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Acyclic Diastereoselection in Prochiral Radical Addition to Prochiral Olefins

Mukund P. Sibi,* Tara R. Rheault,† Sithamalli V. Chandramouli, and Craig P. Jasperse

Contribution from the Department of Chemistry, North Dakota State University, Fargo, North Dakota 58105-5516

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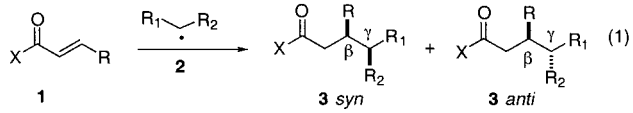
Abstract: The stereochemical preference (syn or anti*)* when prochiral radicals add to prochiral acceptors is of fundamental interest. The primary focus of this research was to determine which factors influence the relative stereochemistry between the β and γ chiral centers when these are formed concurrently. While moderate diastereoselectivity was found for addition of alkyl (**6a**−**d**) and α-alkoxy radicals (**16a**−**c**) (≤6:1 syn) to acceptors **4**, **7**, **8**, **10**, and **14**, consistently high selectivity was observed with less reactive halogenated radicals (**6f**,**g**) (>15:1 anti). Steric influence in alkyl radical additions was difficult to evaluate due to decreased reactivity when using bulky reaction partners; however, more reactive α-alkoxy radicals, it was found that increasing steric bulk leads to moderate increases in selectivity. In addition, higher selectivity was observed when employing lanthanide Lewis acids whose environment (reactivity) was modified using achiral additives, suggesting a potentially simple means for selectivity enhancements in radical reactions. Overall these results indicate that significant stereoelectronic effects are necessary to achieve high levels of selectivity in prochiral radical additions to prochiral acceptors.

Introduction

In recent years effective methods for Lewis acid-activated intermolecular addition of alkyl radicals to enoyl oxazolidinones have been developed.[1] We have shown that radical addition to acrylates as well as nonterminal alkenes in which the acceptor is prochiral proceeds efficiently.[2] Convenient methods are at hand for controlling the absolute configuration at the β center, either diastereoselectively (using a chiral auxiliary)[3] or enantioselectively (using a Lewis acid/chiral ligand combination).[4] In addition, we have developed very selective tandem reactions in which addition at the β center followed by trapping at the α center results in the highly selective formation of two new acyclic stereocenters.[5] Given our ability to control the stereochemistry at both the β and α centers, we were curious to determine whether the relative stereochemistry at the γ carbon could also be controlled in situations where a prochiral radical **2** adds to a nonterminal alkene **1** (eq 1).[6]



R = Me, Ph, *t*-Bu, *i*-Pr, CO_2R
R_1 = alkyl
R_2 = alkyl, OMe, Br, Cl
X = Achiral Template

At the outset of our study we were surprised at the lack of information available regarding fundamental diastereoselectivity[7] when prochiral radicals add to prochiral acceptors. Occasionally, doubly diastereoselective intermolecular radical processes have surfaced in the literature; however, only limited examples have been provided, and the systematic acquisition of essential information regarding factors impacting selectivity has not been pursued.[8] One exception is the intermolecular addition of ketyl radical anions to electron-deficient olefins.[9] Fukuzawa, for example, has reported highly diastereoselective samarium iodide-mediated ketyl radical addition to chiral enoates.[10] Samarium ketyls are ionic compounds, however, and due to their charge and the coordinating ability of the samarium counterion they are not representative of ordinary, nonionic radicals.

In this paper we present our observations on diastereoselectivity in the intermolecular additions of prochiral alkyl, α-ha-

* To whom correspondence should be addressed. E-mail: Mukund.Sibi@ndsu.nodak.edu.

† NSF graduate Fellow (1998−2001). ACS division of Organic Chemistry Fellow (2001−2002).

(1) For general information on radical chemistry, see: *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2.

(2) The rate constants for radical additions to alkenes are highly sensitive to steric and polar effects of both the radical and the acceptor. For an excellent discussion including rate data, see: *Free Radicals in Organic Chemistry*; Fossey, J., Lefort, D., Sorba, J., Eds.; Wiley: Chichester, 1995; Chapter 12.

(3) (a) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779. (b) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090. (c) Sibi, M. P.; Ji, J.; Sausker, J. B.; Jasperse, C. P. *J. Am. Chem. Soc.* **1999**, *121*, 7517.

(4) (a) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (b) Sibi, M. P.; Ji, J.; Wu, J.-H.; Gürtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. (c) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800. (d) Sibi, M. P.; Shay, J. J.; Ji, J. *Tetrahedron Lett.* **1997**, *38*, 5955. (e) Also see: Murakata, M.; Tsutsui, H.; Hoshino, O. *Org. Lett.* **2001**, *3*, 299. (f) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417.

(5) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472.

(6) For discussion on stereoselective radical additions including intramolecular cyclizations, see: Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1995.

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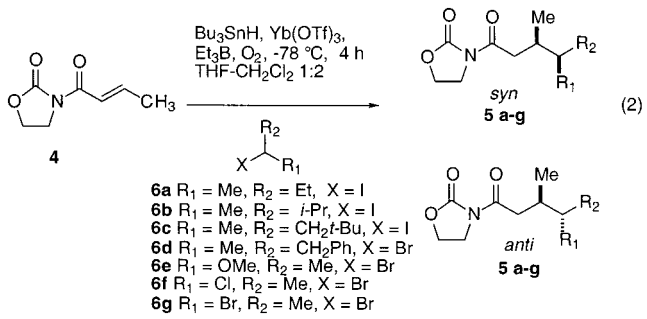
loalkyl, and α-alkoxyalkyl radicals to prochiral enoate acceptors. Our study finds that α-haloalkyl radicals add with remarkably high selectivity and α-alkoxyalkyl radicals with moderate to good selectivity. In contrast, α-alkyl radicals add with low diastereoselectivity, even at low temperature. Issues of steric bulk, electronics, and Lewis acid additives will also be addressed.

