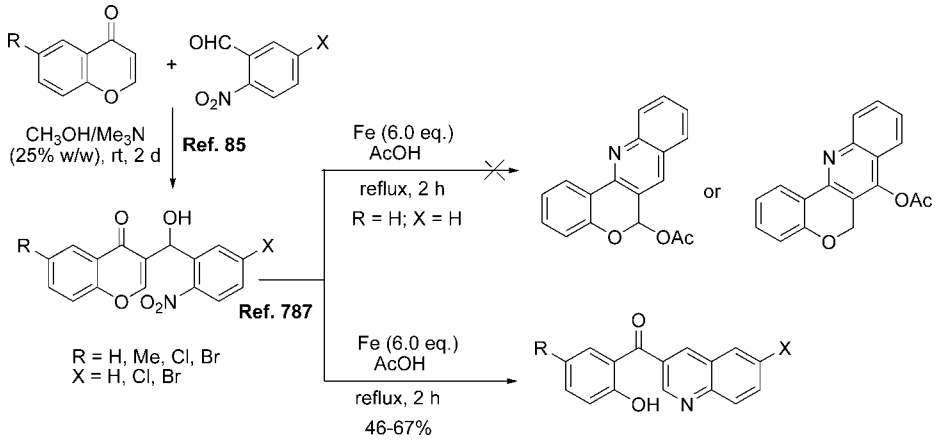
Scheme 315



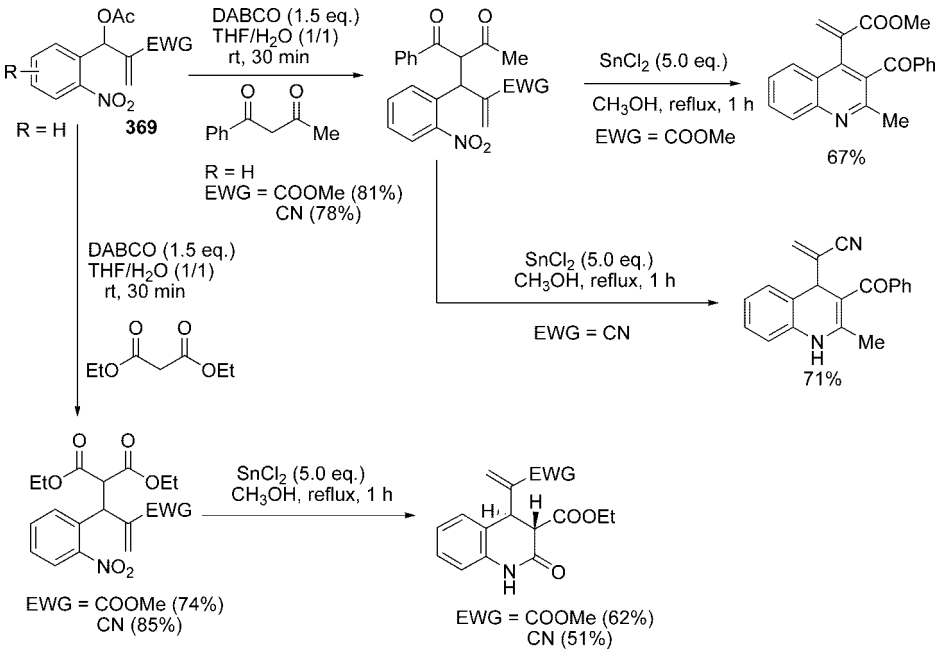
Scheme 316

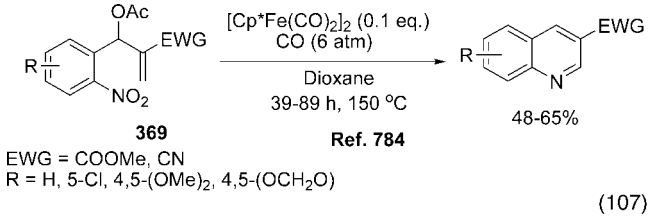


Scheme 317

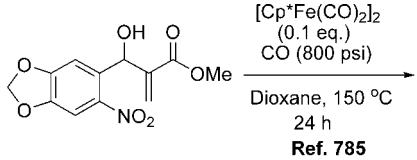


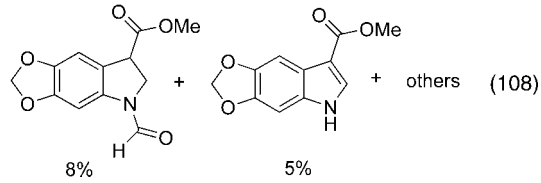
Scheme 318





(107)





(108)

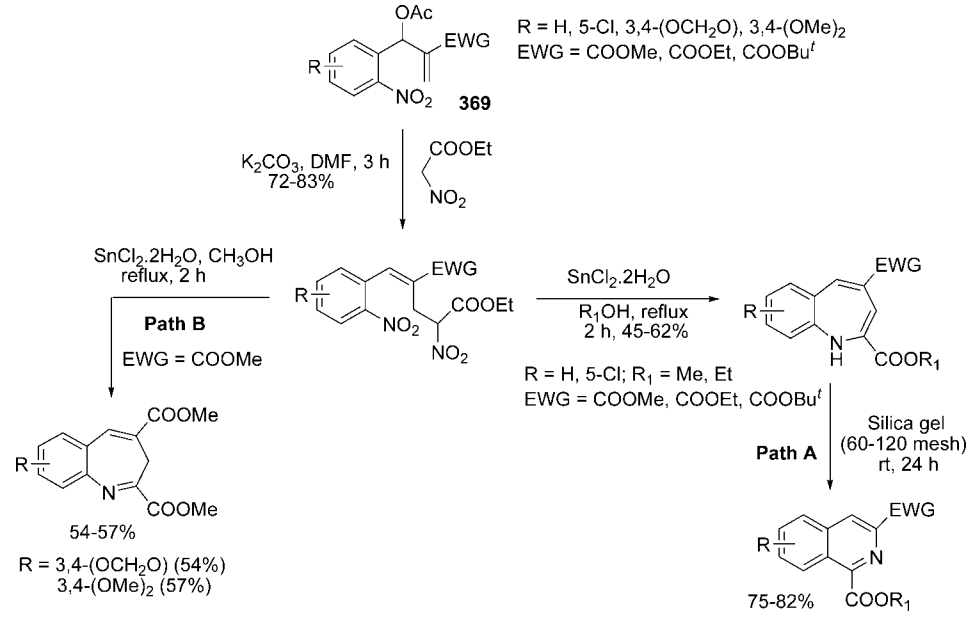
A facile, one-pot synthesis of functionalized 1,2,3,4-tetrahydroacridines from the Baylis−Hillman alcohols derived via the reaction between 2-nitrobenzaldehydes and cyclohex-2-enone derivatives by the treatment with Fe/AcOH as described in Path A, Scheme 316, was reported by our research group.[786] Similarly, the Baylis−Hillman adducts obtained via the reaction of cyclopent-2-enone with 2-nitrobenzaldehydes were transformed into cyclopenta[*b*]quinoline derivatives (Path B, Scheme 316).[786]

Our research group[787] also examined the reaction of Baylis−Hillman adducts obtained via the treatment of chromone derivatives with 2-nitrobenzaldehydes with Fe/AcOH. The expected tetracyclic heterocyclic compounds were not obtained, but 3-(2-hydroxybenzoyl)quinoline derivatives were isolated in good yields. Representative examples are given in Scheme 317.

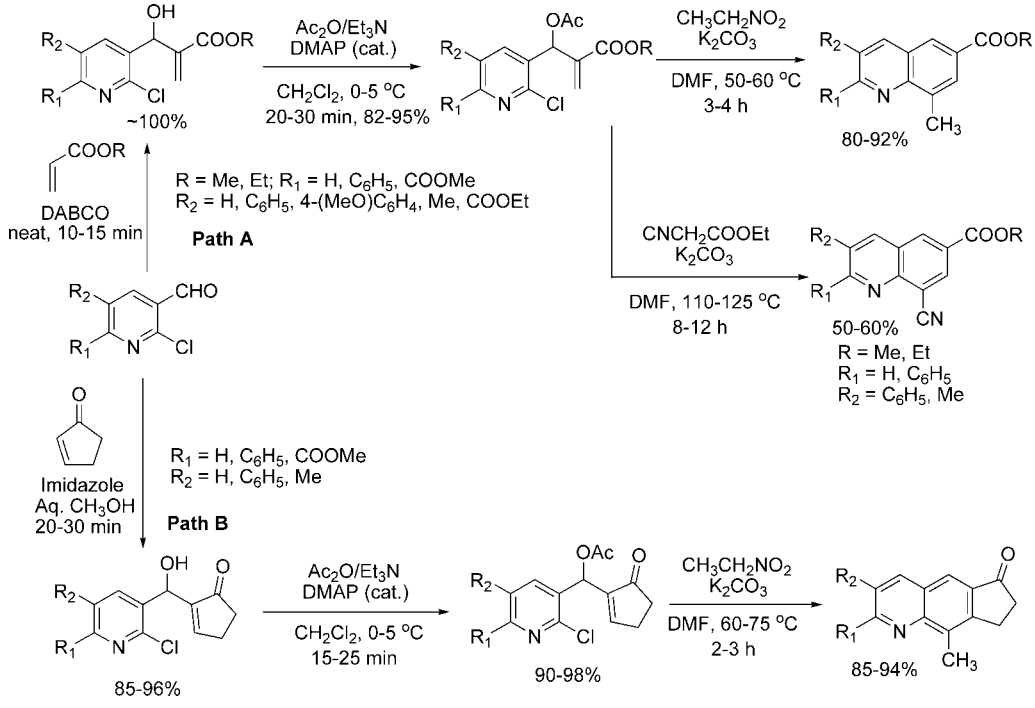
Subsequently Batra and co-workers[788] converted Baylis−Hillman acetates **369** into functionalized quinoline derivatives. This strategy involves the treatment of the Baylis−Hillman acetates with DABCO first and then alkylation with a 1,3-dicarbonyl system followed by reductive cyclization with $SnCl_2$. Representative examples are shown in Scheme 318.

Singh and Batra[789] have reported an interesting synthesis of isoquinoline derivatives, starting from Baylis−Hillman acetate **369** where aromatic ring does not contain an electron-

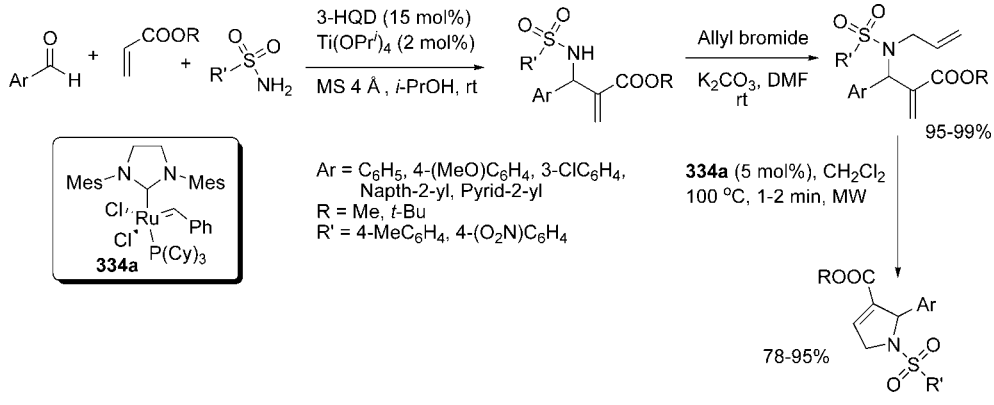
Scheme 319



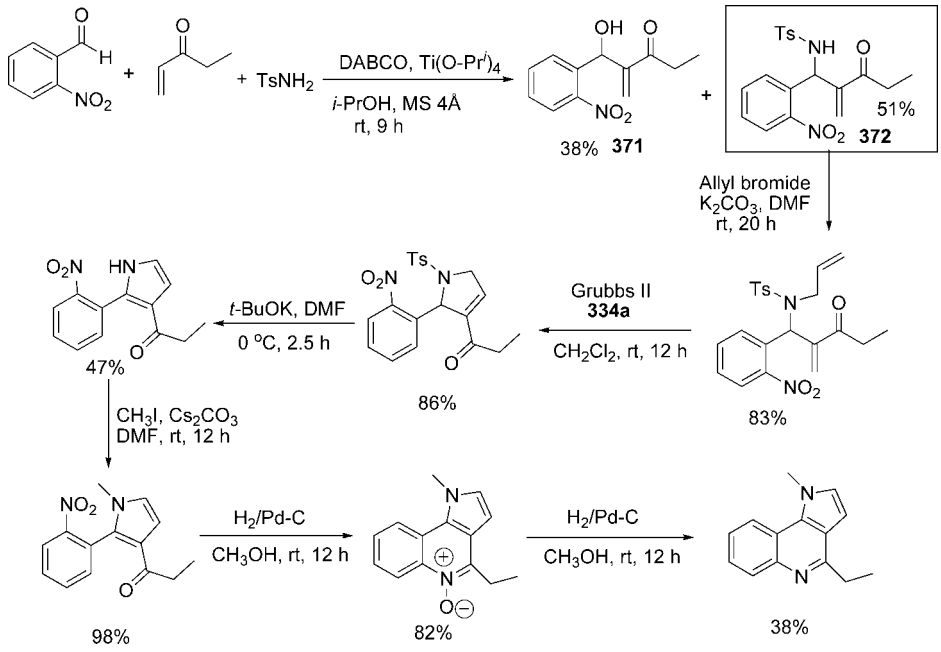
Scheme 320



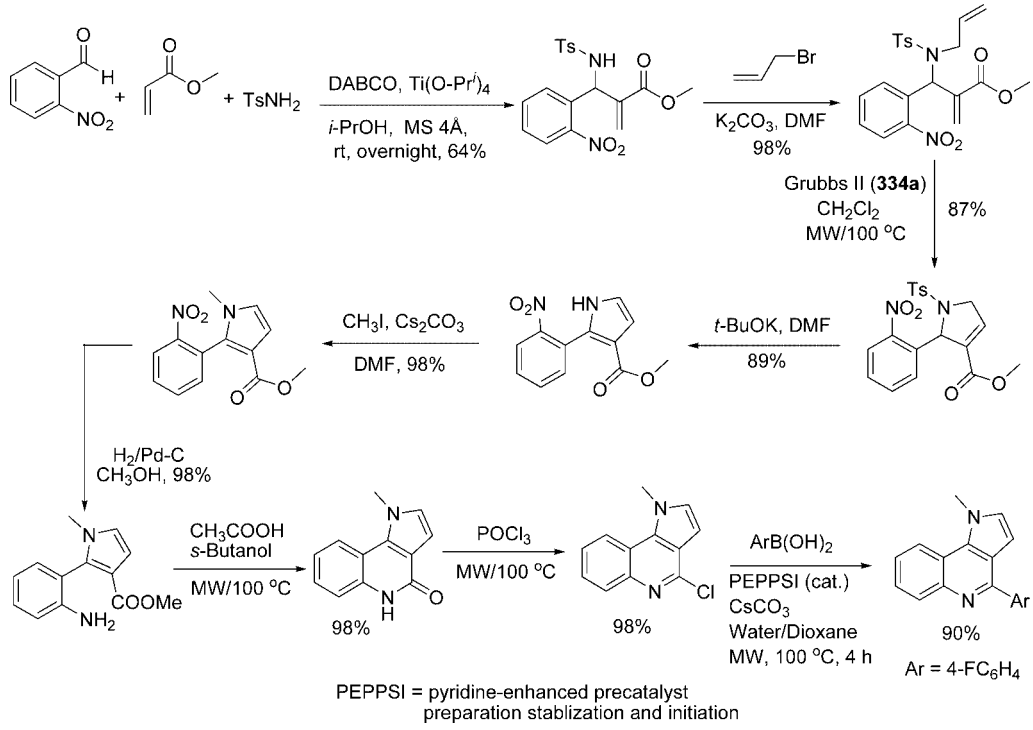
Scheme 321



Scheme 322



Scheme 323



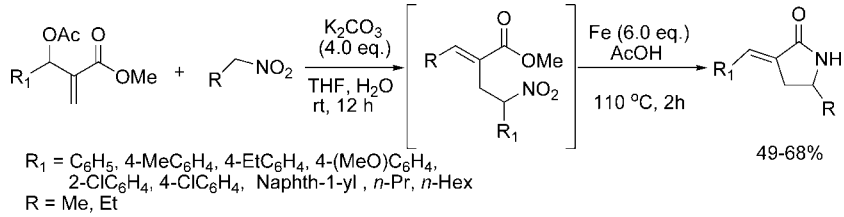
donating group, via the reaction with nitroethylacetate, followed by treatment with $SnCl_2$ to provide 1*H*-1-benzazepine derivatives, which are not stable and spontaneously transformed into isoquinoline derivatives (Path A, Scheme 319). Acetates **369** of Baylis−Hillman alcohols obtained from 2-nitrobenzaldehydes, containing an electron-donating group on the aromatic ring, provided 3*H*-1-benzazepines (Path B, Scheme 319).

Rao and co-workers[790] have reported a simple methodology for the synthesis of multisubstituted quinolines via the reaction of acetate of Baylis−Hillman alcohols (derived from the 2-chloronicotinaldehyde) with nitroethane or ethyl cyanoacetate, following the reaction sequence shown in Path A, Scheme 320. This reaction sequence involves an $S_N2'-S_NAr$ elimination strategy. Similarly, acetates of Baylis−Hillman alcohols derived from the 2-chloronicotinaldehyde and cyclopent-2-enone on reaction with nitroethane followed by cyclization provided cyclopenta[*g*]quinoline derivatives (Path B, Scheme 320).

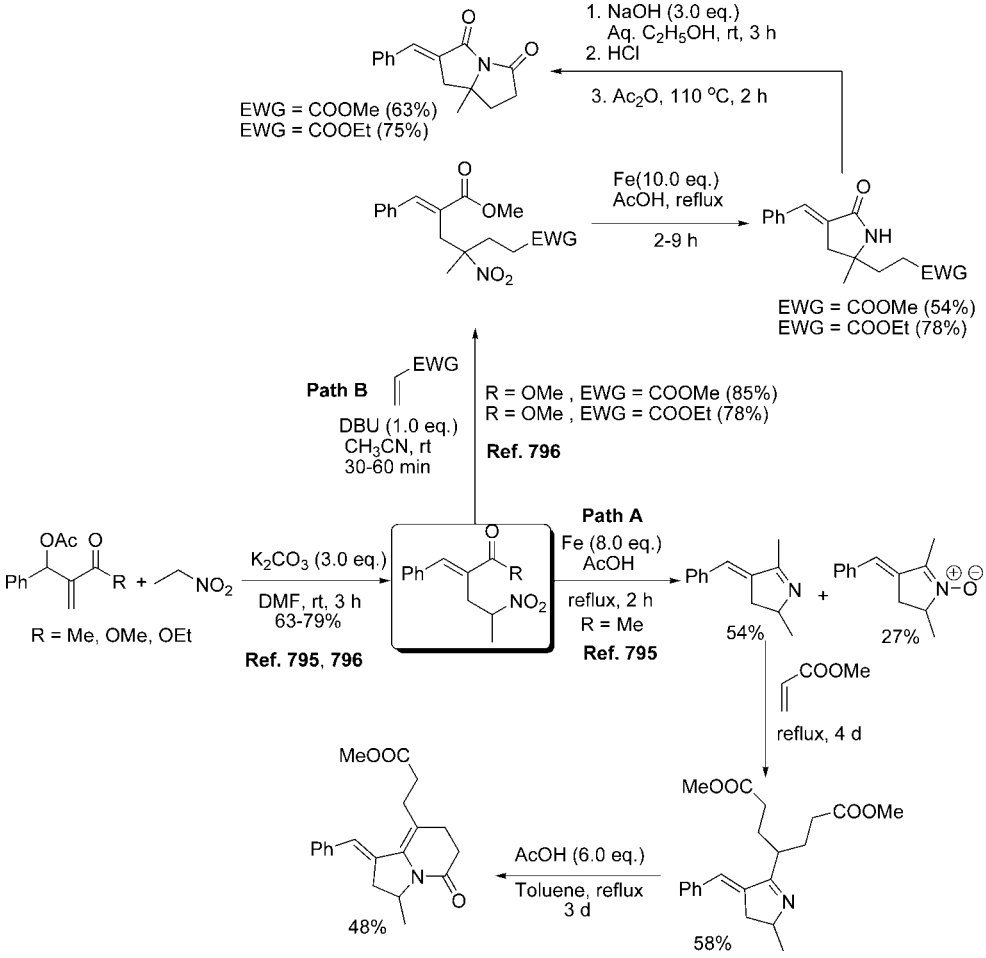
Adolfson and Balan[791] have developed a facile methodology for the synthesis of functionalized 2,5-dihydropyrroles via the ruthenium-catalyzed ring-closing metathesis (RCM) of the diene substrates, obtained from the Baylis−Hillman adducts, under microwave irradiation, following the reaction sequence shown in Scheme 321.

Lamaty and co-workers[792] have developed an interesting synthesis of fused pyrrolo-[3,2-*c*]quinolines starting from Baylis−Hillman adducts **372** following the reaction sequence

Scheme 324



Scheme 325



described in Scheme 322. The required Baylis−Hillman adducts **372** were obtained via the reaction between 2-nitrobenzaldehydes, EVK, and tosyl amine in the presence of DABCO, along with Baylis−Hillman adducts **371** as minor products. Lamaty and co-workers[793] have also developed a similar strategy for obtaining chloro or aryl pyrrolo-[3,2-*c*]quinolines from the Baylis−Hillman adducts derived from methyl acrylate as activated alkene (Scheme 323).

A simple, convenient, and one-pot transformation of the acetates of Baylis−Hillman adducts into substituted γ-lactams, that is, (*E*)-5-alkyl-3-arylidenepyrrolidin-2-ones via treatment with nitroalkanes in the presence of a base, followed by reductive cyclization, using Fe/AcOH, was described by our research group (Scheme 324).[794]

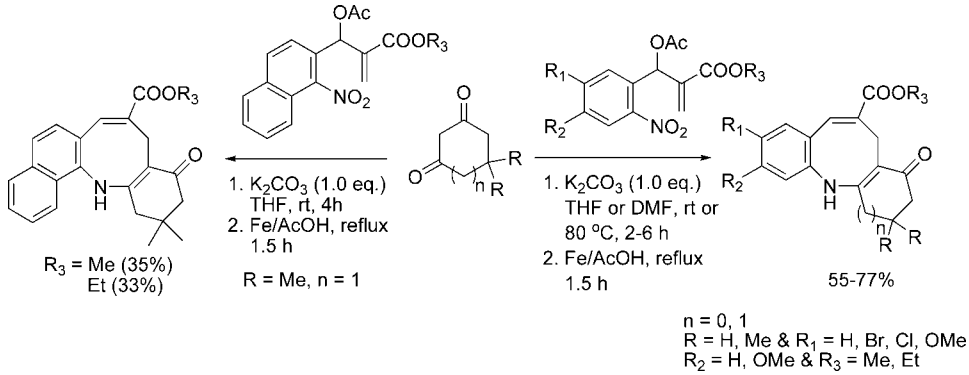
Subsequently Kim and co-workers[795] have transformed the acetate of Baylis−Hillman adducts derived from MVK into dihydropyrrole derivatives via reaction with nitroalkane followed by reductive cyclization with Fe/AcOH. In this reaction, nitrones were obtained as minor products. The dihydropyrroles were subsequently converted into indolizine derivatives via Michael reaction and cyclization. A representative example is given in Path A, Scheme 325. Later on, Kim and co-workers[796] have also converted the acetate of Baylis−Hillman adducts derived from alkyl acrylates into 2-pyrrolidone derivatives, which were then transformed into pyrrolizine derivatives following the reaction sequence described in Path B, Scheme 325.

Recently our research group[797] reported an interesting transformation of Baylis−Hillman acetates into tri- or tetracyclic heterocyclic frameworks containing an important azocine moiety via a one-pot, multistep protocol involving alkylation, reduction, and cyclization sequence (Scheme 326). A plausible mechanism for this transformation is given in Scheme 327.

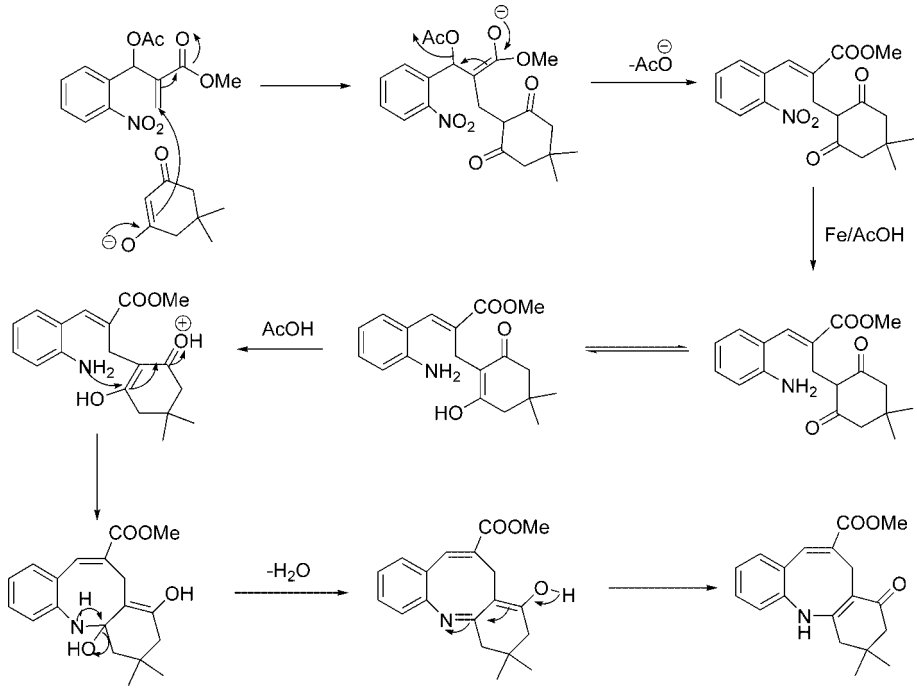
Perez and Horn[798] developed an efficient methodology for the synthesis of 3-nitro-1*H*-indole-2-carboxylic acid ethyl ester derivatives from the Baylis−Hillman acetates via treatment with KNO_2 in DMF (eq 109).

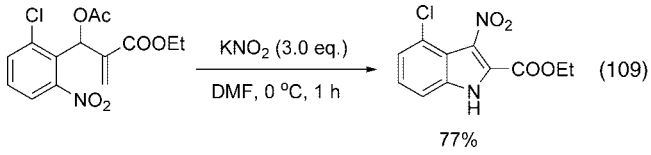
Batra and co-workers[799] reported a simple method for the synthesis of 2-pyrrolidinones and pyrroles from the key intermediates **373** via the reduction of the secondary nitro group. The key intermediates **373** were obtained from the Baylis−Hillman acetate, following the reaction sequence

Scheme 326



Scheme 327





described in Scheme 328. They observed that the formation of products depends on the substitutent as well as on the reducing agent.

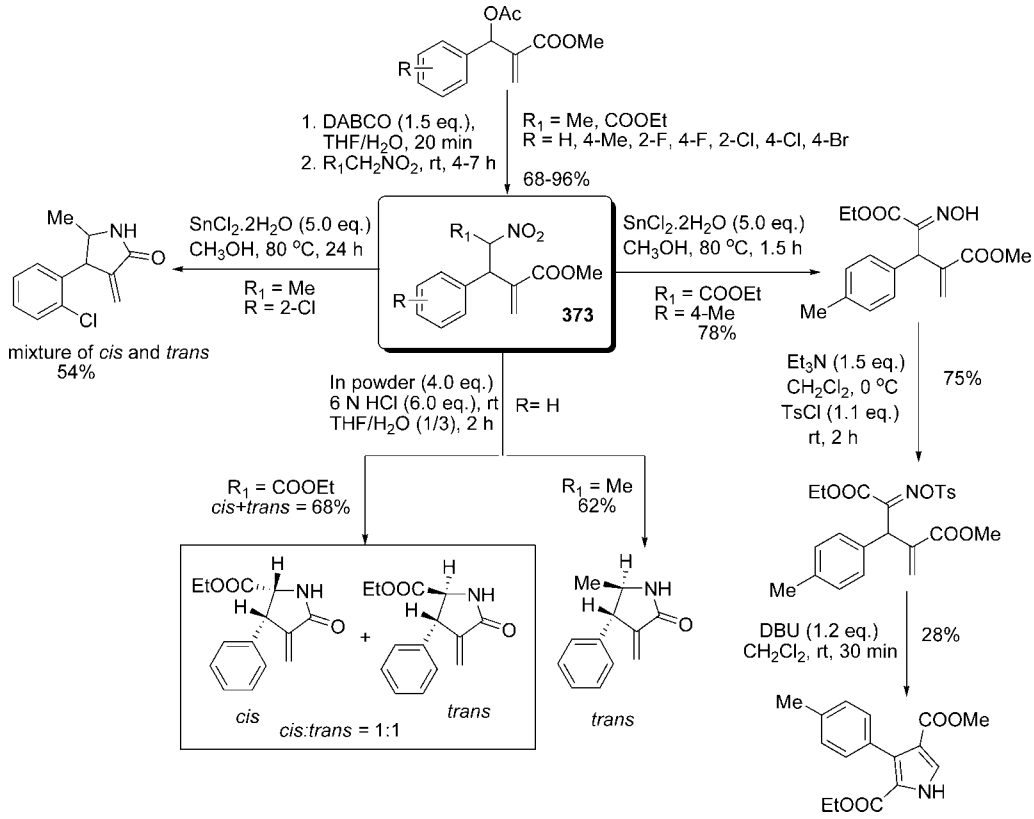
Treatment of the Baylis−Hillman bromide with DABCO first and then with nitroalkane to provide the alkylated products as a mixture of *syn* and *anti* diastereomers (which were separable) was reported by Kim and co-workers.[800] These products were further converted into lactam derivatives by treatment with Fe/AcOH (Scheme 329).

Kim and co-workers[801] have developed an efficient methodology for the synthesis of indenoquinoline skeletons from **374** (S_N2' product) obtained via the treatment of Baylis−Hillman acetate with aniline derivatives, following the reaction sequence described in Path A, Scheme 330. Subsequently, Kim and co-workers[802,803] also reported an interesting synthesis of substituted quinoline derivatives from the product **375** obtained via the reaction of Baylis−Hillman acetate first with DABCO and then with aniline according to Paths B and C, Scheme 330. This reaction proceeds via the aza-Claisen rearrangement as the key step. Later on, Batra and co-workers[804] reported the conversion of **375** into quinoline derivatives according to Path D, Scheme 330. They extended a similar strategy to the acetates of Baylis−Hillman adducts obtained from acrylonitrile to provide 2-aminoquinoline derivatives (Scheme 331). An alternative synthesis of quinoline derivatives from the Baylis−Hillman acetates, involving intramolecular Heck reaction of **376** as one of the key steps, was also described by Kim and co-workers (Path A, Scheme 332).[805] Acetates of Baylis−Hillman adducts were also converted into substituted pyridine derivatives following the reaction sequence shown in Path B, Scheme 332.[805]

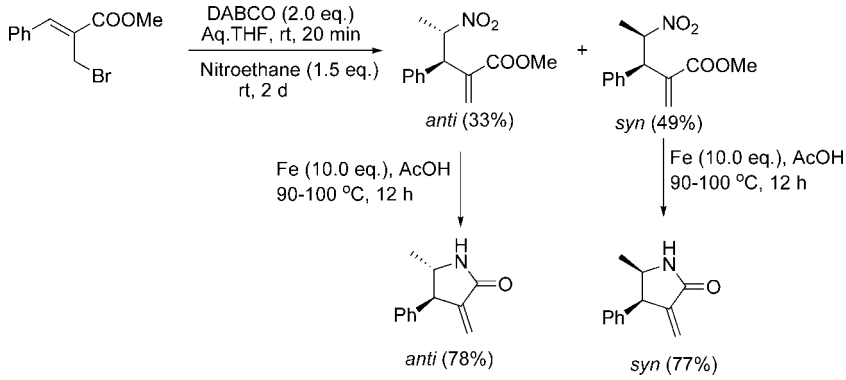
Intramolecular Heck reaction strategy was employed by Kim and co-workers for the synthesis of a tetracyclic heterocyclic system containing an indole moiety, starting from the acetates of the Baylis−Hillman adducts derived from 2-bromobenzaldehyde, according to the reaction sequence shown in Path A, Scheme 333.[806] Later on, they[807] extended this strategy to the synthesis of several poly-fused heterocyclic systems. Some representative examples are given in Paths B and C, Scheme 333.

An interesting methodology for the synthesis of quinolin-5-one derivatives involving the reaction of Baylis−Hillman

Scheme 328



Scheme 329



acetates with cyclic enaminones as the key step has been also reported by Kim and co-workers,[808] following the reaction sequence shown in Scheme 334.

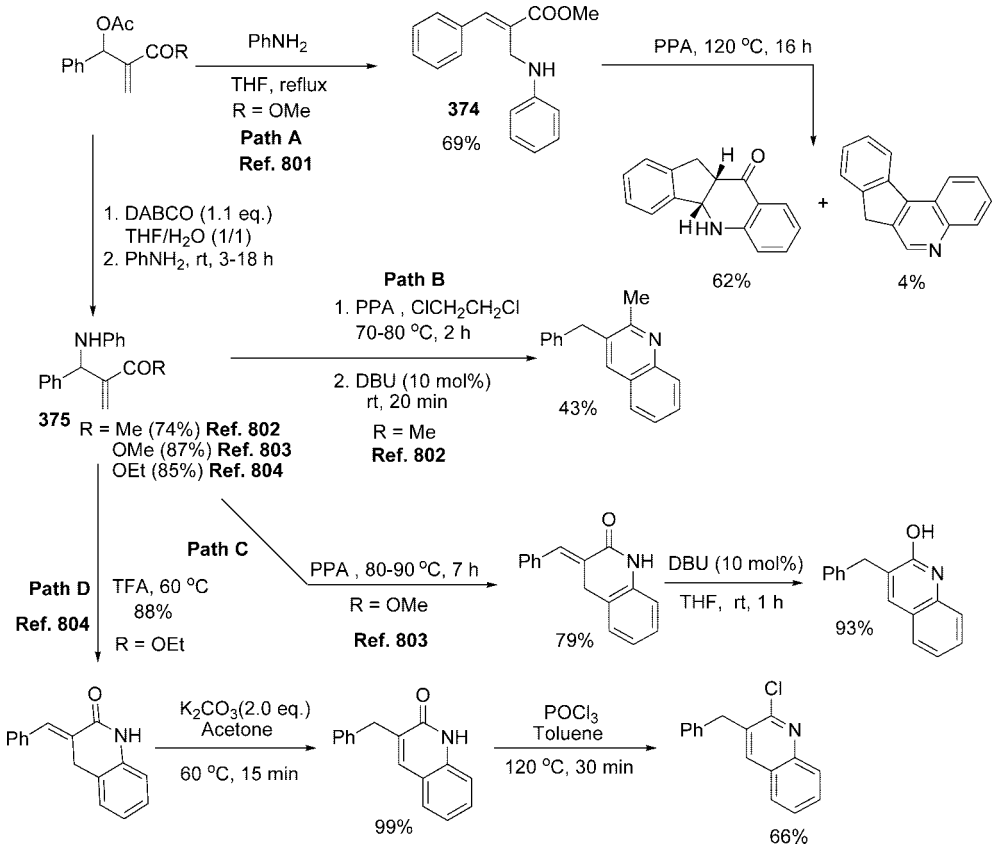
Kim and co-workers[809,810] also developed a facile methodology for synthesis of poly-substituted pyridines via the (3 + 2 + 1) annulation protocol, which involved successive reaction of Baylis−Hillman acetate (three carbon) with active methylene compounds (two carbon) and ammonium acetate (one nitrogen), following the reaction sequence shown in Scheme 335. They have also reported the regioselective *ortho*-hydroxylation[811] of an aryl group adjacent to the nitrogen atom in pyridine rings using oxone in the presence of a catalytic amount of $Pd(OAc)_2$.

Later on, Su and co-workers[812] developed a one-pot strategy for the synthesis of quinolin-5-one derivatives involving the reaction of Baylis−Hillman acetate with cyclohexane-1,3-diones followed by ammonium acetate or primary amines under solvent-free conditions as key steps (Scheme 336).

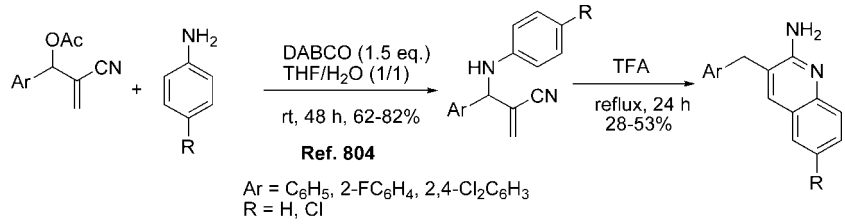
A facile methodology for the synthesis of 3,4-disubstituted and 3,4,5-trisubstituted pyridine derivatives starting from Baylis−Hillman acetates was developed by Kim and co-workers[813,814] following the reaction sequence described in Scheme 337. The allyl amine derivatives **377**, obtained in the first step via the treatment of Baylis−Hillman acetate with tosyl amine, were converted into 3,4-disubstituted pyridines via the Schweizer reaction with vinyltriphenylphosphonium bromide, followed by elimination of *p*-toluensulfonic acid (Path A, Scheme 337). The allyl amine derivatives **377** were also transformed into 3,4,5-trisubstituted pyridine derivatives following the reaction sequence shown in Path B, Scheme 337, involving Michael and aldol reaction. Representative examples are presented.

Kim and co-workers[815] have developed an interesting protocol for the synthetis of poly-substituted pyrrole derivatives via the reaction of phenacyl bromide with the Baylis−Hillman adducts (Path A) or their rearranged derivatives (Path B), involving intramolecular Michael reaction as

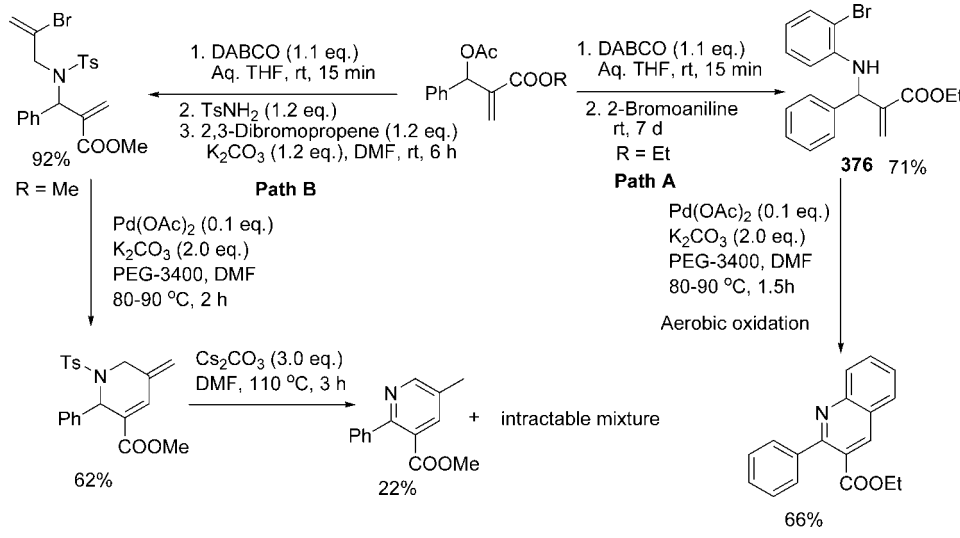
Scheme 330



Scheme 331



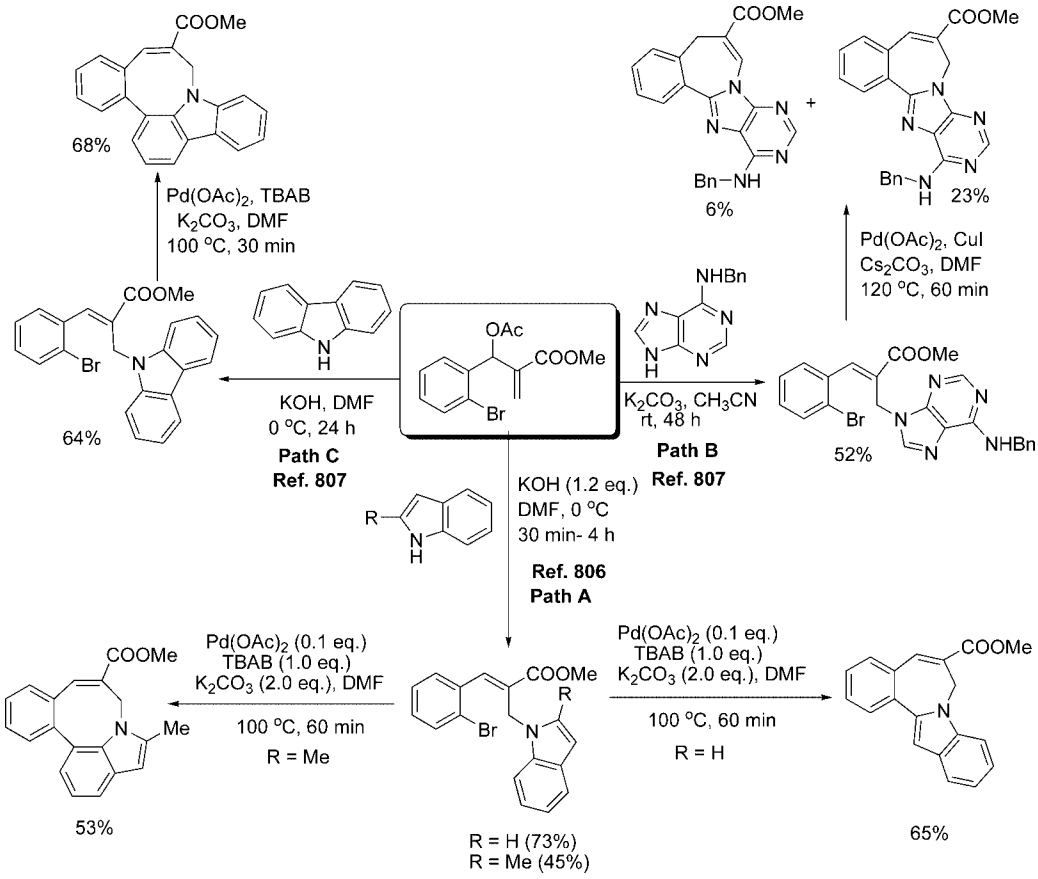
Scheme 332



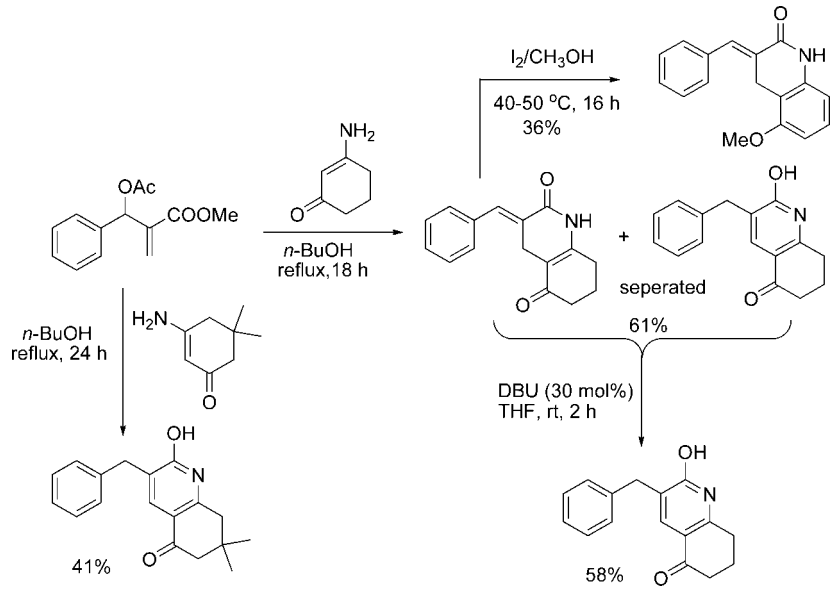
the key step, following the reaction sequence shown in Scheme 338.

The rearranged Baylis−Hillman adducts were transformed into *N*-tosyl-3,3-disubstituted-4-vinylpyrrolidine derivatives in moderate yields with high diastereoselectivity, following the reaction sequence shown in Scheme 339.[816] The key step in this sequence was intramolecular free radical cyclization.

Scheme 333



Scheme 334



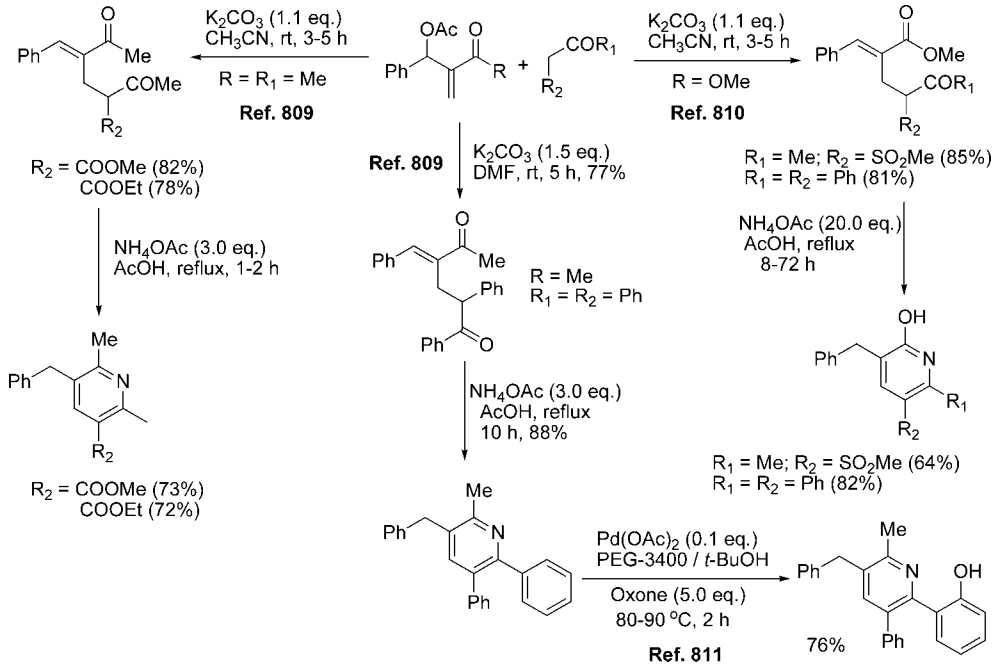
Subsequently Kim and co-workers[817] also synthesized poly-substituted pyrrole derivatives via the reaction of Baylis−Hillman acetates with secondary amines followed by cyclization and aromatization (Scheme 340).

Later on, Kim and co-workers[818] developed an alternative method for the synthesis of trisubstituted pyrroles starting from the Baylis−Hillman bromides. This strategy involves the treatment of Baylis−Hillman bromides with aldehydes in the presence of indium to provide homoallyl alcohols, which on oxidation, followed by treatment with benzylamine, provided pyrrole derivatives. One representative example is shown in Scheme 341.

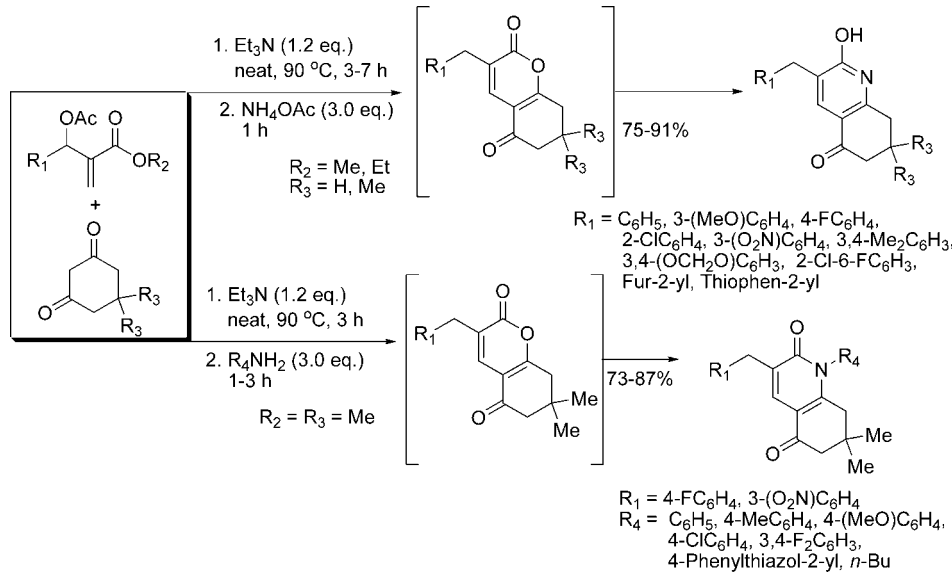
Sa[819] has developed a facile methodology for synthesis of quinoline derivatives from the allyl azides prepared from Baylis−Hillman adducts via treatment with $AlCl_3$ (Scheme 342). One such example is presented.

Hong and Lee[820] have reported an elegant route to various quinolone antibiotic intermediates using the Baylis−Hillman adducts derived from 2-fluorobenzaldehydes as the key synthon, following the reaction sequence described in

Scheme 335



Scheme 336



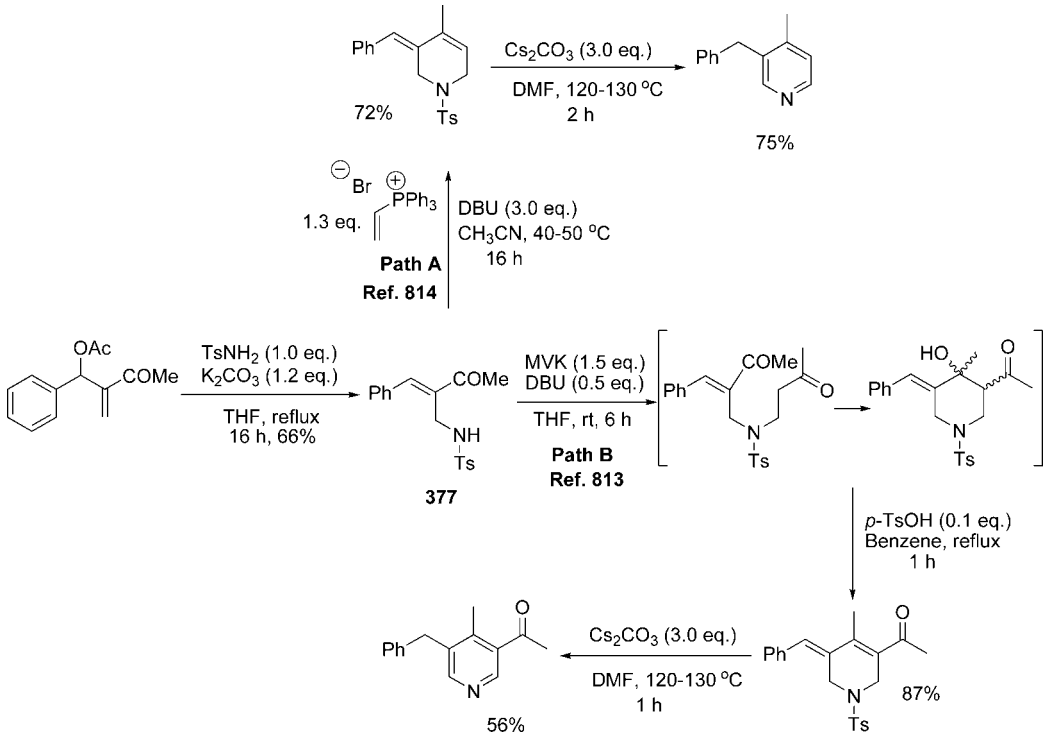
Scheme 343. This strategy involves intramolecular cyclization, fluoride ion serving as leaving group. Representative examples are presented.

Chang and co-workers[821] have reported a facile conversion of Baylis−Hillman adducts into 5-arylidene-3-sulfonylpiperidine-2,6-dione derivatives **379** (major products), along with the formation of 3-sulfonylpiperidine-2,6-dione derivatives (**380**) as minor products, following the reaction strategy presented in Scheme 344. This reaction is believed to proceed through formation of dianion (**378**) and then alkylation followed by intramolecular cyclization. In some cases, the compound **380** was obtained as the major product. This methodology was extended to formal synthesis of tacamonine (**381**) an indole alkaloid, following the reaction sequence shown in Scheme 344.

