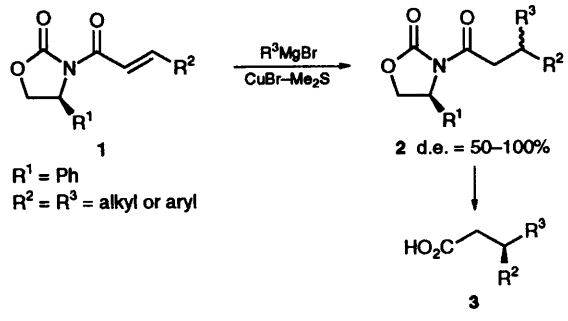
Carboxylic acids and esters

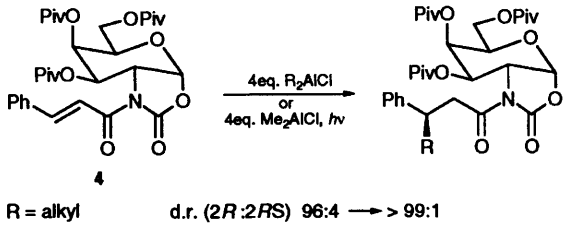
T. HARRISON AND T. LADUWAHETTY

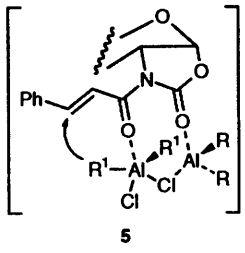
Merck Sharp and Dohme, Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR, UK

Reviewing the literature published between 1 January 1993 and 31 July 1994



Scheme 1





Scheme 2

1 Introduction

This review only covers the literature pertaining to carboxylic acids, and to carboxylic esters and some of their simple derivatives. The chemistries associated with amides and amino acids, and also lactones and macrolides are covered in separate articles in *Contemporary Organic Synthesis.*

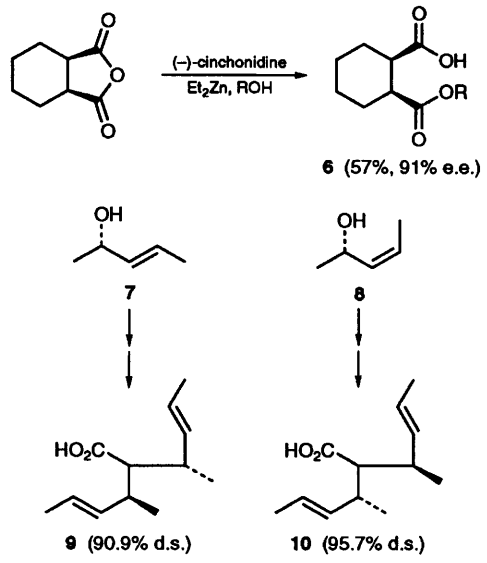
2 Carboxylic acids

2.1 Asymmetric syntheses

Conjugate addition reactions of copper-catalysed Grignard reagents to the 4-phenyloxazolidinone **1** proceed with good to excellent diastereoselectivity to afford the adducts **2** which after hydrolysis provide the β,β'-disubstituted carboxylic acids **3** (**Scheme 1**) in 90–100% yield.[1] The reactions involve initial complexation of the dicarbonyl system in **1** by the metal cation, with the incoming nucleophile approaching *anti* to the phenyl group.

The bicyclic carbohydrate-derived oxazolidinone **4** is also a useful chiral auxiliary for the synthesis of homochiral β,β'-disubstituted carboxylic acids.[2] Organoaluminium reagents undergo conjugate additions to **4** with excellent facial selectivity (**Scheme 2**). The authors rationalize their results in terms of the bis-organoaluminium intermediate **5** where the chloride bridge apparently enhances the electron density of the aluminium near the double bond, resulting in a [1*s*,5*s*] sigmatropic shift of the alkyl group.

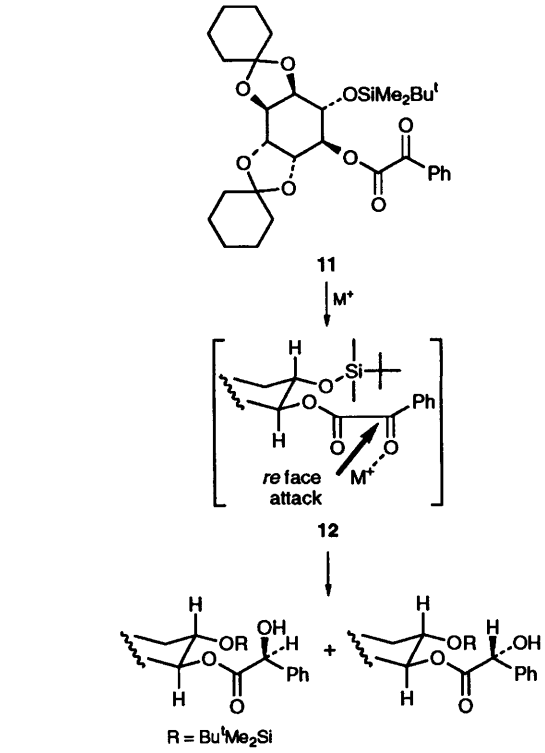
Moderate enantioselectivity in the desymmetrization of *meso*-dicarboxylic anhydrides has been observed when certain substrates are treated with an alcohol in the presence of (−)-cinchonidine and diethylzinc (**Scheme 3**).[3] The enantioselectivity is attributed to one of the enantiotopic carbonyl groups complexing to a metallocycle formed between the alkaloid and the zinc reagent. In the absence of diethylzinc the alkaloid gives the product **6** in only 8% e.e.



Scheme 3

A diastereoselective method for preparing homochiral 2,7-nonadiene-5-carboxylic acids, such as **9** and **10**, involves an iterative Claisen rearrangement starting with the secondary alcohols **7** and **8** which in turn are available from (−)-ethyl lactate.[4] The [3,3] sigmatropic rearrangements proceed through the expected chair transition state to provide the carboxylic acids in > 90% d.s.

Reduction of the α-keto ester **11** (**Scheme 4**) derived from the corresponding chiral cyclitol is a means of obtaining α-hydroxy acids with excellent enantiomeric purity.[5] The alcohol obtained is the product resulting from attack on the *re* face in the chelated transition state **12** where the ester exists in an *s-cis* configuration. There is a complete reversal of facial selectivity in the presence of 18-crown-6 in THF where the product resulting from attack on the *si* face predominates. This interesting result is quoted as one of the first examples in the literature where both antipodes of a compound are obtained from the same substrate under different conditions.



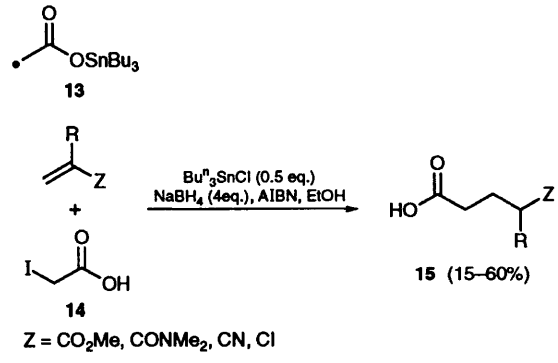
Scheme 4

Improvements in the enantioselective enzymatic hydrolyses of chiral esters in organic solvents are observed in the presence of a crucial amount of a base such as pyrrolidine.[6] The presence of the base increases the solubility of the acids in water saturated organic solvents. The formation of an ion pair with the carboxylic acid which is produced leads to the formation of a second phase in the reaction which also facilitates the isolation of the product. The background chemical hydrolysis, which occurs under aqueous conditions, resulting in the lowering of the e.e.'s, is also prevented in organic solvents.

Amides obtained by the coupling of racemic carboxylic acids, such as 2-tetrahydrofuran carboxylic acid, with amino acids can be separated by distillation. Hydrolysis of the individual diastereoisomers then leads to optically pure carboxylic acids.[7]

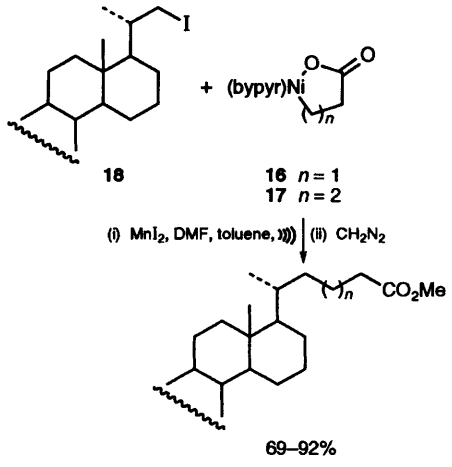
2.2 Homologation reactions

Whilst the trialkyltin ester radical **13** adds only to electron-rich olefins, the radical derived from **14** participates in Michael-type reactions with electron-deficient double bonds to give the homologated acids **15** in moderate yield (**Scheme 5**).[8] Since the dianion of acetic acid adds to acrylate esters to give only 1,2-addition products, this methodology is a useful alternative.



