# Asymmetric Baylis-Hillman Reaction: Use of Novel Chiral Aldehydes as Electrophiles, Chiral Base Catalysts and Auxilliaries#

Palakodety Radha Krishna* and G.V.M. Sharma

*D-206/B, Discovery Laboratory, Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad-500 007, India*

**Abstract:** The present review highlights our recent research findings in the field of asymmetric Baylis-Hillman reaction. In particular, it elaborates on the following efficient aids: 1) utilization of sugar-derived acrylates as chiral auxiliary for diastereoselective Baylis-Hillman reaction; 2) use of novel chiral electrophiles such as sugar-derived aldehydes and chiral 2,3-epoxy aldehydes for the diastereoselective Baylis-Hillman reaction to obtain valuable chiral adducts; 3) a novel prolinol derivative promoted enantioselective Baylis-Hillman reaction and 4) intramolecular Baylis-Hillman reaction wherein both the aldehyde and acrylate component are part structure of the same molecular framework to afford high *de'*s. This review also covers the related research work from other groups on asymmetric Baylis-Hillman reaction.

**Keywords:** Sugar-derived acrylate, sugar-derived aldehydes, chiral 2,3-epoxy aldehydes, *Double Asymmetric Induction*, *N*-methylprolinol, intramolecular Baylis-Hillman reaction.

## INTRODUCTION

The carbon-carbon bond formation is one of the most fundamental reactions in organic chemistry. The development of efficient selective methods for the construction of carbon-carbon bonds is a challenging task in organic synthesis. The Morita-Baylis-Hillman reaction is an emerging carbon-carbon bond forming reaction between a carbonyl compound and an activated alkene under the influence of a suitable catalyst typically a tertiary amine or phosphine. This fascinating reaction has many of the basic properties that an efficient synthetic method should have, e.g., it is selective [1], economical in atom count [2], requires mild conditions and provides densely functionalised products with a newly created stereocenter. Recently, the Baylis-Hillman reaction has been added to the list of useful carbon-carbon bond forming reactions.

## BACKGROUND

In 1968, Ken-ichi Morita and co-workers [3] described the reaction of an aldehyde with electron poor olefins (acrylates and acrylonitrile) catalyzed by tricyclohexylphosphine. They named the transformation "Carbinol Addition". However, the yield of the reaction was extremely poor (20%). Four years later, Anthony Baylis and Melville Hillman [4] were granted a German patent for performing the same reaction using a cyclic tertiary amine catalyst, preferably diazabicyclo[2.2.2]octane (DABCO), with 75% yield (Scheme **1**).

This reaction now commonly known as the Baylis-Hillman reaction [5-9] is a carbon-carbon bond forming reaction between the α-position of activated alkenes (e.g., acrylic esters, acrylonitriles, vinyl ketones, vinyl sulphones, acrolein, vinyl phosphates etc.) and carbon electrophiles (e.g., aldehydes, alkoxy carbonyl ketones, aldimines, π-deficient olefins etc.) under the influence of a suitable catalyst, typically a tertiary amine or phosphine, producing multifunctional molecules (Scheme **2**). Although, more number of tertiary amines are known, DABCO is the most commonly used catalyst for Baylis-Hillman reaction. These densely functionalised molecules are versatile synthetic intermediates in organic synthesis [10-13]. For instance, the Baylis-Hillman products can be stereoselectively transformed into azirines [14], epoxides [15], triols [16] and *anti*-aldol products [17].

Attempts to find out the exact pathway of the reaction by Drewes [5,18], Isaacs [19,20], Kaye [21] and Caubere [22] independently conclude that the Baylis-Hillman reaction is the outcome of an addition-elimination sequence involving tertiary amine, activated alkene and electrophile. The main drawback of the Baylis-Hillman reaction is its extremely slow reaction rate. Numerous efforts [9a] have been made to accelerate this reaction by the use of reactive activated alkenes, reactive electrophiles, microwave irradiation, excess catalyst, hydrogen bonding (having a hydroxyl group in the catalyst or in the substrate), aqueous medium and high pressure and considerable success has been achieved in this direction. More recently, newer interpretation of mechanism have been elucidated by Aggrawal *et al.* [9b] and by McQuade *et al.* [9c] so that Baylis-Hillman reaction could be better understood and used. This review focuses on the asymmetric Baylis-Hillman reaction under the following sub-heads incorporating the results emanating from our laboratories as well as some prominent and relevant contributions from other schools.

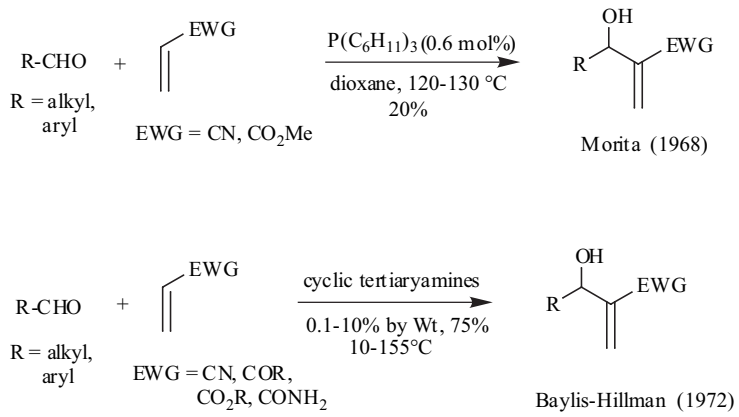
## THE ASYMMETRIC BAYLIS-HILLMAN REACTION

The significance of asymmetric synthesis is probably best appreciated in the context of drug-receptor interactions, because most biological targets are chiral entities. Hence, there is enormous pressure to device viable and practical

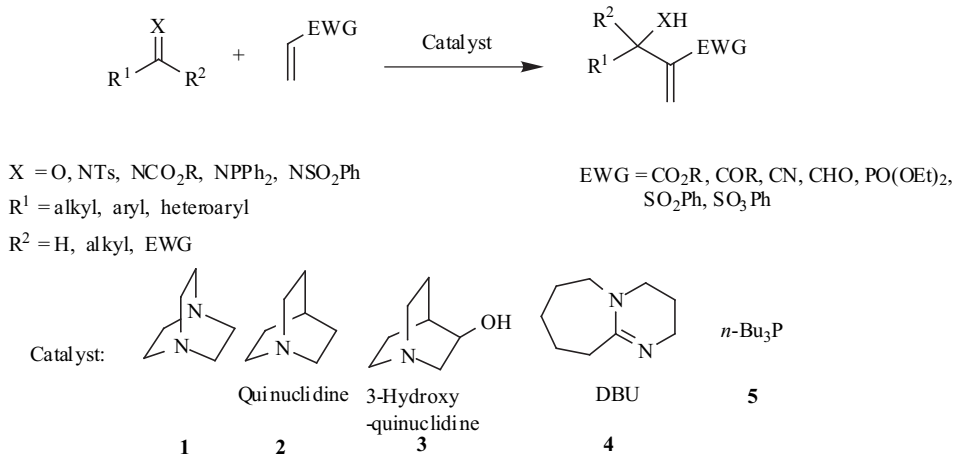
*Address correspondence to this author at the D-206/B, Discovery Laboratory, Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad-500 007, India; Fax: +91-040-27160387 or +91-040-27160575; Email: prkgenius@iict.res.in

#IICT Communication No. 050309.

1570-193X/06 $50.00+.00 




**Scheme 1.**

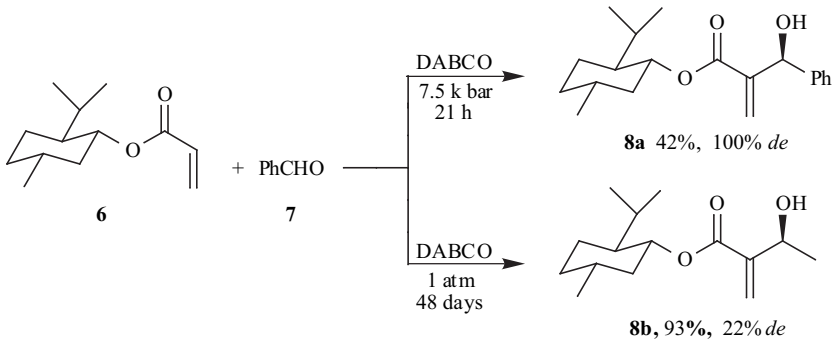



**Scheme 2.**

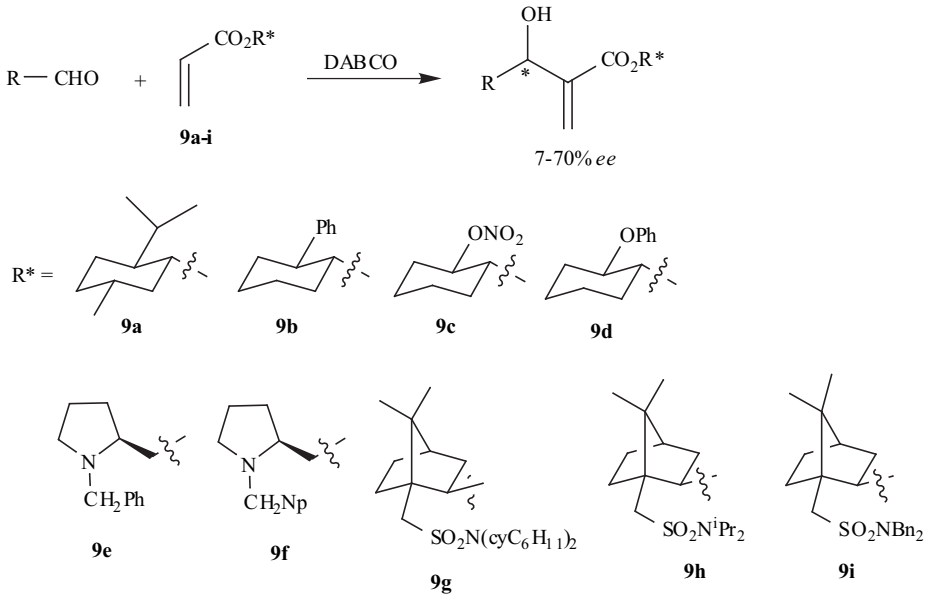
methods for preparing chiral compounds in pure form. Since the Baylis-Hillman reaction results in the creation of new chiral center, there is possibility for asymmetric induction. Unfortunately, there are relatively few methods for performing this task with absolute stereocontrol. There are three main methods that exist for asymmetric version of the Baylis-Hillman reaction: use of (a) chiral Michael acceptor (b) chiral carbonyl compound (c) chiral catalyst.