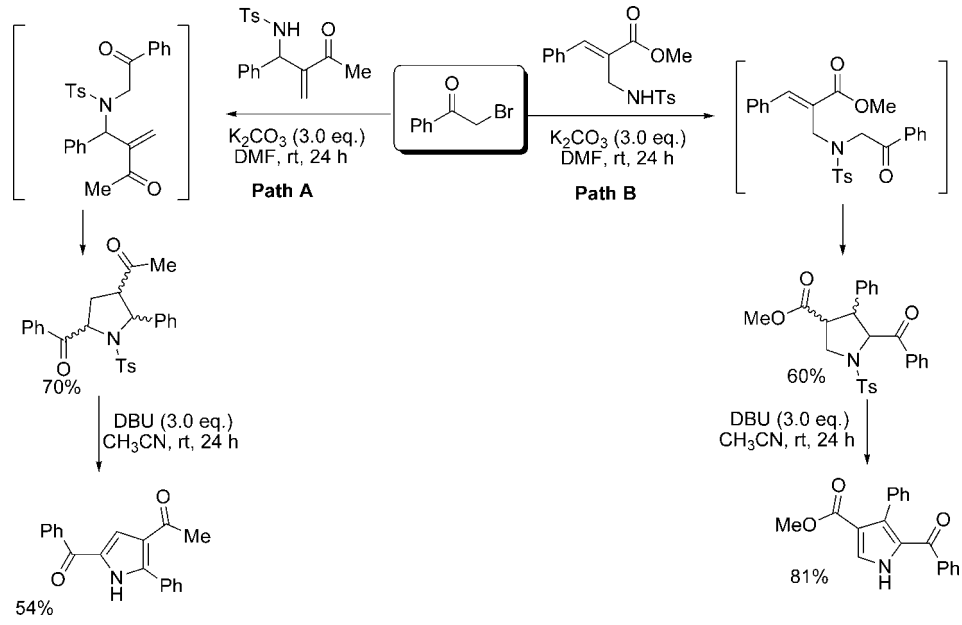
Kamimura and co-workers[822] have developed an interesting protocol for stereoselective addition of thiols to protected Baylis−Hillman adducts (OH protected as TBS group) and subsequently transformed these adducts into β-lactam derivatives following the reaction sequence shown in Scheme 345. One example is given.

Orena and co-workers[823] have reported a facile conversion of Baylis−Hillman adduct **333**, derived from methyl acrylate and ethyl glyoxalate, into chiral 3-hydroxypyrrolidin-2-one (**385**), an important glycosidase inhibitor (Scheme 346). In this reaction sequence, the key step involves the treatment of *O*-silyl derivatives of the Baylis−Hillman adduct with (*S*)-phenylethylamine leading to the formation of a separable equimolar mixture of 4,5-disubstituted pyrrolidin-2-one derivatives (**382** and **383**). Subsequently, Orena and co-workers[824] developed a simple methodology for obtaining chiral 3-aminopyrrolidin-2-one derivatives **388** and **389** starting from the Baylis−Hillman adduct **333**, according to reaction sequence shown in Scheme 347. In this strategy, Overman rearrangement and Michael addition with enan-

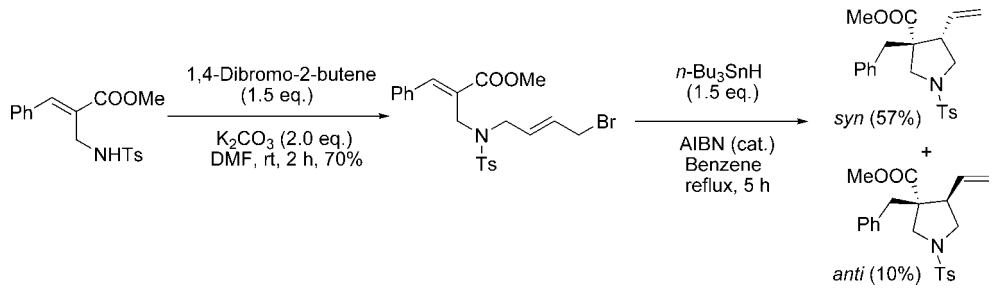
Scheme 337



Scheme 338



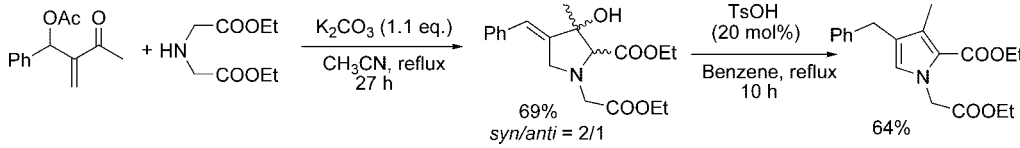
Scheme 339



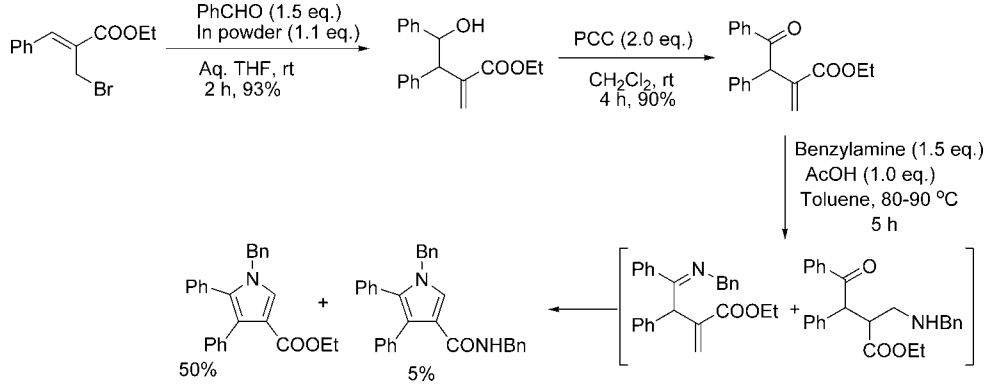
tiopure primary amine (providing a separable mixture of substituted pyrrolidines **386** and **387**) are the key steps.

Lee and co-workers[825] have developed an interesting synthesis of 1-benzazepine-4-carboxylate derivatives from

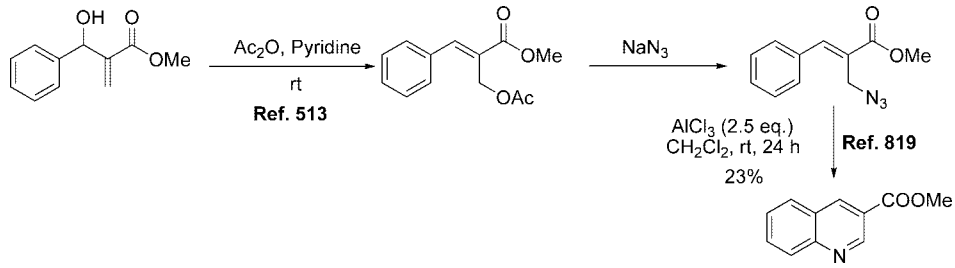
Scheme 340



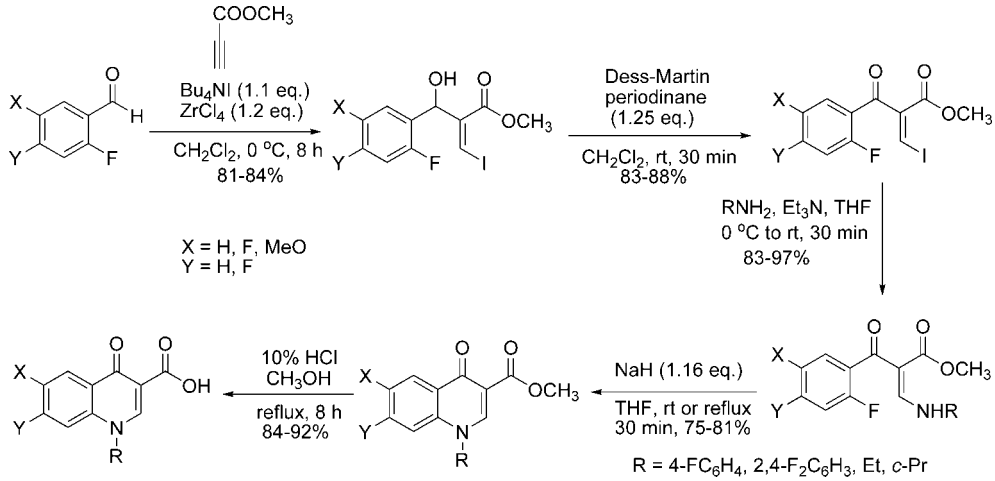
Scheme 341



Scheme 342



Scheme 343

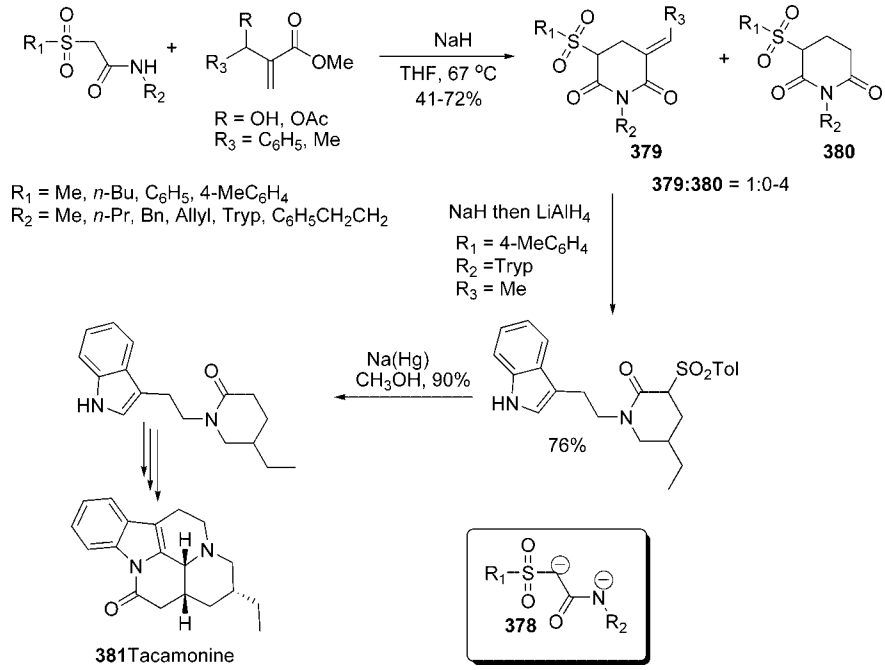


the acetate of Baylis−Hillman alcohols obtained via the reaction of 2-formylaminobenzaldehyde and methyl acrylate. The first step involves the treatment of Baylis−Hillman acetate with KCN, followed by the reaction of the resulting allyl cyanide (**390**) with NaOMe to provide 1-benzazepine-4-carboxylate derivatives, following the reaction sequence shown in Scheme 348. The allyl cyanide obtained from acetates of Baylis−Hillman alcohol prepared via the reaction of 2-acetylamino and 2-propionylaminobenzaldehydes with methyl acrylate was transformed into 1*H*-indole-2-carboxylate derivatives via the treatment with sodium methoxide following the reaction sequence shown in Scheme 348. A similar reaction of the allyl cyanide **390** (when R is phenyl) provided a complex mixture of products.

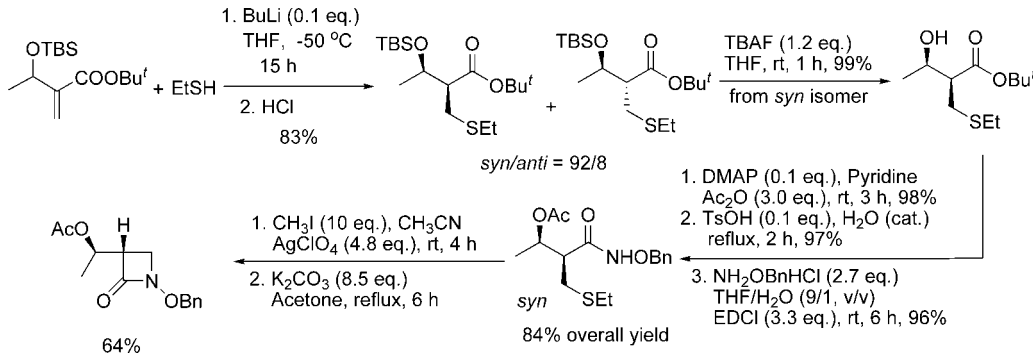
Singh and co-workers[826] have developed an interesting protocol for synthesis of (3*R*,4*R*)-4-acetoxy-3-[1′(*R*)-*tert*-butyldimethylsilyloxyethyl]azetidin-2-one (**393**), which is the key intermediate for the synthesis of penem and carbapenem derivatives, using the enantiomerically pure Baylis−Hillman adduct **391** as the starting material (which was obtained from chiral acrylamide (**138**) via the reaction with acetaldehyde), following the reaction sequence shown in Scheme 349.

Very recently Yadav and co-workers[827] reported a one-pot, highly diastereoselective method for the synthesis of

Scheme 344



Scheme 345



azetidines via the reaction of *N*-arylphosphoramines with Baylis−Hillman alcohols in the presence of NaH, according to Scheme 350.

Clive and co-workers[828,829] have reported an elegant Baylis−Hillman route for synthesis of quinolizines, indolizines, and an [*m.n*.0]-bicyclic framework having nitrogen at the bridgehead. Selected examples are given in Scheme 351. In all these strategies, the first step involves the Baylis−Hillman reaction between appropriate aldehydes (heterocycle-2-yl-ethanal) and methyl acrylate to provide an epimeric mixture of alcohols (more and less polar alcohols, which were separated). The separated alcohols were converted into the corresponding acetates, which on intramolecular cyclization provided bicyclic frameworks as shown in Scheme 351. The same strategy was extended for synthesis of (−)-*δ*-coniceine (**395**) from the Baylis−Hillman alcohols **394** prepared via seleno chemistry according to the reaction sequence shown in Scheme 352.

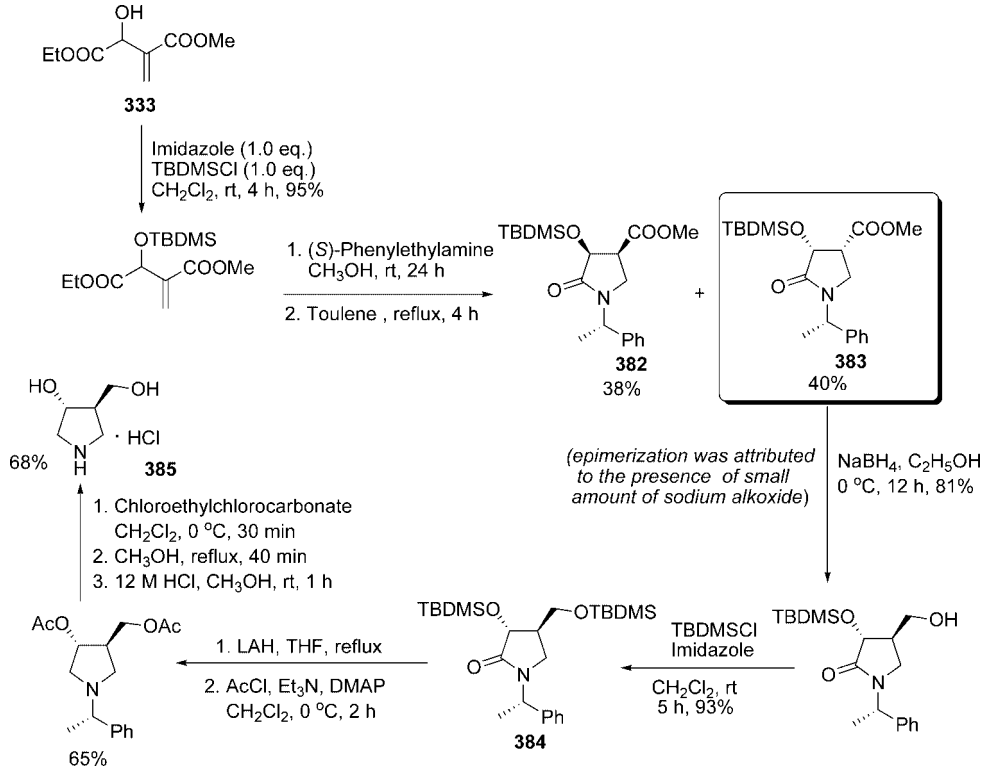
A simple synthesis of diethylphosphono-1,2-dihydroquinolines and 3-acetoxymethylquinolines using the acetates of Baylis−Hillman adduct obtained from 2-azidobenzaldehydes was reported by Lee and co-workers.[830] The key step in this strategy involves the reaction of Baylis−Hillman acetates with triethyl phosphite to generate iminophosphorane intermediates (**396**), which were then transformed into the required quinoline frameworks. Representative examples are given in Scheme 353.

Virieux and co-workers[831] have reported a beautiful synthesis of indolizine carboxylates, following the Baylis−Hillman protocol involving the reaction between 2-pyrrolecarboxaldehyde and allene or propiolate derivatives under the influence of PBu_3 as a catalyst. Representative examples are given in Scheme 354.

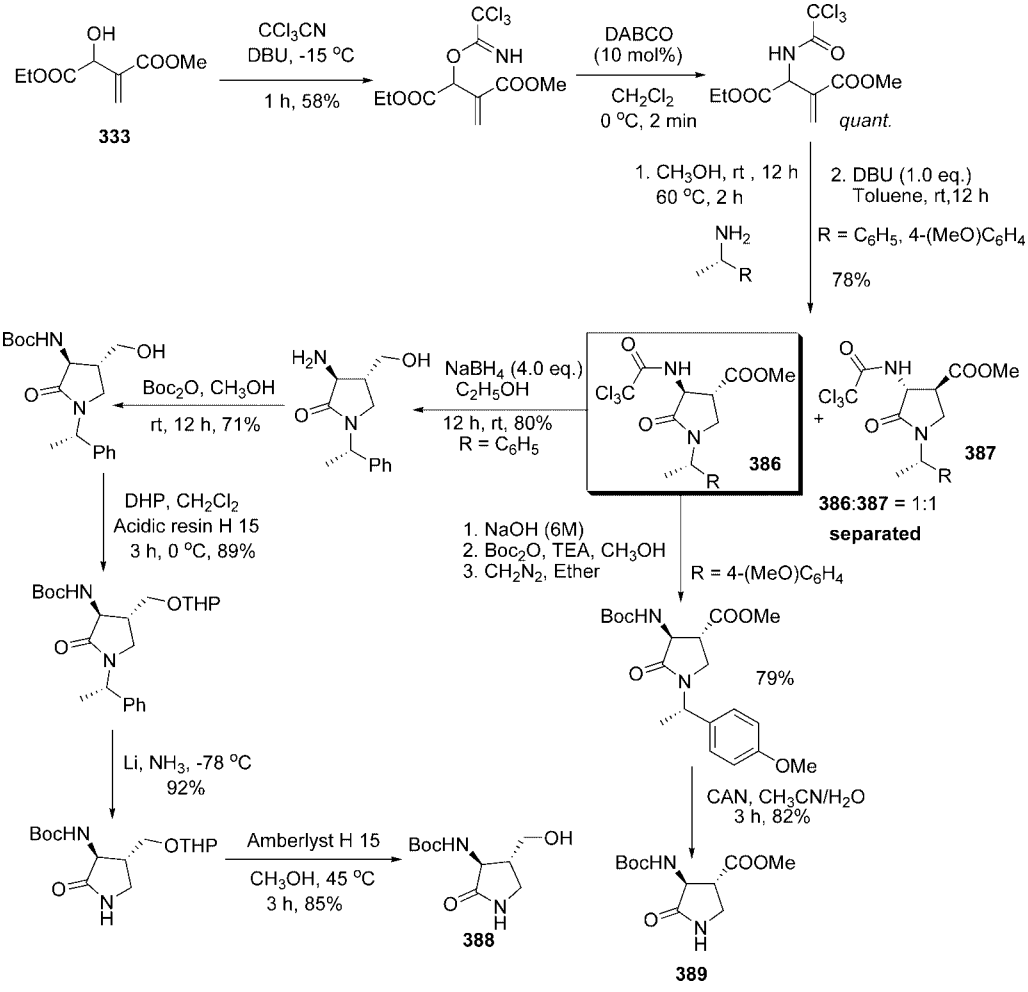
Our research group[648] have developed a novel methodology for synthesis of 2-benzazepine derivatives from the Baylis−Hillman alcohols derived from substituted benzaldehydes containing electron-donating groups at appropriate positions on the benzene ring and alkyl acrylates. This strategy involves tandem construction of C−N and C−C bonds via the simultaneous Ritter and Houben−Hoesch reactions, following the reaction sequence shown in eq 110. We also noticed Baylis−Hillman alcohols derived from simple benzaldehyde containing alkyl groups provided amides with high stereoselectivity (see Scheme 219 of ref 648).

A simple synthesis of methyl α-cyanomethylcinnamates (**397**) from readily available Baylis−Hillman acetates and the subsequent conversion of these cinnamates to several naphthalene (Path A) and benzylidensuccinimide derivatives (Path B) were reported by Lee and co-workers (Scheme 355).[832] Later on, Kim and co-workers[833] converted 2-cya-

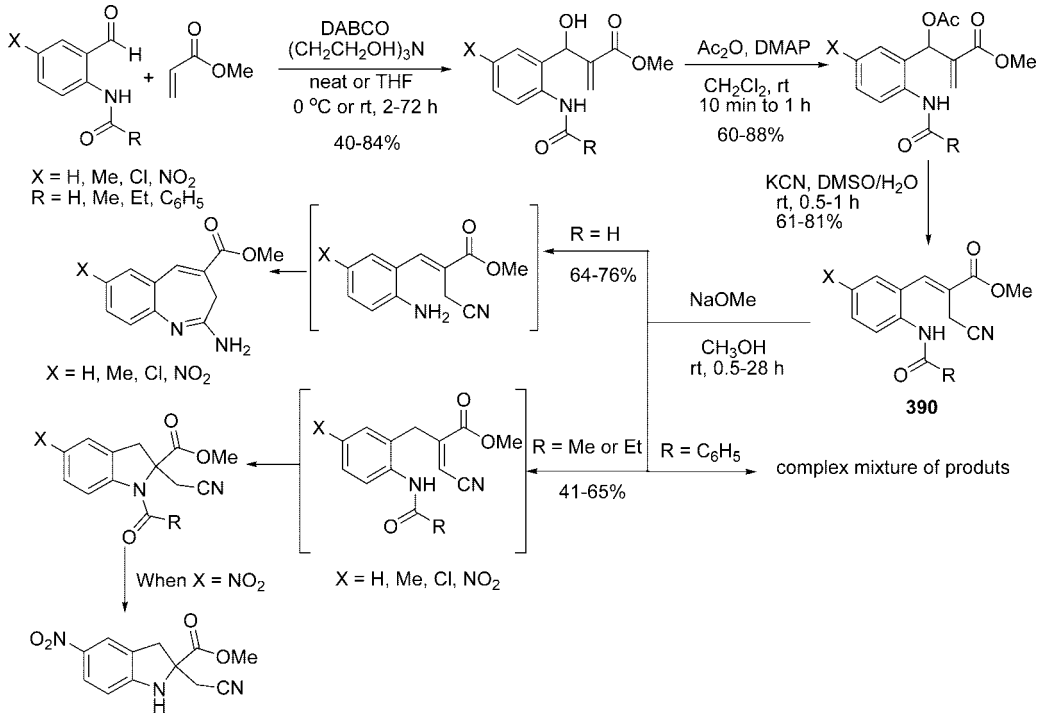
Scheme 346



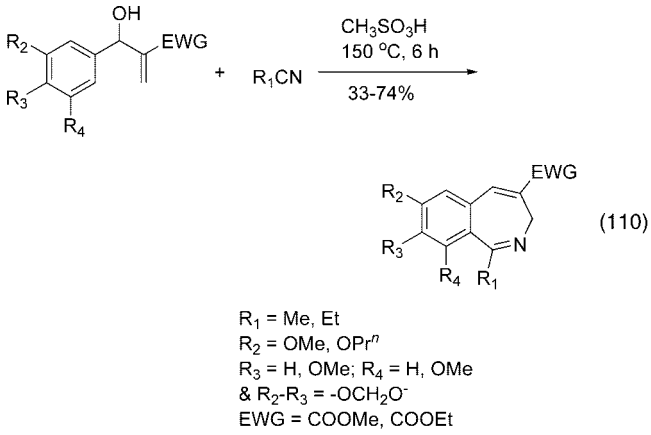
Scheme 347



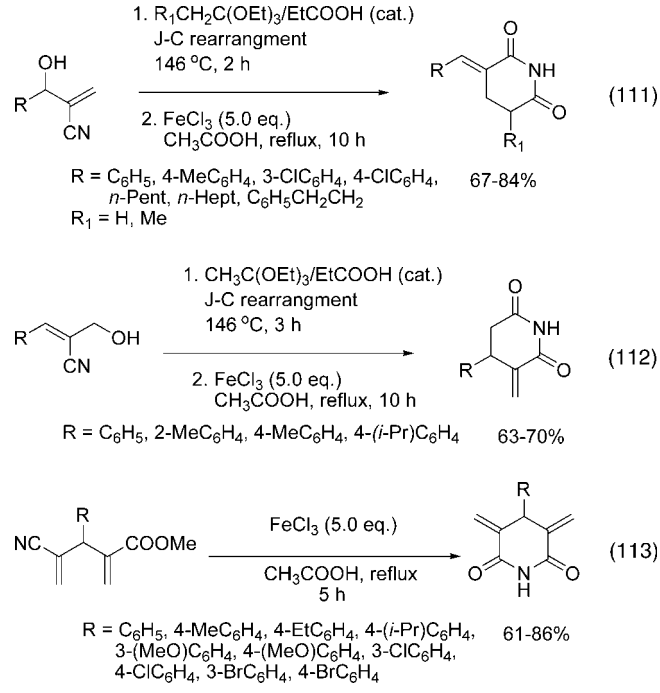
Scheme 348



nomethylcinnamates into 3-benzylidenepyrrolidiene-2,5-diones via treatment first with H_2SO_4 and then with H_2O/CH_3OH (Path C, Scheme 355). They[833] have extended a similar strategy for obtaining a piperidione framework (**398**) from the Baylis−Hillman acetates (Path D, Scheme 355). Representative examples are given in Scheme 355. They have also transformed the Baylis−Hillman products **399** (obtained via the reaction of Baylis−Hillman bromide with acrylonitrile) into glutarimide derivatives (**400**) (Scheme 356).[833]



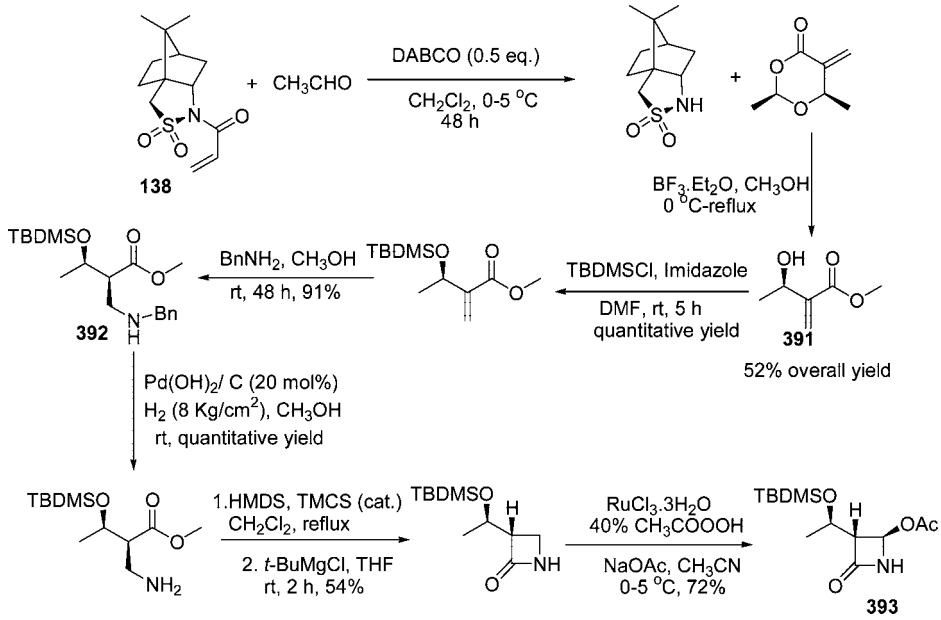
Recently our research group[834] has reported a one-pot multistep transformation of 3-hydroxy-2-methylenealkanenitriles, the Baylis−Hillman alcohols obtained from various aldehydes and acrylonitrile, into 3-arylidene or alkylidene piperidine-2,6-diones. This strategy involves Johnson−Claisen rearrangement, partial hydrolysis of the CN group, and cyclization as key steps (eq 111). Similarly rearranged Baylis−Hillman alcohols, (*E*)-2-hydroxymethyl-3-arylprop-2-enenitriles, were transformed into 4-aryl-3-methylidenepiperidine-2,6-diones (eq 112). A facile strategy for one-pot synthesis of 4-aryl-3,5-dimethylidenepiperidine-2,6-dione framework has been developed using the Baylis−Hillman compounds, 3-aryl-4-cyano-2-methoxycarbonylpenta-1,4-dienes, derived via coupling of Baylis−Hillman bromides with acrylonitrile (eq 113).



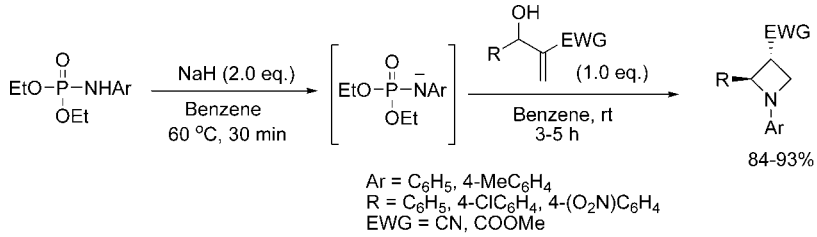
Kim and co-workers[835,836] have reported that Baylis−Hillman alcohols obtained from isatin derivatives and acrylonitrile, on treatment with benzylamine, provided 2-pyrrolidinone derivatives (**401**) as a mixture of diastereomers. Similar treatment of the Baylis−Hillman adducts derived from isatin and methyl acrylate provided tricyclic systems (**402**) as major products along with 2-pyrrolidone derivatives as minor products. Representative examples are given in Scheme 357.

The acetates of Baylis−Hillman adducts derived from acrylonitrile or methyl acrylate have been transformed into

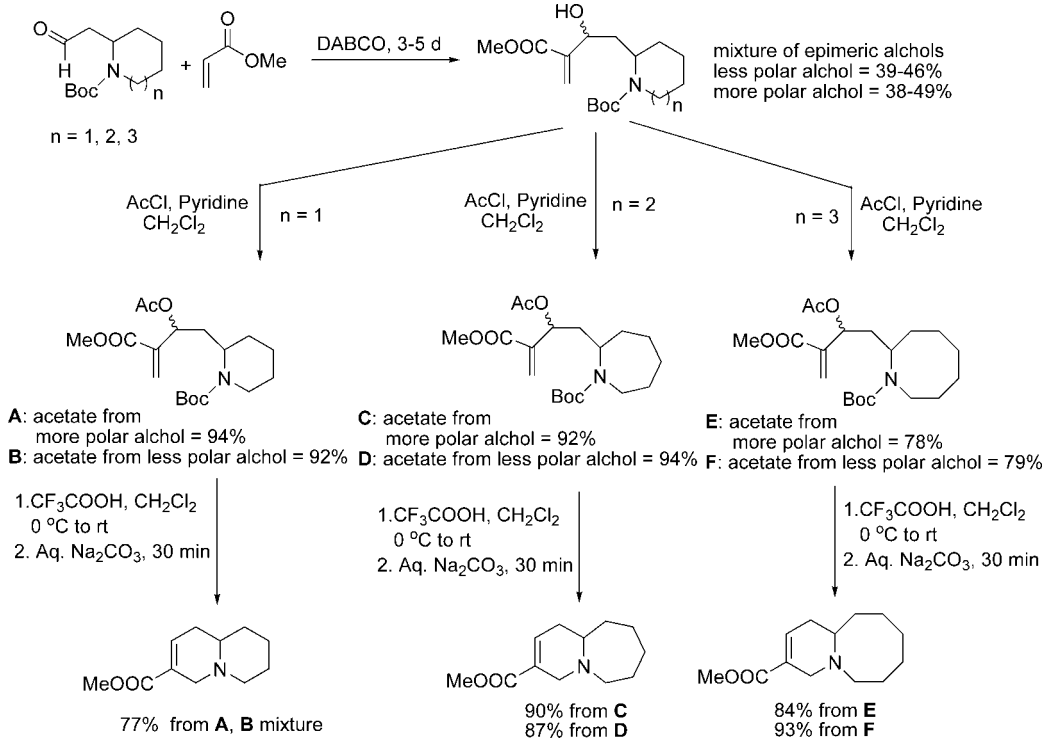
Scheme 349



Scheme 350



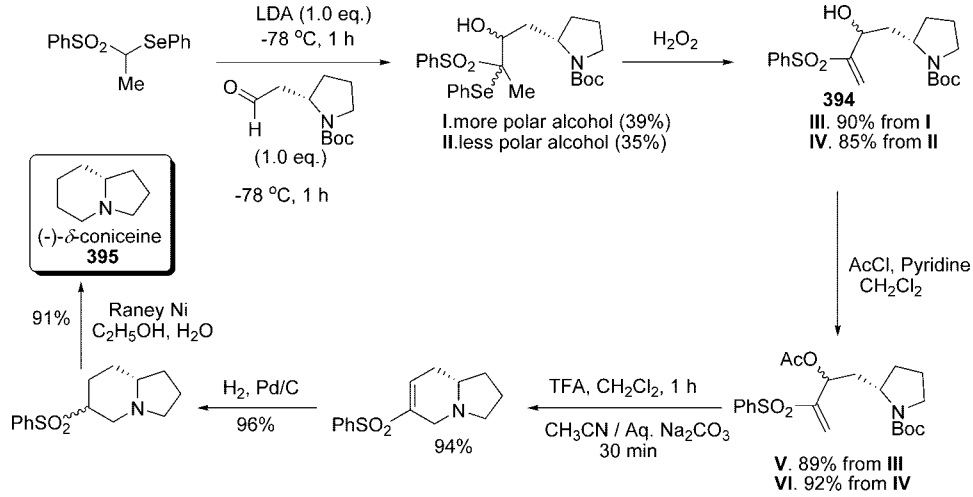
Scheme 351



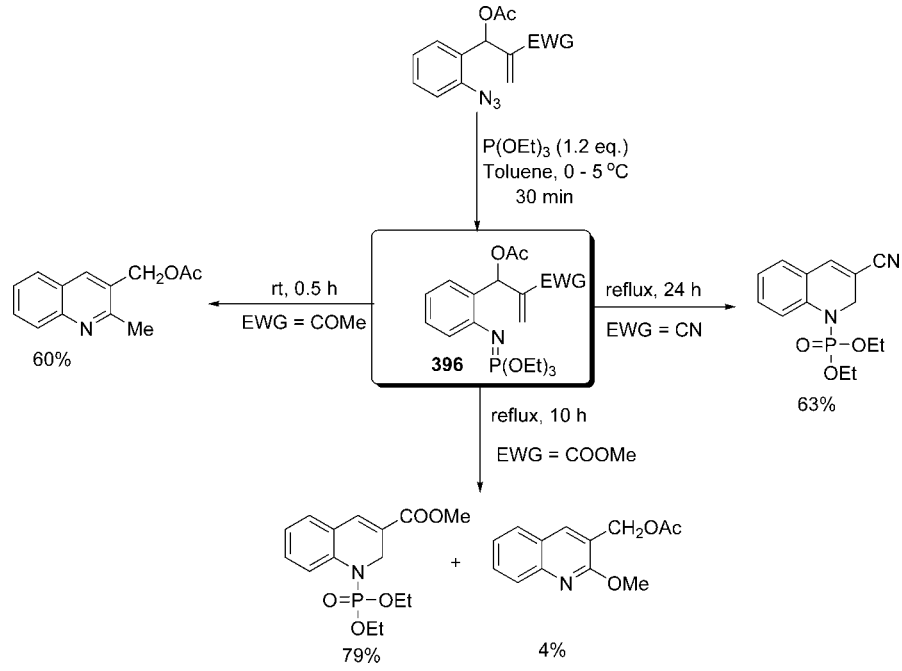
piperidine-2,6-diones and bicyclic and spiro *N*-heterocyclic compounds by Batra and co-workers according to Schemes 358[837] and 359.[838] In this reaction sequence, the key steps involve the treatment of the Baylis−Hillman acetate with DABCO first and then with an appropriate nucleophile, followed by a cyclization strategy.

Our research group[839] has developed a simple and convenient synthesis of di(*E*)-arylidene-tetralone-spiro-gluta-

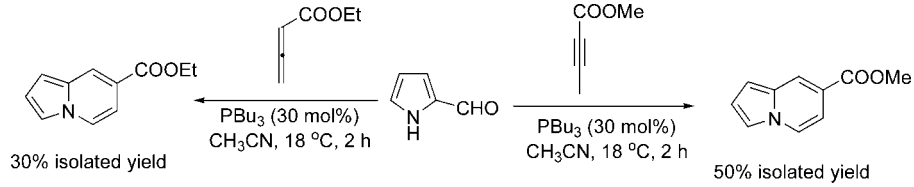
Scheme 352



Scheme 353



Scheme 354

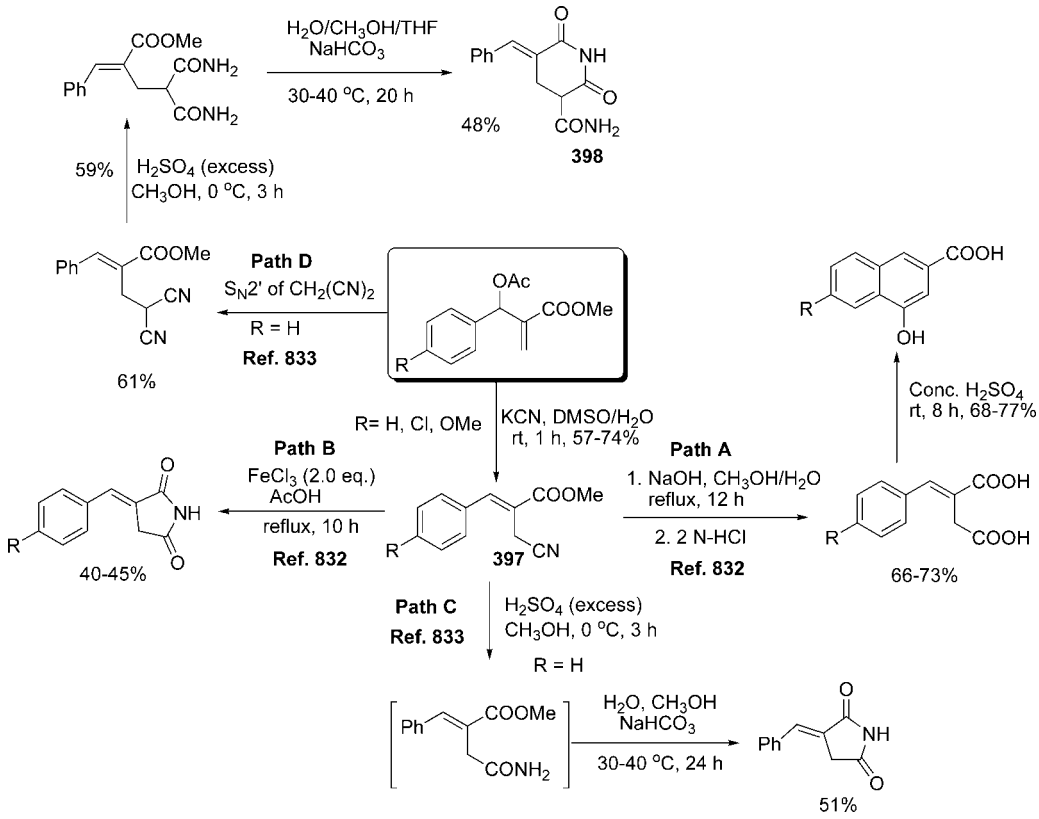


rimides from Baylis−Hillman acetates via an interesting bisalkylation of phenylcyanide and biscyclization strategy involving facile C−C and C−N bond formations following the reaction sequence described in Path A, Scheme 360. Also a simple one-pot, multistep transformation of the Baylis−Hillman acetates into di(*E*)-arylidene-spiro-bisglutarimides was reported by our research group via bisalkylation of malononitrile followed by a biscyclization strategy as shown in Path B, Scheme 360.

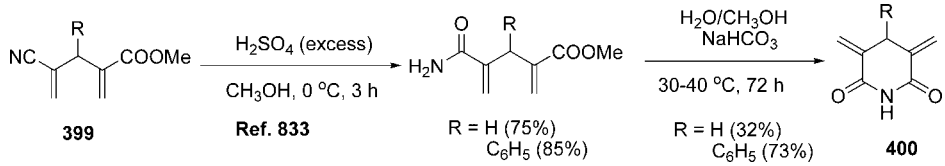
Simple methodology for the synthesis of dihydropyrido[2,1-*a*]isoindolone (Path A) and benzoazepino[2,1-*a*]isoindole (Path B) derivatives starting from Baylis−Hillman alcohols obtained from 2-bromobenzaldehyde was developed by Kim and co-workers. This strategy involves either the radical cyclization (Path A, Scheme 361)[840] or Heck reaction (Path B, Scheme 361)[841] on the key intermediate (**403**) obtained from the corresponding Baylis−Hillman alcohol according to Scheme 361.

Shanmugam and co-workers[842] have reported a facile, stereoselective synthesis of functionalized diastereomeric 3-spirocyclopropane-2-indolones from allyl bromides, derived from the Baylis−Hillman adducts of isatin and alkyl acrylate via reductive cyclization with $NaBH_4$ in high yields (Scheme 362).

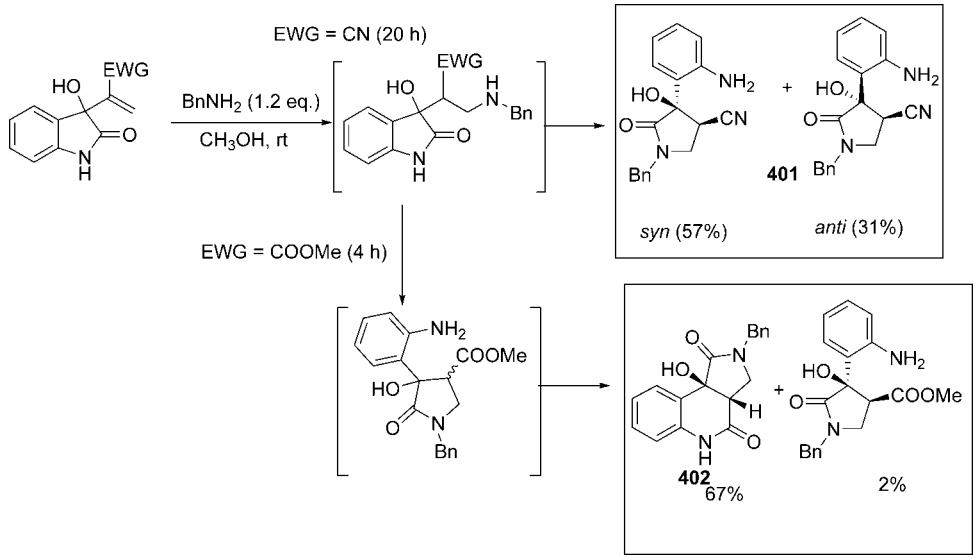
Scheme 355



Scheme 356

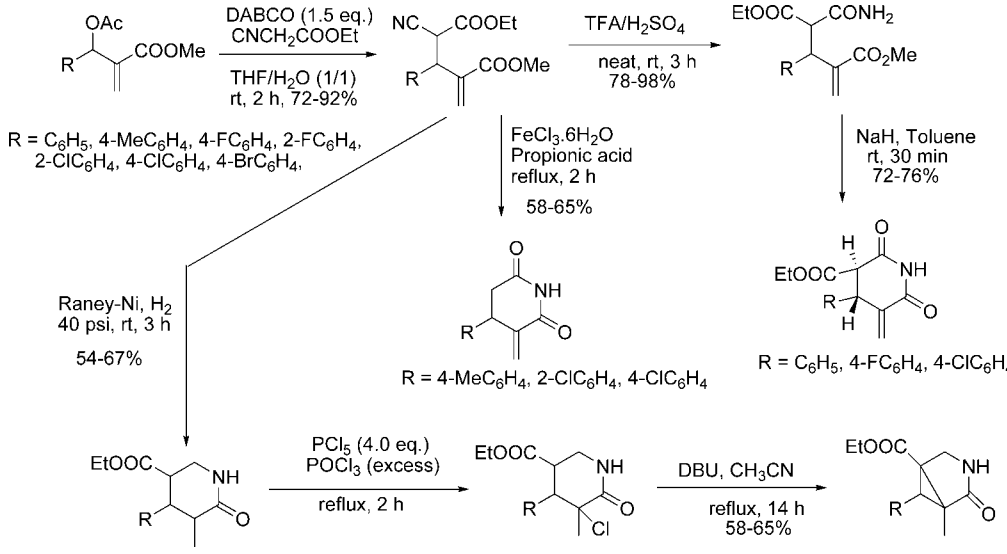


Scheme 357

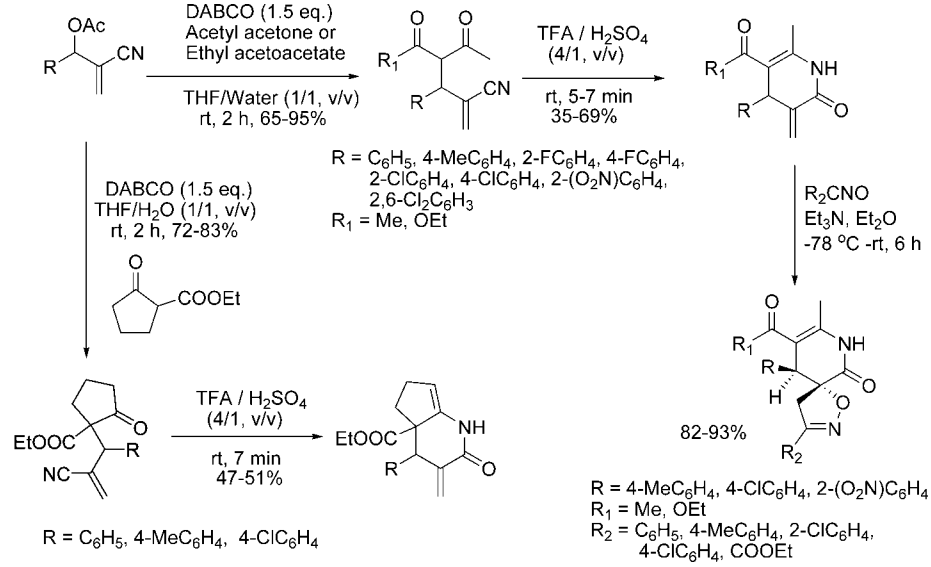


Shanmugam and co-workers[843] have developed an elegant methodology for the synthesis of functionalized 3-spiropyrrolizidine and 3-spiropyrrolidineoxindoles via the reaction of Baylis−Hillman adducts derived from isatin and heteroaromatic aldehydes with azomethine ylides, involving a [3 + 2]-cycloaddition strategy as the key step (Schemes 363 and 364). Representative examples are given. Similar reaction of allyl bromides and allyl ethers obtained from the Baylis−Hillman adducts (derived from isatin derivatives and methyl acrylates), with azomethine ylides provided spiropyrrolidine derivatives **405** and **406**, respectively following the reaction sequence shown in Scheme 364.[844]

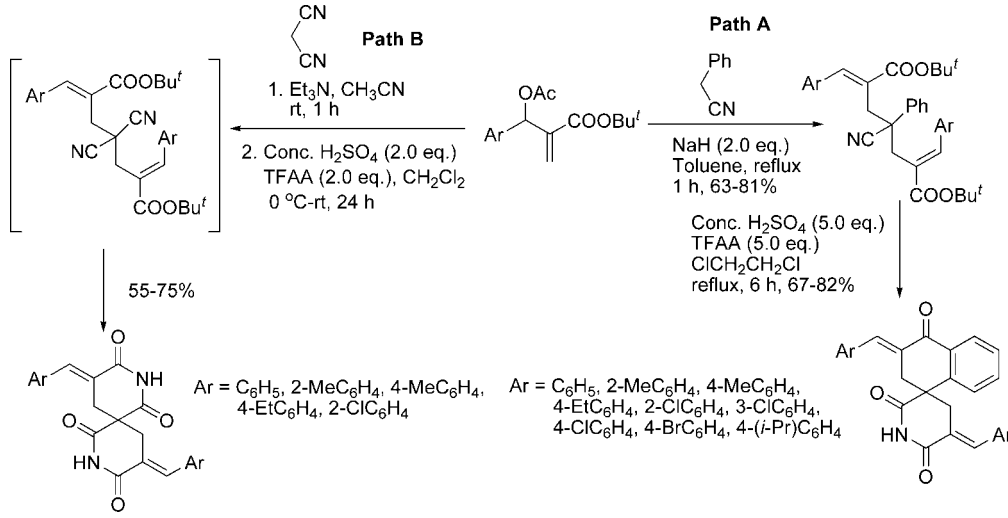
Scheme 358



Scheme 359

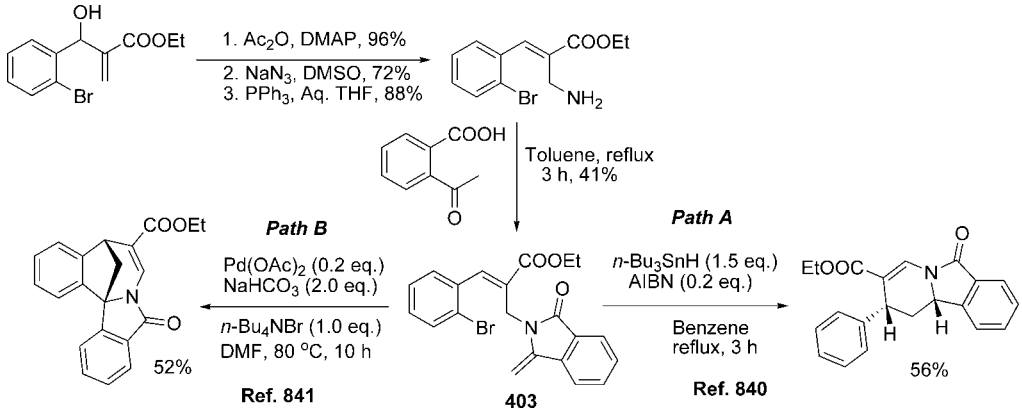


Scheme 360

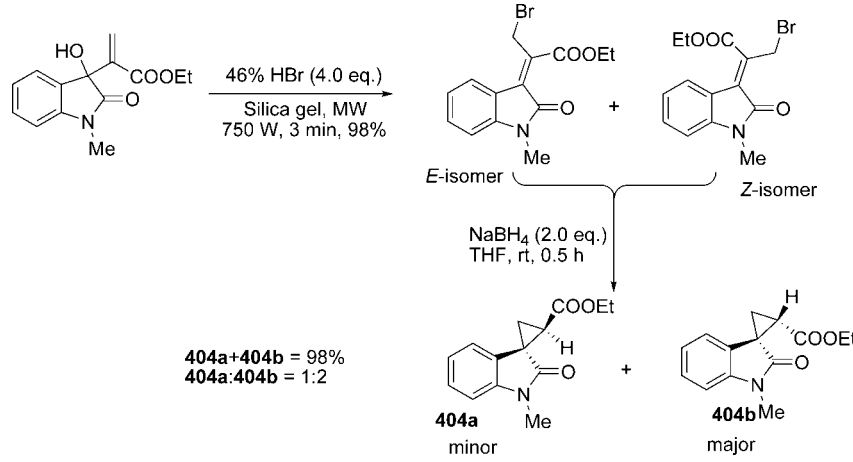


Raghunathan and co-workers[845] have reported a simple methodology for the synthesis of spiropyrrolidines and polycyclic heterocyclic molecules in 40−55% yields via the (3 + 2) cycloaddition reaction of Baylis−Hillman alcohols with azomethine ylides as shown in Scheme 365. Later this strategy was extended for the synthesis of spiropyrrolidines/pyrroliz-

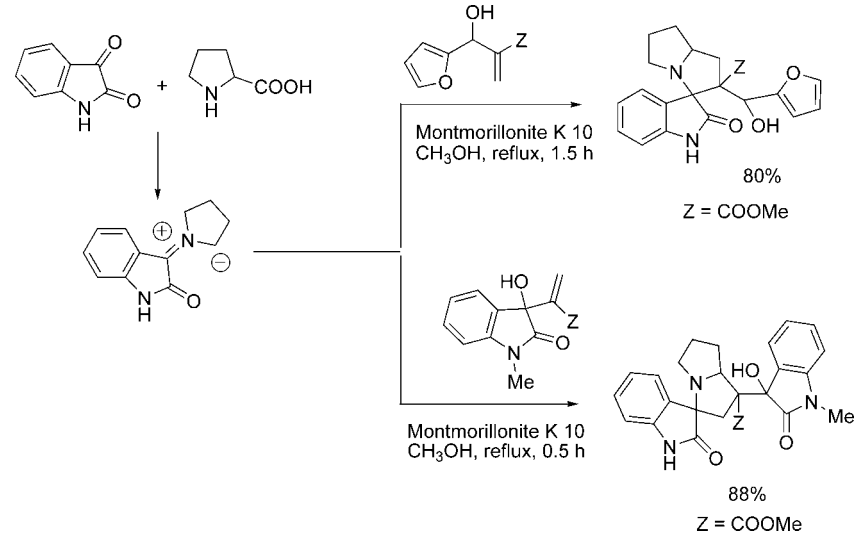
Scheme 361



Scheme 362



Scheme 363

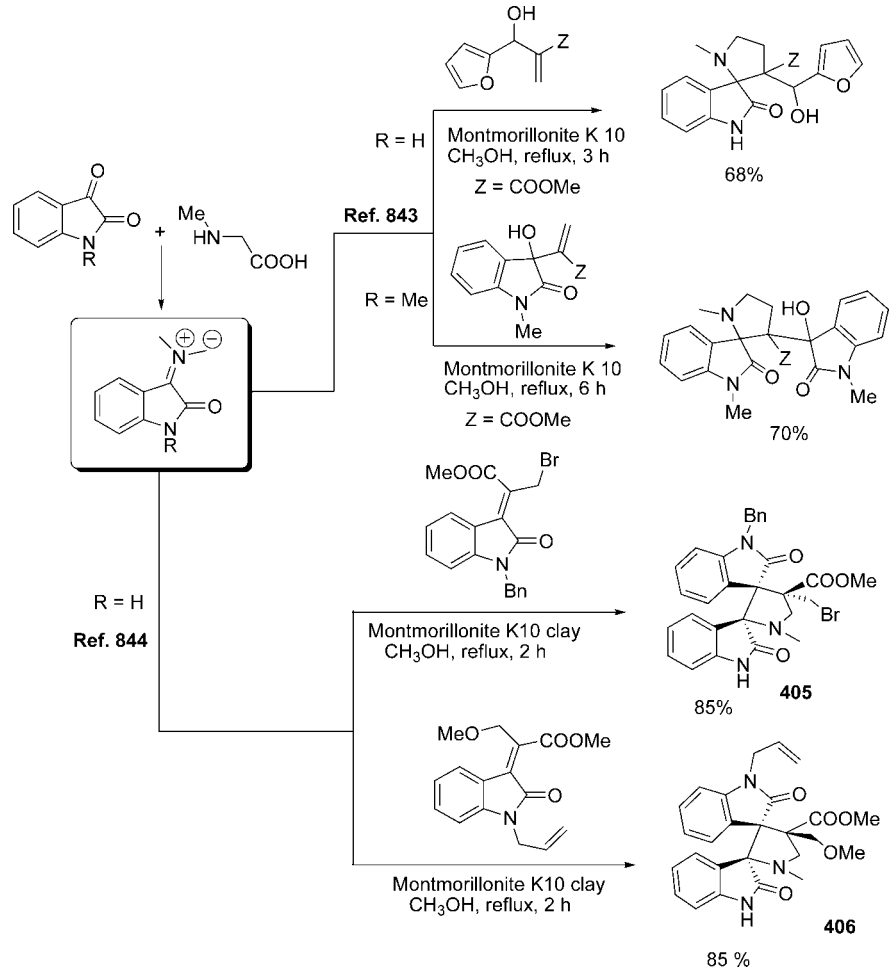


idines using the alkene unit of Baylis−Hillman adducts of ninhydrin under microwave conditions (Scheme 366).[846]

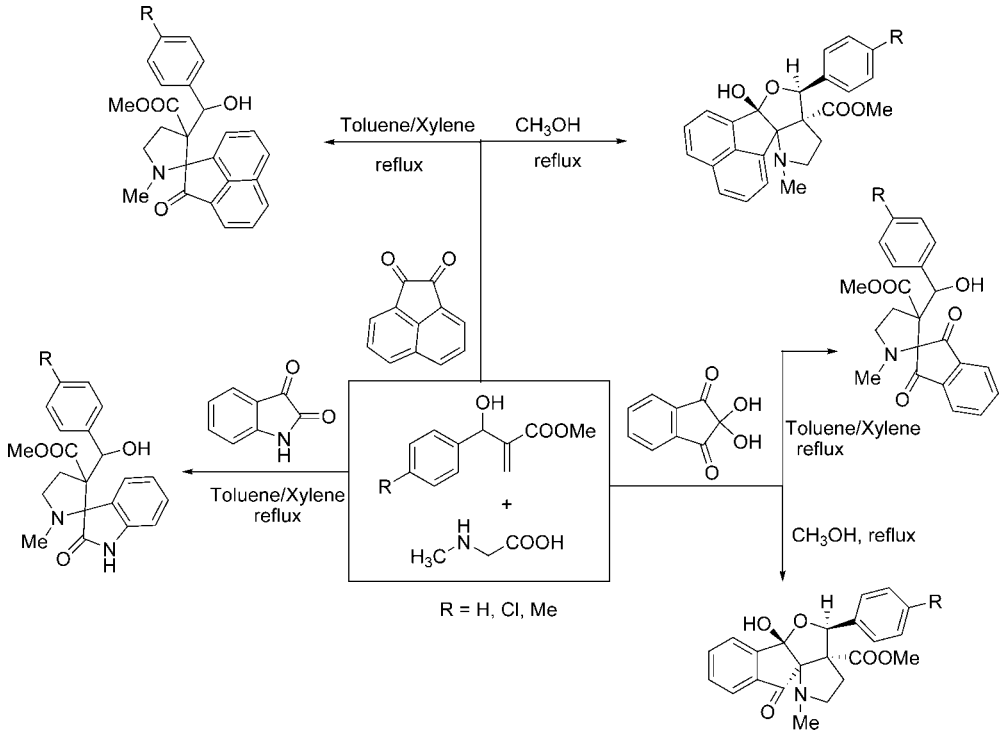
Bakthadoss and co-workers[847] (Path A, Scheme 367) Ramesh and Raghunathan[848] (Path B, Scheme 367) have independently reported a facile route for the synthesis of tricyclic chromenopyrrolidine frameworks from the Baylis−Hillman bromides via the reaction with salicylaldehyde followed by treatment with *N*-methylglycine according to the reaction sequence as described in Scheme 367. One example each is given.

