Carboxylic acids and esters

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REVIEW PERKIN 1

Covering: 1 August 1996 to 31 July 1997
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1 Introduction

This review provides an overview of the methods for the synthesis of carboxylic acids and esters which were published in the organic chemistry literature between 1 August 1996 and 31 July 1997. It focuses on approaches deemed to be novel either because they provide access to interesting substructures or because they exhibit sufficiently broad utility to extend the spectrum of general methods available to the synthetic chemist. The coverage of new chiral auxiliaries and ligands has thus been limited to those which provide improvements over known methodology, for instance by increasing selectivity or by extending the range of accessible products. The use of preparative biotransformations, such as enzyme mediated esterifications and hydrolyses, has not been considered.

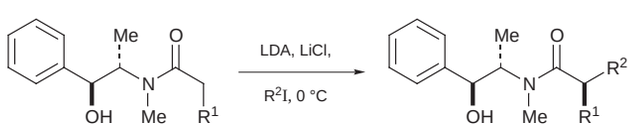
Material is organised based on the functionality present in the target structure. Due to the ready interconversion of carboxylic acid and ester moieties, strategies for the synthesis of their functionalised derivatives are considered simultaneously. The syntheses of polyfunctional molecules are included in the first subsection to which they belong. The chemistry of lactones is detailed in a separate article in this series.

2 Synthetic approaches

2.1 General carboxylic acids

A number of methods for the synthesis of generic carboxylic acids based on ester hydrolysis, oxidation, reduction, alkylation and olefin carboxylation have been reported. A combination of trimethylsilyl trifluoromethanesulfonate and triethylamine has been utilised for the selective cleavage of *tert*-butyl esters in the presence of *tert*-butyl ethers in moderate to good yields (53–90%) without any associated racemisation in α-chiral substrates.[1] Bismuth(III) mandelate has been used for the deprotection of aryl acetates (44–96% yield) and permits the selective hydrolysis of aryl esters in the presence of alkyl esters[2] whilst deprotection of prop-2-ynyl esters without concomitant cleavage of acetate, allyl, benzyl or *tert*-butyl esters can be achieved in excellent yields (80–97%) using benzyltriethylammonium tetrathiomolybdate.[3] The use of stable organic nitroxyl radicals for the oxidation of primary alcohols to acids in aqueous solvent systems has been reviewed.[4] Mioskowski and co-workers have reported the high yielding (67–98%) conversion of primary nitro alkanes and bromides into carboxylic acids using sodium nitrite and acetic acid in dimethyl sulfoxide.[5] The use of *N*-hydroxy-*o*-benzenedisulfonimide for the oxidation of certain aromatic aldehydes has also been reported.[6] Molten 1-*n*-butyl-3-methylimidazolium tetrafluoroborate and propan-2-ol have been utilised as an alternative reaction medium for the ruthenium(II) BINAP mediated asymmetric hydrogenation of 2-aryl acrylic acids. These conditions have been shown to facilitate isolation of the products and to allow reuse of the ionic liquid catalyst solution without adversely affecting the enantioselectivity.[7] Improved reaction rates and enantioselectivities (compared with BINAP) have been observed when 5,5′,6,6′,7,7′,8,8′-octahydroBINAP is used as the ligand in the hydrogenation of a range of 1,2-disubstituted acrylic acids.[8]

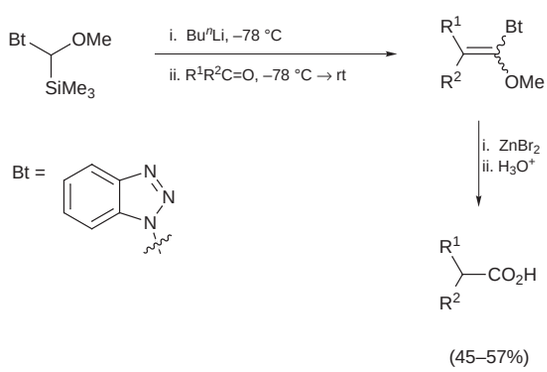
The enantioselective protonation of 2-aryl silyl ketene acetals proceeds with high levels of asymmetric induction (93–94% ee) in the presence of a tin(IV) chloride–methyl BINOL complex as catalyst and 2,6-dimethylphenol as an achiral proton source.[9] Myers *et al*. have investigated the use of pseudoephedrine as an auxiliary for highly diastereoselective asymmetric alkylation reactions (94–≥99% de).[10] The enolate is sufficiently reactive to be alkylated in good yields (80–99%) by a range of electrophiles including β-branched primary alkyl iodides (**Scheme 1**), the selectivity of the latter reactions being defined by the chirality of the pseudoephedrine. Mild hydrolysis of the auxiliary gives the corresponding α-chiral acids in high yields (74–97%) without any epimerisation.



Scheme 1

Katritzky *et al.* have reported a new approach to the one carbon homologation of aldehydes and ketones to the corresponding acids using trimethylsilyl(methoxy)(benzotriazol-1-yl)methane (**Scheme 2**).[11]

Successful approaches which involve introduction of the carboxy moiety have also been developed. The addition of



Scheme 2

organolithium reagents to styrenes followed by carboxylation of the intermediate carbanion provides ready access to α-aryl carboxylic acids. (−)-Sparteine can be used to induce asymmetry in these reactions (up to 72% ee), provided that the aryl ring contains an *o*-substituent which stabilises the benzyllithium intermediate.[12] Tertiary carboxylic acids have been isolated in moderate yields (33–56%) from the gold(I) carbonyl mediated carbonylation of terminal olefins in aqueous sulfuric acid.[13]

The use of biocatalytic deracemisation techniques for the synthesis of chiral acids from esters, nitriles and amino esters has been reviewed.[14] A simple resolution of *O*,*O*′-dibenzoyl tartaric acid by preferential crystallisation of its calcium salt–2-methoxyethanol complex has been developed,[15] and the resolution of a range of racemic carboxylic acid derivatives using titanium α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanolates (TiTADDOLates) has been described.[16]

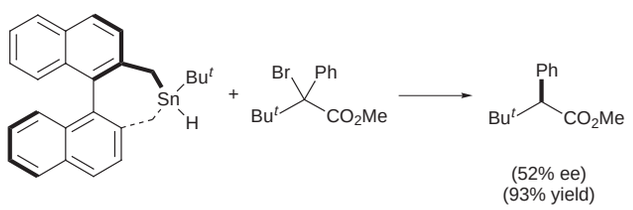
2.2 General carboxylic acid esters

A range of methods for the esterification of carboxylic acids have been developed. A combination of boron trifluoride–diethyl ether and benzyl or allyl 2,2,2-trichloroacetimidate can be used for the preparation of the corresponding esters in good yields (60–98%)[17] whilst addition of dimethyl sulfite expedites the acid catalysed synthesis of adamant-1-yl esters of α-amino acids (70–80% yield).[18] The diphenylmethyl esters of a range of carboxylic acids have been formed in good yields (66–95%) using a combination of Oxone, benzophenone hydrazone, iodine and wet alumina.[19] The use of alumina in organic reactions, including esterifications, has been reviewed.[20] Esterification and transesterification reactions have been shown to be catalysed by the π-acids tetracyanoethene and dicyanoketene dimethyl acetal (40–100% yield), conditions under which acid-labile groups such as *tert*-butoxy and benzyloxy carbamates are stable.[21] The use of magnesium bromide and a tertiary amine permits the high yielding (80–99%) formation of esters of hindered alcohols from anhydrides[22] whilst unhindered, non-conjugated aliphatic carboxylic acids can be esterified in good yields (60–93%) using nickel(II) chloride hexahydrate in refluxing alcohol.[23] Selective monoesterification (>90%) occurs in the presence of aromatic or conjugated acids. The monoesterification of symmetrical dicarboxylic acids can be achieved in high yields (89–95%, 4–6% diester) by the transesterification of butyl formate catalysed by strongly acidic ion-exchange resins.[24] The formation of imidazolides is a standard method of activating carboxylic acids towards nucleophilic attack. *N*-Alkylation of the imidazolide using methyl trifluoromethanesulfonate enhances this activation and leads to high yields (70–90%) of esters, even with hindered alcohols.[25] Aromatic acids can be esterified directly in moderate to good yields (38–96%) using primary alkyl alcohols in the presence of thionyl chloride.[26] Primary amides have been converted into methyl esters in excellent yields (89–96%) by treatment with a methanolic solution of dimethylformamide dimethyl acetal.[27] The reaction also works well for other alcohols.

Benzyl and allyl ethers have been oxidised to the corresponding esters using 1-(*tert*-butylperoxy)-1,2-benziodoxol-3(1*H*)-one in the presence of alkali metal carbonates.[28] The reaction proceeds in moderate to good yields (58–84%) *via* α-oxy carbon-centred radicals and has also been extended to the synthesis of methallyl, prenyl, cinnamyl and alkynyl esters.

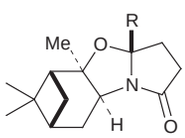
The asymmetric protonation of enolates and silyl ketene acetals provides a method for the synthesis of α-chiral esters; this area has been reviewed as part of a general overview of the enantioselective protonation of enolates.[29] Successful radical based approaches are much rarer although hydrogen transfer from a chiral binaphthyl derived tin hydride to an α-bromo ester has been shown to proceed with moderate enantioselectivity (**Scheme 3**).[30]

A number of approaches to the alkylation of esters have been



Scheme 3

reported. Roth *et al*. have developed polycyclic lactam system **1** which exhibits complementary facial selectivity to Meyers' bicyclic lactam in asymmetric α-alkylation reactions.[31] Benzyl copper reagents add to sterically undemanding α,β-unsaturated esters in the presence of tetramethylethylenediamine and trimethylsilyl chloride to give good yields (70–90%) of the corresponding β-benzyl esters.[32] Alkylation of triazole stabilised homoenolate anion **2** also provides access to β-substituted esters (**Scheme 4**).[33]



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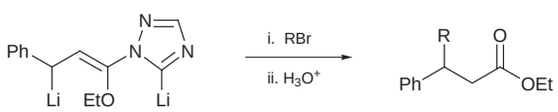
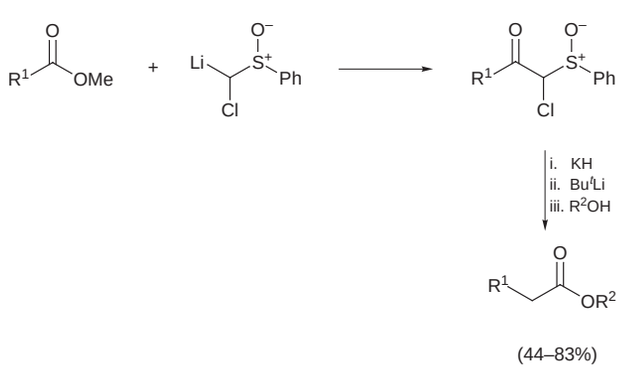


2 (55–84%)

Scheme 4

The one carbon homologation of methyl esters can be achieved by addition of the lithium anion of chloromethyl phenyl sulfoxide followed by treatment of the potassium enolate of the resultant α-chloro-α-sulfinyl ketone with *tert*-butyllithium and an alcohol (**Scheme 5**).[34] The reaction is thought to proceed *via* rearrangement of the alkylidene carbenoid to an alkynolate which is protonated to form a ketene, and hence the carboxylate, upon addition of a range of alcohols or aqueous hydroxide.



