Mastering β-Keto Esters

Simonetta Benetti* and Romeo Romagnoli

Dipartimento di Chimica, Università di Ferrara, I-44100, Ferrara, Italy

Carmela De Risi, Giampiero Spalluto, and Vinicio Zanirato

Dipartimento di Scienze Farmaceutiche, Università di Ferrara, I-44100, Ferrara, Italy

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Born in 1947 in Ferrara, Italy, Simonetta Benetti (seated, left) received her degree in Chemistry in 1971 from the University of Ferrara. Since 1982 she has occupied the position of Associated Professor of Organic Chemistry at the "Dipartimento di Chimica" of the same university. Since 1971 she has carried out research on the synthesis of natural organic substances and their structural analogs of particular pharmaceutical interest and has studied new synthetic methods of general applicability.

Born in 1965 in Ferrara, Italy, Romeo Romagnoli (standing, left) received his degree in Chemistry and Pharmaceutical Technology from the University of Ferrara in 1989. He is now carrying research work on the synthesis of natural compounds of biological interest toward receiving the degree of "Dottore in Ricerca".

Born in Ferrara, Italy, in 1967, Carmela De Risi (seated, right) received her degree in Chemistry from the University of Ferrara in 1992. She is currently carrying out her doctoral work on the synthesis of natural compounds toward the degree of "Dottore in Ricerca" in Chemistry.

Born in S. Maria Maddalena, Italy, in 1963, Giampiero Spalluto (standing, center) graduated in Chemistry and Pharmaceutical Technology in 1987 at the University of Ferrara and obtained the degree of "Dottore in Ricerca" in Organic Chemistry in 1992 from the University of Parma. Currently he is carrying out research at the "Dipartimento di Scienze Farmaceutiche", University of Ferrara. His main interests include the chemistry of heterocycle compounds and the synthesis of biologically active derivatives of antitumor agents.

Born in 1957 in Fenil del Turco, Italy, Vinicio Zanirato (standing, right) received his degree in Chemistry and Pharmaceutical Technology from the University of Ferrara in 1982 and the degree of "Dottore in Ricerca" in Pharmaceutical Sciences in 1986. In 1990 he was appointed as Researcher at the "Dipartimento di Scienze Farmaceutiche", University of Ferrara.

I. Introduction

Reagents containing multiple functionalities are very important in organic synthesis since they can be versatile and effective species for the efficient construction of rather complex structures from relatively simple starting materials.

One important example of such reagents is represented by β-keto esters, which are multicoupling reagents with electrophilic and nucleophilic sites and have proven to be valuable tools in the synthesis of a wide variety of molecular systems. Their importance stems from the facile bond formation at all the four carbon atoms that feature their structural unit composed of two different electrophilic carbonyls and two nucleophilic carbons, which can react selectively under suitable conditions.

In 1942,[1] the methods for their preparation were already important enough to be chosen as the subject of the first issue of the prestigious *Organic Reactions* collection, later to be summarized in books that enjoyed widespread popularity.[2] Although numerous different procedures have been developed and reported since and despite the fact that a significant body of knowledge has gradually accumulated, no

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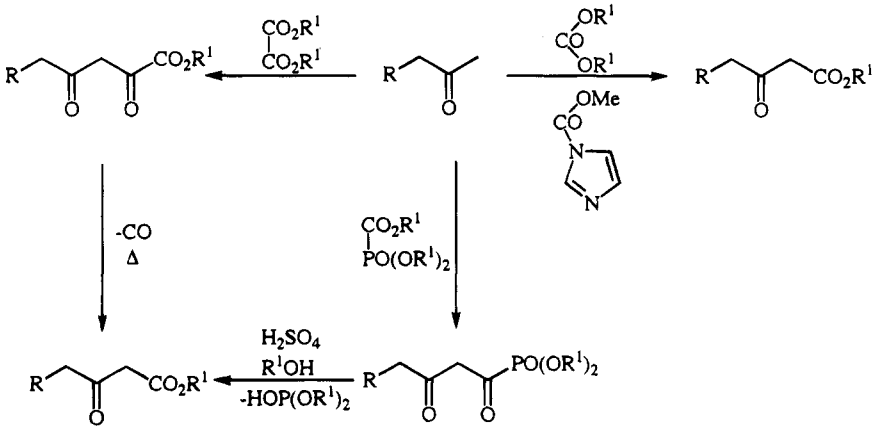
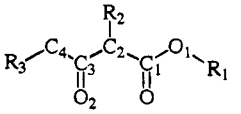
Scheme 1



significant effort has been made to collect and reorganize the data in an exhaustive review.

Considering the increasing interest in the preparation of β-keto esters and in their widespread applications in natural product synthesis, the time seems appropriate for a comprehensive review of their chemistry.

Undertaking the task of updating and organizing the large amount of data accumulated in literature, we have selected as the most convenient and practical organizing criterion the identification of the bond created with a particular transformation to discriminate among the strategies utilized for the numerous different preparations. Thus, referring to the numbering of the different atoms that constitute a β-keto ester moiety, as reported in the general formula (**1**),



(**1**)

seven possibilities of bond formation can be easily identified and will be discussed in separate sections. The present review provides a comprehensive coverage of the subject up to 1993.

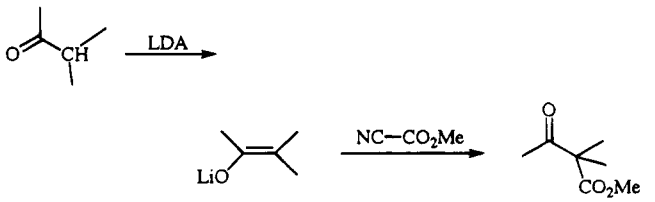
II. C_1–C_2 Bond Formation

The formation of this bond represents an incompletely fulfilled requirement of organic synthesis. Methods for regiospecific C-acylation of unsymmetrical ketones are always welcome.[2a,b] The regiospecificity of usual procedures involving reactions of enolates with dialkyl carbonates,[3] dialkyl oxalates,[4] and (diethoxyphosphinyl)formates[5] is controlled by the different stability of the enolate involved. Accordingly, unsymmetrical ketones are preferentially acylated at the less substituted α-carbon, with poor regioselectivity (Scheme 1).

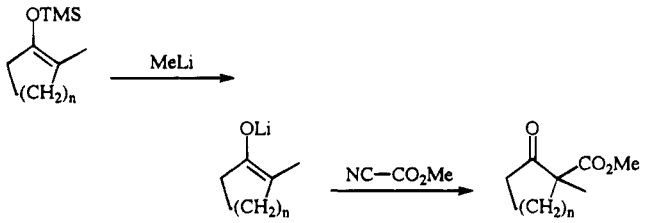
However, all these procedures require different experimental conditions in each case, and the occasionally obtained good results completely depend on the careful choice of base, solvent, temperature, and acylating agent.

A very mild procedure based on the use of carbomethoxyimidazole as an acylating agent at −78 °C in the presence of 2 equiv of lithium diisopropylamide has been introduced in 1979.[6,7] These conditions are well tolerated by base-sensitive substrates, such as α,β-unsaturated ketones. Four years later, Mander[8] suggested a regioselective methodology entailing the reaction of a ketone enolate with methyl cyanoformate. This acylating agent has been shown to be particularly useful with lithium enolates but less efficient with sodium or potassium ones (Scheme 2).

Scheme 2



Scheme 3



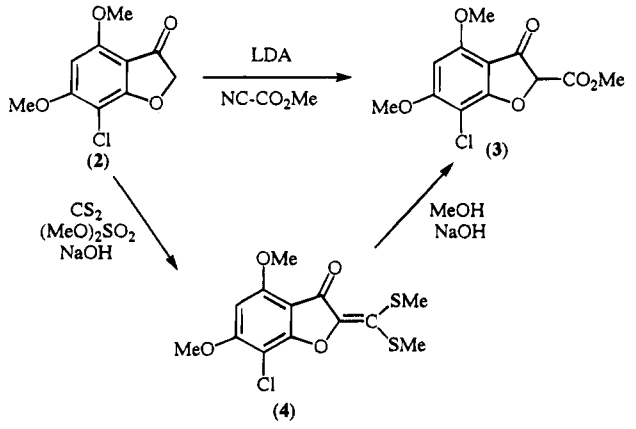
Mander[8] showed this procedure to allow the direct synthesis of non-enolizable β-keto esters via C-acylation of ketones and to be operative in the case of base-sensitive compounds as well. This has been achieved starting from a trimethylsilyl enol ether, in turn converted by treatment with methyl lithium into the corresponding enolate, subsequently acylated with methyl cyanoformate (Scheme 3).

In 1987, Winkler et al.[9] introduced a clever variant of the methodology using anisyl cyanoformate as the acylating agent that allows ester hydrolysis without decarboxylation. This operation is of great significance since the usual acylation−alkylation sequence is reversed.

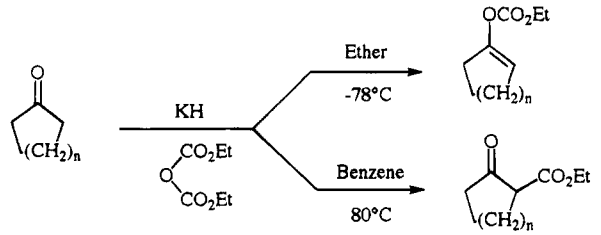
The exceedingly efficient reaction of cyanoformates is also documented by the acylation of **2**, in the presence of lithium diisopropylamide, to produce a 94% yield of 2-chloro-4,6-dimethoxy-2-(methoxycarbonyl)-2,3-dihydrobenzo[*b*]furan-3-one (**3**)[10] (Scheme 4).

The O-alkoxycarbonylated product is obtained when **2** is reacted with different acylating agents. In

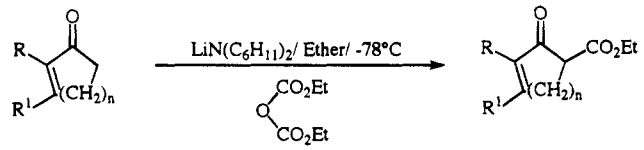
Scheme 4



Scheme 5



Scheme 6



practice, however, the use of cyanoformates in the large scale preparation of β-keto esters is difficult due to the problems posed by their stability and safety.

Yamato et al.[10] have developed a convenient one-pot method for the acylation of aromatic ketones, such as **2**, via the corresponding bis(methylthio)-ketene acetals **4** (Scheme 4). The method is not successful with aliphatic dialkyl ketones.

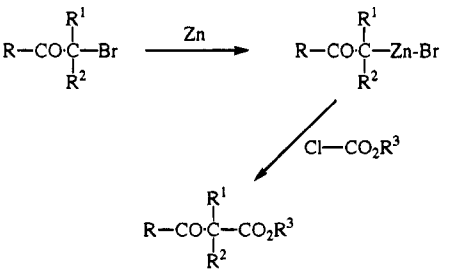
In 1984, Fallis et al.[11] introduced the use of diethyl dicarbonate as a reagent for the preparation of saturated and unsaturated cyclic β-keto esters. In the case of saturated cyclic ketones, the reaction with diethyl dicarbonate in the presence of potassium hydride can be easily controlled by varying the experimental conditions, and both O-acylation (diethyl ether, −78 °C) or C-acylation (benzene, 80 °C) can be produced (Scheme 5).

The introduction of an ethoxycarbonyl group at the α′-position of α,β-unsaturated ketones has been effected by action of diethyl dicarbonate in the presence of lithium dicyclohexylamide in diethyl ether at −78 °C since it requires a strong non-nucleophilic base (Scheme 6).

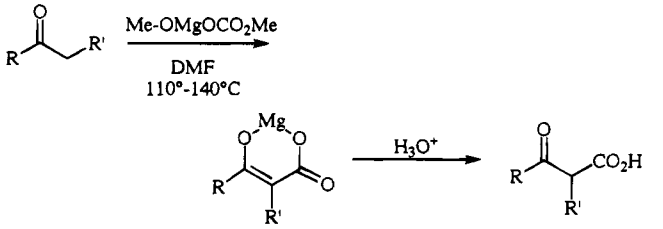
So far, we have not considered chloroformates as acylating agents in view of their known tendency to produce O-acylation products.[12] However, their reaction with organometallic derivatives deriving from α-bromo ketones and zinc furnished good yields of β-keto esters[13] (Scheme 7).

Carboxylation of an enolate followed by subsequent esterification of the derived β-keto acid, as discussed in the section on C_1-O_1 represents a useful alterna-

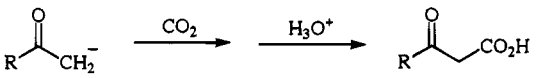
Scheme 7



Scheme 8



Scheme 9



tive procedure to ketone alkoxycarbonylation. This methodology has been briefly surveyed in 1982 by Rosenfeld and Oshry,[14] while more precise information can be found elsewhere.[15] Magnesium methyl carbonate (MMC) is the reagent that features the most common procedure to achieve carboxylation of ketones[16] (Scheme 8).

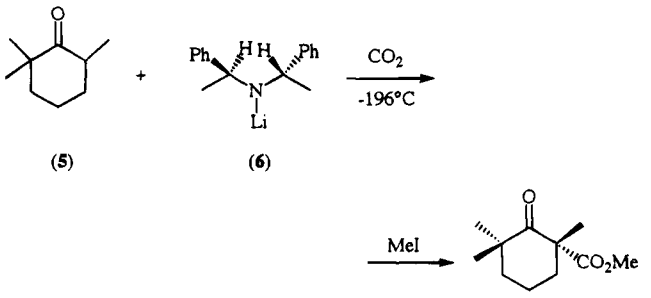
The most salient advantage is represented by the regioselectivity: the outcome of the reaction can be accounted for by the reversibility of the reaction producing the β-keto acid derived by the most stable chelate with magnesium cation. However, the method has several drawbacks: (i) it employs high temperatures; (ii) it uses a large excess (5−20 times) of the rather expensive MMC, which is not easy to prepare in the laboratory, (iii) it involves a difficult separation of the β-keto acid produced from the large volume of DMF required. In addition, the reaction is limited to ketomethylene compounds, the formation of magnesium chelates being strictly required. In view of this, the direct carboxylation by means of carbon dioxide, a well-studied reaction already reviewed,[2a] should be regarded with great attention as a route to β-keto acids (Scheme 9).

In fact, in 1986, new horizons have been opened by Hogeveen and Menge,[17] who first achieved enantioselective carboxylation of 2,2,6-trimethylcyclohexanone (**5**) (e.g., 67%) utilizing lithium bis[(*S*)-α-dimethylbenzyl]amide (**6**) in diethyl ether followed by adding carbon dioxide at −196 °C (Scheme 10).

Studies concerning carriers of carbon dioxide, and hence the trans-carboxylation reactions, should be attentively considered. Matsumura et al.[18] have obtained β-keto acids under very mild conditions (15 °C) by reaction between a ketone and a magnesium complex of the cyclic thiourea **7** (Scheme 11).

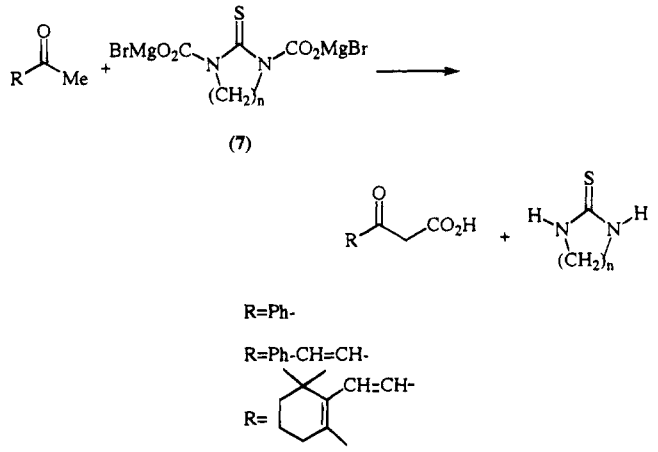
Rathke et al.[19] have proposed ketone carboxylation in acetonitrile using a reaction with carbon dioxide at atmospheric pressure in the presence of triethyl-

Scheme 10



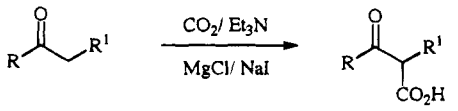
(5) (6)

Scheme 11

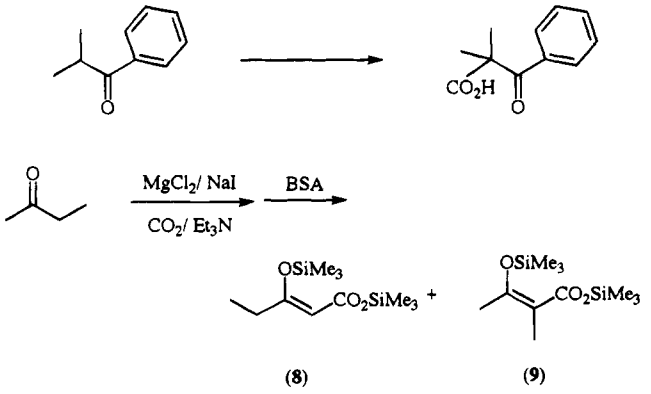


(7)

Scheme 12



Scheme 13



(8) (9)

amine, magnesium chloride, and sodium iodide (Scheme 12).

The novelty of the method is the possibility of affecting the reaction in the absence of enolate. The experimental results seem to rule out the formation of magnesium chelates, the reaction taking place also with ketones possessing only one α-hydrogen, while the characteristic regioselectivity of MMC is not observed (Scheme 13).

The gas chromatographic analysis of the reaction of 2-butanone under the above reported conditions followed by silylation with bis(trimethylsilyl)acetamide (BSA) revealed a mixture of **8** (45%) and **9** (55%).

III. C_2–C_3 Bond Formation

The various routes to gain access to β-keto esters and β-keto acids by forming the C_2–C_3 bond can be divided as follows: A. Acetate Anions; B. Carboxylic Acid Dianions; C. Ketene Acetals; D. Malonate Anions; E. Miscellaneous Procedures.

A. Acetate Anions

Claisen-like condensation or acetoacetic ester synthesis represents the classical methodology to obtain β-keto esters through acylation of an ester enolate with another ester functionality both in the intermolecular or intramolecular (Dieckmann) version. Although the synthetic and mechanistic aspects of the process have been amply discussed in a very successful book by House,[2] the crucial role played by the base used in this reaction should be stressed.

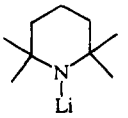
Sodium methoxide or ethoxide, relatively weak bases, have been first utilized with the consequence of only partial deprotonation of the ester, producing almost exclusive self-condensation. The process was not, of course, suitable for the preparation of C-2 disubstituted β-keto esters. However, this operation has become feasible after the introduction of very strong bases, which allow complete deprotonation of the ester as the primary event of the reaction. The following bases have been commonly employed:

a. Alkali Triphenylmethides[2]

They offer the special advantage of being dissociated into a solvated metal cation and the intensely red triphenylmethyl anion in a variety of dipolar aprotic solvents. The major drawback to the use of these bases is the fact that the reaction product must be separated from large quantities of triphenylmethane.

b. Alkali Amides[2]

Enolate generation by sodium amide, a highly nucleophilic base, proceeded slowly, and better results have been achieved using secondary lithium amides, in turn easily accessible by treatment with butyl lithium in tetrahydrofuran of the corresponding amines. Thus, lithium diisopropylamide, lithium cyclohexylpropylamide, and lithium bis(trimethylsilyl)amide are most frequently employed. They allow deprotonation to be effected at very low temperatures; moreover, the steric hindrance of the two bulky substituents minimizes the nucleophilicity of both amide or amine formed by deprotonation. An excessively strong residual nucleophilic character, as in the case of lithium diisopropylamide, can be further weakened by adding an equimolecular amount of hexamethylphosphoric triamide, which forms a 1:1 complex generating a non-nucleophile species of this base. In 1973, Olofson and Daugherty[20] proposed lithium 2,2,6,6-tetramethylpiperidide (**10**) (LiTMP)



(10)

Table 1

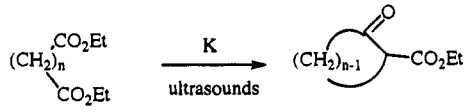
base	yield %
$LiN(i\text{-}Pr)_2$	64
$LiN(i\text{-}Pr)(C_6H_{11})$	66
$LiN(C_6H_{11})_2$	71
LiTMP	89

as a condensing agent that leads to yields of acylation products higher than those obtained with other amides (Table 1) and is easy to remove from the reaction mixture under neutral conditions.

c. Alkali Hydrides[2]

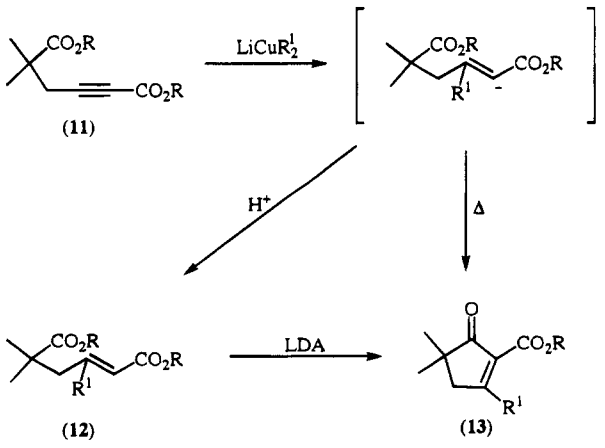
Since it is easy to handle, produces a virtually irreversible reaction, and is a weak nucleophile, sodium hydride represents a valuable base for Claisen condensation. It is, however, a relatively sluggish, heterogeneous agent and often requires prolonged reactions, elevated temperatures, and "activation" by the addition of few drops of alcohol or water. In 1975, Brown[21] utilized the more reactive potassium hydride, which reacts very fast at room temperature (10−15 min), allowing the induction of condensation even with α-disubstituted esters. In 1984, Luche et al.[22] described an original procedure for the cyclization of dicarboxylic acid esters in which, by adding the diesters of adipic or pimelic acid to colloidal potassium obtained by ultrasound treatment of its suspension in toluene, an easy cyclization takes place at room temperature in few minutes (Scheme 14).

Scheme 14

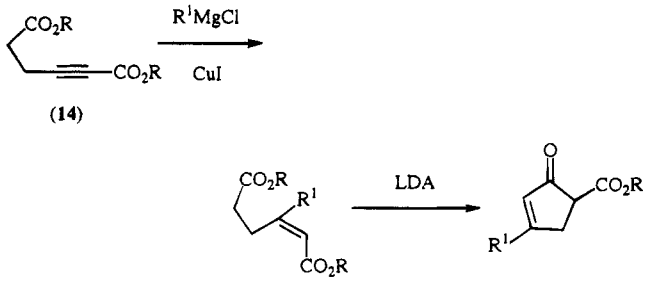


The use of lithium or sodium sand instead of colloidal potassium leaves the starting material unchanged and suberic, azelaic, and sebacic acid diesters do not cyclize under these conditions. In 1984, Crimmins et al.[23] described the synthesis of heavily functionalized cyclopent-2-enones (**13**) by generation of the enolate of the unsaturated ester **12** both directly with lithium diisopropylamide or by conjugate addition of cuprous or magnesium organometallic reagents to the acetylenic ester **11** (Scheme 15).

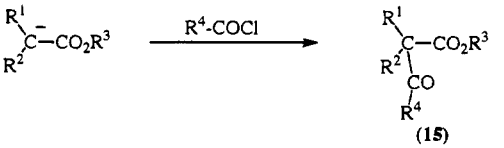
Scheme 15



Scheme 16



Scheme 17



The ethylenic ester (**12**) can be isolated by careful protonation at low temperature of the vinylic organometallic and then cyclized by action of lithium diisopropylamide, but a one-step process can also be effected by adding the organometallic compound to **11** at −78 °C and simply allowing the reaction mixture to reach room temperature. The two-step process seems, however, to proceed with better overall yield. It is also interesting to note that a completely different reaction occurred operating on the unsubstituted acetylenic ester (**14**) (Scheme 16).

In 1971, Rathke et al.[24] discovered that solutions of ester enolates prepared at low temperatures with lithium amides are stable and can be allowed to reach room temperature without the production of condensation products. This observation paved the way to β-keto ester synthesis, and the chemical behavior of these enolates toward different electrophilic reagents has been promptly investigated.

Rathke and Deitch[25] reported that even enolates of α-disubstituted esters do react at −78 °C with acyl halides to produce acylated derivatives (**15**) in good yields (Scheme 17).

To minimize the enolate attack on the formed β-keto ester, suggest adding to the acyl chloride the solution of the anion, prepared using 2 equiv of base, in the specific case lithium isopropylcyclohexylamide, which allows the generation of the scarcely reactive β-keto ester enolate. The acylation of enolates generated from *tert*-butyl esters represents a useful variant introduced by Logue.[26] Thus, both β-keto acids and ketones are obtained from the corresponding β-keto esters. The hydrolysis of *tert*-butyl esters is easily performed by treatment with trifluoroacetic acid at room temperature to obtain β-keto esters or at reflux to obtain ketones (Scheme 18).

Similarly, Lion[27] described the preparation of highly substituted acetoacetates, using acyl halides as acylating agents. The results obtained in different laboratories utilizing this strategy are summarized in Table 2 showing that low yields were only observed in the case of heavily hindered acylating agents. Ester enolates can be generated not only by means of strong bases but also by reaction of haloesters with metals. Magnesium and zinc had usually been employed, but the derived organometallics prepared in tetrahydrofuran solution give rise mainly to self-

Scheme 18

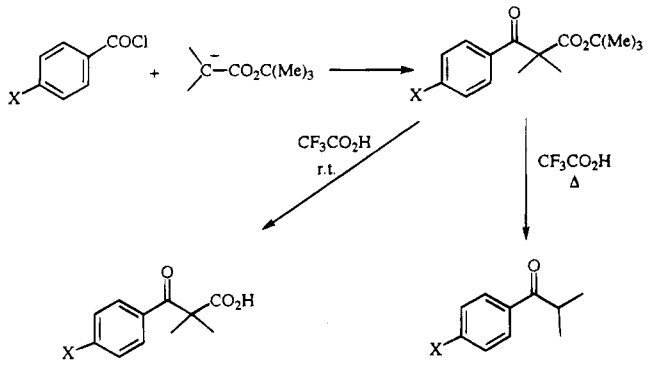
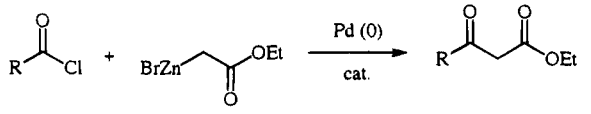


Table 2. Reaction of Ester Enolates with Acid Chlorides

ester enolate			acid chloride		
R^1	R^2	R^3	R^4	yield (%) (**15**)	ref
H	H	Et	Et	60	*25*
H	H	Et	n-Pr	56	*25*
H	H	Et	i-Pr	66	*25*
H	H	Et	t-Bu	70	*25*
H	H	Et	n-C_5H_{11}	78	*25*
n-Bu	H	Et	n-Pr	51	*25*
Me	Me	Me	n-Pr	76	*25*
H	H	Et	Ph	81	*25*
Me	Me	t-Bu	Ph	55	*26*
Me	Me	t-Bu	4-Me-Ph	68	*26*
Me	Me	t-Bu	4-MeO-Ph	80	*26*
Me	Me	t-Bu	4-Cl-Ph	68	*26*
Me	Me	t-Bu	4-NO_2-Ph	22	*26*
Me	Me	Et	t-Bu	92	*27*
Me	Me	Et	t-Bu-C(Et)$_2$	12	*27*
t-Bu	Me	Et	t-Bu	79	*27*
t-Bu	Me	Et	(i-Pr)$_3$C	4	*27*
t-Bu	Et	Et	t-Bu	78	*27*
t-Bu	Et	Et	t-Bu-C(i-Pr)(Et)	3	*27*
Et	Me	i-Pr	n-Bu	69	*31*
Et	Me	i-Pr	i-Pr	78	*31*
Et	Me	Et	i-Pr	80	*31*

Scheme 19

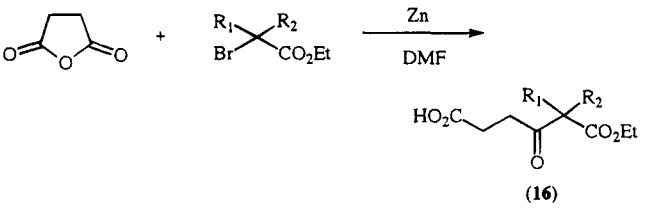


condensation products, and a successful Reformatsky-type condensation of an aroyl chloride had been limited to α,α-disubstituted acetate.[28] Better results were obtained in 1982 by Fujisawa et al.[29] who coupled the Reformatsky reagent of unsubstituted α-bromoacetates with an acyl chloride in the presence of a palladium catalyst (Scheme 19).

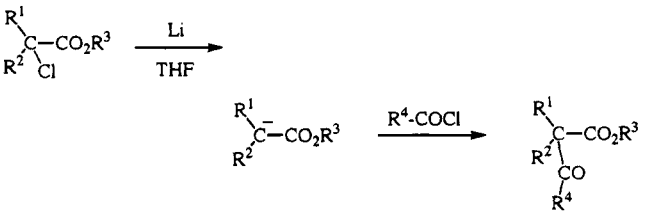
The best results were obtained using a palladium-(0) complex prepared in situ from $Pd(PPh_3)_2Cl_2$ and diisobutylaluminum hydride. The condensation works well with aromatic and heterocyclic acyl chlorides, but the results obtained with aliphatic chlorides are poor. In 1992, Schick and Ludwig[30] described the preparation of 2-alkyl-3-oxoadipate (**16**) utilizing succinic anhydride as the acylating agent (Scheme 20).

The reaction strongly depends on the R_1 and R_2 substituents and on the solvent. The use of dimethylformamide is crucial, and this is the only solvent that allows us to obtain a 55−78% yield of 3-oxoadipates.

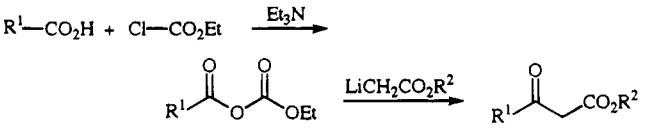
Scheme 20



Scheme 21



Scheme 22



Villieras et al.[31] and Rathke[24] observed that anions derived from α-chloro esters are particularly stable and react at −90 °C by treatment with acyl halides to give the corresponding acetoacetates (see Table 2) (Scheme 21).

Moreover, this procedure suffers some limitations: for instance when R_1 and R_2 are hydrogen atoms, the reaction takes a totally different course during the metallation step. Among the merits, its compatibility even with unhindered esters (see Table 2) must be underlined owing to the absence of the protonated base in the reaction mixture. A comparison between the reactivity of magnesium, zinc, and lithium organometallics derived from the same haloester seems to indicate that Claisen dimerization depends mainly on the Lewis acid features of the metallic salts associated to the organometallic intermediate rather than the nucleophilic character of the latter.

In 1977, Couffignal and Moreau[32] described as an acylating agent the mixed anhydride obtained from a carboxylic acid and ethyl chloroformate in the presence of triethylamine, once more toward lithium ester enolates (Scheme 22).

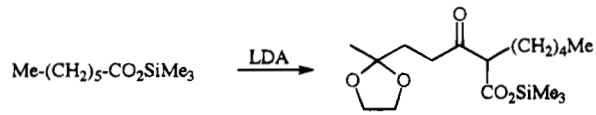
In 1981, the same authors[33] synthesized both jasmone and dihydrojasmone preparing the intermediate **19** by reaction of the mixed anhydride of the ketalized levulinic acid **17** and the lithium derivative of the heptanoic acid trimethylsilyl ester **18** (Scheme 23).

Olsen et al.[34] have developed an efficient synthetic route to γ-hydroxy and γ-amino β-keto esters by condensation of carbonyl-activated derivatives of O-protected α-hydroxy acids or N-protected α-amino acids and lithium enolates. This methodology has been applied to the preparation of the (*S*)-4-hydroxy-5-methyl-3-oxohexanoate (**21**), encountered in didemnins, starting from (*S*)-2-hydroxyisovaleric acid derivatives (**20**) (Scheme 24).

The one-step preparation of the monoesters of β-ketoadipic acid has been achieved by Montforts and

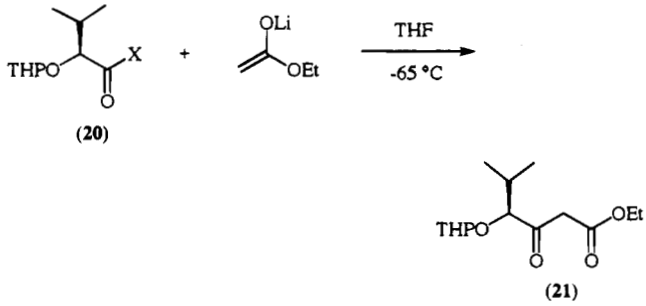
Scheme 23

(17)



(18) (19)

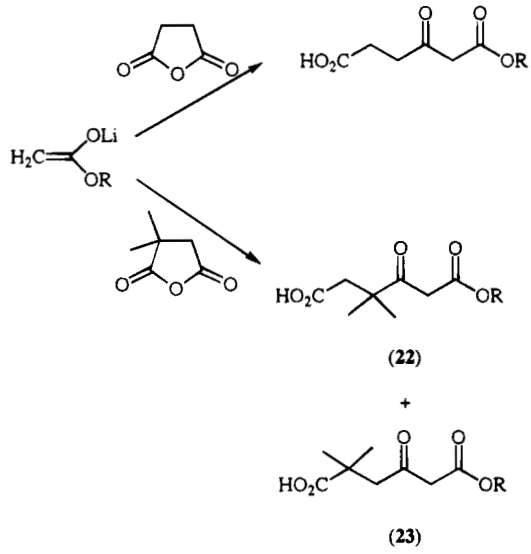
Scheme 24



(20) (21)

X= Cl; OCO_2iBu; 2-oxypyridyl

Scheme 25



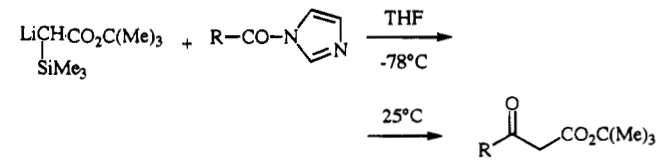
(22) + (23)

Ofner[35] by treatment of succinic anhydride with the lithium enolate of *tert*-butyl or benzyl acetate (Scheme 25). They also investigated the regioselectivity of the reaction by replacing succinic anhydride with dimethylsuccinic anhydride obtaining a 71:29 mixture of **22** and **23**. The preferential attack at the more substituted center is accounted for by the hypothesis that the nucleophilic attack at the carbonyl group requires a trajectory angle wider than 90°.

After unsuccessfully attempting to employ acyl halides and esters as acylating agents, Rathke and Hartzell[36] introduced a convenient preparation of β-keto esters through acylation of lithium *tert*-butyl (trimethylsilyl)acetate with imidazolides (Scheme 26).

A similar approach has been applied by Joullié et al.[37] to the preparation of **24**, a key intermediate in the synthesis of (3*S*,4*R*)-statine, reacting the imidazolilde of Boc-D-leucine with alkyllithium acetate at low temperature (Scheme 27).

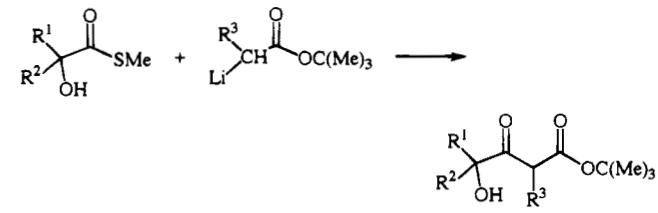
Scheme 26



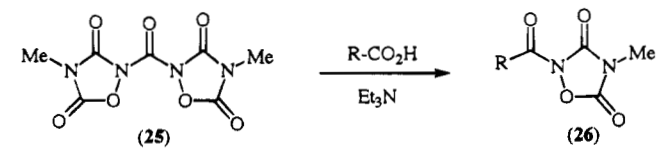
Scheme 27

(24)

Scheme 28

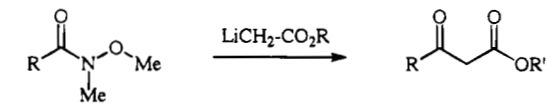


Scheme 29



(25) (26)

Scheme 30

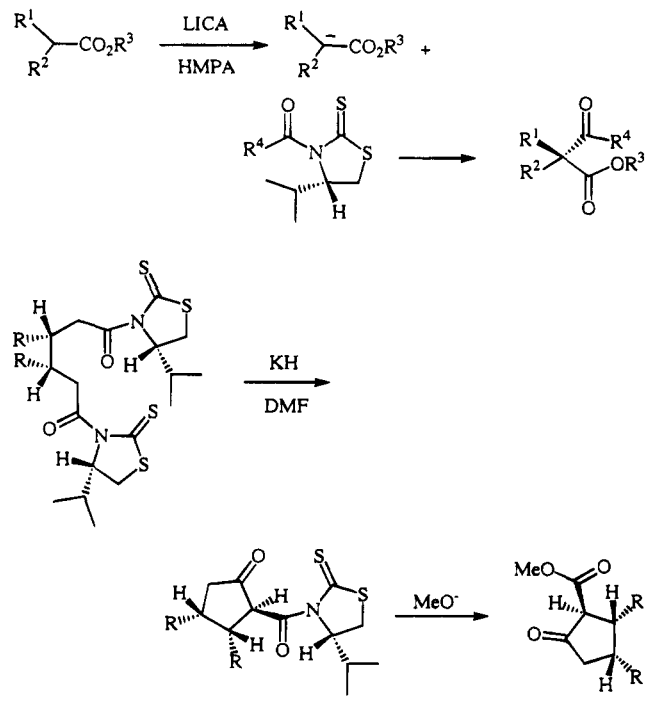


Thiomethyl esters are also excellent acylating agents,[38] which react with simple ester enolates to give very high yields of the corresponding γ-hydroxy β-keto ester adducts. In the case of the reaction with the lithium enolate of *tert*-butyl acetate, 3 equiv of enolate must be employed, while when more complicated ester enolates are used, only 1 equiv of enolate is used along with 2 more equiv of base (Scheme 28).