Garrido and co-workers[849] have reported a novel domino reaction (stereoselective Ireland−Claisen rearrangement and asymmetric Michael addition), starting from the rearranged Baylis−Hillman acetates via the treatment with chiral lithium amide (**411**), which provided optically active γ-substituted δ-amino acids (**407**, Figure 68) with high diastereoselectivities and enantioselectivities, which were further transformed into 2,3-disubstituted piperidines or 2-substituted nipecotic acid derivatives. One example is given in Scheme 368. It was observed that the Baylis−Hillman acetate in the

Scheme 364

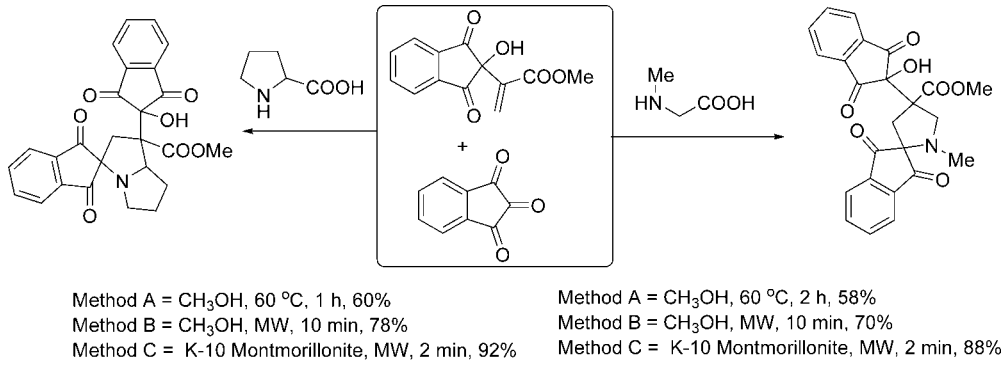


Scheme 365

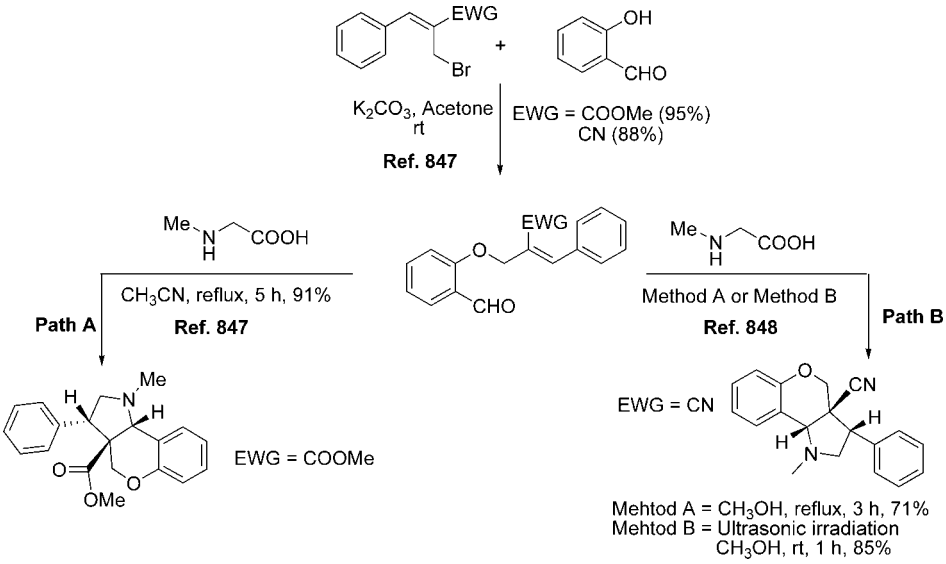


Ireland−Claisen rearrangement provided the required product (**407**) in minor amounts (24%) and the product **409** in major amounts (51%), while the rearranged acetate provided **407** as a major product (56%) along with **408**, **409**, and **410** in 7%, 2%, and 1% yields, respectively. A plausible mechanism for Ireland−Claisen rearrangement is given in Scheme 369.

Scheme 366



Scheme 367



Coelho and co-workers[850] have developed an interesting methodology for the preparation of 3,4-substituted isoquinolin-1(2*H*)-ones starting from the Baylis−Hillman adducts, following the reaction sequence shown in Scheme 370.

Krishna and Reddy[851] have reported a facile methodology for the synthesis of tetrahydropyridine-4-carboxylates from the Baylis−Hillman adducts (**413** and **414**) (which were obtained by the coupling of *N*-allyl-Boc-α-aminal (**412**) and

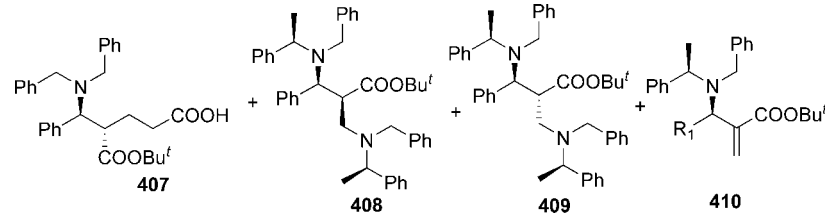
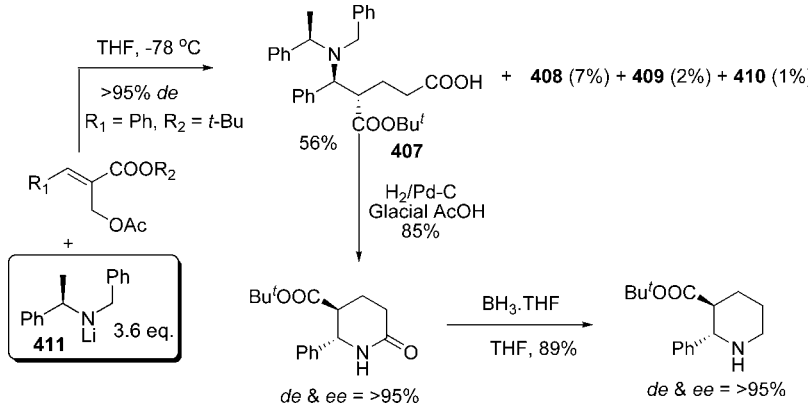
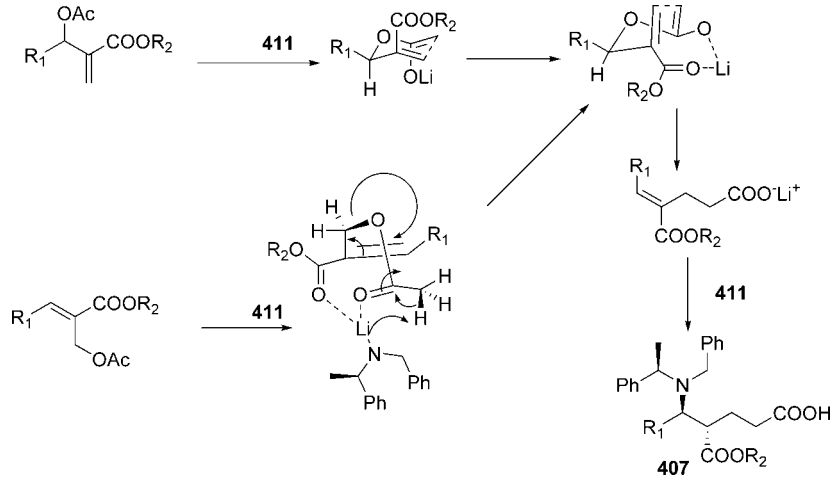


Figure 68.

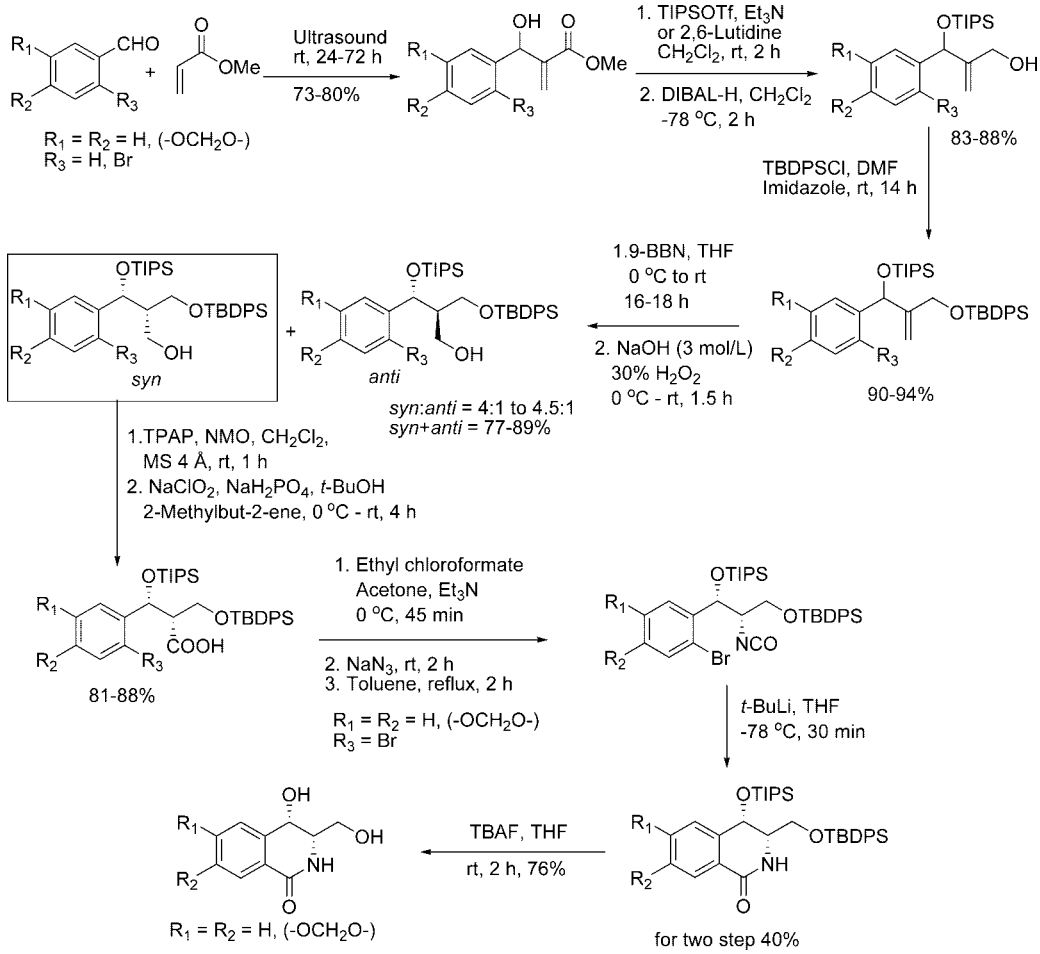
Scheme 368



Scheme 369



Scheme 370



ethyl acrylate) following the reaction sequence shown in Scheme 371, involving RCM as the key step. A representative example is given.

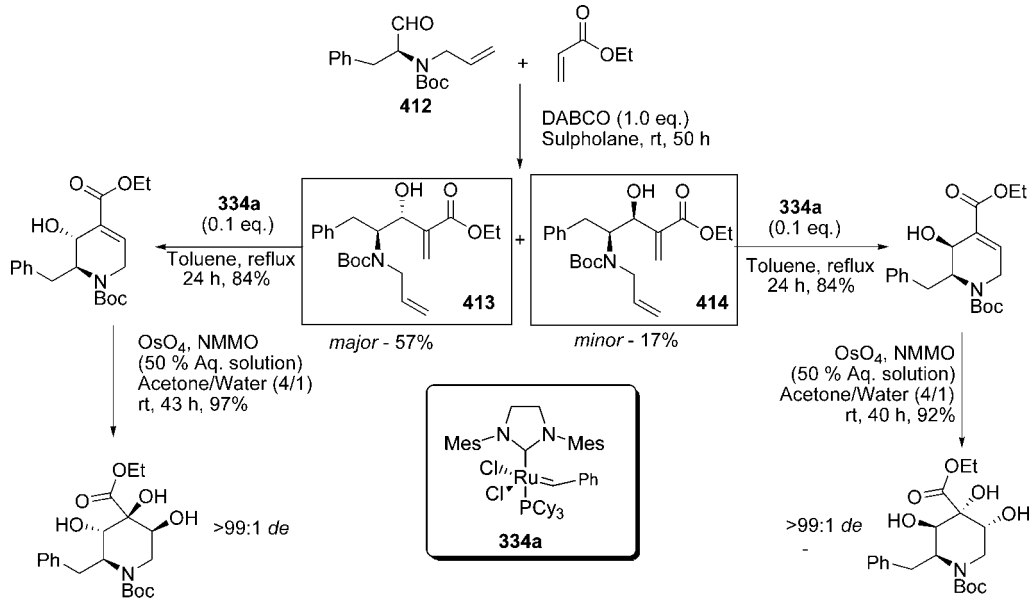
Morizur and Mathias[852] have developed a simple methodology for the synthesis of poly-functionalized 2-pyrrolidinone derivatives starting from the Baylis−Hillman adduct, methyl 2-(ethoxycarbonylhydroxymethyl)acrylate **333**, following the reaction sequence shown in Scheme 372.

Ma and co-workers[853] have reported an interesting synthesis of 1,3,3,4-tetrasubstituted pyrrolidine, a synthon for CCR5 receptor antagonist (**415**), from the Baylis−Hillman adduct obtained from methyl acrylate and ethyl benzoylformate, following the reaction sequence shown in Scheme 373.

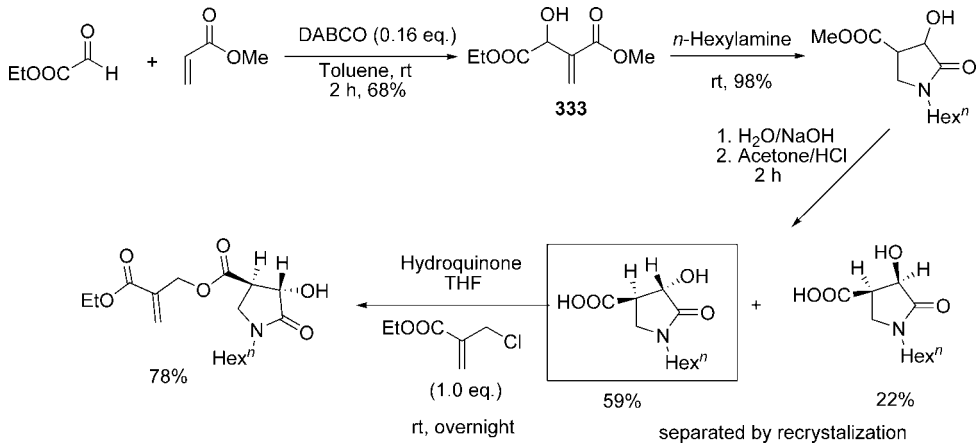
Batra and co-workers[854] have transformed the Baylis−Hillman adducts derived from 5-isooxazole carboxaldehydes into substituted pyrroles derivatives, following the reaction sequence shown in Scheme 374. They[855] have also transformed the Baylis−Hillman adducts derived from 3-isooxazole carboxaldehyde into pyrrolidine derivatives (Scheme 375, one example is given).

Very recently our research group[856] has developed a simple one-pot synthesis of indolizine, benzofused indolizine {pyr-

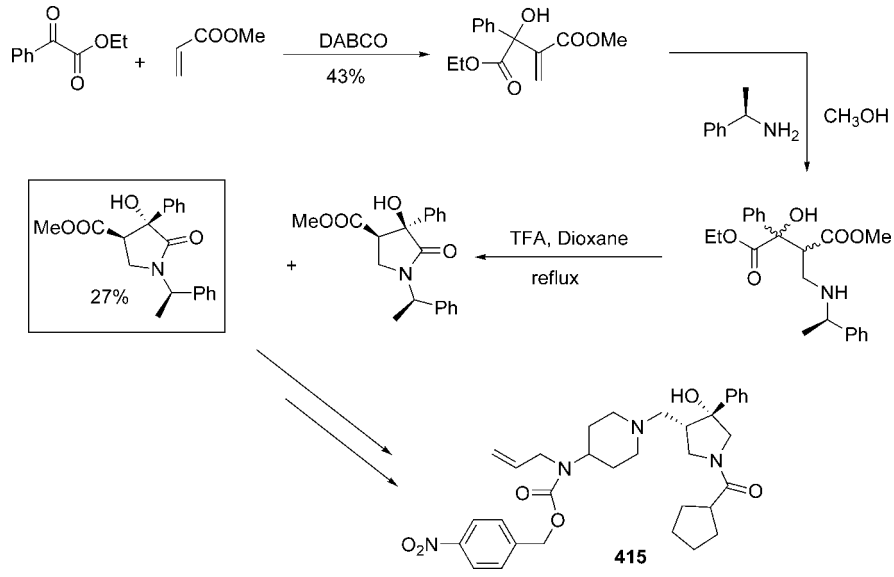
Scheme 371



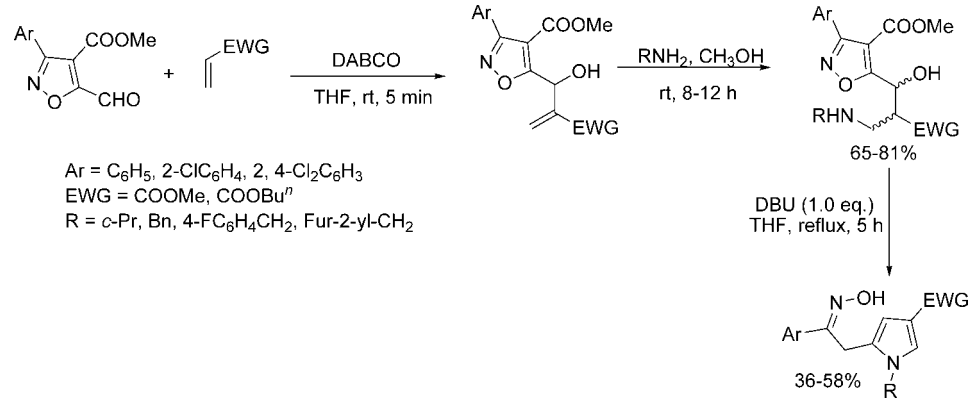
Scheme 372



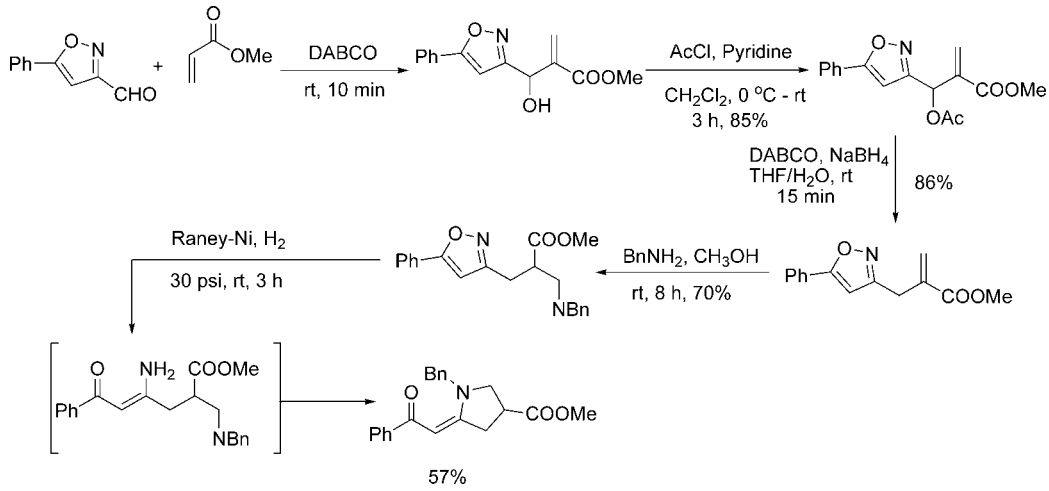
Scheme 373



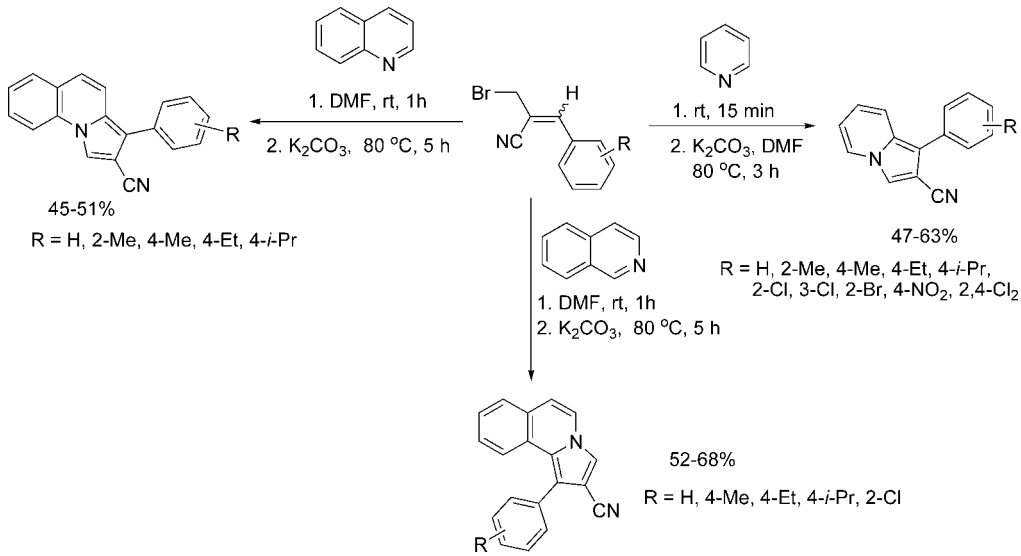
Scheme 374



Scheme 375



Scheme 376

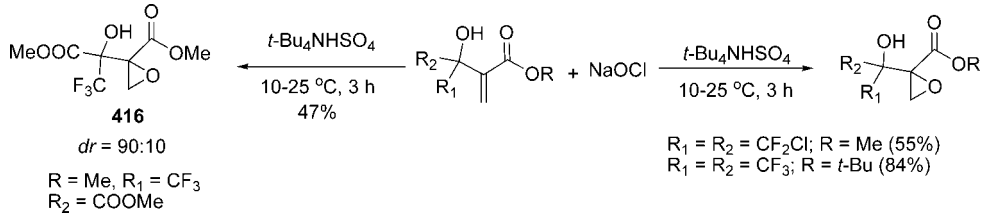


rolo[1,2-*a*]quinoline and pyrrolo[1,2-*a*]isoquinoline} frameworks, from the Baylis−Hillman bromides via an interesting strategy involving 1,5-cyclization of nitrogen ylides (Scheme 376).

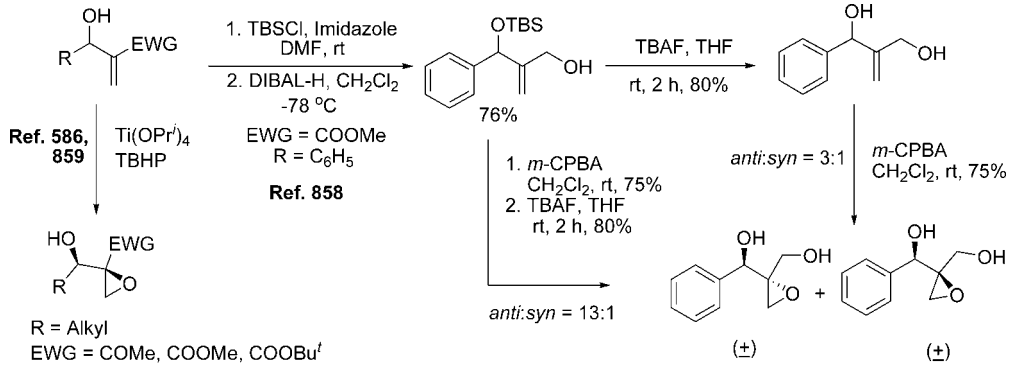
10.5. Synthesis of Oxygen Heterocyclic Compounds

During the studies toward the synthesis of fluorinated epoxides, Petrov and co-workers[857] prepared various achiral fluorinated Baylis−Hillman adducts and transformed them into epoxides using NaOCl as a reagent under the influence of phase transfer catalyst tetrabutylammonium hydrogen sulfate. In the case of the racemic Baylis−Hillman alcohol (R = Me, R_1 = CF_3, R_2 = COOMe) (one example), the corresponding epoxide (**416**) was obtained as a mixture of diastereomers in the ratio of 90:10. Representative examples are shown in Scheme 377.

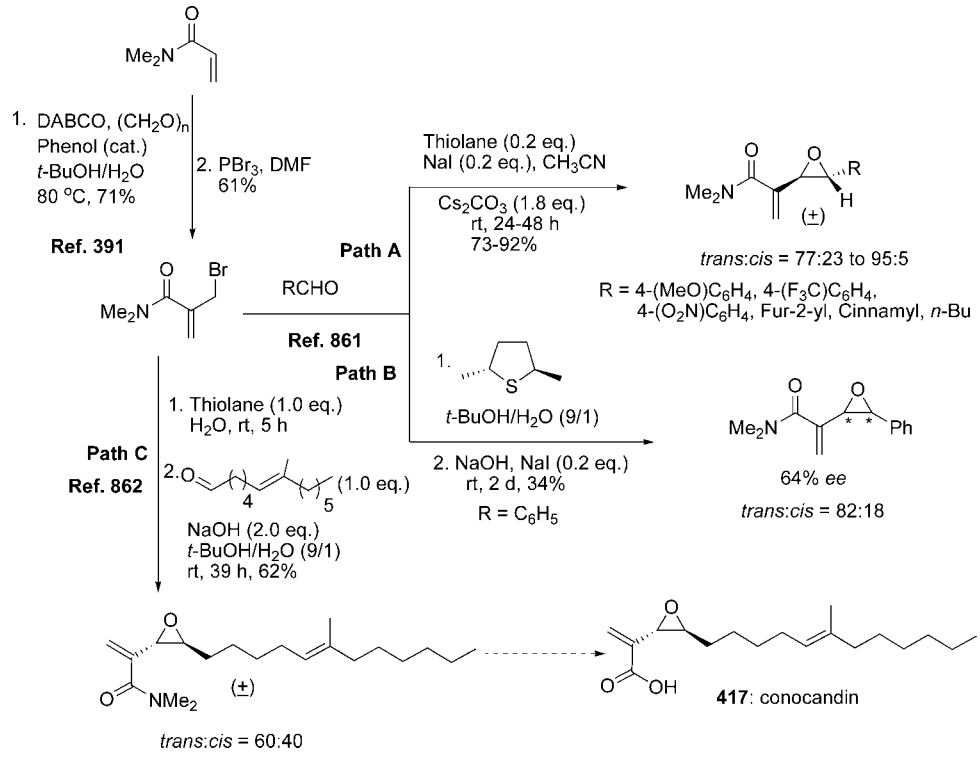
Scheme 377



Scheme 378

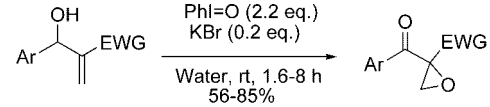


Scheme 379



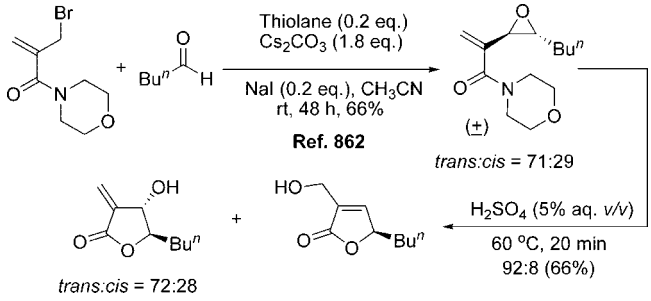
Coelho and co-workers[858] reported an interesting diastereoselective protocol for *trans*-epoxidation of the diols (free diols and monoprotected diols) derived from Baylis−Hillman alcohols using *m*-CPBA as a reagent at room temperature. In this study, they observed that the *tert*-butyldimethylsilyl (TBS) group not only protects the OH group but also directs the stereochemical course of the epoxide formation in the reaction. Representative examples are presented in Scheme 378. It is worth mentioning here that synthesis of *syn* epoxide (99% de) from the Baylis−Hillman adducts was already known in the literature.[586,859]

Subsequently, Das and co-workers[860] reported a simple procedure for epoxidation of Baylis−Hillman alcohols (along with the oxidation of the alcohol into a keto group) employing iodosobenzene (PhI═O) as an oxidizing reagent in the presence of KBr (cat.) in aqueous medium to provide acyloxiranes (eq 114).



(114)

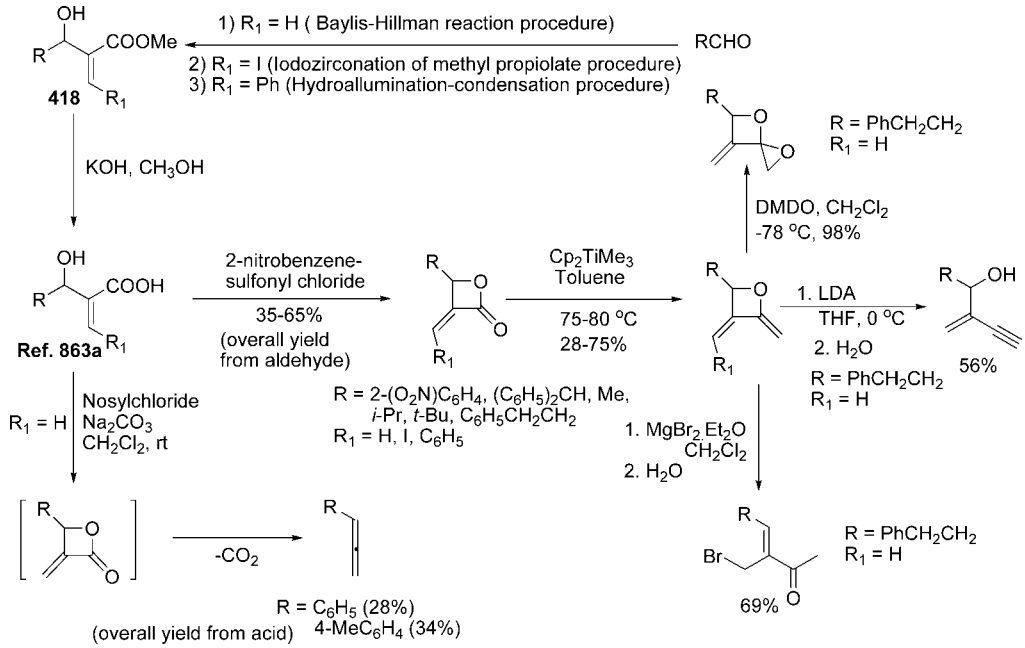
Scheme 380



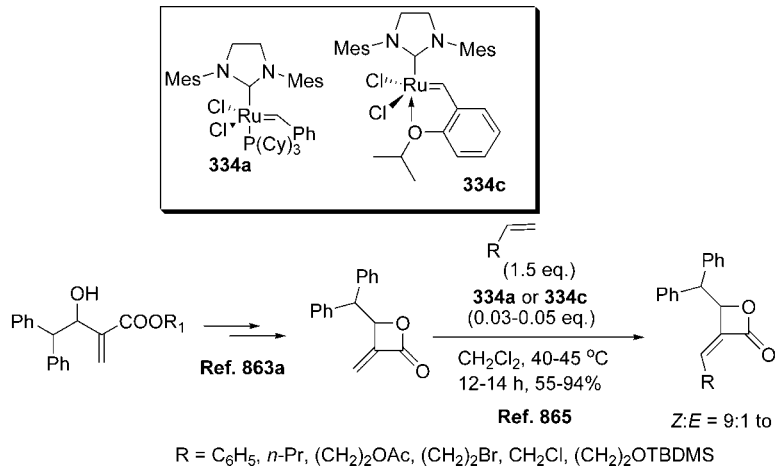
Briere and co-workers[861,862] have reported an interesting strategy for the preparation of vinyl epoxides via the treatment of Baylis−Hillman bromides (derived from Baylis−Hillman adducts obtained via the coupling between *N*,*N*-dimethyl acrylamide and formaldehyde) with aldehydes in the presence of thiolane. Representative examples are shown in Path A, Scheme 379. In the case of ketones, yields and selectivities were low. They have also performed an asymmetric version for this reaction under the influence of (*R*,*R*)-2,5-dimethylthiolane, which provided the resulting epoxide (in the case of benzaldehyde) in up to 64% ee (Path B, Scheme 379). They have also used this strategy for formal synthesis of conocandin (**417**), a biologically active compound, employing an appropriate aldehyde following the reaction sequence shown in Path C, Scheme 379. Subsequently this methodology has been extended for the preparation of dihydrofuran-2-one derivatives according to Scheme 380 (one example is presented). Interestingly the Baylis−Hillman bromide, ethyl 3-bromo-2-methylenepropanoate, derived from the corresponding Baylis−Hillman alcohol, did not provide the expected epoxide (because it underwent rapid polymerization).

Howell and co-workers[863a] have reported a facile synthetic route to 3-alkylidene-2-methyleneoxetane derivatives from 3-alkylideneoxetan-2-one derivatives via the treatment with Cp_2TiMe_3. The required 3-alkylideneoxetan-2-one derivatives were conveniently prepared from various Baylis−Hillman alcohols (**418**), obtained via DABCO-catalyzed coupling of activated alkene and electrophile (R_1 = H),[21] via iodozirconation of methyl propiolate and *in situ* condensation with aldehyde (R_1 = I),[863b] or via a one-pot hydroalumination−condensation procedure as described (R_1 = Ph),[864a−c] via a

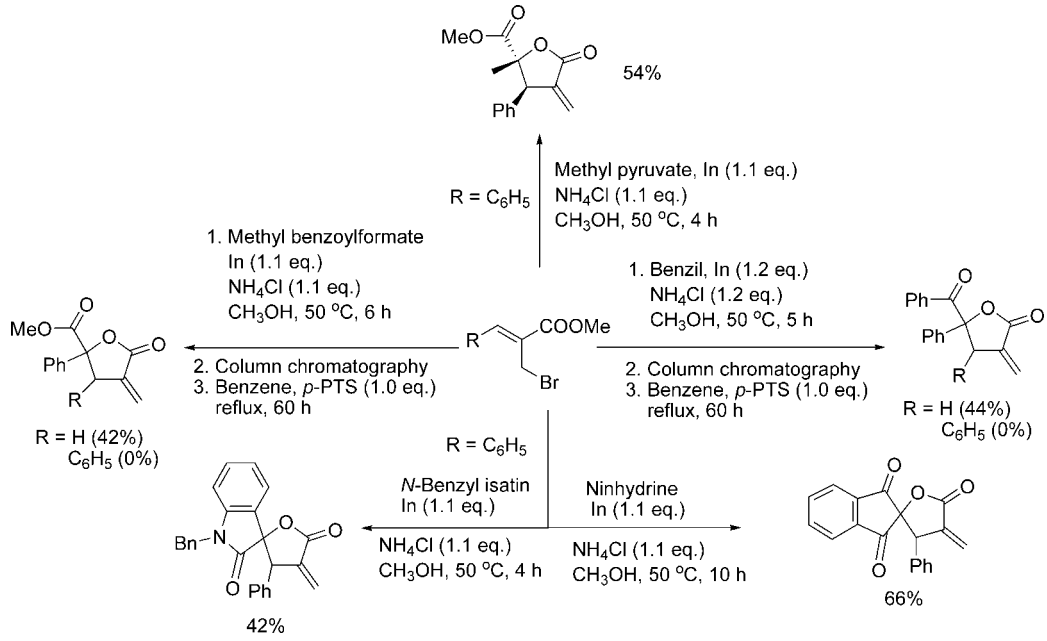
Scheme 381



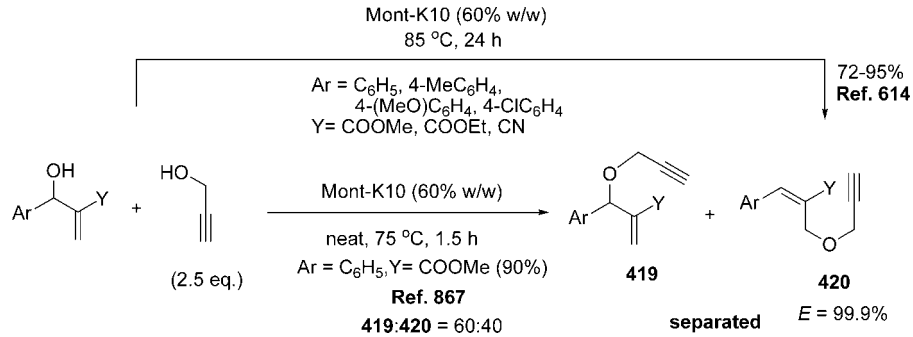
Scheme 382



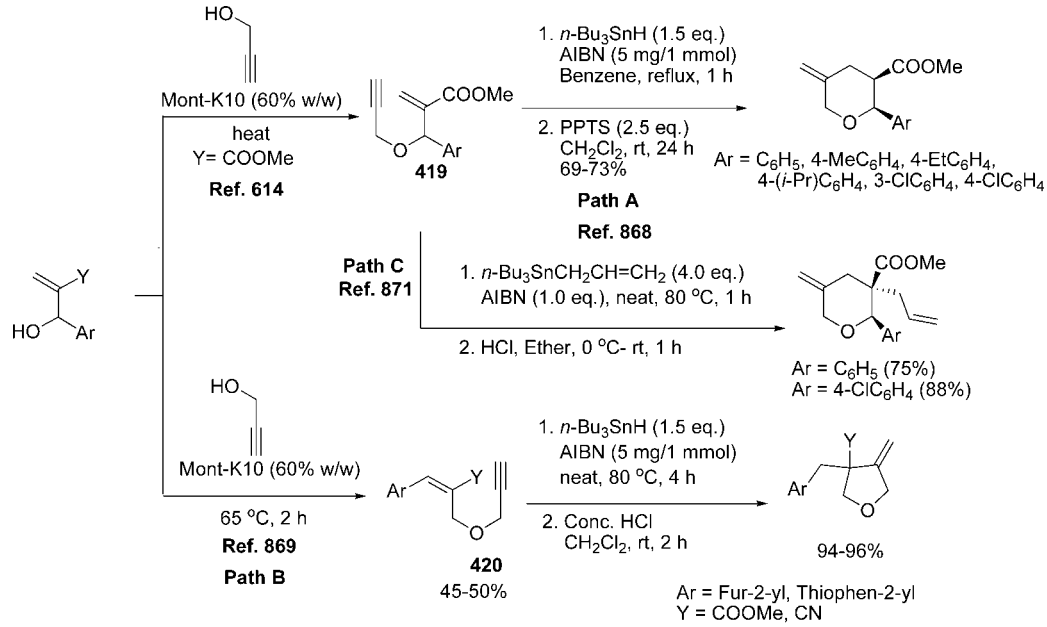
Scheme 383



Scheme 384

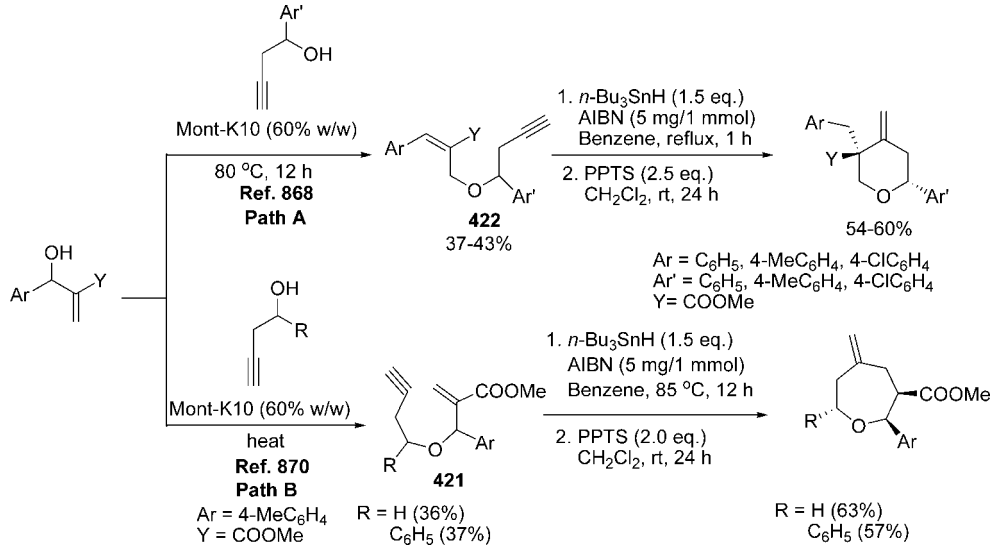


Scheme 385



two- step sequence involving hydrolysis and cyclization (as shown in Scheme 381). Some of the 3-alkylidene-2-methyleneoxetane derivatives were further transformed into 1,5-dioxaspiro[3.2]hexane, enynol, and allylic bromide derivatives by treatment with DMDO (dimethyldioxirane), LDA, and $MgBr_2$, respectively (Scheme 381). It was noticed that Baylis−Hillman adducts derived from benzaldehyde and *p*-tolualdehyde did not provide the expected oxetane deriva-

Scheme 386



tives but provided allenes, which were probably formed from the oxetane via the release of CO_2. Recently Raju and Howell[865] reported an alternative method for obtaining 3-alkylideneoxetane-2-one derivatives via the olefin cross metathesis reaction of 3-methyleneoxetan-2-one derivatives with representative olefins using Grubbs catalysts **334a** or **334c** (Scheme 382).

Kim and co-workers[866] have reported a facile methodology for the synthesis of β,γ,γ-tri- or γ,γ-disubstituted α-methylene-γ-butyrolactones from Baylis−Hillman bromides via the treatment with keto ester (or 1,2-diketones or ninhydrin or isatin). In this study, they have also observed the influence of steric factors. The sterically more demanding allyl bromide (R = Ph) did not provide the expected lactone when treated with methyl benzoylformate or benzil. Representative examples are shown in Scheme 383.

Shanmugam and Rajasingh have transformed the Baylis−Hillman alcohols into its propargyl ethers (**419**) and propargyl (*Z*)-allyl ethers (**420**) via the treatment with propargyl alcohol in the presence of montmorillonite K10 clay (Schemes 384 and 385).[614,867−869] Similarly Baylis−Hillman alcohols were also transformed into homopropargyl ethers (**421**) and homopropargyl (*Z*)-allyl ethers (**422**) (Scheme 386) on treatment with homopropargyl alcohols in the presence of montmorillonite K10 clay.[868,870] Subsequently, Shanmugam and co-workers reported a facile transformation of these allyl ethers (**419**−**422**) into tri- and tetra-substituted tetrahydropyrans[868] (Path A, Scheme 385, and Path A, Scheme 386), tetrahydrofurans[869] (Path B, Scheme 385), or tri- and tetrasubstituted oxepanes[870] (Path B, Scheme 386) via 6-*endo*/6-*exo*-*trig*, 5-*exo*-*trig*, and 7-*endo*-*trig* free radical cyclization strategies mediated by *n*-Bu_3SnH in the presence of AIBN (cat.) according to the reaction sequence shown in Schemes 385 and 386. Subsequently Kim and co-workers[871] extended this strategy for the synthesis of methyl 3-allyl 5-methylenetetrahydropyran-3-carboxylates using allyltributylstannane (which acts not only as a radical source but also as an allyl group source for allylation at the 3-position) following the reaction sequence shown in Path C (Scheme 385).

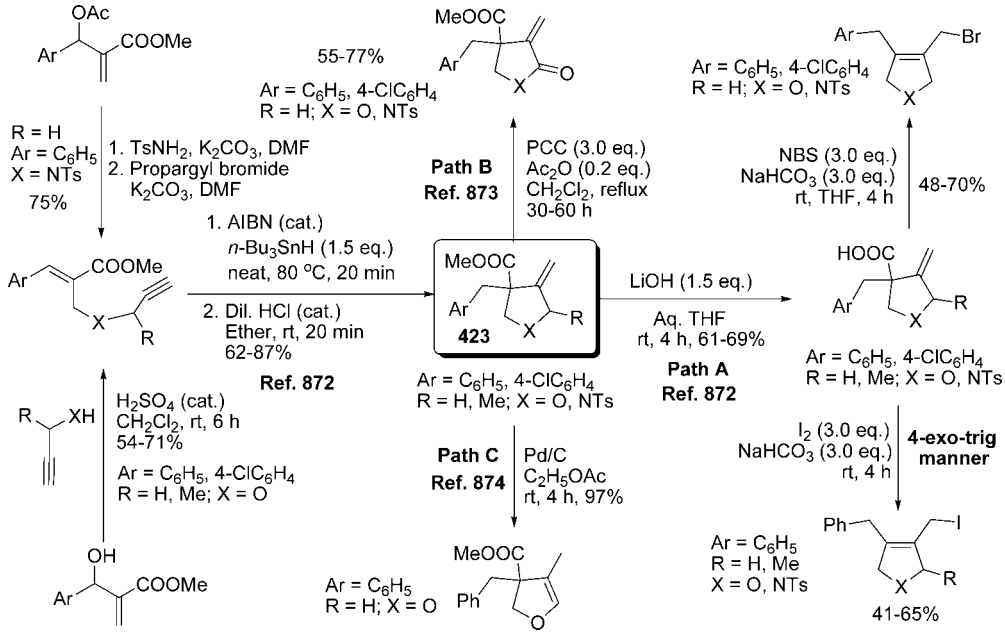
Subsequently, Kim and co-workers also used a similar strategy, involving the free radical mediated cyclization as the key step, for the synthesis of intermediate **423** from the Baylis−Hillman alcohols. The key intermediate **423** has been successfully used for synthesis of 3,4-disubstituted 2,5-dihydrofurans[872] (Path A, Scheme 387), β,β-disubstituted-α-methylene-γ-butyrolactones[873] (Path B, Scheme 387), and dihydrofurans[874] (Path C, Scheme 387). Also this key intermediate **423** has been employed for the synthesis of the furo[3,4-*c*]pyran skeleton[875] using ring-closing metathesis (RCM) as the key step, according to the reaction sequence shown in Scheme 388 (one example is shown).

Later on, Kim and co-workers also employed the free radical cyclization strategy for the synthesis of 3,3-disubstituted 2,3-dihydrobenzofurans[876] (Path A, Scheme 389) and 4,4-disubstituted isochroman[877] (one example is shown in Path B, Scheme 389) from the Baylis−Hillman acetates. This strategy of free radical mediated cyclization has been extended to the synthesis of hexahydrofuro[2,3-*b*]pyran derivatives[878] from the rearranged Baylis−Hillman alcohols according to the reaction sequence shown in Scheme 390 (one example is presented).

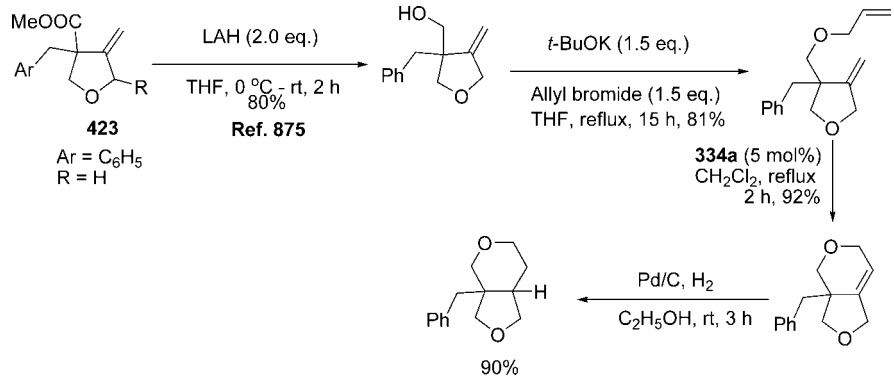
1,6-Enyne derivatives (**424**), obtained from the Baylis−Hillman adducts, were transformed into bicyclo[3.1.0]hexane frameworks, according to Scheme 391 (one example is presented), as reported by Tong and co-workers.[879] The main strategy in this methodology involves cyclization and oxidation using $Pd(OAc)_2$ in the presence of $PhI(OAc)_2$ reagent.[880]

Kim and co-workers[881] reported an interesting strategy for the synthesis of substituted 3,4-dihydro-2*H*-pyrans via the treatment of Baylis−Hillman acetates with acetylacetone and ethyl acetoacetate followed by cyclization (Scheme 392). A similar reaction of Baylis−Hillman acetates with deoxybenzoin[882] provided the 3,5,6-trisubstituted α-pyrones after cyclization following the reaction sequence shown in Scheme 393. Kim and co-workers[883] also extended this strategy to 1,3-cyclohexane dione derivatives, which provided 3-benzyl-7,8-dihydro-6*H*-chromenes and 3-benzoyl-7,8-dihydro-6*H*-chromenes. Representative examples are shown in Scheme 394 (Paths A and B). Su and co-workers[884] very recently reported a similar transformation of acetates of Baylis−Hillman adducts derived from aromatic aldehydes into 3-arylmethyl-7,8-dihydro-6*H*-chromene-2,5-diones under solvent-free conditions (Path C, Scheme 394). Interestingly in the case of Baylis−Hillman adducts derived from aliphatic aldehydes, unexpected pyran derivatives (mixture of stereoisomers) were obtained in moderate yields under similar reaction conditions. Representative examples are shown in Scheme 395.

