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Received (in Cambridge, UK) 9th July 1999

Covering: 1 August 1997 to 31 July 1998

Previous review: *J. Chem. Soc., Perkin Trans. 1*, 1998, 2451

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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 1997 and 31 July 1998 and follows on from the previous coverage.<sup>1</sup> 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 chiral auxiliaries and ligands has thus been limited to those which are comparable to, or provide improvements over, established 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 been reviewed recently<sup>2</sup> and has not been considered here. Methods which simply constitute the application of known solution phase chemistry on a solid support have also been omitted.

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.<sup>3</sup>

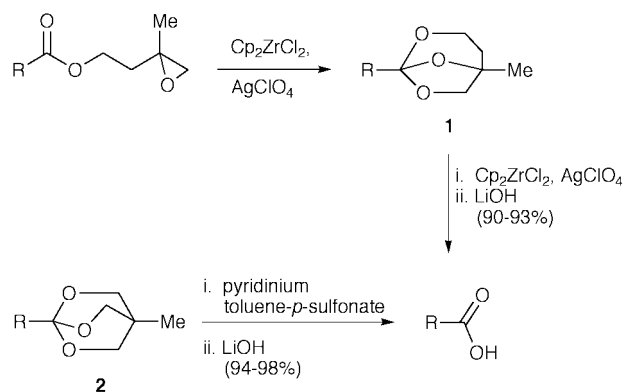
## 2 Synthetic approaches

### 2.1 General carboxylic acids

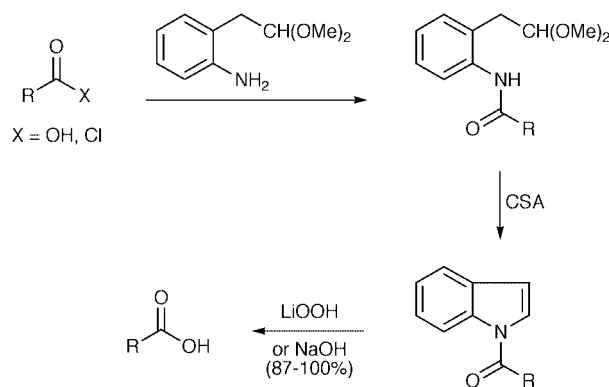
Ester hydrolysis constitutes one of the most fundamental approaches to carboxylic acid synthesis and a number of new, mild methods have been developed. A combination of thiophenol and catalytic potassium fluoride has been employed for the cleavage of esters under neutral, non-hydrolytic conditions in moderate to quantitative yields (50–100%).<sup>4</sup> 3,3-Dimethylallyl and cinnamyl esters can be removed in the presence of alkyl esters (46–100% yield) using kaolinitic clay<sup>5</sup> whilst a perfluoroalkylation–elimination approach gives excellent levels of selective allyl ester cleavage (80–85% yield) in substrates containing acetoxy, hydroxy, ketal, alkenyl and phenylsulfanyl

functionalities.<sup>6</sup> Sulfinic acids and their salts have been used, in combination with a palladium catalyst, for the high yielding (80–99%) deprotection of allyl, methallyl, 2-chloroallyl, but-2-enyl and cinnamyl esters of penems<sup>7</sup> and the nickel catalysed electroreductive cleavage of a number of propargyl (prop-2-ynyl) esters of aliphatic and aromatic acids proceeds in excellent yields (95–99%).<sup>8</sup> Phenacyl esters are cleaved by photolysis in the presence of a 9,10-dimethylantracene sensitiser (90–96% yield)<sup>9</sup> whilst 2,2,2-trichloroethyl esters react with sodium telluride in DMF to give acids in high yields (74–98%).<sup>10</sup> Methyl esters, acetates and *tert*-butyldimethylsilyl ethers are stable under these reaction conditions. Two new protecting group strategies for carboxylic acids have been reported. A zirconocene catalysed epoxy ester-orthoester rearrangement yields the corresponding 2,7,8-trioxabicyclo[3.2.1]octanes **1** (71–100%) which show orthogonal cleavage properties to the related 2,6,7-trioxabicyclo[2.2.2]octanes **2** (Scheme 1).<sup>11</sup> 2-(2-Aminophenyl)acetaldehyde dimethyl acetal provides the corresponding amides from acids or acid chlorides (77–88% yield). These are stable to basic conditions but are readily hydrolysed *via* the corresponding *N*-acylindoles (Scheme 2).<sup>12</sup> Methyl esters are formed in high yields (83–100%) when triethylamine and methanol are used in place of an aqueous base.

A number of new protocols for the oxidative synthesis of carboxylic acids have been reported. The use of Oxone<sup>®</sup> in



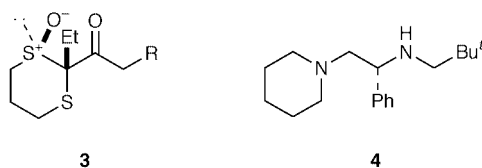
Scheme 1



Scheme 2

aqueous acetone at a controlled, neutral pH provides moderate to good yields (53–94%) of aliphatic and electron-deficient aromatic acids from aldehydes.<sup>13</sup> Good yields (71–87%) are also obtained in the nickel catalysed oxidation of aldehydes in a monophasic toluene–perfluorodecalin solvent system under an oxygen atmosphere.<sup>14</sup> The chromium(vi) oxide catalysed oxidation of primary alcohols proceeds in high yields (73–100%) in the presence of periodic acid in wet acetonitrile,<sup>15</sup> no racemisation occurs during the formation of  $\alpha$ -chiral acids. The use of a tungsten catalyst under phase transfer conditions permits the organic solvent and halide free oxidation of primary alcohols to acids by aqueous hydrogen peroxide in moderate to good yields (52–87%).<sup>16</sup> Microwave irradiation expedites the oxidation of carbonyl compounds bearing electron withdrawing groups (65–92% yield) using aqueous sodium hypochlorite in the absence of organic solvents.<sup>17</sup> Substituted xylenes undergo a regioselective monooxidation to toluic acids (90–98%) in the presence of ruthenium(III) chloride, sodium hypochlorite and a phase transfer catalyst.<sup>18</sup> The asymmetric rhodium(i) diphosphine catalysed transfer hydrogenation of acrylic acids using formic acid proceeds in 57–91% ee<sup>19</sup> whilst a cinchonidine modified palladium(0) catalyst exhibits lower selectivity (20–52% ee) for the hydrogenation of  $\alpha,\beta$ -unsaturated acids.<sup>20</sup> The carbonylation of aryl methanols is catalysed by palladium(II) complexes and hydriodic acid in aqueous solvents and gives aryl acetic acids in 48–90% yield.<sup>21</sup>

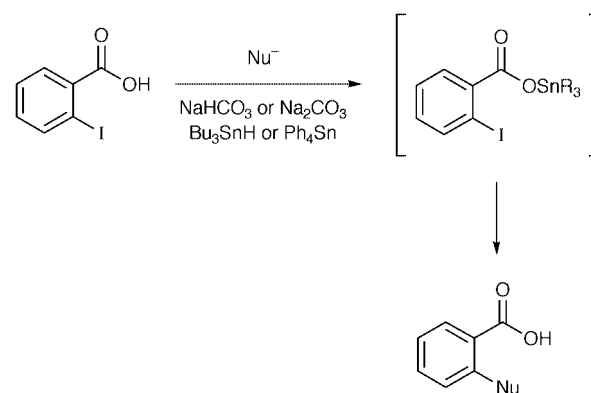
A range of methods for the synthesis of carboxylic acids based on alkylation and substitution reactions have been investigated. 1,3-Dithiane-1-oxides **3** have been employed in the enantioselective synthesis of  $\alpha$ -chiral acids,<sup>22</sup> alkylation proceeds in moderate to good yields (47–84%) with high stereoselectivity (75–100% de). Subsequent basic or oxidative cleavage of the auxiliary provides the corresponding acids (39–77% yield, 81–>99% ee) without concomitant racemisation. The enantioselective  $\alpha$ -alkylation of phenylacetic acid has been achieved using a chiral lithium amide base derived from diamine **4**.<sup>23</sup> Products are obtained in 38–70% yield with moderate levels of asymmetric induction (42–68% ee). The 1,4-addition of organolithium reagents to  $\beta$ -substituted- $\alpha,\beta$ -unsaturated acids followed by electrophilic quenching of the enolate proceeds with moderate to good yields (40–80%).<sup>24</sup> Deprotonation of the carboxylate reduces competing 1,2-addition but low levels of diastereoselection (0–40% de) are observed. The organotin mediated nucleophilic substitution of *o*-iodobenzoic acids is postulated to occur via a stannyl ester intermediate and gives *o*-alkylated and hydroxylated products in 70–86% yield (Scheme 3).<sup>25</sup> The corresponding dehalogenations of iodo and bromobenzoic acids proceed in 82–98% yield in aqueous media. Arylacetic acids are obtained in low to good yields (32–81%) from the photolysis of  $\alpha$ -chloro acetophenones in aqueous acetonitrile.<sup>26</sup>



The chromatographic separation of the diastereomers formed from racemic carboxylic acids and (*S*)-(+)-2-(anthracene-2,3-dicarboximido)-1-propyl trifluoromethanesulfonate is possible, even when the two stereocentres are separated by eight bonds.<sup>27</sup> A method for the assignment of the configuration of  $\beta$ -methylcarboxylic acids based on the <sup>1</sup>H NMR chemical shifts of their diastereomeric 1-arylethyl amides has also been reported.<sup>28</sup>

## 2.2 General carboxylic acid esters

A variety of methods for the esterification of carboxylic acids



Scheme 3

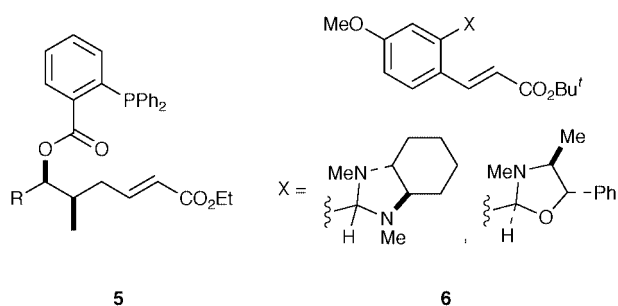
have been developed. The use of acetyl chloride and methanol or ethanol leads to the *in situ* generation of HCl which promotes the formation of methyl or ethyl esters in 57–100% yield.<sup>29</sup> 2-Phenylisopropyl trichloroacetimidate and *tert*-butyl trichloroacetimidate have been utilised for the preparation of the corresponding esters of *N*-protected amino acids in moderate to good yields (40–98%) without the need for an acid catalyst<sup>30</sup> whilst the use of amberlyst-15 in methanol or ethanol leads to the formation of amino acid methyl and ethyl esters in 70–82% yield.<sup>31</sup> Aliphatic acids and diacids react with primary alcohols in the presence of an iron(III) sulfate catalyst to give esters and diesters in good yields (85–98%).<sup>32</sup> A combination of caesium fluoride on Celite and alkyl halides provides the esters of aromatic, heteroaromatic and aliphatic acids in high yields (76–99%) under conditions which do not adversely affect  $\alpha$ -chiral and other base sensitive substrates.<sup>33</sup> The chemoselective esterification of phenolic acids is also possible under these conditions. The reaction of acid chlorides and alcohols, including 2-methylpropan-2-ol, in the presence of zinc affords esters in 83–95% yield<sup>34</sup> whilst *tert*-butyl esters have also been prepared from 2-methylpropan-2-ol in good yields (60–93%) in one pot under neutral conditions by the *in situ* generation of isobutylene using a dispersion of concentrated sulfuric acid on powdered anhydrous magnesium sulfate.<sup>35</sup> *O,O'*-Di-(2-pyridyl)thiocarbonate has been used for the high yielding (72–100%) coupling of acids with hindered alcohols<sup>36</sup> whilst heating secondary or tertiary alcohols with acid anhydrides in the absence of solvent or a catalyst gives moderate to good yields (59–95%) of the corresponding esters.<sup>37</sup> The mild cleavage of secondary and tertiary amides using pyridine and trifluoromethanesulfonic anhydride then ethanol gives good yields (66–93%) of ethyl esters although some racemisation of  $\alpha$ -chiral substrates is observed.<sup>38</sup>

Butylstannoic acid [BuSn(O)OH] has been employed as a transesterification catalyst in the presence of primary and secondary alcohols to give esters in 46–90% yield<sup>39</sup> and the clay catalysed transesterification of  $\beta$ -keto esters with primary alcohols proceeds in good yields (70–90%),<sup>40</sup> no isomerisation of allyl and propargyl esters is observed under these conditions. A range of sterically hindered esters have been formed in moderate to good yields (58–98%) by the titanium(IV) ethoxide catalysed transesterification of the corresponding methyl and ethyl esters<sup>41</sup> and *tert*-butyl esters are available in high yields (88–99%) by a potassium *tert*-butoxide catalysed ester interchange between *tert*-butyl acetate and the methyl and ethyl esters of aromatic and aliphatic acids.<sup>42</sup> The applicability of the latter reaction is, however, limited by the conditions employed – the equilibrium is driven towards the products by removal of the methyl or ethyl acetate formed, thus restricting the remaining reaction components to non-volatile materials. Racemisation of  $\alpha$ -chiral substrates also occurs. The transesterification of *N*-acyloxazolidinones with methyl or benzyl alcohols in the

presence of lanthanum(III) iodide proceeds in 37–100% yield with negligible racemisation.<sup>43</sup>

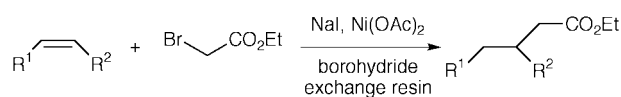
A one-pot conversion of aldehydes to methyl esters (65–96% yield) by oxidation of their *in situ* formed dimethyl acetals with a combination of boron trifluoride–diethyl ether, MCPBA and DBU has been reported,<sup>44</sup> whilst the use of aqueous hydrogen peroxide and hydrochloric acid in alcoholic solvents provides the corresponding esters in 64–99% yield from acetals or aldehydes.<sup>45</sup> The oxidation of benzyl ethers with the 2-nitrobenzenesulfonyl peroxy radical generated from 2-nitrobenzenesulfonyl chloride and potassium superoxide proceeds in 81–93% yield<sup>46</sup> and hypobromous acid has been utilised for the oxidation of symmetrical ethers in aqueous media (78–82% yield).<sup>47</sup>