Scheme 5

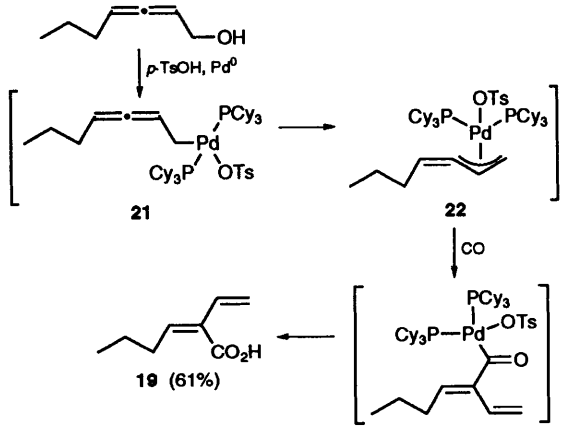
The nickel-acycles **16** and **17**, synthesized from (2,2-bipyridyl)(cycloocta-1,5-diene)-nickel(0) and succinic or glutaric anhydrides (**Scheme 6**), are useful homoenolate synthons.[9] They react with the relatively hindered primary iodide **18** in the presence of



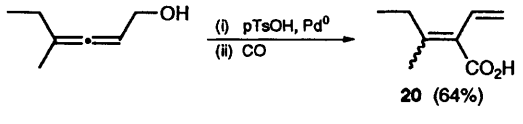
Scheme 6

manganese iodide to give the homologated steroid in one step. The reaction is vastly improved by exposure to ultrasound.

Carbonylations of primary allenyl alcohols to give α-vinyl acrylic acids can be achieved in the presence of $[(Cy_3P)_2Pd(H)(H_2O)]BF_4$, an air-stable source of Pd^0.[10] A variety of disubstituted dienoic acids such as **19** are isolated in 61–74% yield with exclusively (*E*)-geometry (**Scheme 7**). Trisubstituted acids such as **20** are obtained in 43%–64% yield as mixtures of double bond isomers (**Scheme 8**).



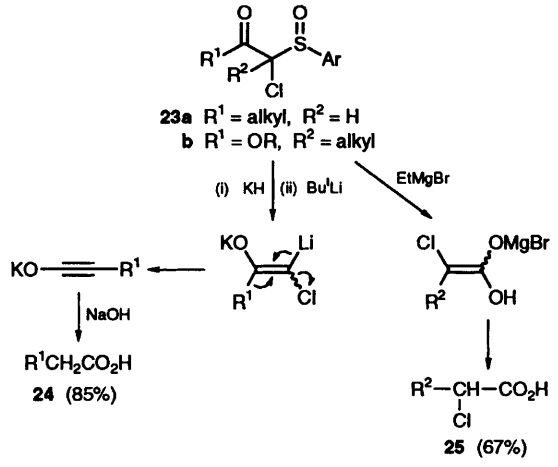
Scheme 7



Scheme 8

p-Toluenesulfonic acid is necessary to protonate the starting alcohol, which is displaced by the Pd^0 species to form a π-allenyl Pd complex such as **21**. Rearrangement of **21** to the corresponding π-allyl species **22**, followed by CO insertion, then leads to the conjugated diene **19**.

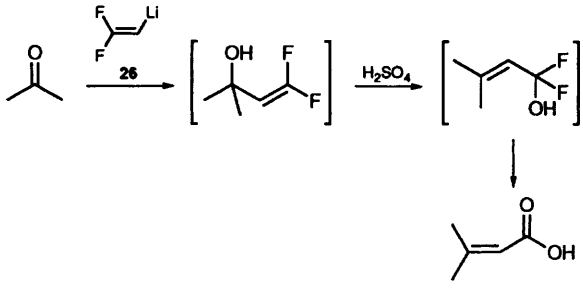
One-carbon homologations of esters to the corresponding acids **24** or α-chloro carboxylic acids **25** can be achieved via the chloro-sulfoxide adduct **23** (**Scheme 9**).[11,12] Initial enolization of **23a** with KH, followed by ligand exchange with Bu^{t}Li results in rearrangement to give **24**, while direct ligand exchange on **23b** with EtMgBr leads to **25**.



Scheme 9

Ketones can be homologated smoothly to give α,β-unsaturated carboxylic acids using the difluorovinyl-lithium reagent **26** (**Scheme 10**).[13]

Trichloroalcohols obtained from aldehydes using the Corey methodology can be converted into α-fluoro-carboxylic acids in 76–100% yields using CsF together wtih Bu^n_4NF.[14] The use of alternative fluoride sources, including CsF and Bu^n_4NF, independently give significant amounts of the chloro carboxylic acid.



Scheme 10

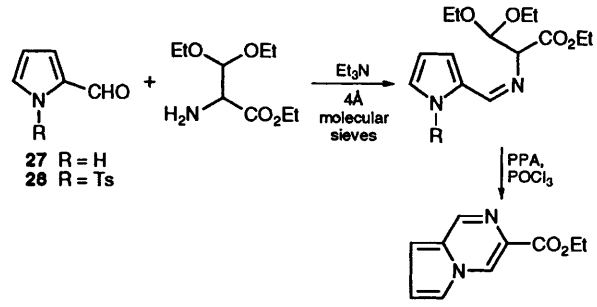
2.3 Acids from esters and amides

An extensive review of methods for the chemical deprotection of the ester functional group has been undertaken by Masceretti *et al.*[15] Primary amides or *O*-methyl hydroxamates can be hydrolysed to the corresponding acids under mild conditions by treatment with catalytic $TiCl_4$ [or $Ti(OR)_4$] and one equivalent of HCl.[16] Strongly acidic or basic conditions that are traditionally used for such transformations result in racemization of adjacent chiral centres.

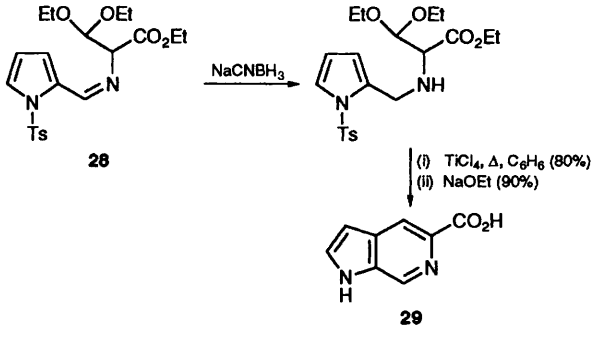
Neutral or acidic alumina, when subjected to microwave irradiation, can hydrolyse benzyl esters in the presence of a variety of other protecting groups, including benzyl ethers.[17]

2.4 Heterocyclic carboxylic acids

Pyrazine formation (**Scheme 11**) is a problem encountered in the direct cyclization of pyrroles **27** or **28** to 6-azaindole-5-carboxylic acid **29**, but can be circumvented by initial reduction of the intermediate imine (**Scheme 12**).[18] The amine thus obtained can be cyclized successfully under Lewis acidic conditions to give **29** in excellent yield after deprotection.

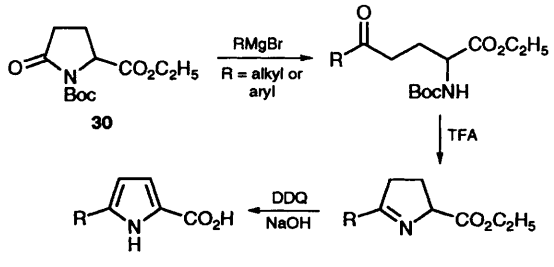


Scheme 11



Scheme 12

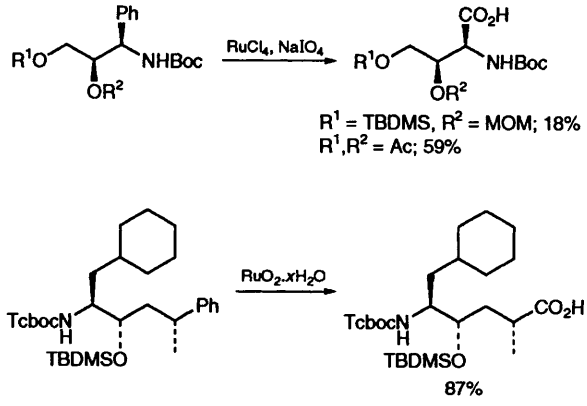
The existing methods for the syntheses of 5-substituted pyrrole carboxylic acids are hampered by the need for starting materials which pose special handling problems. A new route to such compounds involves the ring-opening of the lactam **30**, and deprotection of the Boc-protected amine, followed by oxidation of the resulting imine ion (**Scheme 13**).[19]



