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Enantioselective Free Radical Reactions

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Organic free radicals have historically been regarded as intermediates poorly suited for selective reactions because of their high reactivity. In the past 25 years it has become apparent that radicals can react in a chemo- and regioselective manner. Furthermore, in the past decade, stereoselective transformations of free radicals have been achieved.[1] During this time, a variety of useful synthetic strategies have been developed for radical-based C−C bond-forming reactions, and an understanding of the determining parameters for diastereoselective transformations has emerged.[1]

On the other hand, enantioselective transformations of organic radicals remain uncommon. As recently as 1995, the prevailing view, stated in a review of the field,[1a] was that "*Acyclic diastereocontrol has emerged only recently, but progress has been rapid. Enantioselective reactions of radicals are rare at present, but we believe that their development is now inevitable.*" Since this statement was published, inevitability has become reality, and there are now several examples in the literature of enantioselective radical transformations.

Early enantioselective radical transformations relied on precedents from successful strategies utilized for other reaction types, as was the case in the development of diastereoselective radical reactions. Thus, chiral auxiliaries used in diastereoselective radical transformations were developed based upon precedents elaborated for enolate alkylations,[2] and the enantioselective variants have benefited from strategies used in catalytic Diels−Alder[3] and other processes. In this Account, we present developments in enantioselective radical transformations that have occurred in the past three years in the context of previous efforts to control configuration in diastereoselective radical reactions. We focus principally on advances made in our own laboratories but mention also important developments from other research groups.

Stereoselective Radical Reactions

The introduction of a new stereogenic center by means of free radical chemistry may occur in one of two fundamental ways which are illustrated in Figure 1. A prochiral radical may be trapped selectively (route I), or a radical may add selectively to a prochiral radical trap (route II).[4] Of these, reactions are diastereoselective if either the radical or the radical trap contains a chiral center (Figure 1b,c). Alternatively, the reactions are enantioselective if the substrate is achiral.

Diastereoselective Radical Reactions

A specific diastereoselective example of the general transformation described by route I is shown in Figure 1b. The radical **1** undergoes selective reactions with radical traps such as stannanes or allylstannanes. Selectivity results from these reactions since the stereogenic center adjacent to the radical is fixed in competing transition states by the effects of $A^{1,3}$ strain; see structure **2**.

Figure 1c shows a specific example of the diastereotopic addition of a radical on one of the stereoheterotopic faces of a radical trap, route II. Thus, addition of cyclohexyl radical to the trisubstituted alkene **3** gives product with excellent control of product configuration, the product configuration being consistent with a transition state model as shown in **4**.[5] Radical−radical coupling and disproportionation reactions can also be stereoselective,[6] and recently, trapping of prostereogenic radicals with chiral nitroxides has been shown to occur with modest stereoselectivity.[7]

Complex-Controlled Diastereoselective Transformations

The early work of Guindon and collaborators demonstrated the potential for Lewis acid control of acyclic stereochemistry in free radical transformations.[8,9] The configuration of products derived from tin hydride reduction of **5** was shown dependent on the presence or absence of MgI_2 in the reaction medium. Thus, in the absence of MgI_2, the product distribution **6:7** was >97:3, while in the presence of the Lewis acid, the ratio inverts to 3:97. Allylic strain controls the conformation of transition state **8** in reactions not involving MgI_2. In contrast, chelation of the bidentate substrate to the Lewis acid reorganizes the reactive radical conformation (complexed