Results

Our work began with the examination of simple diastereoselectivity in the addition of prochiral radicals to oxazolidinone crotonate (Table 1, eq 2). The radical additions were conducted according to our standard reported procedure,[3c] involving (1) tin hydride as reducing agent/chain carrier, (2) Et_3B/O_2 as low-temperature radical initiator, and (3) $Yb(OTf)_3$ as an activating Lewis acid.[11,12] We chose $Yb(OTf)_3$ for reasons of convenience, because its stability to water obviated the need for drybox techniques or careful exclusion of air. In addition, $Yb(OTf)_3$ is sufficiently mild to be compatible with the other reactants and can be used in substoichiometric quantities. THF serves to dissolve the $Yb(OTf)_3$ (as well as other lanthanide Lewis acids).

Table 1. Effect of Radical Precursor on Diastereoselectivity



(2)

entry	radical precursor	product	yield[a] (%)	ratio (syn:anti)
1	**6a**	**5a**	80	1.8:1
2	**6b**[d]	**5b**	40	1.3:1
3	**6c**	**5c**	83	2.0:1
4	**6d**	**5d**	93	2.0:1
5	**6e**	**5e**	88	1.2:1
6	**6f**	**5f**	90[b]	1:15
7	**6g**	**5g**	70[c]	1:17

[a] Reactions were run for 4 h using $Yb(OTf)_3$, Bu_3SnH, and Et_3B/O_2 in 2:1 CH_2Cl_2:THF unless otherwise noted. Yields are for the purified product. [b] Five initiation cycles over 24 h, 10% ethyl addition. [c] Five initiation cycles over 24 h, 30% ethyl addition. [d] Reaction using a radical precursor (R_1 = Me, R_2 = *t*-Bu, X = I) gave no desired product.

The addition of simple alkyl radicals (Table 1, entries 1−4) proceeded with modest levels of diastereoselectivity. A slight preference for syn addition was observed, but even at −78 °C maximum selectivities of only 2:1 were observed.[13] Results indicated that increasing the bulk of the R_2 alkyl group had little influence on the diastereoselectivity of the addition. Simple alkyl radicals are relatively nucleophilic, and their additions are uncomplicated by possible electronic effects or chelation. The highly reactive and highly nucleophilic methoxy-substituted radical derived from **6e** also showed low selectivity (entry 5) (see eq 5 for synthesis of **6e**, vide infra).

On the other hand, halogenated radicals derived from **6f** and **6g** added with remarkably high levels of diastereoselectivity (15:1 and 17:1; entries 6, 7). The major diastereomer in each case was determined to be anti by lactonization of the product halides. Due to the electrophilic nature of these radicals, however, several technical problems are encountered in these reactions. Radicals generated from **6f** and **6g** are considerably less reactive than the simple alkyl radicals, which necessitated

(7) (a) For examples and discussions on ionic reactions involving prochiral reagents and prochiral substrates, see: Heathcock, C. H. In *Asymmetric Syntheses*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, Part B, Chapter 2. (b) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992. (c) For some seminal work, see: Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132. (d) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157. (e) For conjugate additions of α-alkoxy organometallics to conjugated systems, see: Chong, J. M.; Mar, E. K. *Tetrahedron Lett.* **1990**, *31*, 1981. (f) Linderman, R. L.; McKenzie, J. R. *Tetrahedron Lett.* **1988**, *29*, 3911. Selected examples of prochiral nucleophile addition to prochiral acceptors under ionic conditions: (g) Lim, S. H.; Curtis, M. D.; Beak, P. *Org. Lett.* **2001**, *3*, 711. (h) Nishwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992. (i) Juhl, K.; Gathergood, N.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995. (j) Liang, B.; Carroll, P. J.; Joullie, M. M. *Org. Lett.* **2000**, *2*, 4157. Selected examples of prochiral nucleophile addition to prochiral acceptors under neutral conditions: (k) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134. (l) Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865. (m) Evans, D. A.; Scheidt, K. A.; Johnston, J. S.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480. (n) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015. (o) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (p) Bernardi, A.; Colombo, G.; Scolastico, C. *Tetrahedron Lett.* **1996**, *37*, 8921. (q) For prochiral radical addition to an aldehyde, see: Ohno, T.; Ishino, Y.; Tsumagari, Y.; Nishiguchi, I. *J. Org. Chem.* **1995**, *60*, 458.

(8) For nitroxyl radical reactions, see: (a) Braslau, R.; Naik, N.; Zipse, H. *J. Am. Chem. Soc.* **2000**, *122*, 8421. (b) Radical addition to substituted stannanes: Damm, W.; Hoffmann, U.; Macko, L.; Neuberger, M.; Zehnder, M.; Giese, B. *Tetrahedron* **1994**, *50*, 7029. (c) Hamon, D. P. G.; Massy-Westropp, R. A.; Razzino, P. *Tetrahedron* **1995**, *51*, 4183. (d) Fliri, H.; Mak, C.-P. *J. Org. Chem.* **1985**, *50*, 3438. (e) Easton, C. J.; Scharfbling, I. M. *J. Org. Chem.* **1990**, *55*, 384. (f) Addition of an arenechromiumtricarbonyl prochiral radical to methyl crotonate: Merlic, C. A.; Xu, D. *J. Am. Chem. Soc.* **1991**, *113*, 9855. (g) Merlic, C. A.; Walsh, J. C. *J. Org. Chem.* **2001**, *66*, 2265. (h) Addition of prochiral radicals to prochiral carbene complexes: Merlic, C. A.; Xu, D.; Nguyen, M. C. *Tetrahedron Lett.* **1993**, *34*, 227. (i) Addition of prochiral radicals to furanones: Bertrand, S.; Hoffman, N.; Pete, J.-P. *Eur. J. Org. Chem.* **2000**, 2227. (j) Bertrand, S.; Glapski, C.; Hoffmann, N.; Pete, J.-P. *Tetrahedron Lett.* **1999**, *40*, 3169. (k) Marinkovi, S.; Hoffmann, N. *Chem. Commun.* **2001**, 1576. For other examples of intermolecular prochiral radical addition to acceptors, see: (l) Mikami, K.; Yamaoka, M. *Tetrahedron Lett.* **1998**, *39*, 4501. (m) Ahn, J. H.; Lee, D. W.; Juong, M. J.; Lee, K. H.; Yoon, N. M. *Synlett* **1996**, 1224. (n) Mero, C. L.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 5155. For some selected examples of intramolecular radical reactions, see: (o) Sasaki, M.; Inoue, M.; Noguchi, T.; Takeichi, A.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 2783. (p) Andres, C.; Duque-Soladana, J. P.; Pedrosa, R. *J. Org. Chem.* **1999**, *64*, 4282. (q) White, J. D.; Shin, H. *Tetrahedron Lett.* **1997**, *38*, 1141. (r) Lee, E. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, Chapter 4.2. (s) Hart, D. J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, Chapter 4.1. (t) For an example on intermolecular radical coupling using chiral Lewis acids, see: Nguyen, P. Q.; Schäfer, H. J. *Org. Lett.* **2001**, *3*, 2993.

