Recent Advances in the Baylis−Hillman Reaction and Applications

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Received October 11, 2002

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1. Introduction

1.1. General

The carbon−carbon bond formation and the functional group transformations are the most fundamental reactions for the construction of a molecular framework and hence represent a forefront of research in organic chemistry.[1−8] Several carbon−carbon bond-forming reactions have been discovered and their applications in organic chemistry have also been well-documented in the literature. The most important ones include the aldol reaction,[9,10] Reformatsky reaction,[11] Claisen rearrangements,[12] Friedel−Crafts reaction,[13,14] Grignard reaction,[15] Diels−Alder reaction,[16,17] Wittig reaction,[18] Heck reaction,[19] Suzuki coupling,[20] Grubb's ring closing metathesis,[21,22] and so forth. The very recent developments in organic chemistry have clearly established that the atom economy, selective (chemeo-, regio-, and stereo-) transformations and catalytic processes have become primary and the most essential requirements for the development of any efficient synthetic reaction.[6−8,23] During the past 15 years, synthetic organic chemistry has seen enormous growth, not only in terms of development of new methodologies for the construction of carbon−carbon bonds and functional group transformations but also in terms of development of new reagents, catalysts, strategies, transformations, and technologies often involving the concepts of atom economy and selectivity. Though the arsenal of synthetic organic chemistry is now very rich in the sense that there are methods available to synthesize any molecule which was once thought to be difficult to prepare, the continuing sophistication in and ever-changing scenario of synthetic organic chemistry requires and even demands the continuous evolution of synthetic methods that meet the requirements of atom economy and very high levels of selectivity. Very recently, the Baylis−Hillman reaction,[24−28] yet another important reaction, has been added to the list of these useful carbon−carbon bond-forming reactions. Since the Baylis−Hillman reaction possesses the two most important requirements, atom economy and generation of functional groups, it

10.1021/cr010043d CCC: $44.00
Published on Web 02/27/2003

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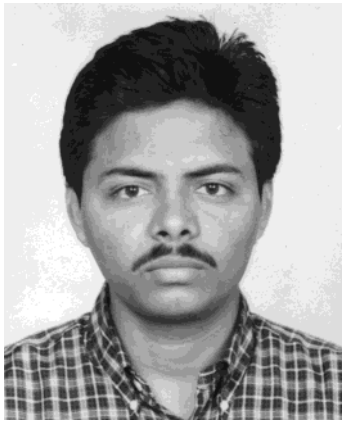

Anumolu Jaganmohan Rao was born in 1975 in Guntur, India. After graduation from the Nagarjuna University, Guntur, he joined as a postgraduate student in 1995 the School of Chemistry, University of Hyderabad, Hyderabad, and obtained his M.Sc. degree in 1997. Presently, he is working for his Ph.D. degree in the same university under the supervision of Professor Basavaiah on the development of new catalysts/catalytic systems for the Baylis–Hillman reaction.

qualifies to be in the list of efficient synthetic reactions.

1.2. Origin and Growth

The origin of this reaction dates back to 1972 to a German patent filed by A. B. Baylis and M. E. D. Hillman.[24] This is essentially a three-component reaction involving the coupling of the α-position of activated alkenes with carbon electrophiles under the catalytic influence of a tertiary amine providing a simple and convenient methodology for synthesis of densely functionalized molecules (eq 1).[24−28] Though this reaction is promising and fascinating, unfortunately, it had missed the attention of organic chemists for almost a decade. It is only in the early 1980s that organic chemists started looking at this reaction and exploring various aspects of this important

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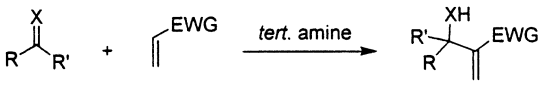
reaction. In fact, now this reaction has become one of the most useful and popular carbon−carbon bond-forming reactions with enormous synthetic utility, promise, and potential. The exponential growth and the importance of this reaction are evidenced by the publication of three major reviews[25−27] and a large number of research papers on this reaction.[24−28] Since the publication of the last review[27] in the year 1997 on this reaction, there has been a quantum jump in the number of papers that have appeared during the past 5 years describing the various aspects and applications of the Baylis−Hillman chemistry. Hence, we strongly felt the necessity of another review covering the literature during the past 5 years so that such a review will be useful to organic chemists. We have therefore undertaken the task of writing another review covering the literature on the Baylis−Hillman chemistry and applications after the publication of the last review,[27] that is, during the past 5 years. Though our review will not present the material that is already described in the earlier reviews, some salient features will be mentioned very briefly or referred to wherever necessary, for continuity and clear understanding of the scientific developments in this reaction.



Eq. 1

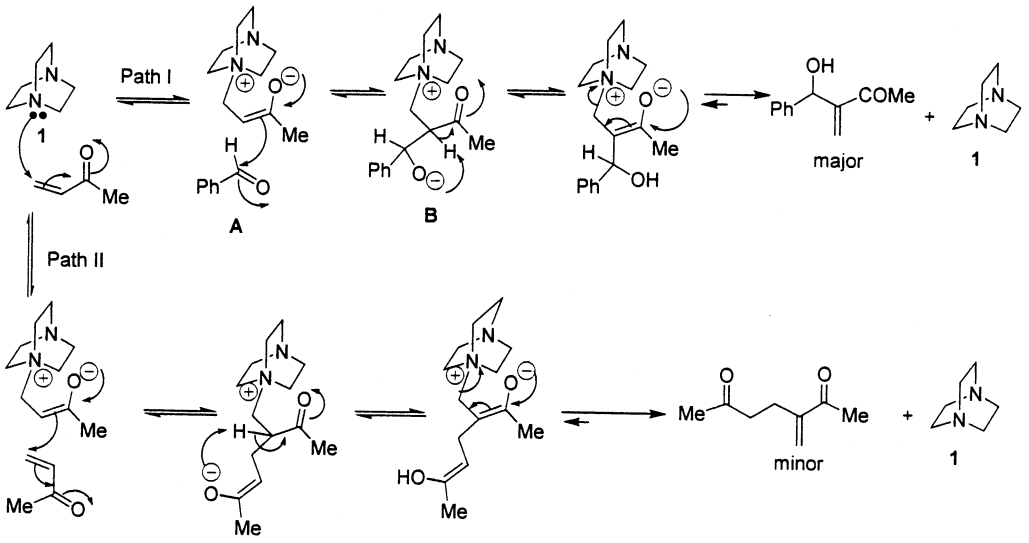
R= aryl, alkyl, heteroaryl; R' = H, COOR, alkyl
X= O, NCOOR, NTs, NSO_2Ph

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

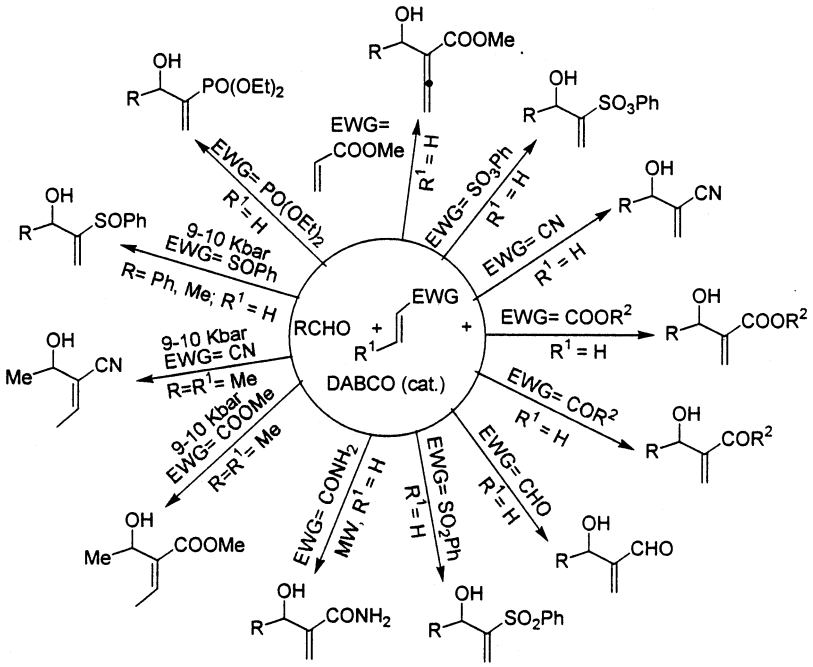
1.3. Mechanism

Mechanism of the reaction is believed to proceed through the Michael-initiated addition−elimination sequence. The most generally accepted mechanism[25−31] of the amine-catalyzed reaction is illustrated in Scheme 1 (Path I), taking the reaction between methyl vinyl ketone (as an activated olefin) and benzaldehyde (as an electrophile) under the catalytic influence of DABCO (**1**), as a model case. The first

Scheme 1



Scheme 2



step in this catalytic cycle involves the Michael-type nucleophilic addition of the tertiary amine to the activated alkene (methyl vinyl ketone) to produce a zwitterionic enolate **A**, which makes a nucleophilic attack onto the aldehyde in an aldol fashion to generate zwitterion **B**. Subsequent proton migration and release of the catalyst provide the desired multifunctional molecules. In the case of reactive activated alkenes (such as alkyl vinyl ketones), Michael-type dimers are formed as side products because they themselves act as electrophiles (Scheme 1; Path II).

Although DABCO (**1**) has been the catalyst of choice, various other tertiary amine catalysts such as quinuclidine (**2**), 3-HQD (**3**), 3-quinuclidone (**4**), and indolizine (**5**) have also been employed to perform the Baylis−Hillman reaction in certain cases (Figure 1).[24−28]

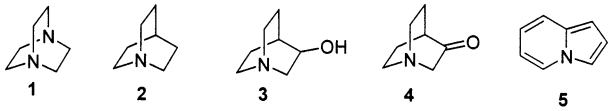
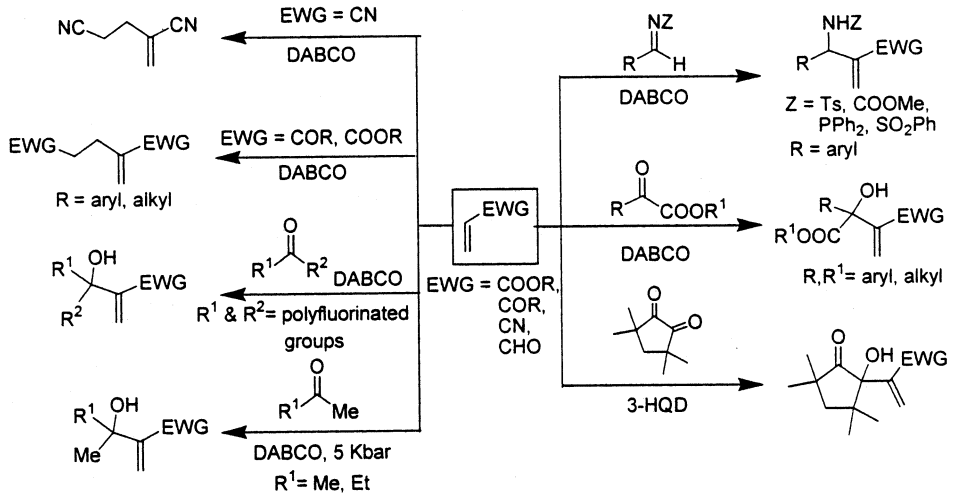


Figure 1.

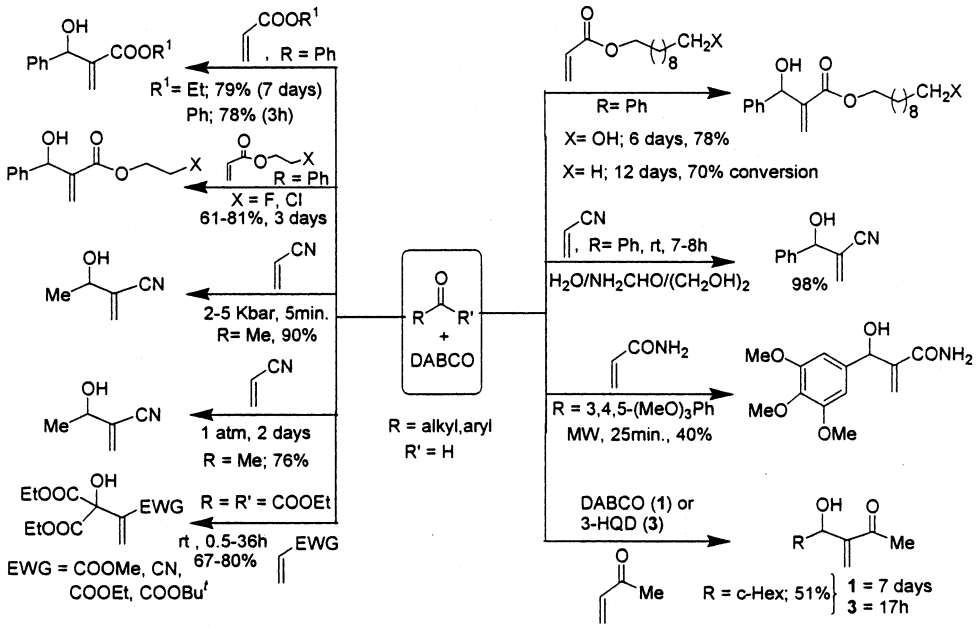
1.4. Essential Components—Earlier Work

During the past 15 years, the Baylis−Hillman reaction has seen exponential growth in terms of all the three essential components, that is, activated alkene, electrophile, and catalyst. Thus, a variety of activated alkenes such as alkyl vinyl ketones,[32−34] alkyl (aryl) acrylates,[31,35,36] acrylonitrile,[33,37] vinyl sulfones,[38] acrylamides,[39] allenic esters,[40,41] vinyl sulfonates,[42] vinyl phosphonates,[43] and acrolein[44,45] couple with a number of carbon electrophiles to provide a wide range of multifunctional molecules (Scheme 2). However, the activated alkenes having β-substituents such as crotononitrile,[46,47] crotonic acid esters,[46] and less reactive alkenes such as phenyl

Scheme 3



Scheme 4



vinyl sulfoxide[48] require high pressure to participate in this reaction (Scheme 2).

Aldehydes[24−27] have been the primary source of electrophiles; thus, various aliphatic, aromatic, and hetero-aromatic aldehydes have been extensively employed in obtaining an interesting class of Baylis−Hillman adducts. Also α-keto esters,[49−51] nonenolizable 1,2-diketones,[45] aldimine derivatives,[52−54] fluoro ketones,[55] and activated alkenes[56−59] have been employed as electrophiles in this reaction (Scheme 3). However, simple ketones require high pressure to undergo Baylis−Hillman reaction.[44,46]

Usually, the Baylis−Hillman reaction is a slow reaction requiring a few days to a few weeks for completion depending upon the reactivities of both the activated alkene and electrophile. Therefore, several efforts were directed to surmount the problem of a slow reaction rate. Thus, applications of reactive activated alkenes,[24−27,30,31,60] reactive electrophiles,[24−27,50] microwave irradiation,[39] use of excess catalyst,[24−27] the concept of hydrogen bonding (having a hydroxy group either in the catalyst or in the substrate),[61−64] aqueous medium,[65] and high pressure[44,46,66] have been examined for rate acceleration and considerable success has been achieved in this direction (Scheme 4).

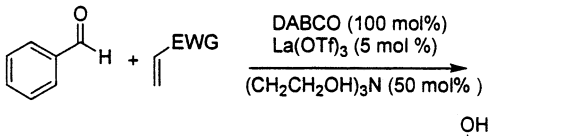
2. Amine-Catalyzed Baylis–Hillman Reaction

2.1. Essential Components—Developments

Aggarwal et al.[67,68] examined the application of metals and ligands in accelerating the Baylis−Hillman reaction. A combination of DABCO (100 mol %), triethanolamine (50 mol %), and $La(OTf)_3$ (5 mol %) was found to accelerate the Baylis−Hillman reaction (eq 2). They also observed that the use of chiral ligands such as (+)-BINOL and (+)-TADDOL did not provide any enantioselectivities in this reaction. Subsequently, they also observed DBU (**6**) as a better catalyst to carry out the Baylis−Hillman reaction at faster reaction rates (eqs 3 and 4).[69]

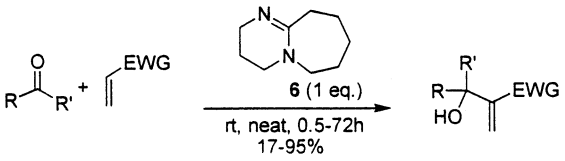
Rezgui and El Gaied,[70] for the first time, used DMAP (**7**) as a catalyst in an aqueous medium for

coupling of the cyclohex-2-en-1-one derivatives with formaldehyde to provide 2-(hydroxymethyl)cyclohex-2-en-1-one derivatives (eq 5). They also noticed that



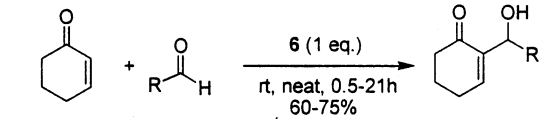
Eq. 2

EWG	time (h)	yield (%)
COOMe	12	83
COOEt	12	84
COOBu^t	72	74
CN	1.5	92



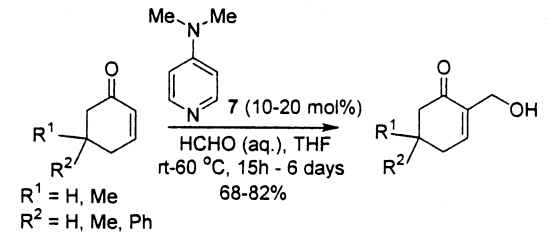
Eq. 3

R = Ph, 2-(NO$_2$)Ph, 4-(NO$_2$)Ph, 2-(OMe)Ph, 4-(OMe)Ph, Et, Bu^t
R' = H, CF$_3$
EWG = COOMe, COOEt, COOBu^t, CN



Eq. 4

R = Ph, 2-(OMe)Ph, *c*-Hex, Bu^t

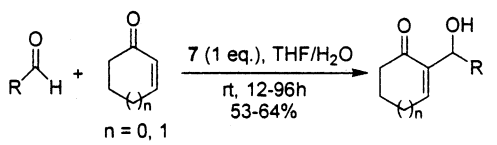


Eq. 5

R^1 = H, Me
R^2 = H, Me, Ph

this reaction does not proceed in the presence of DABCO. Also, β-substituted cyclohexenone derivatives did not undergo Baylis–Hillman reaction under these conditions.

Subsequently, Kim and co-workers also used DMAP (**7**) as a catalyst for the Baylis–Hillman coupling of cycloalkenones with various aldehydes (eq 6).[71]

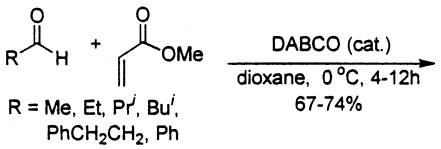


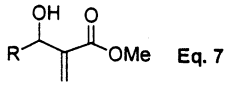
Eq. 6

R = Ph, 2-FPh, 3-(OMe)Ph, 2,4-Cl$_2$Ph, 2-(NO$_2$)Ph, 4-(NO$_2$)Ph, 2-chloroquinolin-3-yl, Pent

Rafel and Leahy observed significant rate acceleration when the reaction was conducted at 0 °C in dioxane (eq 7).[72]

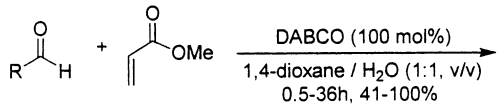
Recently, Hu and co-workers[73] found that a dioxane–water medium accelerates the Baylis–Hillman reaction. Thus, coupling of methyl acrylate with reactive aldehydes in the presence of a stoichiometric

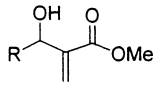




Eq. 7

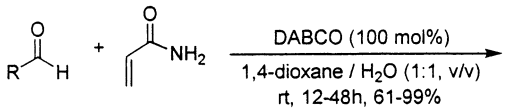
amount of DABCO provides the Baylis–Hillman adducts in shorter reaction times (eq 8). Less reactive activated alkene, acrylamide, also undergoes Baylis–Hillman coupling with reactive electrophiles under these conditions (eq 9).[74]

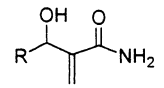




Eq. 8

R = H, Me, Et, aryl, heteroaryl





Eq. 9

R = 2-(NO$_2$)Ph, 3-(NO$_2$)Ph, 4-(NO$_2$)Ph, heteroaryl

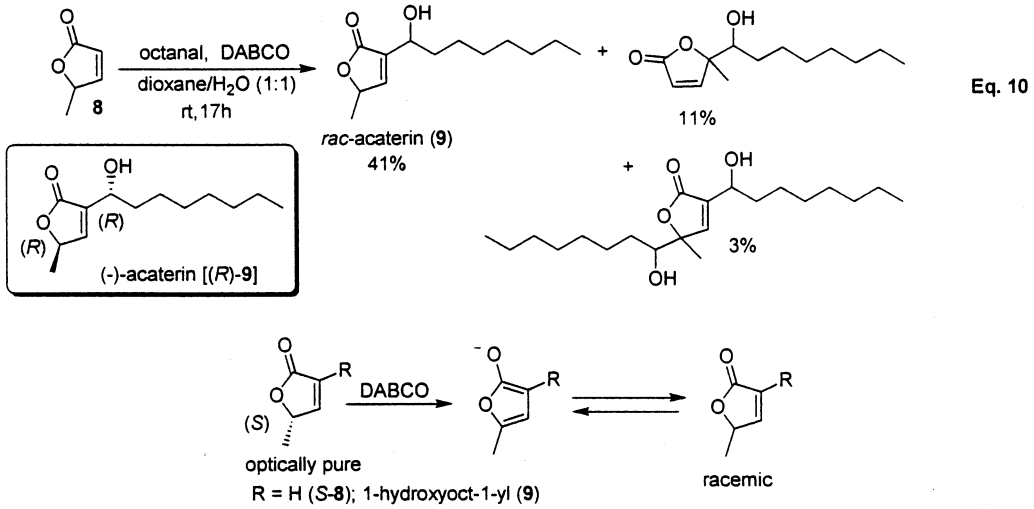
Franck and Figadere[75] later employed these conditions for the synthesis of racemic acaterin (**9**) via the coupling of δ-butyrolactone (**8**) with octanal (eq 10 in Scheme 5). However, their attempts to employ this strategy for obtaining enantiopure acaterin **9** (biologically active molecule) starting from (*S*)-**8** were unsuccessful due to the possible racemization as shown at the bottom of Scheme 5.

Hayashi and co-workers[76] described an interesting rate acceleration of Baylis–Hillman reaction under high pressure induced by freezing water in a sealed autoclave. Representative examples are presented in eq 11.

Kawamura and Kobayashi[77] observed that lithium perchlorate in diethyl ether as an additive (along with a catalytic amount of DABCO) accelerates the Baylis–Hillman reaction, particularly at −20 °C (eq 12). They also noticed that aliphatic aldehydes require 10 mol % lithium perchlorate whereas the benzaldehyde and cinnamaldehyde require 70 mol % lithium perchlorate for better results.

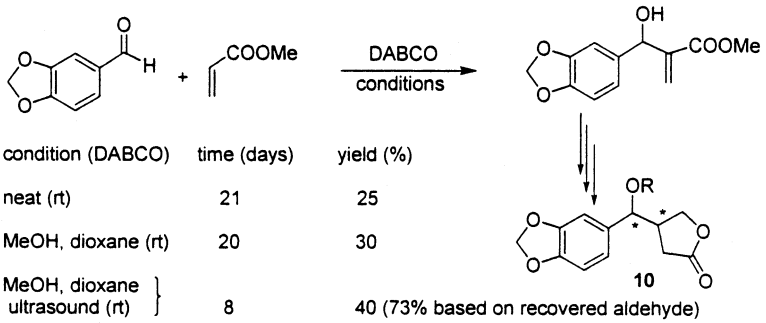
During the synthesis of lignan derivative, butyrolactone **10**, Coelho and co-workers[78,79] performed Baylis–Hillman reaction between the less reactive piperonal and methyl acrylate under ultrasound conditions. The resulting adduct was subsequently transformed into the desired lignan derivative **10** (Scheme 6). Later, they also systematically investigated the influence of ultrasound in accelarating the Baylis–Hillman reaction of various activated alkenes

Scheme 5

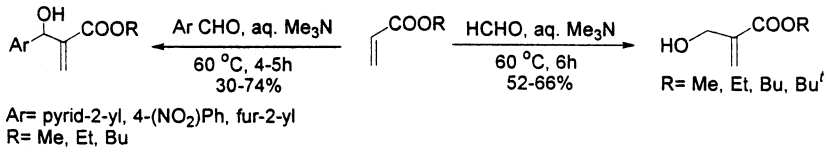


Eq. 10

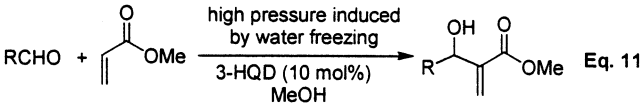
Scheme 6



Scheme 7

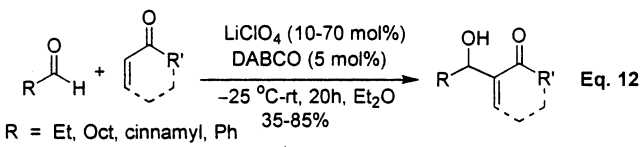


(methyl acrylate, MVK, and acrylonitrile) with several aromatic and aliphatic aldehydes and found that DABCO is a more effective catalyst under ultrasound conditions.[80]



Eq. 11

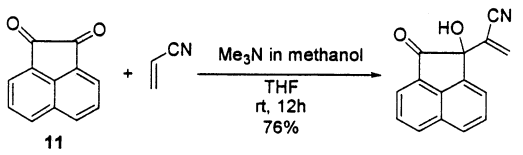
R	pressure (Mpa)	time (h)	temp (°C)	yield (%)
4-(OMe)Ph	200	104	-20	62
4-(OMe)Ph	0.1	104	23	8
Ph	200	24	-20	78
Ph	0.1	24	23	40



Eq. 12

R = Et, Oct, cinnamyl, Ph
R' = H, Me, OCH_2Ph, OEt, OBu^t, CN, $CH_2CH_2CH_2$

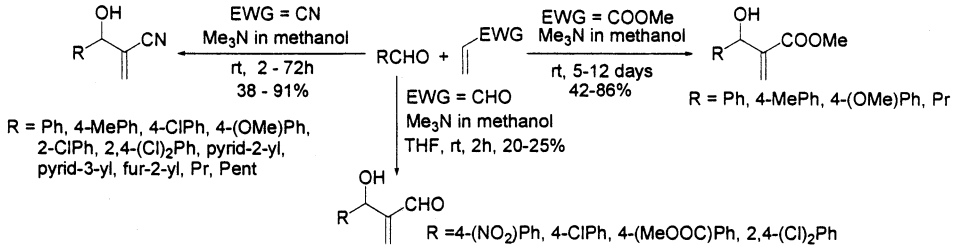
Recently, our research group has employed aqueous trimethylamine as a medium for the Baylis–Hillman coupling of alkyl acrylates with paraformaldehyde and various reactive aromatic aldehydes (Scheme 7).[81] However, our attempts to extend this methodology to benzaldehyde were unsuccessful. Subsequently, we described the application of methanolic trimethylamine for coupling of benzaldehyde with methyl acrylate (Scheme 8). We also used this methanolic trimethylamine for performing Baylis–Hillman reaction between various other activated alkenes and electrophiles. Acenaphthenequinone (**11**), a non-enolizable ketone, was also employed as an electrophile for coupling with acrylonitrile under the influence of methanolic trimethylamine (eq 13).[82]



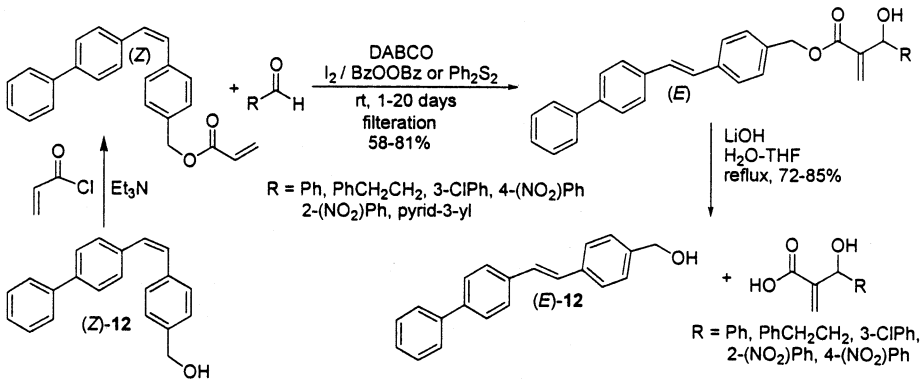
Eq. 13

Our research group has also observed a remarkable rate acceleration of this reaction in a silica gel solid-phase medium.[83] We also found that the less reactive activated alkene, *tert*-butyl acrylate, couples comfort-

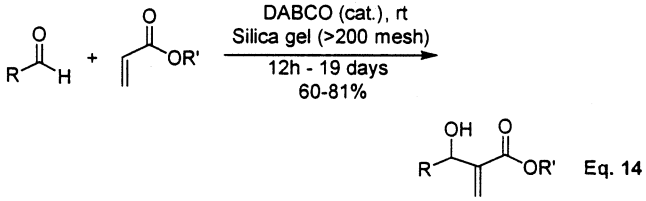
Scheme 8



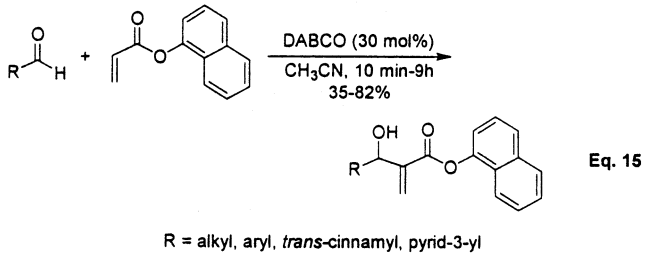
Scheme 9



ably with various aromatic aldehydes under these conditions (eq 14).

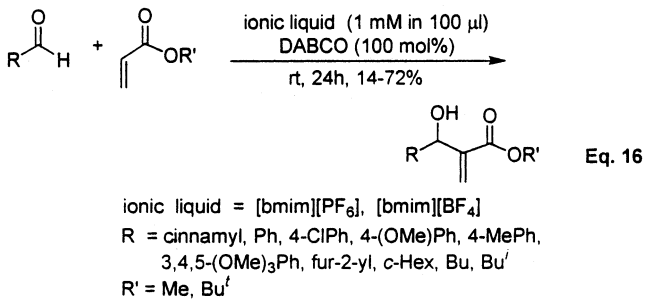


α-Naphthyl acrylate was found to be a fast reactive activated alkene by Chen and co-workers[84] in the Baylis–Hillman reaction. Thus, α-naphthyl acrylate couples with various aldehydes under the influence of DABCO in acetonitrile to provide the desired products in remarkably shorter times (eq 15).

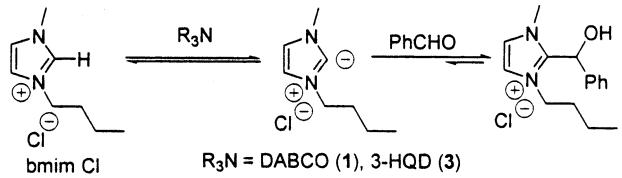


Bosanac and Wilcox used a diaryl alkene alcohol **12** as a precipitating auxiliary for easy isolation of Baylis–Hillman adducts (based on the solubility switch of structural isomerization) (Scheme 9).[85]

Ionic liquids were found to accelerate (33.6 times faster) the Baylis–Hillman coupling between aldehydes and acrylate esters in the presence of DABCO (eq 16). Lithium perchlorate as an additive in this process was found to increase the rate further, but yields of the products were reduced.[86] Later, Aggarwal and co-workers[87] found that when Baylis–Hillman reaction is conducted in the presence of imidazolium-based ionic liquids, the products are obtained in low yields due to the direct addition of deprotonated imidazolium salt to the aldehyde (Scheme 10). Thus they concluded that imidazolium-based ionic liquids are not suitable for Baylis–Hillman reaction as they are not inert under the Baylis–Hillman conditions.

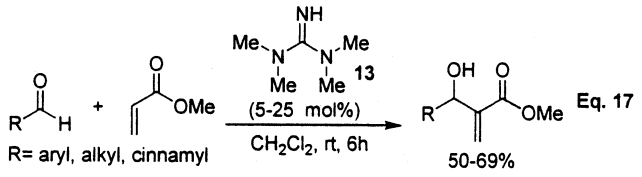


Scheme 10



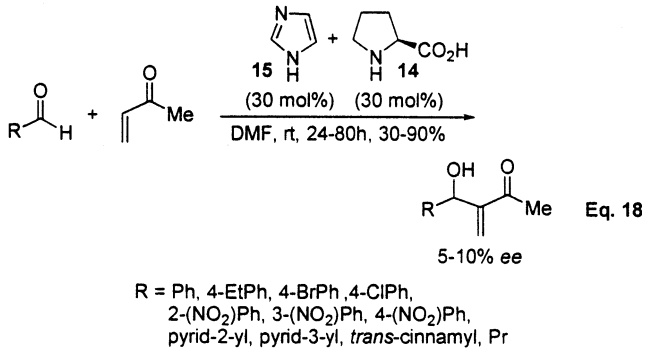
Leadbeater and co-workers[88,89] elegantly used tetramethylguanidine (TMG) (**13**) for the first time as a catalyst for performing the Baylis–Hillman reaction between various aldehydes and methyl acrylate (eq 17). Their attempts to use polymer-supported TMG complexes were unsuccessful. They also exam-

ined the effect of solvent/cocatalyst on the reaction rate.



Eq. 17

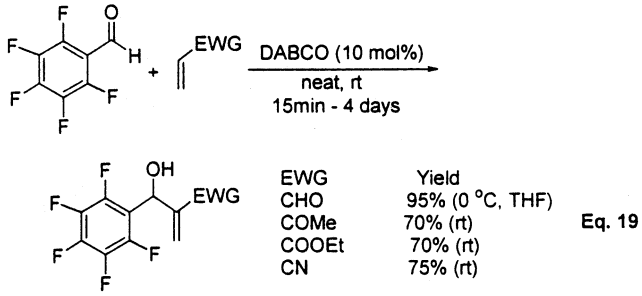
Shi and co-workers[90] investigated proline (**14**) catalyzed Baylis−Hillman reaction between aldehydes and MVK in the presence of Lewis bases such as imidazole (**15**), Et_3N, and DABCO (**1**) to provide the usual Baylis−Hillman adducts in reasonable yields (eq 18). However, enantioselectivities in these reactions were found to be very low (5−10%).



Eq. 18

Cheng and co-workers[91] and Gatri and El Gaied[92] independently reported the Baylis−Hillman reaction of aldehydes with cycloakenones using imidazole (**15**) in stoichiometric and catalytic quantities, respectively, in aqueous media (Scheme 11).[91,92]

Fluorinated aldehydes and aryl fluoromethyl ketones have been employed as electrophiles for coupling with various activated alkenes in the presence of DABCO (Scheme 12 and eq 19).[93,94]

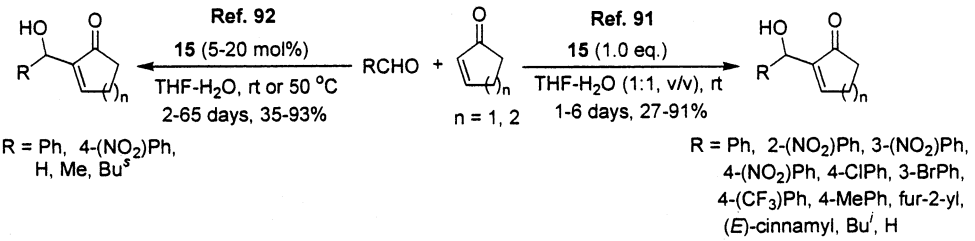


Eq. 19

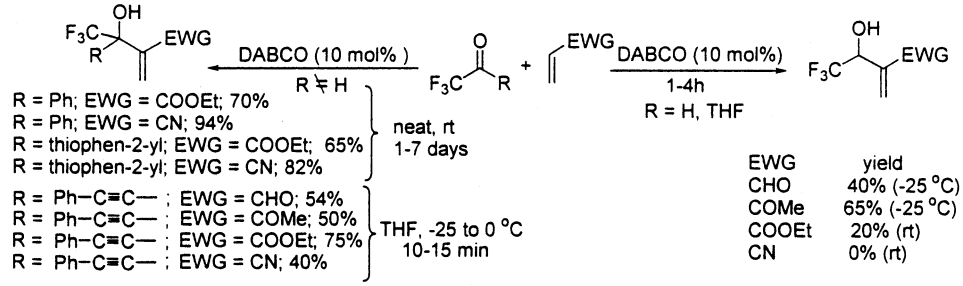
Burger and co-workers,[95] for the first time, used fluorinated imines as electrophiles in Baylis−Hillman coupling with acrylates under the influence of DABCO (100 mol %) in the presence of CaH_2 to provide the desired adducts which were subsequently transformed into the β-amino derivatives (Scheme 13). It is worth mentioning here that in the absence of CaH_2 the reaction was very slow. However, the actual role of the CaH_2 is not known.

Batra et al.[96] reported the Baylis−Hillman coupling of solid-phase-supported 5-isoxazolecarboxaldehyde with ethyl acrylate and 5-isoxazolecarboxaldehyde with solid-phase-supported acrylate esters for the generation of isoxazole-based combinatorial libraries (eq 20 and Scheme 14). These libraries were

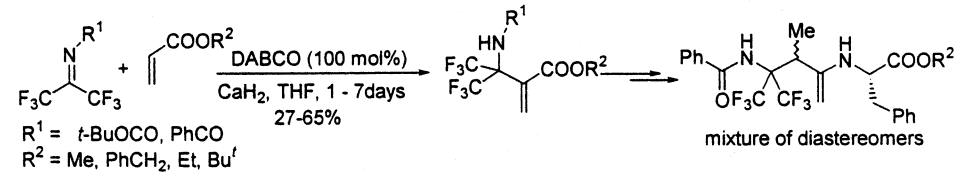
Scheme 11



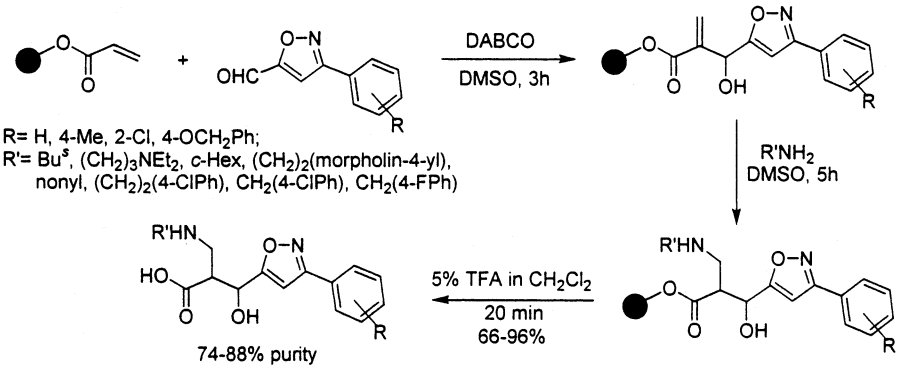
Scheme 12



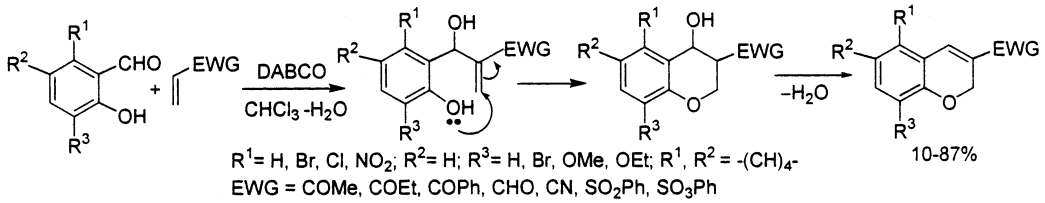
Scheme 13



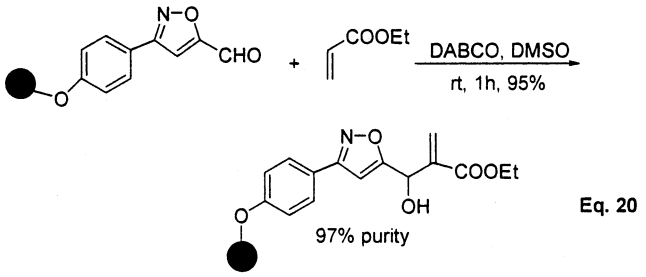
Scheme 14



Scheme 15

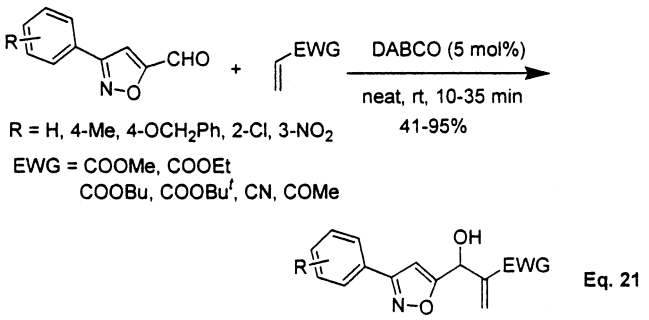


further evaluated for their antithrombin activity in vivo.[97]



Eq. 20

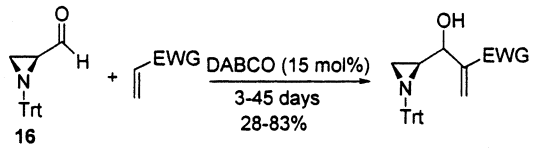
Subsequently, Batra and co-workers[98] found the 5-isoxazolecarboxaldehydes as fast reacting electrophiles in the Baylis–Hillman coupling with various activated alkenes (eq 21).



Eq. 21

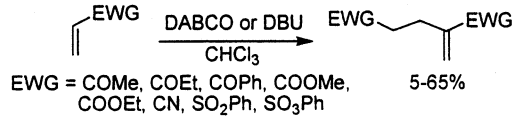
Zwanenburg and co-workers[99] reported the Baylis–Hillman coupling of *N*-tritylaziridine-2-(*S*)-carboxaldehyde (**16**) with activated alkenes. The diastereoselectivities in these reactions were found to be poor (eq 22).

Kaye and co-workers examined the reaction of salicylaldehydes with methyl acrylate in the presence of DABCO and found the formation of a mixture of various chromene and coumarin derivatives.[100] Subsequently, Kaye and Nocanda[101,102] described a simple one-pot methodology for the synthesis of 2*H*-1-chromenes via the reaction between activated alkenes and *o*-hydroxybenzaldehydes catalyzed by DABCO (Scheme 15). They also examined the dimerization of activated alkenes in the presence of DABCO/DBU (eq 23).



Eq. 22

EWG	*syn* : *anti*
COOMe	1:1
COOEt	1:1
CN	2:1
COMe	2:3
SO_2Ph	3:4



Eq. 23

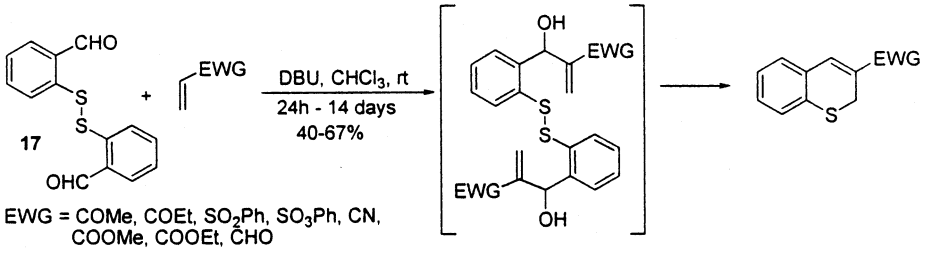
Kaye and Nocanda used 2,2′-dithiobenzaldehyde (**17**) as an electrophile for coupling with various activated olefins in the presence of DBU, to provide a convenient Baylis–Hillman synthesis of benzothiopyran derivatives (Scheme 16).[103]

Isatin derivatives (reactive cyclic α-keto amides) were employed for the first time as electrophiles by Garden and Skakle in the Baylis–Hillman coupling with activated alkenes (eq 24).[104]

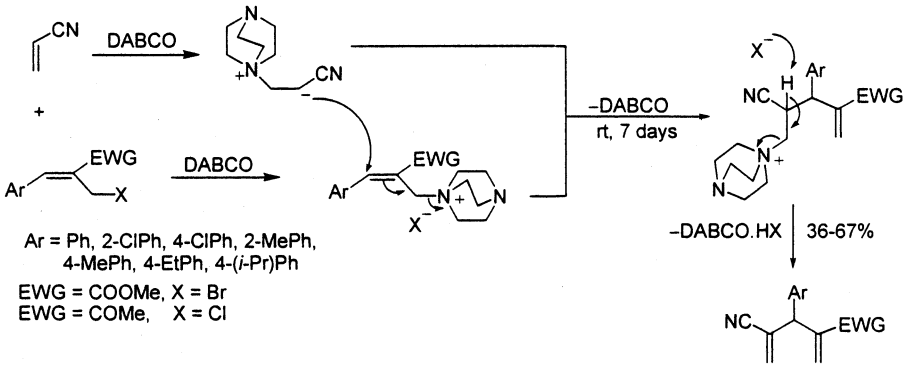
Kitazume and co-workers[105] successfully employed 3-fluoromethylprop-2-enamide **18** as an electrophile in the Baylis–Hillman reaction with activated alkenes under the influence of ionic liquids (eq 25).

Our research group[106] demonstrated, for the first time, the application of allyl halides as electrophiles in the Baylis–Hillman reaction. Thus, the reaction between allyl bromides/allyl chlorides, derived from the corresponding Baylis–Hillman adducts (of meth-

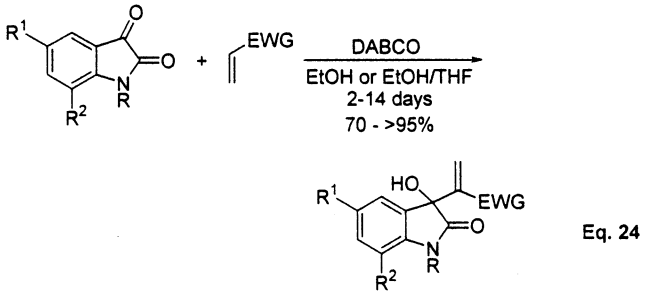
Scheme 16



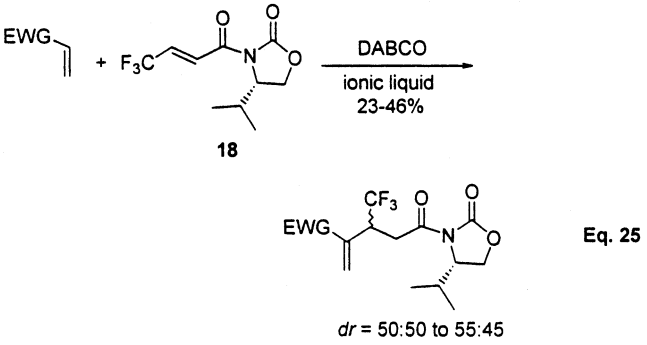
Scheme 17



yl acrylate and MVK) with acrylonitrile in the presence of DABCO, resulted in the formation of 3-substituted functionalized 1,4-pentadienes (Scheme 17). However, the reaction did not work with simple allyl bromide (3-bromoprop-1-ene) or allyl bromides derived from the Baylis–Hillman adducts of corresponding aliphatic aldehydes.



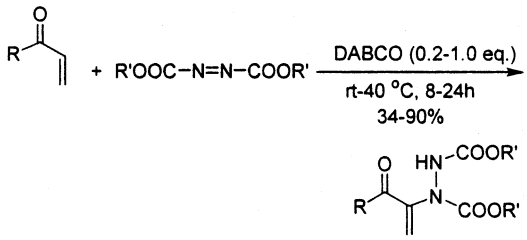
Eq. 24



Eq. 25

Subsequently, our research group has extended this strategy to allyl bromides derived from alkyl 3-hydroxy-2-methylenepropanoates, thus developing a simple methodology for one-pot synthesis of 2,4-functionalized 1,4-pentadienes (Scheme 18).[107]

Kamimura and co-workers[108] employed azodicarboxylates as electrophiles in a Baylis–Hillman reaction with alkyl vinyl ketones in the presence of DABCO as a catalyst (eq 26). However, similar reaction did not proceed with methyl acrylate.



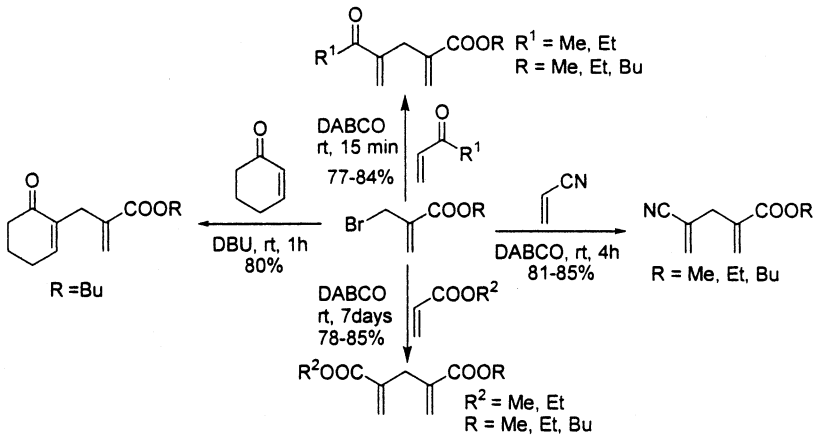
Eq. 26

Azizi and Saidi[109] reported an interesting Baylis–Hillman reaction between in situ prepared iminium salt **19** [obtained via the treatment of aldehyde with (trimethylsilyl)dialkylamine] and activated alkene. These products undergo Michael addition with (trimethylsilyl)dialkylamines to give the diamines in good yields (Scheme 19).