Scheme 13

2.5 Carboxylic acid synthons

A phenyl group can be successfully oxidized to a carboxylic acid (**Scheme 14**) under mild conditions without loss of stereochemical integrity. Whilst the Sharpless methodology employing $RuCl_3$–$NaIO_4$ appears to be successful only when the oxygen protecting groups are electron withdrawing esters,[20(a)] Jones *et al.* have found that $RuO_2.xH_2O$ provide an excellent yield of the carboxylic acid even in the absence of electron-withdrawing protecting groups.[20(b)]



Scheme 14

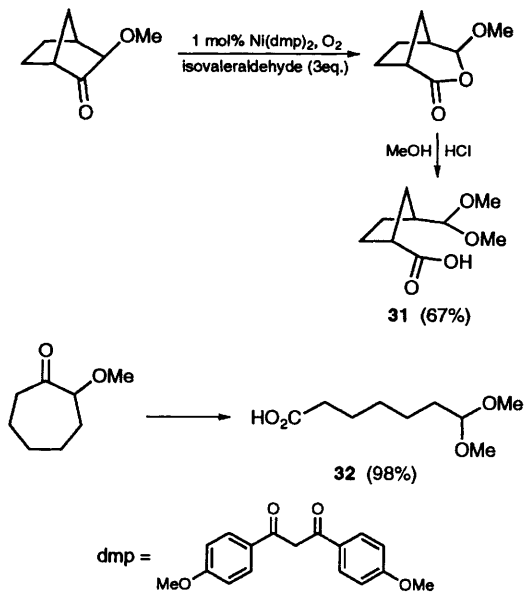
2.6 Miscellaneous substituted carboxylic acids

Amino acids can be oxidized to the corresponding nitro carboxylic acids with the powerful oxygen transfer reagent HOF.MeCN, obtained by bubbling fluorine through aqueous acetonitrile.[21] Despite the fact that this reagent can oxidize aromatic rings, especially activated ones, the very short reaction time (5 min.) ensures selective oxidation of the amine. Serine is oxidized to the corresponding nitro derivative in 70% yield, establishing that even primary hydroxyl groups are stable. Remote chiral centres are also not racemized under these strong oxidizing conditions.

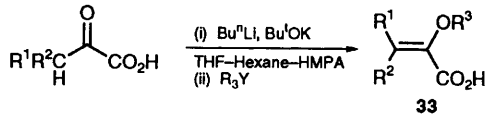
α-Alkoxy cyclic ketones can be converted into the corresponding acetal lactones when treated with $Ni(dmp)_2$ in the presence of oxygen and an aldehyde (**Scheme 15**).[22] These acetal lactones can be ring-opened under acidic conditions to obtain carboxylic acid-acetals, such as **31** and **32**.

α-Alkoxyacrylic acids **33**, which have previously required several steps to synthesize, can be obtained by simply treating α-keto acids with Lochman's base (Bu^nLi/Bu^tOK) in the presence of an alkylating agent (**Scheme 16**).[23] The reaction is limited to small alkyl groups, such as methyl and ethyl, and higher yields are obtained by using the dialkyl sulfate rather than the alkyl triflates or bromides. Increasing substitution on the acid leads to a dramatic reduction in yield.

Although *trans*-substituted cyclopropane carboxylic acids, such as **35**, are available through a variety of synthetic methods, cyclization of the cyano epoxide **34**

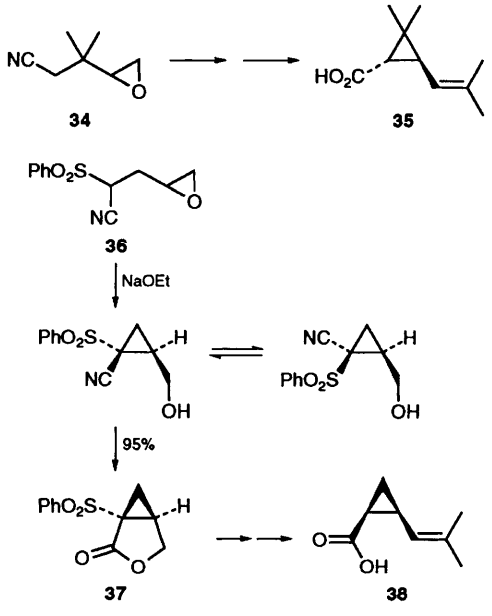


Scheme 15



Scheme 16

being one, the methods for the synthesis of *cis*-cyclopropane carboxylic acids such as **38** are more rare. Activation of a cyano epoxide by a sulfonyl group, as in **36**, followed by intramolecular cyclization provides a novel means of obtaining the *cis*-substituted carboxylic acid via the corresponding lactone **37** (**Scheme 17**).[24]



Scheme 17

Oxidations of alcohols to carboxylic acids by $Pd(OAc)_2$ in the presence of Pd–C and O_2 in a Wacker-type process[25] and the oxidation of aryl/heteroaryl aldehydes to carboxylic acids with hydrogen peroxide in formic acid at low temperatures,[26(a)] have also been reported.

The combination of a catalytic amount of OsO_4 and stoichiometric Jones reagent is an efficient, mild method for the oxidative cleavage of alkenes to carboxylic acids.[26(b)] The reaction can be performed on multigram scale and furthermore allows for the presence of basic amines.

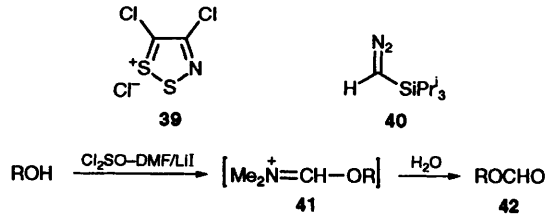
3 Carboxylic acid esters

3.1 General synthesis

The search for simple, mild procedures for the esterification of carboxylic acids continues. Thus, Weinreb *et al.*[27] have reported that esters are generated in good yields under mild conditions from carboxylic acids and alcohols in the presence of Appel's salt (4,5-dichloro-1,2,3-dithiazolium chloride, **39**). This route is mechanistically similar to the 2-halopyridinium salt methodology developed by Mukaiyama.[28] Esters are also formed in excellent yields from near equimolar amounts of free carboxylic acids and alcohols at room temperature by the combined use of 4-(trifluoromethyl)benzoic anhydride and a catalytic amount of active Ti^{IV} salt together with chlorotrimethylsilane.[29] The presence of chlorotrimethylsilane is critical to the success of this reaction.

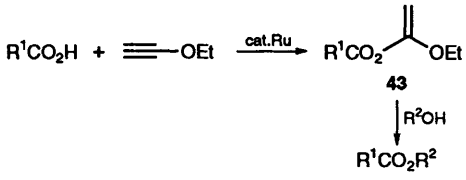
Triisopropylsilyl diazomethane **40** is thermally stable and produces the corresponding silylmethyl esters upon reaction with carboxylic acids.[30] Unlike the reaction with trimethylsilyldiazomethane, concomitant desilylation is not a problem. These silylmethyl esters are considerably more resistant to hydrolysis than the corresponding methyl esters. Triethylorthoacetate is reported to be superior to triethylorthoformate for the preparation of ethyl esters from carboxylic acids under neutral conditions.[31] The rate enhancement is presumably due to the improved stability of the cationic intermediate. t-Butyl esters can be prepared without racemization from chiral acid bromides and t-butyl alcohol in the presence of basic alumina.[32] Clearly basic alumina suppresses the formation of ketene intermediates which would lead to racemization. The beneficial use of microwave irradiation in the synthesis of esters has also been reported.[33]

The use of the thionyl chloride/DMF complex for the conversion of a hydroxyl group into the corresponding chloride is a well known procedure. If this reaction is carried out at or below 0°C in the presence of LiI, attack of halide onto the alkoxyformamidinium intermediate **41** is precluded and hydrolysis yields the corresponding formate ester **42** in high yield (**Scheme 18**).[34] These conditions are much milder than those involving the widely used acetic formic anhydride.



