Carboxylic acids and esters

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Reviewing the literature published between 1 August 1994 and 31 July 1995
Continuing the coverage in *Contemporary Organic Synthesis*, 1995, **2**, 107

1 Introduction

This review covers the literature pertaining to carboxylic acids and esters. Some chemistry of amino acids has also been included, although this area, as well as chemistries associated with amides and lactones is covered in separate articles in *Contemporary Organic Synthesis*.

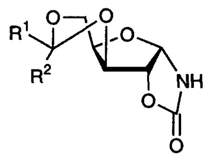
2 Carboxylic acids

2.1 General

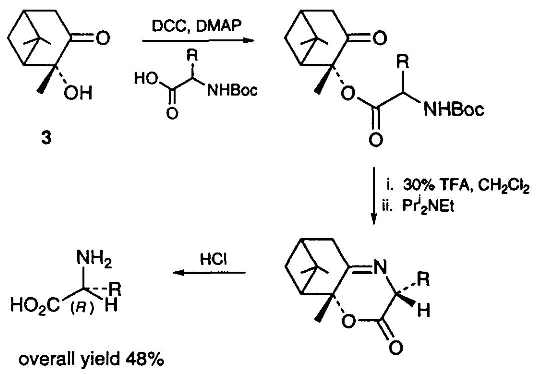
Directed *ortho*-lithiation is a powerful tool for the synthesis of polysubstituted aromatics. The carboxylic acid group, in particular, is a valuable *ortho* directing group due to the fact that it can be readily transformed into other useful functionalities, unlike the more traditionally used groups, *e.g.* amides and sulfonamides. An investigation into the competitive lithiation of substituted benzoic acids reveals that the carboxylic acid moiety is of intermediate capacity as an *ortho* director, being weaker than an amide, but stronger than methoxy and halo substituents.[1]

Novel, inexpensive resolving agents for carboxylic acids are still being sought. Although the use of oxazolidinones as resolving agents for carboxylic acids is known, they have not yet gained wide popularity for this purpose due to the commercially available auxiliaries being too expensive for large scale resolutions. Thus the oxazolidinones **1** and **2** are valuable additions to the literature, being available on multigram scale from inexpensive D-xylose.[2] Their highly crystalline nature is an added bonus, enabling the separation of diastereoisomers by fractional crystallisation as well as by chromatography.

An interesting resolution method for amino acids involves their initial coupling with the commercially available homochiral hydroxyketone **3**, followed by cyclisation of the resulting ester to form the corresponding Schiff base.[3] Only one of the diastereoisomers cyclises, enabling its separation (98% ee, after hydrolysis) by chromatography. The other diastereoisomer is not recoverable by this method (**Scheme 1**).

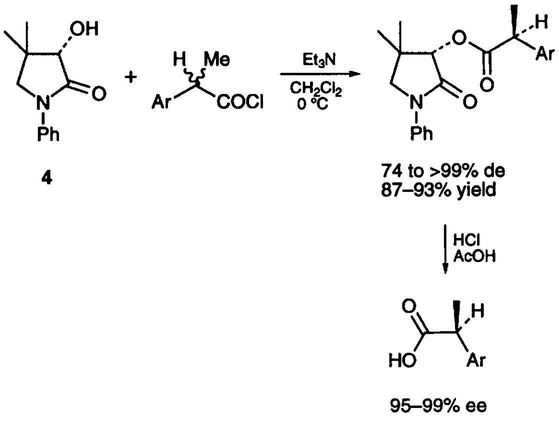


1 $R^1 = Ph; R^2 = H$
2 $R^1 = R^2 = Me$



Scheme 1

Homochiral α-arylpropanoic acids such as (*R*)-ibuprofan can be obtained in >95% ee by the diastereoselective addition of the (*R*)- or (*S*)-pyrrolidinone **4** to the ketene derived from a racemic acid chloride.[4] Although this elegant chemistry has been reported previously using (*R*)-pantolactone, this particular auxiliary has a major advantage in that its full recovery is possible. Both enantiomers of the chiral pyrrolidinone **4** can be synthesised on a multigram scale (**Scheme 2**).

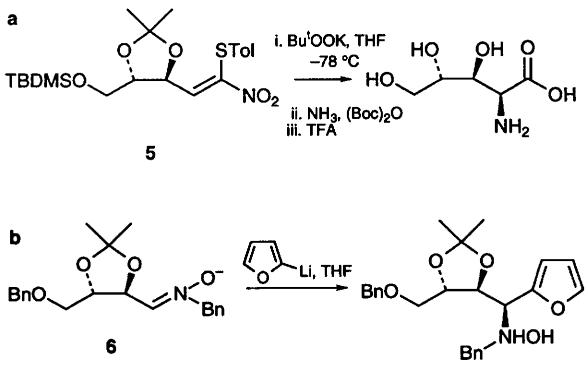


Scheme 2

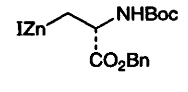
2.2 Amino acids

Novel approaches towards the diastereoselective synthesis of amino acids continue to be a major focus in the area of carboxylic acid chemistry. The stereoselective Strecker reaction, involving the diastereoselective nucleophilic epoxidation of the 1-arylthio-1-nitroalkene **5**, followed by regioselective ring opening with ammonia, provides a novel route to β-hydroxy amino acids in good yield (**Scheme 3**).[5] This facial selectivity in the nucleophilic addition to protected glyceraldehyde derivatives is once again observed in the addition of lithiofuran to the nitrone **6**, where the furan, which is later cleaved oxidatively, is a masked carboxylic acid synthon (**Scheme 3b**).[6]

In addition to the useful organozinc based alanine synthon **7** reported earlier, Jackson *et al.* have extended the scope of this chemistry to include the analogous zinc–copper reagent **8**.[7] This new synthon, based on the Knochel methodology, has enhanced reactivity, undergoing facile S_N2' alkylation with a variety of allylic and propargylic halides.



Scheme 3



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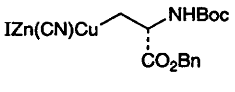

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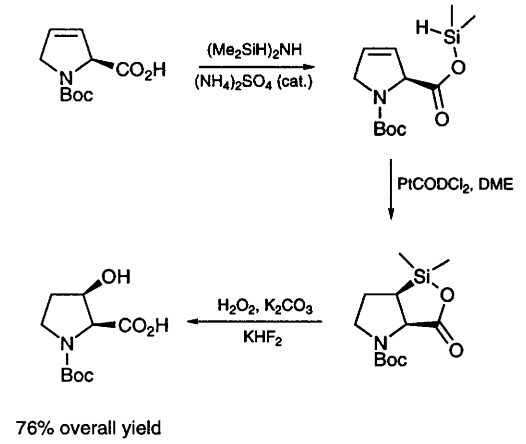
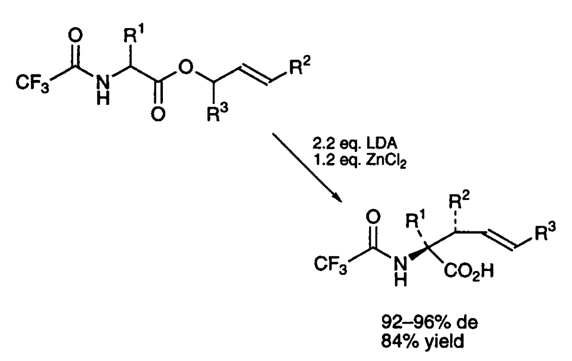
The unprecedented use of a carboxy group to direct the hydrosilation of β,γ-unsaturated acyloxysilanes provides an efficient synthesis of *cis*-β-hydroxy acids.[8] This methodology finds its use in one of the shortest syntheses of (2*S*,3*R*)-hydroxyproline reported to date (**Scheme 4**).

Zinc and magnesium enolates of amino acid esters derived from acyclic[9] and cyclic[10] allylic alcohols, undergo a diastereoselective Claisen rearrangement at 25 °C (−20 °C in the case of cyclic esters) resulting in the formation of α-alkylated γ,δ-unsaturated acids. The lithium enolates do not undergo this rearrangement, since they decompose at 25 °C. The zinc enolate has also been shown to be superior to the ketene silyl acetal in terms of the diastereoselectivity obtained in the rearrangement (**Scheme 5**).