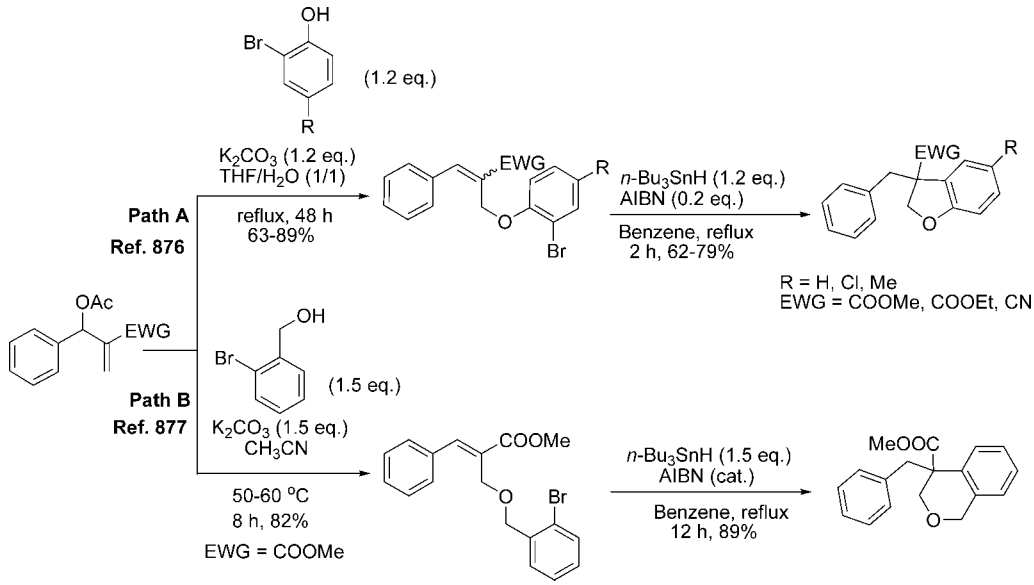
Scheme 387



Scheme 388

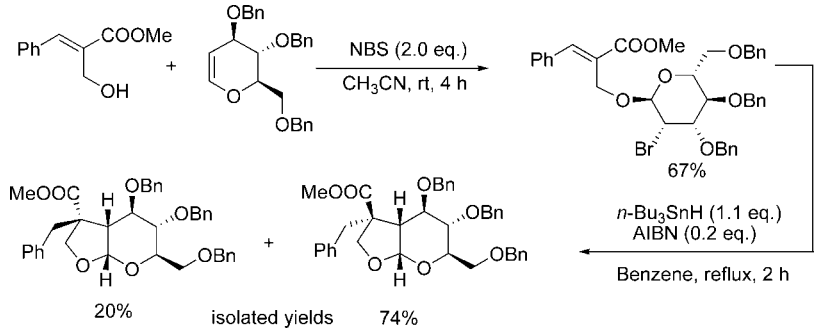


Scheme 389

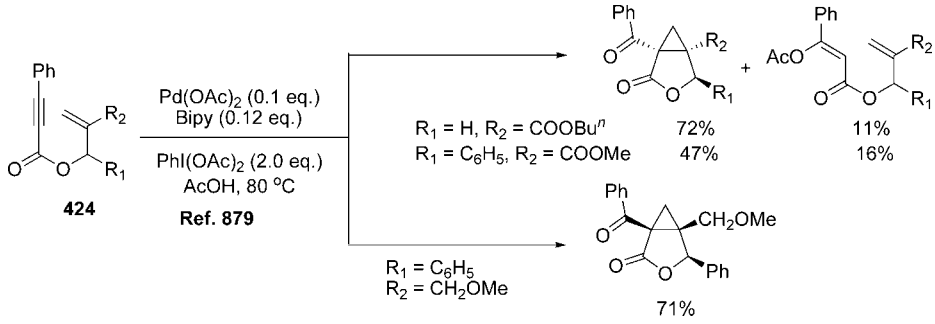


Recently Kim and co-workers[885] have transformed 3-benzylideneflavanones (which were prepared from various 3-arylidenechroman-4-ones following the literature procedure via the reaction between Baylis−Hillman bromides and phenol followed by hydrolysis and cyclization)[578] into 3-benzoylflavanones via PCC oxidation (Path A, Scheme 396). They have also extended this strategy for the preparation of 5,6-tetrahydrobenzochromone 4-(4*H*)one derivatives

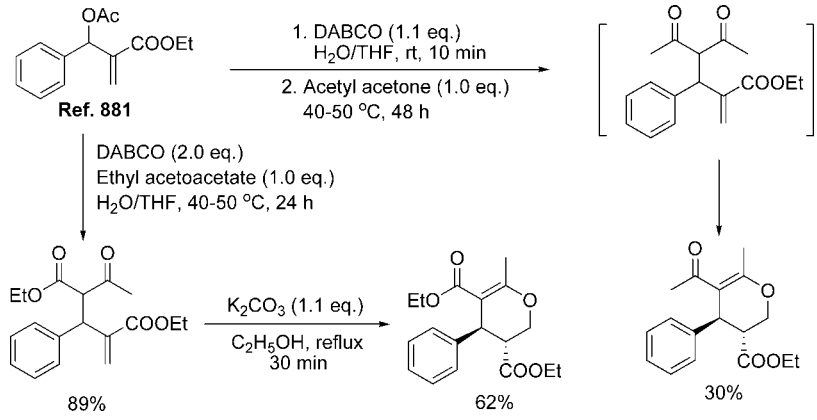
Scheme 390



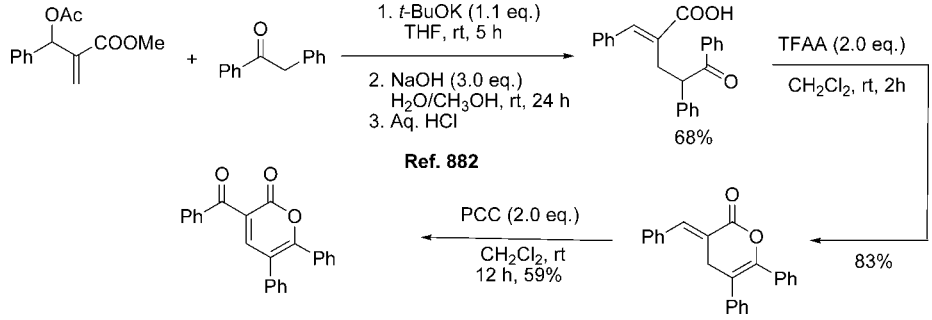
Scheme 391



Scheme 392



Scheme 393

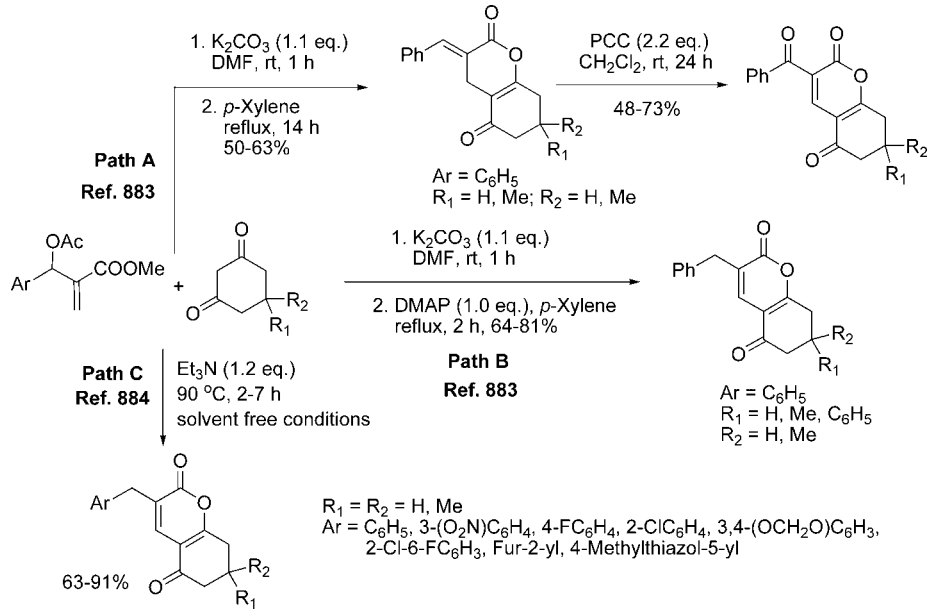


(using 1-naphthol as a nucleophile for reaction with Baylis−Hillman bromides) and oxidized them into the corresponding benzoyl derivatives following reaction sequence shown in Path B, Scheme 396.

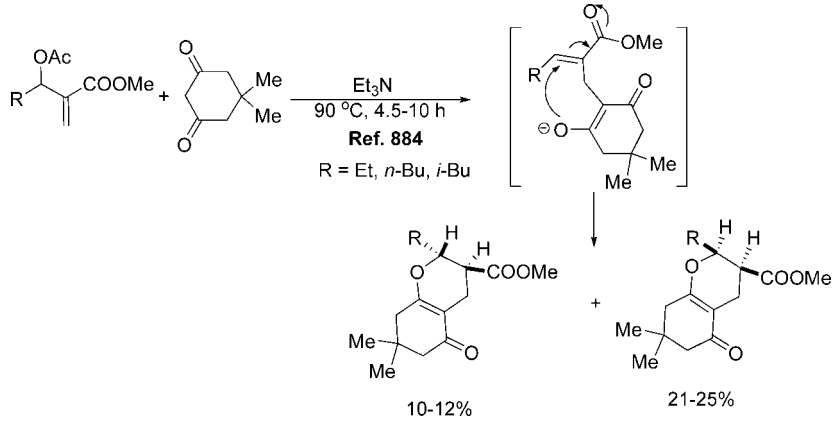
Subsequently, Kanakam and co-workers[886] extended the application of Baylis−Hillman bromides for synthesis of substituted dinaphthyl bis-chromanones following the reaction sequence shown in Scheme 397 (one example is presented). Later on, Rajan and Kanakam also examined biological activity of these compounds. Subsequently, the same strategy has been extended for the synthesis of chiral bis-chromanones via the reaction of Baylis−Hillman bromide with chiral (*S*)-binaphthol (as a nucleophile) (Scheme 398).[887]

The Baylis−Hillman acetates have been transformed into 2-methyl-4-aryl-5-methylene-γ-valerolactones,[888] 3-methylene-3,4-dihydropyran-2-one frameworks,[889] and substituted glutaric anhydride derivatives[889] (with high diastereoselectivity) following the reaction sequence shown in Scheme 399.

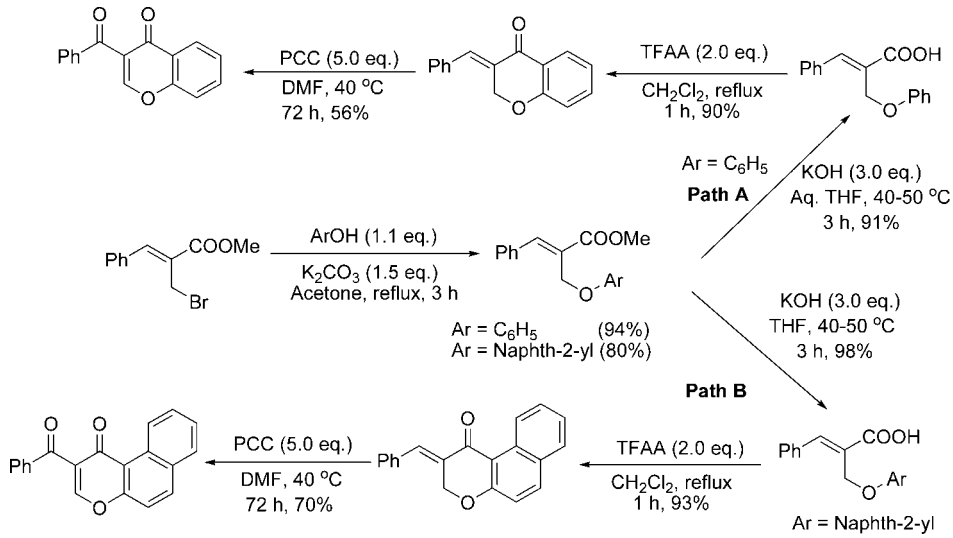
Scheme 394



Scheme 395



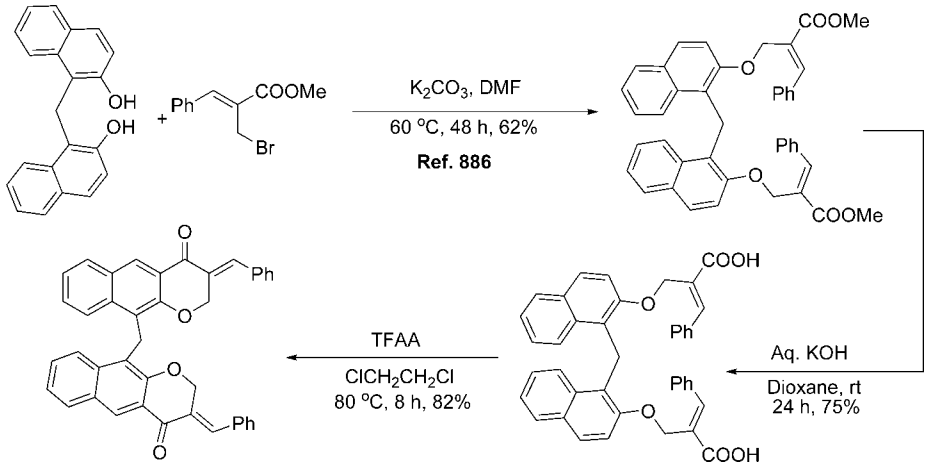
Scheme 396



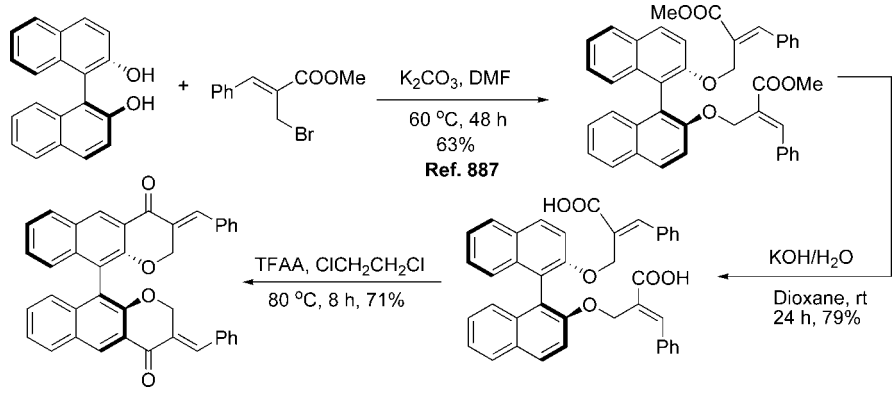
This strategy involves the treatment of Baylis−Hillman acetates first with DABCO and then with appropriate 1,3-dicarbonyl compounds such as acetylacetone (Path A), benzoylacetone (Path B), and methyl acetoacetate (Path C) as nucleophiles followed by cyclization. Representative examples are shown in Scheme 399.

Kim and co-workers[890,891] have transformed the Baylis−Hillman bromides first into S_N2' alkylated product (**373**) with

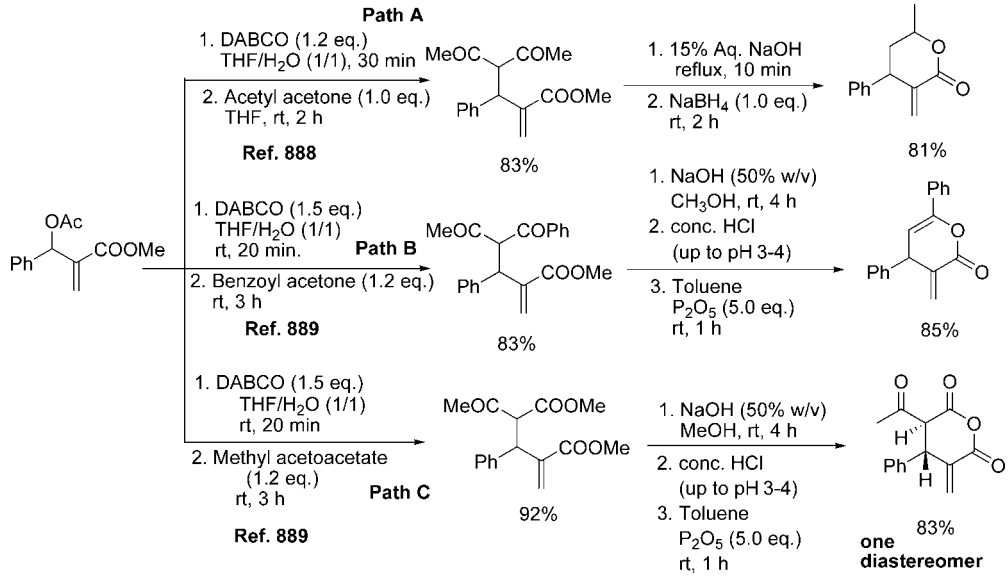
Scheme 397



Scheme 398



Scheme 399

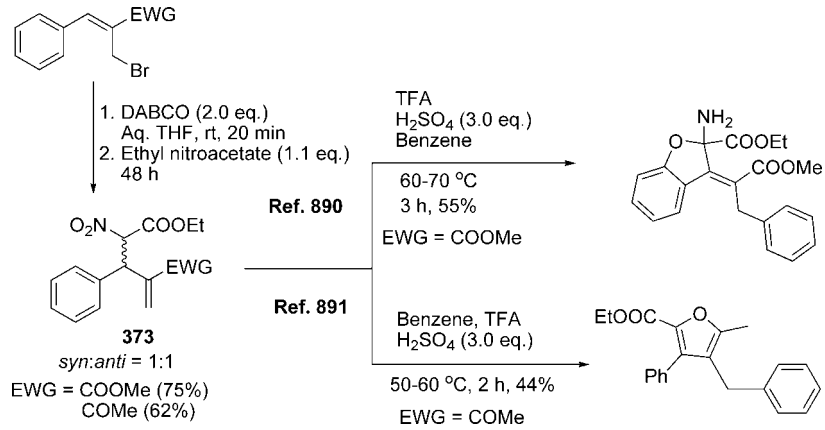


ethyl nitroacetate in the presence of DABCO. The Friedel−Crafts reaction of **373** with benzene in the presence of trifluoroacetic acid provided 2-amino-2,3-dihydrobenzofurans in the case when EWG was COOMe.[890] Similar Friedel−Crafts reaction of **373** with benzene gave tetrasubstituted furan derivatives when EWG was COMe.[891] Representative examples are shown in Scheme 400.

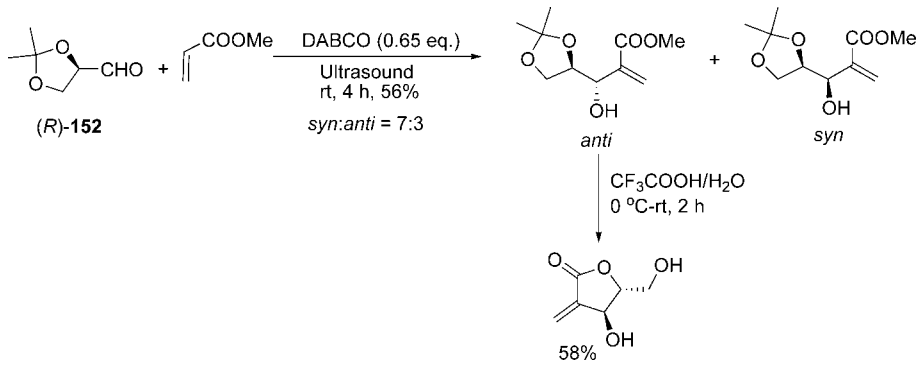
Porto and Coelho[892] have developed a simple methodology for the synthesis of (4*S*)-hydroxy-(5*R*)-hydroxymethyl-3-methylenedihydrofuran-2-one via the treatment of the minor product (*anti* isomer) (obtained by the Baylis−Hillman reaction of 2,3-isopropylidene D-glyceraldehyde and methyl acrylate in the presence of DABCO) with trifluoroacetic acid (Scheme 401).

Our research group[893] has developed a simple and facile methodology for benzoxepine derivatives via the reaction of Baylis−Hillman alcohols with formaldehyde in the presence of H_2SO_4. This reaction involves facile tandem construction of C−O and C−C bonds via Prins-type and

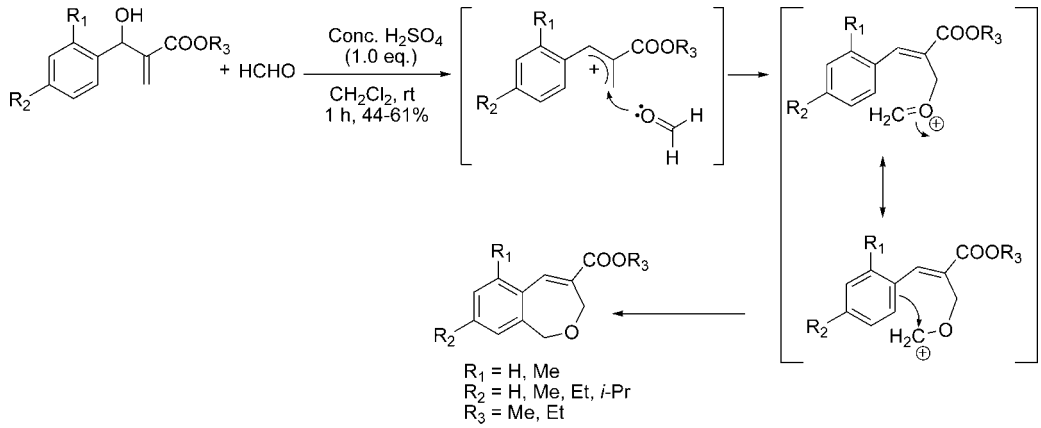
Scheme 400



Scheme 401



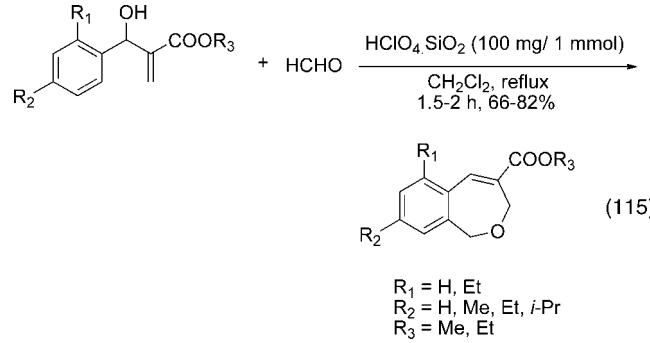
Scheme 402



Friedel−Crafts reactions, respectively. Representative examples are shown in Scheme 402.

Subsequently, Das and co-workers[894] performed the same transformation using silica-supported perchloric acid ($HClO_4 \cdot SiO_2$) or Amberlyst-15 in CH_2Cl_2 as heterogeneous recyclable catalyst. Representative examples are shown in eq 115.

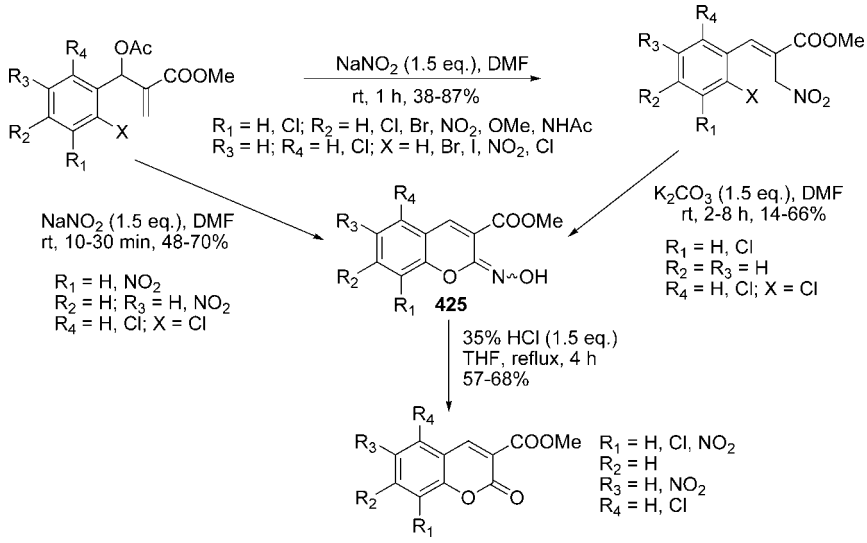
Hang and Lee[895] transformed Baylis−Hillman acetates into α-nitromethylcinnamic esters via treatment with $NaNO_2$. Subsequently, the resulting cinnamic esters containing an *ortho*-chloro group were transformed into oxime derivatives **425** via the treatment with K_2CO_3/DMF. These oximes were then hydrolyzed into coumarin derivatives. Representative examples are shown in Scheme 403. In the case of more reactive substrates containing an *ortho* or a *para* nitro group, the oximes were obtained directly from Baylis−Hillman acetates (when treated with $NaNO_2$), which were then converted further into coumarin derivatives (Scheme 403).



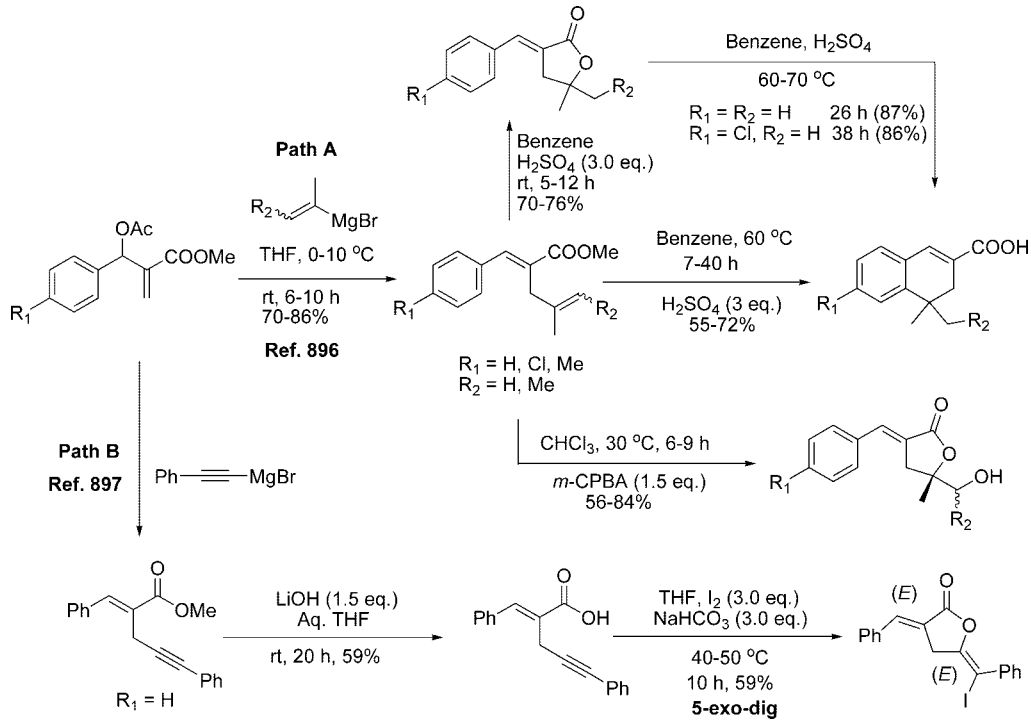
(115)

Kim and co-workers[896] have successfully employed the Baylis−Hillman acetates for synthesis of γ-lactones and dihydronaphthalenes via the reaction with alkenylmagnesium

Scheme 403



Scheme 404



bromide, following the reaction sequence described in Path A (representative examples are shown in Scheme 404). Later on, Kim and co-workers[897] also developed a simple procedure for obtaining iodoenol lactone derivatives from Baylis−Hillman acetates via the reaction with alkynylmagnesium bromide followed by iodolactonization according to the reaction sequence shown in Path B, Scheme 404.

Ramachandran and co-workers[898] examined the reaction of Baylis−Hillman acetates with various diboron compounds such as bispinacolatodiboron **426**, bis(pinanediolato)diboron **427**, and bis(diethyl-L-tartrate glycolato)diboron **428** (Figure 69) to provide the corresponding allyl boronates, which on treatment with aldehydes provided β-substituted-α-methylene-γ-butyrolactones with high diastereoselectivities. Representative examples are shown in Scheme 405. They have also noticed that chiral diboron derivatives **427** and **428** provided low enantioselectivities. The highest ee of 27% was obtained in the case of diboron compound **428** (Scheme 405).

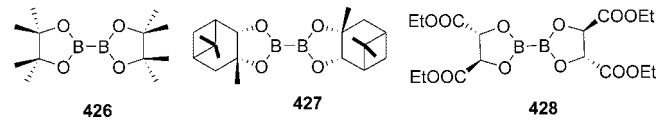
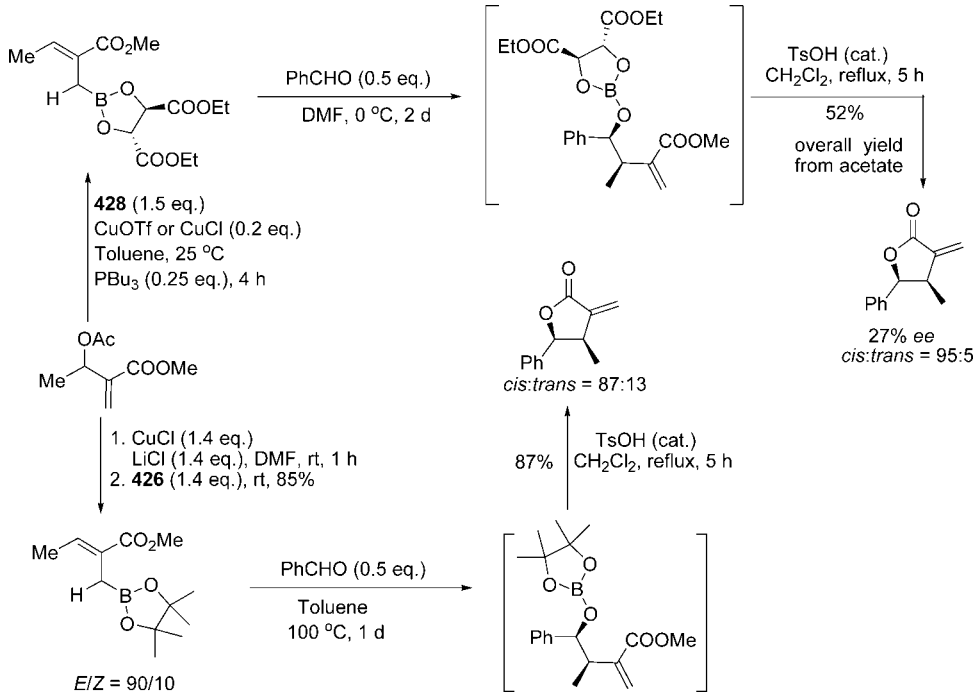


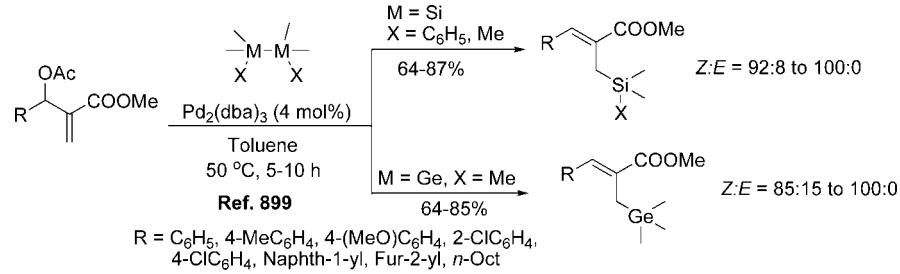
Figure 69.

About the same time, Kabalka and co-workers[899] developed an interesting synthesis of allylsilanes and allylgermanes from Baylis−Hillman acetates via the treatment with bismetallic reagents (Si−Si, Ge−Ge) as shown in Scheme 406. They have also developed an interesting synthesis of allyl boronates via the coupling of diboron compounds with Baylis−Hillman acetates under the catalytic influence of $Pd(OAc)_2$ or $Pd_2(dba)_3$. These allyl boronates were further converted into stable allyl trifluoroborates.[900] Both these derivatives, that is, allyl boronates and allyl trifluoroborates, react with aldehydes to provide *syn* products (Paths A and B, Scheme 407).[900,901] The *syn* homoallylic alcohols have

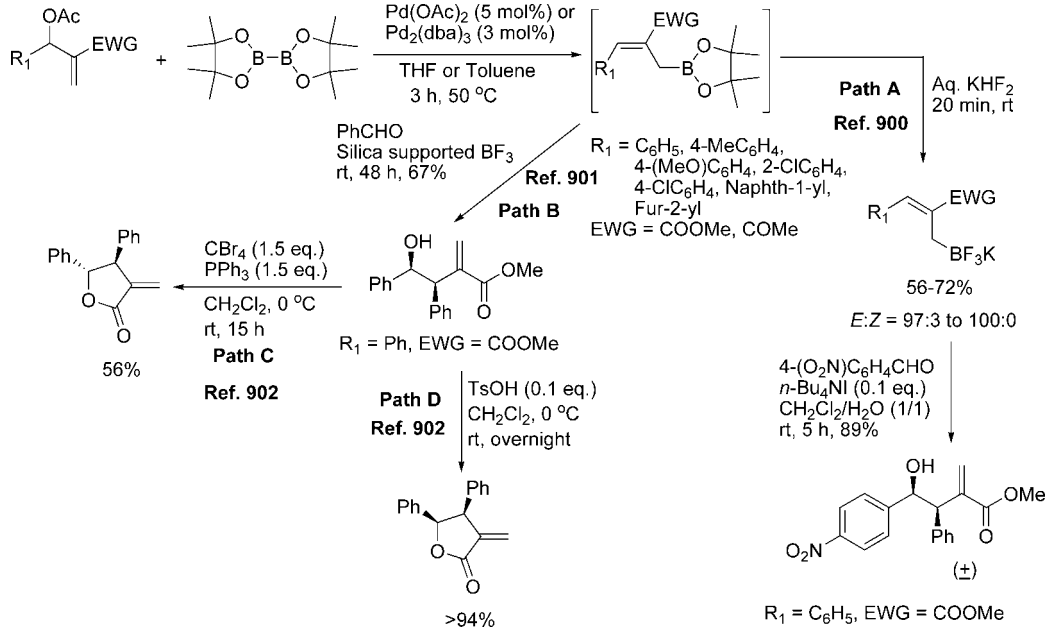
Scheme 405



Scheme 406

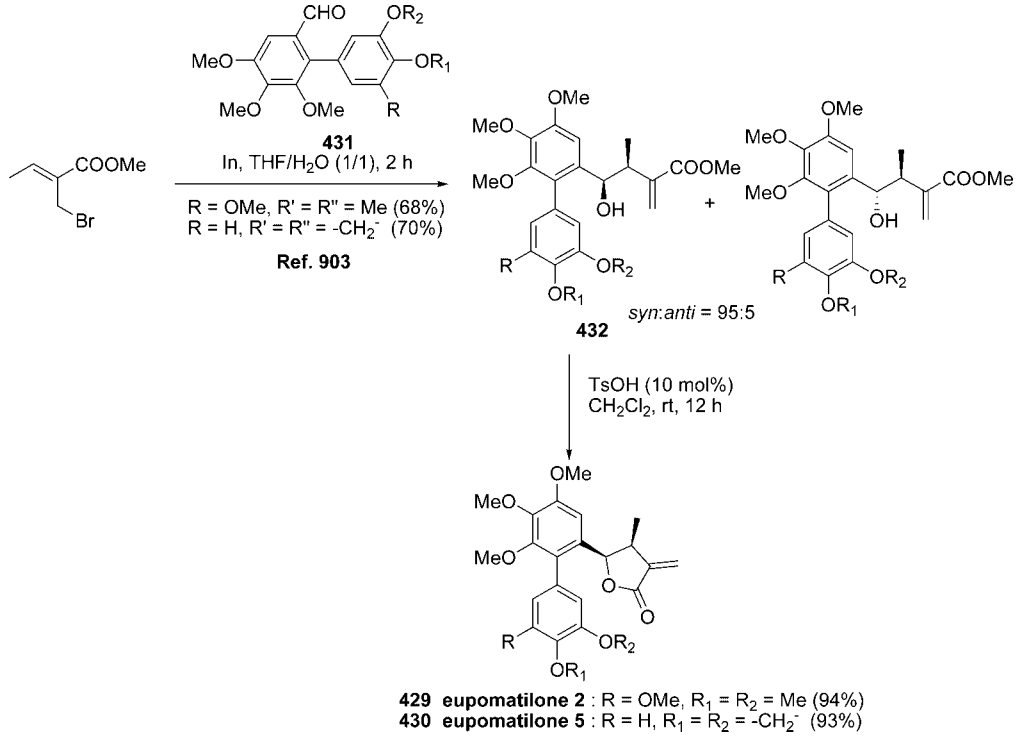


Scheme 407

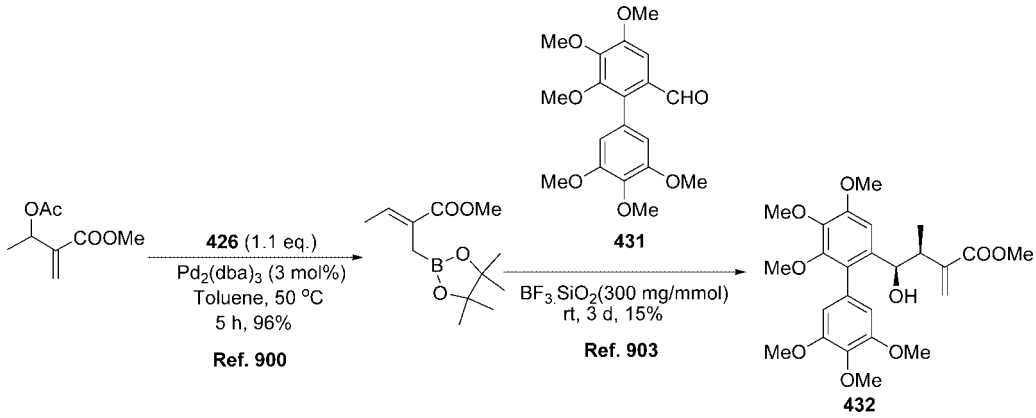


been transformed into *trans* and *syn* α-methylene-γ-lactones by treatment with CBr_4/PPh_3 and *p*-TSA, respectively.[902] One example is shown in Scheme 407 (Paths C and D). They[903] have also developed a facile synthesis of eupomatilone 2 (**429**) and eupomatilone 5 (**430**) starting from the Baylis−Hillman bromide, methyl 2-bromomethylpropanoate, via the reaction with biaryl aldehyde **431** (R = OMe, R′ = R″ = Me) in the presence of indium according to the reaction sequence shown

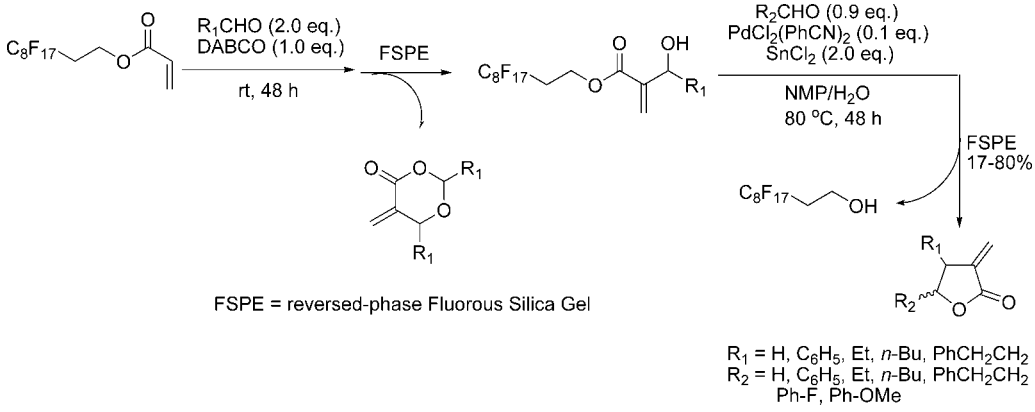
Scheme 408



Scheme 409



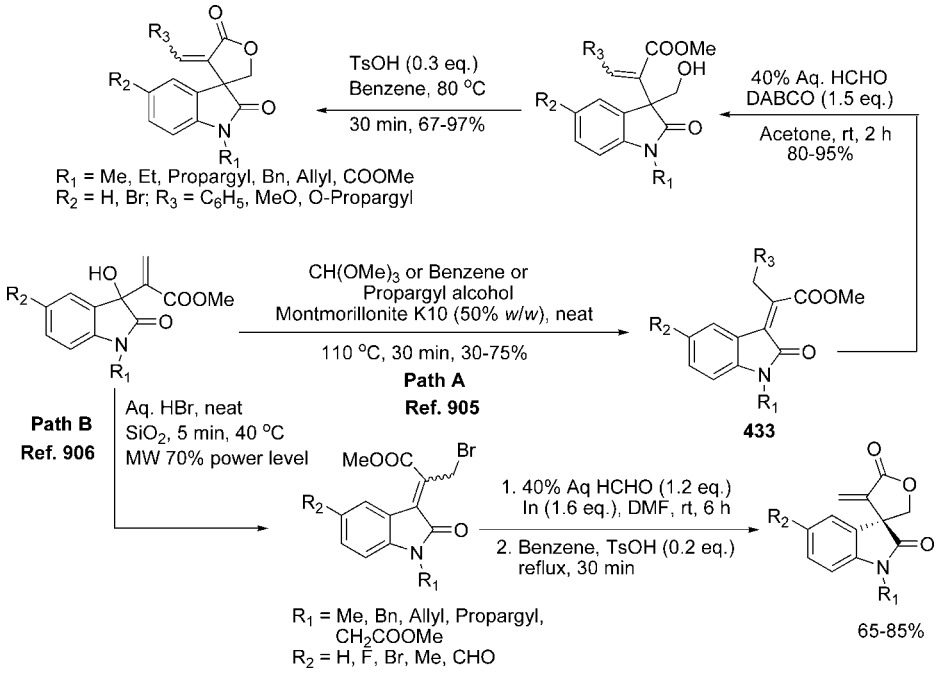
Scheme 410



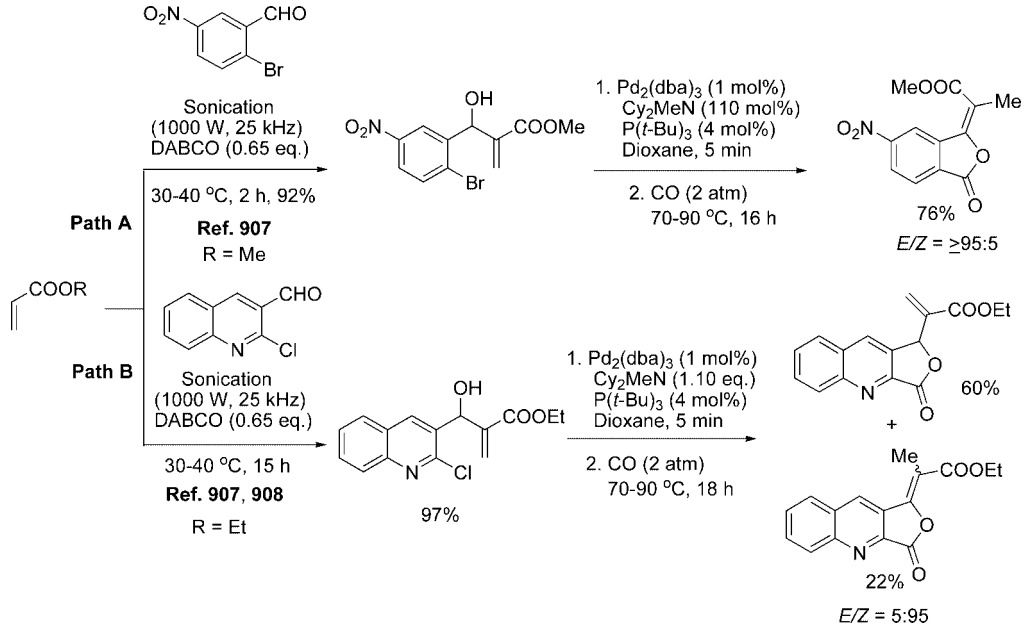
in Scheme 408. Attempts to obtain the required intermediate **432** (R = OMe, R′ = R″ = Me) via the reaction of Baylis−Hillman acetate with bispinacolatodiboron followed by the reaction of the resulting allylboronate with biaryl aldehyde **431** (R = OMe, R′ = R″ = Me) were not successful because the desired product was obtained in low yield (Scheme 409).

Gouault and co-workers[904] used fluorous acrylate as activated alkene in the Baylis−Hillman coupling with aldehydes to provide the corresponding Baylis−Hillman

Scheme 411



Scheme 412

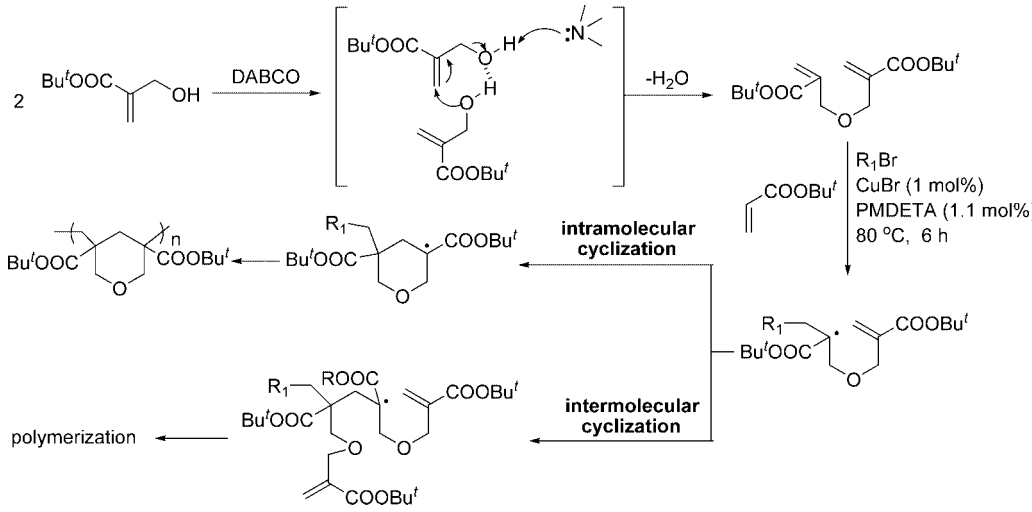


alcohols, which were transformed into disubstituted α-methylene-γ-lactones via the reaction with aldehyde under the influence of $PdCl_2(PhCN)_2$ in the presence of $SnCl_2$ as a Lewis acid. It was clearly mentioned that the workup procedure was easy and convenient in these reactions. Representative examples are shown in Scheme 410.

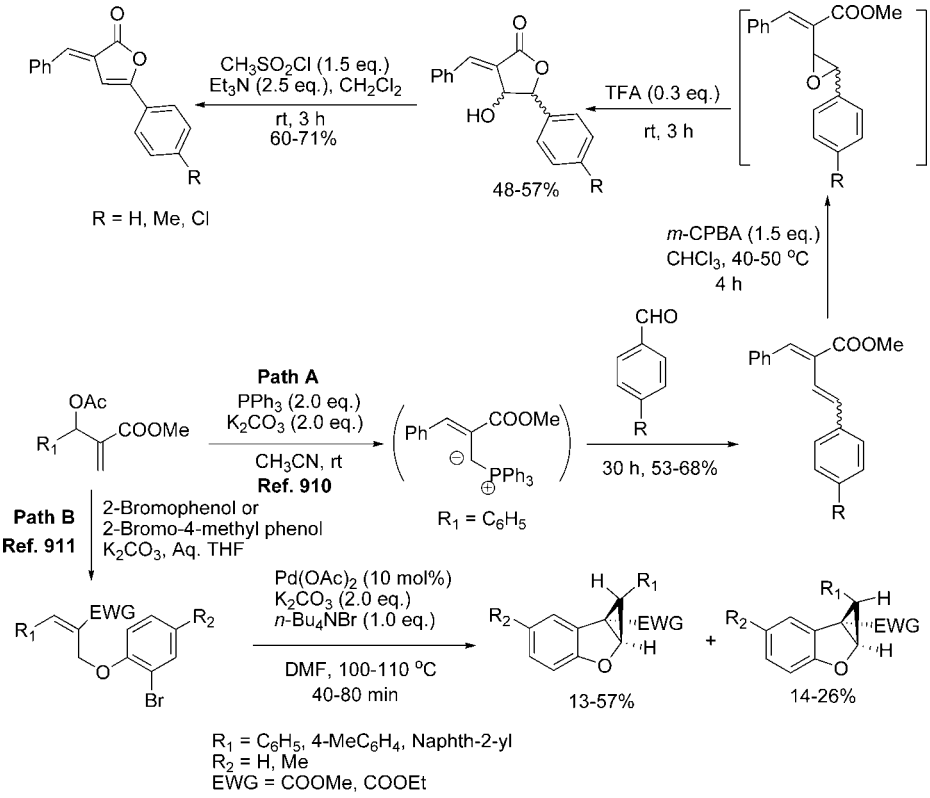
Shanmugam and Vaithiyanathan[905] have transformed the Baylis−Hillman alcohols obtained via the reaction between isatin derivatives and methyl acrylate into spiro-α-methylene-γ-butyrolactone containing an oxindole moiety. The reaction sequence involves the preparation of the tetra-substituted alkenes (**433**) via the treatment of Baylis−Hillman alcohols with $CH(OMe)_3$ or benzene or propargyl alcohol followed by reaction with formaldehyde in the presence of DABCO and subsequent cyclization following the reaction sequence described in Path A (Scheme 411). Subsequently, Shanmugam and Viswambharan[906] also reported an efficient synthesis of 3-spiro-α-methylene-γ-butyrolactone-oxindolones from the allyl bromide derivatives (isomerized) of Baylis−Hillman alcohols obtained from isatin derivatives and methyl acrylate via reaction with formaldehyde in the presence of indium followed by cyclization (Path B, Scheme 411).

Coelho and co-workers[907,908] have described an efficient synthesis of 3-alkenylphthalides (Paths A and B) through palladium-catalyzed carbonylative cyclization of Baylis−Hillman alcohols derived from 2-halo aryl aldehydes. Representative examples are shown in Scheme 412. The quinolinephthalide derivatives (Path B) thus obtained (from 2-chloroquinoline-3-carboxaldehyde) were found to be active toward proliferation of human tumor cell lines.

Scheme 413



Scheme 414



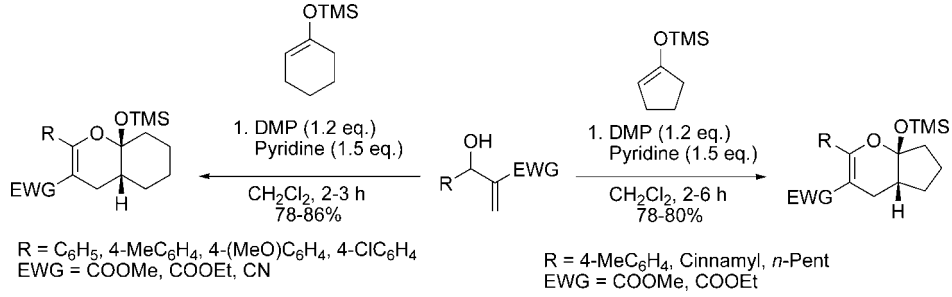
Acar and co-workers[909] have reported interesting cyclopolymerization of allyl ethers obtained from Baylis−Hillman alcohol, *tert*-butyl α-(hydroxymethyl)acrylate (TBHMA), to provide tetrahydropyran derivatives under controlled atom transfer radical polymerization (ATRP) using CuBr/PMDETA in xylene at 70 °C in the presence of *tert*-butyl acrylate as macroinitiator in this strategy (Scheme 413).

A simple procedure for the synthesis of 3-benzylidene-5-aryl-3*H*-furan-2-ones from the Baylis−Hillman acetates was reported by Kim and co-workers.[910] This reaction involves the Wittig reaction and epoxidation as the key steps (Path A, Scheme 414). Kim and co-workers[911] have also reported a facile synthesis of dihydrobenzofuran derivatives fused with cyclopropane moiety starting from the Baylis−Hillman adducts involving the palladium-mediated domino carbopalladation involving activation of the C(sp^3)−H bond as the key step following the reaction sequence shown in Path B (Scheme 414).