Scheme 18

The direct oxidation of primary alcohols to methyl esters is a useful synthetic procedure; calcium hypochlorite in methanol achieves this transformation in high yield.[35] Both aliphatic and benzylic alcohols undergo the reaction, and hypochlorous acid is believed to be the oxidizing species. Ketene acetal derivatives such as **43** have been shown to be useful derivatives for the acylation of alcohols (**Scheme 19**). These novel species can be prepared from carboxylic acids and ethoxyacetylene using a catalytic amount of $RuCl_2(p\text{-cymene})_2$, and they react smoothly with alcohols to provide the corresponding esters in excellent yield.[36]

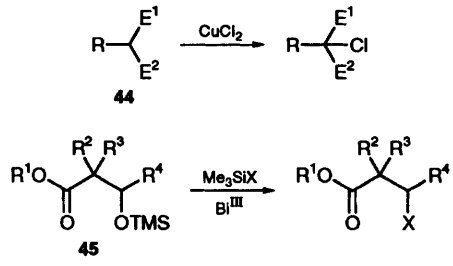


Scheme 19

3.2 Halo esters

α-Halo esters are important synthons for the elaboration of glycidic esters via the Darzens reaction. Recent work has shown that caution should be demonstrated when considering an aldol-type reaction dealing with α-halo esters, since a ketone-enolate-carbenoid manifold exists for α-halo ester enolates. Sodium enolates of α-bromo esters decompose faster than they react with formaldehyde, whereas lithium enolates of α-chloro esters do not decompose at room temperature and they react smoothly with formaldehyde to furnish glycidic esters.[37]

α-Chloro esters are generally prepared through halogenation of carboxylic acids or their derivatives. A particularly mild halogenation of stabilized ester enolates (*e.g.* **44**) can be achieved using cupric chloride.[38] Enolates containing unsaturated functionality react with high chemoselectivity. An alternative route to 2-halo esters involves the oxidation of 2-chloro aldehyde dimethyl acetals using trichloroisocyanuric acid in DMF.[39] The method has recently been extended to the synthesis of α,α-dichloro esters by the oxidation–chlorination of cyclic acetals using this reagent.[40] 3-Halo substituted esters are more difficult to obtain since they can suffer spontaneous dehydrohalogenation if the conditions are too drastic. Compounds of this type can be prepared from the corresponding β-hydroxy or siloxy esters **45** and a trimethyl silyl halide (**Scheme 20**). For the preparation of the chloride derivatives, activation of the silicon–chlorine bond by catalytic bismuth(III) chloride facilitates the reaction.[41]

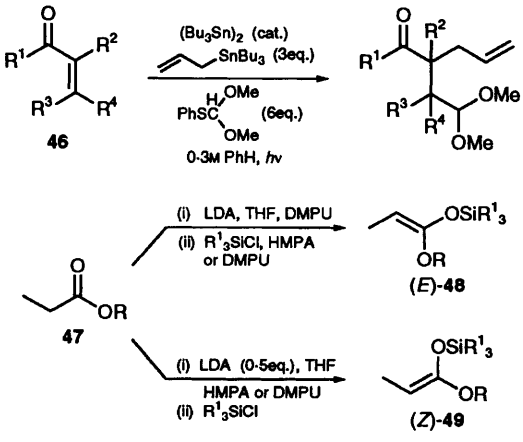


Scheme 20

3.3 Miscellaneous methods of synthesis

The vicinal dialkylation of an α,β-unsaturated ester using radical intermediates has been reported by Keck *et al.*[42] In this reaction the initially formed electron-rich dimethoxymethyl radical reacts more rapidly with the electron-deficient olefin **46**, and the resulting electron-deficient α-carbonyl radical then reacts with the nucleophilic stannane. In general, diastereoselectivity is not high.

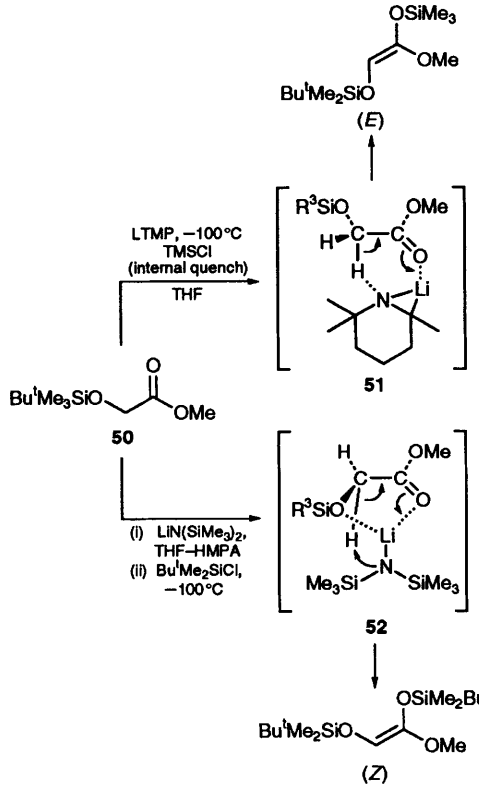
Methods for the stereoselective formation of (*E*)- and (*Z*)-silyl ketene acetals continue to be developed, as these are important intermediates in the ester enolate Claisen rearrangement. In a reinvestigation of the earlier work of Ireland, Otera *et al.* have shown that ketene silyl acetals of propionate esters with high (*E*)-stereochemical purity (*e.g.* **48**) can be obtained by increasing the size of the alkoxy group of the starting ester **47**, whereas employment of an excess of ester relative to base leads to high (*Z*)-selectivity **49** (**Scheme 21**).[43]



Scheme 21

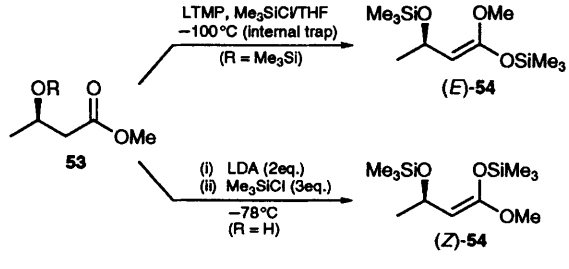
Silyl ketene acetals of α-hydroxy esters are also valuable synthetic intermediates since they allow the stereoselective positioning of hydroxyl groups adjacent to an ester carbonyl via Claisen rearrangement. Yamamoto *et al.* have recently described methods for the stereoselective formation of either (*E*)- or (*Z*)-silyl

ketene acetals starting from α-siloxy esters **50** (**Scheme 22**).[44] Since it seems likely that it is geometric constraints in the transition states for deprotonation which govern the outcome of these selective enolations, it has been suggested that there may be a preferred pericyclic transition state **51** for proton abstraction by LTMP (deprotonation control). Improved chelation in the presence of the weaker base LHMDS and the less reactive TBDMSCl would thus generate the (*Z*)-enolate selectivity via transition state **52** (complexation control).



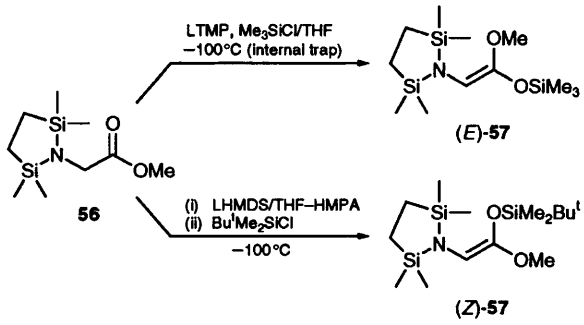
Scheme 22

Yamamoto has extended this method to allow the selective formation of either (*E*)- or (*Z*)-ketene silyl acetals **54** from β-hydroxy ketones **53**, avoiding problems of β-elimination (**Scheme 23**).[45]



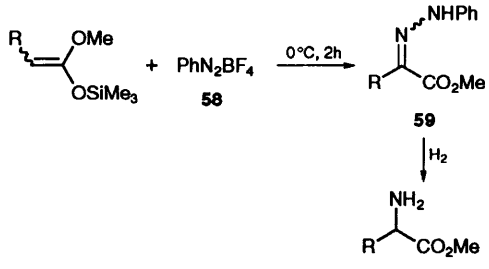
Scheme 23

Similar conditions allow the preparation of (*E*)- or (*Z*)-silyl ketene acetals **57** starting from appropriately protected α-amino esters **56** (**Scheme 24**).[45]



Scheme 24

The direct preparation of α-amino esters by electrophilic amination of esters is an important synthetic process. Tanaka *et al.* have reported that arene diazonium tetrafluoroborates **58** react with ketene-silyl ketals yielding α-hydrazone esters **59** which are converted into α-amino esters by hydrogenation (**Scheme 25**).[46] Interestingly, the less nucleophilic silyl enol ethers of ketones react with **58** in pyridine via a radical mechanism to give α-aryl ketones with concomitant loss of nitrogen.

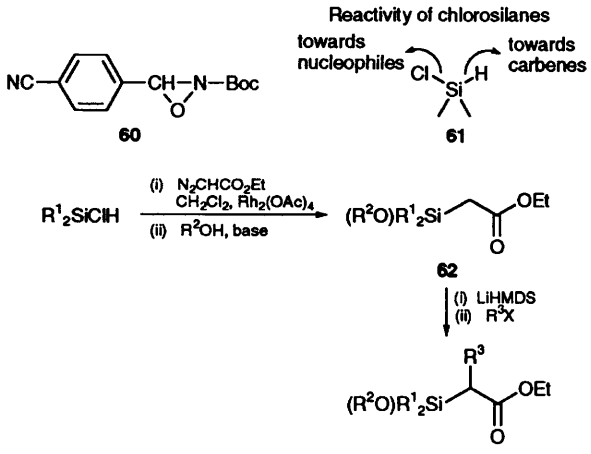


Scheme 25

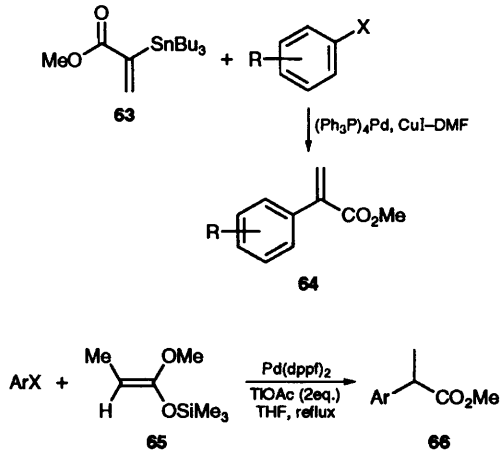
The oxaziridine **60** is a useful reagent for transfer of an N-Boc group to N- and C-nucleophiles. Thus **60** reacts with ester enolates at −78°C affording N-Boc protected α-amino esters directly.[47] Reagents analogous to **60** but containing alternative N-protecting groups can also be prepared.

