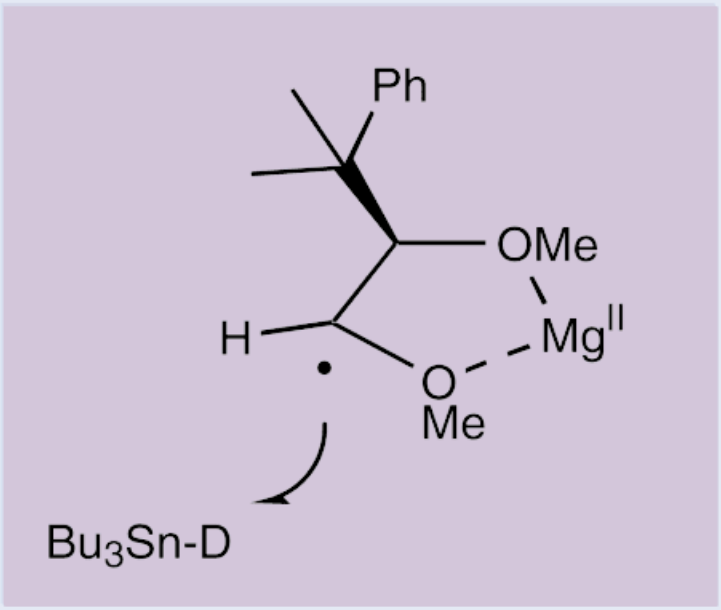
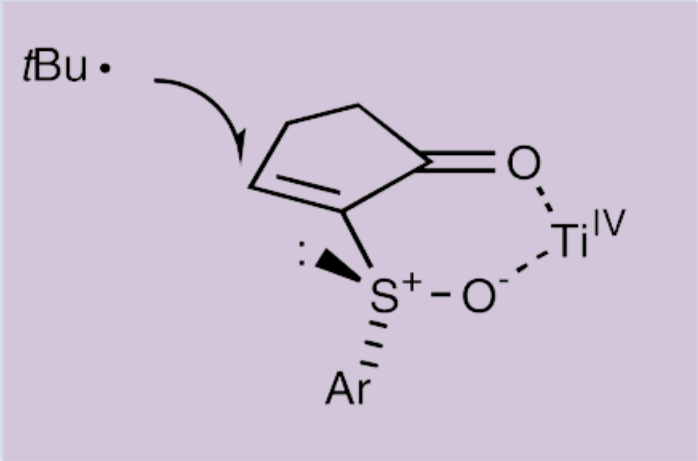
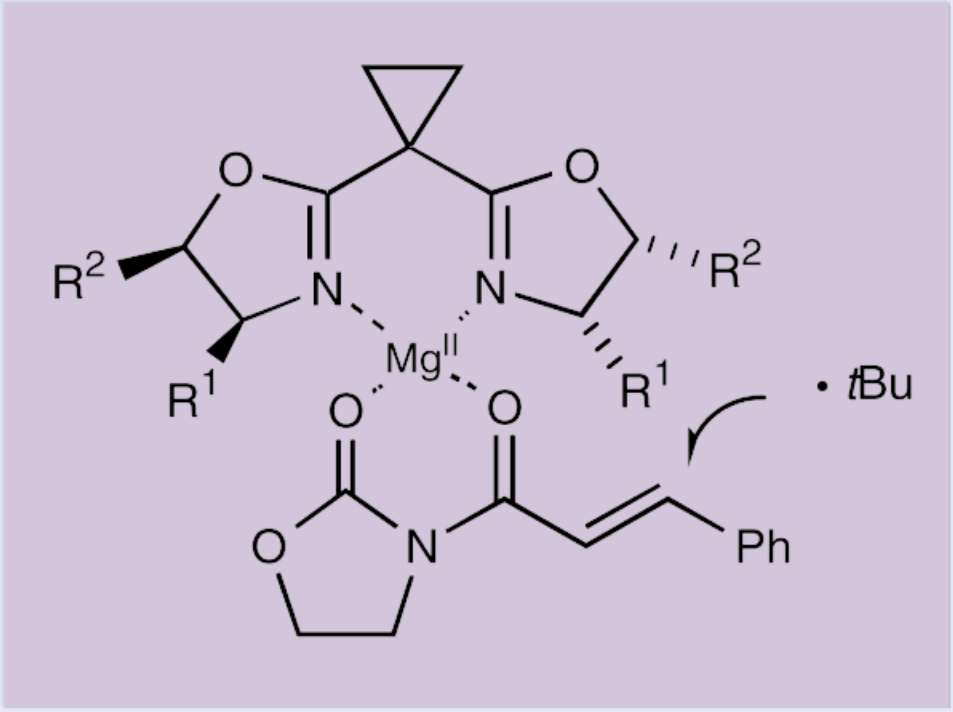


Free Radical Reactions - Lewis Acids

Complexation
Chelation
Catalysis





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Use of Lewis Acids in Free Radical Reactions

Philippe Renaud* and Michèle Gerster

After a long period of neglect, radical chemistry has been investigated seriously, and exciting new developments have been reported. Radical steps are now incorporated in an increasing number of total syntheses. The stereochemical aspect of these reactions has been particularly studied during the last decade. While diastereoselective reactions in cyclic systems as well as cyclization reactions are well established, the possibility of performing diastereoselective reactions in acyclic systems is more recent. However, progress has been extremely rapid in this field. A new dimension was opened wp by the use of Lewis acids, which have been employed first in polymerization reactions and later for controlling reactivity and diastereoselectivity. Enantioselective reactions are being investigated intensively and initial results show great promise. Recently, the first success in enantioselective catalysis of radical reactions was reported. This review gives an overview of the development of radical reactions controlled by Lewis acids. Polymerization reactions, stereoselective reactions based on substrate control, and chiral auxiliary control, as well as enantioselective radical reactions will be discussed. The different roles of the metal center (monocomplexation, chelation, template effect, etc.) will be used to rationalize the results.

Keywords: asymmetric synthesis · chelates · Lewis acids · radical reactions · radicals

1. Introduction

The general feeling of synthetic chemists about free radicals has dramatically changed during the last 15 years. Before that time free radicals were considered mainly as interesting reaction intermediates with very limited synthetic potential, and the few known clean radical reactions were considered as exceptions. However, the 1980s have seen an emergence of new free radical synthetic methods largely based on organomercury and organotin compounds. More recently, atom- and group-transfer reactions, as well as reductive and oxidative single-electron transfer (SET) processes have become very popular.[1]

Parallel to this development, the stereochemistry of radical reactions has been investigated, and results exceeding the initial expectation have been obtained.[2] Interestingly, the rules developed to rationalize the stereochemical outcome of radical reactions are very similar to the ones formerly developed for ionic and concerted reactions. However, because of the neutral nature of radicals, the effect of solvent and other possible complexing agents that are crucial for ionic and concerted reactions were not investigated until very recently. It has been well established that radical reactions can be rationalized by applying the frontier molecular orbital theory. The electronic character of the radical determines whether SOMO–LUMO or SOMO–HOMO interactions are predominating.[3] By analogy to pericyclic reactions it is expected that Lewis acids will strongly influence the outcome of radical reactions and will play a crucial role, similar to the one they play in cycloaddition reactions. Reactivity, as well as regio- and stereoselectivity, should be influenced by the presence of Lewis acidic additives.

Recently, most of these expectations were confirmed and exceptional effects have been obtained on the stereochemical outcome of radical reactions by using complexing agents, mainly Lewis acids. Effects on the reaction rates have also been observed, thus opening the way to catalysis of radical reactions. Since these effects are of great importance for future synthetic applications, we wish to summarize in this account the results concerning the use of Lewis acids in radical reactions with particular emphasis on the stereochemical control.

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2. Reactivity and Regioselectivity Control

The first application of Lewis acids in radical reactions concerned polymerization reactions.[4] For example, it has been observed that homopolymerization of acrylonitrile and methyl methacrylate could be enhanced by the addition of $ZnCl_2$ and very important effects have been observed in

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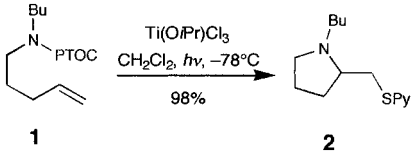
copolymerization:[5] Without Lewis acids regular alternating copolymers are only formed from monomer pairs consisting of one strong electron acceptor and one strong electron donor, but with monomers less differentiated in their electronic character, the alternation was poor. A major breakthrough resulted from the work of Bamford[6] and Hirooka[7] when they described the formation of regular 1:1 copolymers from propylene and acrylonitrile in the presence of $EtAlCl_2$. Following this work, different Lewis acids have been used, and of them zinc, aluminum, boron, and tin derivatives gave the best results. For example, it was found that allylboron halides can be used in a catalytic amount to control the alternation of the monomers.[8] Polymerization of alkyl methacrylates that are initiated by aluminum porphyrins are greatly accelerated in the presence of sterically hindered Lewis acids such as methylaluminum di(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[9] and aluminum tris(2,6-diphenylphenoxide) (ATPH).[10]

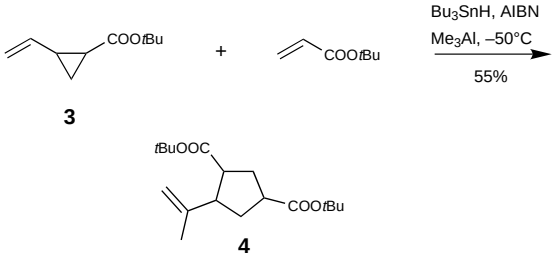
The work on polymerization reactions proves that Lewis acids can be used to control the reactivity of radicals. This possibility has not been used in traditional synthesis until very recently. An early example concerns aminyl radicals that are known to be activated by protonation.[11] It was then demonstrated that Lewis acids could induce the same effects.[12, 13] For example, the PTOC-carbamate **1** cyclizes in almost quantitative yield (GC analysis) to give the pyrrolidine **2** in the presence of $Ti(OiPr)Cl_3$ [Eq. (1); PTOC = pyridine-2-



1 2 (1)

thion-*N*-oxycarbonyl].[12] Under strictly neutral conditions (no Lewis and no Brønsted acid) the cyclic product is not formed. The yield of cyclized product **2** exceeds the amount of Lewis acid employed. This suggests that the Lewis acid is acting as a catalyst.[14]

Complexation of the alkene partner is also expected to lead to enhancement of the radical addition rate with complexed alkenes being more reactive towards alkyl radicals that possess a well established nucleophilic character. This was confirmed by ab initio calculations[15] and by some early observations. For instance, radical alkenylation of vinylcyclopropyl ester **3** with acrylate gives the cyclopentane derivative **4** in high yield in the presence of Me_3Al at low temperature [Eq. (2); AIBN = azobisisobutyronitrile].[16] In the absence of



3 4 (2)

Me_3Al the reaction does not proceed at all at $-50\,^{\circ}C$. This result is attributed to complexation of the ester functionality in either the cyclopropyl or the acrylate moiety.