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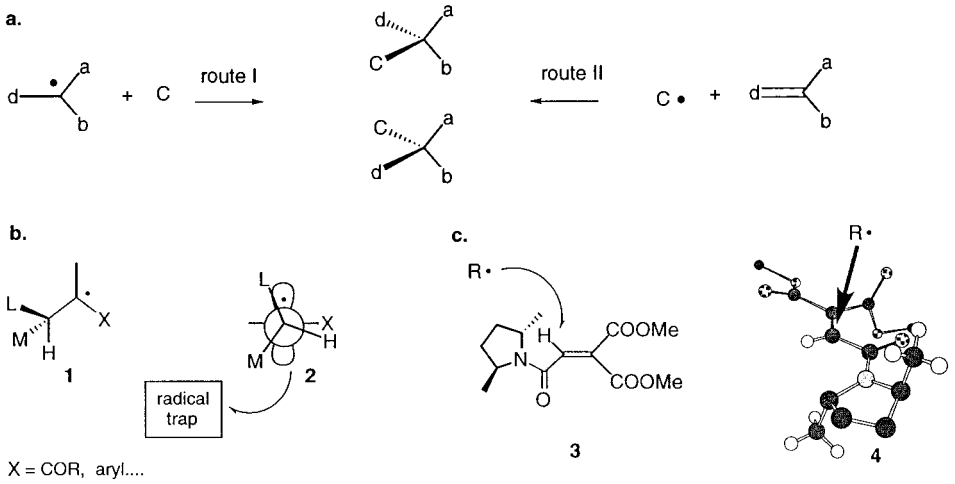
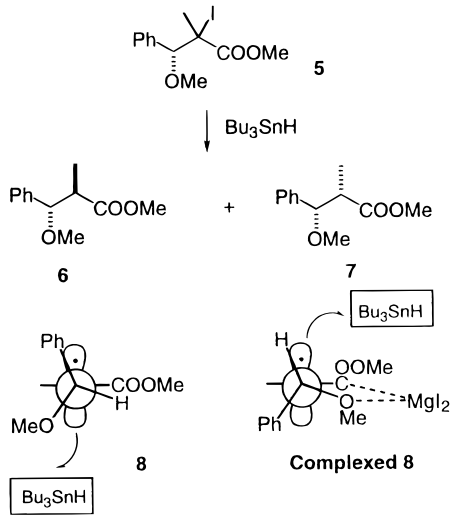
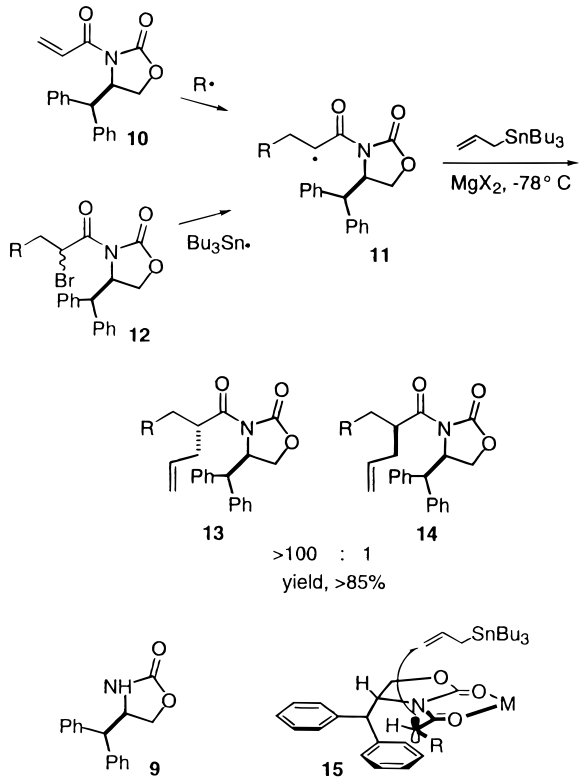


FIGURE 1.

8). Closely related examples involving Lewis acid complex-controlled radical reactions have been reported.[10]



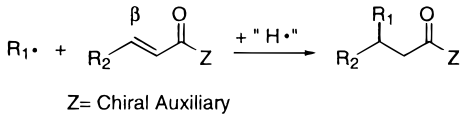
Chiral oxazolidinone auxiliary groups also control reactions of α-acyl radicals. The new diphenylalanine-derived oxazolidinone **9** is particularly effective. The auxiliary can be used in a propagation sequence that involves radical addition to the acrylimide **10** followed by trapping of the adduct radical (**11**) with allyl stannane.[11] An alternate sequence that involves the same intermediate **11** starts from the bromide[12] precursor **12**. In the absence of Lewis acid the reaction is nonselective, giving a product ratio **13:14** of only 1:1.8 (reaction of **12** with allyltributylstannane in dichloromethane initiated by triethylborane at −78 °C). With excess MgI_2 or $MgBr_2$, the product ratio is in excess of 100:1 under otherwise similar reaction conditions. Even at 25 °C, reactions of **12** carried out in the presence of 2 equiv of $MgBr_2$ gave products in a ratio of 30:1. Lanthanide Lewis acids may also be used in the transformation. Exceptionally high diastereoselectivities are obtained from reactions of **12** at −78 °C promoted by Et_3B/O_2 in the presence of an equivalent of Sc, Yb, Y, La, or Sm triflate in reactions usually carried out in ether. The Lewis acids not only affect product distribution from **10** or **12** but also promote the otherwise sluggish low-temperature reaction with **12**.



