The Use of Lewis Acids in Radical Chemistry. Chelation-Controlled Radical Reductions of Substituted α-Bromo-β-alkoxy Esters and Chelation-Controlled Radical Addition Reactions

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The radical reduction of a series of α-bromo-β-alkoxy esters under chelation-controlled conditions is reported. Proceeding with high stereoselectivity in the presence of $MgBr_2 \cdot OEt_2$, reductions give access to *syn* products. Systematic variations in substrate substituents show that these reactions tolerate a wide variety of alkyl functionalities at positions 2 and 3 and are relatively unaffected by the nature of the ester group. Changes to the alkoxy function indicate that a bidentate chelate is involved in the reaction and that an excess of $MgBr_2 \cdot OEt_2$ is required for optimum selectivity by favoring this species in preference to the *anti*-selective monodentate or nonchelated pathways. Competition experiments suggest that the monodentate pathway is kinetically favored over the bidentate one. The suppressibility of the reaction by radical chain inhibitors and the need for initiation indicate the intermediacy of radicals. Further support for this mechanism includes both radical addition to α,β-unsaturated esters and reduction of bromides conducted in the presence of a Lewis acid.

Introduction

The problem of controlling the stereochemical outcome of reactions involving acyclic radicals is receiving considerable attention.[1] Significant levels of diastereoselectivity have already been achieved in strategies involving chiral auxiliaries[2] or a preexisting vicinal chiral center (1,2-induction).[3,4] The scope of these reactions has been expanded by using mono-[5] or bidentate[6,7] Lewis acids, solvent complexation,[8] and intramolecular hydrogen bonding.[9] New developments in this research include reagent control approaches that employ chiral Lewis acids.[10]

Our group has been particularly interested in the reactivity of radicals flanked by both an ester and a stereogenic center in three types of reactions: (1) allylation, (2) atom transfer, and (3) hydrogen transfer reactions.[4,7] These radicals can be obtained via the homolytic cleavage of a halide or phenyl selenide. As shown by Scheme 1, the reaction of iodides such as **1** with

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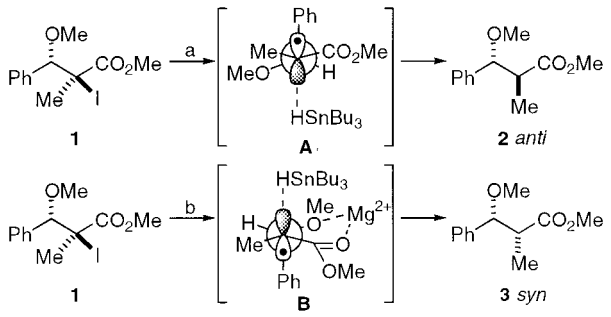
Scheme 1



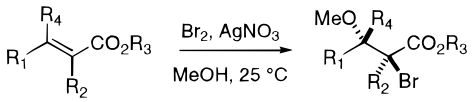
a : Bu_3SnH, AIBN or Et_3B, toluene, -78 °C; b : Bu_3SnH, CH_2Cl_2, -50 °C, $MgBr_2{\bullet}OEt_2$ or MgI_2

tributyltin hydride give primarily products such as **2** which have an *anti* relative configuration.[4a] This stereochemical outcome is best rationalized by transition state **A**,[1–4] which takes into account allylic 1,3-strain,[1a,3c] dipole–dipole repulsion,[4] and hyperconjugative stabilization.[4e]

Inspired by this model, we postulated that facial selectivity could be reversed by the use of a bidentate Lewis acid to promote the intermediacy of transition state **B**.[7a] Thus, the reaction of iodide **1** with tributyltin hydride in the presence of 0.25 equiv of $MgBr_2{\cdot}OEt_2$ afforded *syn* product **3** with excellent diastereoselectivity (>25:1)[7a] and in good yield (81%). Interestingly, neither a full equivalent of Lewis acid nor an initiator[11] was needed to achieve maximal selectivity. However, this reaction was also highly dependent on the relative configuration of the iodide substrates; *anti* iodides gave better selectivity than their *syn* counterparts in the presence of MgI_2. The limited availability of substituted α-iodo-β-alkoxy esters[12] precluded an extensive study of C-2 and C-3 substituent effects on the stereochemical outcome.

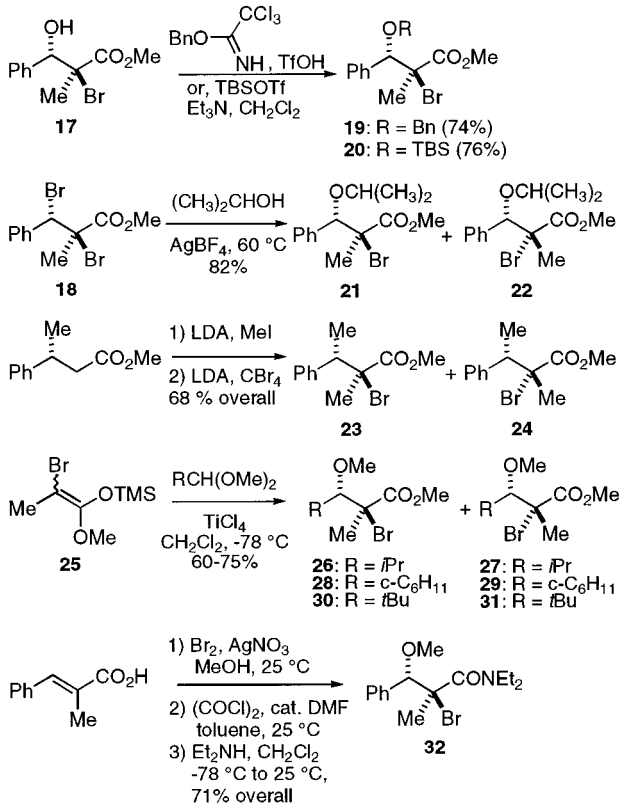
Subsequently, we have found that the limitations inherent to the iodide substrates do not exist in the corresponding bromide series. Reported herein are our studies on the chelation-controlled radical reductions of α-bromoesters, including experimental evidence for the involvement of a chelated intermediate in the free radical chain reaction. Preliminary findings also indicate that chelation control could regulate the addition of radicals to α,β-unsaturated esters.

Table 1. Preparation of Substrates 10–16 by Methoxy-bromination[13]



entry	olefin	R_1	R_2	R_3	R_4	bromide	yield (%)
1	**4**	H	*t*Bu	Me	H	**10**	84
2	**5**	Ph	*i*Pr	Me	H	**11**,**12**	80
3	**6**	Ph	Me	Me	H	**13**	93
4	**7**	Ph	H	Me	H	**14**	89
5	**8**	Ph	Me	*t*Bu	H	**15**	62
6	**9**	Me	Me	Me	H	**16**	69

Scheme 2



Chelation-Controlled Reductions of α-Bromo Esters. The substituted α-bromo-β-alkoxy ester substrates used in this study were prepared in a variety of ways. Substrates **10**–**16** were prepared by methoxy-bromination of the corresponding unsaturated esters **4**–**9** as shown in Table 1.[13,14] Substrates **19** and **20** were prepared from the readily available[3c] alcohol **17** (Scheme 2). Thus, reaction of **17** with benzyl 2,2,2-trichloroacetimidate[15] gave the benzyl ether **19**, whereas TBS ether **20** was smoothly obtained from the treatment of **17** with *tert*-butyldimethylsilyl trifluoromethanesulfonate.[16] Iso-

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(11) For an example of the use of zinc chloride as an initiator, see ref 6d.

(12) The α-iodo-β-alkoxy esters can be prepared by the silver nitrate-mediated alkoxy iodination reaction of an α,β-unsaturated ester; see ref 13. This reaction works well only for substituted cinnamates and crotonates. The presence of a secondary or tertiary alkyl substituent at the β position of the unsaturated ester will preclude formation of the desired regioisomer. A Mukaiyama reaction between the silyl ketene acetal derived from methyl 2-iodopropanoate and a dimethyl acetal could not be used due to the propensity of the intermediate enolate to form a carbene. See Maryanoff, C. A.; Sorgi, K. L.; Zientek, A. M. *J. Org. Chem.* **1994**, *59*, 237.

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(14) The unsaturated esters were either purchased or prepared from the corresponding acids, which were commercially available. Unsaturated esters **4** and **5** were prepared from an aldol condensation (LDA, THF, −78 °C then PhCHO) followed by dehydration (MsCl, pyridine then DBU, toluene).

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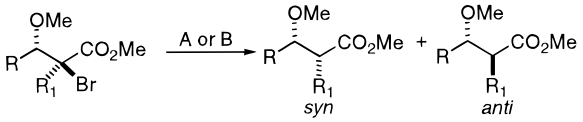
Table 2. Effect of C-2 and C-3 Substitutions in α-Bromoester Substrates on Radical Reductions



				products					
entry	substrate	R	R_1	*syn*	*anti*	conditions,[a] A or B	temp (°C)	ratio[b] *syn*:*anti*	yield[c] (%)
1	**16**	Me	Me	**33**	**34**	A	0	27:1	*d*
2	**16**	Me	Me	**33**	**34**	B	0	1:1.8	–
3	**26**	*i*Pr	Me	**35**	**36**	A	0	32:1	75
4	**26**	*i*Pr	Me	**35**	**36**	B	0	1:8	75
5	**28**	c-C_6H_{11}	Me	**37**	**38**	A	0	27:1	74
6	**28**	c-C_6H_{11}	Me	**37**	**38**	B	0	1:8	93
7	**30**	*t*Bu	Me	**39**	**40**	A	0	33:1	91
8	**30**	*t*Bu	Me	**39**	**40**	B	0	1:21	75
9	**13**	Ph	Me	**3**	**2**	A	0	8:1	78
10	**13**	Ph	Me	**3**	**2**	B	0	1:9	91
11	**13**	Ph	Me	**3**	**2**	A	−78	28:1	70
12	**13**	Ph	Me	**3**	**2**	B	−78	1:20	70
13	**11**	Ph	*i*Pr	**41**	**42**	A	−78	84:1	71
14	**11**	Ph	*i*Pr	**41**	**42**	B	−78	1:13	83
15	**10**[e]	Ph	*t*Bu	**43**	**44**	A	−78	64:1	71
16	**14**	Ph	H	**45**	**46**	A[f]	−78	3:1	70
17	**14**	Ph	H	**45**	**46**	B[f]	−78	1:4	88

[a] Conditions A: 5 equiv of $MgBr_2 \cdot OEt_2$, 2 equiv of Bu_3SnH, 0.2 equiv of Et_3B, CH_2Cl_2; B: 2 equiv of Bu_3SnH, 0.2 equiv of Et_3B, CH_2Cl_2. [b] Determined by GC analysis of crude reaction isolates. [c] Isolated yields. [d] Volatile products. [e] Relative configuration between OMe and Br is *syn*. [f] Bu_3SnD was used.

propyl ethers **21** and **22** were obtained in good yield when dibromide **18** (afforded by bromination of methyl α-methylcinnamate) reacted with silver tetrafluoroborate in 2-propanol at 60 °C. Bromoesters **23** and **24** were prepared by using standard enolate chemistry. Substrates bearing a secondary or tertiary alkyl substituent at the 3-position could not be prepared efficiently by the methoxy-bromination reaction. Instead, these compounds were obtained from a Mukaiyama reaction[17] between silyl ketene acetal **25** and the appropriate dimethylacetal, and the resultant diastereomeric bromides were separated after flash chromatography on silica gel.[18] Finally, diethylamide **32** was derived in a straightforward manner from α-methylcinnamic acid.