A more convincing demonstration of this effect was given by Sato et al. who examined the relative reactivity of *tert*-butyl acrylate **5** and *N*,*N*-dimethyl acrylamide **6** toward the *n*-butyl radical addition [Eq. (3)].[17] In the absence of a Lewis acid the ester reacts more rapidly and **7** is formed preferentially (**7**:**8** = 68:32). The presence of one equivalent of di(2,4,6-trimethylphenoxy)aluminum chloride increases the yield of the addition to the acrylamide and **8** becomes the major product of the reaction (**7**:**8** = 24:76). This result arises from the fact that the amide is a stronger base and is preferentially

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P. Renaud

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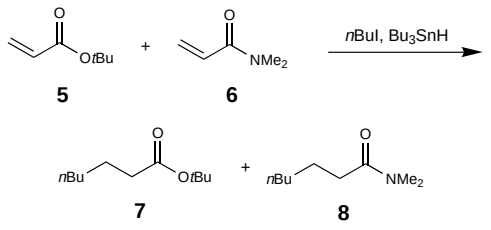
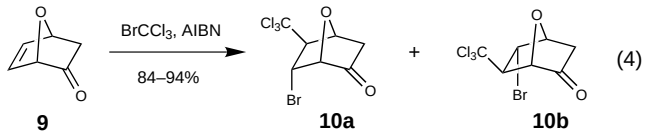
Michele Gerster was born in 1969 in Sion, Switzerland. She studied chemistry at the University of Lausanne. Before starting her Ph. D., she worked for four months with R. K. Haynes in Sydney on the total synthesis of antimalarial compounds. She received her Ph. D. in 1997 under the direction of Professor Renaud at the University of Fribourg with a dissertation entitled: "Study of the Influence of Lewis Acids on the Stereoselectivity of Radical Reactions". She is currently carrying out postdoctoral research in Cambridge, England, in the group of Steven V. Ley where she is involved in the total synthesis of biologically active compounds.



(3)

complexed by the Lewis acid. Interestingly, the activating effect of the Lewis acid has also a positive effect on the overall yield of the reaction (41 →78 %), which confirms the excellent compatibility of Lewis acids and radical chain reactions.

The regioselectivity of the radical addition to 7-oxabicyclo[2.2.1]hept-5-en-2-one (**9**) is influenced by the presence of Lewis acids [Eq. (4)).[18] Kharasch-type addition of bromotrichloromethane to **9** gives **10a** preferentially, which results



(4)

from the addition at C5 (**10a**:**10b** = 74:26). In the presence of Lewis acids such as $Ti(OiPr)_2Cl_2$ the regioselectivity is inverted and **10b** is the major product of the reaction (**10b**:**10a** = 26:74). This inversion can be explained from the HOMO coefficients of alkene **5**. Indeed, it was calculated that protonation of the carbonyl group makes the coefficient at C6 larger than the coefficient at C5.[18]

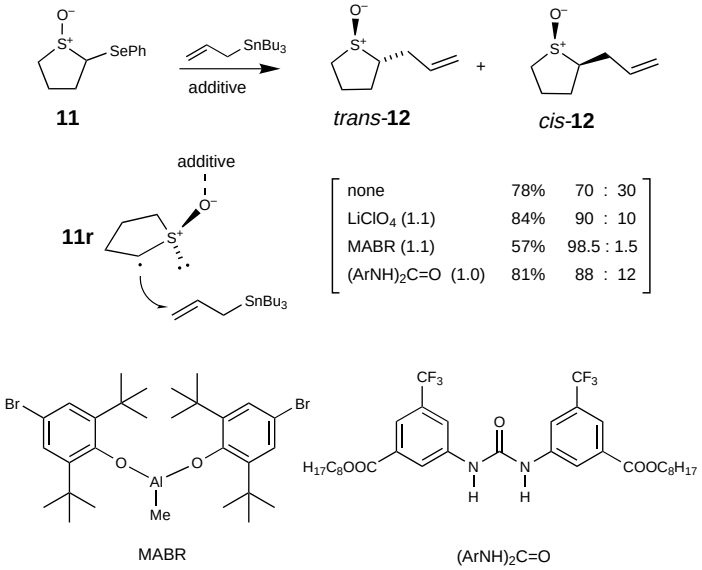
3. Control of Diastereoselectivity

Particular attention has been devoted to the control of the diastereoselectivity but, despite impressive progress, the control of the stereochemistry of radical reactions still represents a barrier for their application in organic synthesis. For the purpose of clarity, we have divided this part of the review between complex formation with monodentate ligands (monocomplexation) and with polydentate ligands (chelation), the ligands being either the radicals or the radical traps. These two approaches lead to remarkable stereoselectivity enhancement and control.

3.1. Monocomplexation

3.1.1. Cyclic Radicals

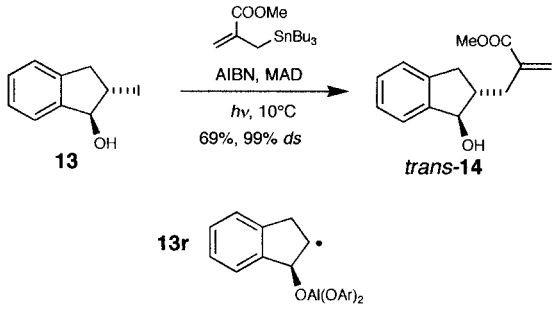
Investigation of 1,2-asymmetric induction in the presence of an additive is reported for radicals derived from cyclic sulfoxides and alcohols. For example, a study of cyclic sulfinamides[19] and sulfoxides[20, 21] shows an interesting solvent effect attributed to hydrogen bonding.[22] The use of oxophilic Lewis acids give even more impressive results: excellent stereoselectivity enhancement is obtained for the allylation of **11** in the presence of lithium perchlorate (Scheme 1).[20, 21] The use of very bulky Lewis acids also



Scheme 1. Allylation of **11** (see text for explanation).

proved to be possible without detrimental effect on yields. With methylaluminum di(4-bromo-2,6-di-*tert*-butylphenoxide (MABR) for example, the *trans* isomer of **12** is formed in 98.5 % *ds*.[21] Good levels of stereoselectivity (up to 90 % *ds*) are still observed when 10 mol % of MABR is used. A similar approach was developed by running the reactions in the presence of diarylureas that form bis-hydrogen-bonded complexes.[23] In all of these systems the additives complex the oxygen atom of the sulfinyl groups and therefore allow a good steric differentiation of the two faces.

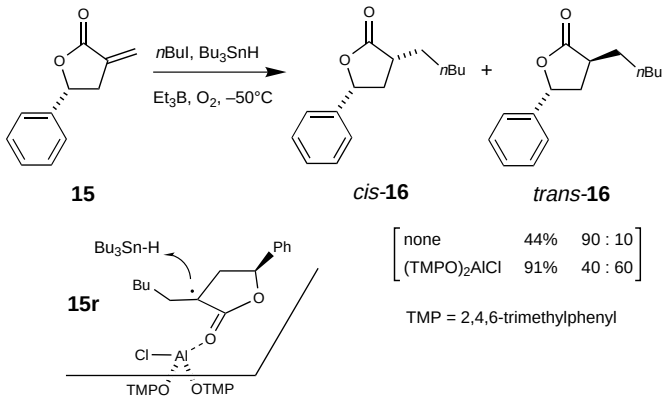
Very bulky methylaluminum diphenoxides also promote selective radical deuteration and allylation of iodohydrin **13** in over 99 % *ds* [Eq. (5)]. Formation of an aluminum alkoxide



(5)

derivative was achieved by treatment of the alcohol with MAD prior to the radical reaction.[24, 25] The extreme bulkiness of the aluminum derivative cannot be rivaled by bulky protective groups. For example, the corresponding *tert*-butyldiphenylsilyl ether is deuterated in only 89 % *ds*.

A single example of 1,3-asymmetric induction controlled by Lewis acids has been reported.[26] Radical addition to the α-methylenebutyrolactone **15** gives *cis*-**16** as the major product (90 % *ds*) in the absence of a Lewis acid (Scheme 2). In the presence of bis(2,4,6-trimethylphenoxy)aluminum chloride, the stereoselectivity is reversed and *trans*-**16** is isolated with a moderate stereoselectivity (60 % *ds*). This difference is ex-

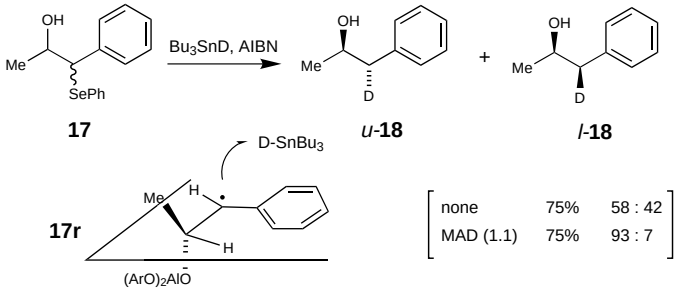


Scheme 2. The influence of a Lewis acid on the yield and product ratio on the radical addition to **15**.

plained by complexation of the carbonyl group of the lactone radical **15r** as shown in Scheme 2.

3.1.2. Acyclic Radicals

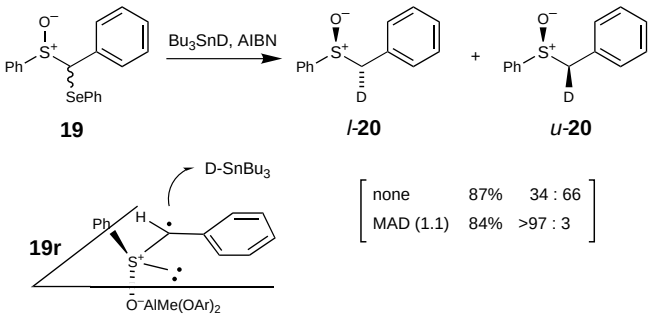
Control of the diastereoselectivity in the acyclic series has been a long standing concern and still remains a formidable challenge for organic chemists. The use of Lewis acids to solve this problem is very promising. Indeed, it has been shown in many examples that radical reactions are characterized by early transition states and therefore the radical conformation is of crucial importance. Chelation is an effective way to fix the conformation of radicals (see Section 3.2). Monocomplexation may also be very efficient to control the conformation and to allow the differentiation between the diastereotopic faces of a radical. However, with this approach a second factor, such as the presence of $A^{1,3}$ strain, is required to control the radical conformation.[27] Benzyl radicals that possess an adjacent chiral center belong to this class with their conformation being controlled by the $A^{1,3}$ strain and excellent levels of stereoselectivity are obtained when the size of the groups at the stereogenic center is well differentiated. For example, the 2-hydroxy-1-phenylpropyl radical generated from **17** is deuterated with Bu_3SnD with low selectivity (*u*-**18**:*l*-**18** = 58:42, Scheme 3).[28] In the presence of MAD (1.1



Scheme 3. Influence of Lewis acids on the radical deuteration of **17**.

equivalents), a *u*-**18**:*l*-**18** = 93:7 ratio is obtained as a result of the formation of the aluminum alcoholate **17r**, in which the three substituents at the stereogenic center are of very different sizes. The model based on minimization of the $A^{1,3}$ strain is depicted in Scheme 3. This example, as well as the reaction of iodohydrin **13** [Eq. (5)], does not involve the formation of a complex, but rather the formation of a covalent O – Al bond.