Tin hydride reagents bearing both a stereogenic tin atom and a chiral ligand have been employed for the asymmetric reduction of racemic  $\alpha$ -bromo esters.<sup>48</sup> High conversions (82–>99%) were obtained, however the tin hydrides employed were not diastereomerically pure, the reactions promoted by the minor diastereomer proved to be highly enantioselective whilst the major diastereomer showed no asymmetric induction. Overall, low optical yields were obtained (0–25% ee). The enantioselectivity of hydroxy containing ligands in the rhodium(I) diphosphine catalysed hydrogenation of  $\alpha,\beta$ -unsaturated esters in aqueous media has been improved from 1.5–34% ee to 40–77% ee by the addition of micelle-forming amphiphiles<sup>49</sup> and the use of ruthenium clays permits the chemoselective hydrogenation of mono- and disubstituted  $\alpha,\beta$ -unsaturated esters in 84–91% yield.<sup>50</sup> The *in situ* generation of a copper hydride conjugate reducing agent from copper(I) chloride and phenyldimethylsilane has been reported to provide saturated esters in 90–96% yield,<sup>51</sup> whilst the factors which influence the diastereoselectivity of cuprate conjugate addition reactions have been surveyed.<sup>52</sup> The *o*-diphenylphosphanylbenzoyl directed addition of cuprates to acyclic enoates **5** is *anti* selective (60–90% de) and proceeds in good yields (60–93%).<sup>53</sup> The conjugate addition of aryllithium reagents to  $\alpha,\beta$ -unsaturated *tert*-butyl esters **6** bearing a chiral imidazoline or oxazolidine at the  $\beta$ -position is both regioselective and diastereoselective (71–97% ee, 45–95% yield after imidazoline/oxazolidine hydrolysis).<sup>54</sup> Enantioselective 1,4-addition to achiral substrates can be achieved in the presence of chiral additives such as sparteine (28–88% ee, 78–92% yield).<sup>55</sup> The conjugate addition of organolithium reagents to 2,6-di-*tert*-butyl-4-methoxyphenyl (BHA) enoates in the presence of chiral ligands is also enantioselective (64–99% ee, 81–96% de, 62–97% yield),<sup>56</sup> and can be achieved using substoichiometric quantities of the ligands (36–85% ee, 91–100% de, 86–99% yield).<sup>57</sup> Mixed alkyl(trimethylsilylmethyl)zinc reagents undergo exclusive 1,4-addition of their alkyl substituent to  $\alpha,\beta$ -unsaturated esters in the presence of trimethylsilyl bromide (68–99% yield),<sup>58</sup> whilst the rhodium catalysed conjugate addition of arylstannanes proceeds in 64–91% yield.<sup>59</sup>



The reductive alkylation of  $\alpha,\alpha$ -disubstituted- $\alpha$ -cyano esters using lithium naphthalenide and primary alkyl halides provides  $\alpha,\alpha,\alpha$ -trisubstituted esters in good yields (67–92%).<sup>60</sup> Tertiary alkyl fluorides have been used in the presence of organoaluminium reagents for the synthesis of quaternary carbon

centres. Addition of the alkyl fluoride to a silyl ketene acetal in the presence of 10 mol% trimethylaluminium provides the  $\beta$ -substituted ester in 38–76% yield.<sup>61</sup> The nickel boride–borohydride exchange resin mediated radical coupling of alkenes with  $\alpha$ -bromo esters proceeds in moderate to good yields (50–90%) in the presence of sodium iodide (Scheme 4).<sup>62</sup> Exocyclic and trisubstituted alkenes undergo a dehydrohalogenation reaction of the intermediate tertiary iodide to give the  $\gamma,\delta$ -unsaturated ester (51–91% yield). The reductive carboxyalkylation of electron-rich alkenes by  $\alpha$ -halo esters in the presence of triphenylsilane is catalysed by thiols (60–88% yield) and also proceeds by a free radical mechanism.<sup>63</sup> Some asymmetric induction was observed when chiral thiols were employed (19–27% ee).  $\alpha$ -Alkyl thioacetates have been utilised for the tin-free reductive photochemical carboxymethylation of terminal alkenes in acetonitrile in 70–90% yield.<sup>64</sup> A reusable silica-supported sulfur–palladium complex has been employed as the catalyst in the formation of *n*-butyl esters in moderate to good yields (45–91%) from aryl iodides and bromides, carbon monoxide and butan-1-ol in the presence of tri-*n*-butylamine.<sup>65</sup> The palladium catalysed alkoxy-carbonylation of aryl tosylates proceeds in low to good yields (4–81%)<sup>66</sup> whilst the reaction of diaryliodonium tetrafluoroborates and tosylates is high yielding (88–93%) and occurs at room temperature and atmospheric pressure.<sup>67</sup> Pyridines and oligopyridines bearing halides or triflates also undergo carboxyalkylation reactions to give *n*-butyl and ethyl esters in 41–90% yield.<sup>68</sup>



Scheme 4

### 2.3 Diacids and diesters

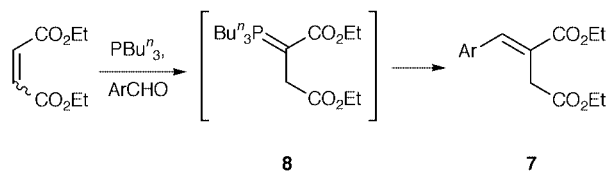
Methods reported for the synthesis of diacids and diesters include a range of coupling reactions where each component contributes one carboxylate to the product or reactions in which there is a diacid or diester already present in one of the fragments as well as reactions where one or two new carboxylates are formed. The cleavage of  $\alpha$ -nitro cycloalkanones with potassium persulfate in alcoholic solvents in the presence of sulfuric acid gives  $\alpha,\omega$ -diesters in 58–93% yield,<sup>69</sup> whilst ethyl diesters are formed in moderate to good yields (55–87%) when cyclic  $\alpha$ -hydroxy ketones are cleaved using catalytic dichloroethoxyoxyvanadium in ethanol under an oxygen atmosphere.<sup>70</sup> The palladium catalysed carbonylation of the dicarbonates of but-2-yne-1,4-diol gives bis(methylene)butanedioates in 51–70% yield,<sup>71</sup> similar reactivity is observed for hex-3-yne-2,5-diol.

The selenium directed conjugate addition of amines to fumarates (Scheme 5) is *anti* selective (4–62% de) and proceeds in high yields (90–98%).<sup>72</sup> Arylidene succinates **7** are formed in one pot from the reaction of diethyl maleate or fumarate with aromatic aldehydes and tri-*n*-butylphosphine (Scheme 6). *In situ* generation of phosphorane **8** leads to high yields (71–94%) of the unsaturated diester.<sup>73</sup> The titanium(IV) oxide catalysed photoalkylation of maleic acid with benzyltrimethylsilanes or phenylacetic acids provides  $\alpha$ -benzylsuccinates in 65–80% yield,<sup>74</sup> whilst the photoinduced electron transfer based generation of radicals and their subsequent addition to dimethyl maleate and dimethyl acetylenedicarboxylate proceeds in low to good yields (15–85%) with better results being obtained for the maleate series.<sup>75</sup>

The conjugate addition of methyl phenylacetate to methyl acrylate in the presence of a chiral crown ether and potassium *tert*-butoxide occurs in 31–100% yield with 0–84% ee.<sup>76</sup> Treatment of the racemic product with potassium *tert*-butoxide in the presence of the same chiral crown ethers leads to the

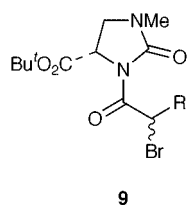


Scheme 5

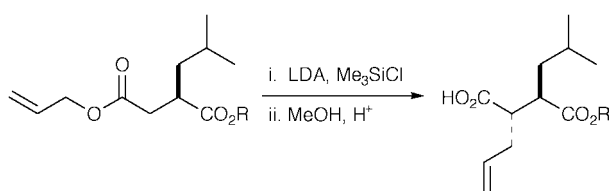


Scheme 6

isolation of material in 5–41% ee. The dynamic kinetic resolution of racemic  $\alpha$ -bromo carbonyl compound **9** by addition of the sodium salt of dibenzyl malonate followed by decarboxylation and auxiliary cleavage gives chiral  $\alpha$ -substituted maleates in 43–51% overall yield.<sup>77</sup> The dynamic kinetic resolution proceeds in 79–82% yield and 88–90% de. 2,7-Diaminosuberates and 2,5-diaminoadipates have been formed in low yields (11–38%) by the Kolbe electrolysis of glutamic and aspartic acid monoesters<sup>78</sup> and the dimethyl esters of 2,6-diamino-2,6-dimethyl-pimelic acid, 2,7-diamino-2,7-dimethylsuberic acid and 2,8-diamino-2,8-dimethylazelaic acid have been obtained in 88–96% de and 26–76% overall yield by reaction of two equivalents of Schollkopf's bislactim ether with dibromoalkanes.<sup>79</sup> 1-Bromo-2-chloroethane was used in place of 1,2-dibromoethane (which causes bromination of the anion) with subsequent conversion of the chloride to the bromide or iodide prior to the second coupling. *cis*-2,3-Diarylsuccinates are formed by the oxidative homocoupling of chiral 3-(arylacetyl)oxazolidin-2-ones (100% de, 17–88% yield) and subsequent cleavage of the chiral auxiliaries (51–89% yield, >98% ee),<sup>80</sup> whilst the intramolecular coupling of  $\alpha,\omega$ -di- $\alpha,\beta$ -unsaturated esters occurs in 55–90% yield (40–70% de) upon photosensitised one electron reductive activation.<sup>81</sup> The Ireland–Claisen rearrangement of (3*R*)-allyl 3-substituted succinates (Scheme 7) gives (2*S*,3*R*)-2-allyl-3-substituted succinate monoesters in moderate yield (36–55%) with good stereoselectivity (72–76% de).<sup>82</sup> 2-Vinylmalonates rearrange to 2-methylsuccinates in the presence of ( $\eta^2$ -propene)titanium(IV) isopropoxide in 76–77% yield.<sup>83</sup>



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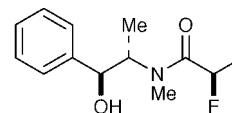
Scheme 7

## 2.4 Halo acids and esters

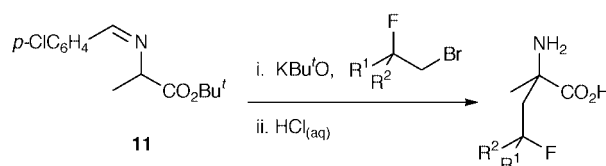
The asymmetric fluorination of a series of  $\beta$ -keto ester and  $\alpha$ -phenyl ester enolates has been achieved in good yields (62–95%) with moderate enantioselectivity (29–70% ee) using *N*-fluoro-2,10-camphorsultams.<sup>84</sup> It is interesting to note that the sense of asymmetric induction in these reactions is the opposite to that observed in the analogous enolate hydroxyl-

ations. The hydrohalogenation of buta-2,3-dienoic acids and esters using lithium or sodium halides in acetic acid gives  $\beta$ -halo- $\beta,\gamma$ -unsaturated acids and esters in moderate to good yields (56–92%) with the free acids giving better yields than their methyl esters.<sup>85</sup> Addition of *N*-bromo and *N*-iodo-succinimides to alkynoates gives the corresponding  $\beta$ -keto or  $\beta,\beta$ -dimethoxy- $\alpha,\alpha$ -dihalo esters in 20–95% yield.<sup>86</sup> Stannylcupration of alk-2-ynoic acids provides access to  $\beta$ -tributylstannyl- $\alpha,\beta$ -unsaturated acids (45–72% yield) with addition of iodine affording the corresponding  $\beta$ -iodo acid (51–66% yield).<sup>87</sup> A reversal of the regioselectivity is observed when tributylstannyl-diethylaluminium and 15 mol% copper(I) cyanide are employed whilst alk-3-ynoic acids give  $\gamma$ -iodo- $\beta,\gamma$ -unsaturated acids (90–98% regioselectivity) in 40–55% yield.