Scheme 5

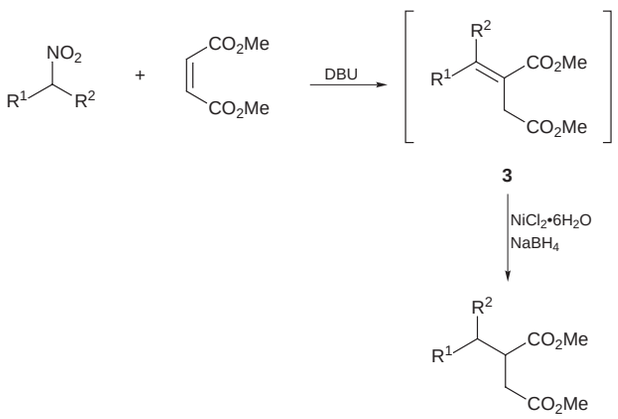
A radical based approach to the carbonylation of alkyl iodides in the absence of metal catalysts has been developed by Ryu and co-workers.[35] Photoirradiation of alkyl iodides in the presence of carbon monoxide, an alcohol and potassium carbonate gives good yields (59–87%) of a range of esters. The reaction conditions tolerate the presence of both chloro and phenylthio substituents.

2.3 Diacids and diesters

A number of different approaches to diacids and diesters have

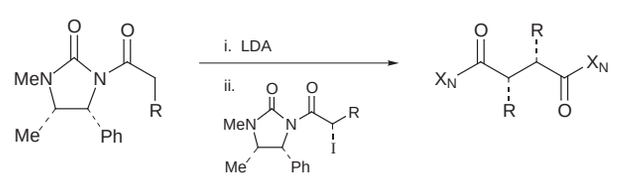
been reported. These are based both on the formation of one or two new carboxylate moieties and on coupling reactions, in which either one carboxylate is contributed by each component, or a dicarboxylate is already present in one of the fragments.

The addition of Grignard derived organocuprates to dimethyl acetylenedicarboxylate and subsequent trapping of the copper enolate with electrophiles provides access to a range of 2,3-disubstituted maleates in good yields (67–83%).[36] The corresponding diacids can be generated by mild basic hydrolysis and have been shown to be protein prenyl transferase inhibitors. The use of nitro alkanes as alkyl anion synthons in the preparation of 2-substituted succinate diesters has been reported.[37] The initial product of base mediated addition of nitro alkanes to dimethyl maleate rapidly eliminates nitrous acid to give α,β-unsaturated ester **3** (**Scheme 6**), which on addition of nickel boride provides the substituted succinate diester in good yields (65–94%).

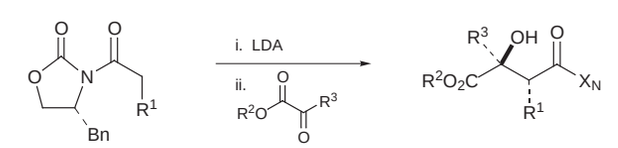


Scheme 6

The oxidative homocoupling reaction of *N*-acyl imidazolidinones proceeds in moderate yields (50–69%) and provides *syn*-2,3-disubstituted succinic acids after cleavage of the chiral auxiliaries (**Scheme 7**).[38] The corresponding heterocoupling reactions lead to mixtures of homo- and hetero-coupled products. 2-Hydroxy-2,3-dialkyl succinates can be prepared in good yields (70–91% before hydrolysis) by addition of α-keto esters to the enolates of phenylalanine derived Evans' auxiliaries (**Scheme 8**).[39] The quaternary centre is formed with moderate selectivity (26–66% de) whilst complete control of the stereochemistry at the tertiary centre is observed.



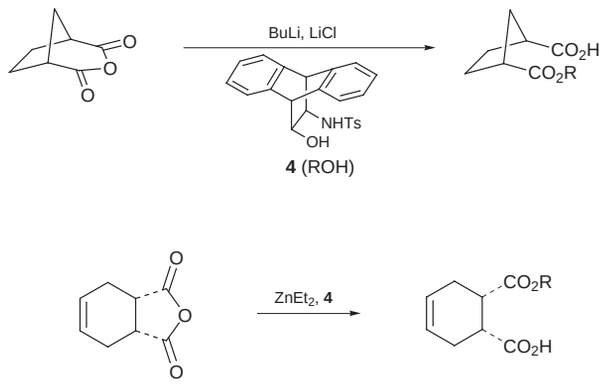
Scheme 7



Scheme 8

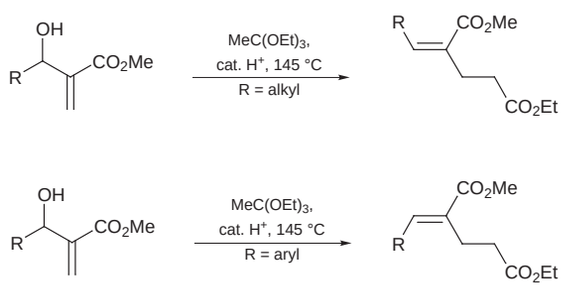
The ruthenium catalysed Michael addition reactions of a series of carbon nucleophiles including malonates, β-keto esters and Meldrum's acid has been reinvestigated. Although the reaction had previously been shown not to proceed in tetrahydrofuran, the use of acetonitrile as solvent leads to activation of the $[RuH_2(PPh_3)_4]$ by ligand exchange and moderate to good yields (42–99%) of addition products.[40]

The ring-opening of bicyclic *meso* anhydrides by metallated derivatives of amino alcohol **4** is diastereoselective (**Scheme 9**).[41] The dilithium salt of **4** and its diethylzinc complex exhibit complementary stereoselectivity, with the butyllithium mediated reactions providing higher diastereomeric excesses (93–>99% de *vs.* 13–93% de).



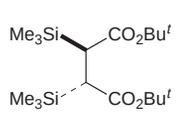
Scheme 9

The Johnson–Claisen rearrangement of methyl (3-hydroxy-2-methylene)alkanoates gives substituted 1,5-diesters in high yields (70–87%) with good *E*:*Z* selectivity (**Scheme 10**).[42] 3-Aryl substrates give *E*-alkenes whilst 3-alkyl substrates favour the *Z* product.



Scheme 10

The butyllithium catalysed addition of 2-methylpropan-2-ol to bis(trimethylsilyl)diketene gives (±)-di-*tert*-butyl 2,3-bis(trimethylsilyl)succinate **5** [91:9 (±):*meso*] in 72% yield whilst addition of methanol provides predominantly the *meso* dimethyl ester [15:70 (±):*meso*, 60% yield].[43] Adipic acid has been prepared in 63% yield by sodium hypochlorite oxidation of cyclohexanol using Aliquat 336® as phase transfer catalyst, while lower yields and significant quantities of oxidised or chlorinated by-products are obtained in the reactions of cycloheptanone and cyclooctanone.[44]



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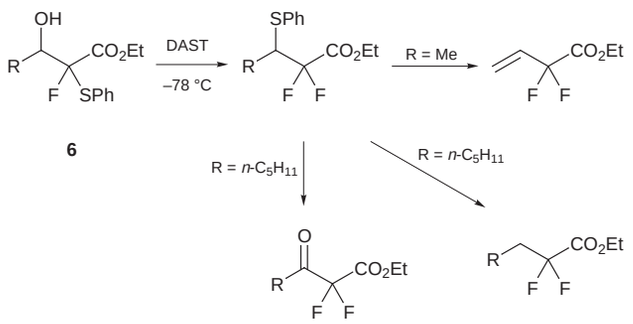
2.4 Halo acids and esters

The halogenation of carboxylic acids and esters has been achieved using a variety of reagent systems. A combination of iodotoluene difluoride and HF–pyridine gives moderate to good yields (50–80%) of mono-α-fluorinated-β-keto esters[45] whilst anodic fluorination of β-thio acrylates and maleates gives low to moderate yields (21–66%) of the corresponding α-fluoro-β-thio-α,β-unsaturated esters.[46] A range of α,α-difluoro esters are available in moderate to good yields (46–94%) by DAST fluorination of readily available α-fluoro-β-hydroxy-α-phenylthio esters **6** and subsequent manipulation of

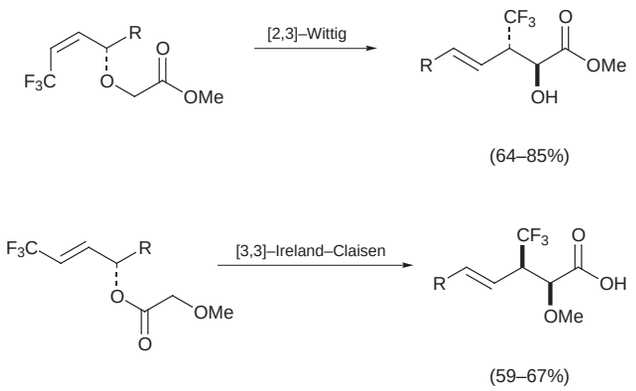
the sulfide moiety (**Scheme 11**).[47] Radical β-bromination of α-chloro carboxylic esters using NBS occurs with good selectivity (9:1–19:1 *anti*:*syn*) and in high yields (78–89%) in substrates where the β-position is either benzylic or tertiary.[48] The multistep synthesis of 2-fluoro-2-phenyl alkanoic acids from the corresponding styrenes has been reported.[49] Two routes have been developed, the first involves addition of triethylamine hydrofluoride and NBS to the alkene followed by displacement of the primary bromide with potassium acetate and subsequent oxidation, whilst the second involves regioselective Lewis acid mediated ring opening of a bromohydrin derived epoxide with triethylamine hydrofluoride. Both routes suffer from low yields (39–50%) in the final oxidation reaction.