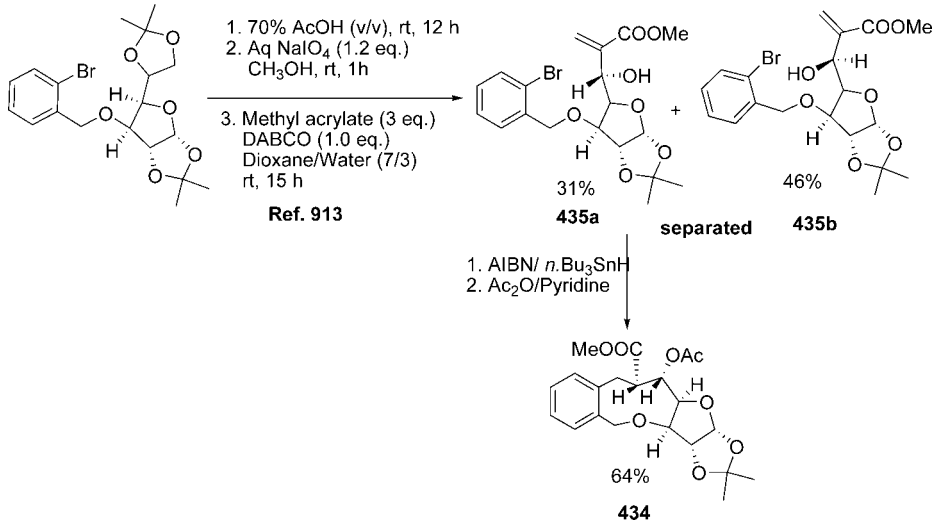
Yadav and co-workers[912] reported a facile method for synthesis of *cis*-fused dihydropyran derivatives from Baylis−Hillman adducts via the reaction with silyl enolethers in the presence of Dess−Martin periodinane (DMP). Representative examples are shown in Scheme 415.

Chattopadhayay and co-workers[913] reported an efficient synthesis of enantiopure benzo-fused *cis*- and *trans*-9,5 oxabicyclic compounds **434** via regioselective intramolecular 9-*endo*-*trig* radical cyclization of the Baylis−Hillman alcohols **435a** obtained via the coupling of *in situ* generated chiral aldehydes (from *O*-2-bromobenzylated-1,2:5,6-di-*O*-isopropylideneglucofuranoside) with methyl acrylate according to the reaction sequence shown in Scheme 416. They have extended this strategy to the synthesis of novel dibenz[*b*-

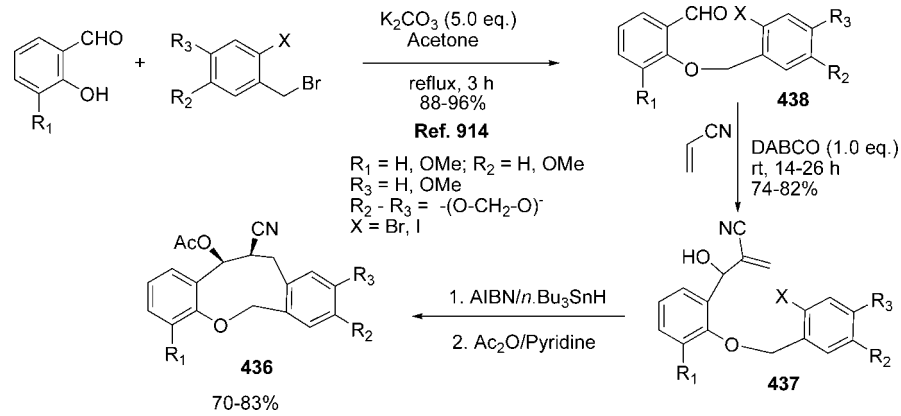
Scheme 415



Scheme 416



Scheme 417



,*g*]oxonins (**436**)[914] using the Baylis−Hillman alcohols **437** obtained via the coupling of the aldehydes **438** with acrylonitrile according to the reaction sequence shown in Scheme 417.

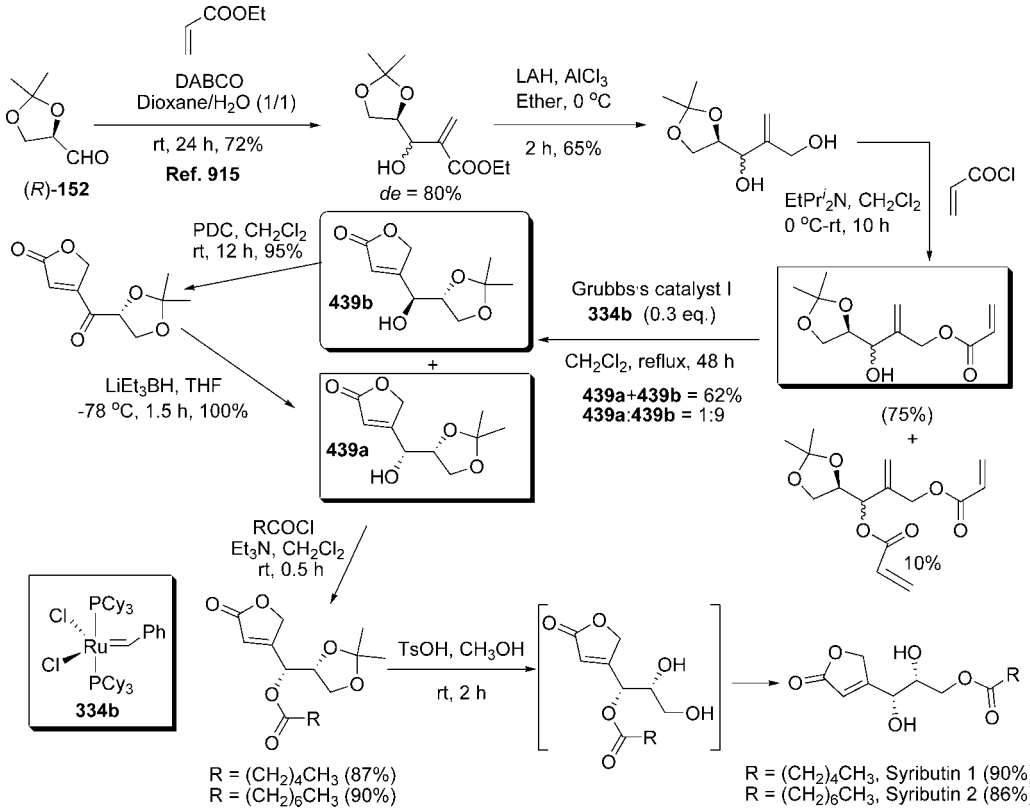
Krishna and co-workers[915] have successfully synthesized syributins 1 and 2 stereoselectively from the Baylis−Hillman adduct derived from 2,3-*O*-isopropylidene-*R*-glyceraldehyde and ethyl acrylate, involving ring-closing metathesis (RCM) as the key step, following the reaction sequence shown in Scheme 418. Subsequently, Krishna and Narsingam[916] extended this strategy to the synthesis of several substituted sugar-linked-α,β-unsaturated γ-lactones from the Baylis−Hillman adduct obtained via the reaction of various aldehydes derived from sugars and ethyl acrylate (Scheme 419).

Subsequently, Kim and co-workers[917] transformed *O*/*N*-allyl derivative of the Baylis−Hillman adducts into 2,5-dihydrofurans and 2,5-dihydropyrroles [involving ring-closing metathesis (RCM) reaction as the key strategy], which were subsequently converted into tetrahydrofurans and tetrahydropyrrole derivatives[874] via catalytic hydrogenation of double bond under the influence of Pd/C in ethanol following the reaction sequence shown in Scheme 420.

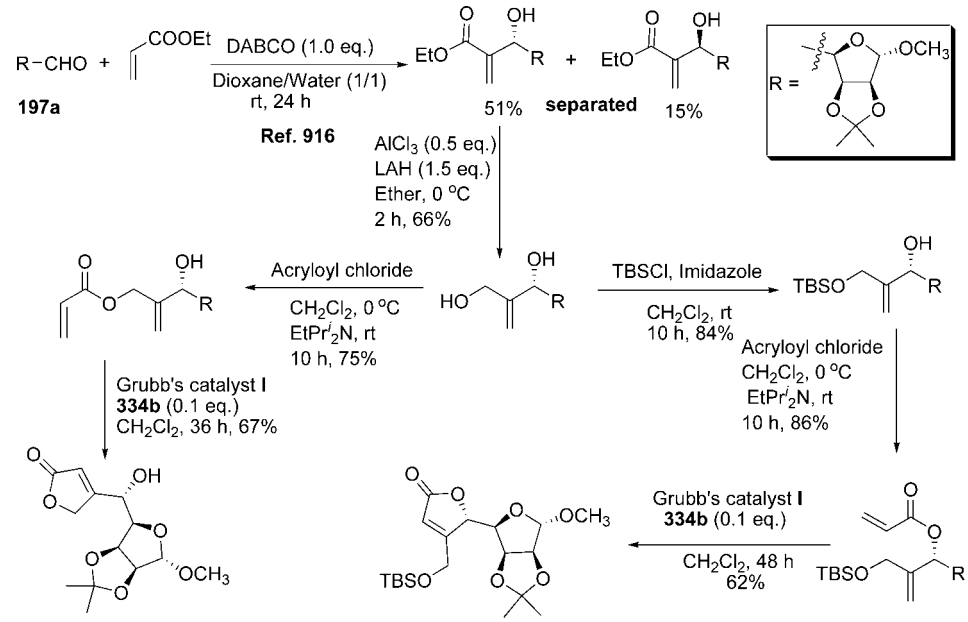
Recently, Selvakumar and co-workers[918] reported an efficient synthetic route for the synthesis of substituted butenolides using RCM promoted by Lewis acid as the key step starting from Baylis−Hillman adducts. They have also employed this methodology for synthesis of phaseolinic acid (**440**) following the reaction sequence shown in Scheme 421.

Cho and Krische[919] have reported an interesting phosphine-catalyzed stereoselective construction of γ-butenolides via the treatment of 2-trimethylsilyloxyfuran with Baylis−Hillman acetates. Representative examples are given in Path A, Scheme 422. They have also used Baylis−Hillman acetates derived from (−)-8-phenylmenthyl acrylate, which provided

Scheme 418



Scheme 419

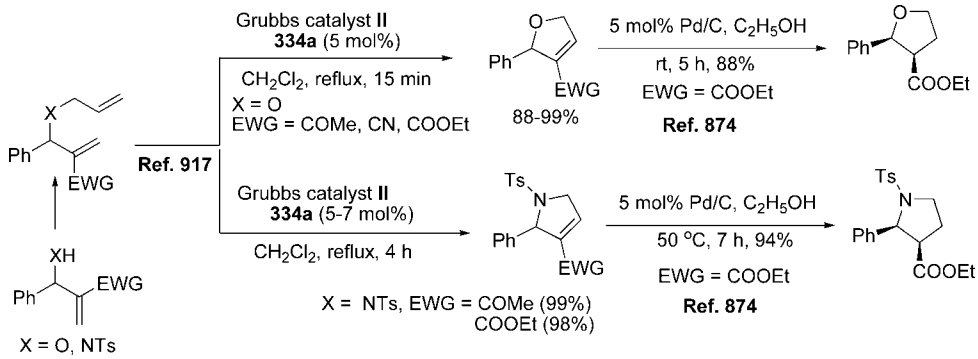


the resulting γ-butenolides in high yield and stereoselectivity (Path B, Scheme 422). Later on, Hou and co-workers[661] have performed this reaction under the catalytic influence of planar chiral [2.2]paracyclophane monophosphine (**327e**) for developing an asymmetric version of this methodology, and the resulting γ-butenolide was obtained in high yield and diastereoselectivity but in low enantioselectivity (Path C, Scheme 422).

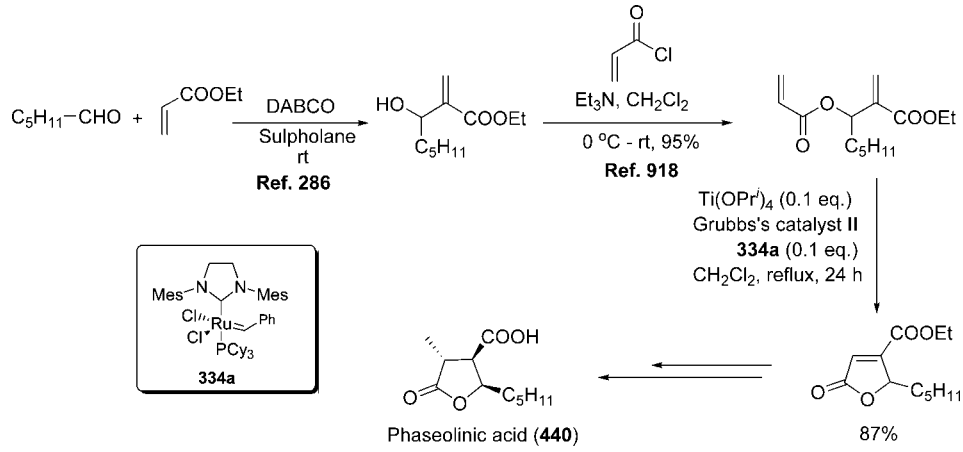
Subsequently, Shi and co-workers[920] have developed an interesting synthesis of highly enantioselective and diastereoselective γ-butenolides from the acetates of Baylis−Hillman alcohols derived from MVK and EVK via treatment with 2-trimethylsilyloxyfuran under the catalytic influence of various chiral phosphines (**232**, **250a**, **250e**, **256b**, or **257**). In these studies, chiral phosphine **250e** provided better selectivity. Representative examples are shown in eq 116.

The TBDMS ethers of Baylis−Hillman alcohols derived from 3-furfural and alkyl acrylates were transformed into β-functionalized γ-hydroxybutenolides (**441a**) by Patil and Liu via oxidation using singlet oxygen in the presence of Hunig base (Path A, Scheme 423).[921] Similarly, the Baylis−Hillman adducts derived from 3-furfural and alkyl acrylates were transformed into α-functionalized γ-hydroxybutenolides (**442a**, along with minor product **441b**) mediated

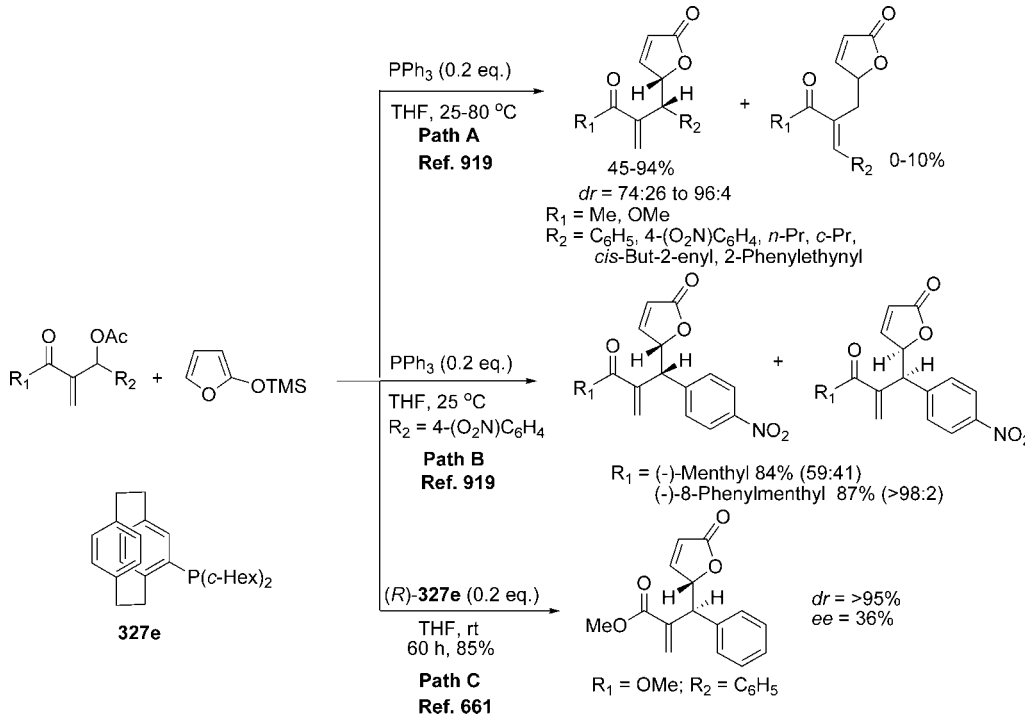
Scheme 420



Scheme 421

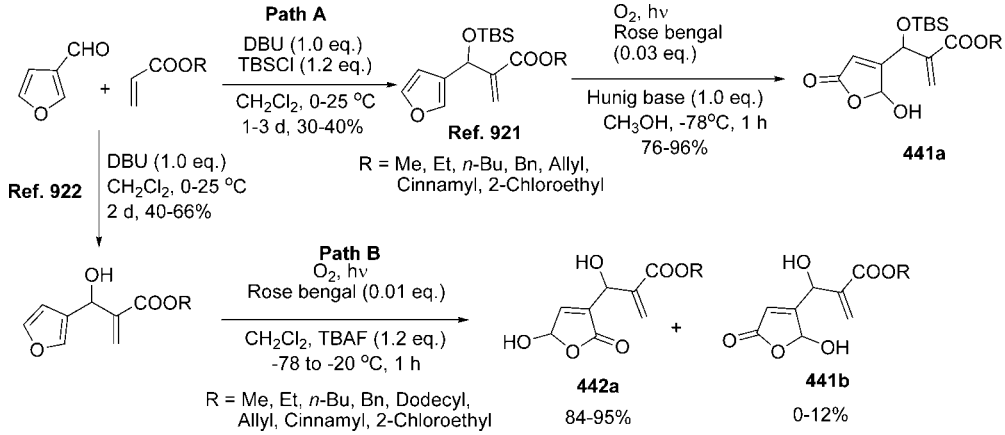


Scheme 422

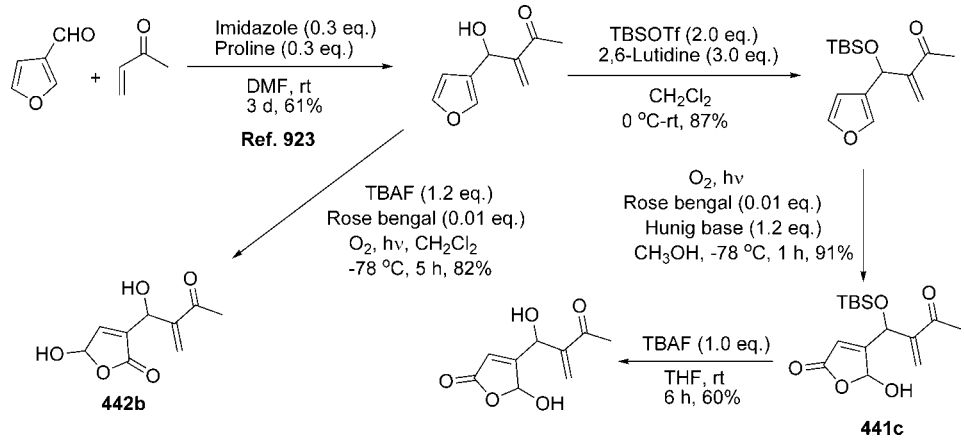


by singlet oxygen in the presence of TBAF (Path B, Scheme 423).[922] Similarly they have extended this strategy to Baylis−Hillman alcohol derived from 3-furfural and MVK and its TBDMS ether to provide α-functionalized γ-hydroxybutenolides (**442b**) and β-functionalized γ-hydroxybutenolides (**441c**), respectively (Scheme 424).[923] From these results, it is quite clear that TBDMS protection of OH in the presence of Hunig base provides different regioselectivity on comparison with simple unprotected Baylis−Hillman alcohols in the presence of TBAF. Liu and co-workers[924] have also extended this same strategy to 2-furfural (Scheme 425). They noticed that protected Baylis−Hillman alcohol provided the expected γ-functionalized γ-hydroxybutenolides, where as unprotected Baylis−Hillman alcohol led to

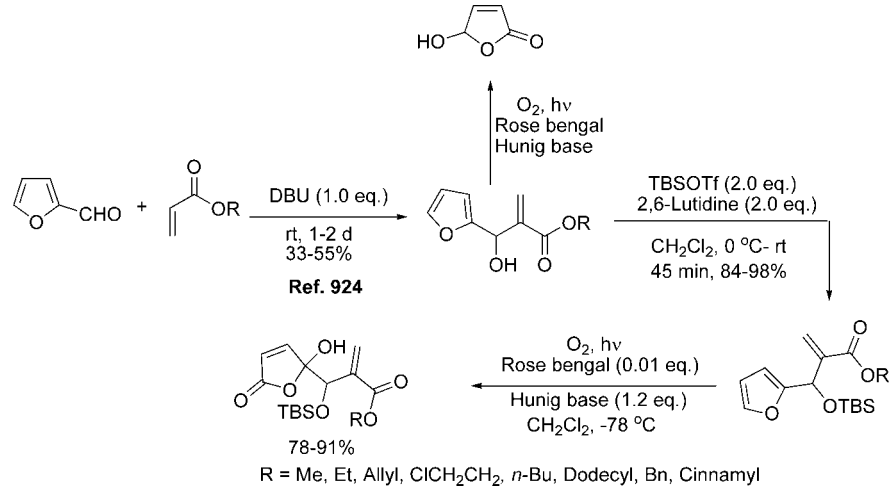
Scheme 423



Scheme 424



Scheme 425



the formation of hydroxybutenolide (base-promoted fragmentation product).

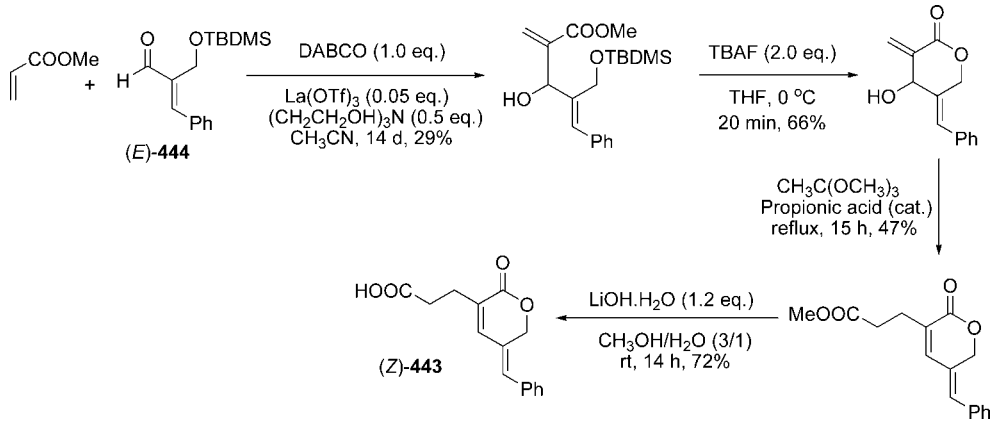
Ko and co-workers[925] have developed a simple synthesis of MMP-inhibitory gelastain analogue (*Z*)-**443** according to the Scheme 426, using the Baylis−Hillman adduct (derived from (*E*)-aldehyde **444** and methyl acrylate) as the starting material. A similar strategy was employed for synthesis of (*E*)-lactone **443** from (*Z*)-aldehyde **444**.

Li and co-workers[926] have reported an interesting protocol for synthesis of epoxy aldehyde (**445**), a precursor of pseudoplexaurol (**446**) and 14-deoxycrassin (**447**) according to Scheme 427, involving the Baylis−Hillman reaction between methyl acrylate and aldehyde **448** as the key step.

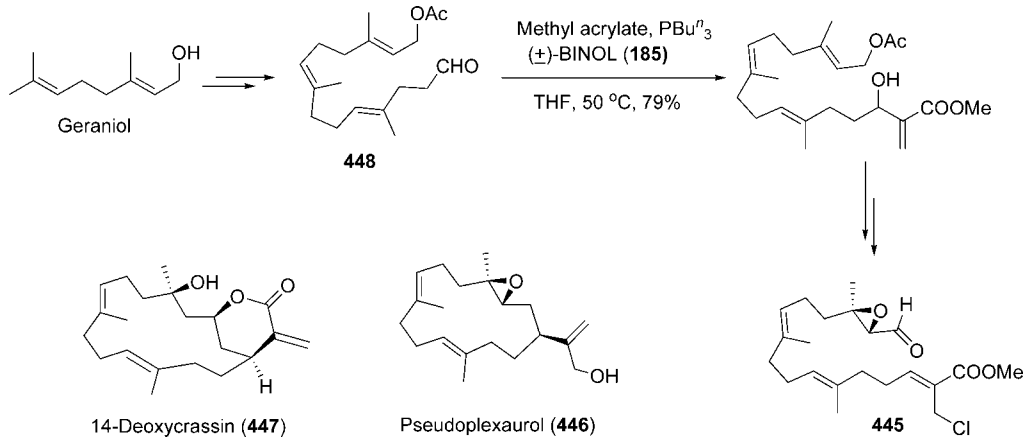
1-Oxaspiro[4.5]decan-2-one derivatives **450** were synthesized according to Scheme 428 involving the Baylis−Hillman coupling between cyclohex-2-enone and ethyl acrylate to provide the adduct (**449**) as the key step by Maier and co-workers.[927] The spiro compound **450** has been transformed into variety of useful spiro compounds (Scheme 428).

Stereoselective synthesis of methyl 7-dihydro-trioxacarcinoside B has been achieved by Koert and co-workers,[928] following the reaction sequence shown in Scheme 429. The

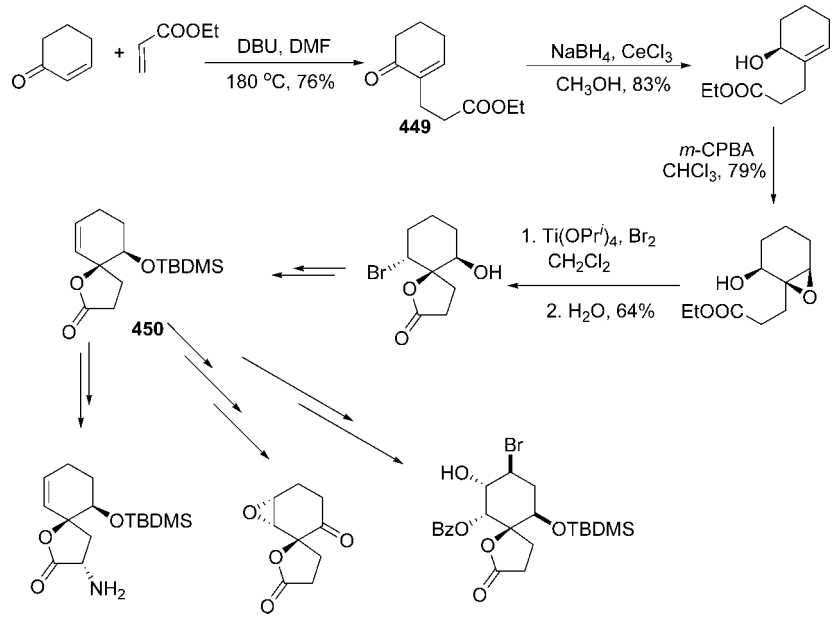
Scheme 426



Scheme 427



Scheme 428

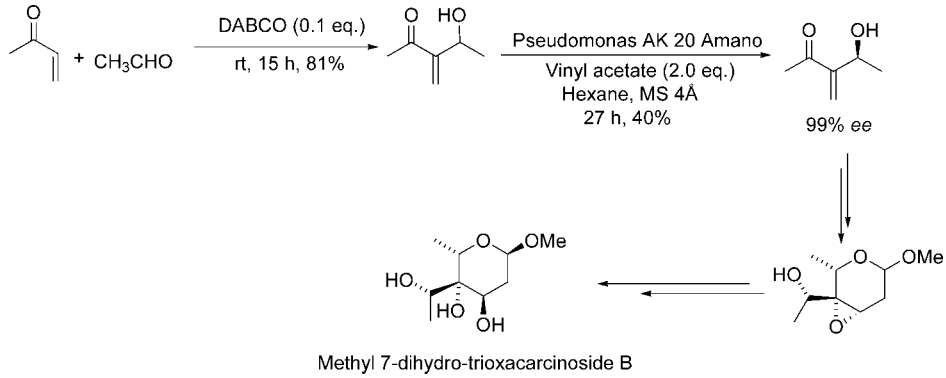


key steps in this strategy involve the Baylis−Hillman reaction between MVK and acetaldehyde and subsequent resolution of this racemic alcohol into chiral alcohol using enzymes.

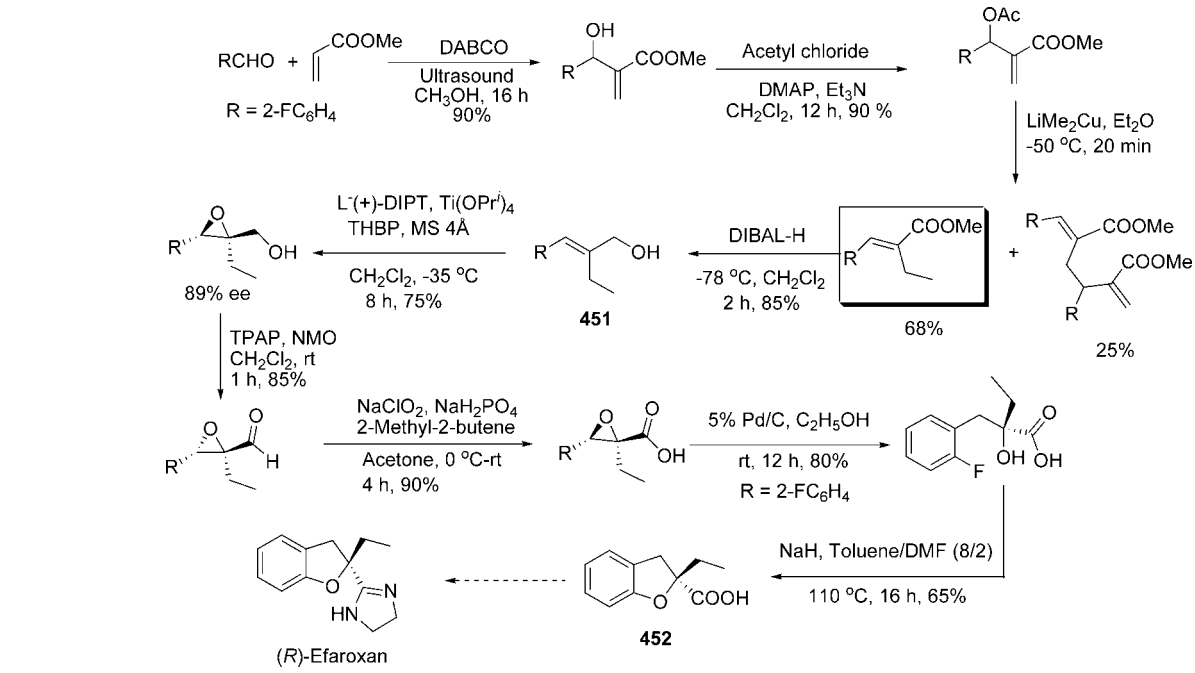
Coelho and co-workers[929] have synthesized 2-ethyl-2,3-dihydrobenzofuran carboxylic acid (**452**), precursor of (+)-efaroxan, in enantiopure form using the Baylis−Hillman adduct derived from 2-fluorobenzaldehyde and methyl acrylate, as the starting material according to the reaction sequence shown in Scheme 430. The key step in this strategy involves the conversion of allyl alcohol (**451**) into the corresponding chiral epoxide using Sharpless asymmetric epoxidation.

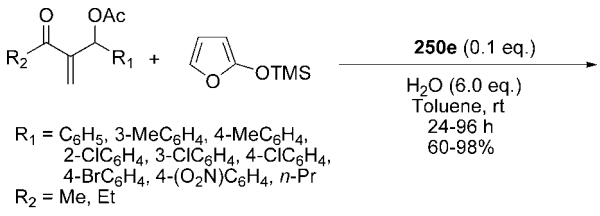
Kim and co-workers[930] have used Baylis−Hillman reaction of *in situ* generated activated alkene with formaldehyde as the key step for the total synthesis of dihydroeponemycin

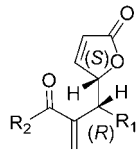
Scheme 429



Scheme 430

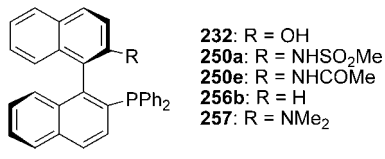






(116)

71-96% *ee*



(**453**), an important immunoproteasome-specific inhibitor, following the reaction sequence shown in Scheme 431.

The Baylis−Hillman alcohol generated via the reaction of triethyl phosphonoacetate with HCHO was used as starting material for obtaining Elliott's alcohols by Righi and co-workers (Scheme 432).[931]

Mehta and Bhat[932] have developed a simple protocol for synthesis of furano-furans from the Baylis−Hillman adducts obtained via the coupling of cyclohex-2-enones and formaldehyde according to the reaction sequence shown in Scheme 433 (one example is shown here).

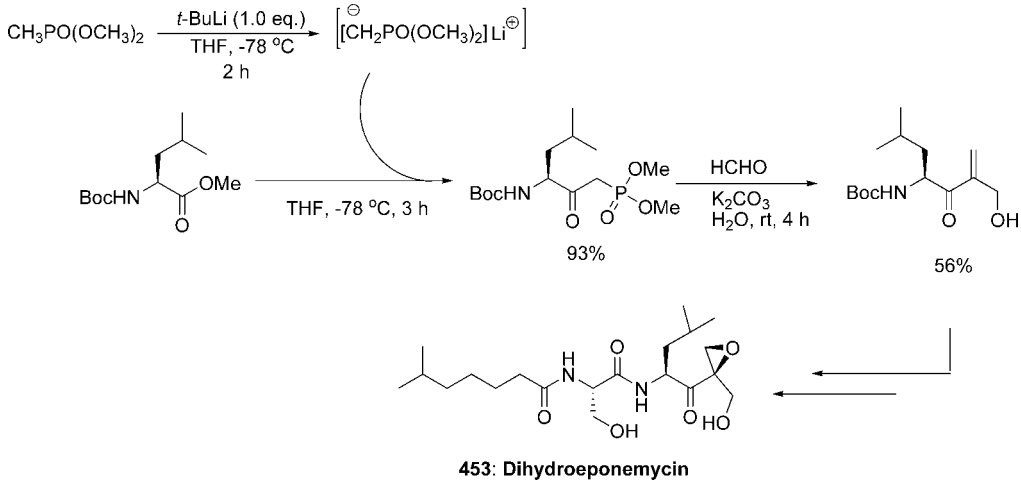
10.6. Synthesis of Selenium Heterocyclic Compounds

Schiesser and co-workers[933] have synthesized selenophene analogue (**454**, X = Se) of the thiophene-containing antihypertensive milfasartan (**454**, X=S) using the Baylis−Hillman alcohol as the starting material according to the Scheme 434. Subsequently, this compound **454** was tested for AT1 receptor antagonist properties.

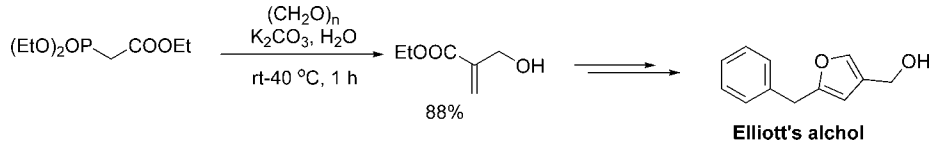
10.7. Synthesis of Heterocyclic Compounds Containing Two or More Hetero Atoms

Kim and co-workers[934] have reported a simple methodology for the synthesis of tetra-substituted pyrazole derivatives in good yields via the reaction of Baylis−Hillman adducts with hydrazine hydrochloride (Path A, Scheme 435). Later

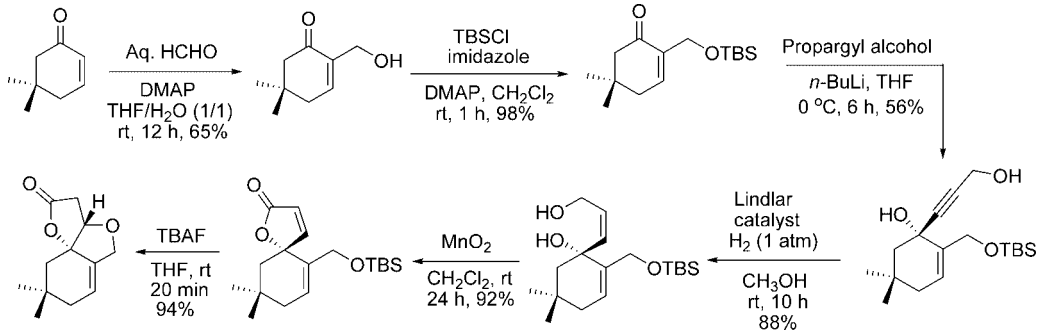
Scheme 431



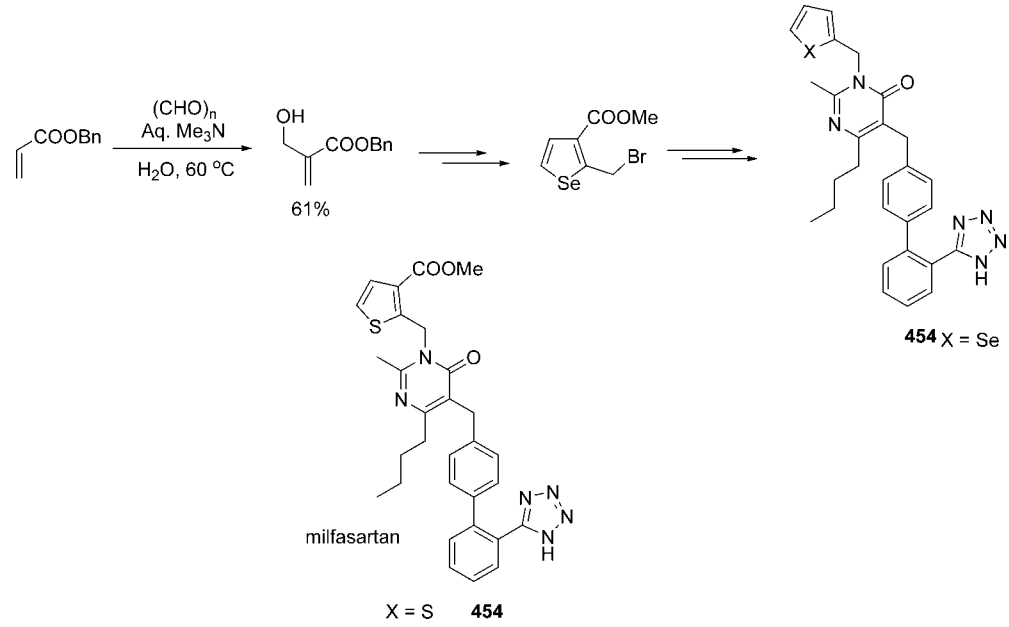
Scheme 432



Scheme 433

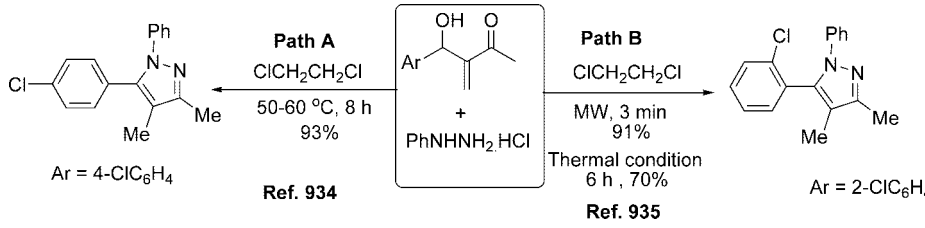


Scheme 434

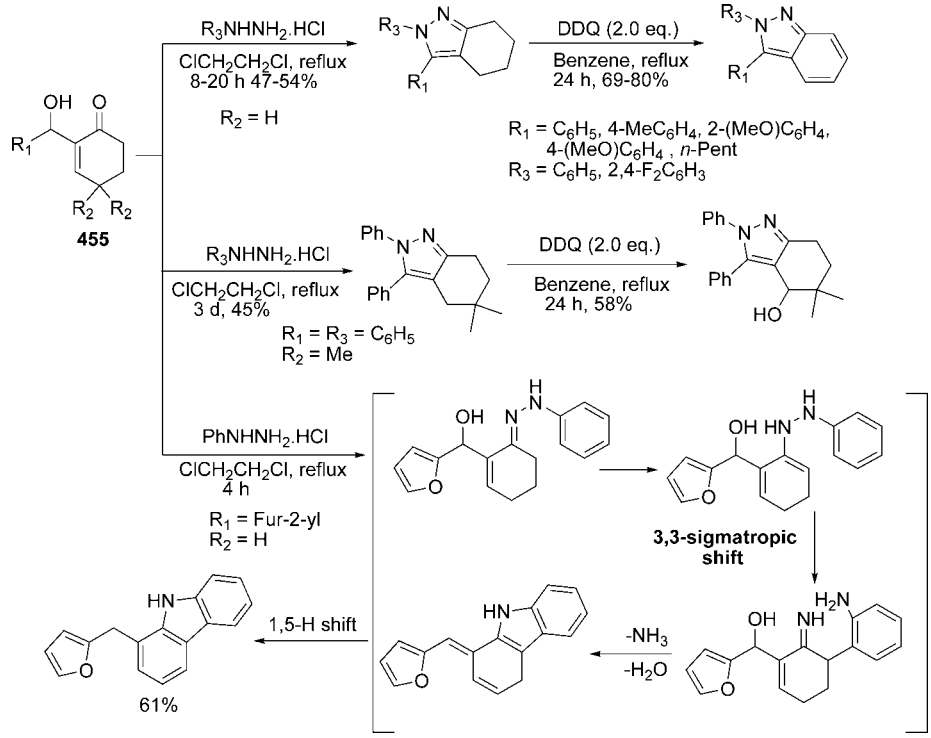


on, Mamaghani and co-workers[935] reported the same reaction

Scheme 435



Scheme 436



under the microwave irradiation conditions in shorter reaction times (Path B, Scheme 435). One example of each is presented.

Subsequently Kim and co-workers[936] extended this methodology for the synthesis of fused pyrazole derivatives starting from the Baylis−Hillman adducts, obtained from various aldehydes and cyclohexenone (Scheme 436). They have also noticed the formation of a carbazole framework in the case of **455** (R = fur-2-yl), instead of pyrazole derivatives. This reaction is believed to proceed via 3,3-sigmatropic rearrangement, following the Fisher indole synthetic pathway.

Kim and co-workers[937] have also reported an alternative route for the synthesis of 1,3,4-trisubstituted pyrazoles via the reaction of hydrazine derivatives with acyloxiranes, which were derived from Baylis−Hillman alcohols. Representative examples are shown in Path A, Scheme 437. Later on, Yadav and co-workers[938] reported a facile synthesis of pyrazolines via the 1,3-dipolar cycloaddition reaction of Baylis−Hillman alcohols with ethyl diazoacetate in the presence of 2-iodoxybenzoic acid (IBX) (Path B, Scheme 437).

Recently our research group[939] has elegantly employed the Baylis−Hillman bromides as a valuable source of 1,3-dipoles for cycloaddition onto dialkyl azodicarboxylates (dipolarophiles) under the influence of dimethyl sulfide in the presence of potassium carbonate to provide functionalized dihydropyrazole derivatives in a simple one-pot [3 + 2] annulation strategy (Scheme 438).

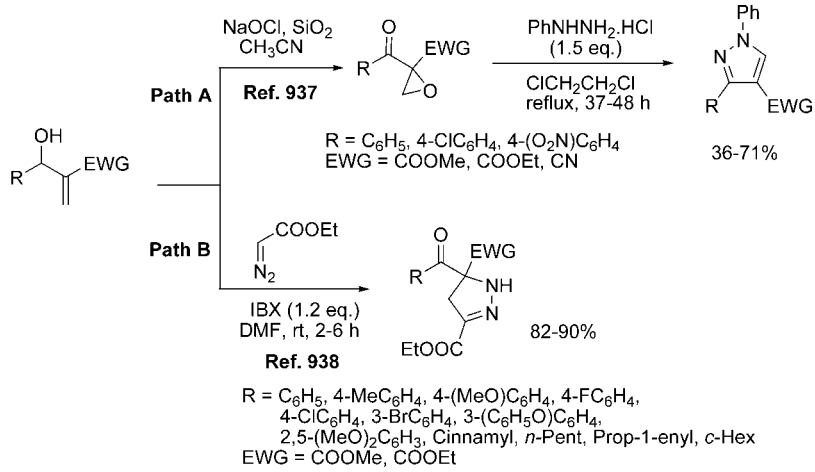
Very recently, Krishna and co-workers[940] reported an $InCl_3$- or DABCO-mediated 1,3-dipolar cycloaddition of Baylis−Hillman alcohols with ethyl diazoacetate to afford 3,5-disubstituted pyrazolines in moderate to good yields under solvent-free conditions (Scheme 439).

Kim and co-workers[941] have reported a facile synthesis of trisubstituted pyrimidines via the reaction of Baylis−Hillman acetate with amidine derivatives according to Scheme 440. Representative examples are given.

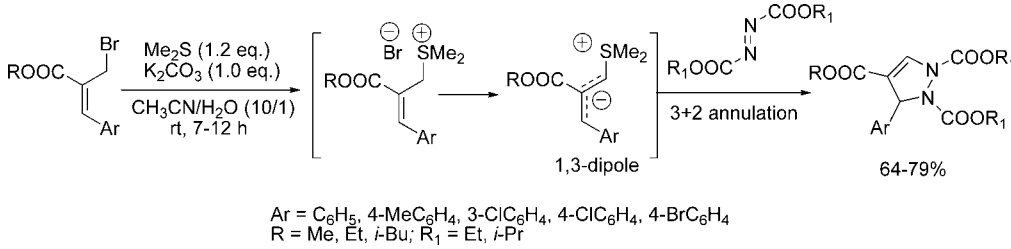
Lee and co-workers[942] have developed an interesting methodology for synthesis of 4-*H*-tetrazolo[1,5-*a*] benzazepines (**458**) via the intramolecular 1,3-dipolar cycloaddition reaction of allyl cyanide (**457**) (intramolecular click reaction), which were in turn obtained from the acetate (**456**) of the Baylis−Hillman alcohols obtained from 2-azidobenzaldehyde via the treatment with KCN (Path A, Scheme 441). Subsequently, Song and Lee[943] reported an alternative procedure for the preparation of 4-*H*-1,2,3-triazolo[1,5-*a*]-benzazepine derivatives from the alkynyl-azido intermediates (**459**), which were obtained via the treatment of the acetate (**456**) with alkynylmagnesium bromide. This reaction also involves intramolecular (3 + 2) cycloaddition reaction (intramolecular click reaction) (Path B, Scheme 441).

Subsequently, Ko and Lee[944] also reported a facile method for the synthesis of 5-*H*-1,2,3-triazolo[4,3-*a*]benzazepines from the acetates (**460**) of Baylis−Hillman alcohols derived from 2-alkynylbenzaldehyde, via the treatment with sodium azide followed by intramolecular 1,3-dipolar addition reac-

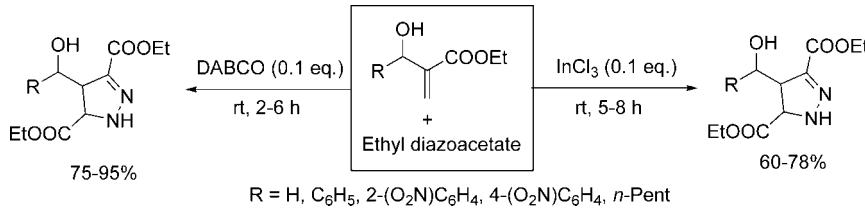
Scheme 437



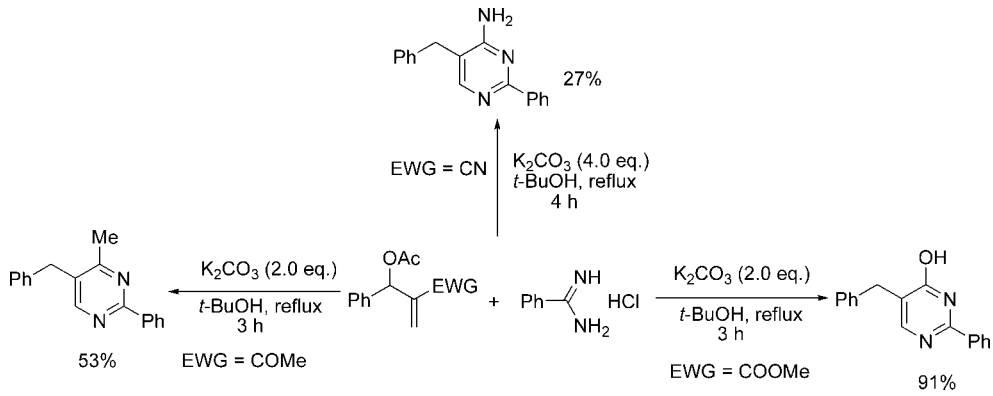
Scheme 438



Scheme 439



Scheme 440

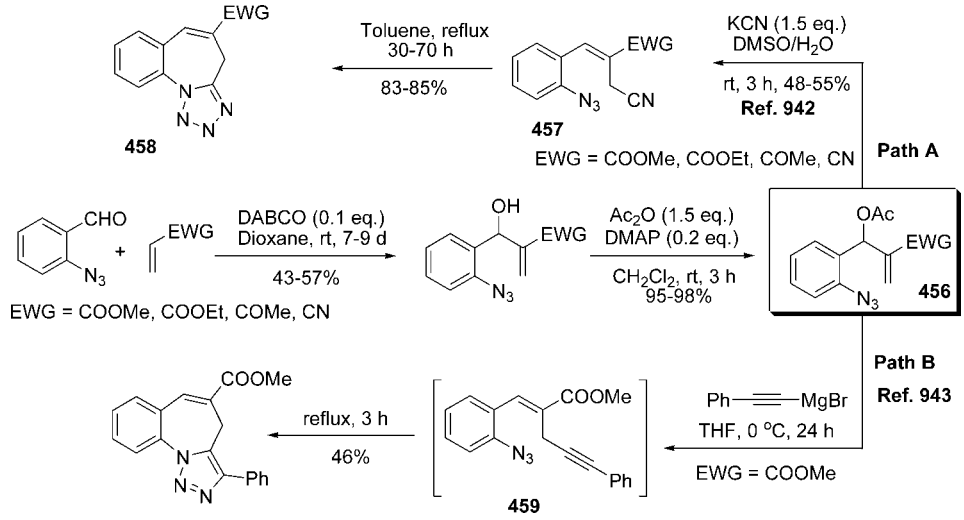


tion, according to the strategy shown in Path A, Scheme 442. These acetates (**460**) were also transformed by Lee and co-workers[945] into naphtho[2,1-*c*]isoxazole derivatives via the treatment with sodium nitrite followed by the formation of nitrile oxide and then intramolecular (3 + 2) cycloaddition strategy according to the reaction strategy shown in Path B, Scheme 442.

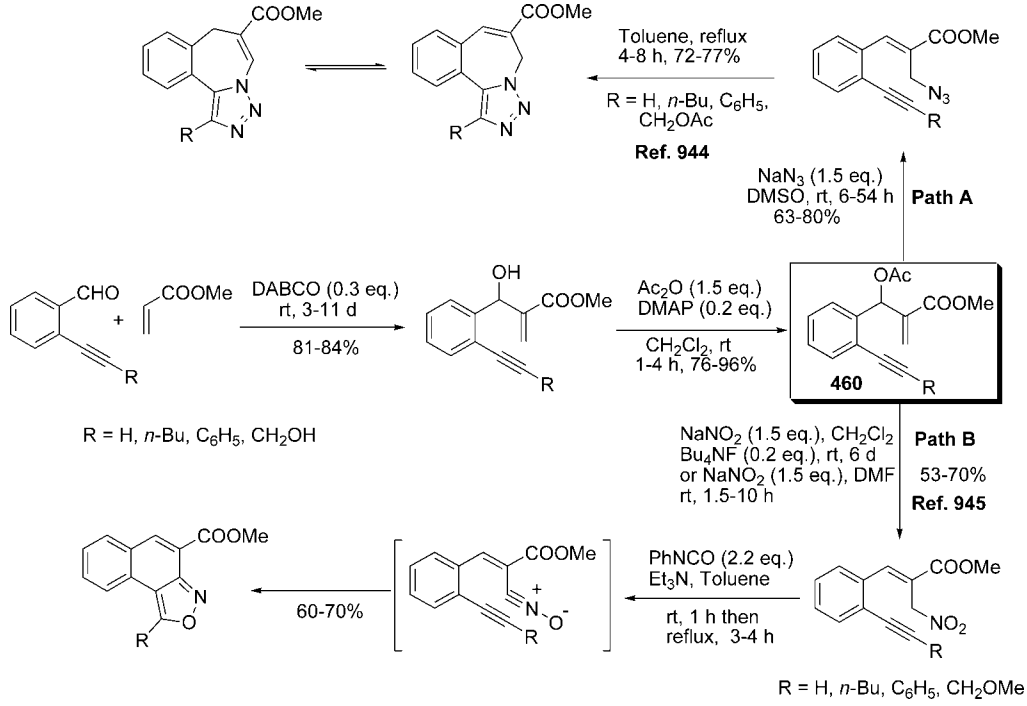
Lee and co-workers[946] have reported a facile methodology for synthesis of tetrahydroimidazolo-benzodiazocine derivatives from the Baylis−Hillman acetates, following the reaction sequence shown in Scheme 443 (one example is presented). The key step of this strategy involves the intramolecular cycloaddition reaction of methyl 2-(1-aziridinylmethyl)-3-[2-(4-chlorophenyl)ureidophenyl]propenoate (**461**), which was obtained by treating the acetate of Baylis−Hillman adduct (obtained from 2-nitrobenzaldehyde) with aziridine, followed by reduction of the nitro group to an amine group and then reaction with alkyl isocyanates, in the presence of PPh_3 and CCl_4 (Appel's dehydration conditions).