(9) (a) For an excellent recent review, see: Molander, G. A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, Chapter 2.1. For other reviews, see: (b) Molander, G. A.; Harris, C. I. *Chem. Rev.* **1996**, *96*, 307. (c) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. For some selected examples, see: (d) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763. (e) Molander, G. A.; Harris, C. I. *J. Org. Chem.* **1997**, *62*, 7418. (f) Taniguchi, N.; Uemura, M. *Tetrahedron Lett.* **1997**, *38*, 7199. (g) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 624. (h) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1669. (i) Inanaga, J.; Ujikawa, O.; Handa, Y.; Otsubo, K.; Yamaguchi, M. *J. Alloys Compd.* **1993**, *192*, 197. (j) Kawatsura, M.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 6900. (k) Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1994**, *35*, 1627. For reactions with stannyl ketyls, see: (l) Enholm, E. J.; Kinter, K. S. *J. Org. Chem.* **1995**, *60*, 4850.

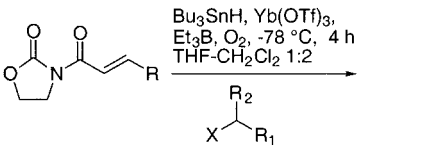
(10) (a) Fukuzawa, S.-i.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482. (b) Matsuda, F.; Kawatsura, M.; Dekura, F.; Shirahama, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2371. (c) Kawatsura, M.; Dekura, F.; Shirahama, H.; Matsuda, F. *Synlett* **1996**, 373. (d) Reference 8l.

(11) For an excellent review on Lewis acid-mediated radical reactions, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562.

(12) Each of these components was important to the success of the additions, as demonstrated by reactions using crotonate **4** and bromide **16c** to give **18c**. In the absence of either Et_3B or tributyltin hydride, no product **18c** formed. These experiments confirm that a radical mechanism is operative.

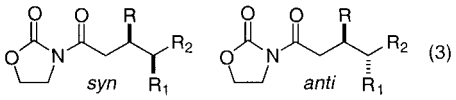
(13) The relative stereochemistry was determined by an independent synthesis of *syn*-3,4-dimethylhexanoic acid and comparison with hydrolyzed **5a**. See Supporting Information for details.

Table 2. Effect of Olefin Substituent on Diastereoselectivity



4 R = Me
7 R = Ph
8 R = *i*-Pr
9 R = CO_2Et
10 R = CO_2t-Bu

6a R_1 = Me, R_2 = Et, X = I
6g R_1 = Br, R_2 = Me, X = Br



(3)

5a R = Me, R_1 = Me, R_2 = Et
5g R = Me, R_1 = Br, R_2 = Me
11a R = Ph, R_1 = Me, R_2 = Et
11g R = Ph, R_1 = Br, R_2 = Me
12a R = *i*-Pr, R_1 = Me, R_2 = Et
12g R = *i*-Pr, R_1 = Br, R_2 = Me
13g R = CO_2Et, R_1 = Br, R_2 = Me
14a R = CO_2t-Bu, R_1 = Me, R_2 = Et
14g R = CO_2t-Bu, R_1 = Br, R_2 = Me

entry	substrate	radical precursor	product	yield[a,f] (%)	ratio[g] (syn:anti)
1	**4**	**6a**	**5a**	80	1.8:1
2	**7**	**6a**	**11a**	80	2:1
3	**8**	**6a**	**12a**	23 (71)[e]	2:1
4	**10**	**6a**	**14a**	85	1:1
5	**4**	**6g**	**5g**	70[b]	1:17
6	**7**	**6g**	**11g**	20[c,d]	1:2
7	**8**	**6g**	**12g**	<5 (95)[e]	
8	**9**	**6g**	**13g**	95	1:2
9	**10**	**6g**	**14g**	95	1:4

[a] Reactions were run for 4 h using $Yb(OTf)_3$, Bu_3SnH and Et_3B/O_2 in 2:1 CH_2Cl_2:THF unless otherwise noted. [b] 30% ethyl addition, separation problems. [c] 50% ethyl addition. [d] Isolated product as lactone. [e] Recovered starting material. [f] Isolated yields for column purified materials. [g] Product ratios were determined by ^1H NMR integration (400 MHz).

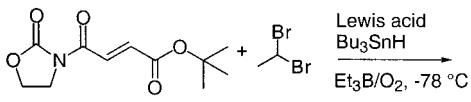
multiple initiation cycles and large excesses of reagents in order to get high yields. Also, the product bromide in **5g** is prone to radical reduction by excess tributyltin hydride and triethylborane, resulting in substantial amounts of a conjugate ethyl addition (R_1 = H) a side product. Finally, the presence of trace amounts of unreacted starting material and ethyl addition side product (R_1 = H) made chromatographic purification of halogenated products **5f** and **5g** difficult.