### a) Asymmetric Baylis-Hillman Reaction using Chiral Michael Acceptors

Chiral auxiliaries have been proven to be a highly effective method of introducing stereochemistry into a molecule in a recoverable fashion [23]. The greatest degree of success in asymmetric Baylis-Hillman reaction has been achieved by using chiral acrylates as chiral Michael acceptor. Brown *et al.* [24] have utilized for the first time (1)-menthyl acrylate **6** for the asymmetric Baylis-Hillman reaction with acetaldehyde using DABCO as catalyst but the diastereomeric excess obtained was only 16%. However, Gilbert *et al.* [25] effectively utilized the same (1)–menthyl acrylate for the diastereoselective Baylis-Hillman reaction at 7.5 k bar pressure with benzaldehyde to afford the product **8a** as a single diastereomer (100% *de*), whereas the same reaction at atmospheric pressure provides the adduct **8b** with only 22% *de* (Scheme **3**). Similarly (-)–bornyl, (-)–nopyl and 8-phenyl menthyl acrylates were also employed by these




**Scheme 3.**



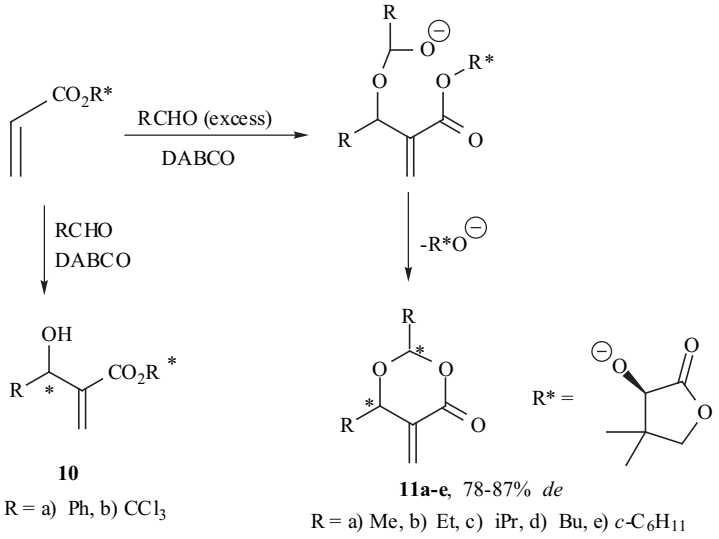

**Scheme 4.**

workers to afford the resulting product with moderate diastereoselectivities. Subsequently, Basavaiah *et al.* [6] studied a variety of chiral acrylates **9a–i** for asymmetric induction in the Baylis-Hillman reaction.

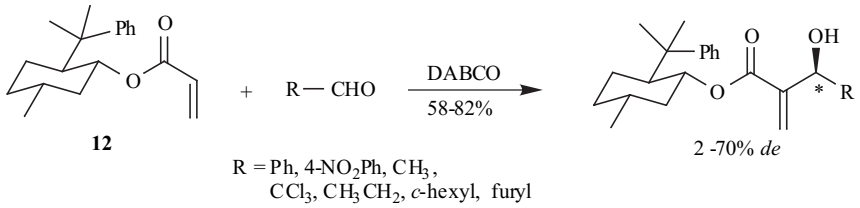
The acrylate **9g**, derived from Oppolzer's chiral auxiliary was found to give higher *de* (70%) on reaction with propionaldehyde. Other chiral acrylates afforded the chiral Baylis-Hillman adducts with a *de* ranging from 7-70% (Scheme **4**).

Drewes *et al.* [26-28] studied the usage of acrylate derived from (*R*)–(+)–pantolactone, with a variety of aldehydes. Except for benzaldehyde and chloral, which gave conventional adducts **10** with 2 and 48% *de* respectively, all other aldehydes gave the corresponding 2,6–dialkyl-5-methylene-1, 3-dioxan-4-ones **11a-e** with 78–87% diastereomeric excess (Scheme **5**).

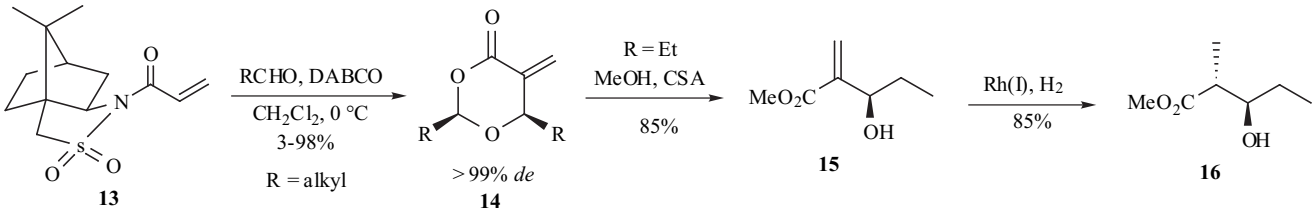
Similarly, 8-phenylmenthyl acrylate [29] **12** has been effectively employed as a chiral Michael acceptor in the




**Scheme 5.**




**Scheme 6.**




**Scheme 7.**

Baylis-Hillman reaction with aldehydes catalyzed by DABCO at atmospheric pressure to afford the corresponding adducts in moderate to good diastereomeric excess (2-70%) (Scheme **6**).

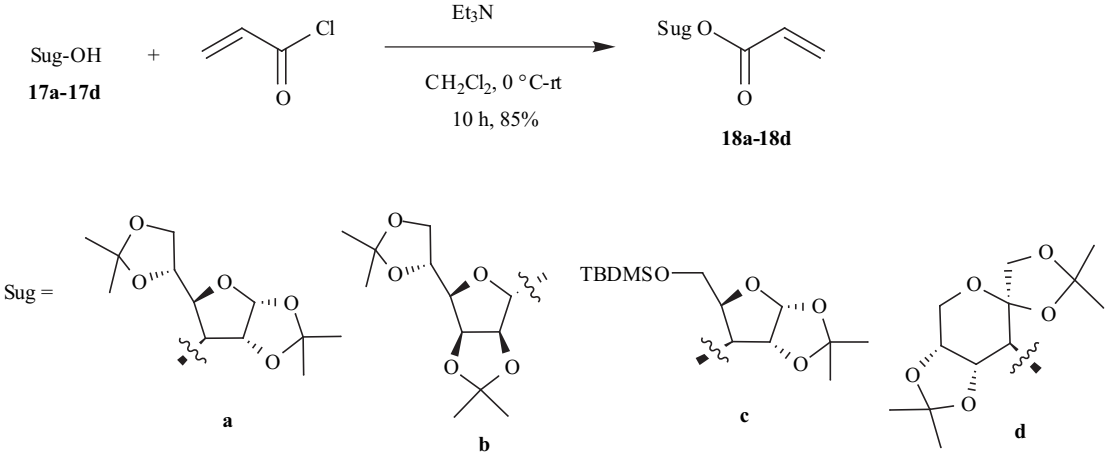
Recently, Leahy and co-workers [30] developed an impressive asymmetric version of the Baylis-Hillman reaction using camphor-derived Oppolzer's sultam as a chiral auxiliary. Oppolzer's sultam is readily available as either antipode and typically leads to excellent transfer of chirality. Moreover L and D Oppolzer's Sultam are equally accessible in two steps from the inexpensive (+) and (-)-camphor-10-sulphonyl chlorides. The camphor sultams can be *N*-acrylated by successive treatment with sodium hydride and acryloyl chloride. The *N*-acyl derivative **13** can be readily purified by crystallization and cleaved (e.g. with LAH, LiOH etc.) under mild conditions without loss of the induced chirality and with virtually complete recovery of the auxiliary. By using second equivalent of aldehyde, the chiral auxiliary can be fortuitously cleaved from the product *in situ* to give an optically active dioxanone **14** in good yields and excellent enantiomeric excess. This method is effective for unbranched aliphatic aldehydes whereas $\alpha$-branched aldehyde afforded lower yields. Thus obtained dioxanone was transformed into the $\alpha$-methylene-$\beta$-hydroxyester **15**, which was subsequently hydrogenated to give the *anti*-aldol product **16** (Scheme **7**).

Chen and Yang [31] have disclosed a highly efficient diastereoselective Baylis-Hillman reaction using hydrazide as a chiral auxiliary for the direct preparation of optically active $\alpha$-methylene-$\beta$-hydroxy carbonyl compounds.

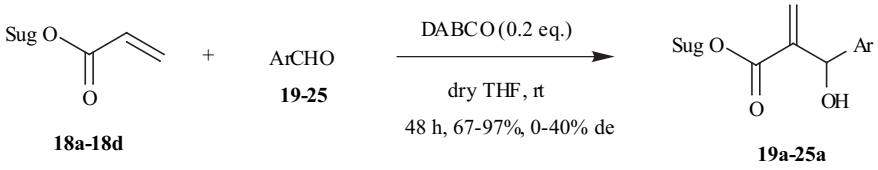
Sugar-derived acrylates [32] (Scheme **8**) were conceived for the first time by us as important chiral auxiliaries due to their wide availability in both D and L-forms and with varied stereochemistries and ring forms, for the diastereoselective Baylis-Hillman reaction with various aryl aldehydes to afford adducts with *de* 0-40% in moderate yields (Scheme **9**).

Interestingly, the addition was adjudged predominantly to occur from the $\alpha$-face due to the formation of an isooxazoline intermediate which was envisaged as the possible enolate of sugar acrylate to result in the diastereoselection. The absolute configuration of the major isomer was determined as '*R*' by a chemical correlation *via* a Sharpless asymmetric epoxidation route.

Alternatively we have exploited *'Double Asymmetric Induction'* [33] for the first time as a mechanistic tool for achieving high diastereoselectivity to the tune of >90% when a chiral aldehyde(s) was/were used as an electrophile(s) and sugar-derived acrylate as a Michael acceptor catalyzed by DABCO (Scheme **10**). The results are rationalized based on a model wherein the 'Matched pair' resulted in adducts with




**Scheme 8.**

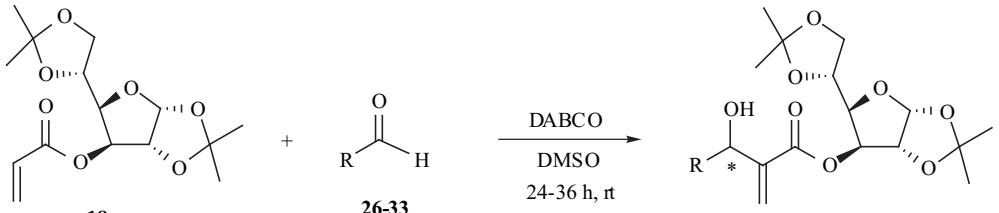



**Scheme 9.**

**Table 1. Asymmetric Baylis-Hillman Reaction of Aldehydes with Sugar Acrylates**

| Entry | Aldehyde | chiral acrylate | Product(s) | Time | Yield (%) | de% |
|---|---|---|---|---|---|---|
| **1** | 2-Nitro benzaldehyde **19** | **18a/18b/18c/18d** | **19a-d** | 48 h | **19a** | 40 (R) |
| **2** | 4-Nitro benzaldehyde **20** | **18a/18b** | **20a-b** | 48 h | **20a** | 40 (R) |
| **3** | Isobutyraldehyde **21** | **18a/18b** | **21a-b** | 48 h | **21a** | 0 |
| **4** | Benzaldehyde **22** | **18a** | **22a** | 84 h | **22a** | 5 (R) |
| **5** | 2,3-Dichlorobenzaldehyde **23** | **18a** | **23a** | 48 h | **23a** | 0 |
| **6** | 2-Nitro-5-n-propoxybenzaldehyde **24** | **18a** | **24a** | 72 h | **24a** | 15 (R) |
| **7** | 2-Nitro-5-methoxybenzaldehyde **25** | **18a** | **25a** | 72 h | **25a** | 34(R) |

