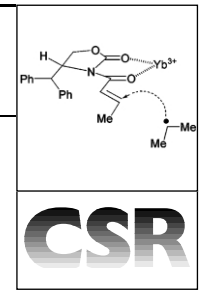
Stereoselective radical reactions



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For many years, the reputed lack of selectivity in some free-radical reactions has resulted in this class of reaction being overlooked in the stereoselective synthesis of important target molecules. More recently, however, the situation has changed as new and milder methods of radical generation have been developed, which have helped researchers to gain a better understanding of the key factors that influence selectivity in radical transformations. As a consequence, the use of radicals in stereoselective synthesis is increasing and there are a number of important intra- and intermolecular additions, where high levels of stereoselectivity have been achieved in the formation of carbon–carbon bonds.

1 Introduction

It is well known that radical reactions can offer a number of advantages over more classical ionic transformations.[1] This includes the use of mild and neutral reaction conditions, which avoids the basic or acidic conditions that can promote decomposition or epimerisation of sensitive organic molecules in ionic reactions. A large number of efficient radical reactions have been developed[2] including tandem and cascade sequences, which can allow the formation of a number of carbon–carbon bonds in concise "one-pot" transformations. Despite these advantages, the use of radicals in synthesis has often been disregarded, due to the perception that all radical reactions are uncontrollable and unselective. This is particularly apparent in the stereoselective synthesis of asymmetric molecules, where ionic and also pericyclic reactions are the tools of choice for the synthetic chemist. However, the situation is gradually changing and a number of highly stereoselective radical reactions are now known which can offer an alternative approach to conventional methods.[3] These developments have been possible as our knowledge of the principal factors that influence radical processes improves. This includes a greater understanding of the importance of bond dissociation energies, steric effects, stereoelectronic effects and radical polarity in radical reactions.[4]

An important problem that needs to be faced when using radical reactions to stereoselectively form asymmetric centres is that most carbon-centred radicals are planar, or nearly so. Once

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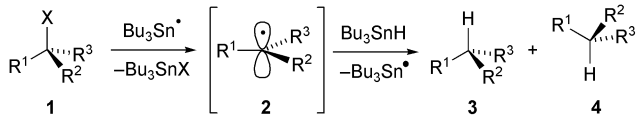
Grégory Bar (left) Andrew Parsons (right)

a carbon radical has been created, it usually adopts a trigonal planar shape and so both faces of the radical are identical. For example, following abstraction of a halogen-atom (by the $Bu_3Sn^{\cdot}$ radical) from the organohalide enantiomer **1**, the planar carbon-centred radical **2** is formed (Scheme 1). This can equally

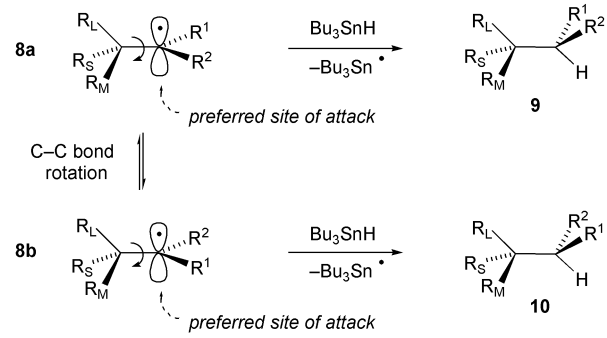


Scheme 1

well abstract a hydrogen atom from the top or bottom face to give a racemic (1:1) mixture of alkanes **3** and **4**.

In order to stereoselectively form an asymmetric centre researchers have employed several strategies, which have been successfully used in ionic transformations. Thus, an adjacent chiral centre can influence the radical reaction leading to the predominant formation of one diastereoisomer (in a 1,2-asymmetric induction). For example, Hanessian and Alpegiani have reported the stereoselective allylation of β-lactam **5** using allyltributylstannane (Scheme 2).[5] The allylation takes place selectively from the bottom face of cyclic radical **7** so as to avoid steric interactions with the sulfone group. This results in the diastereoselective formation of **6** and as the shape of the precursor molecule influences the approach of the incoming reagent this is known as a substrate-controlled reaction.

Stereoselective reaction of an acyclic radical is usually more difficult to achieve than for cyclic radicals (such as **7**) as rotation about the carbon–carbon bond can lead to a mixture of diastereomers. For example, reaction of acyclic radical **8a** with Bu_3SnH is expected to selectively form **9**, as the Bu_3SnH would prefer to attack from the bottom face (to avoid the largest alkyl group, R_L, on the adjacent carbon atom – this is known as *anti* attack) (Scheme 3). However, following rotation of the central carbon–carbon bond of **8a** the alternative conformer **8b** can be formed and this would be expected to react with Bu_3SnH to predominantly form **10**. Therefore, if there is free rotation about the carbon–carbon bond in **8a**/**8b** a 1:1 mixture of the diastereoisomers **9** and **10** can be formed in a non-stereoselective reaction. It is important to note that the selective formation of **9** or **10** should strictly be discussed in terms of the relative stabilities of the transition states that lead to **9** and **10** and not the population ratio of conformers **8a** and **8b** (the Curtin–Hammett Principle). However, as activation energies for radical addition and abstraction reactions are usually low, and their transition states are early (or reactant-like), reactions of preferred (ground state) radical conformers are generally assumed to lead to the major products.[3] Low energy conformers can therefore make a good model for a reactant-like transition state.

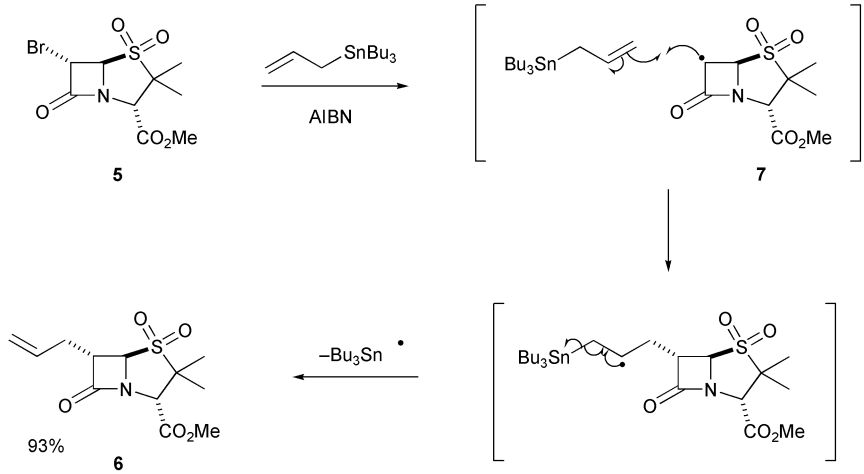


R_L = large sized group; R_M = medium sized group; R_S = small sized group

Scheme 3

This means that for stereoselective radical reactions, rotation around the carbon–carbon bond must be slowed down or prevented so that one particular conformation of the carbon-centred radical is favoured. This review will outline some current strategies for achieving this, which will involve a consideration of stereoelectronic, hydrogen-bonding, steric, polarity and chelation effects. The aim is not to provide a comprehensive review of the area but rather to highlight some common themes that have been employed in the design of stereoselective radical transformations. Initially, some substrate-controlled intramolecular (cyclisations) and then intermolecular radical additions will be discussed, which lead to the predominant formation of a single diastereoisomer. Examples of diastereoselective radical cyclisations have been known for many years, but the development of highly stereoselective intermolecular reactions involving acyclic radicals is relatively new and so this will be covered in greater detail. Most recently, research has focused on intramolecular and intermolecular enantioselective radical additions and some advances in these areas will also be discussed. These reactions can involve chelation of achiral substrates to form chiral complexes and as the shape of the complex influences the approach of the incoming reagent these are usually known as a complex-controlled reactions.

For all of these stereoselective radical reactions the effect of temperature should be emphasised as increasing the reaction temperature generally leads to lower levels of stereoselectivity. At high temperatures the reactants can overcome the activation energies leading to both diastereoisomers, but as the temperature is lowered, a greater proportion will be able to surmount only the lowest activation energy leading to the selective formation of one diastereoisomer. Low reaction temperatures are therefore generally preferred, especially for intermolecular radical additions involving acyclic radicals.



Scheme 2

In some cases however, even low temperature reactions can be non-stereoselective and this could be explained by the early transition states (reactant-like) associated with radical addition and abstraction reactions. This means for example, that when carbon-centred radicals such as **8ab** (Scheme 3) abstract a hydrogen atom from Bu_3SnH there is a relatively long distance between the carbon and tin atoms in the transition state. As the interacting centres are separated by a larger than average distance, this will lead to a weakening of the steric repulsion that is required to influence the diastereoselectivity. This steric repulsion, which may be present between the substituents in the product, will only develop fully after the transition state on the reaction coordinate where it is too late to influence the ratio of diastereoisomers that are formed.

2 Substrate-controlled diastereoselective reactions

2.1 Intramolecular (cyclisation) reactions

Intramolecular radical (cyclisation) reactions to form 5- and 6-membered rings in particular, have found a variety of synthetic applications.[6] This flexible synthetic method can be used to prepare both carbocycles and heterocycles, and the selective formation of mono- and polycyclic products can generally be obtained in good yields. Many diastereoselective radical cyclisations have been reported over the years and the chair-like (Beckwith–Houk) transition-state model **11a** (Figure 1) can be used to explain the stereoselectivity of most 5-*exo*

11a **11b**

Fig. 1

radical cyclisation reactions.[1] Stereoelectronic effects have been used to explain the preference for the chair-like conformation – this allows an efficient overlap of the SOMO orbital of the radical and the HOMO of the alkene. In this conformation, the angle of attack of the radical on the alkene (106°) is close to the angle of attack of a carbon-centred radical on an alkene in an unstrained intermolecular reaction (109°). Substituents at C1-4 generally prefer to adopt pseudo-equatorial positions in the transition state to avoid 1,3-diaxial interactions and this governs the relative positions of the substituents observed in the cyclic products.