The influence of the radical acceptor substituent R on diastereoselectivity is shown in Table 2 (eq 3). Increasing the size of R (R = Ph, *i*-Pr; entries 2, 3) did not significantly affect the selectivity for the addition of the *sec*-butyl radical.[14] It is noteworthy that the larger substituents also decreased the reactivity of the acceptor toward radical additions (entries 3 and 7). In addition, increasing the reactivity of the acceptor alkene by using the fumarate-derived substrates correspondingly reduced the selectivity (entry 4; compare entry 4 with entry 1 and entry 5 with entries 8 and 9).

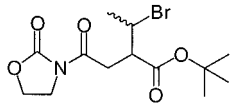
Since the bromoethyl radical had shown higher selectivity than the *sec*-butyl radical in Table 1, we also screened its ability to add to alkenes **7**−**10**. It was observed that the substrate reactivity followed the order R = CO_2Et, CO_2-t-Bu > Me > Ph > i-Pr (in previous work we have likewise found that the

(14) We have attempted to add the radical derived form 3,3-dimethyl-2-iodobutane, but alkylation occurred in <20% yield, presumably due to steric hindrance, and we were unable to determine the selectivity.

Table 3. Effect of Lewis Acid Additives on Diastereoselectivity



10 **6g**



(4)

14g

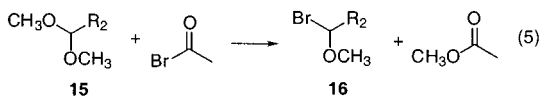
entry	Lewis acid	equiv	solvent	yield[a,b] (%)	ratio[c] (anti:syn)
1	none		CH_2Cl_2	<10	1:1
2	$Yb(OTf)_3$	1.0	2:1 CH_2Cl_2:THF	95	4:1
3	$Sm(OTf)_3$	1.0	2:1 CH_2Cl_2:THF	90	8:1
4	$Sm(OTf)_3$	1.0	CH_2Cl_2	<10	1:1
5	$Sm(OTf)_3$	0.3	2:1 CH_2Cl_2:THF	95	7:1
6	$Sm(OTf)_3$	2.0	2:1 CH_2Cl_2:THF	90	5:1
7	$MgBr_2$	2.0	CH_2Cl_2	43	1:1

[a] Reactions were run for 4 h using Lewis acid, Bu_3SnH, and Et_3B/O_2. [b] Isolated yields for column purified materials. [c] Product ratios were determined by ^1H NMR integration (400 MHz).

fumarate substrates **9** and **10** are orders of magnitude more reactive than their crotonate or cinnamate analogues).[15] Bromoethyl radical additions to the fumarates **9** and **10** proceeded cleanly and efficiently, giving products uncontaminated by starting material or ethyl addition. However, as observed with the *sec*-butyl radical, the more reactive fumarate acceptors gave much reduced diastereoselectivity (compare entry 5 with entries 8 and 9).

Past results on optimizing chloromethyl radical addition to fumarate substrates indicated that $Sm(OTf)_3$ was the optimal Lewis acid for halogenated radical additions to these types of substrates.[16] With this information in hand, a brief study of the effect of the Lewis acid on the diastereoselectivity of bromoethyl radical addition to fumarates was undertaken (Table 3, eq 4). It was again found that $Sm(OTf)_3$ gave the highest diastereoselectivities (8:1) when using substrate **10**, doubling the result previously obtained using the stronger Lewis acid $Yb(OTf)_3$ (Table 3, entries 2 and 3). The effect of increasing temperatures on the double diastereoselective additions was also studied. As expected, increasing reaction temperatures from −78 to 0 °C or room temperature for the reaction shown in eq 4 with $Sm(OTf)_3$ as a Lewis acid resulted in complete erosion of selectivity from 8:1 to 1:1.

Table 4 shows a series of reactions in which prochiral methoxyalkyl radicals add to nonterminal alkenes.[17] We have found that methoxyalkyl bromides **16** are readily prepared from acetals via reaction with acetyl bromide (eq 5),[18] so it was relatively easy to systematically vary the size of the R_2 group.



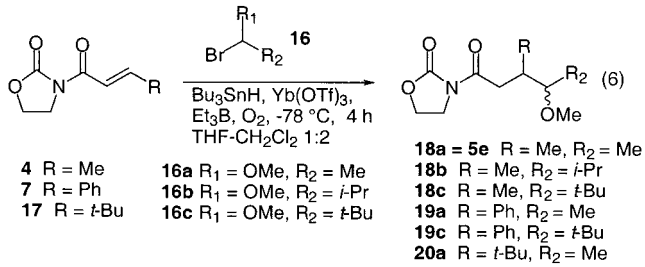
(5)

15 **16**

The α-bromoalkyl ethers **16** were conveniently prepared and used in situ (eq 6), since their formation was quantitative and the α-bromoalkyl ethers **16** were sensitive to workup. The

(15) Sibi, M. P.; Ji, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 274.
(16) (a) Reference 15. (b) Sibi, M. P.; Liu, P.; Ji, J.; Chen, J. Hajra, S. *J. Org. Chem.*, in press.

Table 4. Steric Effect of α-Alkoxy Radicals on Diastereoselectivity[a]



4 R = Me
7 R = Ph
17 R = *t*-Bu

16a R_1 = OMe, R_2 = Me
16b R_1 = OMe, R_2 = *i*-Pr
16c R_1 = OMe, R_2 = *t*-Bu

18a = 5e R = Me, R_2 = Me
18b R = Me, R_2 = *i*-Pr
18c R = Me, R_2 = *t*-Bu
19a R = Ph, R_2 = Me
19c R = Ph, R_2 = *t*-Bu
20a R = *t*-Bu, R_2 = Me

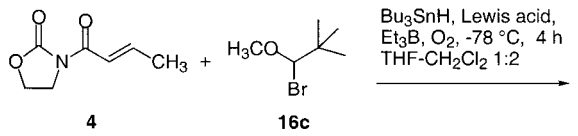
entry	substrate	radical	product	ratio[c] (syn:anti)	yield[b] (%)
1	**4**	**16a**[d]	**18a**[d]	1.2:1	88
2	**4**	**16b**	**18b**	2.3:1	90
3	**4**	**16c**	**18c**	6:1	89
4	**7**	**16a**	**19a**	1.5:1	94
5	**7**	**16c**	**19c**	6:1	90
6	**17**	**16a**	**20a**	5.5:1	35

[a] The general procedure described was followed. Preparative reactions were conducted using 5 equiv of freshly prepared bromoalkyl ether, 5 equiv of Bu_3SnH, 0.1 equiv of $Yb(OTf)_3$, and 2 equiv of Et_3B. [b] Isolated yields for column purified materials. [c] Product ratios were determined by ^1H NMR integration (400 MHz). [d] Table 4, entry 1, corresponds to Table 1, entry 5. Note that **16a** = **6e** and **18a** = **5e**.