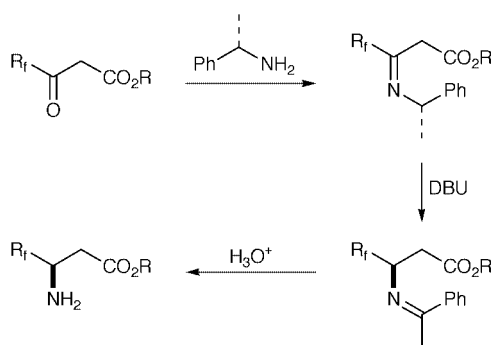
The ruthenium catalysed hydrogenation of  $\alpha$ -(fluorobenzyl)-acrylate has been shown to be highly diastereoselective (86% de, 48% yield), however, racemic products were obtained even when enantiomerically pure (*S*)-BINAP ligands were used.<sup>88</sup> Myers *et al.* have investigated the asymmetric alkylation reactions of  $\alpha$ -fluoro amides bearing a pseudoephedrine chiral auxiliary. The enolate of  $\alpha$ -fluoro propionamide **10** undergoes a highly diastereoselective reaction with allyl and benzyl halides (90–>95% de, 71–80% yield).<sup>89</sup> The  $\alpha$ -fluoro substituent facilitates the hydrolysis of the amide with  $\alpha$ -fluoro acids being obtained in high yields (86–87%, 92–95% ee) upon addition of biphasic alcoholic sodium hydroxide solutions. The  $\alpha$ -fluoro acetamide derivative reacts in an analogous manner, although the instability of the enolate again restricts the range of alkylating agents which can be employed (93–98% ee, 49–88% overall yield).<sup>90</sup>  $\alpha$ -Amino- $\gamma$ -fluoro esters have been obtained in moderate yields (19–62% overall, 24–66% de) by the alkylation of protected alanine **11** with  $\beta$ -fluoroalkyl bromides (Scheme 8).<sup>91</sup> The transamination of  $\beta$ -fluoroalkyl- $\beta$ -keto acids using  $\alpha$ -methylbenzylamine gives chiral  $\beta$ -amino acids (Scheme 9) in moderate to good yields (57–88%, 88–96% ee),<sup>92</sup> the analogous reaction of an  $\alpha$ -methyl- $\beta$ -keto- $\beta$ -trifluoromethyl ester with benzylamine proceeds in good yields (69–91%) but with low diastereoselectivity (8–40% de).<sup>93</sup> The *syn* and *anti*  $\alpha$ -methyl- $\beta$ -amino- $\beta$ -trifluoromethyl acids formed are readily separable, giving each isomer in >98% de. The addition of a lithium acetylide to  $\alpha$ -difluoromethyl and  $\alpha$ -trifluoromethyl imino esters is high yielding (87–95%)<sup>94</sup> and fluorinated imidoyl chlorides react with lithium ester enolates in good yields (75–90%).<sup>95</sup> The products of this latter reaction can exist either as (*Z*)- $\beta$ -fluoroalkyl- $\beta$ -enamino esters or as  $\beta$ -fluoroalkyl- $\beta$ -imino esters with the distribution of these tautomeric forms being influenced by the nature of the fluoroalkyl substituent (Scheme 10). The enantioselective addition of bromofluoro silyl ketene acetal **12** to aldehydes is catalysed by chiral Lewis acid **13**. Both the sense of asymmetric induction and the diastereoselectivity of the reaction are highly temperature dependent with the *anti* product being favoured at  $-20^\circ\text{C}$  (48–78% de, 72–93% ee, 80–90% yield)<sup>96</sup> and the *syn* product predominating at  $-78^\circ\text{C}$  (8–38% de, 83–99% ee, 70–96% yield).<sup>97</sup>



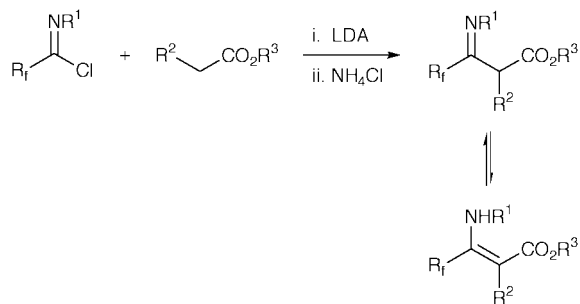
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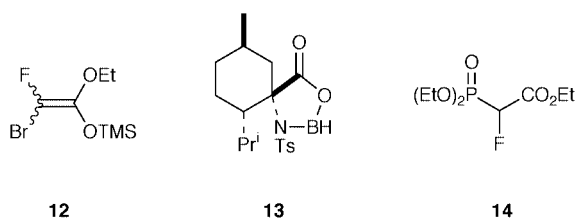
Scheme 8



Scheme 9



Scheme 10

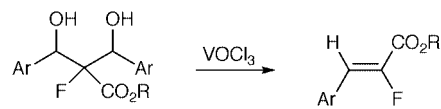


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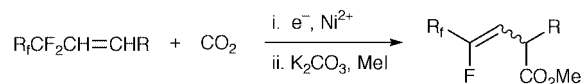
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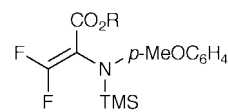
The  $\alpha$ -alkylation and subsequent  $\alpha$ -bromination of methyl acetoacetate proceeds in good yields (72–82%) with a lithium perchlorate and triethylamine mediated deacetylation providing the corresponding  $\alpha$ -bromo esters in 70–83% yield.<sup>98</sup>  $\alpha$ -Fluoro phosphonoacetate **14** has been utilised in the synthesis of a number of  $\alpha$ -fluoro ester derivatives. Ethoxycarbonylation and magnesium chloride mediated phosphorus–carbon bond cleavage provides  $\alpha$ -fluoro malonates in high yields (86–92%)<sup>99</sup> whilst a perfluoroacylation–organolithium addition sequence provides perfluoroalkyl  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters in 56–87% yield (80–100% (*E*)-selectivity).<sup>100</sup> The (*E*)-selective Horner–Wadsworth–Emmons reaction of **14** with aldehydes and alkylaryl ketones is promoted by tin(II) triflate and *N*-ethyl piperidine (73–97% yield, 84–99% (*E*)-selectivity) whilst its magnesium(II) mediated reaction with aldehydes is (*Z*)-selective (74–95% yield, 63–81% (*Z*)-selectivity).<sup>101</sup> (*Z*)- $\alpha$ -Fluoro- $\alpha,\beta$ -unsaturated acids and esters are also available by treatment of  $\alpha$ -fluoro- $\beta,\beta'$ -dihydroxy esters (formed by reaction of dibromofluoroacetates with two equivalents of aldehyde) with vanadium(V) trichloride oxide (Scheme 11). Deoxygenation and elimination of one equivalent of aldehyde gives  $\beta$ -aryl derivatives in 47–76% yield.<sup>102</sup> The reaction of  $\alpha$ -trifluoromethyl- $\beta$ -bromo enol ethers with *tert*-butyllithium then ethyl chloroformate gives  $\beta$ -ethoxy- $\beta$ -trifluoromethyl- $\alpha,\beta$ -unsaturated esters in moderate yields (48–56%).<sup>103</sup> The electrochemical, nickel(II) catalysed addition of carbon dioxide to perfluoroalkyl alkenes gives  $\gamma$ -fluoro- $\gamma$ -perfluoroalkyl- $\beta,\gamma$ -unsaturated esters in 45–56% yield (63–70% (*Z*)-selectivity) by alkene migration and monodefluorination (Scheme 12).<sup>104</sup> *N*-Trimethylsilyl- $\beta,\beta$ -difluoro- $\alpha$ -enamino esters **15** have been generated by the electrochemical reduction of  $\alpha$ -trifluoromethyl- $\alpha$ -imino esters in the presence of trimethylsilyl chloride (50–78% yield).<sup>105</sup> Their subsequent reaction with organolithium reagents or radicals provides access to  $\beta$ -substituted-



Scheme 11



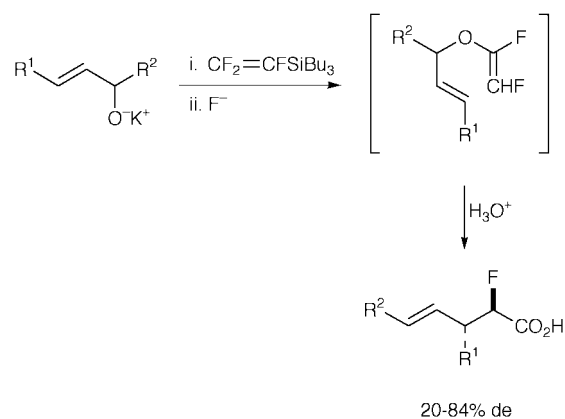
Scheme 12



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$\beta$ -fluoro- $\alpha$ -enamino esters and  $\beta,\beta$ -difluoro- $\alpha$ -imino esters respectively (33–70% yield).

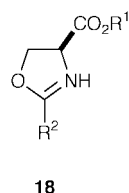
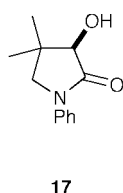
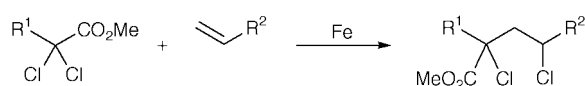
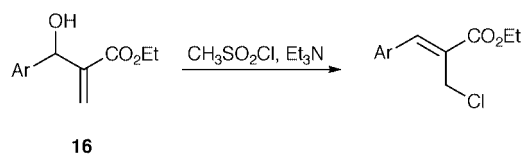
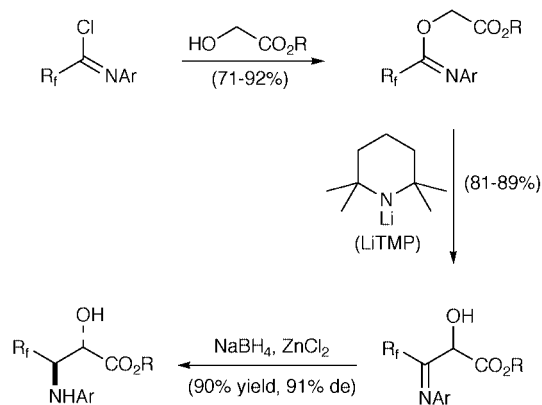
The Claisen rearrangement of allyl fluorovinyl ethers gives  $\alpha$ -fluoro- $\beta$ -substituted- $\gamma,\delta$ -unsaturated acids in 28–72% yield (Scheme 13)<sup>106</sup> whilst the intramolecular rearrangement of imino ethers gives  $\alpha$ -hydroxy- $\beta$ -imino- $\gamma$ -fluorinated esters (Scheme 14).<sup>107</sup> (*Z*)- $\beta$ -Aryl- $\alpha$ -chloromethyl- $\alpha,\beta$ -unsaturated esters have been obtained in 41–81% yield (100% de) by treatment of Baylis–Hillman reaction products **16** with triethylamine and methanesulfonyl chloride (Scheme 15).<sup>108</sup> Chiral  $\alpha$ -chloro acids are formed upon treatment of racemic  $\alpha$ -chloro acyl chlorides with chiral pyrrolidinone **17** and mild alkaline hydrolysis of the intermediate ester (21–99% ee, 45–97% overall yield).<sup>109</sup> The electrophilic ring opening of serine and threonine derived oxazolines **18** with trimethylsilyl halides, ethyl chloroformate or ethyl chloroformate and sodium iodide provides  $\beta$ -halo- $\alpha$ -amino esters in moderate to good yields (30–89%)<sup>110</sup> and the Kharasch addition of  $\alpha,\alpha$ -dichloro esters and trichloroacetates to terminal alkenes in the presence of iron(0) gives  $\alpha,\gamma$ -dichloro and  $\alpha,\alpha,\gamma$ -trichloro esters respectively in 6–89% yields (Scheme 16).<sup>111</sup> The nucleophilic aromatic substitution reaction of dihalofluoro arenes with ethyl cyanoacetate provides 31–61% yields of the corresponding dihalophenylacetic acids after hydrolysis and decarboxylation.<sup>112</sup>



Scheme 13

## 2.5 Amino acids and esters

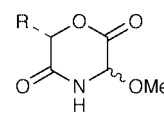
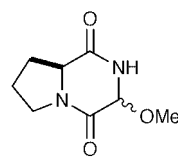
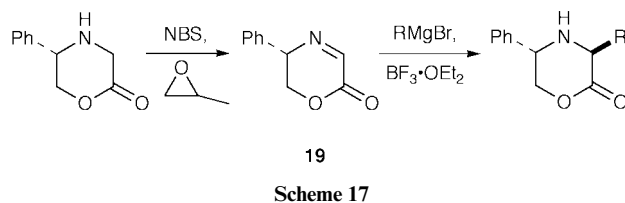
Amino acid synthesis remains an area of extensive research, with both the formation of specific targets and new approaches which are applicable to a range of substrates being investigated. Only the more general methodology is considered here and, in order to minimise any overlap with reviews in this series covering the synthesis of amines and amides,<sup>113</sup> only those methods which involve the formation of a new carbon–carbon bond are discussed.



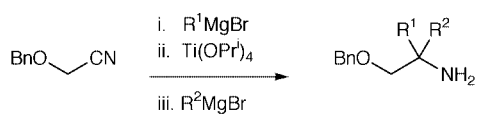
A number of other reviews relating to the synthesis of amino acids have been published recently; Dyker has highlighted approaches involving multicomponent coupling reactions<sup>114</sup> whilst Easton and Hutton have provided an account of the use of *N*-phthaloylamino acid derivatives in synthesis<sup>115</sup> and Agami *et al.* have described the use of chiral masked glyoxal derivatives for the synthesis of cyclic and acyclic  $\alpha$ -amino acids.<sup>116</sup> A general review of the additions of organometallic reagents to carbon–nitrogen double bonds includes a section on imino esters<sup>117</sup> and the use of sulfinimines for amino acid synthesis has been reviewed.<sup>118</sup>

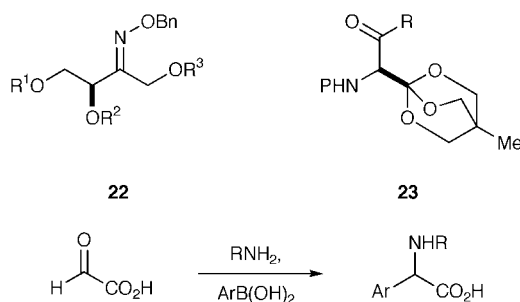
### 2.5.1 $\alpha$ -Amino acids and esters

The addition of organometallic reagents to imines and their derivatives is a popular approach for the synthesis of  $\alpha$ -amino acids. The (–)-sparteine mediated asymmetric addition of organolithium reagents to cinnamyl imines proceeds in moderate to good yield (30–86%, 16–88% ee) with oxidative cleavage of the styryl group providing *N*-protected  $\alpha$ -amino acids (46–84% yield).<sup>119</sup> The Lewis acid mediated diastereoselective addition of Grignard reagents to 2-unsubstituted dehydromorpholinone **19**, formed by NBS oxidation of the corresponding morpholinone (Scheme 17), occurs exclusively at the C=N bond (33–57% yield, 100% de). Hydrogenolytic ring cleavage gives single enantiomers of the corresponding  $\alpha$ -substituted- $\alpha$ -amino acids in 78–98% yield.<sup>120</sup> Diastereoselective allylation of the iminium ions generated upon treatment of chiral glycine equivalents **20**<sup>121</sup> and **21**<sup>122</sup> with titanium(IV) chloride occurs in low to good yields (13–90%, 69–99% de) with the  $\alpha$ -allyl- $\alpha$ -amino acid being liberated upon hydrolysis (62–80% yield). Hydrogenation of the iminium ion formed by the addition of



