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SYNTHETIC POTENTIAL OF THE TERTIARY-AMINE-CATALYSED REACTION OF ACTIVATED VINYL CARBANIONS WITH ALDEHYDES

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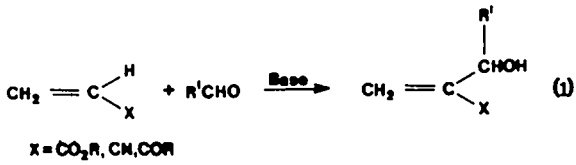
CONTENTS

1. INTRODUCTION

The base-catalysed reaction of activated α,β-unsaturated vinyl systems with suitable electrophiles (generally aldehydes) affords useful synthetic intermediates (Eq. 1). When the base is diazabicyclo[2,2,2]octane (DABCO) the sequence has frequently been referred to as the 'DABCO reaction'. We suggest that this name is inappropriate since it implies a restriction to this particular base.



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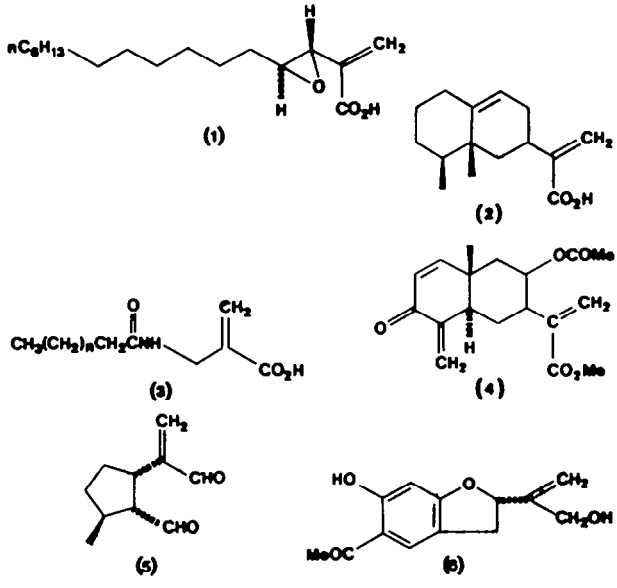
The above reaction has its origin in a patent granted to Baylis and Hillman,[1] of the Celanese Corporation of New York, in 1972. These authors describe the reaction between α,β-unsaturated esters, nitriles, amides or ketones with a broad spectrum of aldehydes. The catalysts listed in the patent, including DABCO, are all cyclic tertiary amines. It is stated that the catalyst, which constitutes between 0.1 and 10% of the reactant weight, should be a relatively strong base. Further, it is stipulated that the reaction may be carried out at temperatures between 0 and 200°C, the pressure may be atmospheric, but it will also proceed at higher pressures or under vacuum. Solvents such as dioxane, tetrahydrofuran, ethanol or chloroform are all suitable but in many instances the solvent is unnecessary.

Despite the obvious potential of the reaction for the introduction of α-substituted acrylates and related systems, little or no interest was shown in it for 10 years. This may reflect an innate weakness of organic chemists to make the fullest use of information in the patent literature. In 1982 we[2] first made reference to the work of Baylis and Hillman[1] in connection with the synthesis of a necic acid precursor and subsequently a steady stream of papers has appeared on the subject. It is our intention in this report to draw attention to the synthetic potential of the reaction. Indeed, we believe that as this reaction becomes better known among organic chemists, many more applications will be found. In the light of this and earlier statements it would seem appropriate to refer to the general sequence in question as the 'Baylis–Hillman Reaction'.

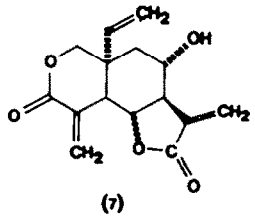
2. ACRYLATE AND RELATED SYSTEMS

2.1. *Natural occurrence*

In a recent review Yu and Helquist[3] have highlighted the fact that the acrylate unit features prominently in a large number of naturally occurring substances that possess biological activity. Some specific examples falling into this category are: conocandin (**1**)[4] (a fungistatic antibiotic from *Hormococcus conorum*), the eremophildienoic acid (**2**)[5] (isolated from *Athanasia* species), the fatty acid derivative of β-alanine (**3**)[6] (from the Red Sea sponge *Fasicospongia cavernosa*), the sesquiterpene gerin (**4**)[7] (isolated from *Geraea viscida*, and which causes allergenic contact dermatitis in humans), the unsaturated monoterpene dialdehyde (**5**)[8] (from *Teucrium marum*), and the tremetone derivative (**6**)[8] (obtained from *Ophryosporus angustifolius*). Probably the best-known of all the



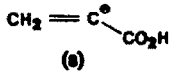
acrylate systems is that present in the α-methylene lactones and exemplified by the much-studied compound vernolepin (7).[10]



(7)

2.2. *Methods of synthesis*

The acrylate moiety can be introduced into the desired system by a direct procedure involving (i) a formal vinyl carbanion (8) or (ii) by making use of a so-called masked acrylate or acrylate anion equivalent.



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2.2.1. *Direct introduction.* Formally the Baylis–Hillman reaction leads to the formation of a vinyl carbanion through the intermediacy of a catalyst. Reaction conditions are extremely mild and very few problems with unwanted side reactions are experienced. This is not the case when the vinyl carbanion is generated from monosubstituted activated ethylenes (acrylates) with strong bases such as lithium diisopropylamide (LDA) or lithium tetramethylpiperidide (LTMP). The elegant work of Feit *et al.*[11] in this area has shown that a severe practical difficulty associated with the formation of vinyl carbanions under the above conditions is the facile anionic polymerisation of the acrylate.

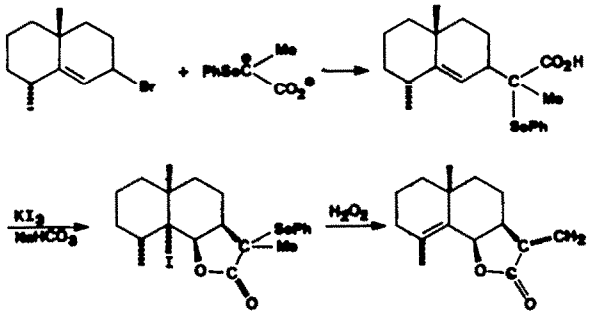
2.2.2. *Masked acrylates.* This technique has been used with considerable success, and the method of Petragnani *et al.*[12] for the synthesis of an α-methylene lactone serves to illustrate the concept (Scheme 1).