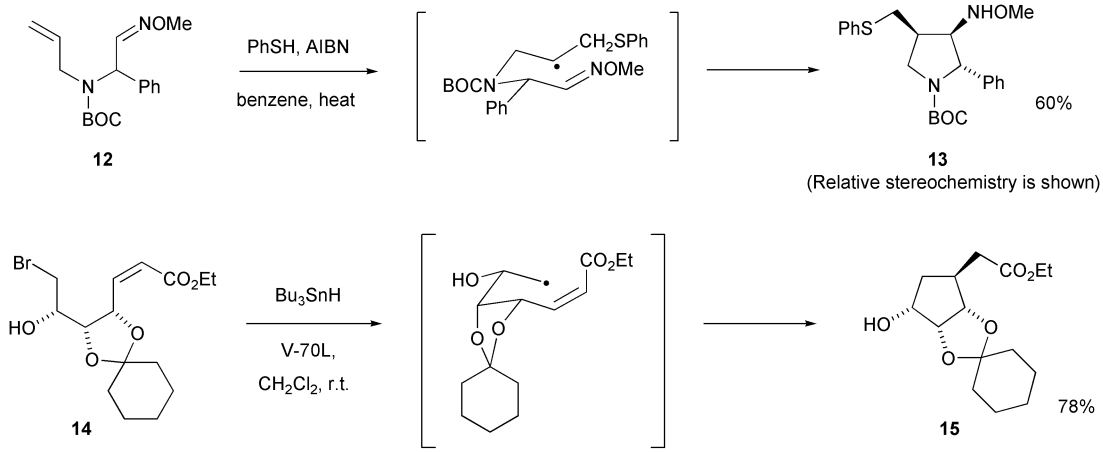
For example, this model can be used to rationalise the diastereoselective formation of substituted pyrrolidine **13**[7] and cyclopentane **15**[8] on 5-*exo* radical cyclisation of oxime ether **12** and primary bromide **14**, respectively. In both cases, the intermediate carbon-centred radicals adopt chair-like conformations, which controls the stereochemistry of the 5-ring products. It should be noted that whereas both reactions are diastereoselective the reaction of **14** to give **15** affords one enantiomer as a single enantiomer of the starting material was employed.

Interestingly, radicals derived from halogeno-acetals can cyclise (in the Ueno–Stork reaction) to give substituted tetrahydrofurans, which have the opposite stereochemistry to that predicted from the Beckwith model.[6] For example, radical **11b** (Figure 1) prefers to adopt a transition state in which the alkoxy group assumes an axial rather than the normal equatorial conformation. This has been explained by an anomeric interaction between the two oxygen atoms. When the OR group is axial the σ*-antibonding orbital of the C–OR bond can form a strong interaction with a lone pair on the oxygen atom that becomes part of the ring and this can stabilise conformation **11b**.

For the formation of 6-membered rings, the chair-like transition state **16** (Figure 2) generally explains the stereoselectivity observed when hept-6-en-1-yl radicals undergo 6-*exo* cyclisation. Both the substituent(s) and alkene prefer to adopt pseudo-equatorial positions, therefore 1-, 3- and 5-substituted heptenyl radicals give predominantly *trans*-disubstituted cyclohexyl products, while 2- and 4-substituted heptenyl radicals give predominantly *cis*-disubstituted cyclohexyl products.

This model can be used to explain the diastereoselective cyclisation of precursors such as the α-iodo-β-keto ester **17** (Scheme 5).[9] On reaction of **17** with 0.1 equivalent of hexamethylditin, an iodine atom transfer cyclisation takes place, which involves 6-*exo* cyclisation of the first-formed carbon-centred radical **18** to give cyclohexanone **20** with excellent diastereoselectivity (≥95:5). As predicted, this proceeds *via* a chair-like transition state, in which the ester group adopts an axial position so as to minimise unfavourable dipole–dipole interactions with the ketone. Following radical cyclisation, secondary radical **19a**/**19b** abstracts an iodine atom from a molecule of starting material **17** (hence the term "iodine atom transfer") to form iodide **20**. As conformer **19a** can be readily converted into conformer **19b** there is little selectivity (as expected from Scheme 3) in the iodine atom transfer step and so iodide **20** was isolated as a mixture of diastereoisomers (in a 2.8:1 ratio). The excellent diastereoselectivity arising from the radical cyclisation step was confirmed by reduction of iodide **20** to form only the 3-propylcyclohexanone diastereomer **21** in 65% overall yield. This reaction neatly illustrates the fact that while diastereoselective radical cyclisations are relatively easy to achieve, acyclic diastereocontrol is much more challenging (see Section 2.2).

Chair-like transition states can also be used to explain the stereoselectivity of products derived from tandem and cascade



Scheme 4

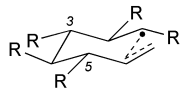


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Fig. 2

(multiple) radical cyclisations. For example, on treatment of β-keto ester **22** with manganese(III) acetate and copper(II) acetate, tricycle **26** was formed as a single diastereomer in 60% yield (Scheme 6).[10] Oxidation of **22** using manganese(III) acetate produces radical **23**, which adopts a chair-like transition state with the ester group in an axial position (to minimise dipole–dipole repulsion with the ketone). Following 6-*exo* radical cyclisation, radical **24** is formed and this can undergo a 5-*exo* cyclisation *via* a chair-like transition state to form primary radical **25**. Finally, on 5-*exo* cyclisation of **25**, a primary radical is formed and this can react with copper(II) acetate to form terminal alkene **26** (presumably *via* an intermediate copper(III) complex).

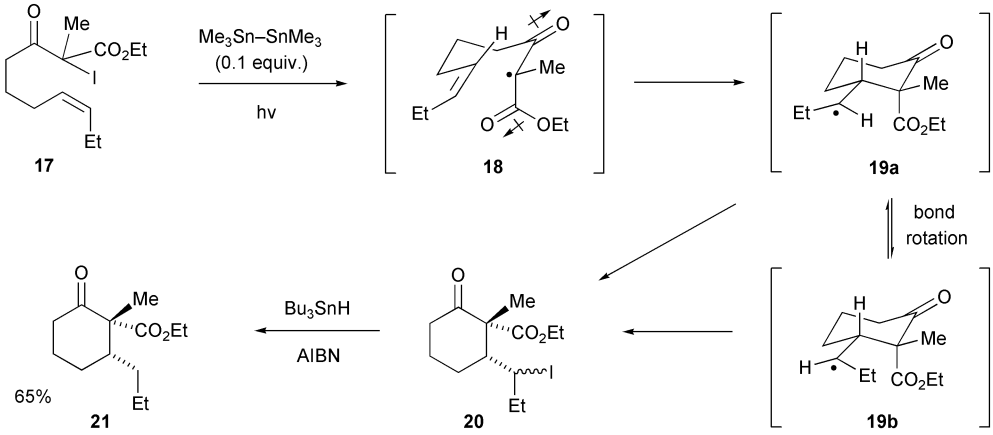
2.2 Intermolecular reactions

2.2.1 Reaction of cyclic radicals. As mentioned in the introduction, the diastereoselective addition of alkenes to cyclic carbon radicals (such as **7**) is relatively straightforward as the number of conformers in 4-, 5- and 6-membered rings is reduced (when compared to acyclic radicals) and an adjacent or nearby substituent can preferentially shield one face of the cyclic radical. Steric effects can therefore explain the preferential addition of alkenes to the face opposite to the bulky shielding substituent.

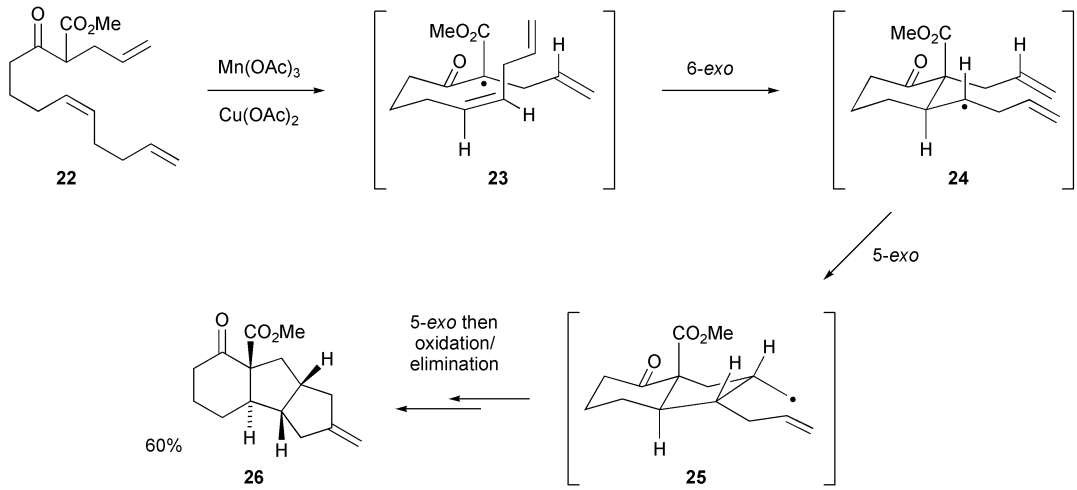
For example, work from our own group has shown that substituted pyrrolidinones can be prepared diastereoselectively on alkylation of 1,3-dicarbonyl **27** with enol ethers in the presence of manganese(III) acetate and copper(II) acetate (Scheme 7).[11] The enol ether preferentially approaches the intermediate radical **28** from the bottom face (to avoid the methoxymethyl group) and this gives rise to the predominant formation of the *anti* addition product **29** in a 1,3-asymmetric induction reaction.