α-(Alkoxysilyl)acetic esters **62** can be prepared in a one-pot operation via insertion of diazoacetates into readily available dialkyl or diarylchlorosilanes, followed by reaction with an appropriate alcohol (**Scheme 26**).[48] This chemistry exploits the dual reactivity of chlorosilanes **61** towards nucleophiles and carbenes. The esters **62** can be alkylated with a range of electrophiles under standard conditions. To date efforts to oxidize the α-silyl esters to α-hydroxy esters under Tamao conditions have proved unsuccessful.

2-Arylpropanoic acid derivatives represent an important class of therapeutically valuable non-steroidal anti-inflammatory agents. The biologically active (*S*)-enantiomers can be prepared by hydrogenation of aryl propenoic acids **64** using a chiral catalyst (**Scheme 27**). A new route to these hydrogenation precursors involves the Pd-catalysed coupling of the α-stannyl acrylate **63** to an aryl iodide



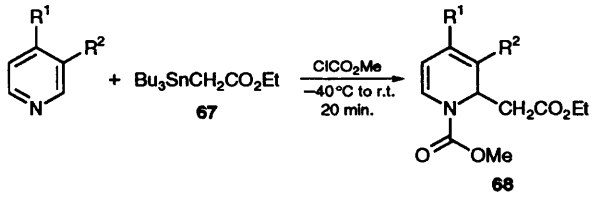
Scheme 26



Scheme 27

or triflate.[49] The use of 0.75 eq. CuI is critical for the success of this reaction. In a related approach, a range of 2-(heteroaryl) propanoic acid derivatives **66** have been prepared by the palladium-catalysed reaction of heteroaryl halides with (*E*)-1-methoxy-1-trimethylsiloxypropene **65**. Thallium acetate has been found to be a useful additive in this reaction. Halo-pyridines, pyrimidines, quinolines, and isoquinolines have been used as the heteroaryl coupling partner; the reaction is sensitive to steric effects.[50]

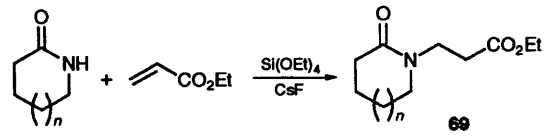
Carboethoxymethylation of functionalized pyridines can be achieved directly by the chemoselective addition of ethyl(tributylstannyl)acetate **67** to acyl pyridinium salts (**Scheme 28**).[51] The resulting dihydropyridines **68** are useful precursors to a variety



Scheme 28

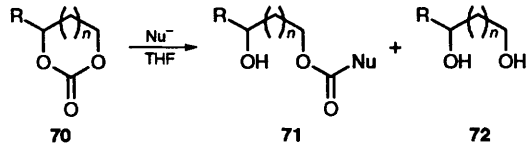
of heterocycles. Quinolinium and isoquinolinium salts can also be used as acceptors.

The Michael additions of lactams and amides to α, β-unsaturated esters are generally unfavourable processes; however, high yields of the addition products **69** can be obtained using an equimolar amount of $Si(OEt)_4$ and catalytic CsF (**Scheme 29**).[52] In this reaction the $Si(OEt)_4$ plays a dual role whereby generation of EtO^- is followed by trapping of the enolate adduct as the corresponding silyl ether, hence suppressing the normally problematic retro-Michael reaction.



Scheme 29

The formation of esters by additions of nucleophiles to carbonates is a synthetic method which has received little attention. During work aimed at preparing C-2 analogues of taxol, Nicolaou *et al.* have observed that esters are formed by the regioselective ring-opening of cyclic carbonates **70** with nucleophiles (**Scheme 30**). The only side-product observed was the diol **72**, and in general the less substituted ester **71** is the major or exclusive product. A range of nucleophiles has been successfully employed in the reaction.[53]



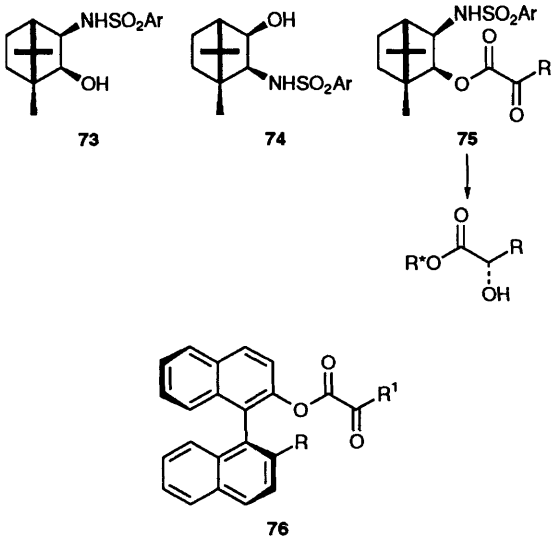
Scheme 30

3.4 Hydroxy esters

A widely used route for the preparation of optically pure α-hydroxy esters is stereoselective reduction of the corresponding α-keto esters bearing a chiral auxiliary. The borneol derivatives **73** and **74** provide extremely high levels of stereocontrol during reductions of the keto esters **75** with $LiAlH(OCEt_3)_3$.[54] The auxiliaries can be removed by mild saponification (LiOH, $THF–H_2O$, r.t.) without racemization of the reduced products.

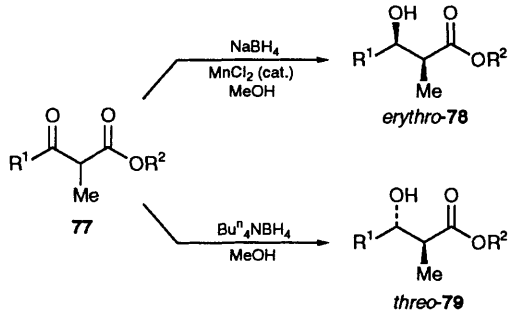
A detailed investigation of the diastereoselectivity of the addition of organometallic reagents to the keto esters **76** bearing a binaphthalen-2-ol auxiliary has been reported. The sense and degree of diastereoselectivity is dependent on the Lewis acidity of the nucleophile.[55]

High diastereoselectivity can be obtained in the direct oxidation of enolates with dimethyldioxirane if the initially formed lithium enolates are transmetallated to the corresponding titanium species prior to oxidation.[56] Furthermore, the aldol reaction of



the enolate with acetone, the unavoidable medium for dimethyldioxirane, is completely suppressed. The titanium enolates react with much higher diastereoselectivity (up to 96% e.e.) than the corresponding sodium enolates or silyl enol ethers.

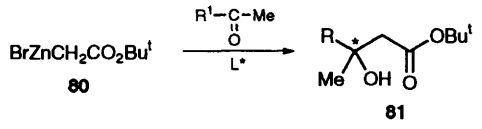
Either *erythro*-**78**- or *threo*-**79**-β-hydroxy-α-methyl esters can be prepared by stereoselective reduction of 2-methyl-3-keto esters **77** (**Scheme 31**). Thus reduction of **77** with $NaBH_4$ in the presence of catalytic $MnCl_2$ provides the *erythro* isomer **78** via a chelated six-membered ring transition state, while reduction of **77** with $Bu^n{}_4NBH_4$ provides the corresponding *threo* isomer **79** via Felkin–Anh control.[57] A further enzymatic method for the diastereo- and enantio-selective reduction of β-keto esters **77** has been reported.[58]



Scheme 31

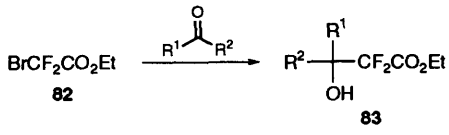
An enantioselective version of the Reformatsky reaction utilizing the bromo-ester **80** and various prochiral methyl ketones in the presence of a chiral ligand provides β-hydroxy esters **81** in moderate yield (**Scheme 32**).[59] E.e.'s of up to 74% have so far been obtained using *N,N*-dialkyl norephedrine derivatives as chiral ligands. The e.e.'s are much lower when (−)-sparteine is used as the chiral controller.