In 1988, two new leaving groups were efficiently used for the activation of carboxylic acid and applied to the synthesis of β-keto esters. The first is represented by 2-acyl-3,5-dioxo-1,2,4-oxadiazolidines[39] (**26**), substances prepared from carboxylic acids and from 2,2′-carbonyl-bis(3,5-dioxo-4-methyl-1,2,4-oxadiazolidine) (**25**) in presence of triethylamine and used in the synthesis of **21**, present in the cyclodepsipeptide didemnins (Scheme 29).

The second is represented by *N*-methoxy-*N*-methyl amides,[40] proven to be effective acylating agents for enolates in a simple one-step reaction. The lack of self-condensation amide products and of side products demonstrates the efficiency of the process. Less satisfactory results are obtained when more stabilized enolates are submitted to more drastic experimental conditions (malonates or phenylacetates) (Scheme 30).

Scheme 31



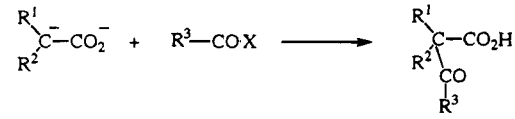
The first example of highly enantioselective Claisen acylation and Dieckmann annulation employing 4(*S*)-isopropyl-1,3-thiazolidine-2-thione as a chiral auxiliary has been reported by Nagao et al.[41] The process is carried out as outlined in Scheme 31.

B. Carboxylic Acid Dianions

Salts of carboxylic acids and esters exhibit quite similar C−H acidity at the α-position (pK_a 24 for the acetate ion and pK_a 24.5 for ethyl acetate), and consequently the same bases can be used for their deprotonation. Two excellent methods allow the effective removal of α-protons and were successfully utilized for generating dianions of carboxylic acids. The first method entails on the use of strong non-nucleophilic bases, typically hindered lithium amides.[27,42,43]

The second one is based on the use of ion radical systems produced from lithium, sodium, or potassium and naphthalene as the base.[44] Thus, the reaction between carboxylic acid dianions with both esters[42,44] and acyl chlorides[27,43] has been successfully utilized as a method for the preparation of β-keto acids (Table 3; Scheme 32).

Scheme 32



C. Ketene Acetals

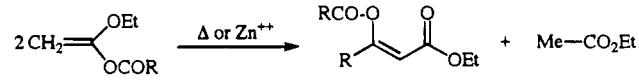
In 1970, Wasserman and Wentland[45] reported that *O*-acyl ketene acetals could be converted into enol-acylated β-keto esters by the action of zinc salts. This

Table 3

R^1	R^2	R^3	X	ref
Me	Et	t-Bu	Cl	*27*
Et	Et	t-Bu-C(Et)$_2$	Cl	*27*
Et	Et	t-Bu-C(i-Pr)(Et)	Cl	*27*
H	Me	Et	OMe	*42*
Me	Me	Et	OMe	*42*
Me	Me	i-Pr	OMe	*42*
Me	Me	t-Bu	OMe	*42*
Me	Me	c-C_6H_{11}	OMe	*42*
Me	Me	Ph	OMe	*42*
−$(CH_2)_5$−		c-C_6H_{11}	OMe	*42*
−$(CH_2)_5$−		c-C_6H_{11}	Cl	*43*
−$(CH_2)_4$−		c-C_6H_{11}	Cl	*43*
−$(CH_2)_4$−		c-C_6H_{11}	Cl	*43*
−$(CH_2)_5$−		c-C_3H_5	Cl	*43*
−$(CH_2)_3$−		c-C_3H_5	Cl	*43*
Me	Me	Ph	Cl	*43*
Me	Me	c-C_6H_{11}	Cl	*43*
Me	Me	t-Bu	Cl	*43*
Et	Et	t-Bu	Cl	*43*
Me	Me	t-Bu-CH_2	Cl	*43*
H	H	Ph	OEt	*44*
H	H	$(Ph)_2CH$	OEt	*44*
H	H	Ph-CH_2	OEt	*44*
H	H	n-C_8H_{17}	OEt	*44*
H	H	n-C_6H_{13}	O-n-C_5H_{11}	*44*
H	H	c-C_6H_{11}-CH_2-CH_2	OMe	*44*
H	H	n-C_8H_{17}	O-n-C_8H_{17}	*44*
H	H	n-C_5H_7-CH_2	OMe	*44*
H	Me	Ph	OEt	*44*
H	Me	C_8H_{17}	OEt	*44*
Me	Me	c-C_6H_{11}-CH_2-CH_2	OMe	*44*

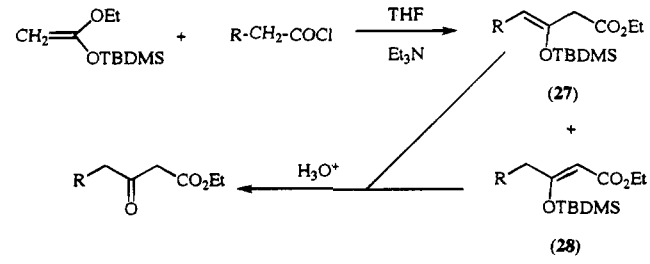
observation complemented the earlier findings of Zwanenburg,[46] who described the thermal conversion of several ethoxyvinyl esters into β-keto ester derivatives (Scheme 33).

Scheme 33



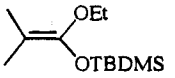
A careful analysis of these results as well as the proposed mechanism suggested the opportunity of acylation of similar substrates possessing a more pronounced nucleophilic character with suitable electrophiles, thus allowing transformations other than self-condensation to be obtained. In fact, in 1973 Rathke and Sullivan[47] were able to perform the acylation of *O*-silyl ketene acetals by means of acyl chlorides in tetrahydrofuran solution in the presence of triethylamine, producing a mixture of **27** and **28**, which provided excellent yields of β-keto esters by acid hydrolysis (Scheme 34).

Scheme 34



The deconjugated product **27**, usually the major component of the mixture, became the sole product

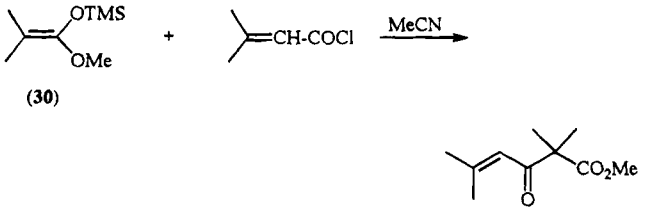
using α,β-unsaturated acyl chlorides as electrophiles. On the other hand, **28** has been obtained using acyl chlorides, such as pivaloyl or benzoyl chlorides, lacking α-hydrogens. The process also works with monosubstituted *O*-silyl ketene acetal, disubstituted ones such as **29** being unreactive.



(29)

A partial solution has been suggested by Rousseau and Blanco[48] as exemplified through the C-acylation of the trimethylsilyl derivatives (**30**) by treatment with 3,3-dimethylacryloyl chloride in acetonitrile in the absence of base (Scheme 35).

Scheme 35



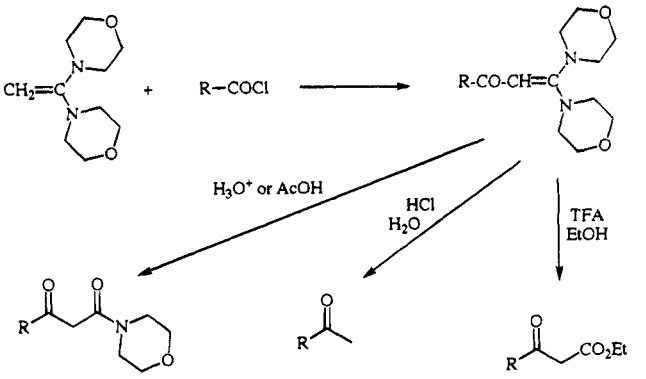
(30)

However, this procedure is limited to α,β-unsaturated β,β-disubstituted electrophiles, and the reaction takes a completely different course with mono- or unsubstituted electrophiles, producing glutaric acid esters via polar [2 + 2] cycloaddition. The methodology has been further extended by Wissner[49] to the preparation of acetoacetates and 2-heterosubstituted methyl ketones (Scheme 36).

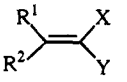
The reaction of a carboxylic acid chloride with 2 equiv of 2-heterosubstituted silylated ketene acetals either under thermal or under Lewis acid catalytic conditions, followed by hydrolysis or hydrolysis–decarboxylation, yields α-functionalized β-keto esters or methyl ketones, respectively. 1,1-Diaminoethenes have been also utilized as synthetic equivalent of the acetate anion. Thus, Stradi et al.[50] investigated the reaction of 1,1-dimorpholinoethene with acyl chlorides elaborating the derived 2-acyl-1,1-dimorpholinoethenes to methyl ketones, β-keto amides, and β-keto esters (Scheme 37).

Better yields are obtained with aromatic acyl chlorides, while the method has poor preparative value when aliphatic acyl chlorides are used. The low yields in the latter case are due to the competitive nucleophilic attack of the amine at the electrophilic center affording morpholides as byproducts. Ketene

Scheme 37



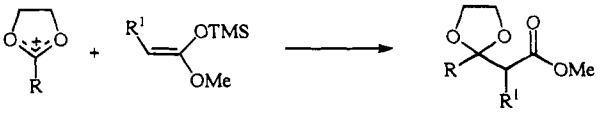
acetals of the general formula (**31**) and the acyl halides utilized are collected in Table 4.



(31)

In 1987, Hayashi et al.[51] described a new synthesis of β-keto esters by reaction of 1,3-dioxolan-2-ylium cations, generated from ethylenacetals by action of trityl tetrafluoborate with ketene silyl acetals and leading to the formation of β-keto esters with a masked carbonyl function (Scheme 38).

Scheme 38



R= Ph-CH_2-CH_2; Ph; Me; H
R^1= H; Ph-CH_2

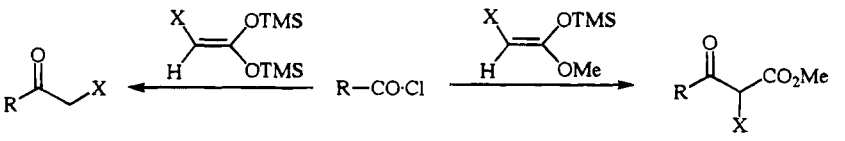
Similarly, Saigo et al.[52] prepared cyclopentenone carboxylates (**35**) from substituted cyclopropane carboxylates (**32**) and ketene silyl acetals in the presence of titanium(IV) chloride. The electrophilic center, generated by Lewis acid-catalyzed ring opening of substituted cyclopropane, reacts with ketene silyl acetal to produce the intermediate **33**, which underwent Dieckmann condensation to give cyclopentanone (**34**), followed by alcohol elimination to give **35** (Scheme 39).

Steric hindrance plays an important role in the development of the reaction. In fact, the use of 3,3-disubstituted ketene silyl acetals gives cyclopentenones in low yield.

D. Malonate Anions

In the classic acetoacetic ester synthesis, esters serve as both nucleophilic and acylating agents.

Scheme 36

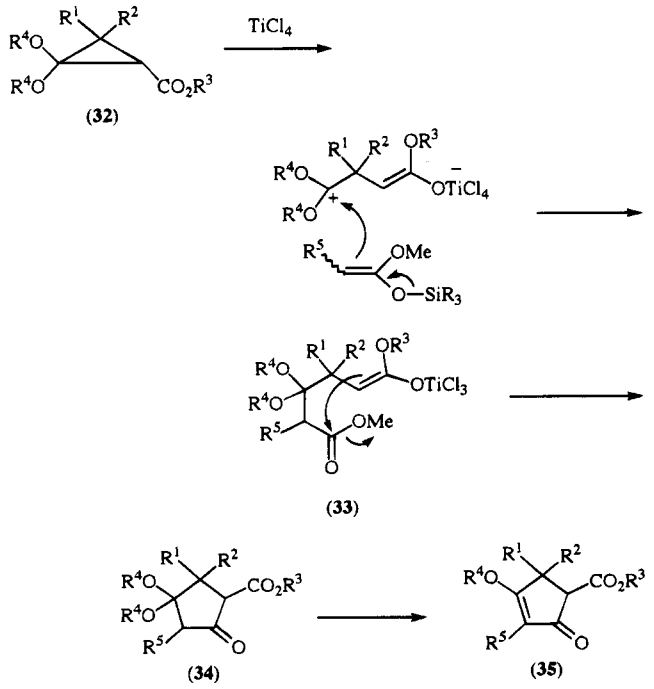


X= -OMe; OTMS; OPh; SMe

Table 4

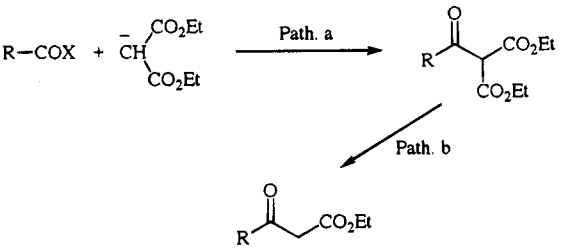
R^1	R^2	X	Y	R^3-COCl	ref
H	H	OEt	OCOPh		*45, 46*
H	H	OEt	OCOMe		*45, 46*
H	H	OEt	OCOEt		*45*
H	H	OEt	$OCOCH_2Ph$		*45, 46*
H	H	OEt	$OCOCH_2Cl$		*45, 46*
H	H	OEt	$OCOCCl_3$		*45, 46*
H	H	OEt	OTBDMS	Me	*47*
H	H	OEt	OTBDMS	n-Pr	*47*
H	H	OEt	OTBDMS	i-Pr	*47*
H	H	OEt	OTBDMS	Me-CH=CH	*47*
H	H	OEt	OTBDMS	Ph	*47*
H	H	OEt	OTBDMS	t-Bu	*47*
H	H	OEt	OTBDMS	$c\text{-}C_6H_{11}$	*47*
H	$n\text{-}C_5H_{11}$	OEt	OTBDMS	Me	*47*
Me	Me	OEt	OTBDMS	Me	*47*
$n\text{-}C_5H_{11}$	H	OMe	OTMS	$(Me)_2C{=}CH$	*48*
n-Bu	H	OMe	OTMS	$(Me)_2C{=}CH$	*48*
Me	Me	OMe	OTMS	$(Me)_2C{=}CH$	*48*
Ph	H	OEt	OTMS	$(Me)_2C{=}CH$	*48*
H	$-CH_2\text{-}CH_2\text{-}O-$		OTMS	$(Me)_2C{=}CH$	*48*
OTMS	H	OTMS	OTMS	$n\text{-}C_7H_{15}$	*49*
OTMS	H	OTMS	OTMS	Ph	*49*
OTMS	H	OTMS	OTMS	$Ph\text{-}CH_2$	*49*
OTMS	H	OTMS	OTMS	$c\text{-}C_6H_{11}$	*49*
OPh	H	OTMS	OTMS	Ph	*49*
OPh	H	OTMS	OTMS	$n\text{-}C_5H_{11}$	*49*
OMe	H	OTMS	OTMS	$n\text{-}C_7H_{15}$	*49*
OMe	H	OTMS	OTMS	Ph	*49*
OMe	H	OTMS	OTMS	$Ph\text{-}CH_2$	*49*
OMe	H	OTMS	OMe	$n\text{-}C_7H_{15}$	*49*
SMe	H	OTMS	OTMS	$n\text{-}C_7H_{15}$	*49*
SMe	H	OTMS	OTMS	Ph	*49*
H	H	morpholine	morpholine	$4\text{-}NO_2\text{-}Ph$	*50*
H	H	morpholine	morpholine	i-Pr-Ph	*50*
H	H	morpholine	morpholine	Ph	*50*
H	H	piperidine	piperidine	Ph	*50*
H	H	morpholine	morpholine	3-Py	*50*
H	H	morpholine	morpholine	$c\text{-}C_6H_{11}$	*50*
H	H	morpholine	morpholine	$n\text{-}C_{15}H_{31}$	*50*
H	H	morpholine	morpholine	EtO	*50*
H	H	morpholine	morpholine	PhO	*50*
H	H	morpholine	morpholine	$Ph\text{-}CH_2O$	*50*

Scheme 39

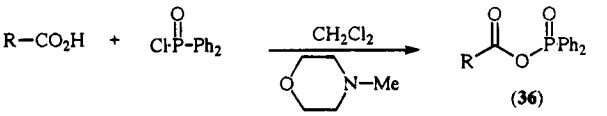


When two different ester fragments are involved, both containing α-hydrogens, the reaction is complicated by the inability to control the nucleophilic and electrophilic character of each individual ester. To avoid this difficulty, sufficiently different electronic properties of the two carboxylic acid moieties are required. The more useful and more thoroughly investigated[2,53] solution employs diethyl malonate anions as nucleophiles and irreversible acylating agents such as acid chlorides. The process, entailing a two-step pathway of acylation and decarboxylation, is presented in Scheme 40.

Scheme 40



Scheme 41



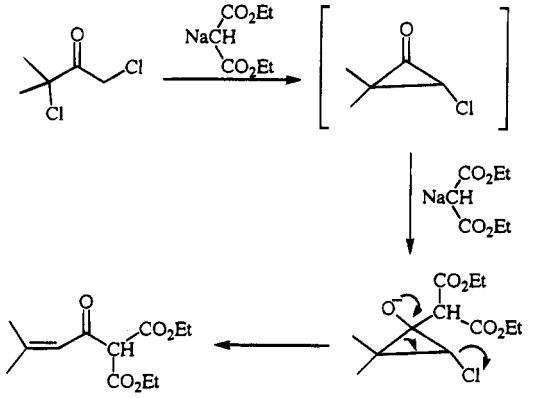
The first step (path a) has several drawbacks, which are mainly due to the experimental conditions required. The acylation step usually involves common acylating agents, such as acyl halides and simple or mixed anhydrides.[2] A rather unusual mixed anhydride has been introduced by Kende et al.,[54] who demonstrated that both aliphatic and carboxylic acids react smoothly with 1 equiv of *N*-methylmorpholine and 1 equiv of chlorodiphenylphosphinite in dry methylene chloride to yield a moderately stable mixed anhydride **36**, which produces acylmalonic esters in good yields when mixed with 2 equiv of sodium diethyl malonate (Scheme 41).

Interestingly, Vlassa and Barabas[55] discovered that β-keto esters can be produced directly by acylation with the pivaloyl chloride of the alkoxymagnesium malonates, prepared by the CCl_4-catalyzed reaction of magnesium turnings with the same alcohol residue, while acylation with propionyl, benzoyl, and trichloroacetyl chlorides furnished the expected acylmalonates. An analogous result was obtained by Mansour[56] using magnesium *p*-nitrobenzylmalonate dihydrate and N-protected aminoacylimidazolides as the acylating agents.

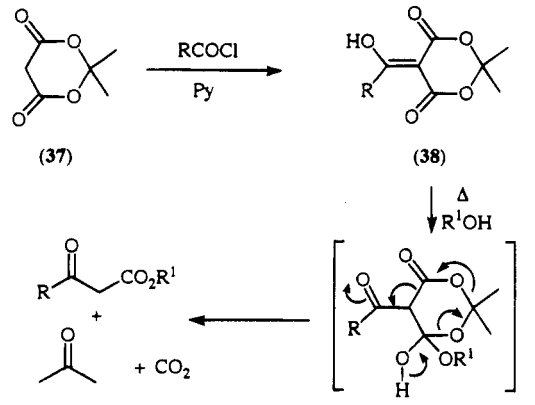
In 1987, Sakai et al.[57] described a new method for the synthesis of γ,δ-unsaturated β-keto esters using a carbanion-induced Favorskii-type rearrangement. The reaction of α,α-dihalo ketones with 2 equiv of sodium malonates in THF at 0 °C and, subsequently, at room temperature gave unsaturated acylmalonates in moderate yield (Scheme 42).

More efforts have been devoted to solving the problems connected with the decarboxylation step (path b). The classical thermal decarboxylation has been carefully examined by House in his book.[2] An improved methodology[58] replaced the high pK_a (13.7) malonic esters with the low pK_a (4.97) 2,2-dimethyl-1,3-dioxane-l,6-dione (**37**), the so-called Meldrum's acid, which readily reacts with acyl chlorides even

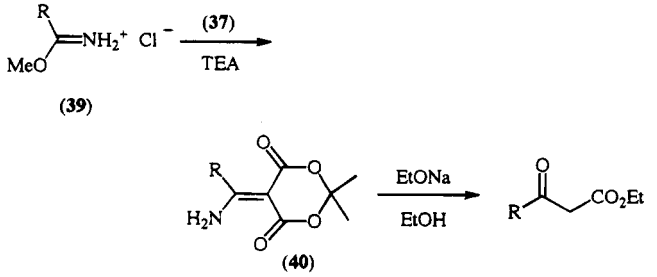
Scheme 42



Scheme 43



Scheme 44

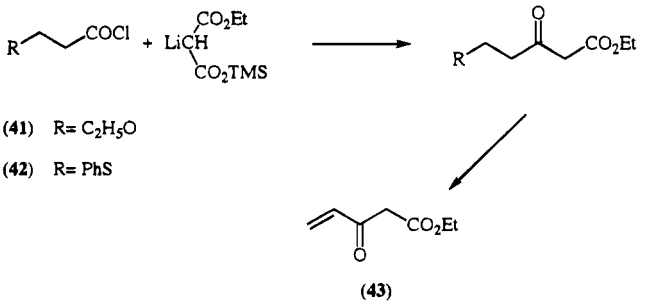


in the absence of a strong base, affording **38**. In heating an alcoholic solution of the acylated Meldrum's acid (**38**), a smooth alcoholysis took place with the evolution of carbon dioxide to give the β-keto ester (Scheme 43).

The alcoholysis of **38** is comparable to that of a diketene, which is converted into acetoacetic acid derivatives by nucleophiles. The application of this procedure to the preparation of methyl phenylacetoacetate has been described in detail in *Organic Synthesis*.[59] The process is an important step in the synthesis of thienamycin described by Melillo et al.[60] In 1982, Houghton and Lapham[61] described a modification of this procedure, based on the formation of the sodium salt of the Meldrum's acid by treatment with sodium hydroxide followed by reaction with anhydrides in dimethylformamide to give **38**. The use of iminoester hydrochlorides as acetylating agents has been also reported[62] (Scheme 44).

Thus, treatment of **39** with **37** in the presence of triethylamine produces **40**, which subsequently furnishes the corresponding acetoacetate by base promoted alcoholysis. The fact that the reaction works

Scheme 45



(41) R= C_2H_5O

(42) R= PhS

(43)

well with the Meldrum's acid but not with malonate esters is due to the different acidity of the two reagents. An alternative way to promote decarboxylation of malonates is based on the differentiation of the two carboxylic functions in order to facilitate the elimination of one of them. This idea was introduced in 1944 by Breslow et al.,[63] who performed the esterification of the ethyl malonic acid half ester with *tert*-butyl alcohol using the *tert*-butyl ester as an acid labile function. Thus, after acylation, decarboxylation took place smoothly by heating in the presence of toluene-*p*-sulfonic acid. Later, Bowmann et al.[64] utilized tetrahydropyranyl esters as acid labile functions. In 1959, Horeau et al.[65] were able to obtain acetoacetates containing unsaturations at positions γ, δ, or ϵ utilizing the above reported procedures. In 1967, Schmidt et al.[66] and some years later Pichat and Beaucourt[67] made use of trimethylsilyl esters for the preparation of **43**, a vinyl β-keto ester known as the Nazarov reagent. The procedure, which involves the acylation of lithium trimethylsilylethylmalonate followed by mild hydrolysis, works well in the case of crotonoyl and methacryloyl chlorides, but is ineffective with acryloyl chloride. However, a suitable device is required to obtain the desired product, involving the use of ethoxypropionyl chloride (**41**) as the acylating agent and leaving the acid-catalyzed elimination as the last step of the process (Scheme 45).

The same concept has been then applied by Trost[68] using phenylthiopropionyl chloride (**42**) as the acylating agent and affecting the elimination reaction after the oxidation of sulfide to sulfoxide with sodium metaperiodate. In 1978, Taylor and Turchi[69] applied this procedure to a great number of acyl halides.

The β-keto esters prepared by acylation of lithium ethyl (trimethylsilyl)malonate are collected in Table 5.

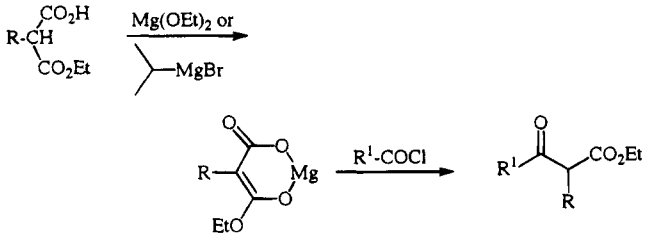
Another way to facilitate decarboxylation, once more based on differently protected malonate carboxylic acid functions, has been proposed by Ireland and Marshall,[70] who used the bisanion of ethyl methyl hydrogen malonate. Its reaction with 2 equiv of magnesium ethoxide or isopropylmagnesium bromide afforded the magnesium chelate, which underwent smooth acylation with acyl halides with concomitant decarboxylation (Scheme 46).

The validity of this methodology, however, is limited to the preparation of α-substituted acetoacetates, the reaction performed on unsubstituted malonate giving rise to the exclusive formation of bisacylation products. This procedure has been successfully utilized by Clezy and Fookes[71] for the

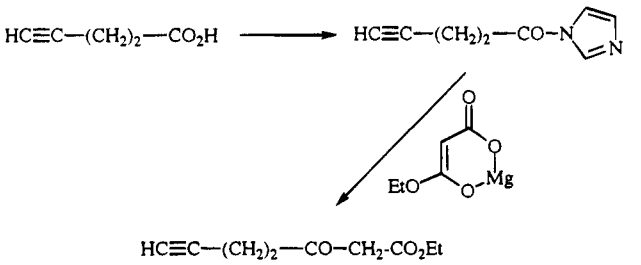
Table 5. Acetoacetates: R-CO-CH_2-CO_2Et

R	yield (%)	ref
Me-CH=CH	75	*67*
CH_2=C(Me)	75	*67*
EtO-CH_2-CH_2	80	*67*
PhS-CH_2-CH_2	77	*68*
t-Bu	84	*69*
t-Bu-CH_2	93	*69*
C_5H_9-CH_2	85	*69*
CH_2=C-CH_2	86	*69*
C_6H_{11}	79	*69*
1-adamantyl	81	*69*
Ph-CH_2	84	*69*
Ph-CH_2-CH_2	90	*69*
Ph	88	*69*
C_6F_5	81	*69*
2-furyl	89	*69*
MeO-CH_2	72	*69*
Cl_3C	58	*69*
FCH_2	33	*69*

Scheme 46



Scheme 47

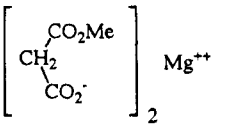


(44)

attachment of a farnesyl group to a porphyrinic acid. Some years later, Gelin and Pollet[72] were able to overcome the problem of bis-acylation simply by use the of a 2.5-fold excess of the magnesium complex in 5:1 THF/CH_2Cl_2 solution. Wierenga and Skulnick[73,74] also operated with a large excess but improved the method by generating the bis anion with 2 equiv of butyl lithium. Bram and Vilkas[75] attributed the bis-acylation to the excessive electrophilic character of the acyl halides and tackled the problem in a completely different way, obtaining exclusive mono-acylation using either mixed anhydride or imidazolides instead of acyl halides. These findings were of great advantage in the preparation of **44**, a crucial intermediate along a synthetic project to prostaglandins developed by Toromanoff et al.[76] (Scheme 47).

Although many progresses had been made in the formation of the C_2-C_3 bond through bis anion methodology, several negative aspects were still to be solved. For instance, the magnesium chelate is highly basic and cannot be used in the presence of substrates sensitive to bases.

This important drawback has been completely overcome by Masamune et al.[77] by acylating the magnesium salt of methyl hydrogen malonate (**45**)

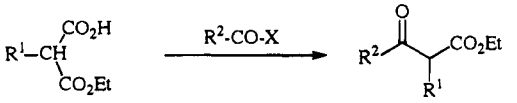


(45)

with imidazolides under practically neutral conditions, obtaining very high yields of acylated products. This decarboxylative carbon acylation is also applied by Mansour et al.[78] to the preparation of β-keto esters of N-protected aminoacylimidazolides.

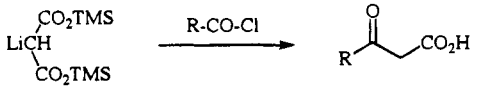
The β-keto esters prepared via ethyl hydrogen malonate following the general reaction shown in Scheme 48 are collected in Table 6.

Scheme 48



In 1979, van der Baan and co-workers[79] developed a route to β-keto acids by hydrolysis and decarboxylation of acylmalonic acid trimethylsilyl esters, prepared by reaction of an excess of lithium bis-(trimethylsilyl)malonate with acyl chlorides or with other suitably activated derivatives (Scheme 49).

Scheme 49



These mild conditions have been studied specifically by the authors and successfully applied to the synthesis of malonomycin.[80]

In 1985, Rathke and Nowak,[81] considering that complexation of a metallic cation with a ligand may enhance the acidity of the latter, reported acylation of bis(trimethylsilyl)malonate with acyl halides in the presence of triethylamine and lithium or magnesium halides. The method offers many advantages, which include the absence of strong bases, the possibility of operating without excess of malonate by using 2 equiv of triethylamine, easy manipulation, and low priced bases.

Taking into account this suggestions, Wemple et al.[82] have developed safe, economical procedures for small as well as for large scale production of aryl and alkyl β-oxo esters using potassium ethyl malonate in either acetonitrile or ethyl acetate solvents in the presence of an already reported salt−base system.

E. Miscellaneous Procedures

There are approaches to the creation of the C_2-C_3 bond that involve more complicated and less immediate pathways, although somewhat related to the methods employing acetate anions. Thus, the phosphorylated derivatives investigated by Bestmann et al.[83] are of great interest. They studied the reactivity of 2,2-diethoxyvinylidenetriphenyl phosphorane (**46**) toward methylene compounds activated by the presence of an ester moiety and found the formation of

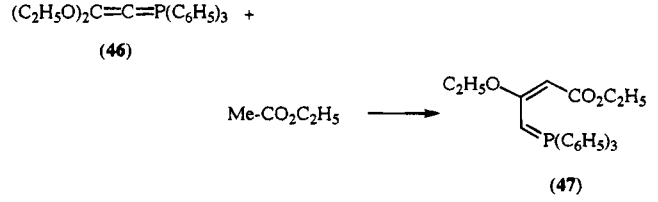
Table 6

R^1	R^2	X	yield (%)	ref
Me	Me	Cl	62	*70*
Me	Me-CH_2-CH_2	Cl	69	*70*
Me	C_6H_5	Cl	52	*70*
Me	EtO_2C-CH_2-CH_2	Cl	71	*70*
Me	*o*-MeO-Ph-CH_2-CH_2	Cl	63	*70*
Ph	Me	Cl	60	*70*
Ph	EtO_2C-CH_2-CH_2	Cl	41	*70*
farnesyl	porphyrin macrocycle	Cl	70	*71*
H	CH_2=C(Me)	Cl	63	*72*
H	Me-CH=CH	Cl	71	*72*
H	Me-CH=C(Me)	Cl	74	*72*
H	$(Me)_2C$=CH	Cl	73	*72*
H	Ph-CH=CH	OCO_{2Et}	53	*75*
H	Ph-CH=CH	Im	30	*75*
H	HC≡C-CH_2-CH_2	Im	70	*76*
H	Ph-CH_2-CH_2	Im	100	*77*[a]
H	n-C_6H_{13}-CHOH-$(CH_2)_9$-CH_2	Im	95	*77*[a]
H	c-C_6H_{11}	Im	85	*77*[a]
Me	Ph-CH_2-CH_2	Im	95	*77*[a]
H	EtO_2C-CH=CH	Cl	61	*72*
H	n-Pr	Cl	62	*73*
H	n-Pr	OCO_2Et	64	*75*
H	n-Pr	Im	74	*75*
H	$(Me)_2CH$-CH_2	Cl	98	*73*
H	n-Bu	Cl	97	*73*
H	Ph-CH_2	Cl	99	*73*
H	Ph-CH_2	OCO_2Et	0	*75*
H	Ph-CH_2	Im	79	*75*
H	Ph	Cl	97	*73*
H	Ph	OCO_2Et	35	*75*
H	Ph	Im	65	*75*
H	4-Me-Ph	Cl	91	*73*
H	4-MeO-Ph	Cl	90	*73*
H	3,4-Cl_2-Ph	Cl	97	*73*
H	4-CN-Ph	Cl	88	*73*
H	3-I-Ph	Cl	97	*73*
H	4-$(Me)_2N$-Ph	Cl	76	*73*
H	2-$C_{10}H_7$	Cl	95	*73*
H	3-furyl	Cl	97	*73*
H	2-Cl-Ph	Cl	93	*73*
H	Et	OCO_2Et	57	*75*
H	Et	Im	68	*75*
H	n-C_6H_{13}	OCO_2Et	62	*75*
H	n-C_6H_{13}	Im	74	*75*
H	EtO_2C-CH_2-CH_2	OCO_2Et	43	*75*
H	EtO_2C-CH_2-CH_2	Im	61	*75*
H	4-NO_2-Ph	OCO_2Et	60	*75*
H	4-NO_2-Ph	Im	77	*75*
H	BocNHCH(Me)	Im	69	*78*[a]
H	FmocNHCH(i-Pr)	Im	45	*78*[a]
H	BocNHCH(i-Bu)	Im	74	*78*[a]
H	BocNHCH(CH_2Ph)	Im	69	*78*[a]
H	ZNHCH(CH_2Ph)	Im	58	*78*[a]

[a] Methyl malonic acid half ester was used.

the stable ylide **47**, derived by Michael addition followed by subsequent ethanol elimination (Scheme 50).

Scheme 50



The phosphorane **47**, actually an enol ether of a β-keto ester, has been elaborated by reaction with an aldehyde as described in the section for the formation of the C_4–R_3 bond. In the meantime, Bestmann et al.[84,85] reported the preparation of β-substituted acetoacetates (**50**) through electrolysis of the phosphonium chloride **49**, in turn obtained by reaction between and acyl halide and [l-(alkoxycarbonyl)-alkylidene]triphenylphosphorane (**48**) in a molar ratio 1:1 (Scheme 51).

The reaction has been carried out in a 1:2 molar ratio on a substrate with $R_3 \neq H$ to produce the allene **54** while for R_3 = H the acetylenic ester **52** is the final product. Both esters **54** and **52** have been subsequently taken to β-keto esters by the addition of piperidine and subsequent hydrolysis.

An alternative procedure has been introduced in 1986 by Sanchez et al.,[86] who prepared the phosphorane **51** (R_1 = H; R_2 = $CH_2OC_2H_5$) as described above and submitted it to reductive elimination by aluminum amalgama catalyzed by trifluoroacetic acid to produce in excellent yield the β-keto ester **53**. In 1988, Hamper[87] suggested a more convenient methodology for the preparation of α-acylmethylene phosphoranes (**55**) by the addition of 2 equiv of triethylamine to a phosphonium salt, followed by 1 equiv of acyl chloride or anhydride. The direct reductive removal of triphenylphosphine from **55** with Al Hg in the presence of a proton donor, developed by Cooke Jr.,[88] afforded β-keto esters in high yields (Scheme 52).

Nokami et al.[89] have described a sulfur-containing Grignard derivative **56** prepared from ethyl (phenylsulfinyl)acetate and alkyl magnesium halide, which can be considered a synthetic equivalent of the acetate anion. (Scheme 53).

Its reaction with aldehydes gave the corresponding α-ethoxycarbonyl β-hydroxy sulfoxides (**57**), which by pyrolitic elimination afforded in good yield the acetoacetates. An elimination reaction has been successfully utilized by Pellicciari et al.[90,91] for the conversion of α-diazo β-hydroxy esters (**58**), the aldol condensation products between lithium ethyldiazoacetate and aldehydes, to the corresponding β-keto esters in the presence of catalytic amounts of rhodium(II) acetate (Scheme 54).

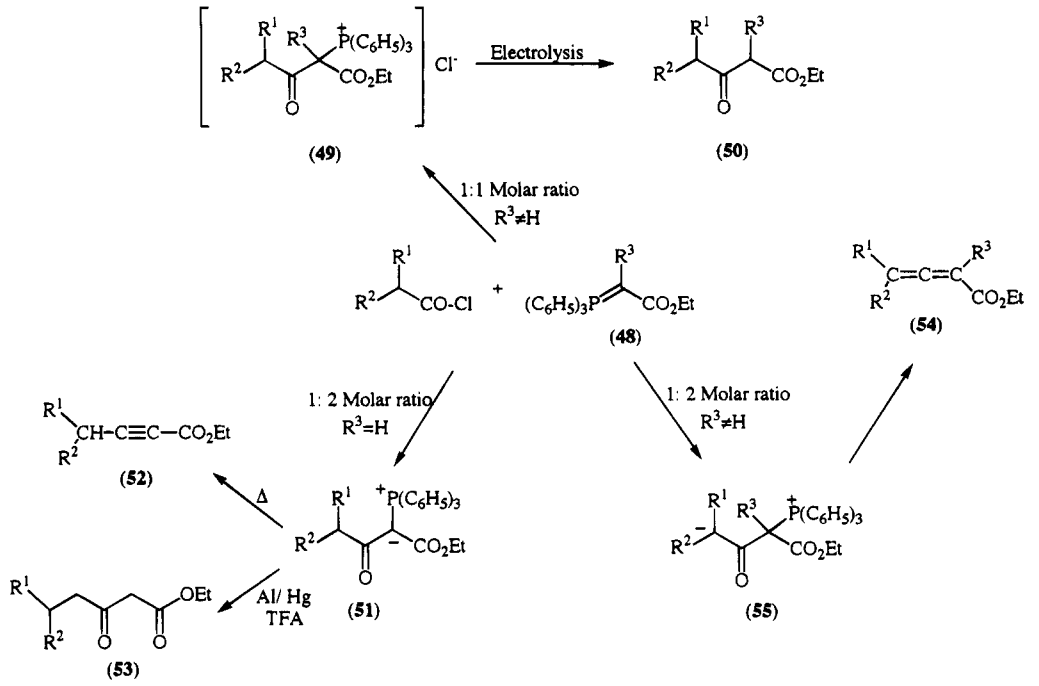
The proposed direct conversion of aldehydes into β-keto esters has also been performed by Roskamp et al.[92,93] in the presence of tin(II) chloride as a Lewis acid catalyst for the addition of ethyl diazoacetate to the carbonyl function.