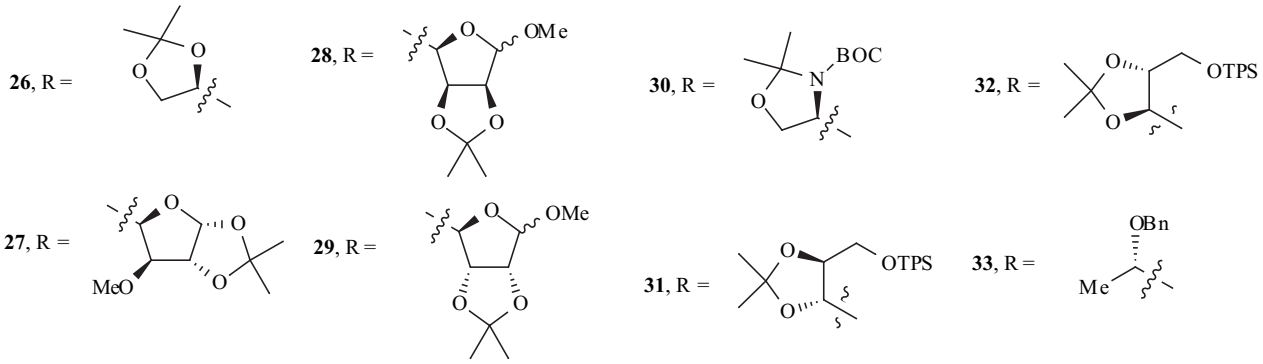
The results (yields, time and d. e. 's ) obtained when sugar acrylate **18a** was used are presented




**18a** **26-33** **26a-33a**

42-84% yield
33- >95% de

**Aldehydes**




**Scheme 10.**

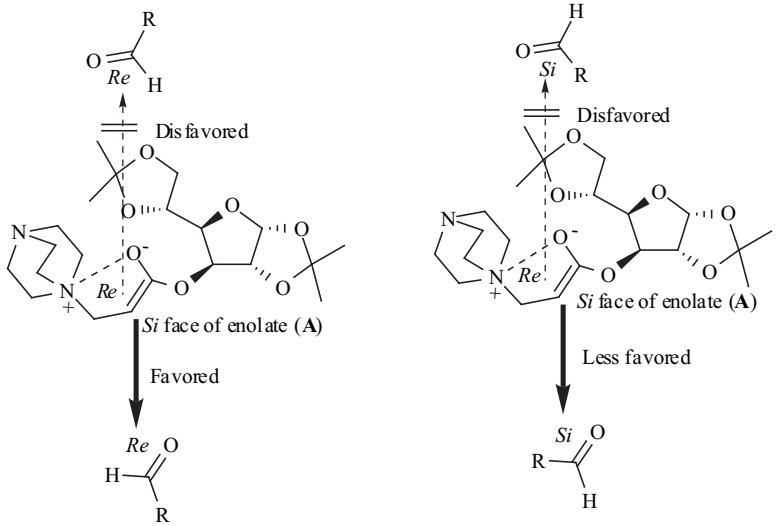


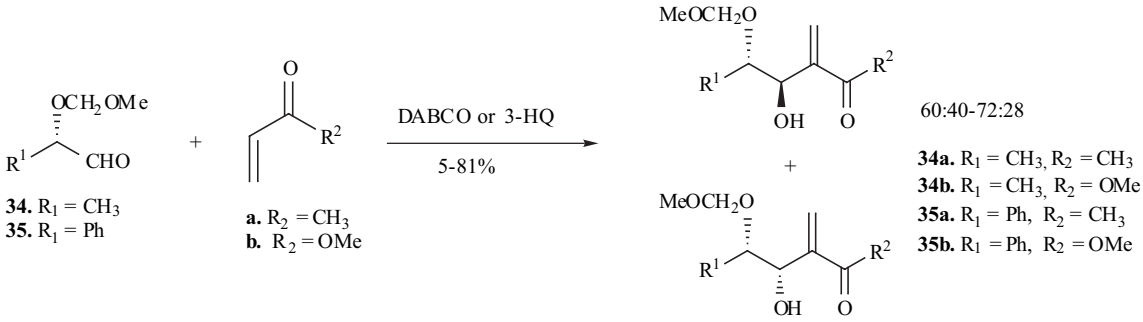

**Fig. (1).** Schematic representation of diastereofacial interactions.

greater selectivity due to steric crowding (diastereofacial interactions) adjacent to aldehyde carbon. More importantly the adducts obtained were *'Syn'* to the preexisting chiral center which clearly means that a diastereoreversal of selectivity was observed. The stereochemical outcome of the study depends on the diastereofacial interactions of the two chiral compounds (aldehyde and acrylate) wherein the matched pair results in adducts with higher selectivity. On the contrary, the mismatched pair either is disfavored or yields adducts with poor selectivity.

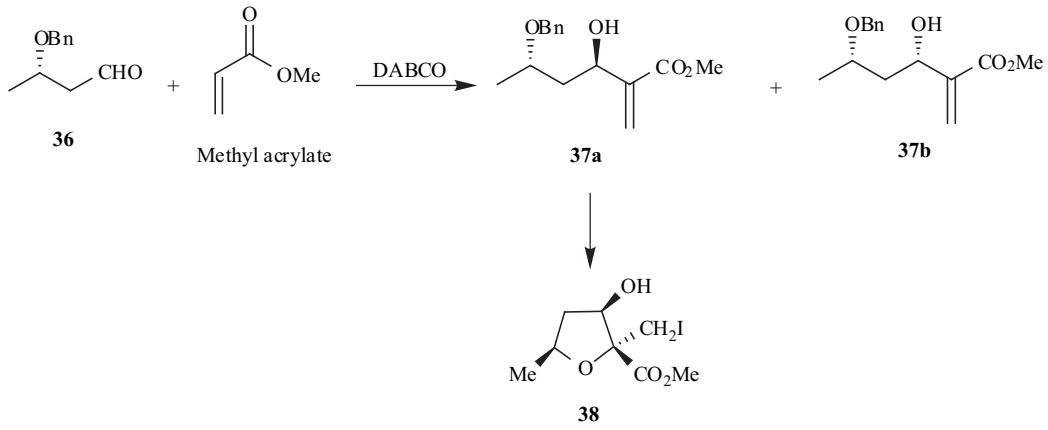
### b) Asymmetric Baylis-Hillman Reaction using Chiral Electrophiles

The use of a chiral electrophile for asymmetric Baylis-Hillman reaction has been least explored in literature. Roos *et al.* [34] have effectively utilized (*S*)–*O*–(methoxymethyl) lactaldehyde (34), (*S*)–*O*–(methoxymethyl) mandaldehyde (35) and α-amino aldehyde as chiral electrophiles in asymmetric Baylis-Hillman reaction with both methyl acrylate and methyl vinyl ketone under the influence of either DABCO or 3–hydroxyquinuclidine to afford mixture of diastereomers with predominant *anti*–isomer (Scheme **10**). Similarly, (*S*)–3benzyloxybutraldehyde[35] **36** reacts under the influence of DABCO with methyl acrylate to furnish a 75:25 mixture of *anti* and *syn*-diastereomers (**37a** and **37b**). The major *anti*-isomer was separated and converted into an interesting tetrahydrofuran derivative **38** with three stereogenic centers (Scheme **12**).

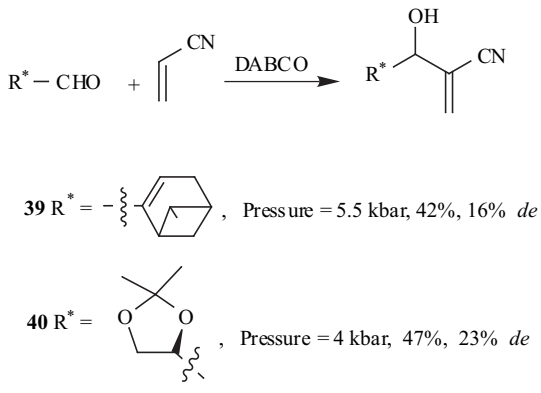
(*R*)-Myrtenal (**39**) and isopropylidine (*R*)-glyceraldehyde [25] (**40**) were employed as chiral electrophiles in the Baylis-Hillman reaction with acrylonitrile at 5.5 and 4 K bar pressure respectively. However, the diastereoselection in this reaction is very low (Scheme **13**).



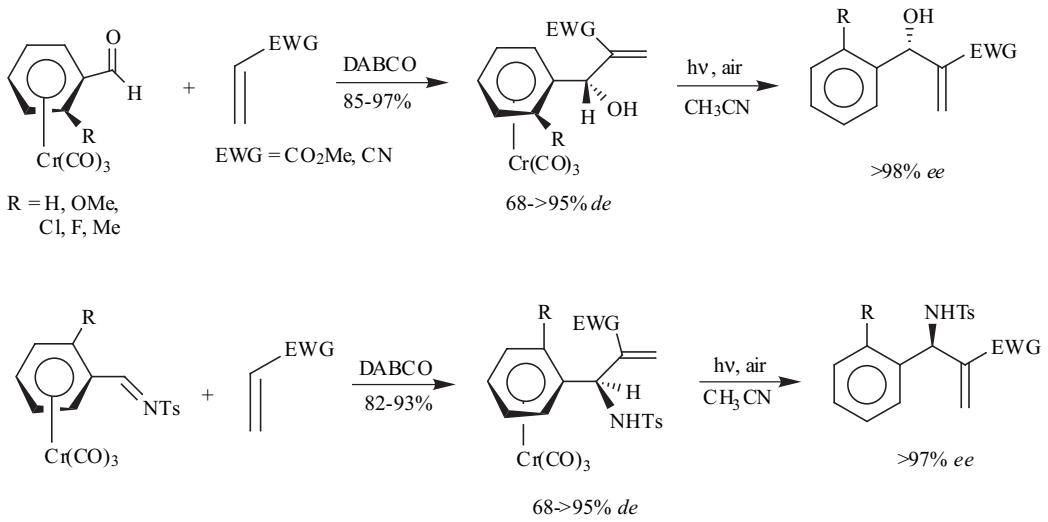

**Scheme 11.**




**Scheme 12.**



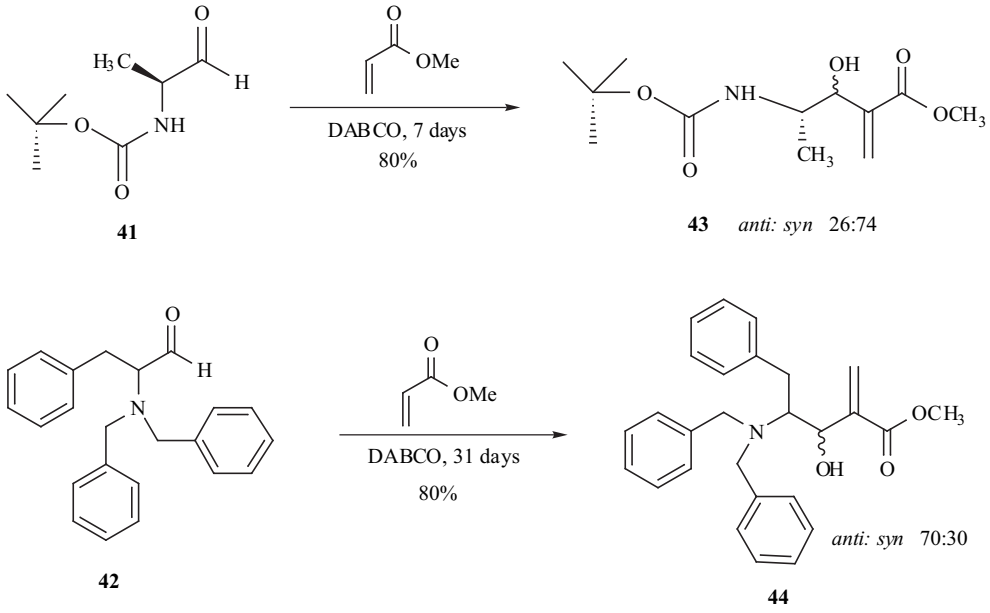

**Scheme 13.**



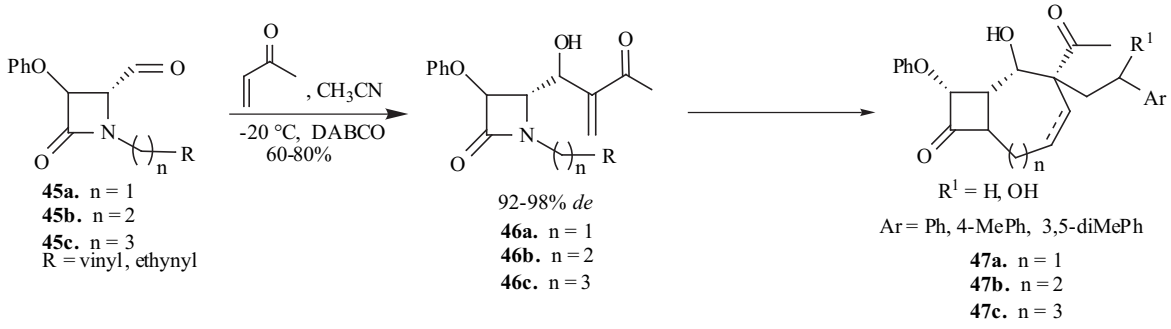

**Scheme 14.**

Recently, Kundig *et al.* [36,37] showed that planar chiral benzaldehyde $Cr(CO)_3$ complexes as electrophiles in the DABCO catalyzed Baylis-Hillman coupling with methyl acrylate and acrylonitrile to obtain corresponding adducts with excellent diastereoselectivities in >98% *ee* (Scheme **14**).