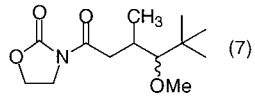
methyl acetate side product was a harmless bystander in the radical reactions. A control reaction also showed that α-bromoalkyl ether **16c** (R_2 = *t*-Bu) is stable to $Yb(OTf)_3$ in solution for over 10 h at room temperature, confirming that cations are not involved in the addition reaction under our low-temperature reaction conditions. Alkoxyalkyl radicals derived from **16** showed high reactivity[19] toward conjugate addition because of the methoxy substituent, so yields in the addition reaction were generally high (Table 4, entries 1−5), except when the R group on the alkene became very large (entry 6).

In the addition of alkoxyalkyl radicals, the syn isomer was consistently preferred over anti (Table 4).[20] Increasing the size of the R_2 group on the radical increased the diastereoselectivity in additions to both crotonate **4** (entries 1−3) and cinnamate **7** (entries 4 and 5). Increasing the size of the R group on the alkene also increased the selectivity (compare entries 1, 4, and 6). Good selectivity was observed only with a very large substituent on either the radical (entries 3, 5) or on the alkene (entry 6).

Table 5. Effect of Lewis Acids on Yield and Diastereoselectivity for α-Alkoxy Radical Additions[a]



4 **16c**



18c

entry	Lewis acid	diastereoselectivity[b] (syn:anti)	yield[c] (%)
1	none	1:1	10[d]
2	$Yb(OTf)_3$	6:1	89[d]
3	$Er(OTf)_3$	4:1	95
4	$Gd(OTf)_3$	2:1	85[d]
5	$Sm(OTf)_3$	4:1	90
6	$Pr(OTf)_3$	1:1	45[d]
7	$Y(OTf)_3$	2:1	90
8	$Sc(OTf)_3$	1.5:1	90
9	$La(OTf)_3$	1:1.5	30
10	$Yb(OTf)_3$ (0.1 equiv)	6:1	89[d]
11	$MgBr_2(OEt_2)$	1:1.2	90[e]
12	$ZrCl_4$	1:3	85[e]
13	$TiCl_4$		<10

[a] The general procedure described was followed. Preparative reactions were conducted using 5 equiv of freshly prepared bromoalkyl ether, 5 equiv of Bu_3SnH, 1 equiv of Lewis acid (unless otherwise noted), and 2 equiv of Et_3B. [b] Diastereomer ratios were determined by ^1H NMR integration (400 MHz). [c] Chemical yields were determined by ^1H NMR integration (400 MHz, pentachloroethane as an internal standard) and GLC. [d] Isolated yields. [e] No THF cosolvent.

Table 5 shows results in which the addition of the methoxyalkyl radical derived from **16c** to crotonate **4** was conducted using several different Lewis acids for activation of the acceptor. The diastereoselectivity is surprisingly sensitive to the Lewis acid (Table 5). We do not have a full explanation for the complex relationship between selectivity and Lewis acid structure, but some of the results are interesting. While simple $Yb(OTf)_3$ gave 6:1 selectivity (entry 2), other Lewis acids tested showed lower syn selectivity or even anti selectivity. Among the metal triflates tested, it is interesting that $Yb(OTf)_3$ is intermediate in both Lewis acid strength and ionic radius (entries 2−9), so there is no simple correlation between diastereoselectivity and either Lewis acid strength or size. Magnesium bromide and zirconium tetrachloride actually give anti selectivity, although the selectivity is low (entries 11, 12). Ytterbium triflate could be used catalytically (entry 10). The very strong Lewis acid titanium tetrachloride provided only trace amounts of product, due to incompatibility with the reactants (entry 13).

Results from a series of reactions in which Lewis basic additives were added to $Yb(OTf)_3$ for the formation of product **18c** are presented in Table 6. Lewis basic additives have been found to effect a number of lanthanide-mediated reactions,[21] and the formation of **18c** reflects a sensitive case study for the

(17) The addition of α-alkoxy radicals to acrylates has been reported. Intermolecular addition: (a) Nishiyama, Y.; Yamamoto, H.; Nakata, S.; Ishii, Y. *Chem. Lett.* **1993**, 841. (b) Giese, B.; Hoch, M.; Lamberth, C.; Schmidt, R. R. *Tetrahedron Lett.* **1988**, *29*, 1375. (c) Bimwala, R. M.; Vogel, P. *J. Org. Chem.* **1992**, *57*, 2076. (d) Kessler, V. H.; Wittmann, V.; Kock, M.; Kottenhahn, M. *Angew. Chem., Int. Ed. Engl.* **1992**, *32*, 902. (e) Garner, P. P.; Cox, P. B.; Klippenstein, S, J. *J. Am. Chem. Soc.* **1995**, *117*, 4183. (f) Garner, P.; Leslie, R.; Anderson, J. T. *J. Org. Chem.* **1996**, *61*, 6754. (g) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139. (h) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986.