A model **15** accounts for the observed selectivity. Several factors contribute to the high selectivity observed in these oxazolidinone-mediated alkylations: (1) both carbonyl oxygens are coordinated to the Lewis acid, (2) minimization of $A^{1,3}$ strain confines the radical intermediate **11** to an *s-cis* conformation, and (3) the oxazolidinone 4-substituent provides shielding of the diastereotopic faces. The transfer of an allyl group to a glycinate free radical bearing a chiral oxazolidinone auxiliary on the glycyl nitrogen has also been shown to occur with significant diastereoselectivity (93:7) when $ZnCl_2$ is present.[13]

Stereoselective conjugate radical addition to α,β-unsaturated systems has been a challenge (Scheme 1).[14]

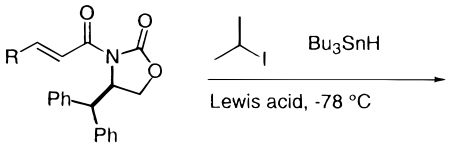
Scheme 1



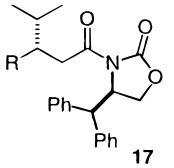
Z= Chiral Auxiliary

The diphenyl oxazolidinone **9** in combination with Lewis acids provides a general solution for diastereoselective reactions. The Lewis acid not only promotes the addition reaction but also controls the rotamer population of the oxazolidinone imide, thus leading to both high yields and high diastereoselectivity.

Steric factors slow the rate of intermolecular addition of radicals to nonterminal alkenes such as **16**. In the absence of a Lewis acid additive, radical additions to the crotonate **16a** or the cinnamate **16b** are inefficient at −78 °C because radical reduction is faster than radical addition. Additionally, the reaction is nonselective in the absence of Lewis acid.[15] When stoichiometric amounts of Lewis acids are added to the reaction, however, both the yield and the diastereoselectivity increase significantly. Thus, $MgBr_2$ gives a **17a**:**18a** ratio of 6:1 while $Yb(OTf)_3$ gives a product yield of 90% in a ratio of 25:1. Use of catalytic $Yb(OTf)_3$ (10 mol %) resulted in only a slight reduction in selectivity (90%, 16:1). Addition to the cinnamate **16b** promoted by $Yb(OTf)_3$ gives a product ratio of **17b**:**18b** of 45:1. This record β diastereoselectivity in



16 a, R=Me
b, R=Ph
c, R=COOEt



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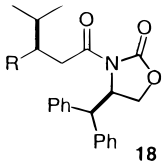
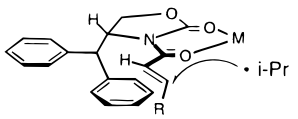


18

		yield %	17 : 18
a, R=Me	$Yb(OTf)_3$	>90	25 : 1
b, R=Ph	$Yb(OTf)_3$	>90	45 : 1
c, R=COOEt	$Er(OTf)_3$	>90	53 : 1



19

radical addition is comparable to or better than that obtained under ionic conditions.[16] A model **19** that involves an *s-cis* substrate−Lewis acid complex predicts the correct configuration of the product and again accounts for the observed high selectivity. High regio- and diastereoselectivities are also observed in the conjugate radical addition to **16c** using two-point binding Lewis acids such as $Er(OTf)_3$ (100:1 regioselectivity and 53:1 diastereoselectivity of **17c:18c**).[17] The preferential complexation of the oxazolidinone functionality instead of the ester by the $Sm(OTf)_3$ further demonstrates the subtle control features available by a proper choice of the Lewis acid.

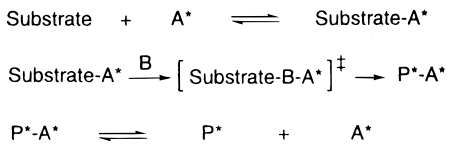
The Lewis acid-mediated diastereoselective radical reactions provide insights into the design of analogous enantioselective reactions. First, a variety of Lewis acids are compatible with radical reaction conditions. Second, control of the reactive conformation of substrates is possible in the presence of chelating Lewis acids. Third, Lewis acid-complexed substrates are much more reactive toward radical conjugate addition than are free substrates. Fourth, the use of catalytic amounts of Lewis acid suggests that the Lewis acid binds to the reactant in preference to the product, and catalytic turnover shows that complex exchange is rapid.

Enantioselective Radical Reactions: General Considerations

For enantioselective processes, substrates are achiral and there is a requirement for reagents that are inherently chiral or that become chiral as a result of chelation or solvation. In enantioselective radical transformations, selection will require π facial discrimination, in which the enantiotopic radical or radical trap faces are made diastereotopic by virtue of a chiral reagent or a chiral complexing agent. There are some inherent advantages to enantioselective transformations including the potential for catalyzed processes.

Enantioselection in free radical reactions can be distinguished as being *complex-controlled* or *reagent-controlled*, and examples of both these types have now been reported. *Complex-controlled* transformations involve an achiral substrate (either a radical or radical trap) being coordinated to a chiral reagent before reaction; see Scheme 2. In this complex, enantiotopic faces of a radical

Scheme 2



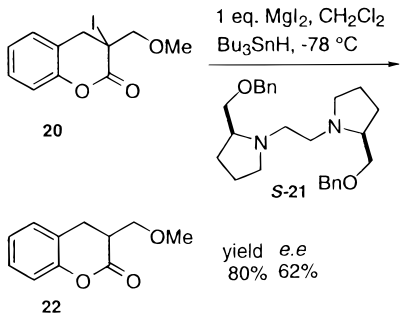
or radical trap become diastereotopic and selectivity is achieved when one of the diastereomeric transition states is favored. When the reagent is a chiral Lewis acid, in theory, such reactions can be catalytic since the source of chirality in the transformation, the Lewis acid, can be reused.