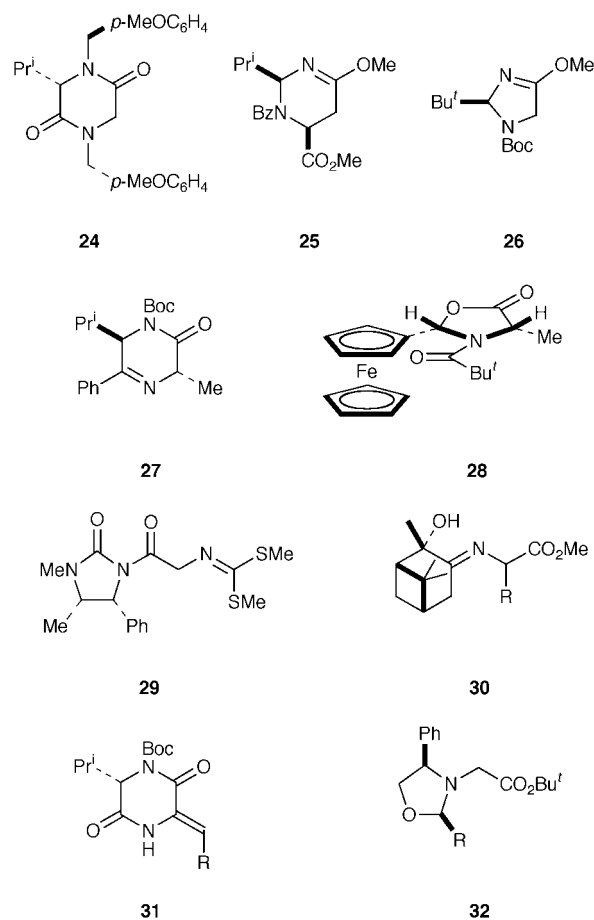
trialkylaluminium reagents to (*S*)-pyroglutamic acid and *in situ* dehydration provides *cis*-5-alkylprolines in high yields with excellent stereoselectivity (85–98% yield, >90–98% de).<sup>123</sup> *O*-Benzyl cyanohydrins undergo a double nucleophilic addition of Grignard reagents if titanium(IV) isopropoxide is added to activate the imine and promote the second addition (43–100% yield).<sup>124</sup> Only allylmagnesium bromide is reactive enough to attack the imine in the absence of the Lewis acid such that two distinct groups can be incorporated by sequential addition of two different Grignard reagents (Scheme 18). However, low yields are obtained during the second addition with  $\beta$ -hydrogen containing Grignards. Debenzylation and oxidation provides the corresponding  $\alpha,\alpha$ -disubstituted- $\alpha$ -amino acids. The addition of organolithium reagents to protected erythrose derived ketoximes **22** is diastereoselective with the two oxime geometries leading to opposite configurations at the new stereocentre. Higher yields and stereoselectivities are observed for the (*E*)-ketoxime (50–95% yield, 50–>90% de) than for the (*Z*)-ketoxime (41–75% yield, 0–74% de).<sup>125</sup> Deprotection and 1,2-diol cleavage provides  $\alpha$ -substituted serines.<sup>126</sup> The zinc bromide mediated addition of Grignard reagents to *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitron (75–77% yield, 80–82% de) provides (*R*)- $\alpha$ -amino acids upon deprotection and diol cleavage whilst complexation with diethylaluminium chloride prior to Grignard addition (63–68% yield, 64–70% de) leads to (*S*)- $\alpha$ -amino acids.<sup>127</sup> The analogous additions of a lithium acetylide occur in high yield (96–100%, 42–>90% de) with conversion of the alkyne to a carboxylate providing (*R*)- and (*S*)- $\alpha$ -amino- $\beta,\gamma$ -dihydroxy esters.<sup>128</sup> Use of a serinal derived nitron provides a route to  $\alpha,\beta$ -diamino acids. Grignard addition to the 2,3-*N,O*-isopropylidene-protected *N*-benzyl nitron gives the *syn* diamine ( $\geq 90\%$  de, 88–91% yield) whilst the *N-tert*-butoxycarbonyl-*O-tert*-butyldiphenylsilyl-protected nitron yields the *anti* diamine (78–82% de, 87–90% yield).<sup>129</sup> The addition of Grignard reagents to serine and threonine derived carbonyl derivatives **23** (R = H, Me) is also diastereoselective (40–98% de, 58–95% yield) with higher selectivity being observed in the threonine series.<sup>130</sup> Petasis *et al.* have extended their three component boronic acid Mannich reaction (Scheme 19) to the synthesis of  $\alpha$ -arylglycines (29–90% yield), however, diastereoselectivities are disappointingly low when  $\alpha$ -methylbenzylamine is employed (28–35% de).<sup>131</sup> The catalytic enantioselective aldol addition of silyl enol ethers to  $\alpha$ -imino esters is mediated by late transition metal phosphine complexes and provides  $\gamma$ -keto- $\alpha$ -amino esters in 65–93% yield with high levels of asymmetric induction (89–98% ee).<sup>132</sup>



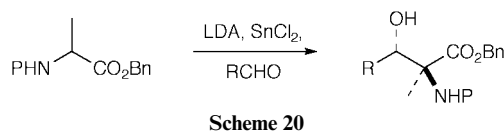


Scheme 19

Both (*R*)- and (*S*)- $\alpha$ -amino acids are available from the reaction of the benzophenone imine of *tert*-butylglycine with alkyl halides and conjugate acceptors under phase transfer conditions using a chiral cinchona alkaloid derived quaternary ammonium catalyst. Use of a pseudoenantiomeric pair of phase transfer catalysts and potassium hydroxide provides (*R*)-acids in 67–89% ee and (*S*)-acids in 72–91% ee and 40–86% overall yield<sup>133</sup> whilst the use of caesium hydroxide gives high yields of the  $\alpha$ -alkylated imines (67–91% yield, 92–99.5% ee)<sup>134</sup> with enones and enoates undergoing 1,4-addition in 85–88% yield (91–99% ee).<sup>135</sup> The reaction with cyclohexenone is also highly diastereoselective (92% de). The asymmetric phase transfer catalysed alkylation of an alanine imine has also been reported. (*R,R*)-2,2-Dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-1,3-dioxolane-4,5-dimethanol provides  $\alpha$ -substituted alanines in 45–96% yield and 22–82% ee.<sup>136</sup> The use of chiral reverse micelles for asymmetric alkylation has also been investigated;  $\alpha$ -amino acids are available both from *N*-benzylidene glycine ethyl ester (33–61% yield, 7–75% ee)<sup>137</sup> and from *N*-phthaloylglycine ethyl ester (41–60% yield, 17–60% ee).<sup>138</sup> The alkylations of a *cis*-aminoindanol derived hippuric acid amide and of *trans* 2-arylcyclohexyl hippurate esters have been shown to be diastereoselective. The former reactions proceed in 80–92% yield (91–99% de)<sup>139</sup> whilst the hippurate esters give >85% yields (55–>98% de) of the  $\alpha$ -benzyl product.<sup>140</sup> Alkylation of diketopiperazine **24** is highly diastereoselective (89–98% de, 63–90% yield) and oxidative cleavage of the *p*-methoxybenzyl groups and hydrolytic ring cleavage provides essentially enantiopure  $\alpha$ -amino acids.<sup>141</sup>  $\alpha$ -Alkylation of asparagine has been achieved by way of imino ether **25** (52–64% yield, >94% de), again hydrolysis yields the free amino acid.<sup>142</sup> Seebach and Hoffmann have reported the preparation and use of **26**, a new chiral glycine equivalent which reacts with primary and secondary alkyl, allyl, propargyl and benzyl halides (21–90% yield, >99% de), enoates (68–80% yield, 66–96% de) and aliphatic and aromatic aldehydes (61–88% yield, 34–>96% de in favour of the *syn* isomer).<sup>143</sup> Conversion of these products to  $\alpha$ -amino acid methyl esters occurs under mild conditions (trimethylsilyl trifluoromethanesulfonate then 0.1 M aqueous trifluoroacetic acid) which are compatible with acid sensitive side chains. The alkylation, conjugate addition and palladium catalysed allylation reactions of chiral alanine template **27** are highly diastereoselective (94–98% de, 47–86% yield). Hydrolysis provides  $\alpha$ -substituted alanines in good yields (72–91%, >97–99% ee).<sup>144</sup> The enantioselective  $\alpha$ -alkylation of alanine by way of chiral ferrocenyl derivative **28** (71–95% yield, 92–>98% de) has also been reported, the (*R*)- $\alpha$ -amino acid is unmasked in 71–95% yield without racemisation.<sup>145</sup> Chiral  $\alpha$ -amino acids are also available by alkylation of (+)-*N*-alkyl-10-camphorsulfonamide imines (20–>90% de, 74–98% yield)<sup>146</sup> and from the alkylation and conjugate addition reactions of an *N*-(diphenylmethylene)glycine-2,10-camphorsultam under phase transfer conditions (74–90% yield).<sup>147</sup> The lithium enolate of imine **29** reacts with alkyl halides in moderate to good yields (58–86%, 46–96% de) with imine hydrolysis and auxiliary cleavage occurring in moderate yields (36–56%, 88–90% ee after recrystallisation).<sup>148</sup>



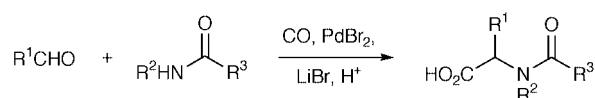
Diastereoselective protonation of the enolates of imines **30**, prepared from the reaction of racemic  $\alpha$ -amino esters with 2-hydroxypinan-3-one, is high yielding (92–96%, 79–>98% de) with the chiral  $\alpha$ -amino esters being regenerated using boric acid (72–94% yield, >98% ee).<sup>149</sup> 2,3-Dideuterio amino acids have been obtained by palladium catalysed reduction of the alkene **31** resulting from the condensation of aldehydes with a chiral diketopiperazine. Product stereochemistries were shown to be dependent both on the alkene geometry and on any nitrogen protecting groups employed; high levels of selectivity were observed (49–94% de) with the free amino acids being formed in moderate to good yields (42–95%, 83–98% ee) upon hydrolysis.<sup>150</sup> The aldol reactions of chiral oxazolidinone bearing glycine *tert*-butyl ester **32** are *anti* selective (80–98% de, 73–94% yield),<sup>151</sup> as are the additions of aldehydes to the chelated tin(II) enolates of *N*-protected alanine benzyl esters (70–98% de, 60–91% yield, Scheme 20).<sup>152</sup> The analogous addition of chelated *N*-tosyl alanine ester enolates to  $\alpha$ -oxygenated- $\alpha$ -chiral aldehydes provides the 2,3-*anti*-3,4-*anti* products in high yields (85–90%, 56–78% de).<sup>153</sup>



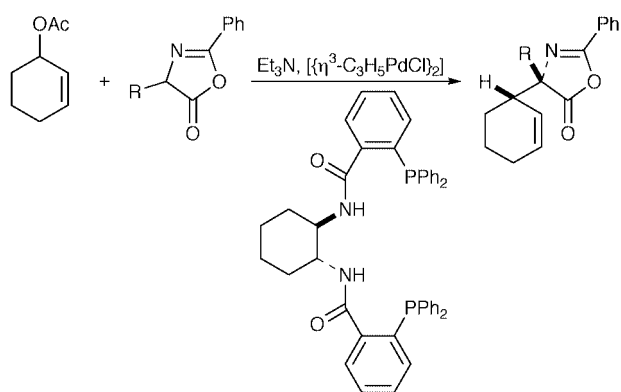
Scheme 20

An enantioselective preparation of phenylglycines based on the reaction of carbon dioxide with the  $\alpha$ -anion of *N*-*tert*-butoxycarbonyl-*N*-trimethylsilyl-arylmethylamines, formed using *sec*-butyllithium and (–)-sparteine (10–86% yield, 29–96% ee), has been reported.<sup>154</sup> The palladium catalysed amidocarbonylation of aldehydes gives racemic *N*-acyl  $\alpha$ -amino acids in 55–99% yield (Scheme 21)<sup>155</sup> with a subsequent enzyme mediated kinetic resolution providing access to optically active materials (24–42% yield, 97–>99% ee (*S*)-amino acid and 30–46% yield, 86–96% ee (*R*)-*N*-acyl amino acid).<sup>156</sup>

The reactions of the organozinc, organocopper and zinc-copper reagents derived from (*S*)- $\gamma$ -iodo- $\alpha$ -amino esters with acid chlorides, allyl chlorides, propargyl chloride and aryl iodides have been investigated.<sup>157</sup> Variable yields (18–78%) of  $\gamma$ -substituted  $\alpha$ -amino acid derivatives are obtained. The addition of alkyl radicals to imines derived from glyoxylates and chiral amines is diastereoselective (16–100% de), although yields are moderate (25–60%),<sup>158</sup> whilst radical additions to a camphorsultam derived glyoxylic oxime are both high yielding and highly diastereoselective (80–86% yield, 90–96% de).<sup>159</sup> The intramolecular 5-*exo-trig* cyclisation of alk-4-enyl amino acid derived aminyl radicals shows some stereoselectivity (20–48% de) and proceeds in moderate to good yields (44–92%).<sup>160</sup> The palladium catalysed reaction of azalactones with allyl acetates in the presence of chiral phosphine ligands is diastereo- and enantioselective (74–90% de, 83–99% ee, 69–97% yield) with  $\alpha$ -amino acids being liberated upon hydrolysis of the azalactone (Scheme 22).<sup>161</sup> The palladium catalysed reaction of *N*-*tert*-butoxycarbonyl-*N*-methyl- $\alpha$ -tosylglycine ethyl ester with allylic carbonates and allylic epoxides also provides unsaturated  $\alpha$ -amino acid derivatives (40–72% yield) the sulfone can be removed using methanolic magnesium (20–69% yield).<sup>162</sup>