A second similar example is based on complex formation between sulfoxide and Lewis acids. The sulfoxide **19** gives *u*-**20** as the major isomer upon deuteration in the absence of a Lewis acid (Scheme 4). In the presence of 1.1 equivalents of

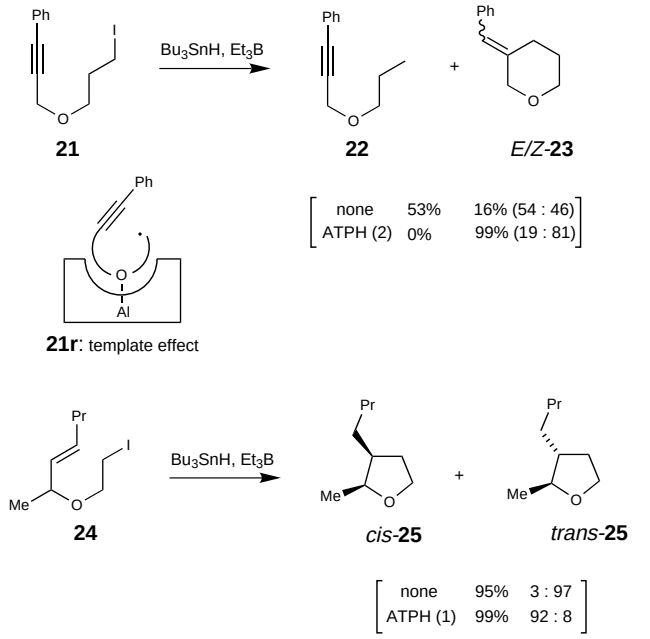


Scheme 4. Influence of Lewis acids on the radical deuteration of **19**.

bulky Lewis acids such as MAD and MABR a reversal of the stereoselectivity is observed and *l*-**20** is formed in over 97% *ds*. The model **19r**, based on the minimization of $A^{1,3}$ strain, was proposed to rationalize this result.[29] Interestingly, the monocomplexation has two consequences: it strongly favors the radical conformation where the pair of electrons are coplanar to the aryl group relative to the conformation having the oxygen atom and the aryl group in the same plane. Secondly, because of its exceptional size, it completely shields one face of the radical. A similar effect, although much more modest, has been observed during the radical reductive alkylation of enamines which is also controlled by $A^{1,3}$ strain. In this case, lithium perchlorate was used to complex a sulfonyl group.[30]

3.1.3. Cyclization Reactions

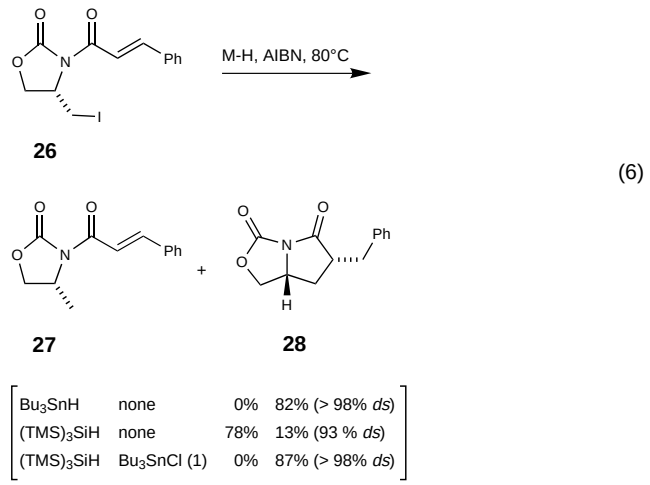
A remarkable template effect is reported by Maruoka and co-workers during the cyclization of substituted propargyl and allyl ethers. Aluminum tris(2,6-diphenylphenoxide) (ATPH) has a dramatic influence on the rate of cyclization.[31] For instance, treatment of **21** with Bu_3SnH/Et_3B under neutral conditions gives mainly the reduced product **22** along with a small amount of the cyclized product **23** (Scheme 5). In the presence of ATPH an almost quantitative yield of **23** is obtained together with good *E/Z* stereocontrol. This result is explained by a template effect, with the complexation enhancing the proximity between the radical center and the alkyne moiety. The same strategy applied to precursor **24** allows not only an enhancement in the yield of cyclized product, but also the complete inversion of the stereochemical outcome. In the absence of a Lewis acid *trans*-**25** (97% *ds*) is produced as the major isomer, which is in good agreement with the Beckwith – Houk rules.[32] In the presence of two equivalents of ATPH, *cis*-**25** becomes the major isomer



Scheme 5. Template effect in the cyclization of a substituted propargyl and allyl ether.

(92% *ds*). Such an inversion of selectivity is unattainable under ordinary radical reaction conditions.

Another example of the influence of Lewis acids upon radical cyclization is depicted in Equation (6).[33] Iodide **26** gives, upon treatment with Bu_3SnH (slow addition technique)



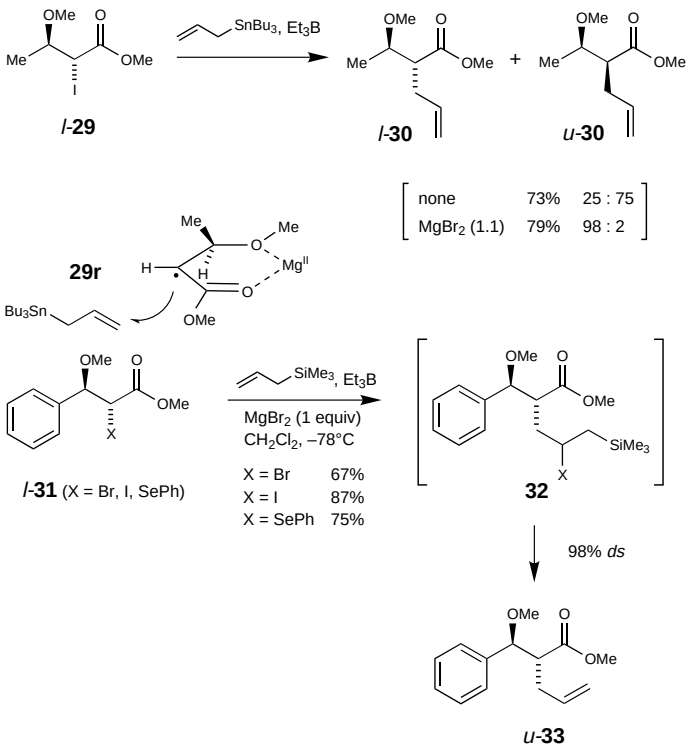
(6)

at 80 °C, the cyclization product **28**. Under analogous conditions, $(TMS)_3SiH$ furnished mainly the product of direct reduction **27** (TMS = trimethylsilyl). This unexpected difference ($(TMS)_3SiH$ is known to reduce primary alkyl radicals slower than Bu_3SnH by one order of magnitude) is caused by the presence of Bu_3SnI, which acts as a Lewis acid. Indeed, the reaction with $(TMS)_3SiH$ in the presence of one equivalent of Bu_3SnCl gave a result very similar to the one obtained when Bu_3SnH was used as the reducing agent. The role of the Lewis acid is to control the rotamer population so that the *N*-enoyloxazolidinone can attain a conformation that favors cyclization. The nature of the Lewis acid (Bu_3SnCl versus Bu_3SnBr) is also of importance for the diastereochemical outcome of the reaction, but the reasons for this are still unclear.

3.2. Chelation

3.2.1. Complexed Radicals

The study of β-hydroxy and β-alkoxy ester enolate radicals has attracted a great deal of attention since the first example of a stereoselective reaction mediated by an acyclic radical discovered by Hart and Huang.[34] In the absence of Lewis acids the stereochemical outcome is controlled by the conformation of the starting radicals, and a model based on the minimization of $A^{1,3}$ and $A^{1,2}$ strains has been proposed.[27, 35] Following this work, Guindon et al. reported the first example of a chelation-controlled radical reaction.[36] A complete reversal of the stereoselectivity is observed when radical reduction of methyl 2-iodo-3-methoxy-2-methylbutyrate is conducted in the presence of MgI_2.[37] Similar results are obtained for the allylation of methyl 3-methoxy-2-iodobutyrate *l*-**29**: in the absence of a Lewis acid, *u*-**30** is formed preferentially (Scheme 6); however, in the presence

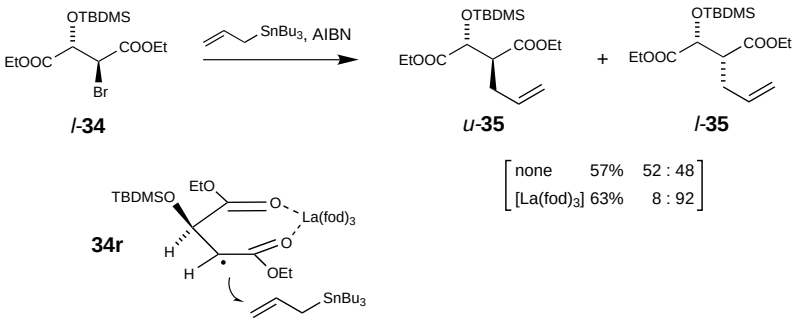


Scheme 6. Chelate-controlled radical reaction.

of three equivalents of $MgBr_2$ the *like* isomer *l*-**30** is produced with an excellent diastereoselectivity.[37] Chelation control (see **29r**) is at the origin of the stereochemical outcome. Interestingly, chelation also has an effect on the efficiency of the process: in the presence of Lewis acids, the reactions proceed more readily even at low temperature (−78 °C) than in their absence. This effect was nicely used to perform

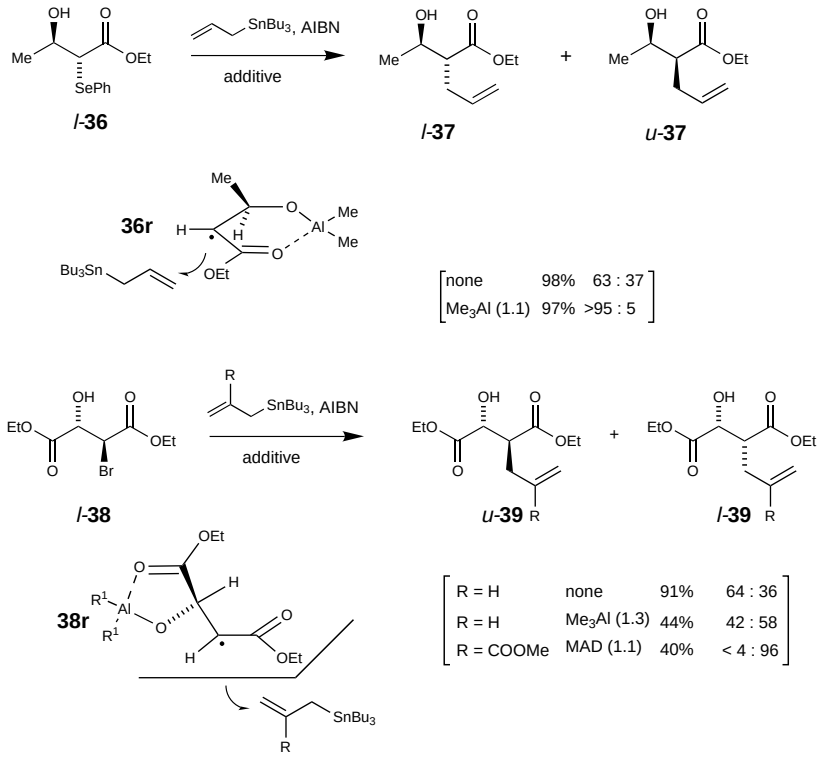
allylation of substrates such as *l*-**31** with allyltrimethylsilane in the presence of triethylborane as the radical initiator.[38] The reaction proceeds through the intermediate **32**, which decomposes readily to give *u*-**33**. The key step of the reaction is an atom (Br/I) or a group (PhSe) transfer, which is promoted by the chelation.