With the α-haloester substrates in hand, we were poised to study their reaction with tributyltin hydride under various conditions. Initial experiments employing conditions optimized for α-iodoesters (2.0 equiv of Bu_3SnH, 0.25 equiv of $MgBr_2 \cdot OEt_2$)[7a] gave results that deviated significantly from our earlier findings. If either $MgBr_2 \cdot OEt_2$, MgI_2, or $AlCl_3$ was used, the reduction of α-iodoesters did not require an initiator. However, the chelation-controlled reduction of α-bromoesters would proceed only if Et_3B[19] was added to the reaction medium. Another important difference between these reductions was the necessity to use an excess (5 equiv) of $MgBr_2 \cdot OEt_2$ to achieve optimal results for the bromide series (vide infra),[20] while only catalytic amounts were required for the reduction of the α-iodoesters. Having ascertained the optimal conditions (2 equiv of Bu_3SnH, 5 equiv of $MgBr_2 \cdot OEt_2$, 0.2−0.6 equiv of Et_3B, CH_2Cl_2)[21] for the reduction of the α-bromoesters, we were able to conduct a systematic analysis of the scope and limitations of the reaction.

As shown in Table 2, the reduction of the α-bromoesters in the presence of $MgBr_2 \cdot OEt_2$ completely reversed the stereoselection of the reaction[7] (cf. conditions A versus B), affording the *syn* isomer with excellent diastereofacial selectivity (entries 1, 3, 5, 7, 9).[22,23] Similar to the nonchelation reaction in exhibiting a sensitivity to temperature,[4a] the chelation-controlled reduction proceeded with greater diastereoselectivity at lower reaction temperatures, as exemplified by the 3-fold enhancement in *syn* selectivity when the reaction was conducted at −78 °C (28:1, entry 11) instead of 0 °C (8:1, entry 9).

Interestingly, the nature of the substituent (R) at position-3 had little effect on the reduction since primary, secondary, and tertiary alkyl groups all gave ratios of ∼30:1 (Table 2; entries 1, 3, 5, 7). This finding contrasts with the results obtained in the absence of $MgBr_2 \cdot OEt_2$[4] which show that larger R substituents at position-3 confer greater selectivity in the nonchelated reduction pathway (entries 2, 4, 6, 8). Table 2 also shows that primary, secondary, and tertiary alkyl substituents at position-2 were well tolerated (entries 11, 13, 15), and that slightly higher ratios were observed with greater R_1 substitution. The reduction of secondary bromides (entry

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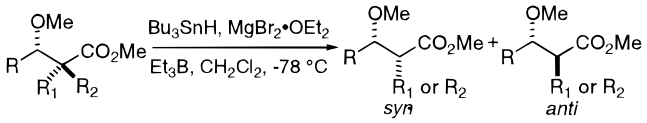
(20) A similar observation has been made in the chelation-controlled allylation of secondary α-iodoesters; see ref 7b.
(21) To ensure that the radical process was quenched at the same temperature at which the reaction was conducted, a radical inhibitor, *m*-dinitrobenzene (*m*-DNB), was added to the reaction mixture prior to workup.
(22) The relative configuration of the reduced products was established by correlation of NMR chemical shifts. In all cases, the methyl group adjacent to the ester function resonated slightly downfield for the *syn* compounds relative to the corresponding resonance of the *anti* isomers. The original NMR reference assignments were verified by X-ray crystallographic structures; see ref 4d.
(23) For purposes of comparison, these reactions were all performed at 0 °C since the *tert*-butyl substrate **31** was insoluble at lower temperatures. Substrates **16**, **26**, and **28** gave higher ratios at −78 °C.

Table 3. Effect of Relative Configuration of α-Bromoester Substrates on Chelation-Controlled Radical Reductions



entry	substrate	R	R_1	R_2	products *syn*	products *anti*	ratio[a] *syn*:*anti*	yield[b] (%)
1	**13**	Ph	Me	Br	**3**	**2**	28:1	70
2	**47**	Ph	Br	Me	**3**	**2**	20:1	–
3	**28**	c-C_6H_{11}	Me	Br	**37**	**38**	42:1	–
4	**29**	c-C_6H_{11}	Br	Me	**37**	**38**	33:1	74
5	**30**	*t*Bu	Me	Br	**39**	**40**	33:1	91
6	**31**	*t*Bu	Br	Me	**39**	**40**	3:1	–
7	**11**	Ph	*i*Pr	Br	**41**	**42**	84:1	71
8	**12**	Ph	Br	*i*Pr	**41**	**42**	81:1	70

[a] Determined by GC analysis of crude reaction isolates. [b] Isolated yields.

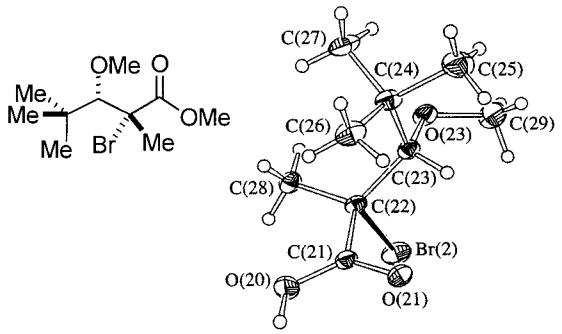


Figure 1.

17) proceeded, however, with considerably reduced *syn* selectivity (vide infra).

Table 3 addresses the impact of the relative configuration at C-2 and C-3 on the reduction. In most cases, the chelation-controlled reductions of *syn* and *anti* bromides (entries 1−4) had similar outcomes. Replacement of the R_1 methyl with an isopropyl group led to a similar conclusion (entries 7 and 8). In other words, excellent diastereoselectivity was observed irrespective of the relative (C-2)-(C-3) configuration of the bromide substrates, except when the R group at C-3 was *tert*-butyl (cf. entries 5 and 6). In this case, the *syn* bromide **31** was reduced with little facial discrimination (3:1) compared to its *anti* counterpart **30** (33:1) under the same reaction conditions.[24] To confirm these results, the relative configuration of the *syn* bromide **31** was verified by X-ray analysis (Figure 1). A rationale based on a mechanistic model of chelation control is proposed for this seemingly discordant result (vide infra).

Involvement of Free Radicals. Do these chelation-controlled reductions actually proceed through the intermediacy of free radicals? The essentiality of an initiator such as Et_3B for the reduction of bromide **13** in the presence of $MgBr_2$•OEt_2 would suggest that radicals do play a key role. Other evidence in support of this includes the complete inhibition of the reaction of **13** when the radical chain inhibitor *m*-dinitrobenzene (*m*-DNB) was added to the reaction mixture prior to the addition of tin hydride; only starting material was recovered under these circumstances.

Scheme 3 illustrates a set of experiments designed to show whether the chelation-controlled reaction proceeds through an intermediate that can be generated through a different approach. More specifically, we wanted to compare the reaction outcomes for **48** and for **49** in the presence of $MgBr_2$•OEt_2. If both reactions were to proceed through the same radical intermediate, the mechanism for its formation would involve halogen abstraction for **48** and a radical transfer (addition) for **49**, but more importantly, the method used to generate the intermediate species should have little bearing on the hydrogen transfer step dictating the outcome of the reaction. As shown in Scheme 4, both the requisite substrates **48** and **49** were prepared from alcohol **52**.[25] In control experiments, these compounds were subjected to radical conditions in the absence of Lewis acid. The treatment of **49** with ICH_2Cl and Bu_3SnH in the presence of Et_3B furnished a 1:4 mixture of **50** and **51** (Scheme 3), demonstrating the expected *anti*-preference, while the reduction of **48** (Bu_3SnH, Et_3B) gave similar results. In the absence of $MgBr_2$•OEt_2, both reactions would therefore seem to proceed through the same radical intermediate. In the presence of $MgBr_2$•OEt_2 (2.0 equiv), reaction of **49** with ICH_2Cl, Bu_3SnH, and Et_3B led to a reversal in facial selection (i.e. *syn*), as anticipated for a hydrogen transfer reaction under chelation control, affording a 6:1 mixture of **50** and **51**.[26] The significance of this experiment lies in the fact that **50** and **51** could arise from **49** only through a radical process. In the crucial experiment where bromide **48** was subjected to Bu_3SnH, Et_3B, and $MgBr_2$•OEt_2, a similar outcome was observed, which strongly suggests a common radical intermediate in both chelation-controlled reactions.

Lending further support to radical involvement in the chelation-controlled reduction is another set of similar experiments based on a radical addition as the initial step. In this study, *tert*-butyl radical was added to the α,β-unsaturated ester **55** in the presence and absence of Lewis acid (Scheme 5). Although the levels of selectivity were modest (1:3), the reaction in the absence of $MgBr_2$•OEt_2 predictably favored the *anti*-isomer **57**, while *syn*-product (**56**) formation was prevalent in the presence of the Lewis acid, presumably through the intermediacy of a bidentate radical.