Steric effects can also explain the stereoselective addition of alkenes to cyclohexyl radicals. For example, alkenes usually selectively add to the axial position when an axial substituent is present on an adjacent carbon atom (*e.g.* in **30**, Figure 3).[12] In contrast, when there is an axial substituent at the 3-position, the alkene can add mainly to the equatorial position as in decalin **31** (so as to minimise 1,3-diaxial interactions). In general, the more substituted (and bulky) the alkene, the greater the selectivity due to increased steric interactions.

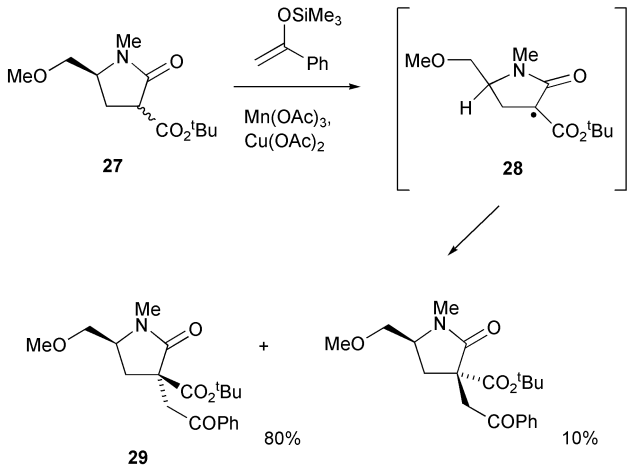
Stereoelectronic effects are also important for the reaction of some 6-ring radicals. Notable examples are radicals at the anomeric position of carbohydrates, which can show a marked preference for axial attack, even though 1,3-diaxial interactions would predict addition of the alkene to the equatorial position. For example, reaction of glycosyl bromide **32** with tributyltin hydride produces a radical at the anomeric position of the ring and this selectively reacts with the double bond of a protected dehydroalanine to give adduct **33** (Scheme 8).[13] The formation of an axial carbon–carbon bond can be explained by the first-formed carbon-centred radical adopting the boat conformation **34**. In this conformation the p-orbital of the radical can be stabilised by interaction with the σ*-orbital of the (coplanar) C–O bond at the C-2 position of the ring. The dehydroalanine adds



Scheme 5



Scheme 6



Scheme 7

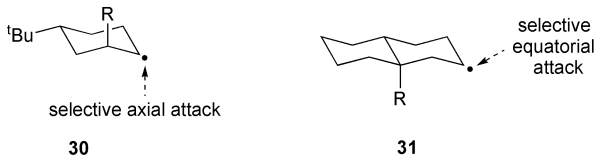
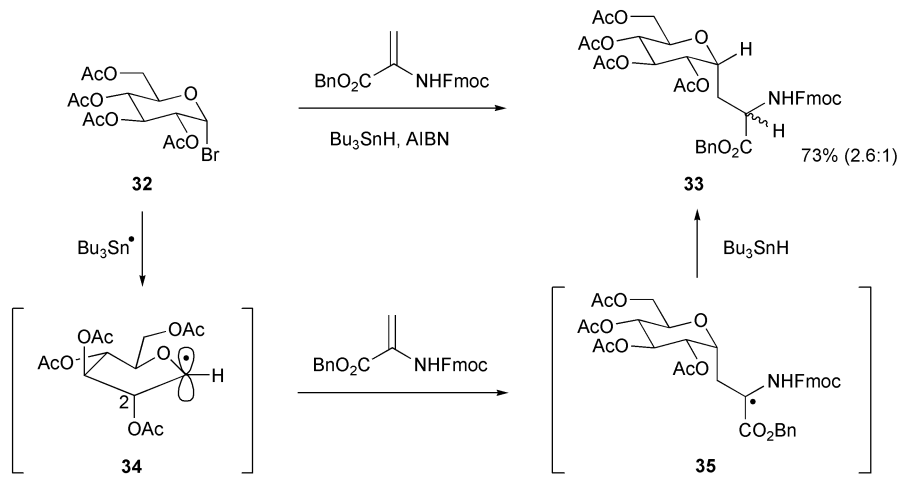


Fig. 3

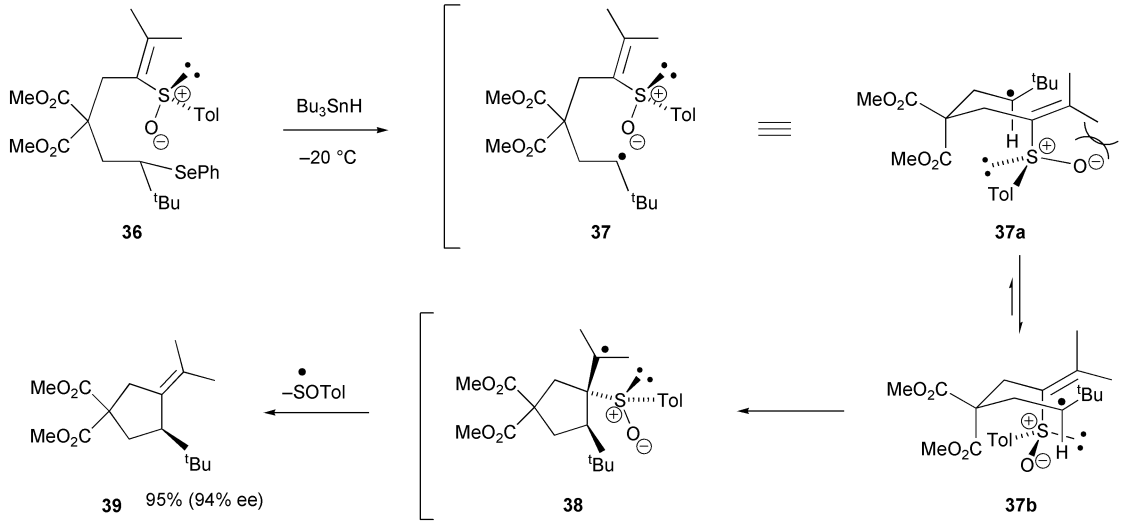
to the equatorial position of **34** (to avoid 1,3-diaxial interactions) but when the adduct radical adopts the preferred chair conformation **35**, the new carbon–carbon bond moves to an axial position. Although the reaction of cyclic radical **34** is highly diastereoselective (> 97%), the subsequent reaction of acyclic radical **35** with tributyltin hydride is not. Tributyltin hydride can donate a hydrogen atom to the top or the bottom face of **35** and so **33** is isolated as a 2.6:1 mixture of diastereoisomers.

More recently, chiral sulfoxide auxiliaries have been employed in diastereoselective radical cyclisations (Scheme 9).[14] In this strategy, following a diastereoselective 5-*exo* cyclisation the intermediate cyclic radical fragments so as to eliminate the chiral auxiliary. Hence on reaction of precursor **36** with tributyltin hydride at low temperature, the substituted cyclopentane **39** is isolated in excellent yield and enantioselectivity. This can be explained by the fact that the first-formed radical **37**, prefers to adopt the chair-like transition state **37b** in preference to **37a**. In both chair-like conformations, the bulky *p*-toluene (Tol) group points away from the ring so as to avoid 1,3-diaxial interactions. However, whereas in **37b** the lone pair on sulfur points in the direction of the substituted alkene, in **37a** the larger oxygen atom on sulfur eclipses the C–Me bond and so this disfavours this particular conformation. Interestingly, the addition of an aluminium-based Lewis acid can reverse the stereochemical outcome of this type of reaction due to complexation of the Lewis acid to the sulfoxide.

2.2.2 Reaction of acyclic radicals. As mentioned earlier, although cyclic radicals have long been known to undergo



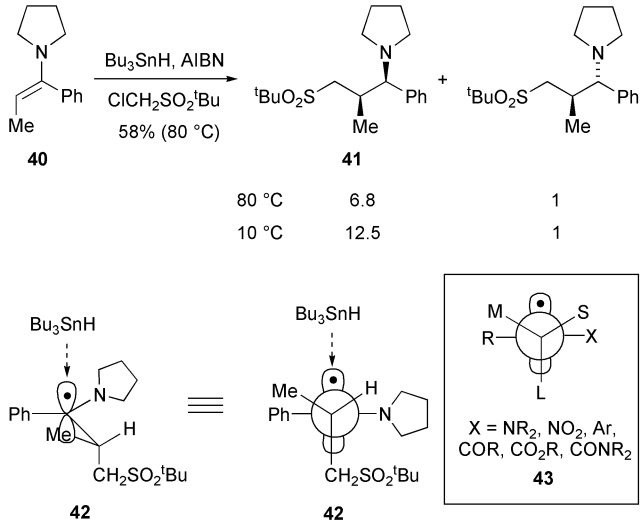
Scheme 8



Scheme 9

diastereoselective reactions it is only in the last 10 years or so that research has shown that the same is true for certain acyclic radicals. Early studies concentrated primarily on 1,2-asymmetric induction reactions whereby an adjacent chiral centre selectively directs the incoming reagent to one particular face of a radical, which exists in one preferred reactive conformation.