Complexed Prostereogenic Radicals Reacting with Radical Trap: Reaction of α-Acyl Radicals

Consideration of the problem of enantioselective acyclic free radical stereocontrol leads to the following general conclusions: (1) the complexing chiral group intended to

control the configuration of the new stereogenic center formed in radical addition must be fixed in the complex relative to that center, (2) the resident chiral group must differentially shield the radical or alkene faces made diastereotopic by complex formation, (3) the reactivity of the substrate−chiral Lewis acid complex must exceed that of the free substrate so that nonselective reactions of the uncomplexed substrate do not interfere, and (4) for use of catalytic chiral Lewis acids, preferential binding of the Lewis acid to the substrate is essential for turnover.

One of the first reports of an enantioselective transformation involving free radicals came from Hoshino and collaborators in 1995.[18] An enantioselective tin hydride reduction of the α-iodolactone **20** gave **22** in 62% enantiomeric excess (ee) in the presence of MgI_2 as Lewis acid and the C_2 symmetric chiral diamine **21**. The enantioselectivity for **22** was dependent on the concentration of the reactants with low ee at high dilution. This suggests nonselective reaction occurs from uncomplexed substrate (which produces racemic product) at low concentrations. At higher concentrations where complex equilibrium is more favorable, selective reaction of Lewis acid complexed species is predominant. This is a consequence of not meeting criterion number three as listed above. It should be noted that the absolute configuration of the major enantiomer of **22** was not established. It was therefore not possible to propose with confidence a transition state model for the transformation. It seems likely, however, that the bidentate radical and multidentate proline derivative **21** are both complexed to the Lewis acid during the stereoselective H-atom transfer step in the reaction. An analogous reduction of a radical substituted α to a lactone proceeded with modest enantioselectivity (28%) when promoted by a binaphthol−aluminum chloride complex.[19]



With few clear precedents, the lessons of enantioselective concerted reactions as well as those of the diastereoselective complex-controlled free radical transformations discussed earlier served to guide our ventures into enantioselective radical carbon−carbon bond construction. An achiral oxazolidinone template was considered as the first choice on the basis of the success of chiral imide auxiliary groups in Lewis acid promoted diastereoselective free radical transformations.[12,13,16] Additionally, the demonstrated efficacy of chiral bisoxazolines in Lewis acid promoted Diels−Alder reactions[3] suggested the use of these ligands in conjunction with oxazolidinone-derived radicals or radical traps. Transition state models for Diels−Alder reactions support the notion that binding of the oxazolidinone and the chiral Lewis acid is bidenate.

Rotamer control issues play a crucial role in the successful execution of complex-controlled enantioselective transformations. We illustrate this concept using an oxazolidinone template for both prostereogenic radicals and radical traps, Figure 2. For both prostereogenic radicals **23** and radical traps **25**, the orientation about the N−C(O) bond and the C(O)−C bond must be controlled. The stereogenic center present in a chiral Lewis acid must be fixed relative to the reacting carbon center. Two point binding Lewis acids control the conformation about the N−C(O) bond by coordinating both carbonyls, and the conformation about C(O)−C is fixed as *s-cis* in both **23** and **25** by $A^{1,3}$ strain. A one point binding model for oxazolidinones or analogous Lewis bases, **24**, leaves the orientation of the chiral Lewis acid and the reactive center ambiguous even if the orientation of the carbonyl reactive center bond is fixed.