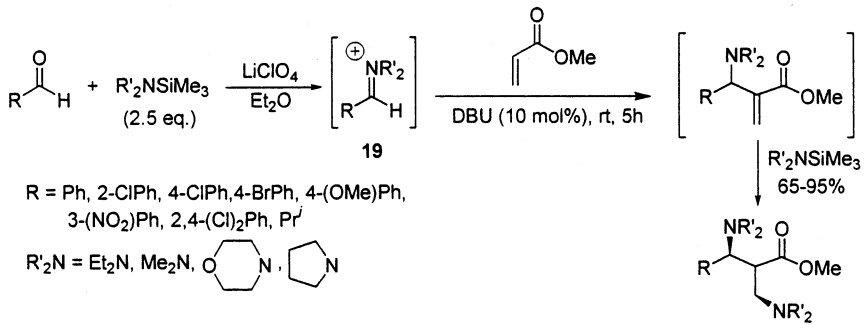
Richter and Jung[110] reported a three-component reaction between a polymer-bound acrylate, aldehydes, and sulfonamides under the influence of DABCO in dioxane to provide the desired Baylis–Hillman adducts in good yields (eq 27). They also examined the application of resin-bound acrylate in performing the Baylis–Hillman reaction with various aldehydes. The resulting products were converted into the amino alcohols via the treatment with amines (Scheme 20).[111]

Kunzer and co-workers[112] described the Baylis–Hillman reaction on solid support and utilized these

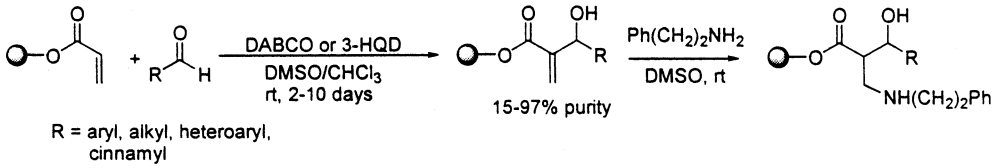
Scheme 18



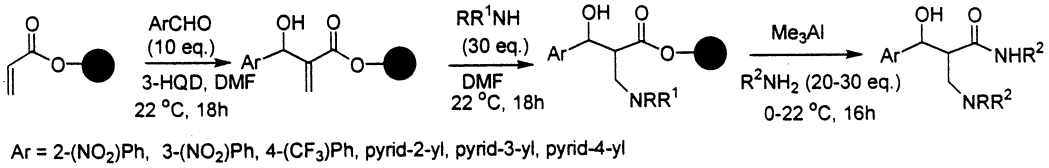
Scheme 19



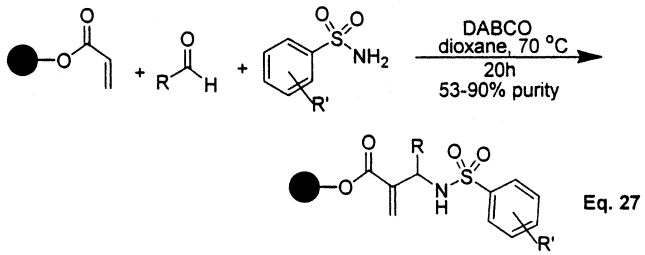
Scheme 20



Scheme 21



adducts for combinatorial synthesis of substituted racemic 3-hydroxypropionamides (Scheme 21).



Kundu and co-workers[113] described a combinatorial synthesis of arylpropanolamines using the Baylis–Hillman methodology according to Scheme 22.

Recently, Balan and Adolfsson reported a three-component reaction between acrylates, aldehydes, and tosylamines, leading to the formation of Baylis–Hillman amine adducts (along with normal Baylis–Hillman alcohols as side products) (eq 28). They also noticed that these reactions are best catalyzed by DABCO or 3-HQD with $La(OTf)_3$ in the presence of molecular sieves in propan-2-ol.[114]

Aggarwal and co-workers[115] examined the role of protic solvents (water, formamide) and hydrogen bonding in the rate acceleration of the Baylis–Hillman reaction. They observed significant rate

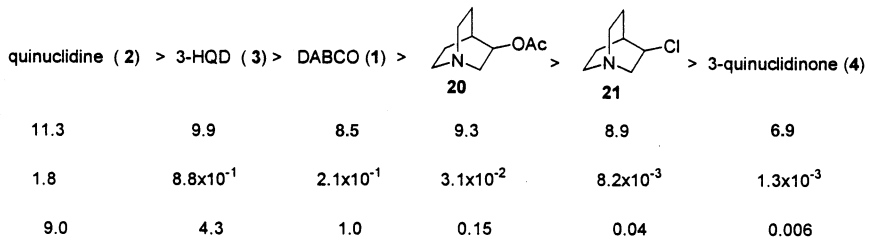
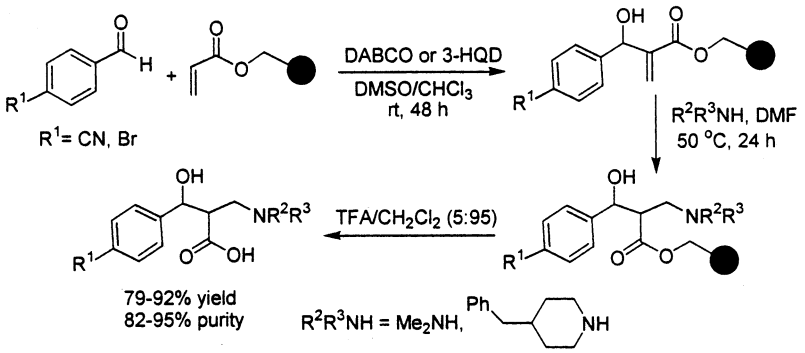
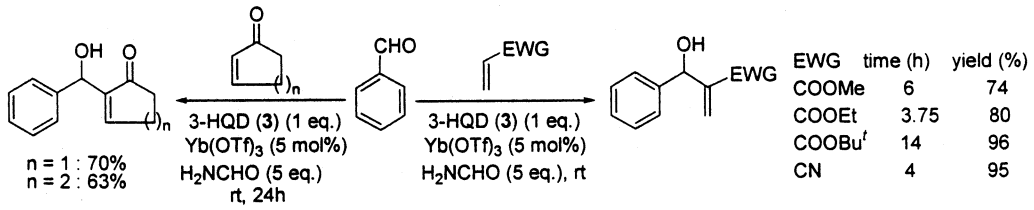


Figure 2.

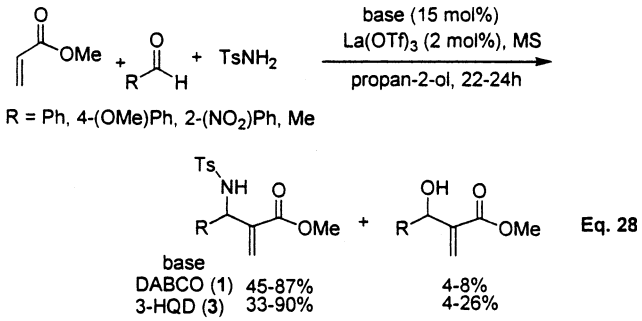
Scheme 22



Scheme 23



acceleration when the reaction was conducted in 5 equiv of formamide. Further acceleration of the reaction is observed in the presence of $Yb(OTf)_3$ (5 mol %) (Scheme 23).



Very recently, Aggarwal and co-workers[116] examined the correlation between pK_a of a variety of quinuclidine-based catalysts (Figure 2) and their reactivities in the Baylis−Hillman reaction. They found that quinuclidine in protic solvents has the highest pK_a (11.3/H_2O) and is the most active catalyst for this reaction. They also observed that a combination of quinuclidine and methanol is the most optimum protocol for the Baylis−Hillman reaction. Less reactive activated olefins such as vinyl sulfones, acrylamides, and β-substituted α,β-unsaturated esters have also been employed in this reaction using quinuclidine as a catalyst (Scheme 24).[116]

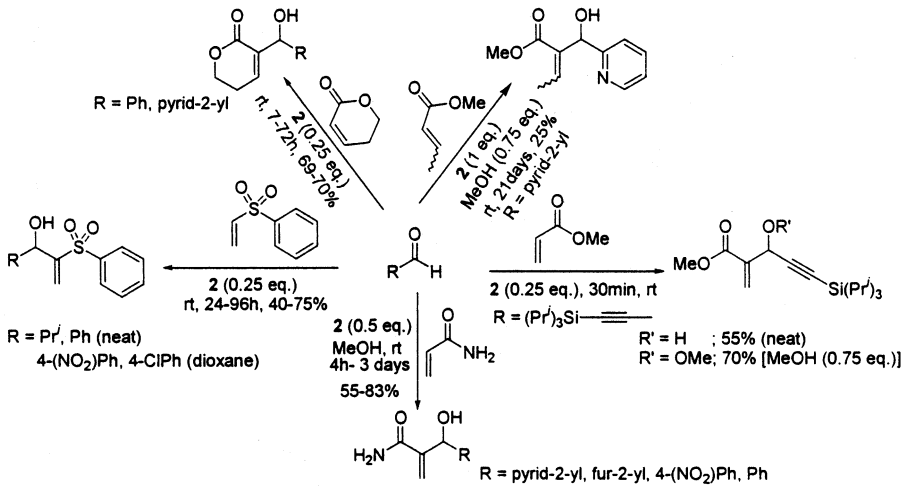
2.2. Asymmetric Baylis–Hillman Reaction

Asymmetric version of the Baylis−Hillman reaction can in principle be carried out with a chiral source in any one of the three essential components (electrophile, activated alkene, and catalyst). In fact, several efforts have been made in this direction using various chiral-activated alkenes such as chiral acrylates and chiral acrylamide derivatives,[24−28,117−126] electrophiles such as enantiopure aldehydes,[24−28,122,127−132] and asymmetric catalysts.[24−28,118,133−136] Gilbert et al. described a remarkable influence of high pressure on the enantioselectivity.[122] Thus, the reaction of (−)-menthyl acrylate (**22**) with benzaldehyde in the presence of DABCO at high pressure (7.5 kbar) provides the corresponding Baylis−Hillman adduct with 100% *de*, whereas the same reaction at atmospheric pressure provides the desired adduct in 22% *de* only (Scheme 25).

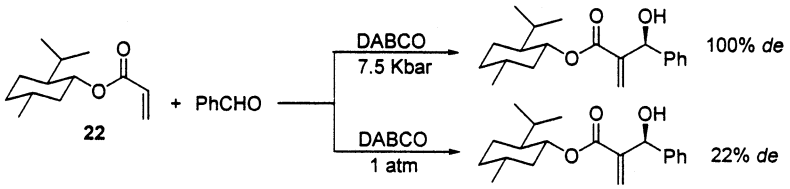
Later on, Marko and co-workers[136] also examined high-pressure mediated Baylis−Hillman reaction between aliphatic aldehydes and MVK using the quinidine (**23**) as a catalyst (eq 29). They obtained the high enantioselectivity of 45% in the reaction of MVK with cyclohexanecarboxaldehyde at 3 kbar in the presence of quinidine.

Applications of various enantiopure electrophiles such as(*S*)-*O*-protected lactaldehyde (**24**),[127] (*S*)-3-benzyloxybutyraldehyde (**25**),[128] α-dialkylamino and α-(*N*-acylamino)aldehydes (**26**),[129,130] *N*-phenylsulfonyl-*L*-prolinal (**27**),[130] enantiopure ortho-substituted

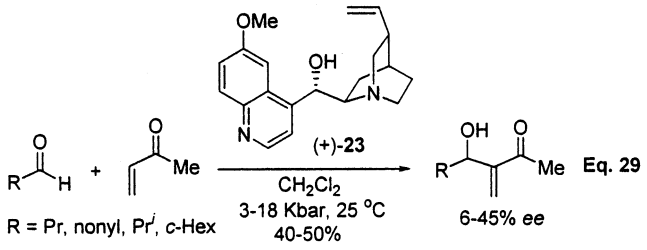
Scheme 24



Scheme 25



benzaldehyde tricarbonylchromium complex (**28**),[131,132] (*R*)-myrtenal (**29**), isopropylidene (*R*)-glyceraldehyde



(**30**),[122] etc. (Figure 3), in achieving high diastereoselectivity in a Baylis−Hillman reaction, have been studied.

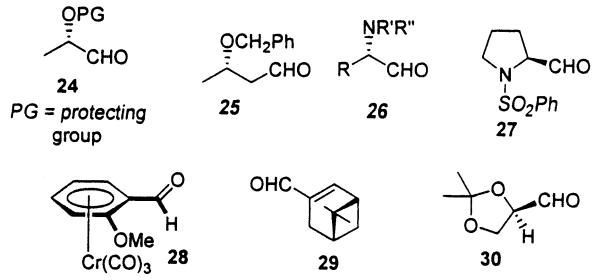


Figure 3.

Recently, Alcaide and co-workers used optically pure 1-alkenyl(alkynyl)-4-oxoazetidine-2-carbaldehydes (**31**) as electrophiles in the Baylis−Hillman reaction with MVK to provide resulting adducts with very high diastereoselectivities (Scheme 26). These adducts were further transformed into functionalized β-lactams fused to medium-sized rings (Scheme 26).[137,138]

Subsequently, Alcaide and co-workers[139] successfully used enantiopure 3-oxo-2-azetidinones **32** for Baylis−Hillman coupling with activated alkenes to provide the resulting products in high diastereoselectivities (eq 30).

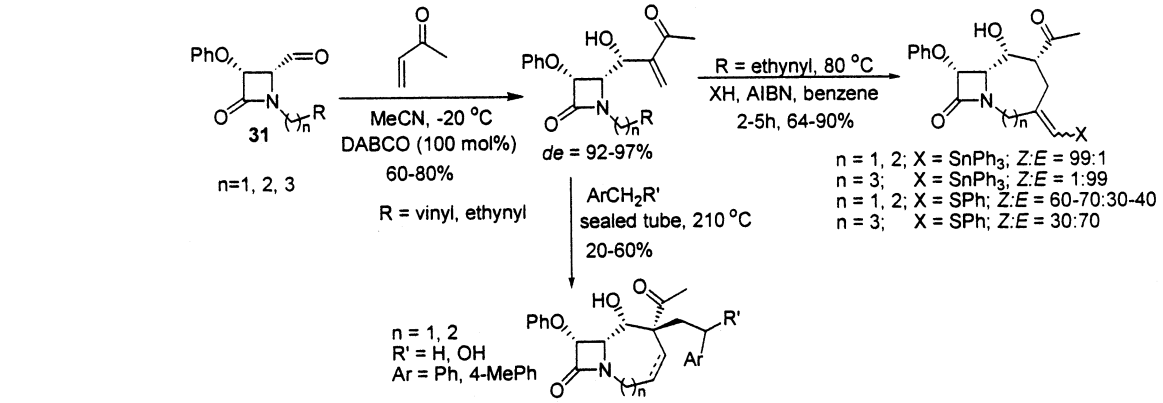
Later on, enantiomerically pure *N*-sulfinimines (**33**) were used by Aggarwal and co-workers, as electrophiles in the Baylis−Hillman coupling with methyl acrylate in the presence of 3-HQD (**3**) and $In(OTf)_3$, to provide the desired adducts in good diastereoselectivities. One representative example is mentioned in eq 31.[140]

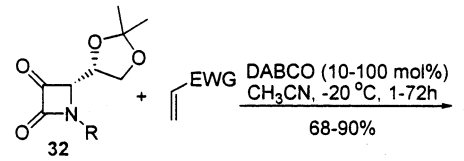
Bussolari et al.[141] reported a reaction between chiral aminoaldehydes **34** and methyl acrylate in the presence of DABCO. The resultant products were obtained in good yields with moderate diastereoselectivities. One such example is described in eq 32. They also observed that reaction between acrylamides and *N*-protected amino aldehydes afforded the *N*-acyl hemiaminals (non-Baylis−Hillman adducts) in moderate to good yields under the Baylis−Hillman conditions (eq 33).

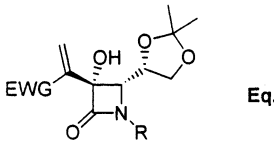
Considerable progress has been achieved in an asymmetric version of this reaction using various chiral acrylate esters (**22**, **35**−**41**) derived from various chiral auxiliaries such as cyclohexanol derivatives, (*R*)-(+)-pentolactone and camphor sultam derivatives (Figure 4).[24−28,117−126]

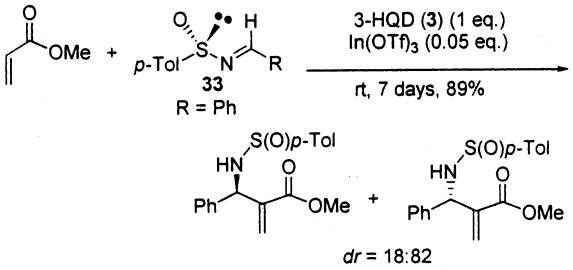
Recently, Leahy and co-workers[142] reported an elegant asymmetric version of the Baylis−Hillman reaction using enantiopure acrylamide **42**, derived from camphor sulfonic acid (Scheme 27). This methodology has been employed for synthesis of biologically important natural product (−)-tulipalin B (**44**) (Scheme 28). They also transformed optically pure dioxane derivatives **43** into various chiral molecules including the ones with chiral quaternary centers (Scheme 29).[143,144]

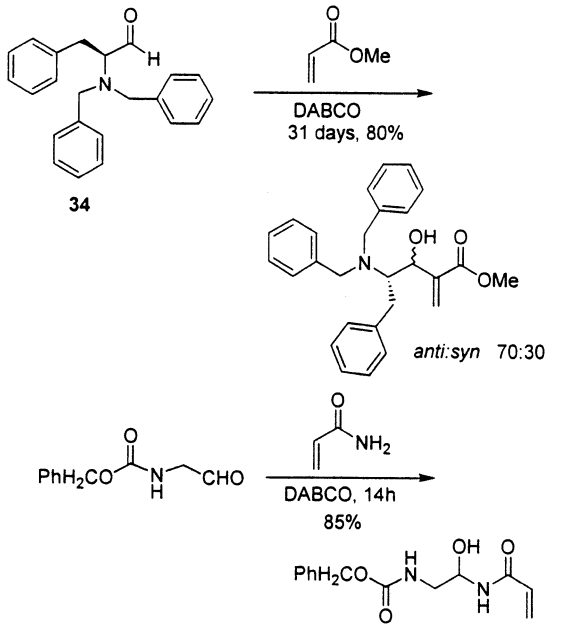
Scheme 26











Subsequently, Yang and Chen[145] designed a highly efficient enantiopure acryloylhydrazide **45** for Baylis−Hillman coupling with various aldehydes to provide the resulting adducts in very high diastereoselectivities. They also observed the reversal of stereoselectivity by changing the solvent from DMSO to THF/H_2O. One representative example is described in eq 34.

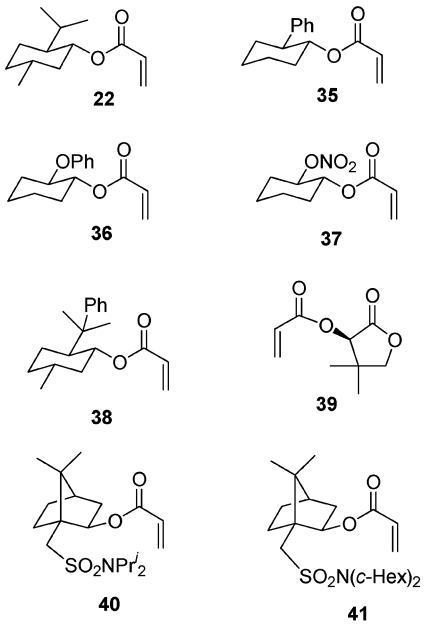
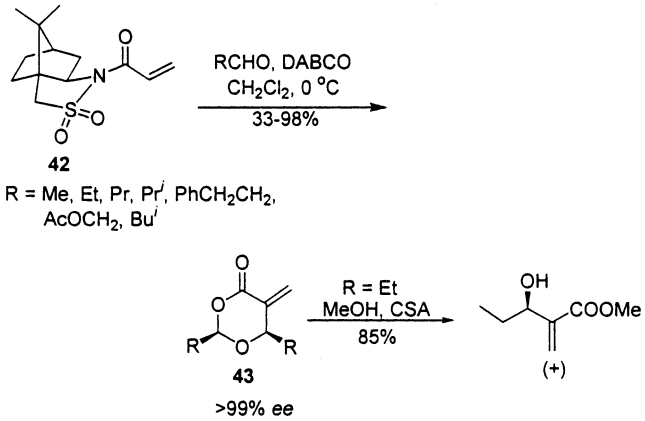


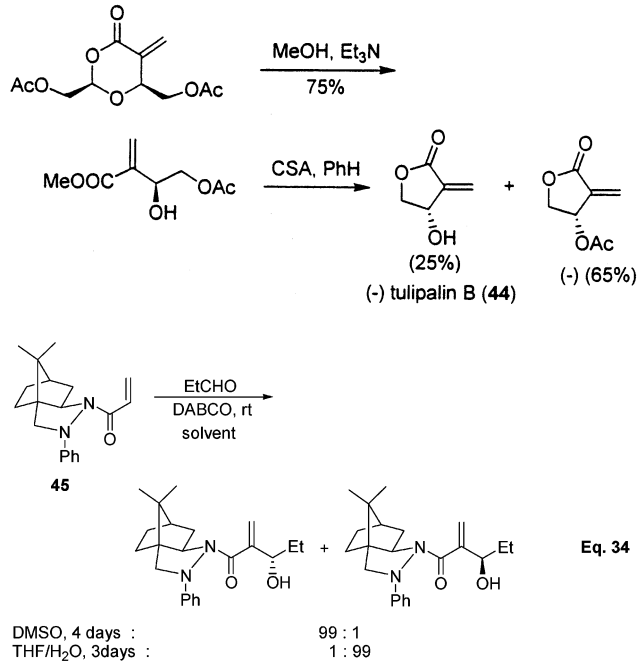
Figure 4.

Scheme 27



Several other activated alkenes **46**−**50** (Figure 5) have also been prepared from various chiral sources and their potential for the asymmetric Baylis−

Scheme 28



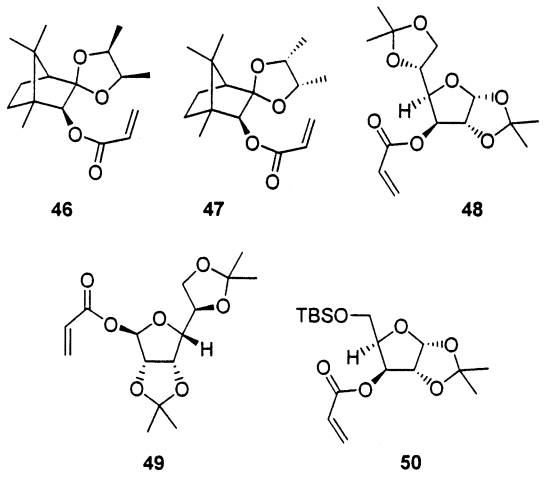


Figure 5.

Hillman reaction has been examined. However, the diastereoselectivities were found to be poor to moderate (0−40% *de*).[146,147]

Organic chemists also directed their efforts at achieving an asymmetric version of Baylis−Hillman reaction using various chiral tertiary amine catalysts.[25−28] Quinidine **23** has been the first catalyst studied in this direction, which provided poor enantioselectivities (maximum up to 20% *ee*).[25,118] Hiroma and co-workers employed enantiopure DABCO {2,3-bis(benzyloxymethyl)-1,4-diazabicyclo(2.2.2)octane} (**51**) (Figure 6) as a catalyst to provide Baylis−

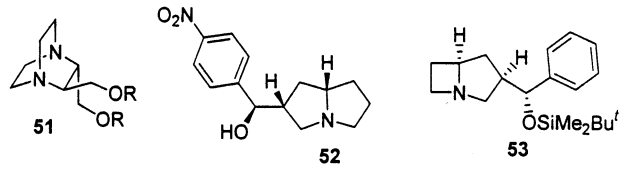


Figure 6.

Hillman adducts up to 47% enantiomeric purity.[134,135] Barrett et al.[148] described an interesting enantiopure pyrrolizidine **52** (Figure 6) mediated Baylis−Hillman reaction of alkyl vinyl ketones (MVK and EVK) with aromatic aldehydes to provide the desired adducts in 21−72% enantiomeric purities (Scheme 30). Subsequently, they employed enantiopure bicyclic azetidine derivative **53** as a catalyst in a Baylis−Hillman reaction of EVK with 2-nitrobenzaldehyde, which provided the desired adduct in 68% yield with 26% *ee* (Scheme 30).[149] However, bicyclic azetidine **53** offered faster reaction rates.[149]

Hatakeyama and co-workers[150,151] examined the application of various tertiary amines **23** and **54**−**57** (Figure 7) derived from cinchona alkaloids for

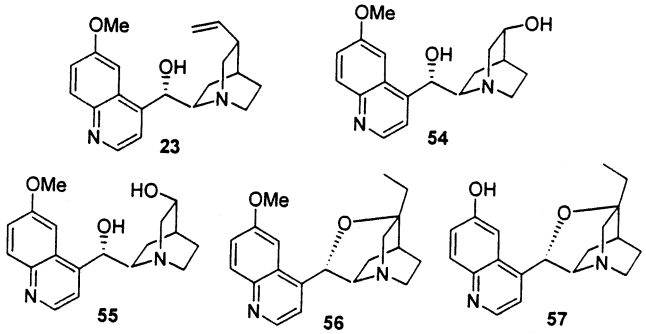
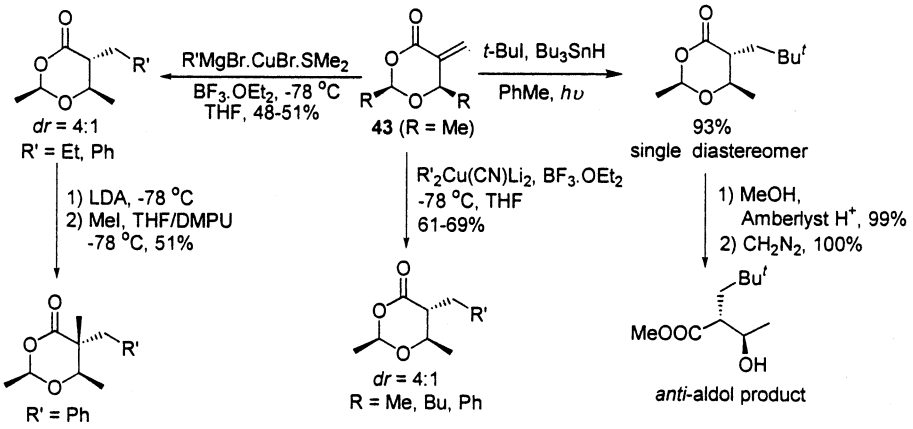


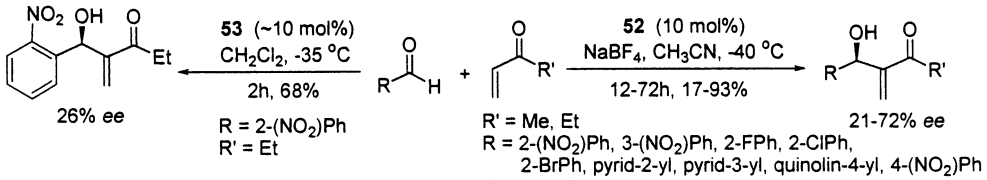
Figure 7.

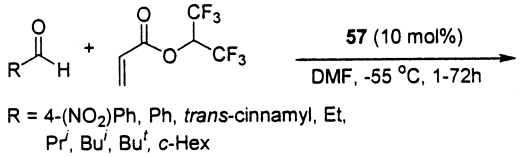
effecting enantioselective Baylis−Hillman reaction. The tertiary amine **57** derived from quinidine (**23**)

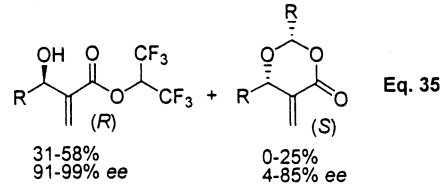
Scheme 29



Scheme 30







Eq. 35

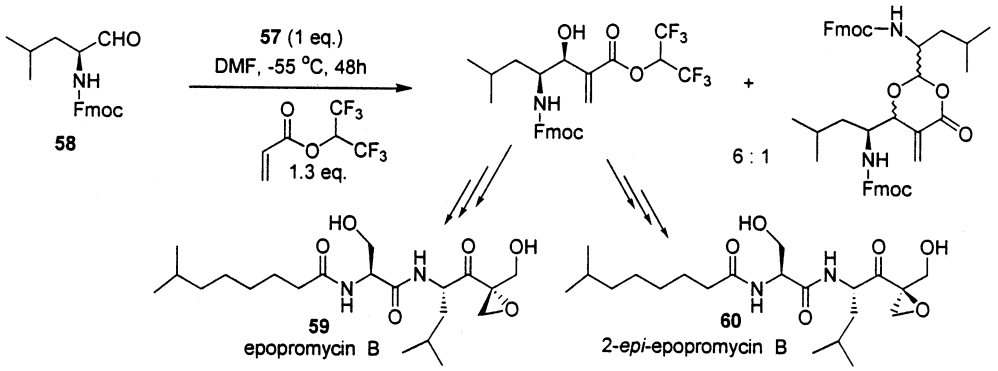
was found to be the best catalyst for Baylis−Hillman coupling between 1,1,1,3,3,3-hexafluoroisopropyl acrylate and various aldehydes, thus providing the desired adducts up to 99% enantiomeric purity (eq 35).

Subsequently, Hatakeyama and co-workers[152] successfully employed this methodology for the synthesis of important biologically active molecules epopromycin B (**59**) and 2-*epi*-epopromycin B (**60**) starting from (*S*)-*N*-Fmoc-leucinal (**58**) (Scheme 31).

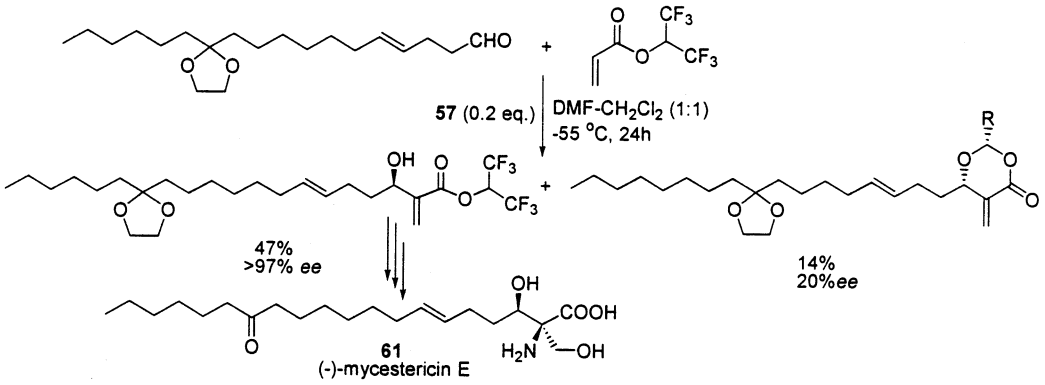
Hatakeyama also reported an elegant synthesis of (−)-mycestericin E (**61**), a potent immunosuppressive agent, which involves asymmetric Baylis−Hillman reaction catalyzed by **57** as the key step (Scheme 32).[153]

Later on, Shi and co-workers[154] employed this catalyst (**57**) for asymmetric coupling of aldehydes with α-naphthyl acrylate and MVK, which provided resulting allyl alcohols in poor to good enantioselectivities (Scheme 33). Subsequently, they also found this catalyst (**57**) provides high levels of enantiosec-

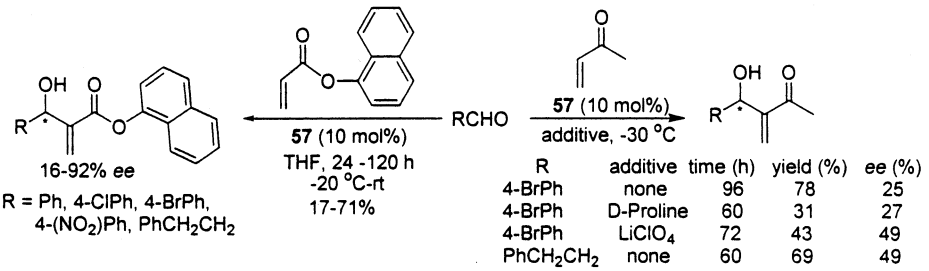
Scheme 31



Scheme 32

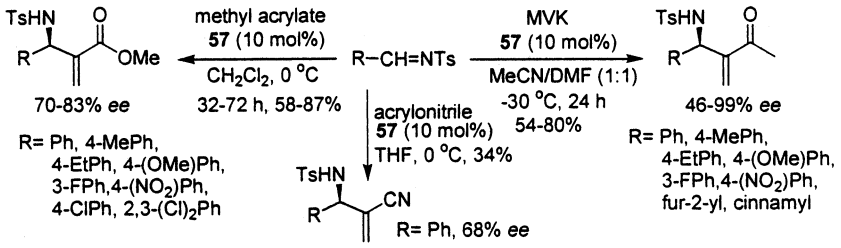


Scheme 33

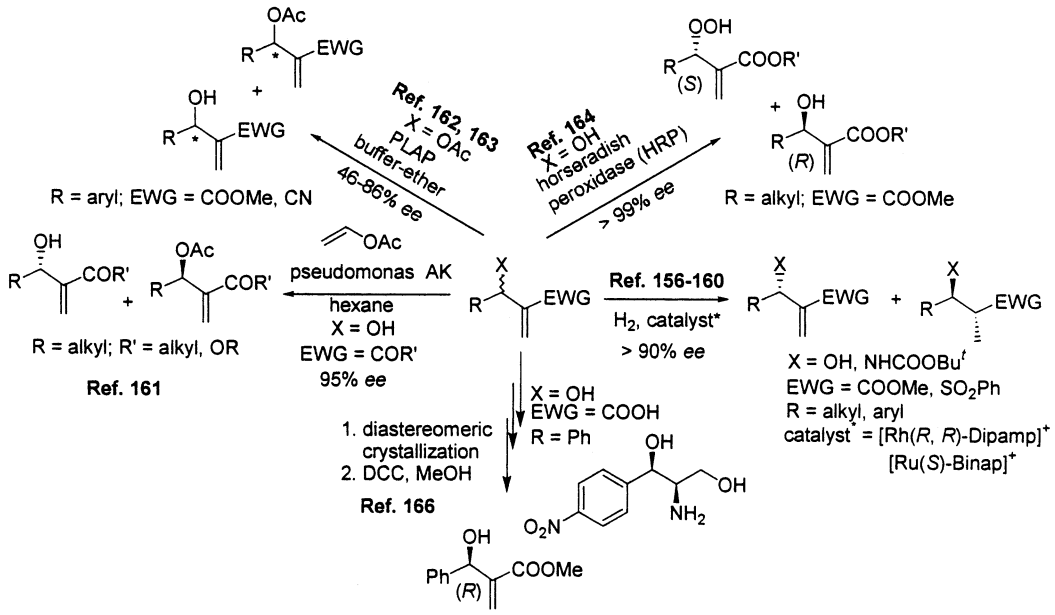


R	additive	time (h)	yield (%)	*ee* (%)
4-BrPh	none	96	78	25
4-BrPh	D-Proline	60	31	27
4-BrPh	$LiClO_4$	72	43	49
$PhCH_2CH_2$	none	60	69	49

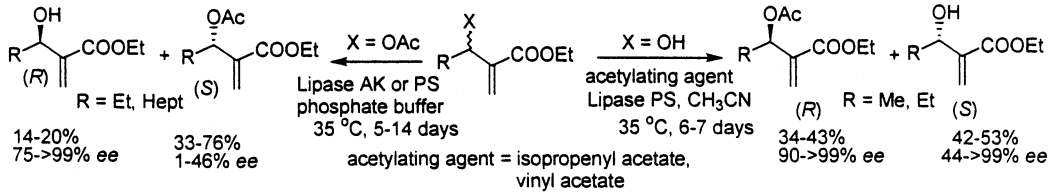
Scheme 34



Scheme 35



Scheme 36



tivities in the coupling of aldimines with MVK/methyl acrylate/acrylonitrile (Scheme 34).[155]

The enantiomerically pure (or enriched) Baylis–Hillman adducts were also obtained via (1) kinetic resolution of alcohols using asymmetric hydrogenation methodology,[53,54,156–160] (2) kinetic resolution of alcohols and their derivatives via chemoenzymatic methodology (Scheme 35),[161–164] and epoxidation[165] (3) diastereomeric crystallization (Scheme 35).[166]

Lipase PS and AK have been successfully employed for kinetic resolution of the Baylis–Hillman adducts (obtained from ethyl acrylate and aliphatic aldehydes) and their acetate derivatives as described in Scheme 36.[167]

Trost et al.[168] reported elegant deracemization of Baylis–Hillman adducts following an alternative approach, DYKAT with $(dba)_3Pd_2{\cdot}CHCl_3$ and enantiopure ligands **62**–**65** (Figure 8). One representative example is described in Scheme 37. They also examined the influence of solvent, ligand, and ligand concentration on regio- and enantioselectivity. Subsequently, Trost et al. applied this methodology for the preparation of enantiomerically pure dihydrobenzofuran derivative **66**, which was further transformed into Furaquinocin E (**67**) (Scheme 38).[169]

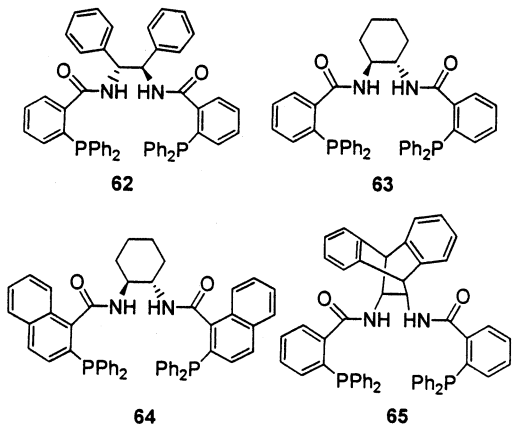
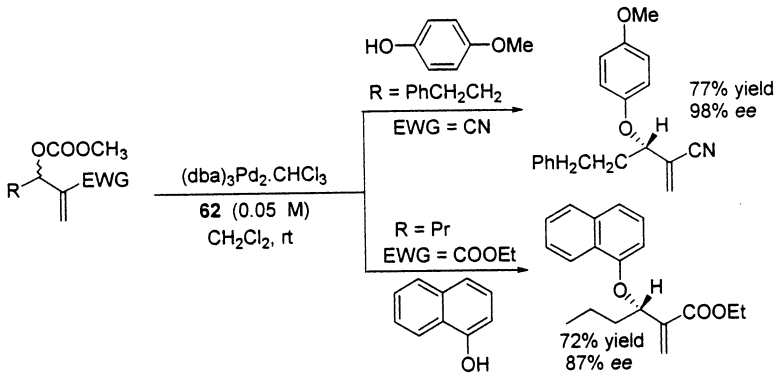
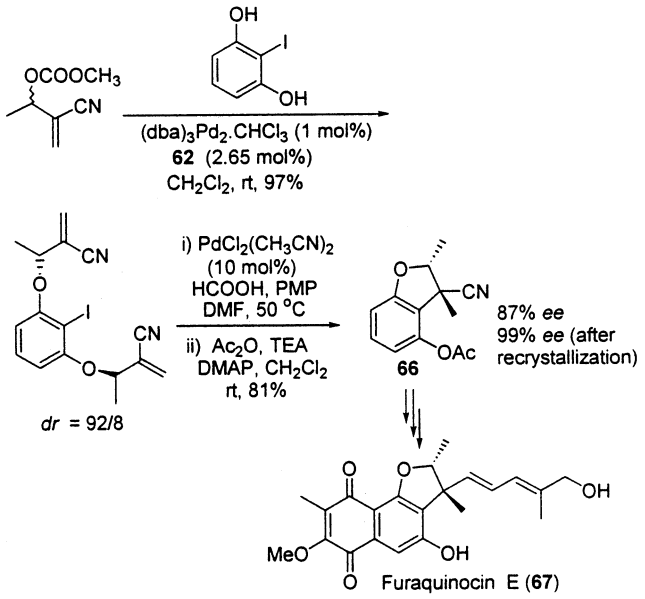


Figure 8.

Scheme 37



Scheme 38

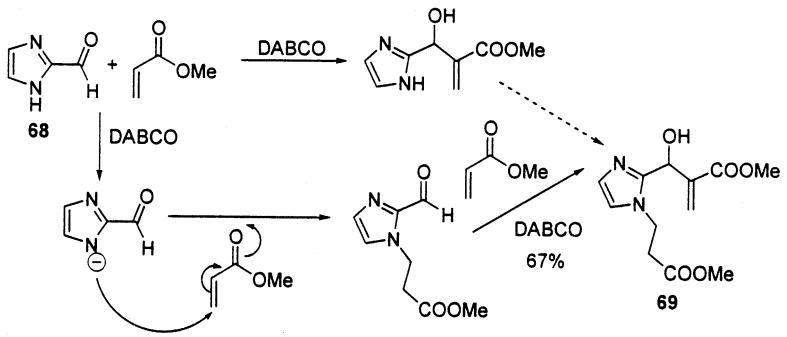


2.3. New Discoveries in the Baylis–Hillman Reaction

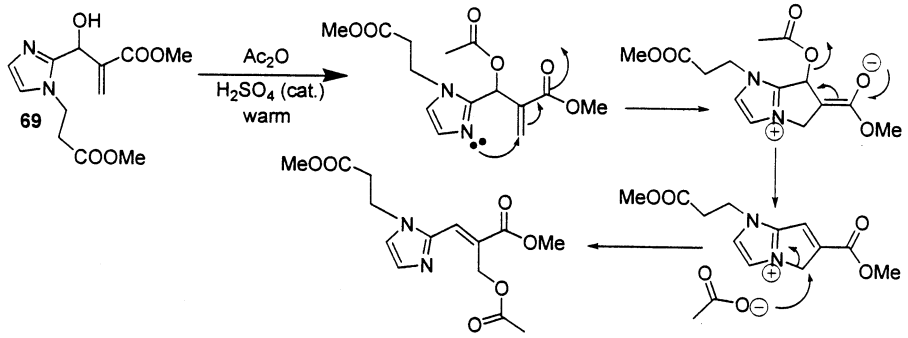
Drewes and Rohwer[170] reported an interesting reaction of 2-formylimidazole (**68**) with methyl acrylate, leading to the formation of disubstituted product **69** via the tandem Michael addition and Baylis–Hillman reactions (Scheme 39). They also observed that acetylation of these allylic alcohols afforded directly the rearranged acetates of Baylis–Hillman adducts (Scheme 40).

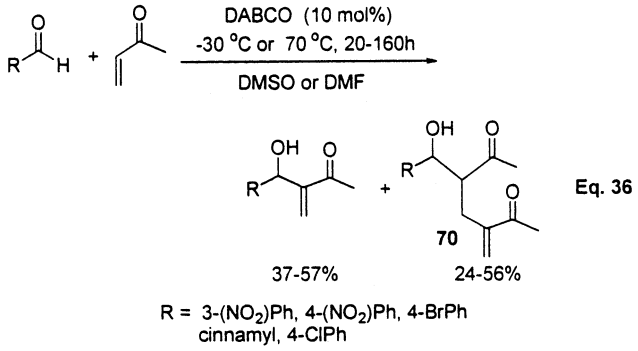
Shi and co-workers[171] have recently found that Baylis–Hillman reaction between aryl aldehydes and MVK (1:4) with DABCO provides the diadducts **70** besides the normal Baylis–Hillman adducts and the yield of diadducts **70** can be increased up to 56% by increasing the amount of MVK (eq 36). However, they found that a similar reaction with DMAP provides predominantly normal Baylis–Hillman adducts. Subsquently, they examined the reaction between PVK and aryl aldehydes, which provided the diadducts **71** predominantly along with minor amounts of PVK

Scheme 39



Scheme 40





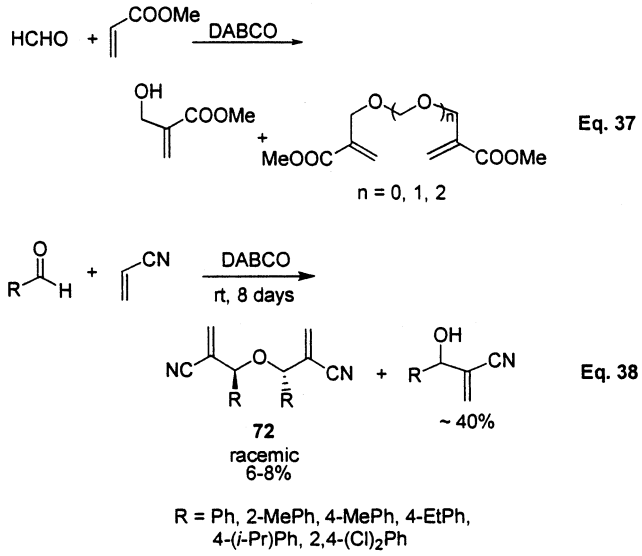
Eq. 36

dimer.[172] They also observed that phenyl acrylate and phenyl thioacrylate gave mostly the usual Baylis–Hillman adducts (Scheme 41).

In the literature it was reported that ethers are formed as side products in the Baylis–Hillman reaction between formaldehyde and methyl acrylate (eq 37).[173,174]

Our research group has reported a new tandem coupling between acrylonitrile and aryl aldehydes under the catalytic influence of DABCO involving the construction of two carbon–carbon bonds and one carbon–oxygen bond, leading to isolation of dl-functionalized bis-allyl ethers **72** (in 6–8% isolated yields) along with the usual Baylis–Hillman adducts (eq 38).[175]

Very recently, Rayner and co-workers[176] conducted the Baylis–Hillman reaction between methyl acrylate and aryl aldehydes in $scCO_2$ and noticed the formation of bis-allyl ethers as side products. In fact, they separately treated Baylis–Hillman adducts with DABCO in $scCO_2$, which provided the bis-allyl ethers **73** in high yields as meso and dl mixtures (Scheme 42). They also found the formation of allyl benzyl ethers **74** when they carried out reaction in the presence of benzyl alcohol and molecular sieves in $scCO_2$, thus describing a novel three-component reaction for the synthesis of fuctionalized allyl ethers (Scheme 42).



Eq. 37

Eq. 38

3. Other Catalytic Sources

3.1. Phosphine-Catalyzed Baylis–Hillman Reaction

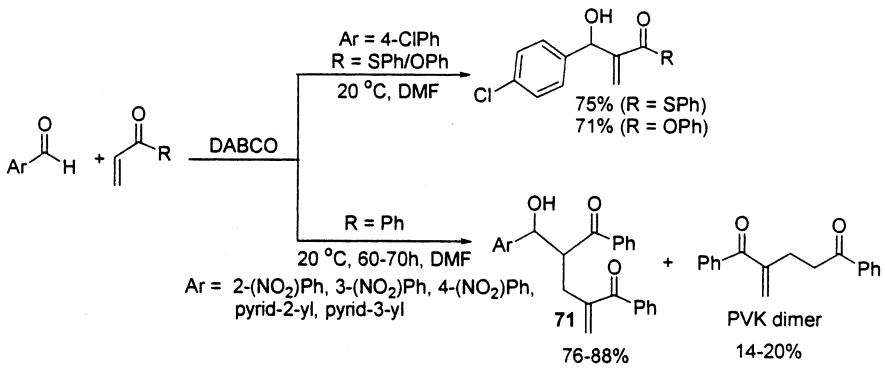
In the year 1963, Rauhut and Currier obtained a patent on phosphine-catalyzed dimerization of activated alkenes.[177] Later (in the year 1965), McClure[178] and Balzer and Anderson[179] independently examined dimerization of acrylonitrile with triarylphosphines. In 1968, Morita and co-workers described an elegant reaction between aldehydes and activated alkenes in the presence of tricyclohexylphosphine, leading to the formation of multifunctional molecules.[180] In the following year (1969) Morita and Kobayashi[181] reported another interesting reaction between activated alkenes and fumaric/maleic esters in the presence of tricyclohexylphosphine to provide an interesting addition product **75** (eq 39). Subsequently, phosphines have been used as catalysts in various reactions involving the coupling of aldehydes and activated alkenes.[182–186]

Recently, Soai and co-workers[187] successfully employed (*S*)-BINAP [(*S*)-**76**] as a catalyst for performing an asymmetric version of Baylis–Hillman reaction between various acrylates and pyrimidine carboxaldehydes to provide the resultant adducts in 9–44% enantiomeric purities (eq 40).

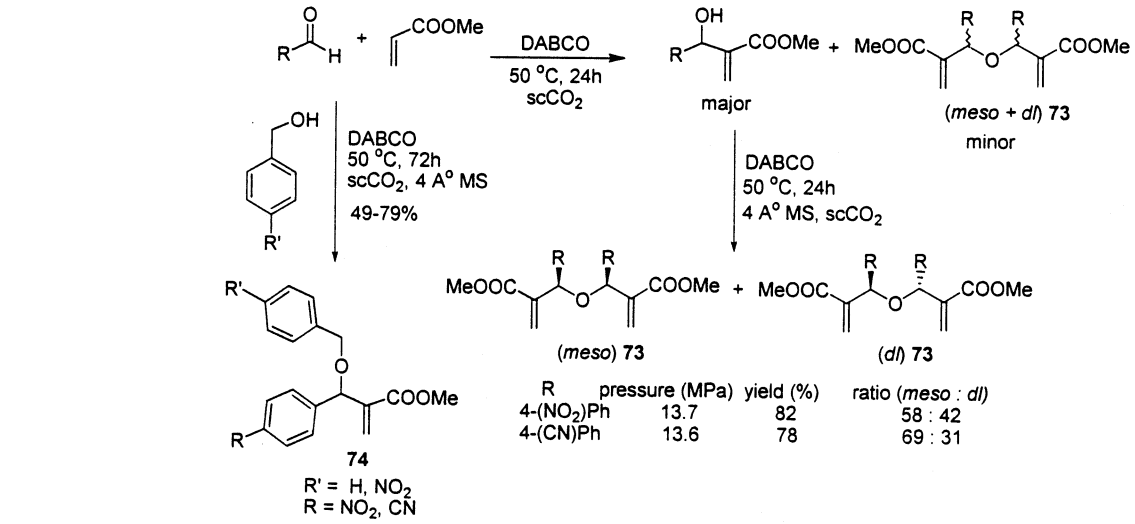
Zhang and co-workers[188] examined the application of various chiral phosphines **77**–**79** (Figure 9) for performing the Baylis–Hillman reaction. Though these phosphine catalysts did not offer any satisfactory enantioselectivities (2–19% *ee*), some rate acceleration was observed in the case of **78** (eq 41).