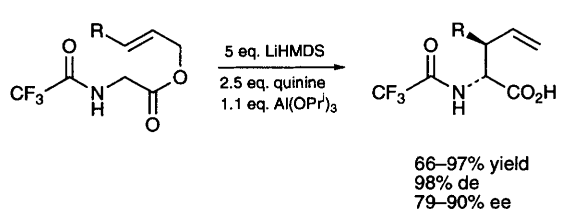


Scheme 4



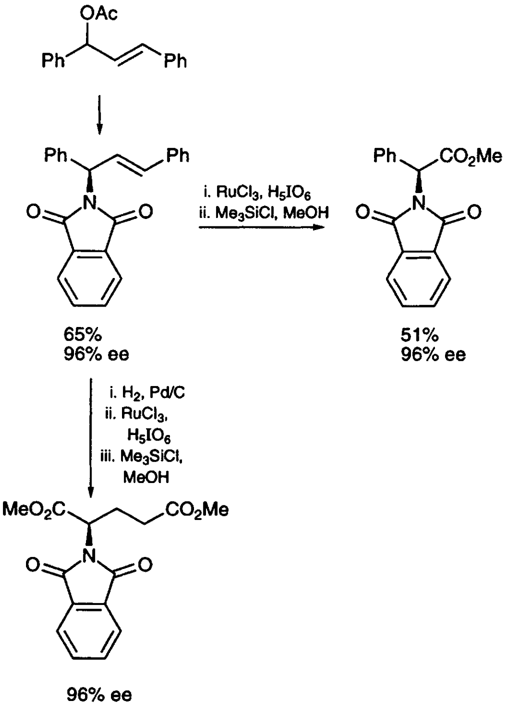
Scheme 5

The enolate driven Claisen rearrangement has also been extended to the enantioselective synthesis of homochiral amino acids (79–90% ee), where the presence of the chiral ligand in the reaction (*e.g.* quinine) has the added effect of improving the diastereoselectivity obtained (**Scheme 6**).[11]



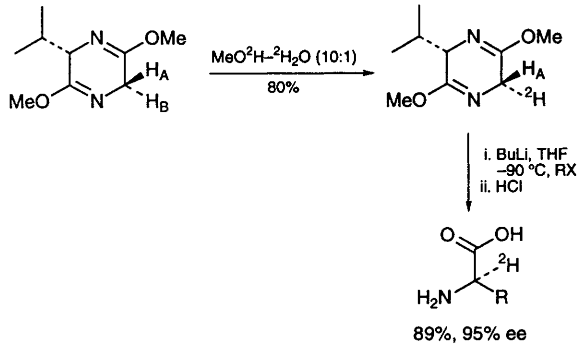
Scheme 6

The products obtained from the enantioselective palladium catalysed allylic substitution of 1,3-diphenylprop-2-enyl acetate can be converted into L-phenylglycine and D-glutamic acid derivatives with no loss of stereochemical integrity (**Scheme 7**).[12]

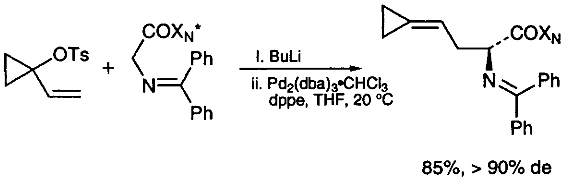


Scheme 7

The Schöllkopf bis-lactim ether has found use in the enantioselective synthesis of β-branched[13] and deuterated amino acids.[14] In the latter case, the judicious choice of deuteration conditions leads to the thermodynamically stable deuterated intermediate in >95% ee, which under kinetic conditions is alkylated exclusively on the opposite, less hindered, face of the auxiliary (**Scheme 8**).



Scheme 8

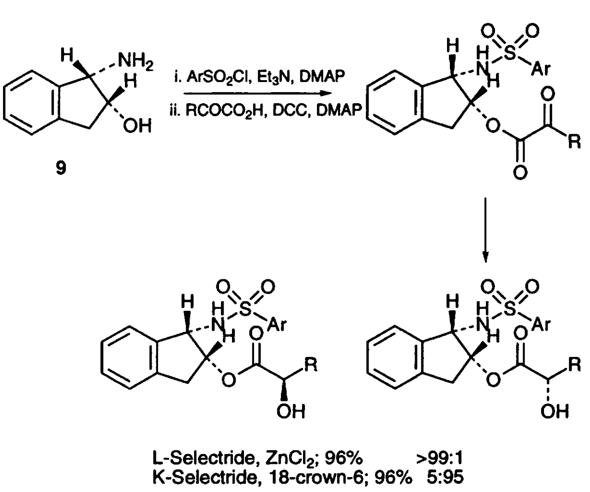


Scheme 9

The palladium catalysed allylation of chiral glycine equivalents provides α-allyl amino acids with good to excellent diastereoselectivity (67–90% de) (**Scheme 9**).[15] In earlier reports concerning diastereoselective Pd catalysed allylations, the presence of a chiral phosphine ligand has been found to be necessary in order to achieve respectable levels of diastereoselectivity.

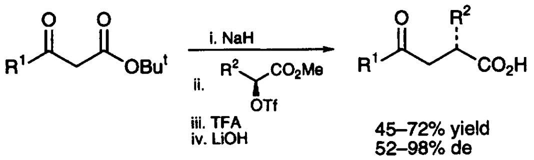
2.3 Oxo acids

The arylsulfonamido derivative of the *cis*-1-amino-2-hydroxyindan **9** can be coupled with α-keto acids and subsequently reduced to give the corresponding α-hydroxy acid of either enantiomer under different conditions (**Scheme 10**).[16] Although this methodology has been reported previously with regard to more esoteric auxiliaries, the advantage of this work lies in the fact that both antipodes of the indan are commercially available.



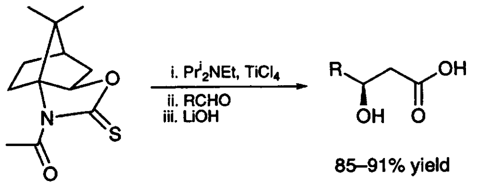
Scheme 10

β-Keto esters can be alkylated with optically pure 2-triflyloxy esters without any loss of stereochemical integrity (**Scheme 11**), providing an elegant, simple method for the synthesis of γ-keto acids.[17]



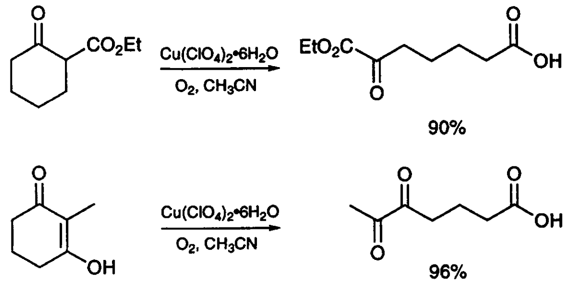
Scheme 11

It is well known that boron enolates of 'propionate' imides and thioimides undergo acylation with excellent diastereoselectivity. The corresponding boron enolates derived from 'acetate' imides and thioimides, on the other hand, give modest selectivity. There is an interesting difference in outcome when switching to the titanium enolate, however. Thus thioimide titanium enolates (**Scheme 12**) give excellent diastereoselectivities,[18] whereas the imide enolates do not; this difference is probably due to the greater affinity of the titanium towards sulfur.



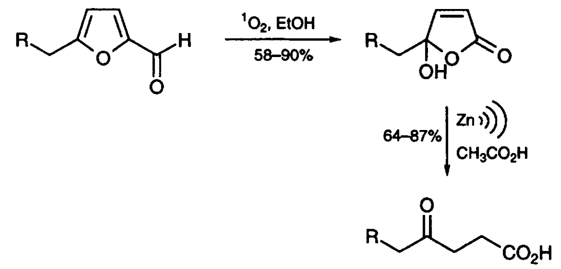
Scheme 12

β-Keto esters and enolisable 2-substituted cycloalkane-1,3-diones can be cleaved oxidatively to give ω-oxocarboxylic acids (**Scheme 13**).[19]



Scheme 13

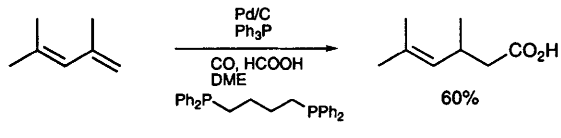
4-Hydroxy-Δ^2-butenolides derived from 2-furfural derivatives can be selectively reduced with zinc to give γ-oxocarboxylic acids. The use of ultrasound in the reaction avoids the need to use activated Zn or high temperatures (**Scheme 14**).[20]



Scheme 14

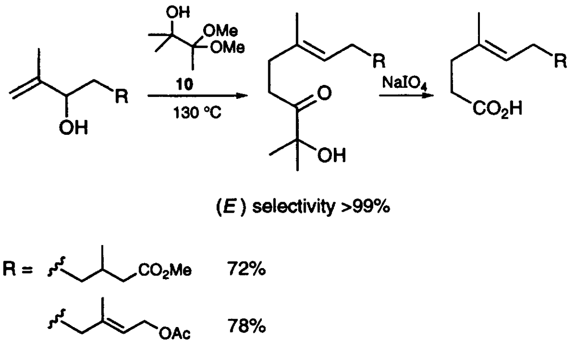
2.4 Unsaturated acids

Trisubstituted and disubstituted 1,3-dienes have been shown to undergo hydrocarboxylation at the least substituted double bond selectively (**Scheme 15**),[21] leading to γ-unsaturated carboxylic acids.



