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Lewis acids in diastereoselective processes involving acyclic radicals

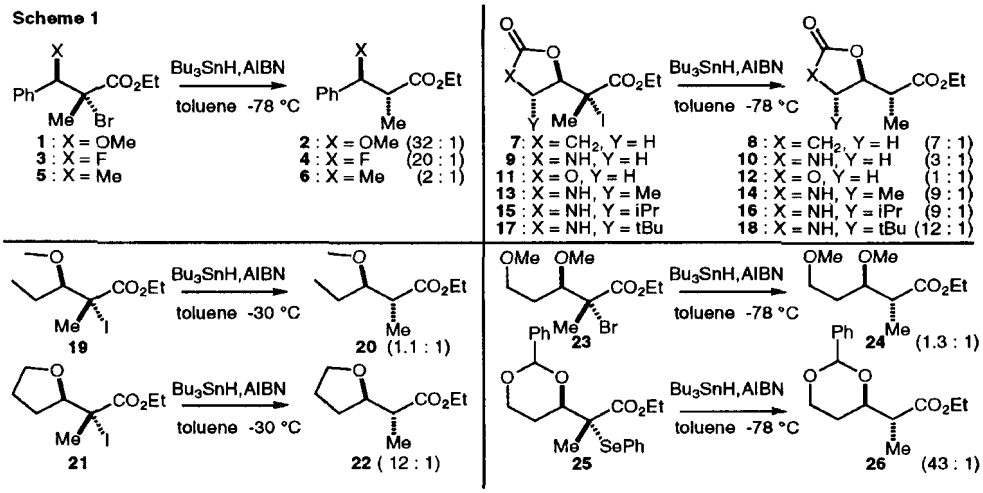
Yvan Guindon,*[a,c] Brigitte Guérin,[c] Jean Rancourt,[b] Catherine Chabot,[b] Nicole Mackintosh,[b] and W.W. Ogilvie[b]

[a]*Dept. de Chimie, Université de Montréal, Montréal, Québec, Canada H3C 3J7*
[b]*Bio-Méga/Boehringer Ingelheim Research, Inc., 2100 Cunard Street, Laval, Québec, Canada H7S 2G5*
[c]*Institut de Recherches Cliniques de Montréal (IRCM), Laboratoire de Chimie Bio-organique, 110 Pine Avenue West, Montréal, Québec, Canada H2W 1R7*

Abstract. The radical reductions and allylations of a series of α-halo-β-alkoxy esters under bidentate chelation-controlled conditions are reported and compared with the analogous reactions under non-chelating conditions. The addition of Lewis acids is shown to give excellent selectivity for the *syn* products in the case of reduction, and the *anti* products in the case of allylation. In some cases, ratios greater than 100:1 are obtained. The reactions require initiation with Et_3B and can be inhibited by *m*- and *p*-dinitrobenzene, which imply a radical-based mechanism. Iodides, bromides and phenyl selenides are all suitable substrates. Investigations also provide a rationale for the large excess of $MgBr_2 \cdot OEt_2$ which is apparently required in these reactions. Competition experiments provide a more detailed explanation of substrate reactivity.

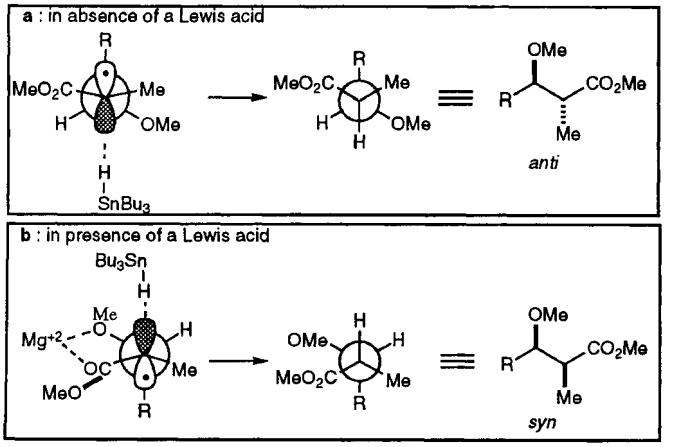
Traditionally radicals derived from acyclic precursors have seldom been considered as intermediates for the generation of asymmetric centers. Recently however, it has been discovered that radicals can indeed react with high levels of diastereoselectivity (1). This has been achieved mainly through the use of chiral auxiliaries (2) or by the influence of a stereogenic center adjacent to a carbonyl (1,2-asymmetric induction) (3, 4, 5). The scope of these reactions has also been expanded by the use of Lewis acids (6, 7), solvent complexation (8) and intramolecular hydrogen bonding (9) to enhance and even reverse the facial bias. In this paper, we describe results we have obtained in chelation-controlled reductions, allylations and atom transfer reactions of α-halo-β-alkoxy esters, and present evidence for radical-based processes. Preliminary experiments designed to elucidate further mechanistic details will also be discussed.