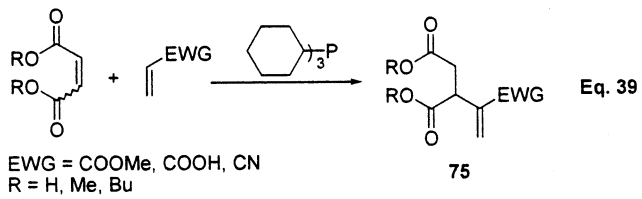
Yamada and Ikegami[189] reported an efficient Baylis–Hillman reaction between aldehydes and activated alkenes catalyzed by Bu_3P in the presence of

Scheme 41

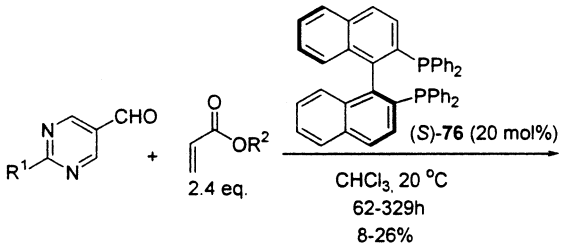


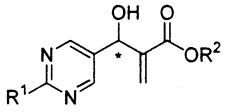
Scheme 42





Eq. 39

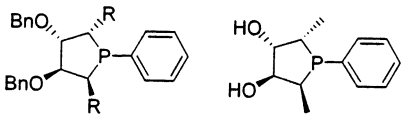


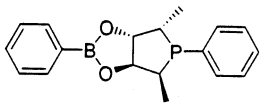


Eq. 40

9-44% *ee*

R^1 = H, Me
R^2 = Me, Et, Pr^i

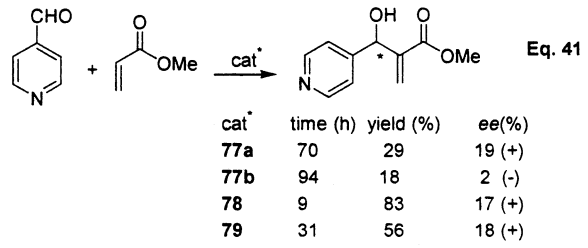




79

Figure 9.

racemic BINOL (**80**) in THF to give the corresponding α-methylene-*β*-hydroxyalkanones in high yields (eq 42). It is proposed that racemic BINOL (**80**) (Figure 10) functions as a Bronsted acid to activate the carbonyl group of an aldehyde and activated alkene. Their attempts to perform a chiral version of this reaction using (*R*)-BINOL [(*R*)-**80**] resulted in low



Eq. 41

cat*	time (h)	yield (%)	*ee*(%)
77a	70	29	19 (+)
77b	94	18	2 (-)
78	9	83	17 (+)
79	31	56	18 (+)

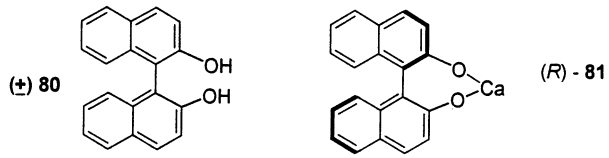
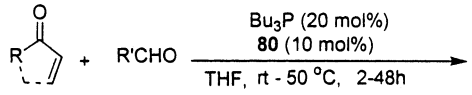


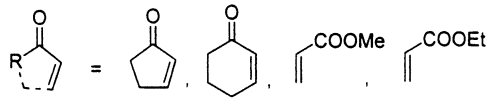
Figure 10.

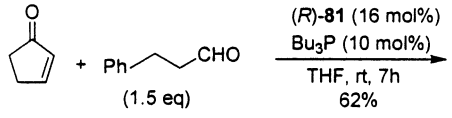
enantioselectivities (<10%). However, they achieved better results using calcium chiral catalyst **81** (Figure 10) along with Bu_3P. Thus, the coupling of cyclopent-2-en-1-one with hydrocinnamaldehyde catalyzed by



Eq. 42

52% - quant.

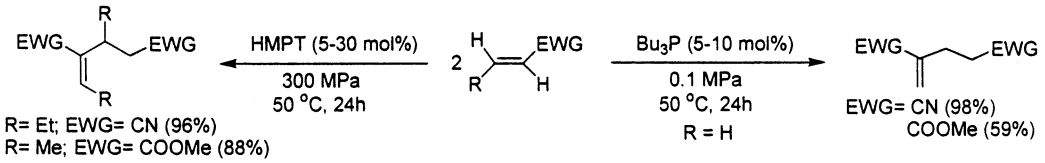




Eq. 43

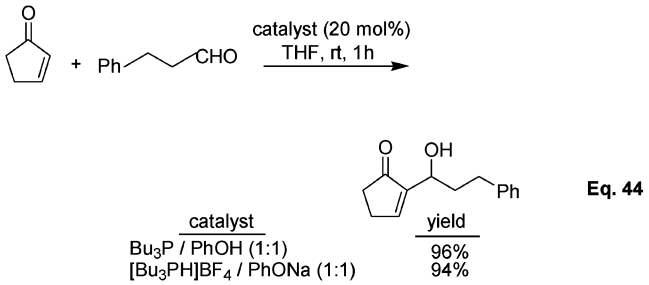
56% *ee*

Scheme 43



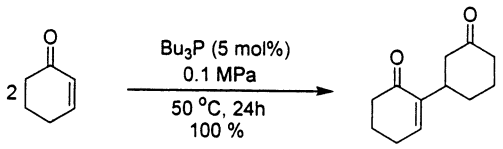
Bu_3P in the presence of **81** provided the desired adduct in 56% enantiomeric purity (eq 43).

Later, Netherton and Fu[190] modified the Ikegamis's procedure using air-stable trialkylphosphonium salt for performing Baylis–Hillman reaction of cyclopent-2-en-1-one with aralkyl aldehyde (eq 44).



Eq. 44

Jenner[191] reported phosphine-catalyzed dimerization of methyl acrylate and acrylonitrile under Baylis–Hillman conditions at ambient pressure (Scheme 43). He also noticed that the β-substituted derivatives generally require high pressures. However, cyclohex-2-en-1-one underwent dimerization smoothly under these conditions with 100% yield (eq 45).

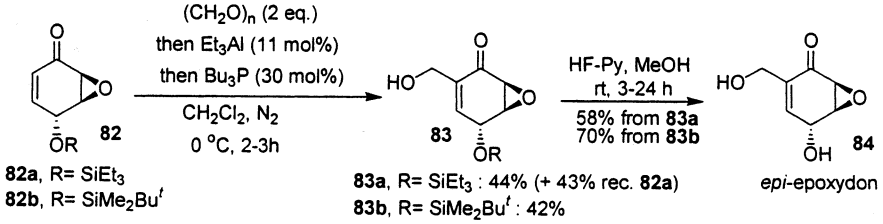


Eq. 45

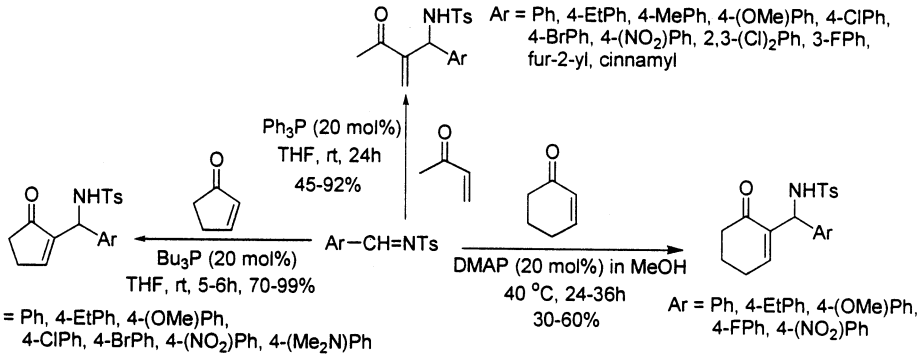
Genski and Taylor[192] successfully employed epoxy-activated alkene **82** for coupling with paraformaldehyde in the presence of Et_3Al/Bu_3P to provide the Baylis–Hillman adduct **83**, which was further transformed into *epi*-epoxydon (**84**), a bioactive natural product (Scheme 44).

Shi and Xu[193] examined the Baylis–Hillman reaction of cyclohex-2-en-1-one and cyclopent-2-en-1-one with DMAP, Bu_3P, and DBU in various solvents. They noticed that the reaction of cyclohex-2-en-1-one with *N*-arylidene-4-methylbenzenesulfonamides in the presence of DMAP provided the usual Baylis–Hillman adducts (Scheme 45). They observed that reaction of cyclopent-2-en-1-one with *N*-arylidene-4-methylbenzenesulfonamides provided the desired Baylis–Hillman adducts both in the presence of DMAP (24h) and Bu_3P (5–6h) (Scheme 45) whereas the reaction between cyclohex-2-en-1-one with *N*-arylidene-4-methylbenzenesulfonamides in the presence of DBU or Bu_3P provided abnormal products **85a** and **85b** in minor amounts along with the usual Baylis–Hillman adducts (Scheme 46). Subsequently, they examined the Baylis–Hillman reaction between MVK and *N*-arylidene-4-methylbenzenesulfonamides using various amine and phosphine bases and found that DMAP, DABCO, Ph_3P, and dppe afforded the usual Baylis–Hillman adducts (best results in the case of Ph_3P) (Scheme 45), whereas Bu_3P provided abnormal Baylis–Hillman products **86a** and **86b** (Scheme 46).[194] Shi and co-workers found that the reaction of cyclohept-2-en-1-one with *N*-arylidene-4-methylbenzenesulfonamides afforded the usual Baylis–Hillman

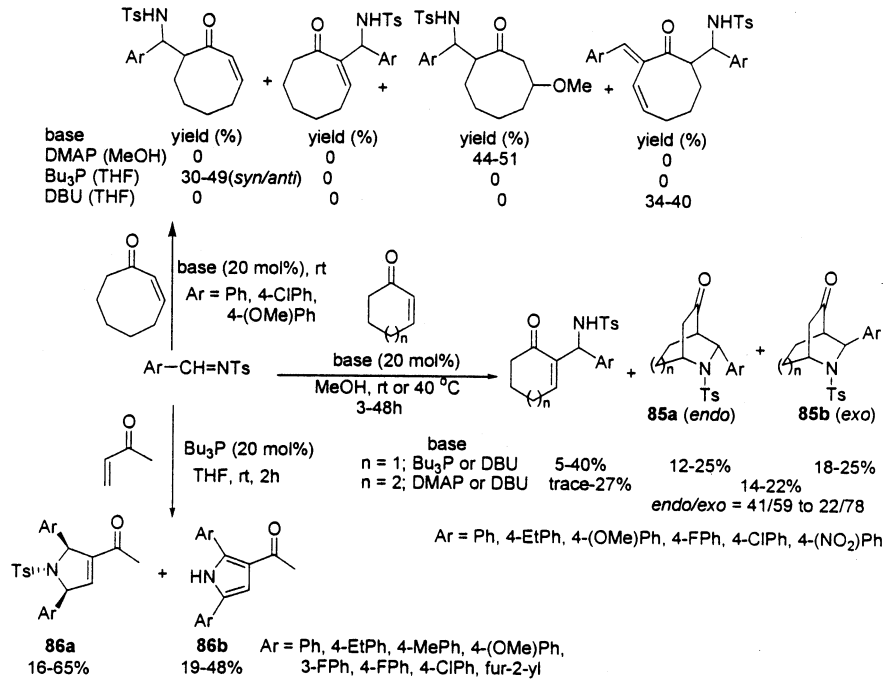
Scheme 44



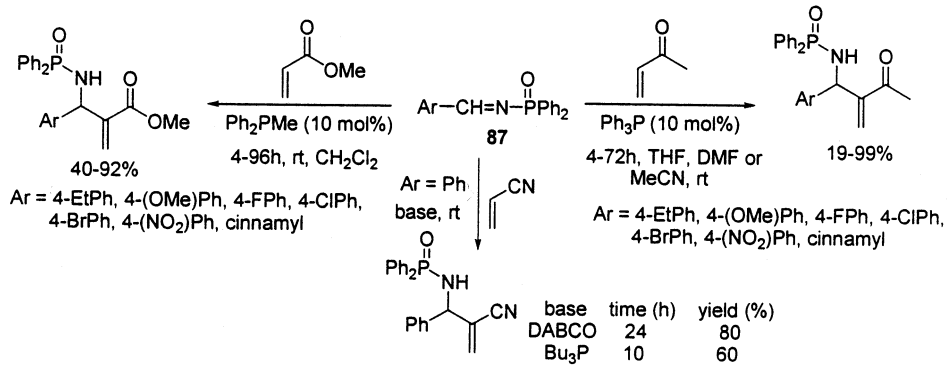
Scheme 45



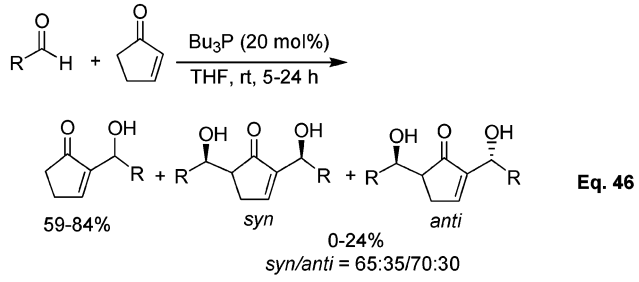
Scheme 46



Scheme 47



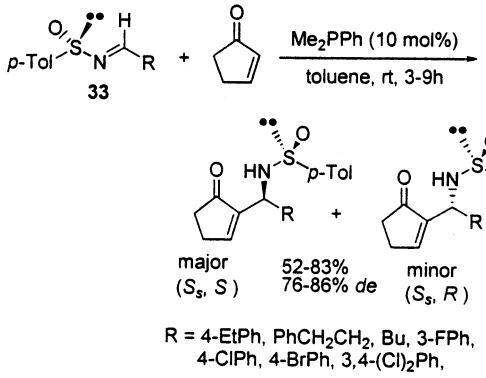
adducts along with abnormal adducts, whereas the reaction of cyclooct-2-en-1-one with *N*-arylidene-4-methylbenzenesulfonamides provided different aldol products depending upon the Lewis base employed (no Baylis–Hillman adduct was formed in any of the cases) (Scheme 46).[195] They observed the formation of aldol products along with the usual Baylis–Hillman adducts in the reaction between cyclopent-2-en-1-one and aromatic aldehydes in the presence of Bu_3P (eq 46).



Eq. 46

R = Ph, 4-ClPh, 4-EtPh, 4-(OMe)Ph

Later, Shi and Xu found dimethylphenylphosphine (Me_2PPh) in toluene as a better catalytic system for diastereoselective Baylis–Hillman reaction between cycolpent-2-en-1-one and enantiopure *N*-sulfinimines 33 (eq 47).[196]



Eq. 47

Subsequently, Shi and Zhao employed *N*-arylidenediphenylphosphinamide **87** as an electrophile in the Baylis–Hillman reaction with various activated alkenes such as methyl acrylate, MVK, and acrylonitrile using Ph_2PMe, Ph_3P, and DABCO, respectively, as catalysts (Scheme 47).[197]

3.2. Chalcogenide-Mediated Baylis–Hillman Reaction

Kataoka et al.[198,199] developed an interesting reaction between vinyl ketones and various aldehydes catalyzed by sulfides or selinides (Me_2S, PhSMe, and **88**−**91**) (Figure 11) in the presence of Lewis acid

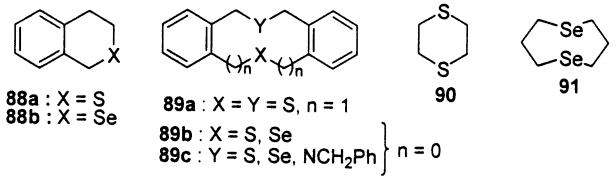


Figure 11.

$TiCl_4$, providing the Baylis−Hillman adducts in moderate to good yields (Scheme 48). Selinide **91** and Me_2S were proved to be the best catalysts for this reaction. They also examined the application of a variety of Lewis acids [BF_3•OEt_2, $SnCl_4$, $AlCl_3$, $EtAlCl_2$, Et_2AlCl, $HfCl_4$, and $Hf(OTf)_4$] and found that $TiCl_4$ offers better results.

Later on, they examined the applicability of 2,6-diphenyl-4*H*-chalcogenopyran-4-ones **92** and **93** (Figure 12) as catalysts in the Baylis−Hillman reaction. They found that **92b** and **93a** offer better results in the presence of $TiCl_4$ (eq 48).[200]

Subsequently, Kataoka extended this strategy to thioacrylates. Thus, the treatment of ethyl thioacrylate with aldehydes under the influence of Me_2S and $TiCl_4$ provided the chloro aldol products as major products along with minor amounts of the usual Baylis−Hillman adducts. Treatment of the crude mixture with DBU or Et_2NH provided the desired Baylis−Hillman adducts, whereas similar treatment with Ti(O-*i*-Pr)$_4$ provided the isopropyl esters of the Baylis−Hillman adducts (Scheme 49).[201,202] On the basis of all these transformations, a plausible mechanism for chalcogeno-Baylis−Hillman reaction proposed by Kataoka is presented in Scheme 50.[203]

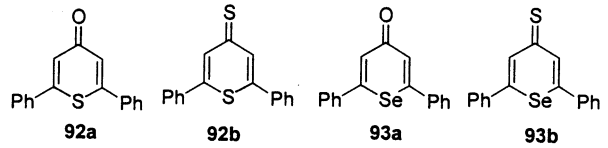
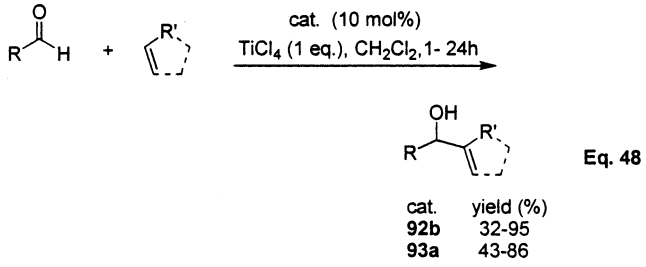
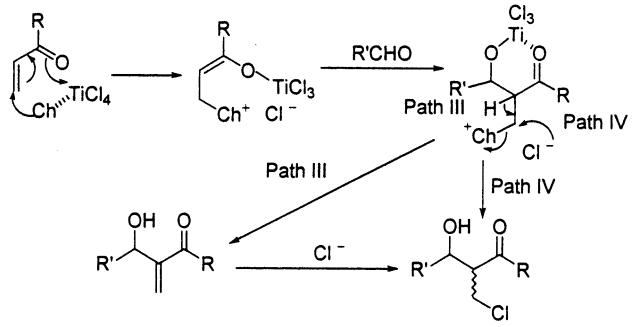


Figure 12.

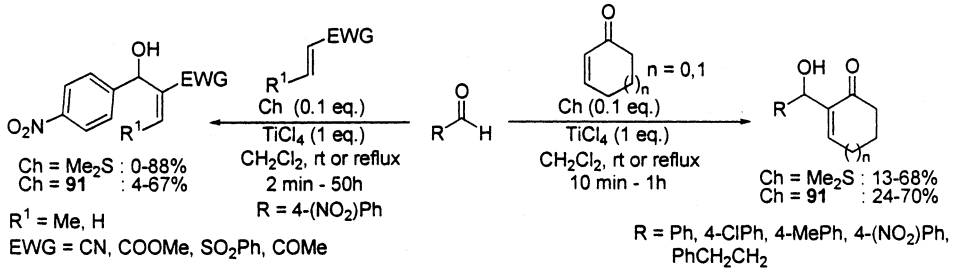


Scheme 50

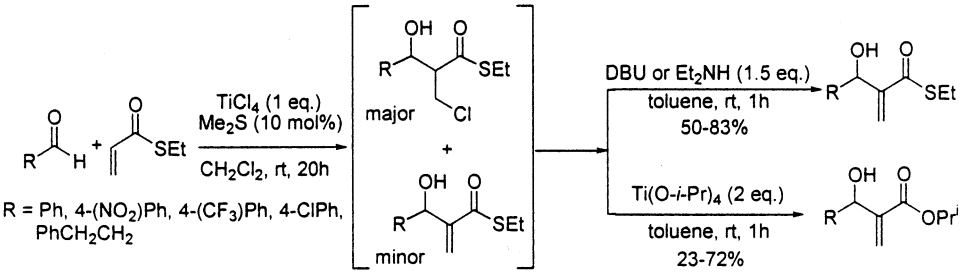


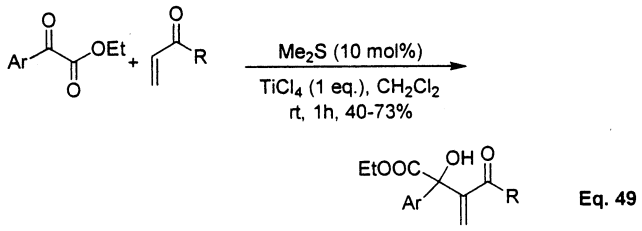
Our research group[204] has described the chalcogeno-Baylis−Hillman reaction between α-keto esters and alkyl vinyl ketones, thus leading to the formation of 2-aryl-2-hydroxy-3-methylene-4-oxoalkanoates in moderate to good yields (eq 49). It was also found that the similar coupling reaction with DABCO as a catalyst is ineffective.

Scheme 48



Scheme 49



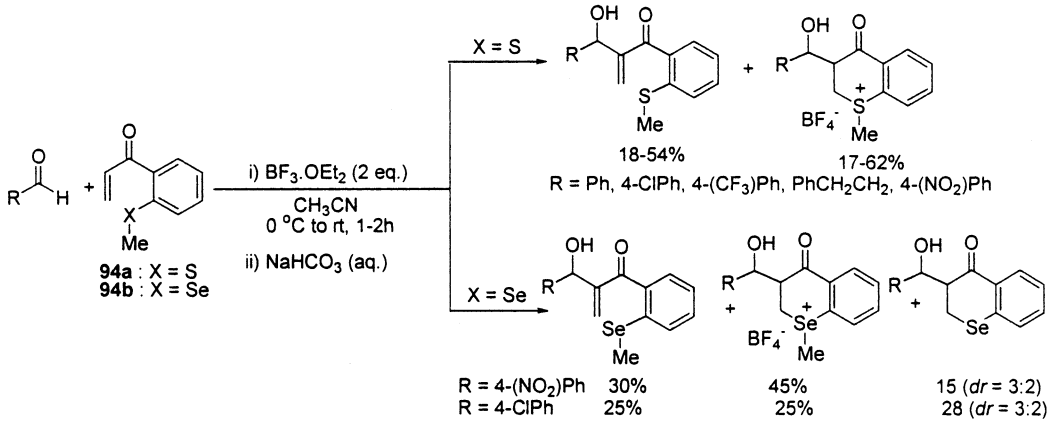


Kataoka et al.[205] has reported a self-assisted (intramolecular) chalcogeno-Baylis−Hillman reaction of 1-[2-(methylsulfanyl)phenyl]prop-2-en-1-one (**94a**) (or selino congener **94b**) with aryl aldehydes catalyzed by BF_3·OEt_2 providing the Baylis−Hillman adducts and onium salts (Scheme 51). Other Lewis acids such as TiF_4 (33% yield) or $Yb(OTf)_3$ (21% yield) did also promote the reaction. Later, they observed that the coupling of **94a** with ketones, α-diketones, and α-keto esters in the presence of BF_3·OEt_2 provided only Baylis−Hillman adducts in moderate yields (Scheme 52).[206]

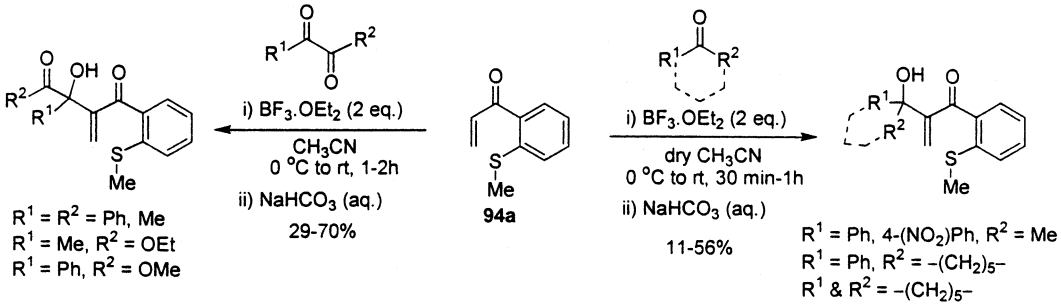
Subsequently, they reported the reaction between alkyl vinyl ketones and aldehydes in the presence of BBr_3·SMe_2 or BCl_3·SMe_2, which provided Baylis−Hillman adducts, aldol products and α-halomethyl enones when the reaction was quenched with $NaHCO_3$, and allyl halides when the reaction was quenched with H_2O.[207] One representative example is presented in Scheme 53. They also observed that reaction of 4-nitrobenzaldehyde with methyl acrylate or cyclohex-2-en-1-one or thioacrylate in the presence BBr_3·SMe_2 gave exclusively Baylis−Hillman adducts when quenched with $NaHCO_3$. A similar reaction of 4-nitrobenzaldehyde with ethyl thioacrylate in the presence of BBr_3·SMe_2 provided the corresponding allyl bromide after aqueous workup. Interestingly, the reaction between 4-nitrobenzaldehyde and cyclohex-2-en-1-one in the presence of BBr_3·SMe_2 provided 4-nitrobenzylphenol **95** and acetal **96** (due to subsequent aromatization) after an aqueous workup (Scheme 54).

Kataoka and co-workers[208,209] also investigated the asymmetric version of the chalcogeno-Baylis−Hillman reaction with enantiopure hydroxy chalco-

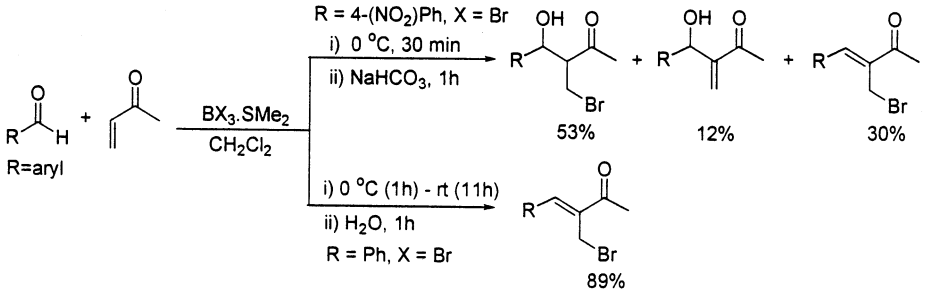
Scheme 51



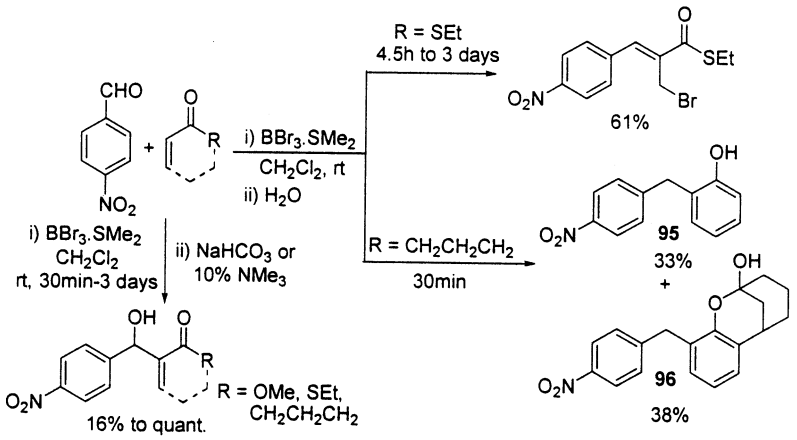
Scheme 52



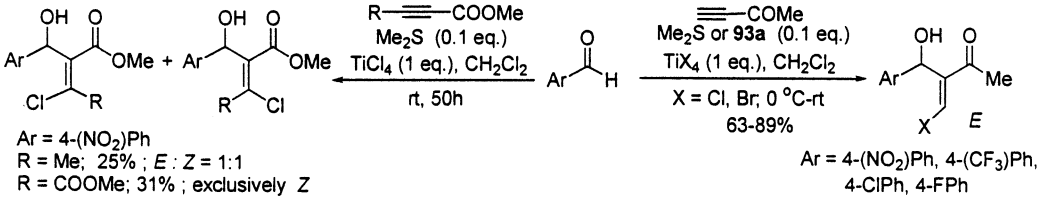
Scheme 53



Scheme 54



Scheme 55



genides **97**−**101** (Figure 13). Some of the hydroxy chalcogenides gave the Baylis−Hillman adducts in

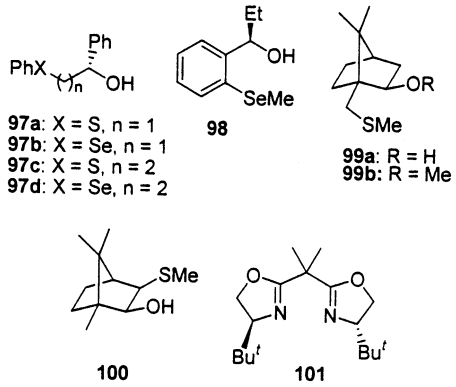
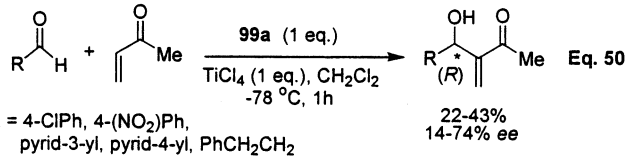


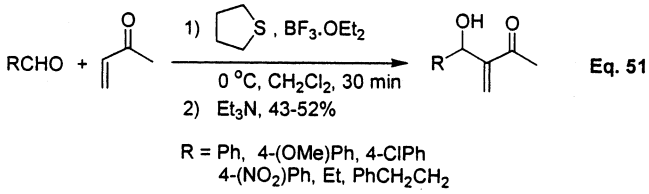
Figure 13.

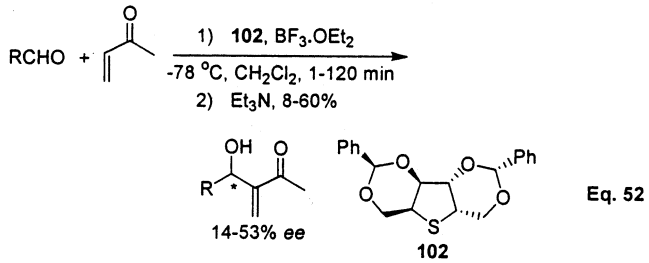
very high yields (93−99%) (eq 50), however, in low enantioselectivities. The best enantioselectivity of



74% was obtained in the reaction between hydrocinnamaldehyde and MVK in the presence of 10-methylthioisoborneol (**99a**). Subsequently, they examined the application of several C_2-symmetric bidentate ligand−$TiCl_4$ complexes [including BINOL (**80**) and bisoxazoline (**101**) (Figure 13)]. However, the resulting adducts were obtained in low enantiomeric purities (maximum up to 7%).

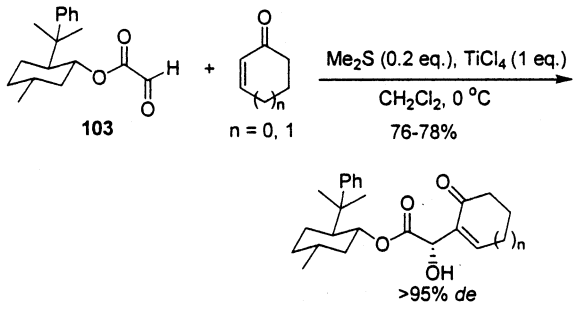
Goodman and co-workers reported tetrahydrothiophene−BF_3·OEt_2-mediated Baylis−Hillman reaction of MVK with aldehydes (eq 51). They also used enantiopure sulfide (**102**), which provided the desired Baylis−Hillman adducts up to 53% enantiomeric excess (eq 52).[210]





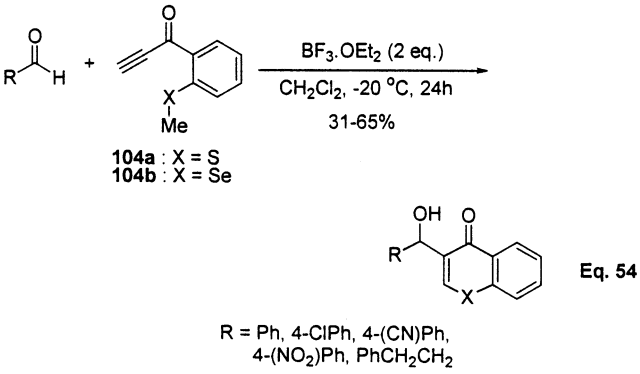
Bauer and Tarasiuk[211] employed (−)-8-phenylmenthyl glyoxylate (**103**) as an electrophile in the chalcogeno-Baylis−Hillman reaction. The desired products were obtained with high diastereoselectivities (>95% *de*). One such example is described in eq 53.

Kataoka et al.further extended chalcogeno-Baylis−Hillman reaction to activated alkynes. Thus, the reaction between activated alkynes with aldehydes in the presence of TiX_4 provided interesting β-halo-α-(hydroxyalkyl)acrylates, that is, β-halo Baylis−Hillman adducts (Scheme 55).[212] Kataoka et al. also reported an interesting intramolecular version involving the coupling of 1-(2-methylchalcogeno-phenyl)propynone **104** with representative aldehydes in the presence of BF_3·OEt_2, leading to the formation



Eq. 53

of 3-(hydroxyalkyl)chalcogenochromen-4-ones (eq 54).[213]

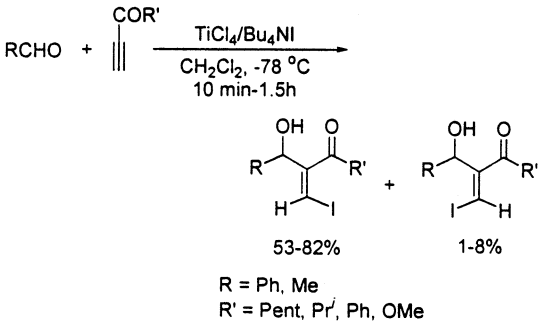


Eq. 54

Recently, Shaw and co-workers employed sugar-derived aldehydes (**105**) as electrophiles in the chalcogeno-Baylis−Hillman reaction (Scheme 56).[214,215] Subsequently, they transformed the resulting allyl chlorides **106** into allylamines **107** via the treatment with various amine derivatives (Et_2NH, pyrrolidine, piperidine, and piperazine derivatives) (Scheme 56). They also evaluated these allyl chlorides and allylamines for their biological activity and found that *Z*-keto allyl chlorides possessed the antimycobacterial activity.[215]

3.3. $TiCl_4$-Mediated Baylis–Hillman Reaction

It is worth mentioning here the earlier pioneering work (1986) of Tanaguchi et al.[216] who examined the reaction between α,β-acetylenic ketones and aldehydes in the presence of various reagents such as $TiCl_4$/TMSI, TMSOTf/TMSI, $TiCl_4/Bu_4NI$, TMSI/Bu_4NF, Et_2AlI, or TiI_4. The best and interesting results were obtained in the case of $Bu_4NI/TiCl_4$, providing the addition compounds (β-iodo Baylis−Hillman adducts) (eq 55).

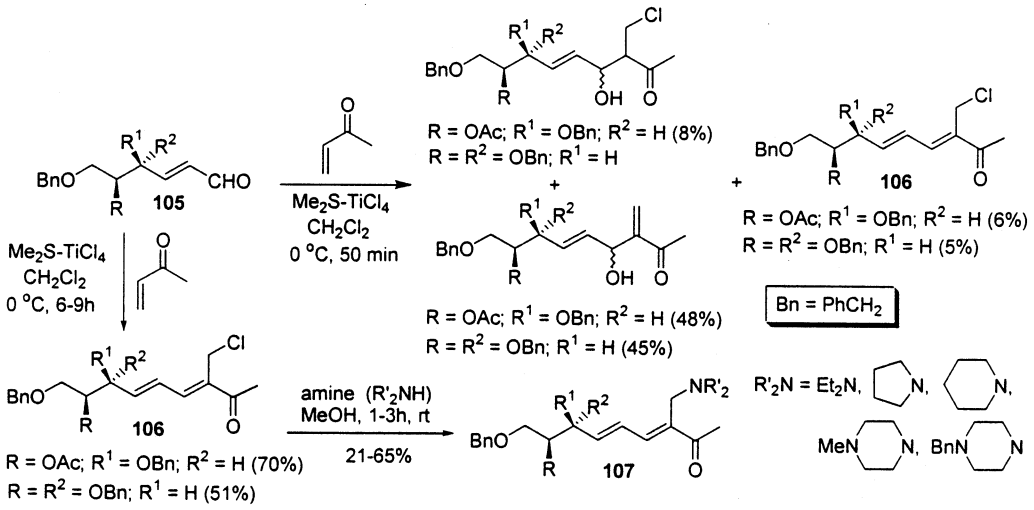


Eq. 55

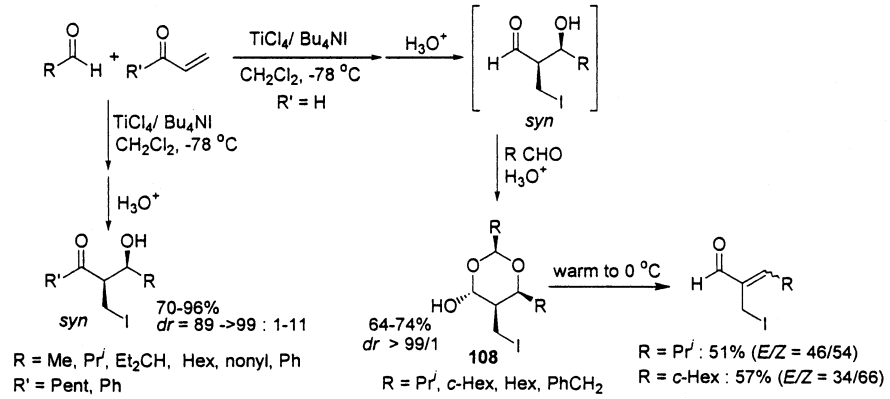
Later on, Oshima and co-workers[217] carried out reaction between acrolein and aliphatic aldehydes in the presence of $TiCl_4/Bu_4NI$, which provided cyclic hemiacetals **108** in high diastereoselectivity at −78 °C (Scheme 57). When the reaction mixture is warmed to 0 °C, they obtained vinyl aldehydes (dehydration products). In the case of benzaldehde, a complex mixture was obtained containing the usual Baylis−Hillman adduct (29% isolated yield) along with trace amounts of cyclic hemiacetal **108**. They also studied the reaction between alkyl vinyl ketones and aldehydes in the presence of $TiCl_4/Bu_4NI$, which provided iodo aldol products in high *syn*-stereoselectivity (Scheme 57).

Li et al.[218] reported an interesting $TiCl_4$-mediated Baylis−Hillman coupling reaction between cycloalkenones and aldehydes (without the direct use of Lewis base) to provide the desired adducts (eq 56). However, when α,β-unsaturated *N*-acylbenzoxazoline **109** was used as activated olefin, β-halogenated aldol products were obtained as the major products (eq 57). The plausible mechanism proposed by them is presented in Scheme 58. Subsequently, Li has synthesized allyl halides in high (*Z*)-stereoselectivity via the reaction of α,β-unsaturated ketones (at room temperature) and thioesters (reflux) with aldehydes in

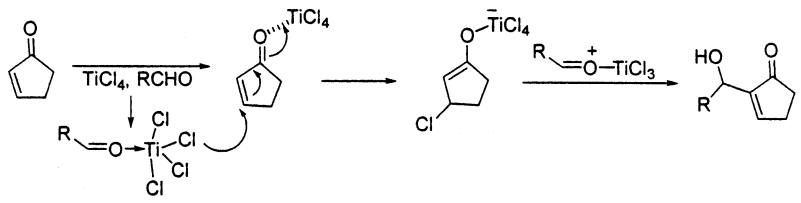
Scheme 56



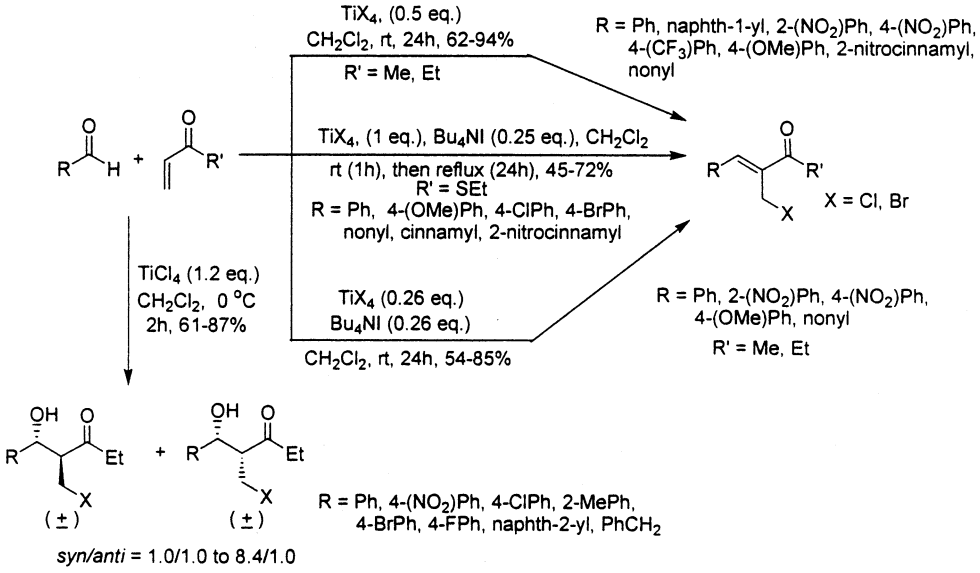
Scheme 57



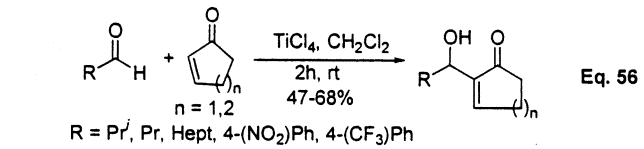
Scheme 58



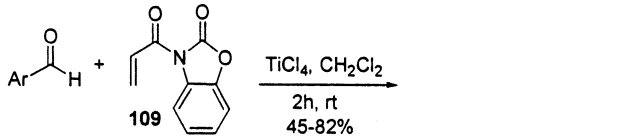
Scheme 59

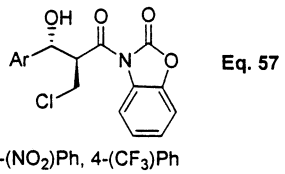


the presence of TiX_4 or TiX_4/Bu_4NI (Scheme 59).[219,220] Li and co-workers also observed the formation of halo aldol adducts in the case of vinyl ketones when the reaction was conducted at 0 °C (Scheme 59).[221]



Eq. 56





Eq. 57

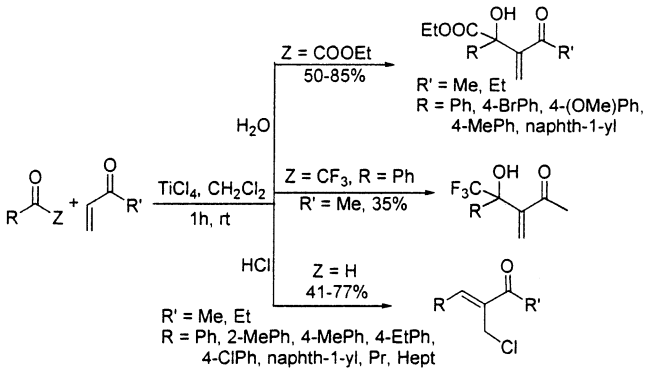
Ar = 2-(NO2)Ph, 3-(NO2)Ph, 4-(NO2)Ph, 4-(CF3)Ph

At about the same time our research group examined the Baylis−Hillman reaction of alkyl vinyl ketones with various electrophiles such as α-keto esters, fluoromethyl ketones, and aldehydes. We noticed an interesting reaction trend. α-Keto esters and fluoro methyl ketones provided the usual Baylis−Hillman adducts, whereas aldehydes provided the (*Z*)-allyl chlorides exclusively (Scheme 60).[222]

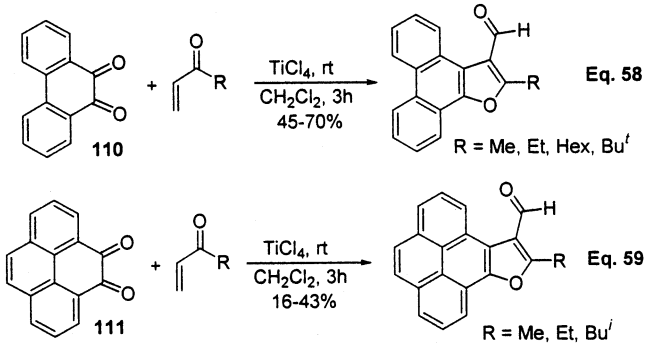
Subsequently, our research group extended this strategy to aryl 1,2-diones **110** and **111**. In these cases the usual Baylis−Hillman adducts were not obtained; instead, we obtained an interesting class of functionalized fused furans (eqs 58 and 59).[223]

Li and co-workers[224−226] reported the reaction between α,*β*-acetylenic ketones and aromatic aldehydes in the presence of $TiCl_4$ or $TiBr_4$ to provide the desired *β*-halo Baylis−Hillman adducts (Scheme

Scheme 60



61) (similar to those obtained by Kataoka). They also obtained similar results employing a mixture of



Bu_4NI (0.3 equiv) and a substoichiometric amount of $TiCl_4$ (only 0.26 equiv). The usually expected iodinated products were not produced in this reaction. The mechanism of the reaction is presented in Scheme 62.

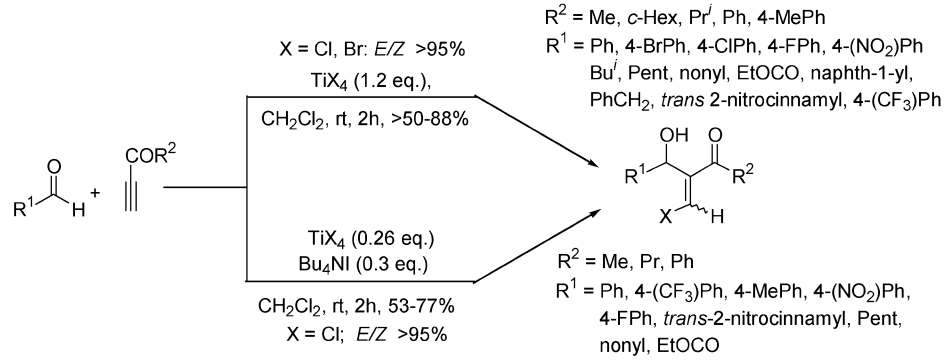
Shi and co-workers[227,228] examined similar $TiCl_4$-mediated coupling of activated alkenes with various aldehydes in the presence of various Lewis bases such as amines (DBU, Et_3N, and Et_2NH),[229] quaternary ammonium salt (TBAB),[230] chalcogenides (Me_2S),[231] oxycompounds (alcohols, ethers, and ketones)[232] (Scheme 63). In the case of oxycompounds, they also studied the applicability of enantiopure oxycompounds **112**−**115** (Figure 14); however, the products were obtained in poor enantioselectivities. Subsequently, they investigated the phosphine-mediated reactions between MVK and aldehydes in the presence of Lewis acids ($TiCl_4$, $ZrCl_4$, or BCl_3), which provided the α-chloro aldol adducts or allyl chlorides depending on the conditions.[233] They observed poor enantioselectivity when they used chiral phosphine (*R*)-BINAP [(*R*)-**76**)] (Scheme 64).

Shi and Wang[234] also examined the reaction between but-3-yn-2-one with aryl aldehydes in the presence of $TiBr_4$ or BBr_3. At −20 °C, β-bromo Baylis−Hillman adducts were formed with high *E*-selectivity (in the case of 2-(NO_2)Ph and 3-(NO_2)-Ph, *Z*-selectivity is favored due to steric factors), whereas at room temperature dibromides **116** were obtained along with β-bromo Baylis−Hillman adducts (Scheme 65). They subsequently subjected the dibromide **116** [Ar = (4-NO_2)Ph] to Heck and Suzuki-type coupling reactions (Scheme 66).

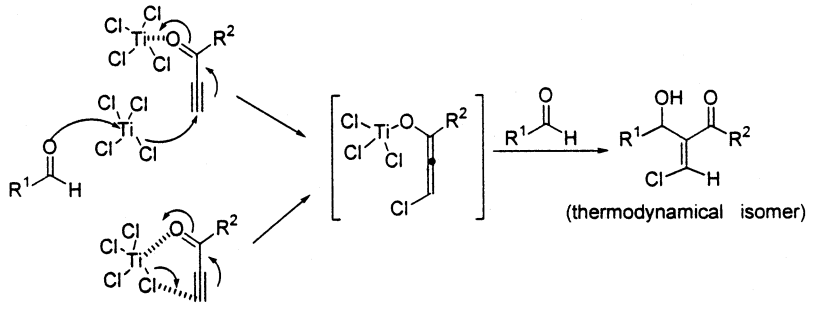
Sato and co-workers have reported an elegant titanium alkoxide promoted Baylis−Hillman reaction between enantiopure acetylenic esters **117**−**119** (Figure 15) and aldehydes. The enantiopure acetylenic ester **117** provided β-trimethylsilylated Baylis−Hillman adducts with high diastereoselectivity (Scheme 67).[235]

A direct synthesis of α-methylene-β-amino acid derivatives via the reaction between aryl aldehydes, sulfonamides, and activated alkenes catalyzed by Ti(O-*i*-Pr)$_4$ and 3-HQD (**3**) in the presence of molecular

Scheme 61



Scheme 62



Scheme 63

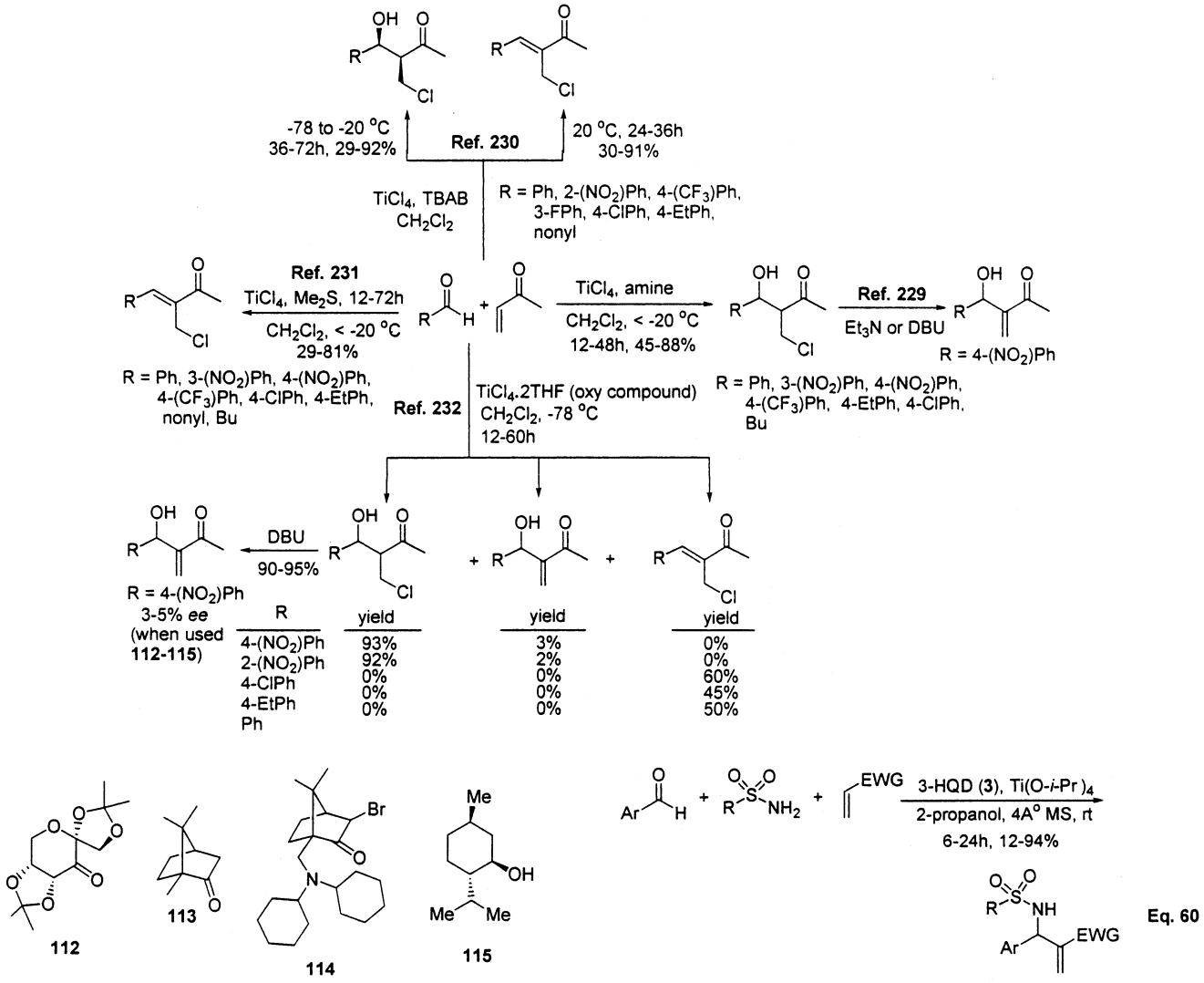


Figure 14.