Subsequently, Sreedhar and co-workers[947] (Paths A and B) and Chandrasekhar and co-workers[948] (Path C) independently reported the synthesis of triazole derivatives from the acetates of Baylis−Hillman adducts via the reaction with

Scheme 441



Scheme 442



sodium azide and terminal alkynes involving click chemistry as the key step under the influence of Cu catalyst (Scheme 444).

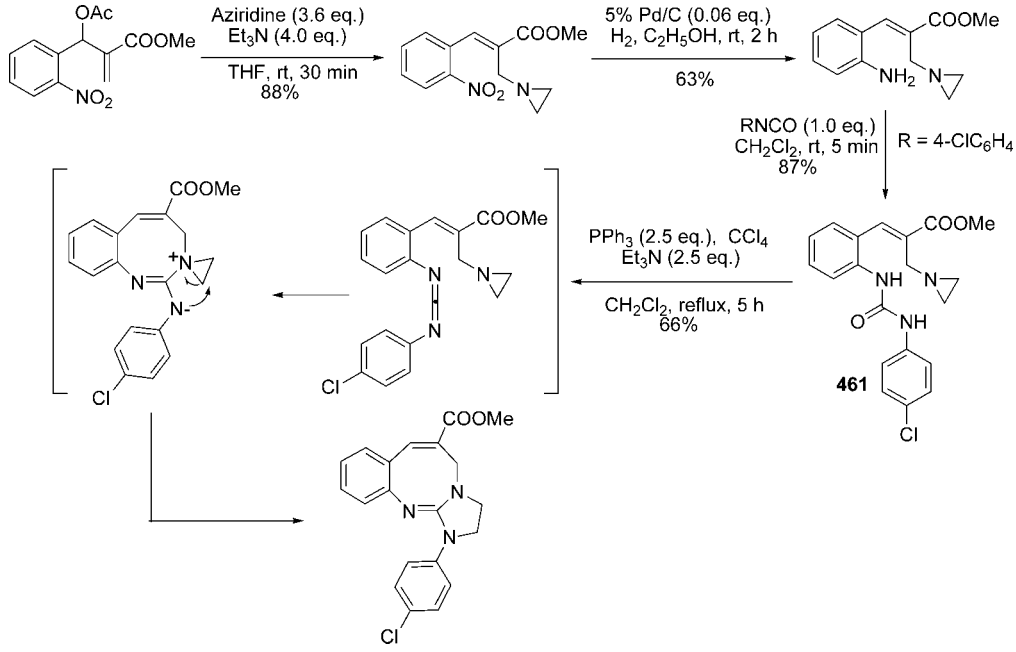
Batra and co-workers[949] have reported a simple synthesis of pyrimidine derivatives (**462**) from the acetates of Baylis−Hillman alcohols derived from acrylonitrile via the successive treatment with NH_3 (to provide allylamines) and alkyl isocyanate (to provide urea derivatives) followed by the reaction with base (Path A, Scheme 445). This strategy has been also extended to the pyrimidinethione framework (**463**) (Path B, Scheme 445). In the case of Baylis−Hillman alcohols, a similar reaction sequence failed to provide the expected 5-substituted pyrimidines because the key intermediate (**464**) expelled benzaldehyde to provide pyrimidine derivative **465** (Path C, Scheme 445). These compounds were tested for their antibacterial activities.

5-Substituted uracil derivatives (**466**, **467**), starting from Baylis−Hillman acetates, were synthesized by Kim and co-workers,[950] following the reaction sequence shown in Paths A and B (Scheme 446). One example is given. Subsequently, Batra and co-workers[951] also synthesized uracil derivatives (**467**) starting from Baylis−Hillman alcohols, following the reaction sequence shown in Path C, Scheme 446.

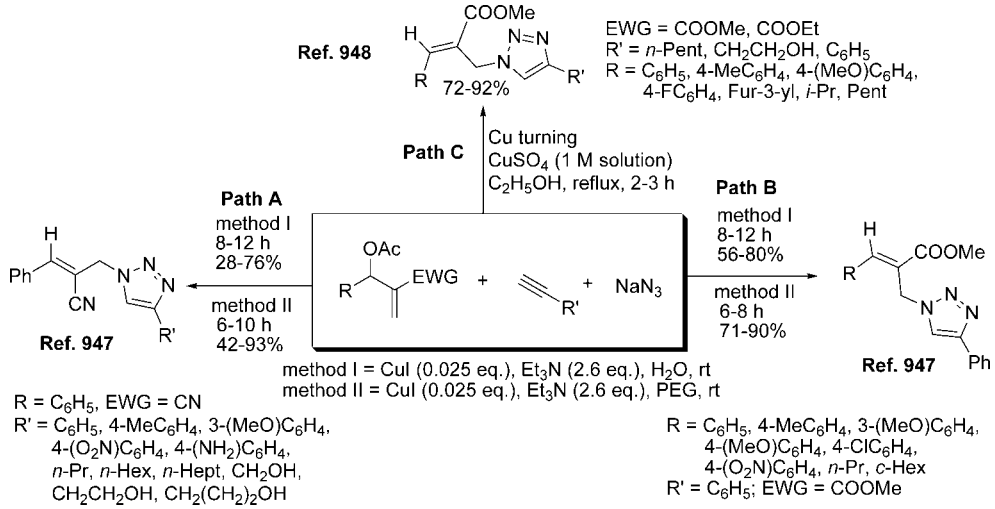
Batra and co-workers[952] have reported an efficient solid-phase synthesis of various fused pyrimidine derivatives from the acetates of Baylis−Hillman adducts derived from 5-isoxazolecarboxaldehydes via Michael addition with appropriate diamines followed by intramolecular cyclization with cyanogen bromide and then base-promoted cyclization according to the reaction sequence shown in Scheme 447.

Pathak and Batra[953] have developed a simple methodology for the synthesis of imidazolo-pyrimidinones and pyrimido-pyrimidinones from the Baylis−Hillman adducts derived from acrylonitrile according to Paths A−C, Scheme 448. Later on, Batra and co-workers[954] have transformed the acetate of the Baylis−Hillman adducts derived from methyl acrylate into 4-chloropyrimidinones and dihydropyrrolizinone frameworks (Path D, Scheme 448). Representative examples

Scheme 443



Scheme 444



are presented. Later on, Batra and co-workers extended a similar strategy for synthesis of 7-aminoimidazolopyrimidine (Path A, Scheme 449)[955] and pyrimido[2,1-*b*]quinazoline frameworks (Path B, Scheme 449).[956] Representative examples are presented.

Yu and co-workers[957] have developed a facile methodology for the synthesis of tetrahydropyridine fused 1,3-diazaheterocyclic compounds via the reaction between the rearranged acetates of Baylis−Hillman alcohols (derived from 2-aryl-1-nitroethylene and formaldehyde) with heterocyclic ketenaminals as shown in eq 117.

Kim and co-workers[958] have transformed the acetates of Baylis−Hillman adducts into benzodiazepine derivatives via treatment with 1,2-diaminobenzene followed by hydrolysis and cyclization. A representative example is shown in Scheme 450.

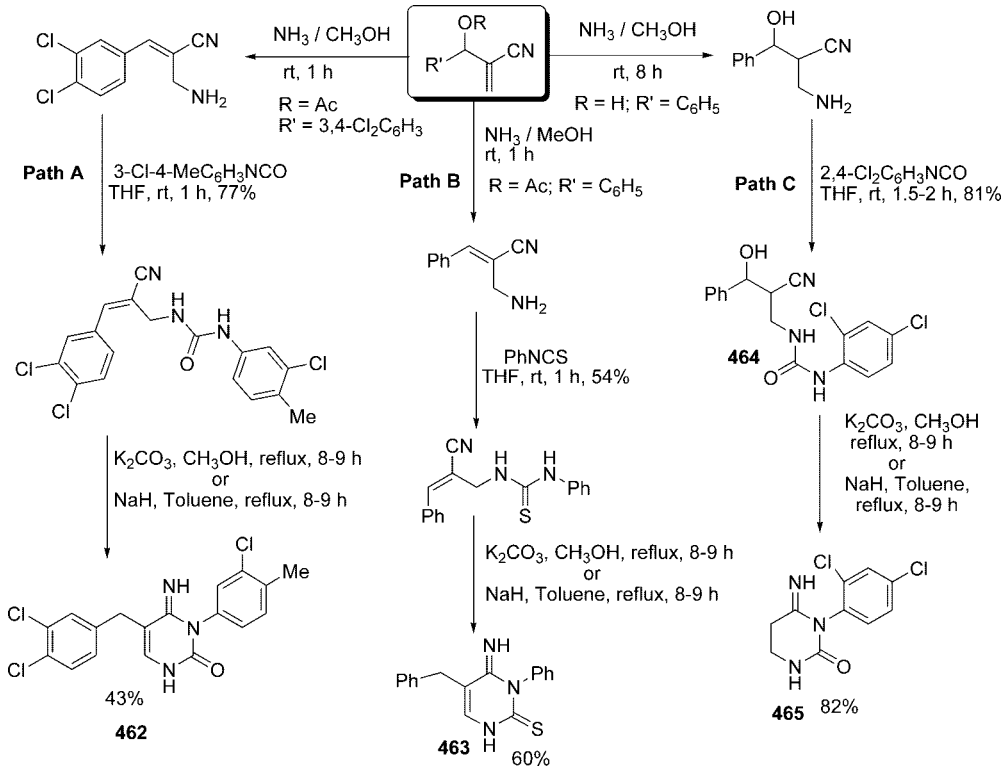
Later on, Pathak and Batra[959] extended a similar strategy to the preparation of 3-methylene-4-aryl-1,3,4,5-tetrahydrobenzo-[*b*][1,4]diazepin-2-ones (**468**) and 3-arylmethylene-4,5-dihydro-3*H*-benzo[*b*][1,4]diazepin-2-ylamines (**469**) according to Scheme 451.

Kim and co-workers[960] have developed a facile synthesis of 4-arylidene-2-substituted isoxazolidin-5-one derivatives starting from Baylis−Hillman acetate via the treatment with alkyl hydroxylamine followed by cyclization, according to the reaction sequence shown in Scheme 452.

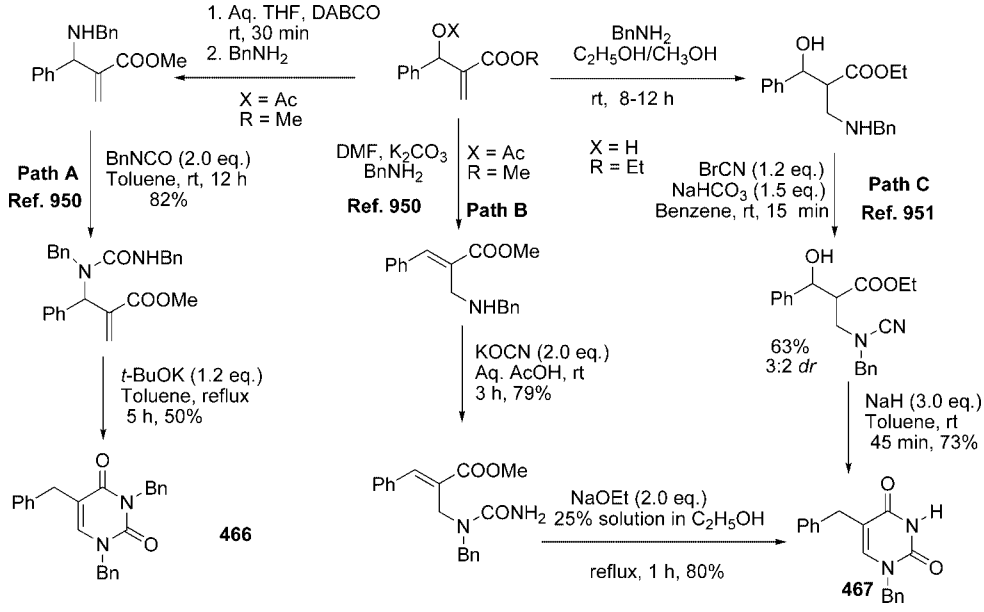
Fisera and co-workers have performed 1,3-dipolar cycloaddition reactions of Baylis−Hillman alcohols with *C*-phenyl-N-methylnitrone (**470**). The reaction was found to be completely regioselective and also highly diastereoselective (along with minor amounts of other isomers). One example is shown in Scheme 453.[961] They have also noticed that TBDPS-protected Baylis−Hillman alcohols provided complete stereoselectivity, although the resulting product was obtained in low yield (Scheme 453).[961] Subsequently, they[962] extended this methodology to chiral nitrone (**471**) to provide the resulting adduct with high diastereoselectivity. When they used TBDMS-protected nitrone (**471**), the product was obtained as a mixture of two diastereomers. Representative examples are given in Scheme 454.

Das and co-workers[963] have reported an efficient methodology for the synthesis of isoxazolines and polyfunctional

Scheme 445



Scheme 446



isoxazolines via the treatment of aldoximes with Baylis−Hillman alcohols under the influence of diacetoxy iodobenzene (DIB) (Path A, Scheme 455). Later on, it was found that ceric ammonium nitrate (CAN) was also effective to perform the same reaction (Path B, Scheme 455).[964]

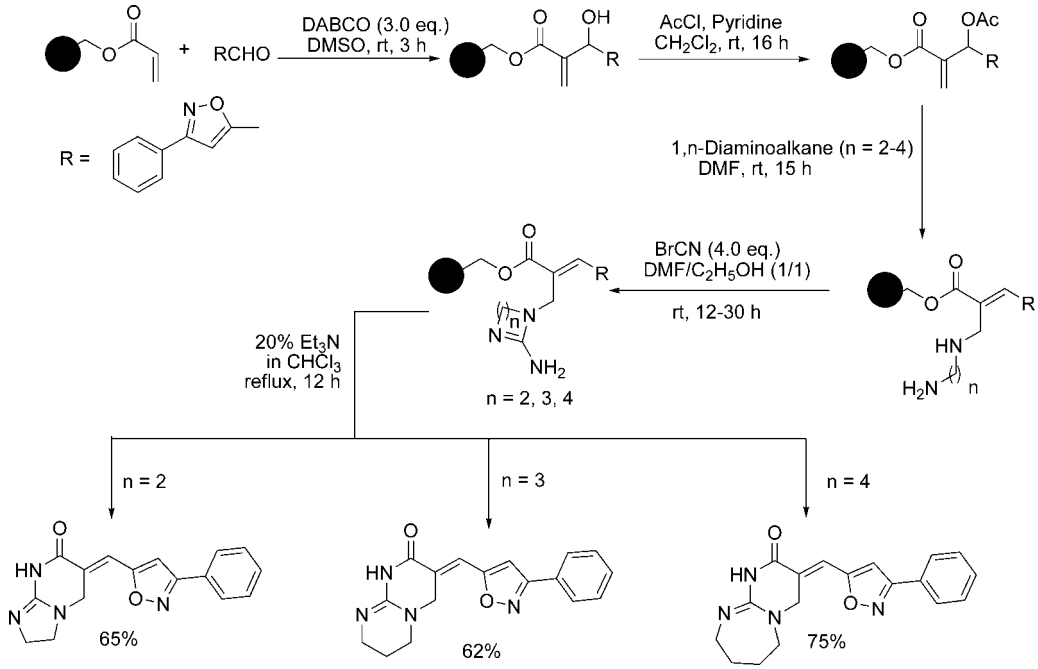
Batra and Roy[965] have reported a facile methodology for the synthesis of isoxazole-annulated heterocyclic compounds, 5,8-dihydroisoxazolo[4,5-*c*]azepin-4-ones, from the acetates of Baylis−Hillman alcohols (generated from 3-aryl-5-formyl-isoxazole-4-carboxylate) following the reaction sequence as described in Scheme 456.

Kim and co-workers[966] have reported a simple methodology for the synthesis of benzo[3,4]azepino[2,1,*a*]isoindole and 4-oxa-9*a*-azafluorene derivatives starting from the acetates of the Baylis−Hillman adducts following the reaction sequence shown in Scheme 457 (one example is presented).

Shang and co-workers[967] reported an interesting cycloaddition of soluble polymer-supported Baylis−Hillman allyl alcohols with nitrile oxides (generated *in situ*) to provide the isoxazole derivative as a mixture of *syn* and *anti* isomers (Scheme 458).

The Baylis−Hillman alcohols derived from acrylonitrile and aryl aldehydes have been conveniently transformed by Batra and co-workers into 5-substituted-2-amino-1,4,5,6-teterahydropyrimidines via reaction with amine followed by reduction and treatment with BrCN according to Scheme 459.[968] The product was further converted into a bicyclic

Scheme 447



imidazole−pyrimidione framework (Scheme 459). One example is given.

Comes-Franchini and co-workers[969] reported 1,3-dipolar cycloaddition of *Z*-α-phenyl-*N*-methylnitrone with chiral allyl fluoride derived from the major *anti*-isomer adduct obtained via the Baylis−Hillman reaction between methyl acrylate and (*S*)-2-*O*-benzylpropanal, which provided fluorine-containing isoxazolidines, following the reaction sequence shown in Scheme 460. Subsequently, these isoxazolidines were converted into aminopolyol derivatives via reduction with LAH.

An interesting stereoselective synthesis of spiro-fused (C-5)isoxazolino (C-3)quinolin-2-one derivatives via the 1,3-dipolar cycloaddition of Baylis−Hillman adducts (obtained from 2-nitrobenzaldehyde and acrylates) with *in situ* generated nitrile oxide followed by reductive cyclization as described in Path A, Scheme 461, was reported by Batra and co-workers.[970] Cycloaddition reaction of *in situ* generated nitrile imines with Baylis−Hillman adducts provided spiro-fused (C-3)pyrazolino-(C-3)quinolin-2-one derivatives as described in Path B, Scheme 461. Similar cycloaddition reactions of 2-methylenealkanoates (**472**) prepared from Baylis−Hillman acetates, with *in situ* generated nitrile oxide and nitrile imines provided spiro-fused (C-5)isoxazolino(C-3)quinolin-2-one derivatives (Path C, Scheme 461) and (C-3)pyrazolino-(C-3)quinolin-2-one derivatives, respectively (Path D, Scheme 461).

The Baylis−Hillman acetates derived from thiazole-2-carboxaldehyde were transformed into pyrrolo[2,1,*b*]thiazoles by Song and Lee[971] following the reaction sequence shown in Scheme 462.

A facile conversion of Baylis−Hillman bromides into allylic thiocyanates (Path A) and 1,3-thiazin-4-one derivatives (Path B) via the reaction with sodium thiocyanate and thiourea, respectively, was described by Sa and co-workers (Scheme 463).[972]

Bakthadoss and Murugan[973] reported a facile synthesis of (*Z*)-3-arylidene-2,3-dihydrobenzo-[*b*][1,4]thiazepin-4-(5*H*)-ones via the treatment of Baylis−Hillman bromides with 2-aminothiophenol, followed by cyclization. It is interesting to note that S-alkylation occurs in the first step (Scheme 464).

11. Total Synthesis of Natural Products, Synthons, and Bioactive Molecules Using Baylis−Hillman Adducts and Derivatives

Almeida and Coelho[974] have developed a stereoselective synthesis of *N*-Boc-dolaproine following the reaction sequence shown in Scheme 465. The key step involved in this strategy is the Baylis−Hillman reaction between N-protected prolinal and methyl acrylate.

Feltrin and Almeida[975] have developed a simple synthesis of a potent and orally available inhibitor of ACE, captopril, from the Baylis−Hillman alcohol derived from *N*-acryloylproline (**473**) via the reaction with formaldehyde, following the reaction sequence shown in Scheme 466.

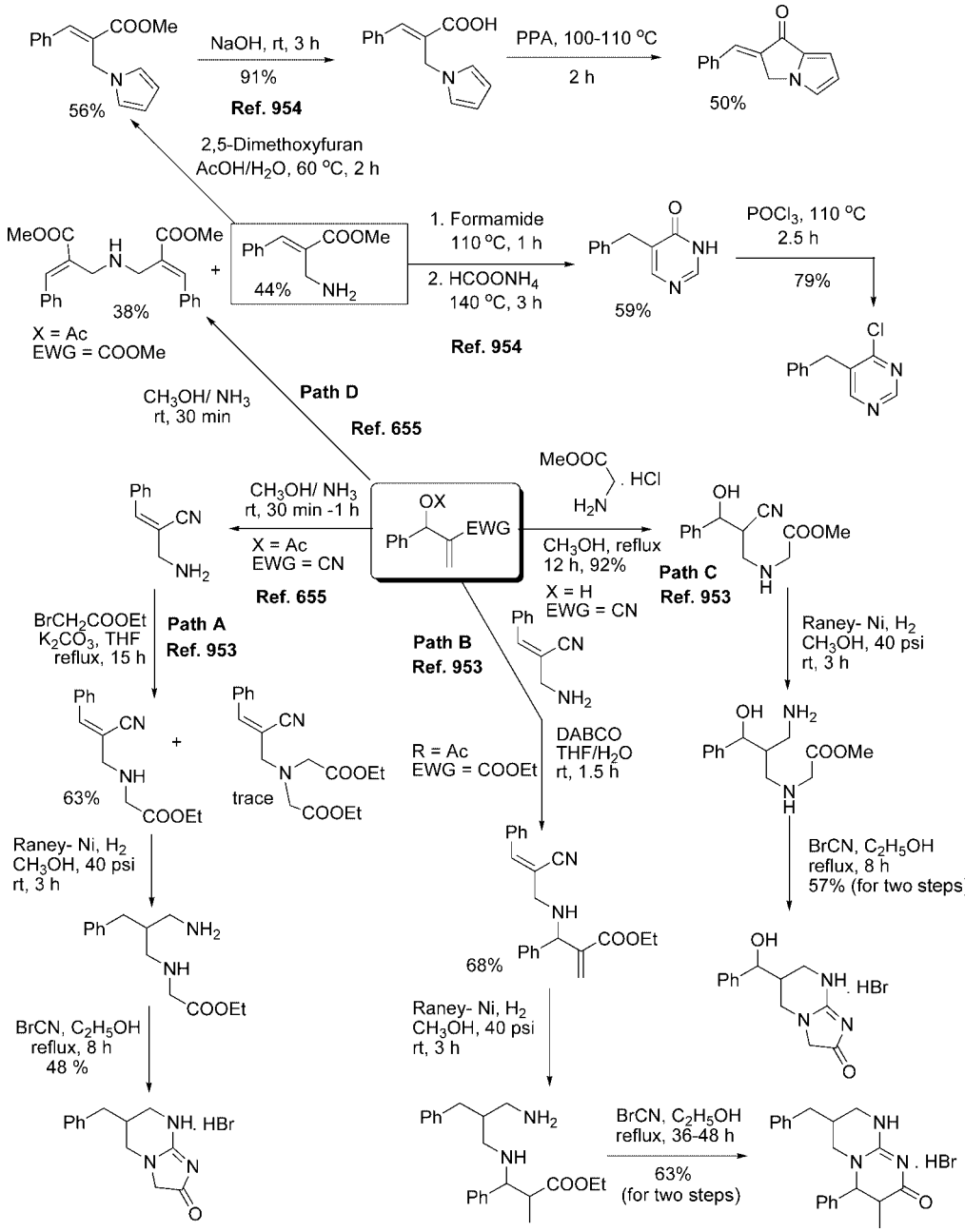
Mateus and Coelho[976] have reported a simple stereoselective synthesis of chloramphenicol (**474a**), fluoramphenicol (**474b**), and thiamphenicol (**474c**) from the key intermediates **475**, which were obtained from the Baylis−Hillman adducts derived from appropriate aldehydes and methyl acrylate, involving Curtius rearrangement and hydroboration as the key steps, following the reaction sequence shown in Scheme 467.

Tadano and co-workers[977] have reported the synthesis of the upper-half (**476**) of (+)-tubelactomicin A (**477**) using the Baylis−Hillman adduct derived from aldehyde **478** and methyl acrylate as the starting material. Subsequently, this upper-half of the segment was coupled with the lower-half using Stille coupling to provide (+)-tubelactomicin A (**477**), a 16-membered macrolide antibiotic (Scheme 468).

Chapuis and co-workers[978] have reported a simple synthesis of *cis*-hedione and methyl jasmonate, following the reaction sequence shown in Schemes 469 and 470, respectively, employing the Baylis−Hillman reaction and Claisen ortho ester rearrangement as the key steps.

The Baylis−Hillman alcohol derived from cyclopent-2-enone via the reaction with formaldehyde was transformed

Scheme 448



into (±)-sarkomycin, a bioactive natural product, in a simple reaction sequence as shown in Scheme 471 by Kar and Argade.[979]

Doutheau and co-workers[980] have synthesized racemic trifluoromethyl analog of (4*S*)-4,5-dihydroxy-2,3-pentanedione (DPD) following the reaction sequence shown in Scheme 472, involving the Baylis−Hillman reaction as the key step. They have also developed asymmetric synthesis of the trifluoromethyl analog of DPD using chiral acrylamide (**138**), prepared from the camphor-derived Oppolzer's reagent, as activated alkene according to the reaction sequence shown in Scheme 473.

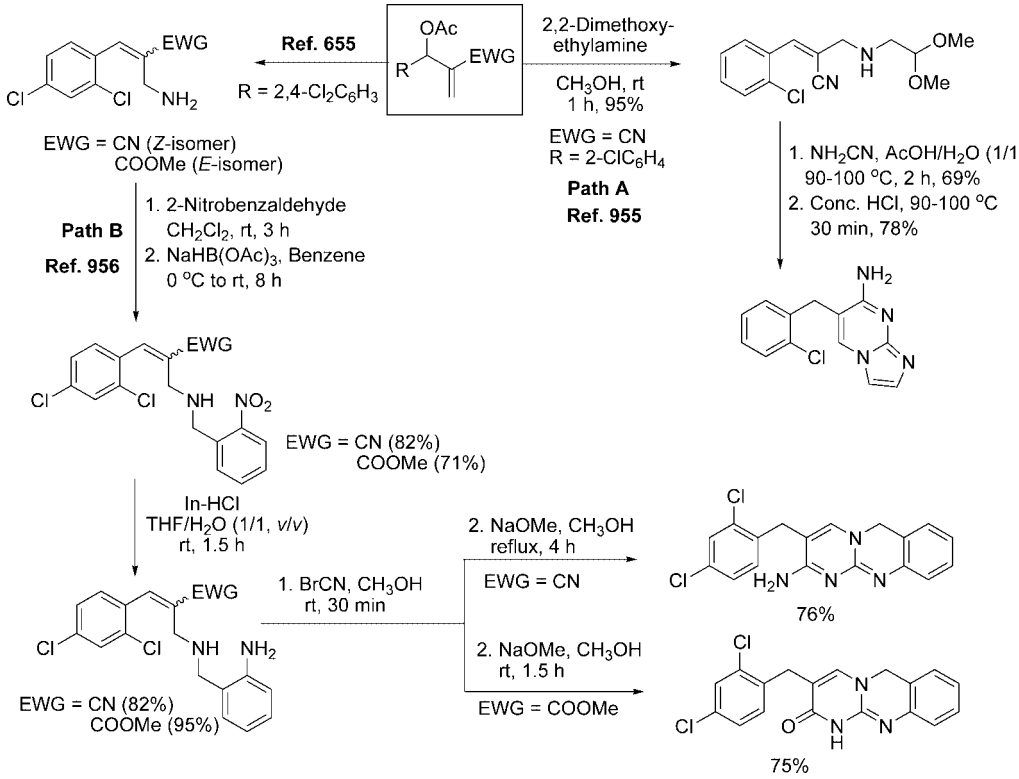
Seck et al.[981] have reported a formal synthesis of the C1−C11 fragment **479** of caribenolide I, a potent antitumor macrolide, isolated from a marine dinoflagellate *Amphidinium* sp, following the reaction sequence shown in Scheme 474. In this reaction sequence, Baylis−Hillman reaction between 3-parametoxylbenzyloxypropanal and methyl acrylate is the key step.

Brase and co-workers[982] have developed a facile route for synthesis of tetrahydroxanthenone mycotoxins via the Baylis−Hillman-type reaction between substituted salicylaldehyde and 4-hydroxycyclohex-2-enone as the key step. They have also extended this strategy to the total synthesis of the secondary metabolite diversonol in racemic form in 14 synthetic steps following the reaction sequence shown in Scheme 475.

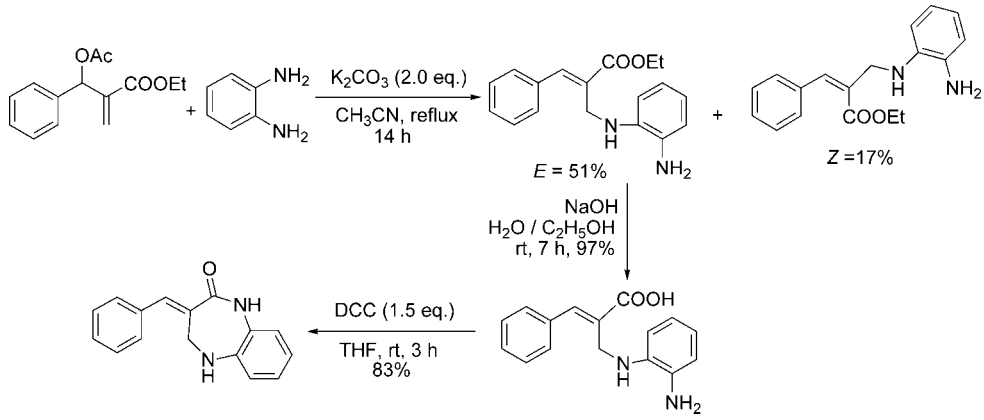
Jogireddy and Maier[983] have developed a novel route for total synthesis of luminacin D and its 6′,8′-epimer. In this strategy, the key intermediate, carbohydrate-sector aldehyde **480**, was prepared from the Baylis−Hillman alcohol methyl 3-hydroxy-2-methylenepentanoate (Scheme 476).

Lei and Porco[984] have developed a facile methodology for total synthesis of the diazobenzofluorene antibiotic (−)-kinamycin C, starting from the Baylis−Hillman adduct derived from the substituted quinine monoketal and formaldehyde, according to the reaction sequence shown in

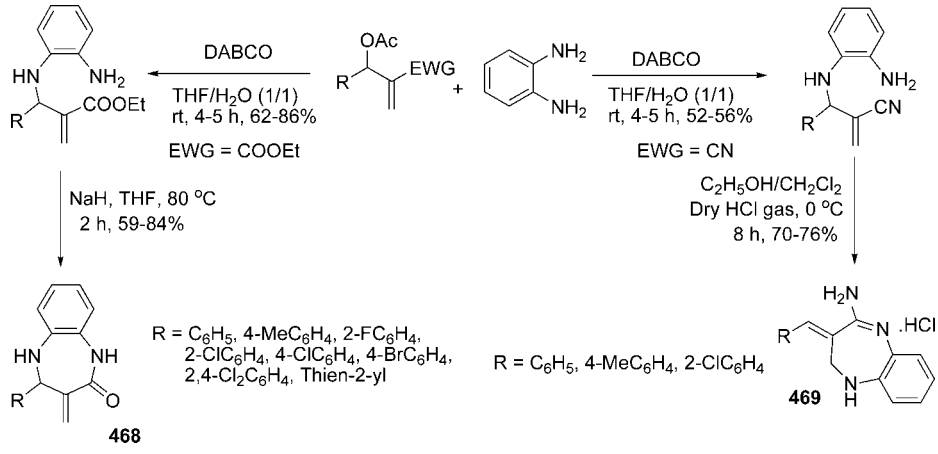
Scheme 449



Scheme 450



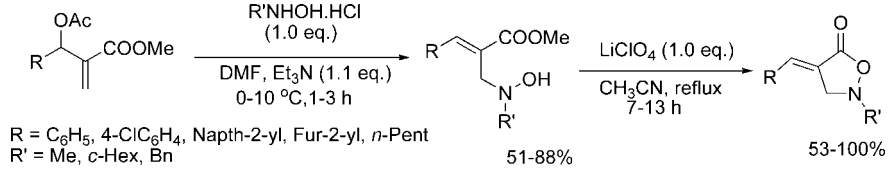
Scheme 451



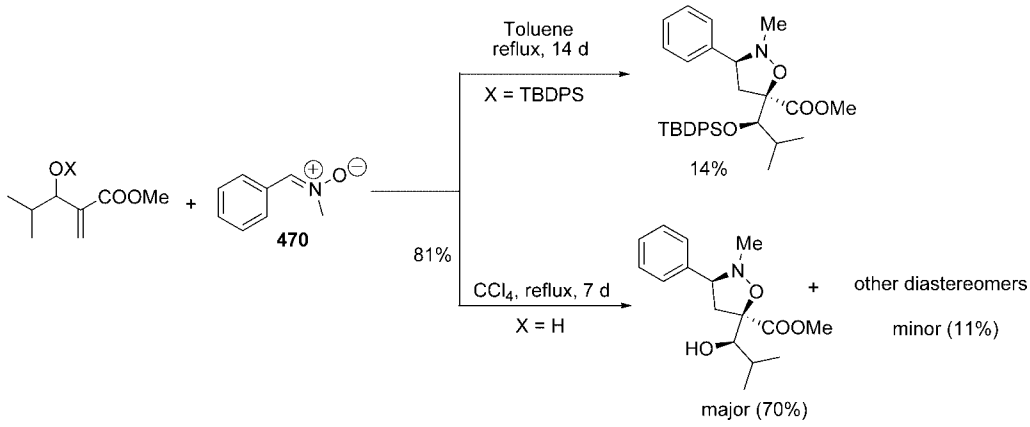
Scheme 477. The tartrate [(+)-DIPT]-mediated asymmetric nucleophilic epoxidation is the key step in this strategy.

Kamal and co-workers[985] have developed asymmetric synthesis of (*R*)- and (*S*)-umbelactones, following the reaction

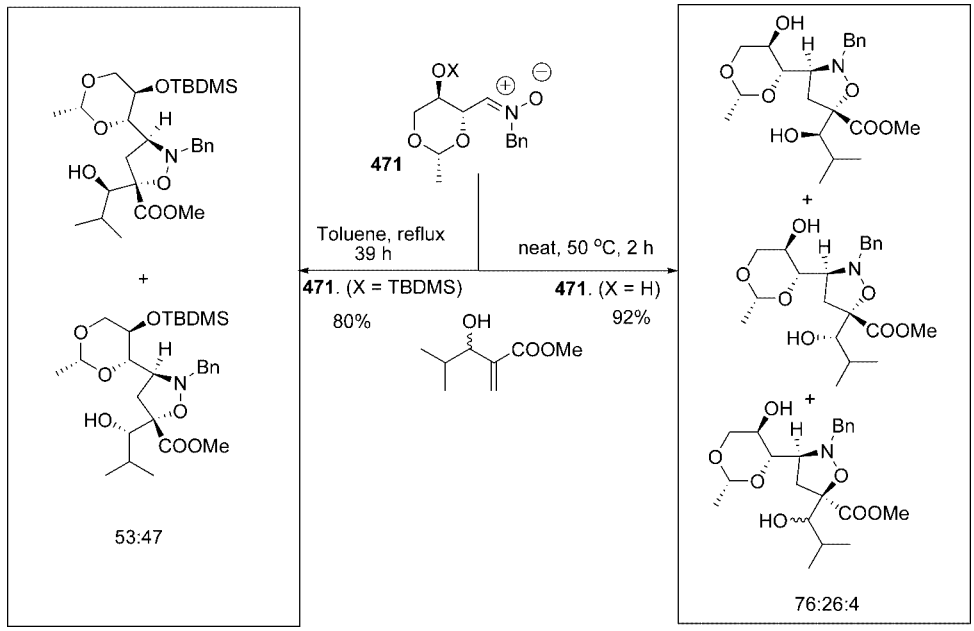
Scheme 452



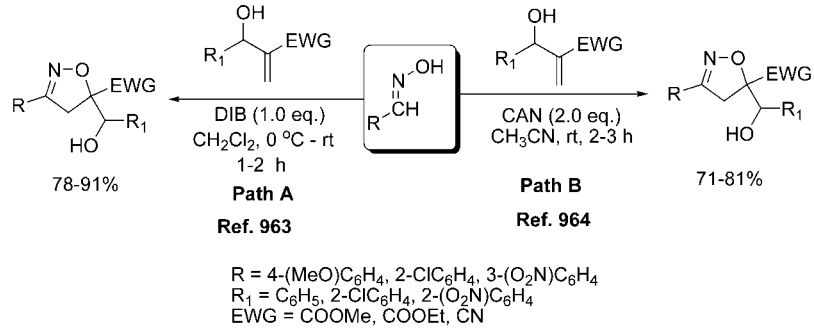
Scheme 453



Scheme 454



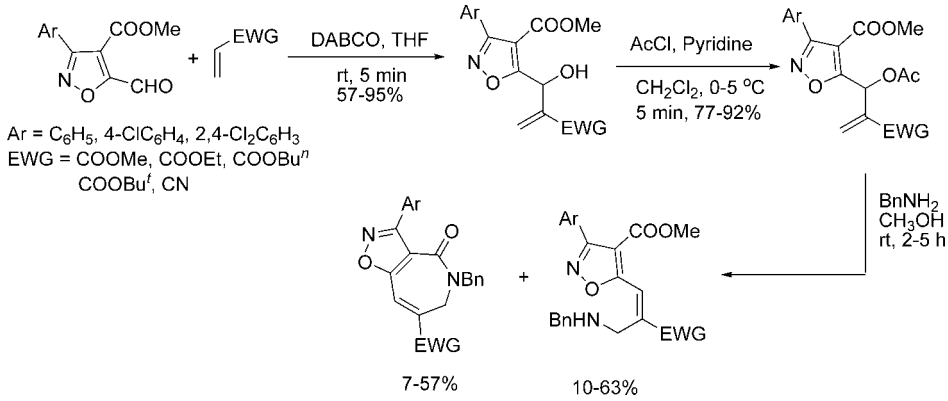
Scheme 455



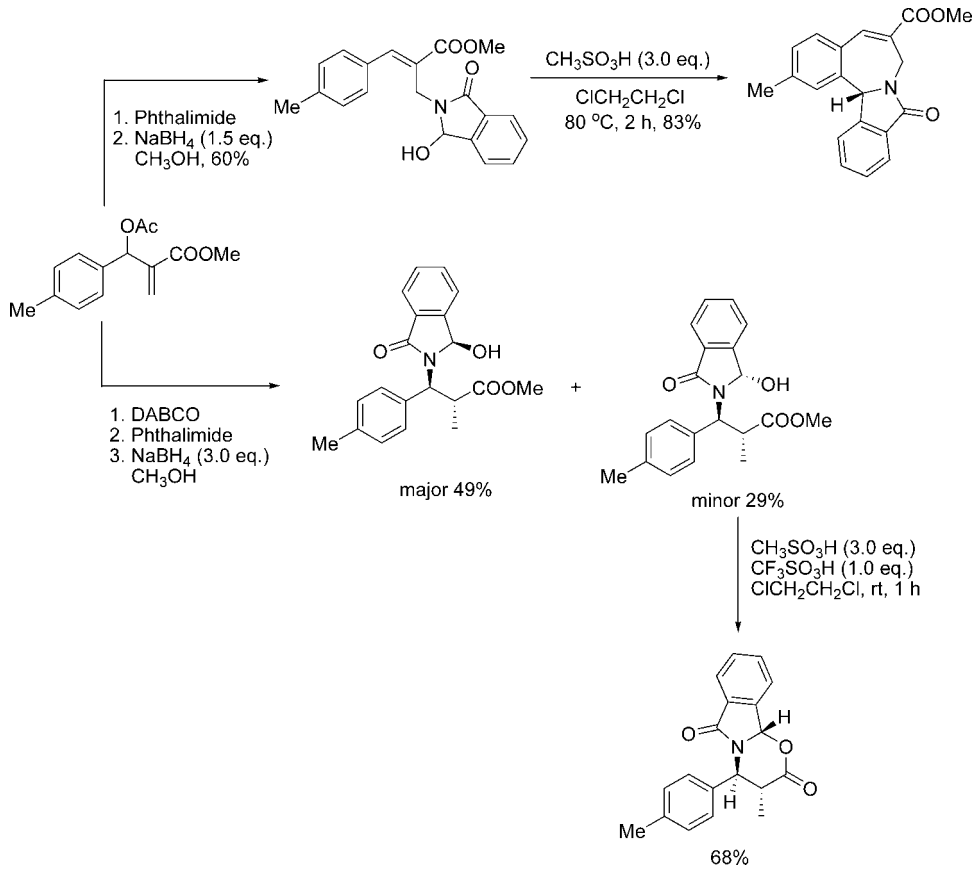
sequence shown in Scheme 478, employing the Baylis−Hillman reaction, enzymatic resolution, and ring-closing metathesis (RCM) as the key steps.

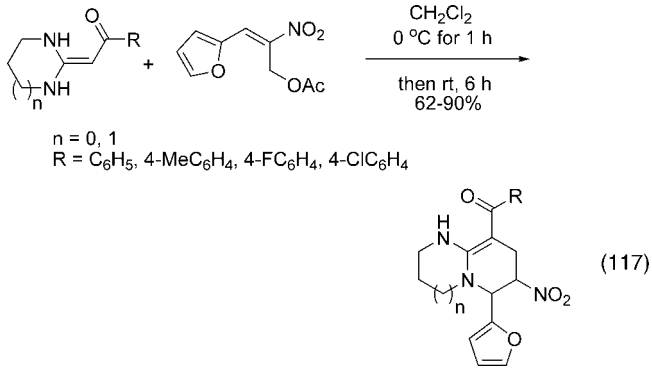
Marquez and Comin,[986] during their studies to understand the binding recognition by herpes thymidine kinase (HSV-tk), have synthesized a novel bicyclic nucleoside using the

Scheme 456



Scheme 457





(117)

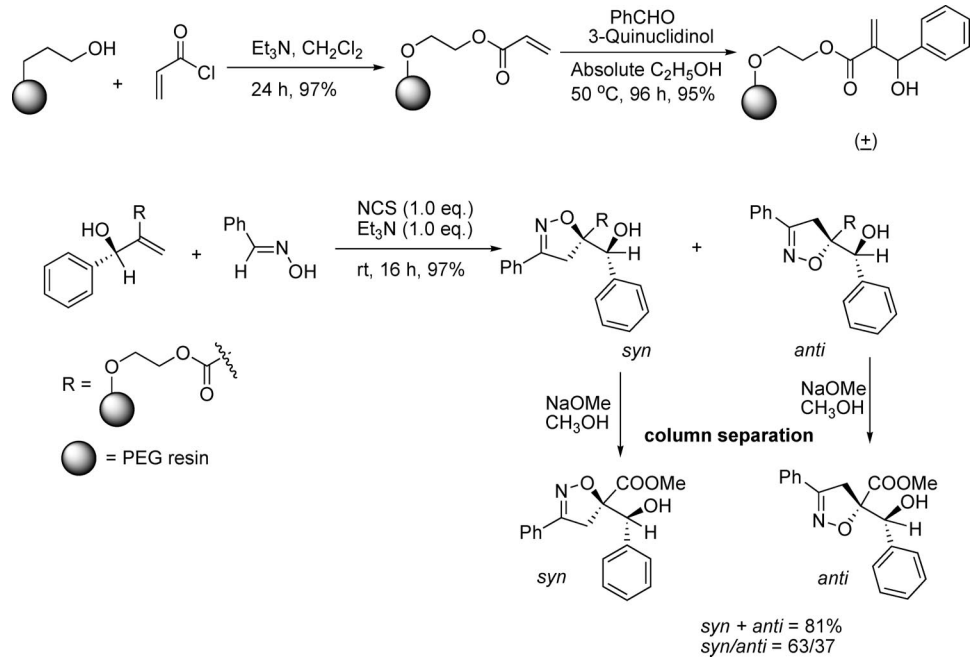
Baylis−Hillman reaction as the key step, following the reaction sequence shown in Scheme 479.

During the investigation toward development of a simple synthesis of the sordarin core framework, Ciufolini and co-workers[987] synthesized the tricyclic frameworks **483**−**485** following the reaction sequence shown in Schemes 480 and 481 starting from the Baylis−Hillman adducts obtained via the reaction of the aldehydes **481** and **482**, respectively, with acrylonitrile.

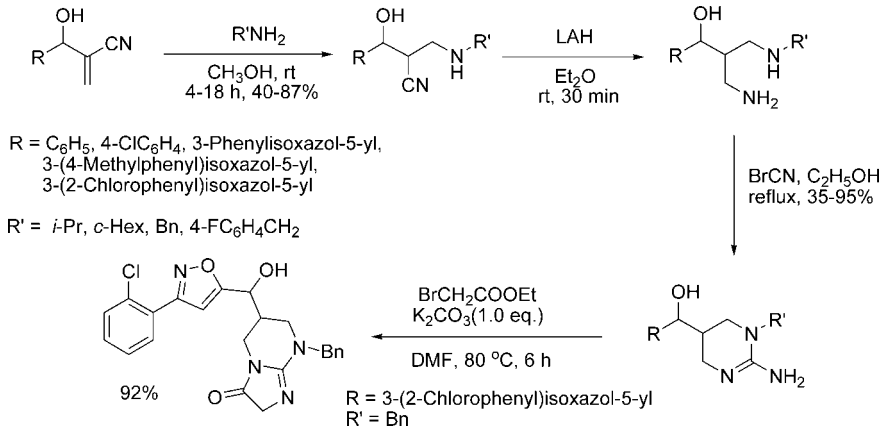
Doddi and Vankar[988] have described efficient methods for the synthesis of imino sugars **486** and **487**, which are moderate inhibitors of β-galactosidase, α-galactosidase, and α-mannosidase, according to the reaction sequence shown in Scheme 482. The key steps involved in this methodology are Baylis−Hillman reaction followed by regiospecific amination, ring-closing metathesis, and diastereospecific dihydroxylations.

Coelho and co-workers[989] have developed total synthesis of (±)-bupropion, following the reaction sequence shown in Scheme 483, starting from the Baylis−Hillman adduct

Scheme 458



Scheme 459



obtained via the reaction of 3-chlorobenzaldehyde with methyl acrylate.

Ubukata and co-workers[990] reported an interesting synthesis of (+)-6-tuliposide B starting from 2,3,4,6-tetra-*O*-acetyl-1-*O*-(2-triethylsilylethyl)-β-D-glucopyranoside, following the reaction sequence shown in Scheme 484. This strategy involves the Baylis−Hillman reaction between 2-trimethylsilylethyl (TMSET) glucoside derivative (**488**) and 2-(*tert*-butyldimethylsilyloxy)acetaldehyde as the key step.

Webber and Krische[991] recently reported an interesting stereocontrolled formal synthesis of (±)-quinine and (±)-7-hydroxyquinine involving the intramolecular Baylis−Hillman reaction of the substrate **489** as the key step (Scheme 485).

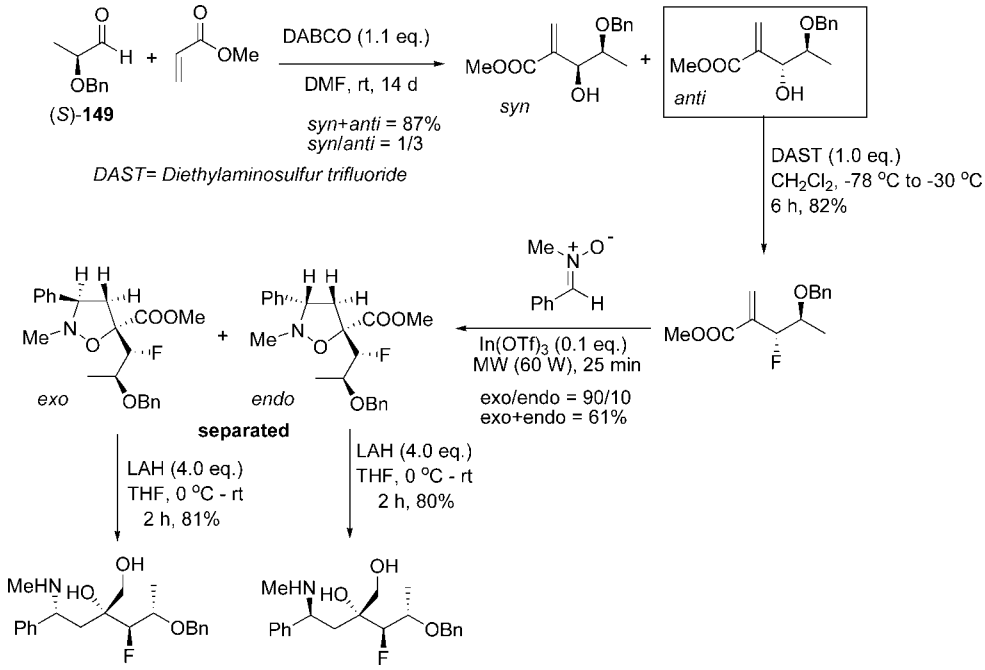
Roe and Stockman[992] have reported a facile synthetic method for the total synthesis of anatoxin-a and homoanatoxin salts from a common intermediate **490**, obtained via intramolecular Baylis−Hillman-type reaction of the substrate **491** as shown in Scheme 486.

12. Mechanism of Baylis−Hillman Reaction: An Intellectual Challenge in Chemistry

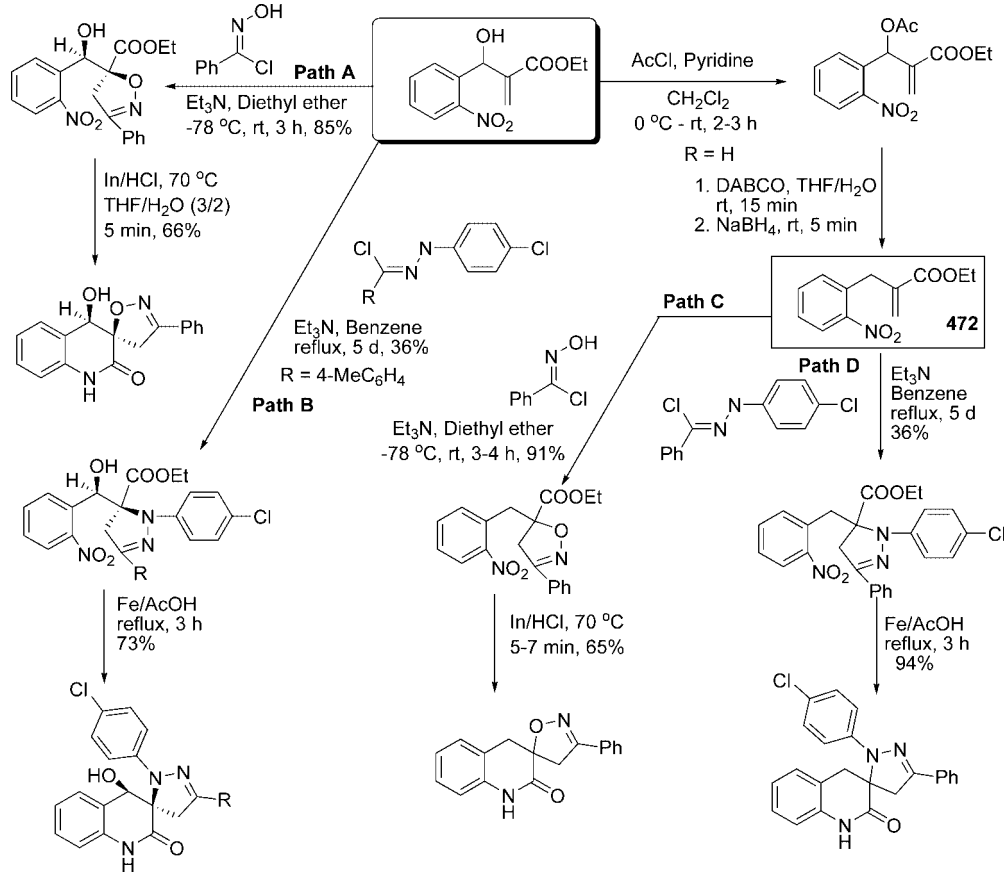
The growth and success of any reaction depend on understanding the mechanistic pathway(s) in which the reaction proceeds and also on the intellectual challenges involved in understanding the mechanism. Normally, all reactions prefer to proceed through the lowest energy transition states among the various possible states (depending on the nature of the reactants and reagents used) thus involving the easiest way of reorganization of atoms or groups present in the reaction leading to the formation of the product (Figure 70).[1,2] Sometimes, the mechanism for simple reactions, in fact, turns out to be the most complicated one, because of large variations of parameters involved, thus creating more complexities in understanding the pathway. The Baylis−Hillman reaction is one such simple and highly useful reaction whose mechanism is not yet completely understood due to large variations of parameters involved. This section is aimed at the presentation of salient features of various efforts from several research groups to understand the mechanism of Baylis−Hillman reaction, and also another major objective of this section is to highlight the challenges involved in understanding the mechanism of this reaction with an invitation to chemists to come out with the most appropriate solution.

