Pergamon

Tetrahedron, Vol. 52, No. 24, pp. 8001-8062, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00154-8

TETRAHEDRON REPORT NUMBER 402

THE BAYLIS-HILLMAN REACTION: A NOVEL CARBON-CARBON BOND FORMING REACTION

Deevi Basavaiah,* Polisetti Dharma Rao and Rachakonda Suguna Hyma

School of Chemistry, University of Hyderabad
HYDERABAD 500 046, India

Contents

1.	Introduction	8002
	1.1. Definition	8003
	1.2. Activated alkenes—Michael-type self-dimerization	8005
2.	Intramolecular Baylis–Hillman Reaction	8007
3.	Mechanistic Aspects	8008
	3.1. Rate enhancement	8009
	3.1.1. Hydrogen bonding	8009
	3.1.2. Substrate structure	8010
	3.1.3. Pressure, temperature, ultrasound and microwave irradiation	8012
4.	Asymmetric Baylis–Hillman Reaction	8013
	4.1. Chiral activated alkenes	8013
	4.2. Chiral electrophiles	8016
	4.3. Chiral catalysts	8018
	4.4. Chiral solvents	8020
	4.5. Optical resolution of Baylis–Hillman adducts	8020
	4.6. Masked acrylate approach to chiral Baylis–Hillman adducts	8022
5.	Synthetic Applications	8023
	5.1. Synthesis of stereodefined alkenes	8023
	5.1.1. Stereoselective synthesis of [*E*]/[*Z*]-allyl halides and sulphides	8024
	5.1.2. Reactions of allylic acetates, halides and sulphides	8026
	5.1.2.1. Carbon nucleophiles	8026
	5.1.2.2. Hydride as nucleophile	8028
	5.1.2.3. Heteroatom-based nucleophiles	8029

5.1.3. Stereoselective rearrangements 8032
5.1.3.1. DABCO catalyzed rearrangement of allyl esters 8032
5.1.3.2. The Arbuzov allyl phosphite–allyl phosphonate rearrangement 8032
5.1.3.3. Claisen ortho-ester rearrangement 8033
5.1.3.4. Mitsunobu reaction with allylic transposition 8034
5.1.3.5. Palladium(0)-catalyzed stereoselective carbonylation 8034
5.2. Cycloaddition reactions 8035
5.2.1. Diels–Alder reactions 8035
5.2.2. Other cycloaddition reactions 8036
5.2.3. Double cyclization of α-methylene-β-hydroxyalkanones 8037
5.2.4. Cycloaddition reactions of α-methylene-β-keto sulphones and esters 8038
5.3. Diastereoselective reactions 8040
5.3.1. Diastereoselective hydrogenation 8040
5.3.2. Diastereoselective epoxidation and aziridination 8042
5.3.3. Diastereoselective Michael-type addition reactions 8043
5.3.4. Diastereoselective allylation of carbonyl compounds 8045
5.4. Other applications 8047
5.4.1. (±)-Sarkomycin ester 8047
5.4.2. Azetidinones and other lactams 8047
5.4.3. Diazacyclophanes 8049
5.4.4. Indolizines 8050
5.4.5. Miscellaneous 8050
6. Variants 8051
7. Conclusion 8053
8. Abbreviations 8053

1. INTRODUCTION

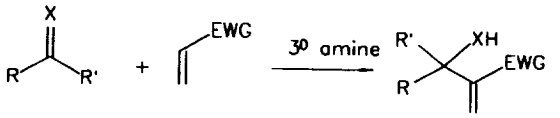
Carbon-carbon bond formation is one of the most fundamental reactions in organic chemistry. The development of efficient and selective methods for the construction of carbon-carbon bonds has been and continues to be a challenging and exciting endeavour in organic synthesis.

The Baylis-Hillman reaction is an emerging carbon-carbon bond forming reaction. It involves the coupling of activated alkenes with carbon electrophiles under the influence of a tertiary amine. It has all the basic properties that an efficient synthetic method should have *i.e.* it is selective (chemo, regio, diastereo and enantio),[1] economical in atom count,[2] requires mild conditions and provides synthetically useful multi-functional molecules. This fascinating reaction was reviewed in 1988 by Drewes and Roos,[3] when the reaction was still in its infancy. Since then the reaction has been drawing increased attention, as evidenced by the good number of publications describing various aspects of the reaction

including its application in the syntheses of several natural products. In this present endeavour all efforts have been made to be comprehensive and cover the literature for the period 1988-1994.

1.1. *Definition:*

The Baylis-Hillman reaction, originating from a German patent,[4] may be broadly defined as *"a reaction that results in the formation of a carbon-carbon bond between the α-position of activated alkenes and carbon electrophiles containing electron-deficient sp^2 carbon atom under the influence of a suitable catalyst, particularly a tertiary amine, producing multifunctional molecules"* (eq. 1).

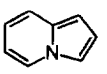


(1)

X = O, NR^2 **EWG = electron withdrawing group**

The Baylis-Hillman reaction involves three components an activated alkene, electrophile and tertiary amine. The research over the last decade has resulted in considerable expansion of the reaction in terms of all the three essential components. Though Baylis and Hillman have originally used DABCO (diazabicyclo[2.2.2]octane) (**1**) pyrrocoline (**2**) and quinuclidine (**3**) as catalysts, DABCO (**1**) has become the catalyst of choice. Several activa-

1



2

3

ted alkenes such as acrylic esters,[5,6] acrylonitrile,[7,8] vinyl ketones,[8-10] phenyl vinyl sulphone,[11,12] phenyl vinylsulphonate,[13] vinyl phosphonate,[14] allenic acid ester,[15,16] and acrolein[17] have been employed in the Baylis-Hillman reaction (Fig.1). A variety of aldehydes such as aliphatic, aromatic, hetero aromatic, α,β-unsaturated aldehydes, paraformaldehyde (or formalin) and functionalized aldehydes have been employed as as electrophiles in the Baylis-Hillman reaction.[18-27] Recently, dialdehydes were also employed by the groups of Foucaud[28] and Caubere[29] in selective mono- and di- Baylis-Hillman coupling with methyl acrylate.

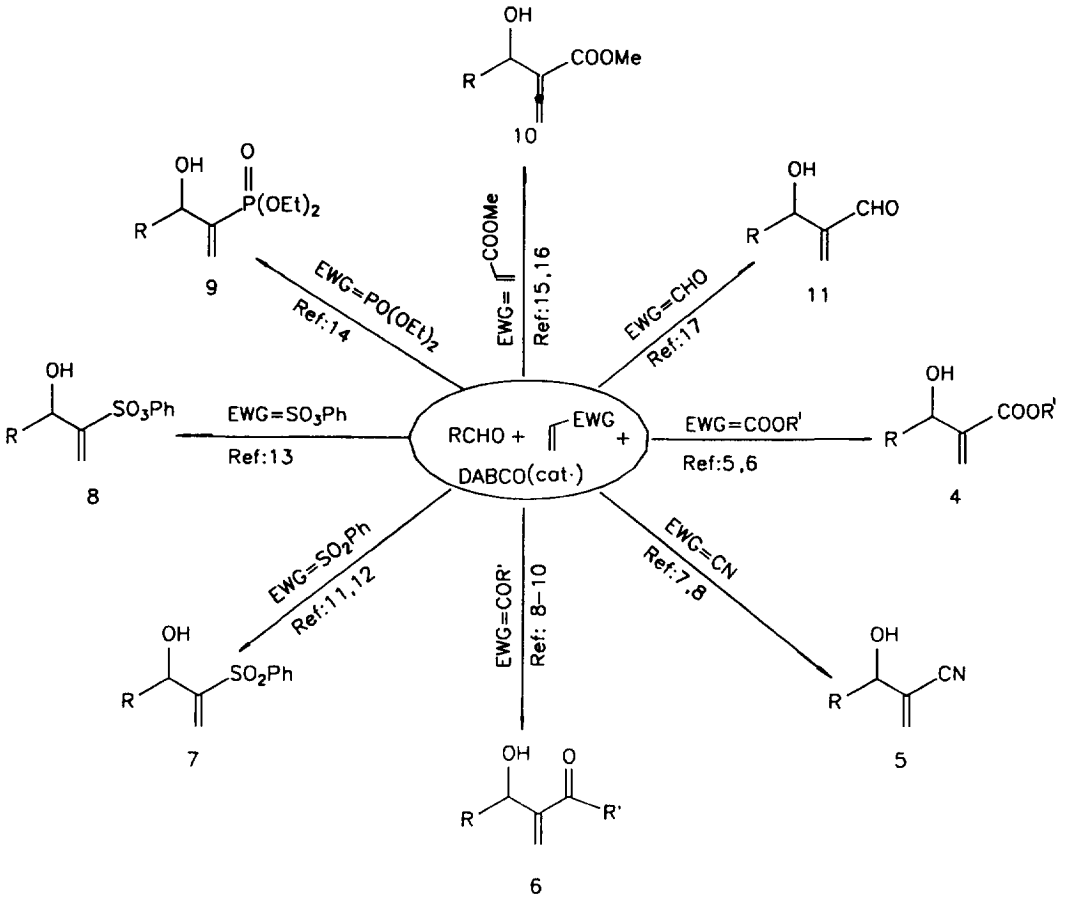
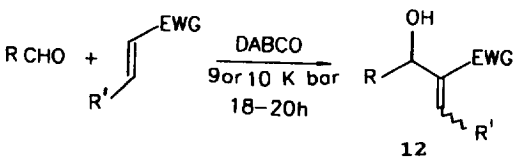


FIGURE 1

The crotonic derivatives (methyl crotonate and crotononitrile) and vinyl sulfoxides that do not undergo Baylis-Hillman reaction at atmospheric pressure, were brought into the scope of the reaction at elevated pressures (eq. 2).[30,31]



(2)

EWG = COOMe, CN ; R = R' = Me

EWG = SOPh ; R = Ph, CH_3 ; R' = H

In addition to aldehydes, α-keto esters,[32-34] fluorinated ketones[35] and aldimine derivatives[36-38] have been employed as electrophiles in the Baylis-Hillman reaction. Ketones were found to be inert substrates for the Baylis-Hillman reaction under the usual conditions. However, Hill and Isaacs have succeeded in bringing the ketones into the scope of the reaction at elevated pressures (Figure 2).[17,30] In addition to DABCO several other tertiary amines *e.g.* 3-hydroxyquinuclidine,[39] triethylamine,[17] quinidine,[3,40] *etc.* have been used as catalysts in special cases.

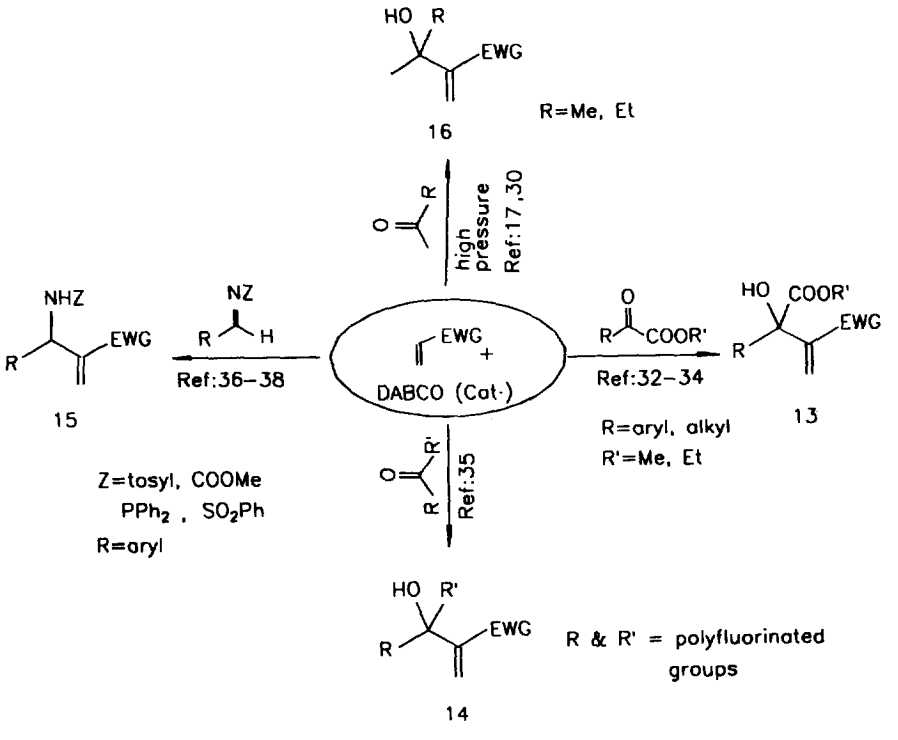


FIGURE 2

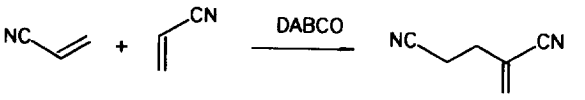
1.2. *Activated alkenes - Michael-type self-dimerization*:

In the absence of an added electrophile, the activated alkenes such as vinyl ketones, acrylonitrile, acrylic esters *etc.* themselves act as electrophiles in these Baylis-Hillman processes. It was in fact observed in our laboratory that vinyl ketones and acrylonitrile undergo Michael type dimerization under the catalytic influence of DABCO to provide corresponding dimers **17** and **18** (eqs. 3 & 4).[41a,b]

(3)

17

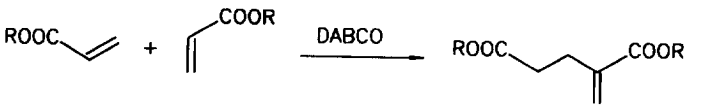
R = aryl, alkyl



(4)

18

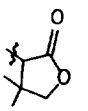
Subsequently, Drewes *et al.*[42] have reported the dimerization of a variety of functionalized alkyl acrylates and aryl acrylates under the influence of DABCO to obtain homo-esters of α-methyleneglutaric acid (**19**) (eq. 5). Methyl acrylate failed to dimerize under these conditions. The dimerization of ethyl and tert-butyl acrylates was also achieved under the influence of tris(dimethylamino)phosphine (TDAP) by Amri *et al.*[43]



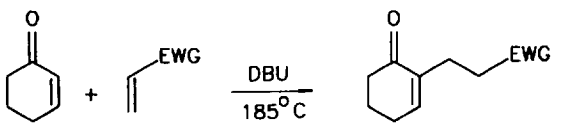
(5)

19

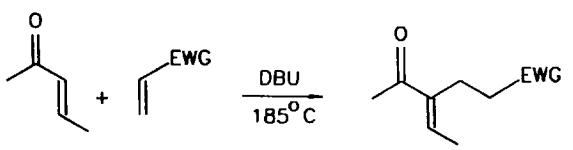
R = phenyl, 4-tolyl, 4-nitrophenyl, CHMeCOOEt, CHPhCOOMe,



Recently Hwu *et al.*[44] reported a closely related process to the above Michael-type reaction *i.e.* the introduction of a substituent at the α-position of α,β-unsaturated ketones using Michael acceptors such as ethyl acrylate, acrylonitrile and phenyl vinyl sulphone, under the catalytic influence of tertiary amine 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) using 1,3-dimethyl-2-imidazolidinone (DMI) as solvent at 185°C (eqs. 6 & 7).



(6)

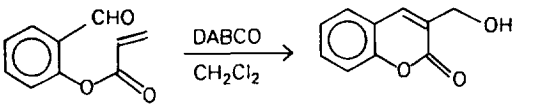


(7)

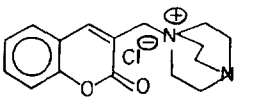
EWG=COOEt, CN, SO_2Ph

2. INTRAMOLECULAR BAYLIS-HILLMAN REACTION

In cases where both electrophile and activated alkene moieties are present in the same molecule and are oriented suitably, a possibility for an intramolecular Baylis-Hillman reaction arises. Recently, Drewes *et al.*[45] carried out intramolecular Baylis-Hillman reaction of 2-acrylyloxybenzaldehyde in presence of DABCO in dichloromethane and obtained 3-hydroymethylcoumarin in only 10% yield (eq. 8). But the major product in this reaction was a quaternary ammonium salt **20**.

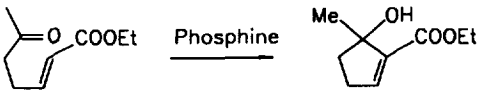


(8)



20

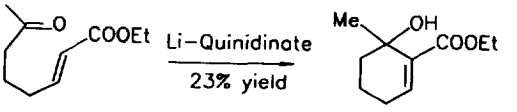
Previously Roth *et al.*[46] reported that an intramolecular process in the cases of both (2*E*)-6-oxohept-2-enoate and (2*E*)-7-oxooct-2-enoate is catalyzed more efficiently by phosphines rather than tertiary amines. In the case of 6-oxoheptenoate (eq. 9), DABCO and quinidine were found to be ineffective. Lithium quinidinate catalyzes the intramolecular reaction in



(9)

Phosphine = PBu_3, $PPhMe_2$, P(i-Bu)MePh, (-)-Camp

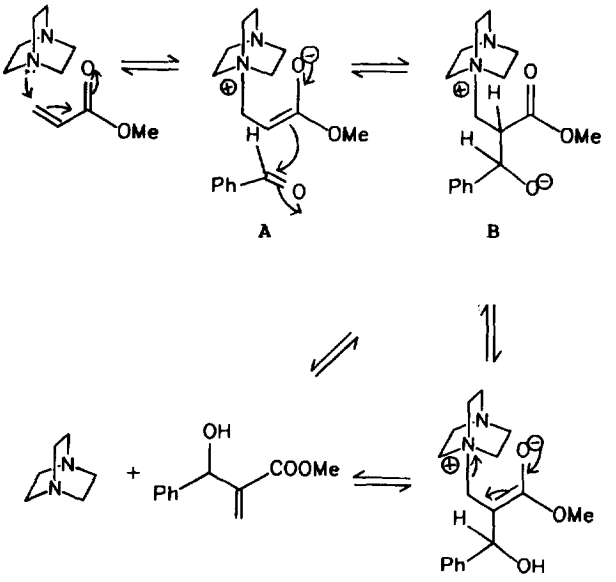
the case of 7-oxooctenoate to produce the cyclic molecule (eq. 10). Although some of the catalysts employed are optically active no appreciable asymmetric induction was observed.



(10)

3. MECHANISTIC ASPECTS

Efforts have been expended to deduce the actual path of the reaction. The efforts of the groups of Drewes,[3,39,45] Isaacs,[17,47] Kaye[48] and Caubere[49] are noteworthy. Invariably, all the studies conclude that the Baylis-Hillman reaction is the outcome of an addition-elimination sequence involving tertiary amine, activated alkene and electrophile. In the light of the experimental observations and proposals, a plausible mechanism of Baylis-Hillman coupling of methyl acrylate with benzaldehyde under the influence of DABCO, as a model case, may be written as shown in the Scheme 1. The reaction is initiated by the Michael type nucleophilic addition of tertiary amine (*e.g.* DABCO) to the activated alkene (methyl acrylate) resulting in a transient zwitter ionic enolate "**A**", which subsequently makes a nucleophilic attack on the electrophile (*e.g.* aldehyde) to produce the zwitter ionic adduct "**B**". The dipolar adduct **B** gives the final product after proton migration followed by the elimination of the tertiary amine. The retrogradation studies of Fort *et al.*[49] point out that the overall reaction is equilibrated(!).[31a,46] Hoffmann and Rabe have even proposed two zwitter ionic conformations "B_1 & B_2" for the adduct "**B**" before the elimination of DABCO[6] (Figure 3).



SCHEME 1

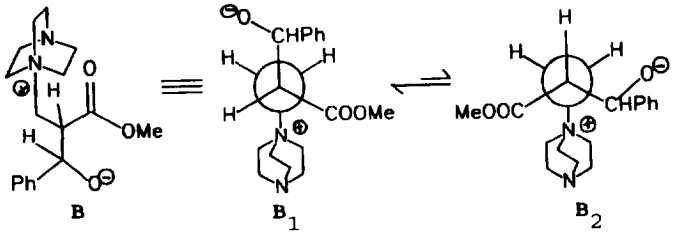


FIGURE 3

Although no intermediate has so for been isolated, probability for the intermediacy of the species '**A**' and '**B**' is very high. In fact this consideration is consistent with the results of kinetic studies of Bode and Kaye.[48] Furthermore their kinetic studies show that the formation of adduct "B" is the rate-determining step and the reaction follows third-order kinetics overall (eq. 11) or pseudo second-order if the concentration of tertiary amine is considered constant (eq. 12). Recent studies of Drewes *et al.*[45] also support the formation of adduct "**B**". The above mechanism should be considered speculative until more evidence is accumulated in support of it.

$$\text{Rate} = K_{obs}[\text{alkene}][\text{electrophile}][\text{amine}] \qquad (11)$$

$$\text{Rate} = K_a[\text{alkene}][\text{electrophile}] \qquad (12)$$
$$\text{where } K_a = K_{obs}[3^0 \text{ amine}]$$

3.1. *Rate enhancement:*

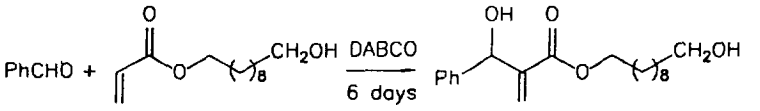
Generally, the Baylis-Hillman coupling of activated alkenes with electrophiles catalyzed by DABCO [α-hydroxyalkylation of acrylate esters can take several weeks to evolve fully] is a very slow process when carried out at room temperature and atmospheric pressure under neat conditions.[3] As it is desirable for any synthetic process, from both a practical and economic point of view, to be accomplished rapidly and with high yields, efforts have been made to circumvent this undesirable nature of the Baylis-Hillman reaction. The first and obvious option of using higher proportions of catalyst has been tried on many an occasion. In addition, the effect of factors such as hydrogen bonding, substrate structure, pressure, temperature, ultrasound and microwave irradiation on the rate of the reaction were studied.