For example, intermolecular radical addition to enamine **40** in the presence of tributyltin hydride has been shown to lead to the predominant formation of diastereoisomer **41**, particularly as the reaction temperature is lowered (Scheme 10).[15] This can



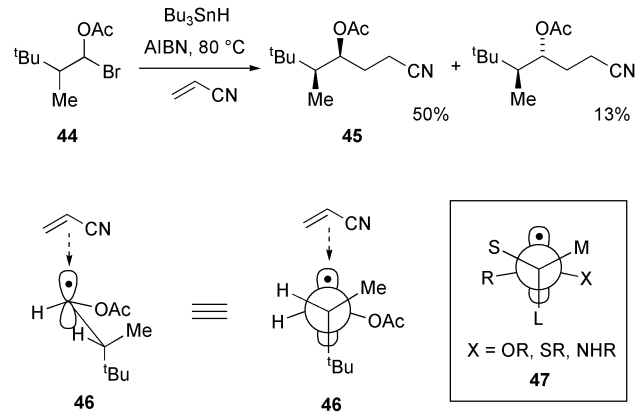
Scheme 10

be explained by the intermediate planar carbon-centred radical preferentially adopting conformation **42**. In this conformation, the small hydrogen atom on the adjacent stereogenic centre points in the direction of the bulky pyrrolidine ring and so steric interactions between the pyrrolidine ring and the Me and $CH_2SO_2{}^tBu$ substituents are minimised – these interactions are known as allylic or $A^{1,3}$-strain effects. The tributyltin hydride approaches radical **42** from the opposite side to the large $CH_2SO_2{}^tBu$ group (*anti* attack) on steric grounds and this leads to the selective formation of diastereoisomer **41**.

Allylic strain effects can also explain the stereoselective reaction of a number of other planar radicals bearing nitro, aryl or carbonyl groups attached to the radical centre – it should be noted that in each case the radical can be delocalised onto these substituents. These radicals generally prefer to adopt conformation **43**, whereby the smallest group (S) on the adjacent chiral centre points in the same direction as the bulky nitro, aryl or carbonyl group.

In contrast, radicals bearing oxygen substituents at the radical centre tend to give the opposite stereoselectively to reactions that are influenced by allylic strain effects. Thus, reaction of bromide **44** with acrylonitrile in the presence of tributyltin hydride affords predominantly diastereoisomer **45** (Scheme 11).[16] In this case, the preferred conformation of the intermediate radical is **46** and this follows the so-called Felkin–Anh rule. The introduction of oxygen substituents can lead to pyramidal carbon-centred radicals so radical **46** can be considered as being bent rather than planar. The oxygen substituent sits in-between the largest and medium-sized groups on the adjacent carbon atom (this looks like the Felkin–Anh conformation of a chiral ketone) and the acrylonitrile approaches radical **46** from the opposite direction to the bulky *tert*-butyl group (on steric grounds). This results in the selective formation of a radical adduct, which gives predominantly **45** after reaction with tributyltin hydride.

The Felkin–Anh rule can also explain stereoselective reactions of other non-planar radicals bearing thio and primary amine groups attached to the radical centre. These radicals generally prefer to adopt conformation **47**.



Scheme 11

Dipole–dipole repulsion has also been shown to be important in controlling the conformation of certain acyclic radicals.[17] This includes planar radicals such as **48** (Figure 4), which bear

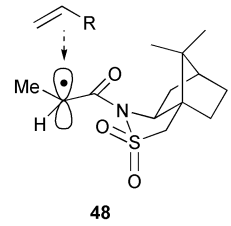


Fig. 4

a chiral auxiliary known as Oppolzer's sultam. The chiral auxiliary, which can be removed after diastereoselective addition of **48** to an alkene, forces the radical to adopt the conformation shown for the following reasons: (i) the oxygen atom of the amide and the oxygen atoms on sulfur point in opposite directions to minimise dipole–dipole repulsion; and (ii) the methyl group at the radical centre points away from the bulky ring system because of steric effects. The dipole–dipole repulsion ensures that rotation about the amide bond is restricted and the axial oxygen atom on the chiral auxiliary preferentially shields the bottom face of the radical. Alkenes therefore prefer to add selectively to the least hindered top face of **48**.

C_2 symmetry has also been employed in diastereoselective acyclic radical reactions.[17] The introduction of a C_2 symmetric 2,5-disubstituted pyrrolidine ensures that planar radicals such as **49a**/**49b** undergo selective addition to alkenes (Figure 5). Even

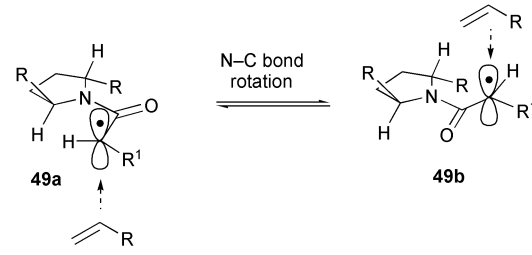
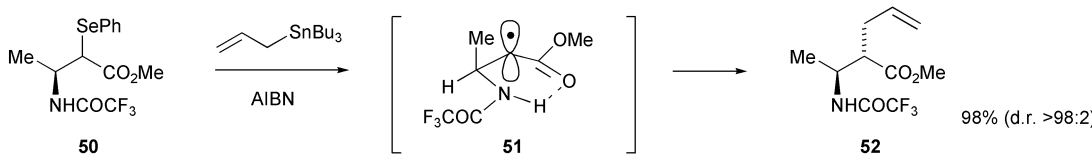


Fig. 5

though rotation about the amide bond is possible, conformer **49a** and **49b** react with an alkene to selectively afford the same diastereoisomer. In both cases the alkene adds to the radical so as to avoid the nearest alkyl (R) group on the pyrrolidine ring and the R^1 alkyl group at the radical centre points away from the ring.

Intramolecular hydrogen bonding can also play an important role as a stereocontrolling element in radical reactions carried out in non-polar solvents. For example, reaction of α-



Scheme 12

phenylseleno ester **50** with allyltributyltin in toluene at low temperature leads to the exclusive (>97%) formation of diastereoisomer **52**.[18] The remarkable diastereoselectivity may be explained by the preferential formation of a radical conformer such as **51**. Intramolecular hydrogen bonding is proposed to form a pseudo 6-membered ring and for conformation **51** it is expected that the allyltributyltin selectively approaches from the opposite side to the methyl substituent to give the observed product **52** (following a radical addition–elimination reaction). The formation of hydrogen bonds in these types of reactions was supported by the fact that when the solvent is changed from toluene to dimethyl sulfoxide the diastereoselectivity is reduced or reversed.

3 Complex-controlled diastereoselective reactions

Radical reactions of complexes has proved to be a very important tool in the stereoselective synthesis of both cyclic and acyclic molecules. In this approach, a complexing agent, typically a Lewis acid[19,20] is added to the organic substrate and complexation with for example, carbonyl or imine groups in the substrate, leads to the preferential formation of one particular conformer of the radical intermediate. As well as locking the radical in a particular conformation by acting as a template, complexation of the Lewis acid can also influence radical reactivity. For example, the complexed α-carbonyl radical **54** is more electrophilic than the non-complexed radical **53** and so would be expected to add more rapidly to an electron-rich double bond (Figure 6). This is because the Lewis acid withdraws electron density and so the electrophilicity of the radical can be tuned by careful choice of the Lewis acid. Typical Lewis acids include $BF_3.OEt_2$, $MgBr_2$, $AlMe_3$, $Yb(OTf)_3$ and $Sc(OTf)_3$.

For radical **54**, the Lewis acid (*e.g.* BF_3 or $AlMe_3$) binds to the substrate at only one point and this is an example of single-point binding. Although this type of binding has found application in stereoselective radical reactions (see below), a more common approach is to use a two-point binding Lewis acid such as $MgBr_2$, $Yb(OTf)_3$ or $Sc(OTf)_3$ as in radical **55**. Binding to two carbonyl groups for example, can provide a very effective strategy in controlling substrate conformation and the use of two point binding has been widely utilised in both diastereoselective and enantioselective radical transformations (Section 4). It should be noted that the choice of solvent is crucial as complexation of the Lewis acid with the solvent can totally suppress complexation with the organic substrate.