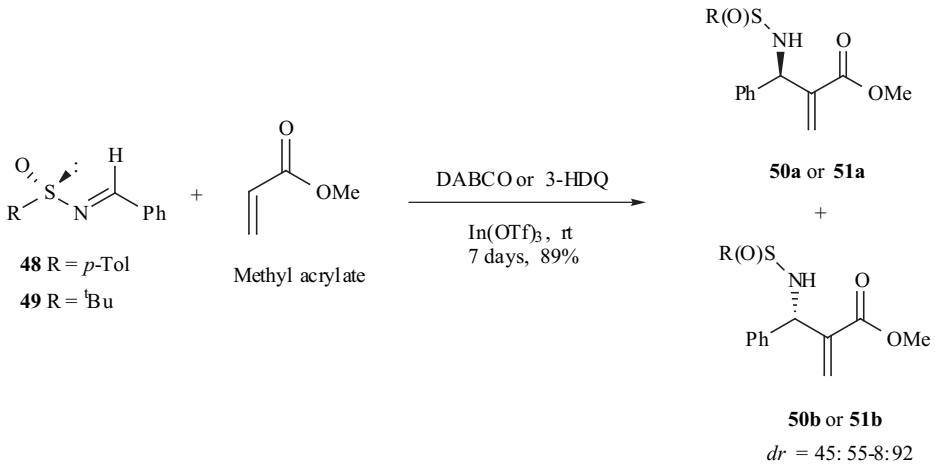
Bussolari *et al.* [38] reported a reaction between chiral aldehyde **41** and **42** and methyl acrylate in the presence of DABCO. The resultant products **43** and **44** were obtained in good yields with moderate diastereoselectivities (50-60%) (Scheme **15**).



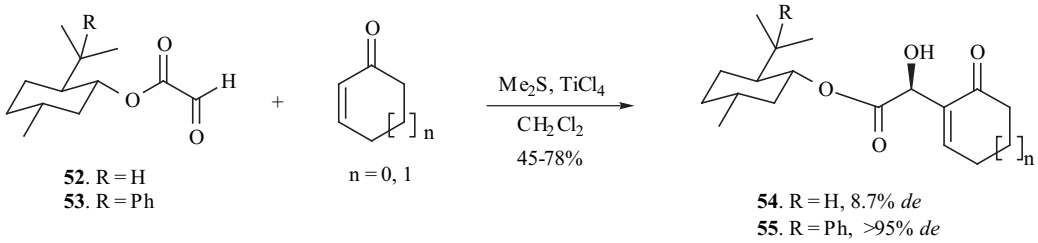

**Scheme 15.**




**Scheme 16.**




**Scheme 17.**




**Scheme 18.**

Recently, Alcaide and co-workers [39,40] have successfully utilized optically pure 1-alkenyl or alkynyl–4–oxoazetidine–2–carbaldehydes as chiral electrophiles in the Baylis-Hillman reaction with MVK to provide adducts with very high diasteroselectivities and which were transformed into highly functionalised β-lactams fused to medium–sized rings through chemocontrolled tandem radical addition–cyclisation sequences (Scheme **16**).

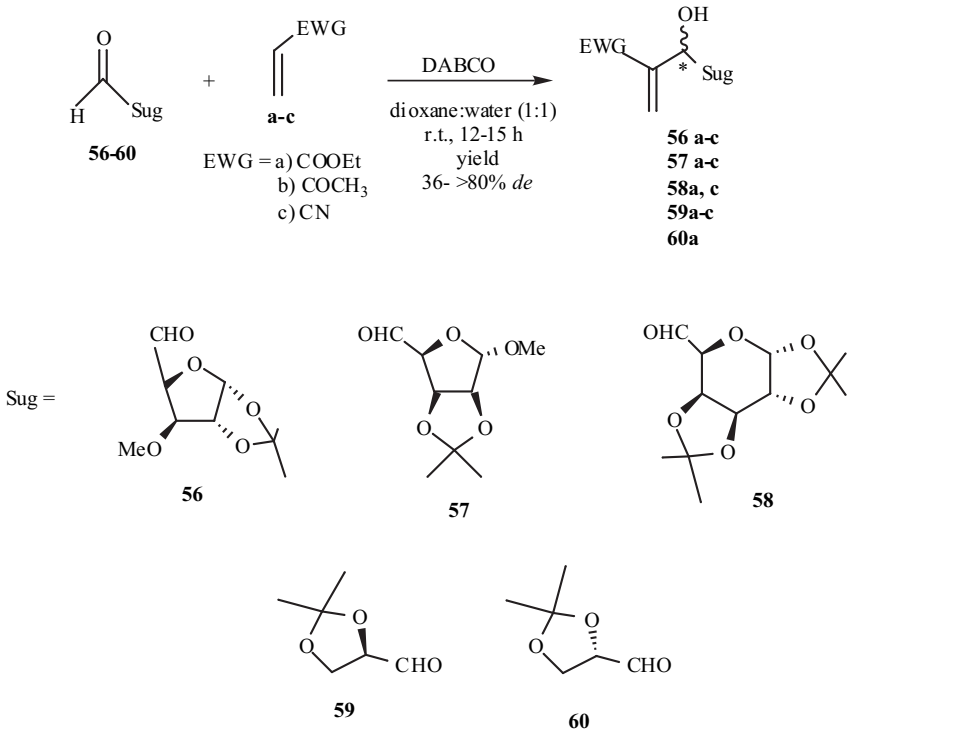
The electrophilic behavior of enantiomerically pure *N–p–* toluenesulfinimines **48** and *N–tert–*butanesulfinimines [41] **49** have been tested by Aggarwal and co-workers in the Baylis-Hillman reaction with methyl acrylate in the presence of Lewis acid. The yield and diastereoselectivity were found to be optimum in the presence of $In(OTf)_3$. The absolute configuration of the major adduct was unequivocally determined as '*S*' at the new sterogenic center by X–ray crystallography. Chiral 3–hydroxy quinucludine was also used in this study but only a small variation in both yield and diastereoselectivity was observed indicating that the stereochemistry of the sulfinimine dominates control in the selectivity of the process (Scheme **17**).

The chiral glyoxylates [42] derived from menthol (**52**) and 8–phenylmenthol (**53**) were also employed as electrophiles for chalcogeno–Baylis–Hillman reaction with cyclic α-β-unsaturated ketones. The sterically more demanding 8–phenylmenthol group not only gave higher yield (76%), but also provided excellent diastereoselectivities (>95%) under Kataoka conditions (Scheme **18**).

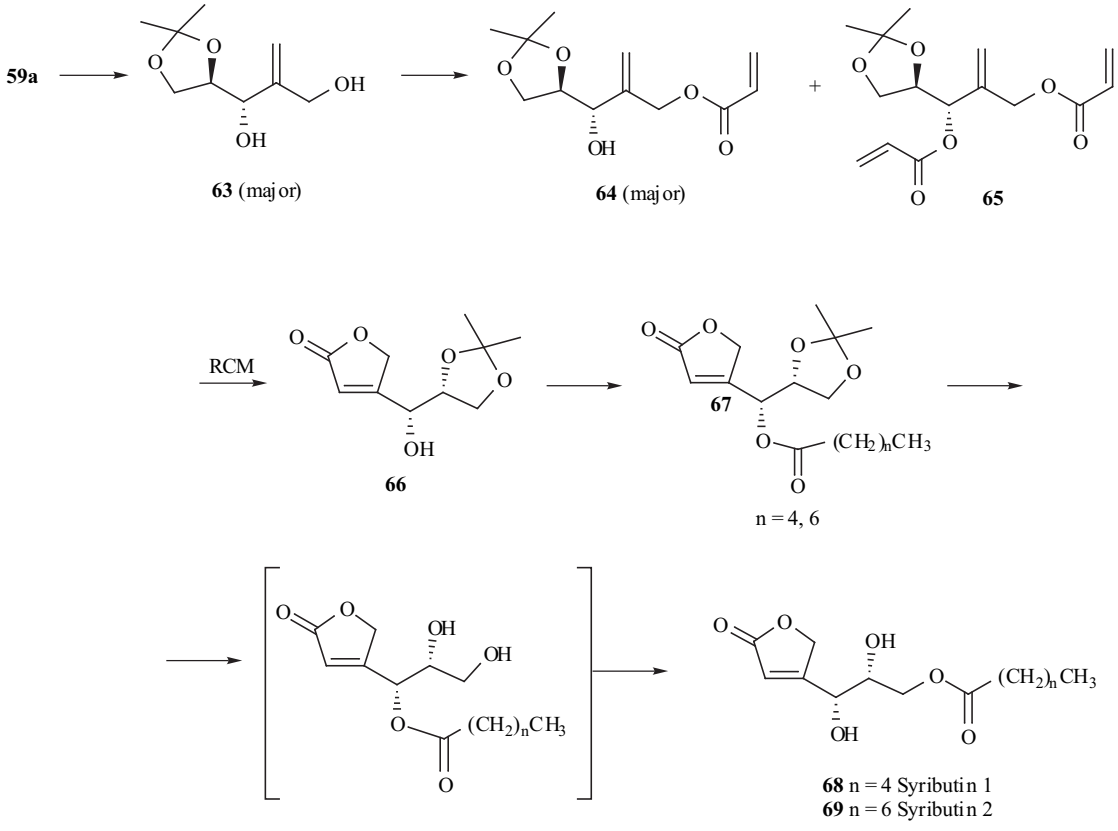
Similarly, sugar-derived aldehydes **56-60**, were thought to be ideal chiral electrophiles for Baylis-Hillman reaction (Scheme **19**) and upon reaction with ethyl acrylate, methyl vinyl ketone and acrylonitrile resulted in adducts **56a-c**, **57a-c**, **58a**, **58c**, **59a-c** and **60a** with the *de*'s varying from 36-95% and yields ranging from 56-85% [43]. The observed stereoselectivity can be explained by the favorable attack of carbanion from *si*-face of the sugar aldehyde leading to 'S' isomer as major product at the newly created center according to Felkin-Ahn model [44] by a non-chelation protocol. Similarly, since the aldehydes are obtained from D-sugars and the Baylis-Hillman reaction was conducted at C-5 site adjacent to C-4, their respective major adducts exhibited larger vicinal coupling constants ($J_{5,4}$). Conclusively, the new stereocenter was defined as 'S' (*threo* relationship between C-4 and C-5) for all aldehydes derived from D-sugars and the opposite was true when the aldehyde is derived from L-sugar.