3.1.1. *Hydrogen bonding:*

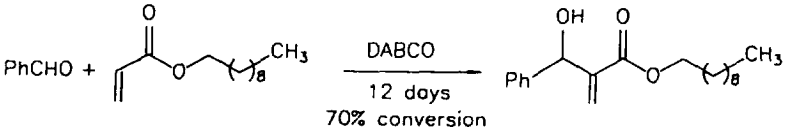
Drewes *et al.*[3,39,50] reported that the rate of DABCO catalyzed α-hydroxyalkylation of methyl acrylate is enhanced by the use of methanol

as solvent or using 3-hydroxyquinuclidine as a catalyst and attributed this enhancement to the involvement of hydrogen bonding. Similar rate enhancement was also observed by Bailey *et al.*[51] in case of α-hydroxyalkylation of methyl vinyl ketone using 3-hydroxyquinuclidine. Recently Bode and Kaye have established the involvement of hydrogen bonding in rate acceleration affected by 3-hydroxyquinuclidine *via* a small deuterium effect.[48]

On the otherhand, the introduction of a hydroxyl group at the terminal position of alkyl acrylates on the rate of α-hydroxyalkylation catalyzed by DABCO was studied in our laboratory.[52] It was shown that the terminal hydroxyalkyl acrylates react faster than the corresponding alkyl acrylates for example, the DABCO-catalyzed reaction of 10-hydroxydecyl acrylate with benzaldehyde is complete in 6 days (78% yield) (eq. 13), whereas the reaction of decyl acrylate with same aldehyde under identical conditions remained incomplete even after 12 days (eq. 14).



(13)



(14)

It is clear from these results and those of Drewes *et al.*[39] that hydrogen bonding does play some role in the rate-enhancement of the Baylis-Hillman reaction. Since nucleophilic attack of the dipolar enolate on the aldehyde is presumably the rate determining step, the hydrogen bonding can in two ways be responsible for the rate-enhancement: (i) by stabilizing the tertiary amine acrylate adduct (which would increase the adduct's concentration), (ii) and or by activating the aldehyde (Figure 4).

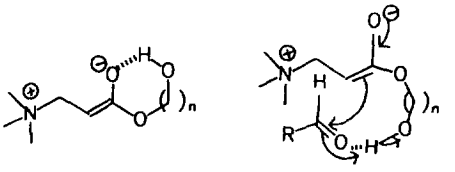
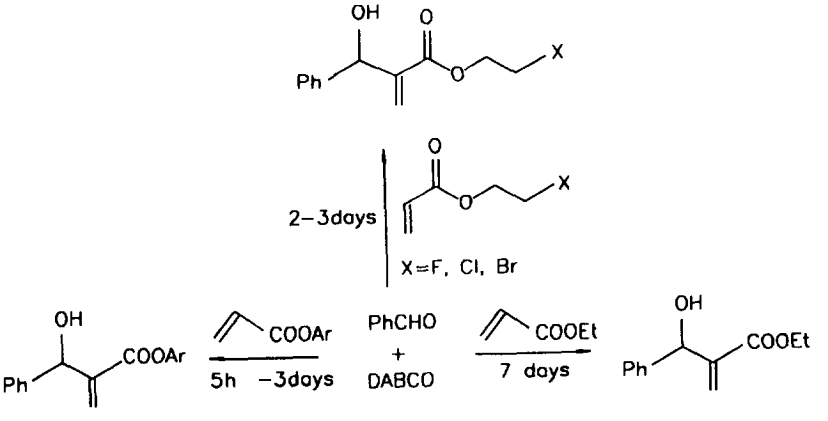


Figure 4

3.1.2. *Substrate structure:*

A close look at the mechanism makes it clear that the groups attached

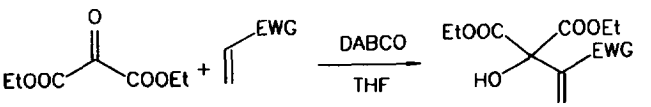
to the chromophore of the activated vinylic system are bound to exert some effect (acceleration/retardation) on the rate of the reaction depending on their electron withdrawing or donating nature and steric features. Recently Fort *et al.*[49] studied the electronic effect on the rate of the reaction of acrylate esters. It is clear from their studies that functionalized alkyl acrylates react faster than simple alkyl acrylates and aryl acrylates react more readily than alkyl acrylates (Scheme 2). Bode and Kaye[48] reported that methyl acrylate reacts faster than ethyl or isopropyl acrylate and attributed this fact to electron-releasing inductive effect. In our laboratory a similar observation was made in the case of α-hydroxyalkylation of alkyl vinyl ketones.[9,10]



Ar = aryl

SCHEME 2

The degree of electrophilicity of the electrophilic component is important. As one would expect, aldehydes undergo the Baylis-Hillman reaction more readily than aldimines, ketones or keto esters. During our search for fast reacting substrates for the Baylis-Hillman reaction we found that diethyl ketomalonate reacts much faster with activated alkenes.[33] Thus it couples with alkyl acrylates, acrylonitrile and methyl vinyl ketone under the influence of DABCO to provide the corresponding adducts in a few hours (0.5 h to 36 h) even when the reaction is performed in THF (eq 15).

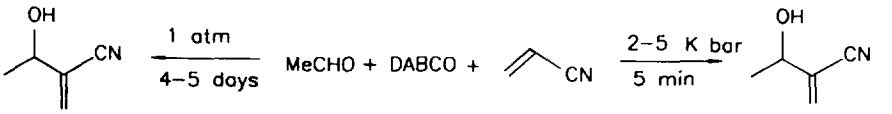


(15)

EWG = COOMe, COOEt, COOBu^t, CN, COMe

3.1.3. *Pressure, temperature, ultrasound and microwave irradiation:*

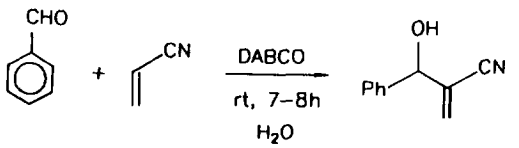
A significant advancement in rate-enhancement of the Baylis-Hillman reaction was achieved by Hill and Isaacs,[17,30,53] who studied the effect of pressure on this reaction and showed that the Baylis-Hillman coupling processes are highly sensitive to pressure and pressures upto 2-5 K bar are highly effective. Thus, the DABCO-catalyzed α-hydroxyethylation of acrylonitrile, which takes 4-5 days at atmospheric pressure to provide the desired product in good yield, goes to completion in 5 minutes when the reactants are kept at 2-5 K bar pressure (Scheme 3). A more important outcome of these studies is that ketones and crotonic derivatives were brought into the scope of the reaction at 10 k bar pressure.[30] In some cases they found that these pressure accelerated processes were better controlled by the less reactive triethylamine rather than DABCO.[17]



SCHEME 3

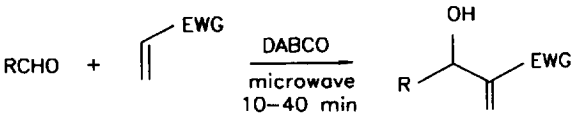
Recently, Roos and Rampersadh[54] have studied the effect of temperature and ultrasound on the rate of DABCO-catalyzed α-hydroxyalkylation of methyl acrylate. They have claimed that although the rate-acceleration due to sonication is not all that remarkable it is helpful where solid reagents are involved. They also claim that it is possible to achieve rate increase by gentle warming (43 ^{O}C) of the reaction mixture rather than refluxing, which may result in the formation of side products and/or polymeric materials.

Auge *et al.* reported that Baylis-Hillman coupling reaction of acrylonitrile with benzaldehyde catalyzed by DABCO was greatly accelerated with water as a solvent. They also noticed that addition of LiI/NaI further enhanced the rate in aqueous media (eq. 16)[55].



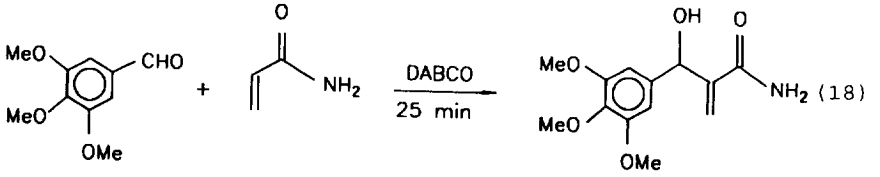
(16)

Bhat and coworkers[56] described that microwave irradiation provides considerable rate enhancement in the Baylis-Hillman reaction between aldehydes and activated olefins (eq. 17). Under normal circumstances acrylamides are inert substrates for the Baylis-Hillman reaction.[40,57] It is worth mentioning here that acrylamide reacts with 3,4,5-trimethoxybenzaldehyde to provide the corresponding adduct in 40% yield under microwave irradiation (eq. 18). Hill and Isaacs described the reaction of acrylamide with acetone at elevated pressure to give the required adduct in only 5% yield.[17]



(17)

R = aryl, alkyl ; EWG = COOMe, CN



(18)

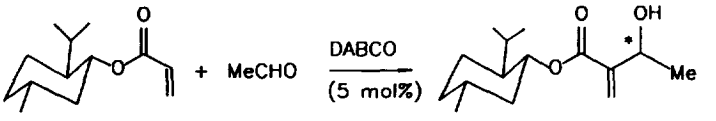
4. ASYMMETRIC BAYLIS-HILLMAN REACTION

The Baylis-Hillman α-hydroxyalkylation or α-aminoalkylation of activated alkenes under the influence of tertiary amines using electrophiles such as aldehydes, prochiral ketones, α-keto esters or aldimines results in the creation of a new chiral center and there exists a possibility for asymmetric induction. Consequently, efforts have been expended to develop an asymmetric version of the Baylis-Hillman reaction. As in the case of any reaction that affords chiral products, the chiral information for an "asymmetric Baylis-Hillman reaction" can lie with any one of the four components essential for the reaction. This had provided new avenues for research and already efforts have been made to study the levels of asymmetric induction by employing any one of the four components, *i.e.* activated alkene, electrophile, tertiary amine or solvent (or additive), in optically active form.

4.1. *Chiral activated alkenes:*

So far only chiral acrylates have been employed as chiral activated alkenes. Probably, the easy accessibility of chiral acrylates and the

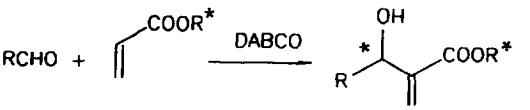
easy removal of the chiral auxiliary from the products made this approach attractive. The use of other activated alkenes *i.e.* vinyl ketones, sulphones and phosphonates in optically active form has been hampered by their inaccessibility. Quite a good number of chiral acrylates were prepared and were employed to good effect in asymmetric Baylis-Hillman reactions, mainly α-hydroxyalkylation with aldehydes. The first such attempt was made by Brown *et al.*[58] when they have carried out the reaction between (l)-menthyl acrylate (**21a**) and acetaldehyde using DABCO as catalyst. The diastereomeric excess was only 16% (eq. 19).



(19)

21a **16% de**

Subsequently, in our laboratory, assymmetric induction in the Baylis-Hillman reaction of a variety of chiral acrylates **21a-21h** [including (l)-menthyl acrylate (**21a**)] with aldehydes was studied (eq. 20).[40,59-61] This resulted in considerable success and a better understanding of the stereo and electronic factors involved in the reaction. The maximum diastereomeric excess, 70%, achieved in these studies was in the case of the reaction of acrylate **21h**, derived from Oppolzer's chiral auxiliary, with propionaldehyde.[62] Other chiral acrylates **21a-21g** afforded the chiral Baylis-Hillman adducts with diastereomeric excess ranging between 7-42%. However, it was possible in many cases to obtain the major stereomer in diastereomerically pure form *via* preferential crystallization. The chiral acrylates **21h** and **21i** were employed in the diastereoselective Baylis-Hillman reaction with various aldehydes under the influence of DABCO by Jensen and Roos.[63]

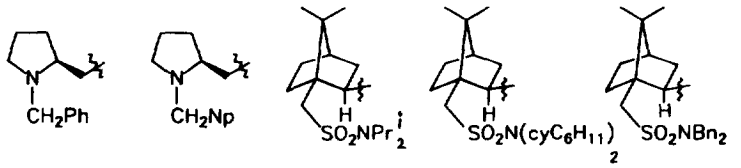


(20)

21a-i

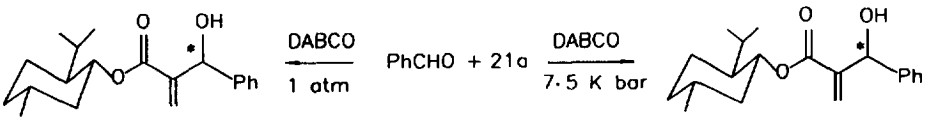
R^* =

a **b** **c** **d**



e **f** **g** **h** **i**

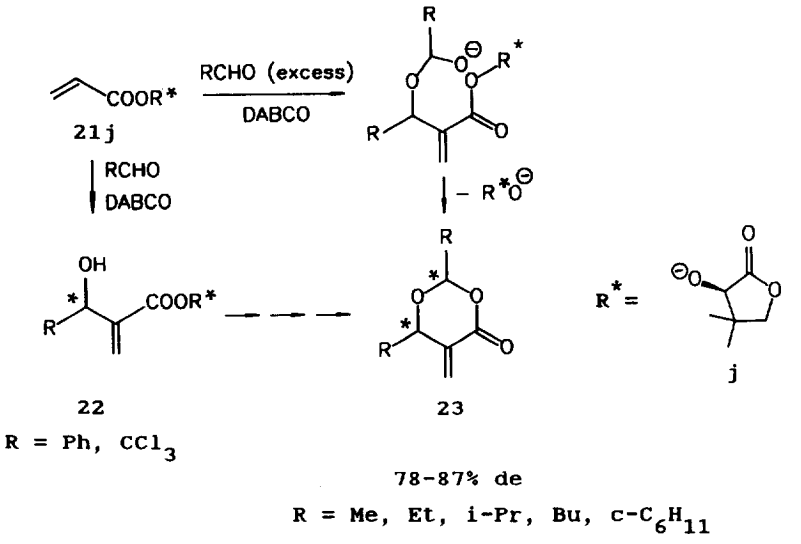
Later, Gilbert *et al.*[64] obtained similar results in the reaction of (l)-menthyl acrylate with a variety of aldehydes at atmospheric pressure. A remarkable improvement in the levels of asymmetric induction was achieved by these workers by performing the reactions at elevated pressures. Thus (l)-menthyl acrylate at 7.5 K bar pressure reacts with benzaldehyde under the influence of DABCO to afford the corresponding Baylis-Hillman adduct as a single diastereomer (100% de), whereas the same reaction at atmospheric pressure provides the adduct with only 22% diastereomeric excess (Scheme 4). At elevated pressures (8.5 K bar), p-tolualdehyde and p-ethylbenzaldehyde react with (l)-menthyl acrylate (**21a**) to provide the the corresponding Baylis-Hillman adducts with 87% and 94% diastereomeric excess respectively. (-)-Bornyl, (-)-nopyl and 8-phenylmenthyl acrylates were also employed by these workers with reasonable success.



22% de **100% de**

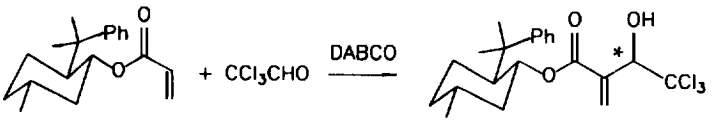
SCHEME 4

The acrylate **21j**,[65-67] derived from (R)-(+)-pantolactone, was treated with a variety of aldehydes under the influence of DABCO to study the diastereoselectivity in the reaction. Except for benzaldehyde and chloral, which gave conventional adducts (**22**) with 2 and 48% diastereomeric purities respectively, all other aldehydes gave the corresponding 2,6-dialkyl-5-methylene-1,3-dioxan-4-ones (**23**) with high diastereomeric excess (78-87%) but with low enantiomeric purities (10-39%). These products are believed to have arisen as delineated in the Scheme 5.



SCHEME 5

Recently, 8-phenylmenthyl acrylate (**21k**) was employed in Baylis-Hillman reactions, with a variety of aldehydes catalyzed by DABCO at atmospheric pressure, to study the levels of asymmetric induction by Drewes and coworkers.[68] The reaction between chloral and the acrylate **21k** gave the best result (70% de) (eq. 21).

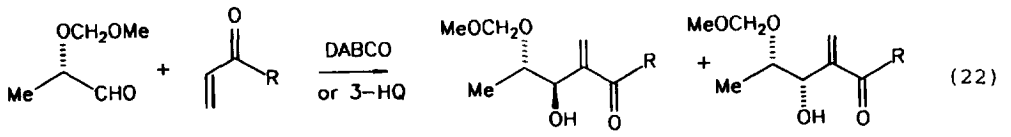


(21)

21k **70% de**

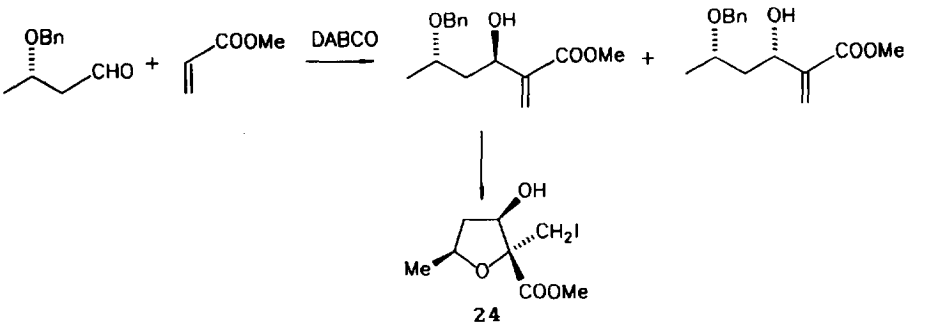
4.2. *Chiral electrophiles:*

Of the various electrophiles only aldehydes have been employed in optically active form thus far. The diastereoselectivity in the Baylis-Hillman reaction of several racemic and non-racemic aldehydes with methyl acrylate and methyl vinyl ketone under the influence of tertiary amine was studied. For example, (S)-*O*-(methoxymethyl)lactaldehyde reacts with both methyl acrylate and methyl vinyl ketone under the influence of either DABCO or 3-hydroxyquinuclidine (3HQ) to afford mixtures of diastereomers with the *anti*-isomer predominating (eq. 22).[69] Both of these tertiary amines provided more or less the same diastereoselection. Similarly (S)-3-benzyloxybutyraldehyde reacts under the influence of DABCO with methyl



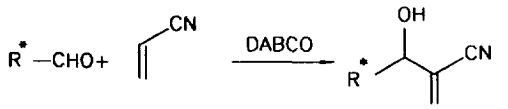
R = OMe, Me **≥70 : ≤30**

acrylate to furnish a 75.5:24.5 mixture of *anti*- and *syn*-diastereomers from which the major *anti*-isomer was separated and converted into an interesting tetrahydrofuran derivative **24** with three stereogenic centers (Scheme 6).[70]

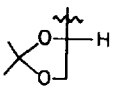


SCHEME 6

(*R*)-Myrtenal and isopropylidine (*R*)-glyceraldehyde[64] were employed in the Baylis-Hillman α-hydroxyalkylation of acrylonitrile at 5.5 and 4 K bar pressure. The diastereoselection in these reactions is very low (eq. 23).

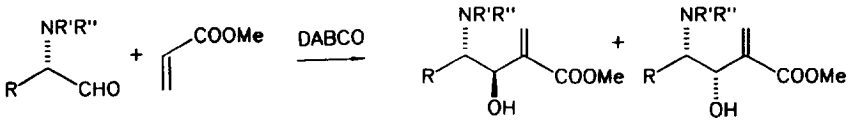


R* =  **, pressure = 5.5 K bar, de = 16%**

R* =  **, pressure = 4 K bar, de = 23%**

Several non-racemic α-dialkylamino and α-(N-acylamino)aldehydes derived from chiral α-amino acids were reacted with methyl acrylate under

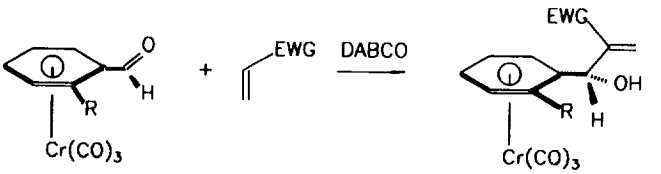
the influence of DABCO to provide the corresponding Baylis-Hillman adducts as mixtures of *anti*- and *syn*-diastereomers. The diastereomeric ratio ranges from 55:45 to 88:12 (eq. 24).[71,72]



(24)

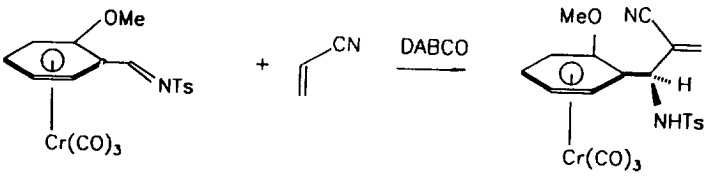
major **minor**

Recently, Kundig *et al.*[73,74] employed racemic and non-racemic ortho-substituted benzaldehyde tricarbonylchrominum complexes (eq.25) and aryl-imine tricarbonylchromium complexes (eq. 26) as electrophiles in the DABCO catalyzed Baylis-Hillman reaction with methyl acrylate and acrylonitrile. These reactions proceeded with exceptionally high diastereoselection. In the case of non-racemic aldehydes, decomplexation afforded metal-free Baylis-Hillman adducts in >98% ee.



(25)

R = OMe, Cl; EWG = COOMe, CN **>95% de**



(26)

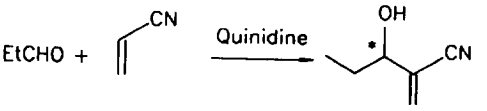
>95% de

4.3. *Chiral catalysts:*

Currently, development of catalytic asymmetric reactions has become a challenging area for organic chemists. The chiral catalysts used to affect asymmetric reactions are often called as "chemzymes" owing to the similarities they exhibit in their functioning to enzymes.[75,76] Development of a chemzyme for catalytic asymmetric Baylis-Hillman reactions, on

the lines of Noyori's Binap-Ru complex[77] or Corey's oxazaborolidine,[78] is a welcome step.