The stereochemical control of the allylation of 3-bromo-2-oxysuccinate has also been investigated.[39] Moderate to good results have been observed with silylethers such as *l*-**34**. The allylation is not stereoselective in the absence of Lewis acids. However, in the presence of lanthanum tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dione) [La(fod)$_3$], the diester *l*-**35** is obtained in 92% *ds* (Scheme 7). The formation of the 7-membered ring chelate **34r** is proposed to account for the observed stereoselectivity. The bulkyness of the *tert*-butyldimethylsilyl protecting group disfavors the five- and six-membered ring chelates involving the ether oxygen atom.



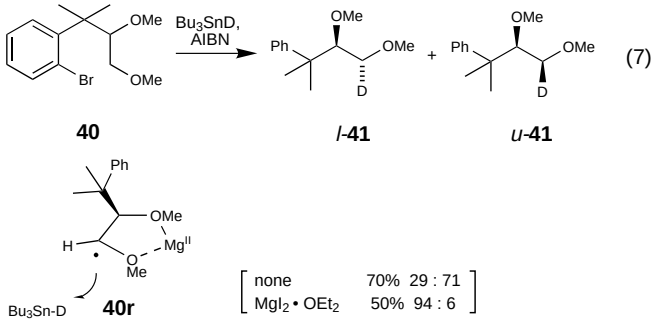
Scheme 7. Increase in the stereoselctivity during the allylation of *l*-**34**.

An excellent level of stereocontrol is obtained when starting directly from the unprotected β-hydroxyesters (Scheme 8). Ethyl 3-hydroxy-2-phenylselanylbutyrate *l*-**36** is allylated to *l*-**37** in the presence of 1.1 equivalents of Me_3Al in over 95% *ds* via the cylic radical **36r**.[40] In the absence of an additive *l*-**37** is also formed preferentially, but the stereoselectivity is much lower (61% *ds*), presumably as a consequence of intramolecular hydrogen bonding.[41] Interestingly, this approach is also successful with the malic acid derivative *l*-**38**. Low levels of stereocontrol are obtained in the absence of an additive and in the presence of Me_3Al. An excellent stereoselectivity (> 96% *ds*) was observed with MAD in favor of the *like* isomer *l*-**39**. This outcome results from the formation of the five-membered ring chelate **38r**, which minimizes $A^{1,3}$ strain. These observations are complementary to the work reported by Nagano et al. in Scheme 7; the absence of the OH protecting group allows for a complete change in the nature of the chelate.



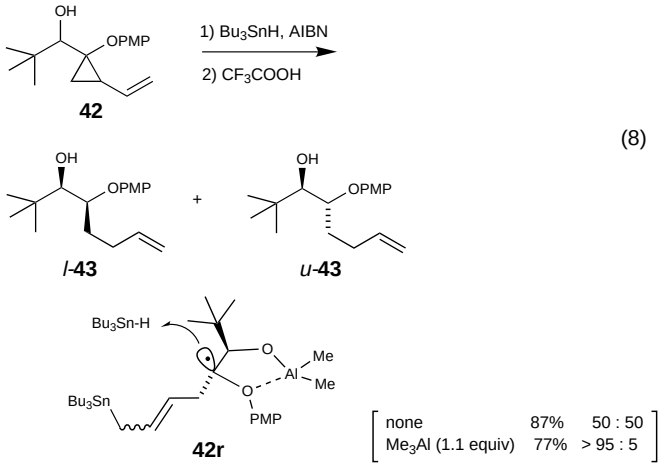
Scheme 8. Increase in the stereoselctivity during the allylation of unprotected β-hydroxy ester.

Another class of synthetically useful intermediates are 1-oxy substituted radicals. In the presence of an adjacent chiral center good levels of 1,2-asymmetric induction are observed. Giese et al. and Curran et al. have rationalized these results by a model very similar to the classical Felkin – Anh model developed for nucleophilic additions to carbonyl compounds.[42] The presence of a heteroatom at the stereogenic center enables chelation control. The first example of such a system is shown in Equation (7).[43] Under neutral conditions *u*-**41** is obtained in



71% *ds* according to the Felkin – Anh model. In the presence of $MgI_2 \cdot OEt_2$ a chelation-controlled reaction occurs and *l*-**41** is obtained in 94% *ds* (50% yield). The proposed model for this reaction **40r** is a radical analogue of the Cram cyclic model for nucleophilic additions.

A surprising result is obtained during the radical opening of the vinylcyclopropane **42**. After protodestannylation of the intermediate allylstannane, the monoprotected diol *l*-**43** is formed with a high (>95% *ds*) and unexpected stereoselectivity when Me_3Al is used as the additive [Eq. (8); PMP = p-methoxyphenol].[44] This major product formation cannot

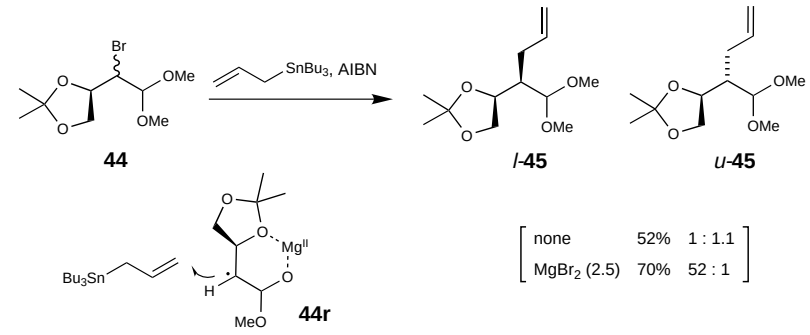


(8)

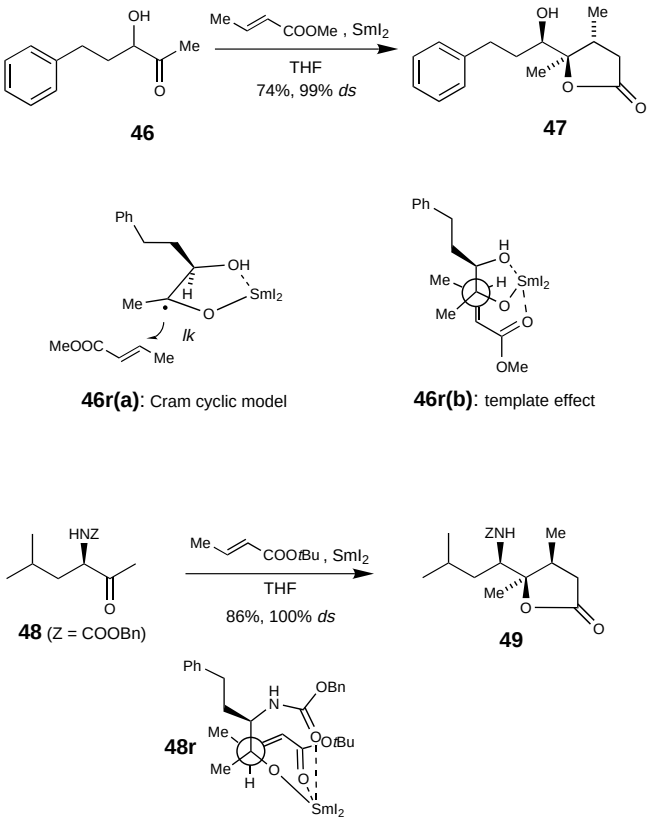
be rationalized by the Cram cyclic model. This result is best explained by invoking pyramidalization of the radical **42r** and attack from the more crowded face *syn* to the *tert*-butyl group (this may be called the "*anti* Cram cyclic model"). Indeed, steric interactions between the two vicinal alkyl groups are critical and dominate the interactions between the *tert*-butyl group and the incoming tin hydride.

Nagano and co-workers have reported highly stereoselective chelation-controlled allylation and deuteration of 2,2′-dialkoxy-substituted radicals.[45] The radical allylation of the bromoacetal **44** in the presence of 2.5 equivalents of $MgBr_2 \cdot OEt_2$ gives *l*-**45** (>98% *ds*; Scheme 9). The stereochemical outcome is best explained by the formation of the six-membered ring chelate **44r**.

Several chelation-controlled radical reactions of ketyl radicals generated by single electron reduction of ketones with samarium iodide are reported and included in recent reviews.[46] Only selected examples will be presented here. Two typical examples of 1,2-asymmetric induction are described in Scheme 10. Reduction of the α-hydroxy ketone **46**



Scheme 9. Chelate-controlled allylation of **44**.



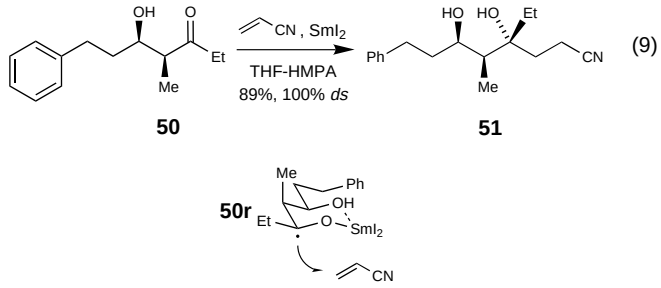
Scheme 10. Example of a 1,2-asymmetric induction.

with SmI_2 in the presence of methyl crotonate gave the lactone **47** with excellent stereocontrol.[47, 48] Formation of a five-membered ring by chelation of the samarium(III) ion explains the *like* topicity (*lk*) for the formation of the first new stereogenic center (see **46r(a)**, Cram cyclic model). The control of the second center occurs via coordination of the ester group of methyl crotonate with the samarium(III) cation as shown in **46r(b)**. The samarium not only controls the conformation of the radical, it also brings the radical trap into the proximity of the radical center (template effect). Similar chelation control coupled with template effects are also observed with 1-aminoketones derivatives. Treatment of **48** with SmI_2 in the presence of *tert*-butyl crotonate gives the lactone **49** as one of the four possible isomers.[48] The stereoselectivity is best explained by chelation and complexation of the radical trap to the samarium cation as shown in **48r**.[49].