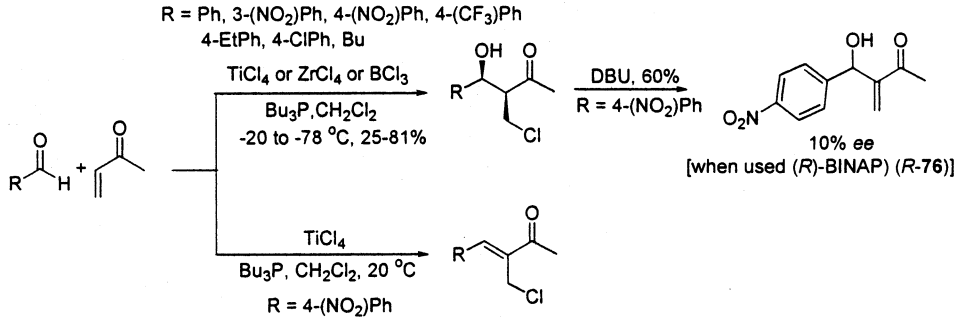
sieves was reported by Balan and Adolfsson (eq 60).[236]

Batra and co-workers[237] described Baylis−Hillman reaction of 5-isoxazolecarboxaldehyde with cyclohex-2-en-1-one and cyclopent-2-en-1-one in the presence of $TiCl_4$. Cyclopent-2-en-1-one provides the usual Baylis−Hillman adducts along with allyl chlorides in minor amounts, whereas cyclohex-2-en-1-one affords the usual Baylis−Hillman adducts along with hemiacetal **120** via aromatization of a cyclohexenone ring (Scheme 68).

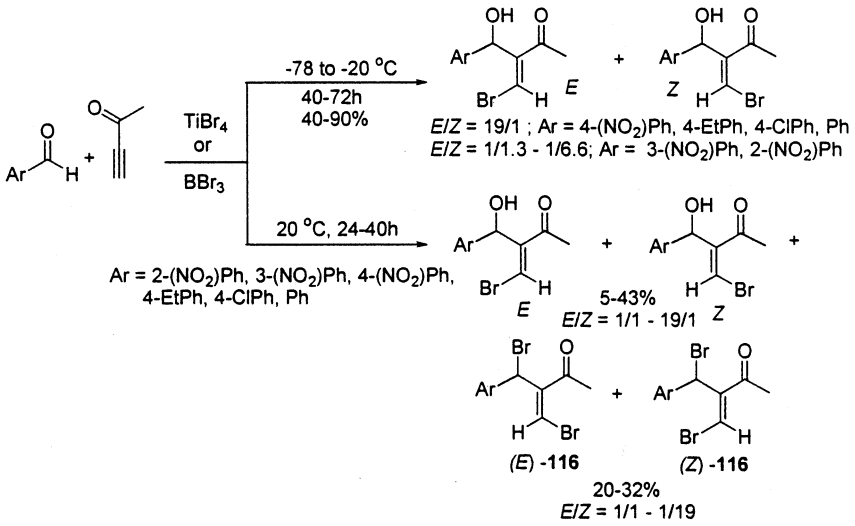
4. Intramolecular Baylis–Hillman Reaction

Although the Baylis−Hillman reaction, in general, has seen a high degree of growth with respect to all three essential components, the intramolecular version of this reaction is not studied in depth.[186,238] Murphy and co-workers[239−241] systematically investigated tandem Michael-aldol intramolecular addition

Scheme 64



Scheme 65



Scheme 66

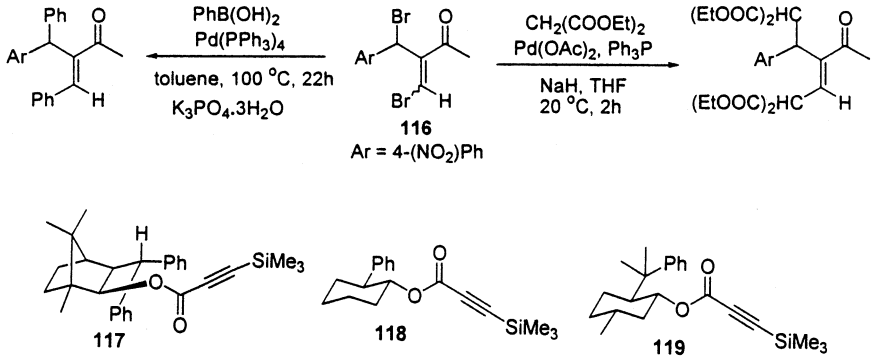
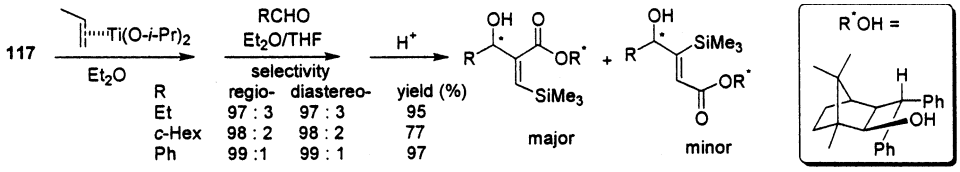
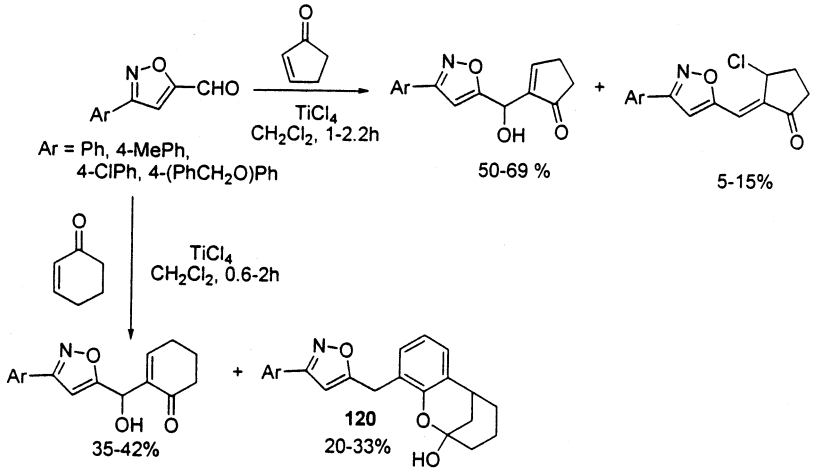


Figure 15.

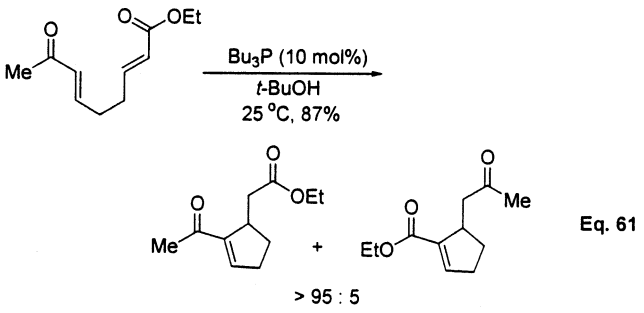
Scheme 67



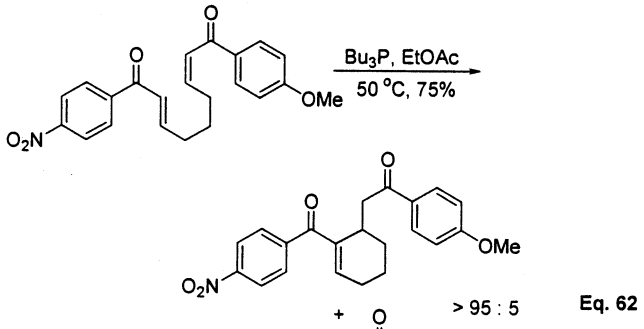
Scheme 68



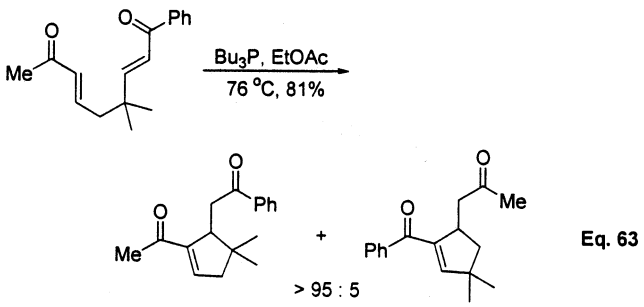
reactions using substrates containing both the activated alkene and electrophile, with various reagents such as amines, phosphines, and thiols. Thiols or thiolates provided the aldol products in the case of five- and six-membered rings. Tributylphosphine gave directly intramolecular Baylis−Hillman adducts in the case of five- and six-membered rings and cycloheptadienes in the case of seven-membered



Eq. 61



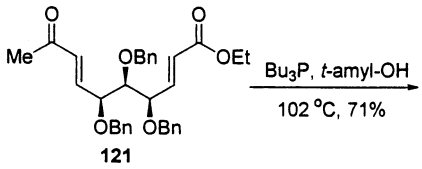
Eq. 62

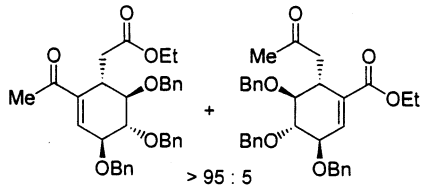


Eq. 63

rings. Stoichiometric amounts of piperidine provided aldol products in the case of five- and six-membered rings in high yields when treated with corresponding phenyl alkenyl ketones, whereas a catalytic amount of piperidine afforded moderate yields of intramolecular Baylis–Hillman adducts in such cases (Scheme 69).

Recently, Krische and co-workers[242] developed an elegant Bu_3P-catalyzed cycloisomerization of bisenones to provide five- and six-membered rings. They investigated the effect of electronic (eqs 61 and 62) and steric (eq 63) factors on cyclization. They also extended this methodology to the enantiopure substrate **121** derived from xylose, which provided the resulting product with high diastereoselectivity (eq 64).



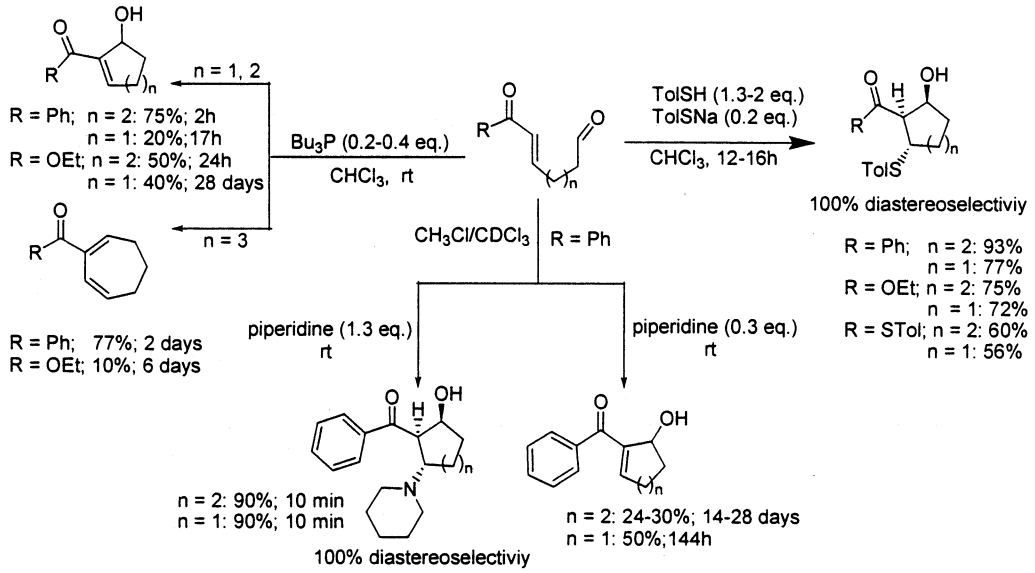


Eq. 64

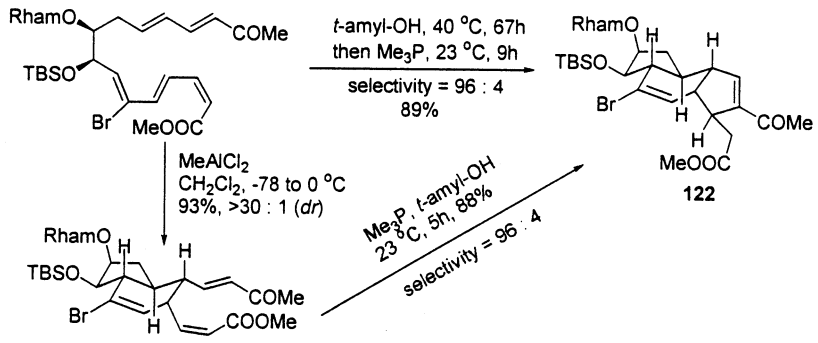
At the same time, Roush and co-workers[243] reported phoshpine-mediated intramolecular Baylis–Hillman reaction of diactivated 1,5-hexadienes and 1,6-heptadienes, thus providing an attractive synthesis of functionalized cyclopentene and cyclohexene derivatives (eqs 65 and 66). They also extended this methodology for the synthesis of substituted dihydrofuran derivatives (eq 67). Subsequently, Roush and co-workers successfully employed this intramolecular Baylis–Hillman strategy to the synthesis of a tricyclic nucleus of spinosyn A (**122**) (Scheme 70).[244]

Recently, Keck and Welch[245] examined intramolecular Baylis–Hillman reaction of α,β-unsaturated esters/thioesters containing an enolizable aldehyde group, at various conditions. In the case of thiol esters cyclopentenol products **123** were formed in

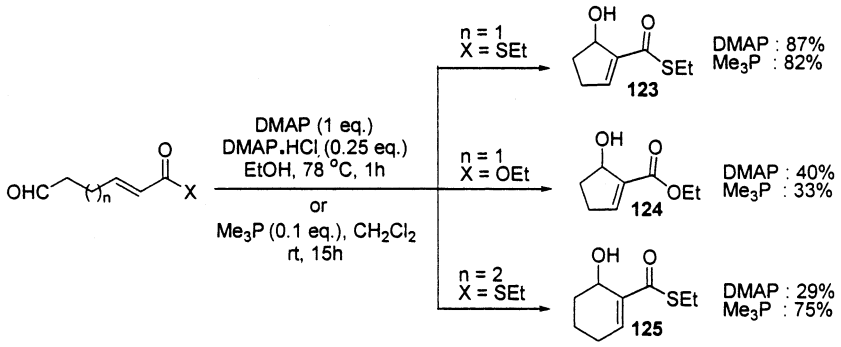
Scheme 69



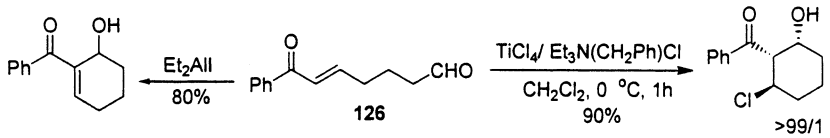
Scheme 70



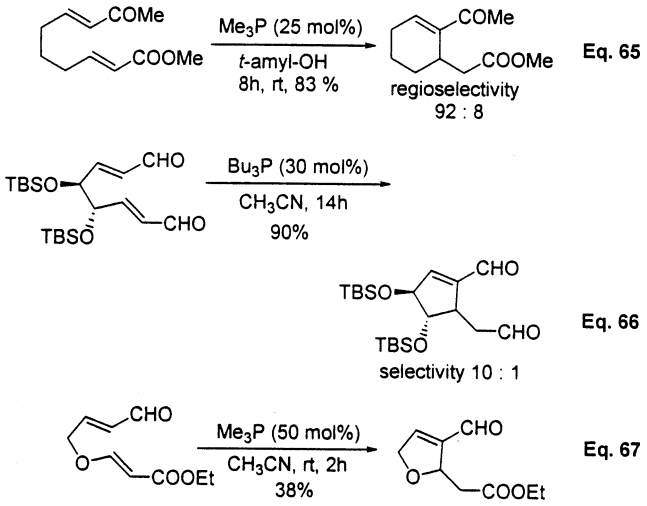
Scheme 71



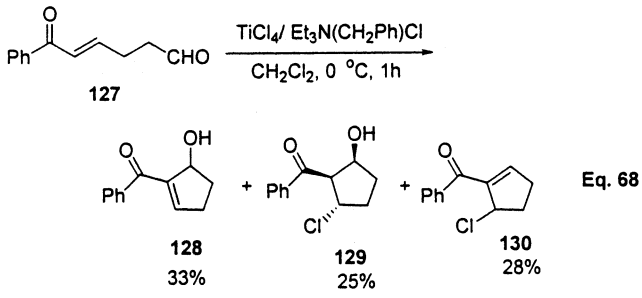
Scheme 72



high yields when DMAP and DMAP·HCl in EtOH (at 78 °C for 1 h) or Me_3P in CH_2Cl_2 (at room temperature for 15 h) were employed. However, in the case of oxyesters, the desired cyclopentenol adducts **124** were obtained in low yields. Cyclohexenol products **125** were obtained in high yields when Me_3P is used as a reagent, whereas DMAP and DMAP·HCl provided **125** in low yields. One representative example for each case is described in Scheme 71.



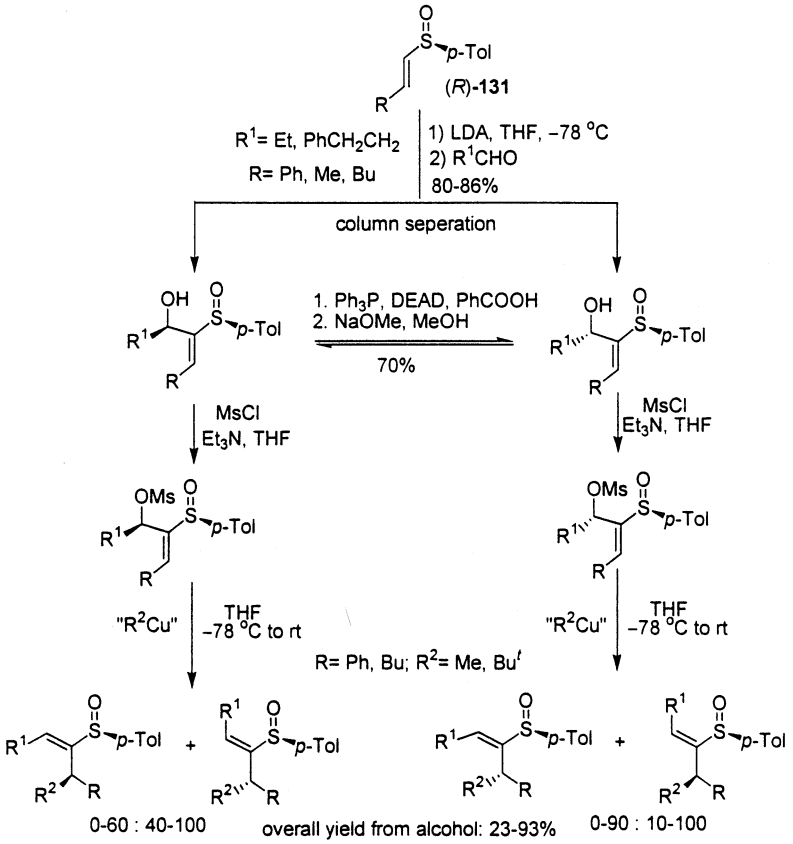
Oshima and co-workers[246] reported intramolecular Michael aldol cyclization of formyl α,β-enones under the influence of Lewis acids. Thus, reaction of **126** with $TiCl_4/Et_3N(CH_2Ph)Cl$ at 0 °C provides 2-benzoyl-3-chlorocyclohexanol (cyclo aldol adduct), whereas the treatment of **126** with Et_2AlI provides an intramolecular Baylis−Hillman adduct (Scheme 72). Similar reaction of **127** with $TiCl_4/Et_3N(CH_2Ph)Cl$ provides intramolecular Baylis−Hillman adduct **128** in 33% yield along with intramolecular chloro aldol product **129** and dehydration product **130** (eq 68).



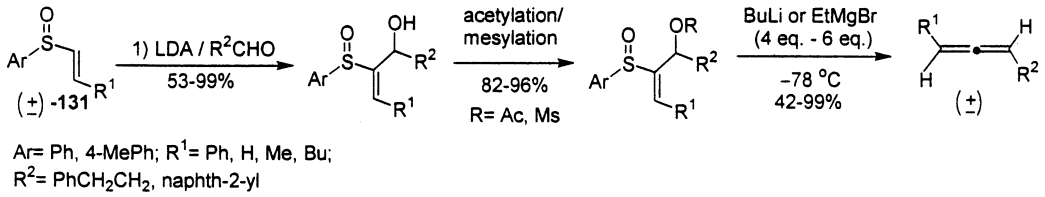
5. Baylis–Hillman-Type Reactions

In addition to the above-mentioned catalysts/catalytic systems for coupling of activated alkenes with electrophiles, literature records some interesting transition metal (Ru, Rh) catalyzed coupling reactions to provide the densely functionalized molecules.[24−28,247−251] Literature also reveals that the Baylis−Hillman adducts have been prepared using different methodologies/strategies, which are described in the following.

Scheme 73



Scheme 74



During their work on enantioselective carbon−carbon bond formation using acyclic allylic mesylates, Marino et al.[252] prepared the Baylis−Hillman-type adducts via the treatment of enantiopure β-substituted vinyl sulfoxides **131** with LDA followed by the reaction with aldehydes. Though the diastereoselectivities in these reactions are low, both the diastereomeric alcohols are separated in stereochemically pure form and used for further transformations (Scheme 73).

Subsequently, Satoh et al.[253] followed a similar strategy for the preparation of Baylis−Hillman-type alcohols having sulfoxide functionality and transformed them into allenes (Scheme 74). They also extended this methodology for the synthesis of optically active allenes from optically pure 2-phenylethenyl *p*-tolyl sulfoxides **131**. One representative example is shown in Scheme 75.

Tius[254,255] and co-workers have described a simple and convenient general methodology for the synthesis of α,β-unsaturated acyl silanes (Baylis−Hillman-type allyl alcohols) via the reaction of allenyl trialkylsilyl ether **132** (which is available in two steps from propargyl alcohol) with aldehydes or ketones in good to excellent yields (Scheme 76).

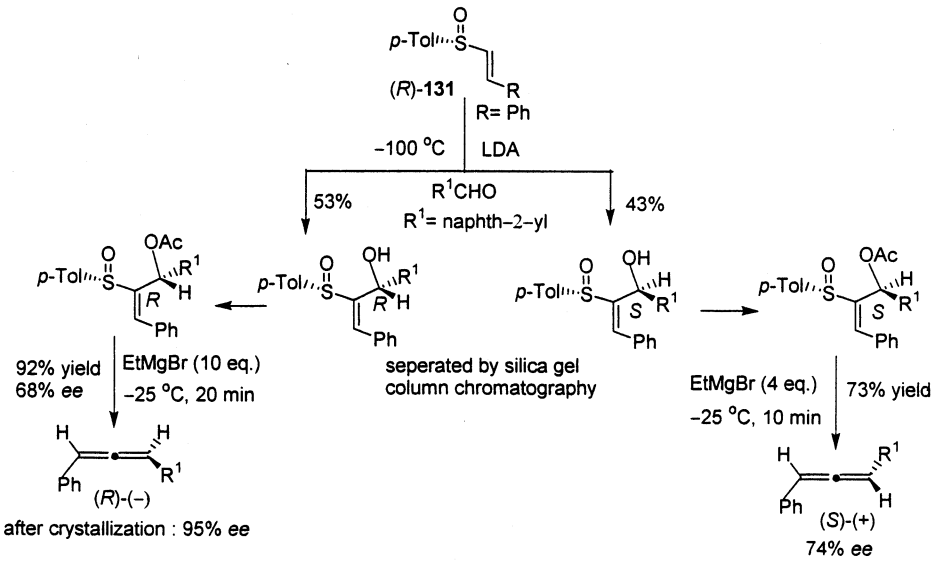
Trehan and co-workers[256] transformed *tert*-butyldimethylsilyloxyallene (generated in situ by the reaction of KOBu^t with TBDMS ether of propargyl alcohol) into Baylis−Hillman alcohols via treatment with aromatic aldehydes in the presence of a Lewis acid. However, similar reaction with aliphatic aldehydes resulted in the formation of polymeric compounds (Scheme 77).

Tomioka and co-workers[257,258] reported an interesting synthesis of α-hydroxy alkenyl-phosphonates via the addition of LDA to vinyl phosphonates followed by the reaction with electrophiles and then the elimination of diisopropylamine. These adducts were further transformed into allenes (Scheme 78). In some cases (when KH is used), minor amounts of alkynes are formed.

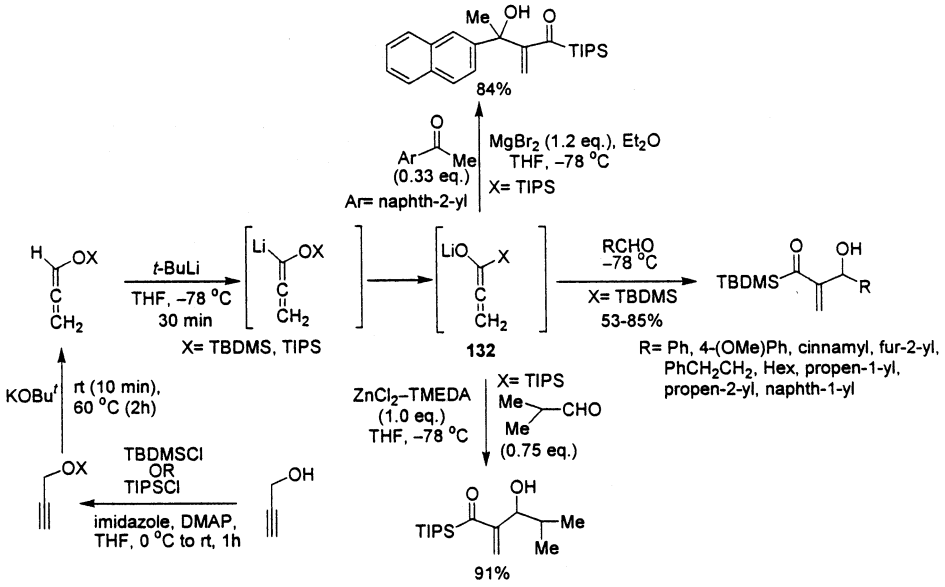
Davies and co-workers[259] developed an asymmetric version of a Baylis−Hillman-type reaction via a three-step process involving diastereoselective Michael addition of chiral lithium amide **133** to cinnamic ester according to Scheme 79.

Subsequently, Warren and co-workers[260] used chiral lithium amide methodology (developed by Davies[259]) for synthesizing enantiomerically enriched Baylis−Hillman-type molecules starting from vinyl phospho-

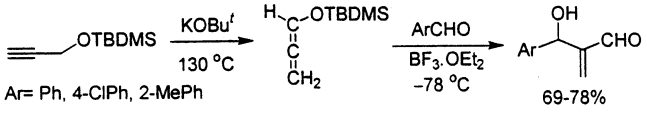
Scheme 75



Scheme 76



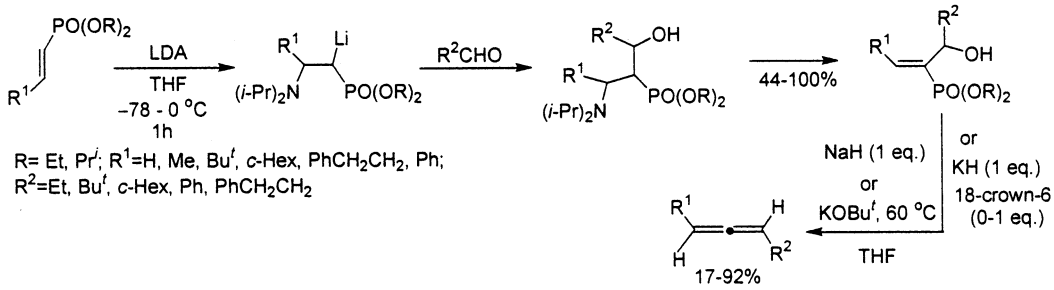
Scheme 77



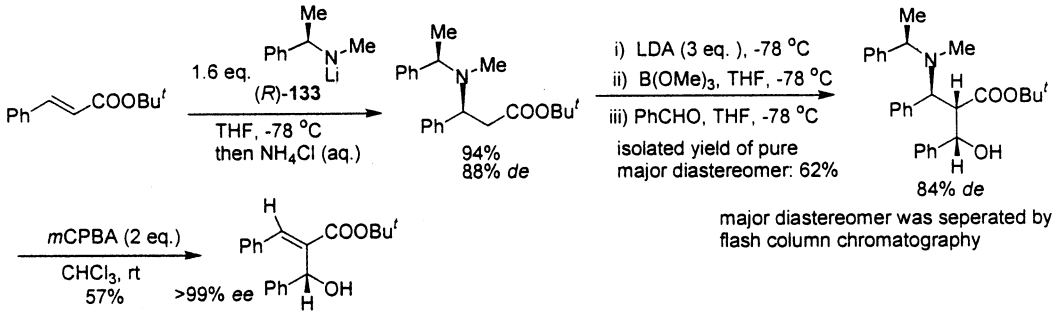
nates. They also converted these allyl alcohols into allenes (Scheme 80).

Jauch[261] reported a novel selenium-based protocol for a highly diastereoselective and enantioselective synthesis of Baylis−Hillman-type adducts using enantiopure activated alkene **134** following the reaction sequence as described in Scheme 81. Jauch also utilized this strategy in the synthesis of various natural products such as kuehneromycin A (**135**) and mniopetals **136** and **137** (Scheme 82).[261−265] Subsequently, Reiser and Jauch extended this strategy for solid-phase organic synthesis and further in the synthesis of natural products such as the core struc-

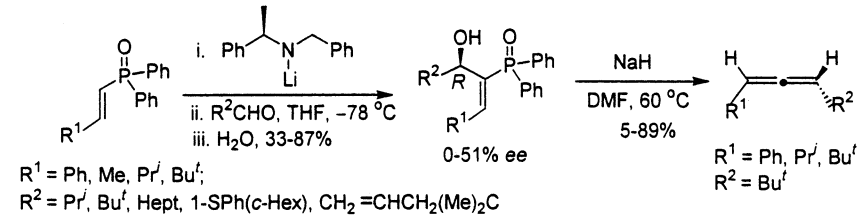
Scheme 78



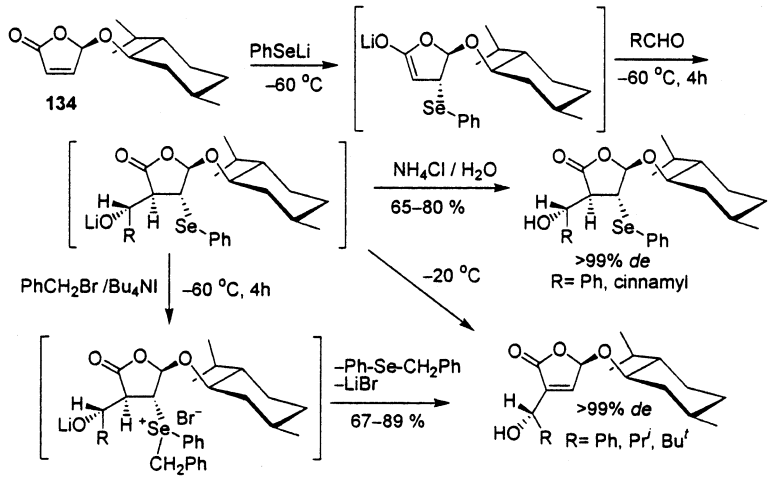
Scheme 79



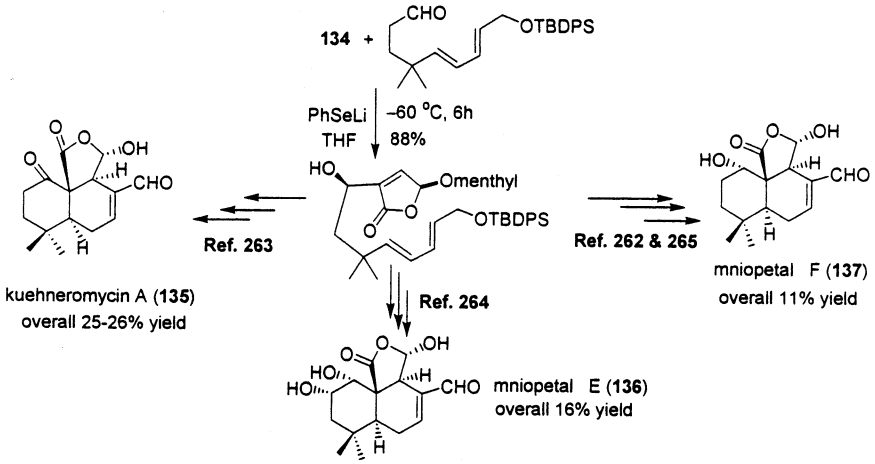
Scheme 80



Scheme 81



Scheme 82

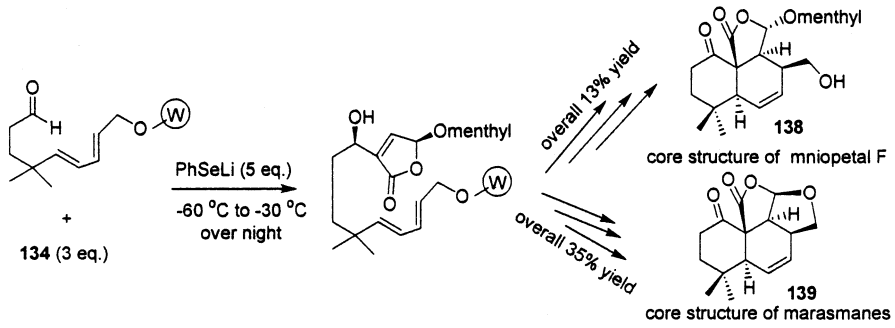


ture of mniopetal F (**138**) and marasmanes (**139**) (Scheme 83).[266]

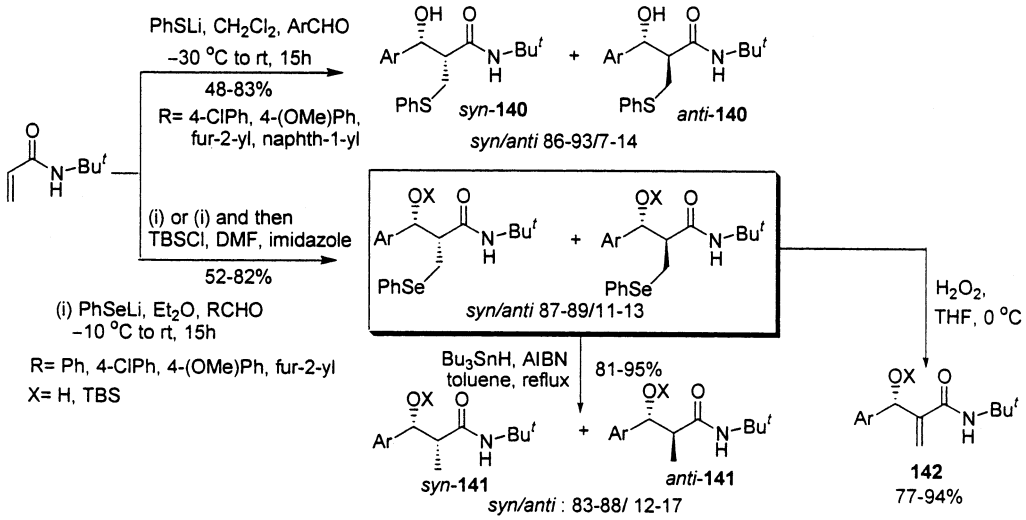
Kamimura et al.[267] reported a simple procedure for the synthesis of *syn*-NH-amide aldols **140** and **141** and Baylis−Hillman adducts **142** via the thiolate- or selenolate-induced Michael-aldol tandem process using secondary α,β-unsaturated amides (Scheme 84).

Huang and Xie[268] successfully employed acetylenic sulfones for the synthesis of corresponding Baylis−Hillman-type adducts via the reaction with phenyl-

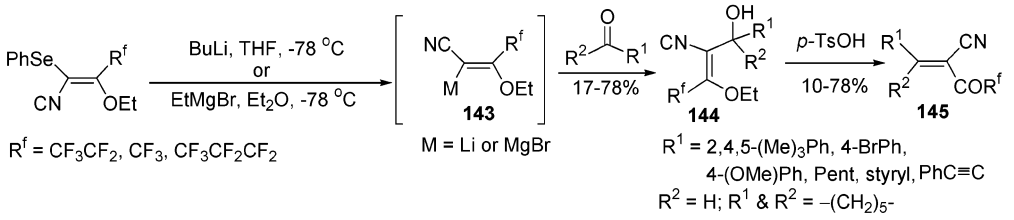
Scheme 83



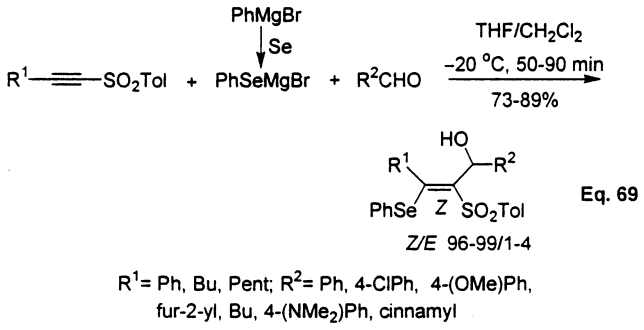
Scheme 84



Scheme 85



selenomagnesium bromide and aryl aldehydes following the reaction sequence as shown in eq 69.



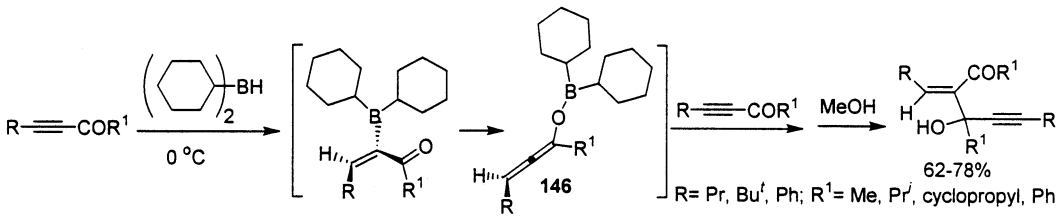
Eq. 69

Recently, Yoshimatsu and Timura[269] reported the reaction of 2-ethoxyperfluoro-2-(phenylselenyl)-alk-2-enenitriles with BuLi or EtMgBr and successive reaction of in situ generated transmetalated compound **143** with a carbonyl group to provide the functionalized allylic alcohols **144** in high yields. Hydrolysis of the resultant allylic alcohols afforded the α-cyano-α,β-unsaturated perfluoroalkyl ketones **145** (Scheme 85).

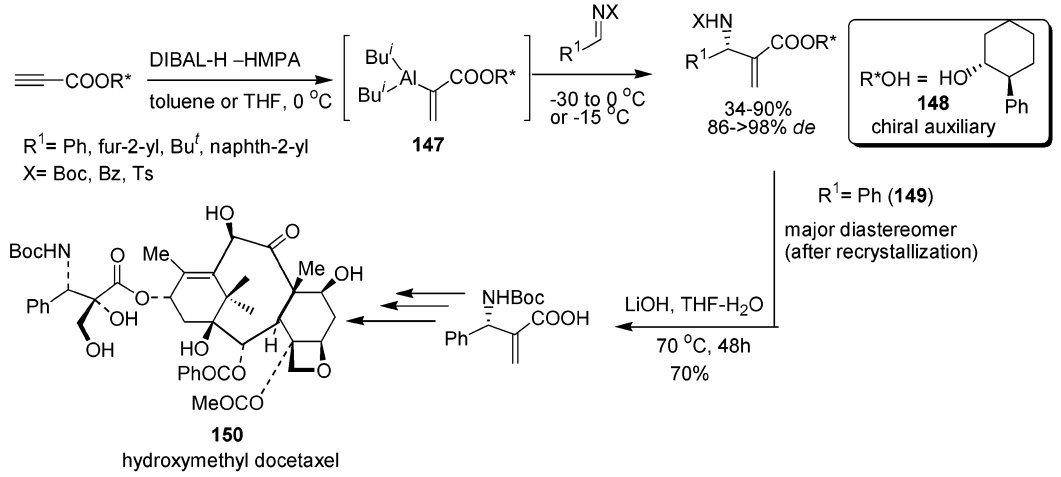
Kabalka et al.[270] successfully synthesized stereodefined functionalized trisubstituted olefins via the reaction of excess α,β-acetylenic ketones with dicyclohexylborane. This reaction is believed to proceed via allenoxy borinate **146** (Scheme 86).

In 1996, Greene and co-workers[271] developed an elegant method for obtaining enantiomerically enriched Baylis−Hillman adducts via the reaction between chiral vinyl aluminum species **147** (generated in situ by the treatment of chiral acetylenic esters with DIBAL-H) and aldehydes. They examined application of various chiral acetylenic esters derived from different chiral auxiliaries. They found that an acetylenic ester derived from (1*R*,2*S*)-phenylcyclohexanol (**148**) offered better diastereoselectivities. The Baylis−Hillman adduct **149** thus obtained was further transformed into C-2′ hydroxymethyl analogues of docetaxel (**150**) (Scheme 87).

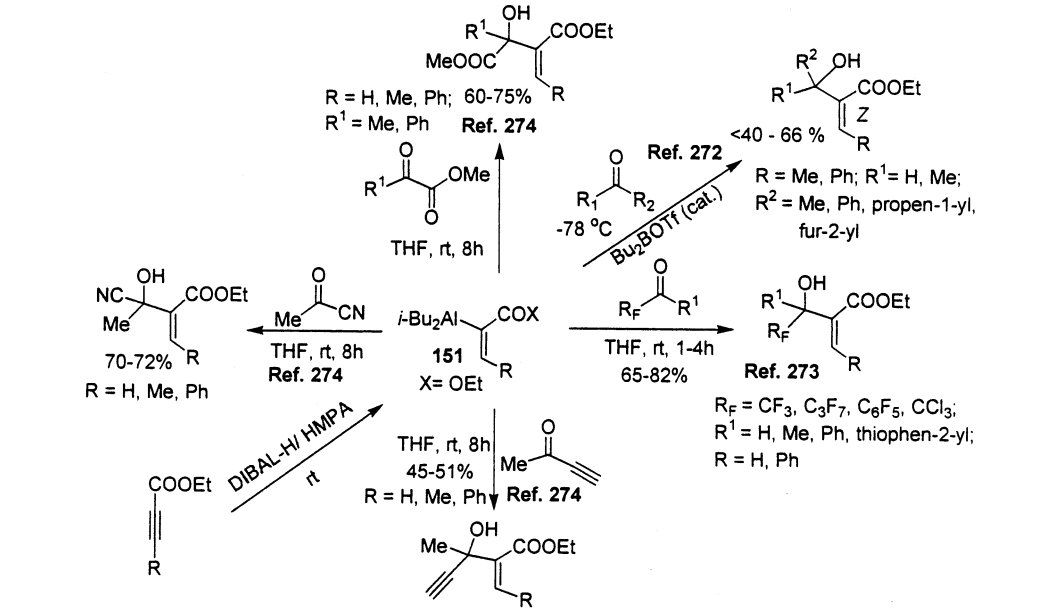
Scheme 86



Scheme 87



Scheme 88

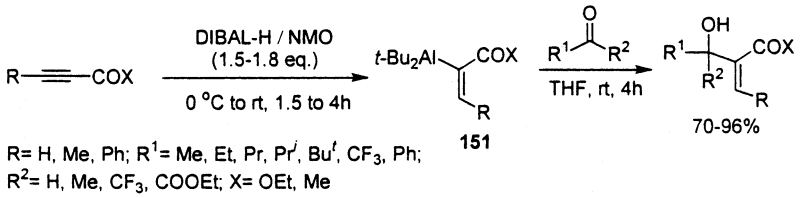


Subsequently, Li et al.[272] described a general synthesis for β-substituted Baylis−Hillman adducts via the generation of anionic intermediates of β-substituted [α-(alkoxycarbonyl)vinyl]aluminum **151**, followed by reaction with carbon electrophiles under the catalytic influence of Bu_2BOTf at −78 °C (Scheme 88). At the same time independently, Ramachandran et al.[273,274] utilized β-substituted vinyl aluminum species for coupling with various electrophiles such as fluoro ketones, α-keto esters, α-acyl cyanides, and α-acetylenic ketones to provide various β-substituted Baylis−Hillman adducts in high yields (Scheme 88).

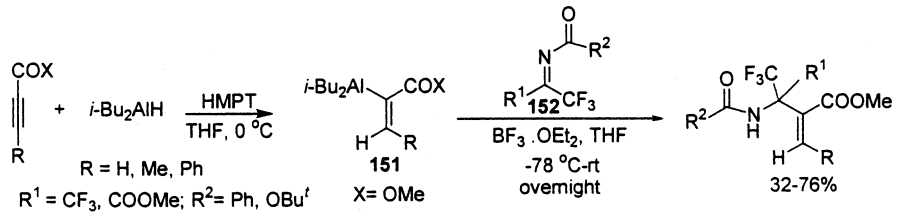
Later on, Ramachandran et al.[275] used NMO as a solvent in place of carcinogenic HMPA, thus developing an environmentally benign procedure for obtaining Baylis−Hillman adducts via the vinyl-alumination of carbonyl compounds (Scheme 89).

Recently, *N*-acylimines of hexafluoroacetone (**152**; $R^1 = CF_3$) and methyl trifluoropyruvate (**152**; R^1 = COOMe) were employed by Burger and co-workers as electrophiles for coupling with [α-(alkoxycarbonyl)-vinyl]aluminum **151** in the presence of Lewis acid ($BF_3{\cdot}OEt_2$) to provide the corresponding trifluoromethyl substituted dehydro-β-amino acid derivatives (Scheme 90).[276]

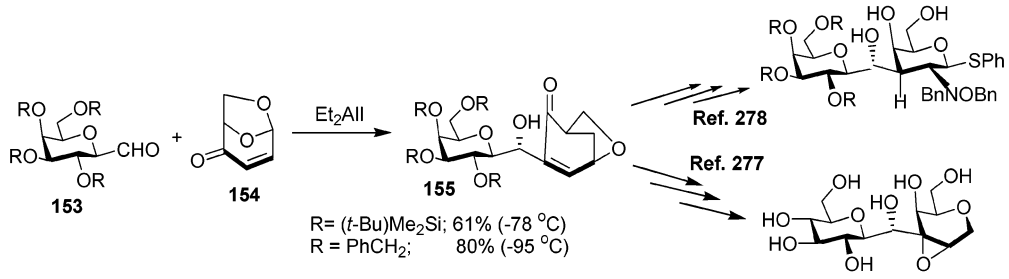
Scheme 89



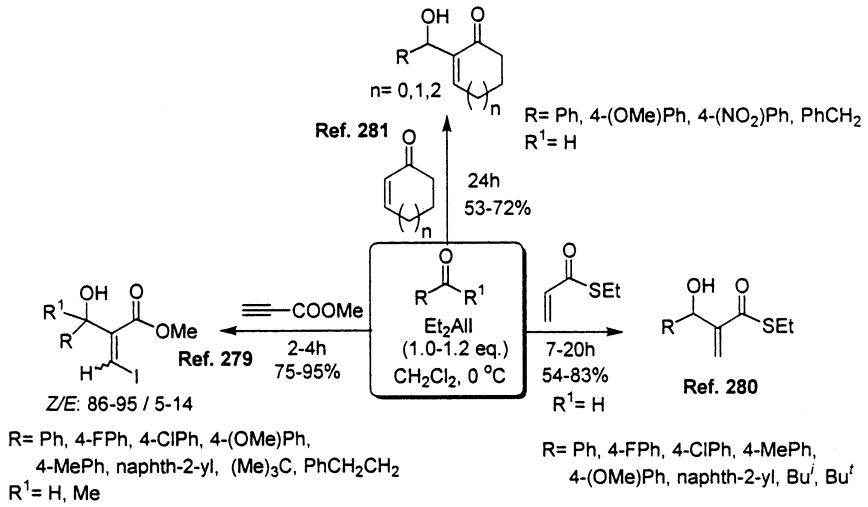
Scheme 90



Scheme 91



Scheme 92



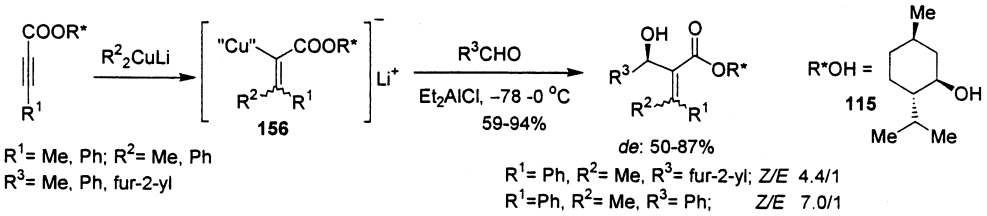
Vogel and co-workers[277,278] synthesized the Baylis–Hillman-type products **155** via the coupling of D-galactose-derived carbaldehyde **153** with isolevoglucosene **154** under the influence of Et_2AlI. These adducts were subsequently employed for the synthesis of C-linked disaccharides and a partially protected C-disaccharide analogue of the oligosaccharide portion of the T-antigen (Scheme 91).

Li and co-workers[279–281] reported an efficient Et_2-AlI-promoted Baylis–Hillman-type coupling of aldehydes with propargylic esters[279] and ethyl thioacrylate[280] to produce β-iodo-α-(hydroxyalkyl)acrylates and α-methylene-β-hydroxy thioesters, respectively. In the latter case they also observed formation of minor amounts of iodo-aldol products. Subsequently, they also successfully employed Et_2AlI for coupling of cycloalkenones[281] with aromatic aldehydes, leading to the formation of the corresponding Baylis–Hillman alcohols in modest to good yields (Scheme 92).