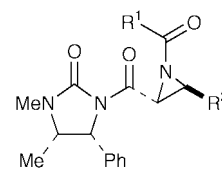


Scheme 21

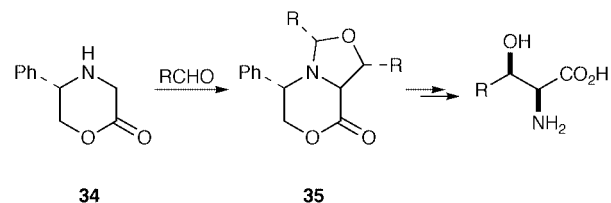


Scheme 22

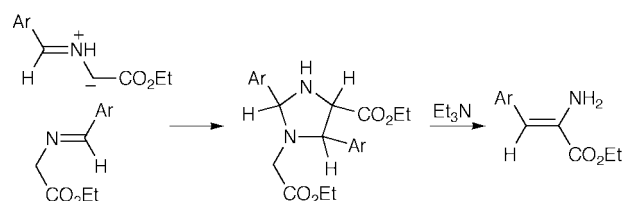
The methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxy) mediated rearrangement of  $\gamma$ -epoxy-*tert*-butyldimethylsilyl ethers proceeds with complete chirality transfer and provides  $\alpha$ -chiral- $\beta$ -silyloxy aldehydes in high yields (79–97%). These aldehydes have been shown to be  $\alpha,\alpha$ -disubstituted- $\alpha$ -amino acid precursors.<sup>163</sup> The ring expansion of *N*-acylaziridine-2-imides **33** provides oxazoline-4-imides in >95% yield. Ring hydrolysis and auxiliary cleavage gives *syn*  $\beta$ -hydroxy- $\alpha$ -amino acids (>63% overall yield).<sup>164</sup> The azomethine ylides, generated from morpholin-2-one **34** and aldehydes, react with a second equivalent of aldehyde to give bicyclic intermediates **35** (Scheme 23) in moderate to good yields (45–86%, 100% de). Hydrolysis and hydrogenolytic cleavage of the auxiliary provides *syn*- $\beta$ -hydroxy- $\alpha$ -amino acids in quantitative yields.<sup>165</sup> An analogous sequence with arylimines yields *syn*- $\alpha,\beta$ -diamino acids (36–45% overall yield, 100% de),<sup>166</sup> and dehydroamino acid esters have been obtained in 15–81% yield by the base catalysed ring opening of the intermediate imidazolidine formed by cycloaddition of an aryl azomethine ylide and the *N*-ethoxycarbonylmethylimine from which it was generated (Scheme 24).<sup>167</sup> 3-Substituted-2-phenyl prolines are produced from the caesium fluoride-tetramethoxysilane mediated 1,4-addition of a diphenylmorpholin-2-one to acrylates (Scheme 25)<sup>168</sup> whilst the base catalysed conjugate addition of nitroalkanes to *N*-protected dehydroalanines provides  $\gamma$ -nitro- $\alpha$ -



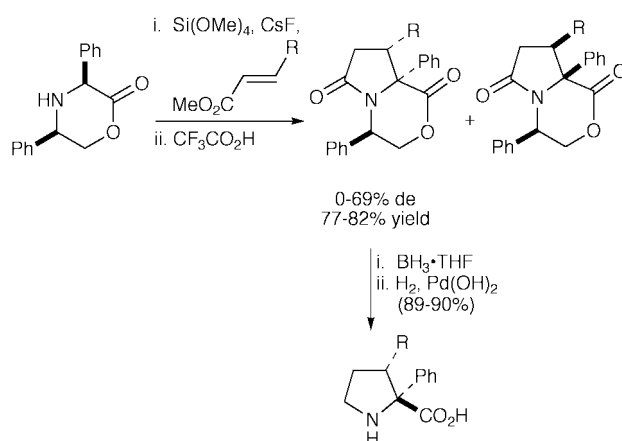
**33**



Scheme 23



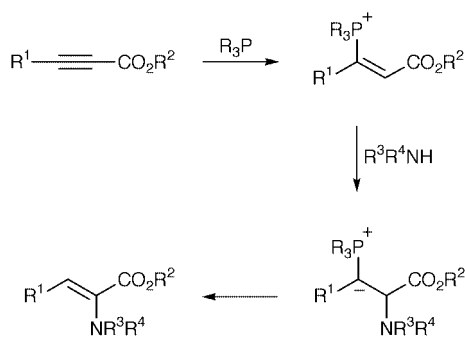
Scheme 24



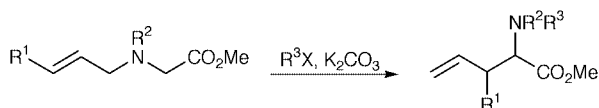
Scheme 25

amino esters (65–93% yield, 0–20% de),<sup>169</sup> although careful control of the reaction conditions is required to ensure that only 1:1 adducts are formed. Conversion of the  $\gamma$ -nitro- $\alpha$ -amino esters to  $\gamma$ -keto,  $\gamma$ -hydroxy and  $\gamma$ -dihydro derivatives (58–87% yield) has been reported.<sup>170</sup> The Knoevenagel reaction of methyl nitroacetate with aldehydes provides  $\alpha$ -methoxycarbonylnitroalkenes **36** (46–88% yield), subsequent addition of organozinc halides (62–97% yield) then  $\alpha$ -alkylation (66–91% yield) and nitro group reduction (64–77% yield) completes a route to  $\alpha,\beta,\beta$ -trisubstituted- $\alpha$ -amino acid derivatives.<sup>171</sup> Dehydroamino acids have been synthesised by the triphenylphosphine catalysed addition of nitrogen nucleophiles to alkynoates which cannot undergo isomerisation to alkenes (56–95% yield).<sup>172</sup> The reaction is believed to proceed *via* the 1,4-addition of the phosphine,  $\alpha$ -nucleophilic attack, proton shift and regeneration of the phosphine by elimination (Scheme 26). The amination of  $\gamma$ -silylated- $\alpha,\beta$ -unsaturated esters provides  $\beta,\gamma$ -unsaturated- $\alpha$ -amino esters in moderate yields (38–66%) after elimination of the silyl moiety.<sup>173</sup> The one-pot *N*-alkylation and [2,3]-Stevens rearrangement of *N*-allyl- $\alpha$ -amino esters gives *N,N*-dialkylallylglycines in 42–65% yield (Scheme 27)<sup>174</sup> whilst the Claisen rearrangement of enynol *N*-protected amino acid esters **37** leads to chemoselective

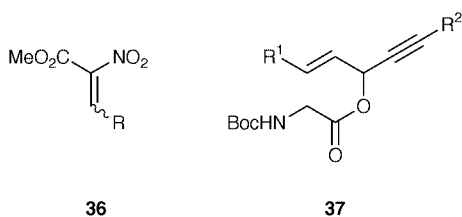




Scheme 26



Scheme 27



36

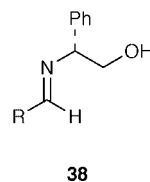
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formation of  $\alpha$ -amino esters bearing an enyne side chain (60–76% yield, 89–>95% selectivity for rearrangement of the alkene).<sup>175</sup>

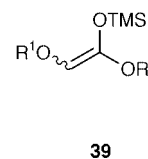
Imidoyllithium reagents have been generated from chloroimines and excess lithium powder and react with ethyl chloroformate to give  $\alpha$ -imino esters in 52–80% yield<sup>176</sup> and a novel phosgene-free procedure for the stereospecific synthesis of chiral  $\alpha$ -isocyanato esters by treatment of chiral  $\alpha$ -amino esters with di-*tert*-butyl dicarbonate and DMAP has been reported (49–95% yield).<sup>177</sup> The Friedel–Crafts acylation of arenes with *N*-protected aspartic anhydrides provides mixtures of  $\alpha$ - and  $\beta$ -amino acids with variable yields (18–83%) and selectivity (100:0–7:93  $\alpha$ : $\beta$ ).<sup>178</sup>

### 2.5.2 $\beta$ -, $\gamma$ - and $\delta$ -Amino acids and esters

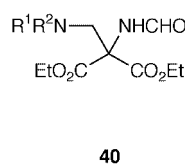
The Lewis acid mediated addition of silyl ketene acetals to chiral imines **38** and their derived *N*-benzyl-1,3-oxazolidines gives (*R*)- and (*S*)- $\beta$ -amino esters respectively (62–98% de, 61–92% yield),<sup>179</sup> whilst the addition of 2-alkoxysilyl ketene acetals **39** to *N*-2-hydroxypyridylimines is catalysed by a chiral 1,1'-binaphthol derived zirconium(IV) species.<sup>180</sup> The latter reactions are both enantio- and diastereoselective with (*E*)-2-*tert*-butyldimethylsilyloxy silyl ketene acetals providing *syn*- $\alpha$ -silyloxy- $\beta$ -amino esters (64–>98% de, 91–98% ee, 65–100% yield) whilst the corresponding reactions of a (*Z*)-2-benzyloxy silyl ketene acetal yield *anti* isomers (14–88% de, 76–96% ee, 41–100% yield). The indium(III) chloride catalysed condensation of aldehydes, amines and silyl ketene acetals gives low to good yields of  $\beta$ -amino esters (21–92%)<sup>181</sup> and the reaction of  $\alpha,\alpha$ -disubstituted and  $\alpha,\alpha,\alpha$ -trisubstituted aldehydes with malonic acid in the presence of ammonium acetate yields  $\beta$ -alkyl- $\beta$ -amino acids (21–59% yield, 0–75% de).<sup>182</sup>  $\beta$ -Secondary amino alanines have been formed by the acidic hydrolysis of the diethyl (*sec*-aminomethyl)formamido malonates **40** derived from the Mannich reactions of diethyl formamido malonate, formaldehyde and secondary amines (39–84% overall yield).<sup>183</sup> The aldol reaction of the lithium enolates of  $\alpha$ -silyl acetates with imines provides *anti*- $\alpha$ -silyl- $\beta$ -amino esters in 43–60% yield (>95% de), protodesilylation or oxidation (72–99% yield) affords  $\beta$ -amino esters or  $\alpha$ -hydroxy- $\beta$ -amino esters respectively.<sup>184</sup>  $\beta$ -Substituted-3,4-dihydroisoquinolone propionates are



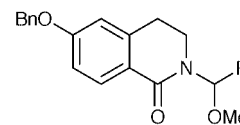
38



39



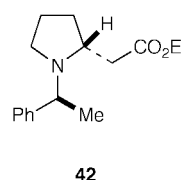
40



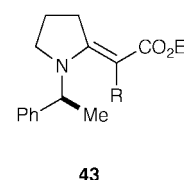
41

produced in the Lewis acid catalysed reaction of a silyl ketene acetal with the acyl iminium ion formed from the corresponding *N*-( $\alpha$ -methoxyalkyl)-3,4-dihydroisoquinolones **41** (45–90% yield).<sup>185</sup> The diastereoselective addition of allylmagnesium bromide to *O*-(1-phenylbutyl)aldoximes (86–>96% de, 78–100% yield) provides  $\beta$ -amino esters after hydroxylamine cleavage and ozonolysis of the alkene.<sup>186</sup> *tert*-Butyl bromoacetate has been utilised as an aminomethyl cation equivalent, reaction with chiral *N*-acyl-1,3-oxazolidin-2-ones followed by a Curtius rearrangement gives  $\beta$ -amino acid derivatives ( $\geq 80\%$  de, 15–25% overall yield).<sup>187</sup> Benzyl *N*-(acetoxymethyl)carbamate provides the analogous products in 34–62% yield (>80% de).

Alkylation of  $\beta$ -amino ester **42** provides the (2*R*,3*R*) ester as a single diastereomer in 25–84% yield,<sup>188</sup> an alternative approach to these targets by hydrogenation of the corresponding tetrasubstituted enamino esters **43** is not stereoselective.<sup>189</sup> The diastereoselective alkylation of 3-silyloxy- $\beta$ -lactams (100% de, 56–84% yield) provides  $\alpha$ -alkyl isoserines after deprotection and ring opening.<sup>190</sup> Three groups have investigated the Arndt–Eistert homologation of *N*-fluorenylmethylloxycarbonyl- $\alpha$ -amino acids. Seebach and co-workers report that yields are highly dependent on the nature of the side chain (33–58%)<sup>191</sup> whilst Müller *et al.* used ultrasound to promote the Wolff rearrangement (65–82% yield)<sup>192</sup> and Ellmerer-Müller *et al.* actively warmed the latter reaction from –20 to 0 °C to prevent base mediated cleavage of the carbamate upon extended exposure to the reaction conditions (80–100% overall yield).<sup>193</sup>

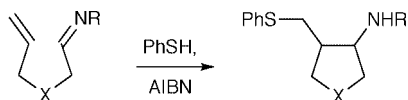


42

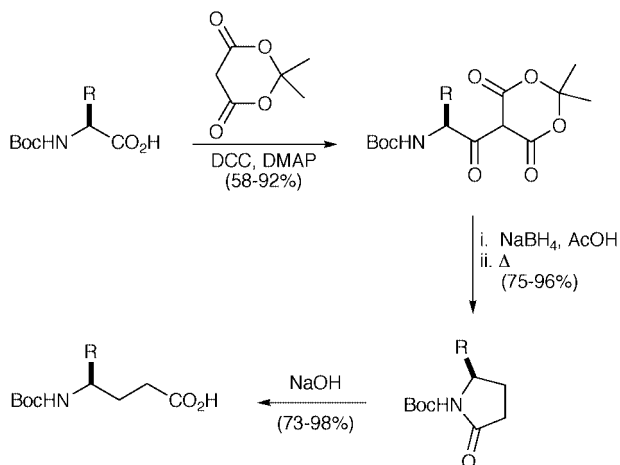


43

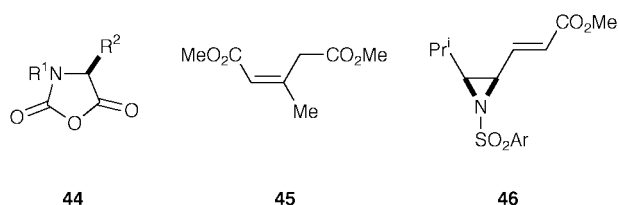
Cyclic  $\beta$ -amino acids have been synthesised by way of the sulfanyl radical addition–cyclisation reactions of tethered  $\omega$ -alkenyl oximes and hydrazones (49–88% yield, Scheme 28).<sup>194</sup> Conversion of the methylphenylsulfanyl substituent to a carboxylate provides the target structures. The palladium catalysed coupling of aromatic iodides with the  $\gamma$ - and  $\delta$ -alkylzinc iodides derived from  $\beta$ - and  $\gamma$ -amino esters respectively provides fair to good yields (20–89%) of the corresponding  $\gamma$ - and  $\delta$ -aryl amino esters.<sup>195</sup> Addition of propiolate acetylides to aliphatic nitrones gives  $\gamma$ -amino- $\alpha,\beta$ -alkynyl esters in 60–94% yield.<sup>196</sup> These have been converted to fully saturated,  $\alpha,\beta$ -unsaturated and  $\alpha,\beta$ -dihydroxy- $\gamma$ -amino esters. The diastereoselectivity of the additions to  $\alpha$ -chiral  $\alpha$ -amino nitrones can be controlled by the addition of magnesium bromide (74% de *anti* in its presence, 100% de *syn* in its absence, 72–78% yield). The addition of lithium ester enolates to urethane *N*-protected-*N*-carboxyanhydrides **44** gives *N*-protected  $\alpha$ -alkyl- $\gamma$ -amino- $\beta$ -keto esters in 25–81% yield,<sup>197</sup> whilst the enolate of dimethyl 3-methylglutaconate **45** reacts with  $\alpha$ -amino aldehydes to give  $\alpha$ -substituted- $\gamma$ -amino- $\beta$ -hydroxy esters (36–70% de, 65–77%