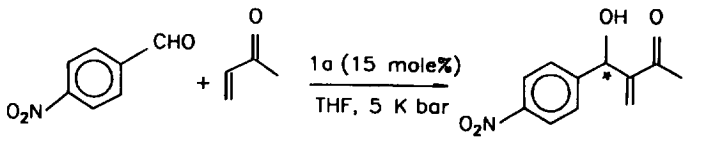
The most commonly used catalysts in the Baylis-Hillman reaction are tertiary amines. The proposed mechanism of this reaction predicts the participation of tertiary amine throughout the course of the reaction including the step in which the chiral center is created. Consequently, the structure of the tertiary amine should have a bearing on the fate of the transition state(s). In other words if the amine is chiral, it should be able to bring about chiral discrimination. A variety of optically active tertiary amines such as quinine, quinidine, cinchonidine and retronecine have been employed[3,40,64] as catalysts in the Baylis-Hillman reaction. All of these studies have met with only limited success. Our efforts to use (6*S*)-1-aza-4-oxabicyclo[4.3.0]nonane as the chiral catalyst also resulted in low enantioselectivities.[40] Quinidine catalyzed coupling of acrylonitrile with propionaldehyde provided the best result thus producing the desired 3-hydroxy-2-methylenepentanenitrile in 20% ee (eq. 27).[40]



(27)

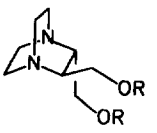
20% ee

1,4-Diazabicyclo[2.2.2]octane (DABCO, **1**) is the most used tertiary amine as catalyst in the Baylis-Hillman reaction. Recently Hirama has utilized chiral C_2-symmetric 2,3-disubstituted 1,4-diazabicyclo[2.2.2]-

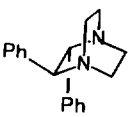


(28)

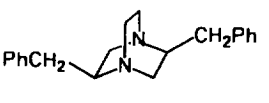
47% ee



1a



1b



1c

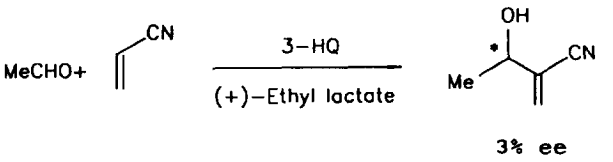
R = Bn, aryl, TBDMS, TBPS

octanes (**1a**) as catalysts for asymmetric Baylis-Hillman reactions. They obtained the best result (47% ee) for the reaction between *para*-nitro benzaldehyde and methyl vinyl ketone using 15 mole% of the catalyst (**1a**, R=benzyl) (eq. 28).[79,80] It is worth mentioning here that the other chiral derivatives of diazabicyclo(2.2.2)octane, **1b** & **1c**, have been synthesized.[81,82] However, their application for asymmetric Baylis-Hillman reaction has not yet been reported.

In fact most of the amines employed are commercially available alkaloids and are not the products of molecular modelling studies. Whilst the aforementioned studies are modest, the prospects for the rational catalyst design are encouraging given the increased understanding of the stereo and electronic requirements of asymmetric synthesis.[83]

4.4. *Chiral solvents:*

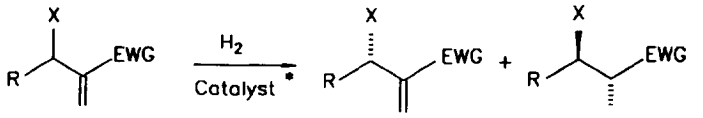
Except in cases where methyl vinyl ketone or diethyl ketomalonate are used, no solvent is required for the Baylis-Hillman processes. However, the reaction of acrylonitrile with acetaldehyde under the influence of (±)-3-hydroxyquinuclidine was carried out in (+)-ethyl lactate to obtain the adduct with only 3% ee (eq. 29).[64]



(29)

4.5. *Optical resolution of Baylis-Hillman adducts:*

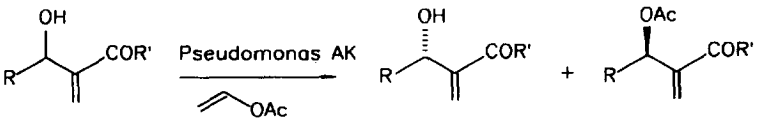
At present, the Baylis-Hillman adducts with high enantiomeric purity are accessible only through resolution. Brown *et al.*[84-87] kinetically resolved α-methylene-β-hydroxyalkanoates, sulphones and α-methylene-β-aminoalkanoates *via* homogeneous hydrogenation using chiral phosphine-rhodium catalysts. The recovered alcohols were obtained in >90% enantiomeric excess (eq. 30). The (S)-Binap-ruthenium diacetate complex was also employed as catalyst for the kinetic resolution of methyl (±)-3-hydroxy-2-methylenebutanoate (>99% ee at 76% conversion) *via* hydrogenation by the group of Noyori.[88] Bailey *et al.* made an attempt to resolve Baylis-Hillman adducts *via* asymmetric Sharpless epoxidation.[89]



(30)

X = OH, $NHCOOBu^t$; EWG = COOMe, SO_2Ph ; R = alkyl, aryl
Catalyst* = $[Rh(R,R)\text{-Dipamp}]^+$, $[Ru(S)\text{-Binap}]^+$

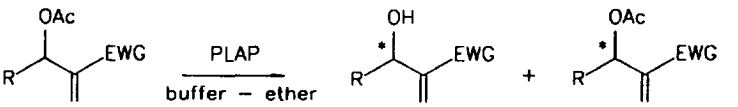
The biocatalytic approach was also shown to be effective for the resolution of Baylis-Hillman adducts. Thus, *pseudomonas* AK lipase catalyzed transesterification of racemic α-methylene-β-hydroxyalkanoates and alkanones results in the production of optically active alcohols with >95% enantiomeric excess (eq. 31).[90]



(31)

R = alkyl, R' = alkyl, *O*-alkyl

On the otherhand pig liver acetone powder (PLAP) catalyzed hydrolysis of acetates of racemic α-methylene-β-hydroxyalkanoates and alkanenitriles furnished the optically active alcohols in 46-88% enantiomeric excess (eq. 32).[91]

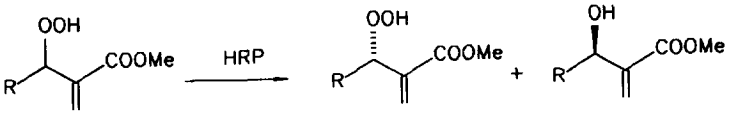


(32)

racemic **46-88% ee**

R = aryl; EWG = COOMe, CN

Recently, Adam *et al.* resolved hydroperoxides of racemic 3-hydroxy-2-methylenebutanoate and pentanoate *via* enantioselective reduction catalyzed by horseradish peroxidase (HRP) (eq. 33).[92]

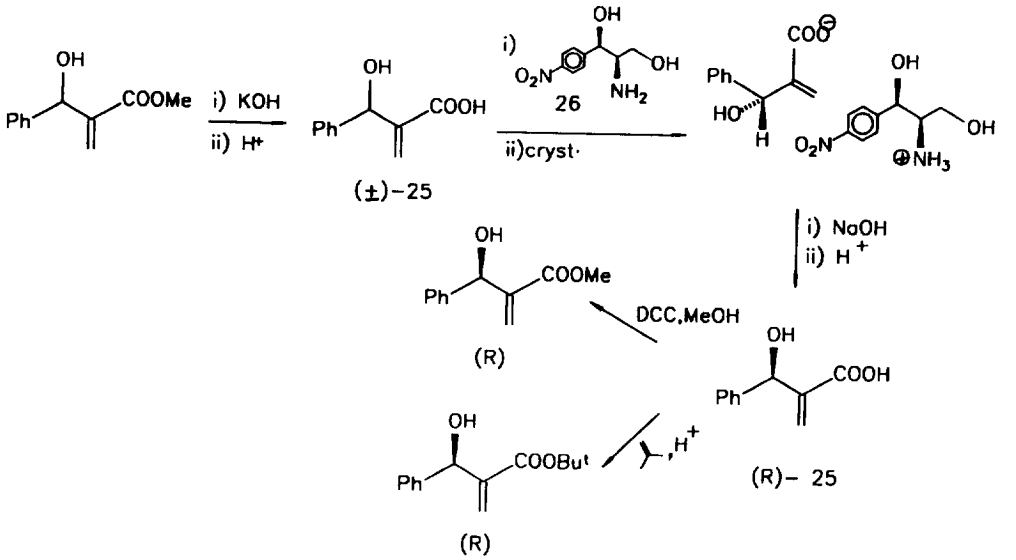


(33)

racemic **(S)** **(R)**

R = Me, Et; >99% ee

Recently, the racemic acid **25** was resolved *via* diastereomer crystallization using the amine-diol **26** and the absolute configuration was

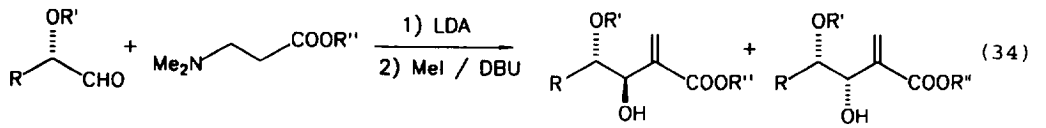


SCHEME 7

assigned.[93] The optically pure acid (R)-**25** was converted into the corresponding methyl and t-butyl esters (Scheme 7).

4.6. *Masked acrylate approach to chiral Baylis-Hillman adducts:*

Some important methods for chiral Baylis-Hillman reactions using the masked acrylate approach are described[94-97] in the following equations (eqs. 34-36).

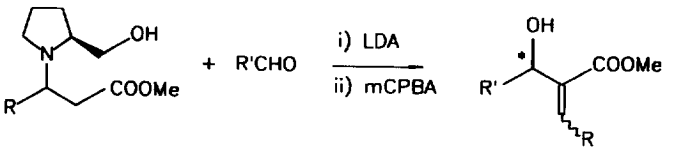


(34)

major **minor**

R = Me, n-hexyl; R' = CH_2OBn, CH_2OMe; R'' = Me, t-Bu

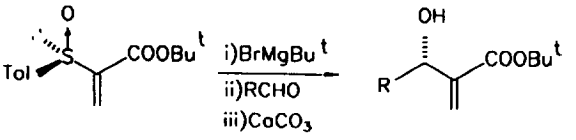
Banfi *et al.* (ref. 94)



(35)

R' = aryl ; R = H, Me

Drewes *et al.* (ref. 95,96)



(36)

R = ethyl, n-butyl

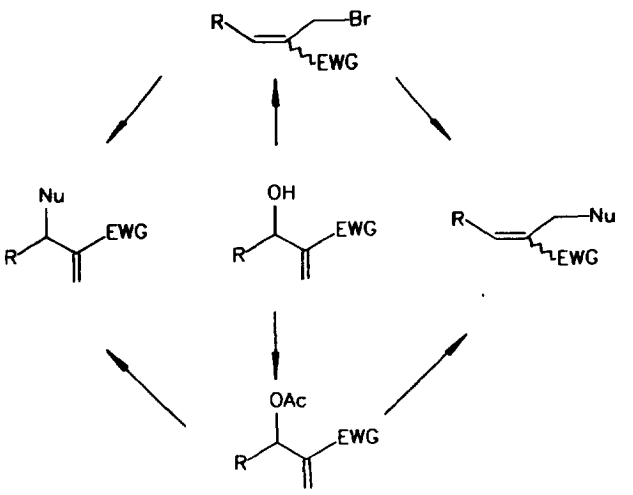
Papageorgiou and Benezra (ref.97)

5. SYNTHETIC APPLICATIONS

The Baylis-Hillman reaction has been increasingly drawing the attention of synthetic organic chemists, as it provides versatile molecules with a minimum of three functional groups (*i.e.* hydroxyl, olefin and ester, ketone, nitrile, sulphone or phosphonate, *etc.*) and a chiral center. The Baylis-Hillman adducts may therefore be expected to undergo a variety of organic transformations involving regio- and stereochemical control. Several successful examples have already been reported and studies are being directed towards utilizing these fascinating molecules in organic synthesis. Moreover, the multifunctionality of these adducts makes them attractive substrates to examine the diastereo- and enantioselectivites of various methodologies. Some of the initial synthetic applications of the Baylis-Hillman reaction were elegantly discussed by Drewes in his 1988 review. The following discussion will mainly focus on the developments which have appeared after the publication of this review. However, some of the aspects discussed by Drewes are also very briefly mentioned in order to have continuity in the text and for easy understanding. Synthetic applications have been broadly divided into four sections: (i) Synthesis of stereodefined alkenes, (ii) cycloaddition reactions, (iii) diastereoselective reactions and (iv) miscellaneous.

5.1 *Synthesis of stereodefined alkenes:*

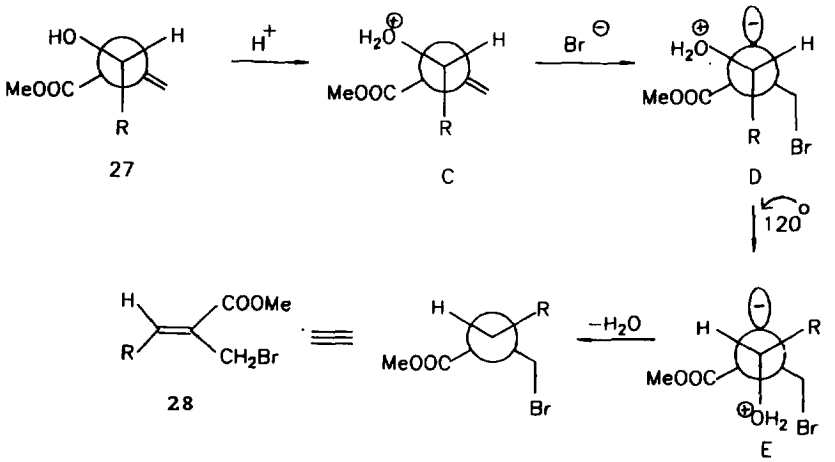
The trisubstituted olefinic moiety[98-100] has been a regular feature of many naturally occurring biologically active compounds such as, terpenoids, pheromones, macrolide antibiotics, *etc.* The Baylis-Hillman adducts α-methylene-β-hydroxyalkanoates, in particular, were shown to be versatile precursors of trisubstituted alkenes. Two approaches have been developed for the conversion of the Baylis-Hillman adducts into stereodefined trisubstituted alkenes: (i) nucleophilic substitution (S_N2) of the allyl bromides obtained from the Baylis-Hillman adducts; (ii) nucleophilic substitution with concomitant allylic rearrangement (S_N2') of the acetates of the Baylis-Hillman adducts. The general strategy for S_N2 and S_N2' reactions is described in the Scheme 8.



SCHEME 8

5.1.1. *Stereoselective synthesis of [E]/[Z]-allyl halides and sulphides:*

The conversion of methyl 3-hydroxy-2-methylenealkanoates (**27**) and 2-benzenesulphonyl-3-hydroxyalkenes (**7**) into the corresponding Z-allyl halides, using a variety of reagents such as NBS-Me_2S, HBr-H_2SO_4, NCS-DMS, HCA-PPh_3, HI-H_3PO_4, has been well documented.[5,11,18,19,101] Recently Hoffmann and Buchholz have explained the origin of stereoselective formation of allyl bromides **28** in the HBr-H_2SO_4 treatment of methyl 3-hydroxy-2-

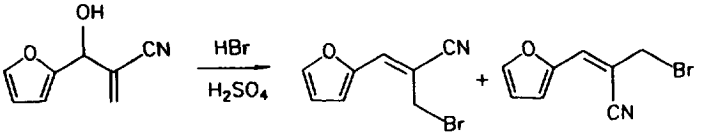


SCHEME 9

methylenealkanoates (**27**) on the basis of molecular modelling studies.[102] According to these workers, the zwitterion **D**, arising from protonation of

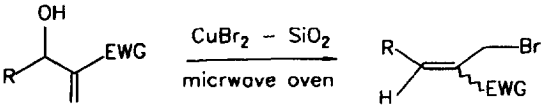
(C) followed by bromide ion attack in Michael fashion, undergoes a 120° counter clock-wise rotation around the central carbon-carbon bond (E) rather than a 60° clock wise rotation as the COOMe group is sterically more demanding than the CH_2Br group, to achieve the required orientation for departure of the leaving group (H_2O), thus resulting in the formation of a [Z]-double bond (Scheme 9).

These arguements are supported by the fact that replacement of COOMe by CN causes loss of [Z]-selectivity,[102] *e.g.* 3-(fur-2-yl)-3-hydroxy-2-methylenepropanenitrile gives a 3:1 mixture of [Z] & [*E*]-allyl bromides (eq. 37).



(37)

Recently Gruiec and Foucaud[103] have reported the stereoselective synthesis of allyl bromides **28** and **29** *via* microwave irradiation of a mixture of silica gel supported copper(II) bromide and the corresponding Baylis-Hillman adducts **27** and **5** in chlorobenzene (eq. 38). While the allyl bromides **28** (EWG=COOMe) were obtained as pure [Z]-isomers, the bromides **29** (EWG=CN) were produced as mixtures of (Z & *E*)-isomers with the [*E*]-isomer strongly predominating.



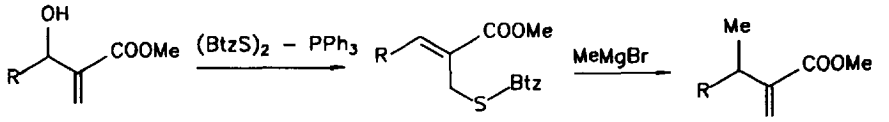
(38)

27 & 5 **28 & 29**

R = aryl

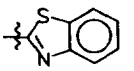
EWG = COOMe (28), CN (29)

A similar reaction of Baylis-Hillman adducts **27** with benzothiazole



27 **30** **31**

Btz =



R = Me, i-Pr, n-octyl

SCHEME 10

disulphide-triphenylphosphine afforded the corresponding allyl sulphides (**30**) with [Z]-stereochemistry in almost quantitative yields. These sulphides were subsequently converted into useful acrylate derivatives (**31**) by treatment with Grignard reagents (Scheme 10).[104]

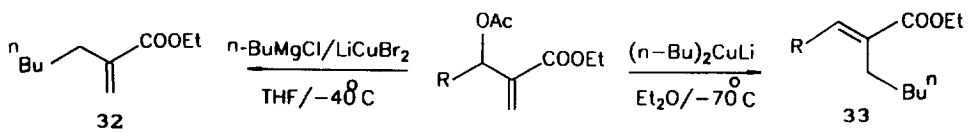
5.1.2. *Reactions of allylic acetates, halides and sulphides:*

The allyl acetates, halides or sulphides derived from the Baylis-Hillman adducts undergo substitution reactions with a variety of nucleophiles. These processes have been shown to proceed with high regio- and stereoselectivity. The various nucleophiles employed so far include carbon nucleophiles, hydride and heteroatom-based nucleophiles such as amines, thiolate ions, phenolate ion, bromide ion, triethyl phosphite *etc.* These processes result in the formation of compounds with a trisubstituted olefinic moiety or a terminal olefin. In either case, the products are attractive and this has been one of the major applications of Baylis-Hillman adducts. Out of these processes, those reactions that result in the stereoselective formation of a trisubstituted olefinic moiety may be considered as attractive alternatives to the well known Wittig-type reaction.

5.1.2.1. *Carbon nucleophiles:*

The reactions of allyl acetates, halides and sulphides derived from the Baylis-Hillman adducts with carbon nucleophiles have been well studied. In fact, the first reported use of the Baylis-Hillman reaction, that appeared ten years after its discovery, emanated from the laboratory of Drewes and dealt with the utilization of this protocol in the stereoselective synthesis of [2*E*]-integerrinecic acid a natural product with trisubstituted olefinic moiety.[5] Subsequently Drewes *et al.*[101,105-109] have carried out stereo- and regioselective addition of carbon nucleophiles derived from ethyl acetoacetate and malonate derivatives to various allyl halides and allyl acetates.

Amri and coworkers have prepared 2-methylenealkanoate (**32**) *via* the treatment of ethyl 2-acetoxymethylprop-2-enoate with Grignard reagents in presence of copper (I) salts.[110] They have extended the same strategy to the synthesis of [2*E*]-alkenoates (**33**) by treating 2-methylene-3-acetoxy-

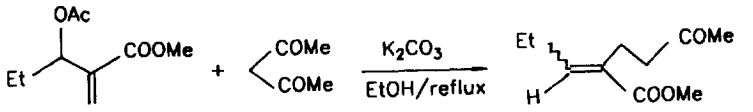


32 **33**

R = H **R = Me, Ph**

SCHEME 11

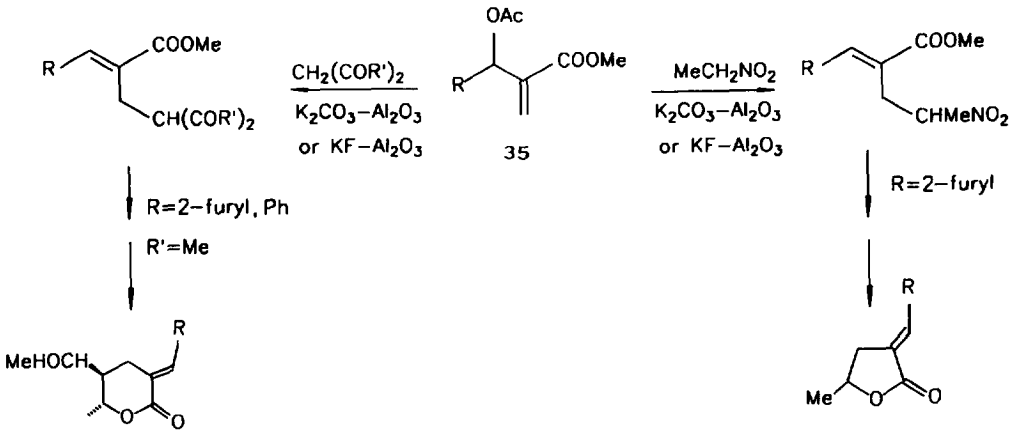
alkanoates with di-n-butyllithium cuprate (Scheme 11).[111] Use of 1,3-diketones as nucleophiles in the presence of K_2CO_3 provided 1,5-keto esters **34** (eq. 39).[112]



(39)

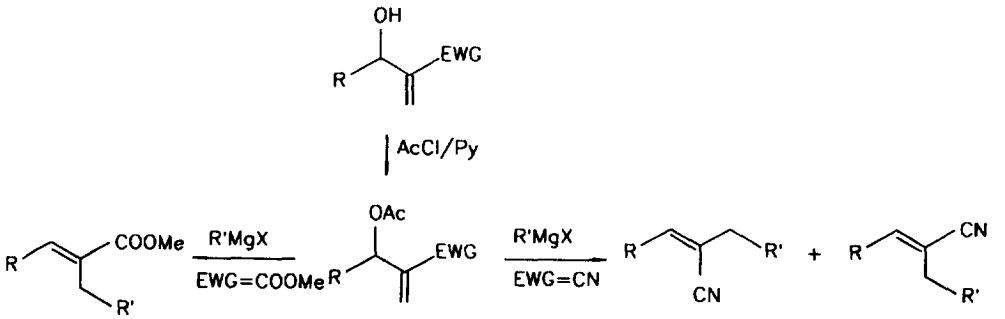
34

Bauchat *et al.*[113] have carried out reactions of acetates **35** with carbanions generated from 1,3-diketone, methyl cyanoacetate or a nitroalkane by treatment with potassium carbonate or potassium fluoride on alumina to provide trisubstituted olefins with [*E*]-selectivity. These products were subsequently transformed into useful γ-lactones and δ-lactones (Scheme 12).