Scheme 1



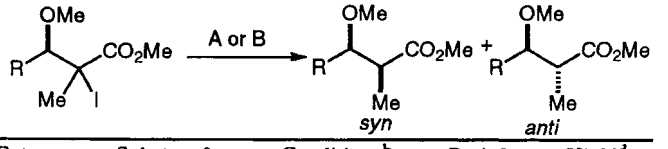
1,2-Asymmetric induction is exemplified by the reduction of α-halo-β-alkoxy esters such as **1** (Scheme 1, note that only major products are shown) which produces the *anti* isomer with excellent selectivity (32:1). Various models have been proposed and refined to account for the selectivities observed (1, 3,

Scheme 2



5). The experimental results which have so far been obtained are most consistent with the transition state model depicted in Scheme 2a. In this model, the radical reacts in a conformation in which the bottom face of the molecule is exposed to reagent attack. Stabilization of this conformer involves a balance of both steric and electronic factors. Potentially destabilizing allylic-1,3 interactions are minimized in this model by placing a hydrogen atom next to the ester group. Secondary steric interactions should also be reduced by orienting the C-R bond orthogonal to the radical plane. Experiments show, however, that one cannot reverse the facial bias simply by increasing the steric bulk of the alkoxy group (relative to R) (5e) and so other factors must be considered. In addition to steric effects, there are two possible electronic factors influencing this transition state. By opposing the ester and alkoxy groups, intramolecular electrostatic repulsions are minimized. This is most strongly suggested by the observation that fluoride **3** is reduced with excellent stereoselectivity (20:1), an observation which cannot be rationalized by steric factors alone (5a). The second electronic effect involves stabilization of the radical by hyperconjugation with an electron donating substituent (R) through the alignment of the $\sigma_{C\text{-}R}$ bond with the radical SOMO (Scheme 2a). This is illustrated by the reduction of rigidified substrates such as **7** (Scheme 1), which makes it possible to differentiate between steric and electronic effects (5f). By systematically changing X from CH_2 to NH to O, the electron-donating ability of the R substituent was reduced, an effect which was reflected by a decrease in the reduction ratio. In the case of carbamate **9**, an increase in the electron-donating ability of the R group by the addition of alkyl substituents (Y=H, Me, *i*Pr, *t*Bu; compounds **9**, **13**, **15**, **17**) results in restored selectivity. The fact that the size of the pendant group does not affect the reduction ratio is a good indication that electronic factors and not steric effects are being manipulated.

Table 1. Reduction of α-iodo esters under chelation-controlled and non-chelation-controlled conditions.



Entry	Substrate[a]	Conditions[b]	Ratio[c] *syn* : *anti*	Yield[d]
1	**27** : R =Ph (anti)	A	1 : >25	86
2	**27** : R =Ph (anti)	B	>25 : 1	78
3	**28** : R =Ph (syn)	A	1 : >25	85
4	**28** : R =Ph (syn)	B	1 : 4	61[e]
5	**29** : R =iPr (anti)	A	1 : 24	87
6	**29** : R =iPr (syn)	B	>25 : 1	79

[a]stereochemical designation refers to the relative configuration between OMe and I in the substrate

[b]A: 2 equiv of $HSnBu_3$, AIBN, toluene, -78. B: 2 equiv of $HSnBu_3$, 2 equiv of MgI_2, CH_2Cl_2, -50 °C.