Several authors proposed sulfur extrusion from thioepoxides as a method for the C_2–C_3 bond formation. The general process outlined in Scheme 55 requires the following: (i) S-alkylation of a thioamide with an α-haloester, (ii) thiirane formation, and (iii) sulfur extrusion with a thiophile and enamine hydrolysis to β-keto ester. The approaches described in the literature are featured by different experimental conditions and utilize a variety of reagents to effect the transformations involved.

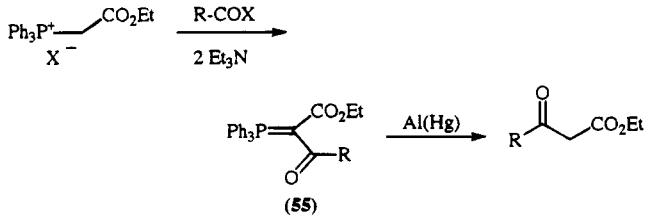
Thus, Gossauer et al.[94] used dithioglutarimides (**59**) or *N*-(thioacyl)urethanes (**60**) instead of thioamides, methyl(triphenylphosphoranylidene) acetate being the alkylating agent and the triphenyl phosphine generated in the reaction the thiophile.

Following the sulfur extrusion methodology introduced by Eschenmoser, Ireland and Brown[95] used the

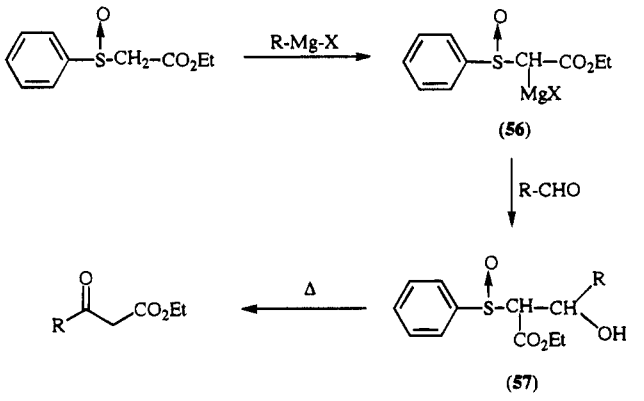
Scheme 51



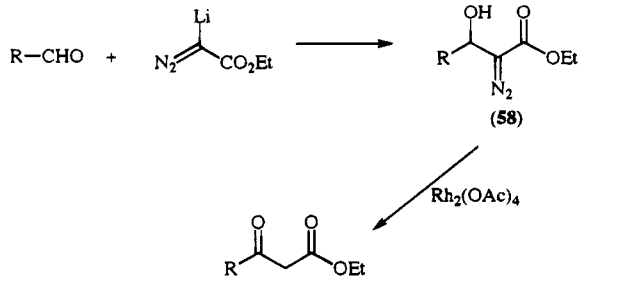
Scheme 52



Scheme 53

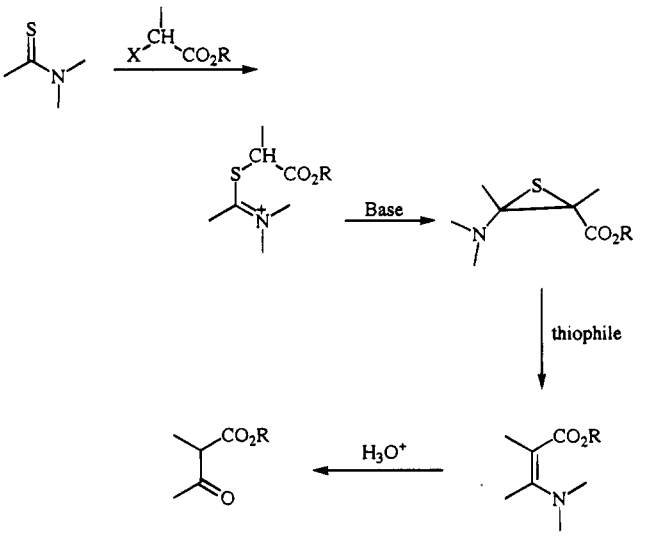


Scheme 54

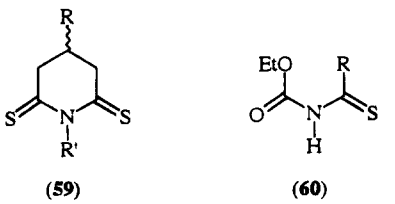


base-thiophile reagent **61** and achieved the preparation of β-keto esters both intramolecularly and intermolecularly. The authors found *N,N*-dialkylthioamides to be more suitable than *N*-monoalkyl-

Scheme 55



thioamides and ascribed the improved behavior to the strong acidity of the acetate proton, probably due to the presence of a positive charge in the thioimmonium salt derived by the alkylation of *N,N*-dialkylthioamides.



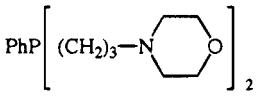
(59) **(60)**

$PhP[(CH_2)_3NMe_2]_2$

(61)

This methodology was subsequently generalized by Rapoport,[96] who also obtained α-substituted β-keto

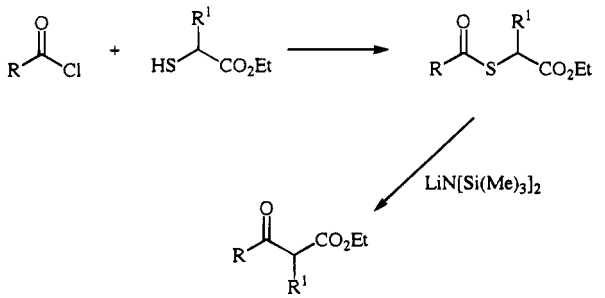
ester. The most salient modifications are as follows: (i) the use of thiopyrrolidides rather than *N,N*-dialkylthioamides; (ii) the possibility of affecting alkylation also with triflates of simple or substituted α-hydroxy esters instead of the usually employed bromo- or iodoacetates; (iii) the introduction of bis-(3-morpholinylpropyl)phenylphosphine (**62**) as the base thiophile.



(**62**)

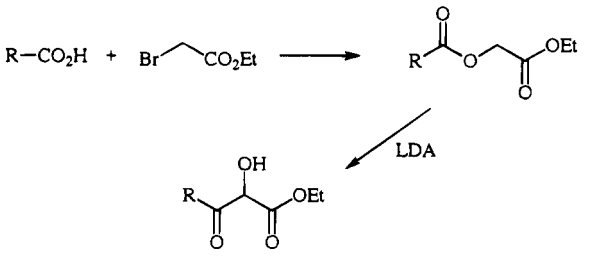
In 1985, Omura et al.[97] discovered a new class of compounds, the α-acylthio esters, which on basic treatment with lithium hexamethyldisilazide, undergo sulfur extrusion with the formation of unsubstituted and of α-substituted acetoacetates in the absence of thiophile (Scheme 56). The same behavior

Scheme 56



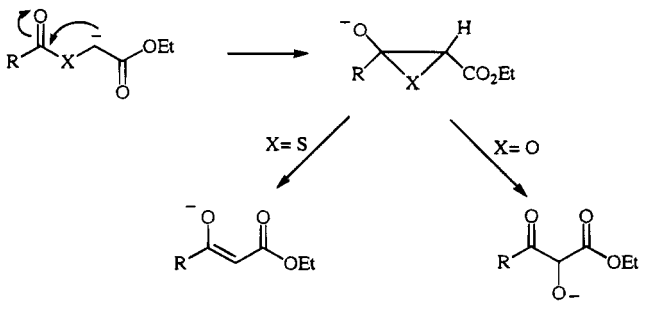
has been observed by Lee et al.[98] for α-acyl esters, which rearrange in the presence of a base to give α-hydroxy β-keto esters without oxygen extrusion (Scheme 57).

Scheme 57

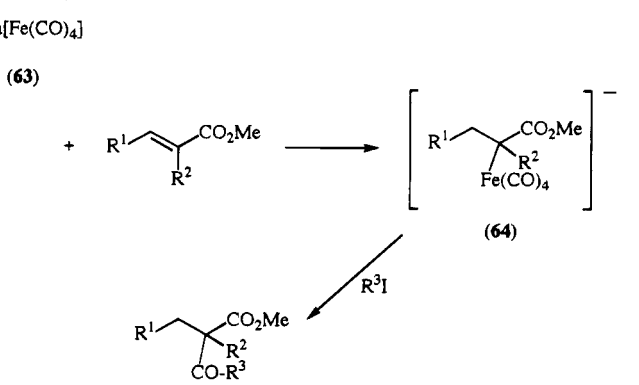


In both cases, the initial event of the sequence is the formation of oxirane or thirane derivatives, which then require the opening of epoxide in the case of α-acyl esters and the extrusion of sulfur in the case of α-acylthio esters (Scheme 58).

Scheme 58



Scheme 59



The preparation of α-substituted β-keto esters through an insertion reaction into the hydrogen−iron bond of tetracarbonyl hydridoferrate(0) (**63**) has been investigated by Mitsudo et al.[99] (Scheme 59).

As an example, the oxidative addition to **63** of α,β-unsaturated esters produces the alkyl−iron complex **64**, which on treatment with primary alkyl iodides leads to the formation of hydroacylation products through eliminative reduction. Owing to steric hindrance the reaction does not work if $R_2 \neq H$.

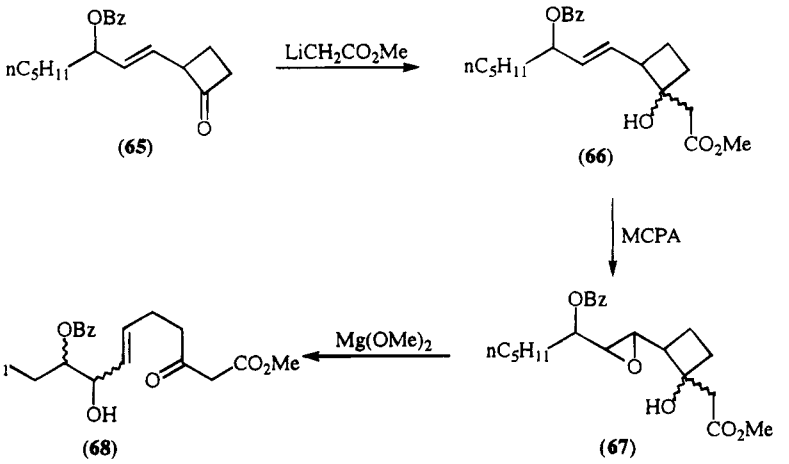
A very ingeneous synthesis of highly substituted acetoacetates based on the base-catalyzed rearrangement of epoxycyclobutenols has been achieved by Trost,[100] as outlined in Scheme 60.

Thus, the lithium enolate of methyl acetate reacts with the substituted vinyl cyclobutanone **65** to give the vinyl cyclobutanol **66**, in turn transformed to **67** by the action of *m*-chloroperbenzoic acid. Rearrangement of the latter in the presence of magnesium methoxide leads to the formation of the ϵ-alkylidene β-keto ester **68**. The α-substituted acetoacetates can also be obtained through aldol condensation with lithium enolates homologous of methyl acetate. The process, known as Blaise reaction and involving nitriles as alkylating agents, has been scarcely investigated until 1982 when Hiyama and Kobayashi[101] suggested a modified procedure involving the condensation of the magnesium enolate of *tert*-butyl acetate, prepared by treatment of the ester with the reagent derived from diisopropylamine (2 mol) and ethyl magnesium bromide (1 mol), with a nitrile followed by acid hydrolysis of the enamino ester to give a β-keto ester (Scheme 61).

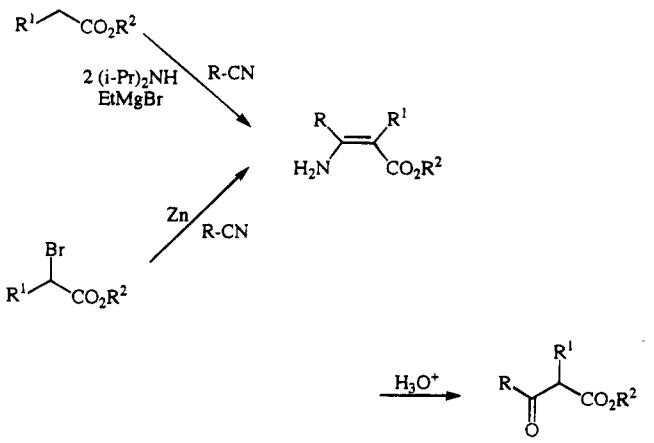
Later, Kishi and Hannick[102] revisited the original procedure described by Blaise and greatly improved the process using tetrahydrofuran as solvent and slowly adding the bromoester to suitably activated zinc (Scheme 61). The authors discovered a very interesting application, namely, the in situ intramolecular alkylation of bidentate organometallics (**69**), in turn derived by a suitably functionalized nitrile (Scheme 62).

In fact, the intermediate **69** can cyclize in two different ways, producing products deriving by N- or C-alkylation, depending on the characteristics of the leaving group X: when X = Br, C-alkylation takes place to give **70**, while for X = OMs, **71** is formed. Another particular acylation of active methylene compounds has been discovered in 1986 by Kobayashi and Tanaka[103] through palladium complex-catalyzed carbonylation of aromatic halides (Scheme 63).

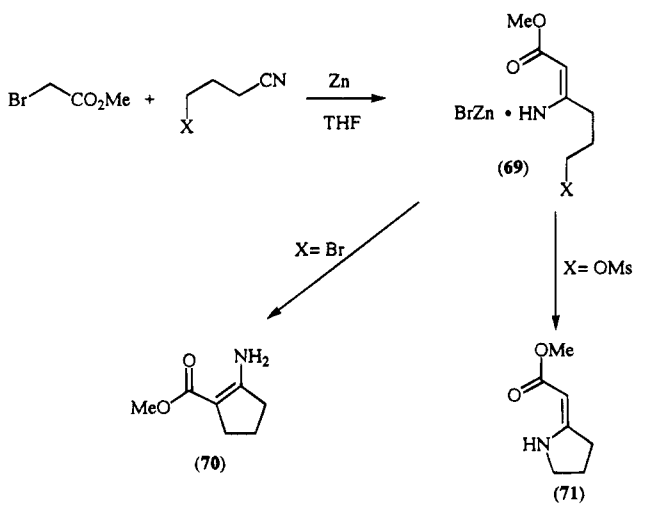
Scheme 60



Scheme 61



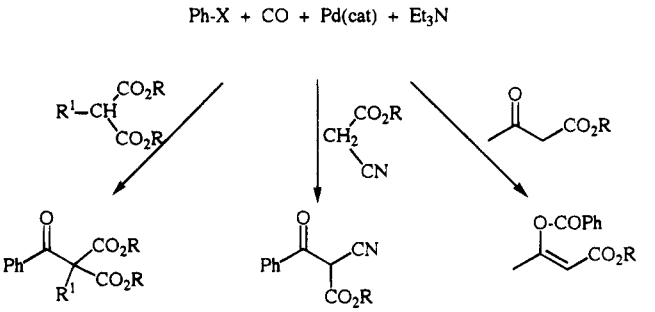
Scheme 62



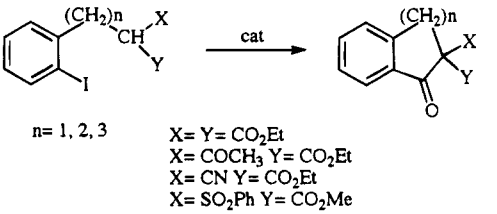
The reaction of diethyl malonate, diethyl alkyl malonate, or ethyl cyanoacetate with iodobenzene in the presence of triethylamine, carbon monoxide, and dichloro[1,1-bis(diphenylphosphino]ferrocene palladium as catalyst produces acylmalonates and acylcyanoacetates. In contrast, the reaction with acetoacetates leads to the formation of the corresponding enol esters through O-acylation.

In 1989, applying the same strategy, Neghishi et al.[104] have reported a potentially general carbonylative cyclization starting from esters of *o*-iodobenzylmalonic acids and related methylene active compounds, CO (600 psi), triethylamine, and a catalytic amount of transition metal complexes prepared from $NiBr_2$ treated with BuLi in the presence of cyclooctadiene, $Pd(PPh)_4$, and $Cl_2Pd(PPh_3)_2$ (Scheme 64).

Scheme 63



Scheme 64



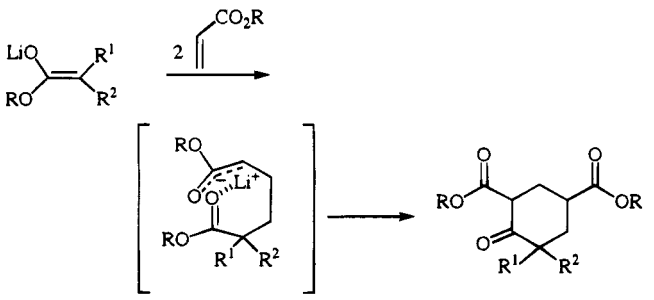
Under analogous conditions, $CpCo(CO)_2$, $Fe(CO)_5$, and $ClRh(PPh_3)_3$ do lead to the same results, but work only in stoichiometric amounts.

In developing synthetic methods based on multicomponent annulations, Posner et al.[105] found that lithio enolates of several different acyclic and cyclic carboxylate esters react with acrylates via a Michael–Michael–Dieckmann cyclization sequence to form cyclohexanones α-carboxylate in good yield (Scheme 65).

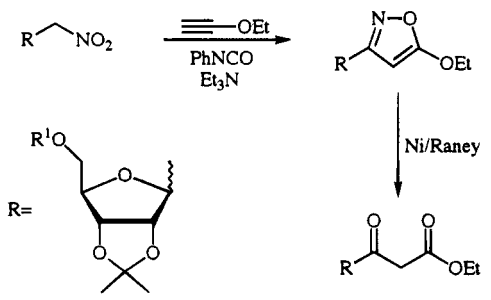
This easy one-pot process represents a simple, convenient, and versatile methodology for joining three 2-carbon components into six-membered substituted carbocycles. Claisen-type condensation requiring a basic agent, an alternative route for its generation, is the involvement of electrogenerated bases produced by the electroreduction of a probase (an aromatic halide).[106] The electrochemical device is an undivided cell fitted with a sacrificial magnesium anode and a nickel cathode on which cadmium had been deposited.

Finally, we will consider two strategies in which heterocyclic compounds act as synthetic equivalent

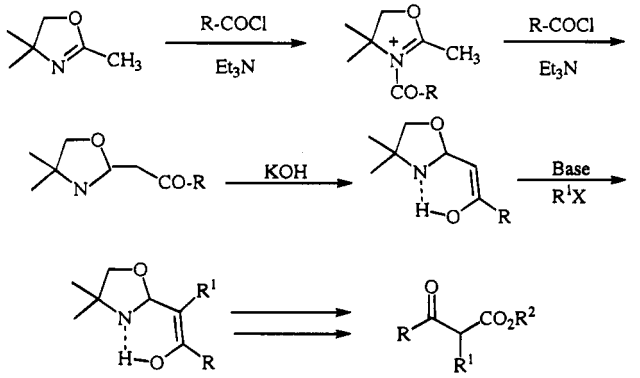
Scheme 65



Scheme 66



Scheme 67



of β-keto esters. The formation of the carbon−carbon bond during the preparation of these heterocyclic compounds constitutes the formation of the C_2-C_3 bond of the acetoacetate moiety.

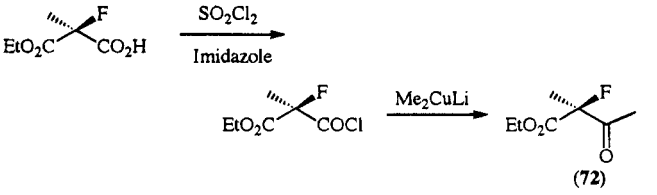
The first strategy was successfully employed in 1983 by Kozikowski and Goldstein[107] in a synthetic approach to C-nucleosides (Scheme 66) based on well-known principles of isoxazole chemistry such as (i) the labile nature of the nitrogen−oxygen bond leads to 1,3-dicarbonyl compounds under hydrogenolytic conditions and (ii) isoxazoles are conveniently prepared through 1,3-dipolar cycloaddition of nitrile oxides to terminal acetylenes.

The second strategy is based on the employment of 1,2,4-trimethyl-2-oxazoline[108] as a synthetic equivalent of the acetate anion, taking advantage of the relevant acidity of hydrogen atoms at the C_2 methyl group after the quaternization of the nitrogen atom, which allows acylation to produce a masked β-keto ester that can be further alkylated to give α-substituted derivatives (Scheme 67).

IV. C_3-C_4 Bond Formation

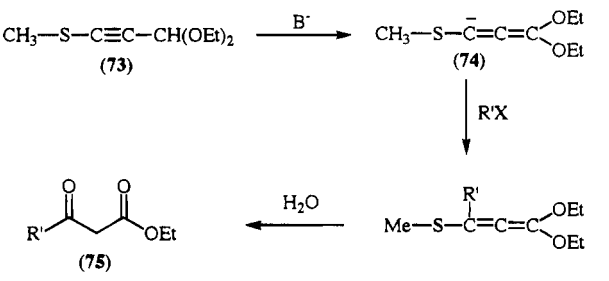
The approach to the preparation of β-keto esters through the formation of this particular bond is undoubtedly the most difficult and the least studied. In principle, the creation of this bond requires a carbanion attack of the center destined to become C_4 at an electrophilic center that will become C_3, following the electronic demand of a three-carbon atom fragment, progenitor of a β-keto ester. Since C_2 must not have H-atoms, the proposed methodologies concern exclusively α,α-disubstituted compounds, as exemplified by the chiral α-fluoro-α-methyl derivative (**72**), easily prepared by reaction of lithium dimethyl copper on the disubstituted ethyl malonyl chloride derivatives[109] (Scheme 68).

Scheme 68



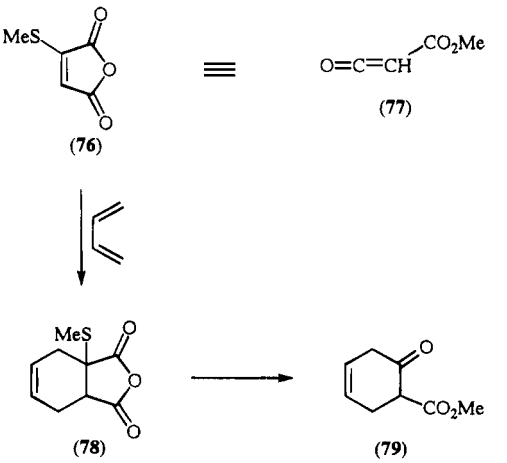
Carlson[110] developed a different approach featuring the "umpolung" of the C_3 carbon atom of three carbon precursor (**73**): thus alkylation of the allenic carbanion **74**, generated by treatment of **73** with lithium diethylamide, with alkyl halides followed by hydrolysis produced the β-keto ester (**75**). This methodology is useful only for unsubstituted compounds (Scheme 69).

Scheme 69



In 1977, an elegant procedure for the synthesis of cyclic β-keto esters entailing the use methylthiomaleic anhydride **76** as the synthon for a protected carbomethoxy ketene **77** has been proposed by Trost[111] (Scheme 70).

Scheme 70



Cycloaddition between the dienophile **76** with a diene counterpart gave rise to the expected adduct **78**, which on oxidative decarboxylation led to the corresponding β-keto ester **79**.

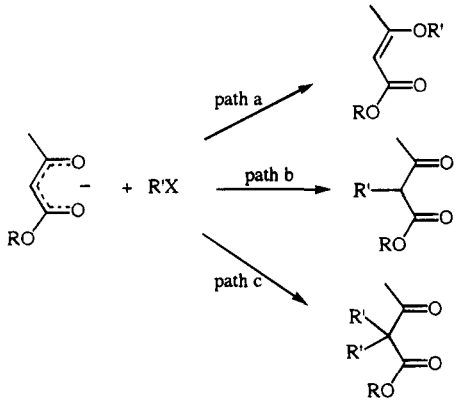
V. C_2–R_2 Bond Formation

The following possibilities can be envisaged for the C_2–R_2 bond formation: A. Alkylations; B. Alkylation via Michael Reaction; C. Lewis Acid-Catalyzed Alkylation; D. Metal-Catalyzed Alkylation; E. Alkylation via Diazoacetates; F. Insertion Reaction with Diazoacetates; G. Heteroatoms–C_2 Bond Formation; H. Alkylation through Rearrangement; I. Other Methods; J. Acylation.

A. Alkylations

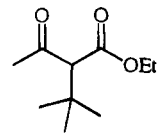
The C_2–R_2 bond usually originates through alkylation of enolates of a β-keto ester. Problems arise from the bidentate nature of the anion, which may react both at the oxygen center (path a)[112] or at the carbon center (path b)[113] as well as from the possibility of bis-alkylation (path c)[114] (Scheme 71).

Scheme 71

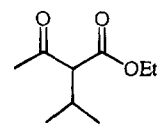


The aspects of β-keto ester ambident reactivity are well known, and various theories have been proposed and examined. A polar aprotic medium, a large counterion, low concentrations of the anion, a hard leaving group, and an alkylating agent of low SN_2 reactivity are usually suggested to promote O-alkylation (path a); the C-alkylation (path b) requiring, of course, opposite conditions. Thus, good yields of C-alkylated products are obtained, employing unhindered primary halides, while with secondary halides the elimination reaction predominates. In such cases, the reaction of the enol rather than the enolate anion with a carbonium ion or carbonium ion-like species is the preferred route. Thus, ethyl acetoacetate reacts with *tert*-butyl bromide and silver perchlorate in nitromethane to give **80**, while its reaction with 2-propanol in the presence of boron trifluoride produces the corresponding C-isopropyl derivative **81**.

Almost exclusive C-alkylation may be achieved through two methodologies: ion pair extraction and phase-transfer catalysis. However, methods that suppress O-alkylation usually lead to the formation of bis-alkylation products (path c). As a logical extension, this technique has been used in asymmetric synthesis, and several chiral ammonium salts (e.g., (−)-*N*-benzyl, *N*-methyl ephedrinium bromide,[115] (+)- and (−)-benzyl-[*cis*-2-(hydroxymethyl)cyclohexyl]-dimethylammonium bromide,[116] (−)-dodecyl,*N*-methyl ephedrinium bromide[117]) and some salts of alkaloids (e.g., cinchonidine, cinchonine, and quinine[117]) have been tested as catalysts. The efficiency of this synthetic methodology is still somewhat limited because the optical purity usually reached is low.



(80)



(81)

Convenient experimental conditions aimed at improving the selectivity of the process regarding mono- and bis-alkylation have been introduced by Kirschleger and Queignec,[118] who carried out the reaction without solvent, in the presence of anhydrous potassium carbonate as the base, using alkyl halides as alkylating agents at temperatures in the range 25–60 °C.

In 1992, Rahn and Bhar[119] reported a simple procedure for the selective control of mono- and bis-C-alkylation of β-oxo esters through a solvent-free reaction on the surface of alumina impregnated with a base. While mono-alkylation is accomplished using 1 equiv of base (potassium *tert*-butoxide or sodium ethoxide) and 1 equiv of alkyl halide, for bis-alkylation the best results were produced using 2.5 equiv of sodium ethoxide and 2 equiv of alkyl halide as summarized in Table 7.

Besides the usual SN_1 and SN_2 type reactions, the alkylation of a β-keto ester can be performed by means of $SN_{2'}$ nucleophilic substitution, the main advantage being high stereospecificity. Toromanoff et al.[76] applied this concept along their synthesis of PGA, where treatment of the enamine of acetoacetate derivative **82** with butyllithium generates the anion **83**, which reacted intramolecularly in a $SN_{2'}$ fashion on the allylic epoxide group producing stereospecifically the substituted cyclopentanone **84** (Scheme 72).

Scheme 72

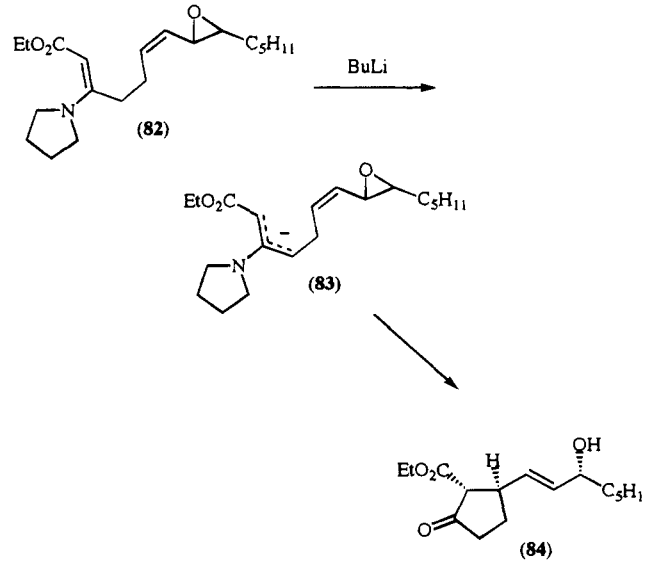
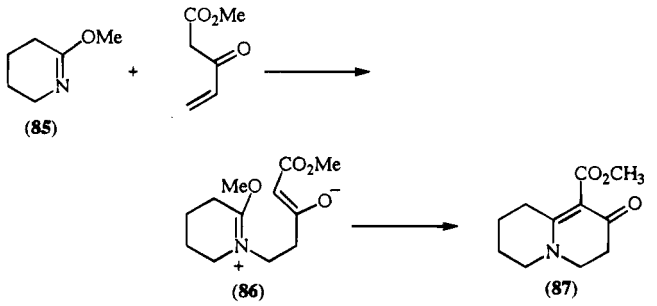


Table 7

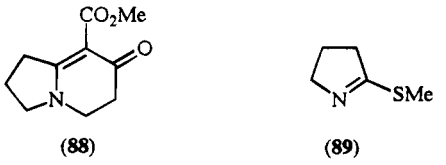
β-keto esters	alkyl halide	yield alkylation mono	yield alkylation bis
ethyl acetoacetate	MeI	90	80
ethyl acetoacetate	CH_2=$CHCH_2Br$	88	85
ethyl acetoacetate	$BrCH_2CO_2Et$	72	70
ethyl acetoacetate	$PhCH_2Br$	85	80
ethyl 2-oxocyclohexanecarboxylate	MeI	92	
ethyl 2-oxocyclohexanecarboxylate	CH_2=$CHCH_2Br$	92	
ethyl 2-oxocyclohexanecarboxylate	$BrCH_2CO_2Et$	86	
ethyl 2-oxocyclohexanecarboxylate	$PhCH_2Br$	92	

The synthesis of the bicyclic system[120] (**87**) offers an interesting example of alkylation in the intramolecular version (Scheme 73). The process is extremely simple and consists of a Michael addition of the Nazarov reagent with the imino ether **85** to produce the intermediate **86**, which undergoes cyclization followed by loss of methanol to give **87**. This route has been advantageously utilized in 1986 by Yamazaki et al.[121] for the preparation of indolizidines (**88**) and quinolizidines (**87**), performing the reaction with thioimidates (**89**) in the presence of mercuric chloride under the same experimental conditions.

Scheme 73



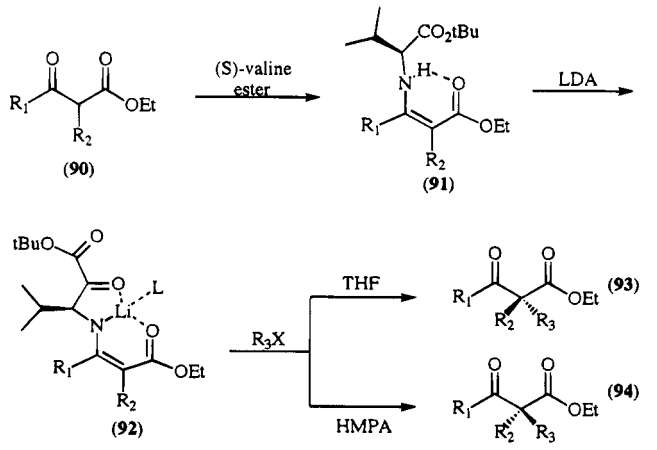
(85) (86) (87)



(88) (89)

During their attempts to develop new methodologies for asymmetric alkylation, Koga et al.[122] applied this procedure to α-alkyl β-keto esters (Scheme 74).

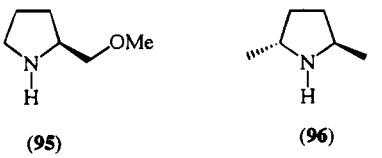
Scheme 74



(90) (91) (92) (93) (94)

The alkylation of the chiral enamine **91**, prepared by reaction of the corresponding β-keto ester **90** with (*S*)-valine *tert*-butyl ester, produced the disubstituted acetoacetates **93** or **94** with good enantiomeric excess. The course of this alkylation heavily depends on the solvent employed and prompted the authors to suggest its direct participation as the fourth ligand of the lithiated complex (**92**).[123]

Different chiral secondary amines have been tentatively used as chiral auxiliary by Hodgson et al.,[124] and their initial effort focused on the incorporation of readily available (*S*)-2-(methoxymethyl)pyrrolidine (**95**) into enamine derivatives.

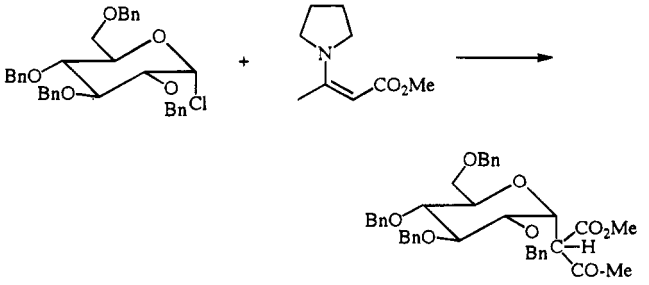


(95) (96)

Thus, the enamine obtained from 2-(ethoxycarbonyl)cyclohexanone and **95** under standard conditions underwent alkylation with a modest induction of asymmetry (33% ee). The authors have also attempted to use (2*R*,5*R*)-2,5-dimethylpyrrolidine (**96**) as an auxiliary, but the presence of two flanking methyl residues increases the steric hindrance and does not allow the formation of the corresponding enamine.

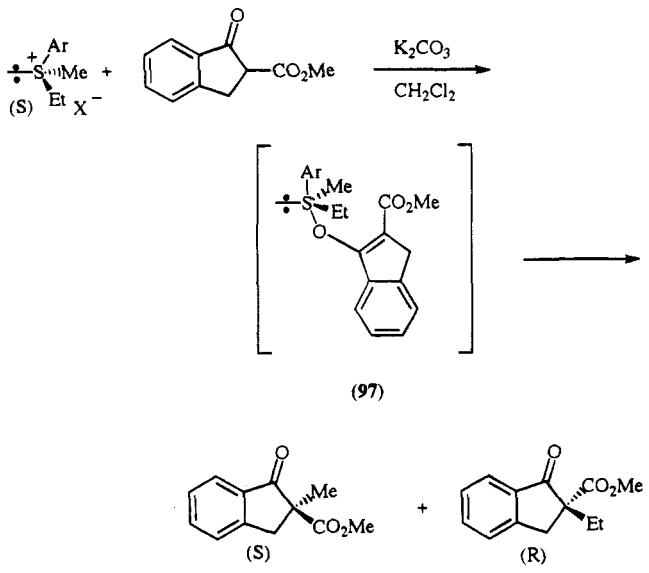
This methodology has been successfully utilized in the preparation of C-glucosides of β-keto esters as reported by Allevi et al.,[125] who were able to obtain exclusive α-C-glucosylation starting from 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride activated by silver(I) triflate and enamines of β-oxo esters (Scheme 75).

Scheme 75

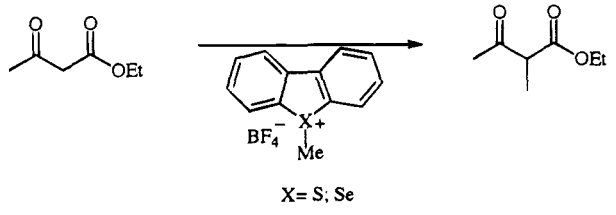


In this direction, though with less encouraging results, Kobayashi et al.[126] investigated β-keto ester alkylation using optically active sulfonium salts, e.g., (*R*)-(+)-(*p*-chlorophenyl)ethylmethylsulfonium *d*-10-camphorsulfonate, dimethyl or diethyl sulfonio D-

Scheme 76



Scheme 77



glucosides[126-128] resulting in the formation of a mixture of C-methylation and C-ethylation products, with very low optical purity and with opposite configuration (Scheme 76). The stereochemical outcome of the reaction has been explained assuming the formation of the S−O sulfurane intermediate (**97**).

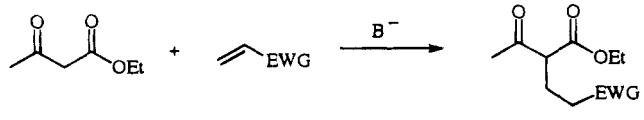
The carbon−carbon bond formation via methyl transfer from a sulfonium salt to the carbon nucleophile of β-oxo esters is well-demonstrated in their previous reports, but the description was limited to nonaqueous systems.

Julia[129] and Garst[130] independently reported that this difference can be attributed to the stabilization of the charged sulfonium salt by water. In 1989, Winkler et al.[131] found that the reaction of the dibenzothiophenium salt as well as the reaction of the more electrophilic selenonium salt leads to the formation of methylated products at neutral pH in aqueous solution (Scheme 77).

B. Alkylation via Michael Reaction

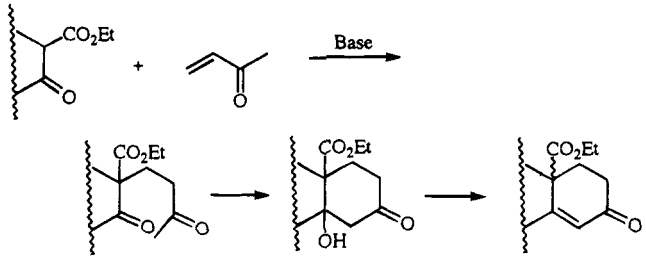
Apart from nucleophilic substitution, β-keto ester alkylation can also be effected through Michael addition as illustrated in the following general equation (Scheme 78).