Scheme 28



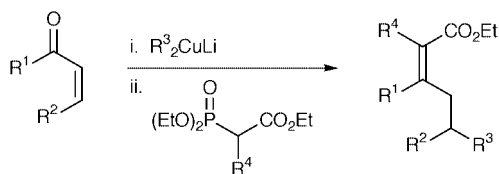
Scheme 29



yield).<sup>198</sup>  $\alpha$ -Amino acids have been converted to  $\gamma$ -substituted- $\gamma$ -amino acids by the addition of Meldrum's acid,  $\alpha$ -keto reduction, decarboxylative ring closure and basic hydrolysis (Scheme 29).<sup>199</sup> The ring opening of (*E*)- $\gamma,\delta$ -aziridinyl- $\alpha,\beta$ -unsaturated esters **46** with methanesulfonic acid or trifluoroacetic acid and subsequent  $S_N2'$  addition of organocuprates provides  $\alpha$ -substituted- $\delta$ -amino- $\beta,\gamma$ -unsaturated esters (78–94% yield).<sup>200</sup> *cis*-Aziridines give *anti* products whilst *trans*-aziridines give *syn* isomers (>98% de). Direct  $S_N2'$  opening of these *cis*- and *trans*-aziridines with organocuprates yields the *syn* and *anti* products respectively (100% yield).

## 2.6 Unsaturated acids and esters

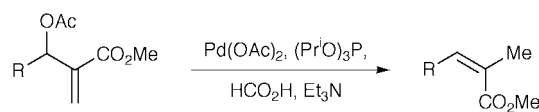
A number of methods for the synthesis of conjugated and non-conjugated unsaturated acids and esters based on the formation of both single and double carbon-carbon bonds have been reported. The reaction of aldehydes, ethyl diazoacetate and triethylphosphite in the presence of a rhenium catalyst provides (*E*)- $\alpha,\beta$ -unsaturated ethyl esters in good yields (65–95%, 50–>90% de)<sup>201</sup> whilst the use of ethyl diazoacetate, triphenylphosphine and a ruthenium catalyst provides (*E*)-esters in 82–92% yield (80–>98% de).<sup>202</sup> Unprotected aldoses react with methyl bromoacetate in the presence of tri-*n*-butylphosphine and zinc to give (*E*)- $\alpha,\beta$ -unsaturated esters (71–89% yield)<sup>203</sup> and (*E*)- and (*Z*)-2-alkoxy and 2-aryloxyalk-2-enoates have been prepared from the reactions of  $\alpha$ -oxy- $\alpha$ -methoxycarbonyl phosphonates and phosphonium salts respectively. (*Z*)-Isomers were obtained in 9–85% yield (>90% de) whilst the (*E*)-isomers were isolated in 18–79% yield (>90% de).<sup>204</sup> The *in situ* oxidation and Wittig reactions of allylic, propargylic and benzylic alcohols has been reported (51–84% yield), providing (*E*)-alkenoates from unstable and isomerisable aldehydes without the need for their isolation.<sup>205</sup> A tandem Michael–Horner–Wadsworth–Emmons reaction of enones provides  $\delta$ -substituted- $\alpha,\beta$ -unsaturated esters in one-pot (41–96% yield, 50–100% (*E*)-product).<sup>206</sup> The intermediate copper enolate is



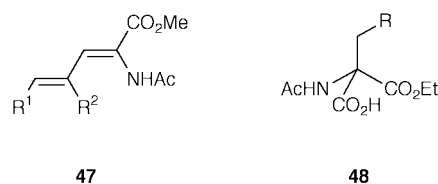
Scheme 30

sufficiently basic to deprotonate the  $\alpha$ -alkoxycarbonyl phosphonate (Scheme 30).

The allylic acetates derived from 3-aryl and alk-3-enyl-3-hydroxy-2-methylene alkanooates (Baylis–Hillman products) can be reduced with formic acid in the presence of triethylamine and a palladium catalyst to give trisubstituted (*Z*)-alkenes (86–100% de, 61–85% yield, Scheme 31)<sup>207</sup> whilst alkynes can be reduced with sodium tetracarbonylhido-ferrate and trimethylsilyl chloride or dichloromethane before oxidation with copper(II) chloride or iodine to give  $\alpha,\beta$ -unsaturated acids in 37–60% yield.<sup>208</sup> The catalytic asymmetric hydrogenation of  $\alpha,\beta,\gamma,\delta$ -unsaturated dienamide esters **47** using an ethyl-DuPHOS bearing rhodium catalyst selectively provides the  $\gamma,\delta$ -unsaturated- $\alpha$ -amino esters (>95% yield, 86–99% ee).<sup>209</sup> Isomerisation of acetylenic pentafluorophenyl esters provides activated (*E,E*)-dienoic esters which can be coupled in one pot with alcohols and amines (63–75% overall yield, 86–98% de).<sup>210</sup> Debromination of methyl 2,3-dibromo-2,3-diarylpropanoates provides 2,3-diarylenoates<sup>211</sup> whilst the oxidative decarboxylation of ethyl hydrogen acetamidomalonates **48** provides dehydroamino esters in 46–71% yield.<sup>212</sup>



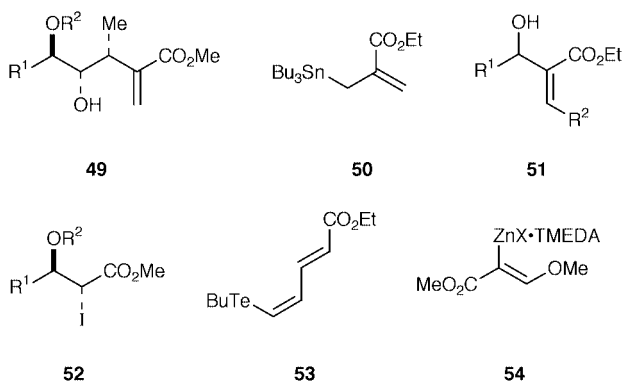
Scheme 31



47

48

The 1,2-addition of lithium ester enolates to  $\alpha,\beta$ -unsaturated aldehydes followed by conversion of the alkoxide to a carbonate and palladium catalysed elimination gives (*E,E*)-dienoic esters (72–90% de, 48–80% yield).<sup>213</sup> The double deprotonation and alkylation of butenoic and 2-methylbutenoic acids has been studied.  $\alpha$ -Alkylation is observed upon addition of two equivalents of diethylolithium amide and alkyl halides but allyl and benzyl halides give substantial competitive  $\gamma$ -alkylation (32–86% overall yield, >99:1–34:66  $\alpha$ : $\gamma$  alkylation).<sup>214</sup> The  $\alpha$ -alkylation of 2-methylbutenoic acid can also be achieved using thienyllithium and substoichiometric quantities of secondary amines (68–72% yield, 62–86%  $\alpha$ -selectivity).<sup>215</sup> The asymmetric glyoxylate ene reaction is catalysed by bidentate bis(oxazolonyl)copper(II) complexes (62–99% yield, 76–98% ee, 74–90% regioselectivity for unsymmetrical alkenes),<sup>216</sup> *in situ* prepared chiral titanium(IV) alkoxides (15–66% yield, 40–97% ee)<sup>217</sup> and chiral ytterbium(III) complexes (78–87% yield, 12–38% ee).<sup>218</sup> Ytterbium(III) triflate provides racemic products in 63–91% yield. The coupling of the indium reagent derived from methyl (*Z*)-2-(bromomethyl)but-2-enoate with  $\alpha$ -benzyloxy and  $\alpha$ -*tert*-butyldimethylsilyloxy aldehydes in water proceeds with high 3,4-*syn*-4,5-*anti* selectivity to give methyl 4-hydroxy-3-methyl-2-methylene-5-oxyalkanoates **49** in 72–92% yield (74–94% de)<sup>219</sup> whilst the radical 1,4-additions of electrophilic allyl tributylstannane **50** to enones proceed in 58–69% yield.<sup>220</sup> The enantioselective Baylis–Hillman reaction of pyrimidine

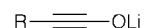


5-carbaldehydes and acrylates is catalysed by BINAP (9–44% ee, 8–49% yield)<sup>221</sup> and (*Z*)- $\beta$ -branched Baylis–Hillman products **51** are formed by coupling  $\beta$ -substituted [ $\alpha$ -(ethoxycarbonyl)vinyl]aluminium intermediates, derived from the hydroalumination of alkynoates, with aldehydes in the presence of di-*n*-butylboron triflate (51–66% yield, >98% de).<sup>222</sup>

The radical allylation of  $\alpha$ -iodo- $\beta$ -alkoxy esters **52** proceeds with inversion of configuration (67–87% yield, 89–>94% de)<sup>223</sup> and the Lewis acid promoted conjugate addition of vinylmagnesium bromide to chiral  $\alpha,\beta$ -unsaturated *N*-acyl oxazolidinones is highly diastereoselective (>90–>95% de) and gives the  $\gamma,\delta$ -unsaturated derivative in 78–89% yield.<sup>224</sup> Only mono-substitution occurs upon addition of (dialkyl)magnesiumcuprates to ethyl (*2E,4Z*)-5-telluropenta-2,4-dienoate **53** affording the (*E,E*)-5-substituted pentadienoate (>96–>98% de) rapidly and in high yields (82–98%).<sup>225</sup> Alkyl  $\beta$ -methyl- $\alpha,\beta,\gamma,\delta$ -unsaturated esters have been prepared from  $\gamma,\delta$ -unsaturated- $\beta$ -keto esters by enol phosphate formation (76–98% yield) and subsequent reaction with dimethylithiumcuprate (54–77% yield), the (*2E*)-isomer predominates but the (*2Z*)- and  $\beta$ -unsubstituted products are also formed.<sup>226</sup> Enoates are also formed by treatment of (*Z*)- $\beta$ -(arylseleno)cinnamates with Grignard reagents in the presence of copper(I) iodide (78–96% yield)<sup>227</sup> and in 20–98% yield by the palladium catalysed cross coupling of vinylzinc halides **54** with aryl halides and vinyl halides and triflates.<sup>228</sup>

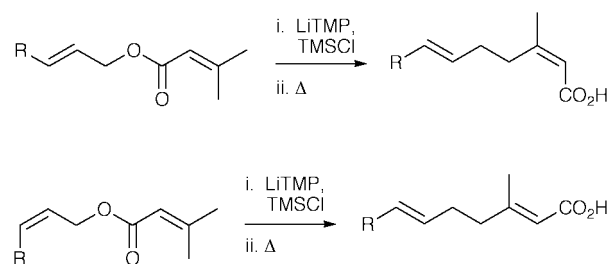
The palladium catalysed Heck reaction of iodobenzene and methyl acrylate occurs in supercritical carbon dioxide when di(perfluoroalkyl)phenylphosphine,<sup>229</sup> tri(difluoromethylphenyl)phosphine and tri-2-furylphosphine ligands<sup>230</sup> are employed (91–96% yield). Nickel(0) catalysed<sup>231</sup> and copper(I) bromide and iodide<sup>232</sup> catalysed Heck reactions have been reported to proceed in 64–87% and 31–85% yields respectively. The Heck cross coupling of propionic acid esters and aryl halides using a palladium(II)–copper(I) based catalyst system in THF gives good yields (92–99%) for electron deficient halides but poor yields (3–35%) when naphthyl halides and phenyl iodides bearing electron donating or additional halo substituents are employed.<sup>233</sup> The Suzuki reaction of cyclopropylboronic acids with bromo acrylates gives cyclopropyl substituted  $\alpha,\beta$ -unsaturated esters in 81–94% yield<sup>234</sup> whilst the rhodium(I) catalysed reductive dimerisation of dialkyl acetylenedicarboxylates gives tetrakis(alkoxycarbonyl)buta-1,3-dienes in 73–91% yield (48–80% (*Z,Z*)).<sup>235</sup> The palladium catalysed reaction of allene, carbon monoxide and phenols gives aryl methacrylate esters in moderate yields (53–68%)<sup>236</sup> and the asymmetric alkoxycarbonylations of cyclohexyl allyl phosphates proceed in 48–70% yield and 2–48% ee.<sup>237</sup> The electrochemical carboxylation of alkyl substituted vinyl bromides in the presence of a nickel(II) catalyst under a carbon dioxide atmosphere gives  $\alpha,\beta$ -unsaturated acids in moderate to good yields (53–82%)<sup>238</sup> whilst 2-bromomethyl-1,4-dibromobut-2-ene gives 3-methylenepent-4-enoic acid (57% yield).<sup>239</sup>

The addition of ynolates **55**, generated *in situ* from  $\alpha,\alpha$ -dibromo esters, to aldehydes and ketones gives di- and