Six-membered ring chelates are also proposed when β-hydroxyketones are employed. A typical example is reported in Equation (9) (HMPA = hexamethylphosphoramide). The β-hydroxyketone **50** is coupled to acrylonitrile under SmI_2 reductive conditions to give **51** with complete stereocontrol via the cyclic intermediate **50r**.[50]

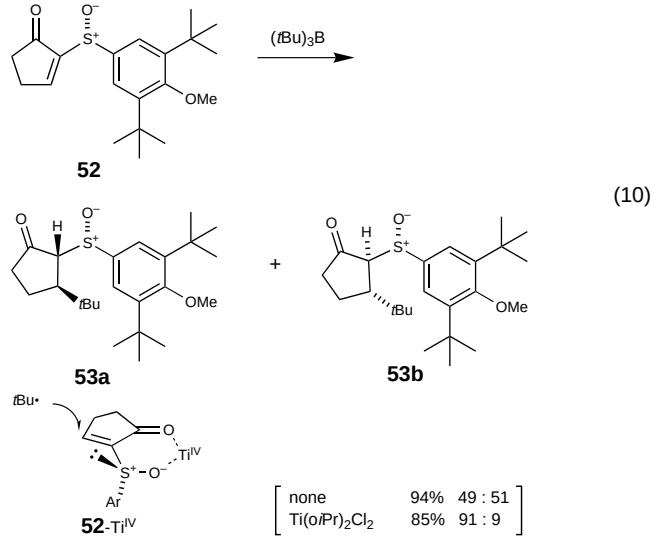
3.2.2. Complexed Olefins

Chelation control during radical addition to chiral olefins has also been investigated. Toru and co-workers have reported high β-stereo-



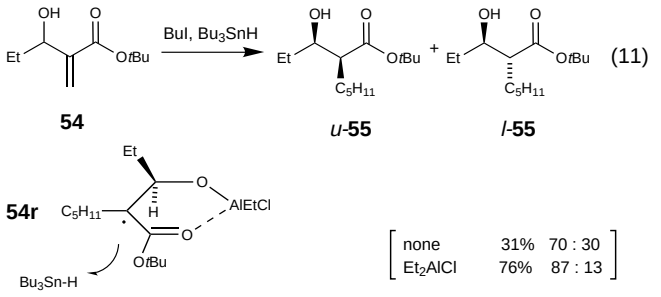
(9)

selectivity in the radical addition to 2-arylsulfinylcyclopentenone **52** in the presence of Lewis acids such as $TiCl_2(OiPr)_2$ (92% ds), ZnBr2, $MgCl_2$, and $ZrCl_4$ [Eq. (10)].[51] The α-diastereoselectivity of radical addition to a α,β-unsaturated



(10)

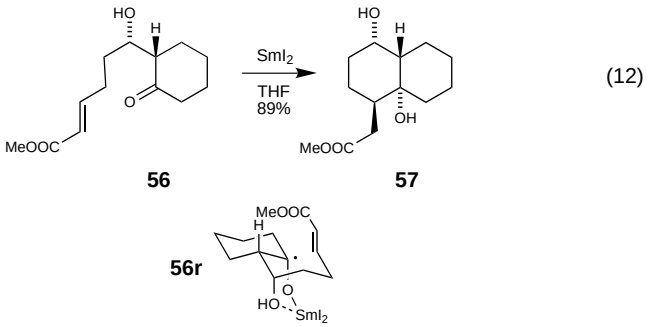
ester such as **54** can also be controlled by Lewis acids [Eq. (11)]. For example, the use of Et_2AlCl provides the *unlike* isomer *u*-**55** as the major product (70 →87% *ds*) via the cyclic radical **54r**.[17] Again, the complexation is beneficial for the yield of the reaction (31 →76%).



(11)

3.2.3. Cyclization Reactions

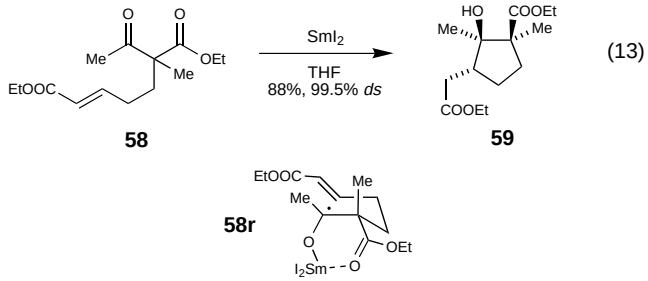
The only examples reported in this area concern the SmI_2-promoted cyclization of ketyl radicals. The recent review of Molander et al.[1h] treats this point in detail and only selected examples will be presented here. Three important reaction classes will be discussed. The first class is the hydroxy-directed intramolecular ketone – olefin coupling.[52–54] One typical example is reported in Equation (12). Treatment of ketone



(12)

56 with SmI_2 affords the *trans* bicyclic compound **57** in 89% yield.[52] The stereochemistry is best explained by the six-membered ring chelate **56r**.

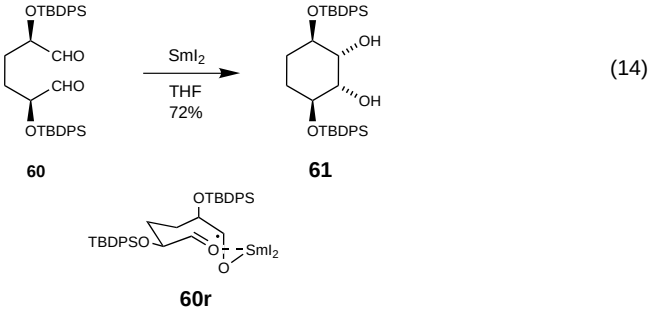
The cyclization of β-dicarbonyl substrates is a second example where chelation is used to achieve excellent yields and control of the stereochemistry. Molander et al. have for example reported the highly stereocontrolled cyclization of β-ketoester **58** to the polysusbtituted cyclopentane **59** [Eq. (13)].[55] Chelation of the samarium(III) ion produces



(13)

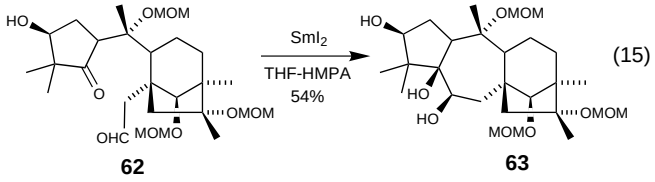
the six-membered ring ketyl intermediate which cyclizes via the chairlike transition state **58r** according to the well established Beckwith – Houk model.[32]

A third class of radical reactions which can be run under chelation control is the pinacolic coupling. For instance, the intramolecular McMurry-type pinacol coupling gives stereoselectivities that arise from chelation control.[56] Samarium iodide offers a very attractive alternative to the McMurry procedure.[57] Coupling of dialdehydes such as **60** yields the *cis*-diol **61** in good yield and excellent stereoselectivity [Eq. (14);



(14)

TBDPS = *tert*-butyldiphenylsilyl] via the 9-membered ring ketyl radical **60r**.[58] Matsuda et al. used a samarium mediated pinacol coupling as a key step in the synthesis of (−)-grayanotoxin III. For this purpose the ketoaldehyde **62** is treated with SmI_2 to afford the *cis*-diol **63** [Eq. (15); MOM = methoxymethyl].[59]

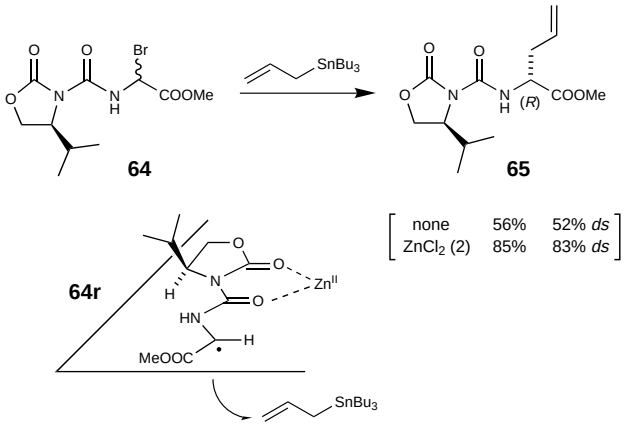


62 63 (15)

3.3. Chiral Auxiliaries

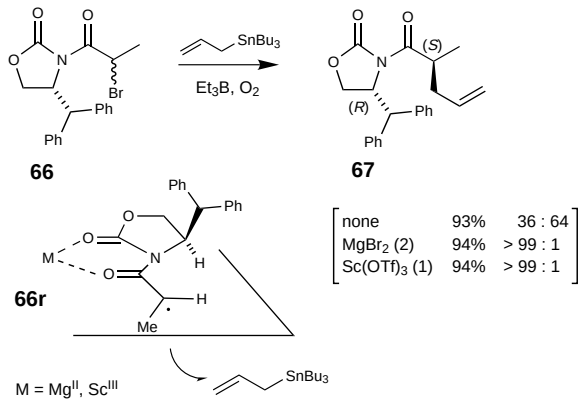
3.3.1. Intermolecular Reactions

The use of chiral auxiliaries proved to be particularly efficient for the preparation of enantiopure materials via radical reactions.[60] When the auxiliary is attached at the radical center excellent levels of stereocontrol have been obtained in conformationally restricted systems such as C_2-symmetric amides, sterically congested systems, and sulfonamides. Complexation with Lewis acids is a promising alternative for controlling radical conformation. Yamamoto et al. have shown that the allylation of the chiral glycine derivative **64** is stereoselective when run in the presence of zinc chloride (Scheme 11).[61] It is noted that zinc chloride also plays the role of a radical initiator.



Scheme 11. Increase in the stereoselctivity during the allylation of **64**.

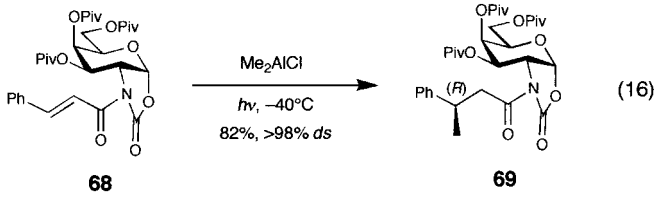
The use of oxazolidinone chiral auxiliaries in radical reactions in the presence of Lewis acids is very promising. Sibi and Ji have reported extraordinary high levels of stereoselectivity with an oxazolidinone derived from diphenylalaninol.[62] The allylation of **66** is not stereoselective in the absence of Lewis acids because of the existence of at least four rotamers of the radical intermediate (Scheme 12). In the presence of two equivalents of magnesium bromide or one equivalent of scandium triflate an excellent stereocontrol is reached and (*R,S*)-**67** is formed preferentially in over 99% *ds*.



Scheme 12. Increase in the stereoselctivity during the allylation of **66**.

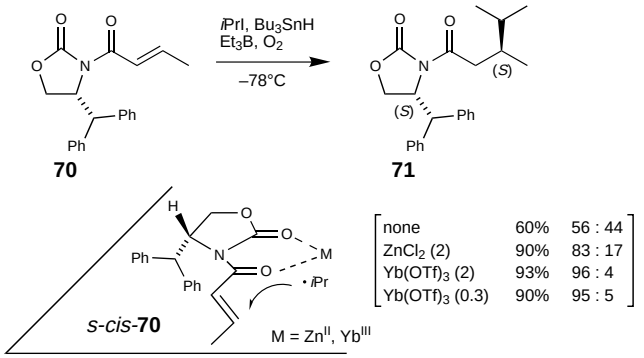
This result is explained by chelation of the Lewis acid with the bidentate radical ligand (see **66r**).

The chiral auxiliary can also be attached to the olefin moiety. This strategy offers several advantages and was investigated thoroughly for cycloaddition reactions. This work has provided important information on the conformation and the reactivity of activated alkenes in the presence of Lewis acids. Moreover, the enhanced basicity of unsaturated systems relative to saturated ones offers a possibility of catalysis.[63] Kunz and Rück have reported early examples of methyl radical additions to chiral oxazolidinones in the presence of Me_2AlCl.[64] Me_2AlCl is used in large excess and acts as a radical source and as a Lewis acid. Excellent diastereoselectivity has been obtained with the bicyclic carbohydrate oxazolidinone **68** [Eq. (16)].

