Enantioselective Radical Methods for Lactone Synthesis: Use of Unprotected Haloalcohols as Radical Precursors

Mukund P. Sibi,* Miguel A. Guerrero

Department of Chemistry, North Dakota State University, Fargo, North Dakota 58105, USA
Fax +1(701)2311057; E-mail: Mukund.Sibi@ndsu.edu

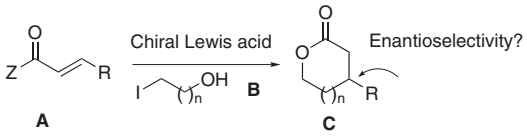
Received 14 March 2005

Dedicated to Bernd Giese in appreciation of his seminal contributions to free radical chemistry

Abstract: We have developed an efficient free radical method for the synthesis of enantioenriched 6- and 7-membered lactones in one synthetic operation.

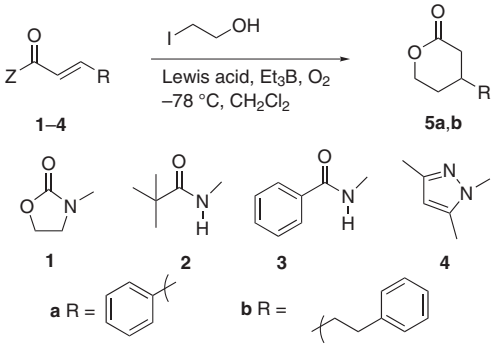
Key words: radical reactions, chiral Lewis acid, lactones, conjugate additions, enantioselective reactions

Free radical chemistry provides an opportunity to explore reactions wherein reactive functional groups can be utilized without protection.[1] In the context of developing new routes to lactones, we have explored the enantioselective addition of radical precursors containing hydroxyl groups to α,β-unsaturated carboxylic acid derivatives (Equation 1, **A** → **B**).[2] The route is flexible and can provide access to functionalized lactones depending on the substitution in the radical precursor or the acceptor. In this work we demonstrate that functionalized 6- and 7-membered lactones can be synthesized in a single operation in good yield and good to high enantioselectivity.



Equation 1

We began our work with the identification of an appropriate acceptor that would undergo conjugate addition effectively using iodoethanol as the radical precursor (Scheme 1).[3] At the outset, we were concerned with the relatively low nucleophilicity of the primary radical derived from iodoethanol and surmised that we would need a very good acceptor with additional Lewis acid activation. To this end, we screened combinations of different acceptors and Lewis acids and these results are shown in Table 1. For these reactions we employed five equivalents of iodoethanol, one equivalent of the Lewis acid, three equivalents of tin hydride, and triethylborane/oxygen as the radical initiator. Radical addition to oxazolidinone cinnamate **1a** using ytterbium triflate as a Lewis acid did not give any product (Table 1, entry 1). We have recently shown that imide templates are quite effective in radical chemistry.[4] However, radical addition to **2a** was also not effective (entries 2 and 3). More encouraging results were obtained with imide **3a** providing the lactone directly in 30% yield (entry 5). Cinnamates are generally less reactive in conjugate radical additions. Changing the β-substituent to a dihydrocinnamyl moiety (**3b**) improved reactivity and gave the lactone product in good yield (entries 6 and 7). 3,5-Dimethylpyrazole has proven to be an effective achiral template in a variety of reactions.[5] This template proved to be ideal in that radical addition to **4a** and **4b** proceeded well giving the lactones **5a** and **5b**, respectively in good yields (entries 9–15).



Scheme 1

Our next task was the identification of an optimal chiral Lewis acid system for the enantioselective radical addition to **3b** and **4b** (Scheme 2).[6] These experiments would allow us to assess the impact on reactivity and/or selectivity due to the presence of the Lewis basic hydroxyl group in the radical precursor and its potential interaction with the Lewis acid. Our group has demonstrated several chiral Lewis acid systems that are effective in enantioselective radical reactions and thus they were reagents of choice for additions to **3b** and **4b**.[7] Radical addition to **3b** using $Mg(ClO_4)_2$ and ligand **6** (1 equiv) gave the lactone **5b** in modest yield and enantioselectivity (Table 2, entry 1). Other chiral Lewis acids (data not shown) did not show any improvement in selectivity and only ytterbium triflate in combination with **8** was effective (entries 2 and 3). Compound **4b** containing a pyrazole template was screened next and it showed superior characteristics with respect to both yield and enantioselectivity. Of the several chiral Lewis acids examined (entries 4–16), magnesium