SCHEME 12

Recently, we have used Grignard reagents as nucleophiles and observed a remarkable reversal of stereoselectivity between esters and nitriles.



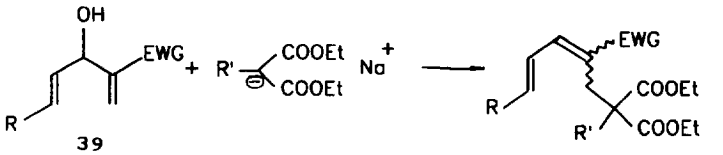
37 **35,36** **major** **38** **minor**

R, R' = alkyl, aryl

SCHEME 13

Thus treatment of 3-acetoxy-2-methylenealkanoates (**35**) with Grignard reagents provided [2*E*]-alk-2-enoates (**37**), while the similar reaction of 3-acetoxy-2-methylenealkanenitriles (**36**) produced [2Z]-alk-2-enenitriles (**38**) predominantly (Scheme 13).[114]

Very recently Heerden and coworkers[115] reported a convenient synthesis of multifunctional stereodefined dienes using Baylis-Hillman adducts (**39**), derived from α,β-unsaturated aldehydes (eq.40).

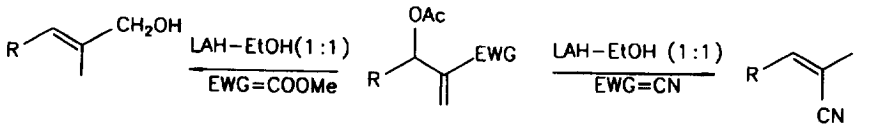


(40)

R = Me, Ph ; R' = Me, allyl ; **EWG = COOMe [E]** **EWG = CN [Z]**

5.1.2.2. *Hydride as nucleophile:*

Hoffmann and Rabe have successfully converted the α-methylene-β-acetoxyalkanoates and 2-bromomethyl-2-alkenoates into [2*E*]-2-methylalkenoates and 2-methylenealkanoates respectively by treatment with $LiEt_3BH$.[18,19] Recently we have successfully used LAH:EtOH reagent as a source of hydride nucleophile.[116] Thus, the treatment of methyl α-methylene-β-acetoxyalkanoates **35** with LAH:EtOH (1:1) gave exclusively [2*E*]-2-methylalk-2- en-1-ols **40** while similar reaction of α-methylene-β-acetoxyalkanenitriles (**36**) with LAH:EtOH provided [2Z]-2-methylalk-2-enenitriles (**41**) (Scheme 14).

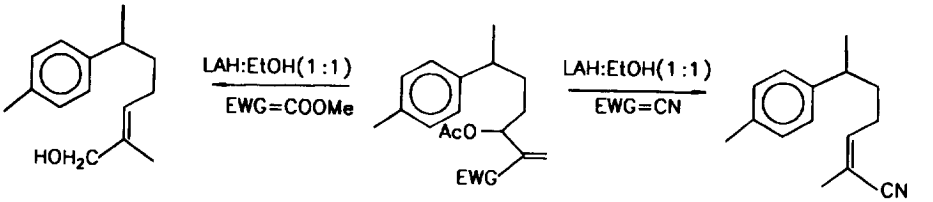


40 **35,36** **41**

R = alkyl, aryl

SCHEME 14

The efficacy of this methodology was amply demonstrated by the synthesis of [*E*]-nuciferol **42** and a precursor **43** of [Z]-nuciferol (Scheme 15).[116]

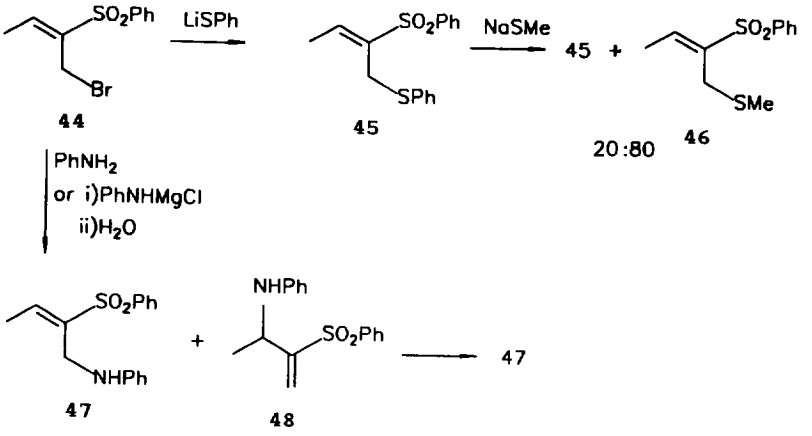


42 **43**

SCHEME 15

5.1.2.3. *Heteroatom-based nucleophiles*:

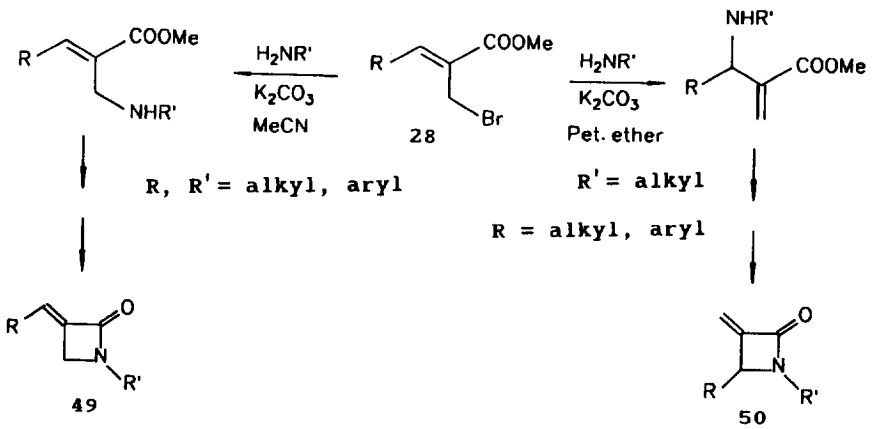
Normant and coworkers[117] carried out a series of nucleophilic substitution reactions on [*E*]-allyl bromide **44** (R=Me) using thiolate ions. Thus the reaction between bromide **44** and lithium phenylthiolate yielded the [*E*]-



SCHEME 16

sulphide **45** exclusively. But this sulphide **45** provided a 20:80 mixture of **45** and [*E*]-methyl sulphide **46** when treated with sodium methylthiolate. They have also discussed the possible mechanism for the observation. Similar reaction of **44** with aniline in excess or its chloromagnesium amide gave a mixture of S_N2 and S_N2' products **47** and **48** which slowly equilibrate to give S_N2 product **47** in 78% yield (Scheme 16).

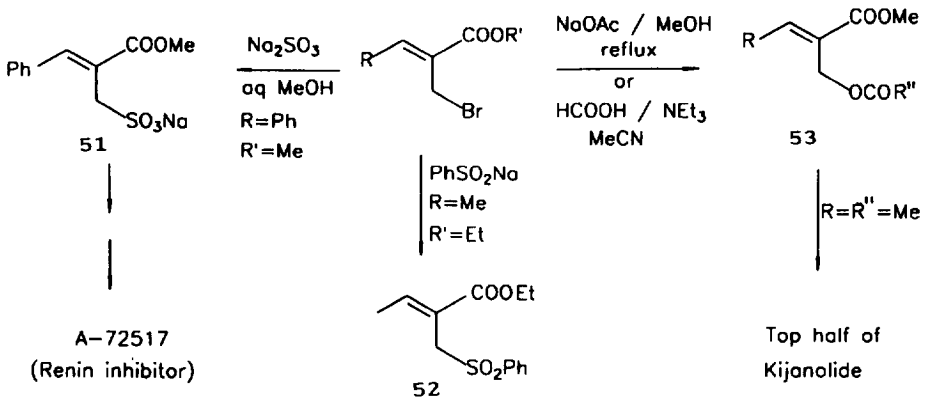
Recently, Hoffmann and Buchholz have carried out nucleophilic addition of aliphatic and aromatic primary amines to allyl bromides **28**.[102] The product distribution (S_N2 or S_N2' process) of these reactions was found to be solvent dependent. In some cases both processes were found to be opera-



SCHEME 17

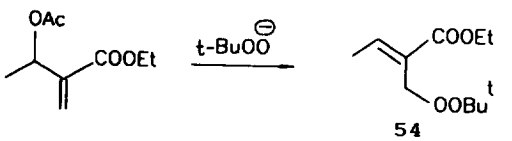
tive. However, in acetonitrile the S_N2 products were formed with high regioselectivity. In contrast, in petroleum ether, the S_N2' products were produced. Thus obtained β-amino acid esters were saponified and lactamized to yield novel α-alkylidene and α-methylidene-β-lactams (**49** and **50**) in good yields (Scheme 17).[102]

Sodium sulphite, phenylsulphinate and carboxylic acid salts were used as nucleophiles to produce the corresponding trisubstituted olefins **51**, **52** and **53**. The molecules **51** and **53** are important synthons for orally active Renin inhibitor A-72517, and kijanolide respectively (Scheme 18).[118-121]



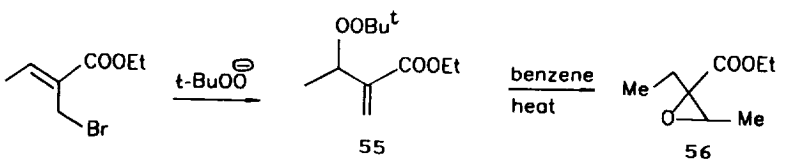
SCHEME 18

The reaction of t-butylperoxylate anion with ethyl 2-methylene-3-acetoxybutanoate (eq. 41) and ethyl 2-bromomethylbut-2-enoate (Scheme 19) were studied by Mailard and coworkers.[122] They found that both provide the



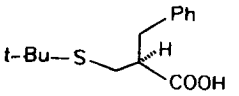
(41)

γ-attack products **54** and **55** with low yields. However, the allyl t-butyl peroxide **55** was obtained in 45% yield when the reaction was carried out in presence of polyethyleneoxide 400.[122] Subsequently the molecule **55** was converted into the corresponding glycidic ester **56** by heating in benzene.[123,124]



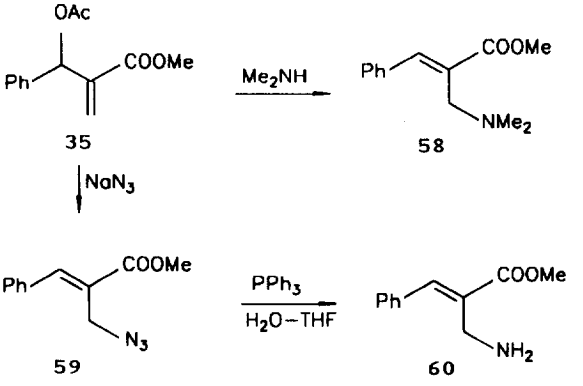
SCHEME 19

Treatment of ethyl [Z]-2-benzylidene-3-bromopropionate with t-butylthiol provided ethyl [2Z]-2-benzylidene-3-(t-butylthio)propionate which was hydrolyzed and hydrogenated in presence of chiral catalyst to produce (*S*)-2-benzyl-3-(t-butylthio)propionic acid (**57**).[125] This acid is useful intermediate for inhibitors of renin and retrovirus protease.



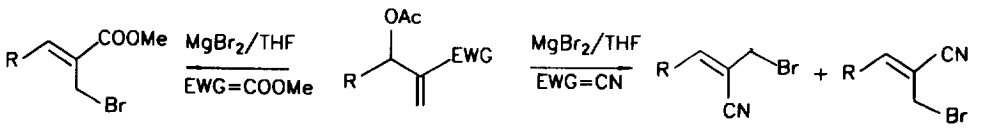
57

The acetate **35** (R=Ph) was stereoselectively converted into corresponding [*E*]-allyl amino compounds. Thus the treatment of acetate **35** with either primary or secondary amines produced [*E*]-amine (**58**) predominantly while the treatment of **35** with sodium azide followed by reduction of the resulting azide **59** with $PPh_3/THF/H_2O$ gave exclusively the primary [*E*]-allyl amine **60** (Scheme 20).[126]



SCHEME 20

Recently, the acetates **35** and **36** were found to undergo a nucleophilic substitution reaction when treated with magnesium bromide to produce corresponding allyl bromides, [Z]-**28** and [*E*]-**29** with high stereoselectivity.[127] This reaction could prove to be an attractive alternative for the synthesis of [Z]-allyl bromides **28** (Scheme 21).



28 **35,36** **major** **minor**

R = aryl, alkyl [*E*]-**29** [Z]-**29**

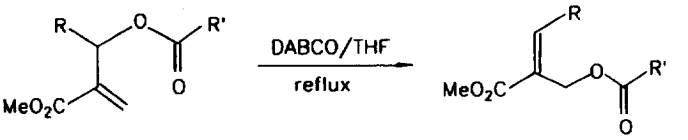
SCHEME 21

5.1.3. *Stereoselective rearrangements:*

The Baylis-Hillman adducts, being reactive substituted allylic alcohols undergo various reactions involving stereoselective rearrangement to produce stereodefined trisubstituted alkenes.

5.1.3.1. *DABCO catalyzed rearrangement of allyl esters:*

During the mechanistic studies of the Baylis-Hillman reaction, Manson and Emslie observed DABCO catalyzed stereoselective allylic transposition of 2-methylene-3-alkylcarbonyloxyalkanoates to provide the 2-alkylcarbonyl oxymethylalk-2-enoates (**61**) with high [*E*]-selectivity (eq. 42).[128]



+ [Z]-isomer (42)

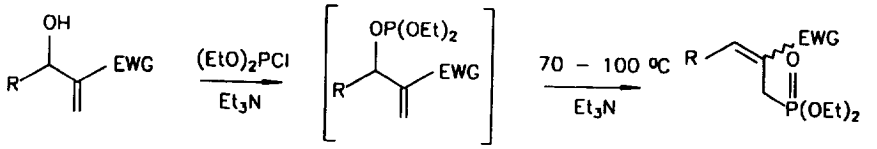
major

61

R = aryl ; R' = Me, Et, CH=CH$_2$, CH$_2$CO$_2$Et

5.1.3.2. *The Arbuzov allyl phosphite-allyl phosphonate rearrangement:*

The Baylis-Hillman adducts **27** and **5** afforded the corresponding phosphites on treatment with diethyl phosphorochloridite in the presence of triethylamine. These phosphites **62** and **63** underwent the Arbuzov rearrangement on heating to produce stereoselectively [Z]-allyl phosphonates **64** and [*E*]-allyl phosphonates **65** respectively (Scheme 22).[129] The



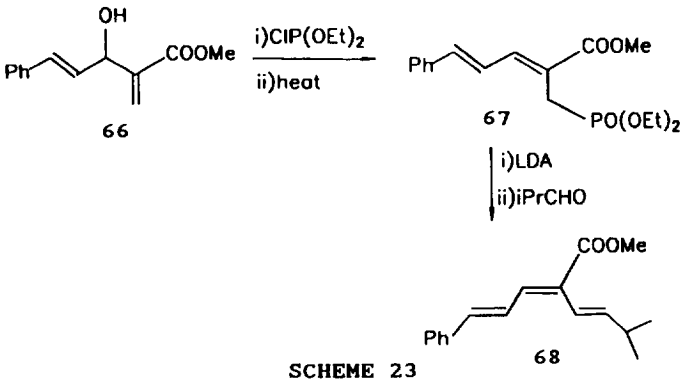
27,5 **62,63** **64 EWG=COOMe [Z]-major**

65 EWG=CN [*E*]-major

R = alkyl, alkenyl, aryl

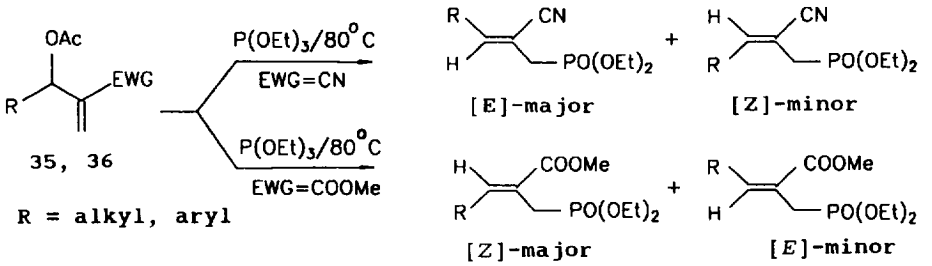
SCHEME 22

allyl phosphonates **64** and **65** are synthetically attractive precursors of substituted 1,3-butadienes. In fact, the allyl phosphonate **67** derived from the Baylis-Hillman adducts **66** was efficiently utilized in the synthesis of stereochemically pure substituted trienes and tetraenes (Scheme 23).[26]



SCHEME 23

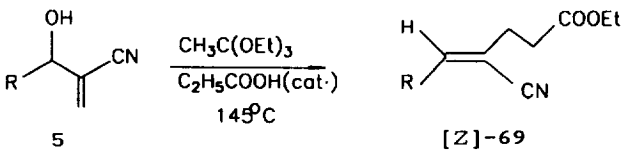
Recently we observed that the reaction of triethyl phosphite with 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles produces [2Z]-2-diethylphosphorylmethylalk-2-enoates and [2*E*]-2-diethyl phosphorylmethylalk-2-enenitriles respectively in high stereoselectivity (Scheme 24).[130]



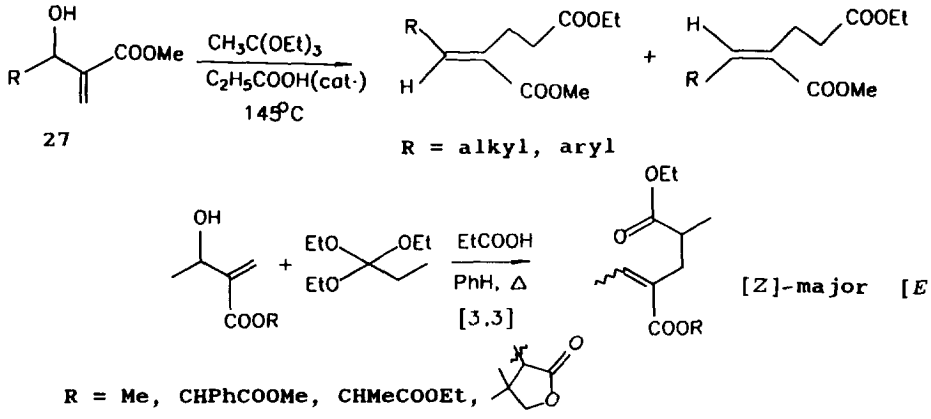
SCHEME 24

5.1.3.3. *Claisen ortho-ester rearrangement:*

Recently we have developed a stereoselective synthesis of ethyl [4Z]-4-cyanoalk-4-enoates **69** *via* the Johnson-Claisen rearrangement of 3-hydroxy-2-methylenealkanenitriles **5** (eq 43).[131] However, Claisen ortho-ester rearrangement of methyl 3-hydroxy-2-methylenealkanoates **27** produced methyl alkenoates as mixture of [*E*]- and [Z]- isomers (eq. 44).[132] Similar observation was also made by Drewes and coworkers in the Claisen ortho-ester rearrangement of alkyl 3-hydroxy-2-methylenepropionates with triethyl orthopropionate (eq. 45).[133]

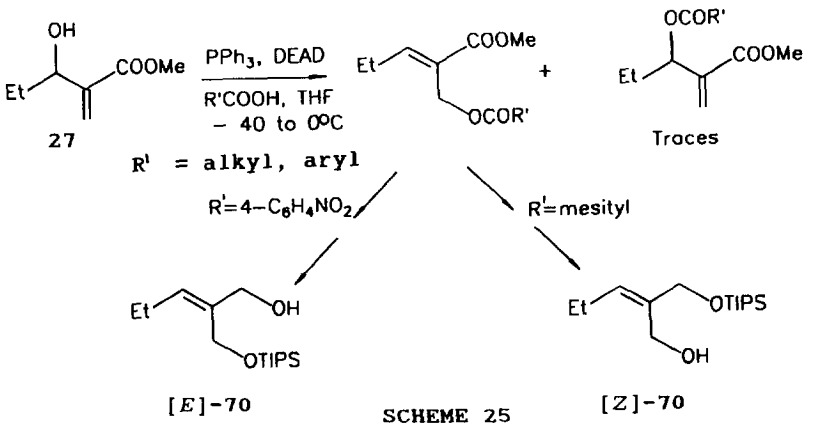


R = alkyl, aryl



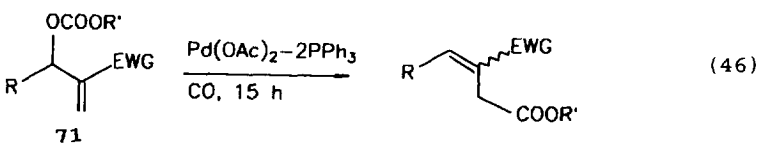
5.1.3.4. *Mitsunobu reaction with allylic transposition:*

Recently, Charette and Cote[118] have observed that the Baylis-Hillman adducts **27** (R=Et), under Mitsunobu reaction conditions gave unusual products. These products could be selectively transformed into either [*E*]- or [Z]-mono protected 2-alkylidene-1,3-propanediols **70** (Scheme 25).