Scheme 78



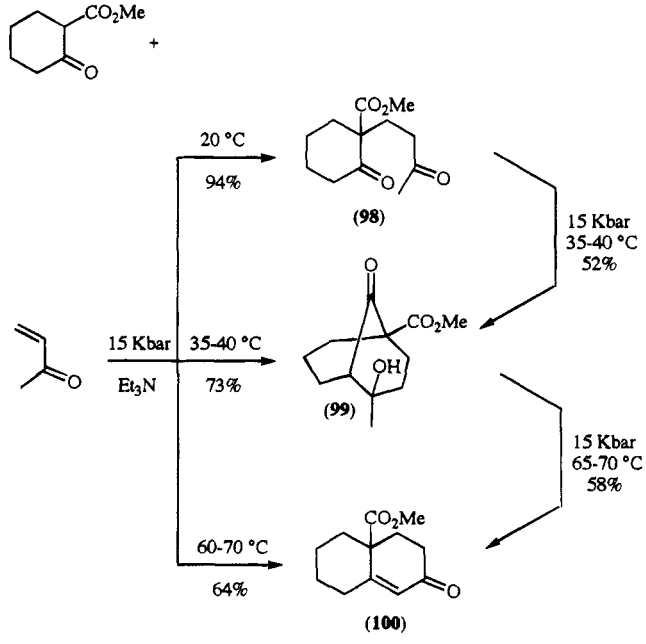
The method is well documented[2] and works with all the usual Michael acceptors, among which the more interesting are certainly the vinyl ketones, which allow the building of cyclic compounds through the classical "Robinson annulation". This involves the sequential base-catalyzed Michael addition of a ketone or keto ester enolate to a vinyl ketone, followed by aldol ring closure of the intermediate 1,4-adduct, and the final dehydration of the resulting ketol (Scheme 79).

Scheme 79



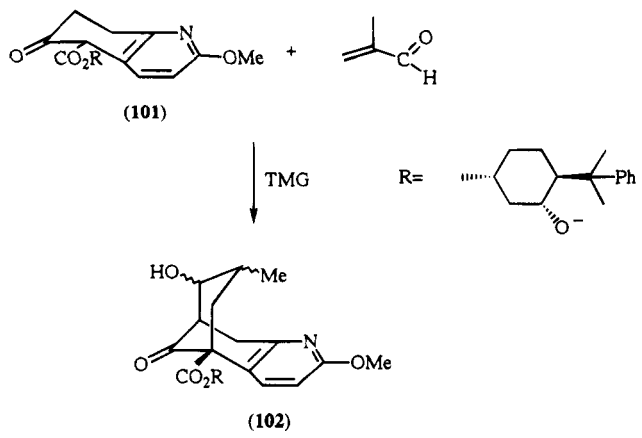
The applicability of this reaction is confined to vinyl ketones possessing no more than one group in the β-position. To overcome the steric inhibition encountered with hindered enones (e.g., mesityl oxide), the enolates of doubly activated β-oxoesters have been cyclized under high pressure (15 kbar) in acetonitrile containing triethylamine or 1,5-diazabicyclo[4.3.0.]-non-5-ene (DBU). Dauben and Bunce[132] reported that the reaction can be controlled to give the simple Michael adduct **98**, the bicyclic ketal **99**, or the fused enone **100** by carefully selecting thermal parameters as shown in Scheme 80.

Scheme 80

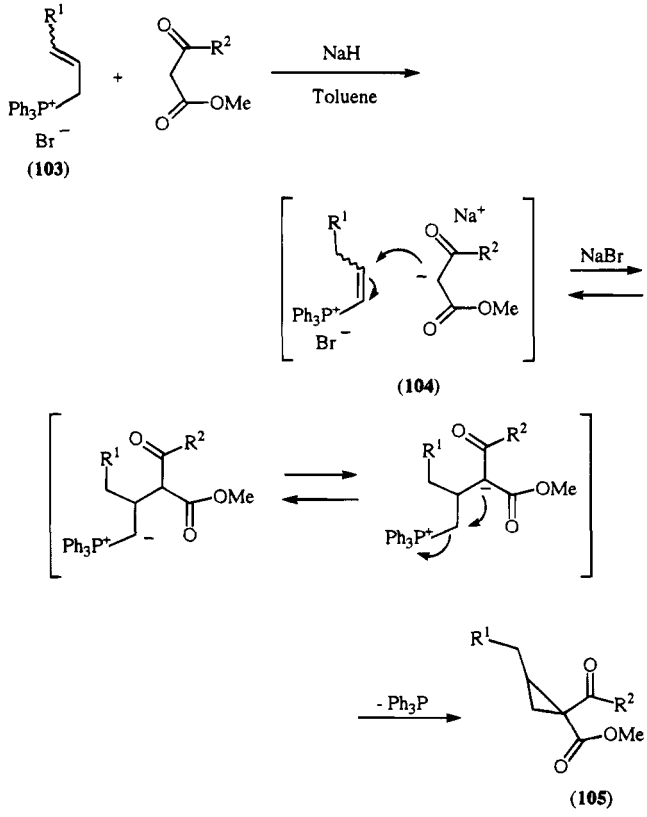


Employing an analogous strategy, Kozikowski et al.[133] have developed an enantioselective approach to huperzine A, starting from the optically active β-keto ester (**101**) and methacrolein in the presence of tetramethylguanidine (TMG) at room temperature and normal pressure, via formation of the bridged ketol **102**, normally undetectable with ketones in comparable experimental conditions (Scheme 81).

Scheme 81



Scheme 82

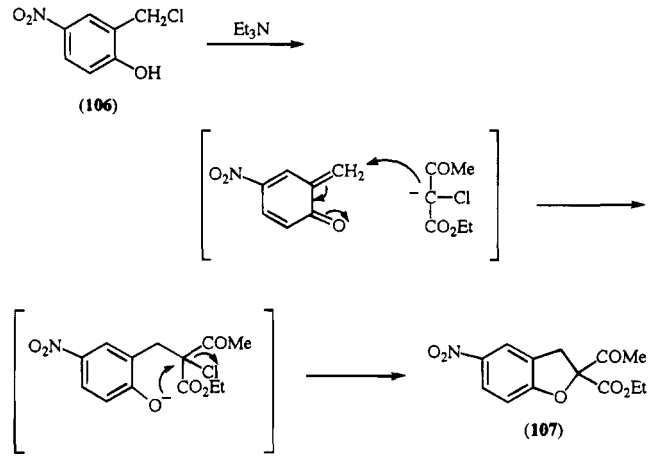


Vinyl phosphonium salts (**104**), obtained by base-catalyzed isomerization of allyl phosphonium salts (**103**), are unusual Michael acceptors and have been used to prepare methyl 1-acyl-2-alkylcyclopropanecarboxylates[134] (**105**) by addition of β-keto esters sodium salts in toluene and subsequent cyclization with elimination of triphenyl phosphine (Scheme 82).

An intriguing β-keto ester bis-alkylation leading to disubstituted benzofurans has been described[135] in 1986. The condensed heterocycle **107** was obtained in a one-step process by treatment of 2-(chloromethyl)-4-nitrophenol (**106**) with the anion derived by ethyl 2-chloroacetoacetate in the presence of triethylamine (Scheme 83).

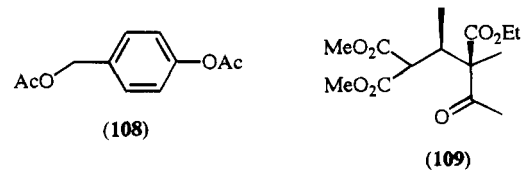
The quinone methide is the Michael acceptor generated from **106**. The same short-lived intermediate, prepared by Sanner et al.[136] from the readily available diacetate (**108**) by treatment with Cs_2CO_3,

Scheme 83



is trapped by ethyl acetoacetate to yield the Michael adduct.

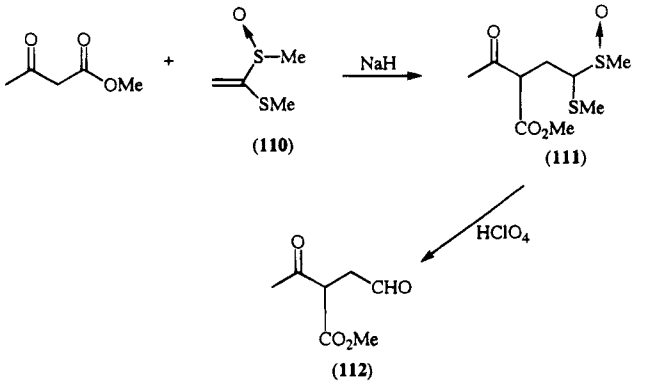
In 1987, Koga et al.[137] described a high enantio- and diastereoselective alkylation involving the use of chiral enamines of α-alkyl β-oxo esters as Michael donors. Thus, the lithioenamine (**91**) can be added to methyl ethylidenemalonate in the presence of hexamethylphosphoramide at −78 °C to give the adduct **109** as the sole product.



Nonactivated Michael acceptors (e.g., methyl vinyl ketone or ethyl acrylate) failed to afford products in these conditions, and the reaction has been carried out in the presence of chlorotrimethylsilane (TMSCl) as an activator.[138] One important feature of the process is that it is capable of the optional control of diastereoface differentiation changing the Lewis acid. The experimental data concerning TMSCl/HMPA and BF_3·Et_2O/HMPA as activators show that in using the first system TMSCl and HMPA play their roles independently (the former as an activator of the Michael acceptor and the latter as a ligand to the lithium cation) while in using the second system BF_3·Et_2O removes HMPA from coordination to the lithium cation. The different behavior affords adducts with opposite configuration. In 1988, Brünner et al.[139] have reported that cobalt chloride catalyzes the addition of chiral β-enamino esters, obtained from commercially available (*R*)- or (*S*)-1-phenylethylamine with a Michael acceptor. Guigant and Hammami[140] have envisaged two different modes of activation of the same enamine, e.g., use of $ZnCl_2$ or $MgBr_2$ as Lewis acids and application of high pressure conditions (11−14 kbar).

The literature describes several particular acceptors possessing a sulfoxide or a sulfonium salt as the electron-withdrawing group. Schlessinger et al.[141] proposed ketene thioacetal monoxide (**110**) as an electron-deficient olefin obtaining the α-substituted acetoacetate (**112**) after hydrolysis of the adduct **111** in aqueous acetonitrile containing perchloric acid (Scheme 84).

Scheme 84



Similar disubstituted products result from the reaction of ketene thioacetal monosulfonium salt (**113**) with active methine compounds such as ethyl 1-oxocyclohexane-2-carboxylate and methyl 2-benzoylpropionate[142] (Scheme 85).

Koppel and Kinnich[143] using phenyl vinyl sulfoxide (**114**) and a cyclic β-keto ester as partners in the Michael addition obtained the adduct **115**, which on pyrolysis in refluxing toluene afforded the vinyl derivative **116** (Scheme 86).

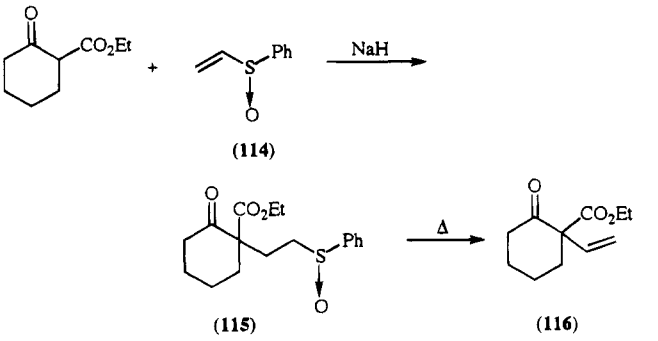
The intramolecular version of the Michael reaction is of significant importance in the construction of cyclic systems with high stereochemical control. For instance, the preparation of *cis*-hydrindane derivatives has been studied in detail, and a very important application has been described along the synthesis of gibberellic acid[144] (Scheme 87).

The stereochemical control has been also observed in the construction of vicinally substituted cyclopentanones and cyclohexanones. To this end, the intramolecular cyclization of **117** ($n = 1$ or 2) has been carefully investigated by Stork et al.,[145] who found that the Michael addition is not selective in polar medium (*tert*-butanol or methanol), a mixture of cis (**118**) and trans (**119**) adducts being obtained (Scheme 88).

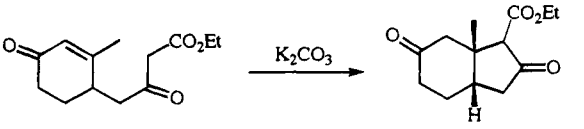
In contrast, the exclusive formation of **118** has been observed performing the reaction in the presence of a catalytic amount of sodium hydride. The high stereoselectivity has been attributed to the involvement of the transition state (**120**) with the orientation of the acceptor chain away from the chelate ring.

A similar process had been previously utilized by Trost and Jungheim[100] for the preparation of mono-

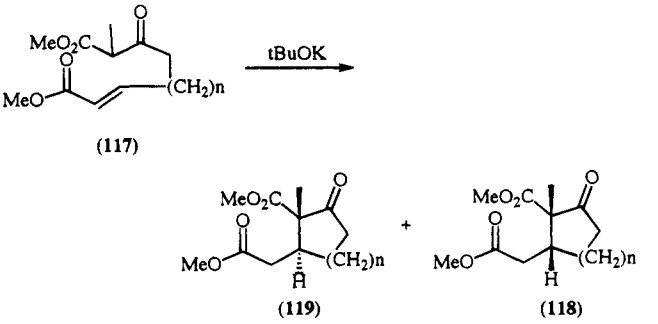
Scheme 86



Scheme 87

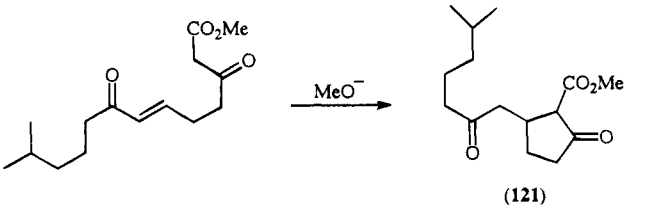


Scheme 88



substituted cyclopentanones of type **121**. In this case, the stereochemical outcome of the addition has not been carefully investigated in view of the planned decarboxylation (Scheme 89).

Scheme 89



Following Stork's suggestions, Barco et al.[146] have developed an elegant route to **122** an advanced

Scheme 85

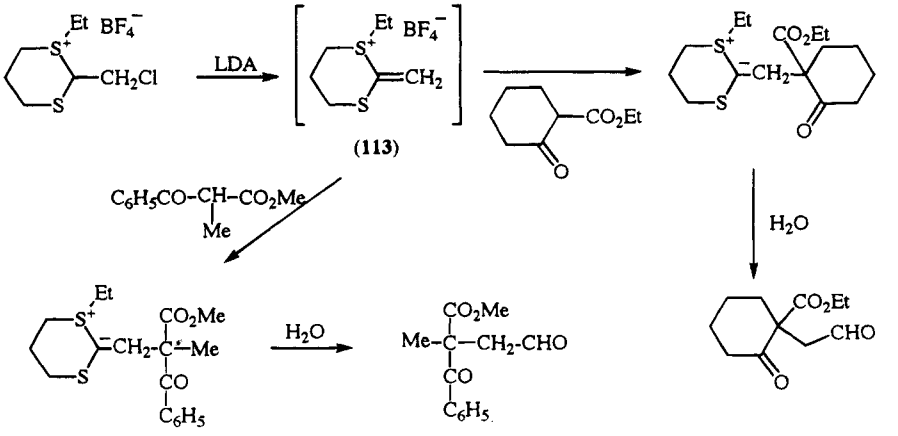
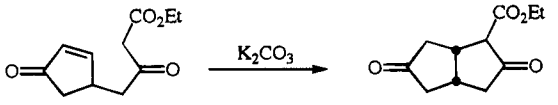


Table 8

acceptor	catalyst	T (°C)	yield (%)	% optical purity (configuration)	ref
acrolein	A				*153*
methyl vinyl ketone	B	25	98	30 (*S*)	*154*
methyl vinyl ketone	C	25	92	42 (*R*)	*154*
methyl vinyl ketone	D	−21	99	76 (*S*)	*155*
methyl vinyl ketone	E	−21	100	69 (*R*)	*155*
methyl vinyl ketone	F	−78	48	99 (*R*)	*156*
methyl vinyl ketone	F	25	75	67 (*R*)	*156*
methyl vinyl ketone	G	20	82	25 (*S*)	*157*
methyl vinyl ketone	H	20	72	21.3 (*R*)	*158*
methyl vinyl ketone	H	−50	50	66 (*R*)	*158*
methyl vinyl ketone	I	−40	74	58.3 (*S*)	*158*

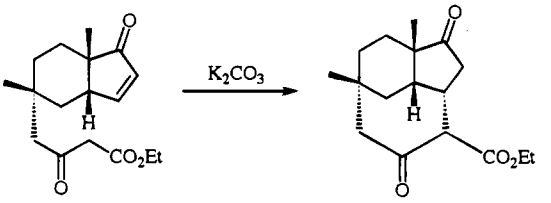
[a] A = (*R*)-(+)-2-(hydroxymethyl)quinuclidine; B = quinine/acrylonitrile copolymer; C = quinidine/acrylonitrile copolymer; D = quinine; E = quinidine; F = chiral crown complex; G = cinchonidine/polystyrene copolymer; H = $Co(acac)_2$/ (+)-1,2-diphenyl-1,2-ethanediamine; I = $Co(acac)_2$/(−)-1,2-diphenyl-1,2-ethanediamine.

Scheme 90



(122)

Scheme 91



(123) (124)

intermediate for the synthesis of 9(*O*)-methanoprostacyclin as outlined in Scheme 90.

The same authors[147] have performed the total synthesis of (±)-isoclovene, an artifact derived by acid treatment of caryophylene oxide characterized by a tricyclo[6.2.2.$0^{5,12}$]dodecane skeleton. The seven-membered ring present into the unusual polycyclic compound **124** has been set up through an intramolecular Michael addition of the suitably functionalized hydrindenone system (**123**) (Scheme 91).

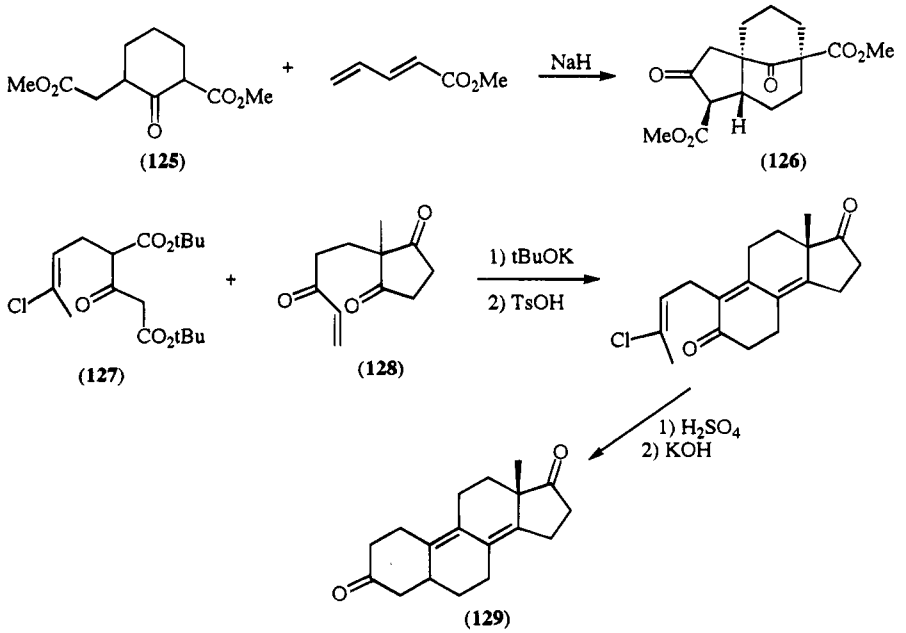
More interesting and complicated instances of additions of several rings at once via Michael reaction have been reported by Danishefsky et al. for the construction of the tricyclic compound[148] (**126**) or of the steroid skeleton[149] (**129**). The first is produced by the reaction of keto ester **125** with methyl 2,4-pentadienoate via a multi-step sequence involving an internal proton transfer (Scheme 92).

The second involves the Michael addition of **127** to the enone **128** followed by acid treatment to construct the tetracyclic compound **129** containing the steroid backbone.

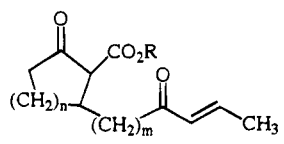
In 1986−1987, Lavallée et al.[150−152] carefully investigated the stereoelectronic control in the intramolecular Michael addition on substrates such as **130** or **131**, finding that formation of the bicyclic product with cis-junction is clearly favored.

As in the case of alkylation, the intriguing problem of how to induce asymmetry in the addition has been studied by different groups with rather encouraging results. The objective has been reached through two strategies. The first entails the use of optically active amines, optically active crown ethers and bases, or

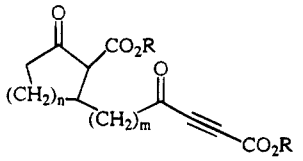
Scheme 92



(125) (126) (127) (128) (129)



(130)



(131)

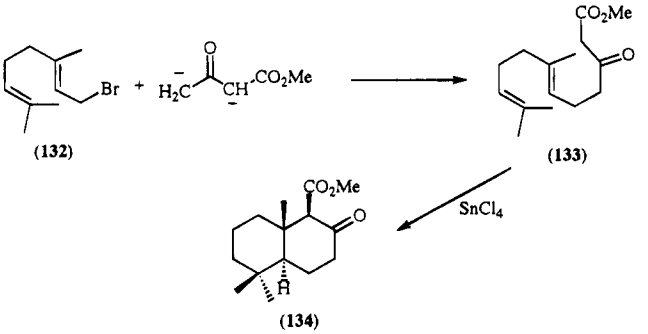
a catalyst system formed by $Co(acac)_2$/chiral amine, which were tested on a specific 1,3-dicarbonyl compound: methyl 1-oxo-2-indancarboxylate. The yields, the temperature reaction, and the optical purity of the adducts are reported in Table 8.[153,158]

The second strategy, already described for the alkylation (Scheme 74), is based on the use as Michael donor of a chiral enamine derived from the condensation of (*S*)-valine *tert*-butyl ester and a β-keto ester.[159]

C. Lewis Acid-Catalyzed Alkylation

The well-known concept of biogenetic-like cyclization of polyolefins was extended by White et al.[160] to olefinic β-keto esters (Scheme 93).

Scheme 93

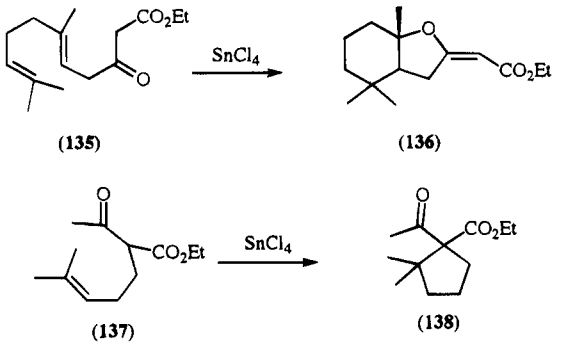


(132) (133) (134)

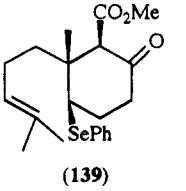
Thus, the stannic chloride-catalyzed cyclization of the β-keto ester (**133**), prepared by alkylation of the dianion of methyl acetoacetate with geranyl bromide (**132**), afforded the bicyclic product **134** in good yields. Curiously, to obtain consistent yields of cyclized products, methylene chloride saturated with water has to be used as the reaction medium. The same idea has been then applied both by Weiler and Sum[161] to the synthesis of Latia Luciferin and by Corey et al.[162] to the synthesis of aphidicolin using mercuric trifluoroacetate as the Lewis acid. The process works well for the formation of cyclohexanone derivatives but fails in the case of a cyclopentanone derivative, as demonstrated by Van Tamelen et al.[163] (Scheme 94).

In fact, the Lewis acid-promoted cyclization of **135** gave rise to **136**, which must be formed by an attack of enolic oxygen on a cyclohexyl cation or its equivalent. In contrast, the submission of **137** to similar treatment afforded **138**. These results suggest that in the case of **138** carbon–carbon bond formation has occurred, as always occurs when the carbonyl function is a substituent of the cyclopentane ring, while carbon–oxygen bond formation takes place as in the case of **136** when the ketone moiety is incorporated into the cyclopentane ring. Analogous results have been obtained by Ley et al.[164,165] studying cyclizations promoted by selenium derivatives, such as *N*-(phenylseleno)phthalimide, $PhSe^+SbF_6^-$, or $PhSe^+PF_6^-$. The formation of the carbon–oxygen bond is more likely: in fact treatment of **133** with phenylselenating agents produced **139**, while with $SnCl_4$ furnished **134** (Scheme 93).

Scheme 94



(135) (136) (137) (138)

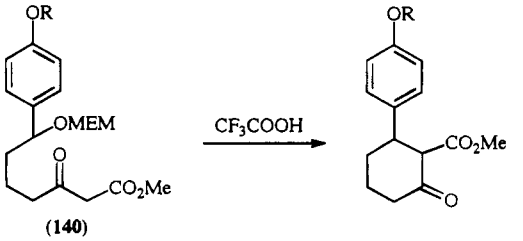


(139)

The strategy has been further extended by Ley et al.[166,167] to the synthesis of natural products such as (*cis*-6-methyltetrahydropyran-2-yl) acetic acid and hirsutene.

Another type of intramolecular cationic cyclization has been performed by Angle and Lonie[168] by generation of a benzyl cation and their subsequent trapping by a β-oxoester as terminator (Scheme 95).

Scheme 95



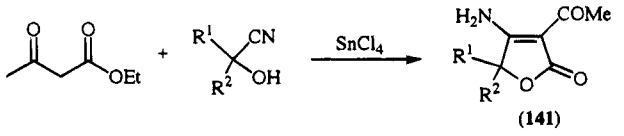
(140)

The cyclization has been carried out at room temperature submitting **140** to the action of trifluoroacetic acid. The reaction is very fast, the yields are excellent, but its outcome is strongly dependent on the substituent on the phenolic oxygen. While good results are obtained with R = H or CH_3, the corresponding acetate fails to give any cyclized product. Intermolecular Lewis acid-promoted cyclizations have been also reported. For example, the preparation of 3-acyl-4-amino-2(5*H*)-furanone[169] (**141**) can be accomplished starting from α-hydroxy nitriles and ethyl acetoacetates in the presence of stoichiometric amounts of tin(IV) chloride (Scheme 96).

Alkyl 1-oxo-2-indancarboxylates (**142**)[170] are obtained by methylenation of 3-oxo-3-arylpropionates with methoxyacetyl chloride–aluminum chloride reagent (Scheme 97).

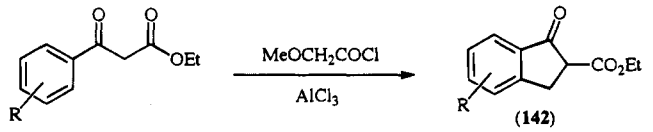
Ti(IV)-mediated coupling of β-keto esters with acetals has been first reported by Williams et al.,[171]

Scheme 96



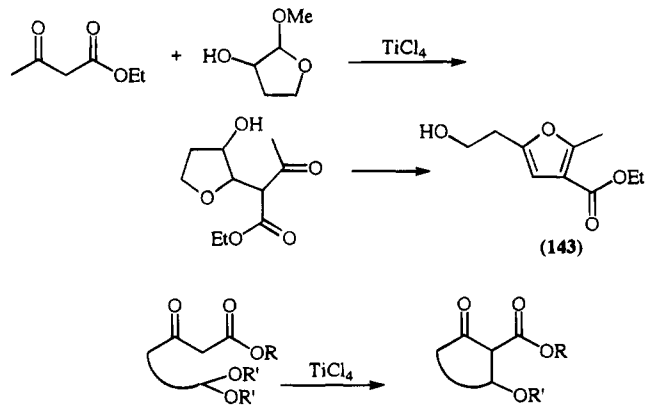
(141)

Scheme 97



(142)

Scheme 98



(143)

who were able to prepare trisubstituted furans (**143**) from β-keto esters and cyclic methylacetals. An analogous cyclization has been performed by Funk et al.[172] on polyfunctionalized acetals such as **144** (Scheme 98). The authors demonstrate that $TiCl_4$ not only generates enolates by complexation of dicarbonyl compounds but also acts as a Lewis acid on acetals, generating reactive oxonium species, which couple with titanium enolates to produce the cyclized compounds.

D. Metal-Catalyzed Alkylation

Palladium-catalyzed allylation of nucleophiles is a well-established synthetic method for the carbon–carbon bond formation. Many useful catalytic reactions involving π-allyl palladium complexes as intermediates have been discovered, and a number of allylic compounds such as halides, acetates, ethers, alcohols, and amines have been used as sources of π-allyl palladium complexes. These allylic compounds behave quite differently (e.g., acetates react generally in the presence of a base, while phenyl ethers are active in neutral conditions and their reactions can proceed with allylic rearrangement). The intramolecular version of the process producing cyclic systems is of particular interest. Tsuji et al.[173] reported the synthesis of five- , six-, and seven-membered cyclic β-keto esters by the palladium-catalyzed alkylation of active methylene compounds with the allylic ether moiety intervening with different results on substrates, ligands, and solvents (Scheme 99; Table 9).

Several 2,3-disubstituted cycloalkanones have been prepared through this methodology and used as starting materials for the synthesis of natural products, including methyl dihydrojasmonate,[173] 18-functionalized steroid intermediates,[174] 18-hydroxyestrone,[175] and sarkomycin.[176] Tsuji and Yamamoto[177] attempted the asymmetric cyclization in the presence of a chiral phosphine as ligand, but the results are of low synthetic potentiality. The technique has also been applied to the construction of spirocyclic compounds[178] (Scheme 100) using an allylic ester as the π-allyl precursor.

Scheme 99

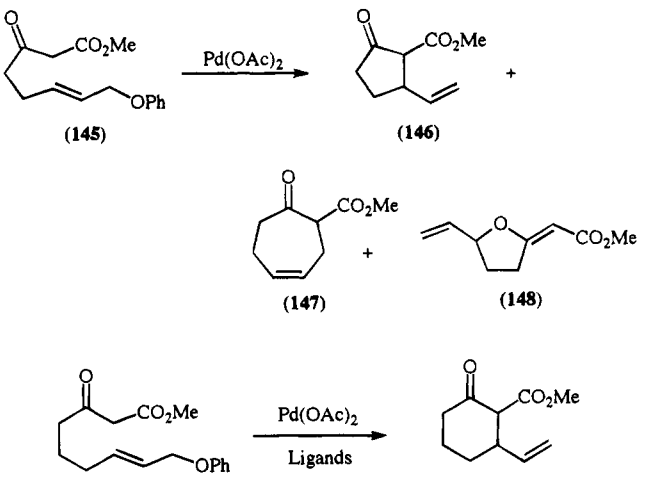
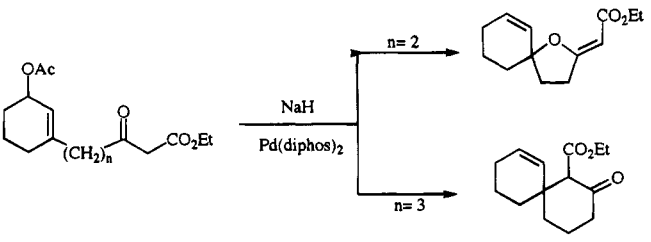


Table 9. Cyclization of 145

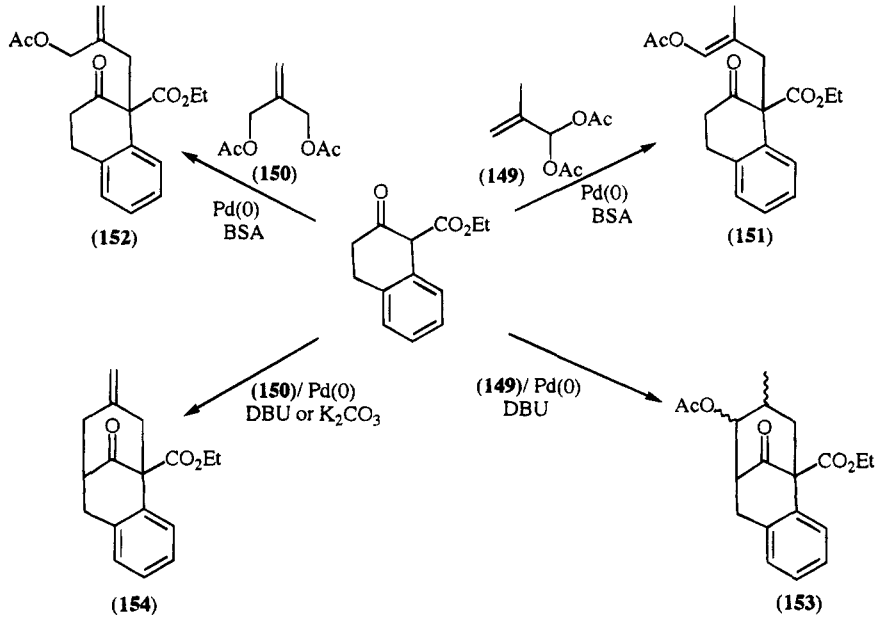
		ratios			
solvent	ligand	**146**	**147**	**148**	others
MeCN	$P(OPh)_3$			100	
MeCN	DIPHOS	76	12		12
MeCN	PBu_3	85	15		
dioxane	PPh_3	46	51		3
benzene	PPh_3	44	49		7
THF	PPh_3	37	57		6
acetone	PPh_3	60	27		13
MeCN	PPh_3	87	13		

Scheme 100

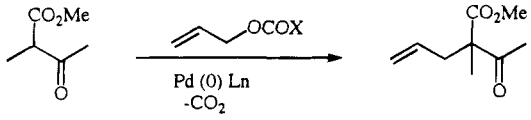


The authors investigated the cyclization of substrates with different tether separating the β-keto ester moiety from the allylic residues, finding carbon–carbon bond formation for $n = 3$ and oxygenated heterocycles for $n = 2$. Unfortunately, the isomerization of O-alkylated compounds to the thermodynamically more stable C-alkylated compounds failed both under Tsuji[173] or Trost[179] conditions. Methallyl-1,1-diacetate (**149**)[180] and 2-(hydroxymethyl)-2-propen-1-ol diacetate (**150**)[181] have also been used as precursors of the π-allyl species. The latter showed an interesting behavior when reacted with β-keto esters, palladium diacetate, triphenylphosphine, and BSA or DBU as a base. In all these cases, using BSA affords the monoalkylation products **151** and **152**. The carbon–carbon bond between the substrate and methallyl-1,1-diacetate formed at the least hindered end. Under the same conditions,

Scheme 101



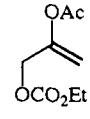
Scheme 102



using DBU as a base, a bicycloannulation process occurred giving **153** and **154**. In the case of 1,3-allylic diacetate (**150**), potassium carbonate can also be used as the enolyzing catalyst; the reaction leading in any case to bicyclic annulation (Scheme 101).

Alkylation under neutral conditions involving complexation through carbon dioxide elimination and subsequent reaction with active methylene compounds could be accomplished with a new class of allylic derivatives (Scheme 102), as experienced with allyl carbamates[182] (X = NR_2) and allyl carbonates[183] (X = OMe).

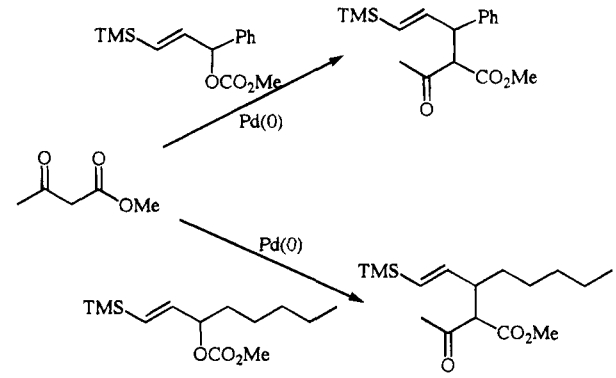
In the latter case, the reactivity of the allyl derivative and the regioselectivity of the reaction catalyzed by Pd, Rh, Ru, Mo, and Ni have been carefully studied. In 1986, beside simple allyl carbonates, Watanabe et al.[184] were able to achieve alkylation with substituted 2-acetoxyallyl carbonates (**155**) with good results.



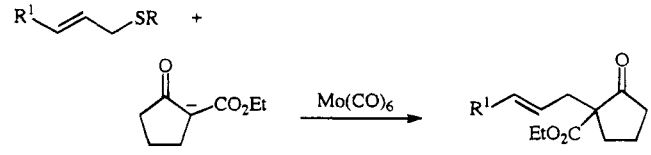
(**155**)

Tsuji et al.[185] also reported that (trimethylsilyl)-allyl methyl carbonates underwent a highly regioselective substitution with acetoacetate, a soft carbon nucleophile. The reaction affords only a vinyl silane, and no regioisomers are detected by GLC, TLC, and NMR analyses. Since this regioselectivity is not satisfactorily explained by the steric bulkiness of the substituents alone, the authors suggested that the electronic factors may also play an important role in the π-allyl palladium complex Scheme 103.

Scheme 103



Scheme 104

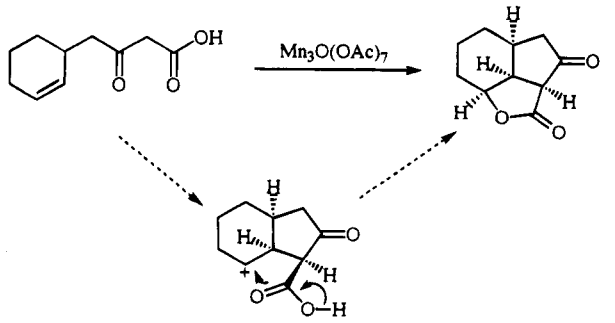


As reported above, the activated allylic alcohols are useful alkylating agents for active methylene compounds, but allyl alcohol itself is less reactive. In 1989, Bergbreiter and Weatherford[186] described a simple procedure to synthesize C-allylated products by heating at 100 °C unsubstituted and substituted acetoacetates, allylic alcohol, and $(PPh_3)_4Pd$ in dry toluene.