SYNTHESIS 2005, No. 9, pp 1528–1532
Advanced online publication: 18.04.2005
DOI: 10.1055/s-2005-865319; Art ID: C02205SS

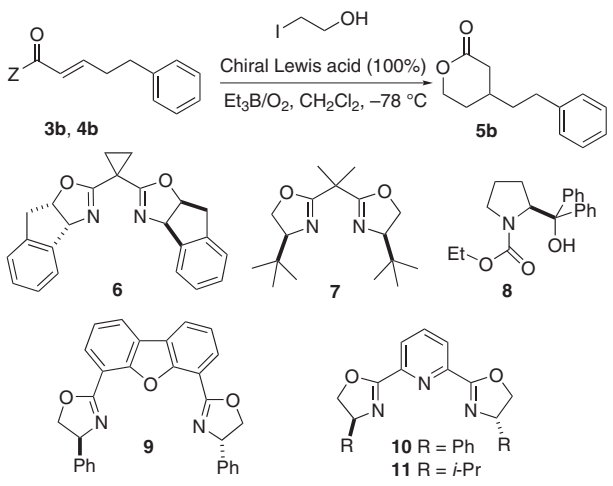
Table 1 Identification of an Optimal Acceptor for Reactions with Iodoethanol

Entry	Substrate	Lewis acid	Product	Yield (%)[a]
1	**1a**	$Yb(OTf)_3$	**5a**	<3
2	**2a**	$MgBr_2$	**5a**	NR
3	**2a**	$Yb(OTf)_3$	**5a**	<3
4	**3a**	$MgBr_2$	**5a**	NR
5	**3a**	$Yb(OTf)_3$	**5a**	30
6	**3b**	$Mg(ClO_4)_2$	**5b**	60
7	**3b**	$Yb(OTf)_3$	**5b**	61
8	**4a**	$MgBr_2$	**5a**	NR
9	**4a**	$Yb(OTf)_3$	**5a**	68
10	**4a**	$Mg(NTf_2)_2$	**5a**	48
11	**4a**	$Mg(ClO_4)_2$	**5a**	56
12	**4b**	$MgBr_2$	**5b**	<3
13	**4b**	$Mg(ClO_4)_2$	**5b**	61
14	**4b**	$Yb(OTf)_3$	**5b**	50

[a] Isolated yield after column chromatography. NR = no reaction.

triflimide and ligand **6** (85% ee, entry 8) and nickel perchlorate and ligand **9** (88% ee, entry 14) gave the highest selectivity. Of these two, magnesium triflimide was more efficient with respect to yield. These experiments demonstrate that lactones can be synthesized in one synthetic operation in modest to good yield and high enantioselectivity. Furthermore, the high selectivity obtained using a small primary radical without any protection of the hydroxyl group is noteworthy.

The synthesis of δ-lactones with different groups at the 4-position was investigated next (Equation 2) and these results are tabulated in Table 3. For these reactions, the chiral Lewis acid derived from $Mg(NTf_2)_2$/ligand **6** was used. The conjugate radical addition followed by cyclization leading to lactones **5a–g** was generally highly selective with ee values ranging from 79–85% (entries 1–7), except for reaction with **4g**, which gave 48%ee (entry 7). The chemical efficiency of the reaction was dependent on the substrate. This underscores the low reactivity of the primary radical and high yields are obtained with electron poor substrate (**4e**, 81%, entry 5) or a small alkyl group (**4g**, 85%, entry 7) only. Substrates **4a–d** gave only modest yields (entries 1–4). Compounds **4f–g** gave good yields.