[c]Ratios determined by ^1H NMR

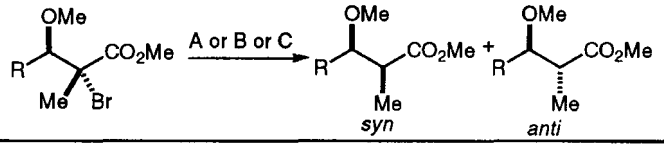
[d]Isolated yield of major product

[e]Combined isolated yield

Systems in which the radical is exocyclic to a ring in general react with higher selectivity than their totally acyclic counterparts (5). For example, tetrahydrofuranyl substrate **21** reduces to give a 12:1 mixture of *anti* and *syn* products, while the respective acyclic substrate **19** reduces with virtually no selectivity. To account for this, several models have been proposed which take into account the transition state leading to the minor isomer (5e). Among these is a model in which the same conformer leads to both the *syn* and *anti* products. That is, the two products arise from approach of the reagent to both faces of the radical. The final ratio obtained would then be a consequence of the blocking ability of the R substituent. This suggests that facial discrimination may be controlled by changes in the dihedral angle between the C-R bond and the radical SOMO. This exocyclic effect has recently been exploited to increase the reduction ratio of acyclic polyols (10). By linking two hydroxyl groups together with a removable protecting group such as an acetal, greatly improved selectivities can be realized. This is illustrated by comparing the reduction ratio of acetal **25** with its acyclic counterpart **23**. The reduction of **25** is much more selective, a consequence of this exocyclic effect.

Consideration of the model depicted in Scheme 2a suggested to us the possibility that the facial selectivity of the reaction could be reversed by bringing the alkoxy group and ester together by Lewis acid complexation (Scheme 2b; 7a). As shown in Table 1, the Bu_3SnH reduction of iodide **27** proceeded with high selectivity in favor of the *anti* product (entry 1). The same substrate in the presence of MgI_2 reacted to give the *syn* product also in high ratio (entry 2). Other α-iodo esters displayed a similar reversal in facial selectivity in the presence of MgI_2 (entries 5, 6). In these reactions, a full equivalent of Lewis acid was not needed to achieve maximal selectivity (7a). Furthermore, in the presence of MgI_2, radical initiation was not required, nor could the reaction be effectively terminated by radical inhibitors (11). This reaction was also highly dependent on the relative configuration of the substrate iodides; *anti* iodides such as **27** gave high *syn* selectivity while the corresponding *syn* iodide (**28**) was reduced with only modest selectivity in the presence of MgI_2. The exact mechanism of these reactions has not yet been elucidated. Since no initiation is required, it is possible that chelation with Lewis acid activates the α-iodo-β-alkoxy esters such that they undergo directly a single electron transfer with Bu_3SnH with subsequent reduction of the radical taking place inside a solvent cage. Since there is no radical chain, no inhibition is observed. To better understand the role of Lewis acid in radical reactions, we have studied the chelation-controlled reduction of the corresponding bromides as well as chelation-controlled allylation reactions.

Table 2. Reduction of various α-bromo esters under chelation-controlled and non-chelation-controlled conditions.



Entry	Substrate	Conditions[a]	Temperature (°C)	Ratio[b] *syn* : *anti*	Yield[c]
1	**30** : R = Me	A	0	27 : 1	-[d]
2	**30** : R = Me	B	0	1 : 1.8	-
3	**31** : R = iPr	A	0	32 : 1	75
4	**31** : R = iPr	B	0	1 : 8	75
5	**1** : R = Ph	A	0	8 : 1	78
6	**1** : R = Ph	B	0	1 : 9	91
7	**1** : R = Ph	A	-78	28 : 1	70
8	**1** : R = Ph	B	-78	1 : 20	70
9	**32** : R = Ph[e]	A	-78	28 : 1	70
10	**32** : R = Ph[e]	C	-78	-	0

[a]A: 5 equiv of $MgBr_2 \cdot OEt_2$, 2 equiv of $HSnBu_3$, 0.2 equiv of Et_3B, CH_2Cl_2. B: 2 equiv of $HSnBu_3$, 0.2 equiv of Et_3B, CH_2Cl_2. C: 5 equiv of $MgBr_2 \cdot OEt_2$, 2 equiv of $HSnBu_3$, 0.2 equiv of Et_3B, 0.25 equiv of 1,4-dinitrobenzene, CH_2Cl_2
[b]Determined by GC using crude reaction mixtures
[c]Isolated yield
[d]Products volatile
[e]Relative configuration between OMe and Br is *syn*