Scheme 15

A route that is complementary to the orthoester Claisen rearrangement, especially in the presence of base labile groups, involves simply heating an alcohol with the ketal **10** (**Scheme 16**) to give a rearranged α-hydroxy ketone, which is then oxidatively cleaved to reveal a carboxylic acid.[22]

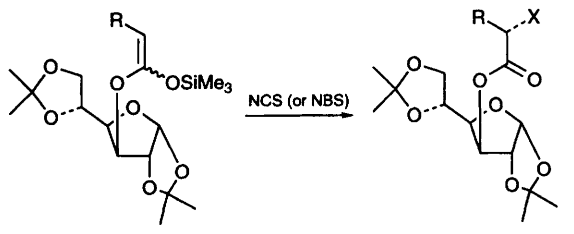


Scheme 16

2.5 Halo acids

The diastereoselectivity observed in the halogenation of chiral ester **11** (80–95% de for chlorination; 70–85% de for bromination) is surprisingly independent on the *Z*- or *E*-configuration of the starting silyl enol ether (**Scheme 17**).[23]

The addition of primary, secondary and tertiary alkyl radicals, generated from Barton esters, to electron deficient fluoroolefins, provides a new Arndt–Eistert type methylene group homologation leading to difluorocarboxylic acids (**Scheme 18**).[24]



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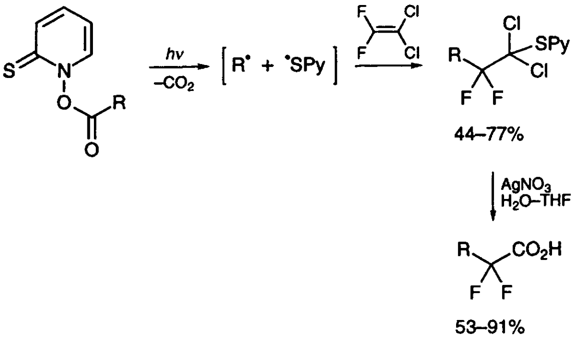
X = Cl, 80–95% de
X = Br, 70–85% de

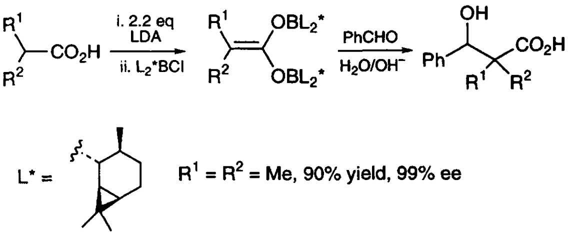
Scheme 17



Scheme 18

2.6 Miscellaneous

Chiral enolborinates of carboxylic acids add to simple aldehydes leading to enantiomerically pure β-hydroxy acids (**Scheme 19**).[25] Optically active succinic acids can be obtained by the novel oxidative homocoupling of chiral 3-acyl-2-oxazolidinones. The base and oxidant can be chosen to give each diastereoisomer selectively (**Scheme 20**).[26]



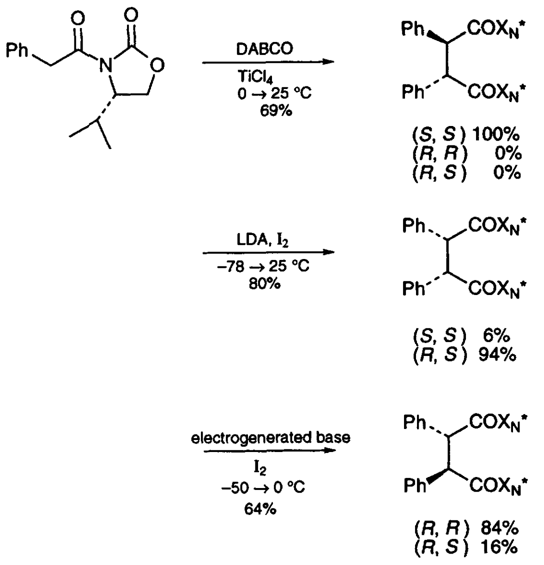
Scheme 19

The desymmetrisation of the anhydride **12** with chiral (R)- or (S)-benzyl mandelate provides a neat route to glutaric acid derivatives of opposing chirality (**Scheme 21**).[27]

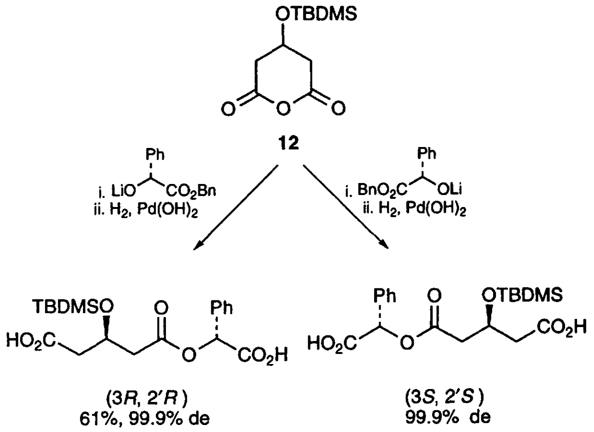
3 Carboxylic acid esters

3.1 General syntheses of esters

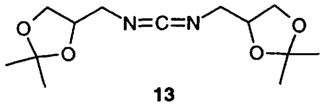
The currently available 'water soluble' carbodiimides that are used extensively for amide bond formation, cannot be used for esterification. Hence, efficient coupling reagents for carboxylic acids and alcohols that enable the facile removal of by products continue to be developed. BDDC (bis-[4-(2,2-dimethyl-1,3-dioxalyl)-methyl]carbodiimide) **13**, a distillable reagent,[28] can be prepared on 200–300 g scale and promises to be an efficient reagent for esterification (77–93% yields). The urea byproduct can be removed with mild acid, the simultaneous cleavage of the ketal groups ensuring its water solubility.



Scheme 20



Scheme 21



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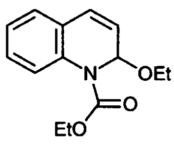
EEDQ (2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline) **14**[29] can be used to couple primary, secondary and tertiary alcohols, and the quinoline byproduct is once again removed with mild acid. No racemisation is observed with chiral substrates. Dialkyl carbonates (under DMAP catalysis)[30] and



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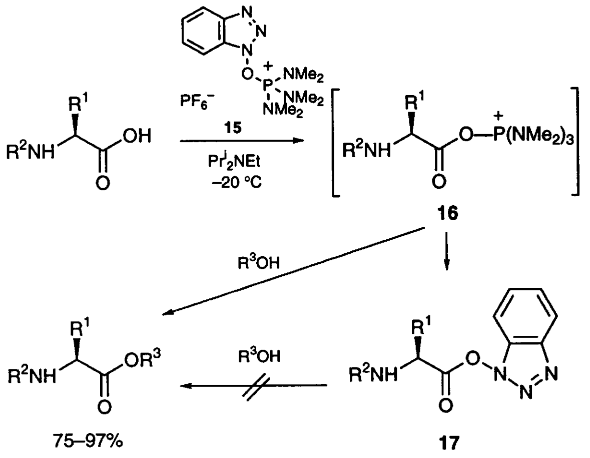
diphosgene[31] have also been reported as efficient coupling reagents.

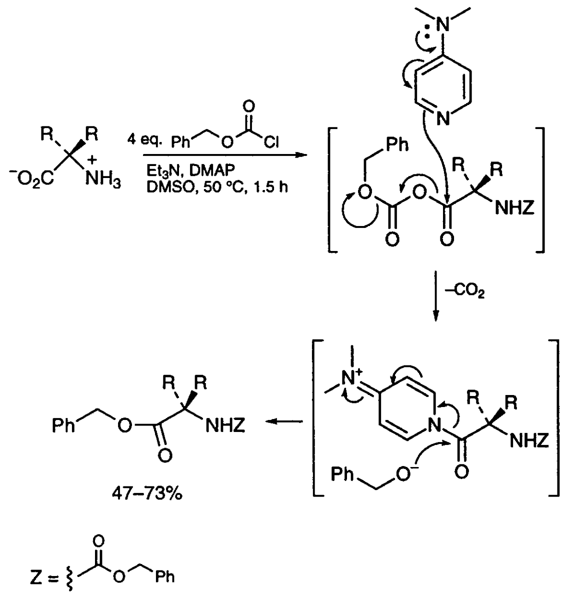
A rare example of esterification under acidic conditions (57–99% yields) that does not require the presence of excess alcohol involves the use of $(Me_2SiO)_4$ with $TiCl(OTf)_3$ catalysis.[32]

The addition of BOP reagent **15** to a premixed solution of an amino acid and an alcohol at low temperature, leads to esterification in excellent (75–97%) yields.[33] The low temperature ensures the stability of the reactive phosphonate intermediate **16** and precludes the formation of the less reactive benzotriazole ester **17** (**Scheme 22**).



Scheme 22

The first reported one-pot procedure for the simultaneous protection of an amino acid with both carbamate and benzyl ester protecting groups,[34] involves simply heating the acid in DMSO with benzyl chloroformate, (**Scheme 23**). The ester formation results from the DMAP induced fragmentation of the initially formed anhydride, followed by the *in situ* trapping of the resulting intermediate with benzyl alcohol. The reaction is limited to more lipophilic amino acids, probably due to their greater solubility in DMSO.