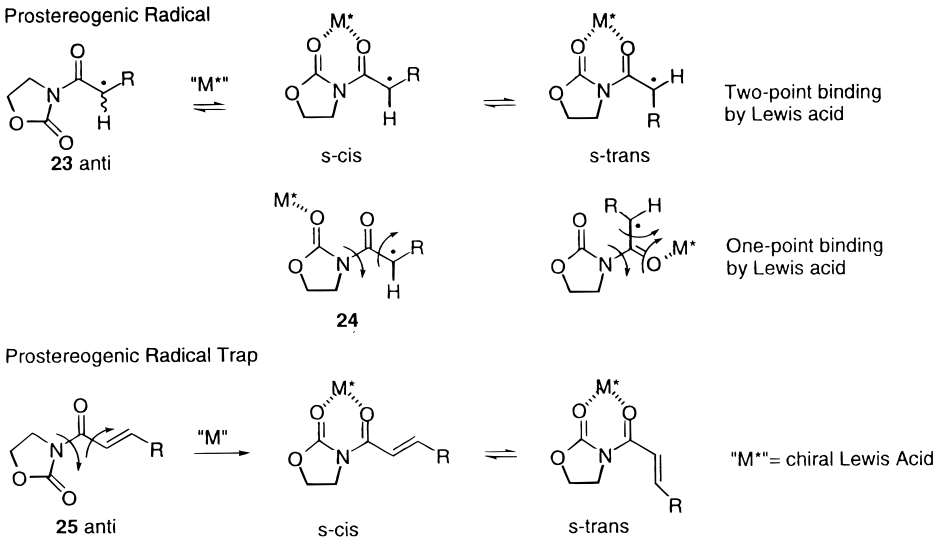
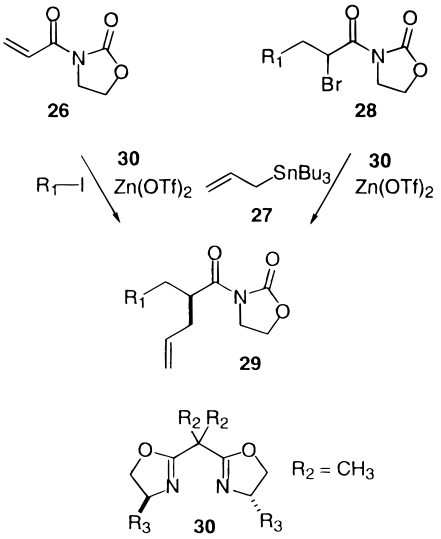


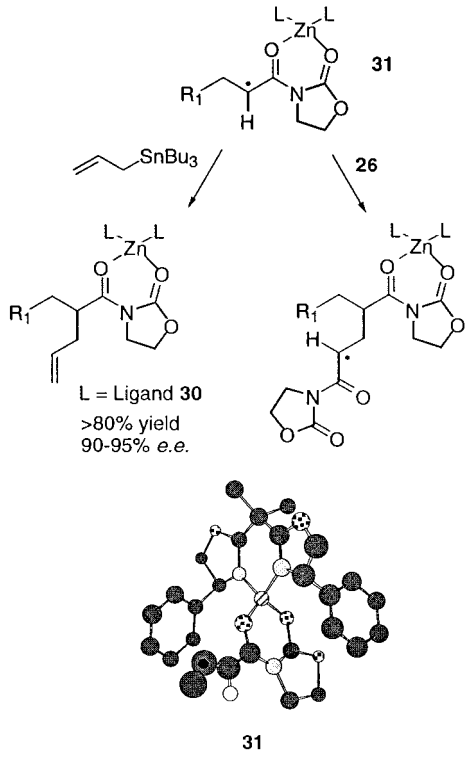
FIGURE 2. Rotamer control for enantioselective radical reactions of oxazolidinone imides.

Our first carbon−carbon bond forming free radical reaction that proceeded with high enantioselectivity utilized a strategy involving the reaction of radicals substituted α to an oxazolidinone.[20] Thus, the addition of alkyl radicals to acrylimide **26** in the presence of stoichiometric amounts of $Zn(OTf)_2$ and bisoxazoline ligand **30** followed by trapping of the intermediate radical with **27** proceeds at −78 °C to give the product **29**. The reaction gives **29**



with ee's as high as 90% when carried out with the **30** having R_2 = Me and R_3 = Ph. Selectivities for the allyl transfer depend on the size of the R_1 group, with a correlation of product ee and the Taft steric parameter for the group attached to the radical center, R_1CH_2-.[21] The reaction carried out under Lewis acid conditions provides little telomeric product that involves the incorporation of two or more units of **26** in the product structure. The transformation (**26** → **29**) does not proceed at low temperature without the added Lewis acid and a free radical initiator (Et_3B/O_2). At 0 °C or above, the reaction does proceed without added Lewis acid but gives, under otherwise identical conditions and concentrations, substantial amounts of telomeric n = 2, 3, and 4 products. These data suggest that the Lewis acid complexed to the intermediate radical (structure **31** and the tetrahedral zinc model) promotes the allyl transfer reaction compared to the chain-growth addition of this complexed radical to **26**.[22]