Scheme 11

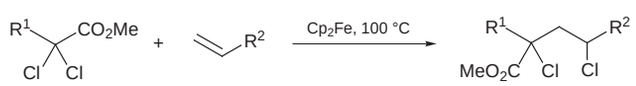
A number of synthetic approaches to halogenated acids and esters based on the formation of new carbon-carbon bonds have been reported. The aldol reactions of *n*-alkyl and acetylenic trifluoromethyl ketones with a chiral nickel(II) complex of a glycine Schiff base provides access to α-amino-β-hydroxy-β-trifluoromethyl acids in moderate to good yields (56–87%) with high levels of diastereoselection (90–>98% de).[50] The analogous addition to a trifluoromethyl imine (98% de, 91% yield) provides the corresponding α,β-diamino-β-trifluoromethyl acid after decomplexation.[51] Trifluoroacetylation of trimethylsilyl ketene acetals with 4-dimethylamino-1-(trifluoroacetyl)pyridinium trifluoroacetate proceeds in moderate to good yields (51–76%).[52] Hydrolysis of the initially formed silyl enol ether gives the corresponding α-alkyl-β-trifluoroacetyl esters, again in moderate to good yields (60–75%). Iseki *et al.* have investigated the generation and asymmetric aldol reactions of α,α-difluoro silyl ketene acetals. α,α-Difluoro-β-hydroxy esters are obtained with good enantioselectivity (81–98% ee) and in high yields (85–>99%) in the presence of chiral Lewis acid catalysts.[53]

The enantioselective Reformatsky reaction of α,α-difluoro esters with aromatic aldehydes is catalysed by chiral amino alcohols and gives α,α-difluoro-β-hydroxy esters with moderate to good levels of asymmetric induction (60–83% ee).[54] The chemoselective addition of Grignard reagents to β-halo-α-keto esters and β-halo-α-imino esters gives the corresponding β-halogenated-α-substituted-α-hydroxy and α-amino esters in good yields (61–92%).[55] A range of α-alkyl- and α-aryl-β,β-difluoro and β-chloro-, β-bromo- and β-iodo-β,β-difluoro esters are available using this methodology. The 1,4-addition of dialkylaluminium chlorides to glucosamine derived α,β-unsaturated *N*-acyloxazolidinones and subsequent halogenation of the intermediate aluminium enolate with either *N*-chloro- or *N*-bromo-succinimide provides chiral β-branched-α-halo carboxylic acids with reasonable levels of diastereoselection (46–84% de).[56] The use of [2,3]-Wittig and [3,3]-Ireland–Claisen rearrangements in the synthesis of *anti*-(*E*)-γ,δ-unsaturated-β-trifluoromethyl-α-hydroxy carboxylic esters and *syn*-(*E*)-γ,δ-unsaturated-β-trifluoromethyl-α-methoxy carboxylic acids respectively has been investigated (**Scheme 12**).[57] Both reactions proceed with high levels of diastereoselection (>99:1); in each case selectivity is lowered when the opposite alkene configuration in the starting material is employed.

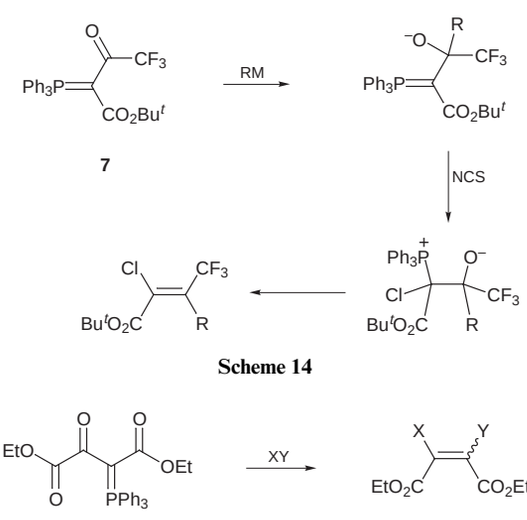


Scheme 12

The addition of methyl 2,2-dichlorocarboxylates to alk-1-enes to give the corresponding 2,4-dichlorocarboxylates in low to reasonable yields (10–72%) is promoted by ferrocene (**Scheme 13**).[58] β-Trifluoromethyl-α-chloro-α,β-unsaturated esters can be obtained in moderate to good yields (65–85%) by addition of organometallic reagents to ylid **7**, chlorination of the intermediate betaine and subsequent elimination of triphenylphosphine oxide (**Scheme 14**).[59] The highly oxygenated ylid **8** can be converted into halogen-containing 2,3-disubstituted diethyl maleates and fumarates in variable yields (26–98%) upon addition of suitable halide donors (**Scheme 15**).[60]



Scheme 13



Scheme 14

Scheme 15

2.5 Amino acids and esters

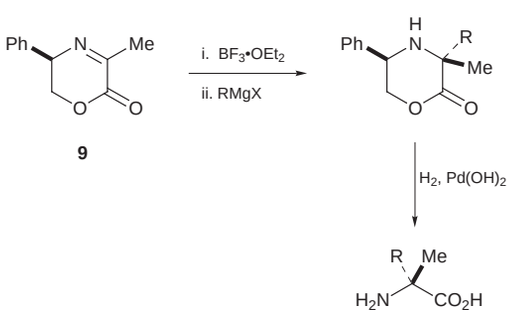
A vast array of methods have been utilised for the synthesis of amino acids and esters. These can be classified either as generally applicable approaches to a range of substrates or as strategies for the synthesis of specific targets; only the former category is considered here. A number of reviews of amino acid chemistry have been published. Their coverage ranges from the synthesis of amino acids incorporating stable isotopes[61] and methods for the synthesis of non proteinogenic heteroarylalanines[62] to the use of carbenes[63] and radicals[64] in amino acid synthesis. Seebach *et al.* have provided an account of their methodology for the use of the self-regeneration of stereocentres (by way of chiral acetals) in the stereoselective alkyl-

ation of amino acids,[65] whilst Wirth has highlighted new strategies for the synthesis of α-alkylated-α-amino acids.[66]

In order to minimise overlap with reviews in this series covering the synthesis of amines and amides,[67] only those general methods for the synthesis of amino acids and esters which involve the formation of a new carbon–carbon bond are discussed here.

2.5.1 α-Amino acids and esters

The addition of organometallic reagents to imines and their derivatives provides direct access to α-alkylated amines, and a number of α-amino acid syntheses based on this approach have been reported. The reactions of erythrulose derived chiral (*E*)- and (*Z*)-ketoximes with organolithium species proceed with high levels of diastereoselectivity (60–>90% de) in good yields (70–95%) with the two oxime geometries leading to opposite configurations at the new stereocentre. The corresponding β-hydroxy-α-substituted-α-amino acids are available upon cleavage of the hydroxylamine and 1,2-diol functionalities.[68] The boron trifluoride–diethyl ether mediated addition of Grignard reagents to dehydromorpholinones **9** occurs exclusively at the C=N bond (**Scheme 16**) and is highly stereoselective (100% de) although yields are variable (20–95%).[69] Cleavage of the trisubstituted morpholinones gives homochiral α-substituted alanine derivatives, again in variable yields (26–74%). Chiral vinyllithium **10** has been shown to react with *N*-sulfonyl imines in a highly stereoselective manner (⩾98% de), and subsequent ozonolysis of the intermediate vinyl bromide provides the corresponding *N*-sulfonyl-α-amino esters (**Scheme 17**).[70]



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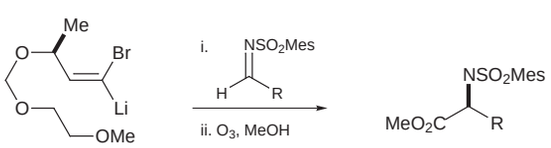
Scheme 16



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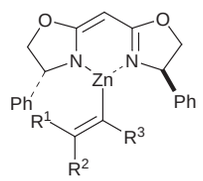
Scheme 17

Allylglycine derivatives can be accessed by enantioselective allylation of α-keto ester oximes using chiral organozinc reagent **11**. The allylation reaction proceeds with high selectivity (74–94% ee) in good yields (62–90%).[71] The addition of a range of α,β-unsaturated organozinc bromides to *N*-(phenylsulfonyl)imino esters provides racemic allyl, crotyl and prop-2-ynyl α,α-disubstituted amino esters in moderate to good yields (54–85%).[72] β-Substituted α-amino acids and esters have been synthesised in good yields (63–79%) from 3-phenyl-2*H*-azirine-2-carboxylates **12**.[73] Methylmagnesium bromide adds to C-3 of the azirine with attack occurring exclusively *syn* to the carboxylate, presumably due to chelation of the incoming reagent. Hydrogenolytic cleavage of the benzylic carbon–nitrogen bond can occur with either retention or inversion at the newly formed stereocentre, selectivity is high (80–92% de) but is both substrate and solvent dependent. The ring opening of aziridines derived from chiral epoxy alcohols by Grignard derived cuprates also provides access to α,α-disubstituted amino acids, after oxidation of the primary hydroxy group.[74] Organometallic attack is high yielding (70–80%) and occurs exclusively at the least hindered end of the aziridine. Oxidation has been shown to occur in 77% yield with complete retention of ee in the synthesis of (*S*)-α-(methyl)phenylalanine. 4-Methoxy-5-(hydrazino)oxazolidin-2-ones **13** have been used as α-amino aldehyde templates in the boron trifluoride–diethyl ether mediated addition reactions of organocuprates. Methoxy group displacement occurs in good yields (72–90%) with complete retention of configuration and subsequent cleavage of the heterocycle provides *N*-protected-α-amino esters in moderate to good yields (60–92%) without any loss of stereochemical integrity.[75]



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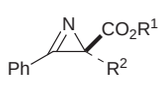

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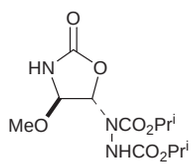
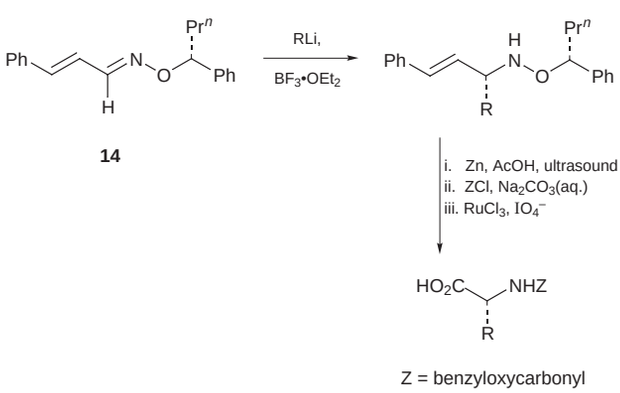


13

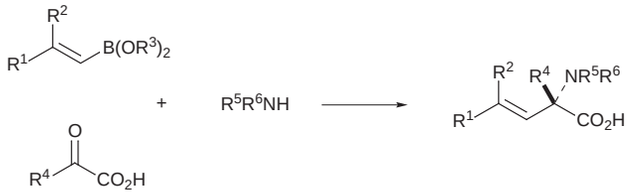
The addition of organolithium reagents to the (*R*)-*O*-(1-phenylbutyl)hydroxylamine oxime of cinnamaldehyde **14** proceeds in good yields (76–95%) with high levels of diastereoselection (90–93% de). Subsequent cleavage of the hydroxylamine and oxidative degradation of the styryl group provides moderate to good yields (31–86%) of the corresponding α-amino acids (**Scheme 18**).[76] This method has been extended to the synthesis of quaternary α-methyl-α-amino acids based on organolithium additions to the corresponding ketoxime of *trans*-4-phenylbut-3-en-2-one. The cerium(III) chloride mediated addition of methylmagnesium bromide to a chiral hydrazone derived from D-glyceraldehyde occurs with moderate stereoselection (56% de) and provides an α-hydrazino acid after oxidative cleavage of the 1,2-diol.[77] Variation of the Grignard reagent should provide access to a range of other substrates.