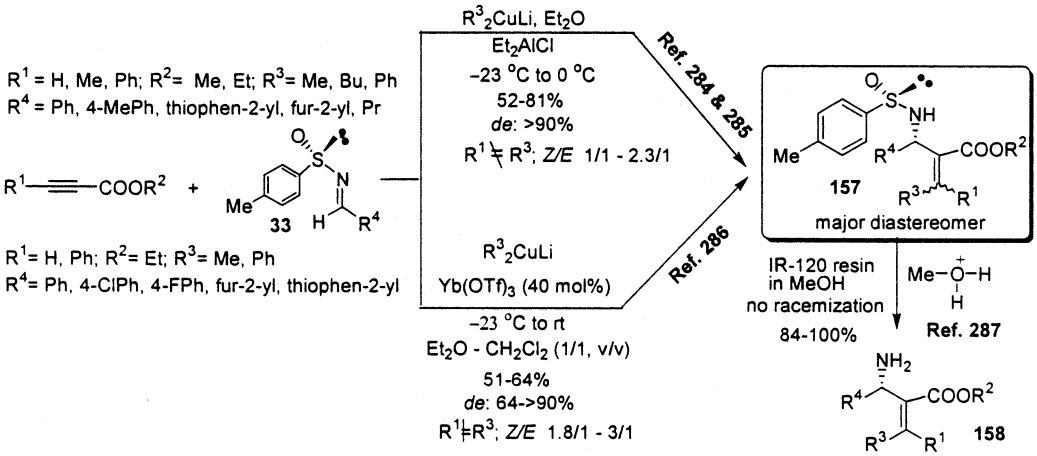
Li and co-workers[282,283] described an interesting approach for diastereoselective synthesis of β,β-disubstituted α-(hydroxyalkyl)acrylates (Baylis–Hillman adducts) via the addition of R_2CuLi to chiral β-substituted α,β-acetylenic esters [derived from menthol (**115**)] followed by the treatment of resulting vinyl copper moiety **156** with aldehydes in the presence of Et_2AlCl (Scheme 93).

Subsequently, Li and co-workers successfully extended this strategy to enantiopure *p*-toluenesulfinimines **33** as electrophiles to provide the desired

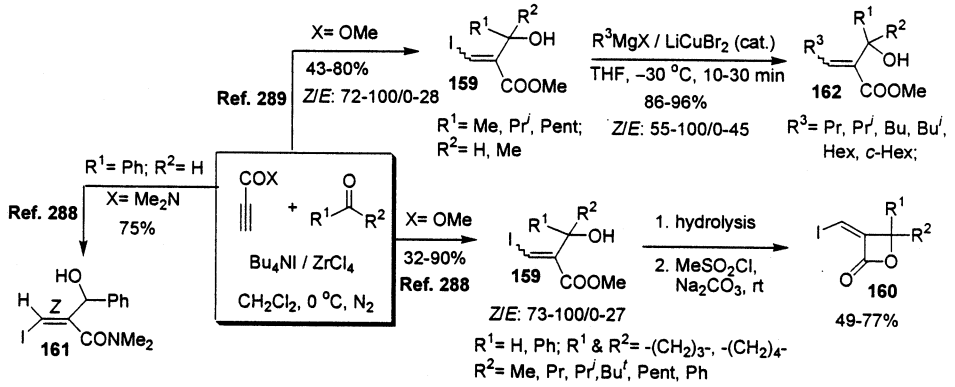
Scheme 93



Scheme 94

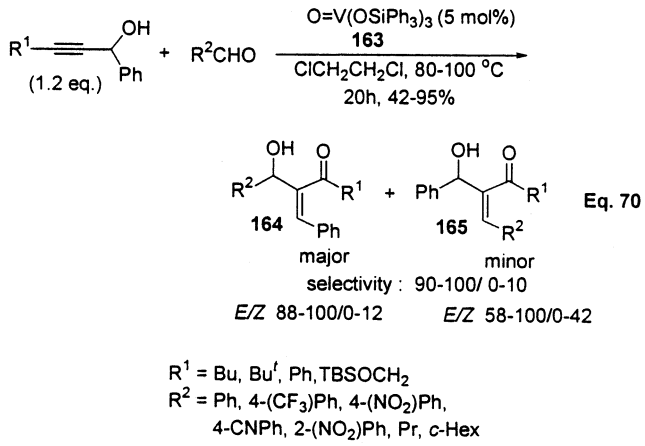


Scheme 95

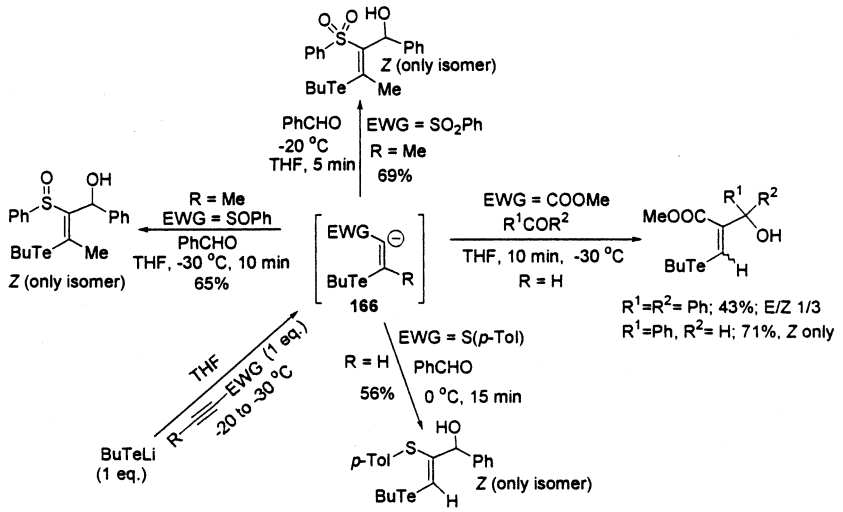


Baylis−Hillman-type adducts, that is, β-monosubstituted and β,β-disubstituted *N*-(*p*-toluenesulfinyl)-α-(aminoalkyl)acrylates **157** in good yields and excellent diastereoselectivities. However, since some of the toluenesulfinimines were insoluble in Et_2O at low temperature, they used $Et_2O-CH_2Cl_2$ as a cosolvent system in the presence of $Yb(OTf)_3$ as a catalyst in this reaction. Subsequently, these adducts **157** were further transformed into β-branched Baylis−Hillman adducts **158** by deprotecting the *N*-*p*-toluenesulfinyl group using amberlyst IR-120 (plus) ion-exchange resin without any racemization (Scheme 94).[284−287]

Zhang and Lu[288] reported a convenient stereoselective synthesis of methyl (2*Z*)-3-iodo-2-(1-hydroxyalkyl)prop-2-enoates **159** via a tandem nucleophilic addition-aldol reaction of methyl propynoate, iodide ion (obtained from Bu_4NI), and carbonyl compounds in the presence of $ZrCl_4$ as a catalyst. The (*Z*)- and (*E*)-isomers were separated and the major (*Z*)-isomers were further transformed into α-(*Z*)-iodomethylene-β-lactones **160** in good yields. They also studied a similar reaction with *N*,*N*-dimethylpropynoamide to provide the corresponding adduct **161** with exclusive *Z*-stereoselectivity (Scheme 95).[288] Later, Amri and co-workers[289] elegantly used the vinyl iodides **159** in the synthesis of β-substituted Baylis−Hillman adducts **162** via the cuprous salt promoted conjugated addition of Grignard reagents (Scheme 95).

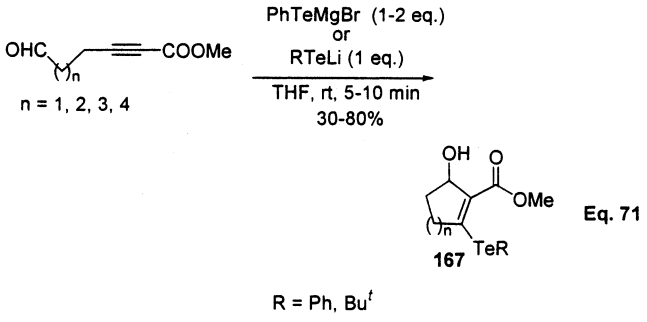


Scheme 96



Trost and Oi[290] described a novel vanadium-catalyzed synthesis of allylic alcohols. Reaction between propargylic alcohols and aldehydes in the presence of a catalytic amount of an oxyvanadium catalyst **163** provided the functionalized allylic alcohols (Baylis−Hillman type) **164** and **165** in good yields with high regio- and stereoselectivity (eq 70).

Recently, Marino and Nguyen[291] reported regio- and stereospecific route to tri- and tetrasubstituted alkenes via the Michael addition of alkyl or aryl tellurate anions onto activated alkynes and subsequent addition of the resulting vinyl anion **166** to various electrophiles such as aldehydes and ketones. Representative examples are presented in Scheme 96. They also described an intramolecular version of this reaction, providing highly functionalized intramolecular Baylis−Hillman-type cycloalkenol derivatives **167** (eq 71).



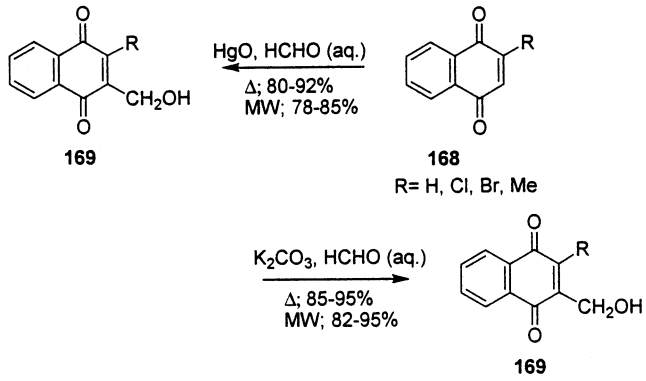
Eq. 71

Khanna and co-workers[292] synthesized the Baylis−Hillman-type alcohols **169** via the hydroxymethylation of 1,4-naphthoquinones **168** using formalin in the presence of K_2CO_3 or HgO by heating or microwave irradiation (Scheme 97).

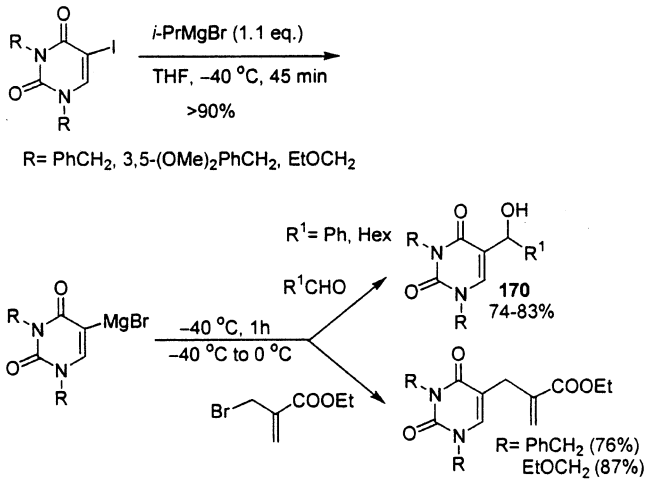
Abarbri and Knochel[293] reported iodine−magnesium exchange reactions of 5-iodouracil derivatives to afford the corresponding polyfunctional Grignard reagents, which further react with various electrophiles to give the Baylis−Hillman-type allylic alcohols **170** in good yields (Scheme 98).

The Nozaki−Hiyama−Kishi reaction was elegantly used to obtain the Baylis−Hillman adducts **171** by Comins and co-workers.[294] Resulting adducts were

Scheme 97



Scheme 98

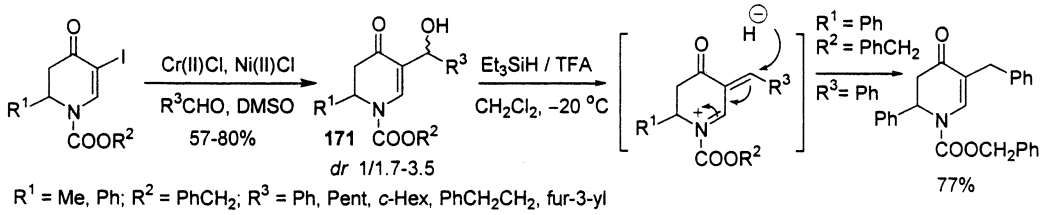


further transformed into various substituted dihydropyridone derivatives. One representative example is shown in Scheme 99.

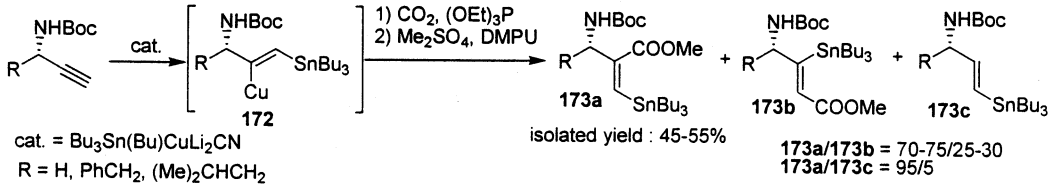
Recently, Reginato and co-workers[295] synthesized chiral stannylated Baylis−Hillman-type adducts **173a** via the addition of stannylcuprates onto enantiopure propargylamine followed by the reaction of in situ generated vinyl copper reagent **172** with CO_2 (Scheme 100).

Recently, Cha et al.[296] reported an efficient stereoselective approach to (*E*)-*β*-methyl Baylis−Hillman

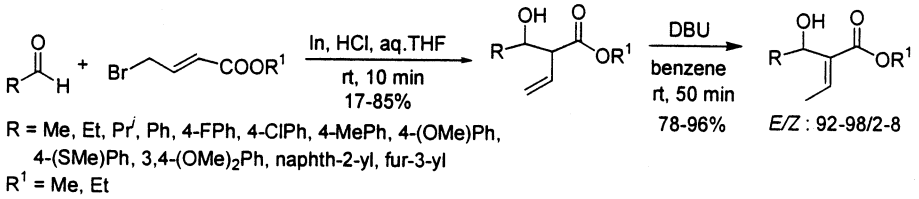
Scheme 99



Scheme 100

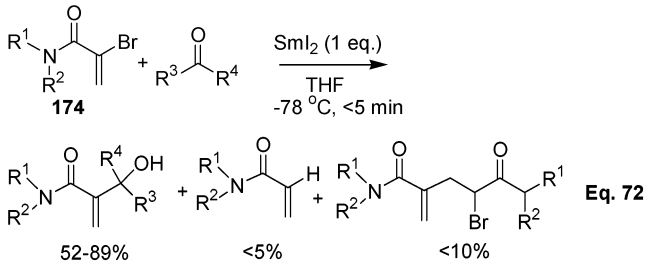


Scheme 101



adducts, via indium-mediated allylation of aldehydes in aqueous media at room temperature, followed by base-induced isomerization (Scheme 101).

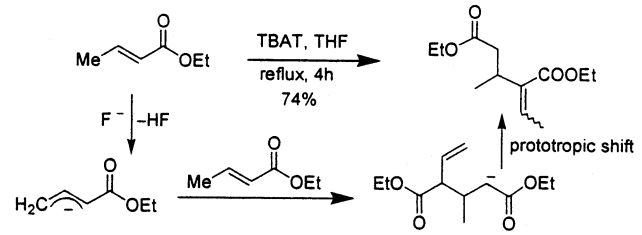
α-Bromoacrylamides **174** have been conveniently transformed by Youn et al.[297] into α-hydroxyalkylacrylamides via treatment with carbonyl compounds in the presence of samarium iodide (eq 72).



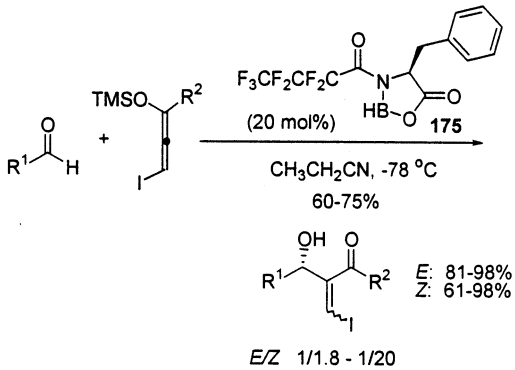
Eq. 72

An interesting Baylis–Hillman-type dimerization of ethyl crotonoate under the influence of fluoride ion (TBAT) was reported by Xuan and Fry.[298] However, this process involves a mechanism different from the usual dimerization of activated alkenes under normal Baylis–Hillman conditions (Scheme 102).

Scheme 102

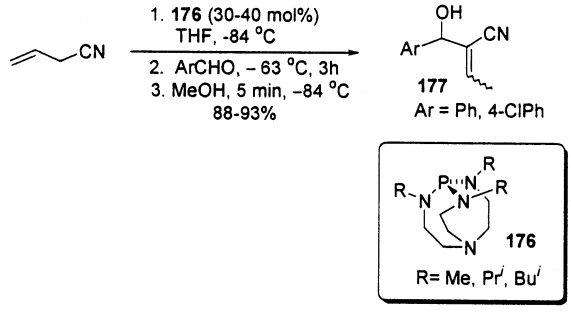


Li and co-workers[299] synthesized enantiomerically enriched β-halo Baylis–Hillman adducts via the aldol reaction of silyl allenolates with aldehydes catalyzed by chiral *N*-C_3F_7CO oxazaborolidine **175** (eq 73).



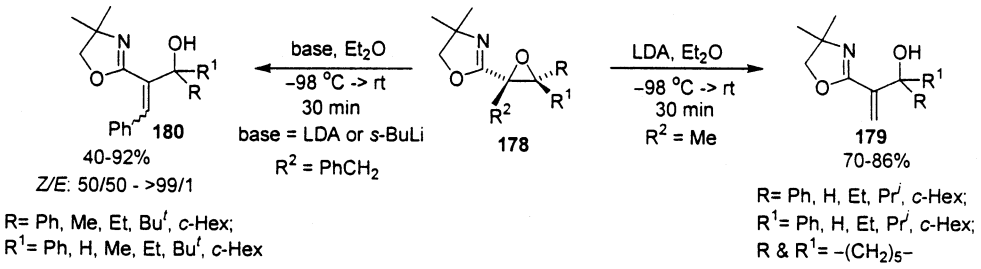
Eq. 73

Kisanga and Verkade[300] described that allyl cyanide reacts efficiently with aromatic aldehydes in the presence of $P(RNCH_2CH_2)_3N$ (**176**) (30–40 mol %)

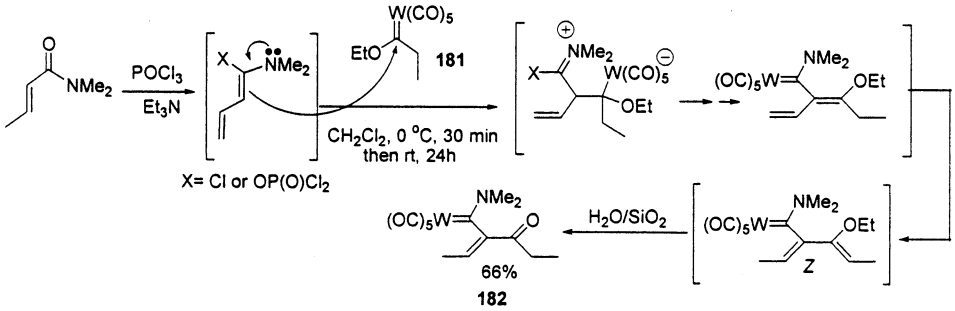


Eq. 74

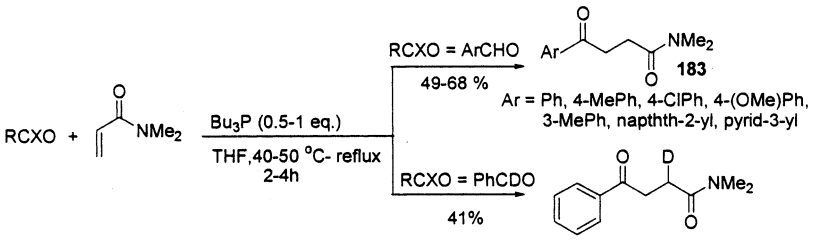
Scheme 103



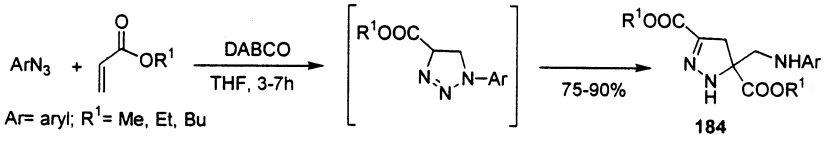
Scheme 104



Scheme 105



Scheme 106



(Verkade base) at −63 °C to give *β*-substituted Baylis−Hillman adducts **177** (eq 74).

Florio and co-workers synthesized oxazolinyl allylic alcohols **179** and **180** (masked Baylis−Hillman adducts) via the ring opening of oxazolinyl alkyl oxiranes (**178**) using LDA (or *s*-BuLi/TMEDA) in Et_2O (Scheme 103).[301]

Aumann and co-workers[302] elegantly employed the Fischer carbene complex **181** as an electrophile in a Baylis−Hillman-type reaction with α,*β*-unsaturated acid amide in the presence of $POCl_3/Et_3N$, to provide acyl aminocarbene derivative **182**. One representative example is described in Scheme 104.

Kim et al.[303] reported that the reaction between *N*,*N*-dimethylacrylamide and aryl aldehydes in the presence of Bu_3P did not provide the usual Baylis−Hillman adducts. Instead, *N*,*N*-dimethyl-3-aroylpropionamides **183** (Stetter reaction) were obtained in moderate yields (Scheme 105).

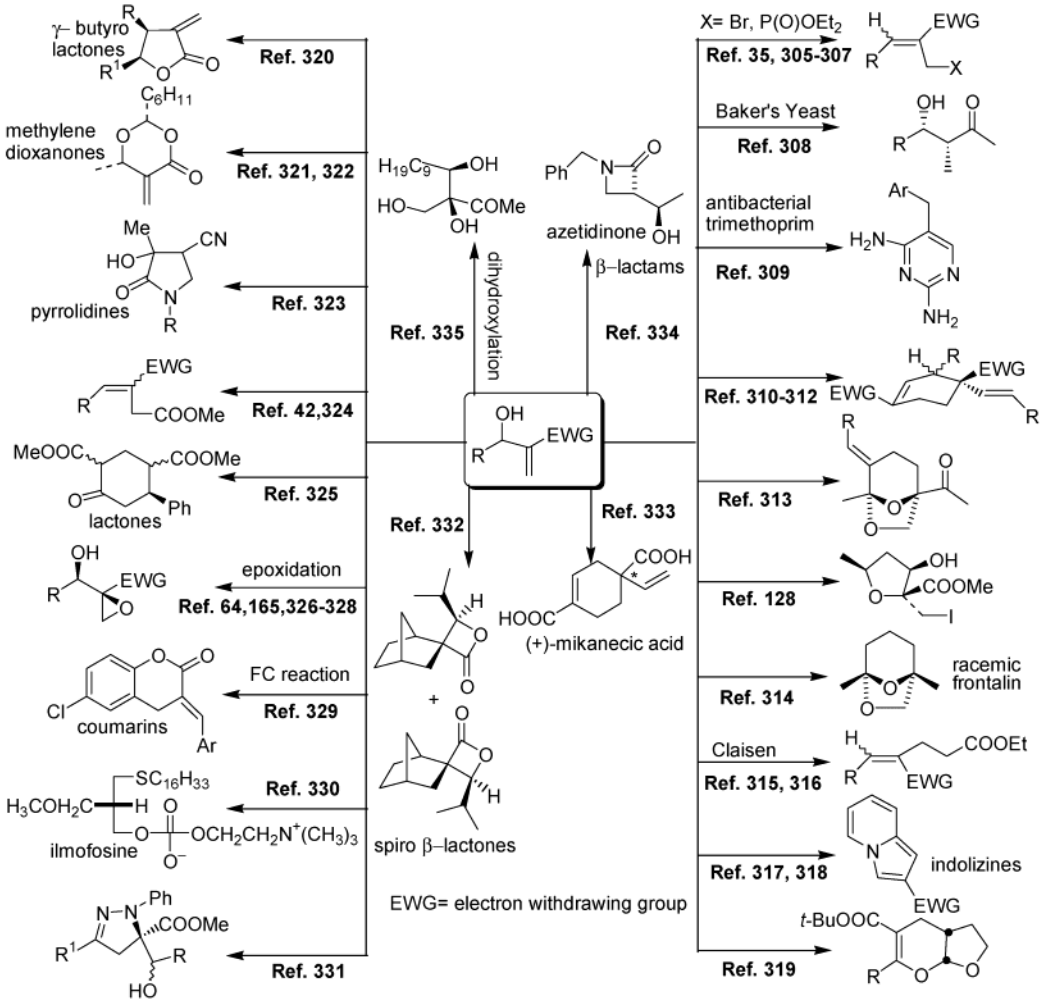
Yadav and co-workers[304] reported an improved synthesis of pyrazolines **184** through the cycloaddition reactions of aryl azides with acrylates (excess) under Baylis−Hillman reaction conditions, in high yields (Scheme 106).

6. Applications of the Baylis–Hillman Adducts

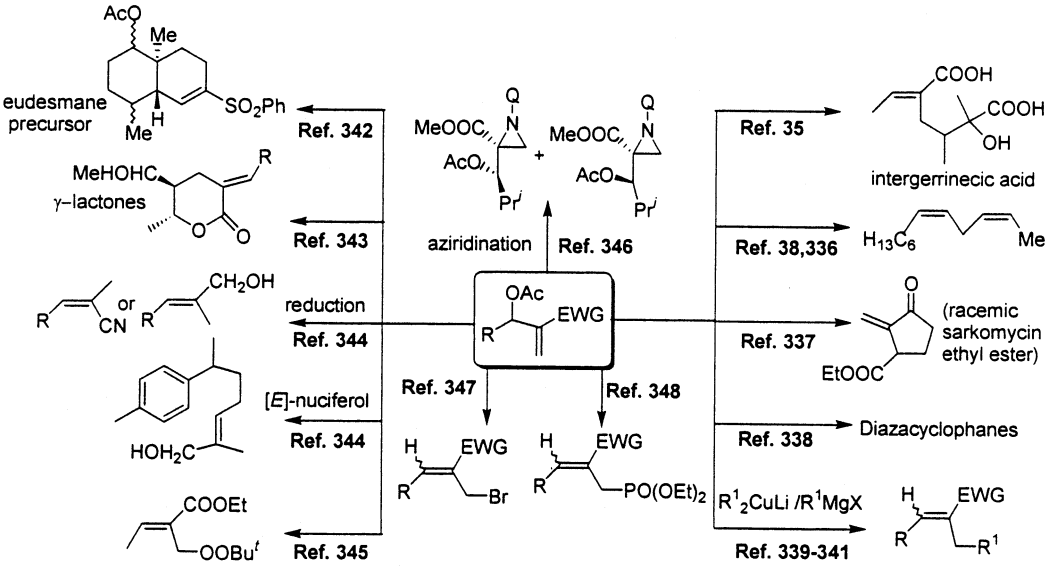
6.1. General—Earlier Work

Functional groups play an important role in bringing latitude to organic synthesis and in the construction of molecular assemblies. The Baylis−Hillman adducts obtained via the reaction between electrophiles and activated vinylic systems contain a minimum of three chemospecific functional groups, that is, hydroxy (or amino), alkene, and electron-withdrawing groups. Since these functional groups are in close proximity, they should in principle be useful in various stereoselective transformations through appropriate tuning of these groups either individually or two at a time or collectively. Several efforts have already been meticulously and articulately made in these directions, leading to the development of facile and simple methodologies for a variety of organic transformations involving high levels of stereoselec-

Scheme 107



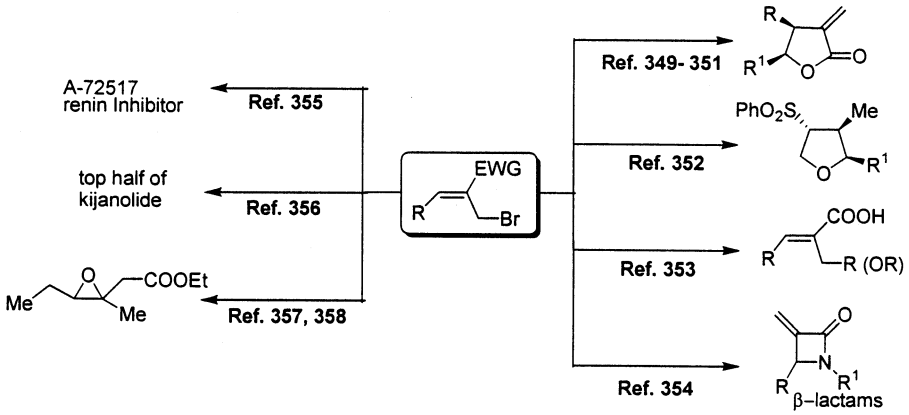
Scheme 108



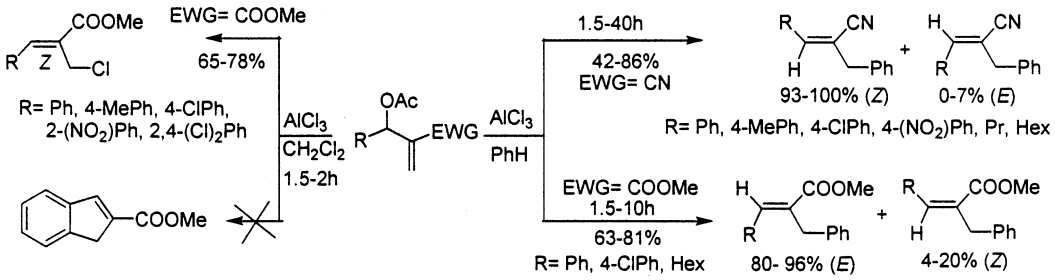
tivities. And in fact, some of these strategies/methodologies were also successfully employed in the synthesis of various biologically active molecules and natural products. All the applications that appeared up to 1995−1996 were well-described in earlier reviews.[25−27] However, to allow for a quick glance and also to have a proper perspective of earlier developments, we are presenting a very brief summary of the earlier applications in pictorial form in Schemes 107−109.

During the past 5 years, applications of the Baylis−Hillman chemistry have been extensively investi-

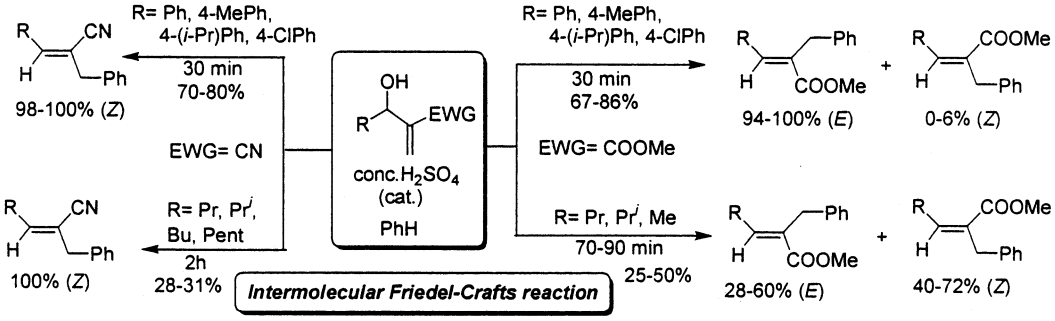
Scheme 109



Scheme 110



Scheme 111



gated and a number of organic transformation methodologies were developed. Every effort has been made to present all these developments in this section systematically. A brief review describing the synthesis of cyclic molecules using Baylis−Hillman adducts by Kim and Lee has just appeared.[359]

6.2. New Developments

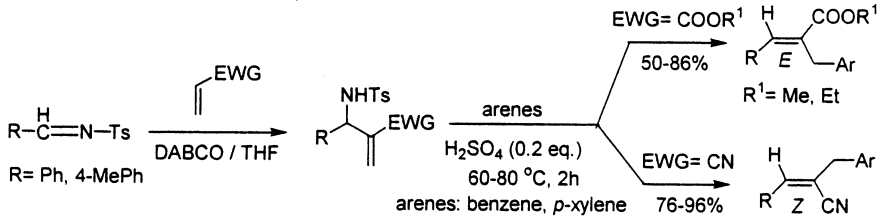
6.2.1. Friedel–Crafts Reaction

Our research group has demonstrated the utility of acetates of the Baylis−Hillman adducts as novel stereodefined β-electrophiles in the Friedel−Crafts reaction with benzene in the presence of $AlCl_3$, leading to the stereoselective synthesis of (*Z*)- and (*E*)-functionalized trisubstituted alkenes (Scheme 110).[360] Our attempts to perform intramolecular Friedel−Crafts reaction in the absence of benzene to obtain indene derivatives met with failure. However, this reaction provided a simple methodology for the synthesis of (*Z*)-allyl chlorides.

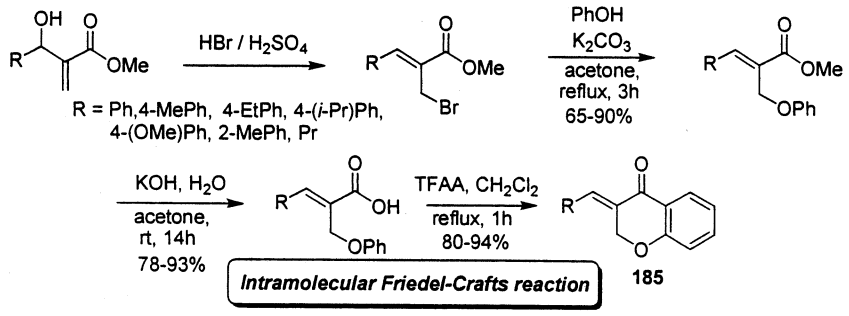
Subsequently, our research group developed a simple and convenient methodology for the stereoselective construction of both (*E*)- and (*Z*)-trisubstituted olefins via the sulfuric acid catalyzed Friedel−Crafts reaction of Baylis−Hillman adducts with benzene, thus avoiding the use of $AlCl_3$ in performing the Friedel−Crafts reaction (Scheme 111).[361] It may be noted that Baylis−Hillman adducts obtained from acrylonitrile provide high (*Z*)-stereoselectivities, whereas the Baylis−Hillman adducts obtained from methyl acrylate and aromatic aldehydes provide high (*E*)-stereoselectivities. However, in the case of Baylis−Hillman adducts derived from methyl acrylate and aliphatic aldehydes, there is no significant stereoselectivity (Scheme 111). This interesting reversal of stereochemical directive effects from ester to nitrile is consistent with our earlier results.[341,344,347,360]

Later on, Kim and co-workers reported Friedel−Crafts reaction of the Baylis−Hillman adducts of *N*-tosylimine derivatives with arenes in the presence of sulfuric acid, providing a stereoselective methodology for the preparation of (*E*)- and (*Z*)-2-benzyl substituted olefins (Scheme 112).[362] They also employed chlorobenzene and toluene for Friedel−Crafts

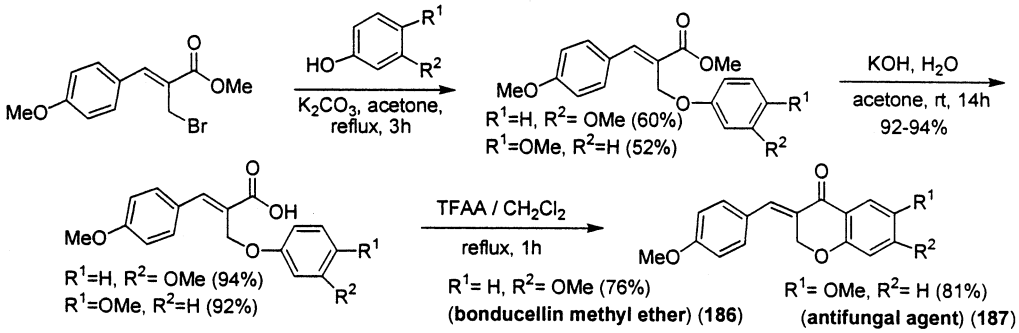
Scheme 112



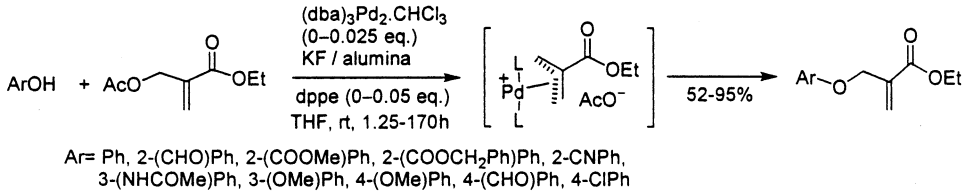
Scheme 113



Scheme 114



Scheme 115



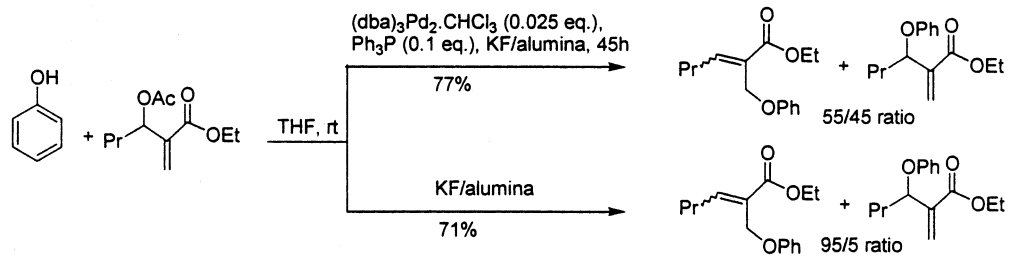
reaction, which provided a mixture of ortho and para isomers.

The Baylis−Hillman adducts, derived from methyl acrylate and aldehydes, were successfully used for the development of a convenient procedure for general synthesis of 3-arylidene(alkylidene)chroman-4-ones **185** following the reaction sequence as described in Scheme 113. This methodology involves intramolecular Friedel−Crafts reaction as the key step (Scheme 113).[363] This synthetic strategy was also applied to the synthesis of representative natural products, that is, bonducellin methyl ether (**186**) and antifungal agent (**187**) (Scheme 114).[363]

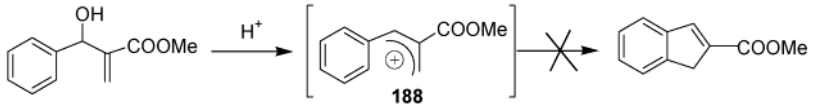
Muzart and co-workers have studied the addition of various substituted phenols to the acetate of the Baylis−Hillman adduct (obtained from formaldehyde and ethyl acrylate) in the presence of a Pd(0) and/or KF/alumina as a catalyst. In general, fast reactions and higher yields were achieved when both the reagents were used together. They also observed the formation of a mixture of ethers in the case of acetate of the Baylis−Hillman adduct obtained from butyraldehyde and ethyl acrylate when Pd(0) and KF/alumina were employed, whereas in the absence of Pd(0), S_N2' product was obtained predominantly (95%) (Schemes 115 and 116).[364]

Our attempts to perform the intramolecular Friedel−Crafts reaction of the Baylis−Hillman adducts obtained from aromatic aldehydes and methyl acrylate to obtain indene derivatives with various reagents were unsuccessful. This may be attributed to less stabilization of the carbocation **188** because of the presence of an electron-withdrawing group (COOMe). However, the Baylis−Hillman adducts containing electron-releasing group(s) on aromatic ring underwent facile intramolecular Friedel−Crafts reaction (probably due to the stabilization of the carbocation) in the presence of P_2O_5, thus provid-

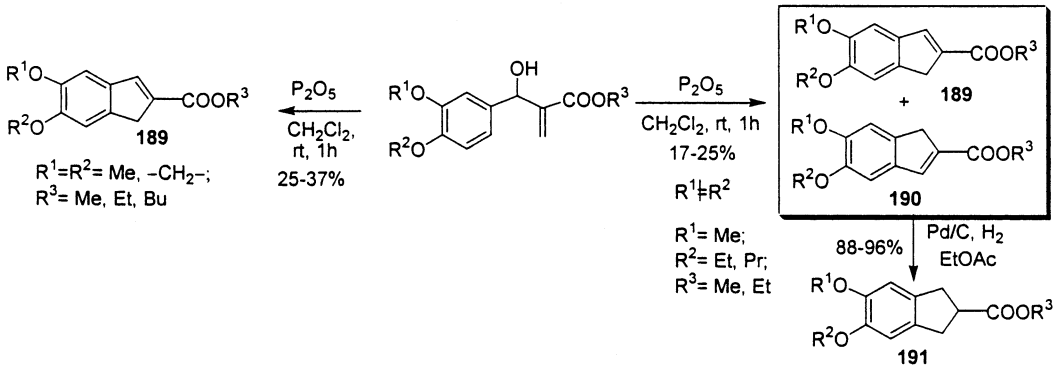
Scheme 116



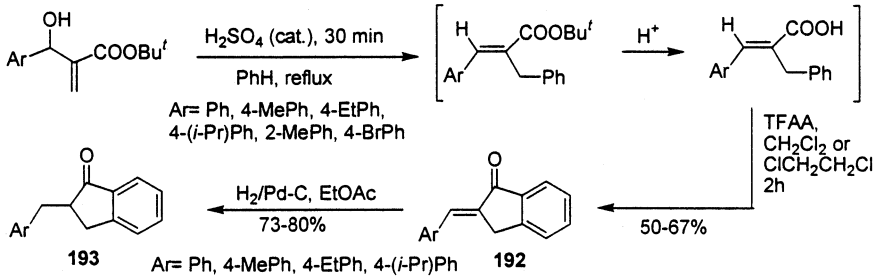
Scheme 117



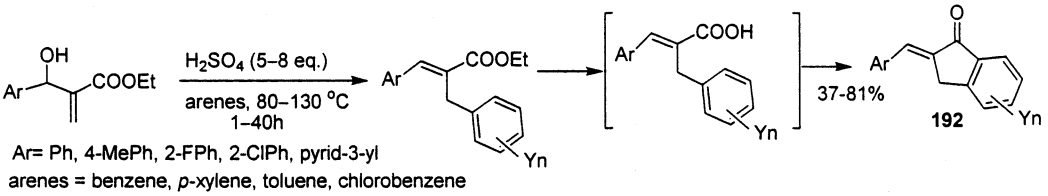
Scheme 118



Scheme 119



Scheme 120



ing a convenient process for the synthesis of indene derivatives **189** and **190**. These indene derivatives were further hydrogenated to the corresponding indane derivatives **191** (Schemes 117 and 118).[365]

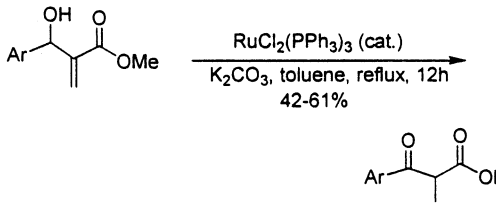
Subsequently, a simple one-pot stereoselective transformation of *tert*-butyl 3-aryl-3-hydroxy-2-methylenepropanoates, the Baylis−Hillman adducts obtained from *tert*-butyl acrylate and aromatic aldehydes, into (*E*)-2-arylideneindan-1-ones **192** involving one inter- and one intramolecular Friedel−Crafts reaction was developed by our research group according to Scheme 119. These compounds were further transformed to the corresponding 2-arylmethylindan-1-ones **193** via catalytic hydrogenation in the presence of 5% Pd/C catalyst (Scheme 119).[366]

Later on, Kim and co-workers also synthesized (*E*)-2-arylideneindan-1-ones **192** in a one-pot operation from the Baylis−Hillman adducts via the successive inter- and intramolecular Friedel−Crafts reactions (Scheme 120).[367]

6.2.2. Isomerization

Our research group has successfully transformed methyl 3-aryl-3-hydroxy-2-methylenepropanoates, the

Baylis−Hillman adducts obtained from methyl acrylate and aromatic aldehydes, into methyl 3-aryl-2-methyl-3-oxopropanoates under the catalytic influence of $RuCl_2(PPh_3)_3$. However, attempted isomerization of methyl 3-hydroxy-2-methylenehexanoate (the Baylis−Hillman adduct obtained from butyraldehyde and methyl acrylate) was not clean in the presence of $RuCl_2(PPh_3)_3$ (eq 75).[368]

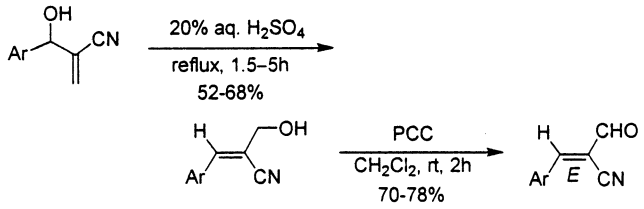


Eq. 75

Ar= Ph, 4-MePh, 4-EtPh, 4-(*i*-Pr)Ph, 4-(OMe)Ph, 2-(OMe)Ph

The α-methylene-β-hydroxyalkanenitriles (secondary allylic alcohols) have been conveniently isomerized into 3-aryl-2-(hydroxymethyl)prop-2-enenitriles (primary allylic alcohols) by our research group via treatment with aqueous sulfuric acid (20%). These primary alcohols were further converted into the corresponding cinnamaldehydes, important synthons in organic synthesis (Scheme 121).[369]

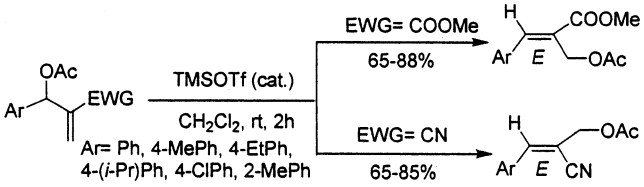
Scheme 121



Ar= Ph, 4-ClPh, 4-MePh, 4-(*i*-Pr)Ph, 2-MePh, 2-(OMe)Ph, naphth-1-yl

Methyl 3-acetoxy-3-aryl-2-methylenepropanoates and 3-acetoxy-3-aryl-2-methylenepropanenitriles were converted under the influence of TMSOTf into methyl (2*E*)-2-(acetoxymethyl)-3-arylprop-2-enoates and (2*E*)-2-(acetoxymethyl)-3-arylprop-2-enenitriles, respectively (Scheme 122).[370] The remarkable reversal in

Scheme 122

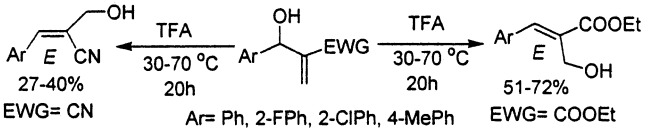


stereochemical directions from ester to nitrile in these reactions is consistent with our earlier results.[341,344,347,360,361]

Kim et al. have reported an interesting facile one-pot stereoselective synthesis of (*E*)-cinnamyl alcohols via the treatment of ethyl 3-aryl-3-hydroxy-2-methylenepropanoates with TFA (Scheme 123). However, similar reaction of 3-aryl-3-hydroxy-2-methylenepropanenitriles with TFA provided the (*E*)-allyl alcohols in low yields (Scheme 123).[371]

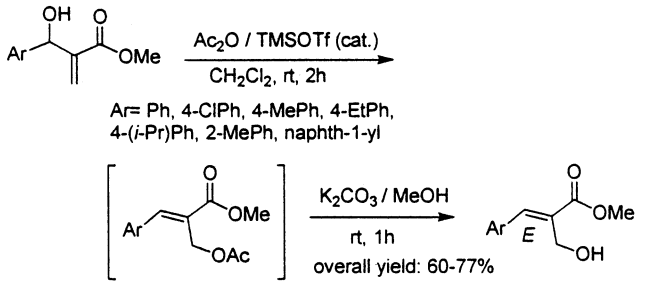
About the same time, we also developed an alternative, simple, and one-pot stereoselective synthesis

Scheme 123

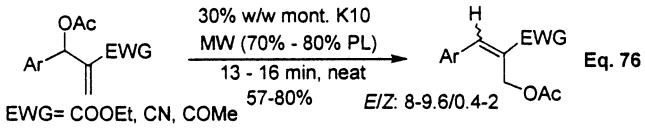


of methyl (2*E*)-3-aryl-2-(hydroxymethyl)prop-2-enoates via the sequential treatment of methyl 3-aryl-3-hydroxy-2-methylenepropanoates with Ac_2O/TMSOTf and K_2CO_3 in methanol (Scheme 124).[372]

Scheme 124



Subsequently, stereoselective isomerization of acetates of the Baylis−Hillman adducts have also been achieved by Shanmugam and Singh using the montmorillonite K10 clay microwave to furnish the (*E*)-trisubstituted alkenes in high yields (eq 76).[373]



Eq. 76

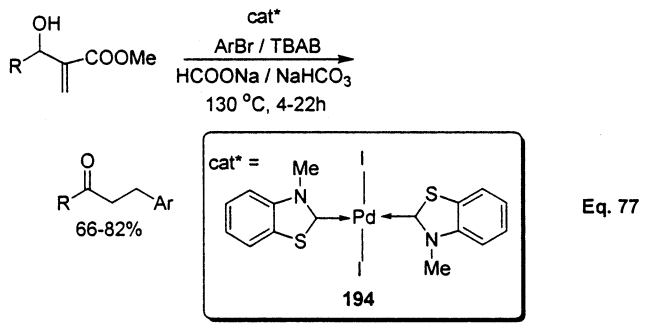
EWG= COOEt, CN, COMe

Ar= Ph, 4-ClPh, 4-MePh, 2,4-(Cl)$_2$Ph, 4-(OMe)Ph, naphth-1-yl, naphth-2-yl

6.2.3. Heck Reaction

The Baylis−Hillman adducts have been successfully utilized as substrates for Heck coupling with various aryl bromides independently by our research group,[374] Sundar and Bhat[375] and Kumareswaran and Vankar[376] (Scheme 125). The acetates of the Baylis−Hillman adducts[376] have also been used for a similar reaction to provide trisubstituted olefins with (*E*)-stereoselectivities (Scheme 125).