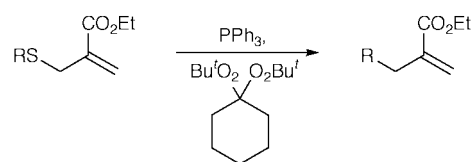


**55**

trisubstituted- $\alpha,\beta$ -unsaturated acids in 24–82% yield with high (*E*)-selectivity (60–>98% de).<sup>240</sup> The  $\gamma$ -alkylation of 3-methylbut-2-enoic acid has been achieved by consecutive Ireland–Claisen (61–74% yield, 78–80% de) and Cope rearrangement (70–80% yield, 100% de) of its allyl esters (Scheme 32).<sup>241</sup> The reactions are stereospecific, with the (*E*)-ester giving the (*2Z,6E*)-product whilst the (*2E,6E*)-isomer is obtained from the (*Z*)-ester. The free radical addition of phenyltrichloroselenide to alkenes provides 2-phenylseleno-1-trichloromethylalkanes (63–88% yield) which can be transformed into  $\alpha,\beta$ -unsaturated acids by base promoted dehydrochlorination (to give the  $\alpha,\alpha$ -dichloroalkene) and a [2,3]-rearrangement of the selenoxide in the presence of water (49–84% yield over two steps).<sup>242</sup> The reaction sequence is highly regioselective but only moderately stereoselective. 2-Methylene-3-alkylthiopropionate esters react with triphenylphosphine in the presence of a peroxide initiator to give the corresponding 2-methylene alkanates (51–71% yield) and triphenylphosphine sulfide (Scheme 33).<sup>243</sup> The [2,3]-sigmatropic rearrangement of  $\alpha$ -propargyloxyacetic acids in the presence of butyllithium and (–)-sparteine gives chiral  $\alpha$ -hydroxy- $\beta$ -allenic acids (35–44% yield, 42–48% ee)<sup>244</sup> and (*E*)- $\beta$ -phosphono acrylates have been formed in 51–69% yield by addition of trimethylsilyloxyphosphorus(III) derivatives to  $\alpha$ -halo acrylates.<sup>245</sup>



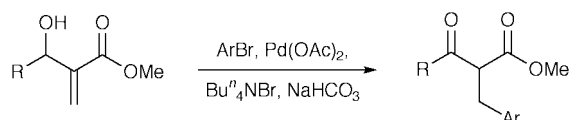
**Scheme 32**



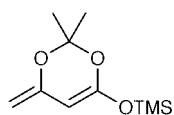
**Scheme 33**

## 2.7 Keto acids and esters

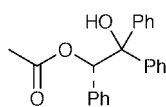
The preparation of  $\beta$ -keto esters, in 54–91% yield, by the titanium(IV) chloride, tributylamine and catalytic trimethylsilyl triflate promoted Claisen condensations of methyl esters has been reported.<sup>246</sup> In all cases higher yields were obtained than for the analogous reactions promoted by dichlorotitanium(IV) ditriflate and triethylamine. The catalytic asymmetric allylation of cyclic  $\beta$ -keto esters using a chiral phosphine–palladium complex affords  $\alpha,\alpha$ -disubstituted- $\beta$ -keto esters in high yields (71–98%) with good levels of asymmetric induction (75–99% ee).<sup>247</sup> The electrochemical carboxylation of alicyclic vinyl triflates provides cyclic  $\beta$ -keto acids in 28–77% yield<sup>248</sup> whilst the palladium catalysed Heck reaction of Baylis–Hillman adducts and aryl iodides yields  $\alpha$ -arylmethyl- $\beta$ -keto esters (60–83%, Scheme 34).<sup>249</sup>  $\delta$ -Hydroxy- $\beta$ -keto esters have been obtained by the chiral phosphine–copper(II) fluoride complex catalysed enantioselective addition of dienolate equivalent **56** to aromatic and unsaturated aldehydes (48–98% yield, 65–95% ee)<sup>250</sup> and by the one-pot 1,2-addition of chiral acetate **57** to  $\beta$ -aryl- $\alpha,\beta$ -unsaturated aldehydes and subsequent Claisen condensation



Scheme 34



56

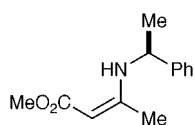


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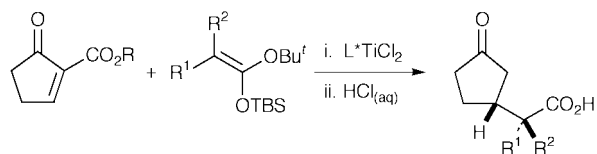
with the lithium enolate of *tert*-butyl acetate (40% yield).<sup>251</sup> The zinc promoted acylation of ethoxycarbonylmethylene triphenylphosphorane proceeds in 80–85% yield.<sup>252</sup>

Conversion of  $\beta$ -keto esters to  $\gamma$ -keto esters has been achieved using diethylzinc and diiodomethane (58–81% yield)<sup>253</sup> whilst reduction of cyclic  $\alpha$ -bromomethyl- $\beta$ -keto esters with samarium(II) iodide provides the ring expanded, one carbon homologated cyclic  $\gamma$ -keto esters in 35–90% yield.<sup>254</sup> The palladium catalysed acylation of 2-(alkoxycarbonyl)cyclopentylzinc iodides is *cis* selective (>90% de) and proceeds in 51–90% yield.<sup>255</sup>

The 1,4-addition reactions of ester enolates and enones, and of enolates and enoates, provide rapid access to  $\delta$ -keto esters. The indium(III) chloride catalysed conjugate addition of silyl enol ethers to enoates occurs in the absence of solvent (14–90% yield), as does the addition of silyl ketene acetals to enones (12–82% yield).<sup>256</sup> The catalyst can be recovered and reused. The catalytic enantioselective 1,4-addition of  $\alpha$ -nitro esters to  $\beta$ -unsubstituted enones in the presence of a chiral lithium tetrahydroaluminate also gives  $\delta$ -keto esters (5–80% ee, 81–87% yield),<sup>257</sup> as does the addition of chiral acyclic  $\beta$ -enaminoesters **58** to acrylates (94–95% de, 66–74% yield) followed by enamine hydrolysis.<sup>258</sup> The asymmetric conjugate addition of silyl ketene acetals to 2-alkoxycarbonylcyclopentenones (Scheme 35), 2-alkoxycarbonylcyclohexenones and enedioates is promoted by chiral titanium(IV) complexes and gives cyclic  $\beta$ -alkoxycarbonylmethyl ketones and esters (25–79% yield, 0–47% ee, 50–97% de) after  $\alpha$ -decarboxylation.<sup>259</sup>



58

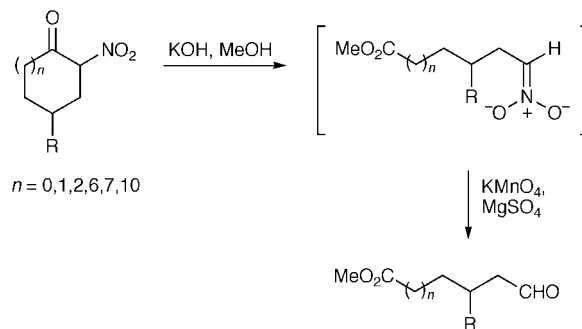


Scheme 35

The dichloroethoxyxyvanadium mediated oxidative cleavage of cyclic tertiary  $\alpha$ -hydroxy ketones gives  $\omega$ -keto esters in 64–73% yield<sup>70</sup> and the ring cleavage and *in situ* Nef reaction of  $\alpha$ -nitro cycloalkanones occurs in the presence of methanolic potassium hydroxide then potassium permanganate and magnesium sulfate (Scheme 36).<sup>260</sup>  $\omega$ -Methoxycarbonyl aldehydes are obtained in good yields (61–84%) whilst diketo esters are available by conjugate addition of the cyclic  $\alpha$ -nitro ketone to an enone prior to ring cleavage (50–93% overall yield).

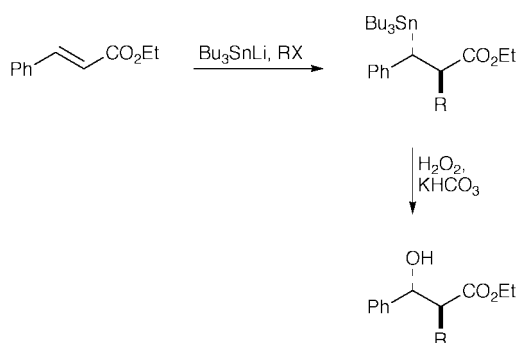
## 2.8 Hydroxy acids and esters

$\alpha$ -Hydroxy acids and esters have been obtained by oxidation of

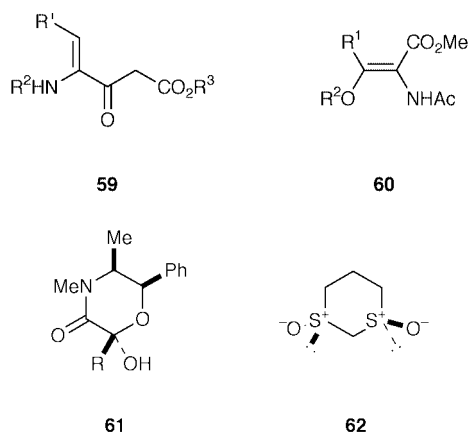


Scheme 36

silyl ketene acetals, malonates and aldehydes. The catalytic enantioselective oxidation of silyl ketene acetals with (salen)-manganese(III) complexes proceeds in good yields (64–85%, 22–68% ee),<sup>261</sup> oxidation with hypervalent iodine in methanol gives  $\alpha$ -methoxy esters in 57–74% yield.<sup>262</sup> The cerium(IV) mediated oxidation of dialkyl malonates under an oxygen atmosphere yields  $\alpha$ -hydroxy- $\beta$ -diesters (23–69%)<sup>263</sup> whilst the diiodomethylation of aldehydes with iodoform and samarium(II) iodide affords  $\alpha$ -diiodomethyl secondary alcohols (40–62%) which rearrange to give  $\alpha$ -hydroxy acids upon addition of aqueous sodium hydroxide (60–65% yield).<sup>264</sup> The dynamic kinetic resolution of  $\alpha$ -bromo acid chlorides with (*R*)-pantolactone ((*R*)-dihydro-3-hydroxy-4,4-dimethylfuran-2(3*H*)-one) and subsequent addition of sodium phenoxides gives  $\alpha$ -aryloxy esters (83–95% yield).<sup>265</sup> The diastereoselectivity of the reaction is solvent dependent with (2*S*)-products being favoured in THF (48–68% de) and (2*R*)-products being preferred in DMSO (47–74% de).  $\alpha$ -Keto acids have been reduced to chiral  $\alpha$ -hydroxy acids using *B*-chlorodiisopinocampheylborane (65–91% yield, 85–98% ee),<sup>266</sup> whilst the asymmetric hydrogenation of pyruvate esters using cinchona alkaloid modified palladium catalysts (1–32% ee),<sup>267</sup> polymer stabilised platinum clusters (76–96% ee)<sup>268</sup> and platinum sols (75–80% ee) has been reported.<sup>269</sup> The enantioselective hydrogenation of  $\alpha$ - and  $\beta$ -keto esters using a ruthenium(II) aminophosphine–phosphinite catalyst gives  $\alpha$ -hydroxy esters with low levels of asymmetric induction (11–41% ee, 52–98% yield) but  $\beta$ -hydroxy esters are formed with higher selectivity (75–85% ee, 52–100% yield).<sup>270</sup> Cationic rhodium DuPHOS complexes have been employed in the hydrogenation of  $\alpha$ -acetoxy and  $\alpha$ -benzoyloxy acrylates (93–99% ee)<sup>271</sup> whilst [2.2]PHANEPHOS ruthenium(II) complexes give  $\beta$ -hydroxy esters from  $\beta$ -keto esters in 95–96% ee at  $-5^\circ\text{C}$ .<sup>272</sup> The sequential hydrogenation of dehydroamino  $\beta$ -keto esters **59** gives (3*R*,4*R*)-3-hydroxy-4-amino esters in >95% ee (90–99% yield)<sup>273</sup> and 2-amino-3-hydroxy esters are available from the asymmetric hydrogenation of  $\beta$ -oxy- $\alpha$ -acetamido acrylates **60**.<sup>274</sup> (*Z*)-Acrylates give (2*S*,3*S*)-products (93–97% ee, 89–99% yield) and (*E*)-acrylates provide the (2*S*,3*R*)-isomers (89–97% ee, 95–99% yield). The organo-selenium mediated reduction of  $\alpha$ -unsubstituted- $\alpha,\beta$ -epoxy esters gives  $\beta$ -hydroxy esters in high yields (83–97%)<sup>275</sup> whilst the  $\beta$ -hydroxy esters are obtained in 85–90% yield by the reaction of the cyclic thionocarbonates of  $\alpha,\beta$ -dihydroxy esters with tributyltin hydride.<sup>276</sup>  $\alpha$ -Substituted- $\beta$ -hydroxy esters have been obtained from the  $\beta$ -stannyl compounds formed in 51–72% yield by the treatment of enoates with tributylstannyl lithium followed by alkylation (Scheme 37).<sup>277</sup> Addition of tin(IV) chloride or titanium(IV) chloride causes inversion of the tin bearing stereocentre (68–99% yield) whilst oxidative cleavage of the stannyl substituent proceeds with retention (57–69%). The bismuth(III) chloride–zinc mediated addition of allyl bromide to  $\alpha$ -,  $\beta$ -,  $\gamma$ - and  $\delta$ -keto acids has been explored,<sup>278</sup> reactions occur in 52–100% yield but the 4- and 5-hydroxy acids cyclise *in situ* to give lactones. Ephedrine derived hemiacetal **61** (formed in 65–71% yield from the corresponding  $\alpha$ -keto acid chlorides) has been utilised for the synthesis of chiral  $\alpha$ -hydroxy acids.<sup>279</sup>