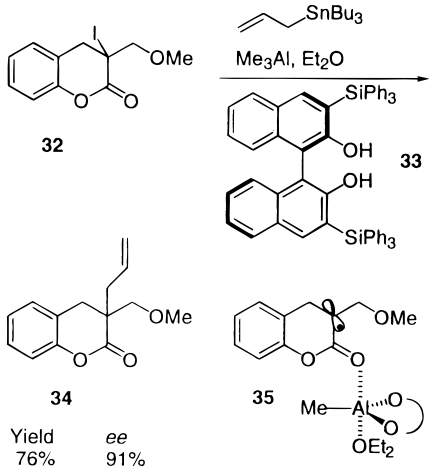
Radical **31** can also be accessed from the bromide precursor **28** in a chain propagation sequence that involves halogen atom transfer to the tributylstannyl radical.[23] Reactions proceeding from the bromide give product with lower enantioselectivity than is observed for reactions of **26** and alkyl iodides, R_1-I. The culprit in the reaction proceeding from bromide is likely the tin bromide, a byproduct of the reaction. This Lewis acid competes for substrate and chiral ligand with zinc and partially neutralizes the effect of the chiral Lewis acid on the reaction.[24] Consistent with this view, addition of tin bromide to reactions of alkyl iodides decreases the selectivity of the transformation. Added tin iodide does not compromise the selectivity of the transformation.



The use of simple allylsilanes in transfer reactions is only possible with radicals that are very electron deficient.[25,26] Lewis acid is apparently critical to the use of allylsilane transfer agents since only the complexed radical **31** or the complexed starting bromide **28** will propagate with allylsilanes. The allylsilane chain-transfer sequence is different from the "standard" allylstannane reaction.[23]

The success of the oxazolidinone template in providing high enantioselectivity can in part be attributed to the availability of two donor sites for chelation and a relatively rigid complex with the chiral Lewis acid. The design of chiral Lewis acids which are capable of activating single point donors such as esters or carbonyl groups is however a more difficult task. Recent work from Hoshino's laboratory illustrates the use of a chiral aluminum Lewis acid in the formation of quaternary carbons using free radical intermediates.[27] The allylation of **32** with allyltributyl stannane using a stoichiometric amount of a chiral Lewis acid derived from **33** and trimethylaluminum gave **34** in low ee (27%). The addition of a stoichiometric amount of an achiral additive, diethyl ether, led to a dramatic improvement in ee (91%). Even catalytic amounts of the chiral Lewis acid with ether as an additive gave high enantioselectivity. Control experiments showed that the Lewis acid was bound to the ester carbonyl only. A tentative structure (**35**) for the reactive complex has been proposed to account for the unusual effect of the achiral additives, but it seems fair to say that the nature of the stereoselectivity is not well understood.

Fhal and Renaud have also investigated chiral aluminum Lewis acids in enantioselective radical allyl transfer reactions.[28] An oxazolidinone template in conjunction with a variety of ligands gave high chemical efficiency in the allylation but only modest enantioselectivity. The



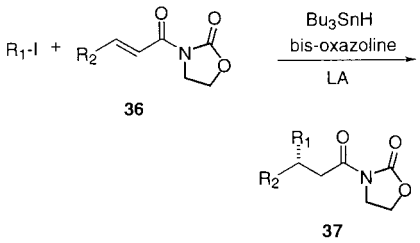
authors propose a model in which only one of the acyloxazolidinone carbonyls is bound to the aluminum.

Radical Addition to Complexed Prostereogenic Radical Traps: Enantioselective Conjugate Additions

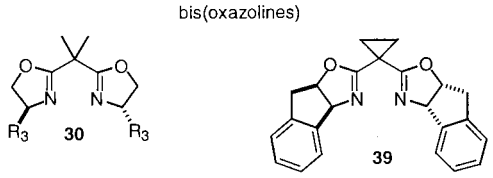
The reactions described in the previous section require, for the most part, stoichiometric amounts of chiral Lewis acid in order to obtain high enantioselectivity. This requirement stems from the lack of differential reactivity between complexed and free α-halo carbonyl compounds such that nonselective reaction of free substrate competes effectively. One of the goals of enantioselective chemistry is to use substoichiometric or catalytic amounts of chiral agent and still maintain high product enantioselectivity. We anticipated that enantioselective conjugate additions might offer the opportunity for catalytic use of chiral agents, and indeed this ultimately proved to be the case.

In our initial effort, several combinations of Lewis acids and ligands of the general structure **30** were screened for enantioselective conjugate radical additions to the crotonate and cinnamate **36** (R_2 = Me or Ph). Magnesium and zinc Lewis acids gave the best results.[29] Excellent chemical yields and high enantioselectivities were obtained for the crotonate and cinnamate using stoichiometric chiral Lewis acid. In general, magnesium halide−aliphatic-substituted bisoxazoline (**30**, R_3 = alkyl) combinations or zinc triflate−phenyl-substituted bisoxazoline (**30**, R_3 = Ph) combination gave high selectivity. The potential for catalytic reactions was then examined using the best ligand−Lewis acid combinations. For example, isopropyl radical addition to cinnamate **36** (R_2 = Ph) using the catalyst MgI_2/**30** (R_3 = ^{i}Bu) proceeds in 82%, 80%, and 70% ee using 100, 50, and 20 mol % chiral Lewis acid, respectively.