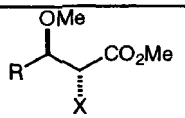
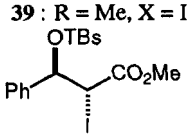
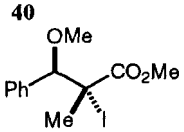
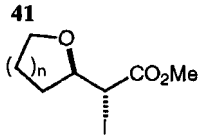
Our initial experiments with α-bromo-β-alkoxy esters employing conditions optimized for α-iodo-β-alkoxy ester (7a) gave significant deviations from the results described above. In the case of the reduction of iodides, no initiator was required for the reaction to proceed in the presence of $MgBr_2 \cdot OEt_2$, MgI_2 or $AlCl_3$. However, the corresponding reactions with α-bromo esters would only proceed if Et_3B (12) was added to the reaction medium. Another important difference was the fact that a large excess of $MgBr_2 \cdot OEt_2$ (5 equivalents) was required for optimal results. As shown in Table 2, a strong preference for the formation of *syn* products was found, regardless of the size of the substituent at the 3 position (entries 1, 3, 5). This is in sharp contrast to the results obtained in the absence of $MgBr_2 \cdot OEt_2$ in which a correlation exists between the reduction ratio and the steric bulk of this substituent (entries 2, 4, 6) (5). In contrast to the chelation-controlled reduction of iodides, in most cases no significant difference in the ratio of reduced products was noted between *syn* and *anti* bromides (entries 7 and 9).

The presence of $MgBr_2 \cdot OEt_2$ has once again led to a complete reversal in the stereochemical outcome of the reaction (compare conditions A and B) producing in high selectivity the *syn* isomer. The reaction is sensitive to temperature, as illustrated by entries 5 and 7 in which an increase in ratio was obtained when the temperature of the reaction was lowered from 0 to -78 °C. These reactions could also be terminated by the presence of radical inhibitors (entry 10). This result combined with the necessity of using Et_3B as an initiator suggests strongly the presence of radical species as intermediates in this reaction.

The formation of carbon-carbon bonds is obviously of prime importance in building organic molecules. We had previously demonstrated that secondary halides can form such bonds diastereoselectively using

allyltributyltin (5b). As in the case of radical reduction, it should be possible to invert the facial selectivity of the radical allylation (from *syn* to *anti*) through the simple expedient of adding a Lewis acid to the reaction mixture. As seen in Table 3, secondary iodides, bromides and phenylselenides can be transformed into their corresponding allyl derivatives in excellent yield and with excellent stereoselectivity. In all cases, the *anti* isomer is formed preferentially to the extent of 38:1, 19:1 and 65:1 respectively when $MgBr_2 \cdot OEt_2$ was present (entries 1, 5, 7) (7b). This is in contrast with the results that were obtained in the absence of Lewis acid (entries 1 and 2) in which a preference for the *syn* isomer was obtained (note that consistent facial bias is observed for both reduction and allylation).

Table 3. Radical allylation of various substrates under chelation and non-chelation control

Entry	Substrate	Conditions[a]	Ratio[b] *anti* : *syn*	Yield[c]
				
1	**33** : R = Ph, X = I	A	38 : 1	80
2	**33** : R = Ph, X = I	B	1 : 5	82
3	**33** : R = Ph, X = I	C	-	2
4	**34** : R = Ph, X = I[d]	A	5 : 1	69
5	**35** : R = Ph, X = Br	A	19 : 1	78
6	**36** : R = Ph, X = Br[d]	A	22 : 1	80
7	**37** : R = Ph, X = SePh	A	65 : 1	90
8	**38** : R = iPr, X = I	A	>100: 1	51
9	**39** : R = Me, X = I	A	51 : 1	79
				
10	**40**	A	1 : 8	90
11	**40**	D	1 : 13	86
				
12	**41**	A	>100: 1	76
13	**41**	B	1 : 16	75
				
14	**42** : n = 1	A	4.6 : 1	91
15	**42** : n = 1	B	1 : 6	90
16	**43** : n = 2	A	18 : 1	84
17	**43** : n = 2	B	1 : 10	89

[a]Conditions: A: 2.0 equiv of $allylBu_3Sn$, 3.0 equiv of $MgBr_2 \cdot OEt_2$, 0.2 equiv of Et_3B, CH_2Cl_2, -78 °C. B: 2.0 equiv of $allylBu_3Sn$, 0.2 equiv of AIBN, hexanes, reflux. C: 2.0 equiv of $allylBu_3Sn$, 3.0 equiv of $MgBr_2 \cdot OEt_2$, 0.2 equiv of Et_3B, 0.25 equiv of 1,3-dinitrobenzene, CH_2Cl_2, -78 °C. D: 2.0 equiv of $allylBu_3Sn$, 0.2 equiv of Et_3B, CH_2Cl_2, -78 °C