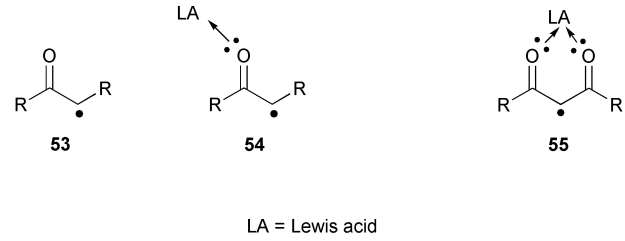
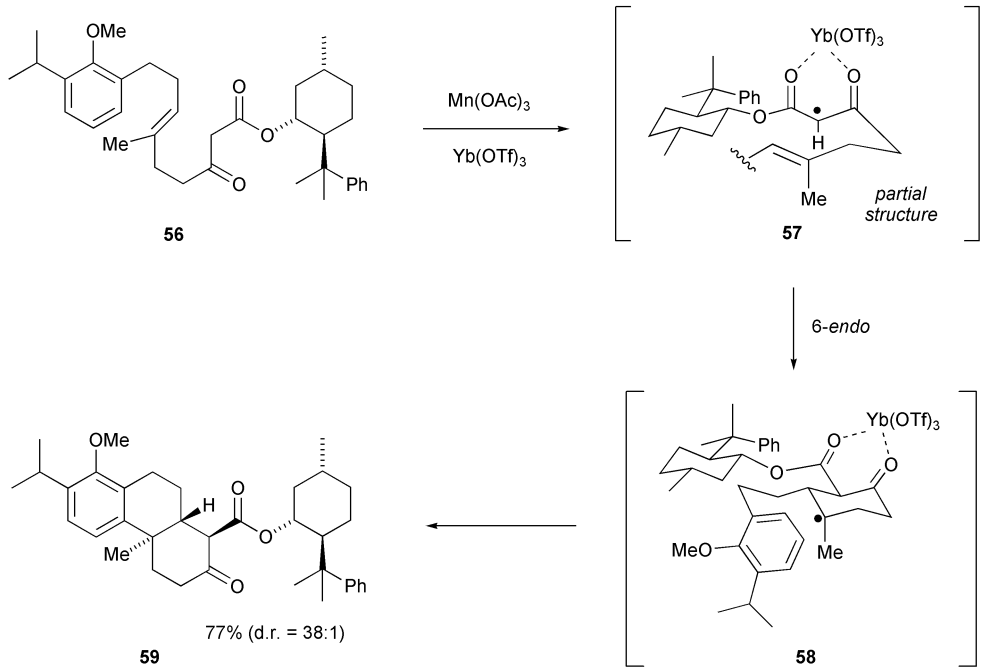


Fig. 6

3.1 Intramolecular (cyclisation) reactions

Good diastereoselectivity has been observed in some manganese(III)-mediated cyclisations of 1,3-dicarbonyls, which have been carried in the presence of $Yb(OTf)_3$ (Scheme 13).[21] A chiral phenylmethanol ester is employed in β-keto ester **56** to act as a chiral auxiliary and following reaction with manganese(III) acetate (2.2 equiv.) and $Yb(OTf)_3$ (1 equiv.) in CF_3CH_2OH, the cyclisation product **59** was isolated in good yield and diastereoselectivity. The preference for diastereomer **59** can be explained by the selective formation of the chair-like transition state **57**. Chelation with the Lewis acid locks the two



Scheme 13

carbonyl groups in a *syn* orientation and the electrophilic radical **57** prefers to cyclise onto the electron-rich double bond from the front face. This is because the back face of radical **57** is shielded by the phenyl substituent on the menthyl auxiliary (introducing larger substituents than phenyl at this position can give even greater diastereoselectivities). Radical **57** presumably undergoes a 6-*endo* (rather than the more common 5-*exo* mode) cyclisation because of steric hindrance by the methyl substituent on the alkene (stabilised radicals are also known to undergo reversible cyclisations that afford thermodynamically more stable 6- rather than 5-membered rings). This produces tertiary alkyl radical **58** and this cyclises onto the benzene ring (*via* a second chair-like transition state) to form a *trans*-decalin ring system. An intermediate cyclohexadienyl radical is formed and on oxidation (by manganese(III) acetate) and loss of a proton the aromatic benzene ring in **59** is formed.

It should be added that lanthanide Lewis acids including $Yb(OTf)_3$, $Sc(OTf)_3$ and $La(OTf)_3$ have attracted particular interest in recent years because they are less moisture sensitive than other Lewis acids and so require less rigorous reaction conditions.

Chelation control has also successfully been employed in a variety of samarium(II) iodide-mediated cyclisations of β-keto esters and β-keto amides.[22] Samarium(II) iodide can reduce a variety of aldehydes and ketones to form ketyl radical anions that can undergo cyclisation reactions onto double bonds. The samarium(III) which is produced is a Lewis acid and can act as a template for controlling the stereochemistry. Following cyclisation the cyclic radical is reduced using a second equivalent of samarium(II) iodide and the resulting carbanion can be protonated to form the organic product. Representative examples of 5-*exo* and 6-*exo* cyclisations are shown in Scheme 14. The diastereoselectivities of the cyclisations are controlled by the ester carbonyl or hydroxy group coordinating to the samarium(III). For the 6-*exo* cyclisation, electronic repulsion between the ketyl oxygen atom and the ester side chain can explain the preferred position of the ester side chain in the decalin product.

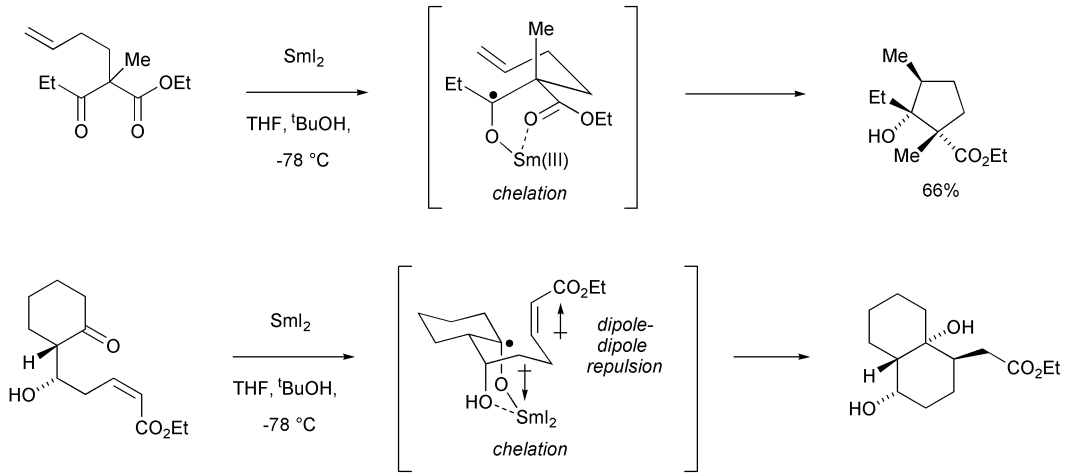
3.2 Intermolecular reactions of cyclic radicals

There are relatively few examples in this category, as many cyclic radicals are known to undergo diastereoselective radical reactions in the absence of complexation (Section 2.2.1). However, one illustrative example of this approach is illustrated in Scheme 15.[23] On reduction of iodide **60** with tributyltin deuteride in the presence of MAD (1.1 equivalent) a highly diastereoselective reduction takes place to afford the deuterated product **62**. In the absence of the aluminium compound, the reaction proceeds with much lower diastereoselectivity (89%, d.r. = 5:1). The pronounced effect of the MAD can be explained by the formation of intermediate **61**, whereby the bulky MAD reagent combines with the substrate to significantly increase the size of the substituent on the top face of the ring. As a consequence, Bu_3SnD selectively approaches **61** from the bottom face of the ring to form diastereomer **62**.

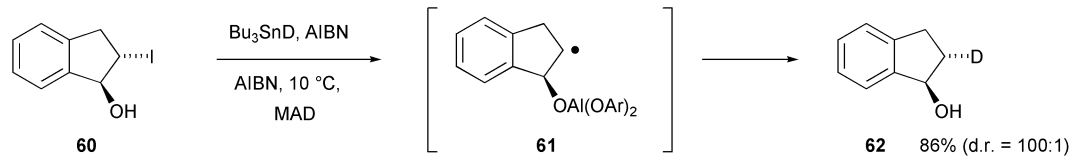
3.3 Intermolecular reactions of acyclic radicals

In recent years, there has been significant activity and some important developments have been made in this research area. An early example of the use of this methodology in stereoselective synthesis is shown in Scheme 16.[24] On reaction of secondary bromide **62** with allytributyltin at room temperature, a radical addition–elimination reaction occurs so as to form the allylated diastereomers **63** and **64** in approximately the same yield. However, when the same reaction is carried out in the presence of a europium(II) salt, the selective formation of diastereoisomer **63** is observed. This can be explained by complexation of both ester carbonyl groups in the intermediate radical to give **65**. The allyltributyltin is expected to selectively attack the top face of radical **65** so as to avoid the bulky trimethylsilyl group.

Oxazolidinone chiral auxiliaries have been widely employed in related allylation reactions. For example, reaction of bromide **66** with allyltributyltin at −78 °C in the absence of a Lewis acid