One such representative adduct **59a** was used for the stereoselective synthesis of Syributins **61** and **62** by a RCM (ring closing metathesis) protocol as shown in Scheme **20**.

Similarly, another class of chiral aldehydes such as chiral 2,3-epoxy aldehydes (**70-76**) were subjected to Baylis-Hillman reaction (Scheme **21**) under the standard reaction conditions to result in densely functionalized adducts in good yields (61-80%) and in moderate diastereoselectivities (40-72% de) [46]. It is beyond the scope of this review to make a mention the significance of epoxides as synthetic intermediates. When such sensitive substrates were subjected to Baylis-Hillman reaction, the general observation that *cis*-epoxy aldehydes yielded major *syn*-adducts than when *trans–*epoxy aldehydes was due to steric crowding. This phenomenon could be rationalized by a Cornforth model [47]. The *syn-anti* ratio of the adducts was determined by $^1H$ NMR and HPLC.




**Scheme 19.**

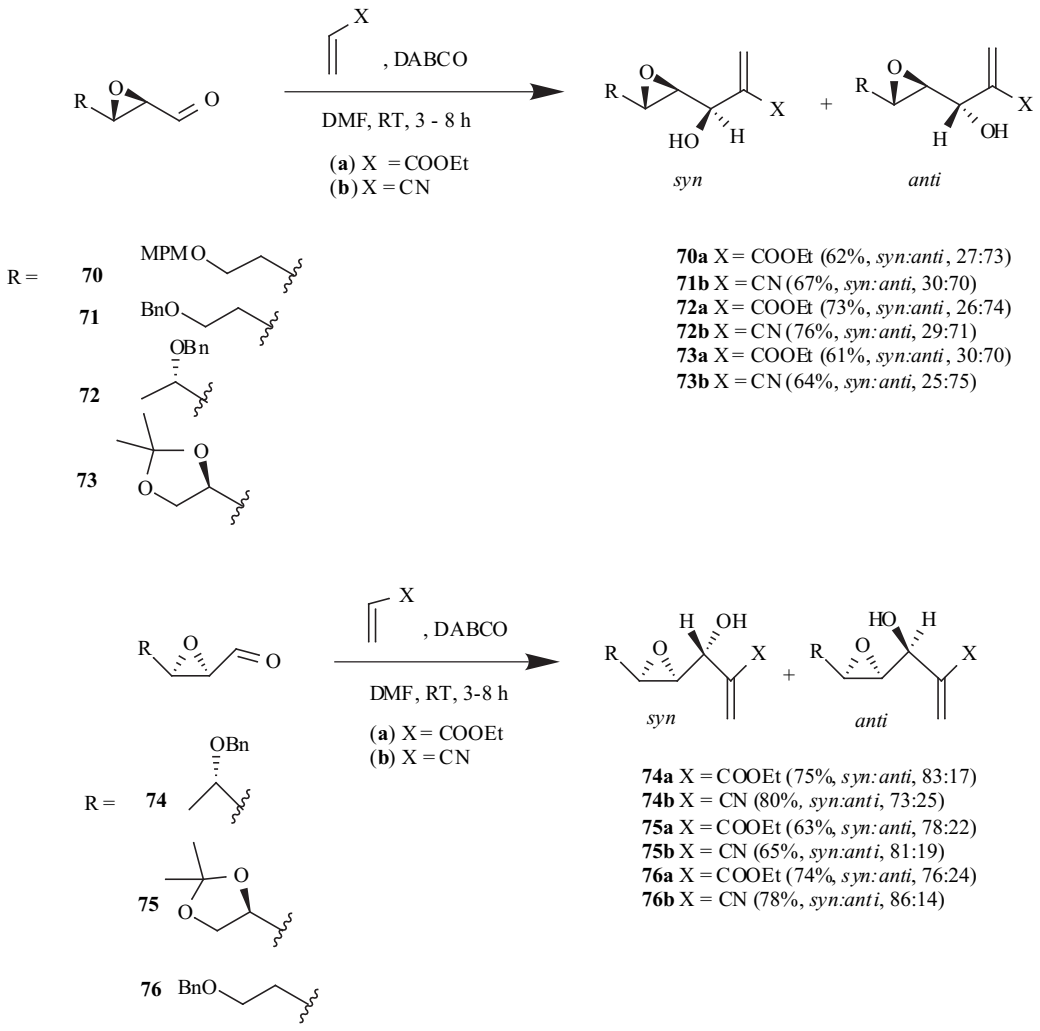



**Scheme 20.**

### c) Asymmetric Baylis-Hillman Reaction using Chiral Catalysts

The chiral catalysts are often called as 'chemenzymes" owing to the similarities in the enantioselectivity and characteristic reactivity to enzymes. Some of the advantages of the chiral catalyst over enzymes are high yield and generality to many substances, which are highly unusual with enzymes.

Drewes *et al.* [5] examined different chiral amine catalysts such as brucine **77**, cinchonidine **78**, quinidine **79**,




**Scheme 21.**

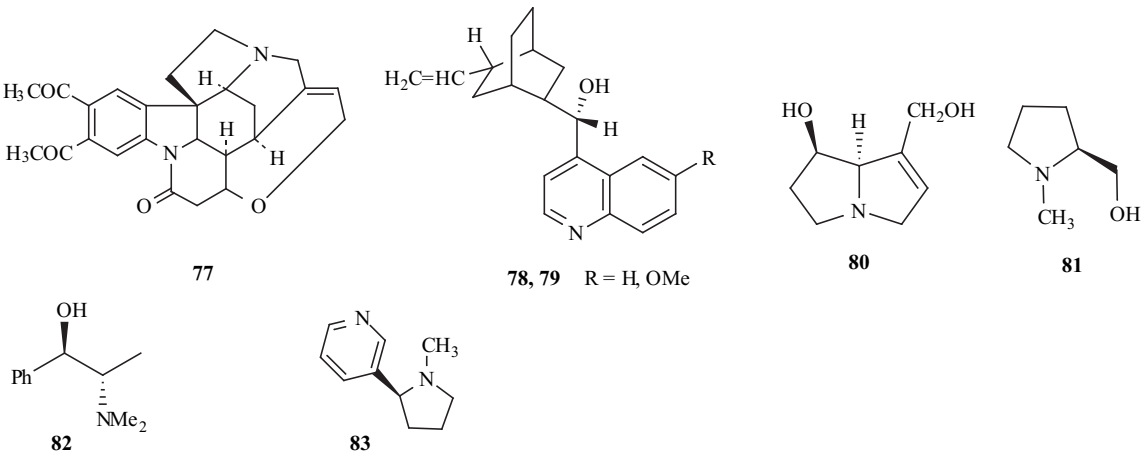
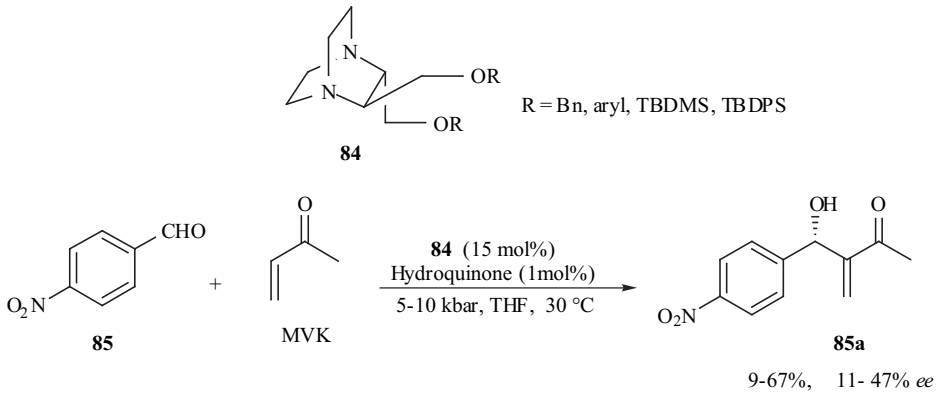



**Fig. (2).**

retronecine **80** and (*S*)-(-)-*N*-methyl prolinol **81** for the Baylis-Hillman reaction. However, the level of asymmetric induction in all cases was very poor (0–12% *ee*). Similarly the other chiral amines 1*R*–2*S*–*N*–methyllephedrine **82**, *S* (-)-nicotine **83** and +/-3-hydroxyquinuclidine catalyzes the Baylis-Hillman reaction under high pressure to afford the desired products in 10–17% *ee* (Fig. **2**).

Oishi *et al.* [48] synthesized chiral $C_2$–symmetric 2,3–disubstituted DABCOs to serve as catalysts for the Baylis-Hillman reaction. They accomplished moderate enantioselectivity (upto 47% *ee*) for the reaction between *p*-nitrobenzaldehyde and methyl vinyl ketone using 15-mol % of the catalyst (R = Bn) under high pressure (5 K bar) (Scheme **22**). In the case of TBPS protected DABCO

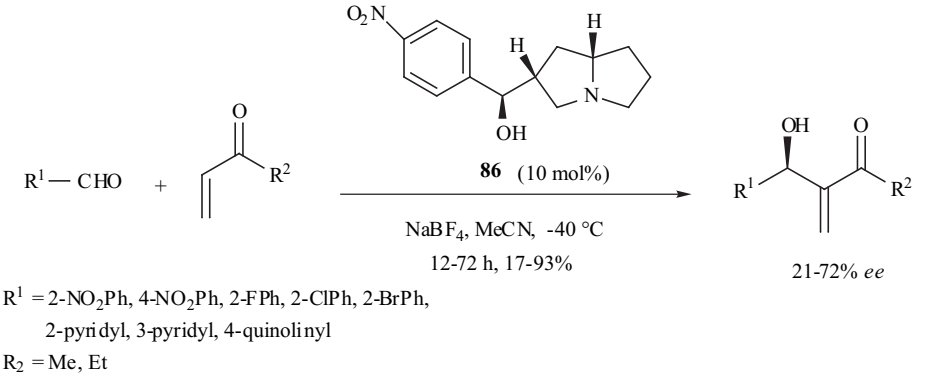



**Scheme 22.**

catalyzed reaction, reversal of stereochemistry of the product was observed. When benzaldehyde was used as electrophile, the asymmetric induction of the product was only 10% *ee* even at high pressure (10 K bar).