[b]determined by GC using crude reaction mixtures

[c]Isolated yield

[d]Relative configuration between OMe and I or Br is *syn*

The presence of a radical chain is indicated by the fact that Et_3B is needed as an initiator (7b), and that radical inhibitors such as 1,3-dinitrobenzene are capable of inhibiting the reaction (entry 3). The use of the *syn* secondary iodide **34** leads to reduced levels of diastereoselectivity (entry 4); however, this problem is not found in the case of the *syn* secondary bromide **36** (entry 6). As seen in entries 8 and 9, excellent ratios of final products are noted when secondary and primary alkyl groups are substituted at position 3. Tertiary halides may also be used as shown in entry 12, affording ratios in excess of 100:1. Given the general difficulty associated with the formation of asymmetric quaternary centers, this represents a reaction of potential synthetic utility (13).

Entries 14 and 16 indicate a lower preference for the *anti* product in cases where the oxygen at position 3 is imbedded in a ring. Tetrahydrofuran derivative **42** gave, under chelation control, a ratio of 4.6:1 which was somewhat lower than that observed for the corresponding tetrahydropyran derivative **43**. The reasons for this finding are not clear at this time. Our working hypothesis is that the formation of a bidentate chelate is impaired with the tetrahydrofuran substrates, by the development of eclipsing interactions between a C-O and a Mg-Br or Mg-O bond in a *cis* bicyclo complex (Scheme 3; presence of etherate ligand on Mg is supported by NMR data). This type of interaction is less severe in the case of tetrahydropyran **43**. The importance of the formation of a bidentate complex in the reaction is inferred by the observation that a *tert*-butyldimethylsilyloxy group at position 3 gave the *syn* product in similar ratios, with or without $MgBr_2 \cdot OEt_2$ (entries 10 and 11).

With conditions for the chelation-controlled reduction and allylation of α-halo esters optimized, we then turned our attention to the problem of why a large excess of $MgBr_2 \cdot OEt_2$ (3 or more equivalents) was

necessary to maximize the level of diastereoselectivity. This finding was surprising to us, since even catalytic amounts of $MgBr_2 \cdot OEt_2$ were always accompanied by insoluble material in the reaction media. We approached this problem by setting out to determine the amount of Mg^{+2} which was actually dissolved in the reaction mixture. To do this, the Lewis acid was allowed to equilibrate at -78 °C in the presence of substrate (5 mL of 0.1 M solution) and allyltin. After the normal mixing time had elapsed, the mixture was filtered and analyzed for the content of magnesium in solution by an EDTA titration (14). As seen in Table 4, in the absence of substrate the solubility of Mg^{+2} in CH_2Cl_2 at -78 °C relative to the amount of substrate normally used was found to be 0.25 equivalents (entry 1) (15). We then measured the amount of Mg^{+2} in different solutions of **33** and allyltin to which 0.25, 1.0, and 3.0 equivalents of $MgBr_2 \cdot OEt_2$ were added. A concomitant increase in the amount of dissolved Mg^{+2} was observed with increasing amounts of $MgBr_2 \cdot OEt_2$ added, reaching a maximum of 1.6 equivalents when 3 equivalents of $MgBr_2 \cdot OEt_2$ was added initially. At the same time, the *anti*:*syn* ratio of allylated products steadily increased, giving a maximum selectivity of 38:1 with 3 equivalents of $MgBr_2 \cdot OEt_2$ added (16). Based on these observations, three conclusions could be reached: a) The intrinsic solubility of $MgBr_2 \cdot OEt_2$ in CH_2Cl_2 is low. b) The substrate brings into solution all of the available $MgBr_2 \cdot OEt_2$ up to a full equivalent of additional Mg^{+2}, suggesting a strong interaction. c) There is *ca* 30 % of the added Lewis acid (see entries 2 and 3) that does not go into solution before the reaction occurs. This precipitate may vary depending on the source of the Lewis acid (17). Our hypothesis at this time is that a significant amount of the less soluble magnesium salts may be present in the commercially available $MgBr_2 \cdot OEt_2$ used.