An alternative eliminative approach was adopted by Yu and Helquist[3] who used a synthon of general structure $ZCH_2CH_2CO_2R$ in which the Z group, after appropriate modification, finally serves as a leaving group in an elimination reaction that unmasks the acrylate system. We have extended this system further by the selection of a chiral Z group which makes possible the synthesis of chiral α-hydroxyalkyl acrylates (Scheme 2).[13,14]

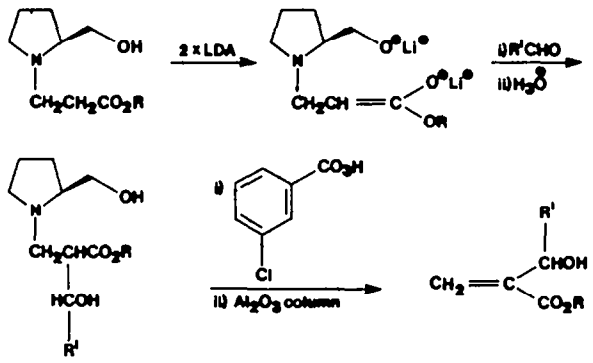
3. CATALYSTS

3.1. *Phosphines*

As far back as 1964 Oda *et al.*[15] investigated the reaction of acrylics with benzaldehyde and triphenylphosphine in roughly equimolar proportions. The reaction was carried out under N_2 at an initial temperature of 130°C which was subsequently raised to 140°C and maintained for 6 hr. After work-up 'Wittig-type' products could be isolated in yields varying between 9 and 45%. Selected results are shown in Table 1.



Scheme 1. Synthesis of an α-methylene lactone.



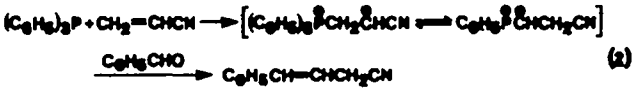
Scheme 2. Synthesis of chiral α-hydroxyalkyl acrylates.

Table 1. Yield of products using triphenylphosphine as catalyst.

Acrylic derivative	Carbonyl compound	Reaction time (hr)	Product	Yield*
CH_2=CHCN	C_6H_5CHO	8	C_6H_5CH=$CHCH_2CN$	23
CH_2=$CHCO_2Et$	C_6H_5CHO	8	C_6H_5CH=$CHCH_2CO_2Et$	28
CH_2=$CHCO_2Et$	Cyclohexanone	14	No reaction	—
Diethyl maleate	C_6H_5CHO	8	C_6H_5CH=$C(CO_2H)CH_2CO_2H$	16

* Based on the quantity of acrylic derivative used.

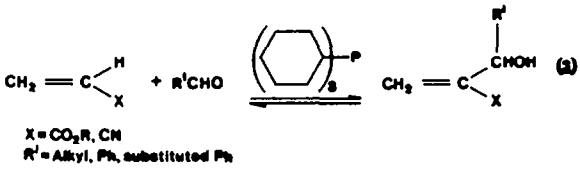
Oda[15] suggests the following mechanism for the reaction (Eq. 2):



(2)

It seems likely that the order of addition (phosphine, aldehyde, acrylic), coupled with the high temperature, leads to formation of a betaine intermediate rather than the vinyl carbanion. Oda also reaches the conclusion that the addition of a proton donor (such as an alcohol or carboxylic acid) has no influence on the overall yield of end product and that the proton shift from the betaine to the phosphorus ylide (Eq. 2) occurs without outside intervention.

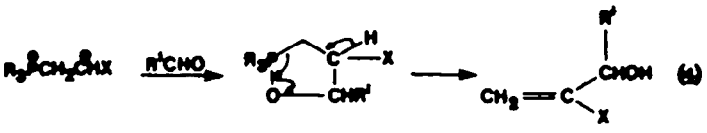
In 1968 Morita *et al.*,[16] using the same reactants as Oda,[15] but employing only a catalytic amount of tricyclohexylphosphine (instead of triphenylphosphine) and allowing reaction to proceed for 2 hr at 120–130°C, report for the first time, isolation of 2-hydroxyalkyl derivatives of acrylate and related systems (Eq. 3). Yields of up to 85% are claimed but the conversion of the α,β-unsaturated



(3)

reactant remained low (23%). Morita[16] suggests that the name 'carbinol reaction' should be used for the above conversion. The mechanism proposed by him is the same as that described later (see Eqs 5–7), but he further considers the cyclic possibility (Eq. 4). While he concedes that ylide formation via isomerisation as described by Oda[15] is possible when triphenylphosphine is used as catalyst, this is not the case when tricyclohexylphosphine or tributylphosphine are employed.[17,18]

No immediate notice was taken of Morita's results,[16] possibly because of the poor conversion of the acrylonitrile and acrylate ester to the desired hydroxyalkyl derivatives. None the less, we believe that some of the credit for this conversion should be accorded to Morita *et al.*[16]



R = Cyclohexyl

X and R' as for Eq. (3)

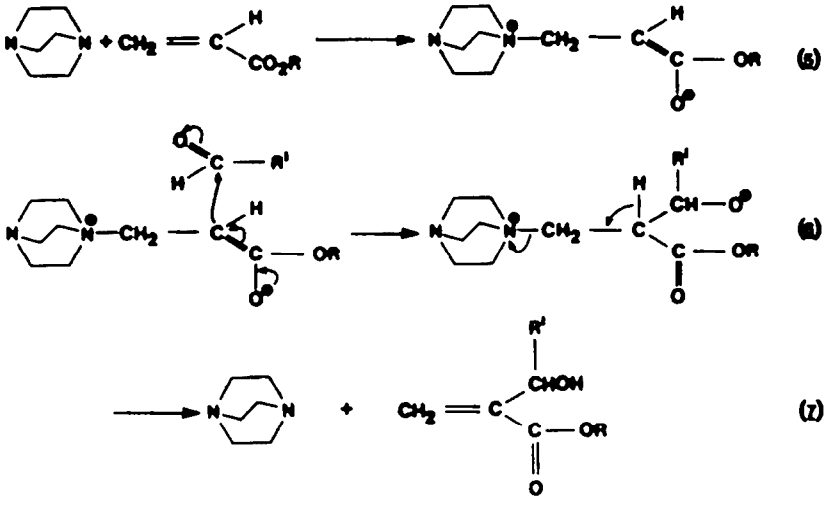
More recently Imagawa,[19] using tributylphosphine catalyst in conjunction with triethylaluminium at elevated temperatures (80°C for 22 hr), obtained much higher conversions for the same carbonyl compounds (up to 47% for decanal). Surprisingly, the reaction with benzaldehyde afforded only 27% of the desired hydroxyalkyl derivative. These authors speculate on the role played by the triethylaluminium chloride and conclude that the enhancement of reactivity is due to the co-ordination of the Lewis acid with the carbonyl oxygen of the aldehyde.

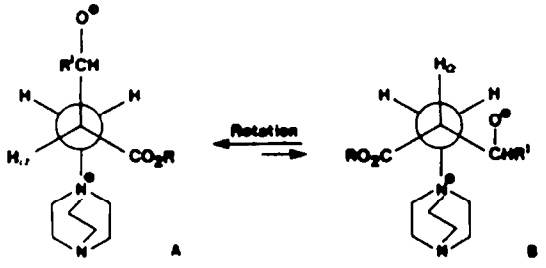
3.2. *Tertiary amines*

Baylis and Hillman[1] refer to the use of teriary cyclic amines such as DABCO (9) and quinuclidine (10), but non-cyclic tertiary amines such as triethylamine have also been employed by other

(9) (10)

researchers.[20] It seems reasonable that the first step in the reaction involves a Michael addition of the tertiary amine to the α,β-unsaturated carbonyl, for example an acrylate ester (Eq. 5).[16] This is followed by nucleophilic attack on the aldehyde (Eq. 6) and subsequent elimination of the tertiary amine (Eq. 7). Hoffmann and Rabe[21] suggest this type of mechanism and also speculate on the possibility of preferred conformations of the intermediate (Scheme 3). The zwitterionic intermediate

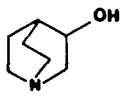




Scheme 3. Conformations of the zwitterionic intermediate.

is considered to exist as an equilibrium mixture of two conformations of which A is preferred on account of possessing fewer unfavourable gauche interactions. To date no such zwitterionic intermediate has been isolated and for the present the mechanistic detail must remain speculative.