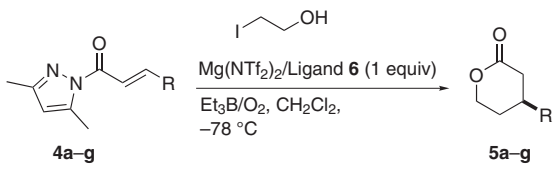


Scheme 2

Table 2 Effect of Lewis Acids on Enantioselectivity

Entry	Substrate	Lewis acid	Ligand	Yield (%)[a]	ee (%)[b]
1	**3b**	$Mg(ClO_4)_2$	**6**	48	40
2	**3b**	$Yb(OTf)_3$	**8**	54	10
3	**3b**	$Sm(OTf)_3$	**8**	48	<3
4	**4b**	$Zn(OTf)_2$	**6**	40	55
5	**4b**	$Zn(NTf_2)_2$	**6**	40	10
6	**4b**	MgI_2	**6**	33	55
7	**4b**	$Mg(OTf)_2$	**6**	58	32
8	**4b**	$Mg(NTf_2)_2$	**6**	50	85
9	**4b**	$Mg(ClO_4)_2$	**6**	53	44
10	**4b**	$Zn(OTf)_2$	**7**	40	4
11	**4b**	$Mg(NTf_2)_2$	**7**	50	<3
12	**4b**	$Yb(OTf)_3$	**8**	59	<3
13	**4b**	$Ni(ClO_4)_2$	**9**	30	49
14	**4b**	$Ni(ClO_4)_2$	**9**	38	88
15	**4b**	$Sc(OTf)_3$	**10**	NR	–
16	**4b**	$Sc(OTf)_3$	**11**	NR	–

[a] Isolated yield after column chromatography.
[b] Determined by chiral HPLC or chiral GC.



Equation 2

We have also assessed few different radical precursors in lactone synthesis and these results are shown in Figure 1. Addition of the radical derived from 1-iodo-2-methyl-2-propanol to **4g** and **4e** gave lactones **12** and **13**, respectively, in modest yield and selectivity. Addition of a primary

Table 3 Radical Addition to Different Substrates

Entry	Substrate R	Product	Yield (%)[a]	Config.	ee (%)[b]
1	Ph (**4a**)	**5a**	48	*S*	85
2	$PhCH_2CH_2$ (**4b**)	**5b**	50	*R*[c]	85
3	2-Furyl (**4c**)	**5c**	40		79
4	2-Thiophenyl (**4d**)	**5d**	52		80
5	4-CF_3Ph (**4e**)	**5e**	81	*S*	80
6	Cyclohexyl (**4f**)	**5f**	68	*S*	81
7	$PMPOCH_2$ (**4g**)	**5g**	85		48

[a] Isolated yield after column chromatography.
[b] Determined by chiral HPLC or chiral GC.
[c] Note the change in priority.

radical derived from enantiopure (*S*)-3-chloro-1-iodo-2-propanol[8] to **4e** gave lactone **14** as a mixture of diastereomers in a ratio of 9:1. The 80% ee in this reaction is similar to that observed for iodoethanol addition to **4e** (see entry 5, Table 2). An analogous experiment using the enantiomer of ligand **6** gave a mixture of diastereomeric lactones in a ratio of 1:2. These experiment suggest that selectivity is optimal when the ligand and the reagent are matched. We have also examined iodopropanol as the radical precursor. Addition of the radical derived from 1-iodo-3-propanol to **4b** and **4e** furnished the 7-membered lactones **15** and **16**, respectively in high yield and selectivity. It is interesting to note that the 7-membered lactone formation proceeds in higher yields and selectivity as compared to the 6-membered ring analogs.

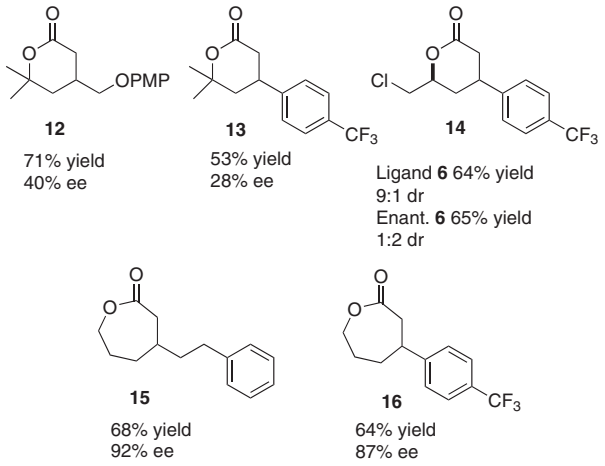
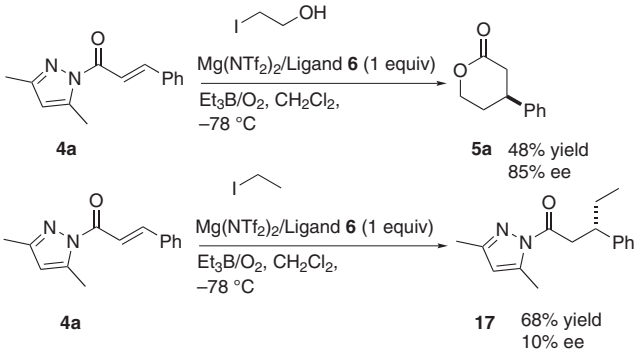