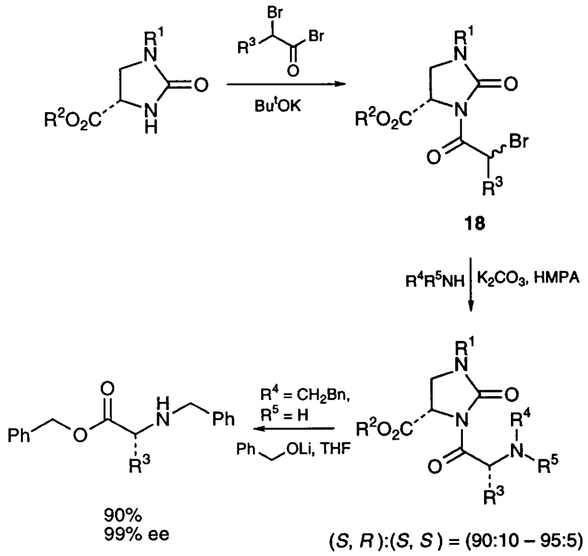
Scheme 23

3.2 α-Amino esters

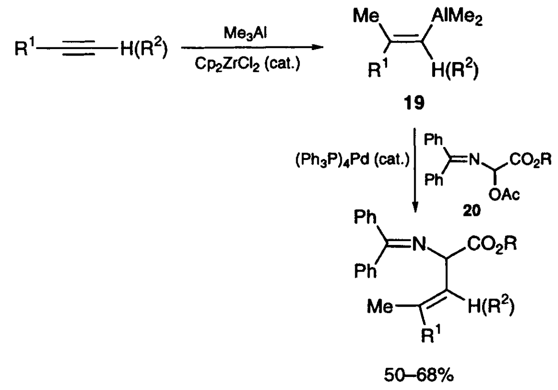
The process of dynamic kinetic resolution, where under the reaction conditions the less reactive diastereoisomer in a mixture is epimerised to the more reactive one, is an attractive concept for the synthesis of homochiral compounds. Hence, the racemic *N*-(α-bromoacyl)imidazolidinone intermediate **18** undergoes S_N2 displacement with various amines resulting in the formation of one diastereoisomer predominantly, providing a route to α-amino acids with excellent enantiomeric excess (**Scheme 24**).[35]

The Negishi reagents **19** couple with the Schiff base acetate **20** to give substituted vinyl glycine esters (**Scheme 25**).[36]

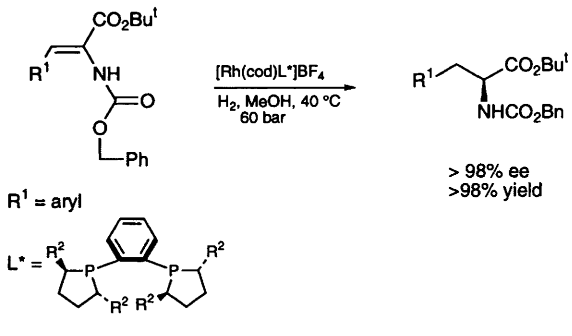
A short and efficient synthesis of optically pure (*R*)- and (*S*)-3-arylalanines involves the rhodium catalysed hydrogenation of (*Z*)-α-amino α,β-dehydro esters in the presence of optically pure diphosphines (**Scheme 26**).[37] The disadvantage in this method lies in the need to use very high (60 bar) pressures.



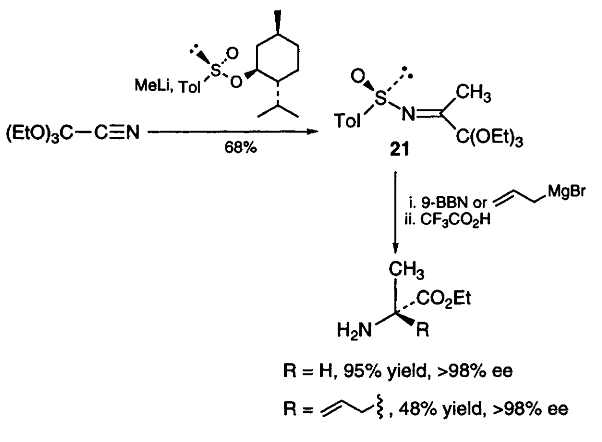
Scheme 24



Scheme 25



Scheme 26

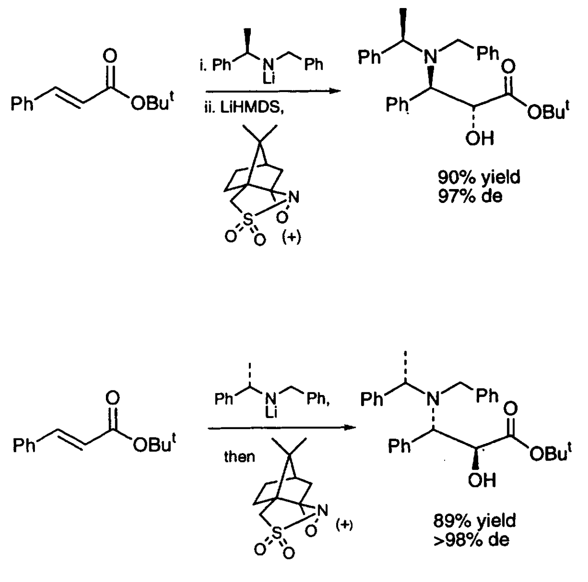


Scheme 27

Homochiral α-substituted amino acid esters can be obtained from the sulfimine **21**, by a chelation controlled reduction with 9-BBN (95% yield, >98% ee) or Grignard addition with allyl magnesium bromide (48%, >98% ee) (**Scheme 27**).[38]

3.3 β-Amino esters

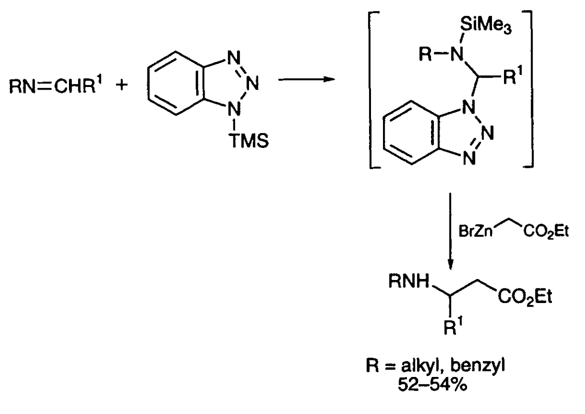
Practical approaches for the diastereoselective synthesis of β-amino-α-hydroxy acid derivatives are necessary due to the presence of this feature in a number important of natural products, *e.g.* the anticancer drug Taxol®. A practical route to chiral *anti*-β-amino-α-hydroxy acids involves the conjugate addition of a chiral amine to an α,β-unsaturated ester, followed by the tandem (*in situ*) or stepwise reaction with a homochiral oxaziridine (**Scheme 28**).[39] There are subtle differences in outcome depending on whether the stepwise or tandem approach is used. The chirality of the oxaziridine used in the reaction does not have a significant effect on the diastereoisomeric ratios obtained in the reaction, suggesting that it is the chirality of the substrate that is the stereodirecting feature in the hydroxylation step.



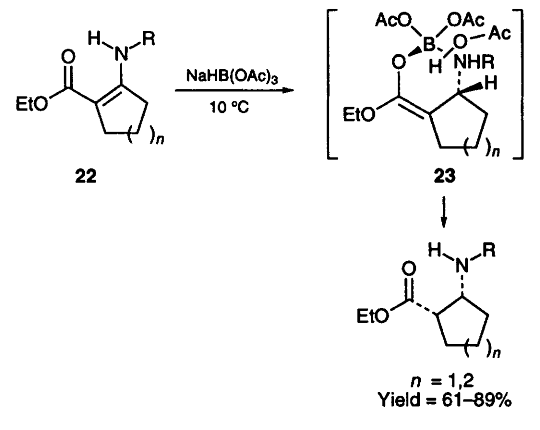
Scheme 28

The presence of 1-(trimethylsilyl) benzotriazole during the addition of a Reformatsky reagent to imines ensures the exclusive formation of the corresponding β-amino ester only; a mixture of the ester and β-lactam is obtained in the absence of the benzotriazole reagent (**Scheme 29**).[40]

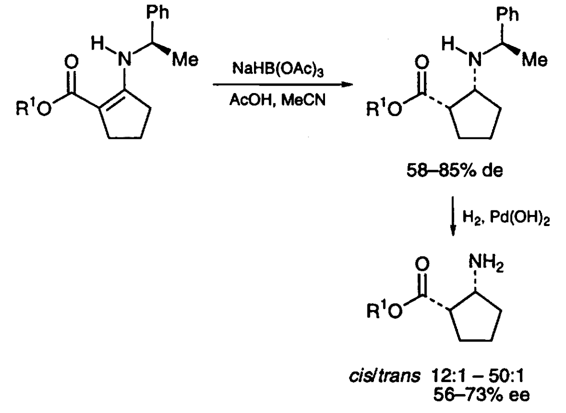
Sodium triacetoxyborohydride mediated reduction of β-enamino esters **22** gives the corresponding *cis*-



Scheme 29



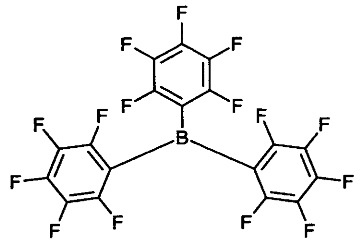
Scheme 30



Scheme 31

β-amino esters exclusively (**Scheme 30**).[41] Reduction of the analogous homochiral β-enamino esters yields β-amino acids with good enantiomeric purity after debenzylation (**Scheme 31**).[42] The stereoselectivity of the reduction arises due to the protonation of the intermediate diacetoxy enol ester **23** from the less hindered face. The reduction of acyclic β-enamino esters, however, is not stereoselective. The classical method for the synthesis of the starting enamino esters, involving the direct condensation of amines with β-keto esters, results in poor yields. An efficient route entails the acylation of lithiated enamines with diethyl carbonate or benzyl chloroformate.[43]

Tris(pentafluorophenyl)boron **24** is an efficient catalyst for the reactions of ketene silyl acetals with enolisable or non-enolisable imines leading to β-amino esters.[44] Some *anti*-selectivity is observed in the reaction.