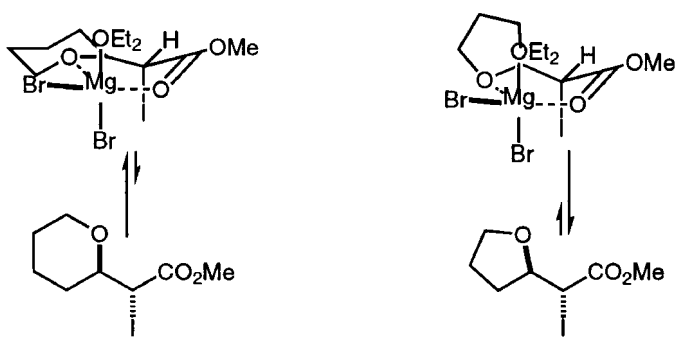
Table 4. Determination of the amount of magnesium dissolved in allylation reaction mixtures by filtration and EDTA titration.

Entry	Substrate	Equivalents $MgBr_2 \cdot OEt_2$ added[a]	Equivalents Mg^{+2} in solution[b]	Allylation ratio *anti* : *syn*
1	none	3.0	0.25	-
2	**33**	0.25	0.18	1.6 : 1
3	**33**	1.0	0.72	7 : 1
4	**33**	3.0	1.63	38 : 1
5	**34**	3.0	1.64	5 : 1
6	**40**	3.0	0.99	1 : 8
7	**42**	3.0	0.88	4.6 : 1
8	**43**	3.0	1.85	18 : 1

[a]equivalents of $MgBr_2 \cdot OEt_2$ relative to the amount of substrate
[b]equivalents of Mg^{+2} measured relative to the amount of substrate

The OTBS derivative **40**, a substrate which does not form a bidentate complex in the presence of Lewis acid, and which does not show reversed facial selectivity in these reactions, nevertheless is able to pull Mg^{+2} into solution (entry 6). This is not surprising in itself since this substrate possesses a Lewis basic site (the ester) that could interact with the Lewis acid. It is possible that this monodentate interaction is less strong than the bidentate one as supported by the fact that only 0.99 equivalents of Mg^{+2} was measured in solution for this substrate as opposed to 1.6 in the case of **33** (entries 4 and 6).

Scheme 3



As discussed before, the formation of a *cis* bicyclic intermediate (Scheme 3) in the reaction of the tetrahydrofuran derivative **42** is perhaps disfavored sterically, a possibility which is reflected by low diastereoselectivity. The total concentration of Mg^{+2} measured in solution seems to support this finding (entry 7). In this case, a magnesium concentration similar to the one found for silyl derivative **40** (entry 6) was measured. Conversely, the tetrahydropyran substrate **43** (entry 8) brought into solution an amount of Mg^{+2} similar to that seen for compound **33** (entry 4), an observation that also correlates with improved diastereoselectivity. Paradoxically, the amount of Mg^{+2} measured in solution for the *syn* iodide **34** is the same as that found for *anti* iodide **33**, even though this substrate (**34**) shows much lower facial selectivity in the allylation reaction (entries 4 and 5).

Previous studies by Eliel (18) on the effects of Lewis acid addition to α-hydroxy ketones, have suggested that the extent of the change in the ^{13}C chemical shift of the carbonyl is an indication of the stability of the bidentate complexes formed. As discussed below, the level of diastereoselectivity in a given reaction is dependent on the contribution of different reaction pathways. The changes in ^{13}C chemical shifts induced by complexation with $MgBr_2{\cdot}OEt_2$ of various substrates may provide an estimate of the relative importance of these pathways to a given reaction process. Preliminary results are found in Table 5. As shown in entries 1-3, the resonances of the carbonyls of *anti* substrates **35**, **33**, and **37** all show large displacements upon addition of $MgBr_2{\cdot}OEt_2$, an observation that correlates with bidentate complex formation and with high stereoselectivity in the subsequent allylation. The carbonyl resonance of OTBS derivative **40** shows a much smaller perturbation suggestive of the formation of a monodentate complex. The *syn* iodide **34** and *syn* bromide **36** apparently form less stable bidentate complexes than the corresponding *anti* analogs (entries 5 and 6 vs 1 and 2). We are presently conducting more studies to define the structural characteristics of these complexes. The data presented should be considered as preliminary and tentative since the Curtin-Hammet principle could always be invoked against any conclusions reached when starting materials are considered.

Table 5. Effect on ^{13}C carbonyl chemical shift by complexation of $MgBr_2{\cdot}OEt_2$ with various substrates.