5.1.3.5. *Palladium(0)-catalyzed stereoselective carbonylation:*

Yamamoto and coworkers[13,134] have studied the palladium(0)-catalyzed stereoselective carbonylation of the carbonates **71** derived from corresponding Baylis-Hillman adducts **27**, **5** and **8**. While the carbonates **71** (EWG=



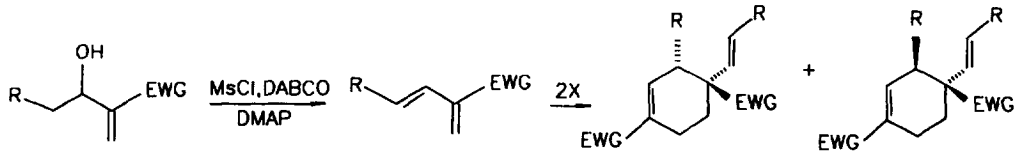
COOMe) gave the corresponding [*E*]-alkylidinesuccinates predominantly the carbonate **71** (R=isobutyl, EWG=CN) exhibited [Z]-selectivity (*E*/Z=1:6). On the otherhand, the carbonate **71** (R=isobutyl, EWG=SO_3Ph) gave stereochemically pure [*E*]-configurated product (eq. 46).

5.2. *Cycloaddition reactions:*

The application of the Baylis-Hillman adducts as hetero dienes or precursors of dienes, and dienophiles for the Diels-Alder cycloaddition reactions was initiated and expanded by the group of Hoffmann.

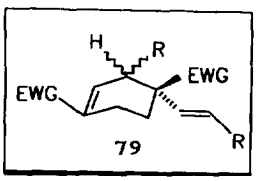
5.2.1. *Diels-Alder reactions:*

In a series of reports Hoffmann and coworkers described the *in situ* Diels-Alder dimerizations of a varitey of dienes **73-75**, generated *via* stereoselective dehydration with MsCl-DABCO-DMAP of the corresponding Baylis-Hillman adducts **27,72,7**.[20,135,136] The elimination of water has always resulted in the exclusive formation of [*E*]-double bond. The dienes **75** generated from adduct **7** (EWG = SO_2Ph) were reasonably stable and



27,72,7 **73-75** **76-78**

R = alkyl, aryl



79

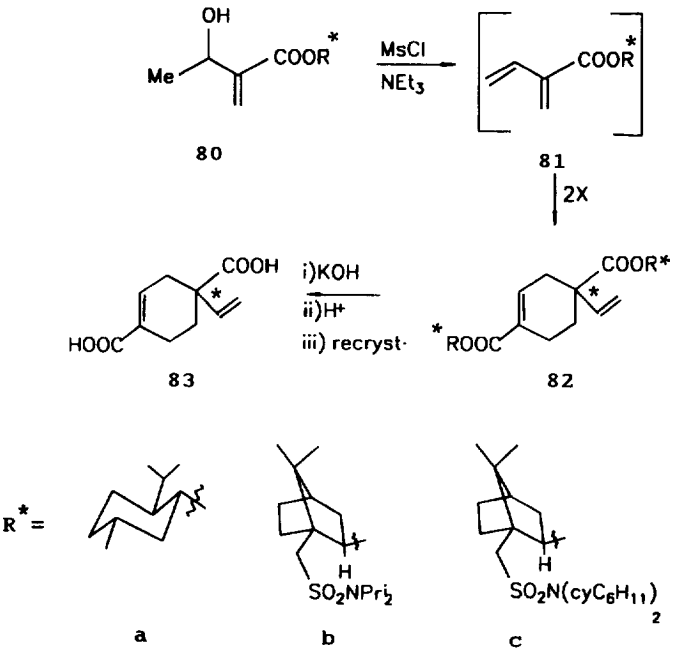
EWG =	**COOMe (76)**	**5-10 : 1**
	COMe (77)	**2-4 : 1**
	SO_2Ph (78)	**100 : 0**

SCHEME 26

allowed full characterization.[136] In contrast the dienes **73** (EWG = COOMe) and **74** (EWG = COMe) dimerized spontaneously under dehydration conditions (Scheme 26). The dimerization had been highly regioselective *i.e. para*-selective. Stereoselectivity in the formation of dimers **76** and **77** from the dienes **73** and **74** was moderate while the dienes **75** always gave *trans*-**78** with regard to sulphonyl and alkyl groups.[136] However, the alkenyl group in all these dimeric products has always been *endo* oriented with respect to roof like cyclohexene ring (**79**) (Scheme 26).

Recently, the first enantioselective synthesis of mikanecic acid (+)-

(83), a terpene dicarboxylic acid in 92% enantiomeric excess was achieved in our laboratory.[137] This was accomplished *via* double stereodifferentiating *in situ* Diels-Alder dimerization of the chiral dienes **81** followed by the hydrolysis of the diesters **82a-c** (25-74% de). The diester **82c** (74% de) upon recrystallization from hexane followed by hydrolysis furnished the (+)-mikanecic acid in 92% ee. The chiral dienes **81a-c** were generated from the corresponding optically active Baylis-Hillman adducts **80a-c** *via* dehydration by the treatment with mesyl chloride-triethylamine (Scheme 27).

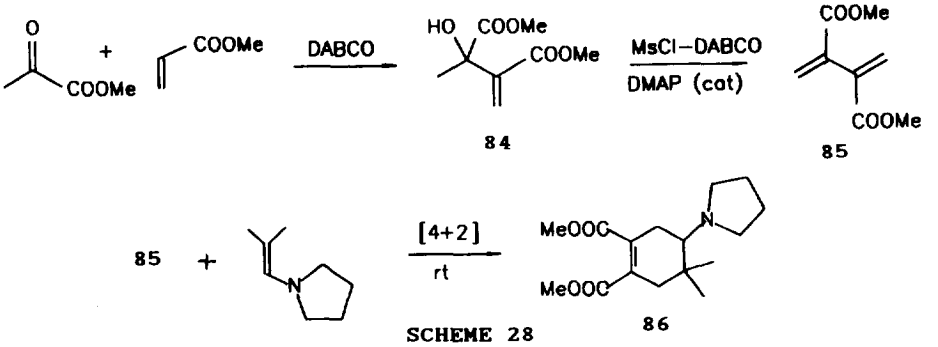


SCHEME 27

Earlier Hoffmann and coworkers described a simple synthesis of racemic mikanecic acid *via* the *in situ* Diels-Alder dimerization of the diene generated from t-butyl 2-bromomethylbut-2-enoate.[6,138]

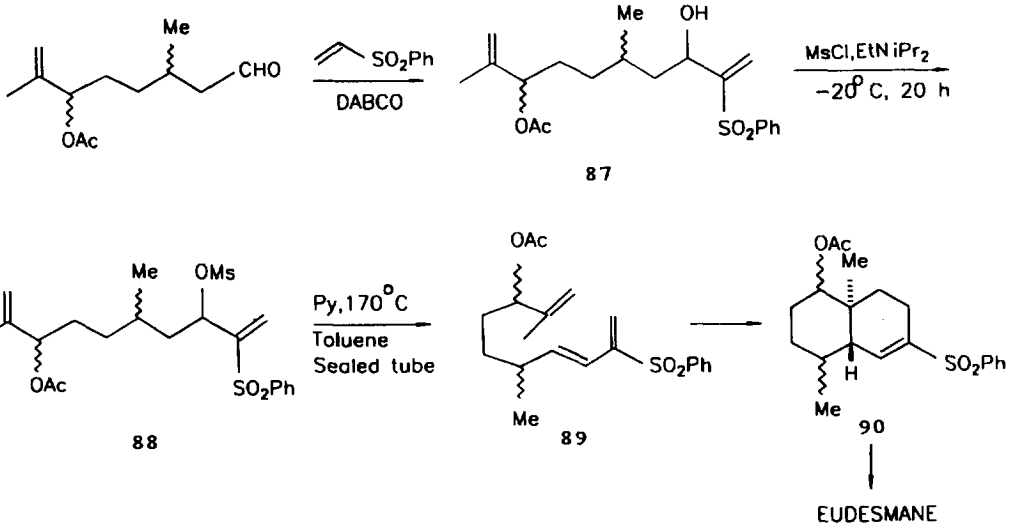
5.2.2. *Other cycloaddition reactions:*

Hoffmann[34] has achieved a simple synthesis of 2,3-dimethoxycarbonyl-1,3-butadiene (**85**) from the corresponding Baylis-Hillman adduct **84** *via* dehydration with MsCl-DABCO-DMAP (Scheme 28). The previous syntheses of this diene had been from either 2,3-butanedione (4 steps; 23% yield)[139] or acrylonitrile (8 steps)[140] which are cumbersome. The diene **85** undergoes an inverse electron demand Diels-Alder cycloaddition reaction with pyrrolidinoisobutene to yield the adduct **86**.



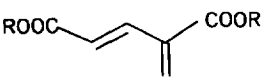
SCHEME 28

Weichert and Hoffmann[141] have synthesized the eudesmane precursor **90** *via* an inverse electron demand intramolecular [4+2] cycloadditon reaction of the triene **89**, generated *in situ* from the mesylate **88** of the Baylis-Hillman adduct **87** (Scheme 29).



SCHEME 29

Oda and coworkers have synthesized butadiene-1,3-dicarboxylate **91** using Baylis-Hillman reaction as the key step and utilized this molecule in polymerization reactions.[142]

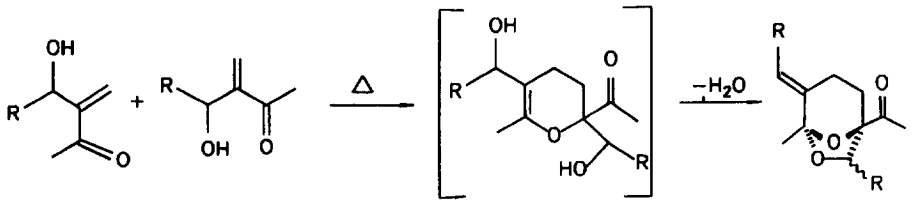


91

5.2.3. *Double cyclization of α-methylene-β-hydroxyalkanones:*

The Baylis-Hillman adducts **72** when heated in a high boiling aromatic hydrocarbon, undergo an intermolecular dehydrative double cyclization to

produce functionalized 6,8-dioxabicyclo[3.2.1]octanes (**92**)[143] (Scheme 30). However, the stereoselectivity in these processes was very poor. The 6,8-dioxabicyclo[3.2.1]octane moiety constitutes the basic framework of a number of pheromones, *e.g.* frontalin, exo- and endo-brevicomins, α-multistriatin, *etc.*

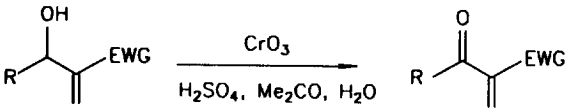


72 **92**

R = H, Me, Et, i-Bu, CH_2CH_2Ph

SCHEME 30

5.2.4. *Cycloaddition reactions of α-methylene-β-keto sulphones and esters:* Synthetically attractive α-methylene-β-keto sulphones **93**[12] and α-

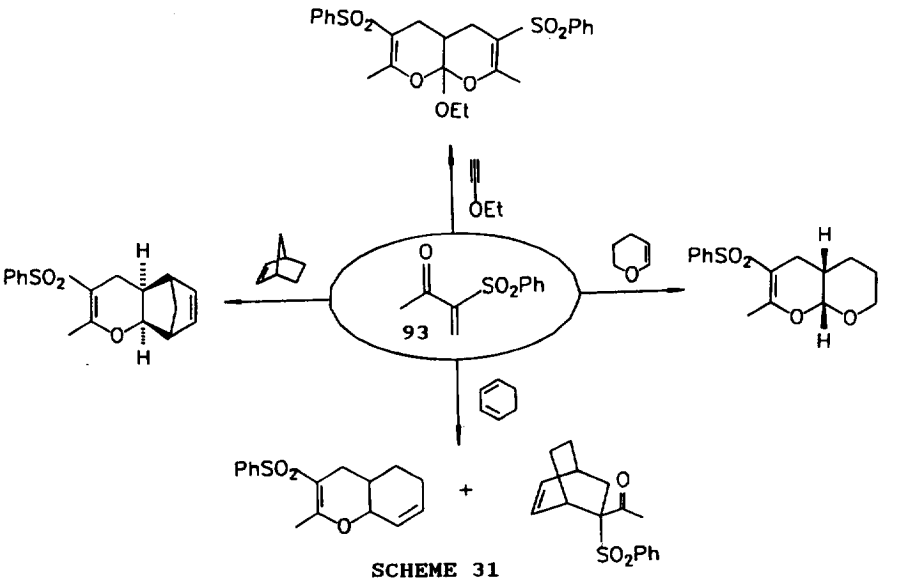


(47)

EWG = SO_2Ph (93)

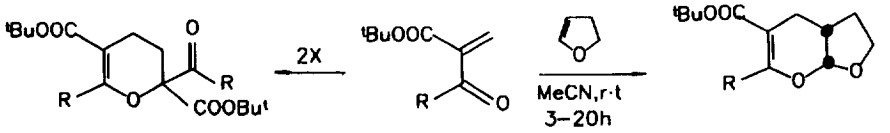
R = alkyl, aryl ; EWG = t-BuOOC (94)

methylene-β-keto esters **94**[144] were prepared from the corresponding Baylis-Hillman adducts *via* modified Jones oxidation procedure (eq. 47). These



SCHEME 31

molecules **93** (R=Me) and **94** participate in a variety of cycloaddition processes (Scheme 31 and 32).

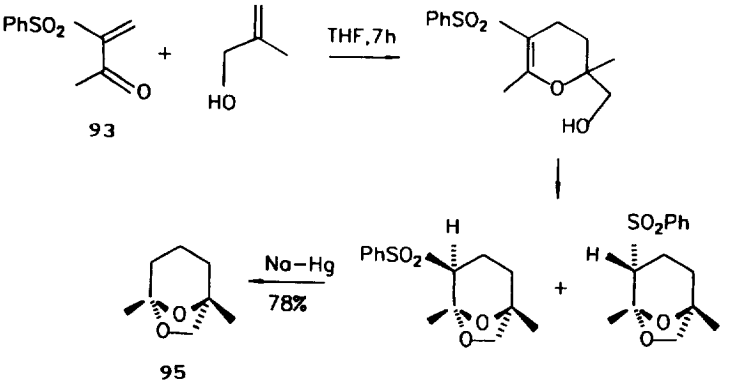


94

R=Et, n-Pr, i-Bu, CH_2CH_2Ph **R=alkyl, aryl**

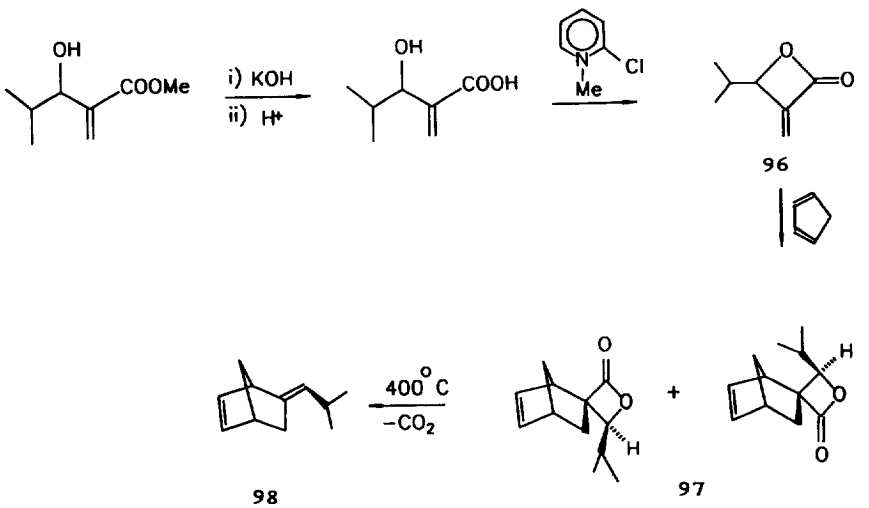
SCHEME 32

The sulphone **93** (R=Me) was efficiently utilized in the synthesis of racemic frontalin **95** (Scheme 33).[12]



SCHEME 33

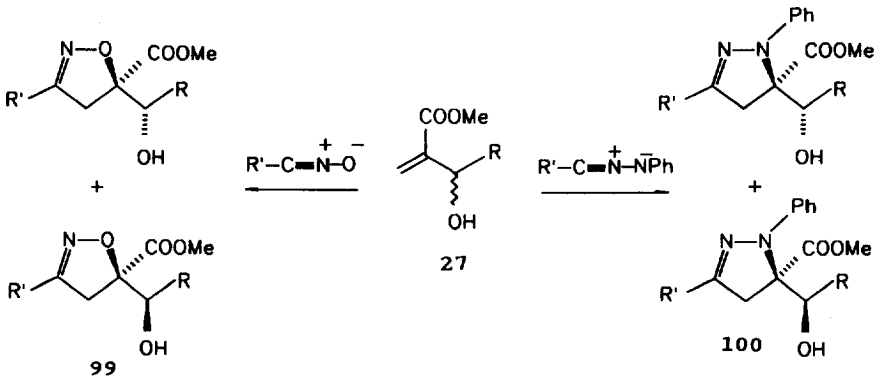
Recently, Adam *et al.*[145] have achieved the synthesis of 3-isopropyl-2-methylenepropiolactone **96** from the corresponding Baylis-Hillman adduct *via* hydrolysis followed by β-lactonization. This α-methylenepropiolactone



SCHEME 34

96 was utilized as an equivalent to isopropylallene in Diels-Alder cycloaddition reactions with a variety of dienes to produce first the spiro β-lactones **97** and then on pyrolysis the desired cyclic alkenes **98** (Scheme 34).

Quite recently, Kanemasa and Kobayashi[146] carried out 1,3-dipolar cycloaddition reactions on the Baylis-Hillman adducts **27**. The dipoles employed are nitrile oxides and nitrile imines, and are employed either in free form or as Lewis acid complexes. The Lewis acid coordinated dipoles undergo *syn*-selective cycloaddition while free dipoles showed *anti*-selectivities but moderate. Thus the adducts, isooxazolines **99** and pyrazolines **100** were obtained in reasonably high diastereomeric purity (Scheme 35).



R = Me, Et, Ph ; R' = Ph, 4-OMePh, t-Bu

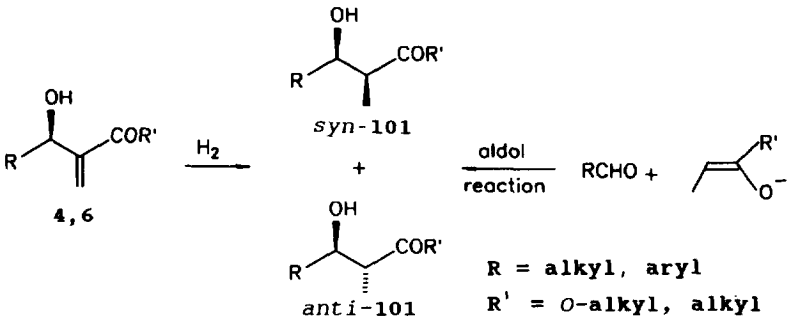
SCHEME 35

5.3. *Diastereoselective reactions:*

The Baylis-Hillman adducts, being chiral molecules, can be suitable substrates for a variety of reactions that create chiral centers diastereo selectively. The diastereoselectivity of several reactions such as, homogenous hydrogenation, epoxidation, Michael type conjugate additions, *etc.* has been studied using these substrates.

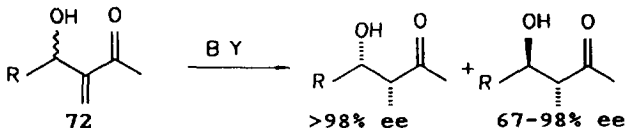
5.3.1. *Diastereoselective hydrogenation:*

Hydrogenation of the Baylis-Hillman adducts **4** and **6** results in the formation of aldol derivatives of the type **101**. If an efficient chiral catalyst is developed for the purpose, this route could prove to be an alternative to the conventional chiral enolate addition to aldehydes,[147] which suffers several disadvantages (Scheme 36).



SCHEME 36

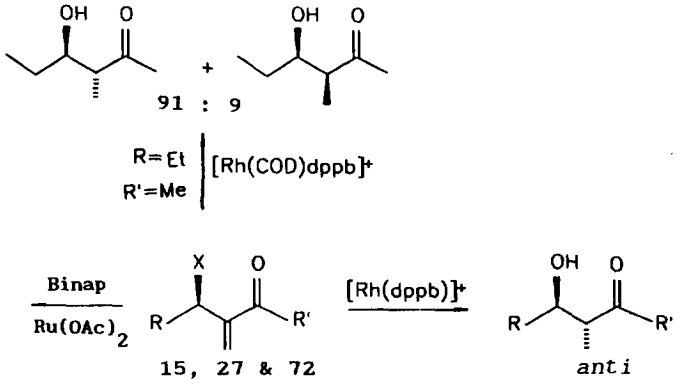
Utaka and coworkers[148] reported the fermenting Baker's yeast mediated reduction of Baylis-Hillman adducts **72** which proceeded with high enantioselection. The *syn*-diastereomers were obtained with >98% ee and the *syn*- and *anti*- products were produced in 1:1.2 ratio (eq. 48).