Barrett *et al.* [49] reported a chiral pyrrolizidine **86** to promote Baylis-Hillman reaction of alkyl vinyl ketone with

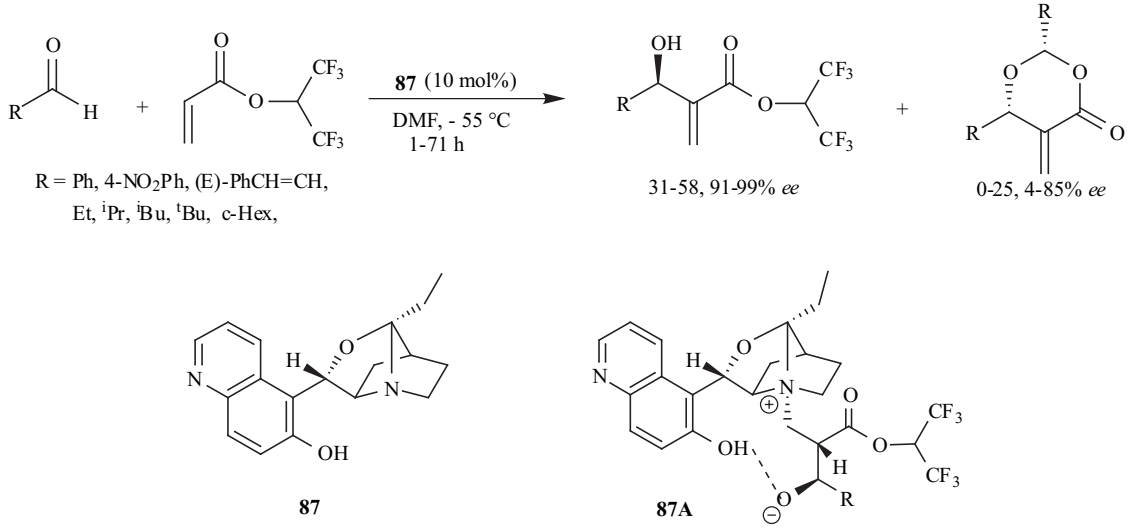
Recently, Hatakeyama and co-workers[50] studied various tertiary amines derived from cinchona alkaloids for enantioselective Baylis-Hillman reaction and arrived at the best catalyst **87** to date (Scheme **24**). The chiral amine **87** catalyzes the reaction of aldehyde and 1,1,1,3,3,3-hexafluoroisopropyl acrylate, at a temperature of –55 °C, providing the desired products with moderate yields and



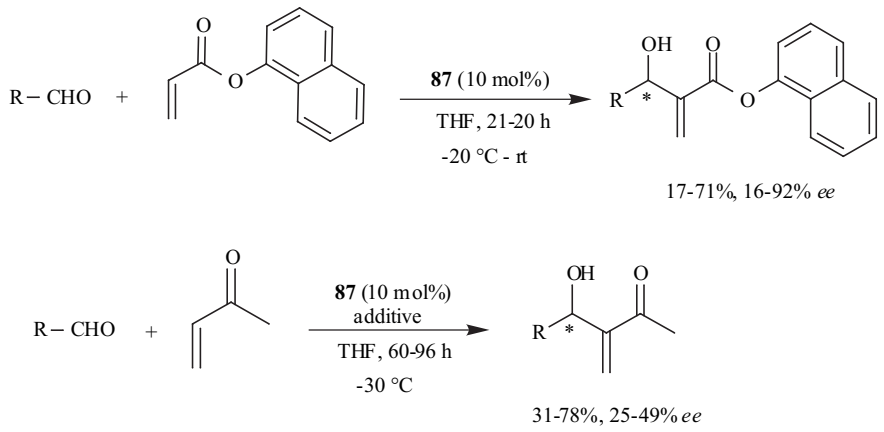

**Scheme 23.**

electron deficient aromatic aldehyde to furnish the corresponding product with 21-72% *ee* and in 17-93% yields (Scheme **23**).

very high enantioselectivities (91-99% *ee*). However, when the chiral amine **87** was employed to catalyze the reaction of *p*-nitrobenzaldehyde with methylacrylate at room




**Scheme 24.**

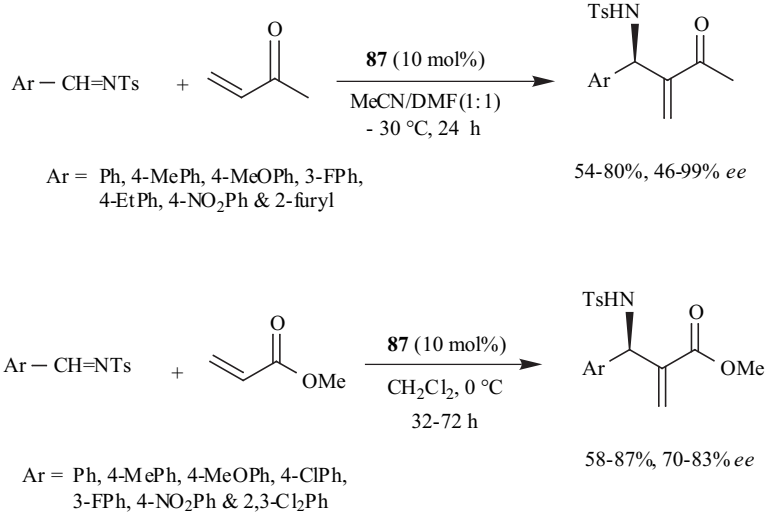



**Scheme 25.**

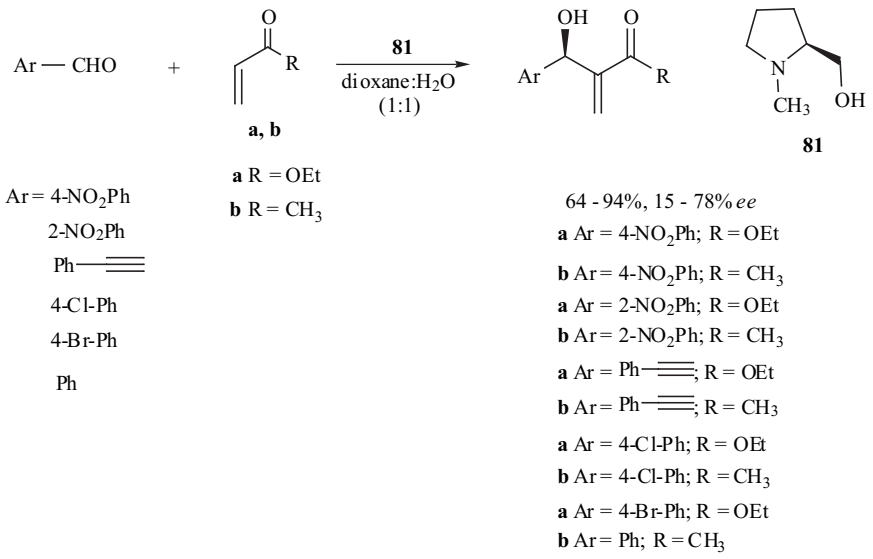
temperature, the enantioselectivity of the reaction was very poor (8% *ee*). Subsequently, Shi and Jiang [51] extended the utility of this chiral amine catalyst **87** to other activated alkenes like α-naphthyl acrylate and MVK in the presence of additive, proline and lithium salt, to obtain the corresponding allylic alcohol in moderate to good enantioselectivities (Scheme **25**). They also reported asymmetric aza Baylis-Hillman reaction [52] of imines with MVK and methyl acrylate catalyzed by **87** to achieve high enantioselectivity (upto 99% *ee*). The reaction of *p*-nitrobenzaldehyde with MVK under the same set of conditions gave the Baylis-Hillman adduct in only 20% *ee* (Scheme **26**).

We have used *N*-methylprolinol **81** as a chiral base catalyst for the enantioselective Baylis-Hillman reaction between aromatic aldehydes and activated alkenes (ethyl acrylate and MVK) to obtain good yields of the adducts with moderate to good enantioselectivity in 1,4-dioxane: water (1:1, v/v) under ambient conditions (Scheme **27**) [53]. It was observed that the pendant hydroxy functionality was an essential component for achieving selectivity as it participated in a 9-membered ring structure stabilizing the intermediate as depicted in Fig. **3**. Intermediate B is more stabilized than C due to the favourable formation of intramolecular hydrogen bonding because the OH group and oxy anion are in the same plane. The absolute configuration of the products was assigned as *R* based on correlation with the known compounds or on analogy. Correspondingly, (*S*)-Baylis-Hillman adducts could be obtained by using *N*-methylprolinol derived from commercially available (*R*)-proline thus providing scope for the facile generation of both the enantiomers.

Another important contribution from our laboratories has been the first diastereoselective intramolecular Baylis-Hillman reaction of the appropriately substituted chiral derivatives to give the corresponding lactones. To date a diastereoselective intramolecular Baylis-Hillman reaction using a chiral substrate wherein both the aldehyde and activated olefin co-exist has not been exploited for the synthesis of α-methylene-β-hydroxylactones that constitute important structural features of many bio-active natural products. Consequently, a novel intramolecular diastereo-




**Scheme 26.**




**Scheme 27.**

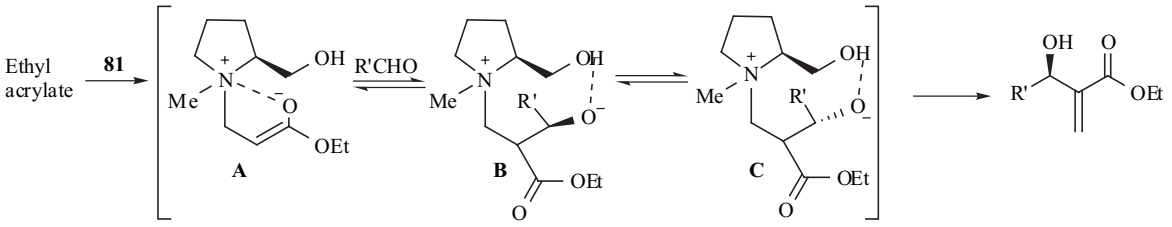
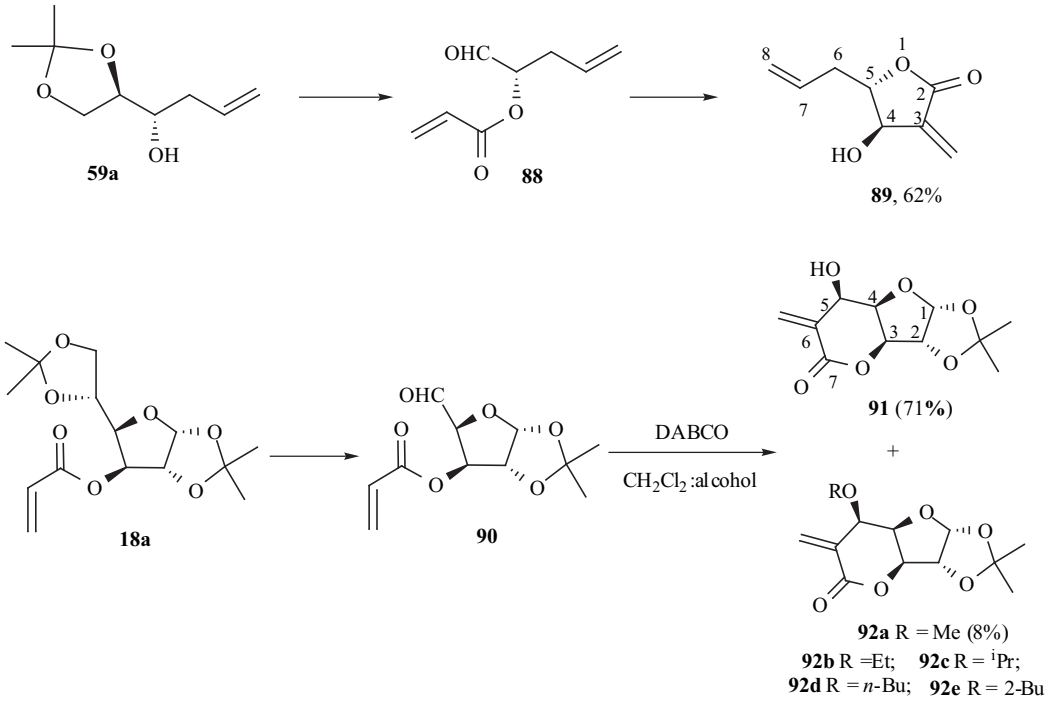
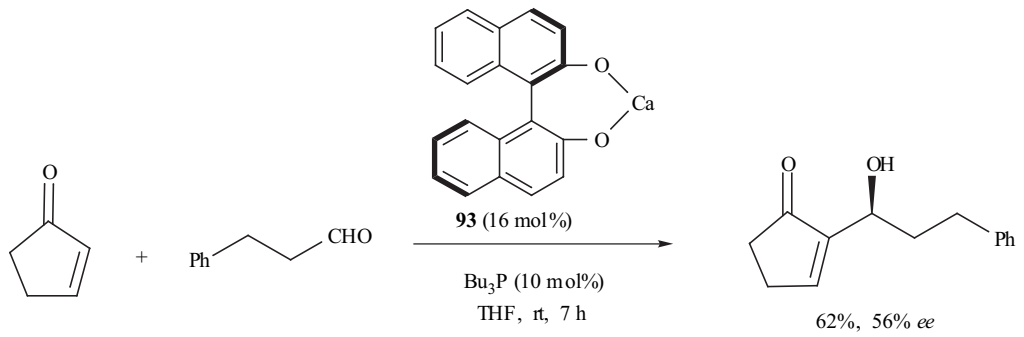