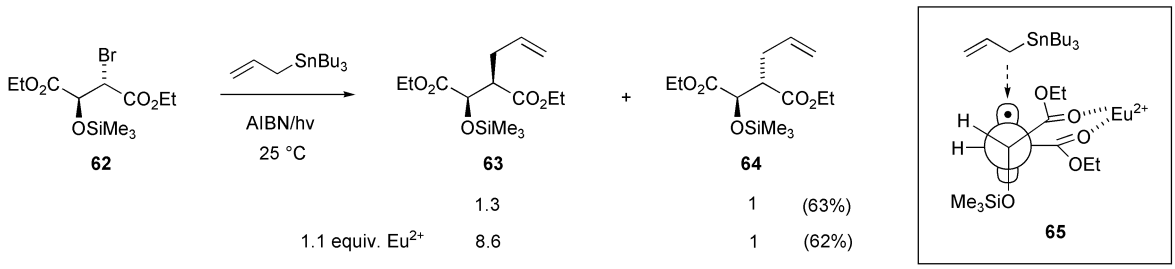


Scheme 14



MAD = methylaluminium bis[2,6-di(*tert*-butyl)-4-methylphenoxide

Scheme 15



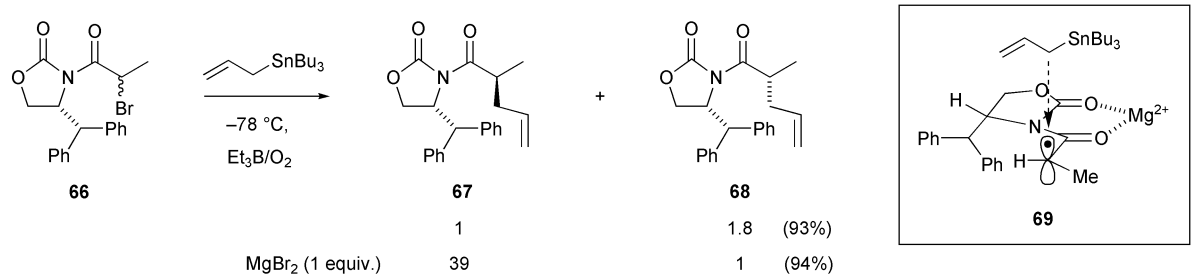
Scheme 16

affords a 2:1 mixture of the allylated diastereoisomers **67** and **68**, respectively (Scheme 17).[25] However, in the presence of 1 equivalent of magnesium bromide the diastereoselectivity of the allylation increases dramatically and **67** is isolated in an excellent 92% yield. This can be attributed to formation of radical **69**, whereby complexation of the magnesium cation with the 1,3-dicarbonyl prevents free rotation about the amide bond. The methyl group at the radical centre of **69** points away from the bulky nitrogen substituent (on steric grounds) and the diphenylmethyl group on the oxazolidinone ring shields the bottom face of the radical from attack by allyltributyltin. The combination of these three factors results in the highly stereoselective formation of the new carbon–carbon bond in **67**. When these allylations are carried out at room temperature, the diastereoselectivity drops due to the less efficient control of the conformer population by the Lewis acid. It is also interesting to note that when $BF_3{\cdot}OEt_2$ is used as the Lewis acid the diastereoselectivity of the allylation also drops because this is a single-point binding Lewis acid. Two-point binding is more effective at controlling the conformation of radical **69** and hence Lewis acids such as $MgBr_2$ work much better.

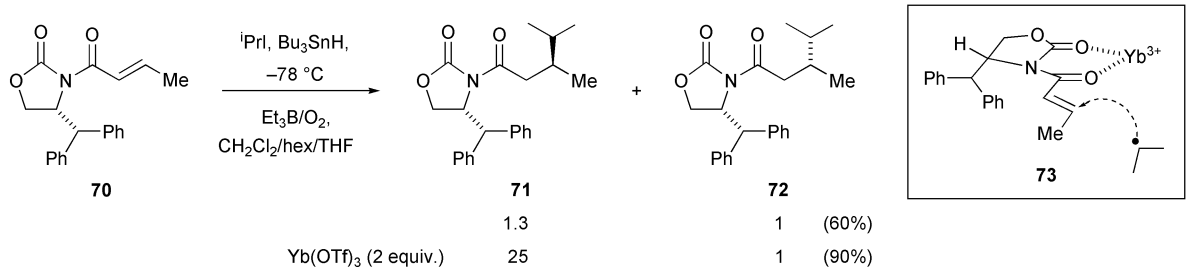
Radical conjugate addition reactions have also been reported in the presence of chiral oxazolidinone auxiliaries.[25,26] On reaction of unsaturated amide **70**, isopropyl iodide and tributyltin hydride, diastereomers **71** and **72** were isolated in similar yields (Scheme 18). These result from a Michael-type addition of the isopropyl radical to the double bond of **70** followed by reduction of the resulting α-carbonyl radical with tributyltin hydride. When the same reaction is carried out in the presence of 2 equivalents of the Lewis acid $Yb(OTf)_3$ the diastereoselective formation of **71** is observed. The preferential formation of **71** presumably results from selective addition of the isopropyl to the top face of complexed radical **73**. Introducing the Lewis acid also increases the yield of the alkylation from 60% to 90%. This is presumably because complexation with the electron-withdrawing Lewis acid makes the alkene more electrophilic and this facilitates addition of the nucleophilic isopropyl radical. The fact that Lewis-acid complexed substrates can be more reactive towards radical conjugate addition has been successfully exploited in enantioselective radical reactions (see Section 4). It should be noted that the diastereoselectivity of this type of radical conjugate addition is comparable or even better than that observed under ionic alkylation conditions.

Excellent diastereoselectivities have also been observed on reduction of α-(arylsulfinyl)alkyl radicals in the presence of zinc bromide (Scheme 19).[27] For example, regioselective radical addition of the *tert*-butyl radical to **74** followed by reduction with tributyltin hydride selectively afforded **75** in 95% yield. In the absence of the Lewis acid, the same reaction produced a similar ratio of the diastereoisomers **75** and **76**. The bidentate Lewis acid (two-point binding) is proposed to form a complex with the pyridine ring and sulfinyl oxygen atom as shown in **77**. The tributyltin hydride approaches from the least hindered face of **77** and on donation of a hydrogen atom this gives rise to diastereoisomer **75**. Addition of the Lewis acid also increases the reactivity of the vinyl sulfoxide as the reaction is complete after only 2 h. This can be compared to an 80% combined yield of **75** and **76** after 24 h in the absence of the Lewis acid.

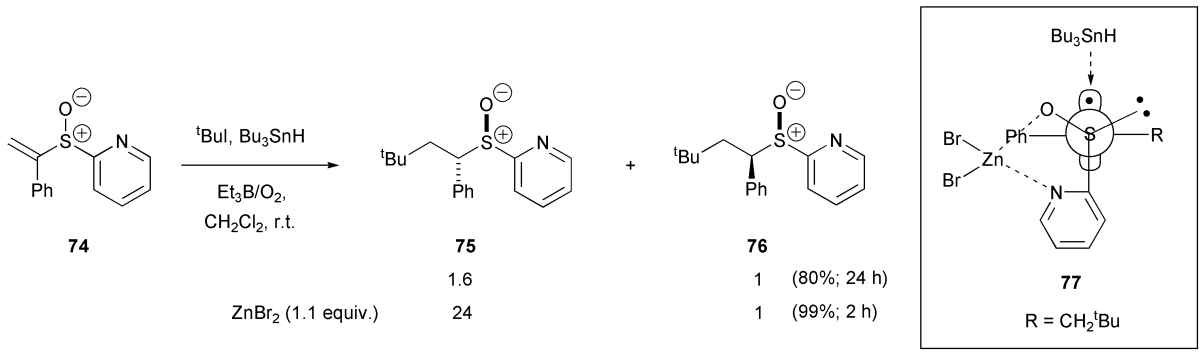
Radical 1,3-asymmetric induction reactions have also been recently investigated (Scheme 20).[28] Addition of the isopropyl radical to unsaturated ester **78** in the presence of magnesium bromide followed by reduction of the radical adduct with tributyltin hydride selectively produced diastereoisomer **79** at 0 °C. The diastereoselectivity has been argued on the basis of the



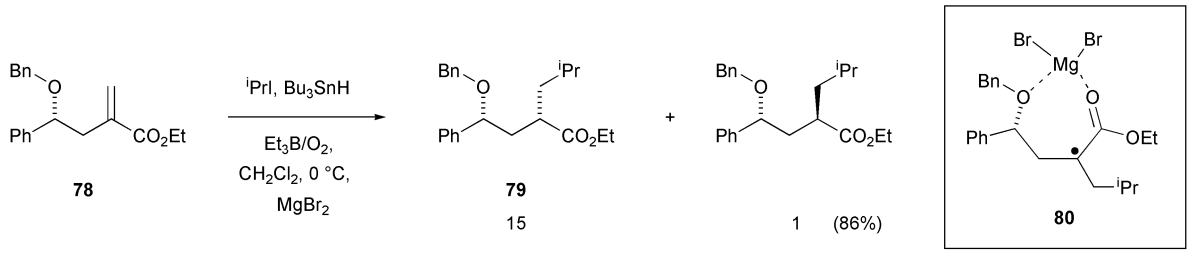
Scheme 17



Scheme 18



Scheme 19

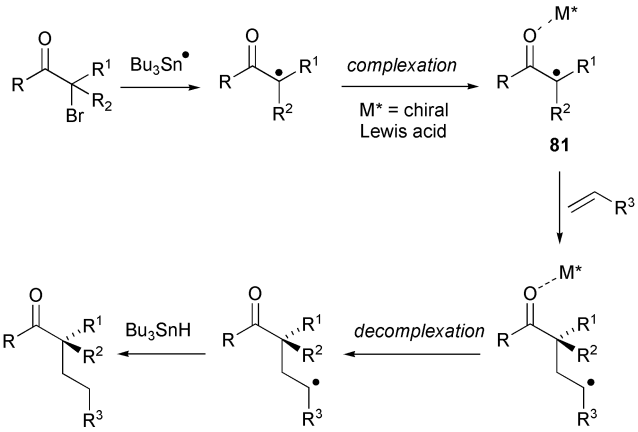


Scheme 20

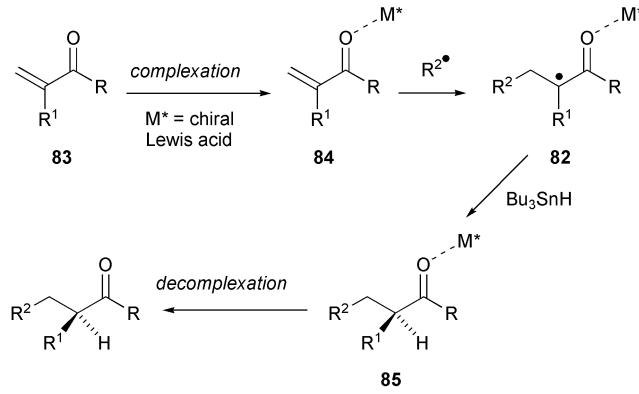
preferred conformation of the seven-membered chelate ring and the geometry of the ester substituent in the radical intermediate **80**.