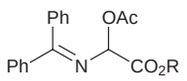
14

Scheme 18

Petasis has developed a novel three component variant of the Mannich reaction (**Scheme 19**) which provides access to β,γ-unsaturated-α-amino acids in moderate to good yields (54–96%) from alkenyl boronic acids, α-keto acids and amines.[78] The use of (*S*)-2-phenylglycinol leads to a highly diastereoselective reaction (>99% de) and provides essentially enantiopure products after hydrogenolytic cleavage of the benzylamine. The addition of diarylzinc reagents to glycine cation equivalent **15** (R = Me) proceeds in good yields (65–80%) to give the corresponding racemic α-aryl-α-amino esters after cleavage of the Schiff base,[79] whilst excellent enantioselectivity (95.5% ee) is observed in the addition of the anion of dimethyl malonate to the analogous *tert*-butyl ester, **15** (R = Bu^t), in the presence of palladium(II) and (+)-BINAP.[80]



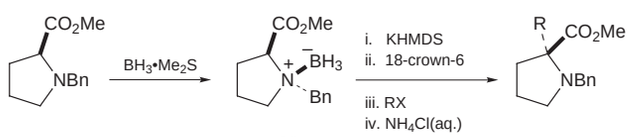
Scheme 19



15

The second major strategy for the synthesis of α-amino acids involves the addition of an electrophile to an α-amino carbanion. This anion is usually stabilised by the presence of an adjacent carboxy function although Beak has developed a novel enantioselective approach to a range of α-aryl amino acids based on his (−)sparteine/butyllithium chiral base chemistry.[81] Carboxylation of the α-anion of *N*-*tert*-butoxycarbonyl-*N*-(*p*-methoxyphenyl)arylmethylamines occurs in high yields (85–95%) with good enantioselectivity (86–92% ee). The sense of asymmetric induction can be controlled either by appropriate choice of the electrophile (carbon dioxide and methyl chloroformate show opposing enantioselectivity) or by trapping the initial carbanion with trimethyltin chloride prior to transmetallation with a second equivalent of (−)-sparteine/butyllithium. Variation of the electrophile also provides access to β- and γ-amino acids although yields are variable (25–95%).

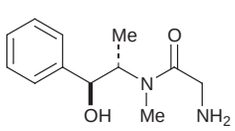
An enantiospecific approach to α-alkylproline derivatives based on alkylation of the potassium enolate of chiral borane–amine adduct **16** has been developed (**Scheme 20**).[82] Products are obtained in moderate to good yields (55–76%) and high enantiopurity (80–92% ee).



16

Scheme 20

Myers *et al*. have explored the asymmetric alkylation of pseudoephedrine glycinamide **17** for the synthesis of α-amino acids.[83] The alkylation proceeds in moderate to good yields (55–89%) with high diastereoselectivity (91–98% de) and provides access to highly enantioenriched *N*-protected-α-amino acids (96–>99% ee) after cleavage of the chiral auxiliary. The synthesis of α-methyl-α-amino acids based on the diastereoselective alkylation (60–>96% de, 60–75% yield) or palladium(0) catalysed allylation (70–>96% de, 53–65% yield) of alanine derived 2,3-dihydro-6*H*-1,4-oxazin-2-one **18** has been described.[84] The alkylation proceeds under mild solid–liquid phase transfer catalysis conditions in the presence of potassium carbonate whilst the amino acid is readily regenerated by acidic hydrolysis of the imine ester.



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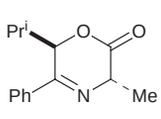
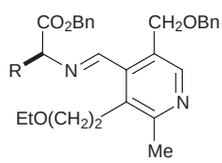


18

Moderate to good yields (54–84%) of racemic α,α-dialkyl-α-amino esters are available by lithium hydroxide mediated alkylation of the pyridoxal model derived aldimine **19**, followed by imine hydrolysis.[85] The acylation of *N*-[bis(methylthio)-methylene]glycine ethyl ester derived aza-allyl carbanions provides moderate yields (45–55%) of α-acyl-α-alkyl-α-amino acid derivatives **20** which have been employed in the synthesis of non proteinogenic amino acids.[86] The ruthenium(II) catalysed reaction of *N*-sulfonyl imines with methyl isocyanoacetate provides *trans*-5-substituted-4-methoxycarbonyl-2-imidazolines in high yields (75–90%) with good stereoselectivity (68–90% de).[87] Acidic hydrolysis of the heterocycle yields 2,3-diamino acids in 92–95% yield. β,β-Disubstituted-β-hydroxy-α-amino acids can be accessed in an analogous manner *via* the copper(I) mediated addition of methyl isocyanoacetate to ketones.[88] The stereoselectivity of this reaction is variable (0–>98% de) but yields are high (74–99%). Arylation of 2-substituted 4-ethoxycarbonyl-4,5-dihydrooxazol-5-ones **21** (R = Me, Ph) with aryllead(IV) triacetates proceeds in good yields with the corresponding racemic α-amino acids being liberated upon hydrolysis (75–94% overall yield).[89] Enantioenriched products (82–99% ee) are available by enzymatic resolution.



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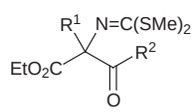

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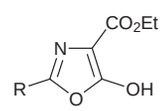
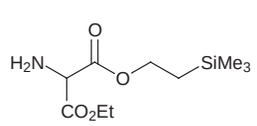


21

A number of transition metal based approaches to α-amino acids have been developed. The anion of α-amino-β-diester **22** has been shown to add to tricarbonyl(η^5-cyclohexadienyl)iron salts in moderate yields (44–63%).[90] Although no selectivity is observed in the addition reaction, a stereoconvergent iron mediated protonation occurs during desilylation–dealkylation and decarboxylation to give low yields (30–51%) of β-cyclohexadienyl-α-amino acids with moderate to excellent diastereoselectivity (50–>95% de). The palladium catalysed addition of serine derived organozinc **23** to tricarbonyl(η^6-chlorobenzene)-chromium complexes has been utilised for the synthesis of a series of substituted phenylalanines in variable yields (30–72% after decomplexation).[91] β-Ferrocenyl-α-amino acids are also accessible by this method. Addition of the zinc/copper reagent derived from **23** to enantiomerically pure (η^3-allyl)tetracarbonyliron salts results in fair to good yields (35–75%) of the corresponding ω-unsaturated products with complete stereocontrol,[92] whilst γ-keto-α-amino acids can be obtained in moderate yields (40–60%) by the palladium catalysed carbonylative addition of **23** to aryl iodides.[93] Stille cross coupling of aryl and vinylstannanes with a protected aspartic acid chloride also provides γ-keto-α-amino acids (37–91% yield).[94]



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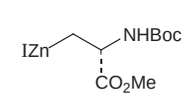
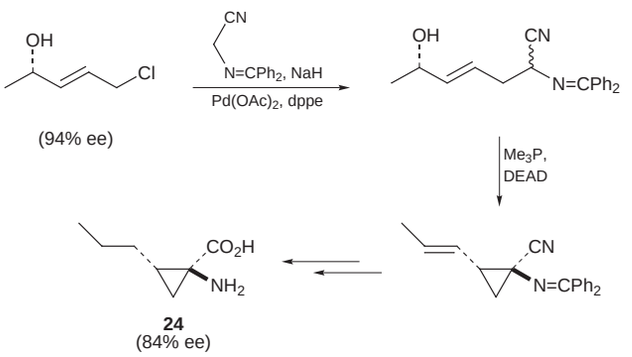


23

The Suzuki reaction of β-substituted-β-bromo dehydroamino acids with vinyl boronic acids proceeds with complete retention of configuration to give α,β,γ,δ-unsaturated products in low to excellent yields (37–94%).[95] Ring closing olefin metathesis has been utilised in the synthesis of a number of unsaturated α-amino acids. Both heterocyclic[96] and carbocyclic[97] products are accessible by this method. Moderate to excellent yields (51–99%) are obtained in the key ring-closing step which has been utilised in the formation of five, six and seven membered rings.

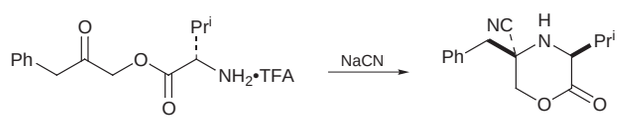
1-Aminocyclopropane-1-carboxylic acid **24** has been synthesised in low yield (29%) in 84% ee *via* the palladium(0) catalysed alkylation of an allyl chloride with a carbon nucleophile and subsequent Mitsunobu cyclisation (**Scheme 21**).[98] The rhodium mediated insertion of α-vinyl diazoester derived carbenoids into amine nitrogen–hydrogen bonds provides moderate yields (62–70%) of α-amino-β,γ-unsaturated esters.[99] α-Hydroxy-, α-silyl- and α-thio-β,γ-unsaturated esters have also been prepared using this approach.