3.2.1. 3-*Hydroxyquinuclidine*. Very recently we have found[22] that racemic 3-hydroxyquinuclidine (3-QDL) (**11**) will also catalyse the Baylis–Hillman reaction and, in fact, leads to a considerable

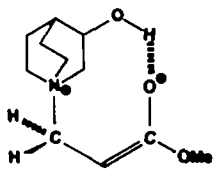


(11)

rate enhancement over DABCO. A comparison of the rates of reaction of methyl acrylate with a range of aldehydes, including heterocyclic ones, illustrates this point (Table 2).

Other points which emerge from this study are that reaction half-lives can be significantly reduced by: (i) the addition of methanol (or other alcohol); (ii) increasing the proportion of catalyst; (iii) using electrophilic heterocyclic aldehydes.

The possibility of hydrogen-bonded stabilisation of the catalyst-acrylate adduct by a protic species such as methanol is attractive, particularly when the catalyst is itself hydroxylated as with 3-QDL. In this instance it is tempting to invoke a cyclically stabilised ambident anion intermediate of the form **12**. Our studies have further shown[23] that reaction times are considerably longer when



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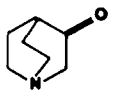


(13)

the hydroxyl group in 3-QDL is blocked by acetylation or when 3-quinuclidinone (**13**) is used. The only other study relating to the effect of hydroxylic solvents (proton donors) in these reactions is that of Oda,[15] as mentioned earlier.

The increased reactivity of heterocyclic aldehydes (Table 2) should also be noted since it could facilitate the synthesis of some alkaloids bearing a pyridine, pyrrolidine or quinoline nucleus. Hoffmann and Rabe[21] report that furfural and nicotinaldehyde (the only other heterocyclic aldehydes studied to date) react rapidly with methyl acrylate due to the fact that the necessary proton migrations leading to restoration of the α,β-unsaturated system (Eqs 5–7) are aided by the basic heteroatoms on the aldehyde.

3.3. *Basicity of DABCO and related bases*

Hine and Chen[24] have related the rate of dedeuteration of isobutyraldehyde-2-*d* with tertiary amines to steric factors present in the amines. For example, 1-azabicycloheptane must have the

Table 2. Rate enhancement with 3-hydroxyquinuclidine (3-QDL)

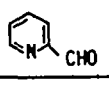
Aldehyde	Catalyst	$t^{1/2} \times 10^{-3}$ (min)	Yield
CH_3CHO	DABCO	3.0	90
CH_3CHO	3-QDL	<0.9	90
	DABCO	0.01	83
	3-QDL	<0.005	83
	DABCO	0.06	82
	DABCO	0.20	94

Table 3. Deuteration rates (10^4k) of $(CH_3)_2CDCHO$ by various bases

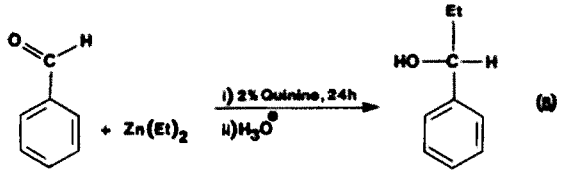
Quinuclidine	370	10.90
1-Azabicycloheptane	83	10.53
3-Quinuclidinol	—	9.48
DABCO	32	8.47
3-Quinuclidinone	4.3	6.93

methylene groups attached to nitrogen pulled back from the non-bonded electron pair relative to the situation in quinuclidine and it is therefore the less-hindered amine. The rate constants obtained by these researchers are shown above (Table 3).

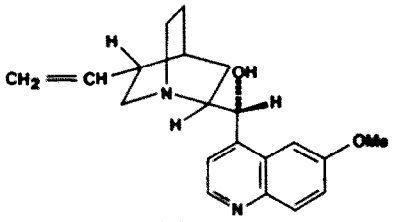
From the limited data available at present (the last three bases above) it appears that basicity and reaction rate in the Baylis–Hillman reaction run parallel.

3.4. *Chiral catalysts*

The concept of chemical enzymes is relatively recent and has been exploited very successfully by Wynberg[25,26] (Eq. 8) and Kitamura *et al.*[27] Thus Wynberg demonstrated that benzaldehyde afforded (*R*)-(+)-1-phenyl-propanol with an enantiomeric excess of 68% and this rose to 90% with 2-ethoxybenzaldehyde.



Inspection of these results and the structure of quinine (**14**) immediately raises the question of the use of chiral catalysts for the Baylis–Hillman reaction. Our preliminary studies in this regard

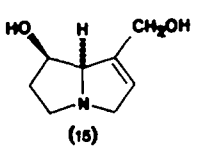


(14)

have been disappointing in the sense that only low *ee*'s are obtained (Table 4). Bearing in mind some of the comments made by Wynberg,[26] such as the use of a 2-alkoxybenzaldehyde and similar more bulky aldehydes, as opposed to acetaldehyde, it seems likely that enhancement of enantioselectivity is possible. The abundance of naturally occurring basic compounds (alkaloids, amino acids), many of which possess one or more hydroxyl groups, ensures that this line of investigation is far from exhausted.

Table 4. Use of chiral catalysts for chiral induction

Catalyst	Aldehyde	Substrate	Time (days)	%*ee*
(i) Brucine	CH_3CHO	$CH_2{=}CHCOCH_3$	4.75	8
(ii) Cinchonidine	CH_3CHO	$CH_2{=}CHCOCH_3$	4.50	10
(iii) Quinidine	CH_3CHO	$CH_2{=}CHCOCH_3$	7.0	12
(iv) Quinine	CH_3CHO	$CH_2{=}CHCOCH_3$	4.5	8
(v) Retronecine (**15**)	$4\text{-}NO_2{-}C_6H_4CHO$	$CH_2{=}CHCOCH_3$	30	0
(vi) Retronecine (**15**)	$4\text{-}NO_2{-}C_6H_4CHO$	$CH_2{=}CHCO_2CH_3$	30	11
(vii) (*S*)-(−)-*N*-methyl prolinol (**16**)	CH_3CHO	$CH_2{=}CHCOCH_3$	4	0



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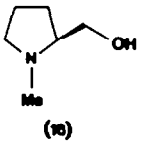