4 Complex-controlled enantioselective reactions

For this type of reaction, an achiral organic substrate is employed and a chiral reagent, such as a chiral Lewis acid, is used to chelate the substrate. For radical addition reactions the chiral Lewis acid can either complex the first-formed carbon-centred radical (Scheme 21) or the alkene acceptor (Scheme 22). In both cases, the resulting chiral complex can undergo diastereoselective radical addition reactions to afford, after decomplexation, enantiomerically enriched (ideally pure) products. For this to be effective the position of the chiral ligand must be fixed relative to the radical centre (in **81** and **82**) and the chiral group must selectively shield one face of the intermediate radical. The complexed substrate (*e.g.* **84**) should also be more reactive than the non-complexed substrate (*e.g.* **83**) to ensure that the non-complexed substrate does not react in non-selective transformations. This is possible because as shown in Section 3, Lewis acids have been used for rate enhancement in radical reactions. Complexation with Lewis acids can make the organic substrates more electrophilic (*i.e.* lower the LUMO energies), which can enhance the rate of addition of nucleophilic radicals (with high energy SOMOs) to alkenes.



Scheme 21

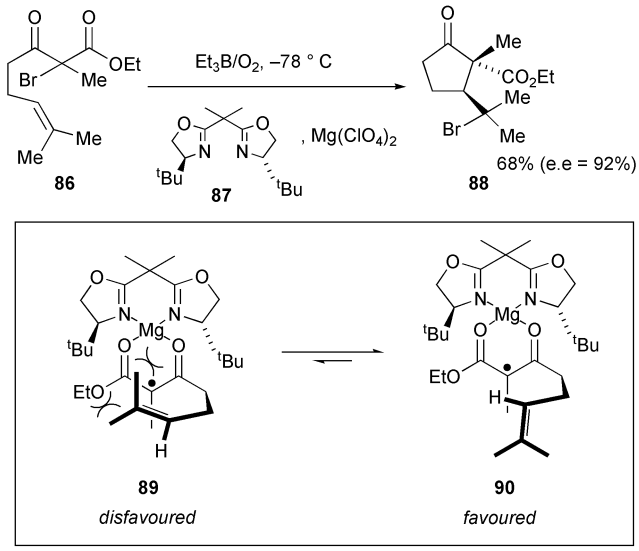


Scheme 22

These types of reactions can be carried out using stoichiometric amounts of Lewis acids in the presence of chiral ligands. However, an important research goal in recent years has been the development of enantioselective radical reactions using catalytic amounts of chiral Lewis acids. This can be achieved when the chiral Lewis acid binds to the substrate in preference to the product. For example, the greater electron-density at the oxygen atom of conjugated alkene **84** can ensure that the chiral Lewis acid binds to **84** in preference to the saturated ketone **85** (*i.e.* as soon as product **85** is formed the Lewis acid transfers from the product to another molecule of starting material **84**).

4.1 Intramolecular (cyclisation) reactions

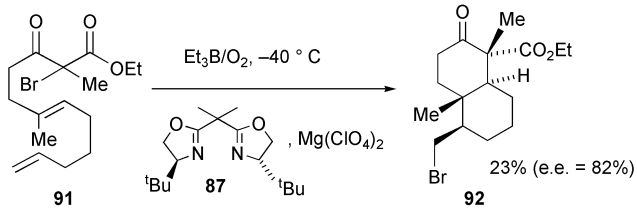
A highly enantioselective bromine atom transfer radical cyclisation has recently reported as shown in Scheme 23.[29] In the presence of 0.3 equivalent of $Mg(ClO_4)_2$ and 0.33 equivalent of the chiral bisoxazoline **87**, bromide **86** underwent 5-*exo* cyclisation to give cyclopentanone **88** in 92% enantiomeric excess. The highly selective formation of **88** can be explained by chelation of the magnesium ion with the chiral ligand and the two carbonyl groups in **86**. This gives a complex with planar geometry at the magnesium and the first-formed carbon-centred radical can cyclise *via* transition state **89** and/or **90**. In both cases, the side chain bearing the acceptor alkene



Scheme 23

prefers to avoid the bulky *tert*-butyl group on the C_2 symmetric ligand (*i.e*. it points towards rather than away from the reader). However, transition state **89** is disfavoured because of steric interactions between the ester substituent and both methyl groups on the alkene. As a consequence, the formation of transition state **90** is preferred and on radical cyclisation (followed by bromine atom abstraction from bromide **86**) this gives rise to the formation of **88**, which has the ethyl ester and bromopropyl substituent in a *trans*-relationship.

Related tandem radical cyclisations have also been reported.[30] For example, on tandem atom-transfer cyclisation of bromide **91** in the presence of 1 equivalent of $Mg(ClO_4)_2$ and 1.1 equivalent of the chiral bisoxazoline **87**, the 6,6-ring fused product **92** was isolated in 82% e.e. (Scheme 24). The



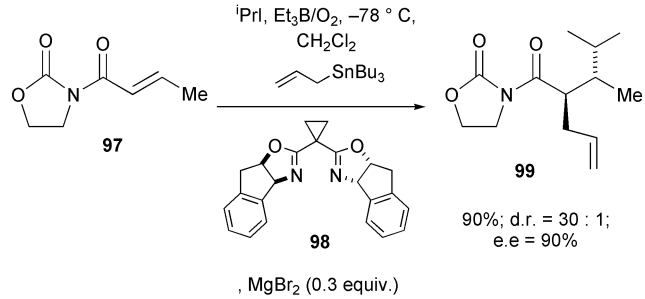
Scheme 24

enantioselective formation of four chiral centres is achieved in a one-pot 6-*endo*-6-*exo* tandem cyclisation process. This type of methodology has tremendous synthetic potential, particularly if the yields of cyclic products such as **92** can be improved.

4.2 Intermolecular reactions of acyclic radicals

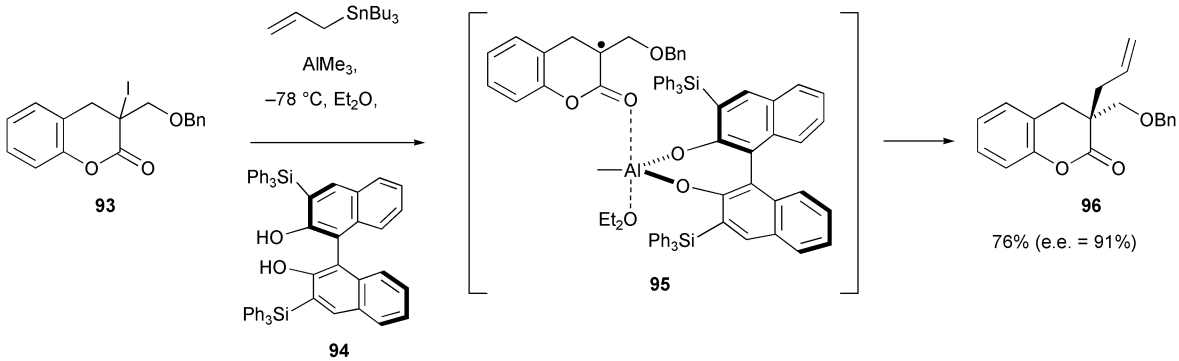
An early example of an enantioselective allylation reaction, which involves the use of a chiral Lewis acid is shown in Scheme 25.[31] Reaction of iodolactone **93** with allyltributyltin, trimethylaluminium and chiral binaphthol **94** (both 1 equivalent) in diethyl ether leads to the highly enantioselective formation of the allylated product **96**. It is shown that the aluminium participates in a single-point binding to the ester carbonyl and the formation of the intermediate trigonal bipyramid chiral complex **95** has been tentatively proposed. In this complex, the chiral binaphthol ligand on the aluminium influences the direction the allyltributyltin approaches radical **95**, which results in the enantioselective formation of the chiral quaternary centre in **96**. Interestingly, when the number of equivalents of the Lewis acid is reduced to 0.1 equivalent, **96** is still formed in good yield (78%) and enantioselectivity (e.e. = 71%).

Although the previous example successfully employed a single-point binding Lewis acid this is rare and most reactions of this type rely on the use of double point binding. Of particular recent interest has been the development of highly enantioselective Michael-type additions using achiral oxazolidinone enoates in the presence of sub-stoichiometric amounts of Lewis acids.[32] Enantioselective tandem radical reactions are possible as shown in Scheme 26. In this approach, conjugate addition of



Scheme 26

the isopropyl radical to unsaturated amide **97** followed by allylation at the α-position of the amide produces **99** in excellent diastereoselectivity and enantioselectivity. This impressive reaction, which uses only 0.3 equivalent of the Lewis acid, therefore leads to the highly selective formation of two chiral centres in a single operation. A working model to explain the selective formation of **99** is shown in Figure 7. In this model the magnesium ion forms a complex with the chiral bisoxazoline **98** and the two carbonyl groups in **97** (*cf*. radical **69** in Scheme 17). This restricts rotation about the amide bond in **97** and the presence of the chiral bisoxazoline ligand forces the isopropyl radical to preferentially attack the top face of the alkene. The intermediate radical then reacts with allyltributyltin, which approaches the radical from the opposite side to the bulky isopropyl group. As only 0.3 equivalent of the Lewis acid is used this suggests that: (i) complexation of **97** results in a faster rate of addition of the nucleophilic isopropyl radical and; (ii) the magnesium Lewis acid binds to alkene **97** in preference to product **99**.