The Reformatsky reaction has also been used to prepare biologically important α,α-difluorinated ester derivatives. In a modification of this reaction α,α-difluoro-β-hydroxy esters **83** are formed in reproducible yield by activation of ethyl



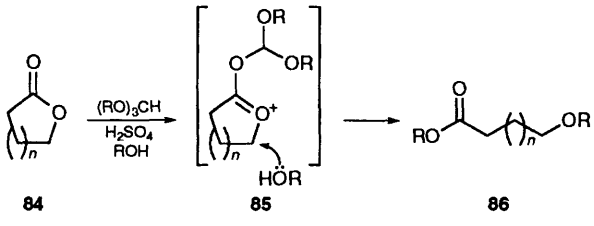
Scheme 32

bromodifluoroacetate **82** using Zn (2 eq.), AgOAc (0.3 eq.), and Et_2AlCl (1.1–2 eq.) to generate a nucleophilic species in the presence of an aldehyde or ketone (**Scheme 33**). When the carbonyl compound is α-substituted, the stereoselectivity is low.[60]



Scheme 33

4-Alkoxybutanoates (**86**, $n = 1$) and 5-alkoxypentanoates (**86**, $n = 2$) can be prepared under mild conditions and in high yield by alcoholysis of the corresponding lactones **84** in the presence of an appropriate orthoester (**Scheme 34**).[61] Mechanistic studies have shown that the ether linkage is formed by an S_N2-like opening of an activated intermediate **85** formed from the lactone and the orthoester. The reaction is much slower for ε-caprolactone derivatives and for lactones which are substituted at the α-position.

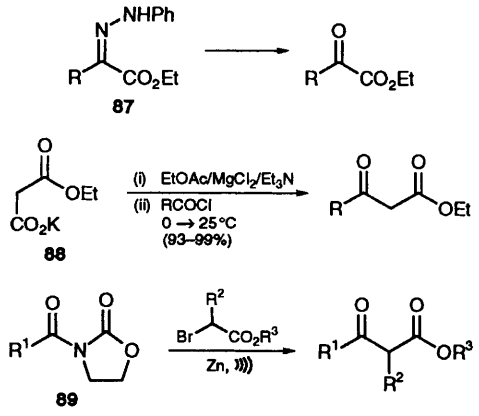


Scheme 34

3.5 Keto esters

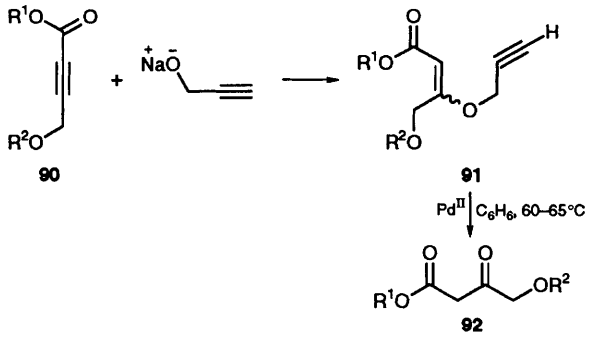
Phenylhydrazones of α-keto esters (**87**) are cleaved efficiently using hypervalent iodine compounds [*e.g.* PhI $(OCOCF_3)_2$]. The reaction proceeds under mild conditions and thus provides a method of protection for the carbonyl group of an α-keto ester.[62]

β-Keto esters are important synthetic intermediates, and they can be prepared in high yield and purity and on a large scale by reaction of acid chlorides with potassium ethyl malonate **88** using a magnesium chloride/triethylamine base system (**Scheme 35**). The method may be of real value in large scale production.[63] Alternatively, 3-acyloxazolidin-2-ones **89** undergo Reformatsky reactions with α-bromo esters in the presence of zinc and ultrasound to provide β-keto esters in moderate to good yield.[64]



Scheme 35

A different approach to the synthesis of β-keto esters involves the hydrolysis of β-alkoxy-α,β-unsaturated ketones **91**, which are prepared by conjugate addition of sodium propargyl oxide to the acetylene **90** (**Scheme 36**).[65]

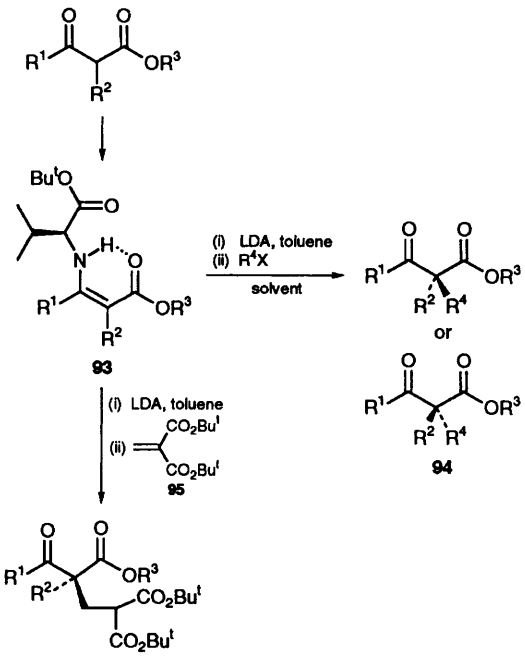


Scheme 36

Chemoselective cleavage of the enol ether moiety occurs under neutral conditions in the presence of a catalytic amount of Pd^{II} complex, affording the acid-sensitive β-keto esters **92** in good yield.[66]

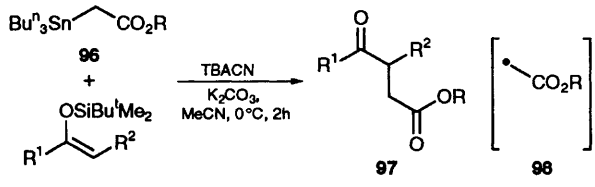
α,α-Dialkyl β-keto esters **94** having either an (*R*)- or (*S*)-chiral quaternary centre can be prepared by asymmetric alkylation of the chiral enamine derivatives **93** (**Scheme 37**). Either enantiomer can be prepared from the same chiral enamine **93** simply by variation of the solvent.[67] A subsequent publication has revealed that chiral enamines such as **93** also undergo a highly stereoselective Michael addition to the reactive Michael acceptor di-t-butyl methylene malonate **95**. The absolute configuration of the newly formed quaternary centre is again predictable, being dependent upon the solvent system used. Enantiomeric purities of > 90% have been obtained.[68]

Several related reports detailing the synthesis of γ-keto esters have appeared in the literature. α-Stannyl esters **96**, which are known to exist predominantly in the C-metallated form, can be oxidized using Ce^{IV} reagents to the corresponding α-radicals **98**. These species undergo efficient coupling with electron-rich olefins (*e.g.* enol ethers) providing γ-keto esters **97** in good yield.[69]



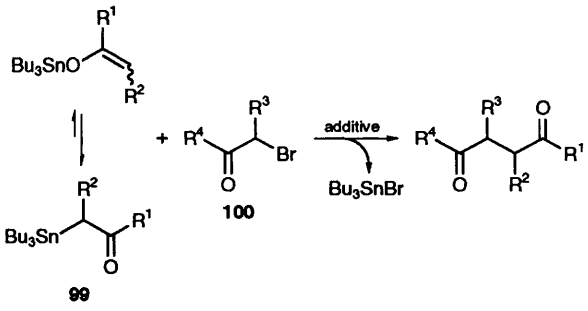
Scheme 37

Alternatively, the radical species **98** can be generated from an α-bromo- or α-iodo ester by reaction with BEt_3 in DMSO in the presence of air.[70] Reaction with silyl enol ethers again provides γ-keto esters **97** in moderate yield. Better yields are observed with α-iodo esters than with α-bromo esters (**Scheme 38**).



Scheme 38

The activation of Sn-heteroatom bonds by coordination of ligands such as phosphine oxides has already been reported.[71] This has been used for the preparation of γ-keto esters by the reaction of tin enolates **99** with α-halo esters **100** (**Scheme 39**). Unlike the previous two examples, this reaction does not occur via a radical mechanism, but rather by direct substitution at the halide moiety.[72]

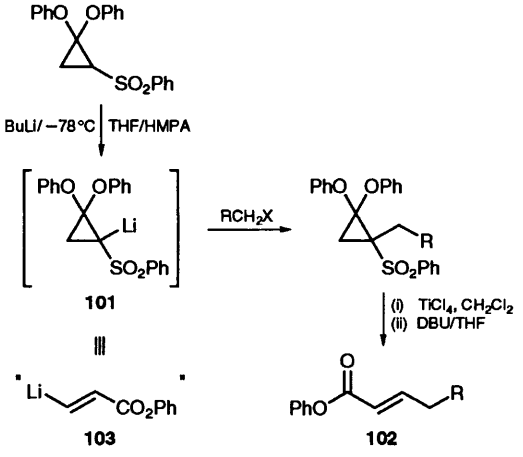


Scheme 39

Eu^{3+} has been reported to be an efficient catalyst for the Michael addition of 1,3-dicarbonyl compounds to α,β-unsaturated esters generating δ-keto esters.[73] Two reports detailing the diastereoselectivity of Michael additions of ketone[74] and ester[75] enolates to α,β-unsaturated esters have appeared.