Allylic sulfides are useful agents for the alkylation of β-keto esters. Masuyama et al.[187] achieved the desulfenylative allylation of ethyl cyclopentanonecarboxylate with allylic sulfides in the presence of molybdenum hexacarbonyl as the thiophilic metal reagent (Scheme 104).

The nucleophile attacks regioselectively at the less substituted end of the allyl unit after the desulfenylation to give only one regioisomer. All the alkylation procedures analyzed in this section are based on a C_2 β-keto ester electron-rich carbon center. However, a different process requiring the opposite electronic

Scheme 105



situation of this center has been proposed. It relies on the action of manganese(III) acetate on an unsaturated β-keto ester, which, fortunately, undergoes faster oxidation than the acetic acid used as solvent. This methodology has been successfully applied by Corey and Kang[188] to the synthesis of polycyclic α-lactones (Scheme 105).

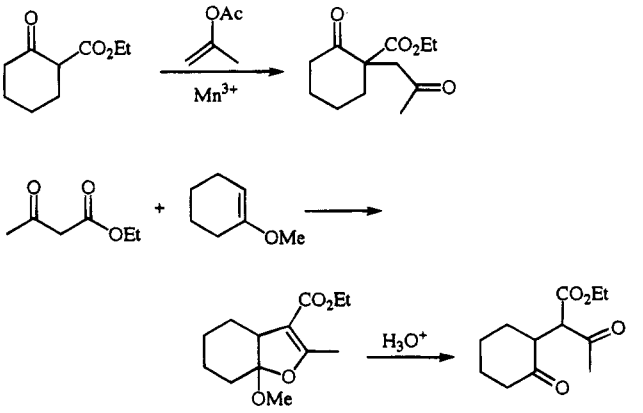
Almost simultaneously, Snider et al.[189,190] investigated a similar oxidative cyclization on different substrates (Scheme 106). The same authors[191] published a more complete report 3 years later.

From a mechanistic point of view, the reaction consists of (i) generation of a C_2 radical that adds to the olefin double bond, (ii) radical oxidation to a carbocation by electron transfer to Mn(III), and (iii) carbocation electrophilic attack to the carboxylic oxygen (Scheme 105) or to the aromatic ring and final proton elimination (Scheme 106). The stereochemical outcome of the reaction is influenced by the presence or absence of a C_2 substituent in the starting β-keto ester (Scheme 106). The method was then extended to intermolecular alkylation. Thus, Corey and Ghosh[192] have described an effective process for the synthesis of fused 2-cyclopentenones via the manganese(III)-promoted addition of cyclic β-keto esters to enol ethers or terminal enol esters (Scheme 107).

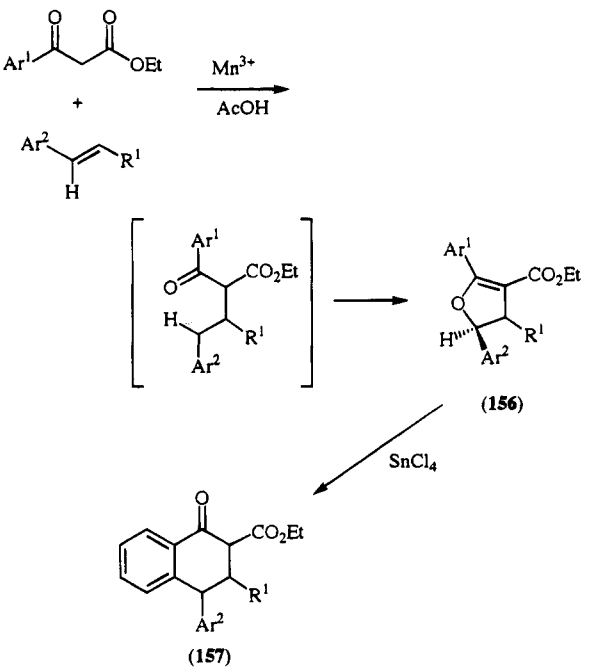
On the other hand, Fristad et al.[193] explored the oxidation of aroylacetate in the presence of substituted styrenes, obtaining a very clean conversion to dihydrofuranes (**156**), which were easily opened by stannic chloride and cyclized to tetralones (**157**) (Scheme 108).

An interesting allylation of cyclic β-keto esters with sulfur derivatives and with a ternary oxidizing mixture (manganic acetate, cupric acetate, and lead dioxide) in acetic acid with acceptable yields has been described by Breuilles and Uguen[194] (Scheme 109).

Scheme 107

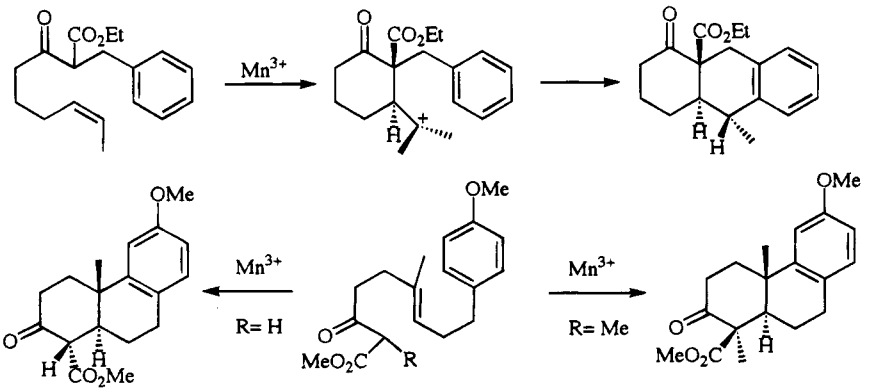


Scheme 108

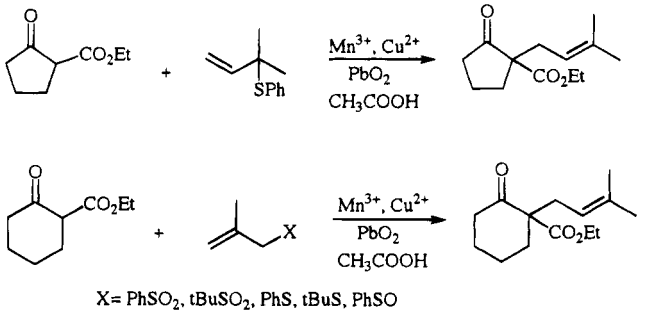


The method provides a valuable alternative to the Trost process[111] since the use of expensive catalysts and the need to work under basic conditions are unnecessary. The reaction can be envisaged as a formal electrophilic displacement of the sulfurated leaving group starting with the formation of the free radical generated by oxidation. Finally, Iqbal et al.[195] have explored with excellent results the possibility of preparing β-alkoxycarbonyl compounds from

Scheme 106



Scheme 109



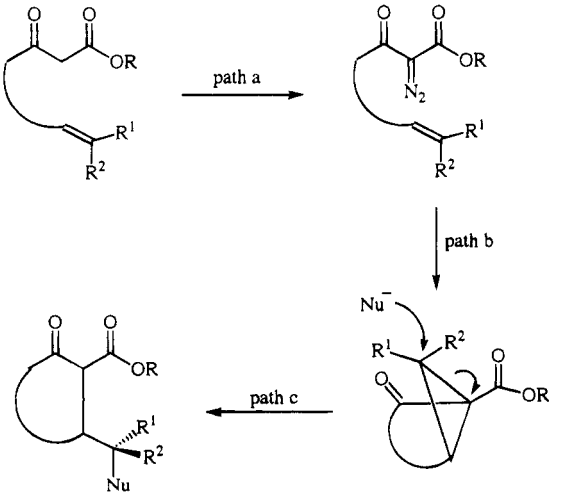
vinyl ethers and acetoacetates in the presence of cobalt(II) chloride. The reaction is diastereoselective, and the trans diastereomer is formed as a major product in all the cases.

The procedure complements the previously reported Corey method[192] and the acid-mediated condensation of active methylene compounds with dihydrofurans and pyrans as described by Bihovsky et al.[196] in 1989.

E. Alkylation via Diazoacetates

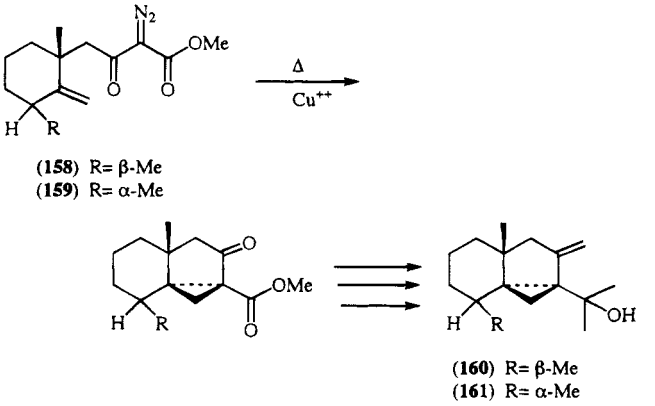
This method has been widely utilized as an indirect method for the formation of the C_2-R_2 bond and can be schematized as follows: path a, preparation of a diazoacetoacetate; path b, intramolecular cheletropic cycloaddition with cyclopropane formation under rigid stereochemical control; path c, regioselective ring opening of the derived cyclopropylketone through homoconjugate addition of nucleophiles (Scheme 110).

Scheme 110

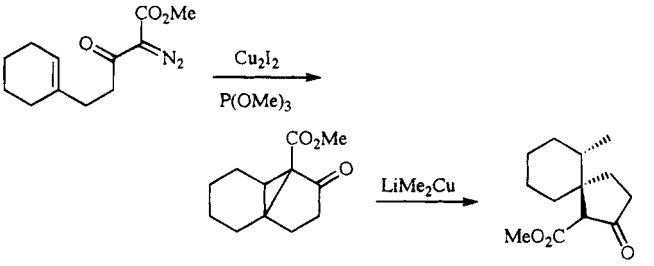


Numerous reagents such as *p*-toluenesulfonyl azide,[197,198] 2-azido-3-ethylbenzothiazolium tetrafluoroborate (Balli's reagent),[199] polymer-bound tosyl azide,[200] 4-carboxybenzenesulfonyl azide,[201] *N,N*-dimethylazidochloromethyleniminium chloride,[202] and azido-tris(−)-phosphonium bromide[203] have been routinely used for the formation of β-keto ester diazoderivatives (path a). The intramolecular cycloaddition (path b) of the carbene, thermally generated in the presence of copper sulfate,[204] copper bronze,[205,206] copper acetyl acetonate,[207,208] or cuprous iodide–trimethyl phosphite complex[209] onto the double bond

Scheme 111



Scheme 112



present in the substrate, allows easy construction of the cyclopropane derivative. This strategy has been successfully applied to the synthesis of cycloeudesmol (**160**) and its epi derivative (**161**)[210] (Scheme 111).

The same sequence has been utilized for the two diastereomeric products performing the thermolysis in different experimental conditions, namely, reflux in cyclohexane for the diazo derivative **158** and reflux in toluene at higher temperature for the analogous **159**.

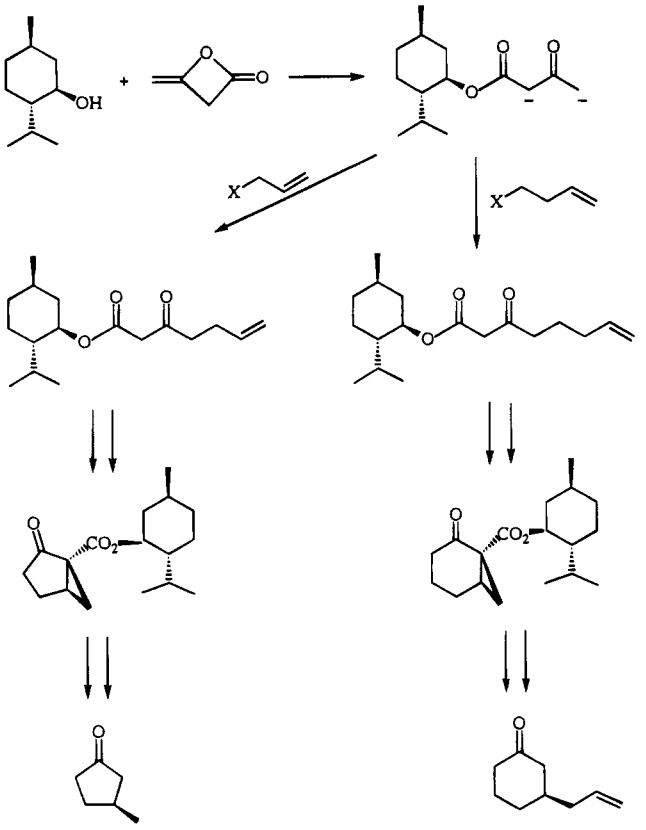
Nucleophilic ring opening of the cyclopropane ring (path c) has been effected by action of thiophenoxide[204,205,210] or lithium dimethyl cuprate,[206,207,208] leading to the formal alkylation of a β-keto ester. An intriguing feature of this step is represented by the unequivocal ring opening of cyclopropane. The examination of the molecular model clearly revealed that the observed bond scission involves the bond that overlaps well with the carbonyl system, while alternative opening involves a bond orthogonal to the system. The effectiveness of the methodology has been amply documented by its application to the synthesis of several prostaglandins.[204,205,207,208] Clark and Heathcock[209] have also achieved the preparation of spiro compounds as shown in Scheme 112.

Since the method allows the preparation of substituted cyclohexanones and cyclopentanones, a logical extension to their convenient preparation with high enantiomeric excess has been investigated using menthol as a chiral auxiliary.[211] The synthetic sequence involves the ring opening of the intermediate cyclopropane with lithium divinyl cuprate or by dissolving metal reduction and subsequent decarboxylation (Scheme 113).

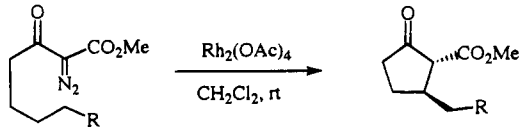
F. Insertion Reaction with Diazoacetates

The insertion of carbenoids into the C–H bonds of alkanes in the presence of Rh(II) observed by Noels

Scheme 113



Scheme 114



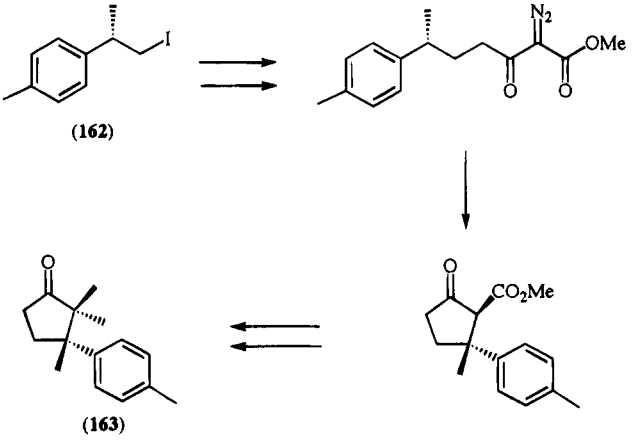
Scheme 115

et al.[212] prompted Taber and Petty[213] to investigate the rhodium acetate-catalyzed cyclization of α-diazo β-keto esters (Scheme 114).

It should be noted that cyclopentane is the sole cyclic system obtainable through this reaction. Moreover, even in the presence of an unsaturated bond, allylic C−H insertion competes effectively with the usual intramolecular cyclopropanation, and the efficiency of the C−H insertion decreases from methine to methylene to methyl. In 1985, Taber and Ruckle[214] were able to extend the methodology studying the diasteroselectivity of the insertion when there is a phenyl substituent on the 4-position of the incipient ring (Scheme 115).

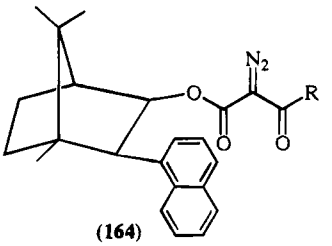
These results demonstrate that the major product is the trans-3,4-disubstituted cyclopentanone; therefore, with a suitable source of an acyclic optically active compound, this method represents a general strategy for enantioselective ring construction. It has been also demonstrated that rhodium-catalyzed intramolecular cyclization proceeds with retention of absolute configuration when the chiral center is the

Scheme 116



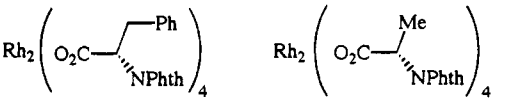
site of C−H insertion, as well exemplified in the synthesis of (+)-α-cuparenone[215] (**163**) starting from the optically active iodide (**162**) (Scheme 116).

Taber and Ramen[216] have also demonstrated that a good level of asymmetry can be induced when a chiral alcohol, easily available from camphor, is incorporated into the diazoester **164**.

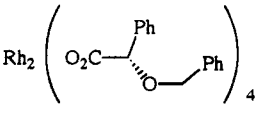


(164)

In 1990, Ikegami et al.[217] have reported an enantioselective intramolecular C−H insertion of diazo esters in the presence of a rhodium catalyst with chiral ligands. Several homochiral rhodium carboxylates have been prepared by exchange reaction between $Rh_2(OAc)_4$ and optically active acids, e.g., *N*-phthaloyl-(*S*)-phenylalanine (**165**), *N*-phthaloyl-(*S*)-alanine (**166**), and (*S*)-2-(benzyloxy)phenylacetic acid (**167**). Their catalytic activity allowed differentiation of enantiotopic methylene hydrogens, albeit inducing only a modest degree of asymmetry.



(165) (166)

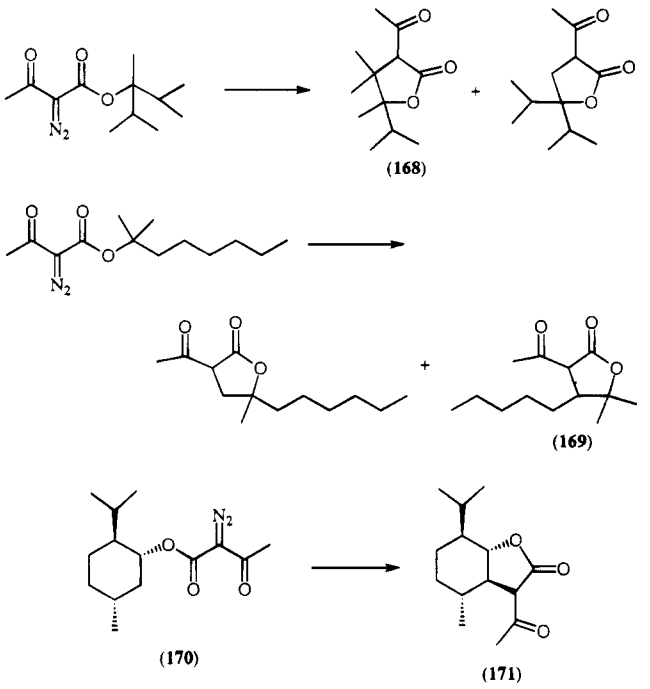


(167)

Usually in intramolecular insertion of C−H the carbon chain is bonded to the carbonyl function. Doyle et al[218] have studied the carbenoid decomposition of compounds having the cyclizing center on the carboxyl function, providing the synthesis of substituted γ-lactones (Scheme 117).

The insertion proceeded with high regio- and stereoselectivity, and the relative reactivities are in

Scheme 117



the order 3° > 2° > 1° as reported by Taber et al.[213] Consequently, **168** and **169** are the major regioisomers. However, the prediction of the outcome of the insertion of C−H in more complex substrates where stereoelectronic or steric factors govern product formation is rather uncertain. In fact, the rhodium-catalyzed decomposition of (1*R*,2*S*,5*R*)-(−)-methyl diazoacetate (**170**) affords in 80% yield only the bicyclic γ-lactone (**171**).

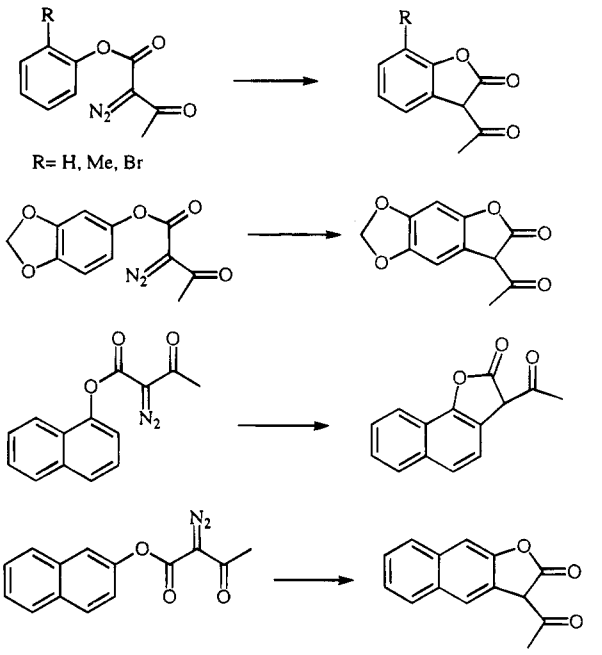
Examples of rhodium-catalyzed carbenoid insertions into aliphatic C−H bond are numerous, while only a few cases in which products resulting from the formal insertion into an aromatic C−H bond are observed. As an example, Durst and Hrytsak[219] have reported the rhodium-catalyzed decomposition of aryl and naphthyl 2-diazoacetoacetates to 3-acetylbenzofuran-2(3*H*)-ones and 3-acetyl naphthofuran-2(3*H*)-ones (Scheme 118).

Interestingly, the insertion strategy has been also applied to the X−H bond, X being a heteroatom, particularly nitrogen, several years before its application to the C−H bond. In fact, in 1980 Ratcliffe et al.[220−222] during their synthetic efforts toward the construction of the bicyclic system of carbapenems, a new class of β-lactam antibiotics, utilized the cyclization of α-diazo β-keto ester (**172**), as outlined in Scheme 119.

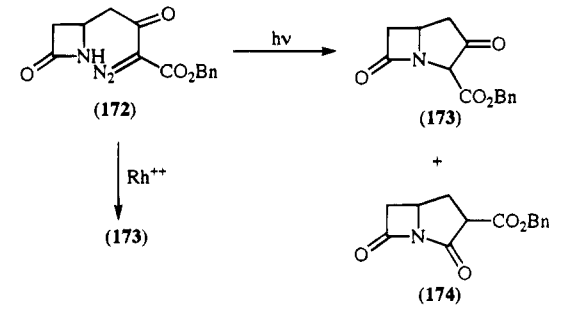
The generation of the carbenoid responsible for the insertion was achieved both photochemically and catalytically. The photochemical decomposition of the diazoderivative **172** produced a 1:9 mixture of carbapenem (**173**) and the imide (**174**), while the rhodium-catalyzed insertion reaction gave exclusively **173** in almost quantitative yields. Through this method, thienamycin[223] (**117**), (+)-thienamycin,[221] (−)-homothienamycin[222] (**176**), 1-oxacepham nucleus[224] (**177**), and aza β-lactams[225] (**178**) have been later synthesized.

Taylor and Davies[226] obtained a rather unexpected mixture of **180** and **181** while attempting the usual

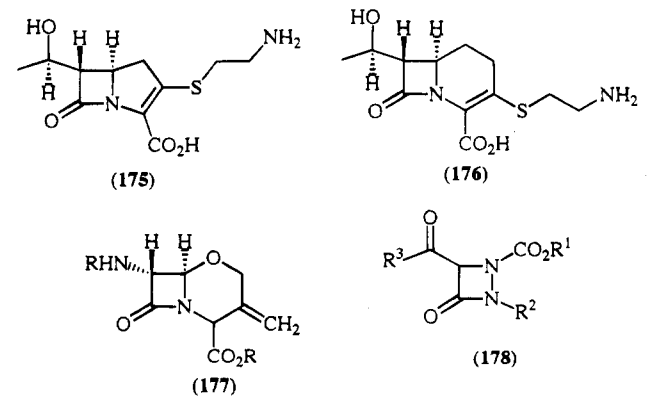
Scheme 118



Scheme 119



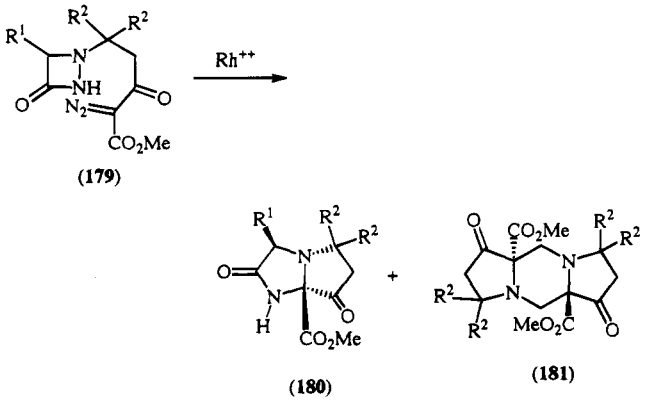
diazo decomposition on the aza β-lactam **179**. (Scheme 120).



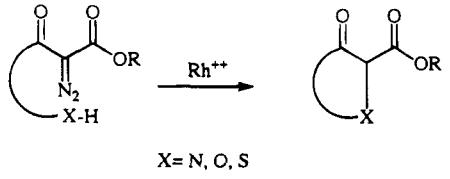
This result has been ascribed to the involvement of the more nucleophilic nitrogen atom not bonded to the carbonyl group in the rather complicated reaction leading to the fission of the nitrogen−nitrogen bond. In 1985, Rapoport et al.[227] reported the results of their studies dealing with the formation of nitrogen, oxygen, and sulfur heterocyclic compounds starting from α-diazo β-keto esters (Scheme 121).

The authors investigated with particular attention the reaction involving nitrogen compounds leading

Scheme 120



Scheme 121

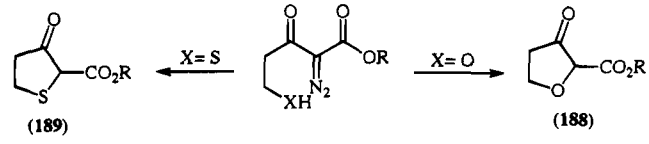


to the formation of differently sized heterocycles (Scheme 122).

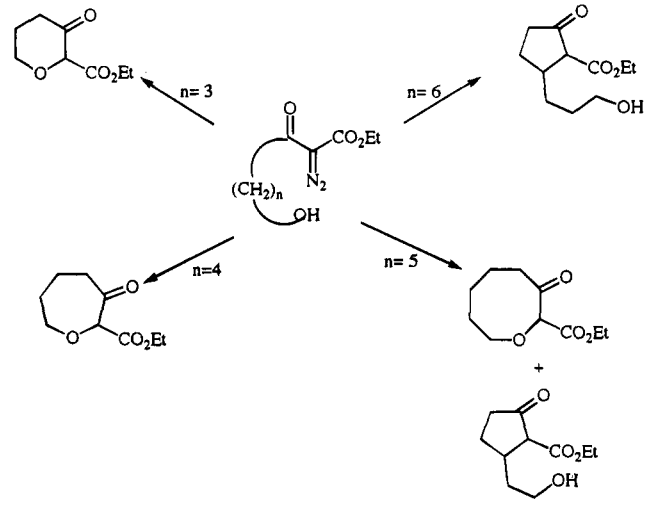
Thus, for $n = 1$ and for $n = 2$, heating **182** in benzene solution in the presence of rhodium acetate produced the expected N−H insertion products **183** and **184**. When $n = 3$, the NH insertion competes with the C−H insertion, producing a mixture containing **185** and **186**, the product distribution being quite dependent on the reaction parameters employed such as solvent, temperature, and amount of catalyst. Finally, when $n = 4$, there is exclusive formation of C−H insertion product **187**. On the other hand, the preparation of 2-(methoxycarbonyl)-3-oxotetrahydrofuran (**188**) and of 2-(ethoxycarbonyl)-3-oxotetrahydrothiophene (**189**) serves to demonstrate the feasibility of intramolecular insertion of O−H and of S−H (Scheme 123).

Moody et al.[228-230] carefully studied the problem concerning the formation of oxygenated heterocycles

Scheme 123



Scheme 124

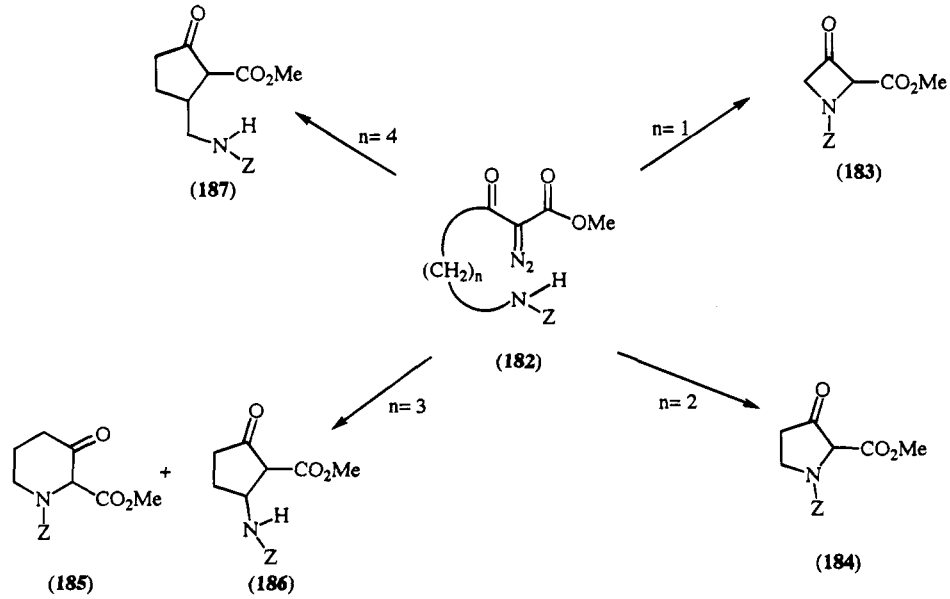


and demonstrated that for six- and seven-membered cyclic ethers there is no competition between the insertion of O−H and of C−H. The yield of cyclization in the case of eight-membered rings is lower, and attempts to form larger rings have been thwarted by competing C−H insertion reactions to give substituted cyclopentanones (Scheme 124).

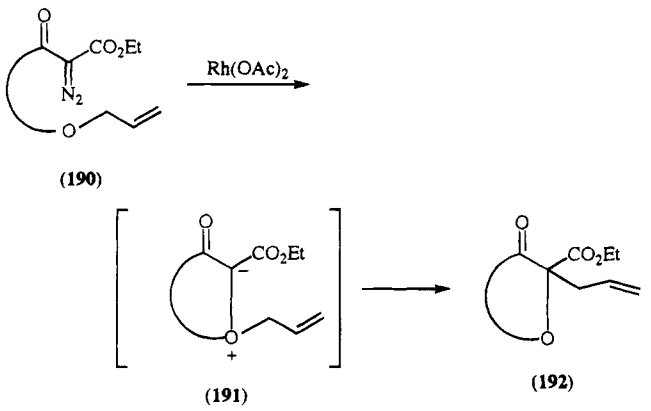
Interestingly, the rhodium-catalyzed decomposition of the α-diazo β-keto ester (**190**) incorporating an allyl ether function furnished the oxygenated heterocycles (**192**) through migration of the allyl residue (Scheme 125).

The authors[231] suggested a mechanism involving the intramolecular generation of the allylic oxonium ylide (**191**), which underwent subsequent (2,3)-sigmatropic rearrangement to give **192**. This strategy

Scheme 122



Scheme 125



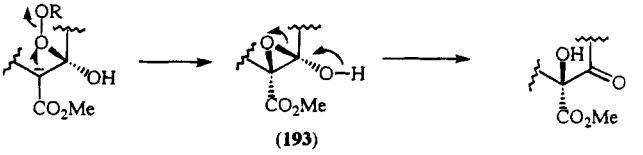
(190) (191) (192)

has been extended to the formation of five-, six-, and eight-membered oxygen heterocycles. The process is rather unusual in the case of ethers, though well-known for sulfides. These give cyclic ylides by intramolecular capture of carbenes, and their rearrangement has been developed into a useful ring expansion procedure.[232] Few are the known examples of stable cyclic ylids: however, Davies and Crisco[233] were able to obtain them by decomposition of diazo derivatives of β-keto esters in the presence of rhodium(II) acetate (Scheme 126). As previously discussed, competition depends on the size of the deriving ring also when the insertion of C–H is involved.

G. Heteroatoms–C_2 Bond Formation

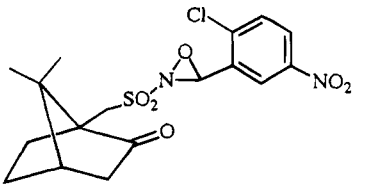
The introduction of a hydroxyl group at the C_2 of a β-keto ester is sometimes required for synthetic purposes. Two methods are usually employed for this operation. The first entails the treatment of the β-keto ester enolate generated by action of a strong base (t-BuOK or KH) with oxidant agents (hydrogen peroxide or *m*-chloroperbenzoic acid) to give the intermediate **193**, which spontaneously collapses to α-hydroxy β-keto ester with high stereospecificity (Scheme 127).

Scheme 127



(193)

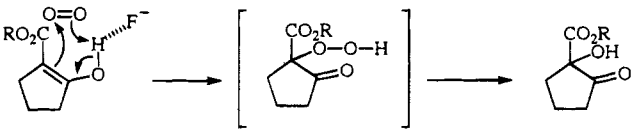
This method has been applied to the synthesis of vindorosine,[234] vindoline,[235] and kjellmanianone[7] where the asymmetric introduction of the hydroxyl group has been satisfactorily accomplished through the reaction of enolate with (−)-*E*-oxaziridine (**194**) as an optically active oxidant.



(194)

The second strategy involves the fluoride ions, which induce the enhancement of the nucleophilicity of the enol form of β-keto ester followed by an oxidative step performed with singlet oxygen.[236,237] The photooxidation probably takes place by an initial enic reaction with the formation of a hydroperoxide intermediate, which then collapses to the hydroxylated compound (Scheme 128).

Scheme 128



Scheme 126

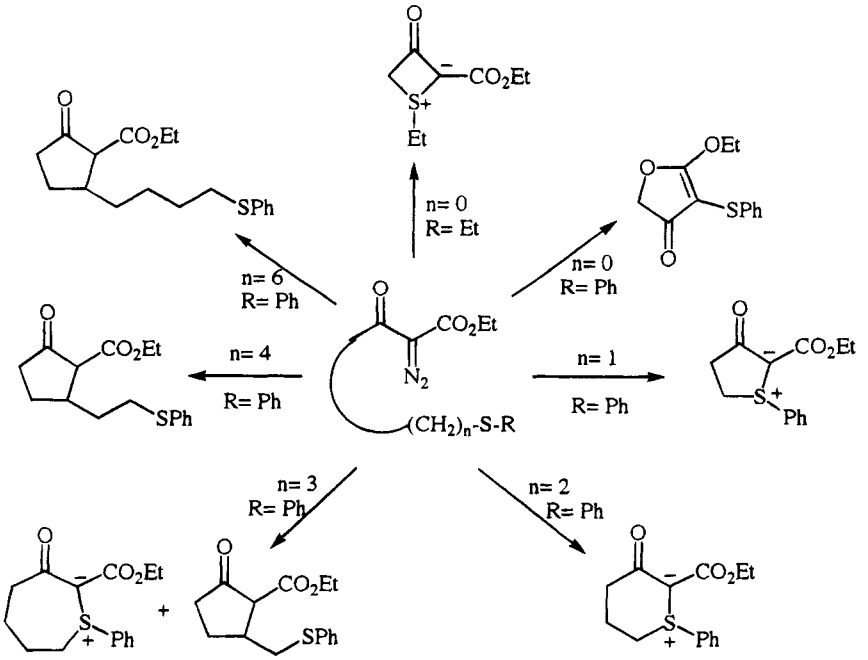
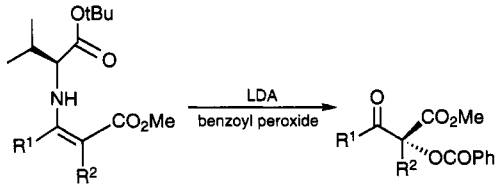


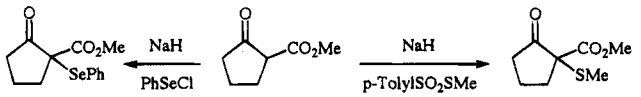
Table 10



195a–f 196a–f

enamine	yield (%)	product	ee (%)
195a $R^1-R^2 = -(CH_2)_4-$	69	(+)-(*R*)-**196a**	92
195b $R^1-R^2 = -(CH_2)_3-$	57	(−)-(*R*)-**196b**	78
195c $R^1-R^2 = -(CH_2)_5-$	58	(+)-(*R*)-**196c**	80
195d R^1 = Me; R^2 = Me	50	(−)-(*R*)-**196d**	85
195e R^1 = Me; R^2 = Et	70	(−)-(*R*)-**196e**	78
195f R^1 = Me; R^2 = H	53	(±)-**196f**	0

Scheme 129



The hydroxylation of silyl enol ether of β-keto ester with *m*-chloroperbenzoic acid has been carried out[238] at 90 °C in 1, 2-dichloroethane in the presence of a catalytic amount of 4,4′-thiobis(6-*tert*-butyl-3-methylphenol) to prevent decomposition of the peroxy compound. The procedure fails with the silyl enol ethers unstable in the reaction conditions. A successful enantioselective oxidation, using the optically active enamines (**195a–f**) obtained from β-oxo esters and (*S*)-valine *tert*-butyl ester, has been reported by Snyder et al.[239] The reaction of metallated (**195a–f**) with benzoyl peroxide produced the benzoate esters (**196a–f**) in acceptable yield and with high optical purity as shown in Table 10. Only the oxidation of enamine (**195a–f**), derived from methyl acetoacetate failure, afforded the racemic α-benzoate.