Figure 1

The absolute stereochemistry of lactones **5a**, **5b**, **5e** and **5f** have been reported in the literature.[9] Comparison of the sign of rotation for **5a**, **5b**, **5e**, and **5f** from our experiments with those in the literature establishes that the *S* products are formed (see Table 3).[10] We also investigated the addition of ethyl radical to **4a** (Scheme 3). The ethyl addition product **17** was obtained in good yield and low selectivity.[11] The absolute stereochemistry for the product was established as *S* by hydrolysis to the known pentanoic acid.[12] Thus the addition of ethyl and hydroxyethyl radicals occurs from the same face. The large difference in the level of enantioselectivity between the two radicals suggests that the hydroxy group could influence the addition through potential coordination to the Lewis acid. This conclusion is corroborated by the match/mismatch in selectivity observed with the chiral alcohols (see Figure 1, data for **14**). The higher selectivity observed for the seven-membered lactones (Figure 1, **15** and **16**) is also instructive in that tether length could play a role in determining the level of enantioselection.



Scheme 3

In conclusion we have developed an efficient free radical methodology for the synthesis of 6-and 7-membered lactones. The use of precursors containing unprotected reactive functional groups highlights the power of free radical methods in the enantioselective synthesis of chiral lactones. The new methodology holds promise for the introduction of a wide variety of substituents on to the lactone ring. The application of the new methodology to the synthesis of natural products is underway in our laboratory.

Conjugate Radical Additions; General Procedure

Under N_2, a mixture of Lewis acid (0.10 mmol) and ligand (0.10 mmol) in CH_2Cl_2 (2 mL) was stirred at r.t. for 45 min. Pyrazole (**4a**; 0.10 mmol) (in 1 mL CH_2Cl_2) was added and the mixture was allowed to stir for an additional 30 min and then cooled to –78 °C. The reaction was then initiated by sequential addition of 2-iodo ethanol (or other radical precursors) (1 mmol), *n*-Bu_3SnH (0.5 mmol), Et_3B (0.5 mmol 1 M solution in hexanes) and oxygen (introduced via syringe). The reaction was monitored by TLC (50% EtOAc in hexane) and when judged complete was quenched with silica gel, concentrated, washed with hexanes and extracted with Et_2O. The Et_2O extract was concentrated over silica gel and purified by silica gel chromatography (hexane–EtOAc) to give the products. The enantiomeric excess of the product was determined by chiral GC or HPLC.

Compound 5a

Ee estimated by chiral GC analysis; column βETA Dex 225 (0.25 cm × 30cm), Temp = 165 °C, t_R (minor) = 68 min, t_R (major) = 74 min, with 85% ee; $[\alpha]_D^{25}$ +3.5 (*c* = 0.34, $CHCl_3$).

IR (neat): 2921, 1720 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36 (t, *J* = 7.0 Hz, 2 H), 7.27 (t, *J* = 7.5 Hz, 1 H), 7.21 (d, *J* = 7.0 Hz, 2 H), 4.51 (ddd, *J* = 11.0, 4.5, 4.0 Hz, 1 H), 4.39 (ddd, *J* = 11.5, 10.5, 3.5 Hz, 1 H), 3.28–3.20 (m, 1 H), 2.92 (ddd, *J* = 17.5, 6.0, 1.5 Hz, 1 H), 2.64 (dd, *J* = 17.5, 10.5 Hz, 1 H), 2.21–2.15 (m, 1 H), 2.1–2.0 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 142.9, 129.2, 127.4, 126.7, 68.8, 37.7, 37.6, 30.5.