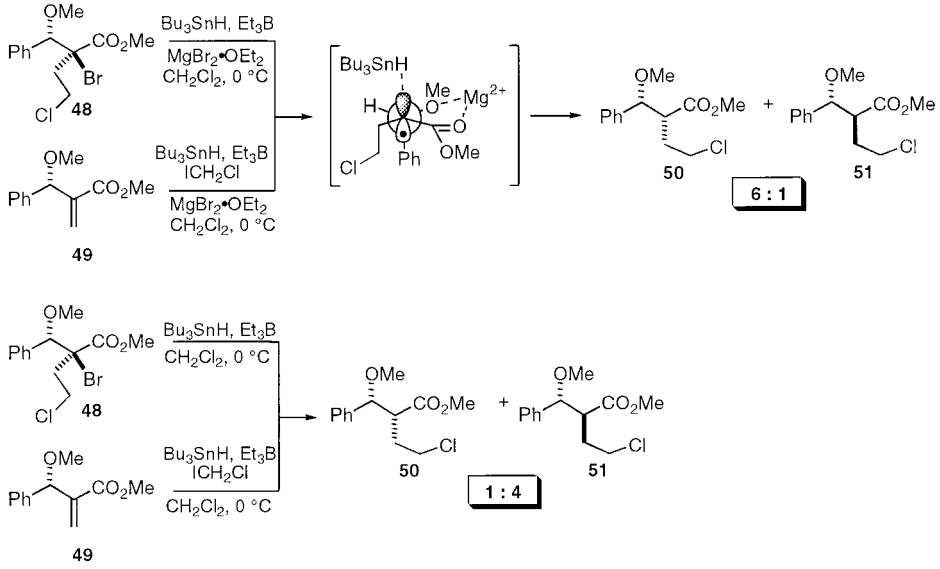
An interesting observation made from these experiments was the apparent kinetic enhancement of the radical addition in the presence of $MgBr_2$•OEt_2. In a typical experiment, Bu_3SnH was introduced slowly by syringe pump to a solution of olefin and alkyl halide to minimize reduction of the radical prior to its addition to the olefin. With an alkyl halide that is very bulky, such as *tert*-butyl iodide, the slow addition of Bu_3SnH was unnecessary in the absence of $MgBr_2$•OEt_2, but the addition to the olefin (**55**) took place very slowly (50% of unreacted substrate was recovered after a reaction time of 20 h). By contrast, an acceleration of the reaction was observed in the presence of $MgBr_2$•OEt_2 since the addition products (**56** and **57**) were obtained in fair yield (68%) after a total reaction time of only 2.5 h (no starting

(24) The difference in reactivity between these two diastereomeric bromides was similar to that observed for the corresponding iodides; see ref 7a.

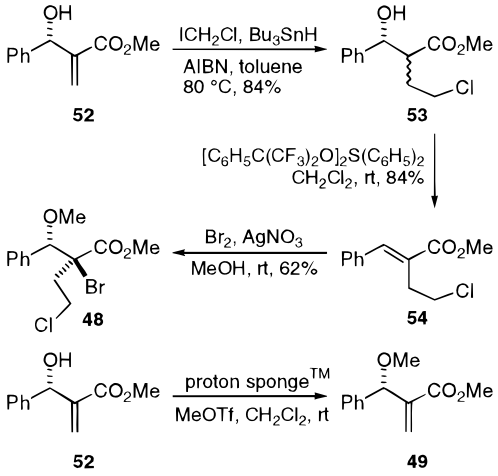
(25) Poly, W.; Schomburg, D.; Hoffmann, H. M. R. *J. Org. Chem.* **1988**, *53*, 3701.

(26) In the Lewis acid mediated reaction of **49**, a competitive process leading to the formation of methyl α-methylcinnamate (45%) was operative.

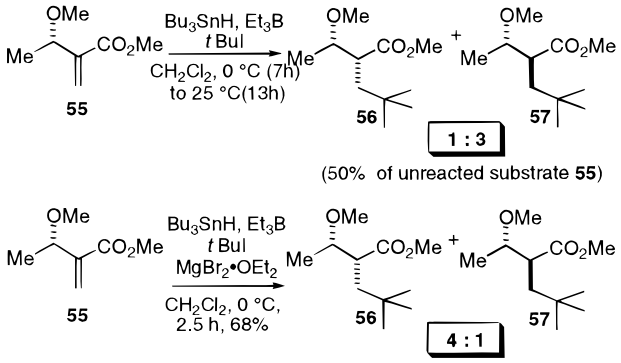
Scheme 3



Scheme 4



Scheme 5



material was recovered).[27,28] The enhanced electrophilicity of the α,β-unsaturated ester due to activation by the Lewis acid may have enhanced the rate of addition of the nucleophilic alkyl radical and/or the subsequent hydrogen transfer step. Based on the assumption that an electron-withdrawing group (i.e. ester) α to the incipient radical center would enhance the rate of radical addition or halogen atom abstraction (by the electropositive tin radical),[29−31] these reactions should accelerate when the ester becomes even more electrophilic upon coordination with a Lewis acid. Similarly, hydrogen transfer between the radical and the incoming tin hydride should accelerate since the radical would be more electrophilic when the ester carbonyl is complexed to the Lewis acid. In fact, the work of Lusztyk and Dolbier supports this argument; in reaction with tin hydride, the more electrophilic perfluoro-*n*-alkyl radicals have been found to be ∼100 times more reactive than *n*-alkyl radicals at 20 °C.[31a]

Involvement of Lewis acid Chelates. We envisioned the coordination of the bidentate Lewis acid with the α-bromo-β-alkoxy ester as the initial step of the reductive process. Subsequently, homolytic cleavage of the C−Br bond would afford the chelated radical (**B**), which would react with Bu_3SnH from the face opposite to that shielded by the phenyl or alkyl R group at C-3 (Scheme 1). Since the $MgBr_2{\cdot}OEt_2$ mediated reduction does favor *syn* product formation, the results presented in Tables 2 and 3 would seem to support this model. However, we had yet to garner experimental evidence for the involvement of the Lewis acid in a bidentate chelate.

One approach to verify the existence of a bidentate chelate between the carbonyl and the β-alkoxyl group of the substrate would entail alteration of the substrate's ability to chelate with the Lewis acid and observation of its effect on the selectivity of the reduction. The modifications of the β-alkoxyl (X) group and its effects on the hydrogen transfer reaction are shown in Table 4. Re-

(27) An increase in the radical based polymerization rate has been observed in the presence of a Lewis acid: (a) Imoto, M.; Otsu, T.; Harada, Y. *Makromol. Chem.* **1963**, *65*, 180. (b) Yabumoto, S.; Ishii, K.; Arita, K. *J. Polym. Sci. A-1*, **1969**, *7*, 1577. (c) Inoue, H.; Otsu, T. *Die Makromol. Chem.* **1972**, *153*, 21. See also ref 29.

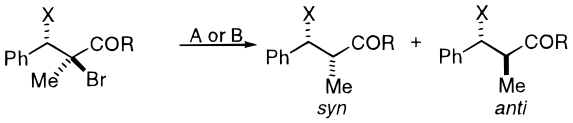
(28) A similar observation has been made by Sato in a study involving radical additions in the presence of diethylaluminum chloride.[6e]

(29) (a) Kuvila, H. G.; Menapace, L. W. *J. Org. Chem.* **1963**, *28*, 2165. (b) Kuvila, H. G. *Adv. Organomet. Chem.* **1964**, *1*, 47. (c) Menapace, L. W.; Kuvila, H. G. *J. Org. Chem.* **1964**, *29*, 3047. (d) Kuvila, H. G. *Synthesis* **1970**, 499.

(30) (a) Coates, D. A.; Tedder, J. M. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1570. (b) Blackburn, E. V.; Tanner, D. D. *J. Am. Chem. Soc.* **1980**, *102*, 692. See also refs 3a−d.

(31) (a) Avila, D. V.; Ingold, K. U.; Lusztyk, J.; Dolbier, W. R., Jr.; Pan, H.-Q.; Muir, M. *J. Am. Chem. Soc.* **1994**, *116*, 99. (b) Xiao, X.; Pan, H.-Q.; Dolbier, W. R., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 4521.

Table 4. Effect of Substrate Modifications on $MgBr_2 \cdot OEt_2$ Chelation in Radical Reductions



				products				
entry	substrate	X	R	*syn*	*anti*	conditions,[a] A or B	ratio[b] *syn*:*anti*	yield[c] (%)
1	**13**	OMe	OMe	**3**	**2**	A	28:1	70
2	**13**	OMe	OMe	**3**	**2**	B	1:20	81
3	**19**	OBn	OMe	**58**	**59**	A	12:1	80
4	**19**	OBn	OMe	**58**	**59**	B	1:13	72
5	**22**	O*i*Pr	OMe	**60**	**61**	A	1:7	76
6	**22**	O*i*Pr	OMe	**60**	**61**	B	1:9	97
7	**20**	OTBS	OMe	**62**	**63**	A	1:4.8	91
8	**20**	OTBS	OMe	**62**	**63**	B	1:4	99
9	**23**,**24**	Me	OMe	**64**	**65**	A	1:2.5	81
10	**23**,**24**	Me	OMe	**64**	**65**	B	1:3.3	90
11	**15**	OMe	O*t*Bu	**66**	**67**	A	57:1	62
12	**15**	OMe	O*t*Bu	**66**	**67**	B	1:22	89
13	**32**	OMe	NEt_2	**68**	**69**	A	6:1	70
14	**32**	OMe	NEt_2	**68**	**69**	B	1:13	83

[a] Conditions A: 5 equiv of $MgBr_2 \cdot OEt_2$, 2 equiv of Bu_3SnH, 0.2 equiv of Et_3B, CH_2Cl_2, −78 °C; B: 2 equiv of Bu_3SnH, 0.2 equiv of Et_3B, CH_2Cl_2, −78 °C. [b] Determined by GC analysis of crude reaction isolates. [c] Isolated yields.

placement of the OMe by an OBn group led to an erosion of *syn* diastereoselectivity under chelation-controlled conditions (cf. entries 1 and 3). When the OMe was replaced by an O*i*Pr (cf. entries 1 and 5), the Lewis acid lost its influence in controlling the stereochemical outcome (cf. entries 5−6). Presumably, the steric congestion furnished by the larger *i*Pr group (relative to Me) precluded chelation of the oxygen with $MgBr_2 \cdot OEt_2$. Similar observations were made for the radical reduction of silyl ether **20**;[32] indeed, in the presence or absence of $MgBr_2 \cdot OEt_2$, the reaction favored *anti*-product formation (entries 7−8). The inability of the X group to chelate due to steric and/or electronic factors therefore produced the same effect as the absence of a coordinating oxygen at the β-position (entries 9−10). From these results, it is clear that the bidentate Lewis acid chelate in these hydrogen transfer reactions is essential for facial discrimination favoring *syn* product.

The effect of modifying the ester R group is also shown in Table 4. While replacement of the ester OMe by O*t*Bu led to a 2-fold enhancement in facial selectivity (cf. entries 1 and 11) under chelation controlled conditions, this change had little impact on the nonchelation pathway (cf. entries 2 and 12). On the other hand, replacement of the ester by a *N*,*N*-diethylamide had a deleterious effect on the reduction mediated by $MgBr_2 \cdot OEt_2$ (cf. entries 1 and 13); the bidentate chelate in this case may be destabilized by a 1,3-allylic interaction between an amide ethyl group and the α-methyl group. Interestingly, the effect of the *N*,*N*-diethylamide on the reduction was less severe in the absence of $MgBr_2 \cdot OEt_2$ (cf. entries 2 and 14).