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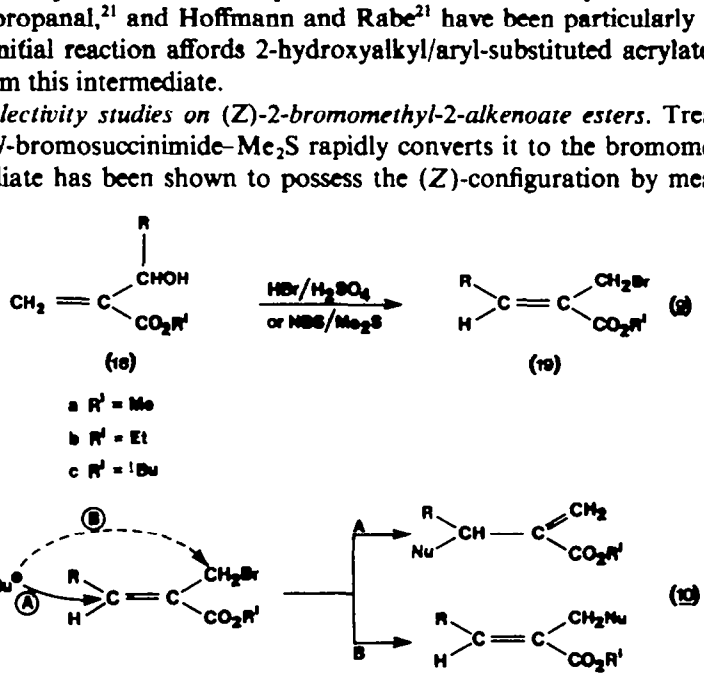
4. SYNTHETIC APPLICATIONS

4.1. *Acrylate esters*

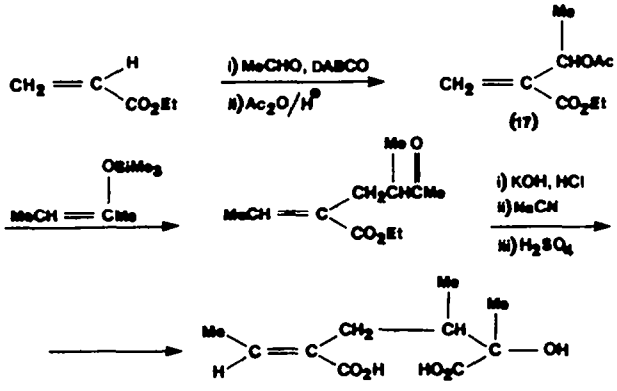
Esters of acrylic acid constitute the major substrate for the Baylis–Hillman reaction. The first serious application of the reaction involved ethyl acrylate and acetaldehyde with subsequent transformation to the necic acid, integerrinecic acid (Scheme 4).[2] While Geissman,[28] in his earlier synthesis of this acid had also made use of the acetylated hydroxy ester (17), his method of synthesis from 3-acetoxybut-1-yne is laborious and several steps are involved.

Acrylate esters have now been reacted with a wide range of aldehydes and there is no longer any doubt regarding the generality of the reaction. Aldehydes have ranged from simple ones such as methanal to more complex ones such as heptanal,[29] trichloroacetaldehyde,[21] 2-furylbenzaldehyde,[21] and 2-methylenepropanal,[21] and Hoffmann and Rabe[21] have been particularly active in this area. In all instances initial reaction affords 2-hydroxyalkyl/aryl-substituted acrylates and elaboration then proceeds from this intermediate.

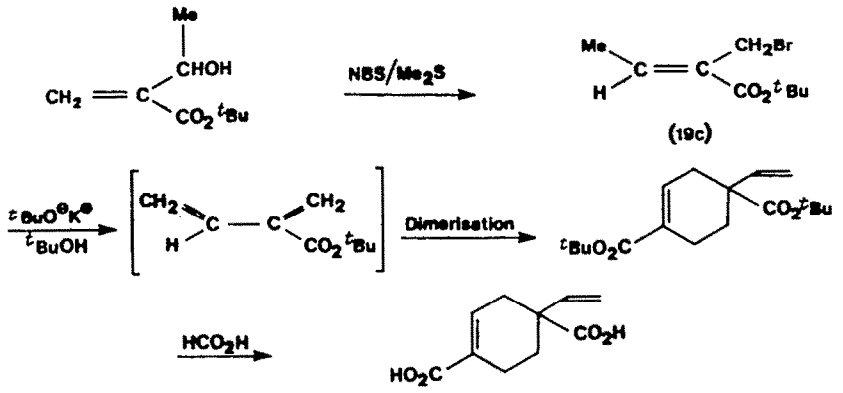
4.1.1. *Regioselectivity studies on* (Z)-2-*bromomethyl*-2-*alkenoate esters*. Treatment of **18** with HBr-H_2SO_4 or *N*-bromosuccinimide–Me_2S rapidly converts it to the bromomethyl ester **19** (Eq. 9). This intermediate has been shown to possess the (*Z*)-configuration by means of X-ray crys-



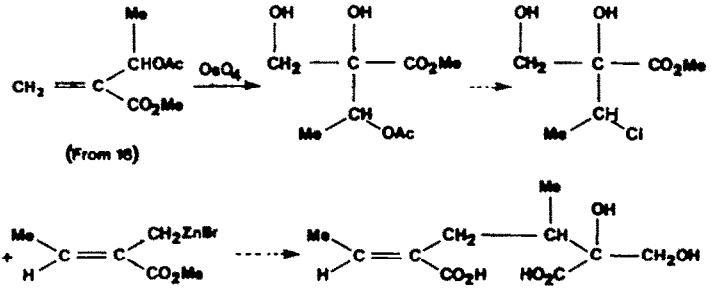
tallography.[30] It is an ambident molecule and nucleophilic attack can take place at the allylic carbon (normal attack, path A) or at the vinylic carbon (C-3 attack, path B) with resultant rearrangement (Eq. 10). Based on results obtained from examination of several nucleophiles, using either NaH–



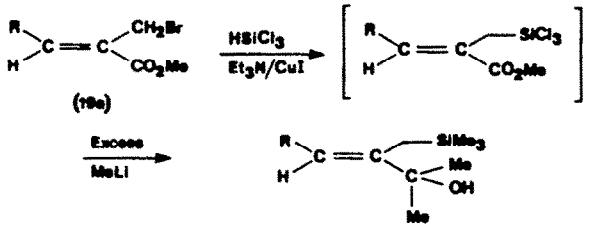
Scheme 4. Synthesis of integerrinecic acid from ethyl acrylate.



Scheme 5. Hoffmann's synthesis of mikanecic acid.[31]



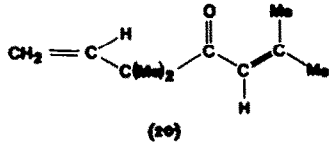
Scheme 6. Synthesis of retronecic acid.[32]

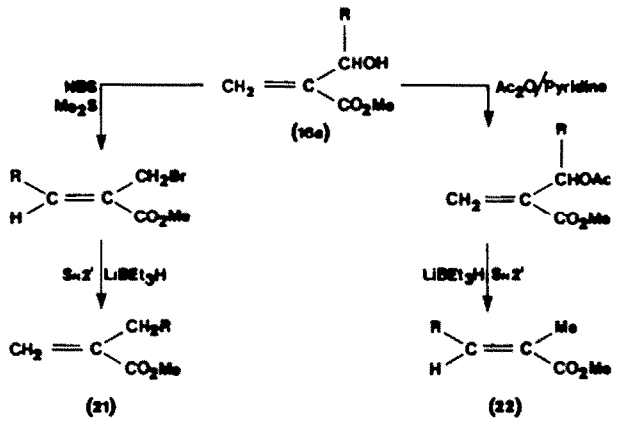


Scheme 7. Synthesis of an allyl silane.