(48)

R = Et, n-Bu, n-pentyl

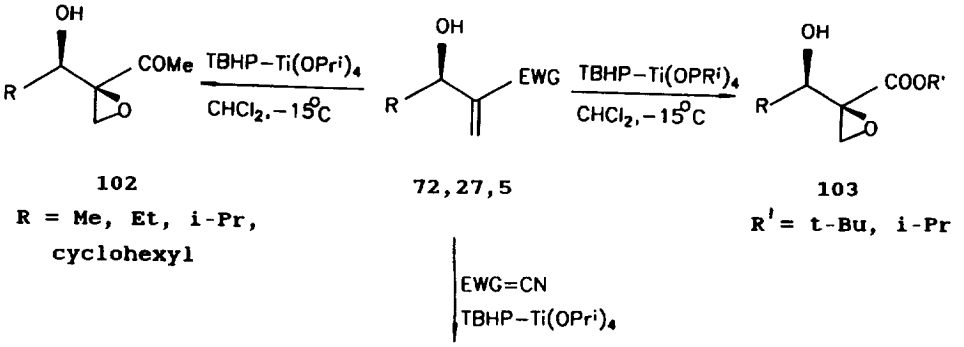
Brown and coworkers[84-87] have carried out the diastereoselective homogeneous hydrogenation of Baylis-Hillman adducts **27** (X=OH, R'=OMe) using Rh^+-diphosphine complexes as catalysts, which resulted in almost exclusive formation of the *anti*-diastereomers. Chiral catalysts, such as Binap-Ru(OAc)$_2$[88] or [Rh(NBD)(*R,R*-dipamp)]BF_4[84,87] are employed to effect kinetic resolution (*cf.* **4.5**). Subsequently, Yamamoto *et al.*[37,38] and Sato *et al.*[149] carried out similar reactions on adducts **15** (X=NHCOOMe, R'=OMe) and **72** (X=OH, R'=Me) (Scheme 37).



SCHEME 37

5.3.2. *Diastereoselective epoxidation and aziridination:*

The Baylis-Hillman adducts **72** and **27** were found to undergo *syn*-selective epoxidation under Sharpless epoxidation conditions producing molecules **102** and **103** respectively.[51,89,150] However, there was no reaction



102
R = Me, Et, i-Pr, cyclohexyl

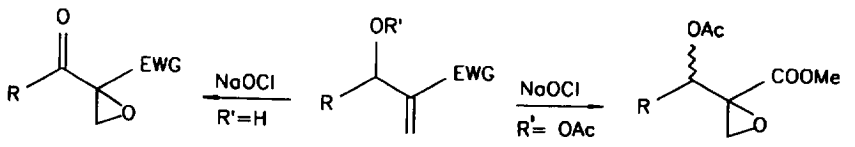
72,27,5

103
R' = t-Bu, i-Pr

SCHEME 38

with nitriles **5** (Scheme 38). The epoxidation was found to be less stereoselective (20-34%) under basic conditions (H_2O_2-NaOH or TBHP-NaOH).

Sodium hypochlorite (NaOCl)[28] converts the hydroxy esters **27** (R = aryl) and nitriles **5** (R=aryl) into the corresponding keto epoxides **104** and the acetoxy ester **35** into acetoxy epoxide **105** in which case the diastereoselectivity was found to be 68% (R = Ph) and 48% (R= 4-ClC_6H_4) (Scheme 39).



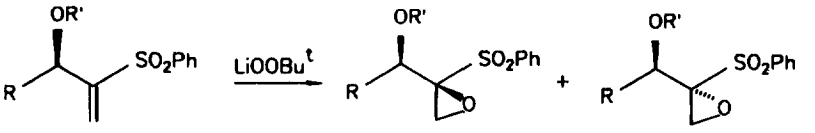
104
R = aryl ; EWG = COOMe, CN

27,5,35

105
R = Ph, 4-ClC_6H_4

SCHEME 39

Lithium t-butylperoxide was used for stereoselective epoxidation of sulphones **7** and their silyl derivative **106**. While the free alcohols gave exclusively the *syn*-epoxides **107**, the silyl ethers produced *anti*-epoxides **108** as major products (eq. 49).[151]



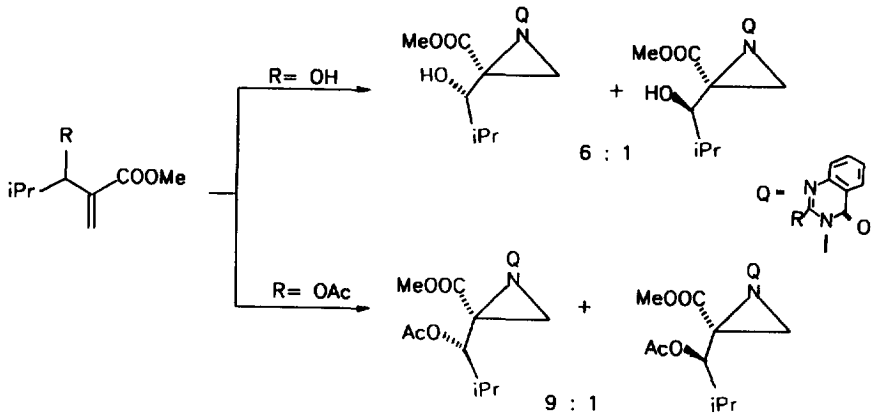
(49)

7,106 107 108

7 (R =H) 25 : 1

R = Me, n-Pr, i-Pr 106 (R =Si i-Pr$_3$) minor major

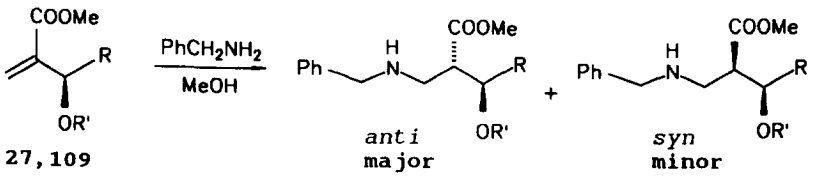
Stereoselective aziridination of 3-hydroxy-2-methylene-4-methylpentanoate and its acetate using 3-acetoxyaminoquinazolin-4(3H)-one is described (Scheme 40).[152] However, yields of the resulting aziridines are very poor.



SCHEME 40

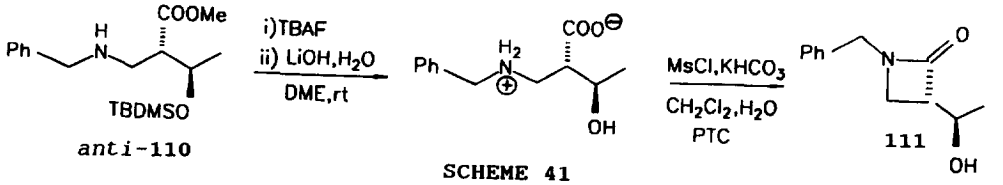
5.3.3. *Diastereoselective Michael-type addition reactions:*

Perlmutter and Tabone[153] carried out nucleophilic addition of benzylamine onto the adducts 27 which proceeded with modest diastereoselectivity



27,109

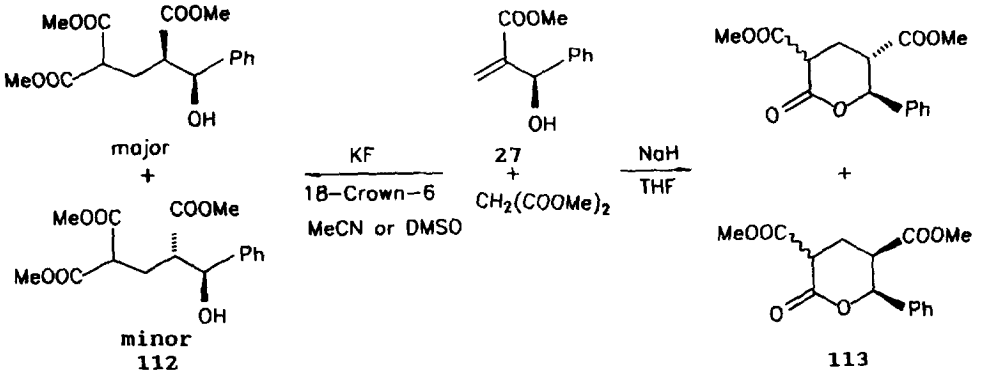
R = Me, Ph, α-Py ; R' = H, TBDMS



SCHEME 41

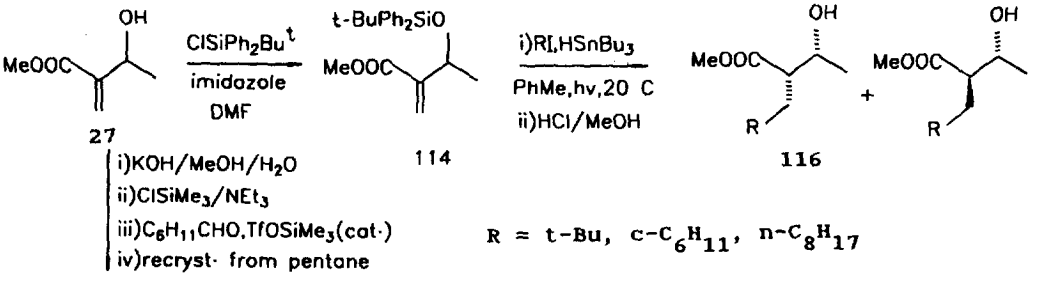
in methanol to produce the desired products as a 4:1 separable mixture of *anti*- and *syn*-isomers. Change of solvent to tetrahydrofuran resulted in a lowering and reversal of stereoselection. The addition becomes highly diastereoselective (≥ 99%) if the hydroxy is converted into TBDMS ether **109**. Thus obtained *anti*-amino ester **110** was transformed into the corresponding azetidinone **111** (Scheme 41).

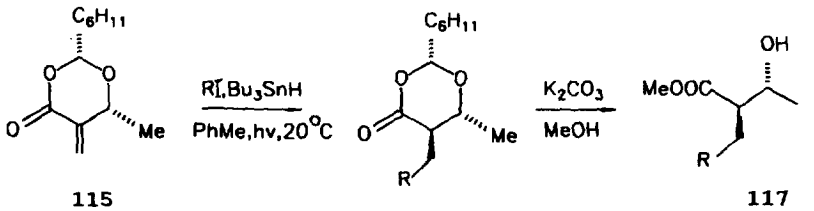
The Baylis-Hillman adducts **27** also undergo the phase-transfer catalyzed diastereoselective Michael reaction with stabilized carbanion derived from dimethyl malonate producing hydroxyester **112**.[154] Good stereoselectivity was obtained in these additions, especially for the reactions carried out in acetonitrile (*syn:anti* = 15-20:1). When the reactions were carried



SCHEME 42

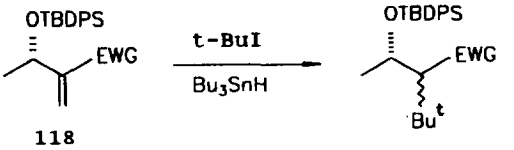
out in tetrahydrofuran using sodium hydride as the base, the lactones **113** were obtained as major products along with small amount of **112** (Scheme 42).





SCHEME 43

Giese *et al.*[155,156] showed that the conjugate addition of radicals to either the silyl ethers **114** or 2-cyclohexyl-5-methylene-6-methyl-1,3-dioxan-4-ones (**115**) derived from the corresponding Baylis-Hillman adduct **27** (R=Me) proceeds with high stereoselection (Scheme 43). Thus the silyl ethers **114** produced, after deprotection, the *erythro*-β-hydroxy esters **116** as major products along with the minor *threo*-isomers whereas the 5-methylidene-1,3-dioxan-4-ones **115** yielded only *threo*-β-hydroxy esters **117** (>99% de). Similar free radical addition on the corresponding silyl derivatives (**118**) (of Baylis-Hillman adduct derived from acrylonitrile and phenyl vinyl sulphone) resulted in low selectivity [157] (eq. 50).

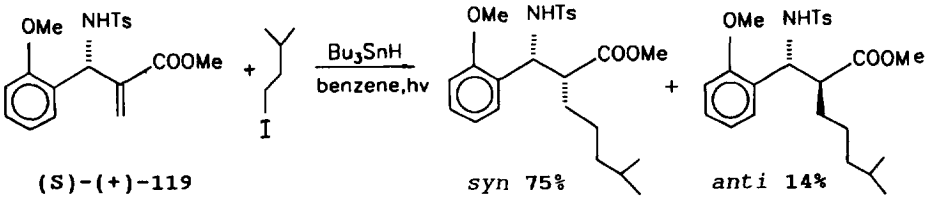


(50)

118

EWG = CN, SO_2Ph

Recently Kundig and coworkers[158] studied diastereoselective addition of alkyl radicals to racemic and enantiomerically pure Baylis-Hillman adduct (**119**) which afforded the *syn*-isomer as major product (eq. 51).



(51)

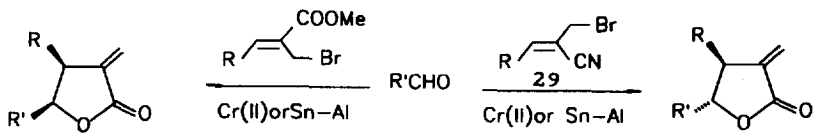
(S)-(+)-119

syn **75%**
>98% ee

anti **14%**
>98% ee

5.3.4. *Diastereoselective allylation of carbonyl compounds:*

The allyl bromides **28** and **29** undergo Drieding-Schimdt reaction[159,160] producing stereochemically defined α-methylene-β,γ-disubstituted-γ-butyrolactones **120** [161-163] (Scheme 44).

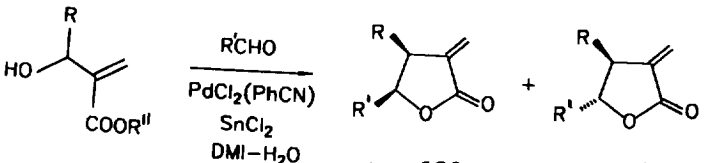


syn-**120** *anti*-**120**

R & R' = alkyl, aryl

SCHEME 44

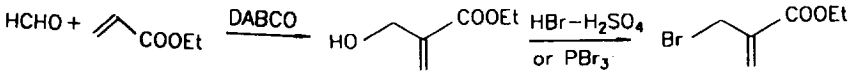
It was recently shown by Masuyama *et al.*[164] that the Baylis-Hillman adducts (allyl alcohols) can directly be converted into α-methylene-γ-butyrolactones (**120**) with high diastereoselectivity using $PdCl_2(PhCN)$ as the catalyst (eq. 52).



(52)

R = n-Bu, cyclohexyl, 4-(COOMe)C_6H_4 ; R' = Me, n-Bu, Ph ; R'' = Me, Et

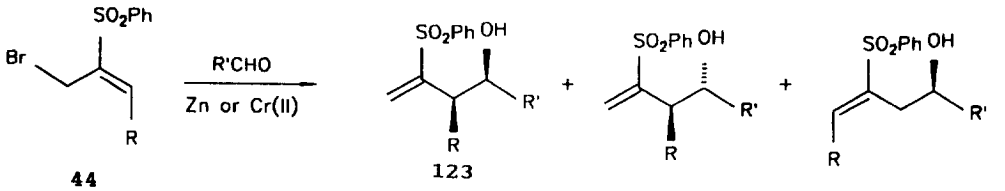
The allyl bromide **122** was extensively used in the synthesis of α-methylene-γ-butyrolactones,[160] lactams[165,166] and several other compounds.[167] This α-bromomethyl acrylate was prevously synthesized *via* routes that are either circuitous or low yielding.[168,169] The Baylis-Hillman reaction provides a simple and efficient procedure for large scale synthesis of allyl bromide **122** (Scheme 45).[23,24]



121 **122**

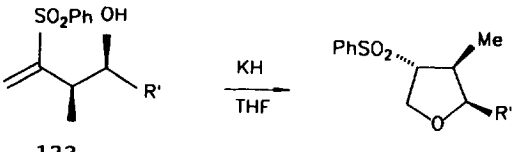
SCHEME 45

[*E*]-Allyl bromides **44** were employed by Normant and coworkers[170] in the zinc or chromium(II) mediated diastereoselective allylation of alde-



44 **123**

R = Me, n-Pr, i-Bu ; R' = alkyl, alkenyl, aryl



123 **124**

R' = Ph, Pentyl

SCHEME 46

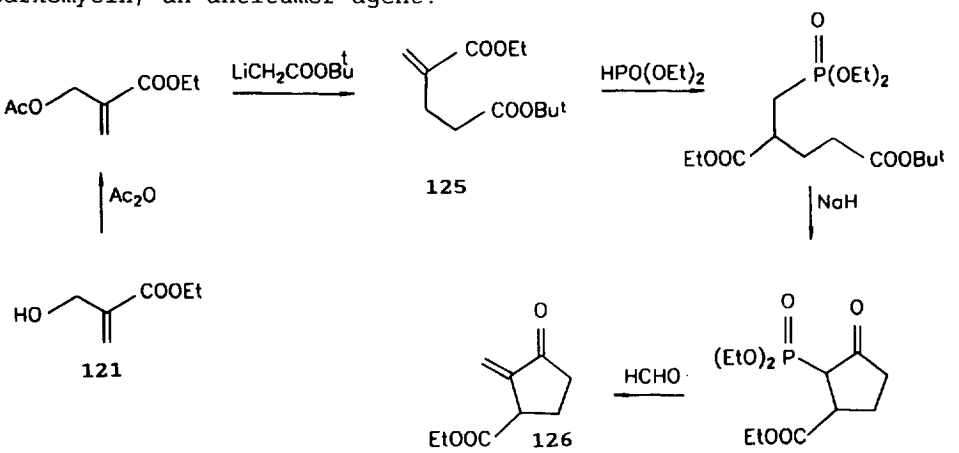
hydes to provide syn-homoallyl alcohol **123** exclusively or predominantly. Some of these *syn*-hydroxy-sulphones were transformed, (after stereochemical purification) into diastereomerically pure 2,3,4-trisubstituted tetrahydrofurans **124** (Scheme 46).

5.4. *Other applications:*

The Baylis-Hillman adducts were also employed in the synthesis of compounds, such as, ethyl ester of (±)-sarkomycin, lactones, lactams, diazacyclophanes, indolizines, liquid crystals, *etc.*

5.4.1. *(±)-Sarkomycin ester:*

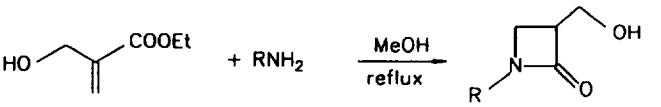
Ethyl α-acetoxymethylacrylate was employed in the preparation of the mixed ester of α-methyleneglutaric acid **125**, which in turn was elaborated, in accordance with Scheme 47, into **126**, the ethyl ester of (±)-sarkomycin, an antitumor agent.[43]



SCHEME 47

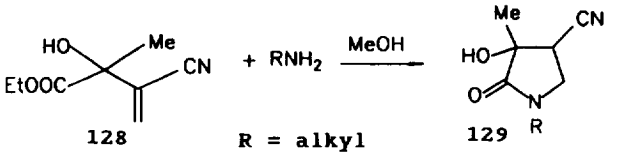
5.4.2. *Azetidinones and other lactams:*

Villieras *et al.* have synthesized α-hydroxymethylazetidinones **127**, *via* conjugate addition of primary amines to Baylis-Hillman adduct **121** (eq. 53).[171] Treatment of the Baylis-Hillman adduct **128**, obtained from acrylonitrile and ethyl pyruvate, with amines produced 1,3,4-trisubstituted 2-pyrrolidines **129** (eq 54).[172] Similar reaction with hydrazine or methyl hydrazine gave polyfunctionalized perhydro-1,2-pyridazin-3-ones **130** and **131**. These reactions exhibited no diastereoselection.

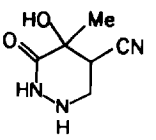


(53)

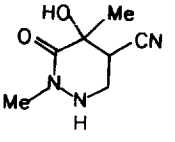
121 **R=alkyl** **127**



128 R = alkyl 129 (54)

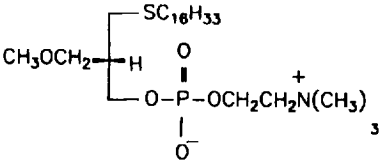


130



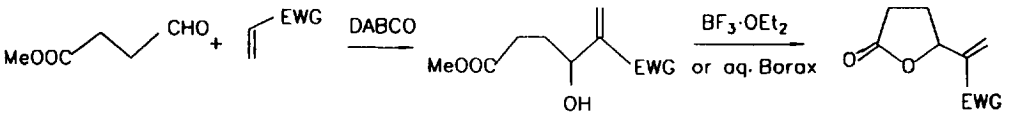
131

Bittmann *et al*. reported the enantioselective synthesis of ilmofosine (**132**) analogue using Baylis-Hillman adduct **121**[173] as the starting material.



132

Recently, Perlmutter and McCarthy[21] have reported synthesis of the lactones **133** in two steps using the Baylis-Hillman reaction as the key step (Scheme 48).