Scheme 25

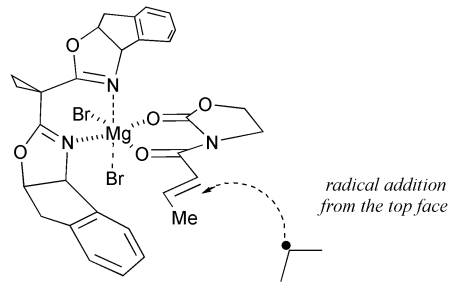


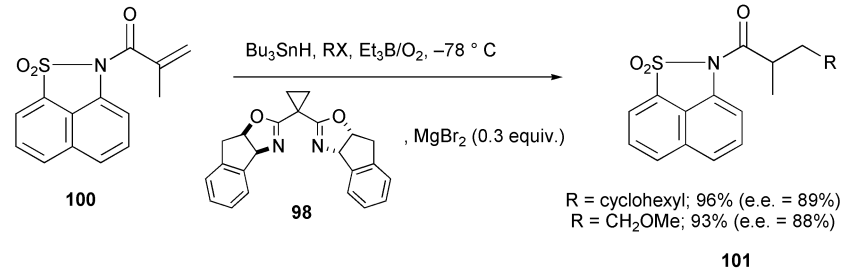
Fig. 7

Other achiral templates besides oxazolidinones can be used including the 1,8-naphthosultam group as shown in Scheme 27.[33] Conjugate addition of nucleophilic alkyl radicals to the double bond of **100** followed by reduction using tributyltin hydride afforded alkylated products **101** in excellent yield and enantioselectivity. For this template, it is proposed that the magnesium complexes to the amide carbonyl and to one of the oxygen atoms of the sulfone group.

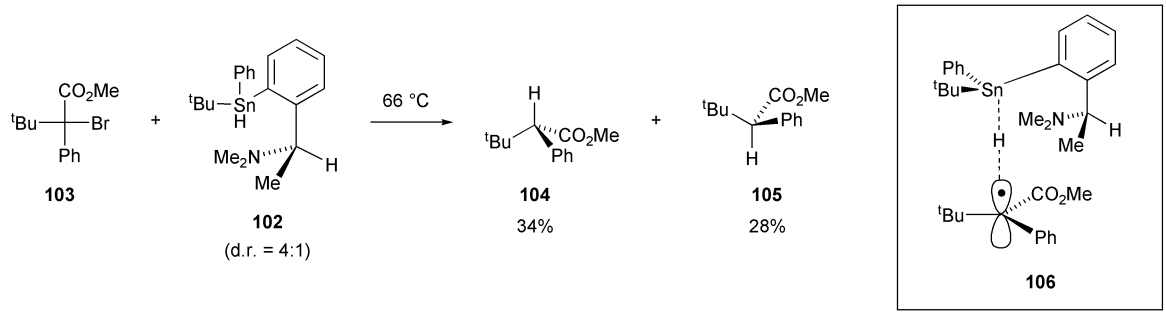
5 Reagent-controlled enantioselective reactions

One final approach for developing enantioselective reactions is to react a radical with a chiral reagent. In these reactions the chiral reagent is able to distinguish the enantiotopic faces of a radical in diastereomeric transition states. Chiral metal hydrides, with weak metal–hydrogen bonds have been investigated and this has involved the incorporation of C_2-symmetric binaphthyl groups on the metal. Alternatively, chiral tin hydrides bearing 2-(1-dimethylaminoalkyl)phenyl ligands have been employed as shown in Scheme 28.[34] Hydrides with chiral ligands such as **102** are hydrogen atom donors that have the potential to trap radicals enantioselectively. This has been investigated in the reduction of α-bromoester **103**, where reaction with a 4:1 mixture of (inseparable) diastereomers of hydride **102** produced the (*S*)-enantiomer **104** in 34% yield and the (*R*)-enantiomer **105** in 28% yield. The predominant formation of **104** could be explained by linear transition state **106**, which shows the reaction of the minor diastereomer of **102** with the intermediate carbon-centred radical. In this transition state the small methyl ester group is positioned close to the bulky dimethylamino group while the phenyl group is orientated beneath the methyl group and the large *tert*-butyl group on carbon is placed between the *tert*-butyl and phenyl groups on tin. Although this model can explain the enantioselective formation of **104** from the minor diastereomer of **102**, analysis of a similar model for reaction of the major diastereomer of **102** predicts that this will react with the radical unselectively. Hence this explains why enantiomer **104** is not formed in significantly higher yield than **105**. As predicted, when the temperature of the reaction is reduced the enantioselectivity increases, although the overall yield of **104** and **105** is reduced (*e.g.* at −30 °C, **104** and **105** are isolated in 12.5% and 7.5% yield, respectively).

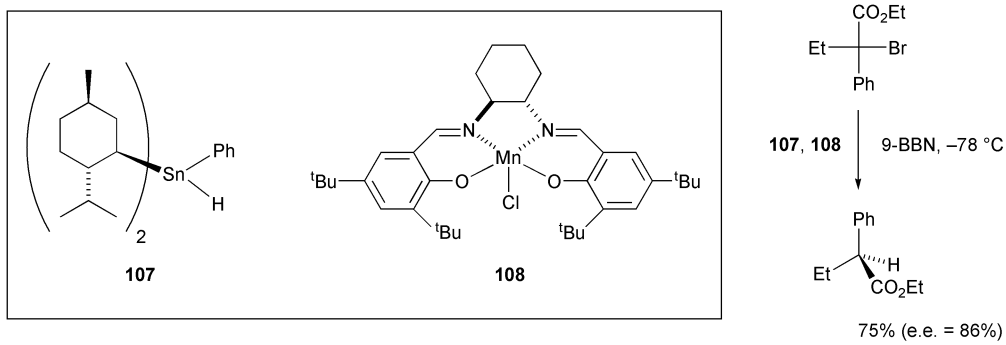
Recently, highly enantioselective reductions have been reported using chiral tin hydride **107** in the presence of a bulky Lewis acid such as **108** and 9-borabicyclo[3.3.1]nonane as the initiator (Scheme 29).[35] Good to excellent enantioselectivities can be achieved at low temperature using both chiral and achiral



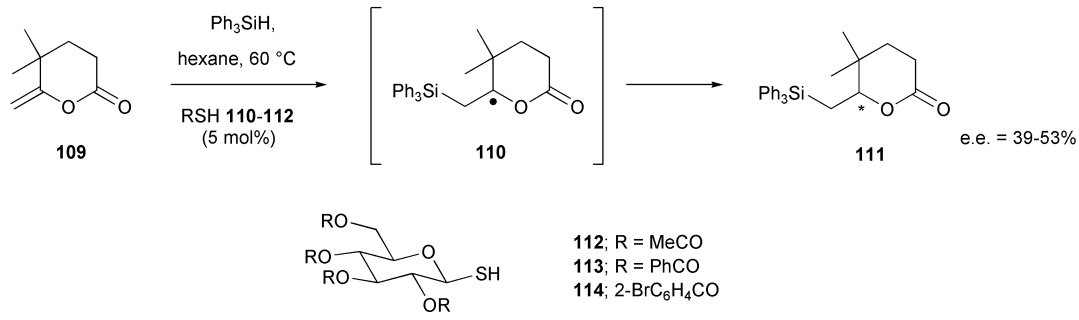
Scheme 27



Scheme 28



Scheme 29



Scheme 30

Lewis acids, which can complex to the halo-ester precursors. The enhancement in enantioselectivity in the presence of the Lewis acid may be explained by the fact that coordination (with the Lewis acid) increases the size of the ester precursor, which is expected to lead to increased steric interactions with the chiral tin hydrides.

Similar reactions are also possible using non-metal hydrides including thiols. For example, reaction of triphenylsilane with unsaturated lactone **109** in the presence of a catalytic amount of β-glucose thiol **112, 113** or **114** produced the hydrosilylation product **111** in good enantioselectivity (Scheme 30).[36] Addition of the triphenylsilyl radical to the alkene double bond of **109** forms the intermediate carbon-centred radical **110** and this reacts with the chiral thiol **112–114** in an enantioselective hydrogen atom abstraction. The resulting sulfur-centred radical then abstracts a hydrogen atom from Ph_3SiH to regenerate thiol **112–114** and the triphenylsilyl radical, which continues the chain reaction. An investigation of different carbohydrate-based thiols has shown that both steric and dipole–dipole interactions between radical **110** and the thiol, as well as the choice of solvent, are important in determining the enantioselectivity.

6 Conclusions

It is clear that the development of stereoselective radical reactions has come a long way over the last 20–30 years. Early studies have highlighted the synthetic potential of diastereoselective reactions and more recently some significant developments have been made in the area of enantioselective radical reactions. The factors that influence radical reactivity are becoming apparent and the once common perception that all radical reactions are uncontrollable and unselective processes has well and truly been proven to be wrong. These exciting findings, particularly those involving the use of chiral catalysts in radical reactions should stimulate further research in this very important area as there is still a way to go before these methods can reach the status of a number of well-established anionic asymmetric reactions. Areas for improvement include the use of inexpensive, easily prepared chiral ligands/reagents and alternative achiral templates as well as the use of robust Lewis acids and the establishment of highly diastereo- and enantioselective tandem and cascade sequences. Further development in these areas could help to promote the use of this methodology on a larger scale as will the establishment of radical methods, which avoid the use of toxic organotin compounds.

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