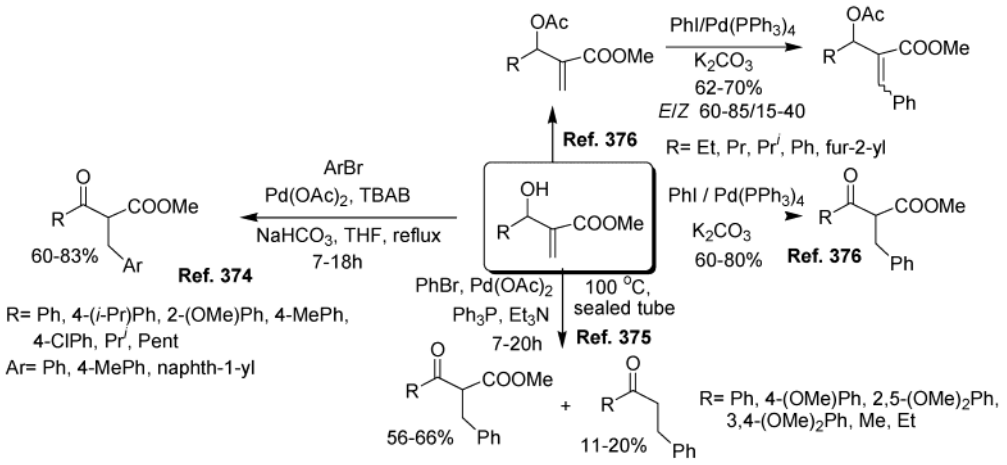
Later on, Kulakarni and Ganesan described a solid-phase synthesis of β-keto esters via sequential Baylis−Hillman and Heck reactions. Subsequent hydrolysis of these keto esters via treatment with TFA provided β-aryl ketone derivatives (Scheme 126).[377]



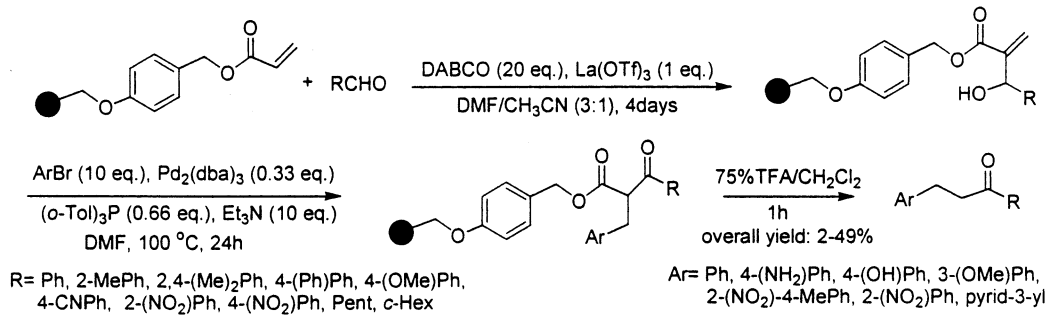
Eq. 77

Ar= Ph, 4-MePh, 4-(OMe)Ph, 4-(COMe)Ph, naphth-1-yl;
R= Ph, Me, Pr, Pr^i, Oct

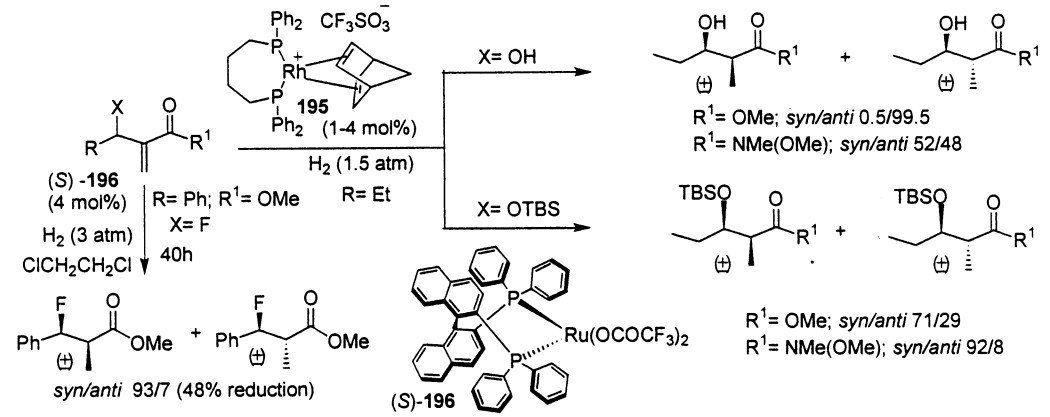
Scheme 125



Scheme 126



Scheme 127



Very recently, Calo et al. observed a very fast and efficient Heck reaction of aryl bromides with methyl 3-hydroxy-2-methylenealkanoates and methyl 3-hydroxy-3-phenylpropanoate (Baylis−Hillman adducts) using Pd-catalyst **194** with benzothiozole carbene as a ligand in TBAB melt as a solvent to give the corresponding β-aryl ketones (eq 77).[378]

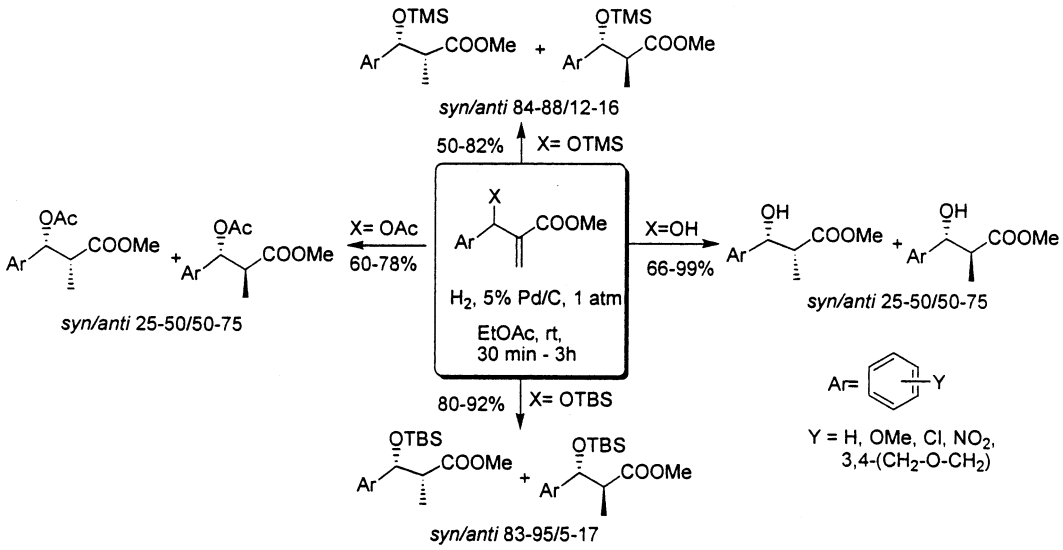
6.2.4. Hydrogenation

The Baylis−Hillman adducts have been successfully employed in various diastereo-/enantioselective catalytic homogeneous hydrogenation processes by Brown and co-workers,[156−159] Noyori and co-workers,[160] Sato et al.,[247] and Yamamoto and co-workers.[53,54] In all these cases *anti*-products were formed predominantly. Recently, Brown and co-workers studied the Rh complex **195** catalyzed hydrogenation of α-(hydroxyalkyl)-*N*-methoxyacrylamides and Ru complex **196** catalyzed hydrogenation of α-(fluoroalkyl)-acrylates, which provided the corresponding *syn*-selective compounds (Scheme 127).[379]

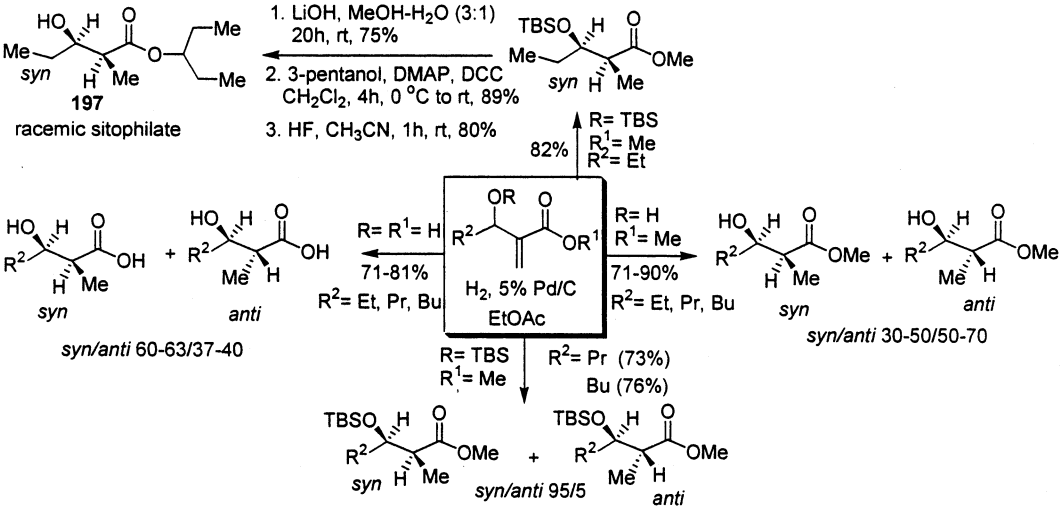
Coelho and co-workers also described a highly *syn*-diastereoselective heterogeneous catalytic hydrogenation of Baylis−Hillman adducts (Schemes 128 and 129).[380] Subsequently, they also successfully applied this methodology in the synthesis of racemic sitophilate (**197**) via the stereoselective heterogeneous catalytic hydrogenation reaction of methyl 3-(*tert*-butyldimethylsilyloxy)-2-methylenepentanoate (Scheme 129).[381]

Bouzide reported a highly *syn*-diastereoselective heterogeneous hydrogenation of Baylis−Hillman ad-

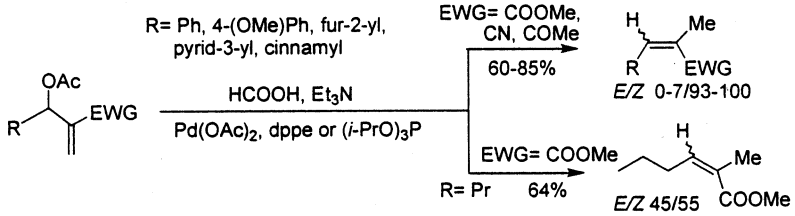
Scheme 128



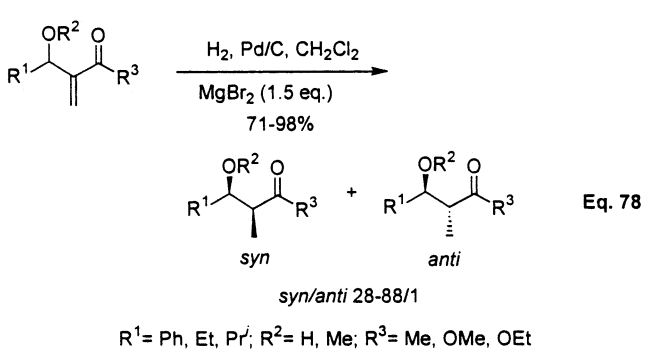
Scheme 129



Scheme 130



ducts in the presence of palladium on carbon combined with $MgBr_2$ to afford the corresponding aldol derivatives (eq 78).[382]



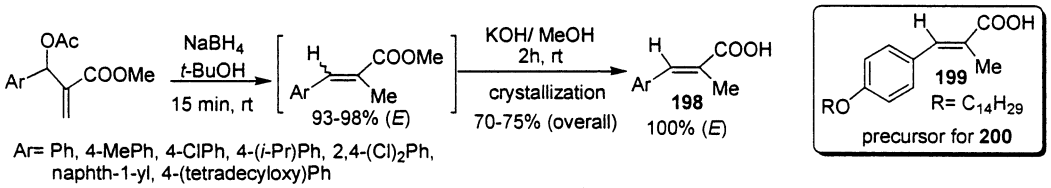
Eq. 78

6.2.5. Hydride Additions

Pachamuthu and Vankar[383] reported that acetates of the Baylis–Hillman adducts derived from aromatic aldehydes undergo reduction with HCOOH in the presence of Et_3N, $Pd(OAc)_2$, and dppe (or triisopropyl phosphite) to give the corresponding trisubstituted olefins with high (*Z*)-stereoselectivities. However, in the case of Baylis–Hillman adducts obtained from aliphatic aldehydes, stereoselectivity was lost (Scheme 130).

We described a simple and convenient synthesis of (*E*)-α-methylcinnamic acids **198** via the nucleophilic addition of hydride ion from $NaBH_4$ to the acetates of the Baylis–Hillman adducts, followed by hydrolysis and crystallization (Scheme 131). This

Scheme 131



Scheme 132

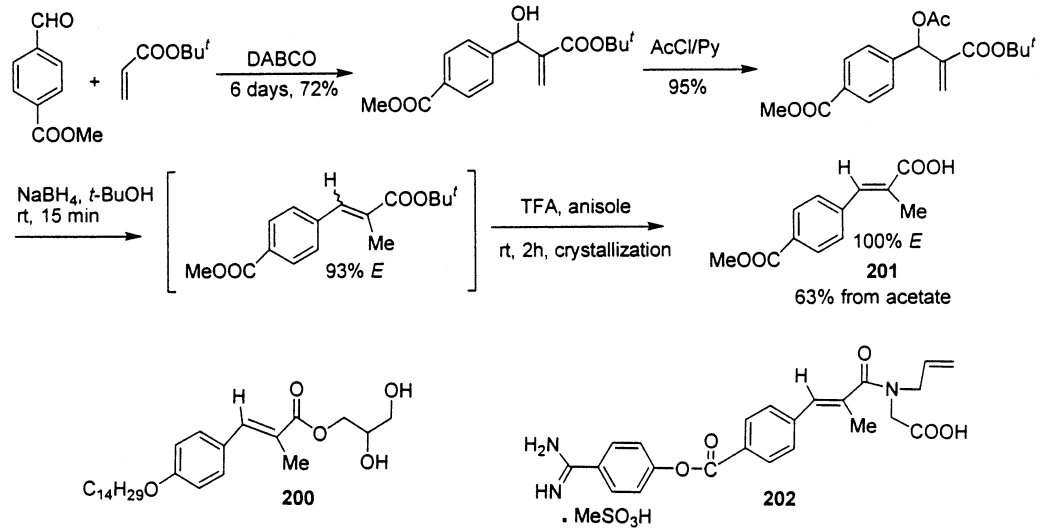
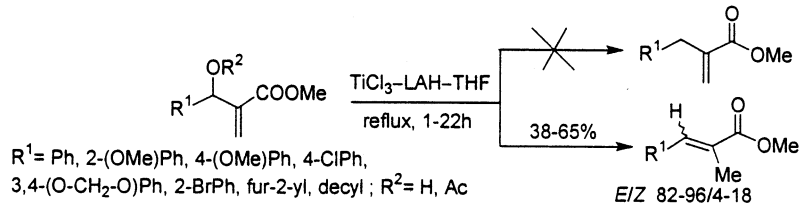


Figure 16.

Scheme 133



methodology was successfully utilized in the synthesis of [*E*]-*p*-(myristyloxy)-α-methylcinnamic acid, a hypolipidemic active agent **199**, which is also a precursor for an another active hypolipidemic agent LK-903 (**200**) and [*E*]-*p*-(carbomethoxy)-α-methylcinnamic acid **201**, a valuable synthon for an orally active seriene protease inhibitor **202** (Scheme 132 and Figure 16).[384]

Shadakshari and Nayak[385] reported a reductive regioselective dehydroxylation of the Baylis−Hillman adducts with low-valent titanium reagent to provide the corresponding trisubstituted alkene esters with high (*E*)-selectivity (Scheme 133).

Our research group described a convenient, general, and efficient synthesis of 2-methylene alkanenitriles and alkanoates via the regioselective nucleophilic (S_N2') addition of hydride ion from $NaBH_4$ to in situ generated DABCO-allylbromide [2-(bromomethyl)alk-2-enenitriles **203** and (2*Z*)-2-(bromomethyl)alk-2-enoates **204**] salts in environment-friendly aqueous media. We also synthesized two hypoglycemic agents **205** and **206** using this methodology (Scheme 134).[386] It is worth mentioning here the elegant work of Corey et al.,[387] Hoffmann and Rabe,[388] and Hall et al.,[389] who have prepared 2-methylenealkanoates from the corresponding alkyl 2-(bromomethyl)alk-2-enoates by using $NaBH_4$/DMSO,[387] superhydride ($LiBEt_3H$),[388] and 9-BBN/HMPA,[389] respectively.

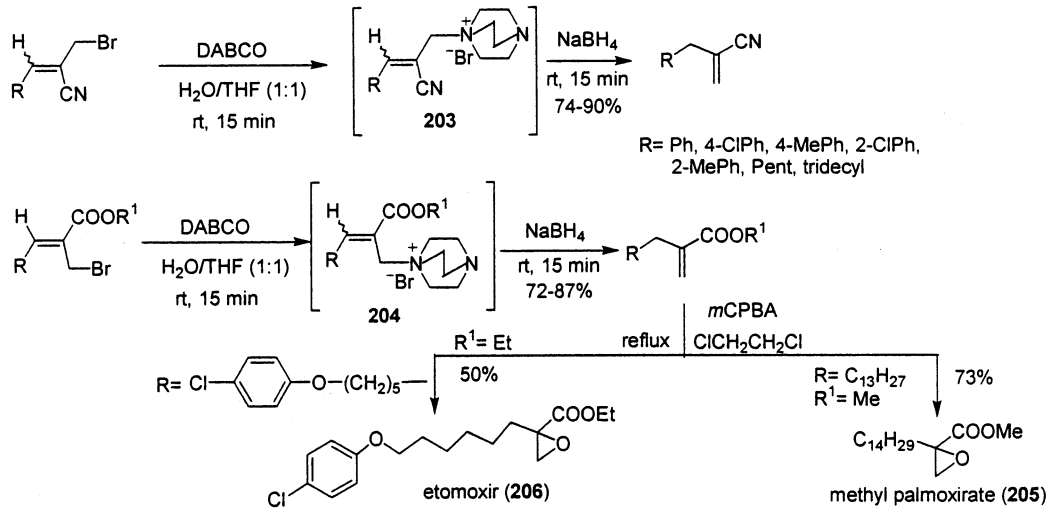
Later, Kim and co-workers[390] also synthesized 2-methylenealkanoates and alkanenitriles via the addition of hydride ion from $NaBH_4$ to the in situ generated DABCO salt of acetates of Baylis−Hillman adduct **207** (Scheme 135).[390]

6.2.6. Photochemical Reactions

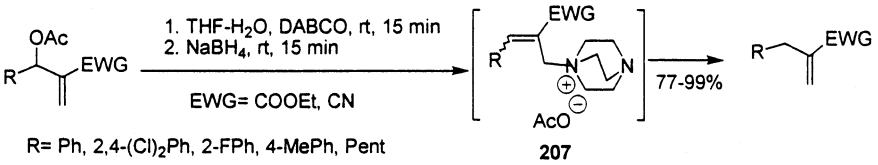
Mikami and co-workers[391−394] published a series of papers on the photochemical studies of the Baylis−Hillman adducts derived from various vinyl ketones and observed an interesting reaction trend. In the case of allyl alcohols derived from MVK, 1,4-diketones **208** were formed via the reaction pathway involving 1,4-H abstraction and cyclopropane formation assisted by the allylic hydroxy group as described in Scheme 136.[391]

In the case of methyl ethers of Baylis−Hillman adducts, the reaction proceeded through β-C−H activation to provide the substituted dihydrofurans, which were subjected to in situ treatment with

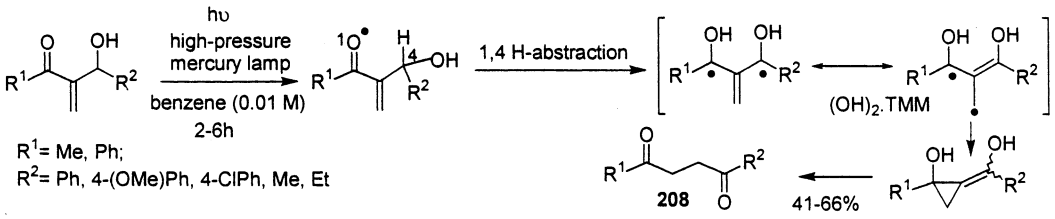
Scheme 134



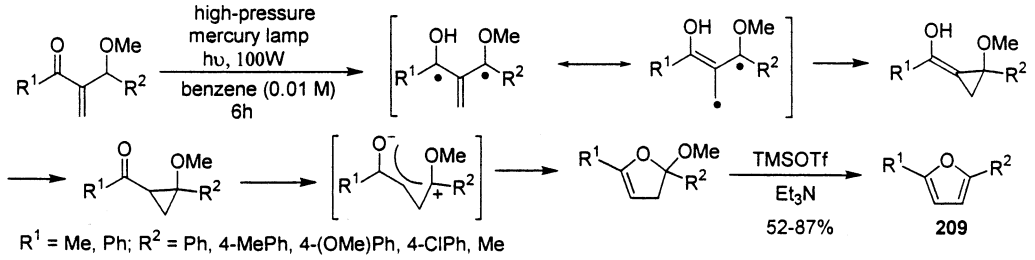
Scheme 135



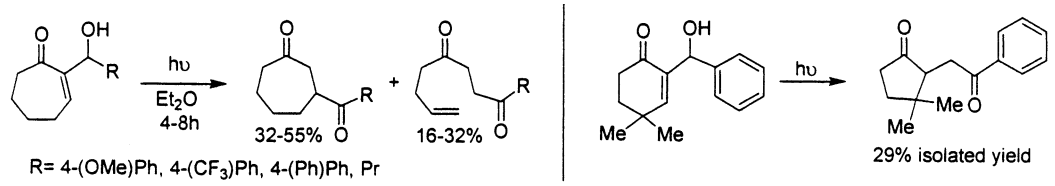
Scheme 136



Scheme 137



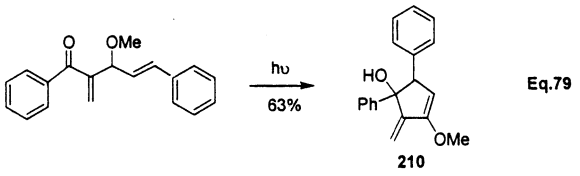
Scheme 138



TMSOTf/Et_3N, leading to the formation of substituted furan rings **209** in moderate to good yields (Scheme 137).[392]

Similar photoreaction of the Baylis−Hillman adduct derived from cyclohept-2-enone gave 1,4-diketones without ring contraction, whereas the Baylis−Hillman adduct obtained from γ,γ-disubstituted cyclohex-2-enone gave 1,4-diketones with the ring contraction under similar conditions (Scheme 138).[393] Methyl ethers of vinylogous Baylis−Hillman adducts provided cyclopentene derivatives **210** under photochemical conditions, rather than cyclopropane (di-π-methane rearrangement) and dihydrofuran (β-hydrogen abstraction) derivatives (generally observed

in nonvinylogous Baylis−Hillman products). One representative example is presented in eq 79.[394]



6.2.7. Indium-Mediated Reactions

Paquette and co-workers[395−398] described a highly diastereoselective synthesis of homoallyl alcohols (3,4-*syn* and 4,5-*anti*) **211** via indium-mediated reaction of allyl bromide (derived from Baylis−Hillman adduct) with α-oxyaldehydes (Scheme 139).[395] They examined the applications of Baylis−Hillman alcohols and the corresponding allyl bromides in indium-mediated diastereoselective reactions with aldehydes in an aqueous medium (Scheme 140).[396,397] They also transformed the Baylis−Hillman adducts into azetidinediones **212** and subjected them to the indium-mediated allylation using allyl bromides derived from Baylis−Hillman adducts to study the diastereoselectivities (Scheme 141).[398]

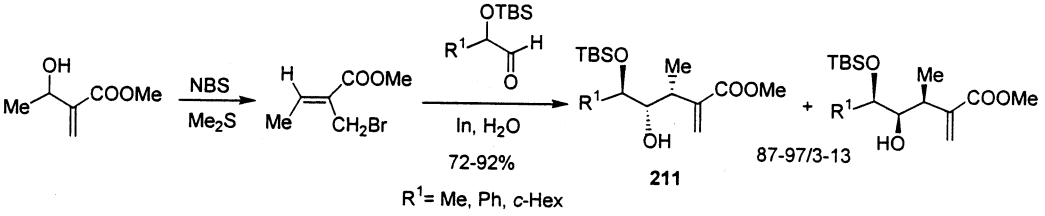
Paquette and Mendez-Andino[399] elegantly utilized the Baylis−Hillman adducts for the preparation of *cis*- or *trans*-lactones **213** following the reaction sequence described in Scheme 142. These lactones were also transformed to larger rings via ring-closing metathesis (RCM). One representative example is shown in Scheme 142.

Yus and co-workers[400,401] developed indium-promoted synthesis of substituted α-methylene-γ-lactones **214** and α-methylene-γ-butyrolactams **215** via the reaction of 2-(bromomethyl)acrylic acid with carbonyl compounds and aldimines, respectively (Scheme 143).

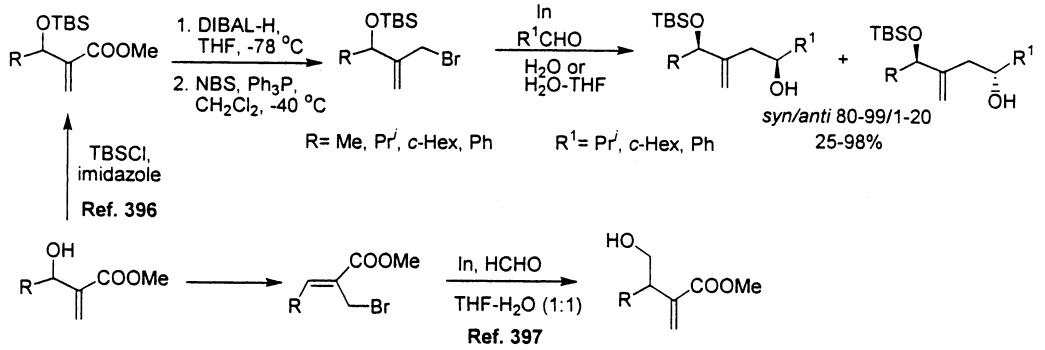
6.2.8. Naphthalenes

Kim and co-workers described a facile synthetic methodology for the synthesis of 2-substituted naphthalenes from the acetates of the Baylis−Hillman adducts involving intramolecular tandem $S_N2'-S_N$-Ar-elimination chemistry according to Scheme 144.[402,403]

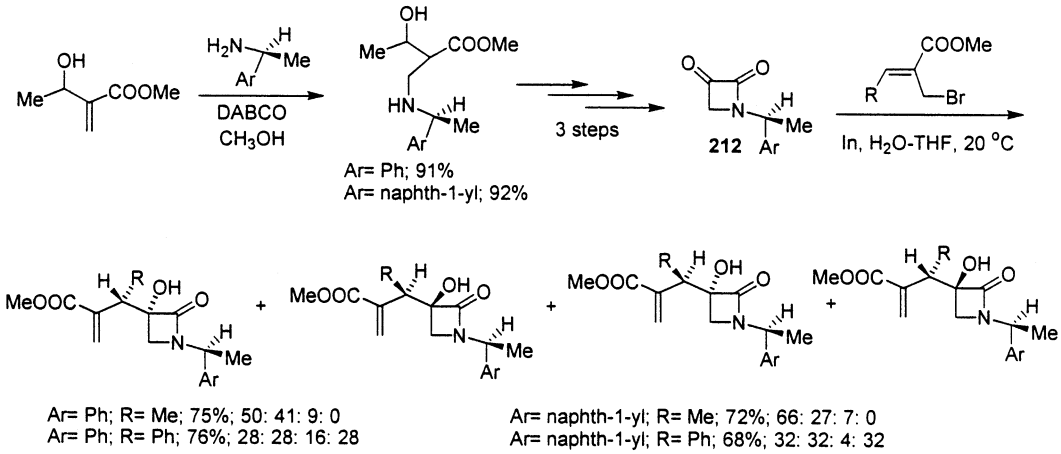
Scheme 139



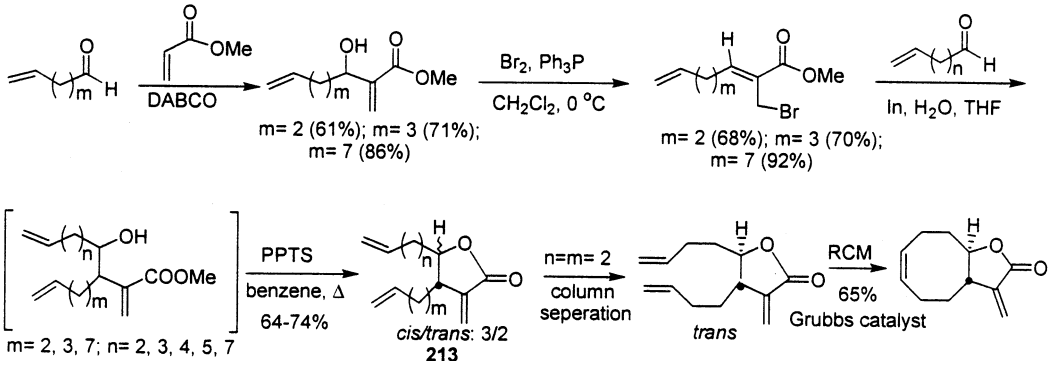
Scheme 140



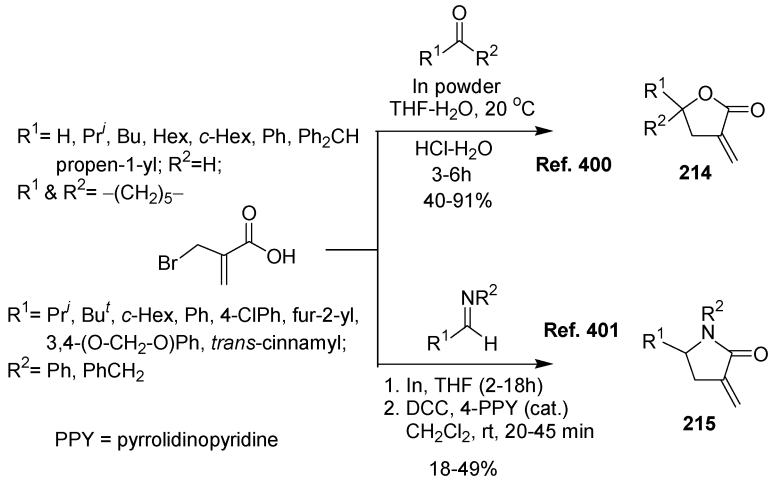
Scheme 141



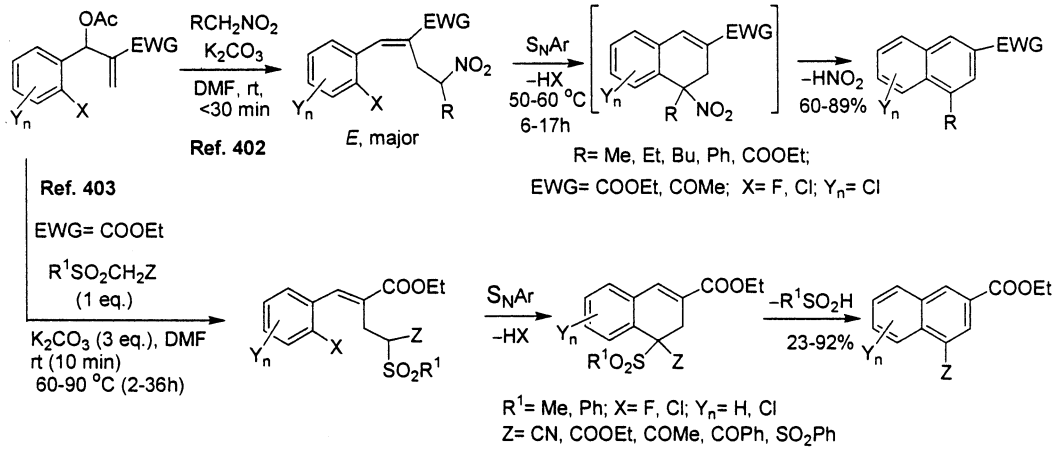
Scheme 142



Scheme 143



Scheme 144



Later on, Kim and co-workers also developed an alternative method for the synthesis of 1,3-disubstituted naphthalenes from the Baylis−Hillman acetates involving manganese(III) acetate assisted radical cyclization and aromatization as the key step according to the reaction sequence as shown in Scheme 145.[404]

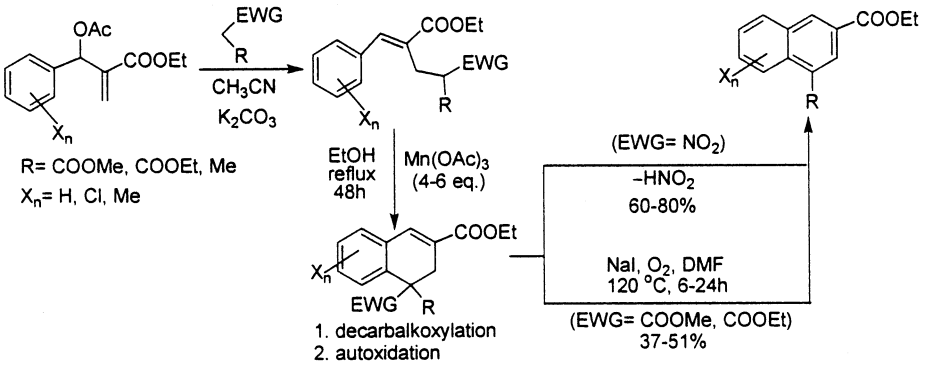
6.2.9. Quinoline, Pyrimidone, and Oxazoline Derivatives

Kaye and co-workers[405] elegantly transformed the Baylis−Hillman adducts derived from *o*-nitrobenzaldehyde and acrylates/alkyl vinyl ketones into quinoline derivatives via catalytic hydrogenation (Scheme 146).

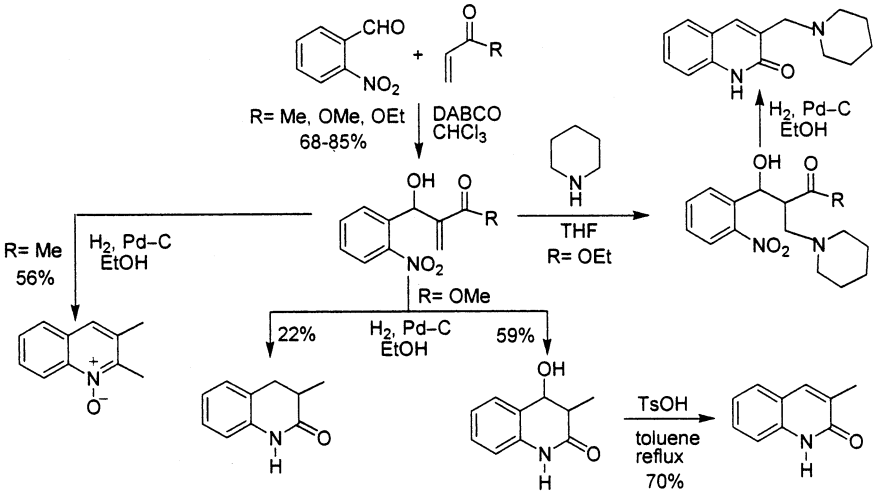
Later, Kim and co-workers[406,407] transformed the Baylis−Hillman adduct obtained from *o*-nitrobenzaldehyde and ethyl acrylate into 3-ethoxycarbonyl-4-hydroxyquinoline *N*-oxides via treatment with TFA at 60−70 °C. However, a similar reaction with the Baylis−Hillman adduct derived from *o*-nitrobenzaldehyde and acrylonitrile was unsuccessful.[406] Subsequently, they reported a photochemical method for the synthesis of 4-hydroxyquinolines (Scheme 147).[407]

Subsequently, Kim and co-workers developed an elegant methodology for the synthesis of quinoline derivatives from the Baylis−Hillman adducts of *o*-halobenzaldehyde *N*-tosylimines (Scheme 148).[408] Also, the acetates of the Baylis−Hillman adducts

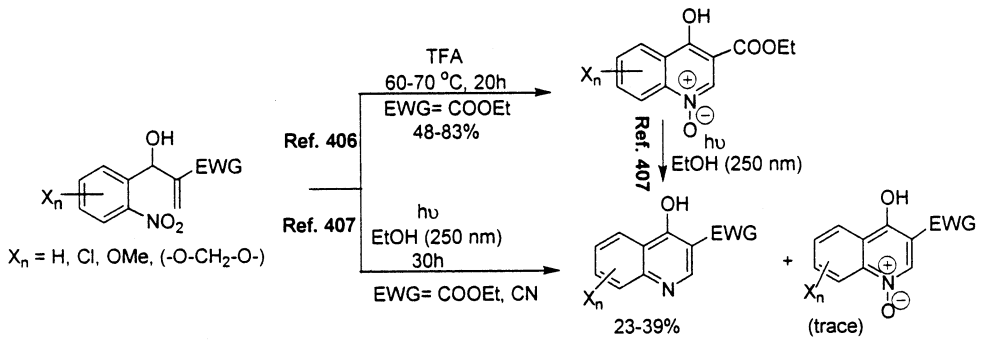
Scheme 145



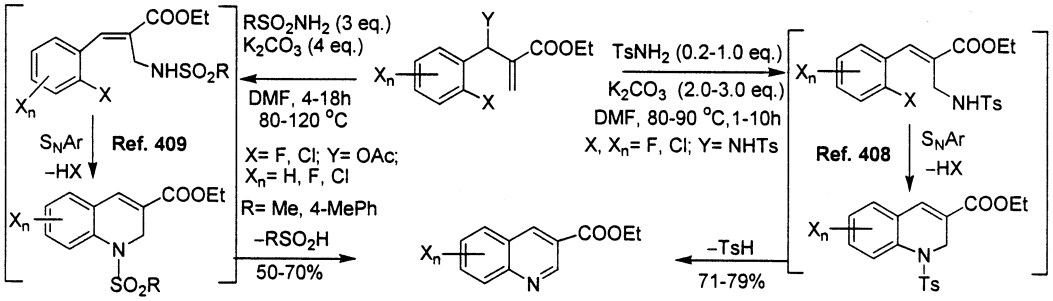
Scheme 146



Scheme 147

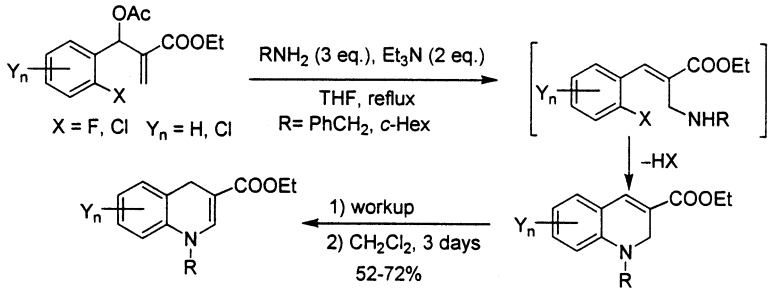


Scheme 148

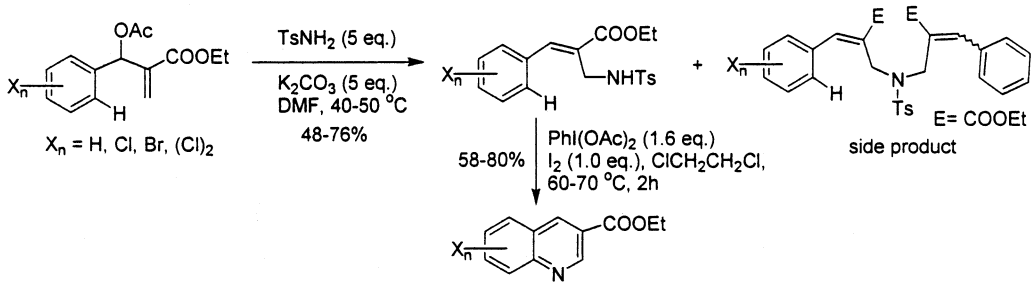


derived from *o*-halobenzaldehydes were converted into quinoline derivatives and *N*-substituted 1,4-dihydroquinolines following the reaction pathways as described in Schemes 148[409] and 149,[410] respectively. The main strategy involved in this methodology is the successive $S_N2'-S_NAr$ isomerization. However, when similar reaction was conducted with 3-(2,4-difluorophenyl)-2-methylene-3-(tosylamino)propane-

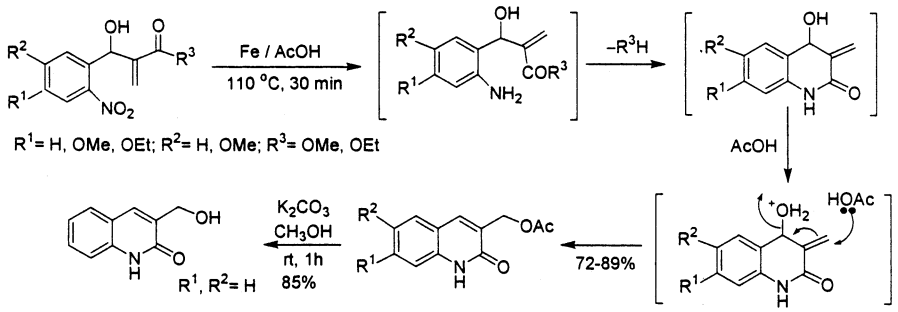
Scheme 149



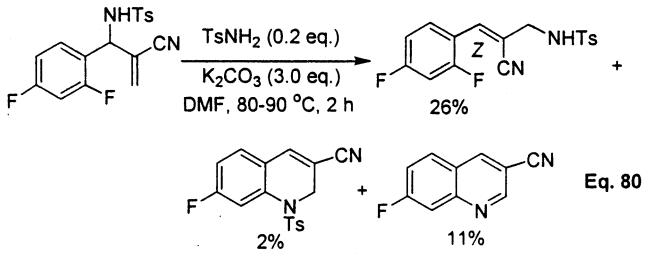
Scheme 150



Scheme 151



nitrile, the expected product was obtained in very low yields (11%), whereas allylamine was obtained as the major product (26% yield) (eq 80).[408]

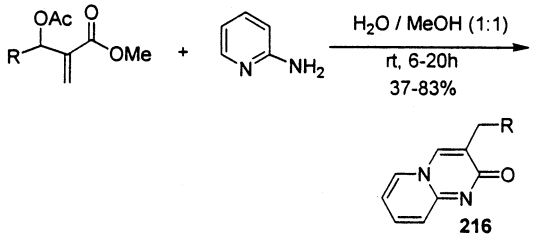


Eq. 80

Kim et al.[411] also employed an alternate method for the synthesis of quinoline derivatives in moderate to good yields from the Baylis−Hillman acetates via oxidative cyclization using $PhI(OAc)_2$ following the reaction sequence as shown in Scheme 150.

Our research group successfully transformed the Baylis−Hillman alcohol derived from *o*-nitrobenzaldehydes and alkyl acrylates into functionalized (1*H*)-quinol-2-ones via treatment with Fe/AcOH (Scheme 151).[412] Similarly, the Baylis−Hillman adducts obtained from *o*-nitrobenzaldehydes and alkyl vinyl ketones have been conveniently transformed into quinolines in a one-pot operation as shown in Scheme 152.[412]

We also described a facile one-pot convenient transformation of the acetates of the Baylis−Hillman adducts into fused pyrimidones **216** via reaction with 2-aminopyridine in environment-friendly aqueous media (eq 81).[413]



Eq. 81

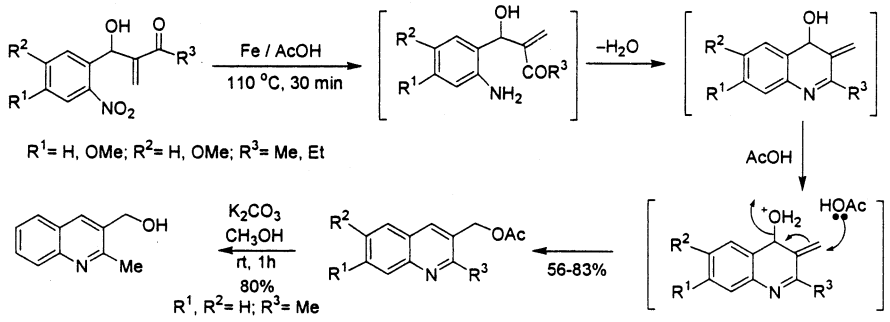
R= Ph, 4-MePh, 4-EtPh, 4-(*i*-Pr)Ph, 2-ClPh, 4-ClPh, 3-(OMe)Ph, 4-(OMe)Ph, Pent

Kurth and co-workers[414] described an efficient and selective synthesis for spiro-fused (C5)-isoxazoline-(C4)-pyrazolones **217** using Baylis−Hillman methodology (Scheme 153).

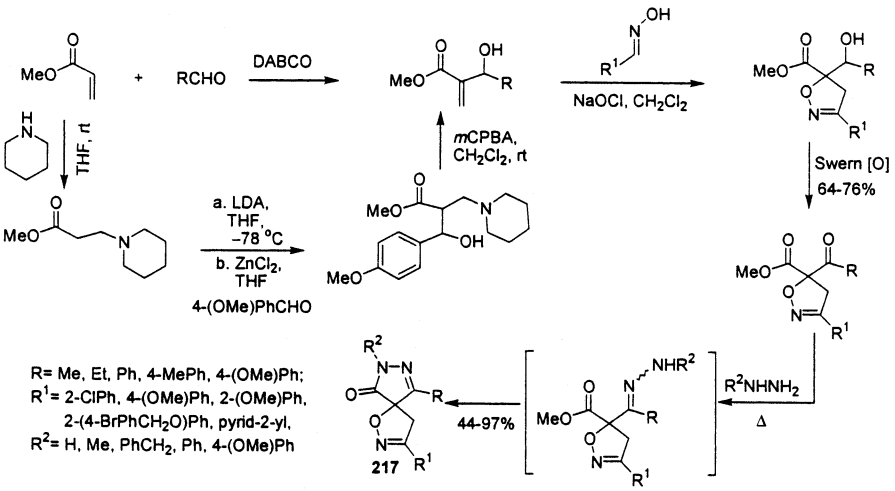
6.2.10. Natural Products

Loh et al.[415] elegantly used the Baylis−Hillman (*Z*)-allyl bromide, that is, methyl 2-(bromomethyl)but-2-enoate, as a starting material for the synthesis of the key intermediate **218** of antillatoxin (**219**), an

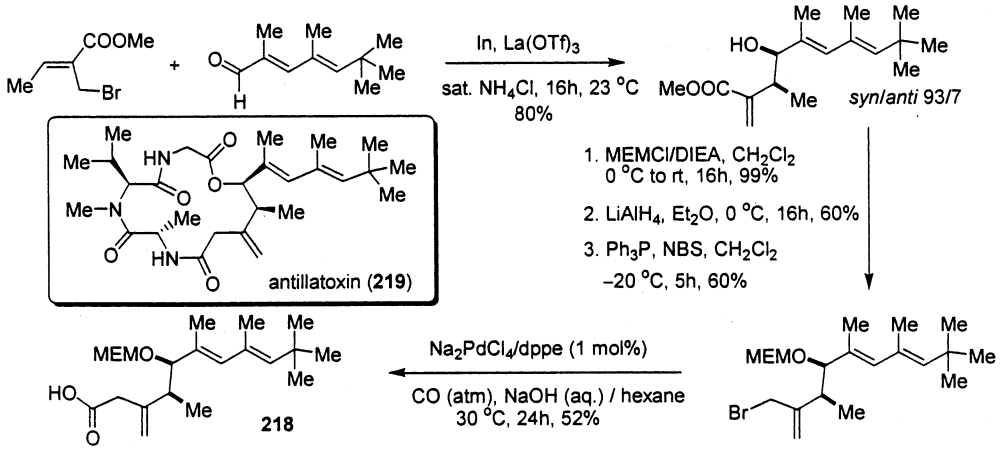
Scheme 152



Scheme 153



Scheme 154



important biologically active molecule following the reaction sequence as shown in Scheme 154.

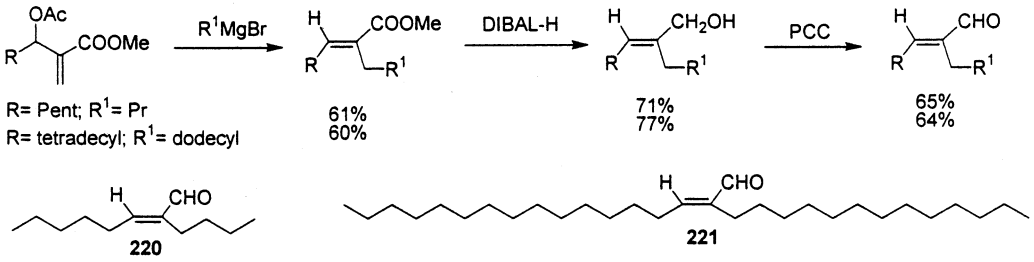
Our research group successfully utilized the Baylis−Hillman methodology in the synthesis of (2*E*)-2-butyloct-2-enal (**220**), an alarm pheromone component of the African weaver ant, *Oecophylla longinoda*, and an unusual metabolite from the red alga, *Laurencia* species (2*E*)-2-tridecylheptadec-2-enal (**221**) (Scheme 155).[416]

Vasella and co-workers[417] synthesized photochemical probes **222** and **223**, which are the analogues of dolichol **224** and dolichol phosphate **225**, obligatory intermediates in the *N*-linked glycosylation pathway in the endoplasmic reticulum, using Baylis−Hillman strategy as one of the steps according to Scheme 156.

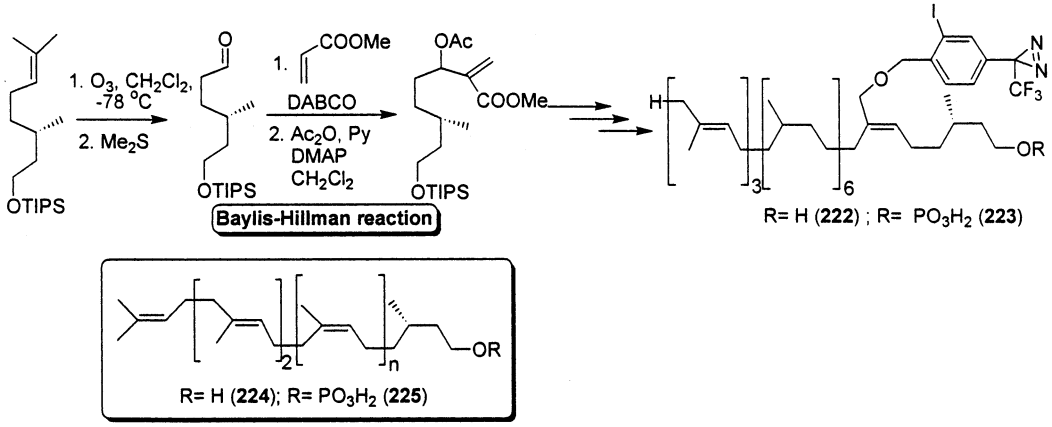
During their studies on the synthesis of tricyclopolyprenols (**227*E*** and **227*Z***), Jenn and Heissler[418] prepared model molecules (both the isomers **226*E*** and **226*Z***) using the Baylis−Hillman strategy via the addition of a cyclohexyl radical to 3-hydroxy-2-methylene-5,9-dimethyldec-8-ennitrile and to methyl 3-hydroxy-2-methylene-5,9-dimethyldec-8-enoate (Baylis−Hillman adducts), respectively (Schemes 157 and 158).

The Baylis−Hillman adducts/acetates were conveniently transformed into *Z*/*E*-allyl phosphonates stereoselectively.[306,348] Very recently, Fields[419] reported convenient synthesis of phosphonothrixin (**228**) (an important natural product) from the (*Z*)-allyl phosphonate [methyl (*Z*)-2-(diethoxyphospho-

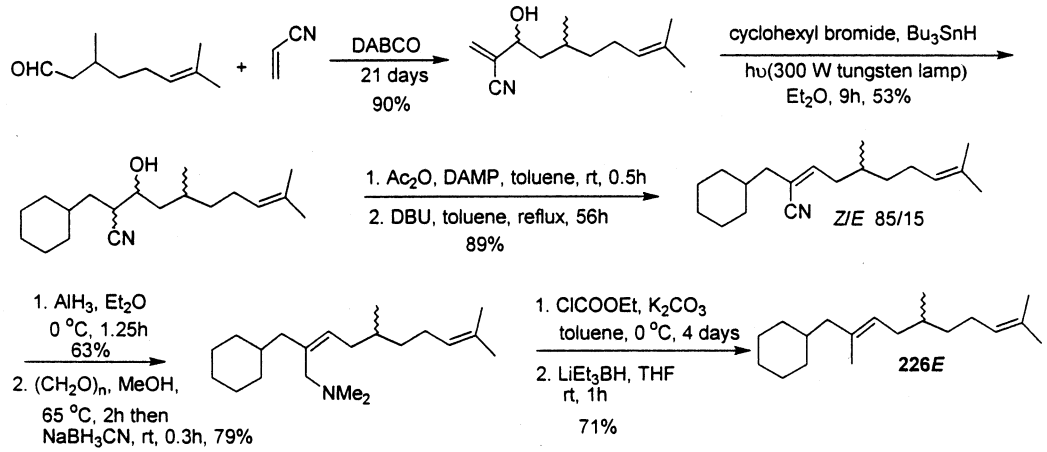
Scheme 155



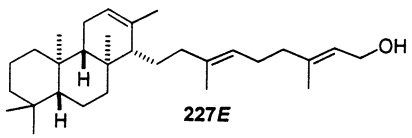
Scheme 156



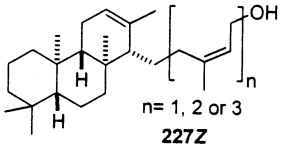
Scheme 157



rylmethyl)but-2-enoate][306] in an overall yield of 24% from the Baylis−Hillman adduct (methyl 3-hydroxy-2-methylenebutanoate) following the reaction sequence as shown in Scheme 159.