24
(84% ee)

Scheme 21

Kazmaier and co-workers have explored the ester enolate Claisen rearrangement of amino acid prop-2-ynyl and allyl esters in the synthesis of γ,δ-unsaturated amino acids.[100] Stereoselectivity is generally high, although yields are variable. The diethylaluminium chloride catalysed 5-*exo* cyclisation of 2,3-epoxy trichloroacetimidates proceeds in moderate to good yields (54–79%) with low to excellent diastereoselectivities (16–100% de) and provides α-substituted serine derivatives upon cleavage of the intermediate 2-trichloromethyl-1,3-oxazoline.[101] α-Benzyl and α-carboxymethyl serines have been synthesised by way of the intramolecular asymmetric Strecker reaction of amino ketone **25** (**Scheme 22**).[102]

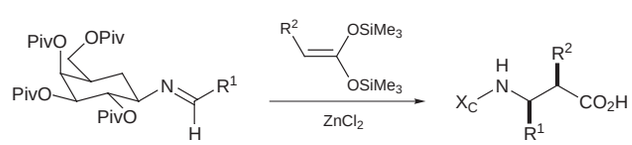


25

Scheme 22

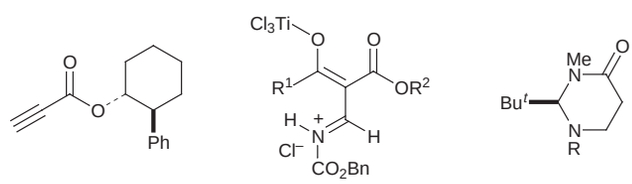
2.5.2 β-, γ- and ω-Amino acids and esters

β-Amino acids have been obtained in moderate to excellent yields (46–84%) by the enantioselective homologation of α-amino acid chlorides using diazomethane and silver(I) benzoate.[103] The addition of the vinylaluminium species derived from alkyne **26** to imines is highly diastereoselective (86–>98% de) and provides moderate to good yields (34–90%) of the corresponding β-amino-α-methylene esters.[104] The addition of silyl ketene acetals to *N*-galactosyl aldimines is selective (78–>90% de) for the *erythro* product, although yields are variable (45–97%), and provides β-amino acids upon cleavage of the auxiliary (**Scheme 23**).[105] Addition of the lithium enolate of *tert*-butyl phenylacetate to the *N*-galactosyl benzaldimine yields the corresponding *threo* diastereomers as a 3:1 mixture with the (2*S*,3*S*)-isomer as the major product.



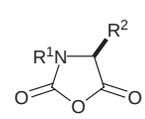
Scheme 23

The addition of a 2,2-dimethyl silyl ketene acetal to a benzaldehyde imine bearing a dioxopiperazine chiral auxiliary is also diastereoselective (85% de, 80% yield) and provides the α,α-dimethyl-β-amino-β-phenyl ester upon hydrolysis.[106] The three component coupling of an aldehyde, a primary amine and a silyl ketene acetal has been shown to proceed in the presence of a polymer-supported scandium catalyst to give α,α-dimethyl-β-amino acids in high yields (73–89%).[107] The addition of silyl ketene acetals to *N*-benzyloxycarbonyl iminium ions **27** also proceeds in high yields (87–99%) although diastereoselectivities are low,[108] decarboxylation provides δ-keto-β-amino esters. The alkylation of asparagine derived pyrimidinone **28** (R = Bz) proceeds in good yields (75–80%) and is highly stereoselective (>90% de). α-Alkyl-β-amino acids are obtained in good yields (80–85%) upon hydrolysis.[109] Epimerisation of the intermediate alkylated pyrimidinones provides access to the enantiomeric products although a slight lowering of stereoselectivity is observed. The addition of electron deficient alkenes to the α-amino radical generated from **28** (R = *o*-bromobenzoyl) by 1,5-hydrogen abstraction provides moderate yields (23–45%) of enantioenriched (97–98% ee) δ-substituted-β-amino acids after cleavage of the auxiliary.[110] α,β-Unsaturated-β-amino esters have been synthesised in moderate to good yields (50–90%) by the sonochemical Blaise reaction of nitriles and ethyl bromoacetate[111] whilst the addition of carboxy containing organozinc reagents to iminium ions provides β-, γ- and δ-*N*,*N*-dialkylamino esters in reasonable yields (52–74%).[112]



26 **27** **28**

N-Protected-γ-amino-β-keto esters can be accessed in moderate yields (50–70%) by addition of the lithium enolate of ethyl acetate to a range of commercially available urethane *N*-protected-*N*-carboxyanhydrides **29**, substrates which are more commonly used in peptide coupling reactions. The addition of amino acid derived 1-amidoalkyl radicals to acrylates provides moderate yields (50–53%) of the corresponding racemic γ-amino esters.[113] The dianions of *N*-trifluoroacetyl- and *N*-*tert*-butoxycarbonyl-γ-amino esters undergo highly stereoselective (>90% de) α-alkylation reactions to give good yields (60–90%) of the 2,4-*anti* products,[114] whilst α-alkyl-ω-amino acids have been obtained by α-alkylation of 2-(ω-phenylsulfonylaminoalkyl)oxazolines (79–>95% de, 50–93% yield).[115]



29

2.6 Unsaturated acids and esters

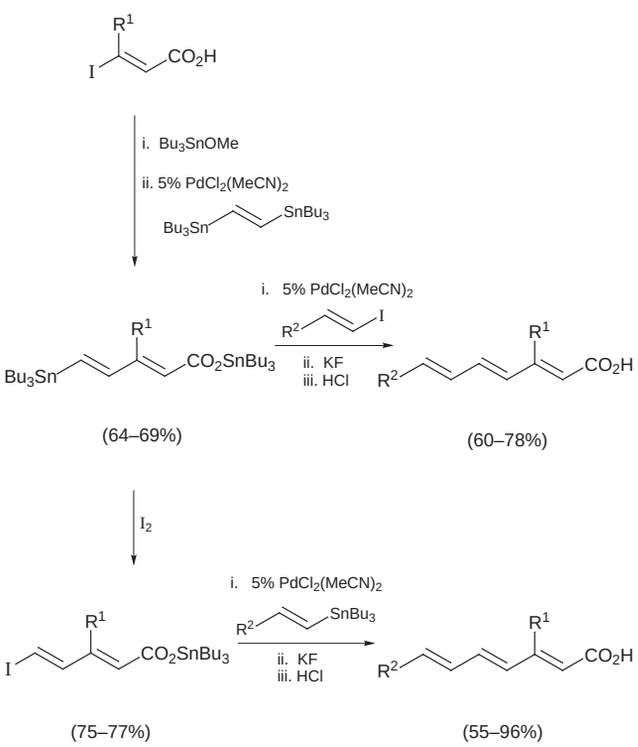
A range of strategies for the synthesis of conjugated and non-conjugated unsaturated acids and esters based on the formation of both single and double carbon-carbon bonds are available. The (*Z*)-selective (93–99%) Horner–Wadsworth–Emmons reaction of ethyl [bis(*o*-alkylphenyl)phosphono]acetates in the presence of sodium hydride or Triton® B provides a range of α,β-unsaturated esters in high yields (70–100%)[116] whilst microwave irradiation has been reported to accelerate the Wittig reactions of stabilised phosphorus ylids.[117] The Horner reaction of 1-(benzotriazol-1-yl)-3-(diphenylphosphoryl)-1-ethoxyprop-1-ene **30** with aldehydes provides γ-substituted-(*E*)-β,γ-unsat-

urated esters in moderate to good yields (55–81%) after hydrolysis (**Scheme 24**).[118] γ,γ-Disubstituted-β,γ-unsaturated esters are accessed in 50–84% yield by the analogous reaction with ketones. A β-substituent may be introduced by α-alkylation of the phosphine oxide prior to the Horner reaction.

30

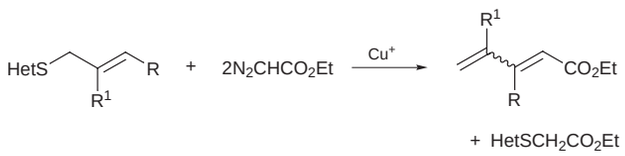
Scheme 24

A number of metal mediated approaches to unsaturated acids and esters, involving both the coupling and the carbonylation/carboxylation of unsaturated fragments, have been investigated. α-Methylcinnamic acids are formed selectively in moderate yields (55–75%) in the Heck coupling of activated aryl bromides and *tert*-butyl methacrylate[119] whilst the Heck coupling of ethyl cinnamates with aryl iodides provides low to excellent yields (32–100%) of 3,3-diaryl propenoates which undergo slow, temperature dependent, *E*–*Z* isomerisation under the reaction conditions.[120] (*E*)-Isomers are formed directly upon coupling of substituted aryl iodides with ethyl cinnamate whilst (*Z*)-isomers are available from ethyl acrylate by successive Heck couplings of a substituted aryl iodide then iodobenzene. Conjugated trienoic acids can be prepared in moderate to good yields by performing two successive Stille reactions, each of which occurs with retention of the alkene geometry (**Scheme 25**).[121] Protection of the carboxylic acid as a tributyltin ester is crucial for the success of the reaction.



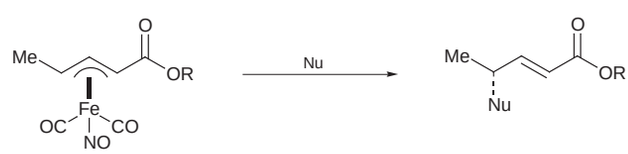
Scheme 25

The electrocarboxylation of vinyl triflates with carbon dioxide in the presence of a palladium(II) catalyst provides α,β-unsaturated carboxylates in low to good yields (32–86%) with superior yields (>70%) being observed for non-conjugated starting materials.[122] Regio- and stereo-controlled hydrocarboxylation of both terminal and internal alkynes can be achieved in moderate yields (37–60%) using sodium tetracarbonylhydridoferrate and dichloromethane in tetrahydrofuran followed by oxidation with copper(II) chloride.[123] The palladium catalysed carbonylation of aryl substituted allylic alcohols in the presence of phenols provides moderate to good yields (53–80%) of the corresponding γ-aryl-β,γ-unsaturated phenolic esters.[124] Conjugated dienoic esters are obtained in good yields (68–94%) by treatment of oxazolin-2-yl, benzimidazol-2-yl and benzothiazol-2-yl allyl sulfides with excess ethyl diazoacetate in the presence of a copper(I) complex (**Scheme 26**).[125]

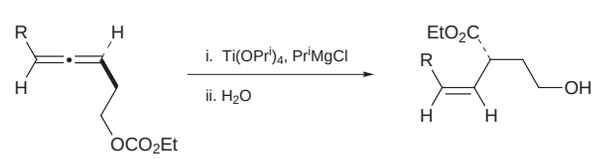


Scheme 26

The addition of nucleophiles to chiral (η^3-allyl)dicarbonylnitrosyliron complexes derived from chiral enoates proceeds in good yields (72–83%) with high selectivity (86–>98% de) to give γ-functionalised-α,β-unsaturated esters (**Scheme 27**).[126] The titanium(IV) isopropoxide–isopropylmagnesium chloride promoted intramolecular nucleophilic acyl substitution of allenylic carbonates is stereoselective (77–>98% *Z*) and gives good yields (56–88%) of α-substituted-β,γ-unsaturated esters after hydrolysis of the organotitanium intermediate (**Scheme 28**).[127] The reactions of chiral allenes are enantiospecific.