The various parameters of the Baylis−Hillman reaction, which generate many directions of flexibilities, are listed in

Scheme 460

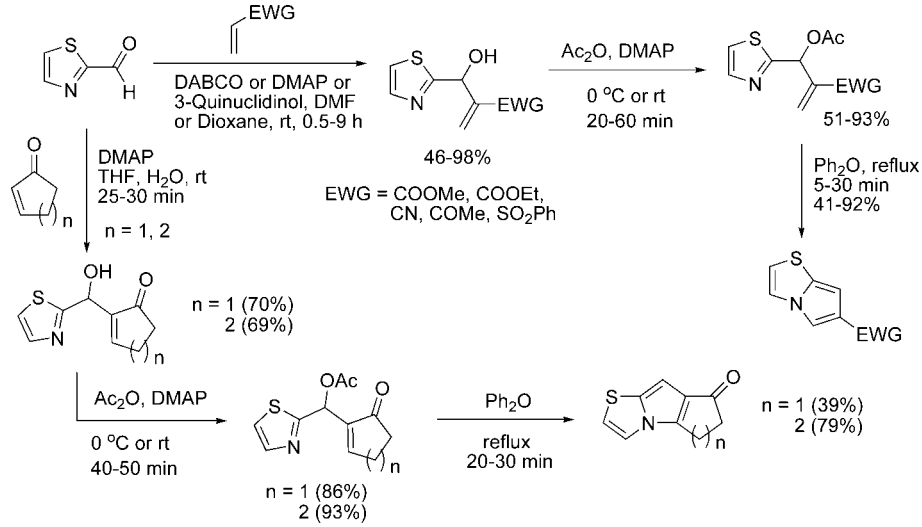


Scheme 461

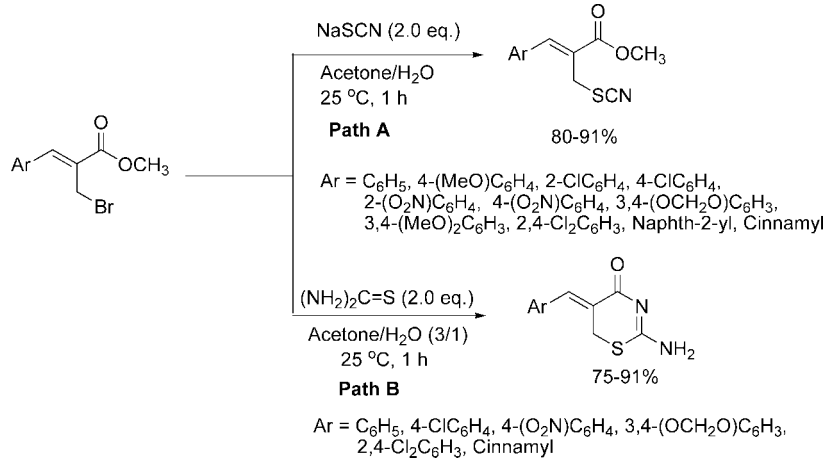


the following: (i) large variations in activated alkene and electrophile components, large and diverse classes of catalysts, and several combinations of these essential components in performing the coupling reactions; (ii) influence of solvent, pressure, temperature, and additives on the rate of the reaction; (iii) large variations involved in designing asymmetric versions of Baylis−Hillman reaction, that is, having chirality in the activated alkene, electrophilic components, catalysts, or additives and using them in a number of combinations; (iv) various ways of designing substrates with different combinations of activated alkene and electrophile components for performing intramolecular versions and also its asymmetric versions; and finally (v) large variations in selecting various combinations of essential components, additives, solvents, etc. (Figure 71). Several interesting publications[47,48,64a,74,80,100,101,103,165,304,306,329,428,993−1018] appeared

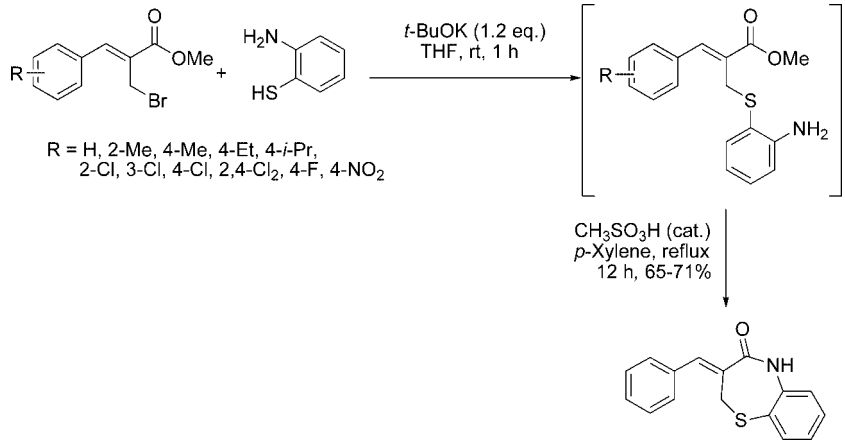
Scheme 462



Scheme 463



Scheme 464

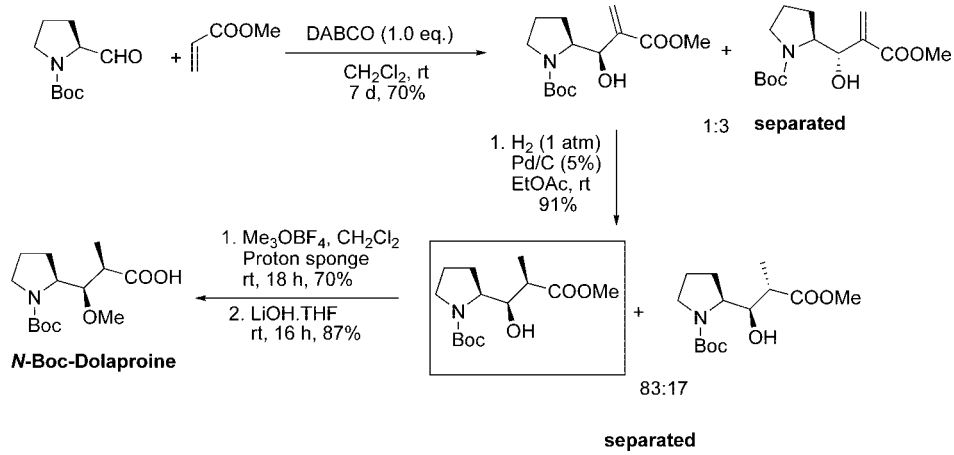


during the last 25 years addressing the problem of mechanism of the Baylis−Hillman reaction.

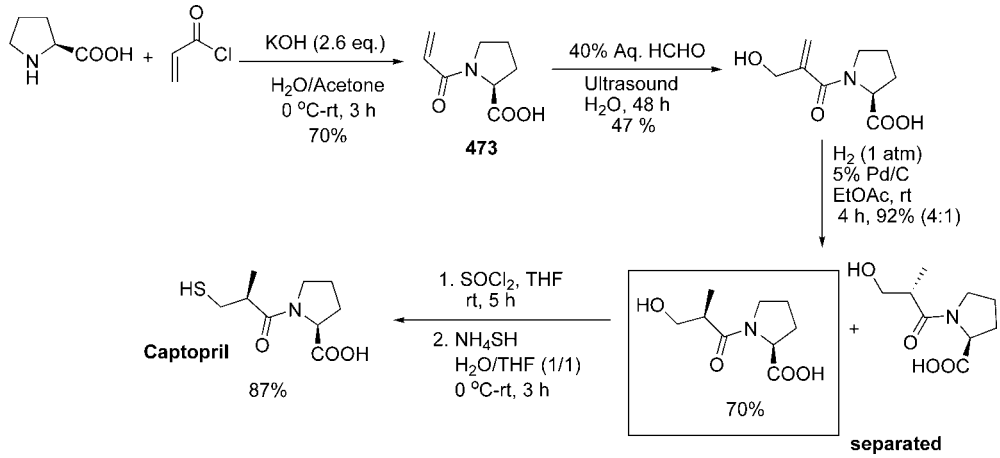
12.1. Amine-Catalyzed Baylis−Hillman Reactions

Based on the initial studies of various workers,[21,993−995] the most generally accepted mechanism of the amine-catalyzed reaction, considering the coupling of methyl vinyl ketone (as an activated alkene) with benzaldehyde (as an electrophile) under the catalytic influence of DABCO as a model case, is presented in the Scheme 487 (Path I). The first step in this catalytic cycle is believed to involve the nucleophilic Michael addition of DABCO to methyl vinyl ketone to produce a zwitterionic enolate **A**. Subsequent aldol reaction of the enolate **A** with benzaldehyde produces zwitterion **A1**, which in fact releases the catalyst after proton migration to provide the desired multifunctional molecules. In the case of very reactive activated alkenes such as MVK, zwitterionic enolate **A** adds onto MVK itself (behaves as an

Scheme 465



Scheme 466



electrophile) in Michael fashion to produce zwitterion **A2**, which provides the Michael-type dimer as the minor product after the release of the catalyst (Scheme 487, Path II).

It should be mentioned here that Hoffmann and Rabe,[47] as early as in 1983, proposed the possible formation of zwitterionic intermediates (**A3**, **A4**, and **A5**, which are generated via the Michael reaction of the catalyst onto the activated alkene followed by the nucleophilic attack of the enolate formed *in situ* onto the aldehyde), which are in equilibrium. Subsequent antiperiplanar elimination of the catalyst provides the Baylis−Hillman product (Scheme 488).

Hill and Isaacs[993] performed the coupling between acrylonitrile and aldehydes and proposed that the rate-determining step (rds) is an aldol-type reaction between zwitterionic enolate and the electrophile leading to the formation of multifunctional molecules (Scheme 489) on the basis of pressure dependence, rate, and kinetic isotope effects in these reactions.

Drewes and co-workers[428] isolated the quaternary salt of DABCO and confirmed the structure by single-crystal X-ray data during their investigations on the intramolecular Baylis−Hillman reaction of 2-acryloyloxybenzaldehyde under the influence of DABCO in CH_2Cl_2 (Scheme 490).

Drewes and co-workers[103] demonstrated that the Baylis−Hillman reactions are faster when 3-hydroxyquinuclidine is used as catalyst. This rate acceleration may be due to intramolecular hydrogen bonding as shown in Scheme 491. They have also examined the Baylis−Hillman reaction in presence of methanol. Subsequently, our research group[48] demonstrated that terminal hydroxyalkyl acrylates react faster with aldehyde than the corresponding alkyl acrylates without having the terminal hydroxyl group (Scheme 492) thus indicating the influence of the terminal hydroxyl group, which might stabilize the enolate or the product (**A6**) via hydrogen bonding (as in the case of Drewes observation as shown in Scheme 491).

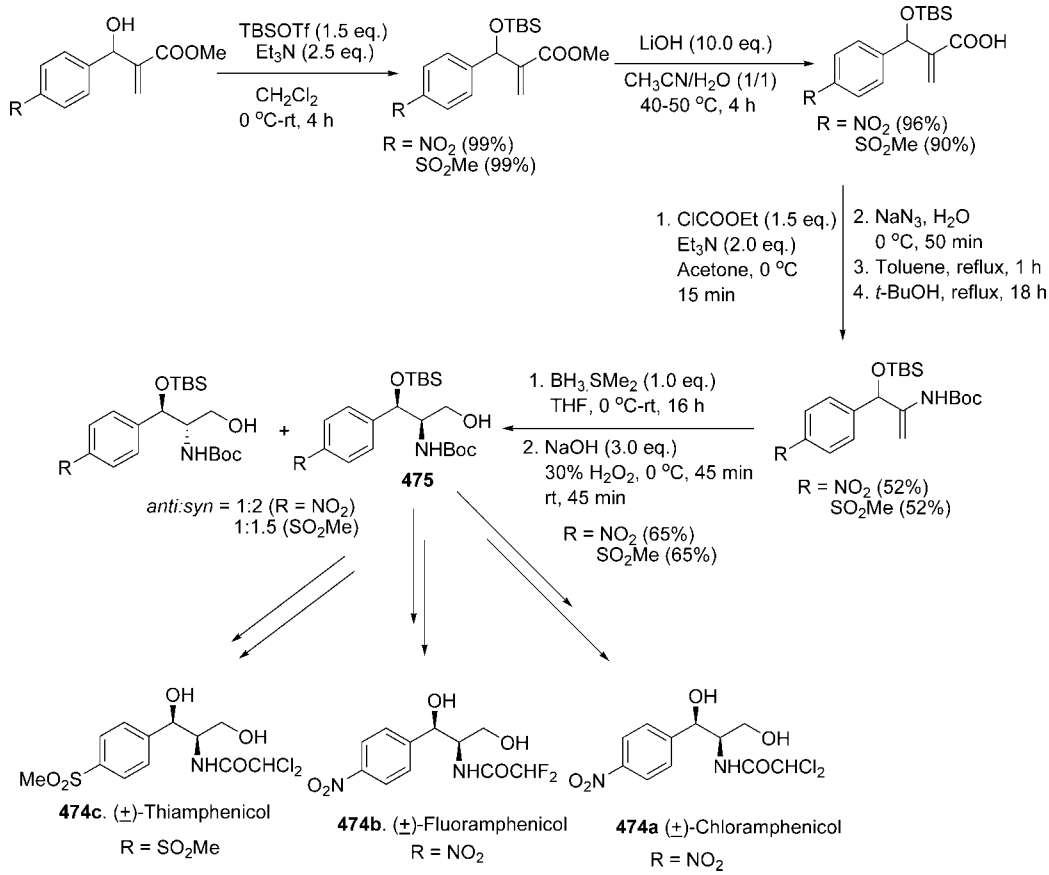
Our research group[100,101] has successfully employed, for the first time, allyl halides (derived from the corresponding Baylis−Hillman adducts of methyl acrylate and MVK) as electrophiles in the Baylis−Hillman reaction with acrylonitrile under the influence of excess DABCO (2.0 equiv) providing 3-substituted functionalized 1,4-pentadienes (Scheme 493). It is understood that this reaction proceeds through the formation of quaternary salt **A7** (isolated)[525] followed by alkylation and elimination. It is also interesting to note that similar reaction with simple allyl bromide (3-bromoprop-1-ene) or other allyl bromides did not work.

12.2. Dioxane Intermediates

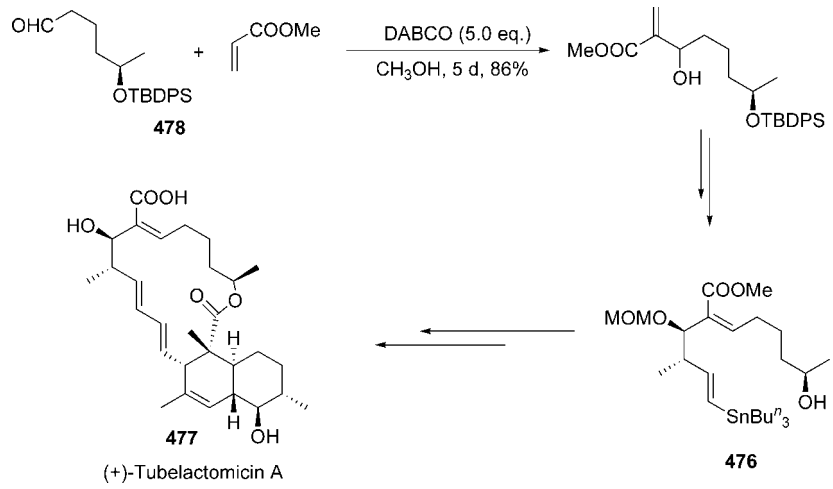
Drewes and co-workers[306] have reported the formation and isolation of 2,6-dialkyl-5-methylene-1,3-dioxan-4-ones in the Baylis−Hillman reaction of chiral activated alkene with aldehydes following the reaction sequence shown in Scheme 494. Formation of 1,3-dioxane derivatives clearly indicates that aldehyde reacts with the *in situ* formed Baylis−Hillman adducts. This information, in fact, is the key for understanding the mechanism of this reaction.

Later on, Leahy and co-workers[304] also reported the isolation of enantiomerically enriched dioxane derivatives during their elegant work on the asymmetric version of

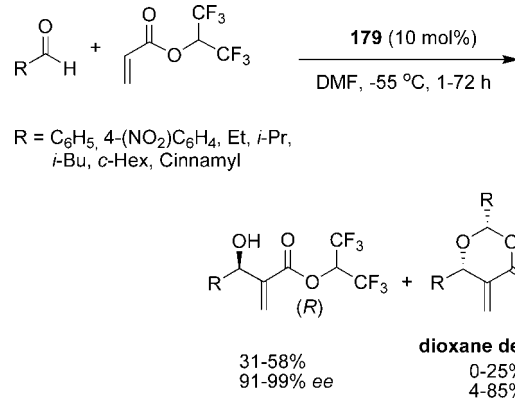
Scheme 467



Scheme 468

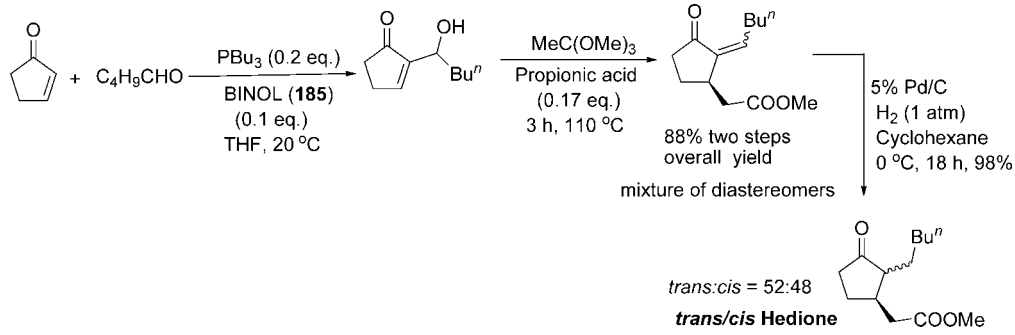


Baylis−Hillman reaction using enantiopure acrylamide **138**, as activated alkene (Scheme 495). Hatakeyama and co-workers[329,1000] have also observed the formation of chiral dioxane derivatives in the asymmetric Baylis−Hillman reaction between 1,1,1,3,3,3-hexafluoroisopropyl acrylate and various aldehydes under the influence of tertiary amine **179** (Figure 72). They have also observed that the tertiary amine **179** containing an OH-group derived from quinidine (**171**) was found to be the best catalyst (in comparison with other catalysts used) for Baylis−Hillman coupling thus providing the desired adducts up to 99% enantiomeric purity (eq 118, part of Scheme 114), thus indicating the role of hydroxyl group (bifunctional catalyst) and also structural rigidity in obtaining high enantioselectivities.

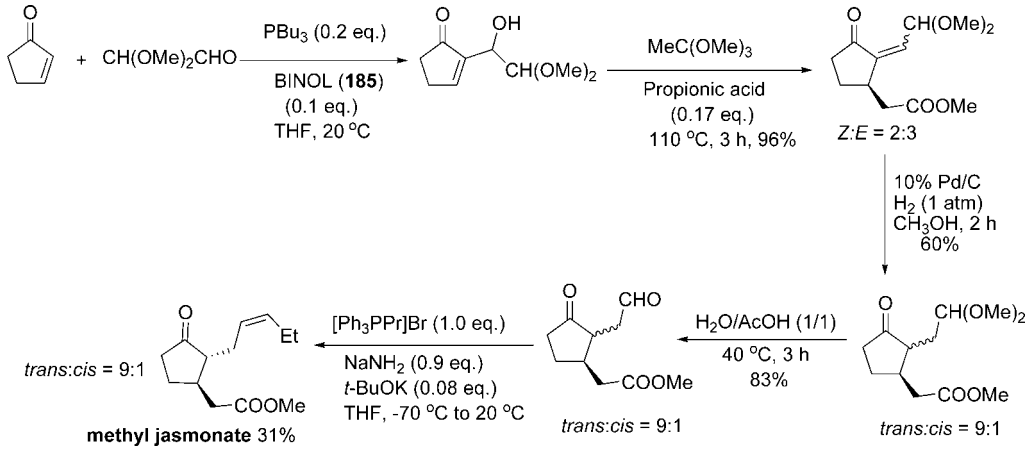


(118)

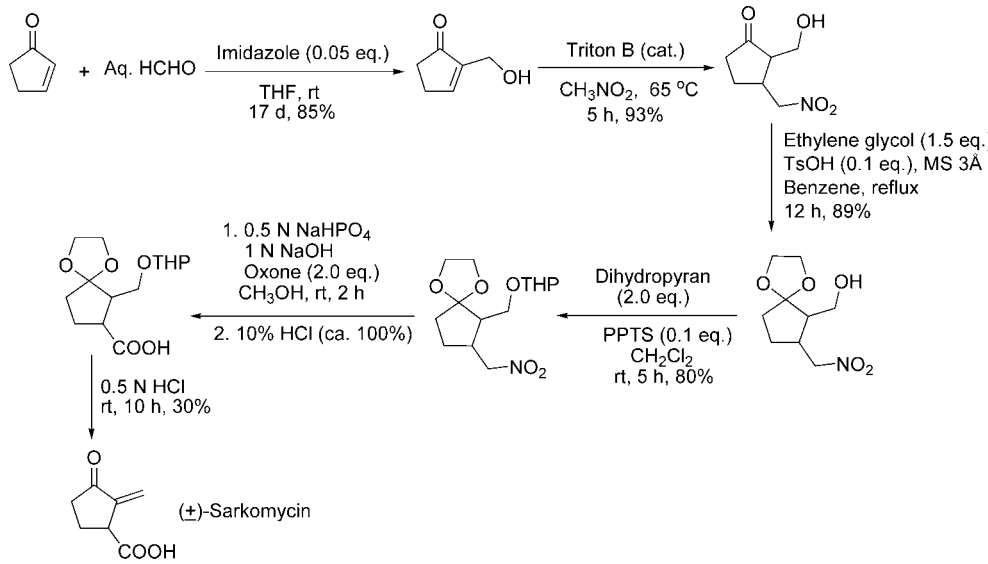
Scheme 469



Scheme 470



Scheme 471



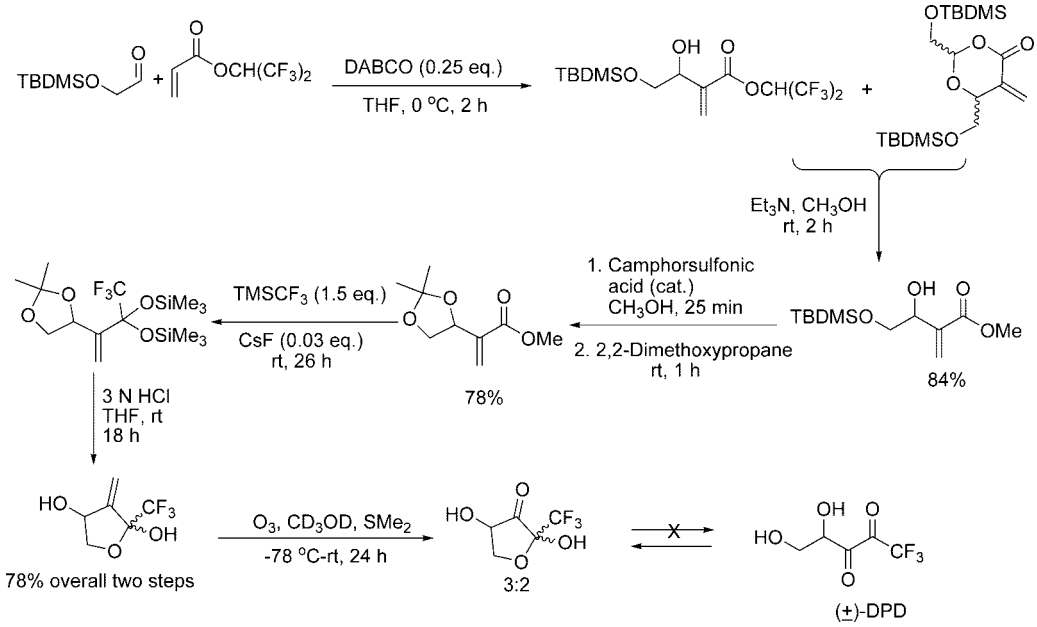
On the basis of observations of Hatakeyama,[329,1000] Leahy,[304] and Drewes,[306] McQuade and co-workers have proposed an interesting mechanism involving dioxane framework formation in the Baylis−Hillman reaction according to the Scheme 496.[1003,1004] They have also proposed that the proton transfer in the zwitterionic intermediate (**A8**) (K_4 step) is the rate-limiting (determining) step (RDS). The RDS is second-order in aldehyde and first-order in DABCO and acrylate (Scheme 496). They have also proposed the formation of a new hemiacetal intermediate(s) (**A9**).

Coelho and co-workers[1002,1010] have examined the Baylis−Hillman reaction between methyl acrylate and aldehydes by ESI and mass spectroscopy and identified the mass peaks of the key intermediates (**A10−12**) (Scheme 497) thus throwing light on the mechanism of the reaction.

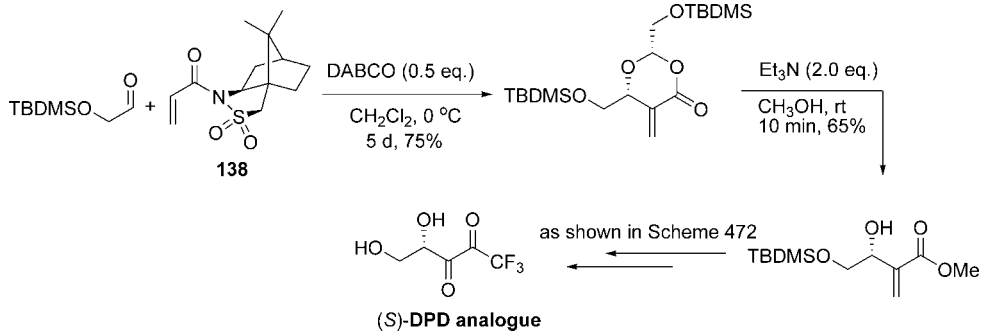
Aggarwal and co-workers[1006,1016] have proposed an interesting mechanism for alcohol- and non-alcohol-catalyzed Baylis−Hillman reactions (Schemes 498 and 499) on the basis of computational studies. This mechanism indirectly supports the mechanism proposed by McQuade (Scheme 495).

Later on, Roy and Sunoj[1014,1015] also reported the first *ab initio* and DFT studies on the mechanism of the Baylis−Hillman reaction, which have shown that the rate-limiting step involves an intramolecular proton transfer in the zwitterionic intermediate generated by the addition of enolate to electrophile. The activation barrier for the C−C bond formation

Scheme 472

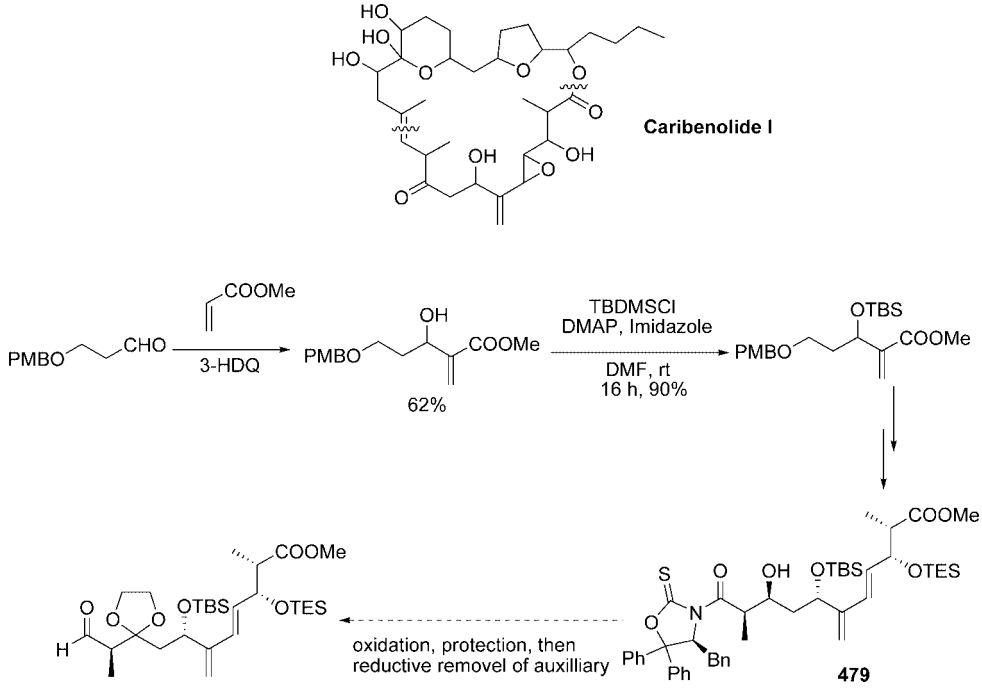


Scheme 473

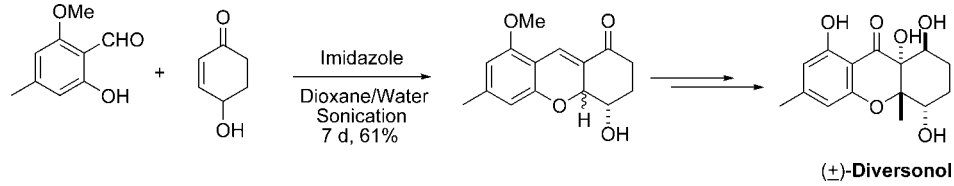


is found to be 20.2 kcal/mol lower than the proton-transfer step for the Baylis−Hillman reaction between methyl vinyl ketone and benzaldehyde catalyzed by DABCO. Thus their observation supports the mechanism proposed by McQuade

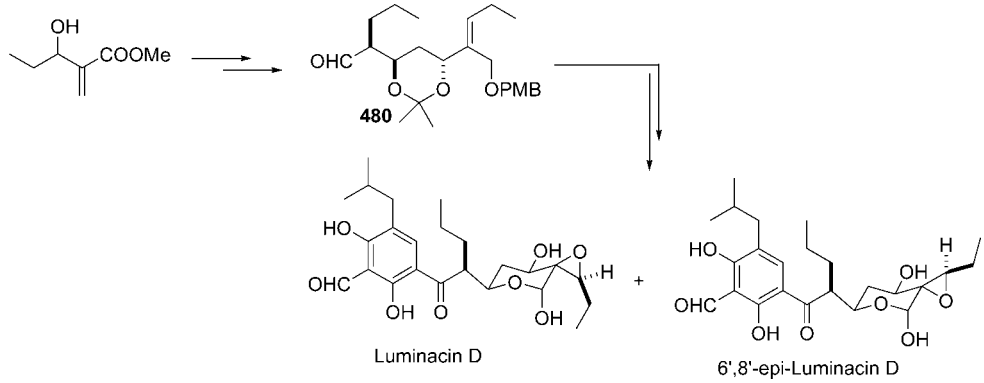
Scheme 474



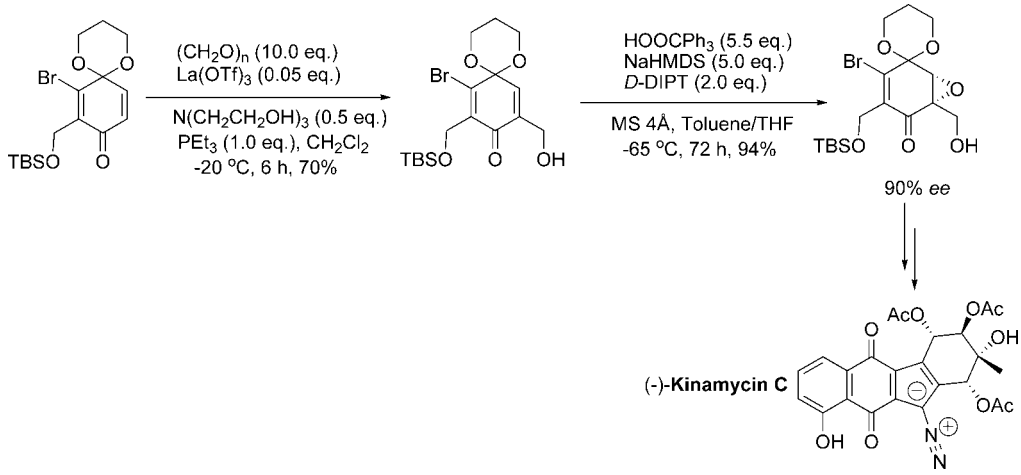
Scheme 475



Scheme 476



Scheme 477



and co-workers. Subsequently, Roy and Sunoj[1015] have also reported their results on water catalysis in the Baylis−Hillman reaction.

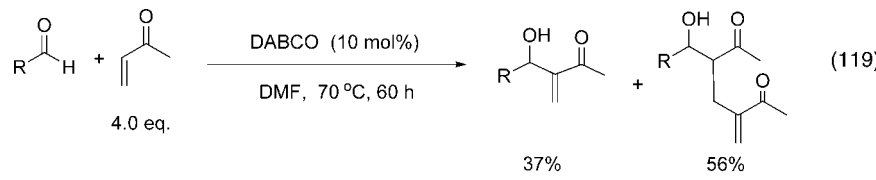
Gruttaduria and co-workers[1017] have provided evidence for proline acting as a bifunctional catalyst in the Baylis−Hillman coupling between alkyl vinyl ketones and aryl aldehydes under the influence of imidazole (Scheme 500) and $NaHCO_3$ (Scheme 501). The reaction is believed to proceed through an iminium ion intermediate (**A13**).

de Souza and Vasconcellos recently proposed the possibility of *cis*-(*Z*-**A14**) and *trans*-(*E*-**A14**) enolates in the first step, that is, Michael addition of tertiary amine onto the methyl acrylate (Scheme 502).[1001]

Shi and co-workers[165,997] have isolated the bis adducts besides the normal Baylis−Hillman adducts in the reaction between aryl aldehydes and MVK with DABCO and also noticed that the yields of diadducts can be increased up to 56% when an excess amount of MVK (4.0 equiv) was employed (eq 119). A similar reaction between PVK and aryl aldehydes provided the diadducts predominantly along with minor amounts of PVK dimer (eq 120).[999] The mechanism for the formation of bis-adducts is given in Scheme 503.

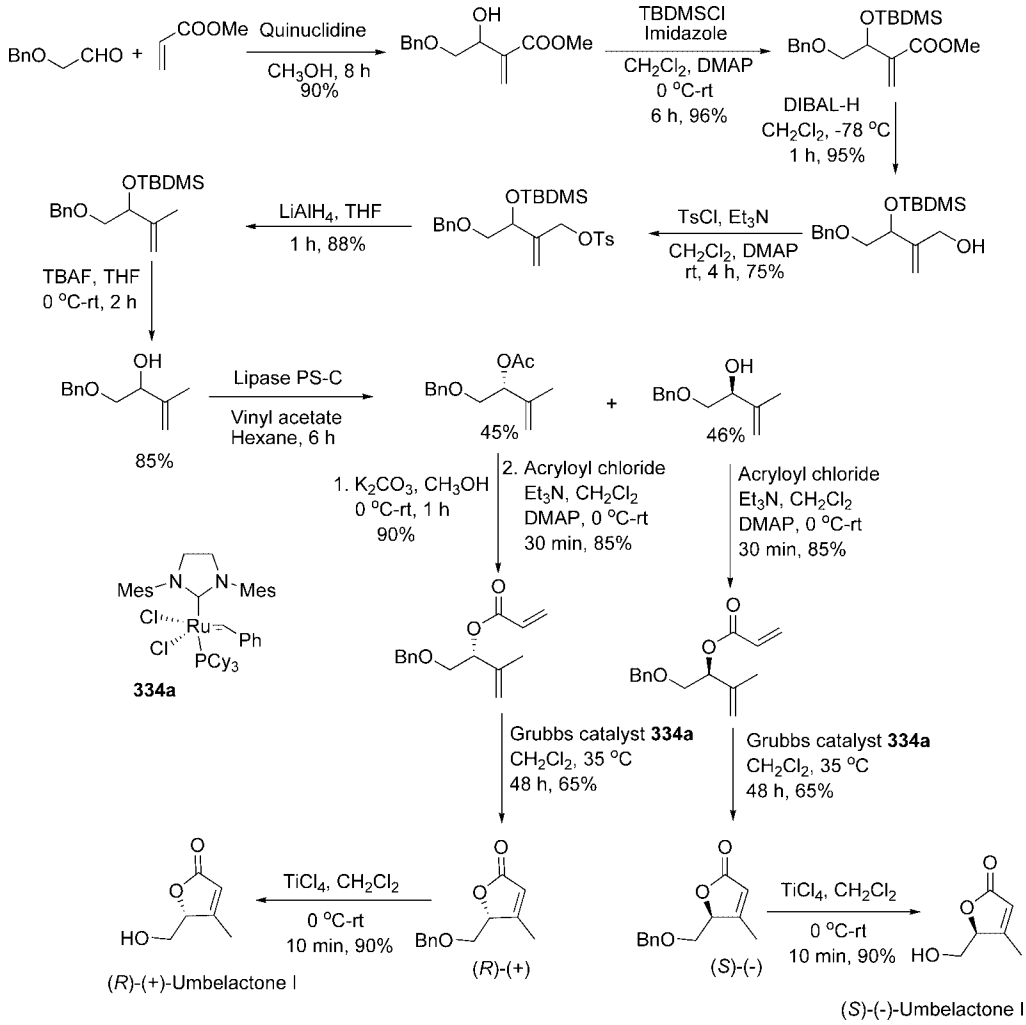
12.3. Chalcogenide/$TiCl_4$-Mediated and $TiCl_4$-Promoted Baylis−Hillman Reactions

Kataoka and co-workers have proposed a plausible mechanism for chalcogeno-Baylis−Hillman reaction according to Scheme 504.[996] It is believed that chalcogenide adds onto the activated alkene in Michael fashion whereas $TiCl_4$



R = 4-$(NO_2)C_6H_4$

Scheme 478



activates the carbonyl oxygen leading to titanium enolate, which then adds onto aldehyde in an aldol manner. Subsequent elimination of HCl and chalcogenide provides the desired Baylis−Hillman adducts. Li et al.[64a] have proposed a possible mechanistic route for the $TiCl_4$-mediated Baylis−Hillman coupling between cycloalk-2-enones and aldehydes (without the direct use of Lewis base) to provide the desired adducts. In this study, Li has proposed that cycloalk-2-enone reacts with $TiCl_4$ first leading to titanium enolate, which will add onto aldehyde (whose carbonyl group is activated by $TiCl_4$) thus providing the required Baylis−Hillman adducts as shown in Scheme 505. Subsequently, a plausible mechanism for $TiCl_4$-mediated coupling of alkyl vinyl ketones with aldehydes and α-keto esters providing, respectively, (*Z*)-keto allyl chlorides and 2-aryl-2-hydroxy-3-methylene-4-oxoalkanoates was independently reported by Li et al.[64b] and by our research group[80] according to Scheme 506. Li and co-workers reported an interesting Et_2AlI-promoted Baylis−Hillman reaction of thio acrylate[66] or cycloalk-2-enone[1018] as activated alkenes with aldehydes and proposed a plausible mechanism (Scheme 507).

12.4. Phosphine-Catalyzed Baylis−Hillman Reactions

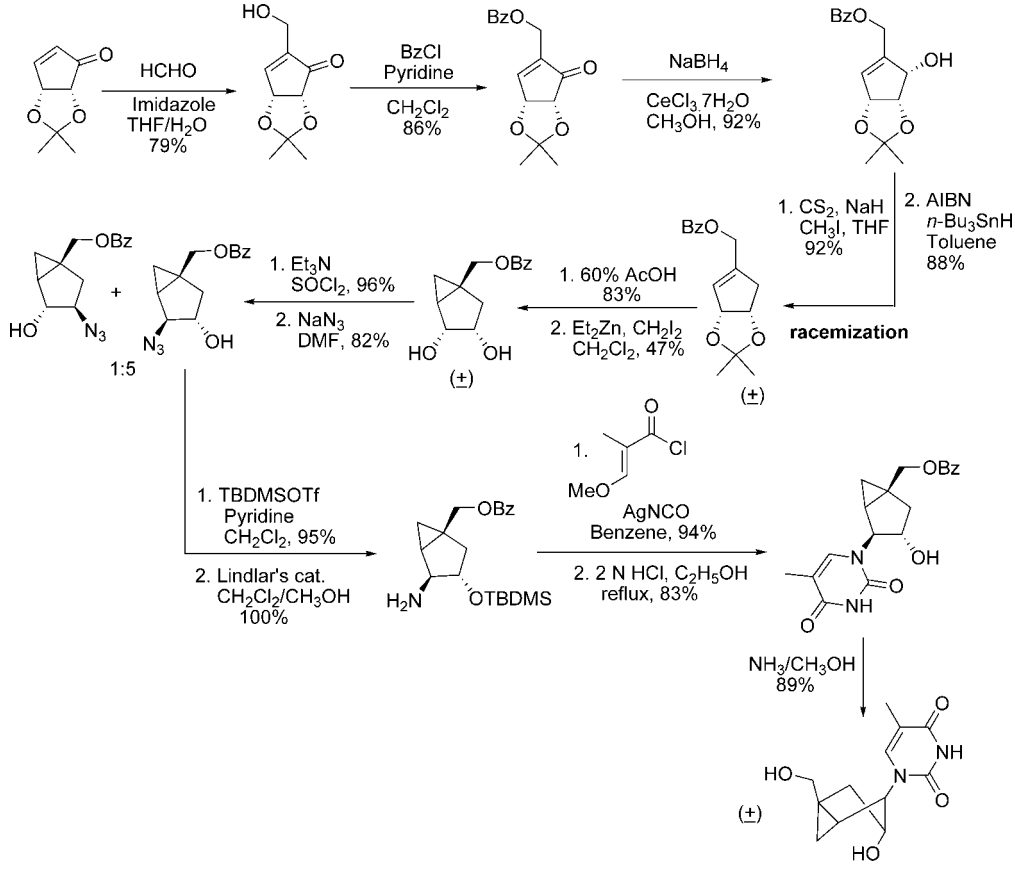
On the basis of density functional theory, Xu has proposed a possible mechanism shown in Scheme 508 taking the Baylis−Hillman reaction between acrylonitrile and ethanal under the catalytic influence of tricyclohexylphosphine as a model case.[1009]

12.5. Stereoselectivity in Asymmetric Baylis−Hillman Reactions: Synthetic and Mechanistic Challenges

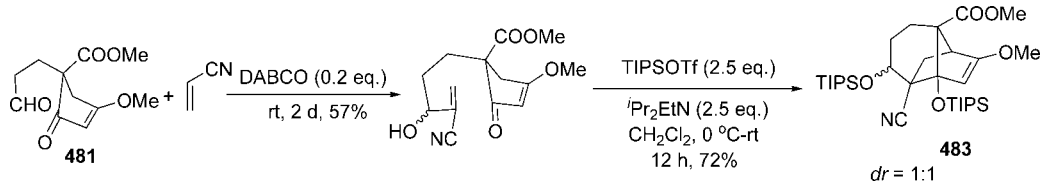
Taking into account all the mechanistic proposals reported in the literature, it is proposed that the most reasonable mechanism involves the Michael, aldol/Michael, and elimination as shown in the Scheme 487.[21,64a,74,80,165,306,993−1018] Despite several studies in this direction, many aspects of the rate-limiting step (RLS) are not yet clearly understood. This might be attributed to the fact that most of the mechanistic studies were investigated using acrylates as activated alkenes and aldehydes as electrophiles, although different kinds of activated alkenes and electrophiles were employed in a number of Baylis−Hillman reactions. All these points will make understanding the mechanism of Baylis−Hillman reaction an intellectual challenge.

The known reports to some extent offer reasonable explanations for the low enantioselectivities in the asymmetric version of the Baylis−Hillman reaction. Aggarwal and co-workers[1006,1016] have proposed the transition state **I** (Figure 73) for the proton migration in the presence of protic source. Aggarwal and co-workers have also proposed that in the asymmetric Baylis−Hillman reaction performed under the influence of chiral catalysts containing a protic source, two diastereomers are formed by the aldol addition of enolate (from the activated alkene) onto the electrophile and in one

Scheme 479

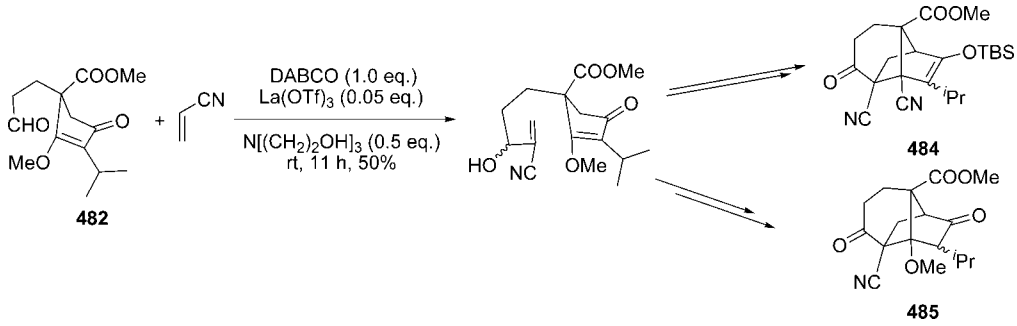


Scheme 480



481 **483**

Scheme 481

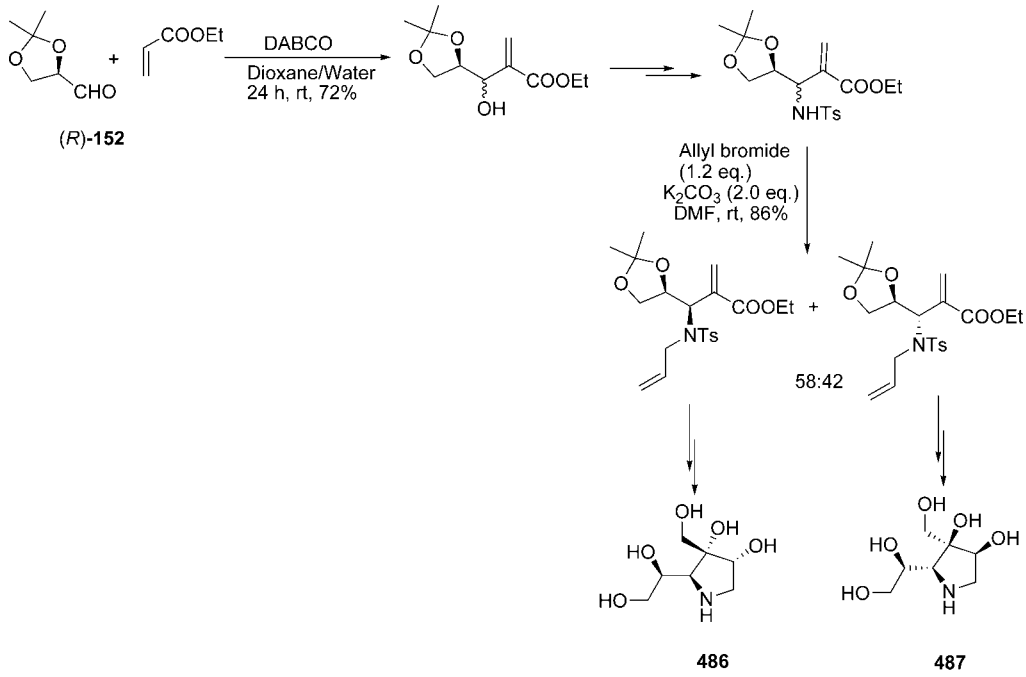


482 **484** **485**

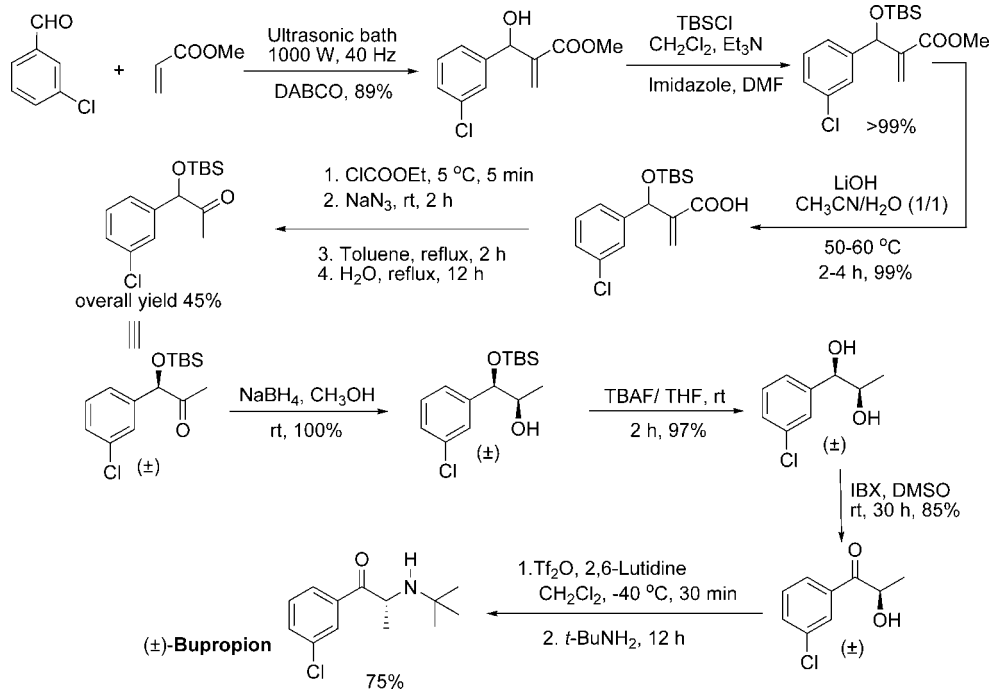
of these diastereomers the proton migration will be faster while the other diastereomers revert back to starting materials thus providing the Baylis−Hillman adducts with high enantioselectivity (Scheme 509).[1006,1016] In fact, Leitner and coworkers[1007] have also postulated a similar transition state (**II**) for the phosphine-catalyzed Baylis−Hillman reaction between aldimines and MVK (Figure 73).

From all these studies, it is quite clear that the key step is the aldol reaction between the enolate, generated by the Michael addition of chiral catalyst to the activated alkene, and aldehyde (electrophile containing an sp^2 carbon). This step generates two chiral centers thereby creating the competing formation of four possible diastereomeric transition states through which the asymmetric reaction actually proceeds. Therefore the real challenge is the development of the most appropriate chiral catalyst(s) that proceeds completely (or to the maximum extent) through the only one of these four possible transition states thus providing high enantioselectivity (either by thermodynamic control or by kinetic control) or allowing only one of the diastereomers to give the product (and forcing the other diastereomers to dissociate back to the starting materials) thus providing high enantioselectivity (as proposed by Aggarwal[1006,1016] and McQuade[1003,1004]).