Scheme 37

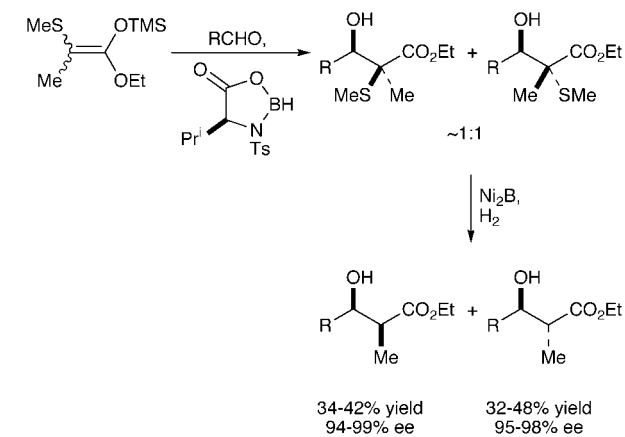


Scheme 38

Titanium(IV) chloride catalysed addition of allyltrimethylsilane proceeds in 67–92% yield (100% de) whilst acid catalysed dehydration of substrates in which R contains a  $\beta$ -hydrogen, followed by hydrogenation and ring cleavage provides  $\alpha$ -chiral acids in 36–53% overall yield. *trans*-1,3-Dithiane-1,3-dioxide **62** has been used as a chiral acyl anion equivalent for the synthesis of  $\alpha$ -hydroxy acids and esters.<sup>280</sup> Diastereoselective addition to aldehydes (6–>96% de, 76–86% yield) followed by a Pummerer rearrangement provides  $\alpha$ -hydroxy thioesters (71–83% yield, 95–100% ee) which can be hydrolysed to the corresponding acids (79–90% yield, 95–100% ee) and esters (86–90% yield, 94–97% ee). The addition of silyl enol ethers and silyl ketene thioacetals to pyruvate esters is mediated by both copper(II) and tin(II) bisoxazoline complexes. Complimentary asymmetric induction is obtained from the two metals, copper(II) gives (*S*)- $\alpha$ -keto esters (93–99% ee, 88–96% de, 77–97% yield)<sup>281</sup> whilst tin(II) gives the (*R*)-isomers (92–99% ee, 80–98% de, 72–94% yield).<sup>282</sup>

The addition of ester enolates to aldehydes and ketones provides rapid access to  $\beta$ -hydroxy esters. Nelson has reviewed the enantioselective aldol reactions of isolable enolate equivalents<sup>283</sup> whilst Ellis and Bosnich have studied the mechanism of the Mukaiyama aldol reaction.<sup>284</sup> Organotin perchlorates have been shown to be effective catalysts for the addition of silyl ketene acetals to aldehydes (45–92% yield),<sup>285</sup> silyl enol ethers and acetals are unreactive under these conditions. Mukaiyama aldol reactions have also been shown to proceed on an alumina surface impregnated with zinc(II) chloride upon sonication (65–93% yield)<sup>286</sup> and in dichloromethane under high pressures but in the absence of a catalyst (78–90%).<sup>287</sup> The latter conditions were also found to be stereoselective (60–68% de *syn*) and to promote reaction at the 2-position of dienolate equivalents. The aldol reaction of  $\alpha$ - and  $\beta$ -benzyloxy aldehydes with silyl ketene acetals is catalysed by zirconocene bistriflate complexes (85–92% yield, 13–43% de).<sup>288</sup> Alkyl aldehydes also react under these conditions (92–97% yield, 0–38% de) with competing pathways involving zirconium and trimethylsilyl triflate catalysis leading to the low stereoselectivity. The stereoselective aldol reaction of (*S*)-3-(*p*-tolylsulfinyl)furfuraldehyde with silyl

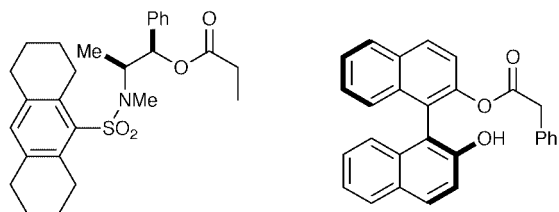
ketene acetals is catalysed by lanthanide triflates (75–99% yield, 90–>99% de).<sup>289</sup> Chiral triarylcations promote the asymmetric addition of benzaldehyde to a silyl ketene acetal (20–99% yield), however, significant levels of competing silyl Lewis acid catalysis were observed (3–50% ee).<sup>290</sup> Similar results were obtained when a macromolecular chiral titanium(IV) catalyst was employed (26% ee, 32% yield).<sup>291</sup> Carreira and co-workers have used their chiral titanium salicylate biaryl catalyst for the acetate aldol reactions of  $\alpha,\beta$ -ynals (84–96% yield, 94–97% ee)<sup>292</sup> whilst *syn* and *anti* propionate aldol products have been obtained by desulfurisation of the products of the enantioselective reaction of a methylsulfonyl containing silyl ketene acetal (Scheme 38).<sup>293</sup>



The addition of aldehydes to the boron enolate of an *N*-acetylbornane-10,2-sultam is diastereoselective (40–82% de, 70–86% yield)<sup>294</sup> whilst the boron mediated addition of chiral propionate **63** is *syn* selective (90–>96% de, 93–98%) when diisopropylethylamine and di-*n*-butylboron triflate are used for enolate formation and *anti* selective (56–78% de, 93–97% yield) when triethylamine and dicyclohexylboron triflate are employed.<sup>295</sup> The lithium enolate of **64** undergoes *anti* selective aldol reactions with aromatic aldehydes (33–82% de, 58–99% yield)<sup>296</sup> whilst the titanium enolate of **65** is *syn* selective in its reactions with precomplexed bidentate aldehydes (88–98% de, 51–84% yield) and *anti* selective in its reactions with isovaleraldehyde (98% de, 83–92% yield).<sup>297</sup>  $\alpha$ -Dimethylsilyl esters, formed by the reaction of ester enolates with chlorodimethylsilane (55–64% yield), react with aldehydes in DMF without the need for an activator (39–93% yield, 20–36% de *syn*).<sup>298</sup> The addition of the lithium enolates of  $\alpha$ -dimethylsilylphenyl acetates to aldehydes gives *anti* products (>95% de) in 64–76% yield,<sup>184</sup> protodesilylation or oxidation gives  $\beta$ -hydroxy and *anti*- $\alpha,\beta$ -dihydroxy esters respectively (48–63%). The asymmetric aldol reaction of 2-cyanopropionates is catalysed by a chiral rhodium(I) diphosphine complex and gives *anti* products (36–62% de, 57–93% ee, 67–88% yield).<sup>299</sup>

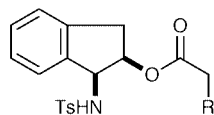
The Reformatsky reaction of ethyl bromoacetate and aromatic aldehydes in chiral micelles proceeds with low levels of asymmetric induction (15–34% ee, 46–60% yield).<sup>300</sup> The iron pentacarbonyl promoted reaction of  $\alpha$ -bromo propionates with ketones shows no diastereoselectivity (20–60% yield)<sup>301</sup> whilst the cobalt(0) mediated addition of  $\alpha$ -bromo esters to (*R*)-2,3-*O*-cyclohexylidene glyceraldehyde gives 2,3-*anti*-3,4-*anti* products (56–88% de, 73–90% yield).<sup>302</sup> *tert*-Butyl enoates, aldehydes and lithium thiophenolate undergo a one-pot tandem conjugate addition–aldol reaction to give *syn*- $\alpha$ -methylphenylsulfanyl- $\beta$ -hydroxy esters **66** in moderate to good yields (52–92%, 22–84% de).<sup>303</sup> The addition of diethylzinc to ethyl diazoacetate generates a zinc derivative which reacts with aldehydes to give  $\alpha$ -diazo- $\beta$ -hydroxy esters (12–86% yield).<sup>304</sup>

The asymmetric Baylis–Hillman reaction of chiral sultam **67**

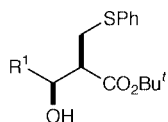


63

64

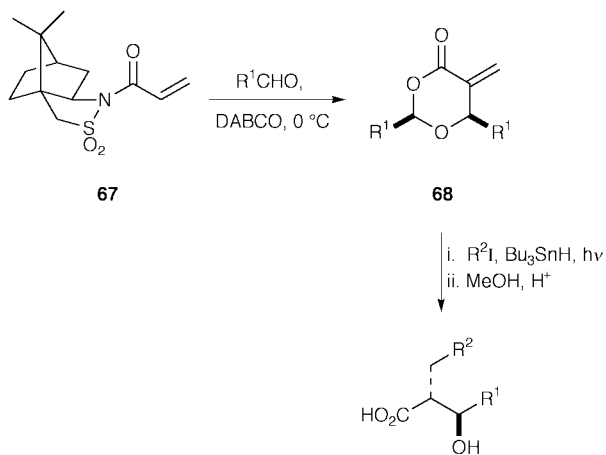


65



66

provides optically pure (>99% ee) dioxanones **68** (33–98% yield) which can be utilised for the synthesis of *anti* aldol products by 1,4-radical addition (57–93% yield) followed by hydrolysis (Scheme 39).<sup>305</sup> Rhodium catalysed hydrogenation of **68** provides the propionate *anti* aldol product (85–89% yield) whilst ring cleavage and epoxidation or dihydroxylation provides epoxy alcohols and triols respectively (80–81% yield).<sup>306</sup> The photosensitised one electron reductive activation of  $\omega$ -oxo- $\alpha,\beta$ -unsaturated esters provides *trans*-2-ethoxycarbonylmethyl cycloalkanols (77–98% yield).<sup>307</sup>



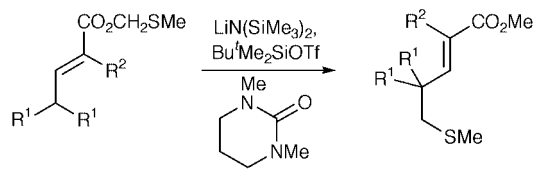
Scheme 39

The coordination mediated optical resolution of carboxylic acids using the neutral calcium salt of *O,O'*-dibenzoyl tartaric acid has been investigated (3–93% ee, 63–99% yield)<sup>308</sup> whilst two methods for the chiroptical determination of the absolute configuration of  $\alpha$ -hydroxy acids have been reported.<sup>309</sup>

## 2.9 Miscellaneous acids and esters

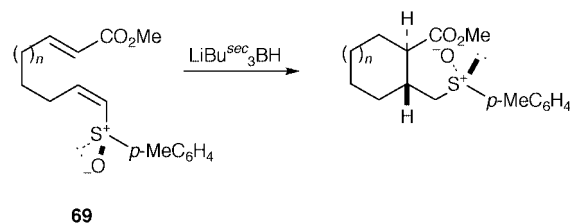
Synthetic approaches to a number of other heteroatom substituted carboxylic acids and esters have been described. The alkylation of ethyl 2-nitropropionate gives disubstituted  $\alpha$ -nitro esters (14–79%) although short reaction times are required to prevent competitive formation of monosubstituted methacrylates.<sup>310</sup> The conjugate addition of nitromethane to  $\alpha$ -cyano- $\alpha,\beta$ -unsaturated esters to give  $\alpha$ -cyano- $\gamma$ -nitro esters is promoted by microwaves (70–100% yield).<sup>311</sup> Reaction of bromobenzoic acids with aryl acetonitriles in the presence of LDA gives 2-cyanobenzoic acids (40–70%) by way of a benzyne intermediate.<sup>312</sup>

Chiral  $\alpha,\beta$ -epoxy esters have been formed from chiral  $\alpha,\beta$ -dihydroxy esters *via* their cyclic sulfates (80–95% overall yield, 97–98% ee)<sup>313</sup> and by the asymmetric Darzen's condensation of aldehydes and ketones with (–)-8-phenylmenthyl

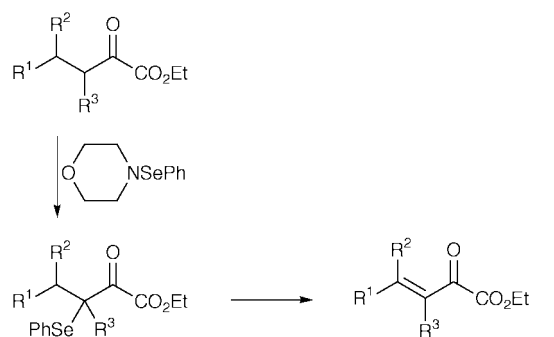


Scheme 40

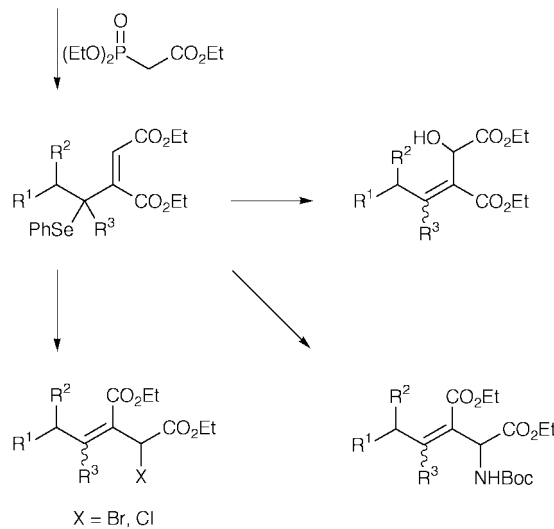
chloro- and bromoacetates (77–96% de, 43–79% yield).<sup>314</sup> The catalytic asymmetric addition of lithium thiophenolates to enoates is promoted by chiral amino alcohols (1–75% ee, 81–99% yield),<sup>315</sup> improved selectivity is observed when 2-trimethylsilylthiophenol is employed (77–97% ee, 66–99% yield).<sup>316</sup> The cobalt catalysed hydrosulfenylation of acrylates provides  $\alpha$ -phenylsulfanyl esters (60–70% yield)<sup>317</sup> whilst  $\gamma$ -methylthiomethyl esters are obtained by rearrangement of the silyl ketene acetals of the methylthiomethyl esters of  $\alpha,\beta$ -unsaturated acids (50–70% yield, Scheme 40).<sup>318</sup> The L-selectride promoted reductive cyclisation of vinyl sulfoxides **69** ( $n = 0, 1$ ) provides a single diastereomeric product in 50–60% yield (Scheme 41).<sup>319</sup>  $\beta$ -Phenylselenanyl- $\alpha$ -keto esters **70** are formed in 58–80% yield from  $\alpha$ -keto esters and can be utilised in the synthesis of a variety of carboxylate containing products (Scheme 42).<sup>320</sup> Alkyl (*E*)- or (*Z*)- $\beta$ -trimethylstannyl-



Scheme 41



70



Scheme 42

$\alpha,\beta$ -unsaturated esters are available from alkynoates by addition of hexamethyldistannane and stereoselective mono-protodestannylation (74–95% yield)<sup>321</sup> whilst the free radical hydrostannylation of (–)-menthyl (*E*)-2,3-disubstituted propenoates is *syn* selective (50–100% de, 11–69% yield).<sup>322</sup>

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Review 8/08136K