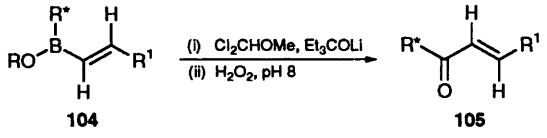
3.6 Unsaturated esters

An interesting approach to α,β-unsaturated esters **102** involves alkylation of the cyclopropyl anion **101** with an appropriate alkyl halide, followed by hydrolysis with $TiCl_4$ in CH_2Cl_2 and elimination of the phenyl sulfonyl group (**Scheme 40**).[76] In this reaction,



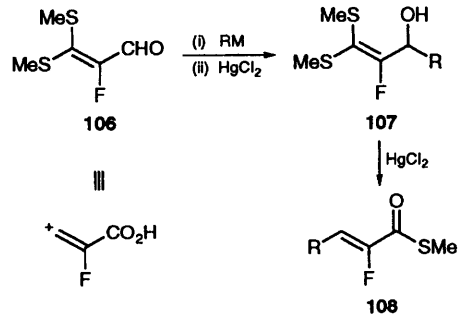
Scheme 40

the cyclopropyl anion is functioning as the β-lithio acrylate synthon **103**. To date it has not proved possible to react the anion **101** with carbonyl compounds. In an extension of their earlier work Brown *et al.* have described a highly enantioselective synthesis of conjugated acyclic α-chiral (*E*)-alkenones **105** from enantiomerically pure (*E*)-1-alkenyl alkyl borinic esters **104** which are in turn prepared by asymmetric hydroboration (**Scheme 41**).[77] Reaction of the esters **104** with α,α-dichloromethyl ether (DCME) in the presence of a hindered base followed by oxidation with H_2O_2 in pH 8 phosphate buffer provides the desired chiral (*E*)-alkenones **105** with > 99% e.e. The chiral group (R) can be cyclic or acyclic.



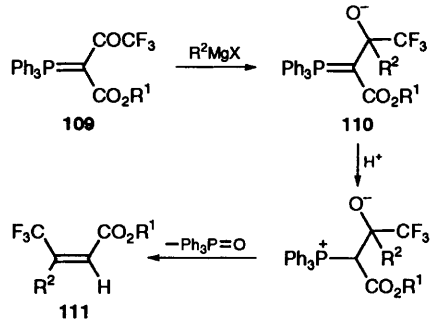
Scheme 41

Pirrung *et al.* have described the fluoroacrylate cation equivalent **106**. This highly functionalized aldehyde reacts with organometallic reagents and enolates to yield allylic alcohol products **107** which can be rearranged under acid conditions to medicinally important (*Z*)-2-fluoroacrylate thioesters **108** (**Scheme 42**).[78]



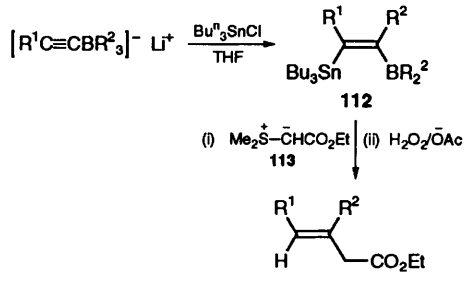
Scheme 42

α,β-Unsaturated esters bearing a trifluoromethyl group at the β-carbon can be prepared with either (*E*)- or (*Z*)-configuration by reaction of the fluorinated phosphorane **109** with a Grignard reagent (**Scheme 43**). The resulting β-oxido ylides **110** are converted into trifluoromethylated α,β-unsaturated esters **111** with either (*Z*)- or (*E*)-configuration depending on the acid used to protonate the intermediate.[79]



Scheme 43

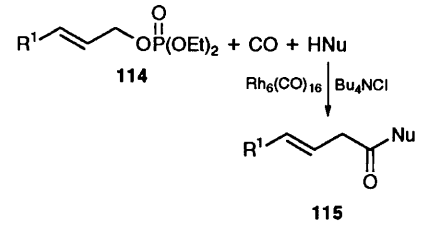
β,γ-Unsaturated esters are often prepared by deconjugation of α,β-unsaturated esters using base; alternatively, trialkyl silyl triflates and a tertiary base can be used.[80] A usual limitation of this method is that mixtures of (*E*)- and (*Z*)-β,γ-unsaturated esters are formed. Stereochemically defined (*E*)-β,γ-unsaturated esters can be formed by reaction of (*E*)-[2-(tributyltin)alkenyl] boranes **112** with the ylide **113** followed by oxidation. Overall yields are generally good (**Scheme 44**). The reaction proceeds via



Scheme 44

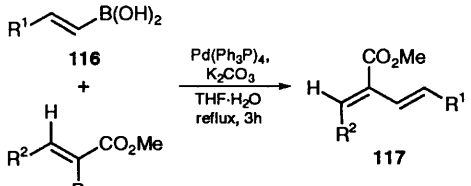
preferential migration of the alkenyl moiety from boron to carbon followed by protonolysis of the resulting alkenyltin intermediate with retention of configuration.[81]

The carbonylation of allylic compounds provides a very mild and efficient method for the preparation of β,γ-unsaturated carbonyl compounds. Allylic phosphates **114** have been shown to be highly reactive substrates for transition metal catalysed transformations, and they react with CO (20 atm.) at 50°C in the presence of a rhodium catalyst and an alcohol to provide β,γ-unsaturated esters **115** in good yield (**Scheme 45**).[82] The reaction in the presence of an amine or H_2O provides the corresponding β,γ-unsaturated amides and acids respectively. These carbonylations occur with high regioselectivity at the less substituted carbon of the allyl unit.



Scheme 45

The Pd^0 catalysed coupling of alkenylboronic acids has become a ubiquitous reaction in organic synthesis. A recent report has described the Pd-catalysed coupling of 1-(*E*)-alkenylboronic acids **116** with α-bromo-α,β-unsaturated esters providing (*E,E*)-dienoates **117** in moderate to good yield (**Scheme 46**). Retention of double bond geometry was observed in all cases.[83] Ketones and aldehydes can be used in place of esters.