Scheme 27

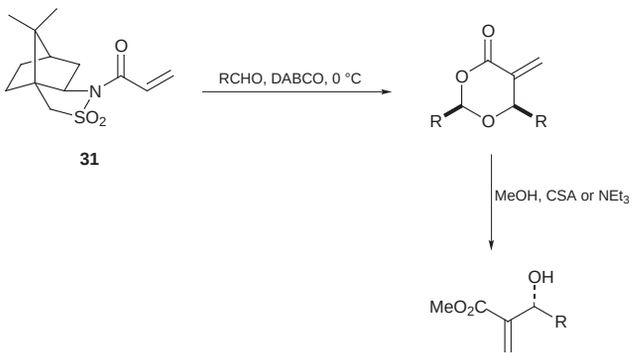


Scheme 28

The Baylis–Hillman reaction provides access to 3-hydroxy-2-methylene alkanoates but its synthetic utility is restricted by the long reaction times required. Rate enhancements have been observed upon addition of lanthanide and Group 3 metal triflates and diols[128] and when tributylphosphine is used instead of DABCO as the promoter.[129] More significantly, lowering the reaction temperature (from ambient to 0 °C) results in a dramatic reduction in reaction time (*e.g.* from 1 week to 8 h) for a range of aldehydes (67–74% yield).[129] This has led to the successful development of an asymmetric Baylis–Hillman reaction (>99% ee, 33–98% yield) with diastereofacial selectivity being controlled by chiral sultam **31** (**Scheme 29**).[130]

The radical allylations of *anti*-α-bromo- or -α-seleno-β-hydroxy esters with allylstannanes in the presence of alkylaluminium compounds are highly diastereoselective (85–94% de, 40–97% yield), α-phenylseleno esters give *anti*-products in the presence of trimethylaluminium whilst *syn*-selectivity is observed in the methylaluminium bis[2,6-di-(*tert*-butyl)-4-methylphenoxide] mediated reaction of α-bromo esters.[131] The radical allylation of α-iodo-β-methoxy esters with allyltrimethylsilane in the presence of magnesium bromide–diethyl ether gives good yields (70–87%) of *anti*-products in >98% de.[132]

The addition of trimethylaluminium to chiral, non-racemic, terminal γ,δ-epoxy acrylates proceeds in a regio- and stereo-

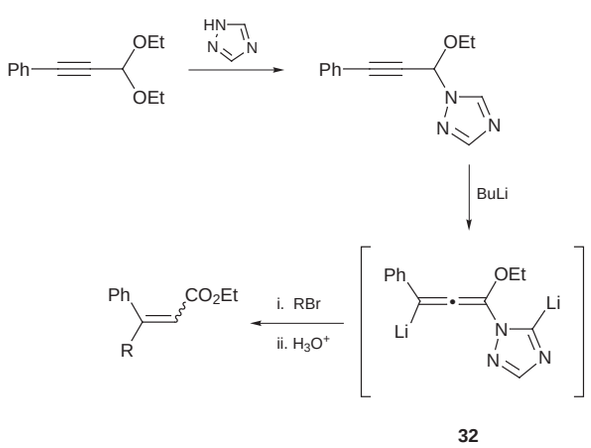


31

Scheme 29

defined manner to give γ-methyl-δ-hydroxy acrylates in good yields (72–87%) with complete retention of enantiopurity.[133] γ-(*p*-Nitrophenylsulfonyloxy)-α,β-unsaturated esters undergo direct displacement by heteroatom nucleophiles to give moderate to excellent yields (41–100%) of the corresponding γ-substituted enoates.[134]

Low selectivities (1:2–1:4, *E*:*Z*) are observed in the synthesis of β-substituted-β-phenyl-α,β-unsaturated esters which are obtained in moderate yields (65–71%) from phenylprop-2-ynyl aldehyde diethyl acetal by addition of 1,2,4-triazole-stabilised allenic anion **32** to alkyl halides (**Scheme 30**).[135] The conjugate addition of the anion of chiral sulfoxide **33** to alkenoates and *n*-halo alkenoates provides high yields (64–93%) of a single product diastereomer (**Scheme 31**).[136] Desulfinylation of the (*n* − 1) cyclic carboxylate formed by intramolecular trapping of the initial enolate gives high yields (91–92% when *n* = 6) of the corresponding *trans*-β-vinyl cyclic carboxylates **34** (R = H or $SiMe_3$).



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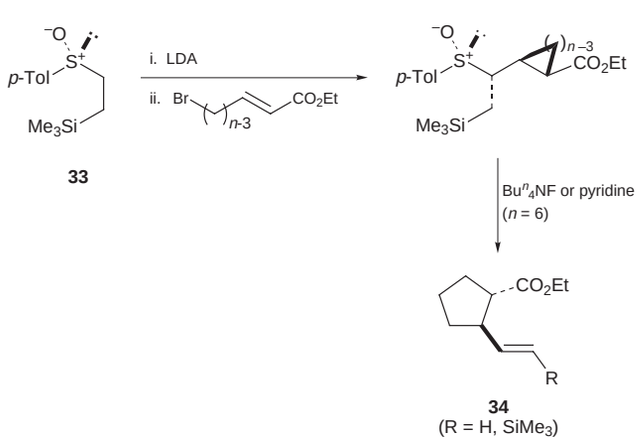
Scheme 30

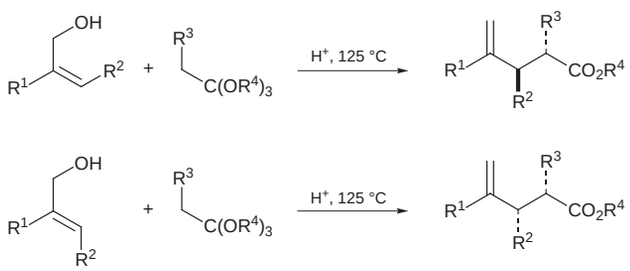


33

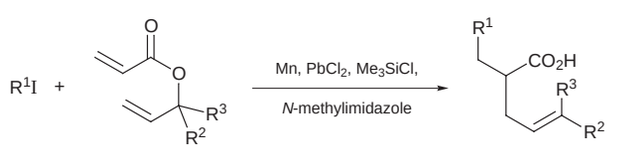
34
(R = H, $SiMe_3$)

Scheme 31

Several syntheses of unsaturated acids and esters based on intramolecular rearrangements have been reported. The enolate Claisen rearrangement of tricarbonyl(η[4]-dienyl)iron complexes proceeds in high yields (70–95%) with moderate diastereofacial selectivity (30–50% de)[137] whilst the orthoester Claisen rearrangement of trisubstituted allylic alcohols is stereospecific (54–88% de) and gives moderate to good yields (41–86%) of the corresponding α,β,γ-trisubstituted-γ,δ-unsaturated esters (**Scheme 32**).[138] The manganese–lead(II) chloride–trimethylsilyl chloride mediated 1,4-addition of alkyl radicals to acrylate allyl esters with subsequent Ireland–Claisen rearrangement provides good yields (75–95%) of α-substituted-γ,δ-unsaturated esters with high (*E*)-selectivity (**Scheme 33**).[139]



Scheme 32



Scheme 33

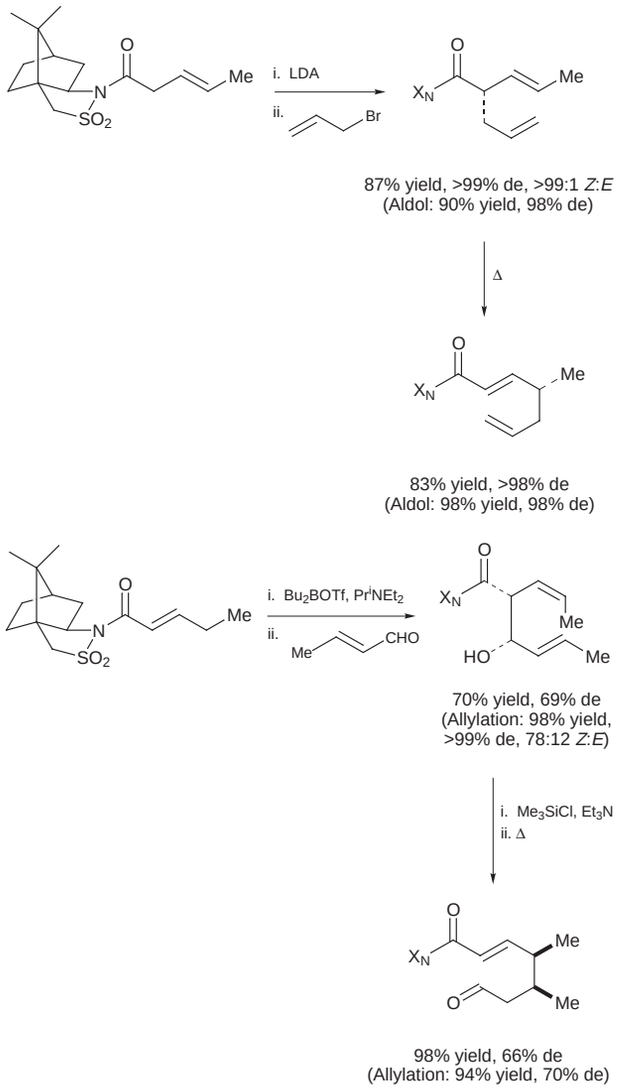
Nakai and co-workers have investigated the application of allylation–Cope rearrangement and aldol–Cope rearrangement sequences for the synthesis of chiral ω-functionalised-α,β-unsaturated acid derivatives (**Scheme 34**).[140] Both processes occur in high yields (69–92%) with good stereocontrol. Silylation of the intermediate aldolate is required to prevent a retroaldol reaction during the Cope rearrangement.

Two methods for the isomerisation of unsaturated esters have been reported. Lithium phenylsulfanyltetraisopropoxytitanate and lithium thiophenoxide mediate the low temperature *Z*→*E* isomerisation of γ-oxygenated-α,β-unsaturated esters (92–100% *E*, 91–100% yield)[141] whilst pentacarbonyliron has been utilised in the synthesis of α,β-unsaturated esters from non-conjugated unsaturated esters in moderate to good yields (67–94%).[142]

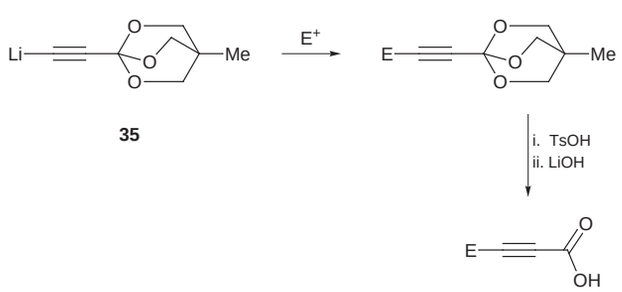
Non-racemic allenic esters have been obtained in good yields (62–91%) and high enantiopurity (60–93% ee) by the palladium mediated alkoxycarbonylation of chiral prop-2-ynylic mesylates[143] and by the dynamic kinetic protonation of racemic allenyl metal species with a chiral proton source [⩾98% ee with (*R*)-pantolactone].[144] 1-(Lithioethynyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane **35** has been shown to act as a propiolate anion equivalent (**Scheme 35**).[145] It reacts with electrophiles in high yields (61–95%) with the carboxylic acid being liberated upon hydrolysis.