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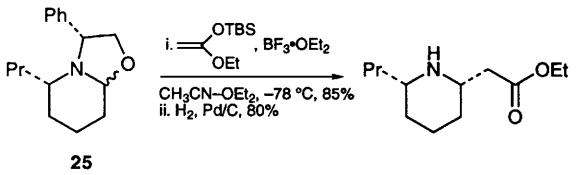
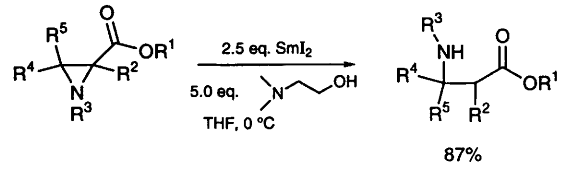
The Lewis acid mediated addition of a silyl enol ether to the chiral aminal **25**, gives two epimeric esters in a 9:1 ratio,[45] with the *cis*-epimer predominating. (**Scheme 32**). This product distribution is due to the $A^{[1,2]}$ strain in the intermediate iminium ion.



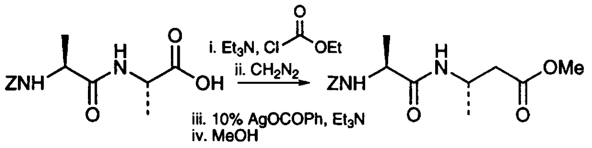
Scheme 32

Sm^{II} mediated regioselective reductions of 2-acylaziridines[46] provide a novel route to β-amino esters (**Scheme 33**). The ethanolamine present in the reaction functions both as a proton source and a chelator for the Lewis acidic Sm^{III}, thus making the reaction stable to acid sensitive protecting groups, *e.g.* Boc (*tert*-butyloxycarbonyl).



Scheme 33

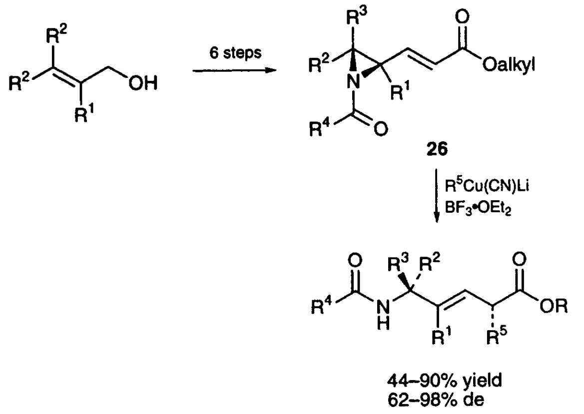
The Arndt–Eistert homologation of an amino acid, where the silver assisted decomposition of the intermediate diazoketone is quenched with methanol, provides a direct synthesis of the corresponding β-amino ester with retention of chirality (**Scheme 34**).[47]



Scheme 34

3.4 δ-Amino esters (5-amino esters)

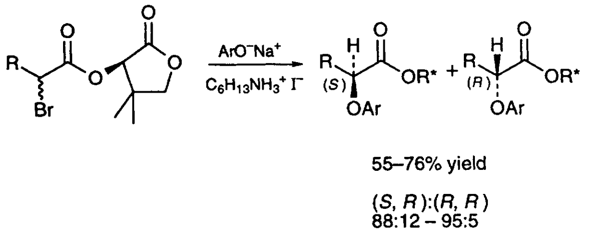
Despite the several electrophilic sites available to alkenylaziridines, exemplified by **26** they react predominantly in a S_N2' fashion with Yamamoto's alkyl copper reagents,[48] dialkylzinc reagents and lower order cuprates (**Scheme 35**).[49] The resulting 2-alkyl-4,5-substituted-5-amino-alk-3-enyl esters are formed in good yields and in excellent diastereoisomeric excess.



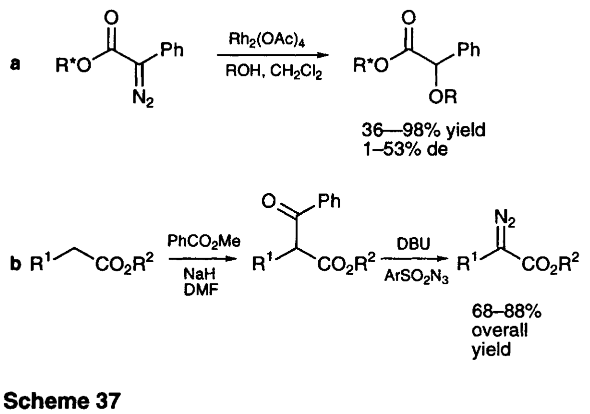
Scheme 35

3.5 α-Hydroxy esters

(S)-2-Aryloxy acids of >75% ee are accessible from racemic α-bromo acids[50] *via* their (*R*)-pantolactone esters (**Scheme 36**). The diastereoselectivity arises due to a dynamic equilibrium where the slower reacting diastereoisomer is rapidly converted into the faster reacting one by the halide ion generated in the reaction. Aliphatic acid nucleophiles do not give any diastereoselectivity.



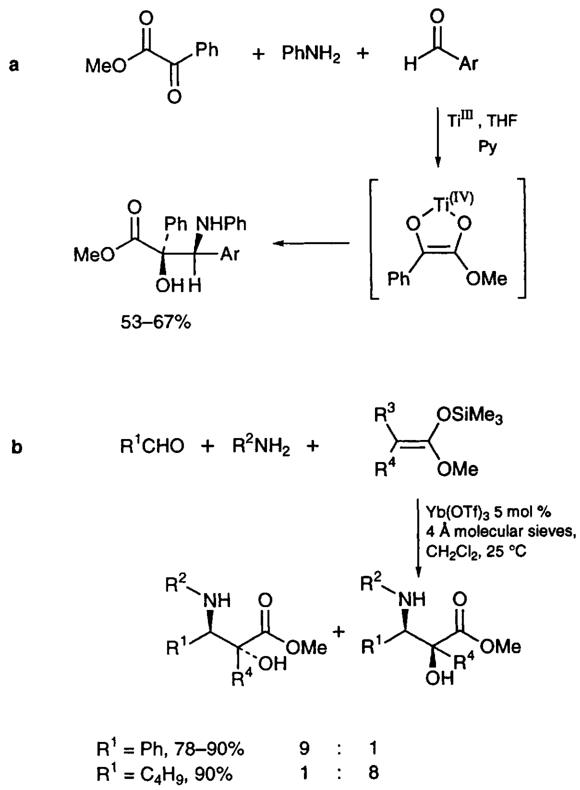
Scheme 36



Scheme 37

The Rh(II) mediated decomposition of chiral phenyldiazoacetates in the presence of simple alcohols provides α-alkoxy esters in good yields, albeit with modest diastereoselectivity (**Scheme 37a**).[51a] A convenient preparation of the diazoesters, which is amenable to large scale synthesis, involves the initial activation of an ester by benzoylation, followed by the DBU promoted diazo transfer (**Scheme 37b**).[51b]

Methyl phenylglyoxylate, aniline and aromatic aldehydes undergo a three-component condensation reaction in the presence of Ti^{III} leading to *syn*-β-hydroxy esters (**Scheme 38a**).[52] The scope of this reaction has been extended to include aliphatic aldehydes and amines by the use of lanthanide triflates such as ytterbium triflate[Yb(OTf)$_3$] (**Scheme 38b**).[53] In contrast to the Ti^{III} catalysed method, aromatic aldehydes give *anti* adducts, while *syn* adducts are obtained from aliphatic aldehydes.



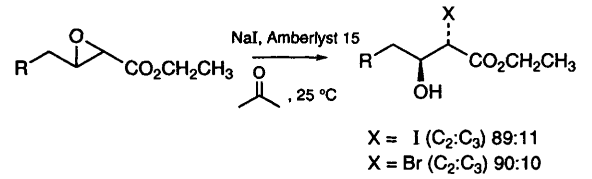
Scheme 38

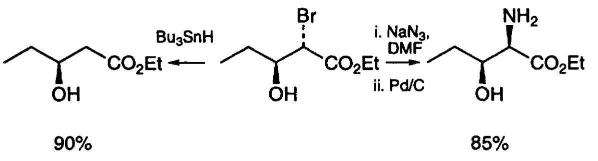
3.6 β-Hydroxy esters

Aliphatic α,β-epoxyesters, which are readily available *via* the Sharpless methodology, ring open almost exclusively at the 2-position with NaI.[54] The resulting halohydrins can be subsequently converted into synthetically useful intermediates such as β-hydroxy esters and *syn*-α-amino-β-hydroxy esters (**Scheme 39**). Other halide salts (LiI, KI) give lower regioselectivity in the ring opening reaction.