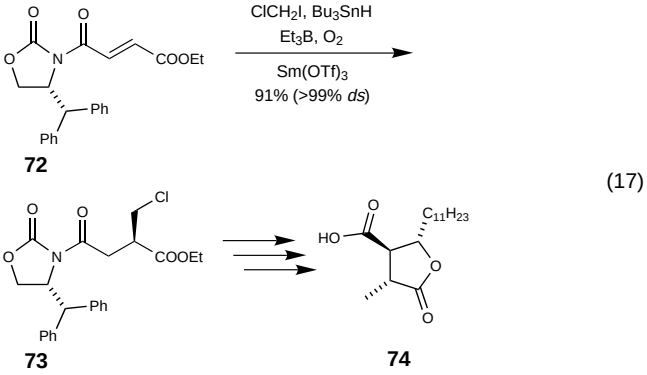


68 69 (16)

Sibi and Ji reported good α-stereoselectivity in radical additions to *N*-propenoyloxazolidinone; the stereocontrol is achieved via chelation control similar to the one described in Scheme 12.[65] The β-stereoselectivity can also be controlled in such systems. Radical addition to *N*-butenoyloxazolidinone **70** gives preferentially (*S,S*)-**71** in the presence of Lewis acids such as zinc chloride (83% *ds*) and ytterbium triflate (96% *ds*) (Scheme 13).[66] In this last case the use of only 0.3 equivalent of the Lewis acid leads to practically no drop in the stereoselectivity and yield. A further advantage of ytterbium triflate is its compatibility with small amounts of water, which is an important practical problem with classical Lewis acids, particularly for catalytic uses. The stereochemical outcome is best explained by the *Si*-face addition of the radical onto **70** lying preferentially in a s-*cis* conformation as a result of the complexation. This strategy was applied for the synthesis of (−)-nephrosteranic acid **74** from **72** [Eq. (17)].[67]

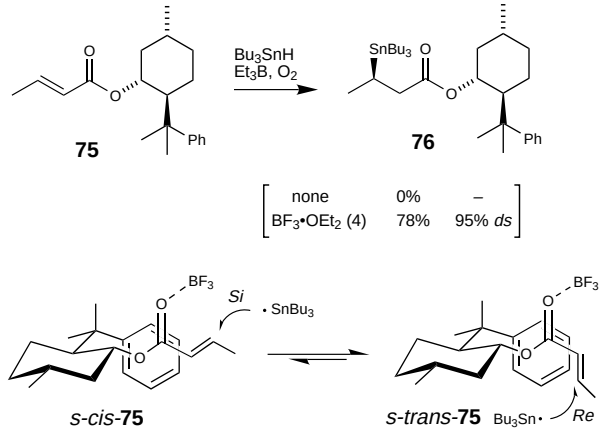


Scheme 13. Increase in the yield and stereoselctivity during the radical addition to **70**.



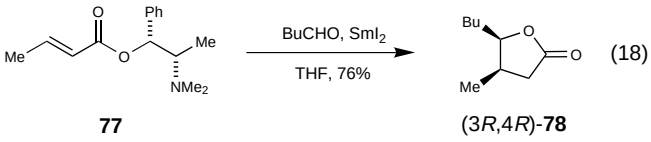
(17)

The use of ester-bound chiral auxiliaries in radical reactions is scarce because of the difficulties in controlling the conformation (*E*/*Z* and s-*cis*/s-*trans*). Nishida et al. reported a solution to this problem for the radical hydrostannylation of 8-phenylmenthyl crotonate **75**.[68] The use of $BF_3 \cdot Et_2O$ favors the s-*trans* conformation, and attack from the *Re* face is preferred (Scheme 14). A highly enantioselective γ-butyrolactone synthesis was developed by Fukuzawa et al. based on



Scheme 14. Example of the use of a chiral ester auxillary.

the samarium iodide promoted coupling of aldehydes and ketones with acrylate and crotonate esters derived from *N*-methylephedrine.[69] A typical example is presented in Equation (18). Addition of the ketyl radical derived from pentanal

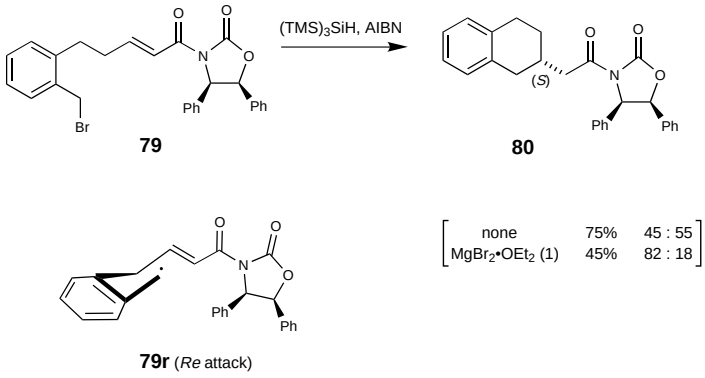


(18)

to crotonate **77** gives the disubstituted γ-butyrolactone **78** in a *cis*:*trans* ratio of 97:3 and with a 94% *ee* for the *cis* isomer. This represents a case where the face selectivity is very high, as well as the coupling of the two prochiral centers. It is worth noticing that the chiral auxiliary is cleaved cleanly during the lactonization step. The importance of samarium chelation in this process is demonstrated by the absence of selectivity when the reaction is run with HMPA as a cosolvent.

3.3.2. Cyclization Reactions

Radical cyclization of *N*-enoyloxazolidinone **79** has been examined by Badone et al. (Scheme 15).[70] The presence of $MgBr_2$ is necessary to obtain a moderate stereoselectivity and

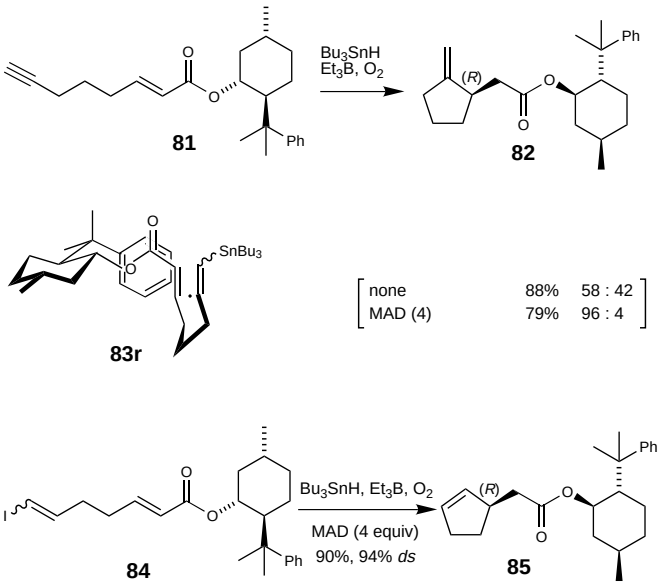


Scheme 15. Radical cyclization of **79**.

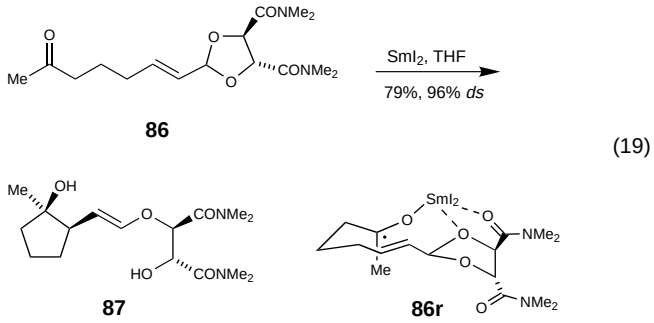
the stereochemical outcome of this reaction is rather surprising. Calculations have indicated that a chelated s-*cis* transition state is preferentially attacked from the *Re* face, presumably because of attractive van der Waals interactions between the arene groups.

Nishida and co-workers have also extended the use of unsaturated phenylmenthyl esters (see Scheme 14 for intermolecular reactions) to cyclization reactions. Good to excellent stereoselectivities are observed during cyclizations of vinyl radicals derived from **81** and **84** (Scheme 16).[71–73] The model is essentially similar to the one reported for intermolecular reactions, with the radical **83r** lying in a *Z* and s-*trans* conformation.

A unique reaction with tartramide acetals as chiral auxiliaries is reported by Molander et al.[74] Treatment of the keto acetal **86** with samarium iodide furnished the cyclopentanol derivative **87** in good yield and with excellent stereocontrol [Eq. (19); *cis*:*trans* = 99:1, 99% *ds* for the *cis* isomer]. The selectivity is rationalized by a highly ordered, tricyclic transition structure **86r** that is made possible by the tridentate nature of the ketyl intermediate.



Scheme 16. Radical cyclization of **81** and **84**.



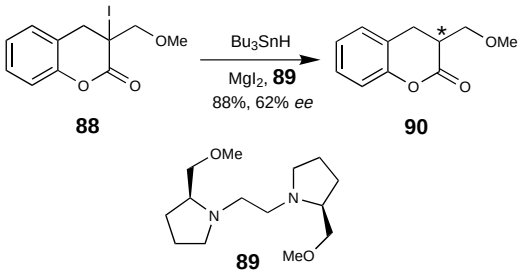
(19)

4. Enantioselective Reactions

Lewis acids have been widely used for highly enantioselective ionic and concerted reactions such as Diels–Alder reactions.[75] The development of enantioselective radical reactions mediated or eventually catalyzed by chiral Lewis acids represents a formidable challenge and preliminary experiments from several research groups have already been reported.

4.1. Complexed Radicals Generated by Homolysis of C–X Bonds

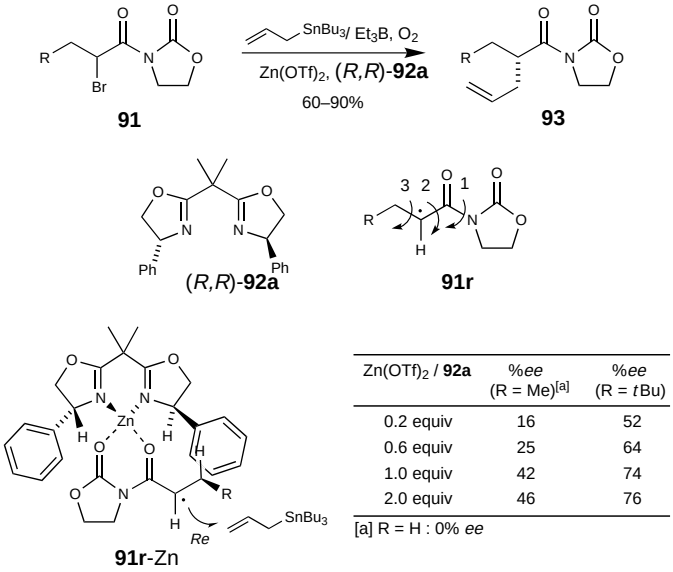
Hoshino and co-workers have reported the enantioselective reduction of the α-iodolactone **88** with tin hydride in the presence of one equivalent of MgI_2 and the diamine ligand **89** [Eq. (20)].[76] Lactone **90** is formed in 88% yield and 62% *ee*. This system offers several important features for enantioselective reactions: first, the cyclic nature of the substrate restricts the number of possible radical conformations. Second, the methoxy group is expected to allow chelation of the Lewis acid and result in a very well defined radical



(20)

conformation. Interestingly, a substoichiometric amount of MgI_2/**89** (0.5 equivalent) leads to a substantial enantioselectivity (52% *ee*).