2.7 Keto acids and esters

α-Keto esters have been prepared from α-sulfonyl esters by way of the thermal decomposition of the corresponding α-phenylsulfonyl-α-methylsulfanyl esters (**Scheme 36**).[146] Solid–liquid phase transfer catalysis is used in the thiomethylation step which proceeds in moderate to good yields (39–96%). The hexamethylditin mediated free radical addition of alkyl iodides to phenylsulfonyl methoxycarbonyl oxime ether **36** also provides α-keto esters in moderate to good yields (64–92% after oxime hydrolysis).[147] The addition of organocuprates derived from



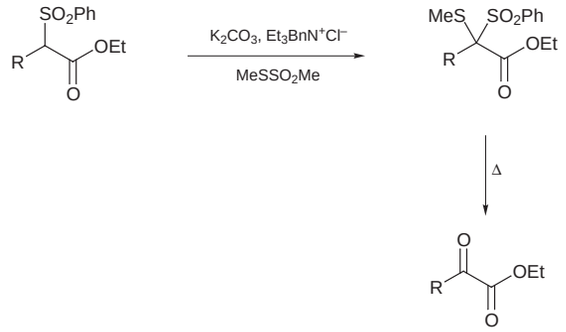
Scheme 34



Scheme 35

Grignard reagents, copper(I) bromide and lithium bromide to dicarboxylic acid chloride monoesters provides good yields (68–98%) of α-, γ-, δ- and ω-keto esters;[148] however, β-keto esters cannot be formed by this method. The chemoselective addition of Grignard reagents to 1-(*N*-alkoxyoxalyl-*N*-methylamino)-3-methylimidazolium salts **37** leads to the formation of α-keto esters in moderate to good yields (56–82%);[149] this reaction has also been extended to the synthesis of higher homologues (53–82% yield),[150] although β-keto esters are again inaccessible due to the preferential formation of enolates.

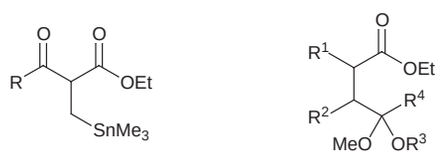
α,α-Disubstituted-β-aryl-β-keto esters have been synthesised in moderate to good yields (30–78%) by the addition of silyl ketene acetals to a range of aryl acid chlorides;[151] a Lewis acid promoter is required if the aryl ring bears an electron withdrawing substituent.



Scheme 36

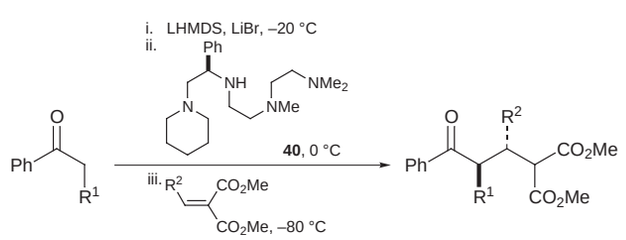
36 **37**

Two methods for the synthesis of γ-keto esters have been reported. Addition of niobium(V) chloride to α-trialkylstannylmethyl-β-keto esters **38** leads to the formation of the homologous γ-keto ester in moderate to good yields (51–88%),[152] whilst the radical coupling of α-halo acid derivatives with vinyl ethers gives good yields (65–95%) of the corresponding γ-dialkoxy carboxylates **39**.[153]



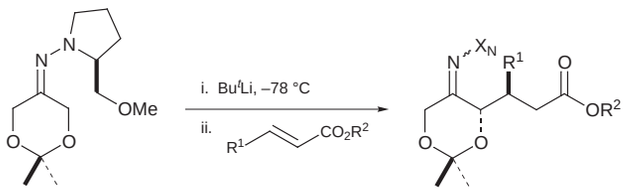
38 **39**

The primary strategy employed for the synthesis of δ-keto esters is the addition of an enolate to a conjugate acceptor. The Michael reaction of ketone lithium enolates with alkylidene malonates has been shown to proceed in excellent yields (95–99%) with high levels of enantio- and diastereo-control (81–99% ee, 68–98% de) in the presence of chiral amine **40** (**Scheme 37**).[154] High levels of stereoselectivity (89–97% ee, 91–96% de) are also observed in the addition of chiral hydrazone **41** to α,β-unsaturated esters (**Scheme 38**).[155] 3-Substituted-4,6-dihydroxy-5-oxo esters are formed in moderate to good yields (40–79%) after cleavage of the chiral auxiliary.



Scheme 37

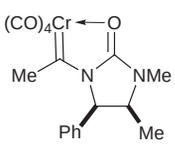
α,α-Dimethyl-β-chiral-δ-keto esters are formed with low to good enantioselectivity (22–92% ee) in low to moderate yields (6–65% after transesterification with methanol) by addition of chiral cinchonyl isobutyrates to β-substituted-α,β-unsaturated ketones.[156] The enolate metal counterion plays a key role in determining the facial selectivity of the addition; iodozinc enolates favour the (*S*)-product whilst lithium enolates are (*R*)-selective in the presence of tetramethyltin. A copper(II) bis-



41

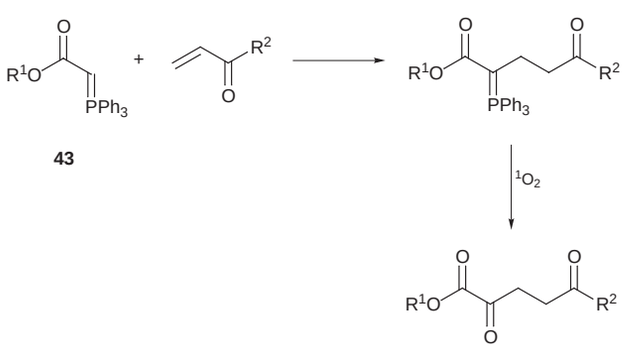
Scheme 38

oxazoline complex has been shown to promote the enantioselective (60–66% ee) Mukaiyama–Michael reaction of a silyl ketene acetal with 2-methoxycarbonylcyclopent-2-enone.[157] Here, the facial selectivity is dependent on the copper complex counterion employed. Europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionate), Eu(fod)$_3$, has been employed in the selective reaction of α,β-unsaturated ketones with silyl ketene acetals in the presence of saturated ketones (95–>99% selectivity for enone derived products).[158] Exclusive 1,4-addition occurs with cyclic enones but predominantly 1,2-addition to acyclic enones is observed. Carbene complex **42** has been used as a chiral acetate enolate equivalent undergoing a diastereoselective (92–94% de) addition to enones in moderate to good yields (46–91% after chromium decomplexation).[159]



42

The asymmetric Michael addition of α-cyano esters to enones is catalysed by a chiral ruthenium(I) complex bearing a bis-phosphine ligand. δ-Keto-α-cyano esters are formed in quantitative yield with moderate enantioselection (66–73% ee).[160] The ytterbium(III) triflate mediated addition of α-nitro esters to enones provides excellent yields (96–99%) of α-nitro-δ-keto esters in aqueous media.[161] The addition of acylphosphonium ylid **43** to enones is high yielding (86–92%), and cleavage of the resultant phosphonium ylid with singlet oxygen gives good yields (76–83%) of the corresponding α,δ-diketo esters (**Scheme 39**).[162]

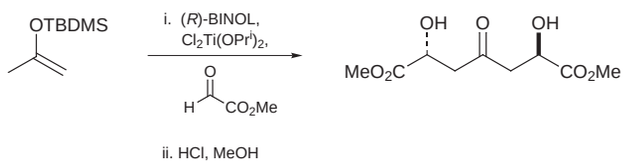


43

Scheme 39

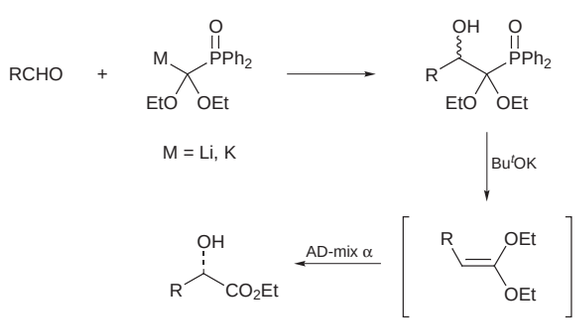
2.8 Hydroxy acids and esters

α-Hydroxy acids and esters have been generated both by carbon–carbon bond forming approaches and by the interconversion of functional groups. The (salen)manganese(III) catalysed asymmetric oxidation of silyl ketene acetals provides low yields (37%) of α-hydroxy esters with moderate enantioselectivity (57% ee).[163] Racemic α-bromo acids have been converted into (*R*)- or (*S*)-α-hydroxy acids by esterification with a 2-hydroxypyrrolidinone chiral auxiliary and subsequent dynamic kinetic resolution during the addition of *p*-methoxyphenol in the presence of sodium hydride and a phase transfer catalyst. Initial products are formed in moderate to excellent yields (48–98%) with good diastereoselectivity (54–98% de). Essentially enantiopure α-hydroxy acids are obtained in moderate yields (46–65%) upon recrystallisation and cleavage of the *p*-methoxyphenyl ether and the chiral auxiliary.[164] The chemoselective reduction of α-aryl-α-keto esters has been achieved in good yields (70–89%) by reaction with a single equivalent of sodium borohydride.[165] The presence of excess reducing agent leads to the formation of 1,2-diols. Rhodium(I) amidophosphine-phosphinite catalysts have been utilised in the enantioselective hydrogenation of α-alkyl-α-keto esters (66–95% ee).[166] Significant reductions in enantioselectivity (8–81% ee) are observed in the hydrogenations of aryl substrates, with a reversal in facial selectivity also occurring. The asymmetric (*R*)-BINOL–titanium(IV) mediated tandem two-directional Mukaiyama aldol reaction of methyl glyoxylate with the silyl enol ether of propan-2-one (**Scheme 40**) proceeds in good yield (77%) with high stereoselectivity (>99% de, >99% ee).[167]