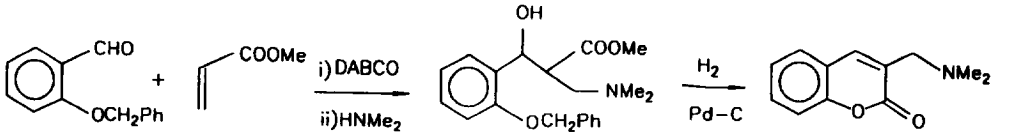


133

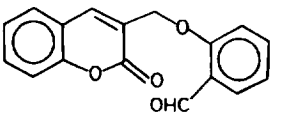
EWG = COOMe, CN, COMe

SCHEME 48

Recently, Drewes and coworkers[45] have synthesized 3-dimethylaminomethylcoumarin *via* DABCO-catalyzed Baylis-Hillman reaction between O-benzylsalicylaldehyde and methyl acrylate followed by addition of dimethylamine and hydrogenolysis (Scheme 49). Previously, 3-(2-formylphenoxy)methylcoumarin (**134**) was isolated in 9% yield from the Baylis-Hillman reaction between salicylaldehyde and acrylate ester by Kaye and cowokers.[174]

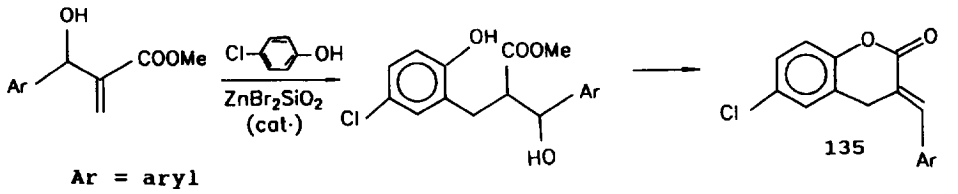


SCHEME 49



134

Foucaud and Brine successfuly converted 3-aryl-3-hydroxy-2-methylene-alkanoates into 3-arylidene-3,4-dihydrocoumarins **135** according to Scheme 50.[175]

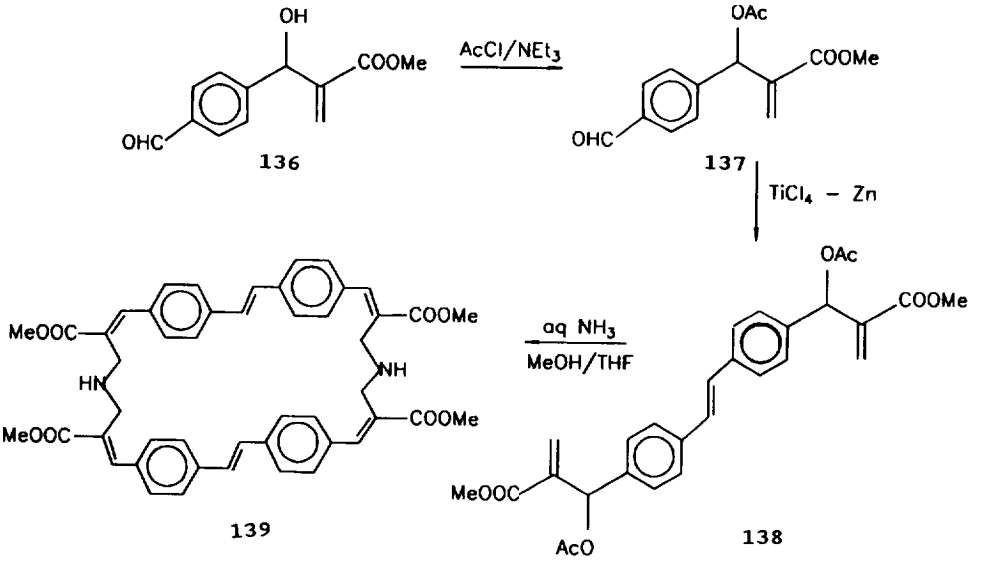


Ar = aryl

SCHEME 50

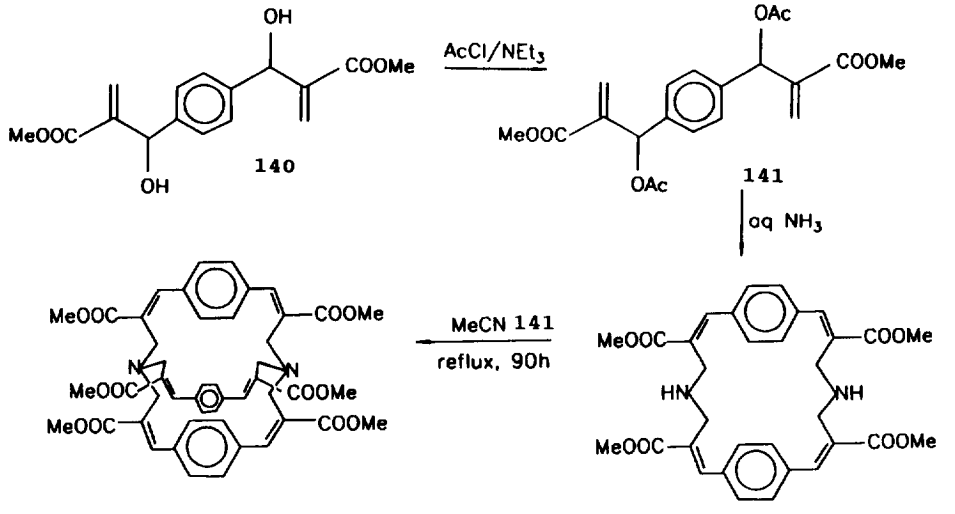
5.4.3. *Diazacyclophanes:*

The acetate **137** of the mono adduct **136** upon reaction with $TiCl_4$ and zinc gave a diacetate **138**, which in turn furnished the diaza[7,2-7,2]-paracyclophane **139** when treated with aqueous ammonia (Scheme 51).[176] On the otherhand, the diacetate **141** of bis-adduct **140** on treatment with



SCHEME 51

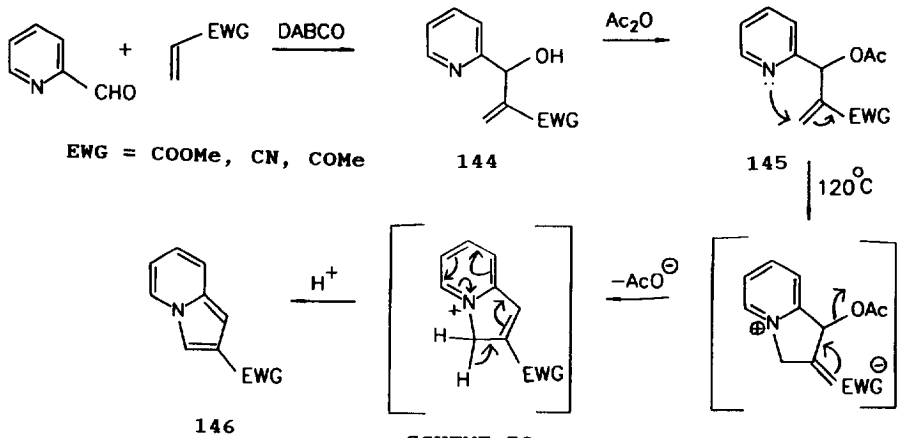
aqueous ammonia gave the diaza[7,7]paracyclophane (**142**) as a single compound. The diazacyclophane **142** when refluxed with the diacetate **141** in acetonitrile for 90h gave diazamacrobicycle **143** in 98% yield (Scheme 52).[176]



SCHEME 52

5.4.4. *Indolizines:*

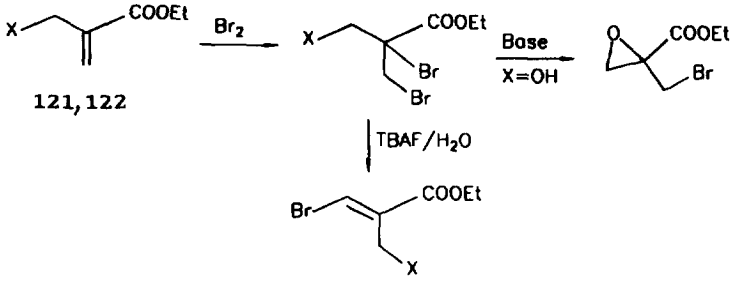
Bode and Kaye[57,177] have synthesized several 2-substituted indolizines **146** using the Baylis-Hillman adduct **144** obtained from pyridine-2-carbaldehyde and activated alkenes such as acrylate esters, acrylonitrile methyl vinyl ketone. Thus the corresponding acetates **145** when heated (120°C), provided the 2-substituted indolizines **146** (Scheme 53). This thermal cyclization presumably proceeds through an addition-elimination path.



SCHEME 53

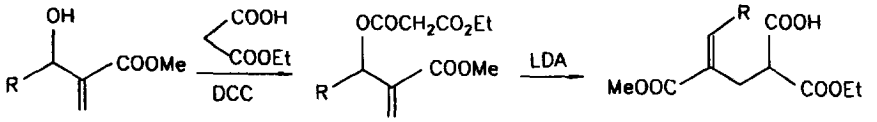
5.4.5. *Miscellaneous:*

Recently, El Gaied and coworkers[178] have utilized **121**, **122** and compounds derived from **122** in the synthesis of 1-bromo-2,3-epoxy-2-ethoxycarbonylpropane and stereodefined β-bromo-α-substituted acrylates (Scheme 54). The same strategy was adopted by Calderon *et al.* in their approaches towards the synthesis of fimbrolides.[179]



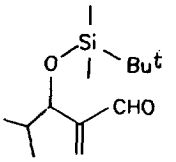
SCHEME 54

Drewes *et al.* have described simple stereoselective synthesis of 2-alkylidene-4-carboxyglutaric acid esters (**147**) using Baylis-Hillman adducts (Scheme 55).[180]

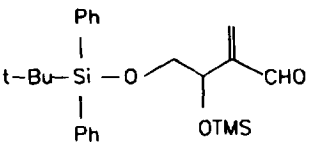


SCHEME 55

Recently, Baylis-Hillman adducts have been utilized for the synthesis of aldehydes **148** and **149**, important synthons for the synthesis of polyether etheromycin.[181,182]

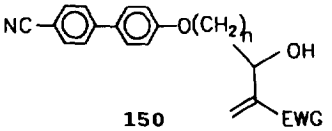


148



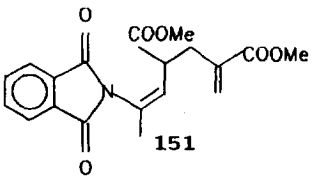
149

Recently Baylis-Hillman adducts **150** have been employed for synthesis of a novel side chain liquid-crystal polymers.[183] Roos and coworkers[184] isolated a novel product **151** in the Baylis-Hillman coupling reaction of 2-phthalimidopropanal with methyl acrylate.



150

EWG = CN, COOMe

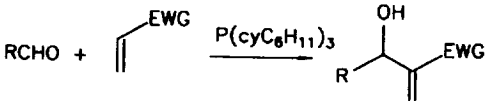


151

6. *Variants:*

It is worth mentioning that the Baylis-Hillman adducts are obtained by using catalysts other than amines. Some of the very important developments have been described.

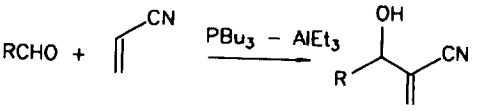
The first of its kind was reported in 1968 by Morita *et al.*[185] They have used tricyclohexylphosphine as the catalyst for the coupling of activated olefins with aldehydes (eq. 55) but the yields are very low.



(55)

R = alkyl, aryl ; EWG = COOMe, CN

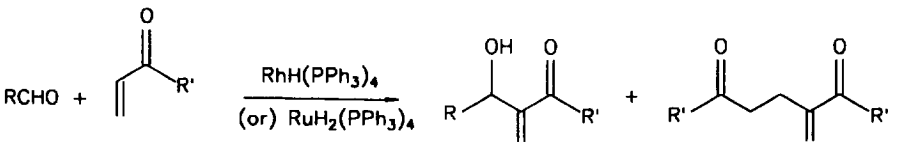
Imagawa *et al.*[186] have reported higher yields in the case of acrylonitrile by employing tributylphosphine and triethylaluminium as catalyst (eq. 56).



(56)

R = alkyl, aryl

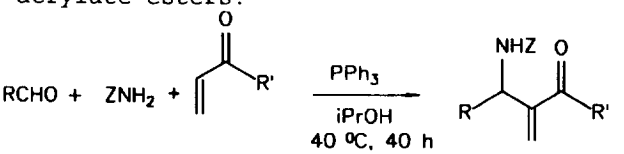
Rhodium(I) and ruthenium(II) complexes were employed as catalysts in the reaction between alkyl vinyl ketones and aldehydes to produce α-methylene-β-hydroxyalkanones (eq. 57).[149, 187-189]



(57)

R = alkyl,aryl ; R' = alkyl

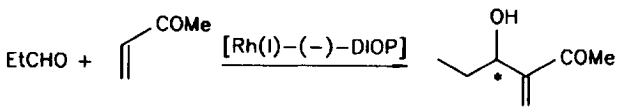
Triphenylphosphine mediated reaction of methyl acrylate with butyraldehyde and tosylamine or carbamates was achieved by Bertenshaw and Kahn (eq 58).[190] Phosphines were used as catalysts for the large scale dimerization of acrylate esters.[191]



(58)

Z = tosyl, t-BuOOC, $COOCH_2Ph$; R = n-Pr, Ph; R' = OMe,

Recently, Roos *et al.*[192] reported the rhodium-chiral bis-phosphine complex catalyzed reaction of methyl vinyl ketone with propanal which produced the Baylis-Hillman adduct in 22% ee. (eq. 59).



(59)

22% ee

Conclusion:

The Baylis-Hillman reaction, originating from a German Patent in **1972** started attracting the attention of organic chemists in 1980's and has significantly advanced in the last ten years as demonstrated by a number of reactions and applications described in the review. Though the reaction is expanding rapidly it is still at an early stage because there is much to learn about the reaction mechanism and the three components of the reaction. A suitable chiral catalyst for asymmetric Baylis-Hillman construction of carbon-carbon bonds is yet to evolve. Applications of this reaction in diastereo- and enantioselective synthesis are beginning to emerge and will certainly represent a forefront of research in organic chemistry. We believe that the coming years will witness more and more advances in this fascinating reaction which will ultimately make this reaction one of the most useful reactions in organic chemistry.

Abbreviations:

Binap	2,2' -bis(diphenylphosphino)-1,1' -binaphthyl
CAMP	o-anisylcyclohexylmethylphosphine
COD	cycloocta-1,5-diene
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethylazodicarboxylate
DIBAL	diisobutylaluminum hydride
DIOP	2,3-O-isoprpylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane
DIPAMP	1,2-bis(anisylphenyl)phosphinoethane
DMAP	4-N,N-dimethylaminopyridine
DMI	1,3-dimethyl-2-imidazolidinone
DMS	dimethyl sulphide
dppb	1,4-diphenylphosphinobutane
EWG	electron-withdrawing group
HCA	hexachloroacetone
3-HQ	(±)-3-hydroxyquinuclidine
HRP	horseradish peroxidase
mCPBA	3-chloroperbenzoic acid
Ms	methanesulfonyl
NBD	norbornadiene
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
Np	1-naphthyl
PLAP	pig liver acetone powder

TBDMS	t-butyldimethylsilyl
TBHP	t-butyl hydroperoxide
TBPS	t-butyldiphenylsilyl
TDAP	tris(dimethylamino)phosphine
Tf	trifluoromethylsulfonyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl

Acknowledgements:

We would like to thank our former coworkers Drs.V.V.L.Gowriswari, T.K. Bharathi, A.K.D. Bhavani and P.K.S.Sarma, and present coworker Dr.S.Pandiaraju who have contributed to the work described in this review. We gratefully acknowledge the help of our coworkers Drs. P. Rama Krishna, S. Bhaskar raju and Mr. K. Muthukumaran during the time of writing this review. We are grateful to UGC (New Delhi) and CSIR (New Delhi) for funding our research on Baylis-Hillman reaction. PDR and RSH thank UGC (New Delhi) for their research fellowships.

REFERENCES

1. Trost, B.M.; *Science*, **1983**, 219, 245.
2. Trost, B.M.; *Science*, **1991**, 256, 1471.
3. Drewes, S.E.; Roos, G.H.P.; *Tetrahedron*, **1988**, 44, 4653.
4. Baylis, A.B.; Hillman, M.E.D.; German Patent 2155113, **1972** , *Chem. Abstr.*, **1972**, 77, 34174q.
5. Drewes, S.E.; Emslie, N.D.; *J. Chem. Soc., Perkin Trans. I*, **1982**, 2079.
6. Hoffmann, H.M.R.; Rabe, J.; *Angew. Chem., Int. Ed. Engl.*, **1983**, 22, 795.
7. Basavaiah, D.; Gowriswari, V.V.L.; *Synth. Commun.*, **1987**, 17, 587.
8. Amri, H.; Villieras, J.; *Tetrahedron Lett.*, **1986**, 27, 4307.
9. Basavaiah, D.; Gowriswari, V.V.L.; *Tetrahedron Lett.*, **1986**, 27, 2031.
10. Basavaiah, D.; Bharathi, T.K.; Gowriswari, V.V.L.; *Synth. Commun.*, **1987**, 17, 1893.
11. Auvray, P; Knochel, P.; Normant, J.F.; *Tetrahedron Lett.*, **1986**, 27, 5095.
12. Weichert, A.; Hoffmann, H.M.R.; *J. Org. Chem.*, **1991**, 56, 4098.
13. Wang, S.-Z.; Yamamoto, K.; Yamada, H.; Takahashi, T.; *Tetrahedron*, **1992**, 48, 2333.
14. Amri, H.; El Gaied, M.M.; Villieras, J.; *Synth. Commun.*, **1990**, 20, 659.
15. Tsuboi, S.; Takatsuka, S.; Utaka, M.; *Chem. Lett.*, **1988**, 2003.
16. Tsuboi, S.; Kuroda, H.; Takatsuka, S.; Fukawa, T.; Sakai, T.; Utaka, M.; *J. Org. Chem.*, **1993**, 58, 5952.
17. Hill, J.S.; Isaacs, N.S.; *Tetrahedron Lett.*, **1986**, 27, 5007.

18. Rabe, J.; Hoffmann, H.M.R.; *Angew. Chem., Int. Ed. Engl.*, **1983**, 22, 796.
19. Hoffmann, H.M.R.; Rabe, J.; *J. Org. Chem.*, **1985**, 50, 3849.
20. Poly, W.; Schomburg, D.; Hoffmann, H.M.R.; *J. Org. Chem.*, **1988**, 53, 3701.
21. Perlmutter, P.; McCarthy, T.D.; *Aust. J. Chem.*, **1993**, 46, 253.
22. Fikentscher, R.; Hahn, E.; Kud, A.; Oftring, A.; *Chem. Abstr.*, **1987**, 107, 7781s.
23. Drewes, S.E.; Loizou, G.; Roos, G.H.P.; *Synth. Commun.*, **1987**, 17, 291
24. Byun, H.-S.; Reddy, K.C.; Bittman, R.; *Tetrahedron Lett.*, **1994**, 35, 1371.
25. Strauss, C.R.; Galbraith, M.N.; Faux, A.F.; *Chem. Abstr.*, **1992**, 116, 128185v.
26. Janecki, T.; *Synth. Commun.*, **1993**, 23, 641.
27. Drewes, S.E.; Emslie, N.D.; Khan, A.A.; Roos, G.H.P.; *Synth. Commun.*, **1989**, 19, 959.
28. Foucaud, A.; Rouille, E.; *Synthesis*, **1990**, 787.
29. Fort, Y.; Berthe, M.C.; Caubere, P.; *Synth. COmmun.*, **1992**, 22, 1265.
30. Hill, J.S.; Isaacs, N.S.; *J. Chem. Res.(S)*, **1988**, 330.
31. a) van Rozendaal, E.L.M.; Voss, B.M.W.; Scheeren, H.W.; *Tetrahedron*, **1993**, 49, 6931.
    b) Ando, D.; Bevan, C.; Brown, J.M.; Price, D.W.; *J. Chem. Soc., Chem. Commun.*, **1992**, 592.
32. Basavaiah, D; Bharathi, T.K; Gowriswari, V.V.L.; *Tetrahedron Lett.*, **1987**, 28, 4351.
33. Basavaiah, D.; Gowriswari, V.V.L.; *Synth. Commun.*, **1989**, 19, 2461.
34. Grundke, C.; Hoffmann, H.M.R.; *Chem. Ber.*, **1987**, 120, 1461.
35. a) Golubev, A.S.; Galakhov, M.V.; Kolomiets, A.F.; Fokin, A.V.; *Bull. Rus. Acad. Sci.*, **1992**, 41, 2193.
    b) *Idem*, *Izv. Akad. Nauk. Ser. Khim.*, **1992**, 2763; *Chem. Abstr.*, **1994**, 120, 54166y.
36. Perlmutter, P.; Teo, C.C.; *Tetrahedron Lett.*, **1984**, 25, 5951.
37. Yamamoto, K.; Takagi, M.; Tsuji, J.; *Bull. Chem. Soc. Jpn.*, **1988**, 61, 319.
38. Takagi, M.; Yamamoto, K.; *Tetrahedron*, **1991**, 47, 8869.
39. Ameer, F.; Drewes, S.E.; Freese, S.; Kaye, P.T.; *Synth. Commun.*, **1988**, 18, 495.
40. Gowriswari, V.V.L.; Ph.D. Thesis, University of Hyderabad, India, **1989**.
41. a) Basavaiah, D.; Gowriswari, V.V.L.; Bharathi, T.K.; *Tetrahedron Lett.*, **1987**, 28, 4591.
    b) Basavaiah, D.; Gowriswari, V.V.L.; Dharma Rao, P.; Bharathi, T.K.;

J. Chem. Res. (S), **1995**, 267.
42. Drewes, S.E.; Emslie, N.D.; Karodia, N.; *Synth. Commun.*, **1990**, 20, 1915.
43. Amri, H.; Rambaud, M.; Villieras, J.; *Tetrahedron Lett.*, **1989**, 30, 7381.
44. Hwu, J.R.; Hakimelahi, G.H.; Chou, C.-T.; *Tetrahedron Lett.*, **1992**, 33, 6469.
45. Drewes, S.E.; Njamela, O.L.; Emslie, N.D.; Ramesar, N.; Field, J.S.; *Synth. Commun.*, **1993**, 23, 2807.
46. Roth, F.; Gygax, P.; Frater, G.; *Tetrahedron Lett.*, **1992**, 33, 1045.
47. Hill, J.S., Isaacs, N.S.; *J. Phys. Org. Chem.*, **1990**, 3, 285.
48. Bode, M.L.; Kaye, P.T; *Tetrahedron Lett.*, **1991**, 32, 5611.
49. Fort, Y.; Berthe, M.C.; Caubere, P.; *Tetrahedron*, **1992**, 48, 6371.
50. Drewes, S.E.; Freese, S.D; Emslie, N.D.; Roos, G.H.P.; *Synth. Commun.*, **1988**, 18, 1565.
51. Bailey, M.; Marko, I.E.; Ollis, W.D.; Rasmussen, P.R.; *Tetrahedron Lett.*, **1990**, 31, 4509.
52. Basavaiah, D.; Sarma, P.K.S.; *Synth. Commun.*, **1990**, 20, 1611.
53. Isaacs, N.S.; *Tetrahedron*, **1991**, 47, 8463.
54. Roos, G.H.P.; Rampersadh, P.; *Synth. Commun.*, **1993**, 23, 1261.
55. Auge, J.; Lubin, N.; Lubineau, A.; *Tetrahedron Lett.*, **1994**, 35, 7947.
56. Kundu, M.K.; Mukherjee, S.B.; Balu, N.; Padmakumar, R.; Bhat, S.V.; *Synlett*, **1994**, 444.
57. Bode, M.L.; Kaye, P.T.; *J. Chem. Soc., Perkin Trans. I*, **1993**, 1809.
58. Brown, J.M.; Cutting, I.; Evans, P.L.; Maddox, P.J.; *Tetrahedron Lett.*, **1986**, 27, 3307.
59. Basavaiah, D.; Dharma Rao, P.; Sarma, P.K.S.; unpublished results.
60. Sarma, P.K.S., Ph.D. thesis, University of Hyderabad, India, **1993**.
61. Basavaiah, D,; Pandiaraju, S.; unpublished results.
62. Basavaiah, D.; Gowriswari, V.V.L.; Sarma, P.K.S.; Dharma Rao, P.; *Tetrahedron Lett.*, **1990**, 31, 1621.
63. Jensen, K.N.; Roos; G.H.P.; *S. Afr. J. Chem.*, **1992**, 45, 112.
64. Gilbert, A.; Heritage, T.W.; Isaacs, N.S.; *Tetrahedron: Asymmetry*, **1991**, 2, 969.
65. Drewes, S.E.; Emslie, N.D.; Karodia, N.; Khan, A.A.; *Chem. Ber.*, **1990**, 123, 1447.
66. Khan, A.A.; Emslie, N.D.; Drewes, S.E.; Field, J.S.; Ramesar, N.; *Chem. Ber.*, **1993**, 126, 1477.
67. Drewes, S.E.; Emslie, N.D.; Field, J.S.; Khan, A.A.; Ramesar, N.; *Tetrahedron Lett.*, **1993**, 34, 1205.
68. Drewes, S.E.; Emslie, N.D.; Khan, A.A.; *Synth. Commun.*, **1993**, 23, 1215.