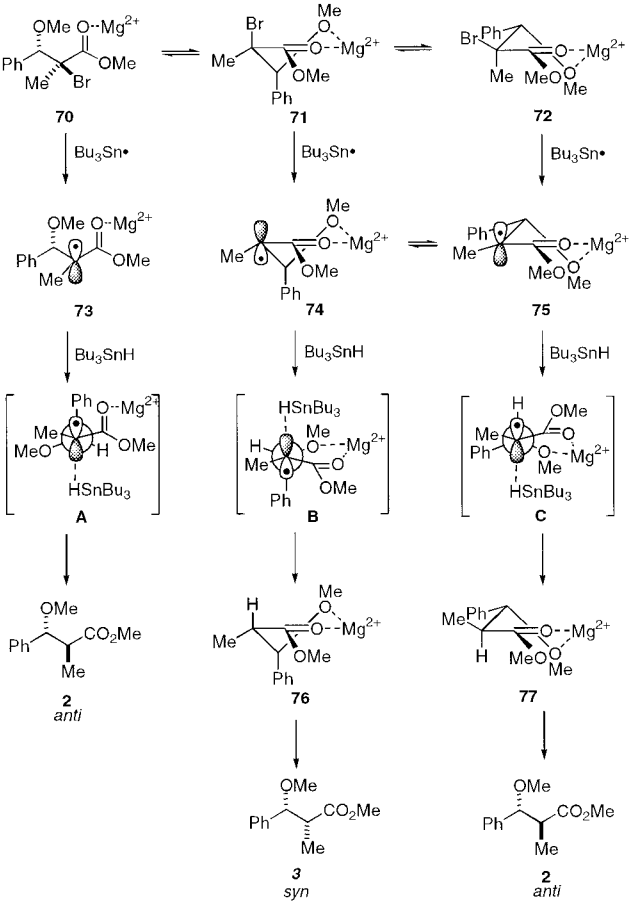
An observation noted earlier was the necessity for an excess of $MgBr_2 \cdot OEt_2$ to be present prior to the addition of Bu_3SnH to achieve good selectivity in the hydrogen transfer reactions. When less than 1 equiv of $MgBr_2 \cdot OEt_2$ was used, no significant preference for the *syn* product was observed. Indeed, to attain an optimum level of facial discrimination, more than 3 equiv of $MgBr_2 \cdot OEt_2$ was required. These observations suggest that the bidentate chelate may be in fact *less* reactive than the nonchelated and/or monodentate species giving rise to *anti*-product, and that an excess of $MgBr_2 \cdot OEt_2$ would then be needed to ensure a maximal concentration of the substrate in its bidentate chelate form for optimal *syn*-selectivity.

Under the conditions of excess $MgBr_2 \cdot OEt_2$, at least three reactive species may play a role in determining the product distribution. One of these would be the bidentate (**71**, Scheme 6) giving rise to the *syn* product. While *anti*-product could arise from the radical reduction of α-bromoesters via a nonchelation pathway, it is more likely that this isomer also arises from an intermediate complexed to $MgBr_2 \cdot OEt_2$, which is present in excess, and that Lewis acid complexation of the ester would enhance the rate of reaction relative to that of the uncomplexed ester. Nevertheless, reduction of a monodentate Lewis acid complex (**70**) involving the ester carbonyl should proceed through an *anti*-predictive transition state (**A**) analogous to the nonchelation pathway. Therefore, depending on the nature and amount of Lewis acid present, an interplay between the uncomplexed, monodentate, and bidentate pathways and their respective reaction rates probably determine the stereochemical outcome of the radical reduction.

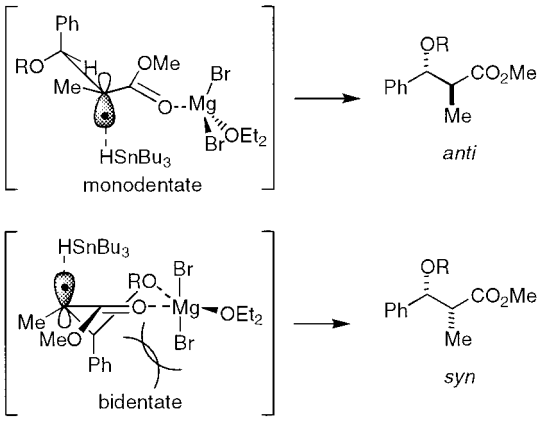
To distinguish between the reactivity of the monodentate and bidentate species, we designed the following competition experiment. A mixture consisting of silyl ether **20** (1 equiv) and methyl ether **13** (1 equiv) was treated with tributyltin hydride (1 equiv) under normal reaction conditions in the presence of $MgBr_2 \cdot OEt_2$. The NMR spectrum of the crude reaction isolate revealed a ∼1:10 mixture of unreacted **20** to **13**, indicating that the silyl ether **20**, reacting through the monodentate species, was consumed ∼10 times faster than the methyl ether **13**, which is expected to react as a bidentate species. In a control experiment to verify that the differential reactivity is attributed to interaction with the Lewis acid and is not inherent to the substrates, the reaction rates of **20** and **13** under radical reduction conditions

(32) Oxygen atoms of hindered silyl ethers are known to be less efficient in complexation with Lewis acids; see Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778 and references therein.

Scheme 6



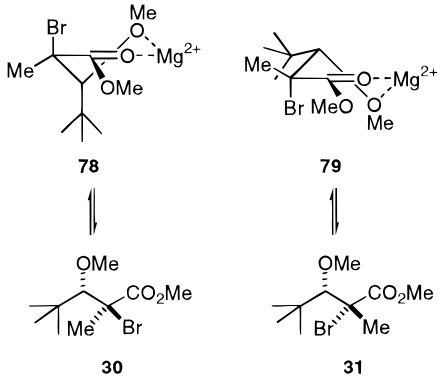
Scheme 7



were found in fact to be similar in the absence of $MgBr_2 \cdot OEt_2$. Therefore, it would appear that the monodentate reacts more rapidly than the bidentate species in the chelation-controlled reduction.

Why is there such a difference between the monodentate and bidentate reaction rates? Assuming that the hydrogen transfer is the rate-determining step, one could attribute the lower reactivity of the bidentate (compared to the monodentate) to destabilization of the bidentate transition state by the developing steric compression between the pseudoaxial Ph and a ligand on the magnesium (i.e. Br or Et_2O) during rehybridization (Scheme 7). An electronic factor contributing to the diminished reactivity of the bidentate may involve the less optimal alignment between the magnesium, ester carbonyl, and the radical p orbital in the bidentate. In such a scenario,

Scheme 8



the SOMO energy of the bidentate radical may actually be greater than that of the monodentate, and the slower reaction rate of the bidentate may be due to a SOMO(bidentate)−HOMO(Bu_3SnH) interaction that is weaker than that of the SOMO(monodentate)−HOMO(Bu_3SnH).

The greater reactivity of the monodentate (compared to the bidentate) may in fact provide a rationale for the anomaly noted earlier, in which the stereochemical outcome appeared to rely on the relative configuration of the substrates **30** and **31** (cf. entries 5−6, Table 3). In a competition experiment in which a mixture of *anti* bromide **30** (1 equiv) and *syn* bromide **31** (1 equiv) was subjected to Bu_3SnH (1 equiv) in the presence of $MgBr_2 \cdot OEt_2$, it was found that **31**, which reacted less selectively (3:1, entry 6), was consumed ∼8 times faster than **30**. By contrast, no difference in rates of reaction was found between the *anti* bromide **13** and its *syn* counterpart **47** (nor between any other pair of diastereomeric bromides shown in Table 3) under similar conditions. The resemblance between the kinetic behavior of *syn* bromide **31** and that of silyl ether **20** in terms of high reactivity and poor selectivity (albeit with opposite stereoselection) would suggest that the bidentate pathway is also disfavored in the Lewis acid mediated reduction of **31**. A comparison of the bidentate chelates **78** and **79** (Scheme 8), which arise from bromides **30** and **31**, respectively, may provide a rationale for the differential reactivity of these diastereomeric substrates. In both *syn*-predictive chelates (**78** and **79**), the bromine would presumably occupy a pseudoaxial position for the maximum overlap with the carbonyl π system to facilitate C−Br bond cleavage. While chelate **78** appears relatively free of destabilizing interactions, the steric compression between the pseudoequatorial *tert*-butyl and α-methyl groups in the bidentate complex **79** may be sufficiently severe to permit the *anti*-selective monodentate pathway to become more competitive.

Taking into account the observations made above, Scheme 6 provides a rationale for the stereochemical outcome of the chelation-controlled hydrogen transfer reaction. At low concentrations (<1 equiv) of $MgBr_2 \cdot OEt_2$, it appears that reaction through the monodentate pathway (**70** → **73** → **2**) is favored to afford *anti* product. Since this pathway is kinetically favored, an excess of $MgBr_2 \cdot OEt_2$ is required to favor bidentate chelate formation prior to homolytic cleavage of the C−Br bond and during the hydrogen transfer step.[33] Although there are two possible bidentate conformers (**71** and **72**) after initial complexation with **13**, chelate **71** should be more reactive

in the homolytic cleavage due to the better overlap of the C−Br bond with the carbonyl π system. This electronic interaction should permit a more facile conversion of **71** to **74** than that of **72** to **75**. Once formed, the radical may exist in the two conformers **74** and **75**, which lead, respectively, to transition states **B** and **C** for the hydrogen transfer step. One would expect a preference for the *syn*-predictive transition state **B** over *anti*-predictive **C** on both electronic and steric grounds. Electronically, the electron-poor radical should be better stabilized by overlap with the C−Ph bond in **B** than with the C−H bond in **C**.[34] From a steric standpoint, **C** appears to suffer from a 1,2-allylic interaction between the phenyl and methyl groups. In the absence of this steric interaction, such as in the case of secondary bromide substrates, the decrease in energy difference between **B** and **C** may well account for the observed erosion in *syn* preference (Table 2, entry 16). Thus the high level of diastereoselectivity exhibited by the chelation-controlled process may be attributed to the prevalence of the *syn*-selective bidentate pathway during both radical formation and the subsequent hydrogen transfer. These hypotheses await verification through kinetic analyses and theoretical evaluation.

Conclusions

Our study of substituent effects clearly establishes the scope and limitations of the chelation-controlled radical reduction of α-bromo-*β*-alkoxy esters. This reaction tolerates a wide variety of substitutions and, except for large groups at position 3, is generally unaffected by the relative configuration of the substrate. In the presence of $MgBr_2{\cdot}OEt_2$, the reduction requires initiation and is inhibited by *m*-DNB, thereby demonstrating behavior typical of radical chain reactions. Other testimony to the intermediacy of radicals are the tandem addition/hydrogen transfer reactions involving α,*β*-unsaturated esters, performed in the presence of a Lewis acid. We are presently evaluating other types of acyclic radical-based reactions that may be subject to kinetic enhancement through chelation.