Scheme 46

4 References

1 E. Nicolàs, K.C. Russel, and V. Hruby, *J. Org. Chem.*, 1993, **58,** 766.
2 K. Rück and H. Kunz, *Synthesis*, 1993, 1018.
3 M. Shimizu, K. Matsukawa, and T. Fijisawa, *Bull. Chem. Soc. Jpn.*, 1993, **66,** 2128.
4 J.C. McKew and M.J. Kurth, *J. Org. Chem.*, 1993, **58,** 4589.
5 T. Akiyama, H. Nishimoto, T. Kuwata, and S. Ozaki, *Bull. Chem. Soc. Jpn.*, 1994, **67,** 180. See also Ref. 54 for a related example.
6 J.L.L. Rakels, A.J.J. Straathof, and J.J. Heijnem, *Tetrahedron: Asymmetry*, 1994, **5,** 93.
7 E. Firtz-Laughals, *Angew. Chem., Int. Ed. Engl.*, 1993, **32,** 753.
8 F. Foubelo, F. Lloket, and M. Yus, *Tetrahedron*, 1993, **49,** 8465.
9 R. Fisher, B. Schönecker, and D. Walther, *Synthesis*, 1993, 1267.
10 M. Piotti and H. Alper, *J. Org. Chem.*, 1994, **59,** 1956.
11 T. Satoh, Y. Mizu, Y. Hayashi, and K. Yamakawa, *Tetrahedron Lett.*, 1994, **35,** 133.
12 T. Satoh, Y. Kitoh, K. Onda, and K. Yamakawa, *Tetrahedron Lett.*, 1993, **34,** 2331.
13 F. Tellier and R. Savêtre, *Tetrahedron Lett.*, 1993, 5433.
14 J.E. Olivier, R.M. Waters, and W.R. Lushby, *Synthesis*, 1994, 273.
15 C.J. Salomen, E.G. Mata, and O.A. Masceretti, *Tetrahedron*, 1993, **49,** 3691.
16 L.E. Fisher, J.M. Caroon, S.R. Stabler, S. Lundberg, S. Zaidi, C.H. Sorenson, M.L. Sparacino, and J.M. Mushowski, *Can. J. Chem.*, 1994, **72,** 142.
17 R. Varma, A. Chatterjee, and M. Varma, *Tetrahedron Lett.*, 1993, **34,** 4603.
18 M. Dekhane, P. Potier, and R.H. Dodd, *Tetrahedron*, 1993, **49,** 8139.
19 J. Esquerra, C. Pedregal, A. Rubio, J. Valenciano, J. Navio, E. Alvarez-Builla, and T. Vaquerro, *Tetrahedron Lett.*, 1993, **34,** 6317.
20 (a) F. Matsuura, Y. Hamada, and T. Shiori, *Tetrahedron*, 1993, **49,** 8211; (b) D.M. Jones, B. Nilsson, and M. Szelke, *J. Org. Chem.*, 1993, **58,** 2286.
21 S. Rozen, A. Bar-Haim, and E. Mishani, *J. Org. Chem.*, 1994, **59,** 1208.
22 E. Hata, T. Takai, T. Yamada, and T. Mukaiyama, *Chem. Lett.*, 1994, 535.
23 R.B. Bates and S. Caldera, *J. Org. Chem.*, 1993, **58,** 6920.
24 F. Benedetti, F. Berti, and A. Risaliti, *Tetrahedron Lett.*, 1993, **34,** 6443.
25 M. Akada, S. Nakano, T. Sugiyama, K. Ichitoh, H. Nakac M. Akita, and Y. Maro-Okai, *Bull. Chem. Soc. Jpn.*, 1993, **66,** 1511.
26 (a) R.H. Dodd and M. Le Hyaric, *Synthesis*, 1993, 295; (b) J.R. Henry and S.M. Weinreb, *J. Org. Chem.*, 1993, **58,** 4745.
27 J.J. Folmer and S.M. Weinreb, *Tetrahedron Lett.*, 1993, **34,** 2737.
28 T. Mukaiyama, *Angew. Chem., Int. Ed. Engl.*, 1979, **18,** 707 and references cited therein.
29 I. Shiina, S. Miyoshi, M. Miyashita, and T. Mukaiyama, *Chem. Lett.*, 1994, 515.
30 J.A. Soderquist and E.I. Miranda, *Tetrahedron Lett.*, 1993, **34,** 4905.
31 J.I. Trujillo and A.S. Gopalan, *Tetrahedron Lett.*, 1993, **34,** 7355.
32 K. Nagasawa, K. Ohhashi, A. Yamashita, and K. Ito, *Chem. Lett.*, 1994, 209.
33 A. Loupy, A. Petit, M. Ramdani, C. Yvanaeff, M. Majdoub, B. Labiad, and D. Villemin, *Can. J. Chem.*, 1993, **71,** 90.
34 I. Fernández, B. Garcia, S. Muñoz, J.R. Pedro, and R. Dela Salud, *Synlett*, 1993, 489.
35 C.E. McDonald, L.E. Nice, A.W. Shaw, and N.B. Nestor *Tetrahedron Lett.*, 1993, **34,** 2741.
36 Y. Kita, H. Maeda, K. Omori, T. Okuno, and Y. Tamura, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2999.
37 C.A. Maryanoff, K.L. Sorgi, and A.M. Zientek, *J. Org. Chem.*, 1994, **59,** 237.
38 X.-X. Shi and L.-X. Dai, *J. Org. Chem.*, 1993, **58,** 4596.
39 M. Boni, F. Ghelfi, U.M. Pagnoni, and A. Pinetti, *Bull. Chem. Soc. Jpn.*, 1994, **67,** 156.
40 F. Bellesia, M. Boni, F. Ghelfi, and U.M. Pagnoni, *Tetrahedron Lett.*, 1994, **35,** 2961.
41 C. Le Roux, H. Gaspard-Iloughmane, and J. Dubac, *J. Org. Chem.*, 1994, **59,** 2238.

42 G.E. Keck and C.P. Kordik, *Tetrahedron Lett.*, 1993, **34,** 6875.
43 J. Otera, Y. Fujita, and S. Fukuzumi, *Synlett*, 1994, 213.
44 K. Hattori and H. Yamamoto, *J. Org. Chem.*, 1993, **58,** 5301.
45 K. Hattori and H. Yamamoto, *Tetrahedron*, 1994, **50,** 3099.
46 T. Sakakura, M. Hara, and M. Tanaka, *J. Chem. Soc., Perkin Trans. 1*, 1994, 289.
47 J. Vidal, L. Guy, S. Stérin, and A. Collet, *J. Org. Chem.*, 1993, **58,** 4791.
48 O. Andrey, Y. Landais, and D. Planchenault, *Tetrahedron Lett.*, 1993, **34,** 2927.
49 J.I. Levin, *Tetrahedron Lett.*, 1993, **34,** 6211.
50 T. Sakamoto, Y. Kondo, K. Masumoto, and H. Yamanaka, *Heterocycles*, 1993, **36,** 2509.
51 T.G. Murali Dhar and C. Gluchowski, *Tetrahedron Lett.*, 1994, **35,** 989.
52 K.H. Ahn and S.J. Lee, *Tetrahedron Lett.*, 1994, **35,** 1875.
53 K.C. Nicolaou, E.A. Couladouros, P.G. Nantermet, J. Renaud, R. Kiplin Guy, and W. Wrasidlo, *Angew. Chem., Int. Ed. Engl.*, 1994, **33,** 1581.
54 Y.B. Xiang, K. Snow, and M. Belley, *J. Org. Chem.*, 1993, **58,** 993. See also Ref. 5 for a related example.
55 Y. Tamai, T. Nakano, and S. Miyano, *J. Chem. Soc., Perkin Trans. 1*, 1994, 439.
56 W. Adam, M. Müller, and F. Prechtl, *J. Org. Chem.*, 1994, **59,** 2358.
57 M. Taniguchi, H. Fujii, K. Oshima, and K. Utimoto, *Tetrahedron*, 1993, **49,** 11 169.
58 Y. Kawai, M. Tsujimoto, S. Kondo, K. Takanobe, K. Nakamura, and A. Ohno, *Bull. Chem. Soc. Jpn.*, 1994, **67,** 524.
59 K. Soai, A. Oshio, and T. Saito, *J. Chem. Soc., Chem. Commun.*, 1993, 811.
60 T.T. Curran, *J. Org. Chem.*, 1993, **58,** 6360.
61 S.A. King, *J. Org. Chem.*, 1994, **59,** 2253.
62 D.H.R. Barton, J.C. Jaszberenyi, and T. Shinada, *Tetrahedron Lett.*, 1993, **34,** 7191.
63 R.J. Clay, T.A. Collom, G.L. Karrick, and J. Wemple, *Synthesis*, 1993, 290.
64 C. Kashima, X. C. Huang, Y. Harada, and A. Hosomi, *J. Org. Chem.*, 1993, **58,** 793.
65 Trialkylphosphines have been reported to catalyse the conjugate addition of alcohols to α,β-unsaturated alkynic esters under neutral conditions, see J. Inanago, Y. Baba, and T. Hanamoto, *Chem. Lett.*, 1993, 241.
66 G.S. Sarin, *Tetrahedron Lett.*, 1993, **34,** 6309.
67 K. Ando, Y. Takemasa, K. Tomioka, and K. Koga, *Tetrahedron*, 1993, **49,** 1579.
68 K. Ando, K. Yasuda, K. Tomioka, and K. Koga, *J. Chem. Soc., Perkin Trans. 1*, 1994, 227.
69 Y. Kohno and K. Narasaka, *Chem. Lett.*, 1993, 1689.
70 E. Baciocchi and E. Muraglia, *Tetrahedron Lett.*, 1994, **35,** 2763.
71 I. Shibata, T. Imoto, A. Baba, and H. Matsuda, *J. Heterocycl. Chem.*, 1987, **24,** 361 and references cited therein.
72 M. Yasuda, T. Oh-hata, I. Shibata, A. Baba, and H. Matsuda, *J. Chem. Soc., Perkin Trans. 1*, 1993, 859.
73 F. Bonadies, A. Lattanzi, L. R. Orelli, S. Pesci, and A. Scettri, *Tetrahedron Lett.*, 1993, **34,** 7649.
74 E.J. Corey and I.N. Houpis, *Tetrahedron Lett.*, 1993, **34,** 2421
75 M. Nomura and S. Kanemasa, *Tetrahedron Lett.*, 1994, **35,** 143.
76 M. Pohmakotr and J. Ratchataphusit, *Tetrahedron*, 1993, **49,** 6473.
77 H.C. Brown and V.K. Mahindroo, *Tetrahedron: Asymmetry*, 1993, **4,** 59.
78 M.C. Pirrung, E. G. Rowley, and C.P. Holmes, *J. Org. Chem.*, 1993, **58,** 5683.
79 Y. Shen and S. Gao, *J. Org. Chem.*, 1993, **58**, 4564.
80 M. Ihara, S. Suzuki, N. Taniguchi, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2251.
81 M.-Z. Deng, N.-S. Li, and Y.-Z. Huang, *J. Org. Chem.*, 1993, **58,** 1949.
82 Y. Imada, O. Shibata, and Ŝ.-I. Murahashi, *J. Organomet. Chem.*, 1993, **451,** 183.
83 N. Urdaneta, J. Ruiz, and A.J. Zapata, *J. Organomet. Chem.*, 1994, **464,** C33.