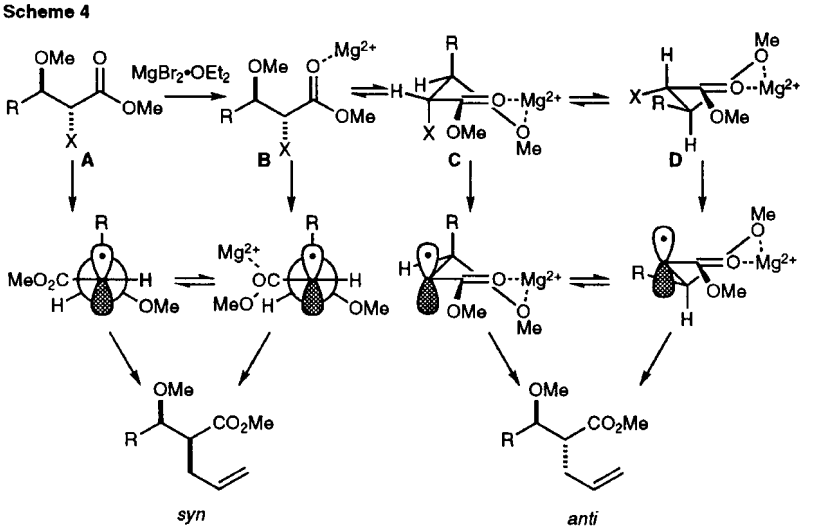
Entry	Substrate	Δδ C=O[a]	Ratio[b]
1	**35**	-6.4	19 : 1
2	**33**	-7.5	38 : 1
3	**37**	-8.4	65 : 1
4	**40**	-2.7	1 : 8
5	**34**	-4.8	5 : 1
6	**36**	-5.7	20 : 1

[a]chemical shift of substrate - chemical shift of substrate with 3 $MgBr_2{\cdot}OEt_2$

[b]see table 3

Possible reaction pathways are shown in Scheme 4. It is important to consider the fact that there are potentially three different sets of reactions, each of which could influence the final outcome of the overall process. First is the non-chelated reaction pathway involving intermediate **A**, which leads to the formation of the *syn* isomer as described above. The second possible pathway involves monodentate complexes such as **B**. Since these two pathways differ only in complexation with the ester carbonyl, it is possible that the transition states are similar in these two cases. Because of the increase in the electronegativity of the complexed ester in **B**, however, both the rate of formation of the radicals and the subsequent carbon-carbon bond formation step may be accelerated relative to that of **A** (19). This is suggested by the observation that when reactions are run in parallel, those containing $MgBr_2{\cdot}OEt_2$ are completed faster than the control reactions which lack a Lewis acid. This is particularly significant in the case of silyl derivative **40** in which the formation of bidentate complexes are precluded. Competition experiments between silyl derivative **40** and β-methoxy substrate **33** indicate that the bidentate chelation pathway may not have clear kinetic advantages over the monodentate pathway. When equimolar amounts of **33** and **34** are mixed and treated with 0.5 equivalents of allyltributyltin, a similar proportion of each substrate is consumed indicating that the reactions of **33** and **34** are proceeding with similar overall rates (20). Since this is true in the presence or absence of $MgBr_2{\cdot}OEt_2$, large amounts of the Lewis acid (three or more equivalents) are required to ensure complete formation of the bidentate complex.

Scheme 4



The bidentate chelate (Scheme 4; the ligands on Mg have been excluded for simplicity) may exist in two conformers as depicted by **C** and **D**. When X is small and strongly electronegative, **D** should be the most stable of the two conformers. In this conformation, the electronegative group will not have

as large an effect on the basicity of the carbonyl as in the case of **C**, in which X is able to better interact with the carbonyl π system. When X is large and less electronegative, conformer **C** should be favored for steric reasons, since in this conformer the two substituents are *anti* to one other. Because the halide is axial, the C-X bond cleavage should be more facile in this conformer due to the electronic participation of the carbonyl π orbital. An increase in the proportion of conformer **C** may be an important factor in the overall competition between the bidentate and the monodentate forms. This remains to be verified, however, as well as the rationale for the low diastereoselectivity of the *syn* iodides.