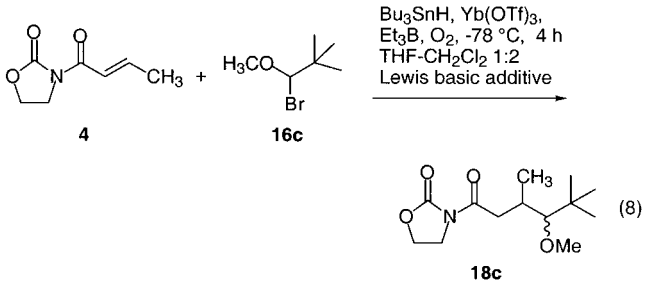
(18) For conversion of a dimethyl acetal to an α-chloroacetal, see: Lokensgard, J. P.; Fischer, J. W.; Batrz, W. J. *J. Org. Chem.* **1985**, *50*, 5609.

(19) Alkoxyalkyl radicals are "nucleophilic". See: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon: Oxford, 1986; Chapter 2. Giese, B.; Dupuis, J.; Hasskerl, T.; Meixner, J. *Tetrahedron Lett.* **1983**, *24*, 703.

(20) The relative stereochemistry was established by conversion of products **5f** and **18c** to known lactones (TMSI, $CDCl_3$). Denmark, S. E.; Forbes, D. C. *Tetrahedron Lett.* **1992**, *33*, 5037. We thank Prof. Scott Denmark for providing us spectral data for the lactone derived from **18c**. In 4,5-disubstituted lactones, the chemical shift of the C_5−H is consistently upfield in the trans compounds relative to the cis, and this relationship was used to assign the lactones derived from **18c**. See: Fang, J.-M.; Liao, L.-F.; Hong, B.-C. *J. Org. Chem.* **1986**, *51*, 2828. Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Okawara, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1351. Carretero, J. C.; Rojo, J. *Tetrahedron Lett.* **1992**, *33*, 7407 and references therein.

(21) For the use of additives in rare earth Lewis acid-mediated reactions, see: (a) Shibasaki, M.; Vogl, E. M.; Groger, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570. (b) Saito, T.; Kawamura, M.; Nishimura, J.-i. *Tetrahedron Lett.* **1997**, *38*, 3231. (c) Mikami, K.; Kotera, O.; Motoyama, Y.; Sakaguchi, H. *Synlett* **1995**, 975. (d) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590. (e) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758. (f) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083. (g) For a review on lanthanide coordination with macrocyclic ligands, see: Alexander, V. *Chem. Rev.* **1995**, *95*, 273. Modification of lanthanide reactivity and or structure by addition of ligands: (h) Aspinall, H. C.; Dwyer, J. L. M.; Greeves, N.; McIver, E. G.; Wooley, J. C. *Organometallics*

Table 6. Effect of Additives to $Yb(OTf)_3$ for α-Alkoxy Radical Additions[a]

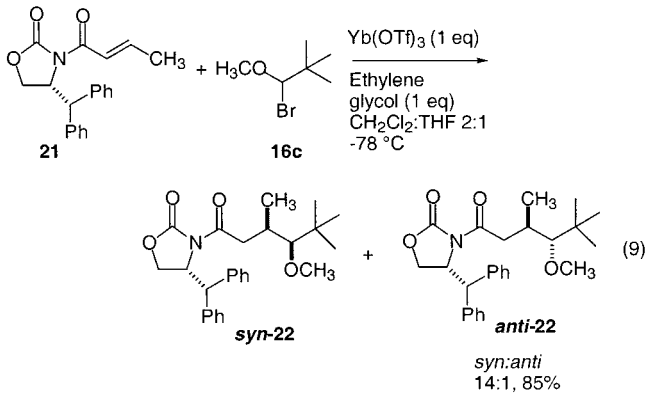


entry	additive (equiv)[b]	$Yb(OTf)_3$ (equiv)	diastereoselectivity[c,d] (syn:anti)
1	none	1	6:1
2	NEt_3 (3)	1	5:1
3	DMSO (3)	1	8:1
4	HMPA (3)	1	10:1
5	$H_2NCH_2CH_2OH$ (1)	1	6:1
6	$HOCH_2CH_2OH$ (1, 2 or 3)	1	10:1
7	$HO(CH_2CH_2O)_2H$ (1)	1	8:1
8	$HO(CH_2CH_2O)_3H$ (1)	1	10:1
9	$HO(CH_2CH_2O)_4H$ (1)	1	14:1
10	$HO(CH_2CH_2O)_5H$ (1)	1	11:1
11	12-C-4 (1)	1	9:1
12	15-C-5 (1)	1	9:1
13	18-C-6 (1)	1	6:1
14	$HOCH_2CH_2OH$ (0.2)	0.1	10:1

[a] The general procedure described was followed. Reactions were conducted using 5 equiv of freshly prepared bromoalkyl ether, 5 equiv of Bu_3SnH, 1 equiv of Lewis acid (unless otherwise noted), the additive (see table), and 2 equiv of Et_3B. [b] Number of equivalents relative to substrate. [c] Yields were generally >90% as determined by isolation or GLC or ^1H NMR. [d] Diastereomer ratios were determined by ^1H NMR integration (400 MHz).

effect of additives.[22] In all cases the chemical yields exceeded 90%. Addition of HMPA or ethylene glycol increased the syn selectivity for **18c** from 6:1 to 10:1 (entries 4, 5). With tetraethylene glycol the selectivity increased to 14:1 (entry 9). Our observations suggest that oxygenated Lewis bases influence the selectivity but that amines have minimal influence. This is in keeping with the known oxophilicity of lanthanides. However, we are uncertain exactly how these additives impact the stereoselectivity. A modest accelerating effect was also observed in reactions using Lewis basic additives. This may suggest that a later transition state may not be the sole contributor for enhanced selectivity. It is possible that coordinating additives suppress a minor competing chelation pathway. While we do not have a clear explanation for these results, they may provide some clues regarding the interaction of ytterbium triflate with additives that may provide insight toward the development of improved rare earth Lewis acid catalysts.[23]

The addition of the radical derived from **16c** to the chiral substrate **21** (eq 9) was also examined. We have previously shown that isopropyl radical addition to **21** occurs with ~25:1 diastereoselectivity.[3a] Radical addition of **16c** to **21** gave **22** as a 14:1 mixture of syn/anti compounds, with no trace of the other two diastereomers. These experiments show that the facial selectivity at the β-carbon is completely controlled (≥25:1) in the conjugate addition.[24] These reactions also demonstrate that absolute as well as relative stereochemistry can be controlled in the addition of prochiral radicals to chiral olefins.