An essential feature of these experiments was the dependence of the product configuration on the nature of the bisoxazoline R_3 group. When R_3 was alkyl, enantiomer **38** was preferred, while when R_3 was aryl, enantiomer **37** was preferred. For example, addition of isopropyl radical to the cinnamate **36** using **30** (R_3 = Ph) and MgI_2 gave **37** in 47% ee, whereas MgI_2 and **30** (R_3 = ^{i}Bu) gave **38** as the major product (82% ee). These results suggested

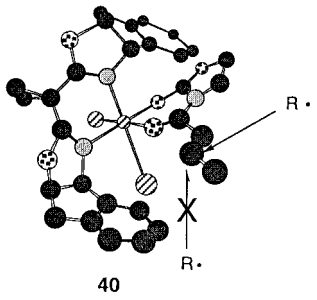


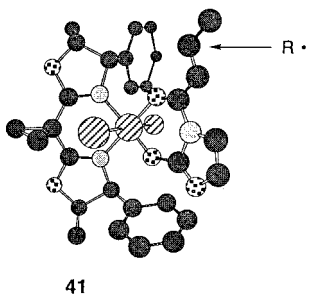
			bis-oxazoline (eq.)	LA (eq.)	yield %	**37 : 38**
R_1=t-Bu	**36**	R_2=Me	**30**, R_3=Ph (1.0)	$Zn(OTf)_2$ (1.0)	65	10 : 1
R_1=t-Bu		R_2= Me	**30**, R_3=t-Bu (1.0)	$MgBr_2$ (1.0)	90	1: 10
R_1=t-Bu		R_2=Me	**39** (1.0)	MgI_2 (1.0)	85	1: 99
R_1= t-Bu		R_2=Me	**39** (0.2)	MgI_2 (0.2)	75	1: 10
R_1=i-Pr		R_2=Ph	**30**, R_3=Ph (1.0)	MgI_2 (1.0)	88	3: 1
R_1=i-Pr		R_2=Ph	**30**, R_3=i-Bu (1.0)	MgI_2 (1.0)	88	1: 10
R_1= i-Pr		R_2=Ph	**39** (1.0)	MgI_2 (1.0)	85	1: 98
R_1= i-Pr		R_2=Ph	**39** (0.1)	MgI_2 (0.1)	75	1: 10



that the substrate−Lewis acid−ligand superstructure varied depending on the bisoxazoline 4-substituent.

The above observations allowed us to carry out a careful ligand optimization study which resulted in a practical solution[30] to the preparation of **38** in high ee using substoichiometric amounts of chiral Lewis acid. The indanyl ligand **39** developed by Davies et al. at Merck[31] in conjunction with MgI_2 has provided for the highest selectivity (97% ee at −78 °C) reported so far for enantioselective radical transformations. Reactions at more convenient temperatures (0 or 25 °C) resulted in only a small decrease in the levels of enantioselectivity (95% and 93% ee). A rigid octahedral superstructure **40** formed

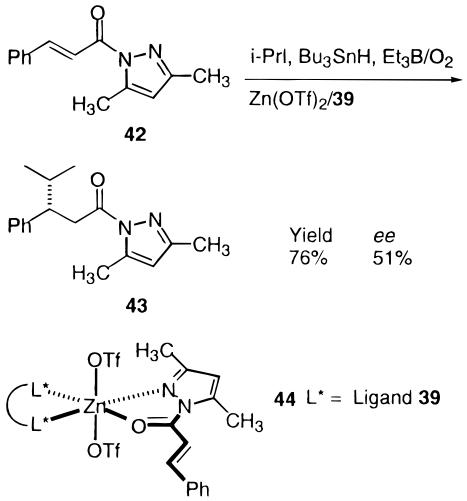




from MgI_2 + **39** + **36** accounts for the product configuration and high enantioselectivity. A similar octahedral complex explains the selectivity with bisoxazolines **30**

when R_3 = alkyl. In contrast with bisoxazolines **30** when R_3 = aryl, an octahedral complex, **41**, in which the carbon−phenyl bond is flexible, is consistent with the reversal of enantioselectivity.