THF or NaOEt–EtOH as solvent systems, the following general features emerge.[29] Attack at the allylic carbon is enhanced by (i) changing the base-solvent system from NaH–THF to NaOEt–EtOH, (ii) increasing the steric bulk of the nucleophile, (iii) increasing the size of the substituent R, where R is alkyl and (iv) introduction of any aryl substituent for R. The flexibility of manipulation of the above system thus allows a wide range of end products and makes it a very versatile procedure. Two typical uses of intermediate **19c** in the synthesis of natural products are shown above (Schemes 5 and 6).[31,32]

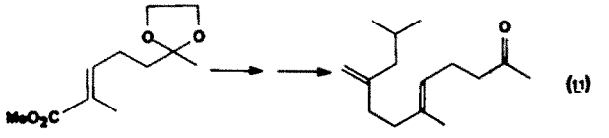
A further useful transformation of **19a** to an allyl silane has been described by Hoffmann (Scheme 7).[33] Initial treatment of **19a** with trichlorosilane and CuI produces the unstable trichlorosilyl intermediate, which, on quenching with a large excess of MeLi, affords the desired allyl silane in 42% overall yield. This route is superior to the conventional Wittig procedure for generating allyl silanes. It is stereocontrolled, proceeds under mild conditions, tolerates a great deal of further functionalisation, and employs simple starting materials. The allyl silanes are useful synthetic intermediates and have many applications. One such example is the synthesis of artemesia ketone **20**, a constituent of exotic perfumes.[34]





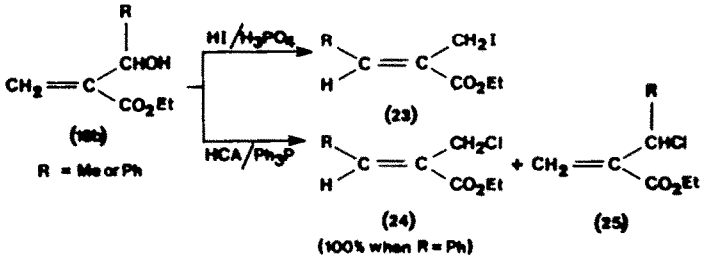
Scheme 8. S_N2' reactions of intermediate (18a).

4.1.2. *S_N2' Reactions of intermediates.* Two reactions, both involving vinylic attack with concomitant rearrangement (Route A, Eq. 10), will be considered.[33] Intermediate **19a** can react with the hydride ion donor, lithium triethylborohydride ($LiBEt_3H$), to produce valuable synthons (Scheme 8). The compound **21** corresponds to an α-alkyl derivative of an acrylate ester and it was generated in remarkably high yield (64%). Direct α-alkylation of acrylic esters with, say, butyl halide and base, is not feasible since the catalyst (DABCO in this instance) is deactivated by quaterisation. The other product (**22**) is interesting insofar as the original acrylate ester has now been transformed into an α-methylated crotyl system (if R = Me). By using this particular route Hoffmann[33] was able to synthesize the unsaturated ketone (Eq. 11) which is a major constituent of *Costus* root oil. Previous attempts to obtain this target molecule suffered from several drawbacks, the most serious being the lack of stereoselectivity.[35,36,37]



4.1.3. *Formation of 2-iodomethyl- and 2-chloromethylbutanoate esters and their reactions.* Whilst the intermediate **18b** readily undergoes brominative allylic rearrangement as shown (Eq. 9), it will also iodinate or chlorinate regioselectively.[38] With HI–conc. H_3PO_4 iodination occurs exclusively at the vinylic carbon whereas treatment with a hexachloroacetone (HCA)–Ph_3P mixture affords both S_N (normal) and S_N' (rearranged) products in a 1 : 1 ratio (Scheme 9).

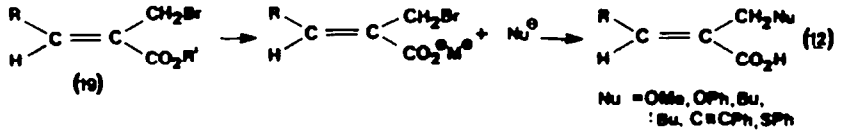
Regioselectivity in allyl alcohols is the subject of a comprehensive review by Magid.[39] Typically secondary allylic alcohols react with HCA–Ph_3P to give predominantly the normal isomer.[40] Our observation[38] that this reagent in the above instance produces an equal mixture of the two isomers indicates that the ethoxycarbonyl group renders the vinylic carbon (C-3) more electrophilic. When the halogeno esters **23**–**25** subsequently react with a nucleophile such as 2-methyl-3-oxobutanoate the product distribution reflects the effect of (i) the nature of the halogen leaving group and (ii) changing the position of the double bond. Thus **23** (R = phenyl) affords exclusively normal sub-



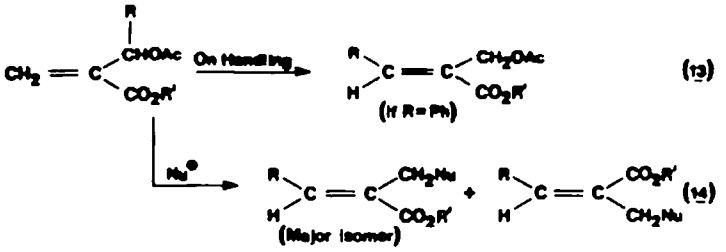
Scheme 9. Normal and rearrangement halogenation products from (18b).[38]

stitution while **24** (also with R = phenyl) gives a mixture of 20% normal and 80% rearranged product.

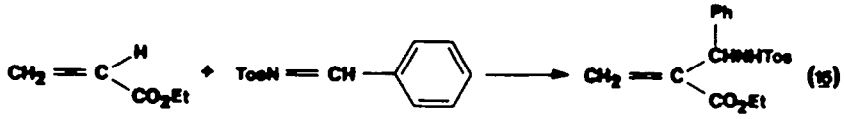
4.1.4. *Acrylic acid synthons.* The intermediate obtained from brominative allylic rearrangement (Eq. 9) has another synthetic use.[41] If the carboxylate anion (rather than the ester) is employed it renders the olefinic bond less reactive towards nucleophilic attack (since it behaves as electron donor) and reaction is then directed at the allylic position. This regioselectivity for almost exclusive allylic substitution was operative for all the common nucleophiles examined (Eq. 12). The choice of this



particular intermediate obviates the potential drawbacks (possible loss of double bond stereochemical integrity, allylic rearrangement) of the route to these substituted acrylate systems via displacement–rearrangement of aceates (Eqs 13 and 14).



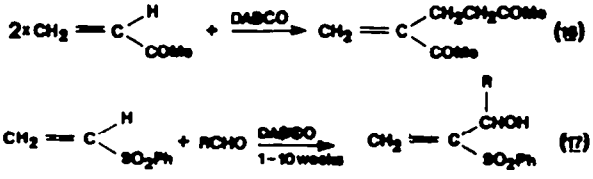
4.1.5. *Coupling of acrylate esters and imines.* Perlmutter and Teo[42] have shown that imines may be substituted for aldehydes in the reaction with acrylate esters. Thus tosylimines of aromatic aldehydes readily reacted with ethyl acrylate (using DABCO as catalyst) (Eq. 15) and the resultant products have obvious value as precursors to β-lactams.