69. Drewes, S.E.; Manickum, T.; Roos, G.H.P.; *Synth. Commun.*, **1988**, 18, 1065.
70. Drewes, S.E.; Njamela, O.L.; Roos, G.H.P.; *Chem. Ber.*, **1990**, 123, 2455.
71. Manickum, T.; Roos, G.; *Synth. Commun.*, **1991**, 21, 2269.
72. Drewes, S.E.; Khan, A.A.; Rowland, K.; *Synth. Commun.*, **1993**, 23, 183.
73. Kundig, E.P.; Xu, L.H.; Romanens, P.; Bernardinelli, G.; *Tetrahedron Lett.*, **1993**, 34, 7049.
74. Kundig, P.; Xu, L.H.; Schnell, B.; *Synlett*, **1994**, 413.
75. Waldrop, M.M.; *Science*, **1989**, 245, 354.
76. Corey, E.J.; *Pure & Appl. Chem.*, **1990**, 62, 1209.
77. Noyori, R.; Takaya, H.; *Acc. Chem. Res.*, **1990**, 23, 345.
78. Corey, E.J.; Bakshi, R.K.; Shibata, S.; Chen, C.-P.; Singh, V.K.; *J. Am. Chem. Soc.*, **1987**, 109, 7925.
79. Oishi, T.; Hirama, M.; *Tetrahedron Lett.*, **1992**, 33, 639.
80. Oishi, T.; Oguri, H.; Hirama, M.; *Tetrahedron: Asymmetry*, **1995**, 6, 1241.
81. Oi, R.; Sharpless, K.B.; *Tetrahedron Lett.*, **1991**, 32, 4853.
82. Soai, K.; Oshio, A.; Yoneyama, H.; *Tetrahedron: Asymmetry*, **1992**, 3, 359.
83. Ojima, I.(Editor), *Catalytic Asymmetric Synthesis*, VCH Publishers inc., New York, **1993**.
84. Brown, J.M.; Cutting, I.; *J. Chem. Soc., Chem. Commun.*, **1985**, 578.
85. Brown, J.M.; James, A.P.; Prior, L.M.; *Tetrahedron Lett.*, **1987**, 28, 2179.
86. Brown, J.M.; *Angew. Chem., Int. Ed. Engl.*, **1987**, 26, 190.
87. Brown, J.M.; *Chem. Soc. Rev.*, **1993**, 25.
88. Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H.; *J. Org. Chem.*, **1988**, 53, 708.
89. Bailey, M.; Staton, I.; Ashton, P.R.; Marko, I.E.; Ollis, W.D.; *Tetrahedron: Asymmetry*, **1991**, 2, 495.
90. Burgess, K.; Jennings, L.D.; *J. Org. Chem.*, **1990**, 55, 1138.
91. Basavaiah, D.; Dharma Rao, P.; *Synth. Commun.*, **1994**, 24, 917.
92. Adam, W.; Hoch, U.; Saha-Moller, C.R.; Schreier, P.; *Angew. Chem., Int. Ed. Engl.*, **1993**, 32, 1737.
93. Drewes, S.E.; Emslie, N.D.; Field, J.S.; Kahn, A.A.; Ramesar, N.; *Tetrahedron: Asymmetry*, **1992**, 3, 255.
94. Banfi, L.; Colombo, L.; Gennari, C.; Scolastico, C.; *J. Chem. Soc., Chem. Commun.*, **1983**, 1112.
95. Brand, M.; Drewes, S.E.; Loizou, G.; Roos, G.H.P.; *Synth. Commun.*, **1987**, 17, 795.
96. Brand, M.; Drewes, S.E.; Emslie, N.D.; Khan, A.A.; *Synth. Commun.*,

1991, 21, 727.

97. Papageorgiou, C.; Benezra, C.; *Tetrahedron Lett.*, **1984**, 25, 1303.
98. Marfat, A.; McGuirk, P.R.; Helquist, P.; *J. Org. Chem.*, **1979**, 44, 3888.
99. Herlt, A.J.; Rickards, R.W.; Thomas, R.D.; East, P.D.; *J. Chem. Soc., Chem. Commun.*, **1993**, 1497.
100. a) Fenical, W.; *Chem. Rev.*, **1993**, 93, 1673.
b) Garson, M.J.; *Chem Rev.*, **1993**, 93, 1699.
c) D'Auria, M.V.; Minale, L.; Riccio, R.; *Chem. Rev.*, **1993**, 93, 1839.
101. Ameer, F.; Drewes, S.E.; Houston-McMillan, M.S.; Kaye, P.T.; *J. Chem. Soc., Perkin Trans. I*, **1985**, 1143.
102. Buchholz, R.; Hoffmann, H.M.R.; *Helv. Chim. Acta*, **1991**, 74, 1213.
103. Gruiec, A.; Foucaud, A.; Moinet, C.; *New. J. Chem.*, **1991**, 15, 943.
104. Calo, V.; Lopez, L.; Pesce, G.; *J. Organomet. Chem.*, **1988**, 353, 405.
105. Ameer, F.; Drewes, S.E.; Esmlie, N.D.; Kaye, P.T.; Mann ; R.L.; *J. Chem. Soc., Perkin Trans. I*, **1983**, 2293.
106. Ameer, F.; Drewes, S.E.; Houston-McMillan, M.S.; Kaye, P.T.; *S. Afr. J.Chem.*, **1986**, 39, 57.
107. Ameer. F.; Drewes, S.E.; Field, J.S.; Kaye, P.T.; *S. Afr. J. Chem.*, **1985**, 38, 35.
108. Ameer, F,; Drewes, S.E.; Kaye, P.T.; Loizou, G.; Malissar, D.G.; Roos, G.H.P.; *S. Afr. J. Chem,*. **1987**, 40, 35.
109. Drewes, S.E.; Slater-Kinghorn, B.J; *Synth. Commun.*, **1986**, 16, 603.
110. Amri, H.; Rambaud, M.; Villieras, J.; *J. Organomet. Chem.*, **1990**, 384, 1.
111. Amri, H.; Rambaud, M.; Villieras, J.; *Tetrahedron*, **1990**, 46, 3535.
112. Beltaief, I,; Amri, H.; *Synth. Commun.*, **1994**, 24, 2003.
113. Bauchat, P.; Le Rouille, E.; Foucaud, A.; *Bull. Chim. Soc. Fr.*, **1991**, 267; *Chem. Abstr.*, **1991**, 115, 91980b.
114. Basavaiah, D.; Bhavani, A.K.D.; Sarma, P.K.S.; *J. Chem. Soc., Chem. Commun.*, **1994**, 1091.
115. Heerden, F.R.; Huyser, J.S.; Holzapfel, C.W.; *Synth. Commun.*,**1994**, 24, 2863.
116. Basavaiah, D.; Sarma, P.K.S.; *J. Chem. Soc., Chem. Commun.*, **1992**, 955.
117. Auvray, P.; Knochel, P.; Normant, J.F.; *Tetrahedron*, **1988**, 44, 6095.
118. Charette, A.B.; Cote, B.; *Tetrahedron Lett.*, **1993**, 34, 6833.
119. Roush, W.R.; Brown, B.B.; *J. Org. Chem.*, **1993**, 58, 2151.
120. Mazdiyasni, H.; Konopacki, D.B.; Dickman, D.A.; Zydowsky, T.M.; *Tetrahedron Lett.*, **1993**, 34, 435.
121. Colombani, D.; Navarro, C.; Degueil-Castaing, M.; Maillard, B.; *Synth. Commun.*, **1991**, 21, 1481.
122. Navarro, C.; Degueil-Castaing, M.; Colombani, D.; Maillard, B.;

Synth. Commun., **1993**, 23, 1025.
123. Colombani, D.; Maillard, B.; *J. Chem. Soc., Chem. Commun.*, **1994**, 1259.
124. Colombani, D.; Maillard, B.; *J. Org. Chem.*, **1994**, 59, 4765.
125. Konno, M.; Yuasa, Y.; Harada, M.; Miura, T.; Kumobayashi, H.; *Jpn. Kokai Tokyo Koho JP* 06,172,300(94,172,300): *Chem. Abstr.*, **1995**, 112 55724g.
126. Foucaud, A.; El Guemmout, F.; *Bull. Soc. Chim. Fr.*, **1989**, 403. *Chem. Abstr.*, **1990**, 112, 76324k.
127. Basavaiah, D.; Bhavani, A.K.D., Pandiaraju, S.; Sarma, P.K.S.; *Synlett*, **1995**, 3, 243.
128. Mason, P.H.; Emslie, N.D.; *Tetrahedron*, **1994**, 50, 12001.
129. Janecki, T.; Bodalski, R.; *Synthesis*, **1990**, 799.
130. Basavaiah, D.; Pandiaraju, S.; *Tetrahedron* (in press).
131. Basavaiah D.; Pandiaraju, S.; *Tetrahedron Lett.*, **1995**, 36, 757.
132. Pandiaraju, S. Ph.D. Thesis, University of Hyderabad, **1995**.
133. Drewes, S.E.; Emslie, N.D.; Karodia, N.; Loizou, G.; *Synth. Commun.*, **1990**, 20, 1437.
134. Yamamoto, K.; Deguchi, R.; Tsuji, J.; *Bull. Chem. Soc. Jpn.*, **1985**, 58, 3397.
135. Hoffmann, H.M.R.; Eggert, U.; Poly, W.; *Angew. Chem., Int. Ed. Engl.*, **1987**, 26, 1015.
136. Hoffmann, H.M.R.; Weichert, A.; Slawin, A.M.Z.; Williams, D.J.; *Tetrahedron*, **1990**, 46, 5591.
137. Basavaiah, D.; Pandiaraju, S.; Sarma, P.K.S., *Tetrahedron Lett.*, **1994**, 35, 4227.
138. Hoffmann, H.M.R.; Rabe, J.; *Helv. Chim. Acta*, **1984**, 67, 413.
139. Bailey, W.J.; Hudson, R.L.; Yates, E.T.; *J. Org. Chem.*, **1963**, 28, 828.
140. a) Bellus, D.; Weis, C.D.; *Tetrahedron Lett.*, **1973**, 999.
b) Bellus, D.; Bredow K.V.; Sauter, H.; Weis, C.D.; *Helv. Chim. Acta*, **1973**, 56, 3004.
c) Dowd, P.; Kang, K.; *Synth. Commun.*, **1974**, 151.
141. Weichert, A.; Hoffmann, H.M.R.; *J. Chem. Soc., Perkin Trans. I*, **1990**, 2154.
142. Oda, R.; *Kagaku (Kyoto)*, **1988**, 43, 208 ; *Chem. Abstr.*, **1988**, 109, 23395r.
143. Daude, N.; Eggert, U.; Hoffmann, H.M.R.; *J. Chem. Soc., Chem. Commun.*, **1988**, 206.
144. Hoffmann, H.M.R.; Gassner, A.; Eggert, U.; *Chem. Ber.*, **1991**, 124, 2475.
145. Adam, W.; Salagado, V.O.N.; Peters, E.-M.; Peters, K;. von Schnering, H.G.; *Chem. Ber.*, **1993**, 126, 1481.
146. Kanemasa, S.; Kobayashi, S.; *Bull. Chem. Soc. Jpn.*, **1993**, 66, 2685.

147. Heathcock, C.H.; in Morrison, J.D.(editor); *Asymmetric Synthesis*, Academic Press, New York, **1984**, 3, 111.
148. Utaka, M.; Onoue, S.; Takeda, A.; *Chem. Lett.*, **1987**, 971.
149. Sato, S.; Matsuda, I.; Shibata, M.; *J. Organomet. Chem.*, **1989**, 377, 347.
150. Bailey, M.; Marko, I.E.; Ollis, W.D.; *Tetrahedron Lett.*, **1991**, 32, 2687.
151. Jackson, R.F.W.; Standen, S.P.; Clegg, W.; McCamley, A.; *Tetrahedron Lett.*, **1992**, 33, 6197.
152. Atkinson, R.S.; Fawcett, J.; Russel, D.R.; Williams, P.J.; *J. Chem. Soc., Chem. Commun.*, **1994**, 2031.
153. Perlmutter, P.; Tabone, M.; *Tetrahedron Lett.*; **1988**, 29, 949.
154. Lawrence, R.M.; Perlmutter, P.; *Chem. Lett.*, **1992**, 305.
155. Bulliard, M.; Zehnder, M.; Giese, B.; *Helv. Chem. Acta*, **1991**, 74, 1600.
156. Bulliard, M.; Zeitz, H.-G.; Giese, B.; *Synlett*, **1991**, 423.
157. Giese, B.; Bulliard, M.; Dickhaut, J.; Halbach, R.; Hassler, C.; Hoffmann, U.; Hinzen, B.; Senn, M., *Synlett*, **1995**, 116.
158. Kundig, E.P.; He-xu, L.; Romanens, P.; *Tetrahedron Lett.*, **1995**, 36, 4047.
159. Loffler, A.; Pratt, R.J.; Ruesch, H.P.; Dreiding, A.S.; *Helv. Chim. Acta*, **1970**, 53, 383.
160. Ohler, E.; Reininger, K.; Schmidt, U.; *Angew. Chem., Int. Ed. Engl.*, **1970**, 9, 457.
161. Drewes, S.E.; Hoole, R.F.A.; *Synth. Commun.*, **1985**, 15, 1067.
162. Nokami, J.; Tamaoka, T.; Ogawa, H.; Wakabayashi, S.; *Chem. Lett.*, **1986**, 541.
163. Drewes S.E.; Taylor, R.B.; Ramesar, N.S.; Field, J.S.; *Synth. Commun.*, **1995**, 25, 321.
164. Masuyama, Y.; Nimura, Y.; Kurusu, Y.; *Tetrahedron Lett.*, **1991**, 32, 225.
165. Alami, N.E.; Belaud, C.; Villieras, J.; *Tetrahedron Lett.*, **1987**, 28, 59.
166. Alami, N.E.; Belaud, C.; Villieras, J.; *Synthesis*, **1993**, 1213.
167. Wanner, M.J.; Koomen, G.J.; *Tetrahedron Lett.*, **1990**, 31, 907.
168. Villieras, J.; Rambaud, M.; *Org. Syntheses*, **1988**, 66, 220.
169. Ferris, A.F.; *J. Org. Chem.*, **1955**, 20, 780.
170. Auvray, P.; Knochel, P.; Normant, J.F.; *Tetrahedron Lett.*; **1986**, 27, 5091.
171. Amri, H.; El Gaied, M.M.; Ayed, T.B.; Villieras, J.; *Tetrahedron Lett.*, **1992**, 33, 6159.
172. Amri, H.; El Gaied, M.M.; Ayed, T.B.; Villieras, J.; *Tetrahedron*

Lett., **1992**, 33, 7345.
173. Reddy, K.C.; Byun, H-S.; Bittman, R.; *Tetrahedron Lett.*, **1994**, 35, 2679.
174. Bode, M.L.; English, R.B.; Kaye, P.T.; *S. Afr. J Chem.*, **1992**, 45, 25, *Chem. Abstr.*, **1992**, 117, 37340w.
175. Foucaud, A.; Brine, N.; *Synth. Commun.*, **1994**, 24, 2851.
176. Bauchat, P.; Foucaud, A.; *Tetrahedron Lett.*, **1989**, 30, 6337.
177. Bode, M.L.; Kaye, P.T.; *J. Chem. Soc., Perkin Trans. I*, **1990**, 2612.
178. Ayed, T.B.; Amri, H.; El Gaied, M.M.; *Tetrahedron*, **1991**, 47, 9621.
179. Calderon, A.; Font, J.; de March, P.; *Tetrahedron*, **1992**, 48, 5347.
180. Mason, P.H.; Emslie, N.D.; Drewes, S.E.; *Synth. Commun.*, **1995**, 25, 183.
181. Paterson, I.; Bower, S.; Tillyer, R.D.; *Tetrahedron Lett.*, **1993**, 34, 4393.
182. Brzezinski, L.J.; Levy, D.D.; Leahy, J.W.; *Tetrahedron Lett.*, **1994**, 35, 7601.
183. Hall, A.W.; Lacey, D.; Hill, J.S.; McDonnel, D.G.; *Supramolecular Science*, **1994**, 1, 21.
184. Field, J.S.; Ramesar, N.; Manickum, T.; Roos, G.H.P.; *S. Afr. J. Chem.*, **1993**, 46, 39; *Chem. Abstr.*; **1994**, 120, 163884b.
185. Morita, K.; Suzuki, Z.; Hirose, H.; *Bull. Chem. Soc. Jpn.*, **1968**, 41, 2815.
186. Imagawa, T.; Uemura, K.; Nagai, Z.; Kawanisi, M.; *Synth. Commun.*, **1984**, 14, 1267.
187. Sato, S.; Matsuda, I.; Izumi, Y.; *Chem. Lett.*, **1985**, 1875.
188. Matsuda, I., Shibata, M.; Sato, S.; *J. Organomet. Chem.*, **1988**, 340, C_5-C_7.
189. Moiseenkov, A.M.; Ceskis, B.; Shpiro, N.A.; Stashina, G.A.; Zhulin, V.M.; *Izv. Akad. Nauk SSSR, Ser. Khim.*; **1990**, 595; *Chem.* Abstr., **1990**, 113, 114922j.
190. Bertenshaw, S.; Kahn, M.; *Tetrahedron Lett.*, **1989**, 30, 2731.
191. Kitazume, S.; *Chem. Abstr.*, **1978**, 88, 89131f.
192. Roos, G.H.P.; Haines, R.J.; Raab, C.E.; *Synth. Commun.*, **1993**, 23, 1251.

NOTE ADDED IN PROOF

Since submitting this review, the following relevant papers have appeared.

193. Marko, I.E.; Giles, P.R.; Janousek, Z.; Hindley, N.J.; Declercq, J-P; Tinant. B.; Feneau-Dupont, J.; Svendsen, J.S., *Recl. Trav. Chim. Pays-Bas* , **1995**, 114, 239.

194. Atkinson, R.S.; Fawcett, J.; Russell, D.R.; Williams, P.J.; *Tetrahedron Lett.*, **1995**, 36, 3241.
195. Marson, C.M.; Pink, J.H.; Smith, C.; *Tetrahedron Lett.*, **1995**, 36, 8107.
196. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L.; *J. Org. Chem.*, **1995**, 60, 4697.
197. Urabe, H.; Yamashita, K.; Suzuki, K.; Kobayashi, K.; Sato, F., *J. Org. Chem.*, **1995**, 60, 3576.
198. Perlmutter, P.; Tabone, M.; *J. Org. Chem.*, **1995**, 60, 6515.
199. Jackson, R.F.W.; Standen, S.P.; Clegg, W.; McCamley, A.; *J. Chem. Soc. Perkin Trans. I*, **1995**, 141.
200. Ciganek, E.; *J. Org. Chem.*, **1995**, 60, 4635.
201. Barrett, A.G.M.; Kamimura, A.; *J. Chem. Soc., Chem. Commun.*, **1995**, 1755.
202. Ayed T.B.; Amri, H.; El Gaied, M.M.; Villieras,; *Tetrahedron*, **1995**, 51, 9633.

(*Received* 29 *January* 1996)