In a recent paper Porter et al. have described the enantioselective allylation of *N*-(α-bromoalkanoyl) oxazolidinones of type **91** in the presence of zinc triflate and bisoxazoline ligands (*R,R*)-**92a** (Scheme 17).[77] The enantioselectivity depends on

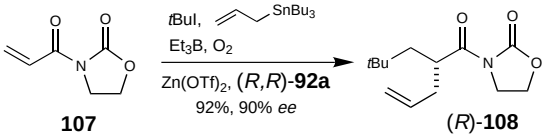


$Zn(OTf)_2$ / **92a**	%*ee* (R = Me)[a]	%*ee* (R = *t*Bu)
0.2 equiv	16	52
0.6 equiv	25	64
1.0 equiv	42	74
2.0 equiv	46	76

[a] R = H : 0% *ee*

Scheme 17. Enantioselective radical allylation.

the size of the R group and on the quantity of chiral Lewis acid, thus suggesting that an equilibrium between the bromide **91** and the Lewis acid precedes the formation of the radical **91r**. The moderate enantioselectivity is explained by a nonselective background reaction involving noncomplexed **91** competing with the Lewis acid promoted reaction. Better enantioselectivities are obtained when the same radicals are formed by radical addition to acryloyloxazolidinone [Eq. (21)]. Chelation of the zinc atom allows rotation 1

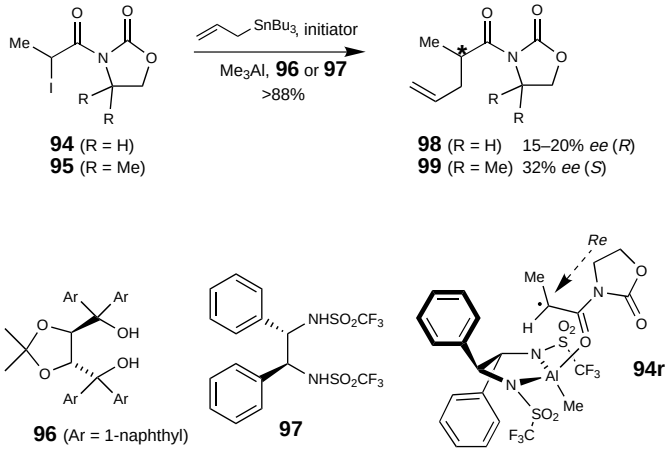


(21)

around the N–C(O) bond of radical **91r** to be controlled. Interestingly, the rotation 2 around the C(O)–C(2) bond is also controlled by the complexation, and the s-*cis* conformer

is favored (this phenomenon is well documented for the complexation of unsaturated esters and amides.[78, 79]) Rotation 3 around the C(2)–C(3) bond is controlled by allylic 1,3-strain. Based on these considerations, the model **91r**–Zn model complex is proposed to account for the preferential *Re*-face allylation.

The allylation of *N*-(α-iodopropionyl)oxazolidinones **94** and **95** was investigated by us (Scheme 18).[80] The resulting radicals **94r** and **95r** were allylated with low enantioselectivities (up to 34% *ee*). An analogy can be drawn between the



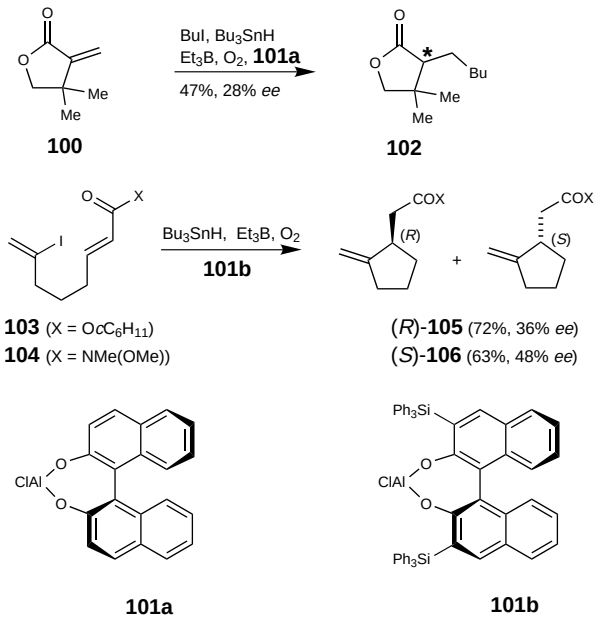
Scheme 18. Allylation of **94** and **95**.

reaction with the Corey (*S*,*S*)-bistriflamide **97** as ligand and the Diels–Alder reaction.[81] A similar model based on the monocomplexation of the radical at the exocyclic carbonyl group and the radical lying in a s-*trans* conformation is proposed. The reactions with TADDOL **96** as the ligand are more difficult to rationalize at the moment.

4.2 Radical Additions to Complexed Olefins

Sato et al. have reported the radical addition to methylene lactone **100** in the presence of aluminum binolate **101a**.[17] α-Alkylated lactone **102** is obtained in a 28% *ee* (Scheme 19). Nishida et al. has reported an intramolecular addition in the presence of four equivalents of aluminum binolate **101b** to the α,β-unsaturated ester **103** with a 36% *ee*.[82] The Weinreb amide **104** gives a similar enantioselectivity (48% *ee*) under identical conditions, but the sense of induction is opposite. These results were rationalized by assuming s-*trans* and s-*cis* conformations of the ester and amide radicals, respectively.

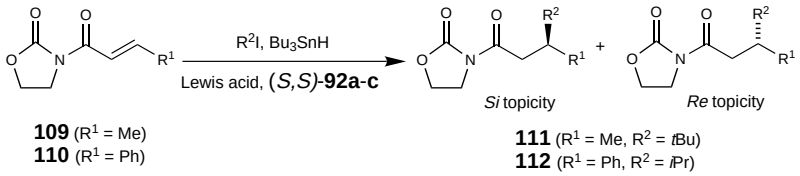
Addition of the *tert*-butyl radical to acrylamide **107** followed by allylation in the presence of bisoxazoline **92a** furnished the amide **108** in excellent

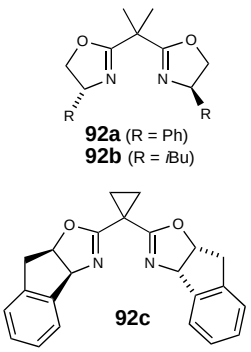


Scheme 19. Additions to a complexed olefin.

yield and enantioselectivity (90% *ee*) [Eq. (21)].[83] Interestingly, this reaction gives much higher selectivities than the allylation of the corresponding bromide **91** described in Scheme 17.[77, 83] This observation is explained by the stronger basicity of enoyloxazolidinone relative to alkanoyloxazolidinone, and by the enhanced reactivity of complexed enoyl systems towards radicals relative to the noncomplexed forms. This reactivity enhancement is certainly less pronounced or even nonexistent for the bromine atom abstraction step when **91** is used as the radical precursor.

The first example of β-enantioselectivity was reported by Sibi and Porter et al.[84] Addition of alkyl radicals to **109** and **110** gives promising *ee* values of up to 82% in the presence of bisoxazolines **92a** and **92b** (Scheme 20). Substoichiometric quantities of Lewis acids (down to 0.05 equivalent) still give a





Substrate / product	Topicity	Lewis acid	Ligand	T [°C]	% Yield	%*ee*
109 / **111**	*Re*	$Zn(OTf)_2$ (1.0)	**92a**	–78	90	82
109 / **111**	*Re*	$Zn(OTf)_2$ (0.2)	**92a**	–78	71	70
109 / **111**	*Re*	$MgBr_2$(1.0)	**92a**	–78	78	82
110 / **112**	*Re*	MgI_2(1.0)	**92a**	–78	88	47
110 / **112**	*Si*	MgI_2(1.0)	**92b**	–78	88	74
110 / **112**	*Si*	MgI_2(0.05)	**92b**	–78	57	40
110 / **112**	*Re*	MgI_2(0.30)	**92c**	–78	91	97
110 / **112**	*Re*	MgI_2(0.05)	**92c**	–78	92	90
110 / **112**	*Re*	MgI_2(0.30)	**92c**	25	87	93

Scheme 20. β-Enantioselective radical addition.

40 % *ee*. Zinc and magnesium are the best metals for this reaction. The rationalization of the results is complicated by the fact that homochiral bisoxazolines bearing aryl (**92a**) and alkyl (**92b**) substituents give opposite reaction topicities. More recently, Sibi and Ji have optimized the reactions.[85] An excellent enantioselectivity of 97 % *ee* is obtained with the ligand **92c** and MgI_2 at $-78\,^{\circ}C$ with 30 mol % of catalyst. The reaction is truly catalytic since an *ee* of 90 % is reached with only 5 mol % of catalyst. Moreover, an enantioselectivity of 93 % *ee* is still obtained with 30 mol % of catalyst at room temperature. A model is proposed where the ligand–MgI_2 complex adopts an octahedral geometry.[86]

5. Summary and Outlook

The use of Lewis acids in radical reactions is opening new applications for this type of chemistry in general organic synthesis and particularly in asymmetric synthesis. The growth of this strategy has developed quickly, particularly if we consider the number of parameters which have to be fulfilled. Radical chain reactions are complex from a kinetic point of view and electron transfer reactions between radicals and the Lewis acid metal centers have to be avoided. Fortunately, several different kinds of Lewis acids based on main group, lanthanides, and other transition metals have proved to be compatible with radical reactions. In numerous examples yield enhancement is observed and highly efficient radical additions to olefins are reported at low temperatures ($-78\,^{\circ}C$ or lower). Moreover, several preliminary results indicate that catalysis of radical reactions is possible. Up to now this point was mainly demonstrated for the radical addition to complexed olefins. However, the possibility of the catalysis of atom abstraction reactions also exists. These catalytic effects are of considerable importance for the development of enantioselective radical reactions.

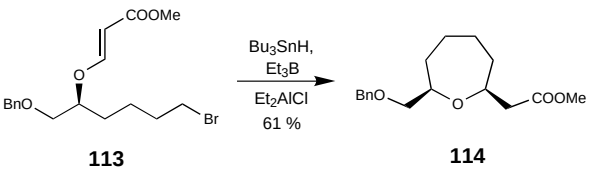
Another noteworthy point for future applications of radical reactions controlled by Lewis acids is their incorporation into reaction cascades. Indeed, formation of several bonds in a one-pot procedure is typical of radical chemistry, and highly attractive from a synthetic point of view. Lewis acids may be used to control the chemo- regio- and stereoselectivity of such processes.

Addendum

During the edition of this manuscript several examples of radical reactions that are controlled by Lewis acids have been reported. These new results are described below following the organization of the main part of the review.