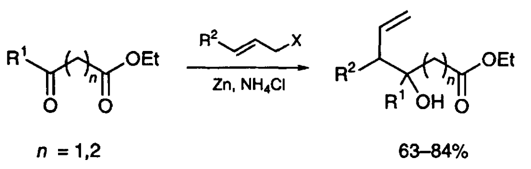
The slow rates of radical additions to α,β-unsaturated esters can be dramatically enhanced by Lewis acid (EtAlCl$_2$) complexation.[55] β- and γ-keto esters react smoothly with allylic halides, in the presence of Zn powder, with complete chemoselectivity to give hydroxyester adducts (**Scheme 40**).[56]

A significant advance in acyclic stereocontrol with respect to radical reactions involves the allylation of

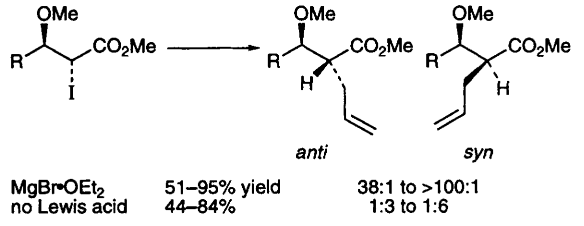




Scheme 39



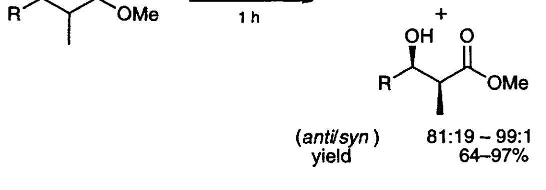
Scheme 40



Scheme 41

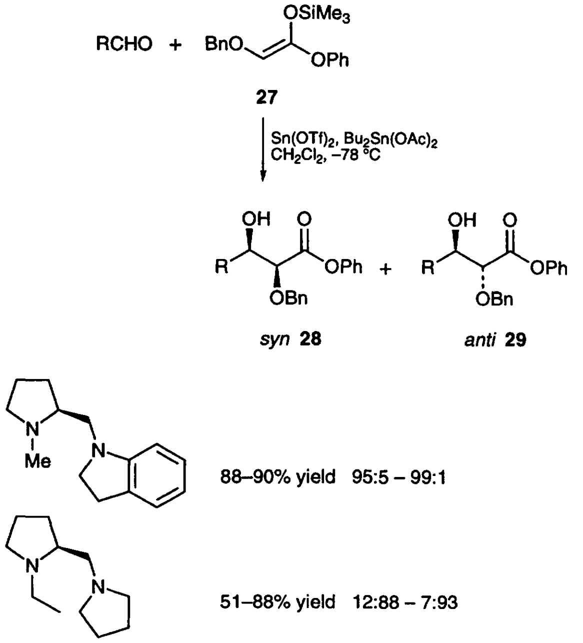
β-methoxy-α-iodo esters in the presence of a Lewis acid.[57] The chelation controlled transition state leads to *anti* adducts predominantly, whereas in the absence of Lewis acids *syn* adducts are favoured to some degree (**Scheme 41**).

Selective reductions of α-methyl-β-keto esters are achieved in the presence of tin hydride and titanium tetrachloride to give *anti*-α-methyl-β-hydroxy esters in good yields (**Scheme 42**).[58]



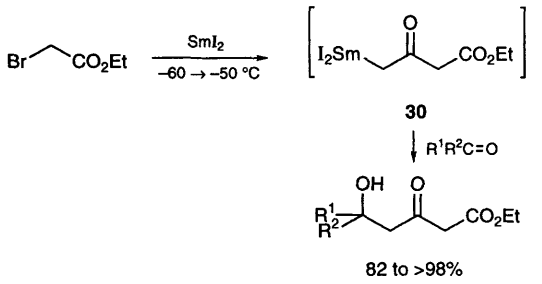
Scheme 42

The Lewis acid mediated addition of the silyl ketene acetal **27** to aldehydes can give the *syn*- or *anti*-2,3-dihydroxy esters **28** and **29** selectively, depending on the chiral ligand present.[59] The phenyl ester is crucial for the unique stereoselectivities observed (**Scheme 43**).



Scheme 43

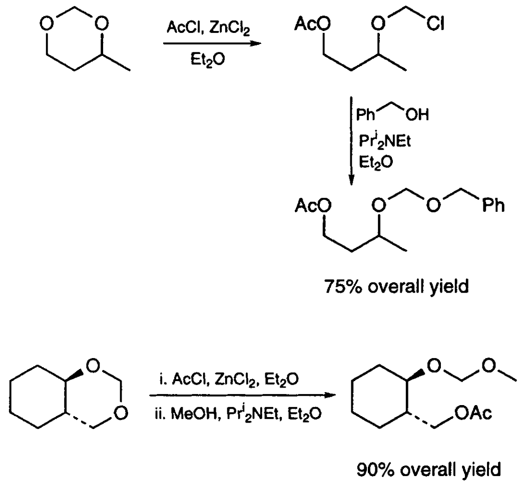
A convenient source of Sm^{II} can be generated *in situ* from $\text{Sm–Me}_3\text{SiCl–NaI}$, and has been demonstrated to be a useful alternative to zinc in the Reformatsky reaction.[60] SmI_2 in the presence of ethyl bromoacetate produces a β-keto ester equivalent **30**, which in turn reacts with ketones and aldehydes to give δ-hydroxy-β-keto esters in excellent yields (**Scheme 44**).[61]



Scheme 44

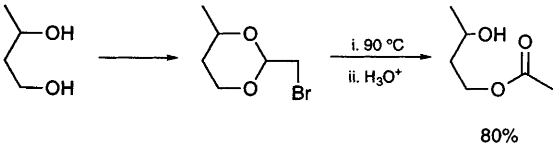
3.7 Miscellaneous hydroxy esters

Selective functionalisations of diols are a useful tool in protecting group chemistry. The regioselective cleavage of cyclic formal derivatives of 1,3-diols results in the formation of the least substituted acetate or pivalate exclusively (**Scheme 45**).[62] The

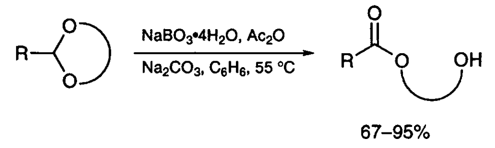


Scheme 45

resulting acetoxy-substituted chloromethyl ethers can be reacted *in situ* with various alcohols to give stable methoxymethyl (MOM) and benzyloxymethyl (BOM) ether derivatives. The analogous cleavage of 1,2-diols is less selective. Diols can also be acetylated selectively *via* hydrolysis of their cyclic ketene aceatal derivatives (**Scheme 46**).[63] An inexpensive method for the large scale protection of symmetrical diols involves the oxidative cleavage of their cyclic acetals (**Scheme 47**).[64]

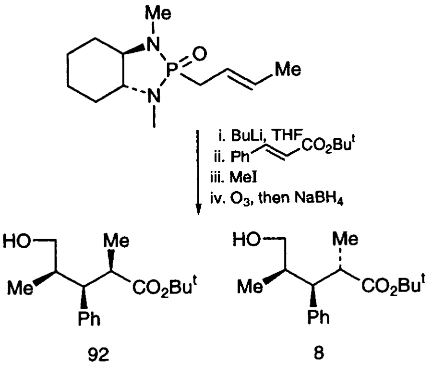


Scheme 46

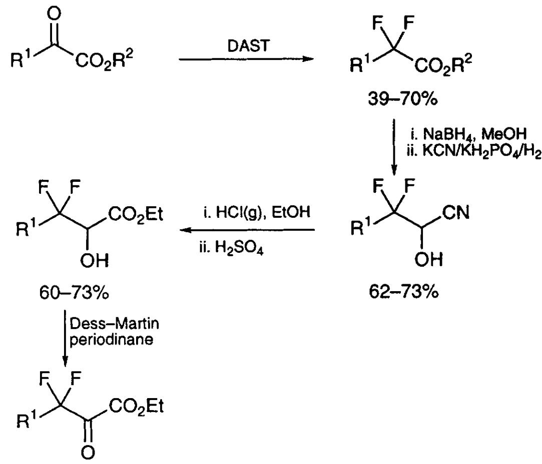


Scheme 47

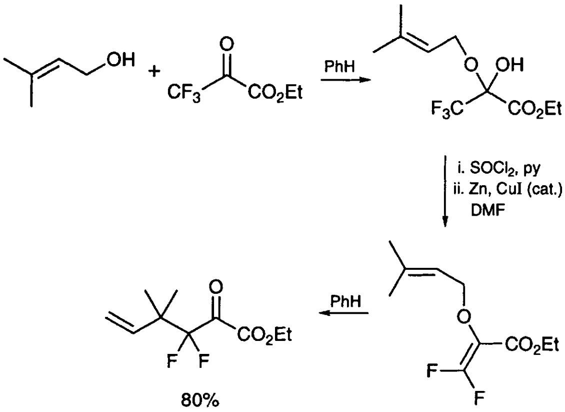
Magnesium methoxide, generated from magnesium in methanol, is a useful reagent for the selective deprotection of a variety of diesters, *e.g.* *p*-nitrobenzoate in the presence of acetate (68%), and acetate in the presence of benzoate (76%).[65] Allyl and crotyl bicyclic phosphonamide anions are 'hydroxyalkyl' synthons that add to α,β-unsaturated esters to give mainly all-*syn* adducts in excellent yields (**Scheme 48**).[66]