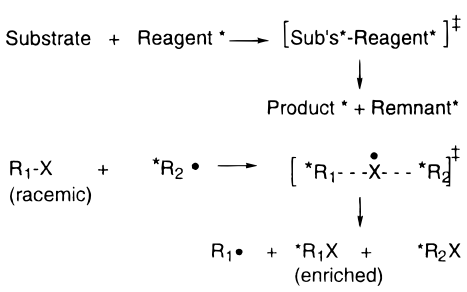
The selection of product based on changes in either the Lewis acid or the ligand led us to examine different achiral templates, the third critical component to a successful enantioselective radical transformation.[32] *N*-Acylpyrazoles, templates capable of forming five-membered chelates with a two point binding Lewis acid, have been evaluated in conjugate radical additions. Addition of isopropyl radical to **42** using a chiral Lewis acid prepared form $Zn(OTf)_2$ and **39** gave **43** with moderate enantioselectivity (51% ee). In comparison isopropyl radical addition to **36**, an oxazolidinone-derived substrate, using $Zn(OTf)_2$ and **39** gave product of opposite configuration (84% yield, 51% ee). Model **44** or a square planar model accounts for the product configuration. These experiments illustrate that achiral templates are thus convenient handles for the formation of products of opposite configuration.



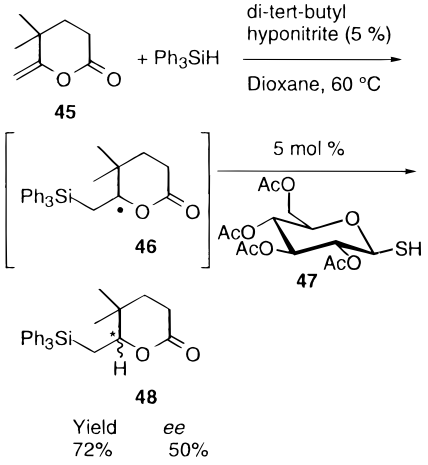
Reagent-Controlled Enantioselective Atom Transfer Reactions

Enantioselection can also be achieved if a prostereogenic radical or radical trap undergoes a reaction with a chiral agent such that transition states are diastereomeric with different energies (Scheme 3). Enantioselection is *reagent-controlled* in this case, and there are many examples that provide precedents for such transformations in nonradical systems, i.e., catalytic epoxidation.[33] In this strategy, outlined in Scheme 3, the radical's (or radical trap's) enantiotopic faces become diastereotopic by virtue of their association with the chiral reagent in the transition state. In this strategy, the process can be made catalytic if the "*remnant*" can be recycled to form the "*reagent**". Another type of reagent-controlled transformation is kinetic resolution in which a chiral radical reacts selectively with one enantiomer of a racemic substrate.

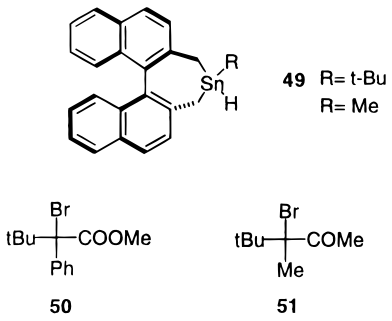
Scheme 3



One of the first examples of the use of chiral tin hydrides in enantioselective reduction of racemic haloalkanes proceeding with low selectivity was reported by Schumann and co-workers.[34] Roberts[35] has studied H-atom transfers and found good levels of kinetic resolution in the H-atom abstraction by amine−boryl radicals. Roberts has also examined several chiral thiol catalysts in the radical-chain hydrosilylation of prochiral alkenes.[36] For example, the addition of triphenylsilane to **45** proceeds in good chemical yield and gave **48** with moderate enantioselectivity (50% ee). The reaction used only 5 mol % sugar-derived thiol **47** as a catalyst: the chiral thiol donates hydrogen atom to prochiral radical **46** and it is regenerated by hydrogen abstraction from triphenylsilane.



Chiral binaphthyl variants of the widely used tin hydrides have been prepared by both Curran[37] and Metzger,[38] and the reduction of α-bromoesters and ketones with these reducing agents has been studied. Thus, **49**, R = ^{t}Bu reduces the bromoester **50** at −78 °C to give product ester in 50% ee, while the tin hydride with R = Me reduces **51** under similar conditions with enantiomeric



excess in the range of 30−35%. These reactions are of interest since the tin hydride reduction can be performed

catalytically; the tin hydride reagent can be regenerated under conditions of reduction by the use of sodium cyanoborohydride. The byproduct of the reaction, tin bromide, can therefore be recycled into the reducing agent and chirality can be reutilized.

Control of stereochemical configuration in free radical transformations is now well established. Developments in diastereoselective radical reactions began in the 1980s and have culminated in guidelines for the use of auxiliaries and the understanding of substrate-controlled processes. Enantioselective reactions of radicals are not common at present, but it is clear that factors that are important in comparable processes (such as enantioselective Diels–Alder cycloadditions) provide a blueprint for progress in free radical reactions as well. While advances in the past two years have been rapid, the "guidelines for enantioselective free radical transformations" is clearly a work in progress.

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