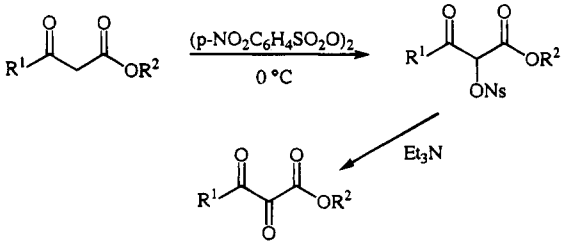
Beside the carbon–oxygen bond, the carbon–sulfur bond can also be obtained through a simple substitution reaction of a β-keto ester enolate on methyl thiotosylate[240,241] (Scheme 129). Similarly, selenyl derivatives can be obtained using phenylselenenyl chloride as the selenenating agent[242,243] (Scheme 129).

Both sulfurated and selenenated compounds have remarkable synthetic interest since their transformation to the corresponding sulfoxides or selenoxides allows easy elimination with the formation of cyclopentenones, which can be further elaborated to cyclopentanoid natural products.

Special interest has been devoted to the 1,2,3-tricarbonyl system, a structural unit featuring biologically interesting compounds including the powerful immunosuppressant FK-506, the antifungal antibiotic rapamycin, and related compounds.

To create these functionalities, Hoffman et al.[244] proposed a two-step process consisting of the oxidation of β-dicarbonyl compounds with *p*-nitrobenzenesulfonyl peroxide to produce 2-[[(nitrophenyl)sulfonyl]oxy] [2-(nosyloxy)] derivatives followed by treatment with triethylamine in benzene at room temperature. The outcome of the reaction is likely due to the base-promoted reductive elimination of *p*-nitrobenzenesulfinate (Scheme 130).

Scheme 130



Numerous other methods have been suggested by various authors: singlet oxygen cleavage or ozonolysis of 2-enamino 3-keto ester,[245] ozonolysis of 2-iodoniumyl 3-keto esters,[246] singlet oxygen cleavage,[247] ozonolysis[245] or potassium peroxymonosulfate (Oxone) oxidation[248] of 2-phosphorous ylide derivatives of 3-keto esters, and hydrolysis of 2-oximino 3-keto esters.[249] Tiecco et al.[250] introduced an advantageous procedure that allows the preparation of 1,2,3-tricarbonyls as α,α-dimethoxy derivatives by simply mixing β-keto esters, ammonium peroxydisulfate, and diphenyl diselenide in methanol.

The acylation of (carboethoxymethylene)triphenylphosphorane with acid chlorides or anhydrides is the classical preparation method for the phosphorane analogues of **55** as previously reported in the section on C_2-C_3 bond formation.

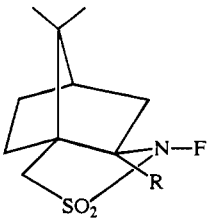
Ohmori et al.[251] have reported the direct formation of the bond between the C_2 carbon of 1,3-dicarbonyl compounds and triphenylphosphine. The transformation is affected by the electrochemical oxidation of a system composed by PPh_3, a β-keto ester in methylene chloride with 2,6-lutidinium perchlorate ($LutClO_4$) or with tetrafluoborate ($LutBF_4$) as a supporting electrolyte. Plausible processes for the formation of analogues of **55** involve the reaction of electrochemically generated triphenylphosphine radical cation [$PPh_3^{\bullet+}$] with the enol form of 1,3-dicarbonyl compounds. The C_2–halogen bond can also be easily generated by a number of halogenating agents. Thus, chlorination of ethyl acetoacetate is usually achieved by treatment with sulfuryl chloride,[252] while bromination of dicarbonyl compounds can be performed in fair to high yield by reaction with magnesium bromide etherate and hydrogen peroxide in THF or ether.[253]

Fluorination of active methylene compounds that exist partly in the enol form can be effected by acetyl hypofluorite[254] or perchloric fluoride[255] in a moderate yield, which can be generally improved by reaction with the corresponding sodium enolate. The potential hazard represented by fluorinating agents has been completely overcome since the introduction of *N*-fluoro-2-pyridone,[256] *N*-fluoroquinuclidinium fluoride,[257] *N*-fluorosulfonamides,[258] and *N*-fluoropyridinium triflates,[259] which are safe reagents.

In 1988, two camphor-derived *N*-fluorosultams (**197** and **198**) have been used as enantioselective fluorinating agents.[260]

H. Alkylation through Rearrangement

Claisen rearrangement of allyl vinyl ethers constitutes a well-established protocol for carbon–carbon bond formation and is particularly useful in creating the C_2-R_2 bond. The presence of a suitably placed

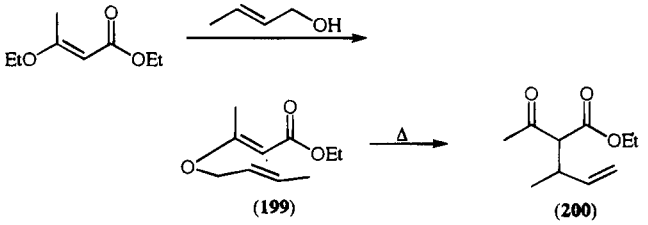


(197) R= H
(198) R= Me

enol ether moiety in the β-keto ester unit as in **199** is an essential requirement for the [3.3] sigmatropic shift.

A nice application of this methodology is the transformation of the allyl vinyl ether (**199**), obtained both by direct O-alkylation of ethylacetoacetate and by transesterification of simpler enol ether derivatives obtaining **200**, a crucial intermediate along the synthesis of the antileukemic agent Botryodiplodin I[261] (Scheme 131).

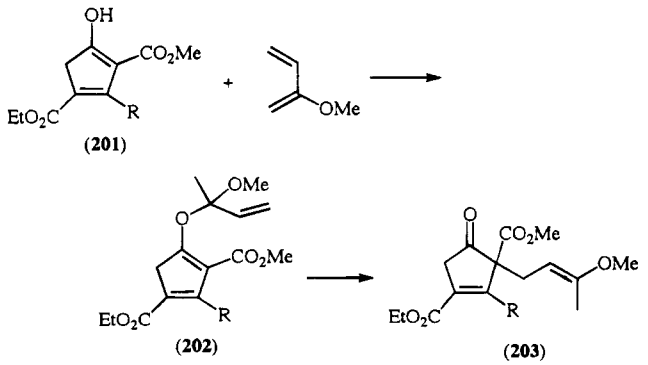
Scheme 131



(199) (200)

Treatment of ethyl enol ether of ethyl acetoacetate with *trans*-crotyl alcohol in hot xylene in the presence of 4:1 dinitrophenol/potassium bisulfate induced a smooth transetherification and Claisen rearrangement, yielding **200**. A particularly interesting process, essentially a variant of the classical Michael reaction, is the α-alkoxyallylation of easily enolizable carbonyl compounds (Scheme 132).

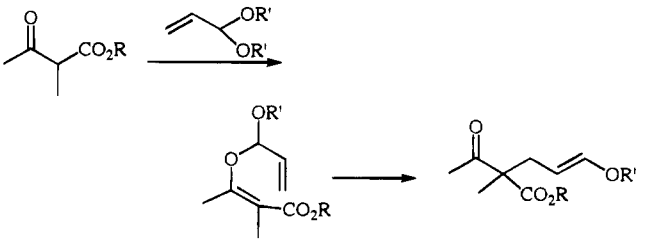
Scheme 132



(201) (202) (203)

Dolby et al.[262] observed that heating a mixture of cyclopentenone (**201**) and 2-methoxy-1,3-butadiene in benzene produced **203**. Since a direct attack at the C_2 of the β-keto ester seems very unlikely, the authors suggested the formation of the acetal intermediate **202**, which led to **203** through Claisen rearrangement. A similar process, involving the reaction of β-keto esters with diethyl acetals of α,β-enals and leading to ethoxyallylation derivatives, has been investigated by Coates and Hobbes[263] some years later (Scheme 133).

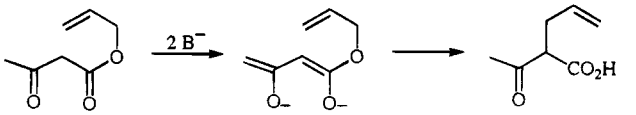
Scheme 133



The final products shown in Schemes 132 and 133 can be formally considered as synthetic equivalents of Michael adducts of β-keto esters on methyl vinyl ketone or on acroleins. Potential advantages of this variant of the Michael reaction include (i) the use of mild acid conditions that presumably can reduce aldol cyclization and (ii) the synthesis of products in protected form.

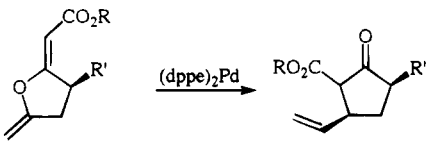
The ester enolate Carroll rearrangement, a variant of Claisen rearrangement, was utilized by Wilson and Price[264] for the synthesis of β-keto acids (Scheme 134).

Scheme 134



The process has rarely been used since the starting β-keto esters were not easily available and the rearrangement required drastic conditions, but both limitations have been successfully overcome. Finally, a noteworthy example of C_2-R_2 bond formation is offered by the rearrangement of 2-alkylidene-5-vinyltetrahydrofurans leading to cyclopentanone derivatives by heating in dioxane at 90 °C in the presence of 6% $(dppe)_2Pd$ (Scheme 135). The stereochemical

Scheme 135



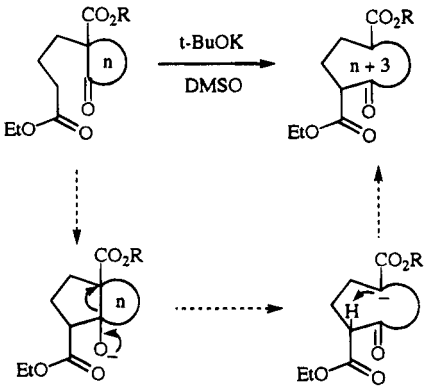
outcome of the reaction on substituted tetrahydrofurans has been carefully investigated.[179,265]

A one-pot three carbon ring expansion has been reported by Xie and Sakai[266] and successfully applied to the synthesis of (−)-muscone. The rearrangement involves an intramolecular aldol condensation, a subsequent retro-aldol cleavage by treatment with potassium *tert*-butoxide in dimethyl sulfoxide and final trapping of the ring-expanded anion by the acidic proton of the generated β-keto ester (Scheme 136).

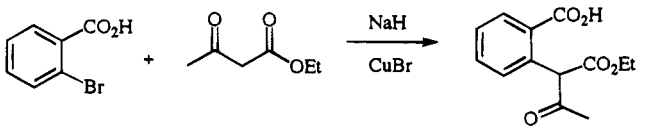
I. Other Methods

The introduction of an aryl substituent at the C_2 of ethyl acetoacetate represents a less facile operation in comparison to alkylation. However, Bruggink and McKillop[267] obtained good results in the direct Cu(I)-catalyzed arylation of β-keto esters with 2-halobenzoic acid (Scheme 137).

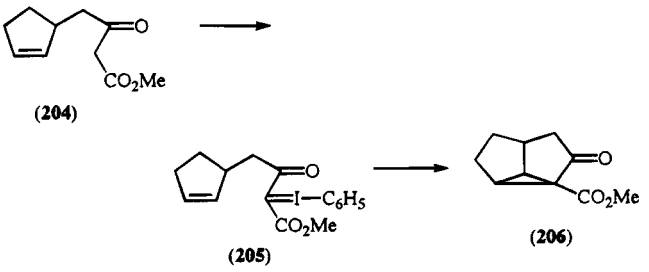
Scheme 136



Scheme 137



Scheme 138



Cuprous chloride also catalyzes the decomposition of iodonium ylide **205**, formally an analogue to dicarbonyl diazo compounds, to give cyclopropanation as shown in the Scheme 138.

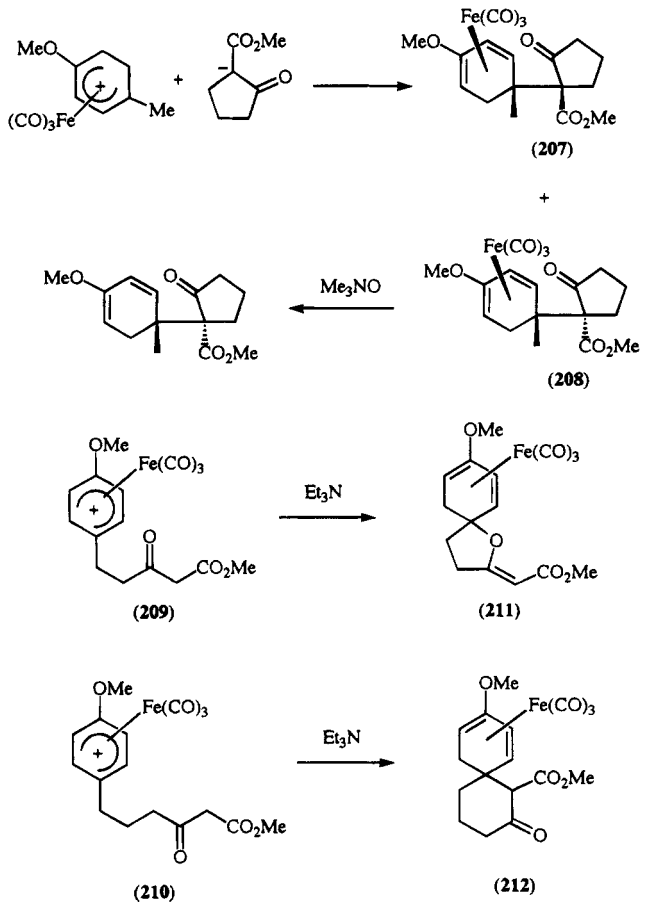
The ylide **205**, derived by the reaction of **204** with diacetoxyiodobenzene in KOH/MeOH at 0 °C, affords the tricyclic compound **206** through intramolecular addition of the electrophilic iodine center to the double bond ring, closure of the zwitterionic intermediate obtained, and final reductive elimination of iodobenzene.[268]

Pearson et al.[269,270] were able to form the C_2-R_2 bond by reaction of tricarbonyl (4-methoxy-1-methylcyclohexadienylium)iron hexafluorophosphate with the potassium enolate of methyl 2-oxocyclopentanecarboxylate, obtaining a diastereoisomeric mixture of **207** and **208**. The intramolecular version of the process on iron derivatives incorporating the acetoacetic unit **209** and **210** leads to the formation of spiro compounds. In this case, both O- and C-alkylation occurred, giving rise to **211** or **212**, respectively, depending on the size of the cycle formed (Scheme 139).

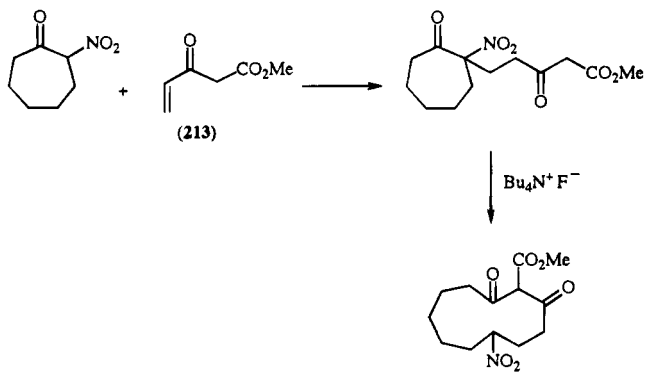
An interesting ring expansion, the carbon zip reaction, allows the carbon–carbon bond formation at the C_2 of β-keto esters. The Michael adducts of seven-, eight-, and twelve-membered 2-nitrocycloalkanones with methyl 3-oxo-4-pentenoate (**213**) react in the presence of tetrabutylammonium fluoride (TBAF) to give cyclic compounds with a ring enlarged by four C-atoms[271] in high yields (Scheme 140).

The introduction of alkenyl and alkynyl groups on active methylene units of β-dicarbonyls can also be

Scheme 139



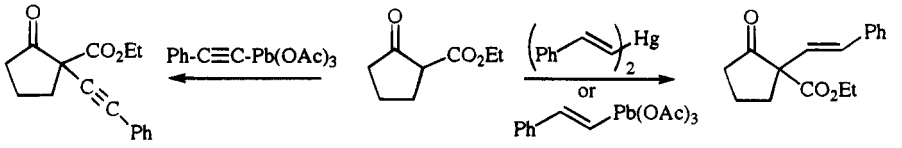
Scheme 140



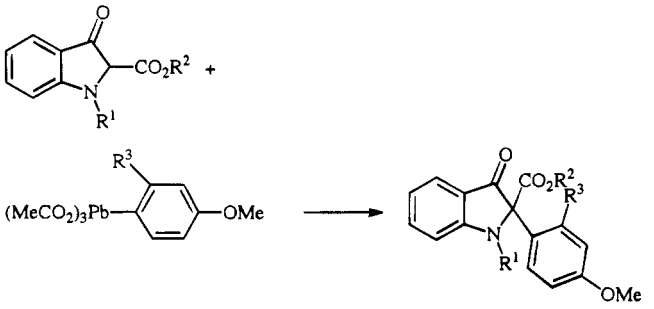
achieved, as exemplified by the addition of lead tetracetate to a solution of dialk-1-enylmercury or alk-1-enyltributylstannane. The unstable intermediate so generated reacts with ethyl cyclopentanone-2-carboxylate to give the alkenylation products.[272] A similar behavior has been encountered generating alk-1-ynyllead triacetate from alk-1-ynyltrimethylstannane and lead tetraacetate[273,274] (Scheme 141).

In 1992, Pinhey et al.[275] found significantly higher yields in vinylations when trimethylvinylstannanes are treated with lead tetrabenzoate. Pinhey's alkynylation is the method of choice for the introduction of akynyl group onto β-keto ester but requires the separate synthesis of moisture-sensitive alkynylstannanes and the troublesome purification of the products from trialkyltin acetates as byproducts. To avoid the hurdles, the alkynyl lead triacetate is generated by the reaction of lead tetraacetate and hexynyl

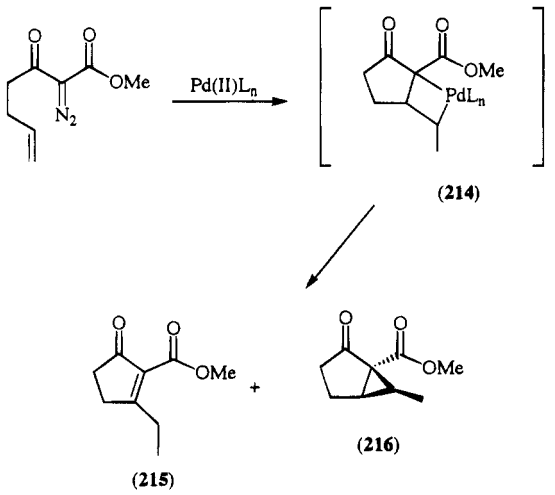
Scheme 141



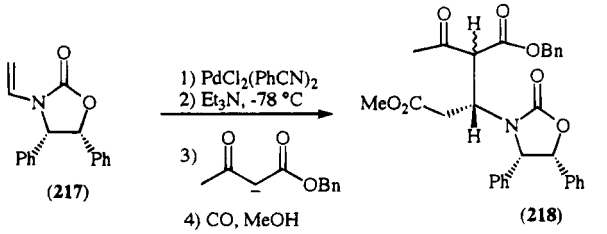
Scheme 142



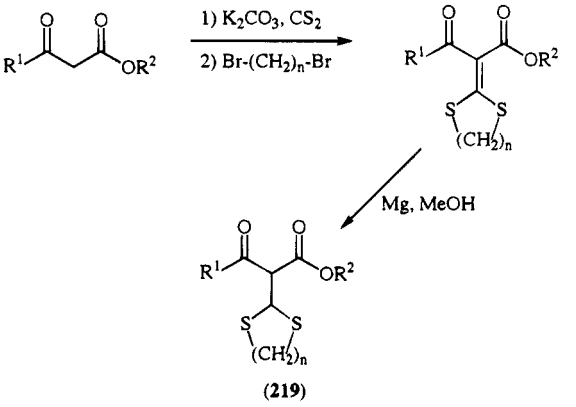
Scheme 143



Scheme 144



Scheme 145



metals as reported by Ikegami et al.[276] An analogous modification has been reported by the same authors[277] for alkenylation developing a more efficient method for the preparation of alkenyllead triacetate. Arylation has also been directly performed[278] with aryllead triacetates.

Thus, 2-(alkoxycarbonyl)-3-oxo-2,3-dihydroindoles are smoothly C-arylated by (4-methoxyphenyl)lead triacetate or (2,4-dimethoxyphenyl)lead triacetate to the corresponding 2-aryl-2-(alkoxycarbonyl)-3-oxo-2,3-dihydroindoles (Scheme 142).

An intriguing diazo insertion[279] reaction induced by a palladium complex, $PdCl_2(PhCN)_2$, offered an extremely useful example for the construction of the cyclopentenone **215** (Scheme 143).

The prevalent formation of **215** with respect to the cyclopropanation product **216** has been accounted for by the intermediacy of a palladium cyclobutane intermediate **214**.

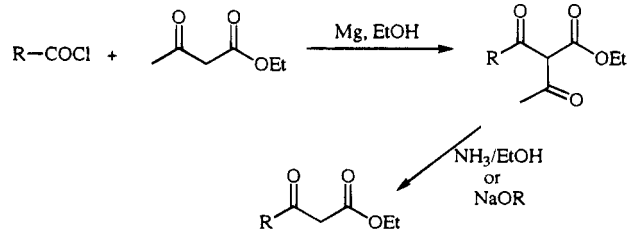
With the aid of suitable palladium catalysts, Hegedus et al.[280] have developed the synthesis of the optically active ene carbamate **217**, which has been used for the preparation of **218**, an intermediate relay to (+)-thienamycin, in good chemical and very high optical yields. The key step of the synthetic approach is the palladium(II)-assisted carboacylation of **217** to give C_2 alkylated benzyl acetoacetate as a mixture of two diastereomers at the epimerizable β-dicarbonyl central carbon (Scheme 144).

Finally, the preparation of acyl(alkoxycarbonyl)-ketene dithioacetals and the subsequent selective reduction with magnesium in methanol to **219** has been described by Pak et al.[281] (Scheme 145).

J. Acylation

The acylation of an acetoacetic ester unit at the C_2 carbon is a well-known process already discussed elsewhere in detail.[2,282,283] A synthetically relevant aspect is represented by the possibility of cleavage of α-acyl β-keto esters to β-keto esters by ammonolysis (Scheme 146) to give products formally arising from a Claisen reaction between different esters.[284]

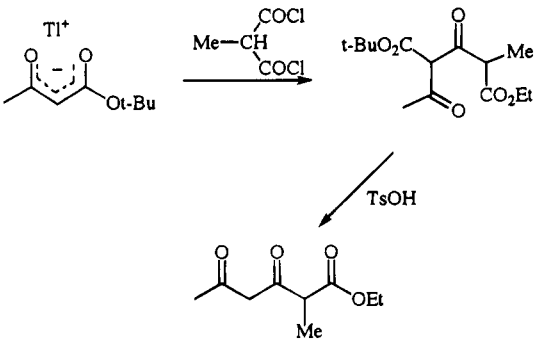
Scheme 146



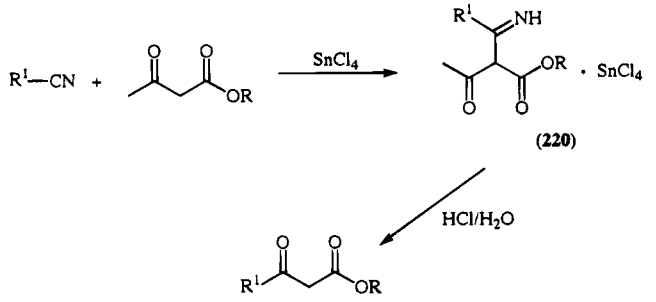
Taking advantage of the properties of *tert*-butyl esters, Suzuki and Inoue[285] obtained cross Claisen products in the presence of an acid catalyst (Scheme 147).

The choice of the base is of crucial importance in the acylation step. Metallic sodium, magnesium

Scheme 147



Scheme 148

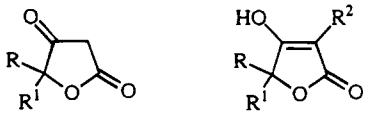


ethoxide, and thallium hydroxide were initially employed. In 1985, the use of pyridine associated to magnesium chloride was proposed,[286] inspired by the principle that metal complexation enhances the acidity of active methylene carbons. Acylation can be also affected in the presence of tin tetrachloride using nitrile as an acylating agent[287] (Scheme 148).

In fact, the addition of tin chloride to a mixture containing both nitrile and acetoacetate precipitates the solid complex **220**, which is then hydrolyzed in a biphasic system of dilute hydrochloric acid/chloroform. In 1985, Takeda et al.[288] discovered an acylation procedure through Favorskii rearrangement that allowed the one-step synthesis of dihydro-4-pyrones (Scheme 149).

The reaction of α,α′-dihalo ketone **221** with the enolate of ethyl acetoacetate yielded the pyrone **224**. Its formation has been rationalized through the formation of the acyl derivative **223** via the chlorocyclopropanone **222**, followed by nucleophilic opening and subsequent intramolecular Michael addition to generate **224**.

Finally, particular attention has been devoted to the C-acylation of the cyclic β-keto ester **225**, which constitutes the basic framework of tetronic acids (**226**).

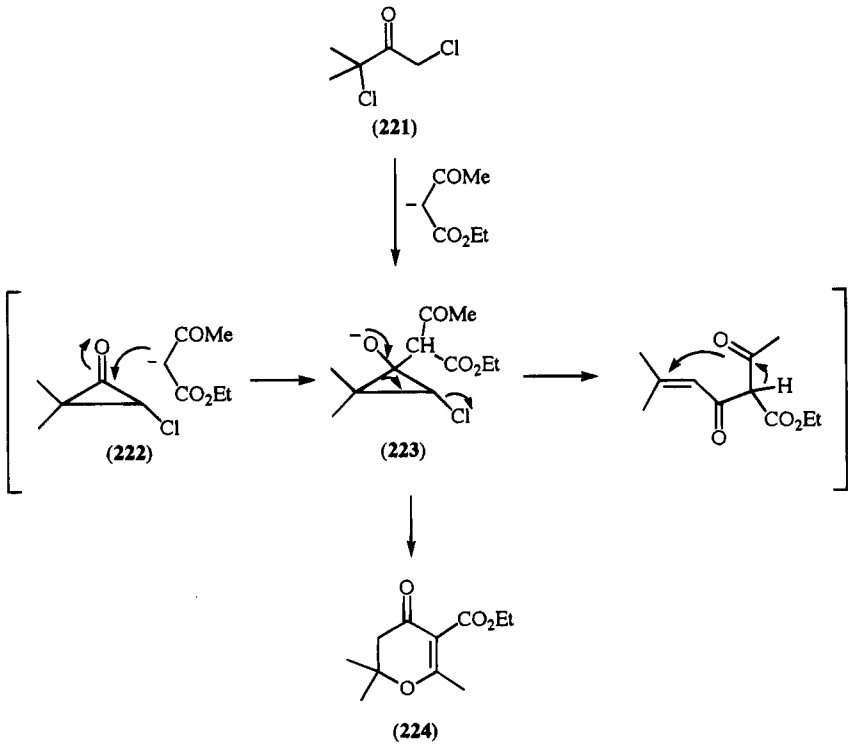


Two types of methodologies have been applied:[289-293] (i) direct acylation of **225** by means of acyl chlorides in the presence of Lewis acids or Fries rearrangement of O-acylated derivatives of **225** promoted by titanium tetrachloride in nitrobenzene solution. Yoshii et al.[294,295] discovered that O-acyl derivatives of **225** rearranged easily to give **226** at room temperature in the presence of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine; (ii) lithiation of *O*-methyl derivatives of **225** in the presence of lithium diisopropyl amide exchange followed by condensation with acyl halides or esters.[296,297]

VI. C_4–R_3 Bond Formation

The γ-alkylation of ethyl acetoacetate represents a practicable route to the formation of C_4–R_3 bond.

Scheme 149



Scheme 150

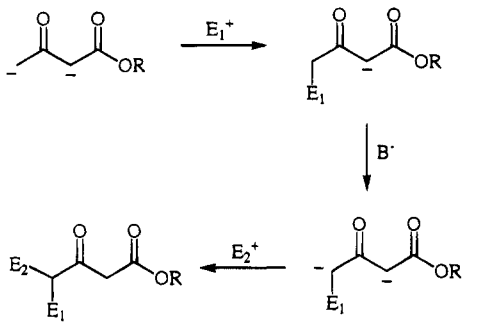


Table 11. Alkylation of Dianion of Methyl Acetoacetate

R-X	yield (%)	R-X	yield (%)
MeI	81	t-BuBr	0
EtBr	84	c-$C_6H_{11}Cl$	0
i-PrI	73	CH_2=CH-CH_2Br	83
n-BuBr	72	$PhCH_2Cl$	81

This operation, previously applied to the alkylation of β-diketones and β-keto aldehydes dianions,[298] can be achieved by generation of the dianion in virtue of the less acid character of the C_4 hydrogen in comparison to that of C_2, followed by reaction with suitable electrophiles. However, incomplete formation of β-keto ester dianions has been observed[299] in liquid ammonia at −33 °C using potassium amide as the base with consistent concomitant ammonolysis of the ester function.

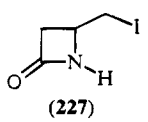
In 1974, Huckin and Weiler[300] were able to solve the problem through a procedure based on the use of a non-nucleophilic base strong enough to achieve complete formation of the dianion, which was allowed to operate in solvents different from ammonia. The acetoacetate dianion has been prepared by treating ethyl acetoacetate with sodium hydride and then butyllithium (Scheme 150).

The subsequent alkylation proceeded very fast (5−15 min) at temperatures in the range 0−25 °C in the presence of different alkyl halides with the yields reported in the Table 11.

The process does not work with hindered halides, but bis-γ-alkylation may also be accomplished in good yield (Scheme 150).

A number of interesting synthetic applications of this methodology have been reported, some of them dealing with the synthesis of (+)-α-cuparenone[215] and the preparation of optically active cyclohexanones and cyclopentanones.[211]

Alkylating agents bearing acid hydrogens have been also utilized as in the case of the iodomethylazetidinone derivative **227** in the synthesis of (−)-



(227)

homothienamycin, where 2 equiv of dianion is required since the primary event of the reaction is the deprotonation of **227** by a dianion equivalent.[222] Aldol condensation products have been obtained by utilizing carbonyl compounds as electrophiles on the dianion of methyl acetoacetate.[301] However, α,β-unsaturated carbonyl compounds gave exclusively 1,2-addition products, owing to the hard nucleophilic character of the dianion.

Both α-hydroxy and α-alkoxy β-keto esters can be prepared by reacting diketene both with carbonyl compounds[302] or their acetals[303] in the presence of titanium tetrachloride (Scheme 151). The use of titanium tetrachloride seems to be crucial for the success of this reaction, since Kucherov and Yufit[304] obtained only the 2-alkoxyalkyl derivative by reacting acetals and diketene in the presence of boron trifluoride etherate (Scheme 151).

The methodology based on the use of $TiCl_4$, originally introduced by Mukaiyama,[303] is highly chemoselective. In fact, the presence of different electrophilic centers, as in the case of a chloroacetal or the dimethyl acetal of methyl levulinate, does not alter the course of the reaction.

Yamaguchi et al.[305] and later Hiyama et al.[306] have envisaged that β,δ-diketo esters are versatile intermediates for polyketide synthesis. One of the best approaches to the preparation of these compounds involves a condensation reaction of anions of acetoacetates with different acylating agents. After having tested with unsatisfactory results cinnamoyl chloride, cinnamoyl imidazolide, and *N,N*-dimethylcinnamoyl amide as electrophilic partners of acetoacetate dianions, they were able to obtain the desired product in 57% yield employing *N*-methoxy-*N*-methylcinnamoyl amide (Scheme 152).

In 1979, Chan and Brownbridge[307] employed 1,3-bis[(trimethylsilyl)oxy]-1-methoxybuta-1,3-diene (**228**) as a synthetic equivalent of the methyl acetoacetate dianion.

Because of the well-known differences between enolates and enol silyl ethers, there is remarkable modification of the reactivity of **228** with respect to the dianion. Thus, this procedure further extends the entries referring to the formation of the C_4-R_3 bond.

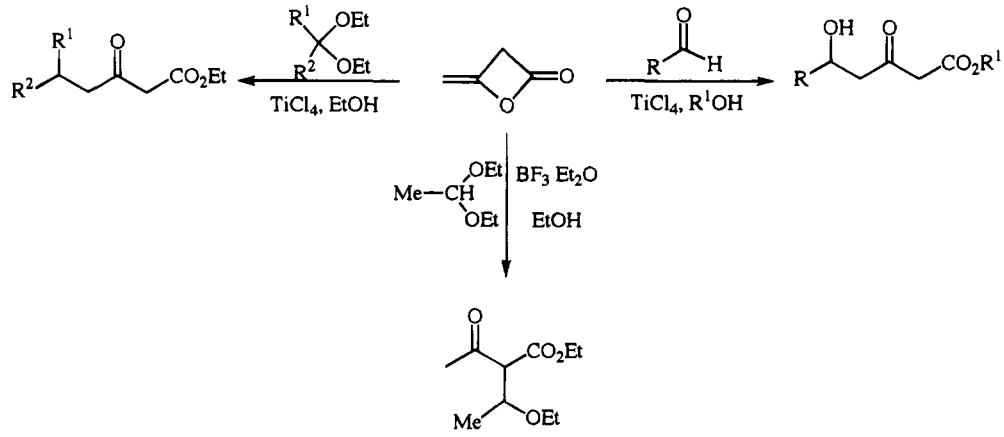
The reaction of **228** with reactive electrophiles proceeds almost spontaneously, as in the case of acetyl chloride, while activation by means of $TiCl_4$ is required with less reactive partners.

Since silyl enol ethers have a softer nature than enolates, the synthon **228** reacts with α,β-unsaturated compounds to produce Michael adducts rather than 1,2-adducts as in the case of the acetoacetate dianion. A general survey of the reactivity of **228** has been depicted in Scheme 153.

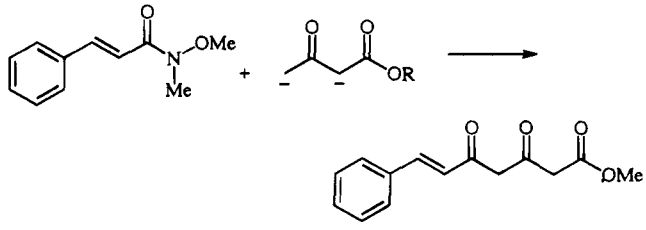
In 1982, Schlessinger[308] proposed the lithium enolate of the vinyl urethane **229** as a new synthetic equivalent of the acetoacetate dianion. Its aldol lactonization process with carbonyl compounds, which proceeded with the formation of **230**, has been carefully studied. Overall yields and diastero- and enantioselectivity were satisfactory with aldehydes, but in marked contrast in the case of ketones, the yields are very low and diasteroselectivity is practically negligible (Scheme 154).

The methodology has been applied to the synthesis of (−)-tirandomycin A[309] and (+)-mosaramicin aglycone.[310] The same author[311] investigated the enatioselectivity of the process using enolates bearing chiral auxiliaries, such as mono- and disubstituted pyrrolidines. They obtained a threo−erythro mixture of

Scheme 151



Scheme 152



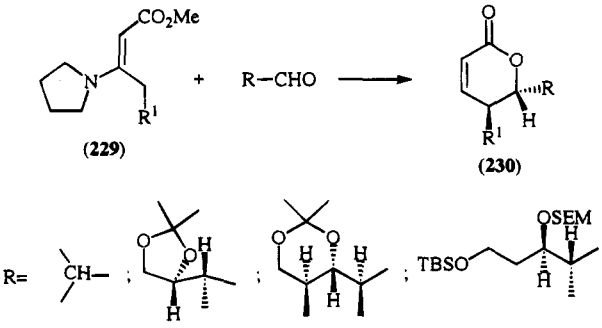
aldol adducts in the case of monosubstituted chiral pyrrolidines but exclusive erythro selectivity in the case of the vinyl urethane **231** containing a 2,5-disubstituted chiral pyrrolidine moiety, then utilized in the synthesis of a C_4 synthon along the route to virginiamycin M_2.

Continuing their studies aimed at overcoming several hurdles encountered in the aldol lactonization process, Schlessinger et al.[312] investigated the acylation and the reduction of vinyl urethanes (Scheme 155).

The readily available acylated derivatives (**232**) were subsequently lactonized to **233** either by reduction with L-selectride or by reaction with methyl lithium with exclusive formation of products reconducible to threo-aldol condensation products with aldehydes (R′ = H) or ketones (R′ = CH_3) (Table 12).