Scheme 48



Scheme 49

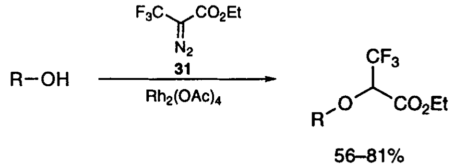


Scheme 50

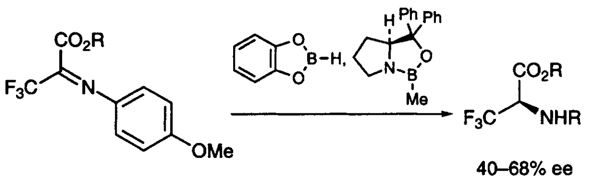
3.8 Halo esters

The study of organofluorine compounds is an ever increasing field within organic chemistry, spurred on no doubt by the demand for new fluorinated synthons in medicinal chemistry. A versatile route to β,β-difluoro-α-keto ester derivatives, by 'insertion' of a difluoromethylene group into an α-keto ester entails a simple four-step sequence (**Scheme 49**).[67] The addition of allylic alcohols to ethyl trifluoropyruvate, followed by a Claisen rearrangement provides a route to unsaturated β,β-difluoro-α-keto esters (**Scheme 50**).[68]

α-Trifluoromethyl alkoxy- and aryloxy-acetates can be obtained in good yields by a rhodium carbenoid mediated insertion of the diazo ester **31** into the O–H bond of the starting alcohol (**Scheme 51**).[69] (*R*)-3,3,3-Trifluoroalanine can be synthesised in moderate enantioselectivity by reduction of an aryl imino ester with the (*S*)-oxazaborolidine–catechol borane combination (**Scheme 52**).[70]

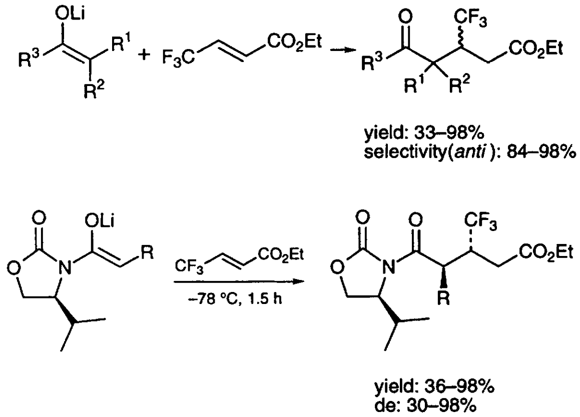


Scheme 51



Scheme 52

The significantly lower LUMO in ethyl (*E*)-3-(trifluoromethyl)acrylate, in comparison with ethyl crotonate, results in its greater reactivity towards nucleophiles, providing *anti* adducts selectively (**Scheme 53**).[71]

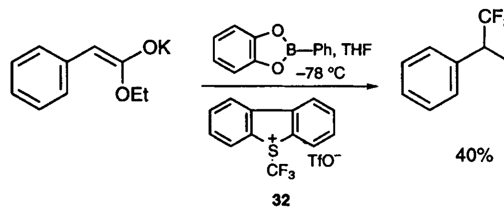


Scheme 53

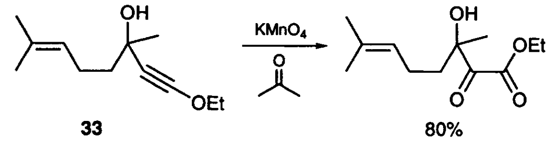
(*S*)-(Trifluoromethyl)dibenzothiophenium triflate **32** is a new electrophilic source of the trifluoromethyl cation, which can be used to alkylate the potassium enolate of phenylacetic acid ester in moderate yields (**Scheme 54**).[72]

3.9 Keto esters

Alkynyl ethers, obtained by the condensation of lithioethoxyacetylene with ketones, can function as keto ester equivalents. Thus the mild potassium permanganate mediated oxidation of **33** to the corresponding β-hydroxy-α-keto ester is possible even in the presence of a double bond (**Scheme 55**).[73]



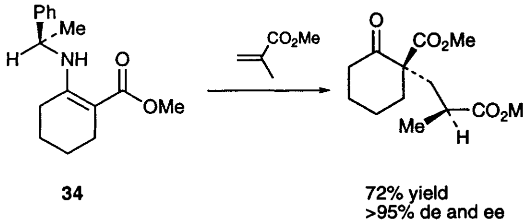
Scheme 54



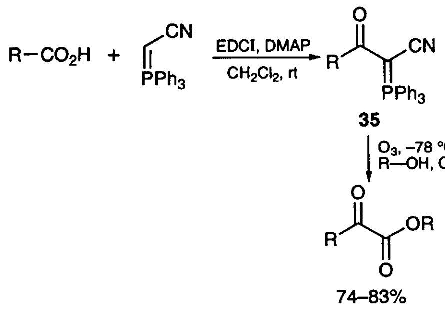
Scheme 55

The addition of the chiral enaminoester **34** to methyl methacrylate gives a single keto ester product (>95% de and ee), allowing the simultaneous control of both a quaternary and tertiary center in one step (**Scheme 56**).[74]

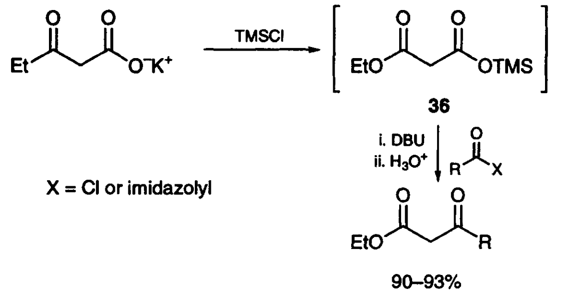
Carboxylic acids can be homologated directly to α-keto esters *via* the cyano phosphorane **35** (**Scheme 57**),[75] and the (trimethylsilyl)ethyl malonate **36**, generated *in situ*, reacts with acyl imidazoles and chlorides to provide β-keto esters (**Scheme 58**).[76]



Scheme 56

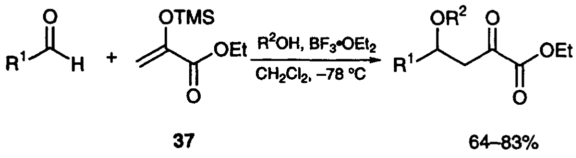


Scheme 57



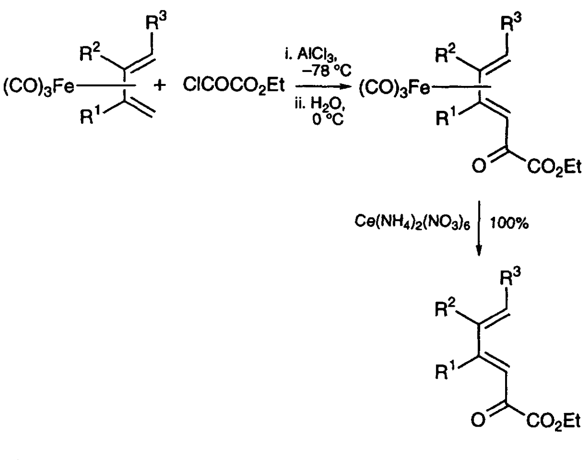
Scheme 58

A hemiacetal, generated *in situ* from an aldehyde and an alcohol in the presence of a Lewis acid, has been shown to react with the acid sensitive ethyl 2-(trimethylsiloxy)acrylate **37**, leading to the corresponding γ-alkoxy-α-keto ester (**Scheme 59**).[77]



Scheme 59

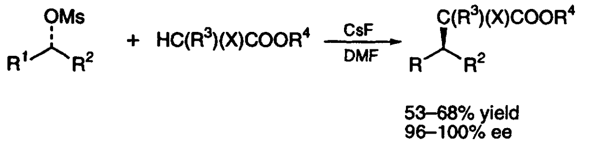
Tricarbonyliron coordinated acyclic dienes undergo Friedel–Crafts acylation to give (*E*,*E*)-3,5-dienyl-2-keto esters selectively. The parent diene can then be obtained after decomplexation with cerium(IV) ammonium nitrate (**Scheme 60**).[78]



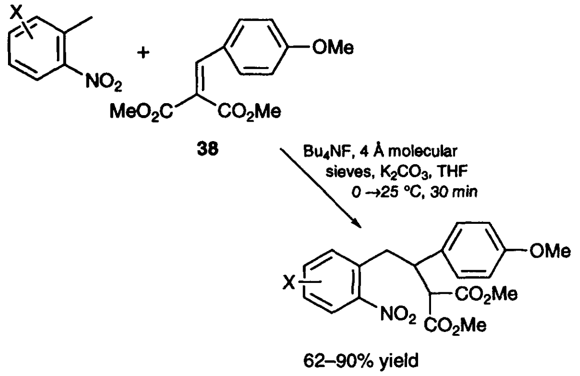
Scheme 60

3.10 Diesters

The caesium fluoride promoted displacement reactions of homochiral secondary mesylates take place with complete inversion to give chiral malonic ester derivatives (**Scheme 61**).[79] Conventional malonic ester alkylation using stronger bases, or Mitsunobu reactions give these adducts in much lower yield and enantiomeric excess. The fluoride-mediated additions of nitrotoluene anions to the α,β-unsaturated ester **38** give the corresponding Michael adducts in good to excellent yield (**Scheme 62**).[80] Stronger bases such as LDA in this case result in dimerisations of the anions.