Experimental Section

General Methods. All reactions requiring anhydrous conditions were conducted under a positive nitrogen atmosphere in oven-dried glassware using standard syringe techniques. The anhydrous solvents purchased from Aldrich were used as received. *i*-Pr_2NH and Et_3N were freshly distilled from CaH_2 under N_2 atmosphere. *n*-BuLi (1.6 M solution in hexane) purchased from Aldrich was titrated prior to use (diphenylacetic acid end-point in dry THF). Bu_3SnH and Et_3B (1 M solution in hexane), also purchased from Aldrich, were used as received. Flash chromatography was performed on Merck silica gel 60 (0.040−0.063 mm) using nitrogen pressure. Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25 mm) Merck silica gel F-254 plates. Melting points were determined on an electrothermal melting point apparatus and are uncorrected.

General Procedure for the Preparation of Methyl Cinnamates 4 and 5. A solution of LDA was prepared by the addition of *n*-BuLi (1.25 equiv) to a solution of *i*-Pr_2NH (1.25 equiv) in anhydrous THF (1.5 M) at 0 °C. After being stirred for 20 min at 0 °C, the solution was cooled to −78 °C, and a solution of an appropriate acetate (1 equiv) in THF (1.5 M solution) was added. The reaction mixture was stirred at this temperature for 45 min before benzaldehyde (1 equiv) was added. The mixture was then quenched by adding a saturated aqueous NH_4Cl solution and extracted with Et_2O (3×). The organic extracts were combined and washed with a saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), filtered, and concentrated. To a cold (0 °C) solution of this residue in dry pyridine (1.5 M) was added mesyl chloride (4.8 equiv). The reaction mixture was stirred overnight at 25 °C, diluted with Et_2O (200 mL), and successively washed with a cold 10% aqueous HCl solution (2 × 50 mL), water, a saturated aqueous $NaHCO_3$ solution, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. To a solution of the residue in dry toluene (2 M) was added DBU (5.5 equiv), and the resultant solution was refluxed for 1.5 h. The reaction mixture was then diluted with Et_2O (150 mL) and successively washed with a 10% aqueous HCl solution (3 × 50 mL), water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. To a solution of the residue in absolute MeOH was added sodium carbonate (1.1 equiv). The reaction mixture was refluxed for 2.5 days, diluted with water (10 mL), and extracted with Et_2O (4×). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was flash chromatographed on silica gel (2% EtOAc−hexane) to afford the desired olefins.

Methyl α-*tert*-Butylcinnamate (4). The olefin **4** was prepared from methyl *tert*-butylacetate (without the transesterification step) and was isolated as a colorless oil (mixture of isomers E/Z = 1/1.5, 54% overall yield); IR (neat) ν_{max} 1720, 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 (s, 9H (minor)), 1.24 (s, 9H (major)), 3.63 (s, 3H (major)), 3.79 (s, 3H (minor)), 6.55 (s, 1H (major)), 7.14 (s, 1H (minor)), 7.16−7.36 (m, 10H (minor + major)); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 29.0, 30.5, 34.9, 35.1, 50.9, 51.0, 126.0, 126.6, 127.1, 127.3, 127.5, 127.7, 127.9, 133.7, 136.1, 137.5, 144.4, 144.5, 170.4 (C═O), 170.5 (C═O); MS (CI, CH_4) *m/e* (relative intensity) 219 (MH^+, 100), 187 (52); HRMS calcd for $C_{14}H_{18}O_2$ (M^+) 218.1307, found 218.1301 (2.5 ppm). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.14; H, 8.53.

General Procedure for the Preparation of Substrates 10−16 by Methoxy-bromination.[13] To a cold (0 °C) solution of the appropriate methyl cinnamate **4**−**9** (1 equiv) in absolute MeOH (3.5 M) were successively added $AgNO_3$ (1.2 equiv) and Br_2 (1.2 equiv). The reaction mixture was stirred at 25 °C for 1 h and then filtered and concentrated. The residue was purified by flash chromatography on silica gel to afford the desired bromides.

Methyl (±)-(2*R,3*S**)-2-Bromo-2-*tert*-butyl-3-methoxy-3-phenylpropionate (10).** After flash chromatography on silica gel (8% Et_2O−hexane), the bromide **10** was obtained as a white solid (84% yield); mp = 58−59 °C; IR (neat) ν_{max} 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 9H), 3.11 (s, 3H), 3.83 (s, 3H), 4.82 (s, 1H), 7.34−7.37 (m, 3H), 7.68−7.71 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.6, 38.4, 52.7, 55.9, 84.4, 86.0, 127.4, 128.5, 130.0, 136.7, 169.6 (C═O); MS (CI, NH_3) *m/e* (relative intensity) 348 (MNH_4^+, 98), 346 (MNH_4^+, 100), 331 (MH^+, 12), 329 (MH^+, 12).

Methyl (±)-(2*S,3*S**)-2-Bromo-2-methyl-3-hydroxy-3-phenylpropionate (17).** To a solution of methyl α-methylcinnamate **6** (1.46 g, 8.3 mmol) in a mixture of acetone (19.4 mL) and water (29 mL) were successively added NBS (2.95 g, 16.6 mmol) and H_2SO_4 (144 μL).[3c] The reaction mixture was stirred overnight at 25 °C and then poured into brine and extracted with Et_2O (3×). The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated. The residue was flash chromatographed on silica gel (15% EtOAc−hexane) to afford the alcohol **17** (1.28 g, 56% yield). White solid (mp = 50−51 °C); IR (neat) ν_{max} 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.80 (s, 3H), 3.16 (d, 1H, J = 5.1 Hz), 3.84 (s, 3H), 5.32 (d, 1H, J = 5.1 Hz), 7.31−7.38 (m, 3H), 7.44−7.48 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.4, 52.8, 61.4, 77.0, 127.1, 127.8, 128.1, 137.1, 171.2 (C═O); HRMS calcd for $C_{11}H_{13}$-

(33) In the same manner that oxygen-containing solvents (e.g. THF) can stabilize Grignard reagents through coordination with magnesium, the bidentate chelate may be more stable than the monodentate form when $MgBr_2{\cdot}OEt_2$ is present in excess relative to the substrate.

(34) (a) See refs 4c and 4e. (b) Curran, D. P.; Balas, L. *Synlett* **1995**, 119.

BrO_3 (M^+) 272.0055, found 272.0048 (−2.5 ppm). Anal. Calcd for $C_{11}H_{13}BrO_3$: C, 48.37; H, 4.80. Found: C, 48.41; H, 4.73.

Methyl (±)-(2*S,3*S**)-2-Bromo-2-methyl-3-bromo-3-phenylpropionate (18).** To a solution of methyl α-methylcinnamate **6** (5.04 g, 28.6 mmol) in CCl_4 (in the dark) was added Br_2 (3.0 mL, 57.3 mmol). The reaction mixture was stirred overnight at 25 °C and then concentrated. The residue was flash chromatographed on silica gel (3% EtOAc−hexane) to afford the desired dibromoester **18** (8.28 g, 86% yield). White solid (mp = 49−50 °C); IR (neat) ν_{max} 1740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.06 (s, 3H), 3.90 (s, 3H), 5.76 (s, 1H), 7.35−7.38 (m, 3H), 7.50−7.60 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 22.0, 53.4, 57.2, 61.3, 127.6, 128.9, 130.7, 135.1, 169.6 (C=O); HRMS calcd for $C_{12}H_{12}Br_2O_2$ (M^+) 333.9205, found 333.9205 (0.1 ppm).

Methyl (±)-(2*S,3*S**)-2-Bromo-2-methyl-3-(benzyloxy)-3-phenylpropionate (19).** To a solution of alcohol **17** (509 mg, 1.9 mmol) in a mixture of cyclohexane (13 mL) and CH_2Cl_2 (7 μL) were successively added benzyl 2,2,2-trichloroacetimidate (694 mL, 3.7 mmol) and trifluoromethanesulfonic acid (98 μL).[15] The reaction mixture was stirred for 2.5 h at 25 °C and then filtered and successively washed with a saturated aqueous $NaHCO_3$ solution, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was flash chromatographed on silica gel (5% Et_2O−hexane) to afford the benzyl ether **19** (505 mg, 74% yield). Colorless oil; IR (neat) ν_{max} 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.79 (s, 3H), 3.75 (s, 3H), 4.30 (d, 1H, J = 11.4 Hz), 4.45 (d, 1H, J = 11.4 Hz), 5.13 (s, 1H), 7.15−7.53 (m, 10 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.5, 52.9, 60.3, 71.7, 83.9, 127.6, 127.7, 128.2, 128.5, 129.6, 134.9, 137.4, 171.0 (C=O); MS (CI, NH_3) *m/e* (relative intensity) 382 (MNH_4^+, 98), 380 (MNH_4^+, 100); HRMS calcd for $C_{14}H_{13}O$ ($M^+ - C_4H_6BrO_3$) 197.0966, found 197.0970 (−2.0 ppm).

Methyl (±)-(2*S,3*S**)-2-Bromo-2-methyl-3-(*tert*-butyldimethylsilyloxy)-3-phenylpropionate (20).** To a cold (0 °C) stirred solution of alcohol **17** (1.51 g, 5.5 mmol) in dry CH_2Cl_2 were successively added Et_3N (1.2 mL, 8.3 mmol) and *t*-$BuMe_2$-SiOTf (1.5 mL, 6.6 mmol).[16] The reaction mixture was stirred at 25 °C for 2 h and then diluted with Et_2O and successively washed with a 10% aqueous K_2CO_3, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was flash chromatographed on silica gel (1.5% EtOAc−hexane) to afford the silyl ether **20** (1.63 g, 76% yield). Colorless oil; IR (neat) ν_{max} 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ −0.35 (s, 3H), 0.01 (s, 3H), 0.84 (s, 9H), 1.80 (s, 3H), 3.82 (s, 3H), 5.37 (s, 1H), 7.29−7.36 (m, 3H), 7.43−7.47 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −5.9, −4.7, 17.7, 20.8, 25.4, 52.6, 61.7, 78.1, 127.1, 128.1, 129.2, 137.8, 170.9 (C=O); MS (CI, isobutane) *m/e* (relative intensity) 389 (MH^+, 10), 387 (MH^+, 9), 257 (100), 255 (100). Anal. Calcd for $C_{17}H_{27}BrO_3Si$: C, 52.71; H, 7.03. Found: C, 52.55; H, 7.28.