Addendum to Section 2

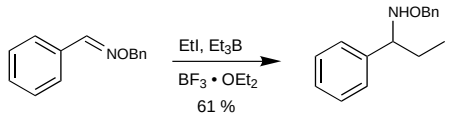
Rate enhancement of intramolecular additions to α,β-unsaturated esters have been reported.[86] For example, starting from the β-alkoxyacrylate **113** the oxepane **114** is obtained in 61 % in the presence of Et_2AlCl at $0\,^{\circ}C$ [Eq. (22); no product is observed at this temperature in the absence of the Lewis acid]. Several reports of intermolecular radical additions to imines and oxime ethers have appeared. Efficient



(22)

113 **114**

rate enhancements are obtained with simple aldoxime ethers;[87] treatment of the aldoxime ether **115** with Et_3B/EtI proceeds smoothly in the presence of $BF_3 \cdot OEt_2$ to give **116** in 61 % yield while in the absence of a Lewis acid it is formed in only 19 % [Eq. (23)]. This reaction compares favorably with

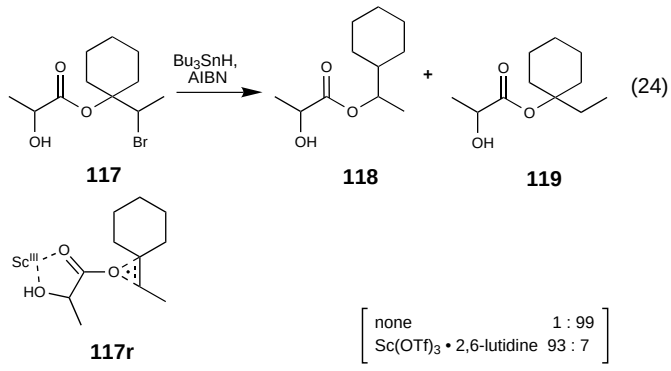


(23)

115 **116**

anionic reactions based on traditional organometallic reagents, particularly when the tolerance of functional groups is considered. Interestingly, this reaction does not require the use of tin hydride when ethyl radicals are added. A similar effect has been reported recently by Bertrand et al. and a chain mechanism involving the formation of ethyl radicals directly from Et_3B and the intermediate nitrogen-centered radical is proposed.[88] Lewis acids have only a marginal effect on the rate and stereoselectivity of radical additions to imines and oxime ethers derived from glyoxylic acid.[88, 89]

The results of reactivity enhancement are best rationalized by the enhancement of the eletrophilic character of the complexed radical or the complexed radical trap. Stabilization of a polarized transition state of a radical reaction represents an alternative explanation that has been examined recently. Lewis acids can enhance efficiently the rate of the 1,2-acyloxy shift of β-(alkoxy)alkyl radicals (Surzur–Tanner rearrangement). Rate enhancement of up to three orders of magnitude have been observed.[90] A typical example is reported in Equation (24). The lactate **117** gives upon reduction with tin



(24)

117 **118** **119**

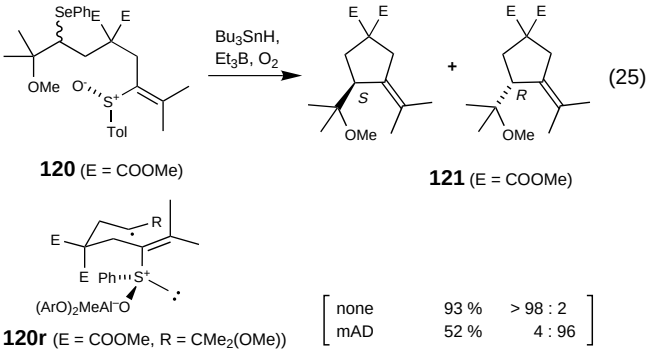
117r

hydride, **118** (rearranged product) and **119** (product of direct reduction) in a 1:99 ratio. In the presence of scandium(III) triflate the rearranged product **118** predominates (**118**:**119** = 93:7). Since the synthetic applications of the Surzur–Tanner rearrangement is severely limited by its slowness, the use of Lewis acids are expected to broaden its scope. Interestingly,

calculations predict that a three-center mechanism (**117r**) is favored by protonation of the ester carbonyl group.[91] This may have some interesting consequences on the stereochemistry of this rearrangement.

Addendum to Section 3.1.3

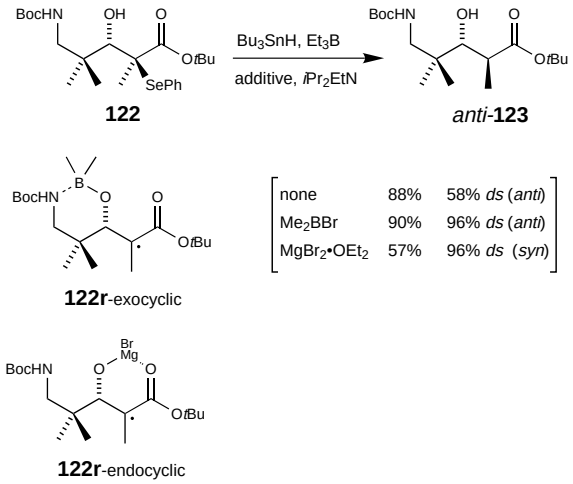
Malacria et al. have reported a radical cyclization–β-elimination tandem process leading to optically active methylenecyclopentane derivatives.[92] The stereochemical outcome of the reaction can be nicely reversed by the use of monocomplexation with the bulky Lewis acid MAD [Eq. (25)]: Cyclization of the alkenyl sulfoxide **120** gives (*S*)-**121** (96% *ee*) in the absence of a Lewis acid while in the



presence of MAD (*R*)-**121** is obtained in a 92% *ee* with a moderate yield. Monocomplexation of the sulfoxides according to **120r** rationalizes this result.

Addendum to Section 3.2.1

An elegant control of the configuration of β-hydroxy-γ-amino ester enolate radicals was reported by Guindon et al.[93] the proper choice of the Lewis acid allows the switch from an endocyclic radical to an exocyclic radical (Scheme 21). For example, reduction of the selenoester **122** in the absence of Lewis acid gives *anti*-**123** with a low diastereoselectivity (58% *ds*), while in the presence of Me_2BBr the *anti* isomer is



Scheme 21. The change from an endocyclic to an exocyclic radical by changing the Lewis acid.

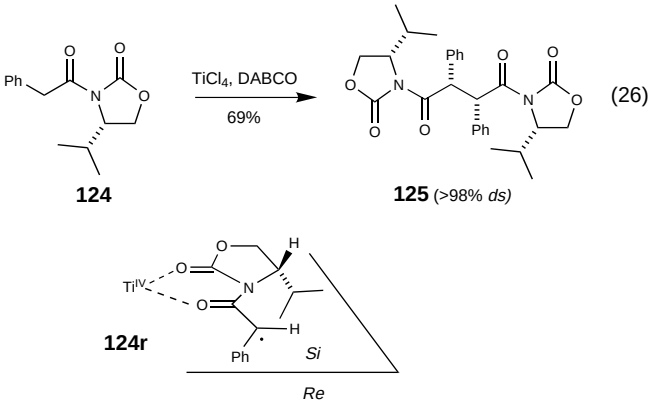
strongly favored (96% *ds*) as a consequence of the formation of an exocyclic radical (**122r**-exocyclic). A reversal of the stereoselectivity is observed with the more oxophilic $MgBr_2 \cdot OEt_2$ (*syn*-**123**, 96% *ds*). This can be explained by the formation of an endocyclic intermediate radical (**122r**-endocyclic).

Addendum to Section 3.2.2

Toru and co-workers have reported full details of this work on cyclic 2-(arylsulfinyl)-2-cycloalkenones[94] [Eq. (10)] as well as related reactions in acyclic systems where hydrogen bonds are playing a key role.[95]

Addendum to Section 3.3

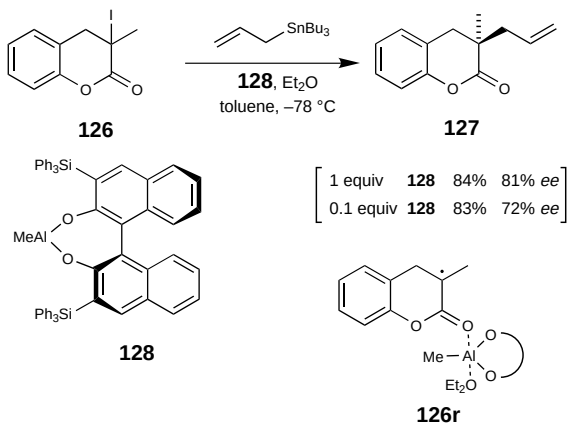
A highly stereoselective oxidative dimerization of in situ generated titanium enolate bearing an oxazolidine chiral auxiliary has been described by Kise et al.[96] Treatment of the *N*-(phenylacetyl)oxazolidinone **124** with $TiCl_4$ gives the dimer (*S,S*)-**125** as a single diastereomer [Eq. (26); DABCO = 1,4-diazabicyclooctane]. The stereochemical outcome is best



rationalized by reaction of the chelate radical **124r** from the less hindered *Si* face. Further investigation of the use of chiral esters have been published,[97, 98] and these results confirm the conclusions from the work of Nishida et al. (Schemes 14 and 16).

Addendum to Section 4

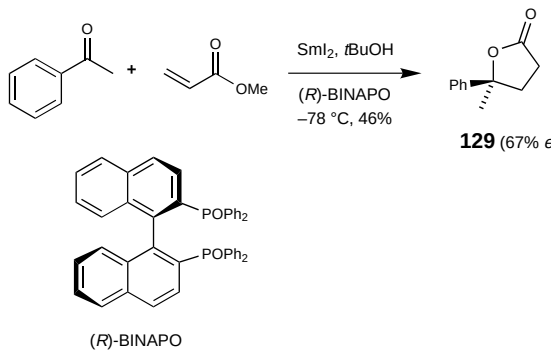
Hoshino et al. have reported an extension of his previous work [Eq. (20)] by performing allylation reactions in the presence of Me_3Al/3,3′-bis(triphenylsilyl)binaphthol **128**.[99] Enantiomeric excesses of up to 91% are obtained. As a typical example, the α-iodolactone **126** is allylated to **127** in 84% yield and 81% *ee* in the presence of one equivalent of **128** (Scheme 22). The degree of asymmetric induction depends dramatically on the presence of one equivalent of Et_2O as additive. Therefore, formation of an unusual five-coordinate aluminum complex was postulated (**126r**), which contrasts with the well-known tendency of aluminum to form four-coordinate complexes. Another interesting aspect of this work is that less than stoichiometric amounts of Lewis acid are able to induce a fair level of induction: **127** is obtained in 72% *ee* when only 0.1 equivalent of the Lewis acid **128** is used.



Scheme 22. Et_2O-dependent allylation of the iodolactones.

Porter et al. have further developed the reaction depicted in Scheme 17. They observed that allylsilanes give higher enantioselectivities than allylstannanes for the allylation of oxazolidinone derivatives.[100] The Lewis acid character of the stannyl bromide byproduct is detrimental to the transformation. This undesired effect can be efficiently suppressed by using the iodide as the starting material. Sibi et al. have investigated the use of pyrazole templates instead of oxazolidinone for β-enantioselectivity.[101] However, the observed enantioselectivities are inferior (and inverse) to those observed with oxazolidinone (Scheme 20).

The first example of an enantioselective samarium diiodide mediated ketyl radical addition to an olefin has been reported by Mikami and Yamakoa.[102] Addition of acetophenone to methyl acrylate furnishes the lactone **129** in 46% yield and 67% *ee* [Eq. (27)]. Two equivalents of the chiral ligand (*R*)-BINAPO are necessary to reach this enantioselectivity.



(27)

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