Discussion

Prochiral alkyl radicals add to electron-deficient alkenes with low levels of diastereoselectivity (Tables 1 and 2). It appears as though steric factors alone are unable to afford substantial diastereoselectivity in the additions of these nucleophilic alkyl radicals to electrophilic alkenes. Radical additions are normally understood to proceed via early transition states, so it is not surprising that early bond formation makes these reactions relatively insensitive to steric factors. The preferred syn products likely arise predominantly via the transition state **25** shown in Figure 1, where gauche interactions are minimized compared to **23** or **24**, also leading to syn products. Ordinarily the largest substituents on a forming bond orient themselves anti to each other, just as they do relative to ethane, so if R acts as the largest substituent on the alkene carbon (as opposed to ═CHCOX), **25** represents the situation where the "large" groups R and R_2 are anti to each other. Transition state **25** also explains why increasing the size of R decreases the reactivity of the acceptor but does not provide substantially increased levels of selectivity, due to unfavorable interactions with the methyl group on the radical. A similar argument can be used to explain the decreasing reactivity when bulky R_2 groups are introduced. The minor anti product may arise from a similar transition state **26** where the methyl and the R_2 group are interchanged, and which experiences similar gauche interactions. The early transition state combined with the modest effective difference in size between R and the ═CH(CO)X groups on the acceptor carbon may limit the energy discrimination between **25** and **26**.

In the case of methoxyalkyl radical additions (see Table 4), we had originally thought that chelation of the methoxy group to the Lewis acid might result in high selectivity (transition states **27** or **30**, Figure 2). However, our results with ytterbium triflate as Lewis acid show that the major diastereomer actually results from an open transition state in which the methoxy substituent on the radical is not complexed to substrate-bound $Yb(OTf)_3$. Although the substrate itself is chelated to the $Yb(OTf)_3$, the incoming methoxyalkyl radical is not. We believe the major diastereomer forms via an open transition state for the following reasons. First is the impact of additives on the reaction **4** +

1998, *17*, 1884. (i) Aspinall, H. C.; Greeves, N.; McIver, E. G. *Tetrahedron Lett.* **1998**, *39*, 9283. (j) Greeves, N.; Aspinall, H. C.; Browning, A. F.; Ravenscroft, P. *Tetrahedron Lett.* **1994**, *35*, 4639. (k) Lacote, E.; Renaud, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2259.

(22) In contrast, addition of Lewis basic additives for the formation of **5a** did not lead to improvement in selectivity.

(23) NMR experiments involving $Y(OTf)_3$ in acetonitrile have shown that ethylene glycol binds preferentially over substrate **4** and indicate that yttrium can accommodate two or three ethylene glycols.

(24) The absolute stereochemistry at the β-carbon is based on analogy from our previous work involving conjugate radi cal additions to chiral substrate **21** (ref 3a).

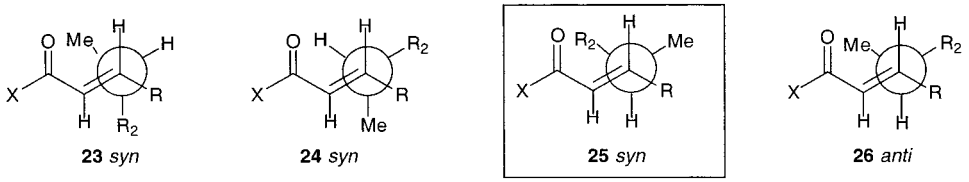


Figure 1.

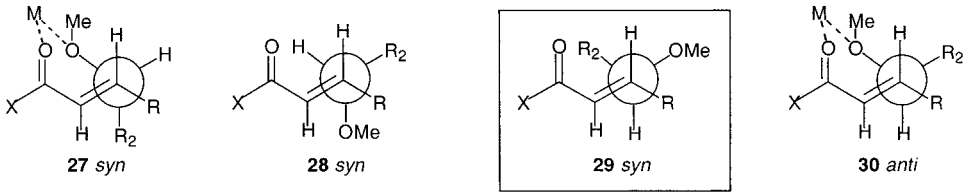


Figure 2.

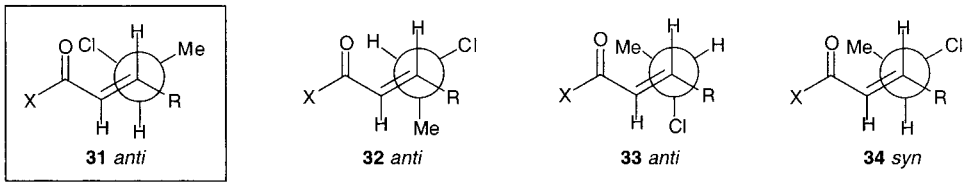


Figure 3.

16c → 18c (see Table 6). Additives such as HMPA and ethylene glycol are strongly coordinating bases with high affinities for lanthanides. If syn product resulted from a chelated transition state, we expected that these additives should disrupt chelation and reduce the syn/anti selectivity, but exactly the opposite occurred. Second, a chelated transition state leading to syn products must proceed via transition state **27**. This chelated transition state appears severely hindered because the R_2 group suffers two gauche interactions, and this should intensify as the sizes of R and R_2 increase. However, increasing the size of either R or R_2 gave enhanced syn selectivity.[25] Third, complexation of a methoxyalkyl radical to a Lewis acid should reduce its nucleophilicity, so it is not surprising that alkoxyalkyl radicals that are not bound to a Lewis acid are the reactive species.[26] It is possible that the anti product, which is modestly preferred when zirconium tetrachloride or magnesium bromide was used as Lewis acid, does result from a transition state **30**, in which the methoxy group is chelated to the Lewis acid.