Methyl (±)-2-Bromo-2-methyl-3-(isopropyloxy)-3-phenylpropionates (21 and 22). To a solution of dibromoester **18** (1.52 g, 4.5 mmol) in *i*-PrOH (14 mL) was added $AgBF_4$ (1.06 g, 5.4 mmol). The reaction mixture was stirred at 60 °C for 1 h and then filtered and concentrated. The residue was flash chromatographed on silica gel (3% Et_2O−hexane) to afford a mixture of isopropyl ethers **21** and **22** (1.18 g, 82% yield). The two diastereomers can be separated using the above conditions. Compound **21** (less polar isomer): colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, 3H, J = 6.0 Hz), 1.07 (d, 3H, J = 6.0 Hz), 1.74 (s, 3H), 3.50 (h, 1H, J = 6.0 Hz), 3.84 (s, 3H), 5.10 (s, 1H), 7.31−7.40 (m, 3H), 7.47−7.50 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.9, 21.4, 23.0, 52.6, 60.7, 71.0, 82.0, 127.3, 128.1, 129.4, 136.3, 170.9 (C=O). Compound **22** (more polar isomer): colorless oil; IR (neat) ν_{max} 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (d, 3H, J = 6.0 Hz), 1.22 (d, 3H, J = 6.0 Hz), 1.77 (s, 3H), 3.58 (h, 1H, J = 6.0 Hz), 3.73 (s, 3H), 4.94 (s, 1H), 7.29−7.37 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.0, 22.6, 23.0, 52.6, 65.3, 71.0, 82.2, 127.8, 128.2, 128.4, 137.3, 170.4 (C=O); Mixture of isomers; colorless oil; MS (CI, isobutane) *m/e* (relative intensity) 317 (MH^+, 100), 315 (MH^+, 100). Anal. Calcd for $C_{14}H_{19}BrO_3$: C, 53.35; H, 6.08. Found: C, 53.19; H, 6.01.

Methyl (±)-2-Bromo-2-methyl-3-phenylbutanoates (23 and 24). A solution of LDA was prepared by the addition of a 1.6 M solution of *n*-BuLi in hexane (16.7 mL, 26.7 mmol) to a cold (0 °C) solution of *i*-Pr_2NH (3.75 mL, 26.7 mmol) in dry THF (20 mL). After being stirred for 20 min at 0 °C, the solution was cooled to −78 °C, and a solution of methyl 3-phenylbutanoate (4.00 g, 22.3 mmol) in THF (15 mL) was added. The reaction mixture was stirred at this temperature for 1 h before MeI (1.67 mL, 26.8 mmol) was added. The mixture was then slowly allowed to warm to 25 °C, diluted with ether, and successively washed with 10% aqueous HCl, 10% aqueous $Na_2S_2O_3$, water, and brine. The residue was then dried ($MgSO_4$) and purified by flash chromatography on silica gel (4% Et_2O−hexane) to afford methyl 2-methyl-3-phenylbutanoates **64** and **65** (3.86 g, 90% yield) as a mixture of diastereomers. The diastereomers can be separated using the above conditions. Less polar isomer: colorless oil; IR (neat) ν_{max} 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, 3H, J = 6.7 Hz), 1.24 (d, 3H, J = 7.0 Hz), 2.56−2.64 (m, 1H), 2.86−2.94 (m, 1H), 3.70 (s, 3H), 7.14−7.21 (m, 3H), 7.24−7.30 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.1, 20.6, 43.4, 46.7, 51.3, 126.4, 127.4, 128.4, 144.2, 176.6 (C=O); HRMS calcd for $C_{12}H_{16}O_2$ (M^+) 192.1150, found 192.1147 (1.6 ppm). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.87; H, 8.59. More polar isomer: colorless oil; IR (neat) ν_{max} 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, 3H, J = 7.0 Hz), 1.27 (d, 3H, J = 7.3 Hz), 2.63−2.70 (m, 1H), 3.02−3.10 (m, 1H), 3.47 (s, 3H), 7.16−7.20 (m, 3H), 7.22−7.29 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.5, 16.9, 41.8, 46.1, 50.5, 125.8, 126.8, 127.7, 144.4, 175.1 (C=O); HRMS calcd for $C_{12}H_{16}O_2$ (M^+) 192.1150, found 192.1146 (4.4 ppm). A solution of LDA was prepared by the addition of a 1.6 M solution of *n*-BuLi in hexane (3.9 mL, 6.2 mmol) to a cold (0 °C) solution of *i*-Pr_2NH (875 μL, 6.2 mmol) in dry THF (5 mL). After being stirred for 20 min at 0 °C, the solution was cooled to −78 °C and a solution of methyl 2-methyl-3-phenylbutanoates **64** and **65** (1.00 g, 5.2 mmol) in THF (3.5 mL) was added. The reaction mixture was stirred at this temperature for 1 h before a solution of CBr_4 (1.90 g, 5.7 mmol) in THF (4 mL) was added. The mixture was then slowly allowed to warm to 25 °C, diluted with Et_2O, and successively washed with 10% aqueous HCl, water, and brine. The residue was then filtered through a pad of silica gel (200 mL, 15% EtOAc−hexane) and flash chromatographed on silica gel (5% Et_2O−hexane) to afford methyl 2-bromo-2-methyl-3-phenylbutanoates **23** and **24** (1.06 g, 75% yield) as a pale red oil (5:1 mixture of diastereomers). Colorless oil; IR (neat) ν_{max} 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, 3H, J = 7.3 Hz (minor)), 1.55 (d, 3H, J = 7.3 Hz (major)), 1.82 (s, 3H (major)), 1.85 (s, 3H (minor)), 3.61 (q, 1H, J = 7.0 Hz (minor)), 3.66 (q, 1H, J = 7.0 Hz (major)), 3.70 (s, 3H (major)), 3.78 (s, 3H (minor)), 7.22−7.32 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) (major diastereomer) δ 17.2, 24.6, 47.8, 52.7, 67.0, 127.3, 128.0, 129.1, 139.6, 171.5 (C=O); ^{13}C NMR (100.6 MHz, $CDCl_3$) (minor diastereomer) δ 16.9, 24.6, 48.3, 52.9, 65.8, 127.2, 127.7, 129.5, 140.2, 171.5 (C=O); HRMS calcd for $C_{12}H_{15}BrO_2$ (M^+) 270.0255, found 270.0262 (−2.5 ppm).

1-Methoxy-1-(trimethylsilyloxy)-2-bromopropene (25). A solution of LDA was prepared by the addition of a 1.6 M solution of *n*-BuLi in hexane (44.8 mL, 71.7 mmol) to a cold (0 °C) solution of *i*-Pr_2NH (10 mL, 71.4 mmol) in dry THF (54 mL). After being stirred for 20 min at 0 °C, the solution was cooled to −78 °C, and a solution of methyl 2-bromopropionate (8 mL, 71.7 mmol) was added. The reaction mixture was stirred for 15 min before Me_3SiCl (20 mL, 157.6 mmol) was added. The mixture was then slowly allowed to warm to 25 °C, stirred at this temperature for 1 h and then filtered and concentrated. The residue was taken up in hexane, and the resultant solution was filtered twice. After concentration, the residue was distilled under reduced pressure (10 mmHg, 85 °C) to afford the desired silyl ketene acetal **25** (12.61 g, 74% yield) as a colorless liquid (mixture of *E* and *Z* isomers, and ∼30% of C-silylated material) that was used without further purification.

General Procedure for the Preparation of Substrates 26−31 and 47 Using Mukaiyama's Protocol.[17] To a cold

(−78 °C) solution of the appropriate dimethylacetal (1 equiv) in dry CH_2Cl_2 (2 M) were successively added a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (1 equiv) and a solution of the silyl ketene acetal **25** (2 equiv) in CH_2Cl_2. The reaction mixture was stirred for 4 h at −78 °C and 15 min at 0 °C and was poured into a 10% aqueous K_2CO_3. After the aqueous layer was extracted with CH_2Cl_2 (3×), the organic extracts were combined, successively washed with water and brine, dried ($MgSO_4$), filtered through a pad of silica gel, and concentrated.

Methyl (±)-2-Bromo-2,4-dimethyl-3-methoxypentanoates (26 and 27). Each diastereomer, prepared from isobutyraldehyde dimethylacetal, can be obtained in pure form by flash chromatography on silica gel (3% Et_2O−hexane, 75% yield). Compound **26** (less polar isomer): colorless oil; IR (neat) ν_{max} 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 7.0 Hz), 1.02 (d, 3H, J = 6.7 Hz), 1.65−1.75 (m, 1H), 1.85 (s, 3H), 3.62 (d, 1H, J = 5.7 Hz), 3.65 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.0, 21.4, 22.1, 32.2, 52.7, 62.9, 65.6, 89.3, 171.1 (C=O); MS (CI, NH_3) *m/e* (relative intensity) 270 (MNH_4^+, 100); HRMS calcd for $C_6H_{10}O_3Br$ ($M^+ - C_3H_7$) 208.9813, found 208.9822 (−4.4 ppm). Compound **27** (more polar isomer): colorless oil; IR (neat) ν_{max} 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, 3H, J = 7.0 Hz), 1.14 (d, 3H, J = 7.0 Hz), 1.84 (s, 3H), 2.21−2.32 (m, 1H), 3.45 (s, 3H), 3.69 (d, 1H, J = 3.2 Hz), 3.80 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.7, 22.5, 24.3, 29.2, 52.7, 61.3, 62.5, 88.5, 171.2 (C=O); MS (CI, NH_3) *m/e* (relative intensity) 270 (MNH_4^+, 100).

***N,N*-Diethyl-(±)-(2*S**,3*S**)-2-bromo-2-methyl-3-methoxy-3-phenylpropionamide (32).** To a solution of α-methylcinnamic acid (1.03 g, 6.3 mmol) and Br_2 (390 μL, 7.6 mmol) in absolute MeOH (36 mL) was added $AgNO_3$ (1.29 g, 7.6 mmol). After being stirred for 45 min at 25 °C, the reaction mixture was filtered and concentrated. The residue was diluted with Et_2O and successively washed with 10% aqueous $Na_2S_2O_3$, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford the desired α-bromoacid (1.72 g, 99% yield). To a solution of the crude acid (1.50 g, 5.5 mmol) in dry toluene (2 mL) were successively added oxalyl chloride (1.44 mL, 16.5 mmol) and a catalytic amount of DMF (100 μL). After being stirred for 1 h at 25 °C, the reaction mixture was concentrated, and the residue was dissolved in dry CH_2Cl_2 (8 mL). To the cold (−78 °C) solution of crude acyl chloride was added Et_2NH (1.25 mL, 12.1 mmol). The reaction mixture was slowly allowed to warm to 25 °C and then diluted with Et_2O and successively washed with saturated aqueous $NaHCO_3$, 10% aqueous HCl, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was flash chromatographed on silica gel (10% EtOAc−hexane) to afford the α-bromoamide **32** (1.31 g, 72% yield). White solid (mp = 68−69 °C); IR ($CHCl_3$) ν_{max} 2990, 2930, 1620, 1450, 1370, 1270, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, 6H, J = 7.0 Hz), 1.85 (s, 3H), 3.26 (s, 3H), 3.30−3.48 (m, 2H), 3.70−3.88 (m, 2H), 4.85 (s, 1H), 7.34−7.39 (m, 3H), 7.43−7.46 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 26.1, 42.5, 57.7, 62.5, 86.8, 127.6, 128.3, 129.4, 135.8, 168.0 (C=O); MS (CI, NH_3) *m/e* (relative intensity) 328 (MH^+, 100), 248 (82); HRMS calcd for $C_{15}H_{23}NO_2Br$ (M^+) 328.0912, found 328.0900 (3.7 ppm).