227*E*



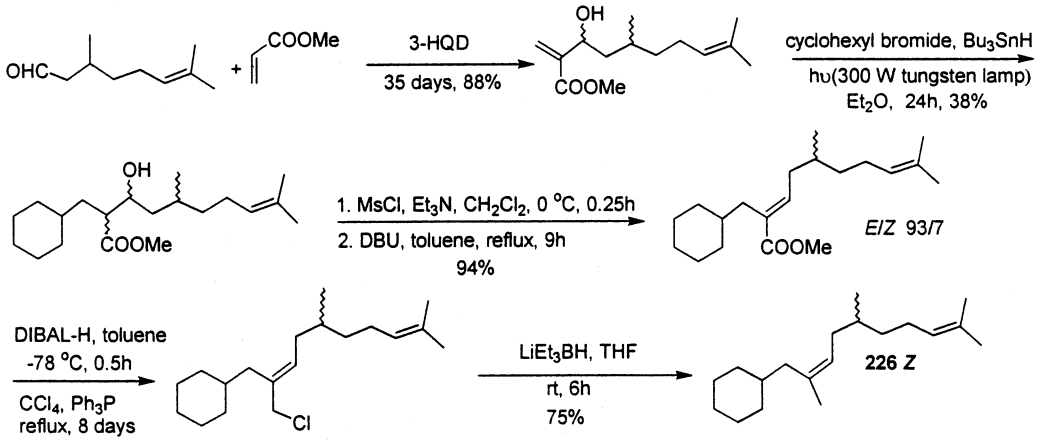
227*Z*

Ogasawara and co-workers[420,421] have performed the Baylis−Hillman coupling between chiral bicyclic enones (+)-KDP and (−)-KDP and formalin. The resulting adducts (+)-**229** and (−)-**229** were transformed into a cyclopentanoid antibiotic (−)-pentenomycin I (**230**)[420] and angular triquinane sesquiterpene (+)-arnicenone (**231**),[421] respectively, according to Scheme 160.

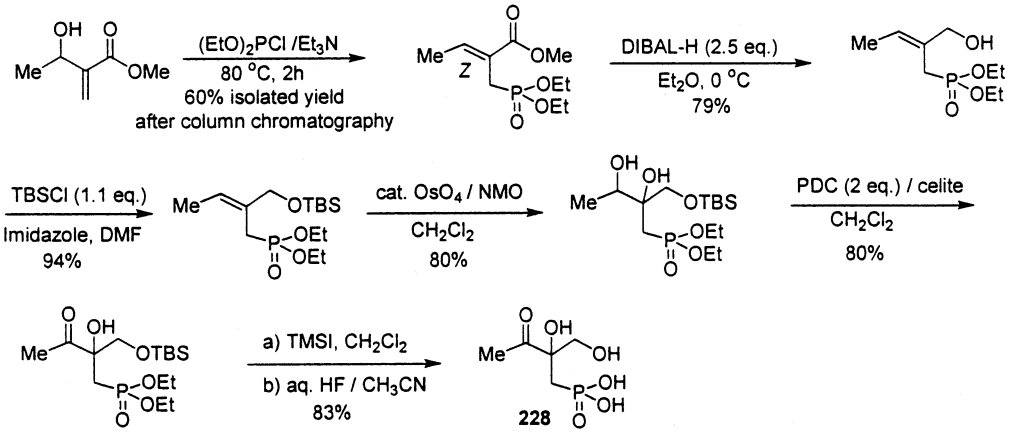
Acetate of the Baylis−Hillman adduct **232** obtained from cyclopentenone and formalin was elegantly used by Banwell et al.[422] for the synthesis of the bicyclic core **233** that appears in tRNA synthetase inhibitors, SB-203207 (**234**) and SB-203208 (**235**) and some biologically active analogues via a multicomponent reaction sequence as shown in Scheme 161.

The Baylis−Hillman adduct derived from piperonal has been successfully transformed into functionalized oxazolidin-2-one **236** by Coelho and Rossi.[423] The molecule **236** was further converted into substituted vicinal amino alcohols **237** and *β*-chloramphenicol derivatives **238** (Scheme 162).[423]

Scheme 158



Scheme 159

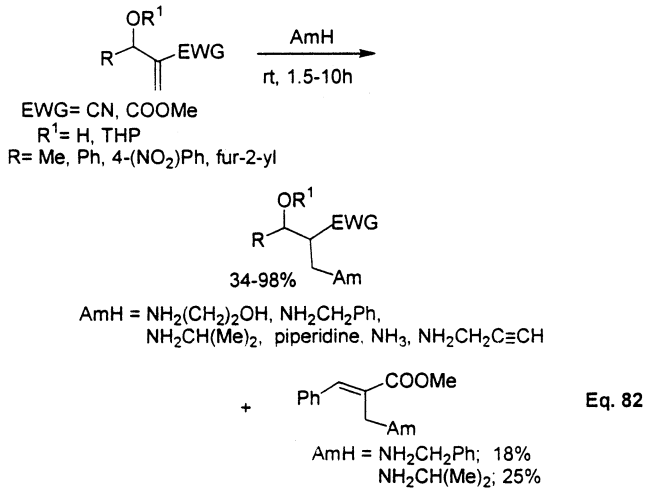


Lin and co-workers[424] successfully described a total synthesis of sphingofungin E (**239**) using Baylis−Hillman methodology as the key step (Scheme 163).

Very recently, Singh and co-workers[425] described a short and efficient synthesis of (−)-acaterin [(−)-**9**], a biologically important natural product, by elaboration of a Baylis−Hillman adduct obtained from octanal and methyl acrylate (Scheme 164).

6.2.11. Allyl Amines

Foucaud and El Guemmout[426] elegantly transformed the acetates of the Baylis−Hillman adducts obtained from methyl acrylate into the corresponding allylamines with high (*E*)-selectivities. Recently, Kundu and Bhat[427] performed the nucleophilic addition of amines onto the Baylis−Hillman alcohols to provide β-aminopropionic acid derivatives. In some cases, they also observed formation of allylamines (eq 82).



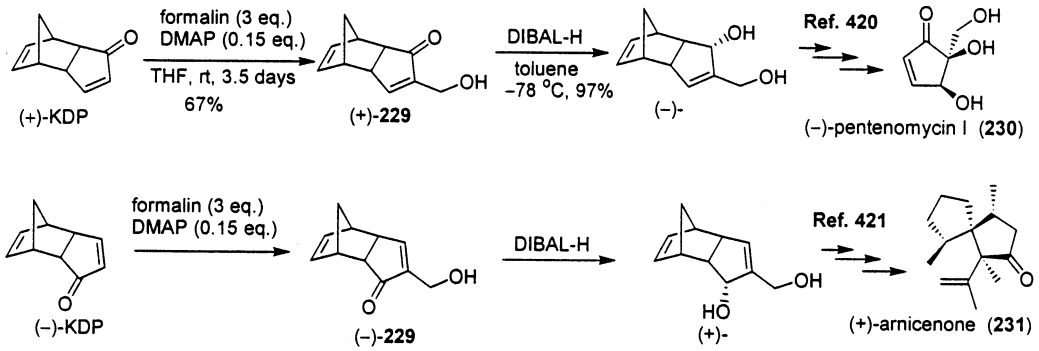
Eq. 82

Later, Amri and co-workers[428] described stereoselective synthesis of 2-ethylidene-3-aminonitriles via the addition of primary or secondary amines to 2-(1-acetoxyethyl)acrylonitrile (Baylis−Hillman acetate) (Scheme 165).

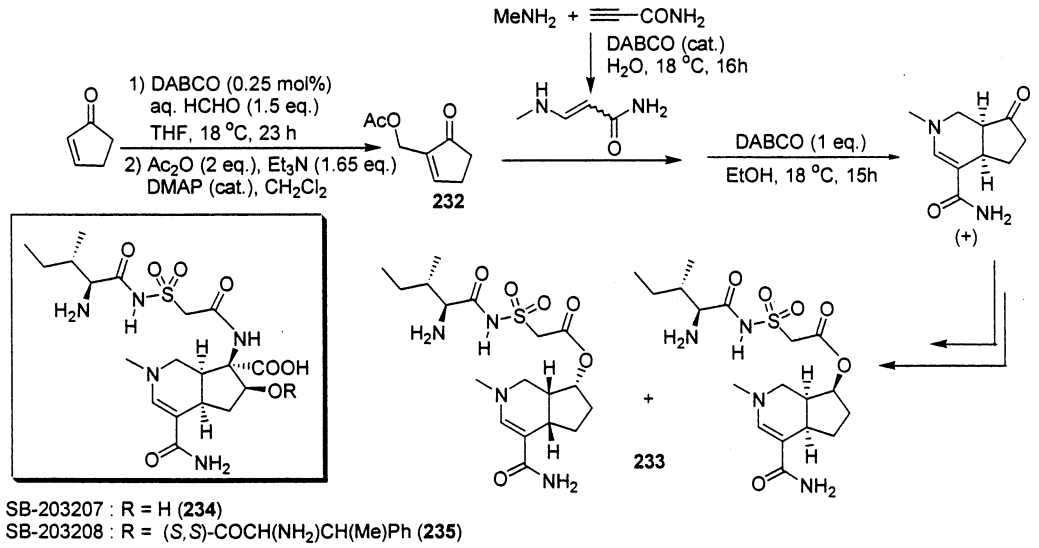
An interesting stereoselective transformation of the Baylis−Hillman adducts into cinnamylamines via treatment with DMF−DMA has been described by Kim and co-workers (Scheme 166).[429,430]

Iqbal and co-workers[431] described an interesting solvent and substituent dependent regioselective (S_N2 or S_N2') palladium(0)-catalyzed synthesis of α-dehydro-β-amino esters via treatment of the acetates of Baylis−Hillman adducts with amines. Representative examples are described in Scheme 167. The (*E*)-allylamine **240** thus obtained was successfully transformed into cyclic peptide **241** according to the reaction sequence shown in Scheme 168. They also observed that the proline-based cyclic secondary amine and serine methyl ester on reaction with allyl acetates under the influence of Pd(0) (catalyst) provide the corresponding (*E*)-allylamines (S_N2') exclusively (Scheme 167).

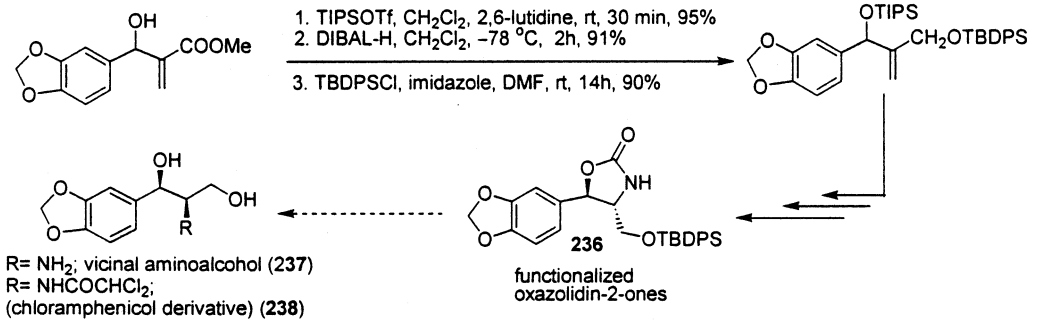
Scheme 160



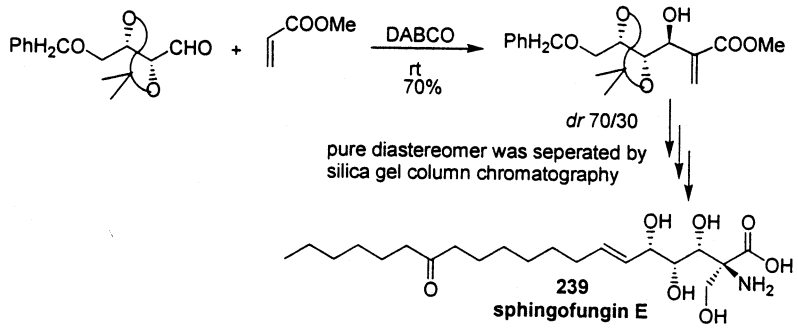
Scheme 161



Scheme 162

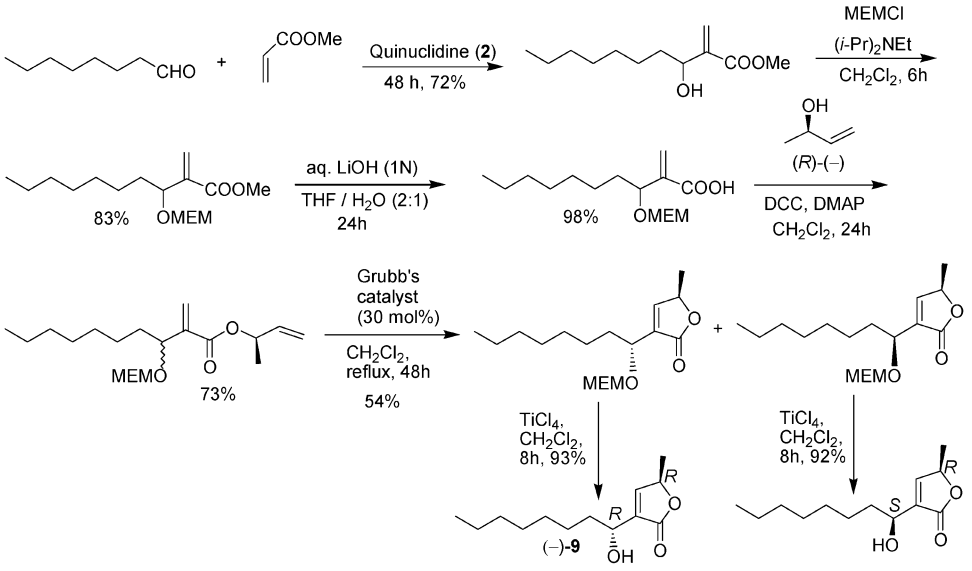


Scheme 163

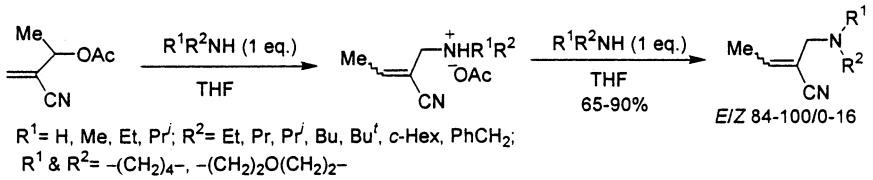


Reiser and co-workers[432,433] reported a combinatorial liquid-phase synthesis of [1,4]oxazepine-7-ones **242**, important building blocks, via Baylis−Hillman reaction and a split synthesis approach using MeOPEG as a soluble polymer support (Scheme 169).[432]

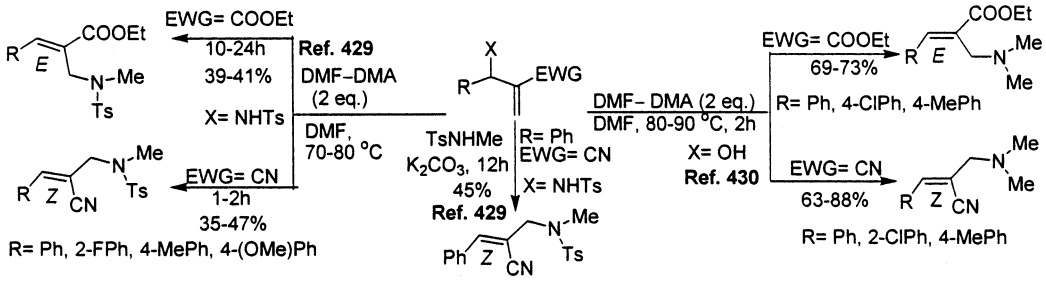
Scheme 164



Scheme 165



Scheme 166



The (*Z*,*Z*)- and (*E*,*E*)-1,4-diallylpiperazines **243** and **244** have been conveniently synthesized by our research group[434] via the treatment of piperazine with acetates of Baylis−Hillman adducts (3-acetoxy-2-methylenealkanenitriles and methyl 3-acetoxy-3-aryl-2-methylenepropanoates) (eqs 83 and 84). In the case of esters, we also obtained (*E*, *Z*)-isomers as minor products (eq 84).

Kim and co-workers[435] elucidated an interesting reaction of DBN or DBU with the Baylis−Hillman acetates, which resulted in the formation of the lactam derivatives **245** (Scheme 170).

Ciclosi et al.[436] reported that the treatment of *N*-*p*-toluenesulfonyl carbamates or *N*-acyl carbamates of the Baylis−Hillman adducts with DABCO in CH_2Cl_2 provided the corresponding 2-methylene-3-(*p*-toluenesulfonyl)amino esters or 2-methylene-3-acylamino esters, respectively, in good yields. However, treatment of *N*-*p*-toluenesulfonyl carbamates of the Baylis−Hillman adduct with DBU gave allylamine derivatives, that is, ethyl (2*E*)-3-aryl-2-(*p*-toluenesulfonylaminomethyl)propenoates exclusively. Acetates of the Baylis−Hillman adducts were transformed into the corresponding secondary allylamines via treatment with tosylamine in the presence of DABCO (Scheme 171).[436]

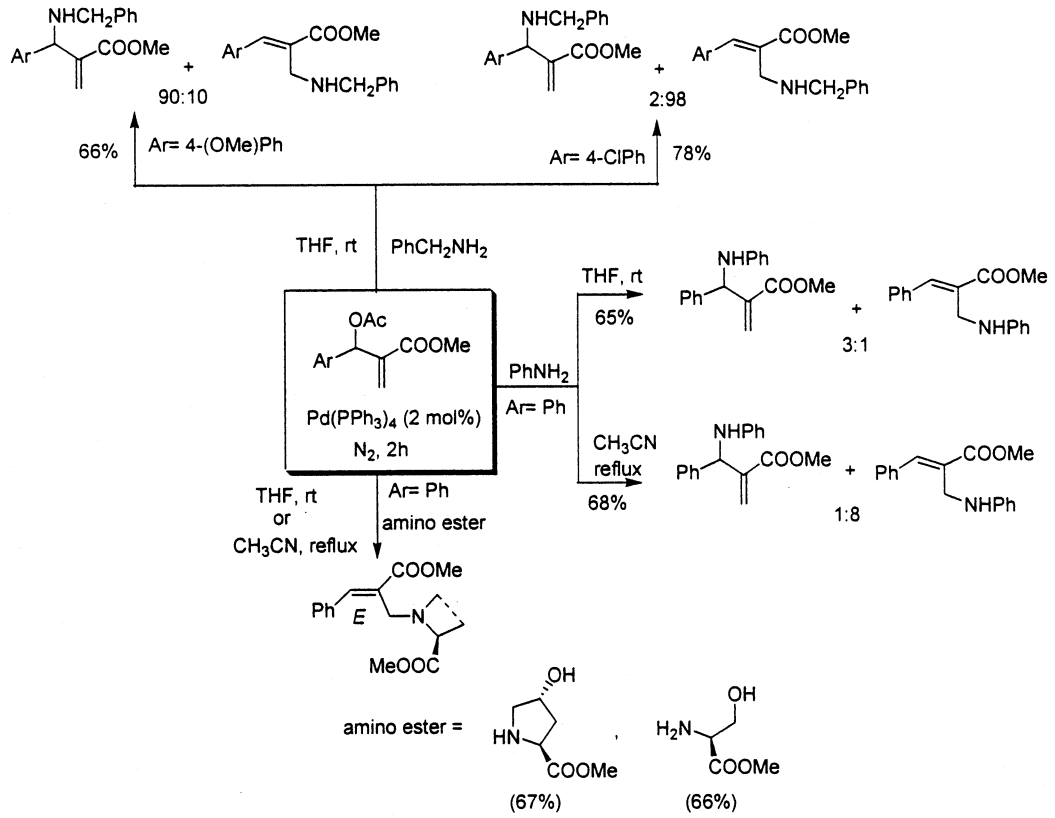
Kim et al.[437,438] used Baylis−Hillman acetate−DABCO salts **207** for the preparation of a Baylis−Hillman adduct of *N*-tosylimine via treatment with tosylamine in aqueous THF. They also used a variety of nucleophiles for an addition (S_N2') reaction with Baylis−Hillman acetate−DABCO salt **207** (in situ generated) to obtain various interesting molecules (Scheme 172).

Batra and co-workers[439] subsequently used these DABCO salts **207** for preparation of allyl azides and allylamine as shown in Scheme 173. They translated this methodology into the solid phase using polymer-bound acrylate.

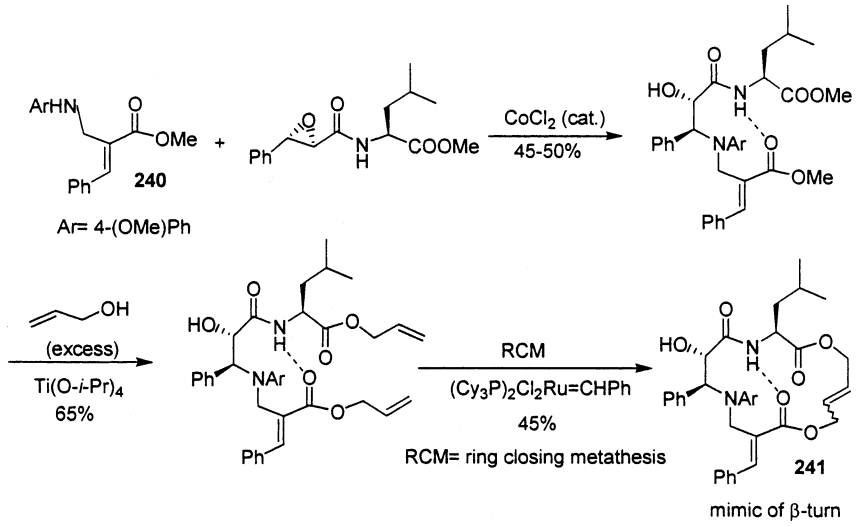
6.2.12. Allyl Halides, Ethers, Nitrates, and Phosphonates

Transformation of the Baylis−Hillman adducts into allyl halides with stereoselectivity have been well-studied in the literature.[35,305,307] Recently, Chavan et al.[440] reported a stereoselective synthesis of

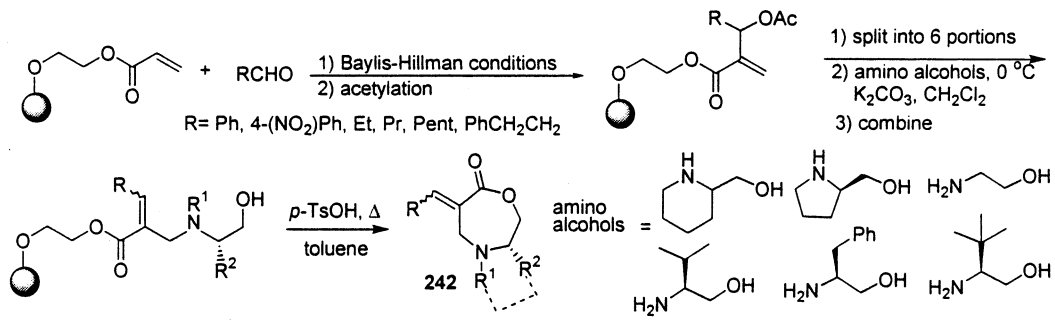
Scheme 167



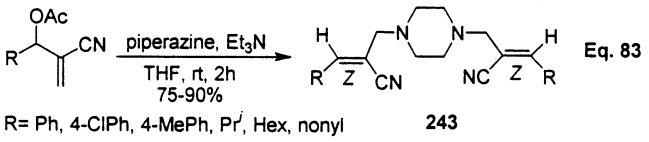
Scheme 168

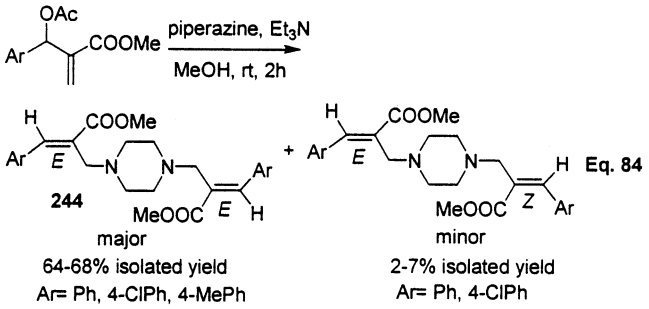


Scheme 169



(2Z)-2-(chloromethyl)-3-arylprop-2-enoates via reaction of the Baylis−Hillman adducts with Et_3N/MsCl (Scheme 174). In this reaction they did not obtain mesylate derivatives.





Our research group[441−443] transformed the Baylis−Hillman adducts obtained from aldehydes and MVK to the (*Z*)-allyl chlorides, (*E*)-allyl ethers and (*E*)-allyl nitrates (Scheme 175).

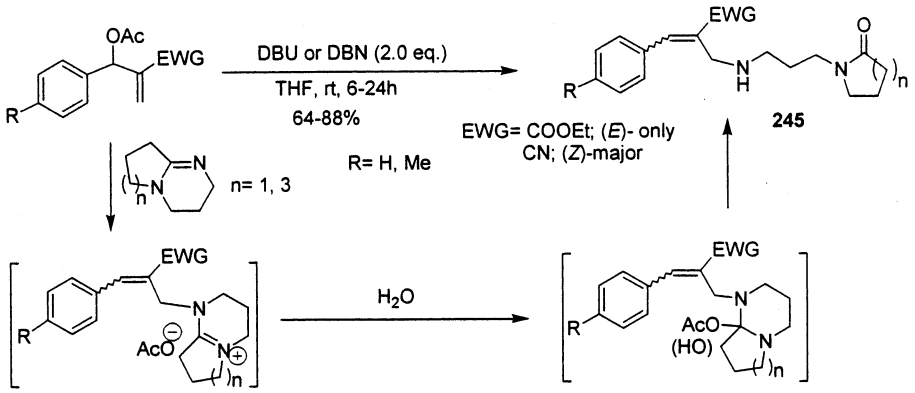
Baylis−Hillman adducts were efficiently oxidized to the corresponding α-methylene-β-keto esters **246** with Dess−Martin periodinane by Lawrence et al.[444] However, their attempts to oxidize the Baylis−Hillman adducts using DMSO/oxalyl chloride (Swern oxidation) did not provide the expected ketones; instead, allyl chlorides were formed (Schemes 176 and 177).[444]

Yadav et al.[445] reported a stereoselective synthesis of (*E*)- and (*Z*)-allyl iodides and bromides via treatment of Baylis−Hillman alcohols with montmorillonite clay supported NaI and NaBr, respectively. They compared the rates and yields by carrying this reaction under conventional heating and under microwave irradiations (Scheme 178).

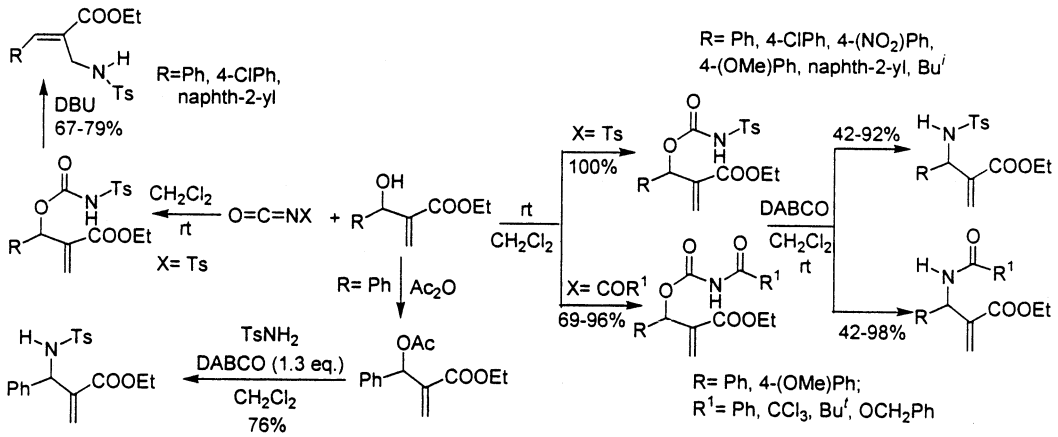
The Baylis−Hillman alcohols and their acetates have been stereoselectively transformed into (*E*)- and (*Z*)-allyl phosphonates.[306,348] These phosphonates were further transformed into dienes.[446] Very recently, Swamy and co-workers[447,448] transformed the Baylis−Hillman adduct obtained from ferrocenecarboxaldehyde and acrylonitrile (Scheme 179)[447] and the Baylis−Hillman adducts obtained from aromatic aldehydes and acrylonitrile (Scheme 180)[448] into the corresponding allyl phosphonates using cyclic chlorophosphite [(−OCH_2−CMe_2−CH_2O−)PCl]. The allyl phosphonates thus obtained were further converted to substituted butadiene derivatives **247** and **248** (Schemes 179 and 180).[447,448]

In continuation of their earlier studies[449,450] on Mitsunobu reaction using Baylis−Hillman adducts, Charette recently reported a highly regioselective S_N2' (γ-attack) Mitsunobu reaction of Baylis−Hillman adducts with triphenylphosphine linked to non-cross-linked polystyrene **249** to provide trisubstituted alkenes almost quantitatively (Scheme 181).[451]

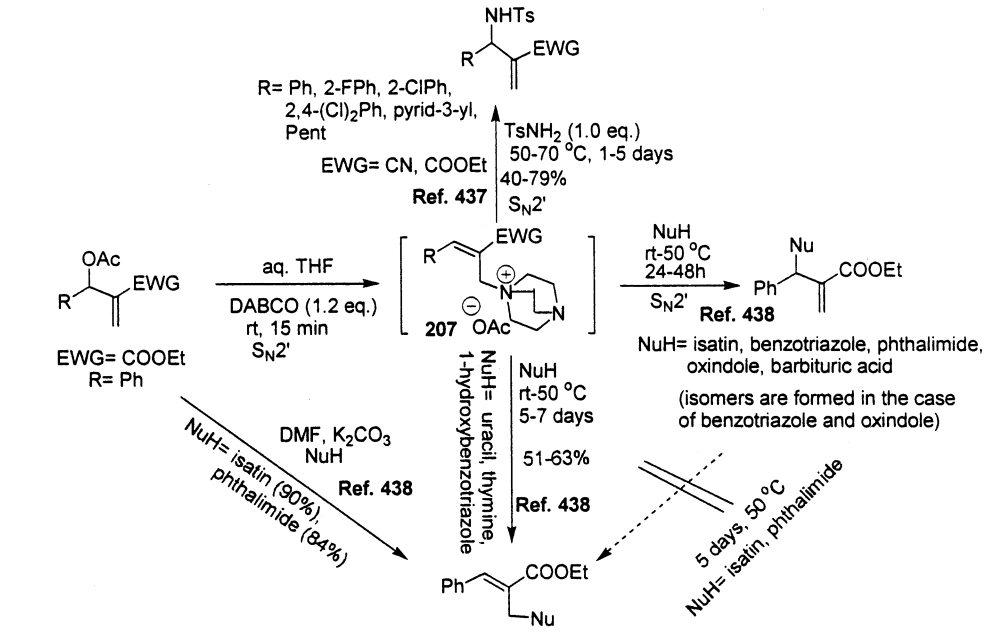
Scheme 170



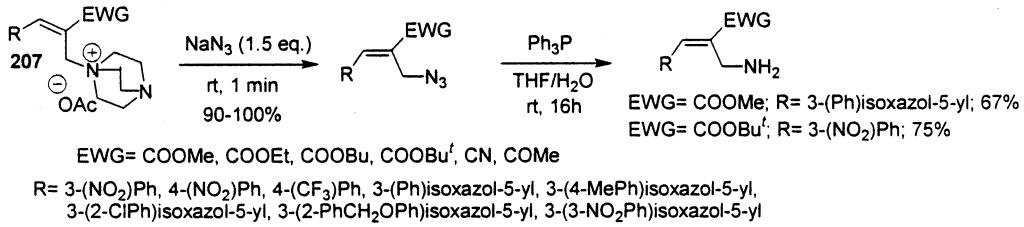
Scheme 171



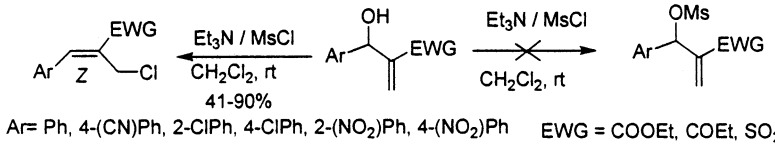
Scheme 172



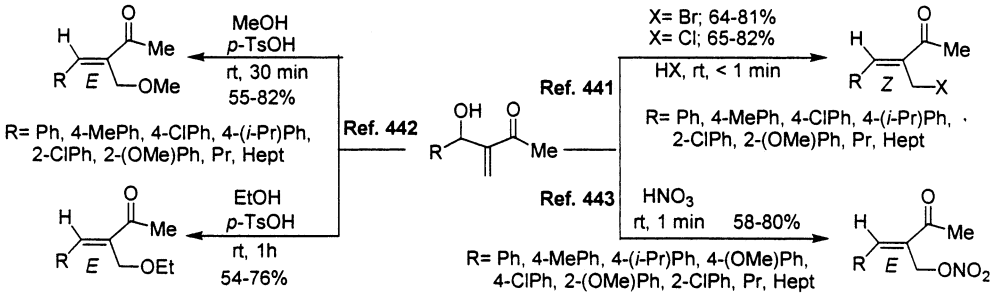
Scheme 173



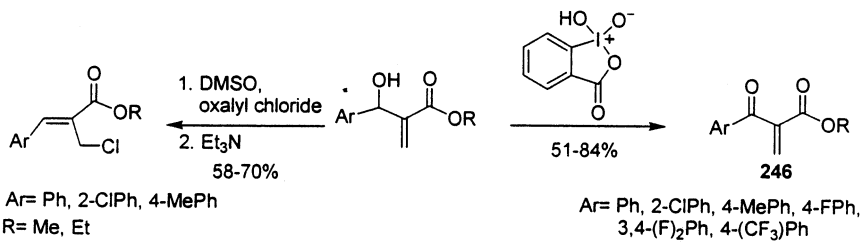
Scheme 174



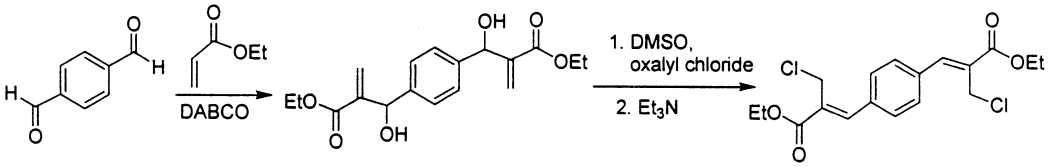
Scheme 175



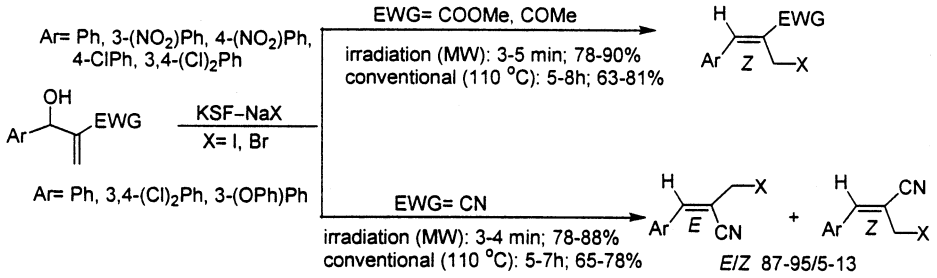
Scheme 176



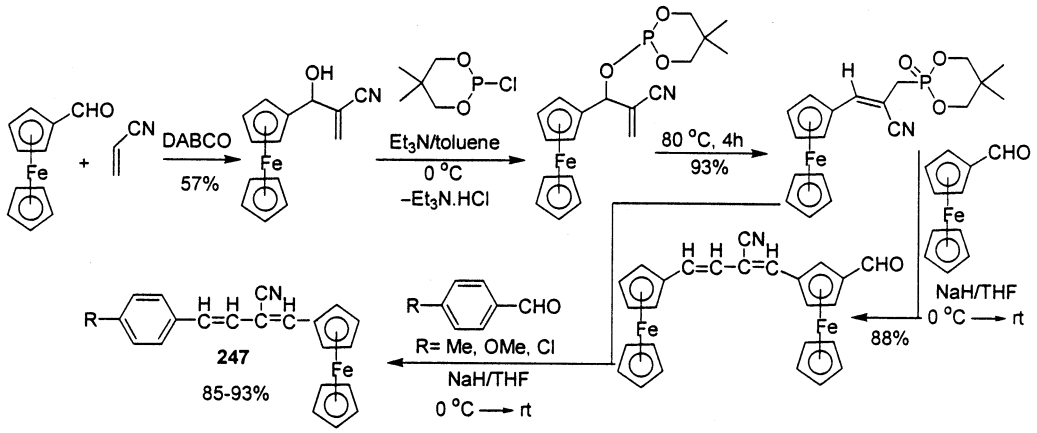
Scheme 177



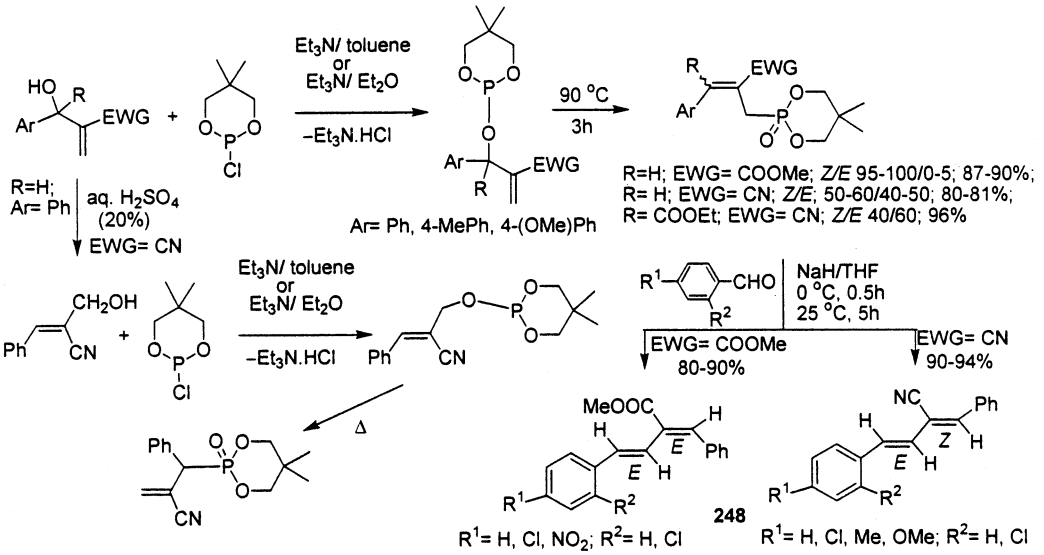
Scheme 178



Scheme 179



Scheme 180

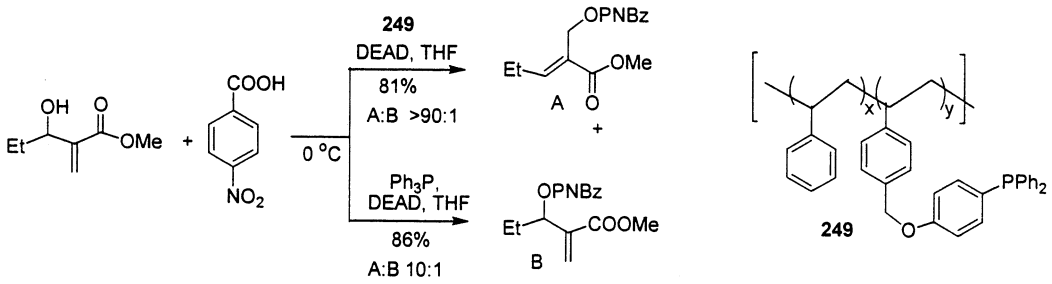


6.3. Miscellaneous Applications of the Baylis–Hillman Alcohols

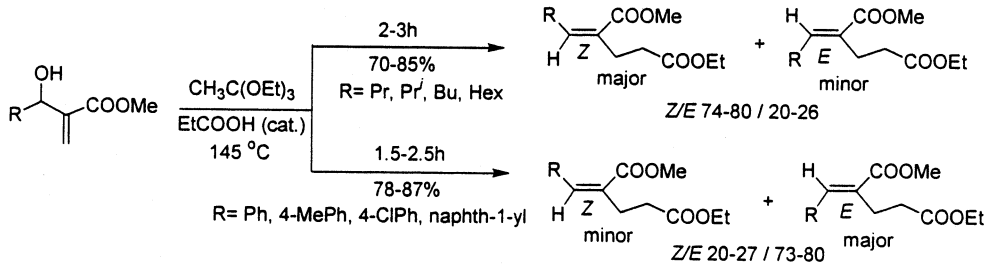
6.3.1. Claisen Rearrangement

Our research group[452] observed an unprecedented stereochemical reversal from alkyl to aryl substituents in the Johnson–Claisen rearrangement of methyl 3-hydroxy-2-methylenealkanoates with triethyl orthoacetate as described in Scheme 182. Thus, we demonstrated the application of Baylis–Hillman adducts as excellent probes for examining the competitive strain of 1,2 and 1,3 interactions in the

Scheme 181



Scheme 182



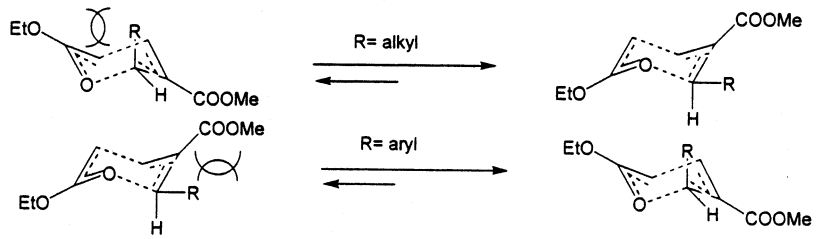
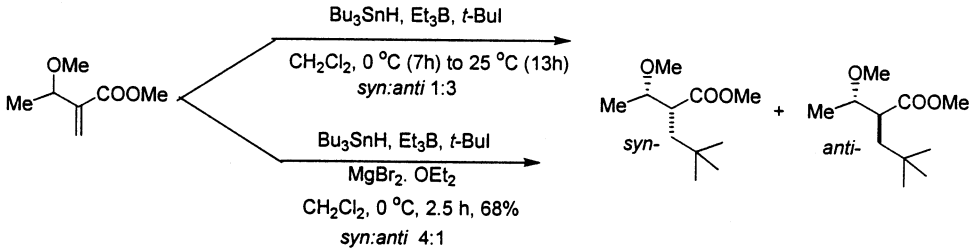


Figure 17.

Scheme 183



course of Johnson−Claisen rearrangement using triethyl orthoacetate (Figure 17).[452]

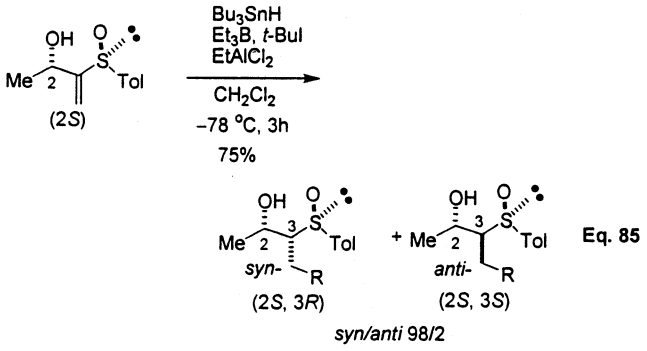
6.3.2. Radical Reactions

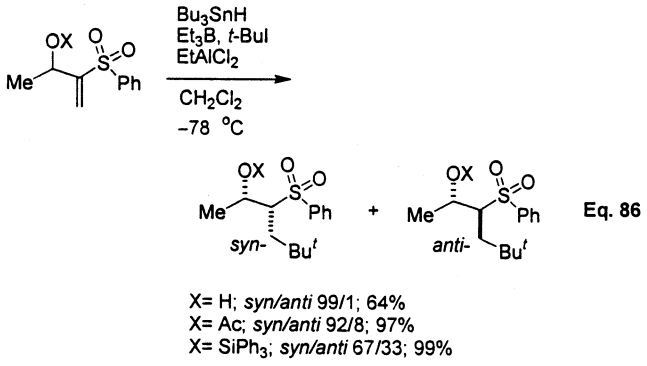
The free radical reactions of the Baylis−Hillman adducts have been well-studied by Giese and co-workers[321,322,453] and Kundig et al.[454] During their studies on Lewis acid controlled radical chemistry (chelation control), Guindon and Rancourt[455] observed that the free radical reactions of methyl ethers of Baylis−Hillman alcohols provided the corresponding products in high *syn*-diastereoselectivities in the presence of Lewis acid ($MgBr_2 \cdot OEt_2$), whereas a similar reaction provided *anti*-products predominately in the absence of Lewis acid. One representative example is presented in Scheme 183.

Toru and co-workers[456,457] elegantly demonstrated the role of intramolecular hydrogen bonding for diastereoselectivity as well as reactivity toward radical addition onto the Baylis−Hillman adducts. Thus, the reaction of (2*S*,S_S)-α-(1-hydroxyethyl)vinyl sulfoxide with alkyl radical and Bu_3SnH gave the addition−hydrogenation product with high diastereoselectivities. However, no product was observed in the case of (2*R*,*Ss*) isomer and *O*-protected (2*S*,*Ss*) isomers.[456] Subsequently, they also used α-(1-hydroxyethyl)vinyl sulfone[457] for free radical reactions, which provides a syn adduct predominately, thus describing the stereoselectivity and also reactivity via intramolecular hydrogen bonding between the hydroxy group and stereogenic sulfonyl oxygen (eqs 85 and 86).

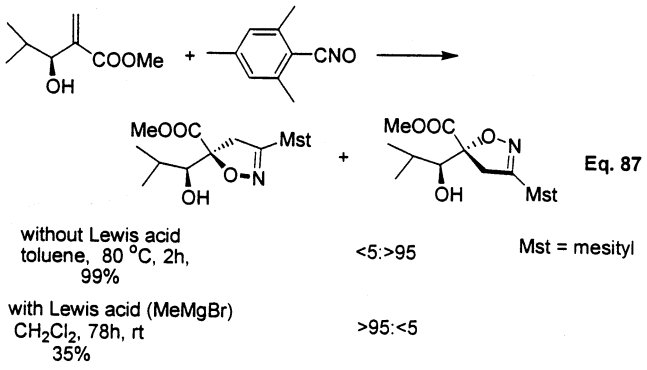
6.3.3. Cycloaddition Reaction

1,3-Dipolar cycloaddition reactions of Baylis−Hillman adducts with nitrile oxides have been well-investigated.[331] Recently, Fisera and co-workers[458,459] reported the 1,3-dipolar cycloaddition reactions of mesitonitrile oxide with the Baylis−Hillman adducts, which proceeded with high diastereoselectivities.





Addition of Grignard reagent reverses the diastereoselectivity of the cycloaddition. The reaction rate is strongly accelerated under microwave irradiation with a small effect on diastereoselectivities. One representative example is shown in eq 87.

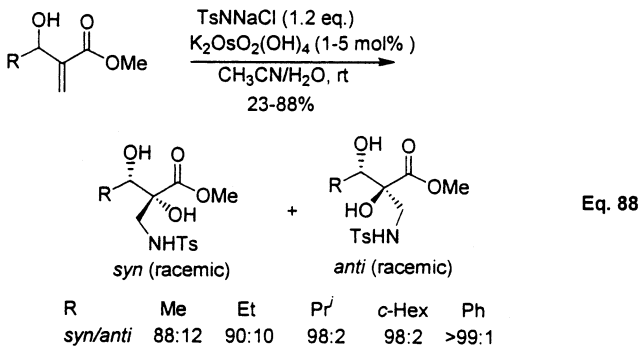


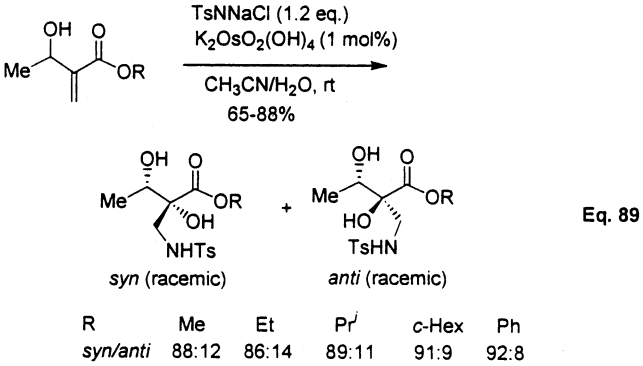
6.3.4. Aminohydroxylation

Marko and co-workers described a highly *syn*-diastereoselective vicinal dihydroxylation of Baylis–Hillman adducts, obtained from alkyl vinyl ketones, with OsO_4 (cat.) in the presence of NMO.[335] Recently, Pringle and Sharpless[460] reported a facile osmium-catalyzed aminohydroxylation of Baylis–Hillman adducts (derived from acrylate) and also of their acetate derivatives. The diastereoselectivity for this reaction is influenced by the aldehyde-derived substituent, whereas the acrylate-derived substituent has a minimum effect (eqs 88 and 89).

6.3.5. Vinyl Epoxide

Ramachandran and Krzeminski[461] have successfully synthesized functionalized vinyl epoxides in high yields via vinyl alumination of α-bromoaldehydes/ketones followed by cyclization with K_2CO_3 or KF under nonaqueous conditions (Scheme 184).





6.3.6. Liquid Crystals

In continuation of their earlier work on liquid-crystalline polymers,[389] Lacey and co-workers[462,463] studied the hydrodynamic and electro-optical (Kerr effect) properties of two side-chain liquid-crystalline polymers **250** and **251**, which are prepared by using Baylis–Hillman methodology. They also related the difference in the mesogenic side-chain mobility of the polymers to the dipole–dipole interactions of the polar groups along the polymer backbone (Scheme 185).