**Fig. (3).** Proposed reaction mechanism.

selective Baylis-Hillman reaction [54] as one of the most practical routes to synthesis of α-methylene-β-hydroxyl-actones with *de'* s >95% was developed (Scheme **28**). Formation of O-alkoxylactones was also observed by an *in situ* derivatisation of adducts when a mixture of $CH_2Cl_2$ and alcohol was used. The absolute stereochemistry at the newly created stereogenic center for the adducts (89, 91, 92a-e) was assigned as *R*.




**Scheme 28.**




**Scheme 29.**

Corey *et al.* [55] have recently utilized diastereoselective intramolecular Baylis-Hillman reaction as the key step in the total synthesis of Salinosporamide A.

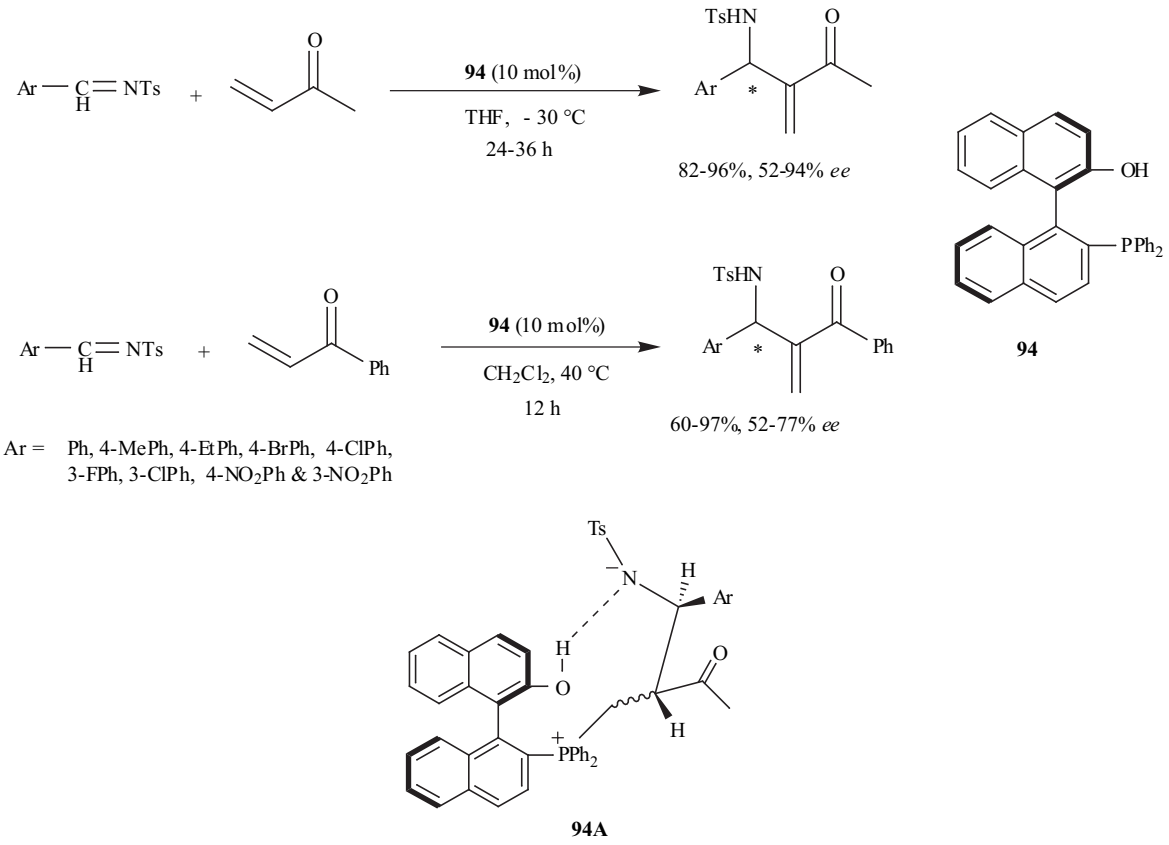
## MISCELLANEOUS

There are relatively few cases where chiral phosphine has been used to catalyze Baylis-Hillman reaction. 2,2[1]-bis(diphenylphophino)–1,1[1]-binaphthyl (BINAP). The various chiral hydroxyl phospholanes derived from D-mannitol have been used by Zhang *et al.* [56] for the catalytic asymmetric Baylis-Hillman reaction between pyridine-4-carbaldehyde and methyl acrylate with low enantioselectivity of 2-19% *ee*.

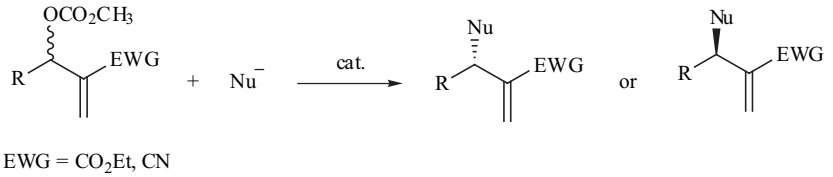
Ikegami and Yamada [57] successfully employed first optically active calcium catalyst **93** for the reaction 2-cyclopenten-1-one with 3-phenyl-1-propanol to afford the corresponding adduct in 62% yield and 56% *ee* (Scheme **29**).

Recently, Shi and Chen [58] have been investigated the chiral phosphine (2[1]-diphenylphosphonyl-[1,1[1]] binaphthalenyl-2-ol **94**) catalyzed aza Baylis-Hillman reaction of *N*-sulfonated imines with MVK and phenyl acrylate to give desired products in high yields with moderate to good enantiomeric excess (Scheme **30**). The intramolecular hydrogen bonding between phenolic OH and nitrogen anion plays key factor to give relatively stable intermediate **94A** to produce the aza Baylis-Hillman product with *S* configuration.

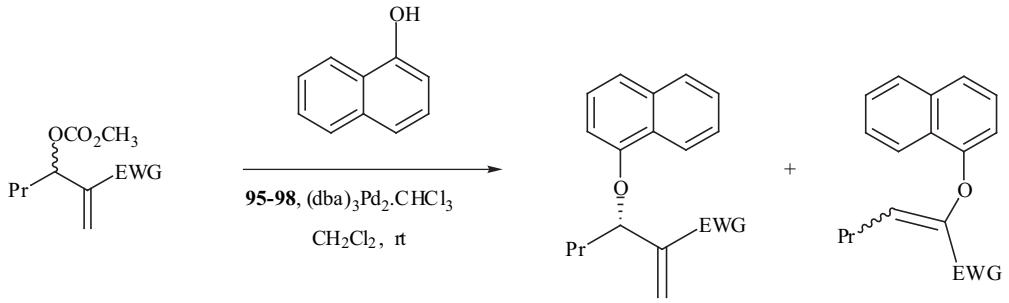
The first enantioselective chalcogeno-Bayis-Hillman reaction has been developed by Kataoka *et al.* [59,60] using a hydroxy chalcogenide $TiCl_4$ complex under atmospheric pressure. Chen and coworkers [61] screened the various




**Scheme 30.**




**Scheme 31.**




**Scheme 32.**

chiral dimerized ligands for the asymmetric Baylis-Hillman reaction of benzaldehyde with methylacrylate in the presence of a Lewis acid.

Trost and coworkers [62] considered an alternative strategy to obtain α-methylene-β-hydroxy ester or nitriles in enantiomerically enriched forms using the dynamic kinetic asymmetric transformation (DYKAT) process (Scheme **31**). The process could be considered as a '*deracemization'* of the Baylis-Hillman adducts. The variation of ligand was also studied during the reaction of carbonates with α-naphthol as nucleophile. The least rigid **96** gave the best regioselectivity and enantioselectivity (Scheme **32**).

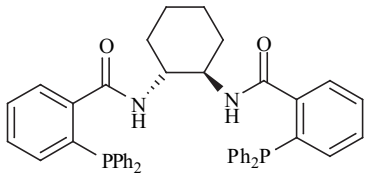
The other methods currently available for realizing optically active α-methylene-β-hydroxy compounds are 1) kinetic resolution of alcohol and their derivatives by the use of enzyme as biocatalyst [63], 2) kinetic resolution of alcohol using asymmetric hydrogenation methodology [64], 3) diastereomeric crystallization [65] and 4) dynamic kinetic resolution of Baylis-Hillman acetates [66].

## Chiral Bronsted Acid Catalyst

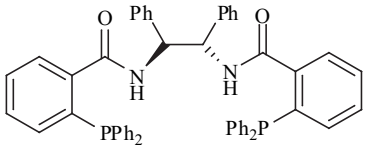
Recently, Schaus *et al.* [67] (Scheme **33**) reported highly enantioselective Baylis-Hillman reaction of cyclohexenone with aldehydes using chiral BINOL as Bronsted acid catalyst and trialkylphosphine as nucleophilic promoter. Triethyl phosphine was found to be better nucleophilic promoter which gave more enatioselectivities compared to $PMe_3$ and $P(n\text{-}Bu)_3$.