Scheme 482



Scheme 483



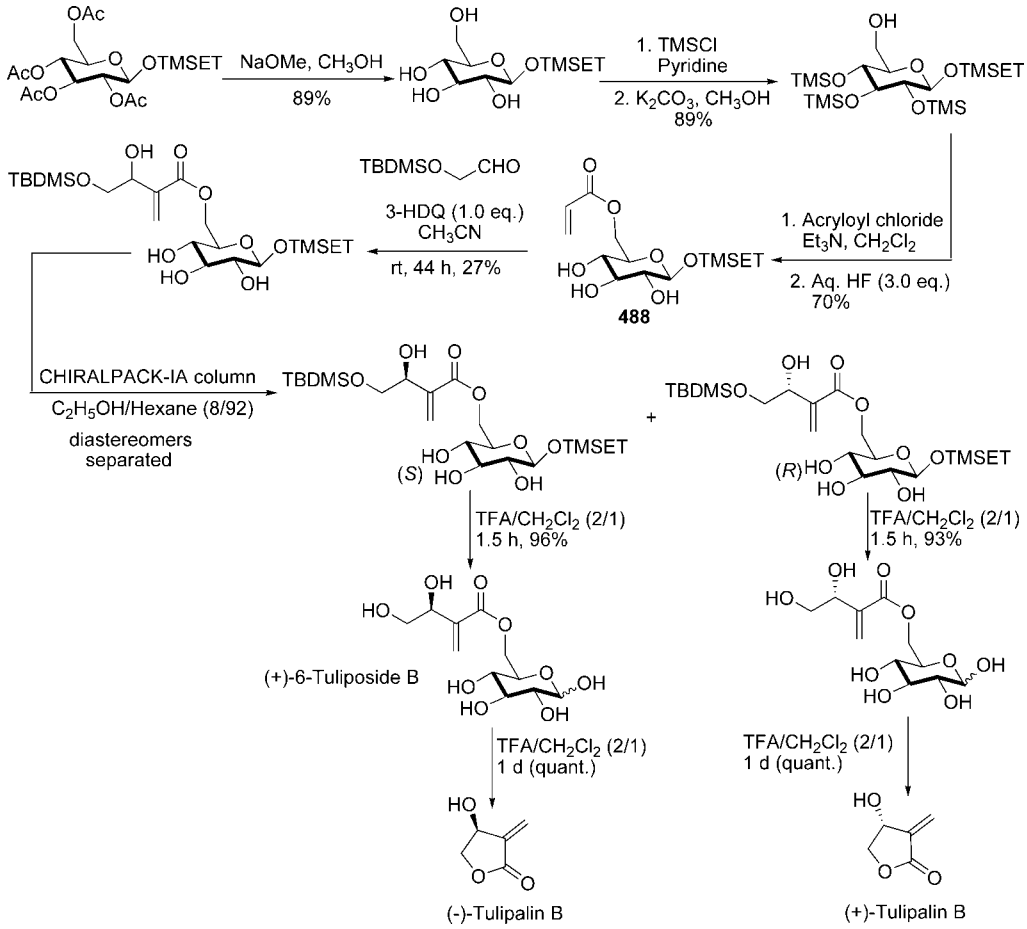
12.6. Intramolecular Baylis−Hillman Reactions: An Emerging Challenge

Although there has been increasing interest in the intramolecular Baylis−Hillman reactions in recent years and some interesting examples have been reported in the literature,[21] this aspect still is in its infancy. Most of the known reports are based on the cyclizations of various activated alkene and electrophile combinations, such as enone−enone, enone−acrylate, enone−aldehyde, unsaturated thioester−aldehyde, and enone−allylic carbonate frameworks (see Section 7, Intramolecular Baylis−Hillman Reaction). Recently Krafft and co-workers have also isolated ketophosphonium salt (**A15**) with a view to understanding the mechanism, which, in fact, supports the proposed mechanistic pathway (as shown in Scheme 508) for the analogous of Baylis−Hillman reaction (Scheme 510).[1008]

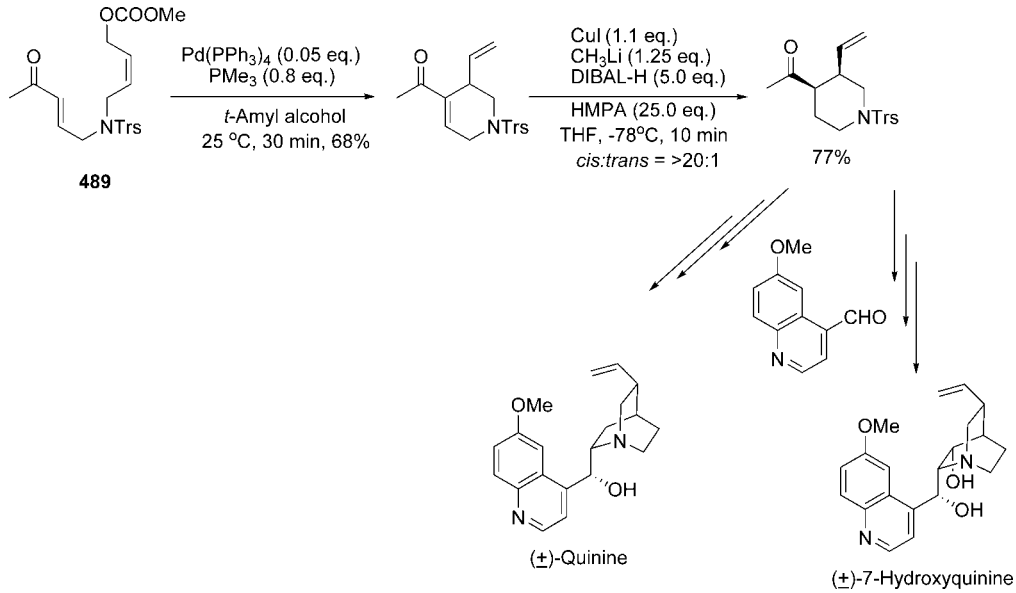
Kwon and co-workers have isolated the key intermediate (**A16**) and determined the structure by single-crystal X-ray analysis, which clearly supports the initial Michael type addition of PR_3 to methyl alkynoate and subsequent aldol reaction onto the pyridine-4-carboxaldehyde (Scheme 511).[1013]

Although there is no clear evidence, the first step in any amine-catalyzed, phosphine-catalyzed, or $TiCl_4$-induced reaction is the Michael-type addition to activated alkene to generate enolate. Addition of enlolate onto the electrophile,

Scheme 484



Scheme 485

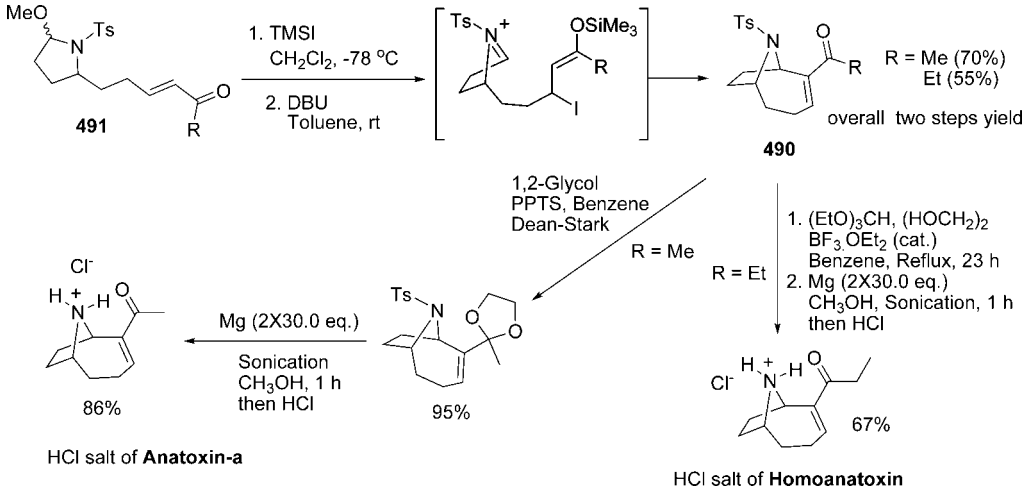


proton transfer, and release of the catalyst are the other key steps (Scheme 487). However, the low enantioselectivities in several asymmetric versions indeed generate many questions to understanding the rate-determining step(s) and also formation of other key intermediates like dioxane derivatives. Complete understanding of these aspects would certainly throw light on the design of appropriate chiral catalysts to provide high levels of enantioselectivities and would require much more work to be done in this direction.

13. Conclusions and Future Projections and Directions

As we predicted several years ago in our past major reviews (refs 21, 23, and 26), the Baylis−Hillman reaction has grown from an unknown patent level to the levels of high popularity and usefulness during the last 25 years. Several new activated alkenes and electrophiles have been employed comfortably in different types of Baylis−Hillman

Scheme 486



reactions. The scope of the catalysts has been really expanded; thus various new catalysts have been employed in performing Baylis−Hillman reactions. Although there has been tremendous progress with respect to activated alkenes, still several kinds of activated alkenes, such as β-substituted acrylates, acrylonitriles, alkyl vinyl ketones, and vinyl sulfones or sulfoxides, could not be accommodated properly in coupling reactions with aldehydes and other electrophiles. Despite considerable success in the case of electrophiles, there are many substrates, such as acid chlorides, alkyl

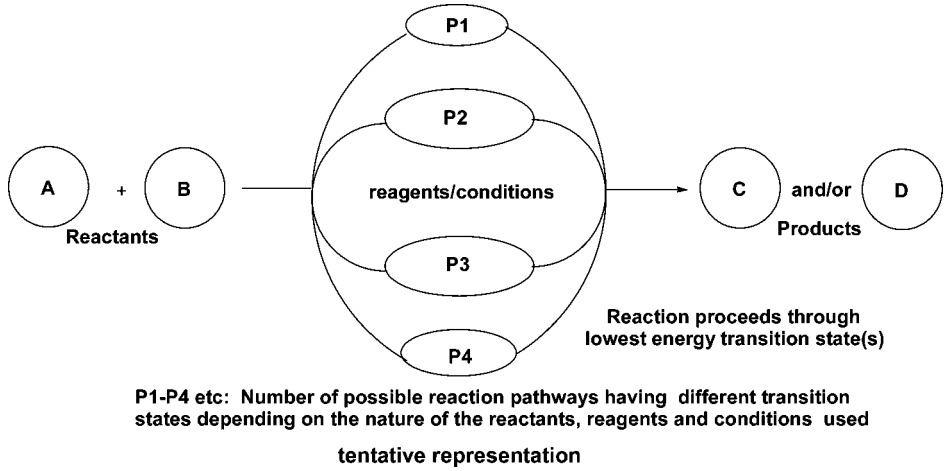


Figure 70.

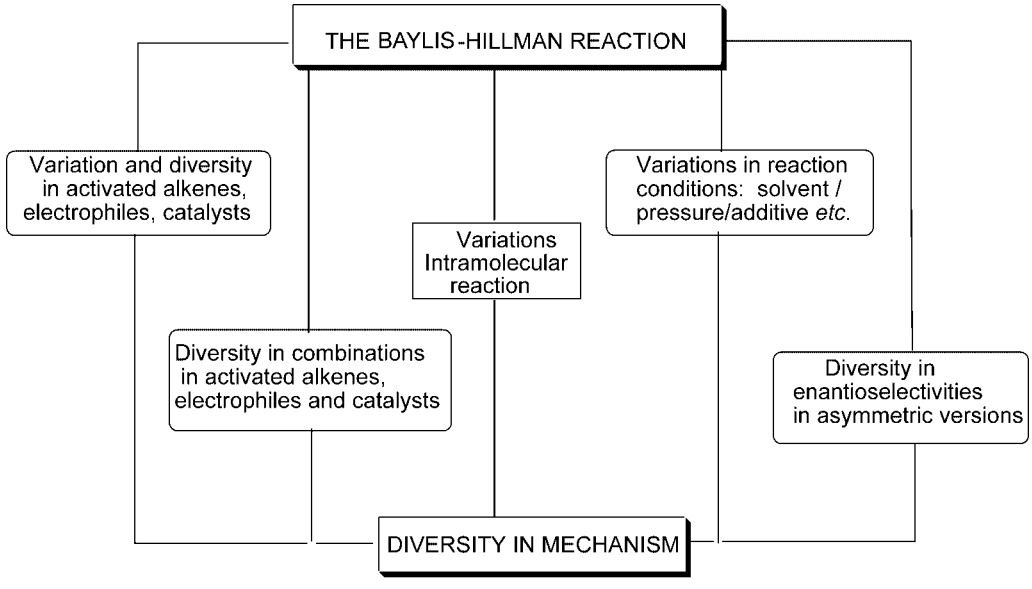
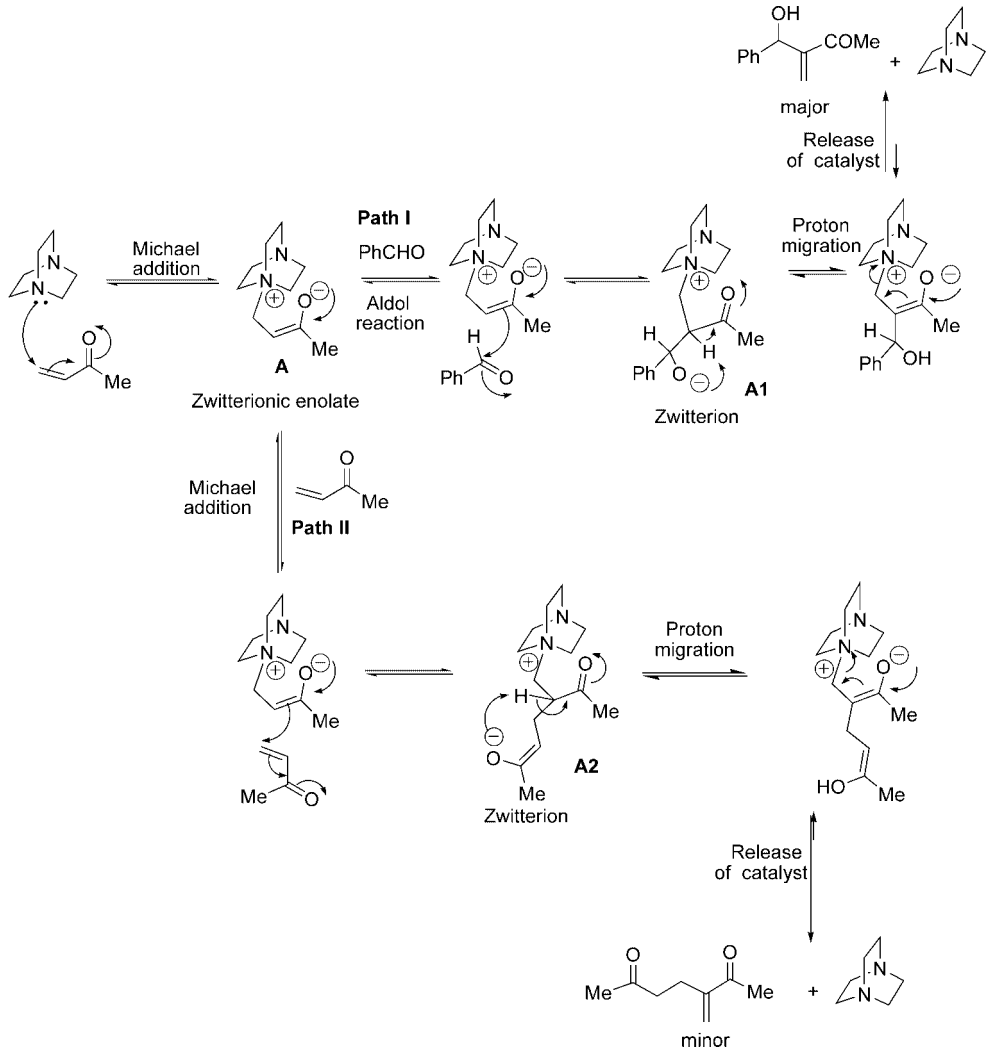
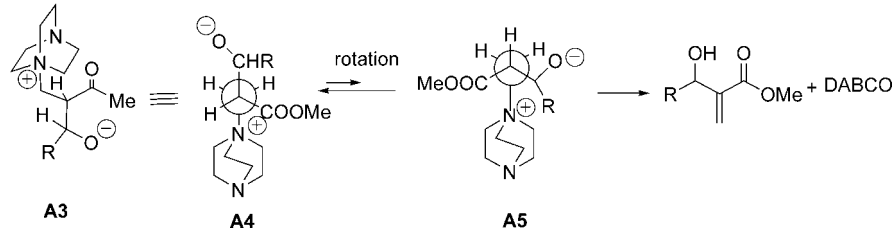


Figure 71.

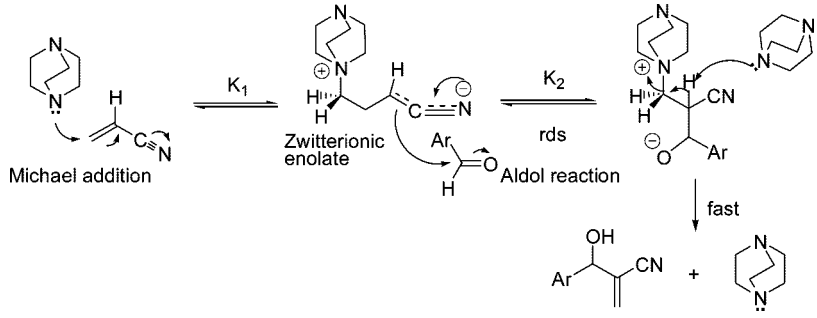
Scheme 487



Scheme 488. Hoffmann's Hypothesis

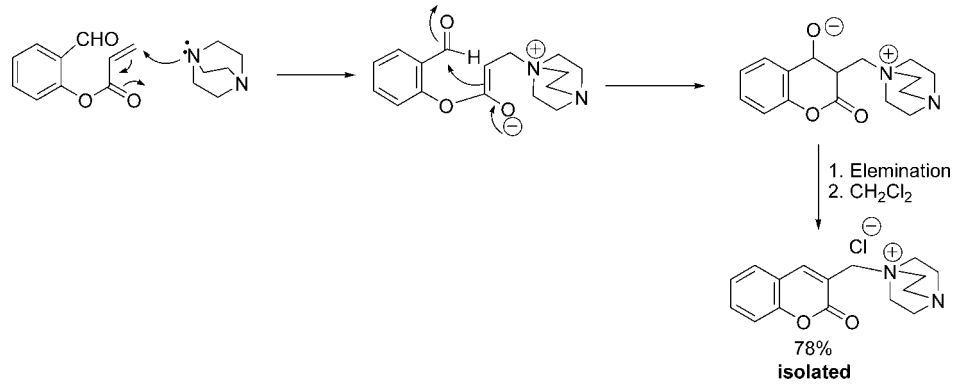


Scheme 489

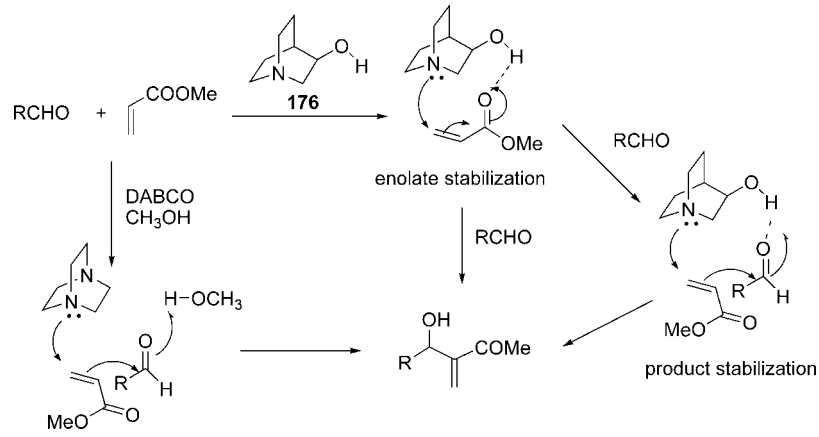


halides, allyl halides, simple ketones, acetals, ketals, epoxides, and aziridines, that could not find a proper place in the list of electrophiles though there are few examples reported. Applications of carbenes, particularly *N*-heterocyclic carbenes (NHCs), for promoting or catalyzing the Baylis−Hillman reaction between selected activated alkenes and electrophiles have been well documented during the past few years. We envision that NHCs will prove to be very

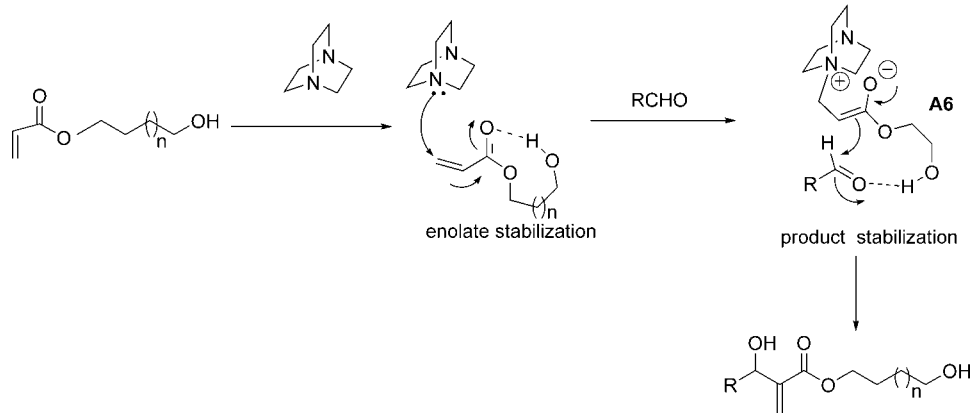
Scheme 490



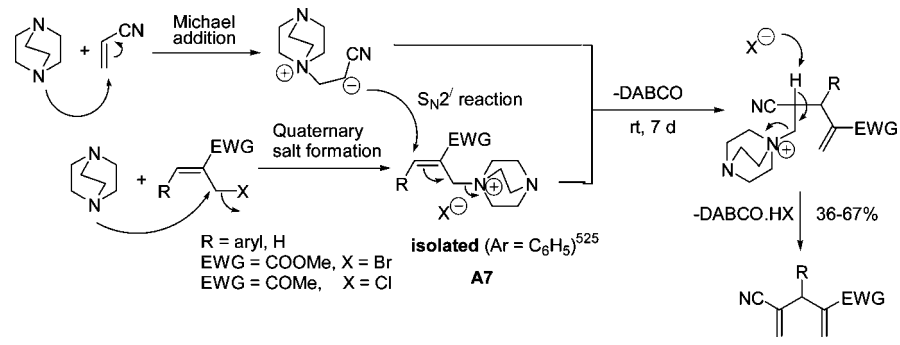
Scheme 491



Scheme 492



Scheme 493

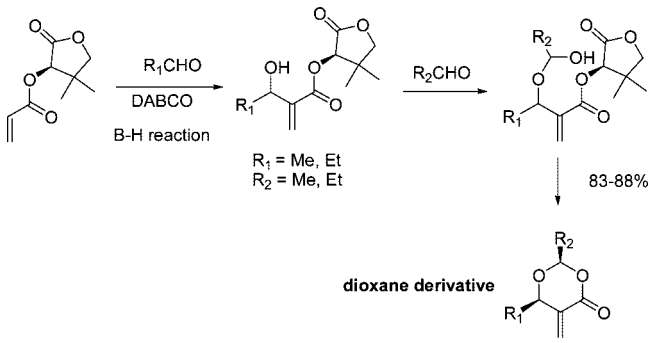


useful catalysts for this reaction in the years to come and several unsolved problems in the Baylis−Hillman reaction will be surmounted with the design of new NHCs.

During the past few years, a number of chiral activated alkenes and electrophiles have been employed in this reaction, thus further expanding the scope in the asymmetric Baylis−Hillman reaction. In fact, significant developments have been made in the design of new chiral catalysts such as chiral amines, phosphines, and thioureas based on the concept of bifunctionality for the asymmetric version of the Baylis−Hillman reaction, and high enantioselectivities have been achieved. However, all these developments are applicable only to certain kinds of activated alkenes and some specific electrophiles. Therefore, the development of effective catalysts for asymmetric Baylis−Hillman reactions that are applicable to most of the common activated alkenes and electrophiles still continues to be a challenging endeavor. In this connection, we foresee that design of new chiral NHCs will play a key role in achieving high levels of success in most aspects of the asymmetric version of the Baylis−Hillman reaction in the near future.

The intramolecular version of the Baylis−Hillman reaction has seen certain progress during the past few years. However, the large scope of the intramolecular version, which in fact will be useful for constructing various carbocyclic and heterocyclic rings, has not yet been completely exploited by synthetic chemists. It is predicted that this aspect will receive utmost attention in the coming years and a number of methodologies or strategies for synthesis of different classes of carbocyclic and heterocyclic compounds of different ring sizes will be developed. Asymmetric intramolecular Baylis−Hillman reaction is still at the initial stages and needs to be

Scheme 494



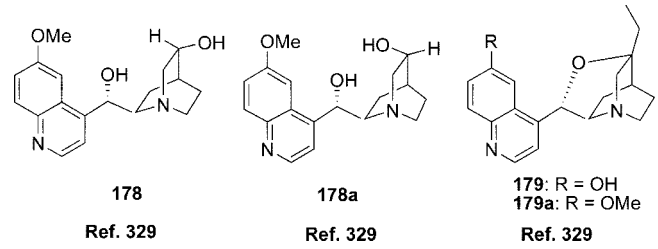
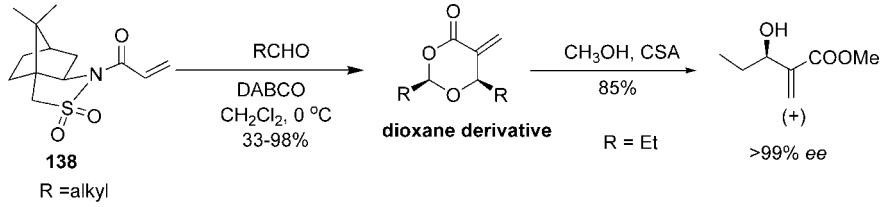
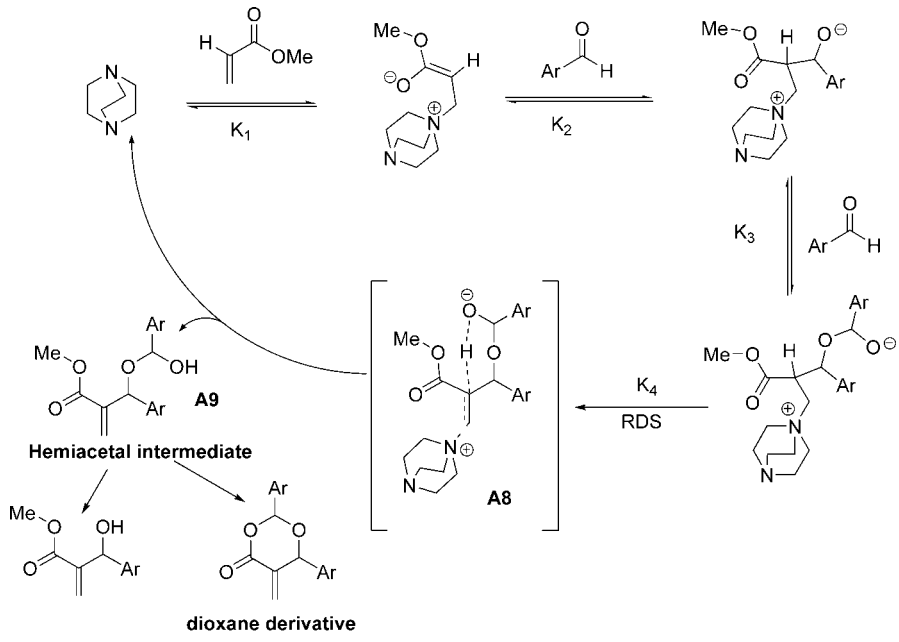


Figure 72. Part of Figure 28.

Scheme 495



Scheme 496[a]



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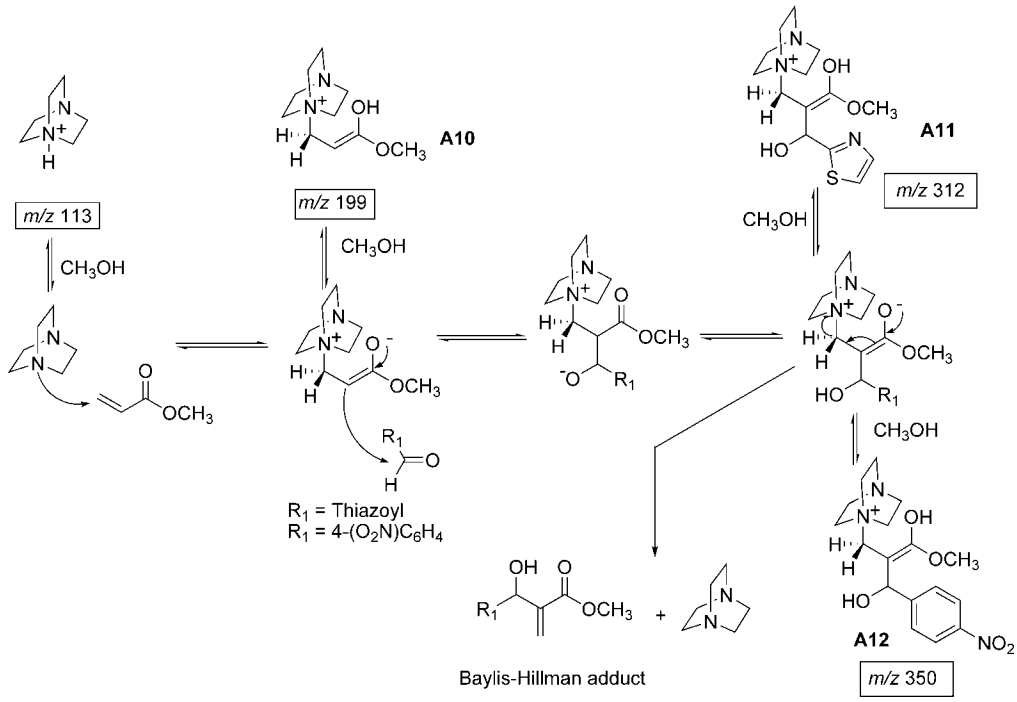
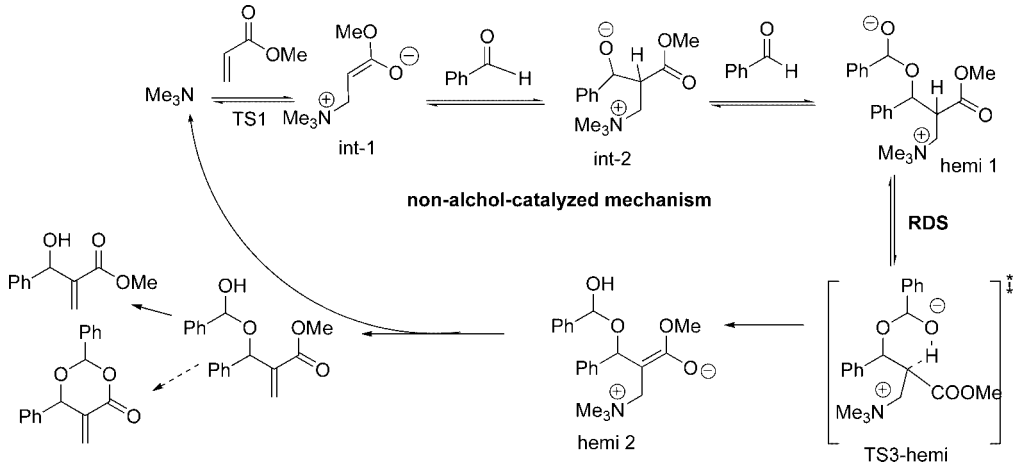
Scheme 497[a]



[a] Reprinted with permission from ref 1002. Copyright 2004 Wiley-VCH, Verlag GmbH & Co.

Scheme 498[a]



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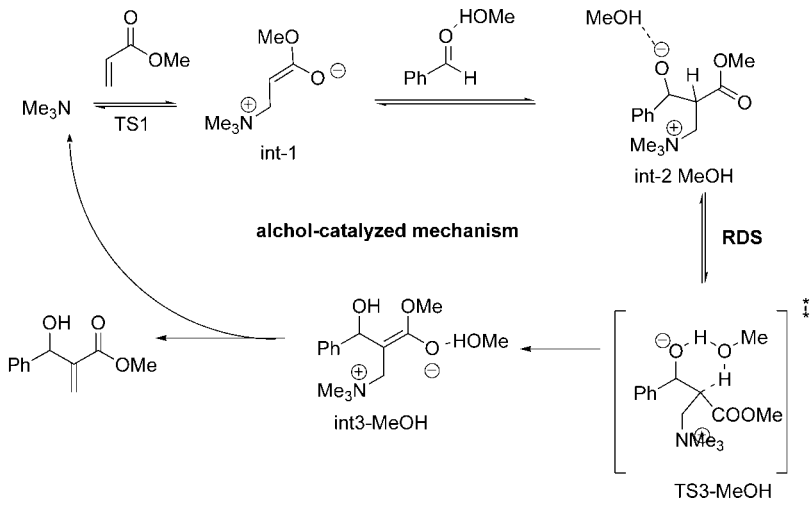
Scheme 499



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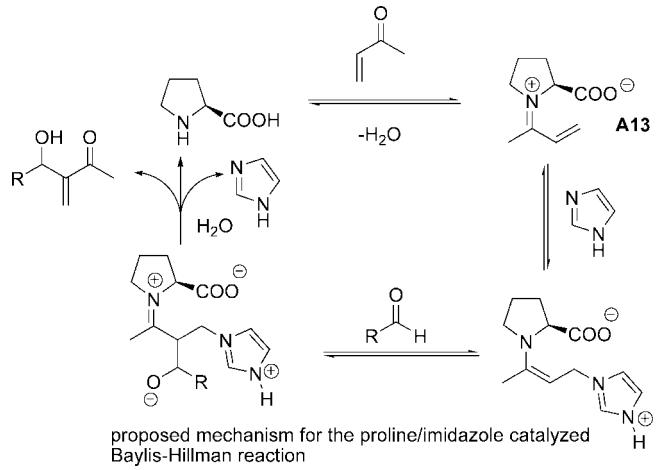
Scheme 500[a]



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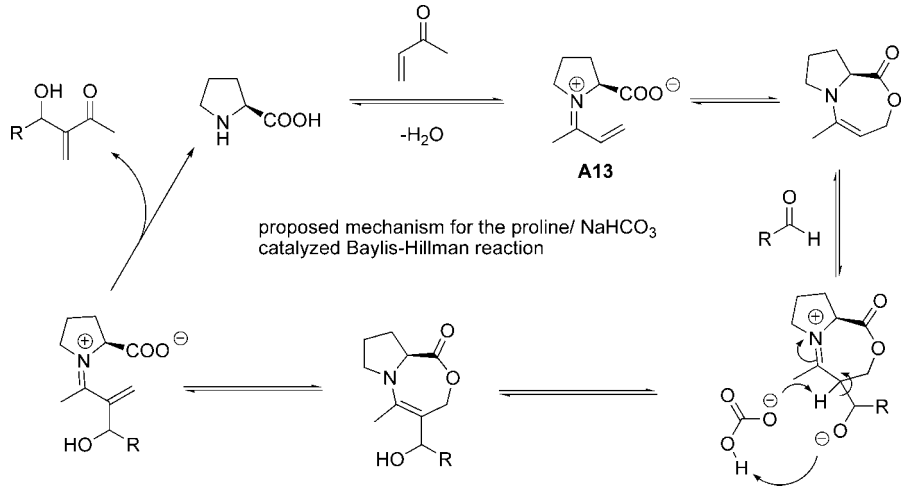
Scheme 501[a]



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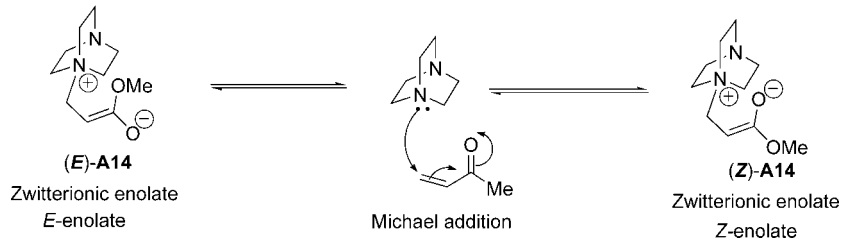
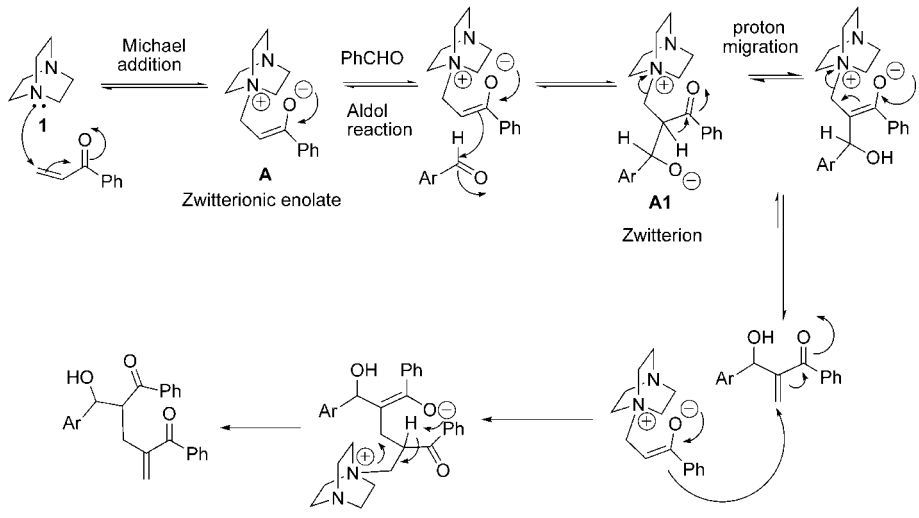
Scheme 502



Scheme 503

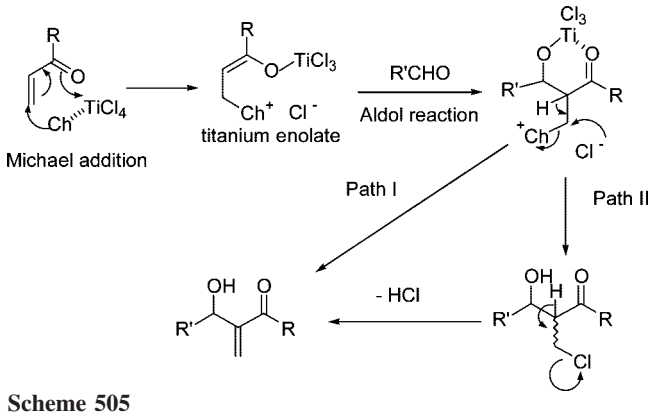


developed with an objective of developing enantioselective methodologies for obtaining different cyclic frameworks. This would require the design of appropriate substrates containing suitable activated alkene and electrophile components and the development of the right chiral catalysts for achieving the asymmetric version of the intramolecular Baylis−Hillman reaction. It is expected that these aspects will be addressed in the coming few years. The concept of multi-Baylis−Hillman reactions, that is, where two or more Baylis−Hillman reactions can be performed simultaneously or consecutively in a one-pot operation will be one of the future challenging objectives in this reaction. We foresee that this aspect of multi-Baylis−Hillman reaction strategy will be addressed in the coming years and significant developments will be made in this direction. It is also interesting to note that the development of the corresponding asymmetric version will be another attractive endeavor in the history of the Baylis−Hillman reaction. We feel that the most interesting and intellectually exciting target will be the development of simple strategies for synthesis of catenanes using the concept of multi-Baylis−Hillman reactions involving two simultaneous intramolecular versions, and developing the corresponding asymmetric version will be more exciting.

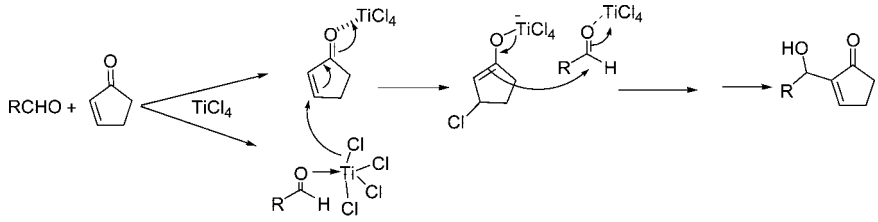
Due to the proximity of functional groups, the Baylis−Hillman adducts have been successfully utilized as substrates in a number of organic transformations, in various reactions and as synthons for obtaining a number of natural products and bioactive molecules. Because of variations of parameters in the functional groups located in proximity, the Baylis−Hillman adducts offer enormous opportunities in many organic reactions and strategies thereby inviting synthetic chemists to develop new methodologies, reactions, and transformations that are applicable for synthesis of bioactive and other important molecules. The Baylis−Hillman adducts offer opportunities and challenges to the synthetic chemists for the appropriate use of these adducts in whatever fashion they want to use, and we believe that these opportunities will never end because these adducts will indeed form a huge source for synthetic strategies, and it is up to the users to use them in suitable ways.

Although there has been impressive developments in many aspects of the Baylis−Hillman reaction, the mechanism of this reaction is not clearly understood. Several publications appeared on the mechanism in recent years. All these are directed toward acrylate−aldehyde reactions. Because of variations of parameters, flexibilities in using various combinations of activated alkenes, electrophiles, and catalysts, the understanding of the mechanism of this reaction has indeed become an intellectual puzzle. Selected theoretical calculations have been carried out to predict the reaction pathway and also to understand the rate-limiting step. However, there has been no key conclusion so far in understanding the mechanism of this reaction. It looks to us that there is a possibility for a number of mechanisms, and all these are believed to involve initial Michael addition of the catalyst to activated alkenes to generate zwitterionic enolates, which would then add onto electrophiles to provide

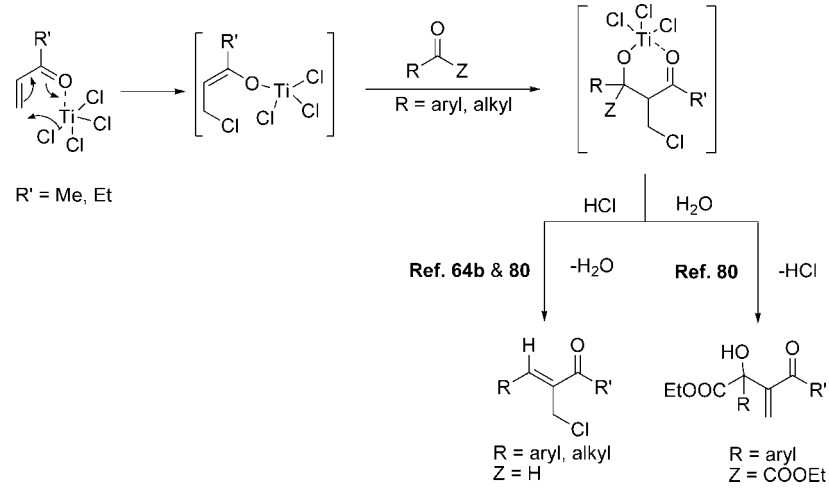
Scheme 504



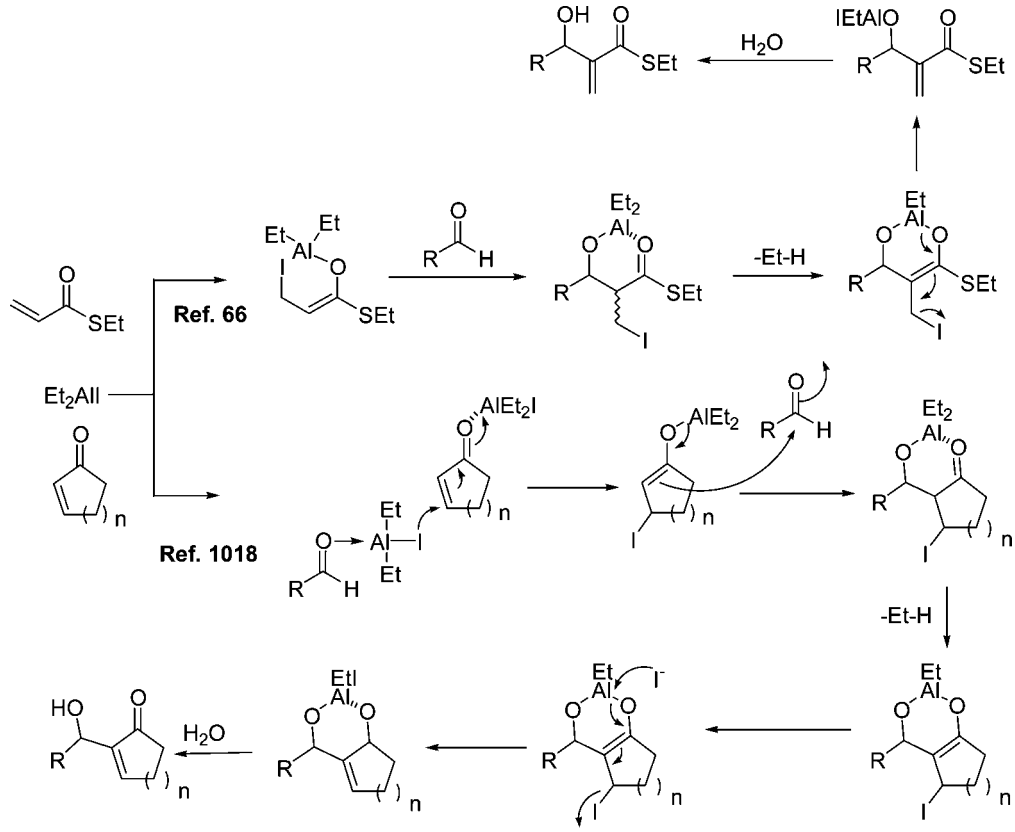
Scheme 505



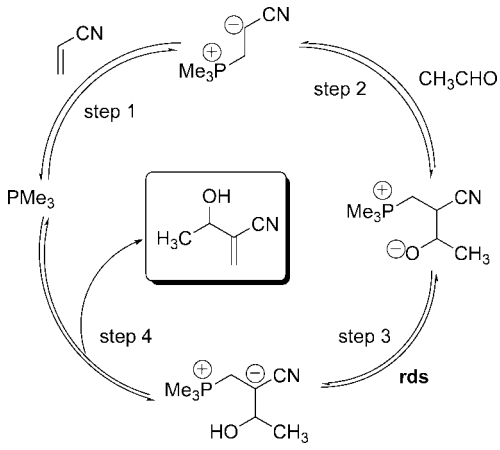
Scheme 506



Scheme 507



Scheme 508



the products after release of the catalysts depending on the electrophiles employed as they follow different pathways (for example, aldehydes and allyl halides involve different reaction pathways). Due to a large number of parameter variations involved in this reaction with respect to all three essential components and also other effects, such as additives, solvent, and temperature, understanding of this mechanism really is a challenging task that demands intellectual output.

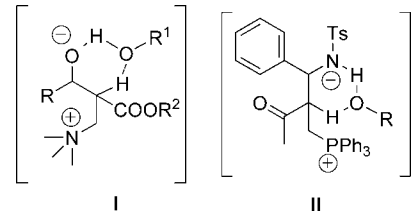
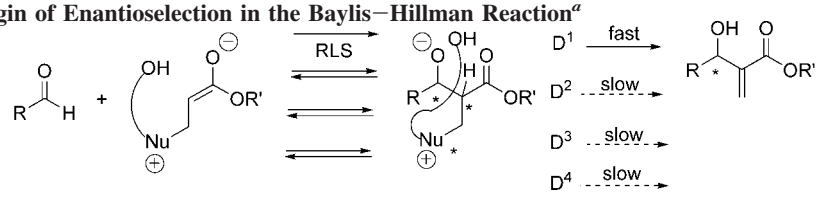


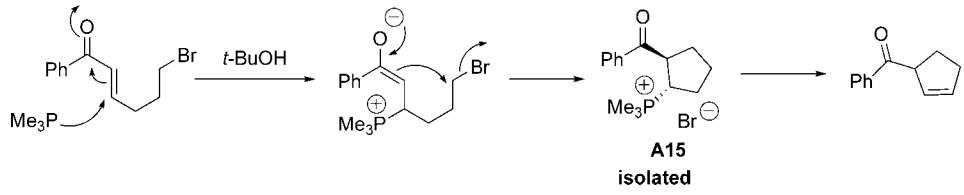
Figure 73. Transition state for the proton migration.

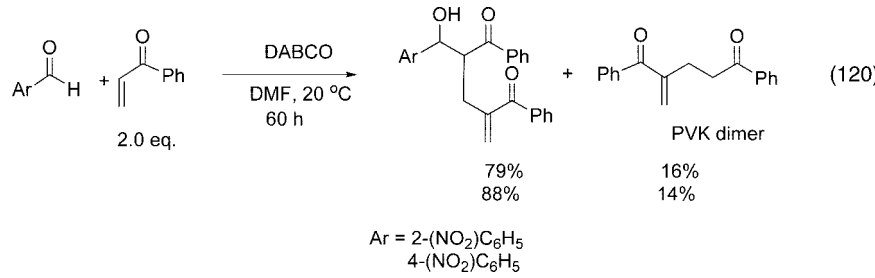
Scheme 509. Likely Origin of Enantioselection in the Baylis−Hillman Reaction[a]



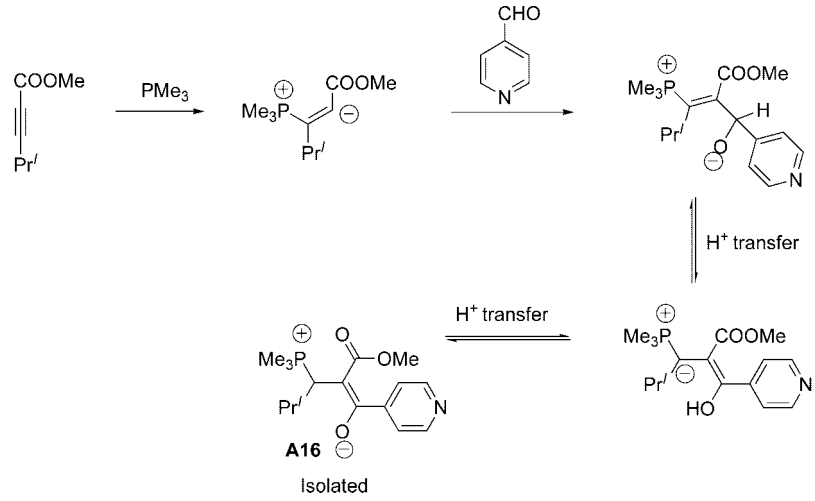
[a] D^1-D^4 are diastereomers of the alkoxide adduct. Reprinted with permission from ref 1006. Copyright 2005 Wiley-VCH.

Scheme 510





Scheme 511



Thus, this reaction provides opportunities for intellectuals to provide a clear understanding on the mechanism.

We may add here that a new continent in organic chemistry has been discovered with fertile land having avenues for discovering new transformations, methodologies, concepts, and challenges, and it is up to the younger generation of synthetic chemists to understand the value of this emerging reaction and make use of its riches to solve problems in synthetic and medicinal chemistry, thereby helping society.

14. Abbreviations

Ac	acetyl
acac	acetylacetonyl
AIBN	2,2′-azobisisobutyronitrile
ATRP	atom transfer radical polymerization
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	2,2′-dihydroxy-1,1′-binaphthyl
Bipy	2,2′-bipyridyl
bmim	1-butyl-3-methyl-1*H*-imidazolium
Bn	benzyl
Boc	*t*-butoxycarbonyl
NBS	*N*-bromosuccinimide
BSA	bovine serum albumin
Bt	1-benzotriazolyl
CAN	ceric ammonium nitrate
CBS	Corey−Bakshi−Shibata reagent
Cbz	benzyloxycarbonyl
cce	electrochemical cyclization
γ-CD	γ-cyclodextrin
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
m-CPBA	*meta*-chloroperbenzoic acid
NCS	*N*-chlorosuccinimide
CTAB	cetyltrimethylammonium bromide
Cy	cyclohexyl
DABCO	1,4-diazabicyclo(2.2.2)octane
DAST	diethylaminosulfur trifluoride
DBA	dibenzylideneacetone
DBN	1,5-diazabicyclo(4.3.0)non-5-ene
DBP	dibutyl phthalate
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DHP	3,4-dihydro-2*H*-pyran
$(DHQD)_2AQN$	hydroquinidine anthraquinone-1,4-diyl diether
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
$(DHQD)_2PYR$	hydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether
DIAPHOXs	diaminophosphine oxides
DIB	(diacetoxyiodo)benzene
DIBAL-H	diisobutylaluminium hydride
DIC	*N*,*N*′-diisopropylcarbodiimide
dioxane	1,4-dioxane
DIPEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DMDO	dimethyldioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMF-DMA	*N*,*N*-dimethylformamide dimethyl acetal
DMP	Dess−Martin periodinane
2,2-DMP	2,2-dimethoxypropane
DMSO	dimethyl sulfoxide
DPD	4,5-dihydroxy-2,3-pentanedione
DPEN	diphenylethylenediamine
dppe	1,2-diphenylphosphinoethane
DYKAT	dynamic kinetic asymmetric transformation
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EVK	ethyl vinyl ketone

EWG	electron-withdrawing group
Fmoc	9-fluorenylmethoxycarbonyl
FSPE	reverse-phase fluorous silica gel
FVP	flash vacuum pyrolysis
H_8-BINAM	(*R*)-(−)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine framework
HFIPA	1,1,1,3,3,3-hexafluoroisopropyl acrylate
HMDS	hexamethyldisilazane
Hmim	1-methylimidazolium
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
3-HQD	3-hydroxyquinuclidine
HRP	horseradish peroxidase
IBX	2-iodoxybenzoic acid
β-ICD	β-isocupreidine
Im	imidazole
NIS	*N*-iodosuccinimide
JJ-PR_3	Janda Jel-PR_3
KDP	ketodicyclopentadiene
LAH	lithium aluminum hydride
LBBA	Lewis base−Brønsted acid
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
MEMCl	(2-methoxyethoxy)methyl chloride
Mes	mesityl
MS	molecular sieves
Ms	mesyl
MVK	methyl vinyl ketone
MW	microwave
NaHMDS	sodium bis(trimethylsilyl)amide
NHC	*N*-heterocyclic carbene
NMM	*N*-methylmorpholine
NMMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl 2-pyrrolidinone
PAP	polymer-bound 4-(*N*-benzyl-*N*-methylamino)pyridine
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PEG	poly(ethylene glycol)
PEPPSI	pyridine-enhanced precatalyst preparation, stabilization, and initiation
PLAP	pig liver acetone powder
PMDETA	*N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine
PMHS	polymethylhydrosiloxane
PMP	*p*-methoxyphenyl
PPA	poly(phosphoric acid)
PPTS	pyridinium *p*-toluenesulfonate
PTA	1,3,5-triaza-7-phosphaadamantane
PTC	phase transfer catalyst
PVK	phenyl vinyl ketone
RhFAP	rhodium-exchanged fluorapatite
SDS	sodium dodecyl sulfate
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDMS/TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBHMA	*tert*-butyl α-(hydroxymethyl) acrylate
TBHP	*tert*-butyl hydroperoxide
TCT	trichlorotriazine
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TMCS	trimethylchlorosilane
TMEDA	tetramethylethylenediamine
TMG	tetramethylguanidine
TMPDA	*N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine
TMS	trimethylsilyl
TMSET	2-(trimethylsilyl)ethyl
TPAP	tetra-*n*-propylammonium perruthenate
Tol	*p*-tolyl
Trs	2,4,6-triisopropylbenzenesulfonyl
Ts	*p*-toluenesulfonyl
TTMPP	tris(2,4,6-trimethoxyphenyl)phosphine

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