6.3.7. Combinatorial Chemistry

Jung and co-workers[464] demonstrated the use of polymer-supported Baylis–Hillman adduct **252** as a template for the synthesis of multiple core structure libraries (Scheme 186).

6.3.8. Diene (Hetero Diels–Alder Reaction)

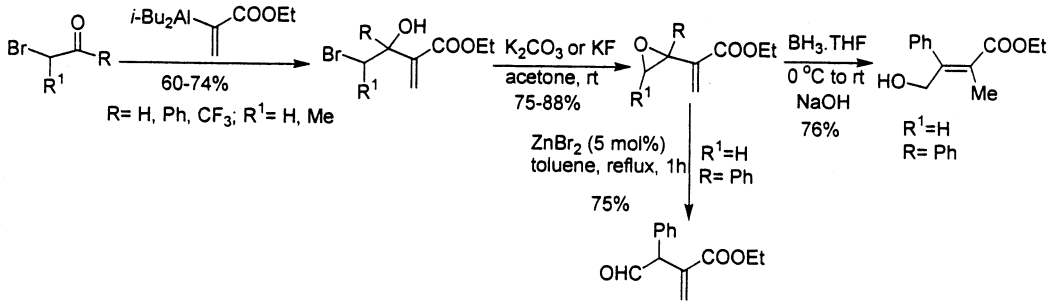
During their work on π-facial selectivities Yadav et al. studied the Diels–Alder cycloaddition reactions of various dienophiles with diene (**253**) [obtained from the Baylis–Hillman adduct, that is, 2-(hydroxymethyl)cyclohex-2-enone]. One representative example is shown in Scheme 187.[465]

6.4. Nucleophilic Additions to the Baylis–Hillman Acetates

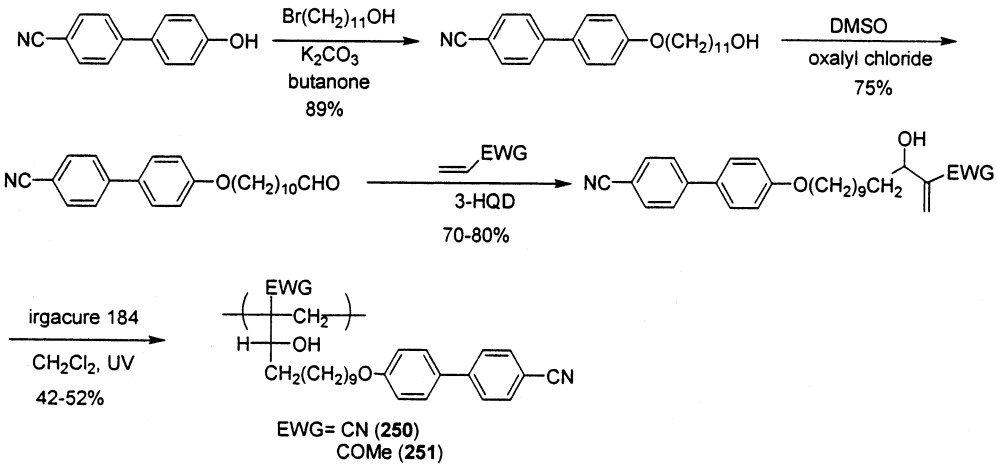
Rezgui and El Gaied[466,467] have reported an interesting synthesis of bicyclic dienones in sequential and also in a one-pot process via the reaction of 2-(acetoxymethyl)cyclohex-2-enone with 1,3-dicarbonyl compounds in the presence of K_2CO_3 following the reaction sequence as described in Scheme 188.

Chamakh and Amri[468] described a one pot synthesis of (*E*)-4-alkylidene-2-cyclohexen-1-ones **254** via a

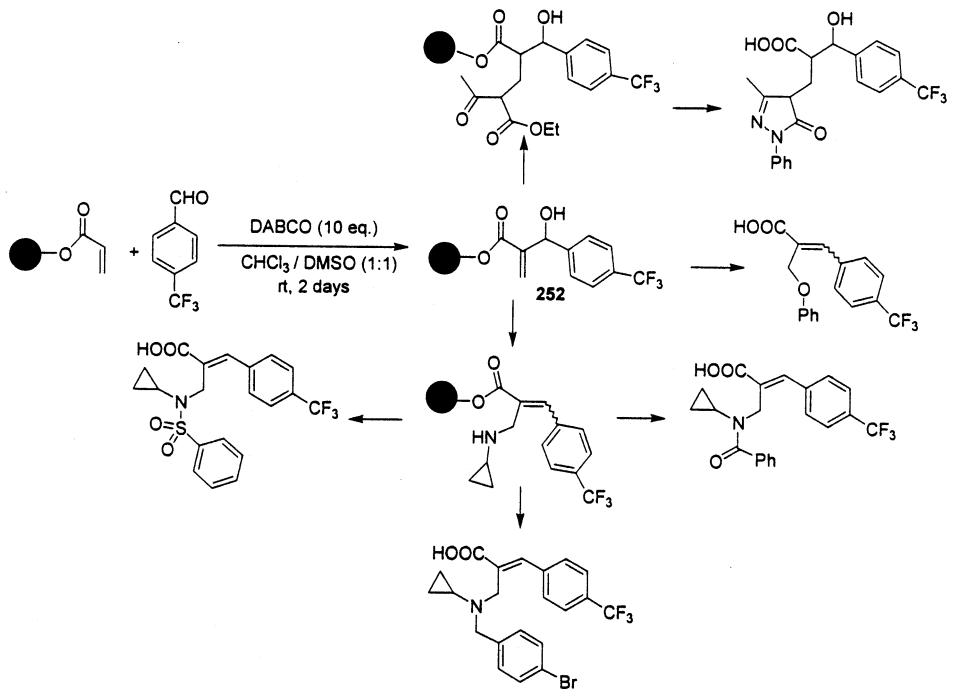
Scheme 184



Scheme 185



Scheme 186

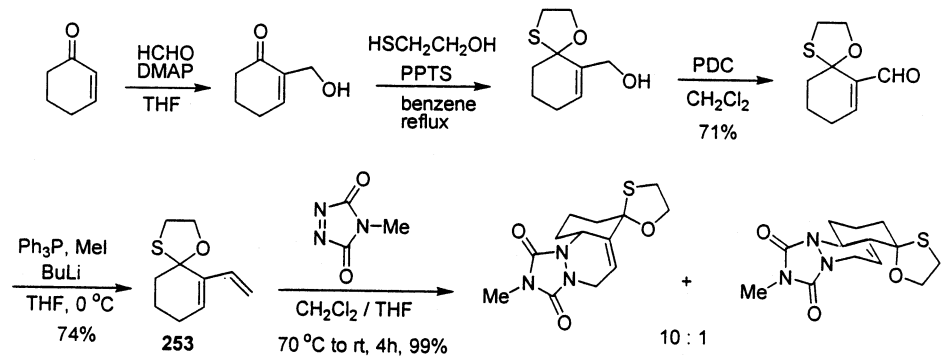


cross coupling of acetates of the Baylis−Hillman adducts with aliphatic 1,3-diketones in the presence of K_2CO_3 in absolute ethanol at reflux temperature (Scheme 189).

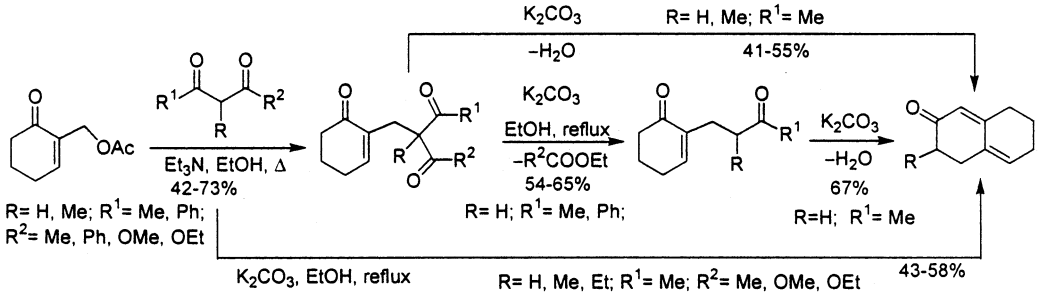
Amri and co-workers[469,470] also successfully transformed the acetates of the Baylis−Hillman adducts obtained from various activated alkenes into β-nitro alkene derivatives via treatment with nitroalkanes. The resulting nitroalkane derivatives were further transformed into the corresponding 1,4-diketones **255** and keto alkene derivatives **256** via the Nef reaction (Schemes 190 and 191).

Subsequently, Kim and co-workers[471] also followed a similar strategy using different conditions to obtain 2-arylidene-4-nitroalkanoates (Path V, Scheme 192). They also transformed the acetates of the Baylis−

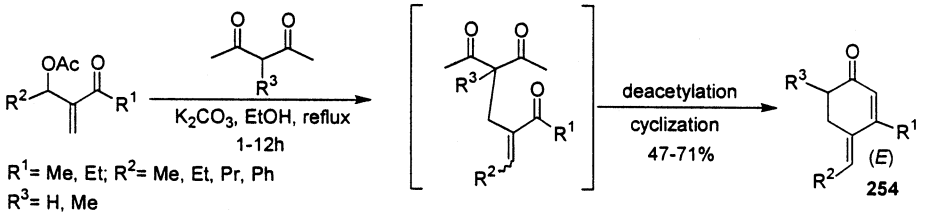
Scheme 187



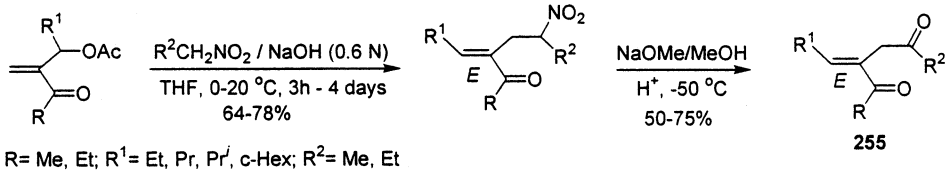
Scheme 188



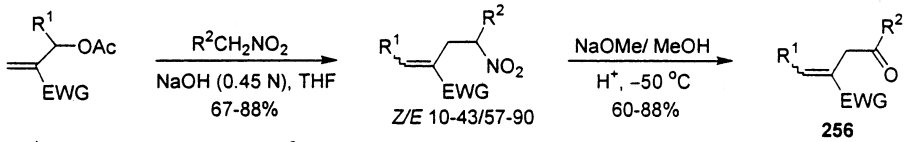
Scheme 189



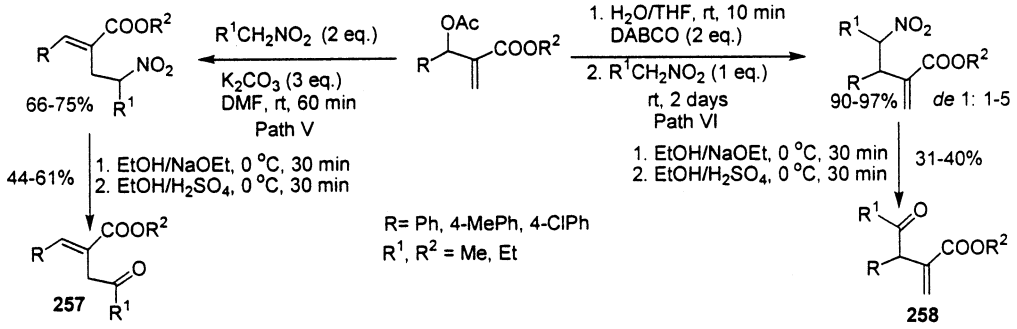
Scheme 190



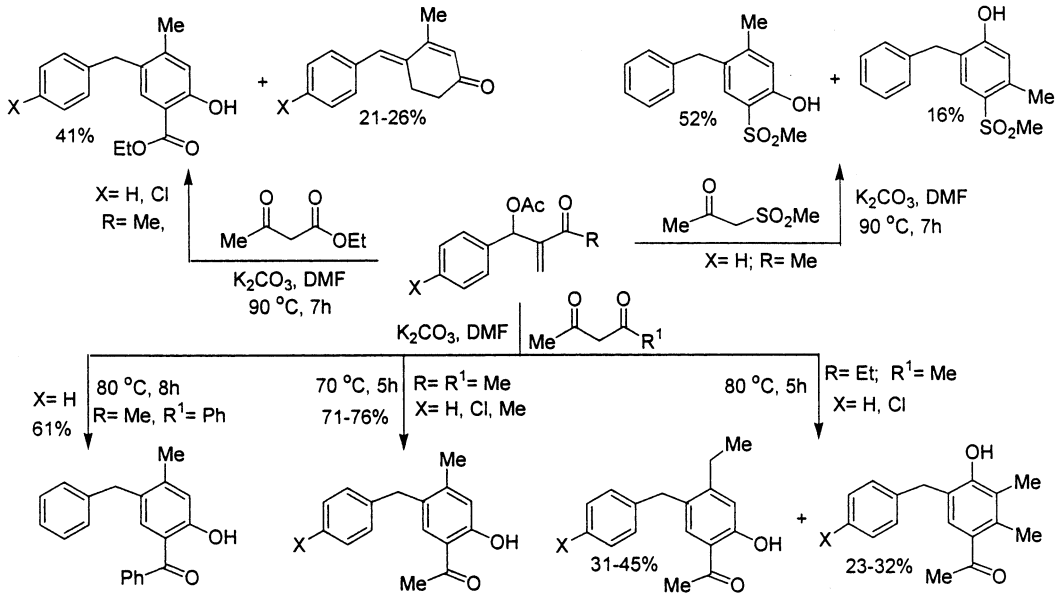
Scheme 191



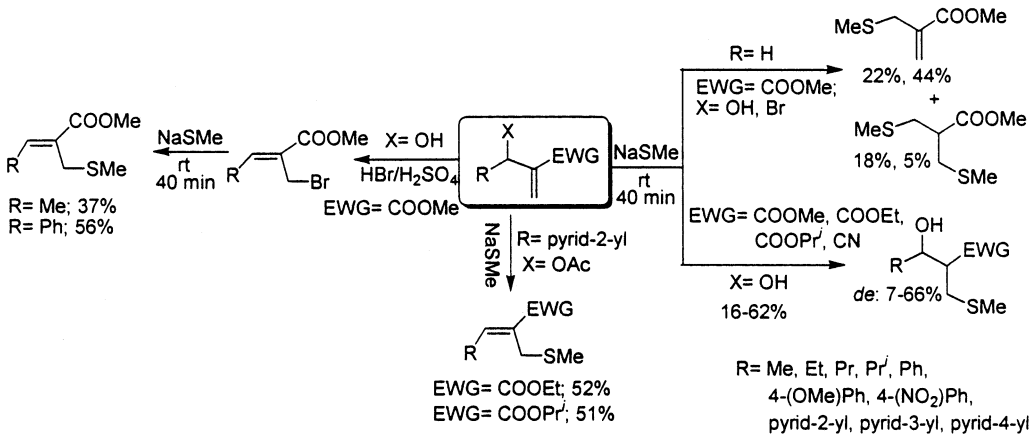
Scheme 192



Scheme 193



Scheme 194



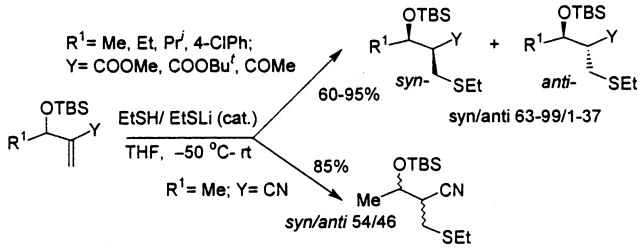
Hillman adducts into the corresponding 2-methylene-4-nitroalkanoates via treatment of in situ generated DABCO salt with nitroalkanes (Path VI, Scheme 192). Finally, they transformed these adducts into the corresponding keto esters **257** and **258** via Nef reaction (Scheme 192).

Kim et al.[472] successfully transformed the Baylis–Hillman acetates to *o*-hydroxyacetophenone derivatives via treatment with 1,3-dicarbonyl compounds in the presence of K_2CO_3 (Scheme 193).

Kaye and co-workers[473] investigated the regio- and diastereoselectivity in the reaction of α-(1-hydroxyalkyl)acrylate derivatives with sodium methanethiolate. The hydroxy derivatives underwent conjugate addition with up to 66% *de*, whereas the acetoxy and bromo analogues underwent S_N2' and S_N2 reactions, respectively (Scheme 194).

Very recently, Kamimura and co-workers[474] developed a diastereoselective methodology (up to 99%) for the synthesis of *syn*-*β*-hydroxy-α-thiomethyl carbonyl compounds via nucleophilic addition of ethanethiol (EtSH) to the TBS ether of Baylis–Hillman adducts in the presence of catalytic amounts of lithium thiolate (EtSLi). These adducts were further successfully transformed into *β*-lactams **259**. However, when

Scheme 195

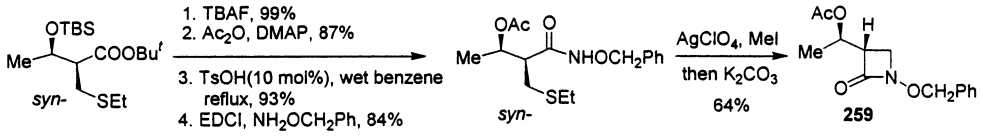


a similar reaction was extended to TBS ether of a Baylis–Hillman adduct obtained from acrylonitrile and acetaldehyde, the stereoselectivity was lost (Schemes 195 and 196).

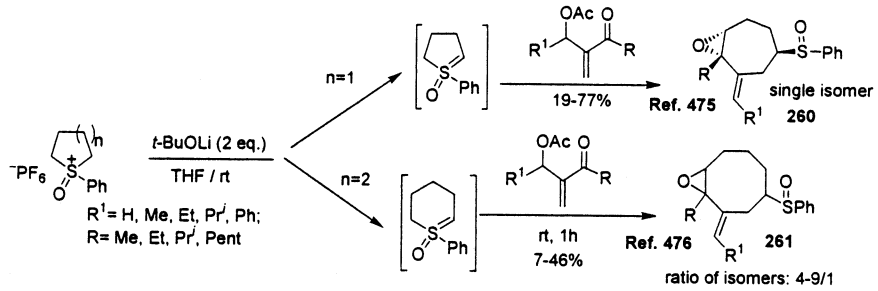
Fujimoto and co-workers[475,476] reported a tandem Michael-intramolecular Corey–Chaykovsky reaction of the five-membered cyclic oxosulfonium ylide with acetates of the Baylis–Hillman adducts in the presence of base-producing cycloheptene oxide derivatives **260** as a single stereoisomer. However, in the case of six-membered oxosulfonium ylide, the cyclooctane oxide derivatives **261** were obtained as a mixture of stereoisomers in moderate yields (Scheme 197).

Kim and co-workers[477] reported an interesting synthesis of tetrasubstituted alkene, that is, ethyl

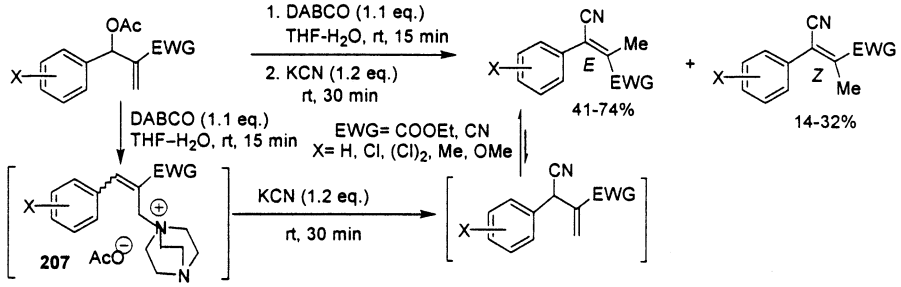
Scheme 196



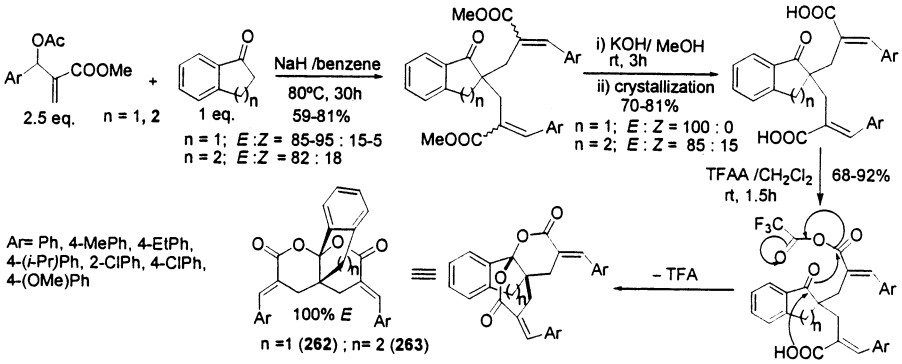
Scheme 197



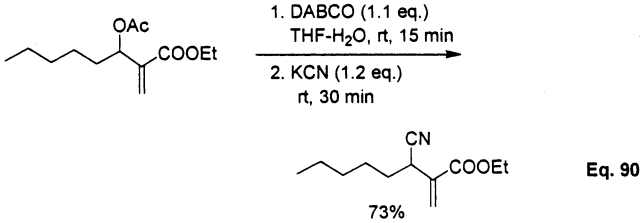
Scheme 198



Scheme 199



β-cyano-α-methylcinnamates and β-cyano-α-methylcinnamonitriles with (*E*)-selectivities via a successive $S_N2'-S_N2'$-isomerization strategy as described in Scheme 198. However, they could obtain only ethyl 3-cyano-2-methyleneoctanoate in the case of a Baylis–Hillman adduct obtained from hexanal and ethyl acrylate (Scheme 198 and eq 90).



Eq. 90

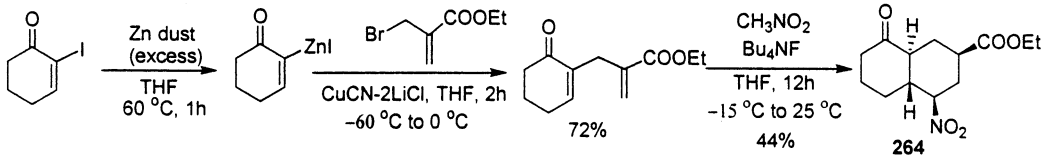
Recently, our research group[478] developed a simple and convenient three-step synthesis of 2,10-dioxa-[4.4.3]propellane-3,9-diones **262** and 2,10-dioxa[4.4.4]-propellane-3,9-diones **263** using the acetates of Baylis–Hillman adducts following the reaction sequence as described in Scheme 199.

6.5. Other Applications of the Baylis–Hillman Bromides

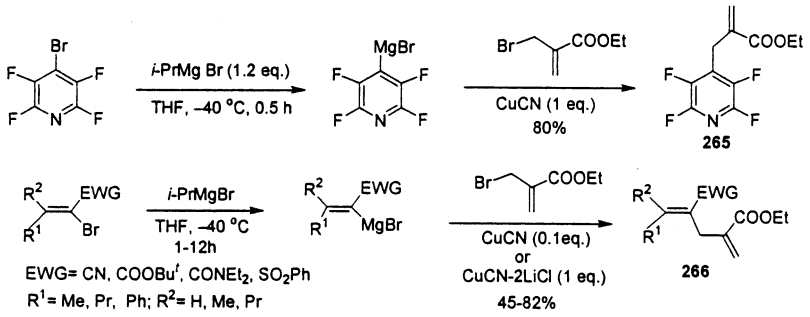
Prasad and Knochel[479] used ethyl 2-(bromomethyl)-prop-2-enoate in the synthesis of polyfunctionalized decalin **264** via the reaction with 2-zincated cyclohexenone (obtained by the reaction of 2-iodocyclohexenone with zinc dust in THF) in the presence of Cu(I) catalyst according to Scheme 200.

Knochel and co-workers[480,481] also utilized ethyl 2-(bromomethyl)prop-2-enoate in the preparation of allyl-substituted heteroaromatic compounds **265** and functionalized dienes **266** (Scheme 201). This meth-

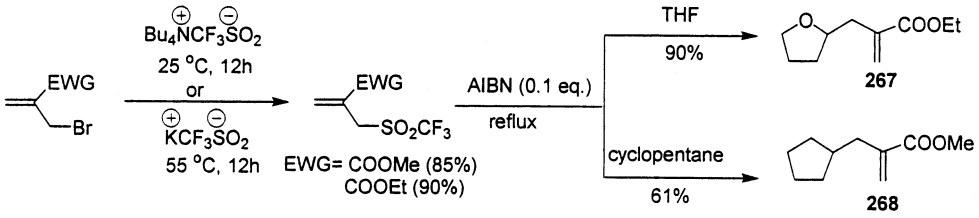
Scheme 200



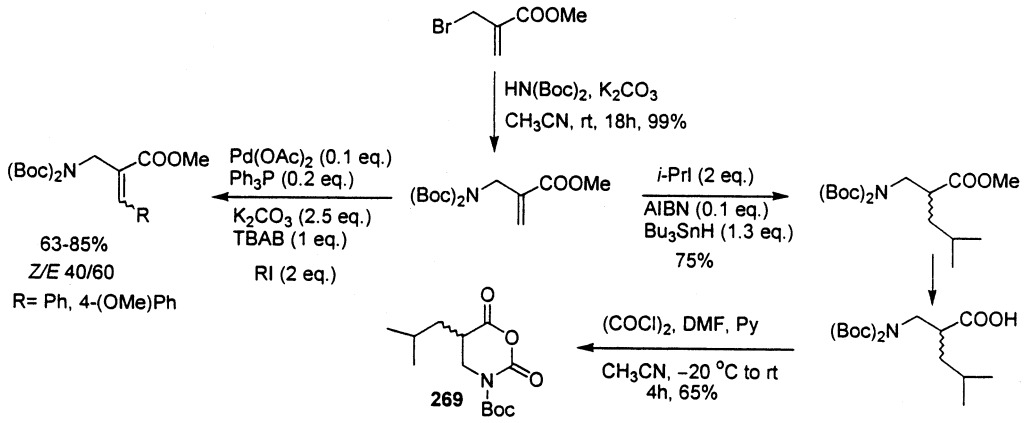
Scheme 201



Scheme 202



Scheme 203



odology involves a halide−magnesium exchange with *i*-PrMgBr in THF.

Fuchs and co-workers[482] elegantly used allyl triflone obtained from methyl(ethyl) 2-(bromomethyl)-prop-2-enoate successfully for allylation of the C−H bond, thus providing a simple synthesis of α-substitued activated alkenes. Two representative examples **267** and **268** are shown in Scheme 202.

Receveur and co-workers[483] described an efficient synthesis of urethane *N*-carboxyanhydrides (*β*-UNCAs) **269** from methyl 2-(bromomethyl)prop-2-enoate according to Scheme 203. The key intermediate, allylamine, in this reaction is further transformed into *β*-substituted allylamines via the Heck reaction (Scheme 203).

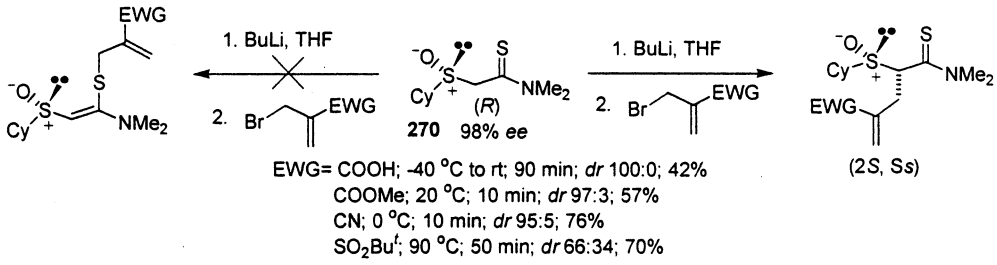
Highly stereoselective C-allylation of lithium enolate of enantiopure cyclohexylsulfinyl thioacetamide **270** is described by Nowaczyk et al.[484] via reaction with Baylis−Hillman allyl bromides containing various electron-withdrawing groups (Scheme 204).

Blechert and co-workers[485] described an efficient synthetic approach toward substituted oligomeric macrolactones by treatment of 2-(bromomethyl)alk-2-enoic acids with DBU. Tri- and tetrolides **271** and **272** were obtained selectively in acceptable yields in a consecutive sequence (Scheme 205). Similar reaction of 2-(bromomethyl)acrylic acid with DBU provided lactone **273** (Scheme 205).

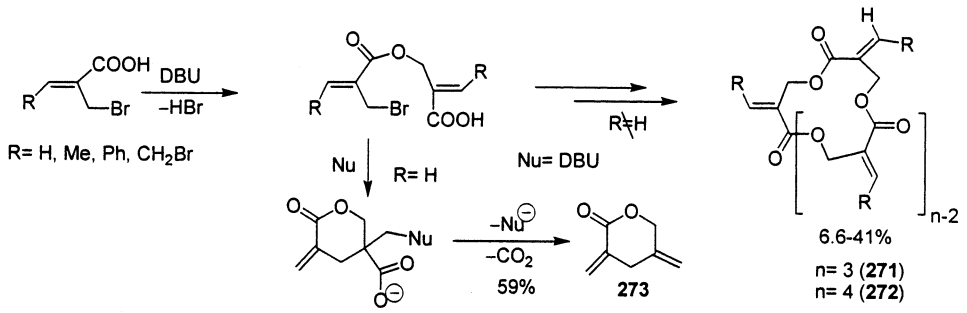
Amri and co-workers[486] developed a simple, efficient, and stereoselective synthesis of alkylidene-*γ*-lactams **274** from the Baylis−Hillman-type bromides following the reaction sequence as described in Scheme 206.

Borhan et al.[487] reported a convenient stereoselective synthesis of 1,4-bis-^{13}C-labeled isomeric compound (*E*,*E*)-2-ethoxycarbonyl-1,4-diphenylbutadiene

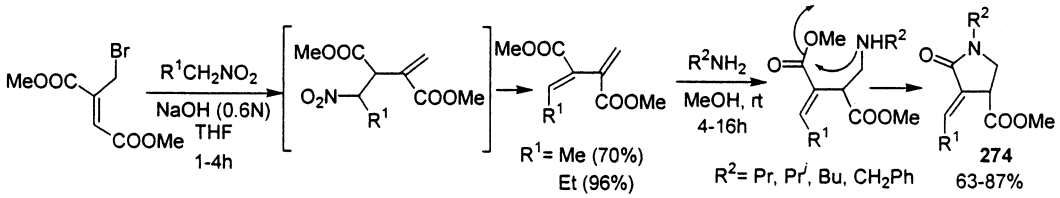
Scheme 204



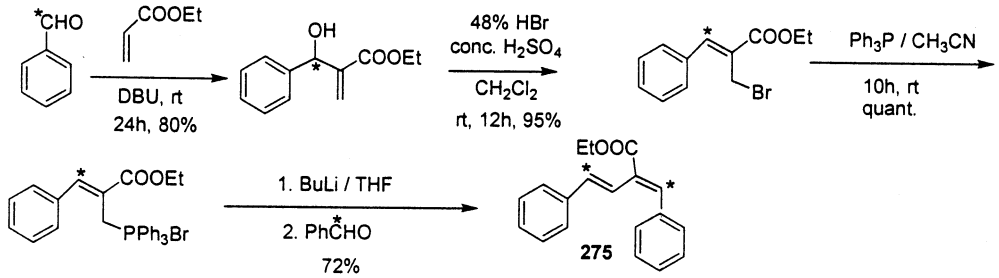
Scheme 205



Scheme 206



Scheme 207



275 via the Baylis−Hillman protocol starting from benzaldehyde (^{13}C-labeled carbonyl carbon) according to Scheme 207.

Woodward et al.[488] reported copper-catalyzed asymmetric chemo- and regiospecific S_N2' addition of organozinc reagents to (*Z*)-allyl chlorides, derived from the Baylis−Hillman adducts, in the presence of chiral ligand **276** to provide the corresponding products **277** up to 64% *ee* (Scheme 208).

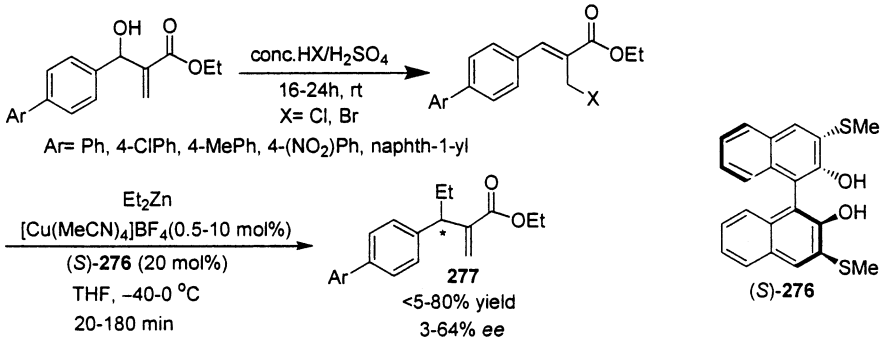
Our research group[489] described the nucleophilic additions of phenols and propargyl alcohols to the Baylis−Hillman bromides in the presence of Et_3N to provide the corresponding methyl 3-aryl-2-methylene-3-phenoxypropanoates and methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)propanoates, respectively. We also carried out the reaction of propargylic alcohols with Baylis−Hillman bromides in the presence of quinidine [in situ generated quinidine−allyl bromide salt **278**] to provide the resulting product (−)-methyl 3-aryl-2-methylene-3-(prop-2-yn-1-yloxy)-propanoates (propargyl ether of Baylis−Hillman adducts) **279** in 25−40% enantiomeric purities following the chiral-leaving group strategy as shown in Scheme 209.

6.6. Biological Activity

Bhat and co-workers[490] investigated the antimalarial activity of 3-hydroxy-3-aryl(heteroaryl)-2-methylenepropanenitriles (Baylis−Hillman adducts derived from acrylonitrile and aryl or heteroaryl aldehydes) and found that adducts **280**−**282** (Figure 18) were shown to have antimalarial activity against *P. falciparum* in vitro.

2-(Hydroxymethyl)cyclohex-2-enone (the Baylis−Hillman adduct obtained from cyclohex-2-enone and formaldehyde) has been used in the preparation of 2-crotonyloxymethyl-2-cyclohexenone (COMC) (**283**) (biologically active molecule) by Creighton and coworkers.[491] They hypothesized that **283** is an enzyme-

Scheme 208



Scheme 209

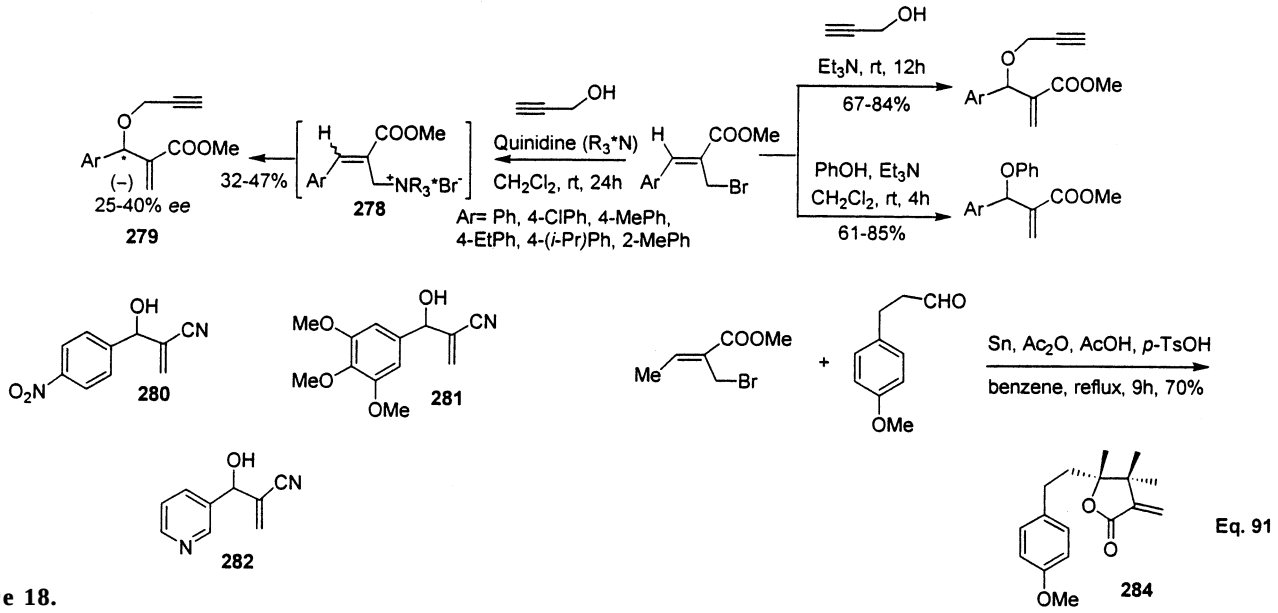


Figure 18.

activated prodrug in which the crotonate ester serves as a leaving group, in a process triggered by glutathionyl transferase (Scheme 210).[491]

Bermojo et al.[492] synthesized and studied the biological activity of the compound **284** and found that it has extremely interesting properties with regard to its apoptosis-inducing ability in HL-60 cells (eq 91).

Lin et al.[493] synthesized a new class of pyrimidinyl agents, **285**−**290** (Schemes 211 and 212), using the Baylis−Hillman strategy and studied their in vitro antimalarial activities against *Plasmodium falciparum*. Out of all these molecules, the compound **290** exhibits the most antimalarial activity, which is comparable to that of chloroquine.

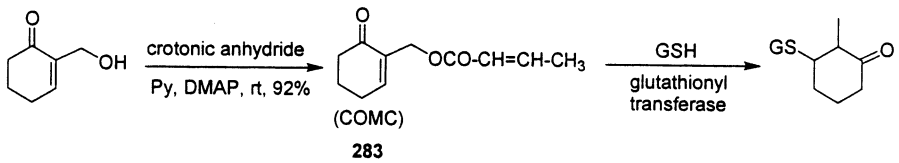
Asymmetric synthesis for pregabalin (**291**) (future drug for the treatment of neuropathic pain, epilepsy, a variety of anxiety disorders, and chronic pain conditions) has been developed at Pfizer[494] via the Baylis−Hillman methodology according to Scheme 213.

The Baylis−Hillman alcohol obtained from formaldehyde and *tert*-butyl acrylate has been elegantly used by Dunn[495,496] at Pfizer for the synthesis of sampatrilat (**292**), an important drug, following the reaction sequence as described in Scheme 214.

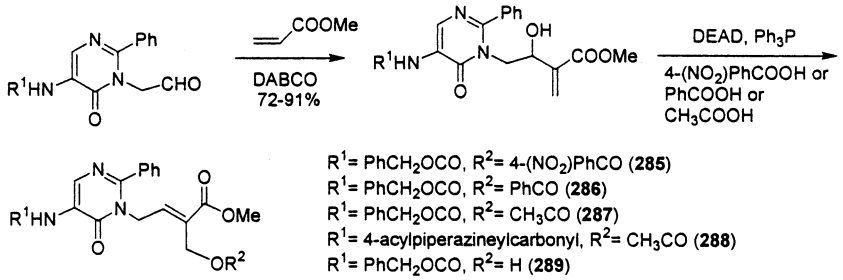
7. Conclusions

In our last review, we predicted that this reaction would witness more and more advances both in reaction development and application point of view. Our prediction has indeed come true to a large extent and this present review is a testimony. The details in this review clearly establish that the Baylis−Hillman reaction involving the coupling of activated alkenes with electrophiles has become one of the most powerful and useful carbon−carbon bond-forming

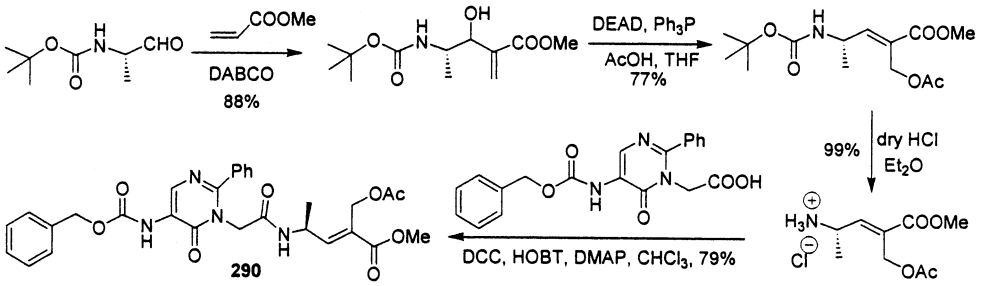
Scheme 210



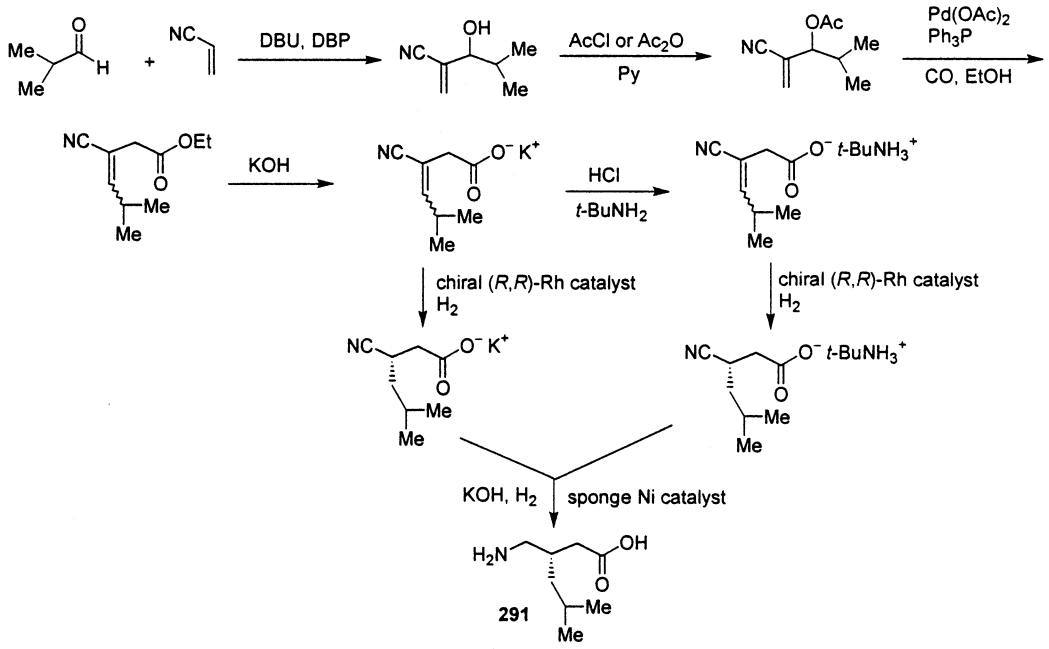
Scheme 211



Scheme 212



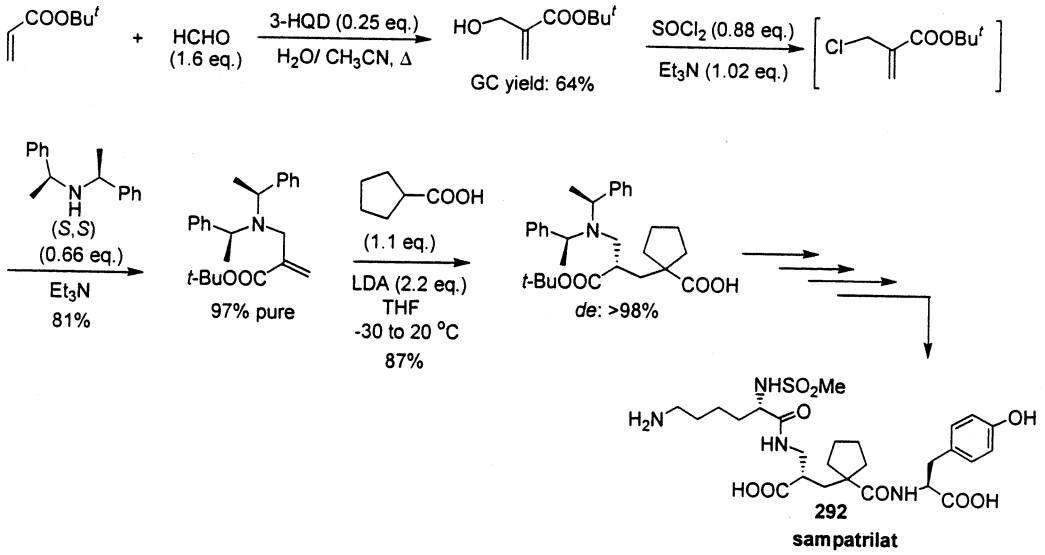
Scheme 213



reactions, providing a variety of densely functionalized molecules. In addition to tertiary amines, originally reported in the patent, various other catalysts/catalytic systems have been successfully employed for coupling of activated alkenes with electrophiles during the last several years, thus increasing and demonstrating the scope for further discovery of new catalytic sources. Also, in addition to the activated alkenes and electrophiles, which are described in the patent, several activated vinylic systems and electrophiles with different substitution profiles have been successfully utilized over the years in this fascinating C−C bond-forming reaction. However, still several other activated alkenes such as β-substituted vinylic esters, nitriles, ketones, and amides have not been comfortably accommodated in this reaction. Also, various electrophiles such as simple ketones, alkyl halides, and epoxides did not get their share in this reaction. Therefore, there are challenges in front of organic chemists to address and solve these problems for better and appropriate applications of this reaction in various aspects of organic synthesis.

Although there is considerable progress in designing and synthesizing various chiral catalysts, to date there is only one effective chiral catalyst that is applicable only to selected vinylic systems and electrophiles for performing the asymmetric Baylis−Hillman reaction with a high degree of enantioselectivities. It is, therefore, absolutely essential for the organic chemists to discover more and more efficient chiral catalysts, which would be applicable to all or at least to most of the commonly used activated alkenes and electrophiles so that these new developments in an asymmetric version will certainly make

Scheme 214



this reaction a valuable chiral source for asymmetric synthesis of various molecules of biological importance. Though there have been some interesting developments in the intramolecular version of the Baylis–Hillman reaction during the past 5 years, still this aspect remains at infancy. There is much to be done to understand and explore this approach from several directions so that an appropriate intramolecular version accommodating various substitution patterns will be developed, which would ultimately lead to the construction of cyclic molecules of different ring sizes with stereochemical and regiochemical control, and in fact, this aspect needs more attention and concentration from organic chemists.

The Baylis–Hillman adducts have already been recognized as an excellent source for various stereochemical transformation methodologies. Thus, they have been employed as valuable substrates for various reactions such as Friedel–Crafts reaction, Heck reaction, Diels–Alder reaction, radical reactions, cycloaddition reactions, hydrogenation, photochemical studies, Claisen rearrangement, dihydroxylation, epoxidations, aziridination, aminohydroxylation, and so forth, thus leading to the discovery of various new reactions, pathways, and strategies with high levels of stereochemical control. These adducts have also been used in the synthesis of various carbocycles, heterocycles, tri- and tetrasubstituted alkenes, and molecules of various substitution patterns and structural organizations. Several natural products and biologically active molecules have also been synthesized using the Baylis–Hillman methodology. This methodology has also become an innovative source for combinatorial chemistry and also for synthesis of molecules which show liquid-crystalline properties.

However, we feel that the proximity and chemeospecificity of the functional groups in the Baylis–Hillman adducts have not been fully exploited by the organic chemists and there is much more to understand and design the most appropriate strategies for proper tuning of these functional groups so that novel reaction pathways and methodologies can be discovered for further applications in organic synthesis.

We further predict that the simplicity of this reaction in the easy construction of the C–C bond under green conditions and its ability to accommodate a wide range of electrophiles, activated alkenes, and catalysts will provide the opportunities and also challenges to organic chemists to discover innovative methodologies to understand and solve problems in synthesizing drugs and other important molecules of biological importance, in the years to come.

8. Abbreviations

AIBN	azobisisobutyronitrile
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-bi-2-naphthol
bmim	1-butyl-3-methyl-1*H*-imidazolium
NBS	*N*-bromosuccinimide
mCPBA	*m*-chloroperbenzoic acid
CSA	10-camphorsulfonic acid
DABCO	1,4-diazabicyclo(2.2.2)octane
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
DEAD	diethyl azodicarboxylate
DIEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF–DMA	dimethylformamide dimethyl acetal
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
dppe	1,2-diphenylphosphinoethane
DYKAT	dynamic kinetic asymmetric transformation
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
emim	1-ethyl-3-methyl-1*H*-imidazolium
EVK	ethyl vinyl ketone
Fmoc	9-fluorenylmethoxycarbonyl
GSH	glutathione
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorus triamide
HOBT	1-hydroxybenzotriazole
$(OH)_2$·TMM	dihydroxytrimethylenemethane
3-HQD	3-hydroxyquinuclidine
KDP	ketodicyclopentadiene
LAH	lithium aluminum hydride

LDA	lithium diisopropylamide
MEMCl	(2-methoxyethoxy)methyl chloride
MS	molecular sieves
MsCl	mesyl chloride
MVK	methyl vinyl ketone
MW	microwave
NMO	*N*-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PEG	polyethyleneglycol
PLAP	pig liver acetone powder
PNBZ	*p*-nitrobenzoyl
PMP	1,2,2,6,6-pentamethylpiperidine
PPTS	pyridinium *p*-toluenesulfonate
PVK	phenyl vinyl ketone
Rham	rhamnosyl
$scCO_2$	supercritical carbon dioxide
TADDOL	*trans*-α,α′-(dimethyl-1,3-dioxolane-4,5-diyl)-bis(diphenylmethanol)
TBAB	tetrabutylammonium bromide
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDPSCl	*tert*-butyldiisopropylsilyl chloride
TBSCl	*tert*-butyldimethylsilyl chloride
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TMEDA	tetramethylethylenediamine
TMG	tetramethylguanidine
TMSI	trimethylsilyl iodide
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TsOH	*p*-toluenesulfonic acid

9. Acknowledgments

We gratefully acknowledge the many colleagues who furnished reprints/preprints and also for their valuable suggestions and helpful discussions. We would like to thank our former co-workers Drs. V. V. L. Gowriswari, T. K. Bharathi, P. Dharma Rao, P. K. S. Sarma, P. Rama Krishna, S. Bhaskar raju, S. Pandiaraju, R. Suguna Hyma, A. K. D. Bhavani, K. Muthukumaran, N. Kumaragurubaran, M. Bakthadoss, K. Padmaja, M. Krishnamacharyulu, R. Mallikarjuna Reddy, and B. Sreenivasulu whose significant contributions to the Baylis−Hillman reaction are presented or referred to in this review. We are thankful to our present co-workers Ms. D. S. Sharada and Mr. J. Sreevardhan Rao for their timely help and cooperation during the preparation of this review. Thanks are also due to Messrs. G. Jayapal Reddy, V. Chandrasekhar, D. Lenin Babu, B. Devendar, and Ms. P. Anupama and Messrs. J. Raju, A. Veerendhar, and K. Venkateswara Rao who are presently working on various aspects of this reaction. We are grateful to UGC, CSIR, and DST (New Delhi) for funding our research projects on the Baylis−Hillman reaction at various times. A.J.R. thanks CSIR (New Delhi) and T.S.N. thanks UGC (New Delhi) for their research fellowships.

10. Note Added in Proof

Since the submission of the accepted version of the manuscript, several relevant publications have appeared on various aspects of this fascinating reaction. See refs 497−517.

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CR010043D