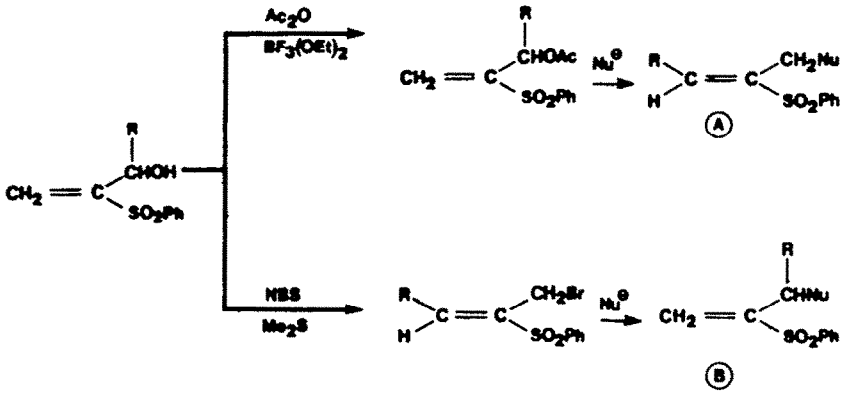
4.2. *Activated vinyl systems other than acrylates*

4.2.1. *Vinyl ketones.* In a recent paper Basavaiah[43] reports "a straightforward and simple synthesis of α-methylene-β-hydroxyalkanones via the reaction of methyl vinyl ketone with representative aldehydes catalysed by DABCO in THF as solvent". The use of α,β-unsaturated ketones is covered in the original patent by Baylis and Hillman[1] but the work of Basavaiah does extend it to include some lone chain aldehydes—up to C_{15}. Basavaiah[43] reports yields of 50–73% with reaction times of up to 15 days for $C_{15}H_{31}CHO$. He also finds that propanal and furfural did not afford pure products but no reason is advanced for this.

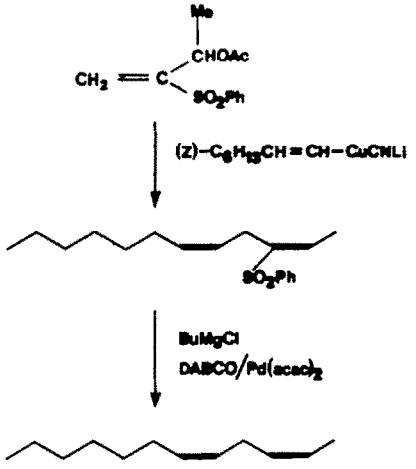
Villieras[44] also reports on the reaction of methyl vinyl ketone with selected aldehydes and concludes that reaction is considerably faster than for acrylate esters. When methyl vinyl ketone is employed as electrophile as well, a slow (7 days) Michael addition occurs to give 3-methylenehepta-2,6-dione (Eq. 16).



4.2.2. *Phenyl vinyl sulphones.* An obvious extension of the Baylis–Hillman reaction would be to replace the 'normal' vinylic electron withdrawing group such as ester or ketone with a sulphone. This is in fact what Normant *et al.*[45,46] have done through the use of phenyl vinyl sulphone (Eq. 17). It is of interest to note here that reaction was extremely slow, in some instances extending to



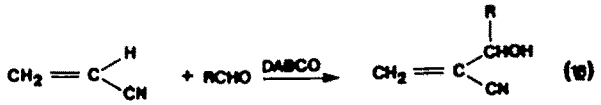
Scheme 10. Reaction of vinyl sulphone derivatives with a nucleophile.



Scheme 11. Synthesis of (2*Z*, 5*Z*)-dodecadiene.

11 weeks. Typical transformations executed by Normant[45] are shown in Scheme 10. The allylic acetates and bromides react regioselectively with carbon nucleophiles to give S_N2' substitution products respectively of type A and B. The synthesis of 2*Z*,5*Z*-dodecadiene in 73% yield and very good isomeric purity is shown in Scheme 11. In this instance the addition of 2 equivalents of $BF_3(OEt)_2$[47] increases the S_N2'/S_N2 ratio to 9:1. At the end of reaction the sulphone is readily removed.

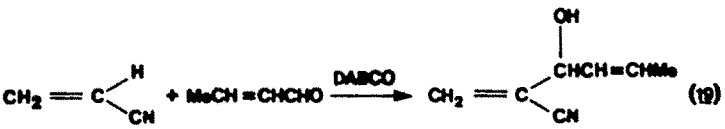
4.2.3. *Acrylonitrile.* In a very recent publication Basavaiah[48] has drawn renewed attention to the synthesis of α-hydroxyalkyl acrylonitriles from the reaction between acrylonitrile and selected aldehydes in the presence of DABCO (Eq. 18). Whilst the paper adds little to what is already stated



(18)

in the original patent, Basavaiah[48] does comment on the fact that DABCO afforded a much cleaner product than DBU(1,8-diazabicyclo[5,4,0]undec-7-ene), or diisopropylethylamine. For the shorter aldehydes—up to C_5—total reaction time is typically 40 hr. This reaction rate is considerably faster than with the acrylate esters.

Villieras[44] has also described the preparation of α-methylene-β-hydroxynitriles with DABCO as catalyst. The work again adds very little to that which is recorded in the patent other than the fact that an α,β-unsaturated aldehyde (crotonaldehyde) is employed as electrophile. In this instance a 59% yield of the 1,2-addition product is obtained after 48 hr (Eq. 19).

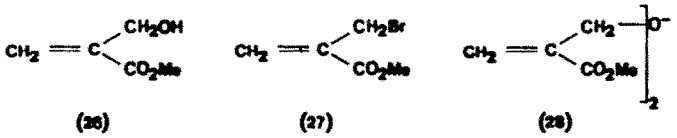


From the results available at present it appears that the α,β-unsaturated systems all react with aldehydes and that the rate of reaction is:

ketone > nitrile > ester > sulphones.

4.3. *Reaction of acrylate esters with formaldehyde*

α-Hydroxymethylacrylate esters (**26**) and the corresponding bromomethyl derivative (**27**) have found many uses as synthetic intermediates.[49] Their inherent bifunctional reactivity towards nucleophiles has led to application in bicyclic[50,51] and spirocyclic ring[52] formation. Numerous routes to **26** are known[53] with one of the more recent ones being described by Villieras *et al.*[54] These authors employ a Wittig–Horner type reaction and this affords **26** in 77% yield.

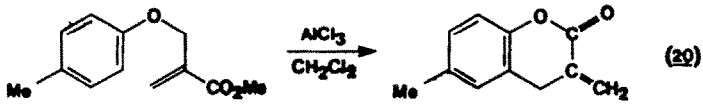


(26) (27) (28)

We have found that **26** can readily be obtained by coupling methyl acrylate and formaldehyde with DABCO as catalyst by carrying out the reaction in a sealed container. Although **26** is contaminated by the ether **28**, the mixture of the two can be converted to **27** in good yield.[55]

4.4. *Claisen rearrangement of α-hydroxyalkyl acrylates*

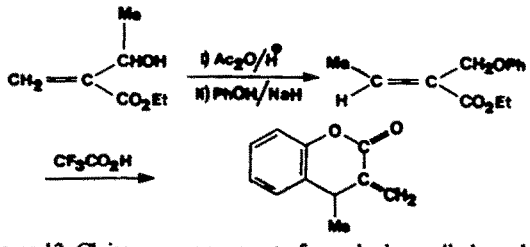
There are few reports on the synthesis of 3-methylene-coumarins and the published procedures are circuitous.[56,57] Recently Rajagopalan *et al.*[58] have published an elegant route to these compounds via a Lewis acid catalysed Claisen rearrangement of methyl α-aryloxymethyl acrylates (Eq. 20).