Given an open transition state for the usual addition of methoxyalkyl radicals, transition state **29**, where gauche interactions are minimized and in which the large groups R and R_2 are anti to each other, again seems best, especially when R ≠ methyl. In terms of steric volume, the methoxy group is smaller than even a methyl group, and obviously much smaller than *tert*-butyl.[27] That transition state **28** is not the source of the syn products is evident from the dependence of diastereoselectivity on R. As R gets larger, **28** should be increasingly destabilized, but experimentally enlarging R increased rather than decreased the syn selectivity (Table 4, compare entries 1, 4 and 6). That transition state **29** is operative is also consistent with the observation that syn product is preferred in all cases, and that selectivity increased when the size of either R or R_2 increased (Table 4, entries 1−3, 4 and 6). The preference for transition state **29** may also have a stereoelectronic component. In **29**, the oxygen lies anti relative to the alkene. Analogous anti relationships of oxygen substituents to alkenes in radical additions have been noted previously and attributed to stereoelectronic effects, and effects of this type are probably key to the high selectivity associated with addition of samarium ketyl radicals to alkenes.[28] The stereoelectronic effects are probably much smaller in the case of methoxyalkyl radicals than in samarium alkoxy radicals (samarium ketyls) because the oxygen has greater negative charge density in the latter. The R_2 group and the carbonyl carbon have a pseudo syn pentane relationship in **29**, but because of the early transition state and the trigonal (planar) geometry of the α-carbon, we suggest that the inside position is not significantly encumbered.[29]

Haloalkyl radicals add with remarkably high anti selectivity, especially in additions to crotonate **4**. Of the three projections **31**−**33** that would lead to the anti product, transition state **31** seems the best, since **32** and **33** would likely experience more allylic strain and more severe gauche interactions (Figure 3). In contrast to alkyl and alkoxyalkyl radicals, haloalkyl radicals are relatively electrophilic and much less reactive, so that the transition state is probably relatively late. As is to be expected, reactions involving a later transition state are much more sensitive to both steric and electronic factors.

What is surprising is that the haloalkyl radicals give anti selectivity, whereas alkyl and methoxyalkyl radicals give syn

(25) On the other hand, the R_2 group has a syn pentane-type arrangement relative to the carbonyl group in transition state **29**. While R_2 would also suffer syn pentane relationships with R when R ≠ Me (Table 1, entries 4, 5), it is possible that when R = Me the syn product arises from transition state **28**, and when R ≠ Me the syn product arises from transition state **29**. While it is possible that **18c** forms via **28**, the cinnamate **7** also underwent syn-selective addition by **16c** (6:1), which should proceed via **28**.

(26) The involvement of an open transition state is not all that surprising. Even in the absence of additives, the methoxy group is less basic than the cosolvent THF, especially since the basicity of the oxygen atom is reduced by electron donation to the radical. Also, if a methoxyalkyl radical was coordinated to a Lewis acid, the radical should be less nucleophilic and less reactive toward alkene addition.

(27) The *A* values for −Cl, $-OCH_3$, $-CH{=}CH_2$, $-CH_3$, $-CH(CH_3)_2$, $-C_6H_5$, and $-C(CH_3)_3$ are 0.5, 0.6, 1.7, 1.8, 2.1, 2.9, and >4.5, respectively. *Stereochemistry of Organic Compounds*; Eliel, E., Wilen, S., Eds.; Wiley: New York, 1993.

(28) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073.

(29) An alternate explanation is that due to incipient syn pentane interactions, the inside position is the most hindered, and that syn product is formed via **28**. When R_2 = *t*-Bu, however, an even more severe syn pentane interaction occurs with R.

selectivity. The *A* values for −Cl and $-OCH_3$ are very similar, so if steric factors are the only consideration, haloalkyl and methoxyalkyl radicals should both prefer the same isomer, whether syn or anti. Why do haloalkyl radicals add via **31** rather than via **34**? Clearly, the differing outcomes between haloalkyl and methoxyalkyl radicals have an electronic basis. The less reactive haloalkyl radicals add with much later transition states. Under these conditions, **34** may be destabilized due to developing syn pentane interactions between the methyl group and the carbonyl carbon. Another possible explanation is that transition state **31** benefits from favorable dipole/dipole interactions (attractive interaction of the halogen with the carbonyl carbon or the Lewis acid). The same dipolar advantages do not apply in the reaction of alkoxyalkyl radicals because the much earlier transition state and the shorter C−O bond length make too great a spatial distance for significant dipole/dipole interactions. Further, unlike chlorine and bromine, the methoxy group is a strong π donor to the radical, so that the C−O bond has drastically reduced or even reversed dipolar character.

Conclusions

In this work we have examined factors that are fundamental to understanding reactions between two prochiral fragments. We have shown that alkoxyalkyl and haloalkyl radicals add to enoates with moderate to good diastereoselectivity, and the methodology could have synthetic potential. The diastereoselectivity in our study using alkyl radicals is modest, and may be of limited synthetic value, but the results are of fundamental interest. The alteration of the environment (reactivity) of the lanthanide Lewis acids with achiral additives detailed in this work suggests a potential and simple route for selectivity enhancements in radical reactions.

Overall, our results show that additions of prochiral radicals to prochiral alkenes via open transition states are not uniformly highly diastereoselective. The selectivity is only slightly higher than observed in anionic nucleophilic addition of α-alkoxylithiums, for example.[7e] To be highly diastereoselective, it appears that intermolecular addition of achiral prochiral radicals to prochiral alkenes will require either strong stereoelectronic effects[30] or chelation control to provide sufficient organization.

Acknowledgment. This work was supported by the National Institutes of Health (GM-54656). T.R.R. thanks NSF and the ACS Division of Organic Chemistry for graduate fellowships. We thank Megan Kirsch, Mei Liu, and Sarah Steffl for technical assistance.

Supporting Information Available: Characterization data for compounds and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA017510T

(30) Fukuzawa, ref 10a, gets highly syn-selective addition of samarium ketyl radicals to crotonate esters. Stereoelectronic and/or chelation plays a major role in these reactions.