General Procedure for Radical Reduction under Chelation-Controlled Conditions (Conditions A). To a stirred suspension of $MgBr_2 \cdot OEt_2$ (5 equiv) in dry CH_2Cl_2 was added α-bromoester in CH_2Cl_2 (0.1 M). After being stirred for 5 min at 25 °C, the reaction mixture was cooled to 0 °C, and Bu_3SnH was then added. Triethylborane (1 M solution in hexane) was subsequently added in three equal portions during the first 15 min of the reaction (3 × 0.2 equiv, total of 0.6 equiv). After 2 h at 0 °C, *m*-dinitrobenzene (0.5 equiv) was added, and the mixture was poured into a saturated aqueous $NaHCO_3$. The aqueous layer was extracted (3×) with CH_2Cl_2, and the organic extracts were combined, successively washed with water and brine, and dried ($MgSO_4$). GC analysis was performed on the crude reaction isolate. After filtration and concentration, the residue was taken up in hexane and *n*-Bu_4NF was added (2.5 equiv). After being stirred for 5 min at 25 °C, the mixture was filtered through a short pad of silica gel (100 mL, 15% EtOAc−hexane) and concentrated.

Methyl (±)-2-(2-Chloroethyl)-3-hydroxy-3-phenylpropionate 53. To a warmed (80 °C) solution of alcohol **52**[25] (1.00 g, 5.2 mmol) and ICH_2Cl (1.9 mL, 26.1 mmol) in dry toluene (19 mL) was slowly added, over a period of 2 h, a solution of Bu_3SnH (2.80 mL, 10.4 mmol) and AIBN (128 mg, 0.8 mmol) in toluene (8 mL). The reaction mixture was then stirred overnight at 25 °C, concentrated, diluted with hexane, and treated with a 1.0 M solution of *n*-Bu_4NF in THF (12.5 mL, 12.5 mmol). The mixture was filtered through a short pad of silica gel (200 mL, 40% EtOAc−hexane) and concentrated. The residue was flash chromatographed on silica gel (20% EtOAc−hexane) to afford a mixture of alcohols **53a** and **53b** (1.03 g, 82% yield). Less polar alcohol; colorless oil; IR (neat) ν_{max} 3470, 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.96−2.32 (m, 2H), 2.76 (d, 1H, J = 3.3 Hz), 2.93−3.04 (m, 1H), 3.37−3.65 (m, 2H), 3.66 (s, 3H), 5.08 (dd, 1H, J = 3.3, J = 4.8 Hz), 7.28−7.37 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 29.6, 42.7, 50.2, 51.5, 73.6, 125.6, 127.4, 128.0, 141.1, 173.7 (C=O). More polar isomer; colorless oil; IR (neat) ν_{max} 3460 (br), 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72−1.89 (m, 1H), 2.01−2.19 (m, 1H), 2.88 (d, 1H, J = 5.5 Hz), 2.99−3.10 (m, 1H), 3.34−3.56 (m, 2H), 3.71 (s, 3H), 4.83 (dd, 1H, J = 5.5, J = 7.5 Hz), 7.28−7.44 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 31.2, 41.8, 50.2, 51.3, 74.4, 126.1, 127.6, 127.9, 141.0, 174.0 (C=O); HRMS calcd for $C_{12}H_{16}ClO_3$ (MH^+) 243.0788, found 243.0795 (−2.9 ppm). Anal. Calcd for $C_{12}H_{15}ClO_3$: C, 59.39; H, 6.23. Found: C, 59.03; H, 6.13.

Methyl α-(2-Chloroethyl)cinnamate 54. To a cold (0 °C) solution of the Martin sulfurane dehydrating agent[35] (1.07 g, 1.6 mmol) in dry CH_2Cl_2 (4 mL) was added a solution containing a mixture of the alcohols **53a** and **53b** (320 mg, 1.3 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was slowly allowed to warm to 25 °C, stirred for 1 h and then diluted with Et_2O and successively washed with aqueous 10% NaOH, water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was flash chromatographed on silica gel (4% EtOAc−hexane) to afford the olefin **54** (237 mg, 1.1 mmol, 84% yield). Colorless oil; IR (neat) ν_{max} 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.03 (t, 2H, J = 7.5 Hz), 3.73 (t, 2H, J = 7.5 Hz), 3.85 (s, 3H), 7.37−7.45 (m, 5H), 7.85 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 30.8, 42.5, 52.0, 128.5, 128.6, 128.7, 129.0, 134.8, 142.1, 167.8 (C=O); HRMS calcd for $C_{12}H_{14}O_2Cl$ (MH^+) 225.0682, found 225.0678 (1.9 ppm). Anal. Calcd for $C_{12}H_{13}ClO_2$: C, 64.34; H, 5.85. Found: C, 64.03; H, 5.75.

Methyl (±)-(2*S,3*S**)-2-Bromo-2-(2-chloroethyl)-3-methoxy-3-phenylpropionate 48.** To a solution of olefin **54** (174 mg, 0.8 mmol) in absolute MeOH (1 mL) were successively added Br_2 (48 μL, 0.9 mmol) and $AgNO_3$ (158 mg, 0.9 mmol). The reaction mixture was stirred for 5 h at 25 °C, filtered, and concentrated. The residue was diluted with Et_2O, successively washed with 10% aqueous $Na_2S_2O_3$, water, and brine, and dried ($MgSO_4$). After filtration and concentration, the residue was flash chromatographed on silica gel (3% EtOAc−hexane) to afford the α-bromoester **48** (158 mg, 62% yield). Colorless oil; IR (neat) ν_{max} 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.27−2.35 (m, 1H), 2.65−2.73 (m, 1H), 3.26 (s, 3H), 3.59−3.66 (m, 1H), 3.83 (s, 3H), 3.84−3.92 (m, 1H), 4.85 (s, 1H), 7.36−7.47 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 38.2, 41.6, 53.2, 57.9, 64.8, 87.1, 127.9, 128.8, 129.1, 134.2, 169.6 (C=O); HRMS calcd for $C_{13}H_{17}BrClO_3$ (MH^+) 335.0050, found 335.0065 (−4.6 ppm).

Methyl (±)-2-(1-Methoxy-1-phenylmethyl)propenoate 49. To a solution of alcohol **52**[25] (500 mg, 2.6 mmol) in dry CH_2Cl_2 (3 mL) were successively added proton sponge (2.80 g, 13.0 mmol) and MeOTf (1.5 mL, 13.0 mmol). The reaction mixture was stirred overnight at 25 °C, diluted with Et_2O, and successively washed with 10% aqueous HCl (2×), water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was flash chromatographed on

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silica gel (5% EtOAc−hexane) to afford the methyl ether **49** (460 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.71 (s, 3H), 5.14 (s, 1H), 5.94 (s, 1H), 6.34 (s, 1H), 7.27−7.38 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 50.9, 56.1, 80.4, 123.8, 127.0, 127.7, 139.1, 140.9, 165.4 (C=O); IR (neat) ν_{max} 1720, 1630 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.90; H, 7.05.

Methyl (±)-2-(1-Methoxyethyl)propenoate 55. To a solution of methyl 2-(1-hydroxyethyl)propenoate[36] (2.01 g, 15.5 mmol) in dry CH_2Cl_2 (19 mL) were successively added proton sponge (16.6 g, 77.5 mmol) and MeOTf (8.7 mL, 77.5 mmol). The reaction mixture was stirred overnight at 25 °C, diluted with Et_2O, and successively washed with 10% aqueous HCl (2×), water, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford the methyl ether **55** (1.55 g, 70% yield). IR (neat) ν_{max} 1720, 1630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, 3H, J = 6.4 Hz), 3.31 (s, 3H), 3.78 (s, 3H), 4.22 (q, 1H, J = 6.4 Hz), 5.86 (s, 1H), 6.29 (s, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 20.7, 51.2, 55.9, 75.0, 123.8, 141.4, 166.0 (C=O).

General Procedure for Radical Reduction in the Absence of a Lewis Acid (Conditions B). To a cold (0 °C) stirred solution of the α-bromoester in dry CH_2Cl_2 (0.1 M) were added Bu_3SnH (2 equiv) and Et_3B (3 × 0.2 equiv during the first 15 min of reaction). After the reaction mixture was stirred at 0 °C for 2 h, *m*-dinitrobenzene (0.5 equiv) was added, and the mixture was concentrated. GC analysis was performed on the crude reaction isolate. The residue was taken up in hexane, and the resultant solution was treated with *n*-Bu_4NF (2.5 equiv). After being stirred for 5 min at 25 °C, the mixture was filtered through a short pad of silica gel (100 mL, 15% EtOAc−hexane) and concentrated.

Methyl (±)-2-Methyl-3-methoxy-3-phenylpropanoates (2 and 3). The ratio of **2** and **3** was determined by GC analysis of the crude isolate arising from the radical reduction of **13** or **47**. They were purified by flash chromatography on silica gel by using 5% EtOAc−hexane. Compound **2**[37] **(2*S**,3*S**)** was isolated as a colorless oil; IR (neat) ν_{max} 1740 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, 3H, J = 7.1 Hz), 2.77 (dq, 1H, J = 9.8, J = 7.1 Hz), 3.15 (s, 3H), 3.76 (s, 3H), 4.24 (d, 1H, J = 9.8 Hz), 7.25−7.42 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 13.9, 46.9, 51.7, 56.7, 85.9, 127.6, 128.2, 128.4, 138.9, 175.7 (C=O); HRMS calcd for $C_{12}H_{16}O_3$ (M^+) 208.1099, found 208.1094 (−2.3 ppm).

Compound 3[36] **(2*R**,3*S**).** Colorless oil; IR ($CDCl_3$) ν_{max} 1735 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (d, 3H, J = 7.1 Hz), 2.74 (dq, 1H, J = 7.1, J = 6.7 Hz), 3.24 (s, 3H), 3.55 (s, 3H), 4.44 (d, 1H, J = 6.7 Hz), 7.19−7.41 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 12.2, 47.3, 51.3, 57.0, 84.2, 126.9, 127.7, 128.1, 139.6, 174.3 (C=O); HRMS calcd for $C_{12}H_{16}O_3$ (M^+) 208.1099, found 208.1105 (−3.0 ppm).

Methyl (±)-2-Methyl-3-methoxybutanoates (33 and 34).[38,39] The ratio of **33 (2*R**,3*S**)** and **34 (2*S**,3*S**)** was determined by GC and ^{1}H NMR analyses of the crude isolate arising from the radical reduction of **16**.