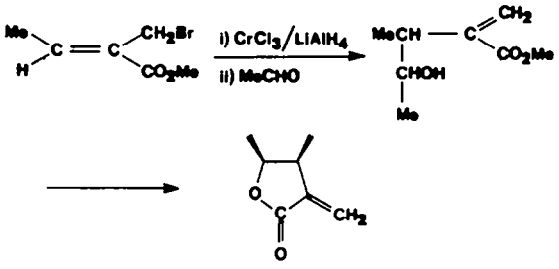
Synthesis of the starting material for this reaction is not simple but the Baylis–Hillman reaction readily leads to the requisite allyl ether systems (Scheme 12) which can then be rearranged to the substituted 3-methylenecoumarin. We have found that this conversion occurs in good overall yield but that a large substituent in the C-4 position hinders cyclisation.[59]

4.5. *α-Methylene-γ-lactones from α-hydroxyalkyl acrylates*

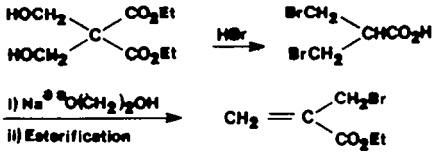
The synthesis of variously substituted α-methylene-γ-lactones has continued to be a topical subject on account of their biological activity.[60–62] As we have demonstrated, allylic organometallic intermediates derived from the Baylis–Hillman reaction can readily be utilized for this purpose (Scheme 13).[63] The allylic chromium intermediate reacts with acetaldehyde to give *cis*-4,5-dihydro-4,5-dimethyl-1,3-methylene-2(3H)-furanone. The reaction proceeds diastereoselectively and in good



Scheme 12. Claisen rearrangement of an α-hydroxyalkyl acrylate.



Scheme 13. Synthesis of an α-methylene-γ-lactone.

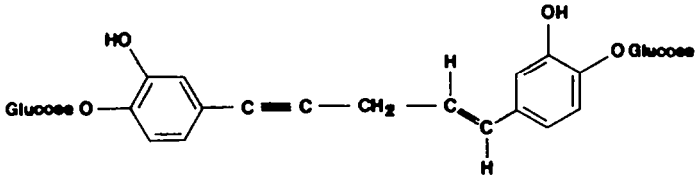


Scheme 14. Alternative synthesis of α-bromomethyl acrylate.

yield. It is of interest to note that Oshima *et al.*[64] published simultaneously an identical procedure for the synthesis of α-methylene lactones. These authors proceeded by a lengthy procedure from diethyl*bis*-(hydroxymethyl)malonate via β,β′-dibromoisobutyric acid[55] to the desired α-(bromomethyl)acrylate (Scheme 14).

4.6. *Pent-1-en-4-yne derivatives with medicinal value*

The pent-1-en-4-yne derivative **29**, named hypoxoside by Marini-Bettolo *et al.*[65] and isolated from *Hypoxis* spp., is used against urinary ailments by the indigenous people of Southern Africa.

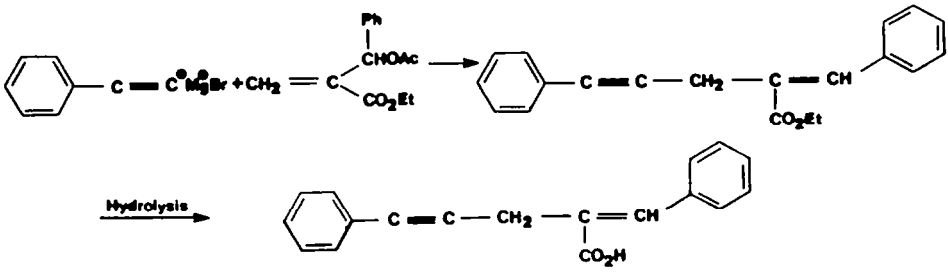


(29)

This compound also possesses anti-tumour properties as the aglycone and numerous analogues of it have been synthesized.[66,67] One of the drawbacks of many of these analogues centres round their insolubility in an aqueous medium. This problem was partly overcome through the incorporation of carboxylic acid groups in the system and the Baylis–Hillman reaction products have been utilized for this purpose (Scheme 15).[68]

4.7. *Pressure-modified reactions*

In 1986 Hill and Isaacs[15] reported on an aspect of the Baylis–Hillman reaction not previously covered—the use of pressure to enhance reactivity. At a pressure of 2–3 kbar the reaction between



Scheme 15. Synthesis of pentenyne derivatives containing a modified acrylate system.

acrylonitrile, acrylate esters, amides, and acrylic aldehyde with aldehydes and ketones is greatly accelerated. This contrasts with the situation at atmospheric pressure where ketones are wholly unreactive. Further points to note from the above are:

(i) the reaction is better controlled using the less reactive triethylamine as base rather than DABCO. These authors found the rate of acceleration to be DABCO > quinuclidine > Me_3N > Et_3N.

(ii) With acrylonitrile and simple aldehydes the reaction is complete (90%) within 5 min whereas the normal reaction time is 4–5 days.

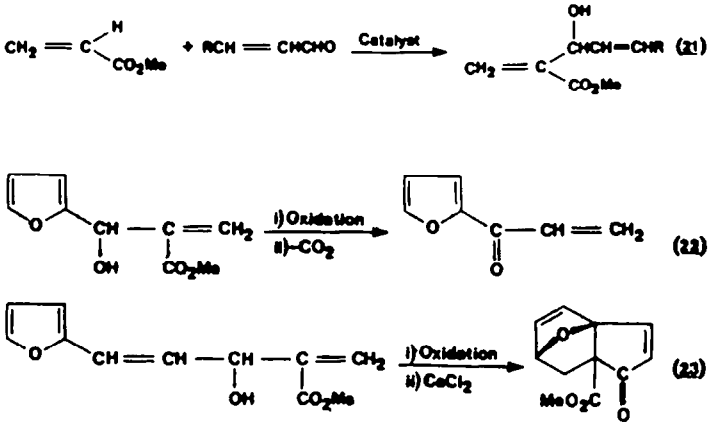
(iii) The order of reactivity of the α,β-unsaturated component follows the sequence: $XCH{=}CH_2$ X = CHO > COMe > CN > CO_2R > $CONH_2$.

(iv) When α,β-unsaturated aldehydes are used as electrophiles, e.g. acrolein, the yield falls to 20%.

(v) With crotyl systems as substrate no reaction occurs even at 10 kbar.

4.8. *α,β-Unsaturated aldehydes as electrophiles*

No systematic study of this class of compounds has been undertaken but isolated aldehydes have been examined by Basavaiah,[43] Hoffmann,[21] Villieras,[44] and Isaacs.[15] Our studies[69] on a series of α,β-unsaturated aldehydes with methyl acrylate (Table 5) have shown that 1,2-addition takes place in all instances (Eq. 21). (10% 3-QDL as catalyst).