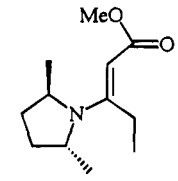
In view of these promising results, the same experimental conditions were applied to the chiral

Scheme 154



R[1]= Me; SMe; CH_2-CH_2-OBn

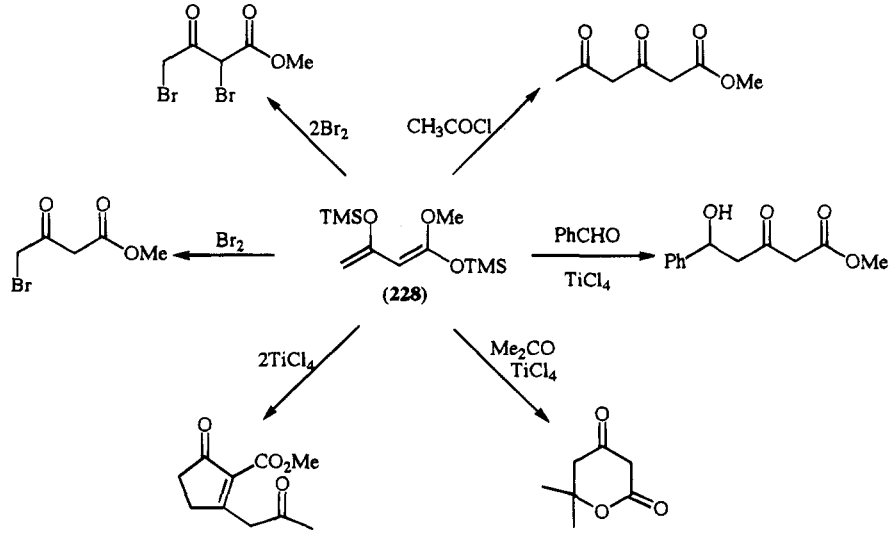
vinylogous urethane **231**, but rather surprisingly, a mixture of C_2 and C_4 acylation products of the



(231)

acetoacetic unit was obtained. Conversion of **231** to the trimethylsilyl keteneacetal **234** allowed a re-

Scheme 153



Scheme 155

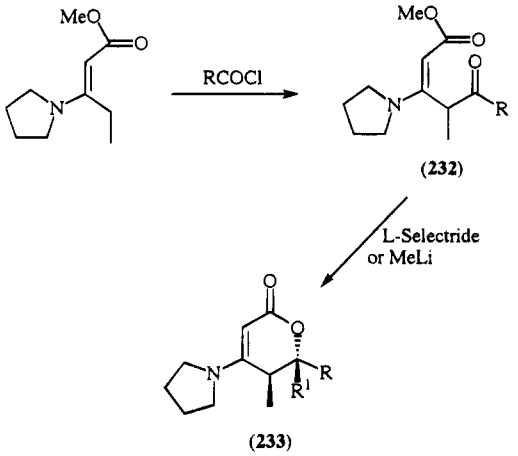
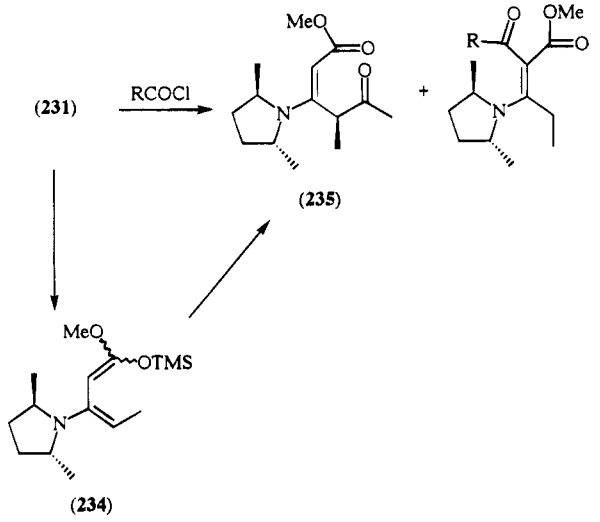


Table 12

RCHO or RCOCl R =	aldol		acylation–reduction	
	threo:erythro	yield (%)	threo	yield %
Me	9.5:1	71	99	82
n-Pr	10:1	74	99	82
n-Bu	11:1	80	99	86
t-Bu	7.5:1	81	99	68
Ph	7:1	84	99	90

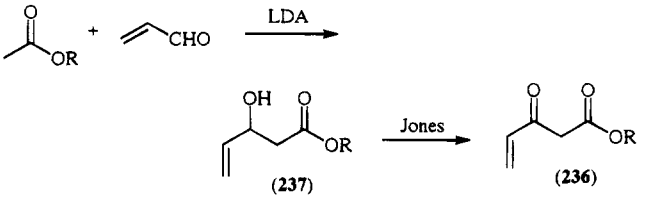
Scheme 156



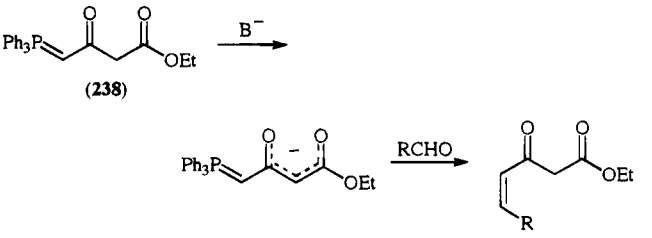
giospecific acylation at C_4 to be produced after the usual workup good yield of threo derivative **235** with a 94% of ee (Scheme 156).

Alkylidene derivatives at the C_4 position of the acetoacetic ester unit can also be obtained via usual aldol condensation. The synthetic importance of these derivatives is noteworthy as demonstrated by the wide applications of the simplest term (**213**) in the Robinson annealation studied by Nazarov[313] on cyclic β-diketones and subsequently extended by Stork[314] to enamines of cyclic ketones. At first sight, the elaboration of the previously described α-hydroxy β-keto ester to α-alkyliden-β-keto esters would seem to be a trivial operation. However, since the rather obvious dehydration is hardly a practicable method, the process requires methodologies involving the utilization of sulfoxides and α-phosphorylated derivatives of acetoacetic ester. In view of these difficulties, Trost[68] proposed the dehydrosulfenylation as a way

Scheme 157



Scheme 158



to create the unsaturation. Thus, alkylation of the acetoacetate dianion with iodomethylphenylsulfide, followed by oxidation and heating at reflux for 12 h in chloroform solution, furnishes a good yield of methyl 3-oxopent-4-enoic acid (**236**).

In 1989, to avoid the polymerization encountered in the Trost procedure, Zibuck and Striber[315] prepared **236** by Jones oxidation of the β-hydroxy esters (**237**) obtained by condensation of acrolein and alkyl acetates (Scheme 157).

Phosphorylated derivatives have been also utilized: as far as phosphoranes are concerned, the stabilized ylide **238** reacted with aromatic aldehydes only under acid catalysis and drastic conditions not tolerated by aliphatic aldehydes.

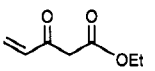
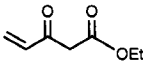
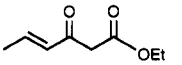
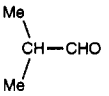
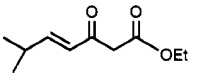
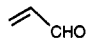
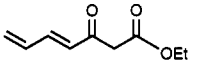
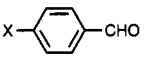
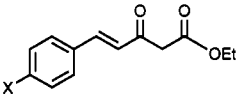
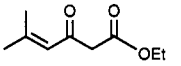
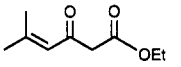
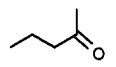
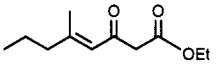
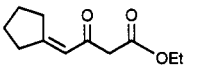
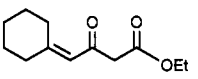
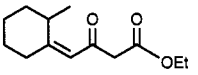
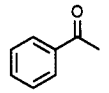
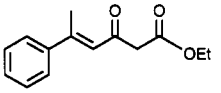
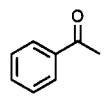
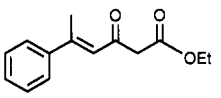
Two solutions are known to overcome this problem: thus, Bestmann and Saalfrank[83] prepared the phosphorane **47**, previously mentioned in this review, which reacts smoothly with aldehydes allowing *E*-α-alkylidene β-keto esters to be obtained after acid demasking of the carbonyl function.

In 1986, Pietrusiewicz and Monkiewicz[316] were able to enhance the reactivity of the phosphorane (**238**) through the simple and brilliant device of transforming its stabilizing carbonyl group into the corresponding enolate (Scheme 158).

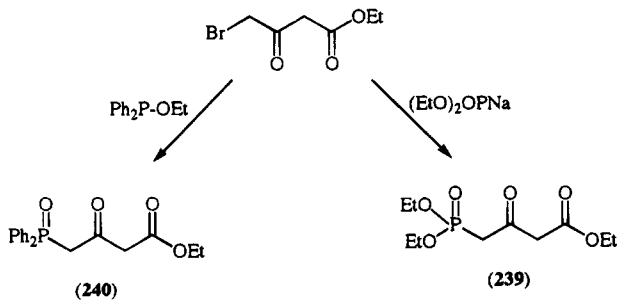
Thus, a fast reaction takes place mixing equimolecular amounts of ylide **238** and aldehyde with 2 equiv of sodium hydride in tetrahydrofuran containing a few drops of water to produce almost exclusively (*Z*)-γ,γ-alkylidene β-keto esters in the case of aliphatic aldehydes, a rather unexpected stereochemical outcome for condensations of stabilized phosphoranes, prevalent *E*-isomers being obtained with aromatic aldehydes.

In 1980, Bodalski et al.[317] obtained **239** by reaction of the sodium salt of ethyl γ-bromoacetoacetate with sodium diethyl phosphite while **240**, another phosphorylated derivative, has been prepared[318] by using ethyl diphenylphosphinite as the electrophile. Reaction of both **239** and **240** with aldehydes in the presence of 2 equiv of base allowed (*E*)-γ,δ-unsaturated β-keto esters to be obtained, while the reaction with ketones produced *E*/*Z* mixtures (Scheme 159; Table 13).

Table 13

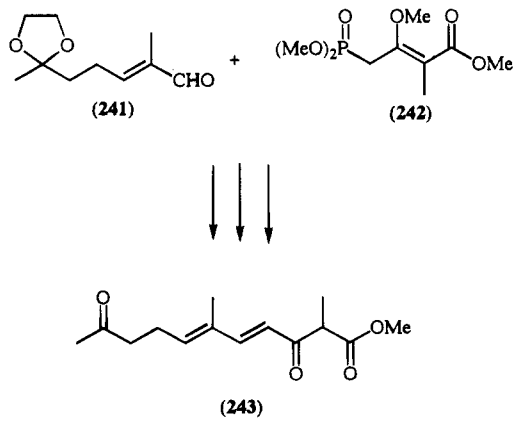
phosphorylated derivative	carbonyl compds	product	yield (%)	*E*/*Z* ratio	ref
174	CH_2O		52	100:0	*318*
174	Me-CHO		81	100:0	*318*
173	Me-CHO		89	100:0	*317*
173			96	100:0	*317*
173			91	100:0	*317*
					
173	X =H	X =H	84	100:0	*317*
174	X = H	X = H	90	100:0	*318*
174	X = Me	X = Me	80	100:0	*318*
174	X = OMe	X = OMe	80	100:0	*318*
174	X = NO_2	X = NO_2	81	100:0	*318*
174	X = $N(Me)_2$	X = $N(Me)_2$	84	100:0	*318*
174			72	100:0	*318*
173			70	85:15	*317*
174			65	100:0	*318*
173			85	100:0	*317*
174			63	100:0	*318*
174			63	85:15	*318*
174			65	90:10	*318*
173			60	75:25	*317*

Scheme 159



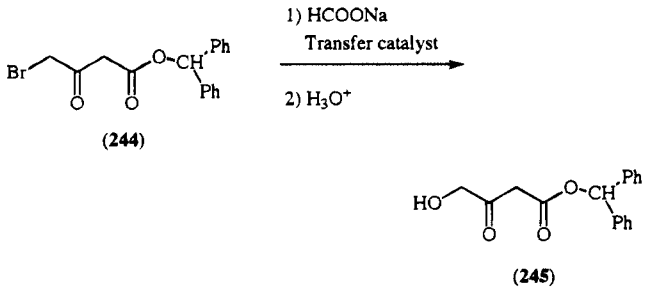
The condensation of the aldehyde **241** with the phosphonate of the masked β-keto ester **242**, in turn prepared starting from 2-methyl-4-bromo-3-methoxybut-2-enoic acid methyl ester and trimethyl phosphite, had been previously utilized by Edward et al.[319] to construct a useful intermediate for the synthesis of trisporic acid B (**243**) (Scheme 160).

Scheme 160

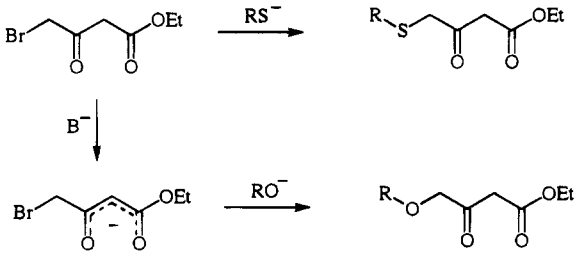


The methods for the formation of the C_4-R_3 bond so far reviewed in this section are all based on the reactivity of C_4 as a nucleophilic center, but methods involving the C_4 carbon as an electrophilic center are

Scheme 161



Scheme 162



also known. 4-Bromoacetoacetate derivatives represent the most obvious substrates for nucleophilic substitutions, offering possibilities for bond formation with different heteroatoms. However, this kind of reaction usually fails because of the acidity of the C_2 hydrogens.

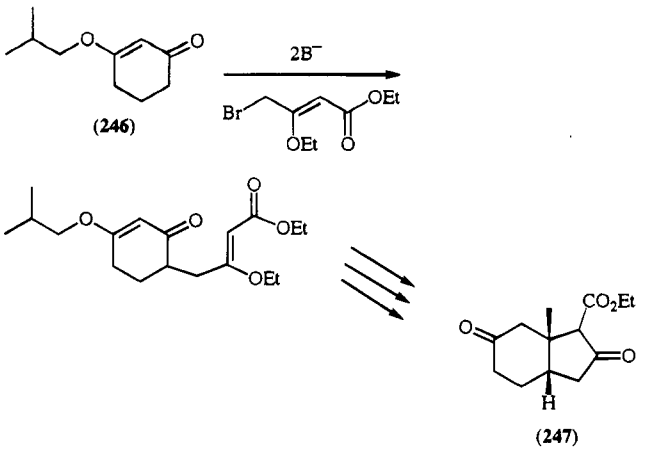
Inspection of the literature reveals two cases in which the nucleophile, being a weak base, allows a direct substitution. The first one[224] concerns the preparation of diphenylmethyl 4-hydroxyacetoacetate (**245**) by reaction of the bromo derivative **244** under phase-transfer catalysis with sodium formate followed by acid hydrolysis of the intermediate (Scheme 161). The second case,[320] describes the preparation of thioether derivatives by reaction of ethyl 4-bromoacetoacetate with thiolate anions (Scheme 162).

In order to obtain C_4 substitution products by reaction with strong bases such as alkoxides or metalated amines, a preliminary salification with sodium hydride is required. The substitution can then be achieved as described by Kellogg and Troostwijk.[320] Stork,[144] who developed a new synthesis of *cis*-hydrindan nucleus (**247**), was forced to operate the alkylation of the dianion of 1,3-cyclohexanedione isobutyl enol ether **246** with a bromoacetoacetate unit in masked form (Scheme 163).

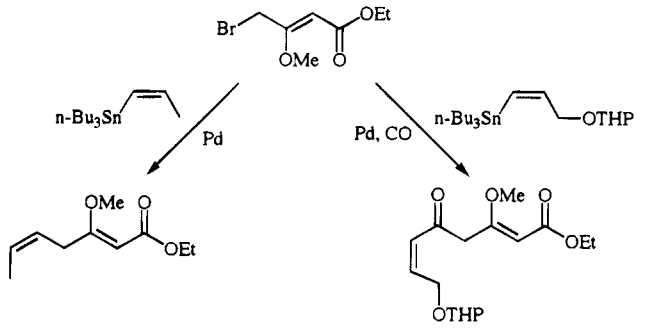
Finally, cross-coupling of organometallic derivatives starting from the ethyl ester of 4-bromo-3-methoxybut-2-enoic acid has been also employed. In 1983, Stille and Sheffy[321] made use of this strategy using tin derivatives and palladium complexes as catalysts (Scheme 164).

This reaction offered a good example of stereo- and regiospecific carbon–carbon bond formation, which not only is compatible with the presence of other functions but also allows alkylation and acylation in the presence of carbon monoxide of the acetoacetic unit. Several particular cases of C_4–R_3 bond formation must also be taken into account. For instance, Hewson et al.[322] were able to obtain bridged bicyclic systems by treatment of prenylated β-keto esters with tin(IV) chloride, applying a more general concept

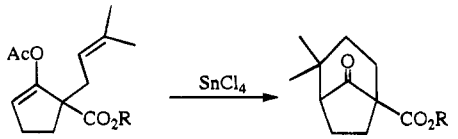
Scheme 163



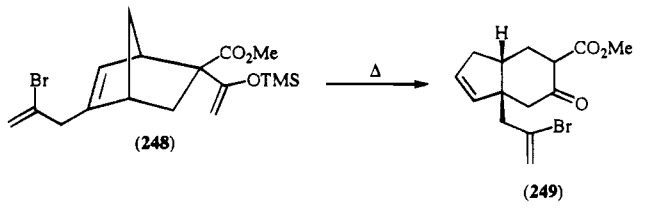
Scheme 164



Scheme 165



Scheme 166



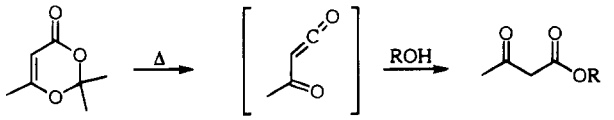
based on Lewis acid-catalyzed intramolecular alkylation of enol ethers[323] (Scheme 165).

Finally, Corey and Munroe[324] prepared an advanced intermediate toward the synthesis of gibberellic acid through an elegant β-keto ester α-alkylation featuring a sigmatropic reaction. Heating at 160 °C, the silyl enol ether **248** in toluene containing propylene oxide as an acid scavenger promotes a Cope rearrangement, leading to the formation of the *cis*-hydrindene **249** (Scheme 166).

VII. C_1–O_1 Bond Formation

The most direct formation of this bond consists in the esterification of a β-keto acid. This apparently simple method requires careful choice of experimental conditions in order to minimize the propensity of these substrates to decarboxylate. In addition to the

Scheme 167



(250) (251)

esterification, vinyl ether formation can also take place. An efficient procedure has been reported by Stodola,[325] who suggested the use of dicyclohexylethylamine as base and alkyl sulfates as alkylating agents in refluxing acetone. An improvement of the process has been suggested by Horwell and Fairhurst,[326] avoiding the possible decarboxylation by using 1,5-diazabicyclo[4,3,0]non-5-ene (DBN) at room temperature.

Acetoacetylation of an alcohol can be effected by reaction with diketene in the presence of suitable catalysts. Boese[327] was the first to use *p*-toluenesulfonic acid as a catalyst, but later better results have been achieved in the presence of basic catalysts such as alcoholates,[328] sodium acetate,[329] and triethylamine.[330,331] In 1984, Wilson[264] suggested the use of 4-(dimethylamino)pyridine for the preparation of allylic, primary, secondary, and tertiary acetoacetates under mild conditions, and the method has been widely generalized by Nudelman et al.[332] This topic was reviewed by Clemens[333] in 1986.

Several procedures have the additional advantage of introducing a resolving agent allowing optically active building blocks to be produced after suitable elaboration.[211,330]

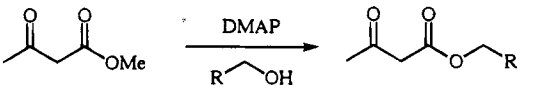
In 1985, a methodology involving the use of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**250**) as acylating agent of alcohols without added catalyst was reported as a useful alternative to diketene methodology[334] (Scheme 167).

It should be noted that **250** has been previously utilized in the preparation of β-keto esters through acid-catalyzed transesterification with alcohols.[335] However, Clemens and Hyatt[334] demonstrated that **250** can be considered a synthetic equivalent of acetylketene **251**, generated by loss of acetone by heating and trapped with an alcohol to give highly pure β-keto esters, even with hindered tertiary hydroxyl groups and polyhydroxylated alcohols. For instance, glucose, which cannot be completely acylated by reaction with diketene, gave rise to an excellent yield of a pentaacetoacetyl derivative by heating with 5 equiv of **250**. It is known that transesterification of methyl acetoacetate, a variant in the formation of title bond, proceeds with unsatisfactory results.[336]

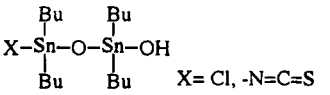
Taber et al.[337] introduced a procedure of more general applicability based on the use of 4-(dimethylamino)pyridine (DMAP) as catalyst. This protocol gives valuable results although with some limitations, for instance, non-enolizable β-keto esters and the formation of esters with tertiary alcohols are still evident (Scheme 168).

Gilbert and Kelly[338] modified the experimental conditions adding 4-Å molecular sieves for the removal of ethanol and to bias the equilibrium, but the same serious shortcomings previously encountered still remain.

Scheme 168



These problems have been partially solved by Otera et al.,[339,340] who were able to achieve transesterification of non-enolizable β-keto esters under practically neutral conditions under the catalysis of 1,3-disubstituted tetrabutyldistannoxanes (**252**) as showed in Table 14.[341]

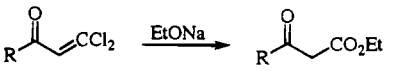


(252)

An alternative process, based on the thermal reaction of *tert*-butyl acetoacetate with 1-butanol in xylene, was reported by Witzeman[342] in 1990. The mechanism of the transacetoacetylation has been examined in detail, and the author suggests that the reaction must proceed via a unimolecular rate-determining decomposition of *tert*-butyl acetoacetate to acylketene (**251**). The latter can then react with 1-butanol to give the transacetoacetylated product. The formation of the reactive intermediate **251** is supported by the observation that 2,2-disubstituted acetoacetates do not undergo exchange reactions owing to their inability to form **251**.

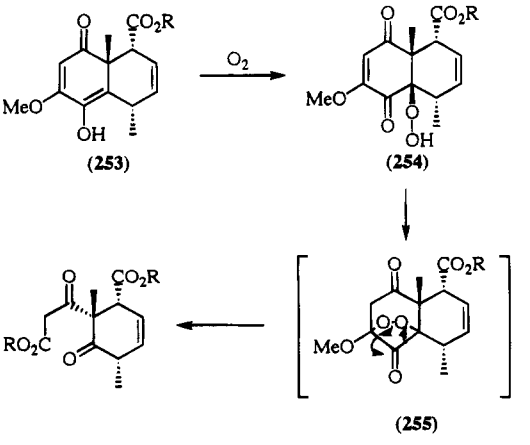
A method for the preparation of these β-keto esters by treatment of β,β-dichlorovinyl ketones with sodium ethoxide has been reported by Julia[343] and subsequently utilized by other workers on chlorinated polyenones[344] (Scheme 169).

Scheme 169



The rearrangement of the hydroperoxide **254** through the endoperoxide **255** followed by oxidative decarboxylation represents an intriguing method for the formation of the C_1-O_1 bond.[345] In the author's opinion, the reaction takes place if **253** is in enolic

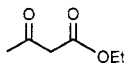
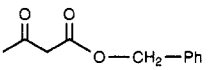
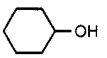
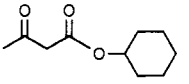
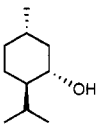
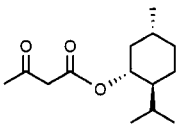
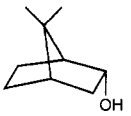
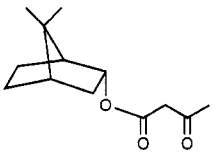
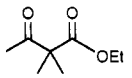
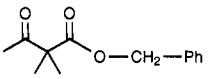
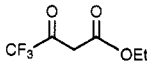
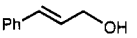
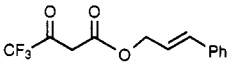
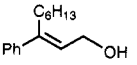
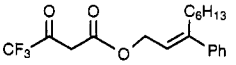
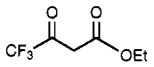
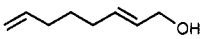
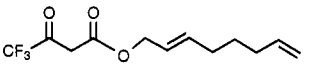
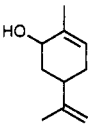
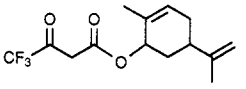
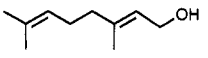
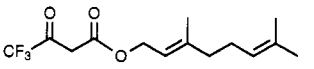
Scheme 170



(253) (254) (255)

form, the presence of the methoxy group being crucial to ensure complete enolization. In fact, when the

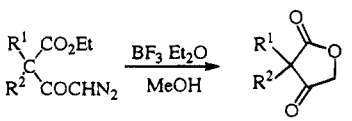
Table 14

β-keto ester	alcohol	product	yield (%)	ref
	Ph-CH_2OH		96	*339*
			91	*339*
			93	*339*
			95	*339*
	Ph-CH_2OH		88	*339*
			90	*341*
			90	*341*
			53	*341*
			87	*341*
			95	*341*

methoxy group is substituted for a methyl group, the reaction does not take place (Scheme 170).

2,4-(3*H*,5*H*)-Furandione derivatives often referred to as tetronic acids are commonly prepared by cyclization of a variety of α-substituted β-keto esters. A new strategy based on the cyclization of diazoketones derived from substituted ethyl hydrogen malonates in the presence of catalytic amounts of boron trifluoride etherate in methanol was suggested by Miller[346] in 1987 (Scheme 171).

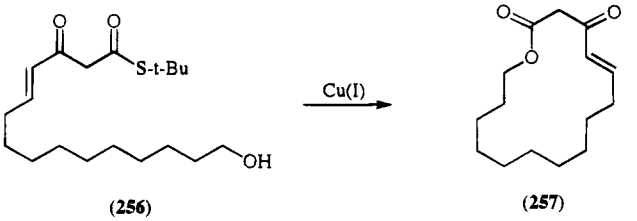
Scheme 171



Ley and Woodward[347] have demonstrated the effectiveness of the *tert*-butyl thioester group in an intramolecular transesterification to construct macrolides. Thus, treatment of **256** with copper(I) trifluoroacetate in buffered (Na_2HPO_4) dichloromethane produced the macrocyclic compound **257** in 35% yield (Scheme 172).

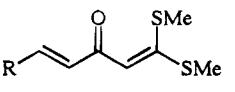
Finally, β-keto esters are obtained in good yield when dithioacetals, structurally related to **258**, are refluxed in methanol in the presence of the

Scheme 172



(256) (257)

ether–boron trifluoride complex and mercury(II) chloride.

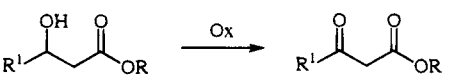


(258)

VIII. C_3–O_2 Bond Formation

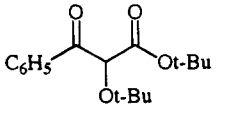
The most direct and convenient method for the formation of this bond undoubtedly consists in the oxidation of a β-hydroxy ester, in turn easily obtained through aldol condensation[348] (Scheme 173).

Scheme 173



It is interesting to observe that this rather obvious transformation has not been carefully investigated

for a long time, but it is now a general methodology. The most suitable protocols utilize Collins and Swern reagents, but the yields are highly dependent both on the number and on the type of substituents on C_2. For instance, the high yield of β-keto ester **259**



(259)

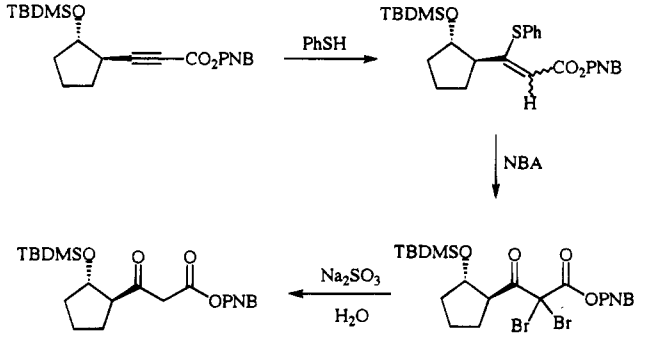
utilizing the Jones reagent, an oxidizing agent which requires unsuitable acid conditions, has been accounted for by the presence of a *tert*-butoxy group at C_2.[349]

The oxidation process is also dependent on the features of the R_1 group. In fact, the Swern reagent gives good yields when R_1 = alkyl or phenyl but gives poor yields if R_1 = vinyl. However, Nakata[350] obtained an 82% yield carrying out the oxidation on a substrate bearing $R_1 = CH_2{=}C(CH_3)$.

A general procedure to affect the Moffatt oxidation using P_2O_5 to activate DMSO in the presence of triethylamine was introduced with excellent results in 1987 by Taber et al.[351]

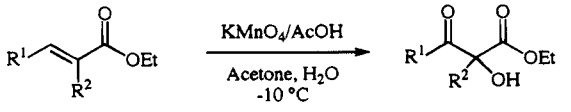
A β-keto ester can be obtained by direct hydration of acetylenic esters,[352-354] as well as by hydrolysis of enamino esters[355] or by treatment of thiol adduct, easily obtained through the addition of a thiol to a propiolic ester, with *N*-bromosuccinimide or *N*-bromoacetamide[356] (Scheme 174).

Scheme 174



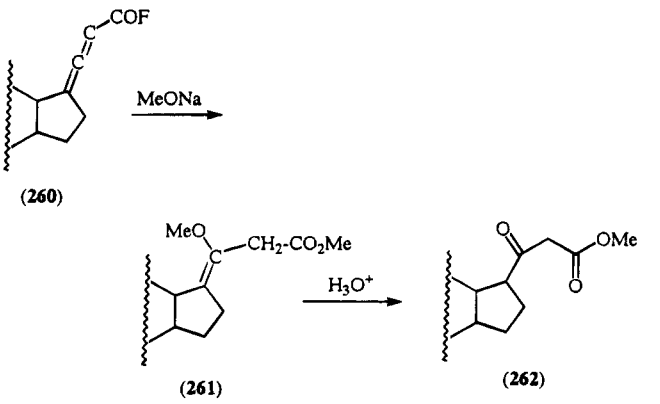
An interesting oxidation of α-substituted α,β-unsaturated esters to 2-alkyl-2-hydroxy-3-oxocarboxylic esters has been developed by Crout and Rathbone.[357] It also works well with simple aliphatic systems giving 2-hydroxy derivatives that are practically inaccessible with the method of Adriamialisoa et al.[238] The procedure is based on the oxidation of a conjugated double bond by potassium permanganate under mild acidic conditions (acetic acid) in aqueous acetone (Scheme 175).

Scheme 175



A rather unusual example of hydration of a cumulated system is offered by the steroidal allenic acid fluoride **260** prepared by Crabbè[358] through an intriguing procedure. Exposure of **260** to sodium methoxide followed by treatment of the derived enol ester **261** with dilute hydrochloric acid produced the β-keto ester **262** in excellent yield (Scheme 176).

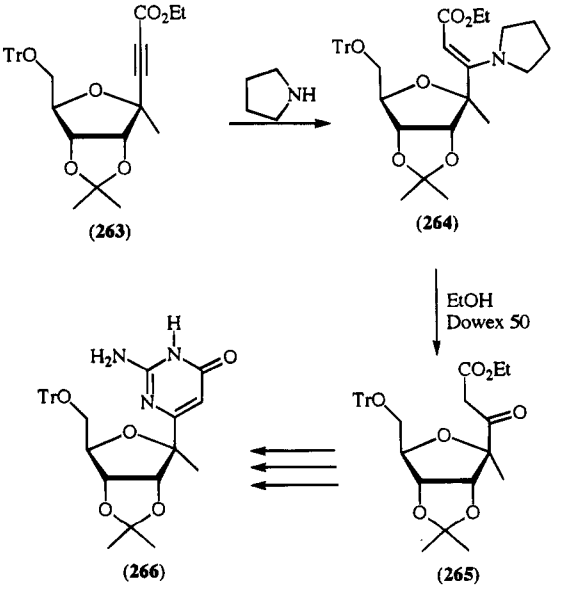
Scheme 176



Bestmann et al.[84,85] investigated the addition of piperidine both to the substituted allene **54** or to the acetylenic ester **52**. Both procedures gave rise to the formation of an intermediate enamino ester, subsequently taken to the corresponding acetoacetate acid. Only in the first case was it possible to obtain derivatives bearing a substituted C_2.

A similar strategy has been applied by Klein[359] to the synthesis of the pyrimidine C-nucleoside **266**. To this end, pyrrolidine was added to the acetylenic ester **263** to give the corresponding enaminoester **264**, subsequently hydrolyzed in the presence of wet Dowex-50 to the β-keto ester **265**, precursor of the pyrimidine ring (Scheme 177).

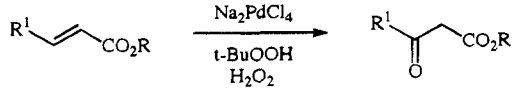
Scheme 177



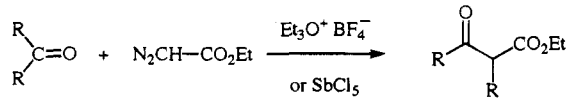
A variant of the Wacker process involving *tert*-butyl hydroperoxide or hydrogen peroxide as oxidizing agents in the presence of Pd catalyst has been utilized by Tsuji[360] for the oxidation of an α,β-unsaturated ester to a β-keto ester (Scheme 178).

Ketone homologation to a β-keto ester can be achieved by reaction with ethyl diazoacetate both directly or with isolation of α-diazo β-hydroxy ester intermediates (Scheme 179).

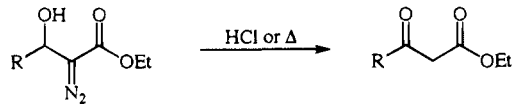
Scheme 178



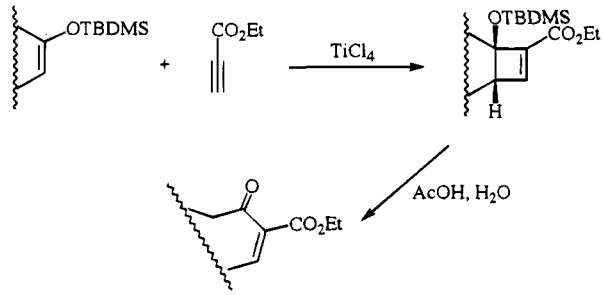
Scheme 179



Scheme 180



Scheme 181



Mock and Hartman[361] have investigated the direct procedure, obtaining the best results in the presence of triethyl oxonium fluoborate or antimony pentachloride and establishing that the rearrangement occurs usually through the migration of the less substituted residue attached to the carbonyl group.

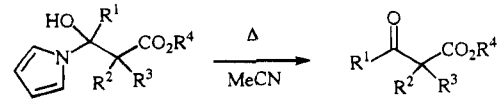
The alternative procedure, which consists in the reaction of ethyl diazoacetate with aldehydes or ketones followed by the rearrangement of the derived products catalyzed by transition metals, demonstrated that α-diazo β-hydroxy esters could be easily transformed to the corresponding β-keto esters either by refluxing in the presence of hydrochloric acid or by vacuum pyrolysis[90,362] (Scheme 180).

The rather severe limitations due to the drastic experimental conditions and to the poor yields have been later overcome performing the reaction at room temperature in the presence of catalytic amounts of rhodium(II) acetate. The method, previously applied to α-diazo β-hydroxy esters derived by condensation of ethyl diazoacetate with aldehydes, has been further expanded by Kim et al.[363] to the condensation products of the same reagent with ketones. Beside rhodium acetate, other less expensive and more efficacious salts such as Wilkinson catalyst, palladium, and cobalt chloride have been used. The regiospecificity of the transposition is of particular interest: alicyclic ketones gave rise exclusively to rearranged products derived by migration of the less substituted group. All the procedures introduced for ketone homologation are, however, unsuitable for α,β-unsaturated ketones.

The conrotatory opening of substituted cyclobutenes offers the last example of formations of the bond discussed in this section (Scheme 181).

The most general way to prepare these compounds involves [2 + 2] cycloaddition of acetylenic esters on

Scheme 182



(267)

enamines or silyl enol ethers, as reported by Clark and Untch.[364] The ring opening to produce β-keto esters can occur both at room temperature or by heating. The more or less pronounced lability of the cycloadduct can be attributed to different factors such as the nature of substituents, the relative stereochemistry, and the type of junction in the case of polycyclic systems.

In 1987, Brandange and Rodriguez[365] reported the preparation of β-keto esters by heating the pyrrolyl carbinols **267** easily obtained from lithium ester enolate and *N*-acylpyrroles with basic reagents (Scheme 182).

IX. Concluding Remarks

It is superfluous to stress the well-established ubiquitous importance of β-keto esters in organic chemistry and the consequent interest currently manifested in this area. During the years, organic chemists have offered a plethora of preparative methods to the subject of this review, whereas the progress in the control of the regiochemistry and the stereoselectivity in C−C bond-forming reactions have provided useful levels of efficiency and of induction of asymmetry. However, many methodologies employed in this context occasionally require reaction conditions that cannot be tolerated by the reagents involved, and new procedures or conceptually novel ideas need to be invoked to increase the potentiality of β-keto esters.

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X. References

(1) Hauser, C. R.; Hudson, B. E., Jr. *Org. Reactions*, **1942**, *1*, 266.
(2) (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; p735−760. (b) Caine, D. *Carbon-Carbon Bond Formation*; Augustine, R. L.,, Eds.; Marcel Dekker: New York, 1979; Vol. 1, p 250−258. (c) Barton, D.; Ollis, W. D. *Comprehensive Organic Chemistry*, 1st ed.; Pergamon Press: Oxford, 1979; Vol. 2, pp 707−708 and 785−787.
(3) Krapcho, A. D.; Diamanti, J.; Cayen, C.; Bingham, R. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 198.
(4) Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React.* **1954**, *8*, 59.
(5) Shahak, I. *Tetrahedron Lett.* **1966**, *7*, 2201.
(6) Koreeda, M.; Liang, Y. P.; Akagi, H. *J. Chem. Soc. Chem. Commun.* **1979**, 449.
(7) Boschelli, D.; Smith, A. B., III; Stringer, O. D.; Jenkins, R. H., Jr.; Davis, F. A. *Tetrahedron Lett.* **1981**, *22*, 4385.
(8) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(9) Henegar, K. E.; Winkler, J. D. *Tetrahedron Lett.* **1987**, *28*, 1051.
(10) Tomozane, H.; Takeuchi, Y.; Yamato, M. *Chem. Pharm. Bull.* **1988**, *36*, 401.
(11) Hellou, J.; Kingston, J. F.; Fallis, A. G. *Synthesis* **1984**, 1014.
(12) House, H. O.; Auerbach, R. A.; Gall, M.; Peet, N. P. *J. Org. Chem.* **1973**, *38*, 514.
(13) Saitkulova, F. G.; Kadirmatova, T. P.; Abashev, G. G.; Lapkin, I. I. *Isv. Vyssh. Uchebn, Zaved. Khim. Khim. Tekhnol.* **1977**, *20*, 1078; *Chem. Abstr.* **1977**, *87*, 201013*b*.
(14) Oshry, L.; Rosenfeld, S. M. *Org. Prep. Proced. Int.* **1982**, *14*, 249.