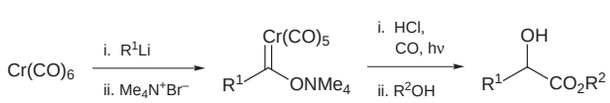


Scheme 40

The *C*-acylation of methyl phenylglyoxylate by acyl halides and anhydrides is promoted by titanium(III) chloride–pyridine. Products are obtained in moderate to good yields (45–90%).[168] An olefination–dihydroxylation sequence provides the products of the asymmetric addition of an ethyl formate anion equivalent to aldehydes (**Scheme 41**) in moderate to good yields (27–94%) and with high levels of enantioselectivity (70–>99% ee).[169] The photolytic reaction of *in situ* generated pentacarbonyl(hydroxyalkylidene)chromium complexes **44** with alcohols under a carbon monoxide atmosphere gives low to moderate yields (4–62%) of the corresponding α-hydroxy esters (**Scheme 42**).[170]



Scheme 41

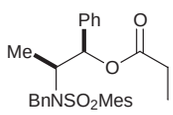


44

Scheme 42

The addition of ester enolates to aldehydes and ketones provides rapid access to β-hydroxy esters. Carreira has reported the *in situ* preparation of his chiral titanium salicylate biaryl catalyst for asymmetric acetate aldol reactions.[171] No diminution of yield or enantioselectivity is observed. The additions of lithium ester enolates to (R_S)-2-(*p*-tolylsulfinyl)cyclohexanone proceed in high yields (81–90%) with good diastereocontrol

(82–100% de).[172] Elimination of the sulfoxide provides the corresponding β-hydroxy-γ,δ-unsaturated ester. The dicyclohexylboron triflate mediated *anti*-aldol reactions of chiral carboxylate **45** are highly diastereoselective (90–>98% de, 90–98% yield),[173] whilst the products of the enantioselective addition of acetic acid to aldehydes can be accessed by the use of chiral ligands on boron in the aldol reactions of α-(thiomethyl)-ethanoic acid (**Scheme 43**).[174] (−)-Di(isocaran-2-yl)chloroborane yields *syn*-products (78–>99% ee, 60–82% de) whilst (−)-di(isocaran-4-yl)chloroborane is *anti*-selective (14–98% ee, 50–80% de). Desulfanylation provides β-hydroxy esters in good yields (70–75%). Highly enantioenriched acetate aldol products (83–99% ee) have also been obtained in high yield (83–92%) by desulfurisation of the products of the chiral oxazaborolidinone mediated Mukaiyama aldol reaction of aldehydes with silyl ketene acetal **46**.[175] Excellent diastereoselectivities (100% de) are observed when β-hydroxy aldehydes are employed in this reaction.[176] High yields (77–83%) are obtained, with the configuration of the new stereocentre being dictated by the chirality of the catalyst.



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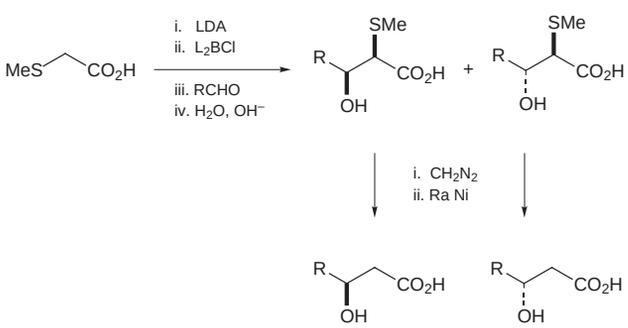
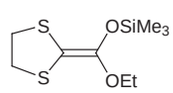
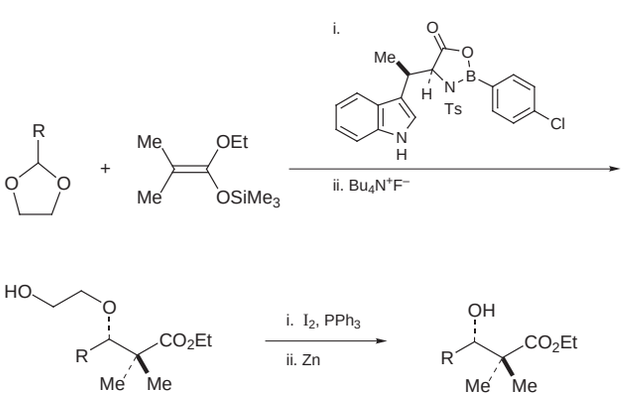


Scheme 43



46

An amino acid derived oxazaborolidinone has been employed in the enantioselective reaction of silyl ketene acetals with achiral 1,3-dioxolanes (**Scheme 44**). The β-hydroxy ester products are obtained in good yields (82–88%) with high levels of asymmetric induction (86–92% ee).[177]

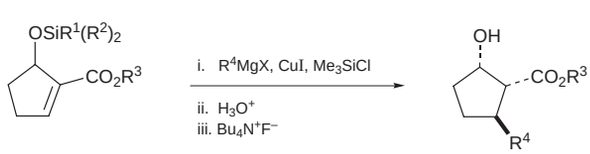


Scheme 44

The stereoselective zinc chloride mediated insertion of ketenes into 1,3-dioxolanes has also been investigated.[178] Moderate to good yields (55–82%) and high levels of diastereoselection (91–>95% de) were observed when a chiral 2-*p*-methoxyphenyl-4,5-dimethyl-1,3-dioxolane was employed. A chiral aluminium Lewis acid has been shown to provide reasonable levels of enantioselectivity (55–82% ee) in the addition of a 2,2-dimethyl silyl ketene acetal to aldehydes,[179] whilst the catalytic asymmetric aldol reactions of a trichlorosilyl ketene acetal proceed in high yields (89–99%) but with low enantioselectivity (20–62% ee) in the presence of chiral phosphoramides.[180] Tartrate derived silyl ketene acetals undergo diastereoselective addition reactions to both aldehydes and α-keto esters.[181] The α-stereocentre is formed with excellent stereocontrol (>90% de) whilst lower selectivity (76–>90% de) is observed in the formation of the β-stereocentre. Tributyltin perchlorate and dibutyltin bis(triflate) have been shown to mediate the selective (80–100%) 1,2-addition of silyl ketene acetals to α,β-unsaturated aldehydes in the presence of saturated aldehydes.[182] Good yields (61–81%) of β-hydroxy-γ,δ-unsaturated products are obtained.

A chiral β-amino alcohol has been employed in the enantioselective Reformatsky reactions of *tert*-butyl α-bromoacetate; moderate to good yields (35–90%) and enantioselectivities (33–78% ee) are observed.[183] The chromium(II) mediated Reformatsky reaction has been studied by Wessjohann and co-workers: aldehydes react selectively in the presence of ketones[184] and, in contrast to the zinc mediated process, *anti*-products are favoured (36–58% de, 63–95% yield) when α-substituents are present.[185] Moderate yields (34–67%) are observed in the reactions of methyl ketones.[186] 3-Bromo-2-chloroprop-1-ene adds to aldehydes in aqueous solution in the presence of indium, good yields (64–99%) of β-hydroxy esters are obtained upon ozonolysis of the vinyl chloride thus formed.[187]

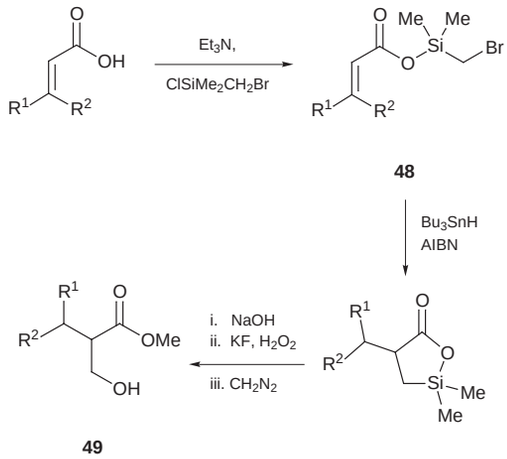
The addition of organocuprates to α,β-unsaturated esters bearing a γ-benzyloxymethyl ether proceeds in good yields (60–93%) with high *anti*-selectivity (78–>96% de).[188] Subsequent enolisation and α-substitution of the ester is *syn*-selective (>90% de). Cuprate addition to 3-trialkylsilyloxycyclopent-1-ene-2-carboxylates **47** (**Scheme 45**) is also highly diastereoselective (86–>99% de).[189] The presence of trimethylsilyl chloride in the reaction mixture suppresses the formation of S_N2' type addition products. The regioselective boron trifluoride–diethyl ether promoted ring opening of enantiopure styrene oxides with lithium cyanocuprates results in moderate yields (55–67%) of α-substituted-β-hydroxy carboxylic acids after oxidative cleavage of the phenyl ring.[190] Optically active dicarbonyl(η^5-cyclopentadienyl)(vinyl ether)iron salts behave as 3-hydroxypropionate-2,3-dication equivalents, providing β-hydroxy-δ-keto esters as mixtures of diastereomers in moderate to good yields (40–70%) upon addition of copper(I) enolates.[191]



47 (42–77%)

Scheme 45

The hydroxymethylation of carboxylic acids has been achieved by the intramolecular radical cyclisations of α,β-unsaturated esters **48** (**Scheme 46**). The substitution pattern of the alkene determines the mode of cyclisation (5-*exo vs.* 6-*endo*) with attack occurring at the least hindered end. Moderate yields (34–38%) of β-hydroxy esters **49** are obtained upon cleavage of the silicon tether.[192]



Scheme 46

2.9 Miscellaneous acids and esters

Synthetic approaches to a number of other heteroatom substituted carboxylic acids and esters have been described. Landais *et al*. have investigated the asymmetric synthesis of α-substituted-α-silyl esters based on the alkylation of chiral α-silyl esters and on the enantioselective insertion of an α-pantolactone diazoester into a silicon–hydrogen bond.[193] Preliminary studies indicate that products are available in good yields but with low levels of enantioselection. The stereoselective addition of methyl and phenyl disulfides to the α-lithio anions of 2-(γ-phenylsulfonylaminoalkyl)-1,3-oxazolines gives low to moderate yields (25–63%) of the corresponding enantioenriched (80–>90% ee) γ-amino-α-sulfanylated carboxylic acids after cleavage of the chiral auxiliary.[194] Cyclic β-keto sulfones have been shown to undergo carbon–carbon bond cleavage upon reaction with aqueous sodium hydroxide in the presence of cetyltrimethylammonium chloride to give good yields (64–98%) of the corresponding ω-sulfonyl carboxylic acids.[195] α-Seleno esters have been obtained in moderate to good yields (48–96%) by the tin(0) mediated addition of diselenides to α-bromo esters.[196] Sonication increases the rate of the reaction, which is carried out in aqueous media under an inert atmosphere.

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