Table 6. Radical allylations with allyltrimethylsilane under chelation and non-chelation control

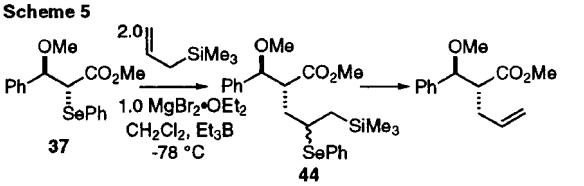
Entry	Substrate	Conditions[a]	Ratio[b] *anti* : *syn*	Yield[c]
1	**40**	A	1 : 9.5	82
2	**40**	B	1 : 13	39
3	**33**	A	42 : 1	87
4	**33**	B	1 : 5	39

[a]A: 2.0 equiv. of $CH_2CHCH_2SiMe_3$, 1.0 equiv. of $MgBr_2 \cdot OEt_2$, 0.2 equiv. of Et_3B, CH_2Cl_2, -78 °C. B: 2.0 equiv. of $CH_2CHCH_2SiMe_3$, 0.2 equiv. of Et_3B, CH_2Cl_2, -78 °C
[b]determined by NMR using crude reaction mixtures
[c]isolated combined yield

We have recently utilized the activating ability of Lewis acids to promote atom transfer reactions. Although α-halo esters make good substrates for other radical processes due to the activating effect of the carbonyl, these types of substrates do not in general perform well in atom transfer reactions. Chelation of the carbonyl of such an ester with a Lewis acid would presumably increase the rate of the reaction by making the ester more electrophilic and decreasing the energy of the radical SOMO. To test this hypothesis, silyl derivative **40** was treated with allyltrimethylsilane and Et_3B. This reaction resulted in only a poor yield of allyl transfer product (Table 6, entry 2). In the presence of $MgBr_2 \cdot OEt_2$, however, this same transformation proceeded readily (entry 1). The next obvious step was to try the same experiment with compound **33** to see if this process would occur in the presence of a bidentate complex. As shown in entries 3 and 4, the addition of $MgBr_2 \cdot OEt_2$ resulted in an increase in reactivity and also a reversal in the facial selectivity of the reaction. To prove that an atom transfer mechanism was operative, we examined the reaction of phenylselenide substrate **37** since the initially formed adduct should be relatively stable (Scheme 5). This was in fact the case as we noticed in the crude NMR spectrum the presence of a new product. Careful chromatography afforded the intermediate phenylselenide **44** as a 4:1 mixture of isomers. These reactions could be inhibited by 1,3-dinitrobenzene. This observation and the requirement of Et_3B to initiate the reaction, suggest the involvement of radicals as intermediates. *To our knowledge, this represents the first example of an atom transfer reaction in which facial selectivity is controlled by Lewis acid complexation.*

Similar principles to the ones described above can be applied to control the diastereoselectivity of radical addition reactions. In this case, the radical center (flanked by and OMe and ester) could be obtained as a result of the addition of another radical to an α-β-unsaturated ester. The use of Lewis acid could be used to control the facial selectivity of the terminal hydrogen transfer step. The reaction should also be facilitated by the presence of the Lewis acid. On one hand, the activation of the ester by complexation will render the double bond electron-poor, facilitating the attack of an electronrich radical. The chelated α-carboxy radical formed would then be potentially of very low SOMO energy, thus increasing the electrophilicity of this subsequent acceptor.

Scheme 5



Diastereoselective processes involving acyclic radicals are rapidly emerging. Chelation-control through the formation of bidentate chelates is one of the most promising of these and has begun to find application in controlling the stereoselectivity of reduction, allylation, atom transfer and alkyl transfer reactions of acyclic radicals.

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15. The number of equivalents reported is relative to the number of mmoles of substrate normally used. This was kept constant for entries 1 through 4.
16. The use of more than 3 equivalents of $MgBr_2 \cdot OEt_2$ did not further increase the amount of Mg^{+2} in solution nor the allylation ratio.
17. It is possible that this precipitate could play a role if the reaction takes place at the interface between the solid and the solution. To address this, we prepared a reaction as usual using 3 equivalents of $MgBr_2 \cdot OEt_2$, but filtered off the precipitate at -78 °C before the addition of Et_3B. The reaction proceeded normally without changes to the yield nor to the level of diastereoselectivity. This indicates that the insoluble material does not participate in the reaction after the pre-equilibration phase.
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20. We have obtained different results when reductions are considered, the monodentate complex reacting faster than the bidentate complex.