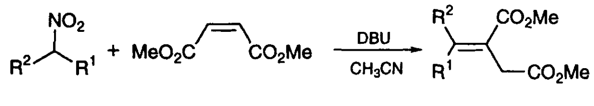


Scheme 61



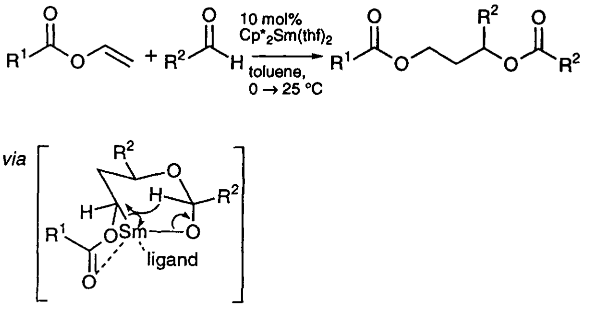
Scheme 62

The addition of nitroalkanes to dimethyl maleate, followed by the *in situ* elimination of nitrous acid, provides a direct synthesis of Stobbe type α,β-unsaturated diesters (**Scheme 63**).[81]



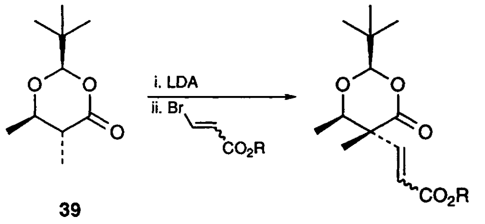
Scheme 63

The catalytic organosamarium mediated coupling between vinyl esters and aldehydes lead to diesters of propane-1,3-diols (**Scheme 64**).[82] The reaction is presumed to be due to the formation of an eight-coordinated alkoxy samarium species, which undergoes an intramolecular hydride shift.



Scheme 64

The addition–elimination reaction of the anion derived from the chiral synthon **39** with (*E*)-bromo acrylates takes place with excellent diastereoselectivity [(*R*):(*S*) >20:1)] (**Scheme 65**).[83]



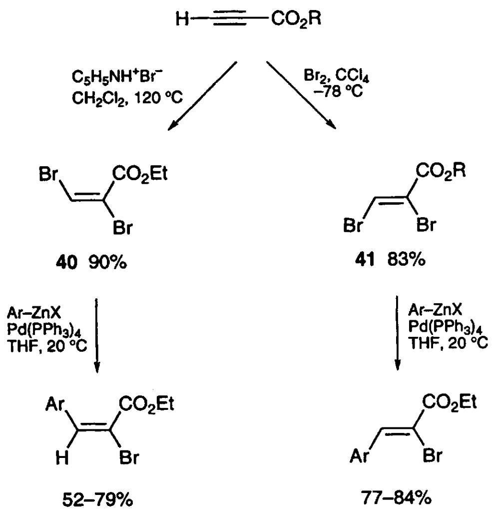
39

(*E*)-bromoacrylate, R = Me, 71% yield, (*R*):(*S*) >20:1
(*Z*)-bromoacrylate, R = Et, 51% yield, (*R*):(*S*) 6:1

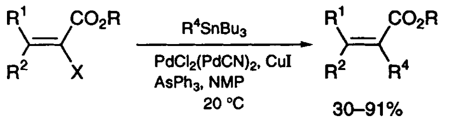
Scheme 65

3.11 Unsaturated esters

Stereochemically pure (*Z*)- and (*E*)-2-bromo-3-arylpropenoates have been prepared by the regioselective Pd^0 mediated cross coupling of (*Z*)- and (*E*)-2,3-dibromopropenoates **40** and **41** with arylzinc halides (**Scheme 66**).[84] The 2-bromopropenoates can then be reacted further with organostannyl reagents in a Stille type coupling to afford tri- and tetra-substituted α,β-unsaturated esters (**Scheme 67**).[85]

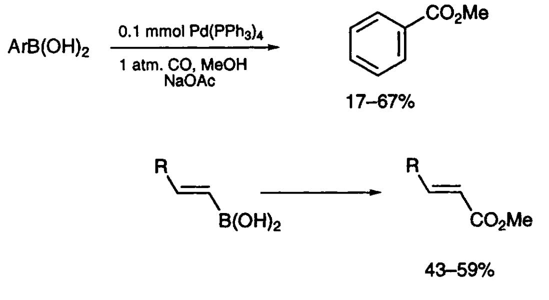


Scheme 66



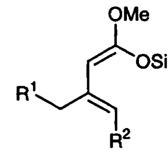
Scheme 67

Aryl and alkenyl boronic acids react with carbon monoxide in the presence of 1–5 mol% Pd^0 and sodium acetate in methanol to give α,β-unsaturated esters directly (**Scheme 68**).[86] Aryl halides do not react under these conditions. This reaction has been reported previouly using stoichiometric amounts of Pd^{II}.



Scheme 68

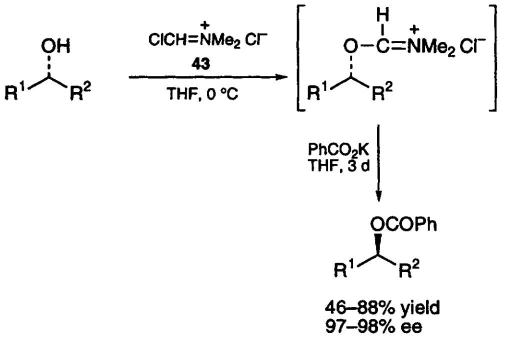
(*Z*)-Enol esters have been prepared by acylation reactions of ketones *via* their manganese enolates,[87] and by the reaction of silyl enol ethers with acyl fluorides.[88] The conversion of α,β-unsaturated esters into silyl enol ethers under kinetic conditions leads to a single (*Z*)-siloxydiene **42**.[89]



42

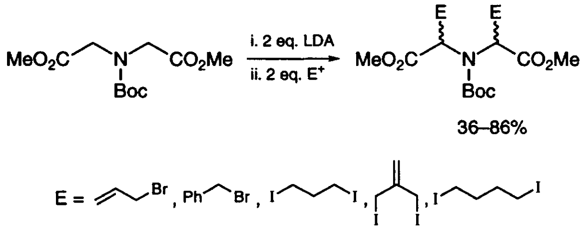
3.12 Miscellaneous

Secondary alcohols can be converted into benzoate esters with inversion of configuration *via* sequential reaction with the Vilsmeier reagent **43** and potassium benzoate (**Scheme 69**).[90] Although not suitable for chiral benzylic alcohols, this reaction has distinct advantages over the Mitsunobu reaction in terms of purification, the by-products being DMF and KCl. The displacement of the Vilsmeier intermediate, however, is very slow, taking up to three days in the examples cited.



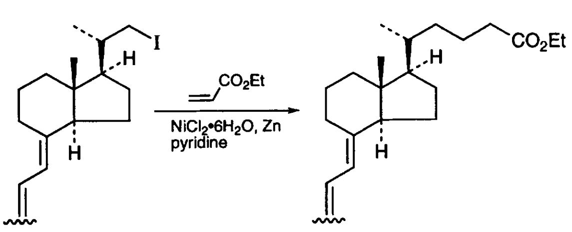
Scheme 69

Inverse addition of the dianion of *N*-Boc iminodiacetic esters to a variety of electrophiles gives moderate to good yields of dialkylated products (**Scheme 70**).[91]



Scheme 70

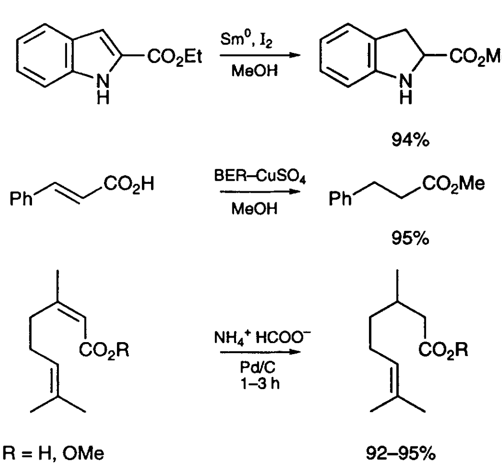
The nickel promoted addition of the steroidal intermediate **44** to ethyl acrylate gives a good yield of adduct, whereas the corresponding tin radical mediated addition failed to yield any product (**Scheme 71**).[92]



44

Scheme 71

The chemoselective reduction of α,β-unsaturated esters in the presence of isolated olefins is a useful process which can be achieved under transfer hydrogenation conditions (**Scheme 72**)[93] and with borohydride exchange resin (BER).[94] Metallic samarium, in the presence of iodine, has also been shown to reduce α,β-unsaturated esters to the corresponding saturated analogues (**Scheme 72**).[95] These conditions do not need the strictly anaerobic conditions necessary for SmI_2.



Scheme 72

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