## Ionic Liquids

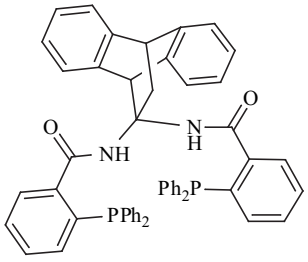
Giang Vo-Thanh *et al.* [68] conceptually used *N*-alkyl-*N*-methylephedrinium salts as chiral ionic liquids towards the



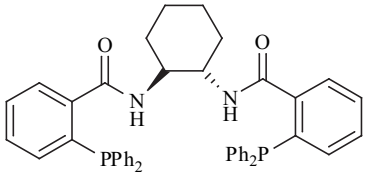

**95**




**96**

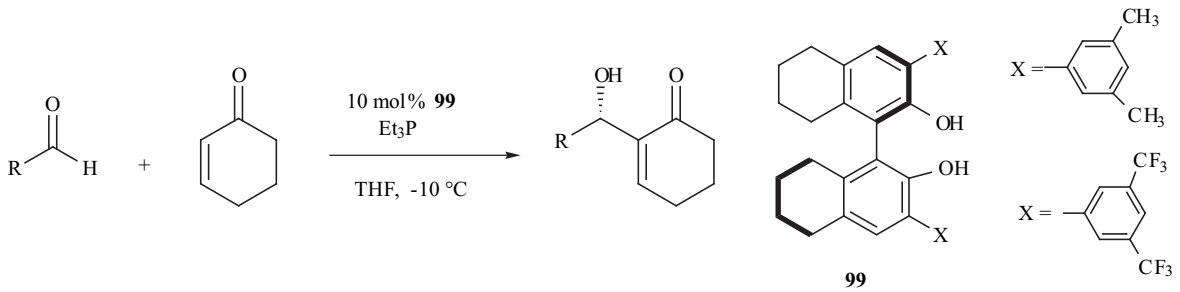



**97**




**98**

**Fig. (4).**




**Scheme 33.**

first application in enantioselective Baylis-Hillman reaction, wherein the *ee*'s ranged from 20-44%.

## CONCLUSION

The Baylis-Hillman reaction provides versatile molecules with a newly created center that are important building blocks in organic synthesis and also serve as synthetic equivalent to anti-propionate aldol addition products. The most impressive results obtained in asymmetric Baylis-Hillman reaction were while using sugar-derived chiral acrylate. More interestingly, reversal of selectivity was observed when the chiral aldehydes were reacted with a sugar-derived chiral acrylate to obtain adducts in high '*Syn selectivity*' (*de* >95%) by a '*Double Asymmetric Induction*' protocol than when the same chiral aldehydes were used directly in a diastereoselective Baylis-Hillman reaction. It is pertinent to note that by switching the chiral acrylate either enantiomer (with respect to the major isomer) can be accessed. The only one best catalyst known to date for highly enantioselective Baylis-Hillman reaction is quinidine derivative **87** though *N*-methyl prolinol **81** gave us moderate enantioselectivity. Fortunately, both the isomeric proline forms are commercially available and make valuable contributions as chiral bases for enantioselective Baylis-Hillman reaction. Herein the first ever diastereoselective intramolecular Baylis-Hillman reaction was also showcased as an easy access to chiral α-methylene-β-hydroxylactones with >95% *de*. However, there still remains scope to develop more protocols for enantioselective Baylis-Hillman reaction.

## ACKNOWLEDGEMENTS

The authors thank their graduate students namely: Dr. V. Kannan, Mr. L. Krishna Rao, Mr. M. Narsingam, Mr. P. V. Narasimha Reddy, Ms. Rachna Sachwani and Ms. A. Manjuvani whose work was cited in this article.

## REFERENCES

[1] Trost, B. M. *Science* **1983**, *219*, 245.
[2] Trost, B. M. *Science* **1991**, *256*, 1471.
[3] Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn*. **1968**, *41*, 2815.
[4] Baylis, A. B.; Hillman, M. E. D. *German Patent 2155113*, **1972**; *Chem. Abstr*. **1972**, *77*, 34174q.
[5] Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.
[6] Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.
[7] Ciganek, E. The Morita-Baylis-Hillman reaction. *Org. React.* Paquette, L. A. Ed. John Wiley & Sons, New York, **1997**, Vol. *51*, pp. 201.
[8] Langer, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 3049
[9] a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811; b) Aggarwal, V. K.; Fulford, S. Y.; Jones, G. C. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 1706; c) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980.
[10] Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev*. **1993**, *93*, 1307.
[11] Basavaiah, D.; Bhavani, A. K. D.; Pandiaraju, S.; Sarma, P. K. S. *Synlett* **1995**, 243.
[12] Annunziata, R.; Benaglia, M.; Einquini, M.; Cozzi, F.; Raimondi, L. *J. Org. Chem*. **1995**, *60*, 4697.
[13] Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *Tetrahedron* **1997**, *53*, 16423.
[14] Atkinson, R. S.; Fawcett, J.; Russel, D. R.; Williams, P. J. *J. Chem. Soc. Chem. Commun*. **1994**, 2031.
[15] Bailey, M.; Marko, I. E.; Ollis, W. D. *Tetrahedron Lett*. **1991**, *32*, 2687.
[16] Marko, I. E.; Giles, P. R.; Janousek, Z.; Hindley, N. J.; Declereq, J. -P.; Tinant, B.; Feneau-Dupont, J.; Svendsen, J. S. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 239.
[17] Brown, J. M. *Angew. Chem. Int. Ed.* **1987**, *26*, 190.
[18] Ameer, F.; Drewes, S. E.; Freese, S.; Kaye, P.T. *Synth. Commun*. **1988**, *18*, 495.
[19] Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett*., **1986**, *27*, 5007.
[20] Hill, J. S.; Isaacs, N. S. *J. Phys. Org. Chem.* **1990**, *3*, 285.
[21] Bode, M. L.; Kaye, P. T. *Tetrahedron Lett*. **1991**, *32*, 5611.
[22] Fort, Y.; Berthe, M. C.; Caubere, P. *Tetrahedron* **1992**, *48*, 6371.
[23] Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.
[24] Brown, J. M.; Cutting, I.; Evans, P. L.; Maddox, P. J. *Tetrahedron Lett*. **1986**, *27*, 3307.
[25] Gilbert, A.; Heritage, T. W.; Isaacs, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 969.
[26] Drewes, S. E.; Emslie, N. D.; Karodia, N.; Khan, A. A. *Chem. Ber*. **1990**, *123*, 1447.
[27] Khan, A. A.; Emslie, N. D.; Drewes, S. E.; Field, J. S.; Ramesar, N. *Chem. Ber*. **1993**, *126*, 1477.
[28] Drewes, S. E.; Emslie, N. D.; Field, J. S.; Khan, A. A.; Ramesar, N. *Tetrahedron Lett*. **1993**, *34*, 1205.
[29] Drewes, S. E.; Emslie, N. D.; Khan, A. A. *Synth. Commun*. **1993**, *23*, 1215.
[30] a) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc*. **1997**, *119*, 4317; b) *Chemtracts*; Commentary by Venkatesan, H.; Liotta, D. C. **1998**, 29.
[31] Yang, K. -S.; Chen, K. *Org. Lett*. **2000**, *2*, 729.
[32] Radha Krishna, P.; Kannan, V.; Ilangovan, A.; Sharma, G. V. M. *Tetrahedron: Asymmetry* **2001**, *12*, 829.
[33] Radha Krishna, P.; Rachna Sachwani, Kannan, V. *Chem.Comm* **2004**, 2580.
[34] Drewes, S. E.; Manickum, T.; Roos, G. H. P. *Synth. Commun*. **1988**, *18*, 1065.
[35] Drewes, S. E.; Njamela, O. L.; Roos, G. H. P. *Chem. Ber*. **1990**, *123*, 2455.
[36] Kundig, E. P.; Xu, L. H.; Romanens, P.; Bernardinelli, G. *Tetrahedron Lett.* **1993**, *34*, 7049.
[37] Kundig, E. P.; Xu, L. H.; Schnell, B. *Synlett* **1994**, 413.
[38] Bussolari, J. C.; Beers, K.; Lalan, P.; Murry, W. V.; Gauthier, D.; McDonnell, P. *Chem. Lett*. **1998**, 787.

[39] Alcaide, B.; Almendros, P.; Aragoncillo, C. *J. Chem. Soc. Chem. Commun*. **1999**, 1913.
[40] Alcaide, B.; Almendros, P.; Aragoncillo, C. *J. Org. Chem*. **2001**, *66*, 1612.
[41] Aggarwal, V. K.; Catsro, A. M. M.; Mereu, A.; Adams, H. *Tetrahedron Lett*. **2002**, *43*, 1577.
[42] Bauer, T.; Tarasiuk, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1741.
[43] a) Radha Krishna, P.; Kannan, V.; Sharma, G. V. M.; Ramana Rao, M. H. V. *Synlett* **2003**, 888; b) Radha Krishna, P.; Manjuvani, A.; Kannan, V. *Tetrahedron: Asymmetry* **2005**, *16*, 2691.
[44] Roush, W. R.; Adam, M.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc*., **1986**, *108*, 3422.
[45] Radha Krishna, P.; Narsingam, M.; Kannan, V. *Tetrahedron Lett*. **2004**, *45*, 4773.
[46] Radha Krishna, P.; Krishna Rao Lopinti; Kannan, V. *Tetrahedron Lett*. **2004**, *45*, 7847.
[47] a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Am. Chem. Soc.* **1959**, *81*, 112; b) Evans, D. A.; Siska, S. J.; Cee, V. C. *Angew. Chem. Int. Ed*. **2003**, *42*, 1761.
[48] Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241.
[49] Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *J. Chem. Soc. Chem. Commun*. **1998**, 2533.
[50] Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219.
[51] Shi, M.; Jiang, J. -K. *Tetrahedron: Asymmetry* **2002**, *13*, 1941.
[52] Shi, M.; Xu, Y. -M. *Angew. Chem. Int. Ed*. **2002**, *41*, 4507.
[53] Radha Krishna, P.; Kannan, V.; Narasimha Reddy, P. V. *Adv. Synth. Cat.* **2004**, *346*, 603.
[54] Radha Krishna, P.; Kannan, V.; Sharma, G. V. M. *J. Org. Chem.* **2004**, *69*(19), 6467.
[55] Reddy, L. R.; Sarvanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230.
[56] Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489.
[57] Yadama, Y. M. A.; Ikegami, S. *Tetrahedron Lett*. **2000**, *41*, 2165.
[58] Shi, M.; Chen, L. -H. *J. Chem. Soc.Chem. Commun.* **2003**, *11*, 1310.
[59] Kataoka, T.; Iwama, T.; Tsujiyama, S. -I.; Kanematsu, K.; Iwamura, T.; Watanabe, S. -I. *Chem. Lett*. **1999**, 257.
[60] Iwama, T.; Tsujiyama, S. -I.; Kinoshita, H.; Kanematsu, K.; Tsurukami, Y.; Iwamura, T.; Watanabe, S. -I.; Kataoka, T. *Chem. Pharm. Bull*. **1999**, *47*, 956.
[61] Chen, K. -Y.; Lee, W. -D.; Pan, J. -F.; Chen, K. *J. Org. Chem.* **2003**, *68*, 915.
[62] a) Trost, B. M.; Tsui, H. -C.; Toste, F. D. *J. Am. Chem. Soc*. **2000**, *122*, 3534; b) *Chemtracts*, commentary by Ley, S. V.; Rodriguez, F. **2000**, 596.
[63] a) Burgess, K.; Jennings, L. D. *J. Org. Chem*. **1990**, *55*, 1138; b) Wang, M. -X.; Wu, Y. *Org. Biomol. Chem*. **2003**, *1*, 535.
[64] a) Brown, J. M. *Angew. Chem. Int. Ed*. **1987**, *26*, 190; b) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 708.
[65] Drewes, S. E.; Emslie, N. D.; Field, J. S.; Khan, A. A.; Ramesar, N. *Tetrahedron: Asymmetry* **1992**, *3*, 255.
[66] Cho, C. -W.; Kong, J. -R.; Krische, M. J. *Org. Lett.***2004**, *6*, 1337.
[67] McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094.
[68] Pegot, B.; Thanh, G. V.; Gori, D.; Loupy, A. *Tetrahedron Lett.* **2004**, *45*, 6425.

**Received: March 16, 2005** **Revised: May 30, 2005** **Accepted: June 28, 2005**