Methyl (±)-2,4-Dimethyl-3-methoxypentanoates (35 and 36). The ratio of **35** and **36** was determined by GC analysis of the crude reaction isolate arising from the radical reduction of **26** (conditions A and B). The residue was purified by flash chromatography on silica gel by using 5% Et_2O−hexane.

Methyl (±)-2-Methyl-3-cyclohexyl-3-methoxypropanoates (37 and 38). The ratio of **37** and **38** was determined by GC analysis of the crude reaction isolate arising from the radical reduction of **28** or **29**. They were separated by flash chromatography on silica gel by using 4% EtOAc−hexane.

Methyl (±)-3-Methoxy-2,4,4-trimethylpentanoates (39 and 40). The ratio of **39** and **40** was determined by GC analysis of the crude reaction isolate arising from the radical reduction of **30** or **31**. The compounds were separated by flash chromatography on silica gel by using 2% Et_2O−hexane.

Methyl (±)-2-Isopropyl-3-methoxy-3-phenylpropanoates (41 and 42). The ratio of **41** and **42** was determined by GC analysis of the crude reaction isolate arising from the radical reduction of **11**. The compounds were purified by flash chromatography on silica gel by using 6% Et_2O−hexane.

Methyl (±)-2-*tert*-Butyl-3-methoxy-3-phenylpropanoates (43 and 44). The ratio of **43** and **44** was determined by GC analysis of the crude reaction isolate arising from the radical reduction of **10**. The compounds were separated by flash chromatography on silica gel by using 5% Et_2O−hexane.

Methyl (±)-2-Deutero-3-methoxy-3-phenylpropanoate (45 and 46). The ratio of **45** and **46** was determined by ^{1}H NMR analysis of the crude reaction isolate arising from the radical reduction of **14**. The compounds were purified by flash chromatography on silica gel (4% EtOAc−hexane).

Methyl (±)-2-Methyl-3-(benzyloxy)-3-phenylpropanoates (58 and 59). The ratio of **58** and **59** was determined by ^{1}H NMR analysis of the crude reaction isolate arising from the radical reduction of **19**. The compounds were separated by flash chromatography on silica gel by using 7% Et_2O−hexane.

Methyl (±)-2-Methyl-3-(isopropyloxy)-3-phenylpropanoates (60 and 61). The ratio of **60** and **61** was determined by ^{1}H NMR and GC analyses of the crude reaction isolate arising from the radical reduction of **22**. The compounds were separated by flash chromatography on silica gel by using 4% EtOAc−hexane.

Methyl (±)-2-Methyl-3-(*tert*-butyldimethylsilyloxy)-3-phenylpropanoates (62 and 63). The ratio of **62** and **63** was determined by ^{1}H NMR analysis of the crude reaction isolate arising from the reduction of **20**. The compounds were purified by flash chromatography on silica gel by using 2% EtOAc−hexane.

Methyl (±)-2-Methyl-3-phenylbutanoates (64 and 65). The ratio of **64** and **65** was determined by ^{1}H NMR analysis of the crude reaction isolate arising from the radical reduction of a 5:1 mixture of **23** and **24**. The compounds were separated by flash chromatography on silica gel by using 4% Et_2O−hexane.

***tert*-Butyl (±)-2-Methyl-3-methoxy-3-phenylpropanoates (66 and 67).** The ratio of **66** and **67** was determined by GC analysis of the crude reaction isolate arising from the radical reduction of **15**. The compounds were separated by flash chromatography on silica gel by using 4% Et_2O−hexane.

***N,N*-Diethyl (±)-2-Methyl-3-methoxy-3-phenylpropionamides (68 and 69).** The ratio of **68** and **69** was determined by ^{1}H NMR analysis of the crude reaction isolate arising from the radical reduction of **32**. The compounds were separated by flash chromatography on silica gel by using 25% EtOAc−hexane.

Methyl (±)-2-(2-Chloroethyl)-3-methoxy-3-phenylpropionates 50 and 51. The ratio of **50** and **51** was determined by GC analysis of the crude reaction isolate arising from the radical reduction of **48** or from the addition reaction on **49** as described below.

Under Chelation Control. To a cold (0 °C), stirred suspension of $MgBr_2{\cdot}OEt_2$ (735 mg, 2.8 mmol) in dry CH_2Cl_2 (33 mL) were successively added a solution of ester **49** (293 mg, 1.4 mmol) in CH_2Cl_2 (6 mL), ICH_2Cl (518 μL, 7.0 mmol), a 1.0 M solution of Et_3B in hexane (280 μL, 0.28 mmol), and Bu_3SnH (765 μL, 2.84 mmol). After being stirred for 2 h at 0 °C, the mixture was poured into a saturated aqueous $NaHCO_3$, and the aqueous layer was extracted (3×) with CH_2Cl_2. The organic extracts were combined, successively washed with water and brine, and dried ($MgSO_4$). ^{1}H NMR analysis of the crude reaction isolate, performed to determine the ratio of **50** and **51**, revealed also the presence of methyl α-methylcinnamate **6** (ca. 45%) and unreacted substrate **49** (ca. 13%).

In the Absence of Lewis Acid. To a cold (0 °C), stirred solution of olefin **49** (207 mg, 1.0 mmol) and ICH_2Cl (366 μL, 5.0 mmol) in dry CH_2Cl_2 (23 mL) was slowly added over 2.5 h a solution of Bu_3SnH (541 μL, 2.0 mmol) in CH_2Cl_2 (5 mL). During the addition of Bu_3SnH, a 1.0 M solution of Et_3B in

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hexane was added in three equal portions (3 × 67 μL, 0.2 mmol). The reaction mixture was stirred for an additional 30 min at 0 °C and then concentrated. ^{1}H NMR analysis of the crude reaction isolate was performed to determine the ratio of **50** and **51**. The residue was taken up in hexane, and to the resultant solution was added a 1.0 M solution of *n*-Bu_4NF in THF (2.4 mL, 2.4 mmol). After being stirred for 5 min at 25 °C, the mixture was filtered through a short pad of silica gel (200 mL, 20% EtOAc−hexane) and concentrated. The residue was flash chromatographed on silica gel (4% EtOAc−hexane) to afford a mixture of ester **50** and **51** (125 mg, 49% yield). The two diastereomers can be separated by performing a second flash column chromatography using the above conditions. Ester **50** (*syn*): colorless oil; IR (neat) ν_{max} 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.18−2.29 (m, 2H), 2.88−2.93 (m, 1H), 3.22 (s, 3H), 3.45−3.61 (m, 2H), 3.50 (s, 3H), 4.40 (d, 1H, J = 7.3 Hz), 7.24−7.37 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 31.0, 42.9, 50.9, 51.5, 57.0, 83.9, 126.9, 128.0, 128.3, 138.9, 172.8 (C═O).

Ester **51** (*anti*): colorless oil; IR (neat) ν_{max} 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50−1.58 (m, 1H), 1.90−2.00 (m, 1H), 2.92−2.98 (m, 1H), 3.13 (s, 3H), 3.20−3.38 (m, 2H), 3.75 (s, 3H), 4.29 (d, 1H, J = 9.5 Hz), 7.27−7.39 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 31.6, 42.0, 50.4, 51.8, 56.7, 84.7, 127.4, 128.4, 128.5, 138.3, 174.0 (C═O); MS (CI, isobutane) *m*/*e* (relative intensity) 257 (MH^+, 1.5), 225 (100). Anal. Calcd for $C_{13}H_{17}ClO_3$: C, 60.82; H, 6.67. Found: C, 60.73; H, 6.72.

Methyl (±)-2-Neopentyl-3-methoxybutanoates (56 and 57). Under Chelation Control. To a cold (0 °C), stirred suspension of $MgBr_2$·OEt_2 (760 mg, 2.9 mmol) in dry CH_2Cl_2 (34 mL) were successively added a solution of ester **55** (212 mg, 1.5 mmol) in CH_2Cl_2 (6.4 mL), *t*-BuI (877 μL, 7.4 mmol), a 1.0 M solution of Et_3B in hexane (295 μL, 0.295 mmol), and Bu_3SnH (792 μL, 2.9 mmol). After being stirred for 2.5 h, the mixture was poured into a saturated aqueous $NaHCO_3$, and the aqueous layer was extracted (3×) with CH_2Cl_2. The organic extracts were combined, successively washed with water and brine, and dried ($MgSO_4$). GC analysis of the crude reaction isolate was performed to determine the ratio of **56** and **57**. After filtration and concentration, the residue was taken up in hexane, and to the resultant solution was added a 1.0 M solution of *n*-Bu_4NF in THF (3.5 mL, 3.5 mmol). After being stirred for 5 min at 25 °C, the mixture was filtered through a short pad of silica gel (100 mL, 20% EtOAc−hexane) and concentrated. The residue was flash chromatographed on silica gel (4% EtOAc−hexane) to afford a mixture of esters **56** and **57** (203 mg, 68% yield).

In the Absence of Lewis Acid. To a cold (0 °C), stirred solution of olefin **55** (214 mg, 1.5 mmol) and *t*-BuI (885 μL, 7.4 mmol) in dry CH_2Cl_2 (41 mL) were successively added a 1.0 M solution of Et_3B in hexane (300 μL, 0.297 mmol) and Bu_3SnH (800 μL, 2.97 mmol). The reaction mixture was stirred at 0 °C for 7 h, slowly allowed to warm to 25 °C, and stirred at this temperature overnight. ^{1}H NMR analysis of the concentrated crude reaction isolate, conducted to determine the ratio of **56** and **57**, revealed substrate **55** (∼50%). A 4:1 mixture of **56** and **57** was recovered as a colorless oil; major diastereomer: IR (neat) ν_{max} 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 9H), 1.14 (d, 3H, J = 6.0 Hz), 1.26 (dd, 1H, J = 1.6, J = 14.0 Hz), 1.77 (dd, 1H, J = 10.8, J = 14.0 Hz), 2.55−2.60 (m, 1H), 3.30 (s, 3H), 3.38−3.41 (m, 1H), 3.68 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.3, 29.2, 30.3, 41.1, 47.9, 51.4, 56.6, 78.7, 175.9 (C═O); MS (CI, isobutane) *m*/*e* (relative intensity) 203 (MH^+, 20), 171 (100); HRMS calcd for $C_{10}H_{19}O_3$ ($M^+ - CH_3$) 187.1334, found 187.1335 (−0.5 ppm).

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Supporting Information Available: Characterization data for compounds **5**, **11**−**16**, **28**−**31**, **47**, **35**−**46**, **58**−**69**; ^{13}C NMR spectra for compounds **10**, **12**, **15**, **16**, **18**, **19**, **23**, **24**, **26**, **27**, **30**, **32**, **37**−**42**, **44**, **47**, **48**, **50**, **55**−**57**, **59**, **66**−**69** (39 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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