The products from this reaction are useful synthetic intermediates in their own right but, in addition, mild oxidation of the secondary alcohol should afford substrates which will (a) decarboxylate to vinyl ketone derivatives and (b) undergo intramolecular Diels–Alder reactions [entries

Table 5. Reaction of α,β-unsaturated aldehydes with methyl acrylate

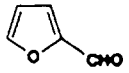
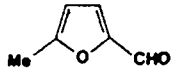
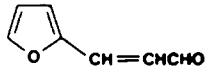
	α,β-Unsaturated aldehyde	Time	Product yield (%)
i)	$CH_3CH{=}CHCHO$	14 days	25
ii)	$PhCH{=}CHCHO$	14 days	28
iii)		20 hr	65
iv)		14 days	33
v)		14 days	38

Table 6. Yields of α-methylene-β-hydroxy-γ-alkoxy esters and ketones

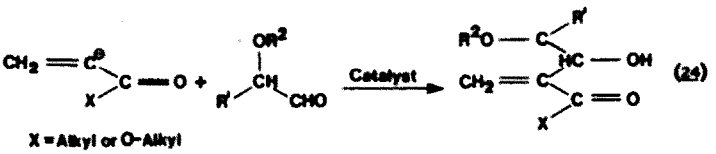
Entry	Aldehyde*	Vinyl system	Catalyst†	Reaction time	*anti*:*syn* Ratio	Yield (%)‡
1	1	4	A	14 days	60:40	68
2	2	4	A	4 days	70:30	55
3	2	4	B	36 hr	72:28	60
4	2	5	A	2.5 hr	71:29	54
5	2	5	B	< 20 min	71:29	80
6	2	5	B	2 hr	71:29	80
7	3	5	A	6 days	62:38	70

* Aldehydes 1 and 3 were racemic and 2 was optically active.
† A = DABCO, B = 3-QDL.
‡ Refers to isolated yield after chromatography.

(iii)–(v)] (Eqs 22, 23). There is considerable interest in this latter transformation[70–72] particularly since the adduct is a cyclohexene–furan derivative.

4.9. *Stereoselective synthesis of α-methylene-β-hydroxy-γ-alkoxy esters and ketones*

An aldol-type condensation between an α-alkoxy aldehyde and the synthetic equivalent of a vinylcarbonyl α-anion represents a logical route to the title compounds (Eq. 24). This is the approach

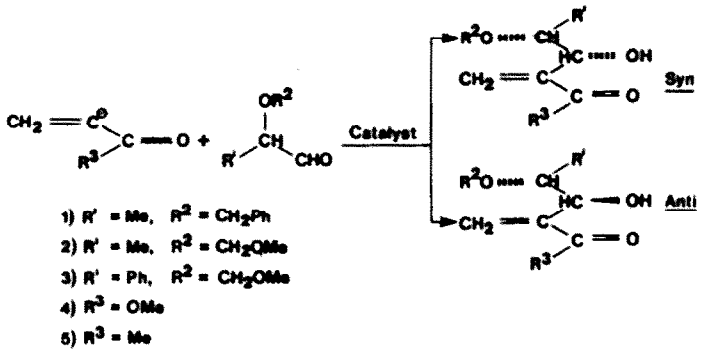


(24)

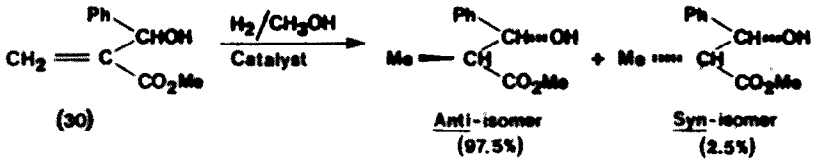
adopted by Scolastico *et al.*[73] in their attempts to establish a viable route for the stereoselective synthesis of the title compounds. The multifunctionality of this system renders it of value in the synthesis of natural products. With the ready availability of optically pure α-alkoxy aldehydes the title compounds were readily obtained from interaction of these aldehydes with LDA-deprotonated β-(dimethylamino)propionate anions.[3] It seemed to us[74] that an alternative and simpler approach would be to utilize the Baylis–Hillman reaction to generate the appropriate vinyl anion since this would (i) avoid the problems associated with low temperature carbanion generation and (ii) obviate the need for masking and subsequently releasing the acrylate moiety. Our initial results for the diastereoselectivity of the catalysed coupling of α-alkoxyaldehydes with activated vinyl systems (Scheme 16) are shown in Table 6. Our studies indicate predominant *anti*-selectivity, in agreement with the prediction of Felkin's model.[75] This finding, coupled with respectable yields, places the procedure within the synthetically useful range.

4.10. *Mechanistic studies on α-hydroxyalkyl acrylates*

α-Hydroxyalkyl acrylates obtained by application of the Baylis–Hillman reaction have been used as substrates by Brown[76,77,78] for his elegant studies on the directed hydrogenation of olefins



Scheme 16. Synthesis of α-methylene-β-hydroxy-γ-alkoxy esters and ketones.



Scheme 17. *anti*-Selectivity during reduction of α-hydroxyalkyl acrylate esters.

employing cationic rhodium or iridium catalysts. These hydroxy-esters are considered to be the best substrates for asymmetric hydrogenation since the chelating hydroxyl group α to the α,β-unsaturated ester or acid is precisely what is required. All rhodium-catalysed hydrogenations of α-hydroxylalkyl acrylates have been found to be highly *anti*-selective. Using the least favourable reaction conditions (H_2, CH_3OH, rhodium catalyst) only 2.5% of *syn*-isomer is obtained from racemic methyl 3-hydroxy-3-phenyl-2-methylenepropanoate (**30**) (Scheme 17). From his studies Brown was able to demonstrate *anti*-selectivity as a general phenomenon for his chosen system. It provides an equivalent to an *anti*-selective aldol condensation with two straightforward steps.

4.11. *Future developments*

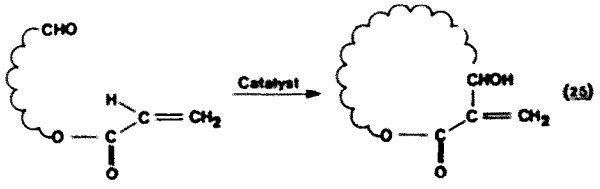
We believe that the value of the Baylis–Hillman reaction to synthetic organic chemistry is only beginning to emerge. Future areas of application which readily come to mind include the following:

(i) utilization of the acetylated hydroxyalkyl acrylate (**18a**) or the bromomethyl ester (**19a**) in enamine reactions.

(ii) Hydrazones and oxazolines instead of the currently used esters, ketones, nitriles and sulphones with the obvious extension to chiral derivatives.

(iii) General extension of the initial hydroxyalkyl products (such as **18a**) and the rearranged products (**19a**) to a range of dienophiles and dienes for Diels–Alder reactions.

(iv) The synthesis of biologically active macrocyclic molecules (Eq. 25).



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NOTE ADDED IN PROOF

Since submitting this review three further papers have appeared which are relevant. Hoffmann and Grundke,[79] and Basavaiah *et al.*[80] have used α-keto esters to react with activated vinyl carbanions while Yamamoto *et al.*[81] have employed benzylidenecarbamate for the same purpose.

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