(15) Inoue, S.; Yamazaki, N. *Organic and Bio-organic Chemistry of Carbon Dioxide*; John Wiley: New York, 1982; pp 5−78.
(16) Stiles, M.; Finkbeiner, H. L. *J. Am. Chem. Soc.* **1959**, *81*, 2598.
(17) Hogeveen, H.; Menge, V. M. P. B. *Tetrahedron. Lett.* **1986**, *27*, 2757.
(18) Matsumura, N.; Asai, N.; Yoneda, S. *J. Chem. Soc. Chem. Commun.* **1983**, 1487.
(19) Tirpak, R. E.; Olsen, R. S.; Rathke, M. W. *J. Org. Chem.* **1985**, *50*, 4877.
(20) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582.
(21) Brown, C. A. *Synthesis* **1975**, 326.
(22) Luche, J. L.; Petrier, C.; Dupuy, C. *Tetrahedron Lett.* **1984**, *25*, 753.
(23) Crimmins, M. T.; Mascarella, S. W.; DeLoach, J. A. *J. Org. Chem.* **1984**, *49*, 3033.
(24) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318.
(25) Rathke, M. W.; Deitch, J. *Tetrahedron Lett.* **1971**, *12*, 2953.
(26) Logue, M. W. *J. Org. Chem.* **1974**, *39*, 3455.
(27) Lion, C. *C. R. Acad. Sci.* **1978**, *284*, 401.
(28) Bayless, P. L.; Hauser, C. R. *J. Am. Chem. Soc.* **1954**, *76*, 2306.
(29) Sato, T.; Itoh, T.; Fujisawa, T. *Chem. Lett.* **1982**, 1559.
(30) Schick, H.; Ludwig, R. *Synthesis* **1992**, 369.
(31) Villieras, J.; Perriot, P. O.; Bourgain, M.; Normant, J. F. *J. Organomet. Chem.* **1975**, *102*, 129.
(32) Couffignal, R.; Moreau, J. L. *J. Organomet. Chem.* **1977**, *127*, C65.
(33) Moreau, J. L.; Couffignal, R.; Arous-Chtara, R. *Tetrahedron* **1981**, *37*, 307.
(34) Kim, H. O.; Olsen, R. K.; Choi, O. S. *J. Org. Chem.* **1987**, *52*, 4531.
(35) Montforts, F. P.; Ofner, S. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 632.
(36) Hartzell, S. L.; Rathke, M. W. *Tetrahedron Lett.* **1976**, *17*, 2757.
(37) Harris, B. D.; Bhat, K. L., Joullié, M. M. *Tetrahedron Lett.* **1987**, *28*, 2837.
(38) Damon, R. E.; Luo, T.; Schlessinger, R. H. *Tetrahedron Lett.* **1976**, *17*, 2749.
(39) Jouin, P.; Poncet, J.; Dufour, M. N.; Maugrs, I.; Pantaloni, A.; Castro, B. *Tetrahedron Lett.* **1988**, *29*, 2661.
(40) Turner, J. A.; Jacks, W. S. *J. Org. Chem.* **1989**, *54*, 4229.
(41) Nagao, Y.; Hagiwara, Y.; Tohjo, T.; Hasegawa, Y.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1988**, *53*, 5983.
(42) Neng Kuo, Y.; Yahner, J. A.; Ainsworth, C. *J. Am. Chem. Soc.* **1971**, *93*, 6321.
(43) Krapcho, A. P.; Kashdan, D. S.; Jahngen, E. G. E., Jr. *J. Org. Chem.* **1977**, *42*, 1189.
(44) Angelo, B. *C. R. Acad. Sci.* **1973**, *276*, 293.
(45) Wasserman, H. H.; Wentland, S. H. *J. Chem. Soc. Chem. Commun.* **1970**, 1.
(46) Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 593.
(47) Rathke, M. W.; Sullivan, D. F. *Tetrahedron Lett.* **1973**, *14*, 1279.
(48) Rousseau, G.; Blanco, L. *Tetrahedron Lett.* **1985**, *26*, 4195.
(49) Wissner, A. *J. Org. Chem.* **1979**, *44*, 4617.
(50) Armati, A.; De Ruggeri, P.; Rossi, E.; Stradi, R. *Synthesis* **1986**, 573.
(51) Hayashi, Y.; Wariishi, K.; Mukaiyama, T. *Chem. Lett.* **1987**, 1243.
(52) Saigo, K.; Shimada, S.; Shibasaki, T.; Hasegawa, M. *Chem. Lett.* **1990**, 1093.
(53) Pollet, P. L. *J. Chem. Educ.* **1983**, *60*, 244.
(54) Kende, A. S.; Scholz, D.; Schneider, J. *Synth. Commun.* **1978**, *8*, 59.
(55) Vlassa, M.; Barabàs, A. *J. Prakt . Chem.* **1980**, *322*, 821.
(56) Mansour, T. S. *Synth. Commun.* **1989**, *19*, 659.
(57) Sakai, I.; Ishikawa, M.; Amano, E.; Utaka, M.; Takeda, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2295.
(58) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087.
(59) Oikawa, Y.; Yoshioka, T.; Sugano, K.; Yonemitsu, O. *Org. Synth.* **1985**, *63*, 198.
(60) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783.
(61) Houghton, R. P.; Lapham, D. J. *Synthesis* **1982**, 4510.
(62) Célérier, J. P.; Deloisy, E.; Kapron, P.; Lhommet, G.; Maitte, P. *Synthesis* **1981**, 130.
(63) Breslow, D. S.; Baumgarten, E.; Hauser, C. R. *J. Am. Chem. Soc.* **1944**, *66*,1286.
(64) Bowman, R. E.; Fordham, W. D. *J. Chem. Soc.* **1952**, 3945.
(65) Arsenijevic, V.; Horeau, A. *Bull. Soc. Chim. Fr.* **1959**, 1943.
(66) Schmidt, U.; Schwochau, M. *Monatsh. Chem.* **1967**, *98*, 1492.
(67) Pichat, L.; Beaucourt, J . P. *Synthesis* **1973**, 537.
(68) Trost, B. M.; Kunz, R. A. *J. Org. Chem.* **1974**, *39*, 2648.
(69) Taylor, E. C.; Turchi, I. J. *Org. Prep. Proced. Int.* **1978**, *10*, 221.
(70) Ireland, R. E.; Marshall, J. A. *J. Am. Chem. Soc.* **1959**, *81*, 2907.
(71) Clezy, P. S.; Fookes, C. J. R. *Aust. J. Chem.* **1977**, *30*, 1799.
(72) Pollet, P.; Gelin, S. *Synthesis* **1978**, 142.
(73) Wierenga, N.; Skulnick, H. I. *J. Org. Chem.* **1979**, *44*, 310.
(74) Wierenga, Y.; Skulnick, H. I. *Org. Synth.* **1981**, *61*, 5.
(75) Bram, G.; Vilkas, M. *Bull. Soc. Chim. Fr.* **1964**, 945.
(76) Martel, J.; Blade-Font, A.; Marie, C.; Vivat, M.; Toromanoff, E.; Buendia, J. *Bull. Soc. Chim. Fr.* **1978**, II-1310.
(77) Brooks, D. W.; Lu, L. D. L.; Masamune, S . *Angew. Chem. Int. Ed. Engl.* **1973**, *18*, 72.
(78) Mansour, T. S.; Evans, C. A. *Synth. Commun.* **1990**, *20*, 773.
(79) Barnick, J. W. F. K.; Van der Baan, J. L.; Bickelhaupt, F. *Synthesis* **1979**, 787.
(80) Van der Baan, J. L.; Barnick, J. W. F. K.; Bickelhaupt, F. *Tetrahedron* **1978**, *34*, 223.
(81) Rathke, M. W.; Nowak, M. A. *Synth. Commun.* **1985**, *15*, 1039.
(82) Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. *Synthesis* **1993**, 290.
(83) Bestmann, H. J.; Saalfrank, R. W. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 367.
(84) Bestmann, H. J.; Graf, G.; Hartung, H.; Kolewa, S.; Vilsmaier, E. *Chem. Ber.* **1970**, *103*, 2794.
(85) Bestmann, H. J.; Geismann, C. *Liebigs Ann. Chem.* **1977**, 282.
(86) Sànchez, I. H.; Larraza, M. I.; Breña, F. K.; Cruz, A.; Sotelo, O.; Flores, H. J. *Synth. Commnun.* **1986**, *16*, 299.
(87) Hamper, B. C. *J. Org. Chem.* **1988**, *53*, 5558.
(88) Cooke, M. P., Jr. *J. Org. Chem.* **1982**, *47*, 4963.
(89) Nokami, J.; Kunieda, N.; Kinoshita, M. *Tetrahedron Lett.* **1975**, *16*, 2841.
(90) Pellicciari, R.; Fringuelli, R.; Ceccherelli, P. O.; Sisani, E. *J. Chem. Soc. Chem.Commnun.* **1979**, 959.
(91) Pellicciari, R.; Natalini, B.; Cecchetti, S.; Fringuelli, R. *J. Chem. Soc. Perkin Trans. 1* **1985**, 493.
(92) Holmquist, R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.
(93) Holmquist, R.; Roskamp, E. J. *Tetrahedron Lett.* **1990**, *31*, 4991.
(94) Gossauer, A.; Roebler, F.; Zilch, H.; Ernst, L. *Liebigs Ann. Chem.* **1979**, 1309.
(95) Ireland, R. E.; Brown, F. R., Jr. *J. Org. Chem.* **1980**, *45*, 1868.
(96) Shiosaki, K.; Fels, G.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 3230.
(97) Tsuzuki, K.; Akeyoshi, M.; Omura, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 395.
(98) Lee, D. S.; Chan, T. H.; Kwon, K. S. *Tetrahedron Lett.* **1984**, *25*, 3399.
(99) Mitsudo, T. A.; Watanabe, Y.; Yamashita, M.; Takegami, Y. *Chem.Lett.* **1974**, 1385.
(100) Trost, B. M.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 7910.
(101) Hiyama, T.; Kobayashi, K. *Tetrahedron Lett.* **1982**, *23*, 1597.
(102) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833.
(103) Kobayashi, T.; Tanaka, M. *Tetrahedron Lett.* **1986**, *27*, 4745.
(104) Neghishi, E.; Zhang, Y.; Shimoyama, T.; Wu, G. *J. Am. Chem. Soc.* **1989**, *111*, 8018.
(105) Posner, G. H.; Shulman-Roskes, F. M. *J. Org. Chem.* **1989**, *54*, 3514.
(106) Barhdadi, R.; Gal, J.; Heintz, M.; Troupel, M. *J. Chem. Soc. Chem. Commun.* **1992**, 50.
(107) Kozikowski, A. P.; Goldstein, S . *J. Org. Chem.* **1983**, *48*, 1139.
(108) Tohda, Y.; Kawashima, T.; Ariga, M.; Akiyama, R.; Shudoh, H.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2329.
(109) Kitazume, T.; Kobayashi, T. *J. Fluorine Chem.* **1986**, *31*, 357.
(110) Carlson, R. M.; Isidor, J. L. *Tetrahedron Lett.* **1973**, *14*, 4819.
(111) Trost, B. M.; Lunn, G. *J. Am. Chem. Soc.* **1977**, *99*, 7079.
(112) Le Noble, W. J. *Synthesis* **1970**, 1.
(113) Brändström, A.; Junggren, U. *Acta Chem. Scand.* **1969**, *23*, 2204.
(114) Durst, H. D.; Liebeskind, L. *J. Org. Chem.* **1974**, *39*, 3271.
(115) Fiaud, J. C. *Tetrahedron Lett.* **1975**, *15*, 3495.
(116) Saigo, K.; Koda, H.; Nohira, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3119.
(117) Julià, S.; Ginebreda, A.; Guixer, J.; Tomàs, A. *Tetrahedron Lett.* **1980**, *21*, 3709.
(118) Kirschleger, B.; Queignec, R. *C. R. Acad. Sci. Ser. 2* **1985**, *301*, 143.
(119) Ranu, B. C.; Bhar, S. *J. Chem. Soc. Perkin Trans. 1* **1992**, 365.
(120) Trost, B. M.; Kunz, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 7152.
(121) Takahata, H.; Yamabe, K.; Suzuki, T.; Yamazaki, T. *Heterocycles* **1986**, *24*, 37.
(122) Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2719.
(123) Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *Tetrahedron Lett.* **1984**, *25*, 5677.
(124) Hodgson, A.; Marshall, J.; Hallet, P.; Gallagher, T. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2169.
(125) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Fiecchi, A; Scala, A. *J. Chem. Soc. Chem. Commun.* **1988**, 57.
(126) Kobayashi, M.; Umemura, K.; Watanabe, N.; Matsuyama, H. *Chem. Lett.* **1985**, 1067.
(127) Umemura, K.; Matsuyama, H.; Kobayashi, M.; Kamigata, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3026.
(128) Umemura, K.; Matsuyama, H.; Watanabe, N.; Kobayashi, M.; Kamigata, M. *J. Org. Chem.* **1989**, *54*, 2374.
(129) Badet, B.; Julia, M.; Lefebvre, C. *Bull. Soc. Chim. Fr.* **1984**, 431.
(130) Garst, M.; Mc Bride, B. *J. Org. Chem.* **1983**, *48*, 1362.
(131) Winkler, J. D.; Finck-Estes, M. *Tetrahedron Lett.* **1989**, *30*, 7293.
(132) Dauben, W. G.; Bunce, R. A. *J. Org. Chem.* **1983**, *48*, 4642.
(133) Yamada, F.; Kozikowski, A. P.; Reddy, E. R.; Peng, Y. P.; Miller, J. H.; Mc Kinney, M. *J. Am. Chem. Soc.* **1991**, *113*, 4695.
(134) Jacoby, D.; Célérier, J. P.; Lhommet, P. G. *Synthesis* **1990**, 301.

(135) Fanghänel, E.; Bockelmann, J.; Grossmann, N.; Pfeifer, D. *J. Prakt. Chem.* **1986**, *328*, 724.
(136) Sanner, M. A.; Stansberry, M.; Weigelt, C.; Michne, W. F. *Tetrahedron Lett.* **1992**, *33*, 5287.
(137) Tomioka, K.; Yasuda, K.; Koga, K. *J. Chem. Soc. Chem. Commun.* **1987**, 1345.
(138) Tomioka, K.; Seo, W.; Ando, K.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 6637.
(139) Brünner, H.; Kraus, J.; Lautenschlager, M. J. *Monatsh. Chem.* **1988**, *119*, 1161.
(140) Guignant, A.; Hammami, H. *Tetrahedron: Asymmetry* **1991**, *2*, 411.
(141) Herrmann, J. L.; Kieczylowski, G. R.; Romanet, R. F.; Wepplo, P. J.; Schlessinger, R.H. *Tetrahedron Lett.* **1973**, *14*, 4711.
(142) Oishi, T.; Takechi, H.; Ban, Y. *Tetrahedron Lett.* **1974**, *15*, 3757.
(143) Koppel, G. A.; Kinnick, M. D. *J. Chem. Soc. Chem. Commun.* **1975**, 473.
(144) Stork, G.; Taber, D. F.; Marx, M. *Tetrahedron Lett.* **1978**, *19*, 2445.
(145) Stork, G.; Winkler, J. D.; Saccomano, N. A. *Tetrahedron Lett.* **1983**, *24*, 465.
(146) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Gandolfi, C. *J. Org. Chem.* **1980**, *45*, 4776.
(147) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Polo, E.; Simoni, D. *J. Org. Chem.* **1985**, *50*, 23.
(148) Danishefsky, S.; Hatch, W. E.; Sax, M.; Abola, E.; Pletcher, J. *J. Am. Chem. Soc.* **1973**, *95*, 2410.
(149) Danishefsky, S.; Crawley, S. L.; Solomon, D. M.; Heggs, P. *J. Am. Chem. Soc.* **1971**, *93*, 2356.
(150) Berthiaume, G.; Lavallée, J. F.; Deslongchamps, P. *Tetrahedron Lett.* **1986**, *27*, 5451.
(151) Lavallée, J. F.; Berthiaume, G.; Deslongchamps, P.; Grein, F. *Tetrahedron Lett.* **1986**, *28*, 5455.
(152) Lavallée, J. F.; Deslongchapms, P. *Tetrahedron Lett.* **1987**, *28*, 3457.
(153) Langström, B.; Bergson, G. *Acta Chem. Scand.* **1973**, *27*, 3118.
(154) Kobayashy, N.; Iwai, K. *J. Am. Chem. Soc.* **1978**, *100*, 7071.
(155) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238.
(156) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc. Chem. Commun.* **1981**, 625.
(157) Hodge, P.; Khoshdel, E.; Waterhouse, J. *J. Chem. Soc. Perkin Trans. 1* **1983**, 2205.
(158) Brunner, H.; Hammer, B. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 312.
(159) Tomioka, K.; Ando, K.; Yasuda, K.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 715.
(160) Skeean, R. W.; Trammell, G. L.; White, J. D. *Tetrahedron Lett.* **1976**, *17*, 525.
(161) Sum, F. W.; Weiler, L. *Tetrahedron Lett.* **1979**, *20*, 707.
(162) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742.
(163) Van Tamelen, E. E.; Jih Ru, H.; Leiden, T. M. *J. Chem. Soc. Chem. Commun.* **1983**, 62.
(164) Jackson, W. P.; Ley, S. V.; Morton, J. A. *J. Chem. Soc. Chem. Commun.* **1980**, 1028.
(165) Jackson, W. P.; Ley, S. V.; Whittle, A. J. *J. Chem. Soc. Chem. Commun.* **1980**, 1173.
(166) Ley, S. V.; Lygo, B.; Molines, H.; Morton, J. A. *J. Chem. Soc. Chem. Commun.* **1982**, 1251.
(167) Ley, S. V.; Murray, P. J. *J. Chem. Soc. Chem. Commun.* **1982**, 1252.
(168) Angle, S. R.; Louie, M. S. *Tetrahedron Lett.* **1989**, *30*, 5741.
(169) Veronese A. C.; Callegari, R.; Bertazzo, A. *Heterocycles* **1991**, *32*, 2205.
(170) Sartori, G.; Bigi, F.; Tao, X.; Casnati, G.; Canali, G. *Tetrahedron Lett.* **1992**, *33*, 4771.
(171) Williams, R. M.; Esslinger, C. S. *Tetrahedron Lett.* **1991**, *32*, 3635.
(172) Funk, R. L.; Fitzgerald, J. F.; Olmstead, T. A.; Para, K. S.; Wos, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 8849.
(173) Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 1475.
(174) Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 3393.
(175) Tsuji, J.; Okumoto, H.; Kobayashi, T.; Takahashi, T. *Tetrahedron Lett.* **1981**, *22*, 1357.
(176) Kobayashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1981**, *22*, 4295.
(177) Yamamoto, K.; Tsuji, J. *Tetrahedron Lett.* **1982**, *23*, 3089.
(178) Godleski, S. A.; Valpey, R. S. *J. Org. Chem.* **1982**, *47*, 381.
(179) Trost, B. M.; Runge, T. A.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 2840.
(180) Gravel, D.; Benoit, S.; Kumanovic, S.; Sivaramakrishnan, H. *Tetrahedron Lett.* **1992**, *33*, 1403.
(181) Gravel, D.; Benoit, S.; Kumanovic, S.; Sivaramakrishnan, H. *Tetrahedron Lett.* **1992**, *33*, 1407.
(182) Minami, I.; Ohashi, Y.; Shimizu, I.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 2449.
(183) Minami, I.; Shimizu, I.; Tsuji, J. *J. Organomet. Chem.* **1985**, *296*, 269.
(184) Hori, Y.; Mitsudo, T.; Watanabe, Y. *Tetrahedron Lett.* **1986**, *27*, 5389.
(185) Tsuji, J.; Yuhara, M.; Minato, M.; Yamada, H.; Sato, F.; Kobayashi, Y. *Tetrahedron Lett.* **1988**, *29*, 343.
(186) Bergbreier, D. E.; Weathford, D. A. *J. Chem. Soc. Chem. Commun.* **1989**, 883.
(187) Masuyama, Y.; Yamada, K.; Kurusu, Y. *Tetrahedron Lett.* **1987**, *28*, 443.
(188) Corey, E. J.; Myung-Chol, K. *J. Am. Chem. Soc.* **1984**, *106*, 5384.
(189) Snider, B. B.; Mohan, R.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659.
(190) Mohan, R.; Kates, S. A.; Dombroski, M. A.; Snider, B. B. *Tetrahedron Lett.* **1987**, 845.
(191) Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 2427.
(192) Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1987**, *28*, 175.
(193) Yang, F. Z.; Trost, B. K.; Fristad, W. K. *Tetrahedron Lett.* **1987**, *28*, 1493.
(194) Breuilles, P.; Uguen, D. *Tetrahedron Lett.* **1990**, *31*, 357.
(195) Iqbal, J.; Srivastava, R. R.; Khan, M. A. *Tetrahedron Lett.* **1990**, *31*, 1485.
(196) Bihovsky, M. U.; Kumar, S. D.; Goyal, A. *J. Org. Chem.* **1989**, *54*, 4291.
(197) Regitz, M. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 733.
(198) Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 179.
(199) Balli, H.; Löw, R. *Tetrahedron Lett.* **1966**, *7*, 5821.
(200) Roush, W. R.; Feitler, D.; Rebek, J. *Tetrahedron Lett.* **1974**, *15*, 1391.
(201) Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610.
(202) Kokel, B.; Boussouira, N. *J. Heterocycl. Chem.* **1987**, *24*, 1493.
(203) McGuiness, M.; Shecher, H. *Tetrahedron Lett.* **1990**, *31*, 4987.
(204) Tunemoto, D.; Araki, N.; Kondo, K. *Tetrahedron Lett.* **1977**, *18*, 109.
(205) Taber, D. F. *J. Org. Chem.* **1977**, *42*, 3513.
(206) Trost, B. M.; Taber, D. F.; Alper, J. B. *Tetrahedron Lett.* **1976**, *17*, 3857.
(207) Kondo, K.; Umemoto, T.; Takahatake, Y.; Tunemoto, D. *Tetrahedron Lett.* **1977**, *18*, 113.
(208) Kondo, K.; Umemoto, T.; Yako, K.; Tunemoto, D. *Tetrahedron Lett.* **1978**, *19*, 3927.
(209) Clark, R. D.; Heathcock, C. H. *Tetrahedron Lett.* **1975**, *16*, 529.
(210) Chen, E. Y. *J. Org. Chem.* **1984**, *49*, 3245.
(211) Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699.
(212) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssié, P. *J. Chem. Soc. Chem. Commun.* **1981**, 688.
(213) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808.
(214) Taber, D. F.; Ruckle, R. E., Jr. *Tetrahedron Lett.* **1985**, *26*, 3059.
(215) Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.
(216) Taber, D. F.; Xaman, K. *J. Am. Chem. Soc.* **1983**, *105*, 5935.
(217) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 5173.
(218) Doyle, M. P.; Bagheri, V.; Pearson, M. M.; Edwards, J. D. *Tetrahedron Lett.* **1989**, *30*, 7001.
(219) Hrytsak, M.; Durst, T. *J. Chem. Soc. Chem. Commun.* **1987**, 1150.
(220) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31.
(221) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.
(222) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 1193.
(223) Melillo, D. C.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783.
(224) Yamamoto, S.; Itani, H.; Takahashi, H.; Tsuji, T.; Nagata, W. *Tetrahedron Lett.* **1984**, 25, 4545.
(225) Moody, C. J.; Pearson, C. J.; Lawton, G. *Tetrahedron Lett.* **1985**, *26*, 3171.
(226) Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 113.
(227) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223.
(228) Heslin, J. C.; Moody, C. J.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron Lett.* **1986**, *27*, 1403.
(229) Moody, C. J.; Taylor, R. J. *Tetrahedron Lett.* **1987**, *28*, 5351.
(230) Moody, C. J.; Taylor, R. J. *J. Chem. Soc. Perkin Trans. 1* **1989**, 721.
(231) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060.
(232) Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358.
(233) Davies, H. M. L.; Crisco, L. van T. *Tetrahedron Lett.* **1987**, *28*, 371.
(234) Büchi, G.; Matsumoto, K. E.; Nishimura, H. *J. Am. Chem. Soc.* **1971**, *93*, 3299.
(235) Ando, M.; Büchi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880.
(236) Irie, H.; Katakawa, J.; Tomita, M.; Mizumo, Y. *Chem. Lett.* **1981**, 637.
(237) Wasserman, H. H.; Pickett, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 4695.

(238) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *Tetrahedron Lett.* **1985**, *26*, 3563.
(239) Lee, J.; Oya, S.; Snyder, J. K. *Tetrahedron Lett.* **1991**, *32*, 5899.
(240) Hewson, A. T.; MacPherson, D. T. *Tetrahedron Lett.* **1983**, *24*, 647.
(241) Hewson, A. T.; MacPherson, D. T. *J. Chem. Soc. Perkin Trans. I* **1985**, 2625.
(242) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
(243) Marx, J. N.; Minaskanian, G. *J. Org. Chem.* **1982**, *47*, 3306.
(244) Hoffman, R. V.; Kim, H. O.; Wilson, A. L. *J. Org. Chem.* **1990**, *55*, 2820.
(245) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; Van Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371.
(246) Schank, K.; Lick, C. *Synthesis* **1983**, 392.
(247) Wasserman, H. H.; Rotello, V.; Williams, D. R.; Benbow, J. W. *J. Org. Chem.* **1989**, *54*, 2785.
(248) Wasserman, H. H.; Vu, C. B. *Tetrahedron Lett.* **1990**, *31*, 5205.
(249) Wasserman, H. H.; Lombardo, L. J. *Tetrahedron Lett.* **1989**, *30*, 1725.
(250) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D.; Marini, F. *J. Org. Chem.* **1991**, *56*, 5207.
(251) Ohmori, H.; Maeda, H.; Tamaoka, M.; Masui, M. *Chem. Pharm. Bull.* **1988**, 36, 613.
(252) Boehme, W. R. *Organic Syntheses*; Wiley: New York, 1960; Collect. Vol. IV, p 590.
(253) Inukai, N.; Iwamoto, H.; Tamura, I.; Yanagisawa, Y.; Ishii, Y.; Murakami, M. *Chem. Pharm. Bull.* **1976**, *24*, 820.
(254) Lerman, O.; Rozen, S. *J. Org. Chem.* **1983**, *48*, 724.
(255) Machleidt, H. *Justus Liebigs Ann. Chem.* **1964**, *676*, 66; *Chem. Abstr.* **1965**, 62, 436e.
(256) Purrington, S. T.; Jones, W. A. *J. Org. Chem.* **1983**, *48*, 761.
(257) Banks, R. E.; Du Boisson, R. A.; Tsiliopoulos, E. *J. Fluorine Chem.* **1986**, *32*, 461.
(258) Barnette, W. E. *J. Am. Chem. Soc.* **1984**, *106*, 452.
(259) Umemoto, T.; Kawada, K.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 4465.
(260) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *29*, 6087.
(261) McCurry, P. M., Jr; Abe, K. *Tetrahedron Lett.* **1973**, *14*, 4103.
(262) Dolby, L. J.; Elliger, C. A.; Esfandiari, S.; Marshall, K. S. *J. Org. Chem.* **1968**, *33*, 4508.
(263) Coates, R. M.; Hobbs, S. J. *J. Org. Chem.* **1984**, *49*, 140.
(264) Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722.
(265) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7559.
(266) Xie, Z. F.; Sakai, K. *J. Org. Chem.* **1990**, *55*, 820.
(267) Bruggink, A.; McKillop, A. *Tetrahedron* **1975**, *31*, 2607.
(268) Moriarty, R. M.; Prakash, O.; Vaid, R. K.; Zhao, L. *J. Am. Chem. Soc.* **1989**, *111*, 6443.
(269) Pearson, A. J.; Raithby, P. R. *J. Chem. Soc. Perkin Trans. 1* **1980**, 395.
(270) Pearson, A. J. *J. Chem. Soc. Perkin Trans. 1* **1980**, 400.
(271) Nakashita, Y.; Hesse, M. *Helv. Chim. Acta* **1983**, *66*, 845.
(272) Moloney, M. G.; Pinhey, J. T. *J. Chem. Soc. Chem. Commun.* **1984**, 965.
(273) Moloney, M. G.; Pinhey, J. T.; Roche, E. E. *Tetrahedron Lett.* **1986**, *27*, 5025.
(274) Moloney, M. G.; Pinhey, J. T.; Roche, E. E. *J. Chem. Soc. Perkin Trans. 1* **1989**, 333.
(275) Parkinson, C. J.; Pinhey, J. T.; Stoermer, M. J. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1911.
(276) Hashimoto, S.; Miyazaki, Y.; Shinoda, T.; Ikegami, S. *J. Chem. Soc. Chem. Commun.* **1990**, 1100.
(277) Hashimoto, S.; Miyazaki, Y.; Shinoda, T.; Ikegami, S. *Tetrahedron Lett.* **1989**, *30*, 1100.
(278) Mérour, J. Y.; Chichereau, L.; Finet, J. P. *Tetrahedron Lett.* **1992**, *33*, 3867.
(279) Taber, D. F.; Amedio, J. C., Jr; Sherrill, R. G. *J. Org. Chem.* **1986**, *51*, 3382.
(280) Montgomery, J.; Wieber, G. M.; Hegedus, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 6255.
(281) Choi, E. B.; Youn, I. K.; Pak, C. S. *Synthesis* **1988**, 792.
(282) Shriner, R. L.; Schmidt, A. G.; Roll, L. J. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, pp 266.
(283) Guha, M.; Nasipuri, D. *Org. Synth.* **1962**, *42*, 41.
(284) Viscontini, M.; Merckling, N. *Helv. Chim. Acta* **1952**, *35*, 2280.
(285) Suzuki, E.; Inoue, S. *Synthesis* **1975**, 259.
(286) Rathke, M. W.; Cowan, P. J. *J. Org. Chem.* **1985**, *50*, 2622.
(287) Singh, B.; Lesher, G. Y. *Synthesis* **1978**, 829.
(288) Sakai, T.; Miyata, K.; Ishikawa, M.; Takeda, A. *Tetrahedron Lett.* **1985**, *26*, 4727.
(289) Mulholland, T. P. C.; Foster, R.; Haydock, D. B. *J. Chem. Soc. Perkin Trans 1* **1972**, 1225.
(290) Jones, R. C. F.; Sumaria, S. *Tetrahedron Lett.* **1978**, *19*, 3173.
(291) Tanaka, K.; Matsuo, K.; Nakaizumi, Y.; Morioka, Y.; Takashita, Y.; Tachibana, Y.; Sawamura, Y.; Kohda, S. *Chem. Pharm. Bull.* **1979**, *27*, 1901.
(292) Bloomer, J. L.; Kappler, F. E. *Tetrahedron Lett.* **1973**, *14*, 163.
(293) Bloomer, J. L.; Kappler, F. E. *J. Org. Chem.* **1974**, *39*, 113.
(294) Takeda, K.; Kubo, H.; Koizumi, T.; Yoshii, E. *Tetrahedron Lett.* **1982**, *23*, 3175.
(295) Nomura, K.; Hori, K.; Arai, M.; Yoshii, E. *Chem. Pharm. Bull.* **1986**, *34*, 5188.
(296) Clemo, N. G.; Pattenden, G. *Tetrahedron Lett.* **1982**, *23*, 581.
(297) Miyata, O.; Schmidt, R. R. *Tetrahedron Lett.* **1982**, *23*, 1793.
(298) Harris, T. M.; Harris, C. M. *Org. React.* **1969**, *17*, 155.
(299) Wolfe, J. F.; Harris, T. M.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3249.
(300) Huckin, S. N.; Weiler; L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(301) Huckin, S. N.; Weiler, L. *Tetrahedron Lett.* **1971**, *12*, 4835.
(302) Izawa, T.; Mukaiyama, T. *Chem. Lett.* **1975**, 161.
(303) Izawa, T.; Mukaiyama, T. *Chem. Lett.* **1974**, 1189.
(304) Kucherov, V. F.; Yufit, S. S. *Chem. Abstr.* **1961**, *55*, 9273, 15395.
(305) Yamaguchi, M.; Shibato, K.; Hirao, I. *Chem. Lett.* **1985**, 1145.
(306) Hanamoto, T.; Hiyama, T. *Tetrahedron Lett.* **1988**, *29*, 6467.
(307) Chan, T. H.; Brownbridge, P. *J. Chem. Soc. Chem. Commun.* **1979**, 578.
(308) Schlessinger, R. H.; Poss, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 357.
(309) Schlessinger, R. H.; Bebernitz, G. R.; Lin, P.; Poss, A. J. *J. Am. Chem. Soc.* **1985**, *107*, 1777.
(310) Schlessinger, R. H.; Poss, M. A.; Richardson, S. *J. Am. Chem. Soc.* **1986**, *108*, 3112.
(311) Schlessinger, R. H.; Iwanowicz, E. J.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 3070.
(312) Schlessinger, R. H.; Tata, J. R.; Springer, J. P. *J. Org. Chem.* **1987**, *52*, 708.
(313) Nazarov, I. N.; Zavyalov, S. I. *Chem. Abstr.* **1954**, *48*, 13667*h*.
(314) Stork, G.; Guthikonda, R. *Tetrahedron Lett.* **1972**, *13*, 2755.
(315) Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, *54*, 4717.
(316) Pietrusiewicz, K. M.; Monkiewicg, J. *Tetrahedron Lett.* **1986**, *27*, 739.
(317) Bodalski, X.; Pietrusiewicz, K. M.; Monkiewicz, J.; Koszuk, J. *Tetrahedron Lett.* **1980**, *21*, 2287.
(318) Van den Goorbergh, J. A. M.; Van der Gen, A. *Tetrahedron Lett.* **1980**, *21*, 3621.
(319) Edwards, J. A.; Schwarz, V.; Fajkos, J.; Maddox, M. L.; Fried, J. H. *J. Chem. Soc. Chem. Commun.* **1971**, 292.
(320) Troostwijk, C. B.; Kellog, R. M. *J. Chem. Soc. Chem. Commun.* **1977**, 932.
(321) Sheffy, F. K.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7173.
(322) Evans, E. H.; Hewson, A. T.; Wadsworth, A. H. *Synth. Commun.* **1985**, *15*, 243.
(323) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 96.
(324) Corey, E. J.; Munroe, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 6129.
(325) Stodola, F. H. *J. Org. Chem.* **1964**, *29*, 2490.
(326) Fairhurst, J.; Horwell, D. C. *Synth. Commun.* **1976**, *6*, 89.
(327) Boese, A. B., Jr. *Ind. Eng. Chem.* **1940**, *32*, 16.
(328) Kimel, W.; Cope, A. C. *J. Am. Chem. Soc.* **1943**, *65*, 1992.
(329) Lawesson, S. O.; Gronwall, S.; Sandberg, R. *Org. Synth.* **1962**, *42*, 28.
(330) Mauz, O. *Liebigs Ann. Chem.* **1974**, 345.
(331) Kato, T.; Chita, T. *Chem. Pharm. Bull.* **1975**, *23*, 2263.
(332) Nudelman, A.; Kelner, R.; Broide, N.; Gottlich, H. E. *Synthesis* **1989**, 387.
(333) Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241.
(334) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431.
(335) (a) Carroll, H. F.; Bader, A. R. *J. Am. Chem. Soc.* **1952**, *74*, 6036. (b) Carroll, H. F.; Bader, A. R. *J. Am. Chem. Soc.* **1953**, *75*, 5400.
(336) Bader, A.; Cummings, L. O.; Vogel, H. A. *J. Am. Chem. Soc.* **1951**, *73*, 4195.
(337) Taber, D. F.; Amedio, J. C., Jr; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618.
(338) Gilbert, J. C.; Kelly, T. A. *J. Org. Chem.* **1988**, *53*, 449.
(339) Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383.
(340) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307.
(341) Shimizu, I.; Ishii, H.; Tasaka, A. *Chem. Lett.* **1989**, 1127.
(342) Witzeman, J. S. *Tetrahedron Lett.* **1990**, *31*, 1401.
(343) Julia, M. *Annu. Chim.* **1950**, 635.
(344) Pochat, F.; Levas, E. *Bull. Soc. Chim. Fr.* **1972**, 3151.
(345) Hayakawa, K.; Ueyama, K.; Kanematsu, K. *J. Chem. Soc. Chem. Commun.* **1984**, 71.
(346) Miller, R. D. *Tetrahedron Lett.* **1987**, *28*, 1039.
(347) Ley, S. V.; Woodward, P. R. *Tetrahedron Lett.* **1987**, *28*, 345.
(348) Smith, A. B., III; Levenberg, P. A. *Synthesis* **1981**, 567.
(349) Touzin, A. M. *Tetrahedron Lett.* **1975**, *16*, 1477.
(350) Nakata, T.; Fukui, M.; Ohtsuka, H.; Oishi, T. *Tetrahedron* **1984**, *40*, 2225.
(351) Taber, D. F.; Amedio, J. C., Jr.; Kang-Yeoun, J. *J. Org. Chem.* **1987**, *52*, 5621.
(352) Miocque, M.; Hung, N. M.; Yen, V. O. *Annu. Chim.* **1963**, *8*, 157.
(353) Hudrlik, P. F., Hudrlik, A. M. *The Chemistry of the Carbon-Carbon Triple Bond*; Patai, S., Ed.; Wiley: New York, 1978; Part 1, p 199.
(354) Ishino, Y.; Nishiguchi, I.; Nakao, S.; Hirashima, T. *Chem. Lett.* **1981**, 641.
(355) Stamhuis, E. J. *Enamines: Synthesis, Structure and Reactions*; Cook, A. G., Ed.; Marcel Dekker: New York, 1969; p 101.

(356) Shibasaki, K; Nishida, A.; Ikegami, S. *Tetrahedron Lett.* **1982**, *23*, 2875.
(357) Crout, D. H. G.; Rathbone, D. L. *Synthesis* **1989**, 40.
(358) Crabbé, P.; Carpio, H.; Velarde, E. *J. Chem. Soc. Chem. Commun.* **1971**, 1028.
(359) Tam, S. Y. K.; Klein, R. S.; Fox, J. J.; De las Heras, F. G. *J. Org. Chem.* **1979**, *44*, 4854.
(360) Tsuji, J.; Nagashima, H.; Hori, K. *Chem. Lett.* **1980**, 257.
(361) Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42*, 459.
(362) Wenkert, E.; Ceccherelli, P.; Fugiel, R. A. *J. Org. Chem.* **1978**, *43*, 3983.
(363) Nagao, K.; Chiba, M.; Kim, S. W. *Synthesis* **1983**, 197.
(364) Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 248.
(365) Brandänge, S.; Rodriguez, B. *Acta Chem. Scand.* **1987**, 740.

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