Compound 5b
Yield: 50%; colorless oil.

Ee was estimated by chiral HPLC (254 nm, 25 °C) [chiralcel OD column (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd), hexane–*i*-PrOH (90:10), flow rate = 0.8 mL/min], t_R (major) = 36 min, t_R (minor) = 48 min, with 85% ee; $[\alpha]_D^{25}$ +14.5 (*c* = 0.48, $CHCl_3$).

IR (neat): 2919, 1738, 1254, 1080 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 7.5 Hz, 2 H), 7.20 (t, *J* = 7.5 Hz, 1 H), 7.16 (d, *J* = 7.5 Hz, 2 H), 4.41 (ddd, *J* = 11.0, 4.5, 4.0 Hz, 1 H), 4.24 (td, *J* = 11.0, 4.0 Hz, 1 H), 2.73 (ddd, *J* = 17.5, 6.0, 1.5 Hz, 1 H), 2.66 (t, *J* = 8.0 Hz, 2 H), 2.19 (dd, *J* = 17.5, 10.5 Hz, 1 H), 2.01–1.95 (m, 2 H), 1.74–1.66 (m, 2 H), 1.61–1.54 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3, 141.4, 128.7, 128.4, 126.3, 68.6, 38.0, 36.6, 32.8, 31.0, 29.0.

HMRS (ESI): *m*/*z* calcd for $C_{13}H_{16}O_2Na$: 227.1048; found: 227.1029.

Compound 16
Yield: 64%; white solid; mp 109 °C.

Ee was estimated by chiral HPLC (254 nm, 25 °C) [chiralcel OD-H column (0.46 cm × 25 cm) (from Daicel Chemical Ind., Ltd), hexane–*i*-PrOH (90:10), flow rate = 1.0 mL/min], t_R (major) = 17 min, t_R (minor) = 20 min, with 87% ee; $[\alpha]_D^{25}$ –41.5 (*c* = 0.8, $CHCl_3$).

IR (neat): 2925, 1730, 1326, 1180, 1111, 1025 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.5 Hz, 2 H), 7.30 (d, *J* = 8.5 Hz, 2 H), 4.43–4.36 (m, 1 H), 4.31 (dd, *J* = 13, 10.5 Hz, 1 H), 3.07 (dd, *J* = 12.0, 12.2 Hz, 1 H), 3.01 (ddd, *J* = 12.0, 12.2, 2.5 Hz, 1 H), 2.81 (dd, *J* = 12.0, 1.0 Hz, 1 H), 2.15–2.06 (m, 2 H), 2.00–1.90 (m, 1 H), 1.85–1.75 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.1, 149.5, 129.5 (q, *J* = 32 Hz), 126.9, 126 (q, *J* = 3 Hz), 124 (q, *J* = 272 Hz), 69.2, 41.3, 40.7, 37.7, 29.1.

HMRS (ESI): *m*/*z* calcd for $C_{13}H_{14}F_3O_2$ ($M + H^+$): 259.0946; found: 259.0944.

Acknowledgment

We thank the National Institutes of Health (NIGMS-54656) for financial support. We also thank Conacyt-Mexico for providing a fellowship to M. Guerrero.

References

(1) (a) *Radicals in Organic Synthesis*, Vol. 1; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**. (b) *Radicals in Organic Synthesis*, Vol. 2; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**.

(2) For lactone synthesis using radical intermediates, see: (a) Tsunoi, S.; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 8692. (b) Tsunoi, S.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* **1994**, *116*, 5473. (c) Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. *Org. Lett.* **2000**, *2*, 389. (d) Castle, K.; Hau, C.-S.; Sweeney, J. B.; Tindall, C. *Org. Lett.* **2003**, *5*, 757. (e) Molander, G. A.; St. Jean, D. J. Jr. *J. Org. Chem.* **2002**, *67*, 3861. (f) Clive, D. L. J.; Zhang, J.; Subedi, R.; Bouetard, V.; Hiebert, S.; Ewanuk, R. *J. Org. Chem.* **2001**, *66*, 1233. (g) Berlin, S.; Ericsson, C.; Engman, L. *Org. Lett.* **2002**, *4*, 3. (h) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071. (i) Kim, K.; Okamoto, S.; Sato, F. *Org. Lett.* **2001**, *3*, 67. (j) Fischer, J.; Reynolds, A. J.; Sharp, L. A.; Sherburn, M. S. *Org. Lett.* **2004**, *6*, 1345. (k) Fukuzawa, S.-I.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482. (l) Kerrigan, N. J.; Upadhyay, T.; Procter, D. J. *Tetrahedron Lett.* **2004**, *45*, 9087. (m) Kerrigan, N. J.; Hutchison, P. C.; Heightman, T. D.; Procter, D. J. *Org. Biomol. Chem.* **2004**, *2*, 2476. (n) Fang, X.; Xia, H.; Yu, H.; Dong, X.; Chen, M.; Wang, Q.; Tao, F.; Li, C. *J. Org. Chem.* **2002**, *67*, 8481.

(3) For selected examples on the use of achiral templates in enantioselective transformations from other laboratories, see: (a) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559. (b) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1731. (c) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (d) Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471. (e) Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710. (f) Palomo, C.; Oiarbide, M.; Garcia, J. M.; Gonzalez, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942. (g) For work from our laboratory see the following: Sibi, M. P.; Sausker, J. B. *J. Am. Chem. Soc.* **2002**, *124*, 984. (h) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615. (i) Sibi, M. P.; Liu, M. *Org. Lett.* **2000**, *2*, 3393. (j) Sibi, M. P.; Prabagaran, N. *Synlett* **2004**, 2421.

(4) Sibi, M. P.; Petrovic, G.; Zimmerman, J. *J. Am. Chem. Soc.* **2005**, *127*, 2390.

(5) Sibi, M. P.; Shay, J. J.; Ji, J. *Tetrahedron Lett.* **1997**, *38*, 5955.

(6) For reviews on stereoselective radical chemistry, see: (a) Renaud, P.; Gèrster, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 2563. (b) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (c) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263. (d) Bar, G.; Parsons, A. F. *Chem. Soc. Rev.* **2003**, *32*, 251. (e) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8303.

(7) Enantioselective conjugate radical reactions: (a) Sibi, M. P.; Ji, J.; Wu, J. H.; Gurtler, S.; Porter, N. A. *J. Am. Chem. Soc.* **1996**, *118*, 9200. (b) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1997**, *62*, 3800. (c) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472. (d) Sibi, M. P.; Manyem, S. *Org. Lett.* **2002**, *4*, 2929. (e) Sibi, M. P.; Petrovic, G. *Tetrahedron: Asymmetry* **2003**, *15*, 2879. (f) Sibi, M. P.; Zimmerman, J.; Rheault, T. R. *Angew. Chem. Int. Ed.* **2003**, *42*, 4521. (g) Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417. (h) Murakata, M.; Tsutsui, H.; Hoshino, O. *Org. Lett.* **2001**, *3*, 299. (i) Sibi, M. P.; He, L. *Org. Lett.* **2004**, *6*, 1749.

(8) The compound was prepared from optically pure epichlorohydrin.

(9) Compound **5a** and **5e**: (a) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (b) Irwin, A. J.; Jones, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 556. (c) Evans, D. A.; Johnson, J. A.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635. (d) Compound **5b**: Jones, J. B.; Lok, K. P. *Can. J. Chem.* **1979**, *57*, 1025. (e) Compound **5f**: Lam, L. K. P.; Hui, R. A. H. F.; Jones, J. B. *J. Org. Chem.* **1986**, *51*, 2047.

(10) Note the change in priority for compound **5b**. The radical reaction occurs from the same face for all compounds.

(11) This reaction proceeds with 39% ee when magnesium bromide is used as the Lewis acid. See ref. 5.

(12) (a) Elzner, S.; Maas, S.; Engel, S.; Kunz, H. *Synthesis* **2004**, 2153. (b) Chiacchio, U.; Corsaro, A.; Gambera, G.; Rescifina, A.; Piperno, A.; Romeo, R.; Romeo, G. *Tetrahedron: Asymmetry* **2002**, *13*, 1915.