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Reagent-Controlled Asymmetric Homologation of Boronic Esters by Enantioenriched Main-Group Chiral Carbenoids

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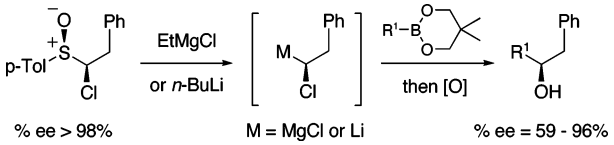
ABSTRACT



Putative enantioenriched carbenoid species, (*R*)-1-chloro-2-phenylethylmagnesium chloride (9) and (*S*)-1-chloro-2-phenylethyllithium (26), generated in situ by sulfoxide ligand exchange from (−)-(R_S,*R*)-1-chloro-2-phenylethyl *p*-tolyl sulfoxide (8), effected the stereocontrolled homologation of boronic esters. *sec*-Alcohols derived from the product boronates by oxidation with basic hydrogen peroxide exhibited % ee closely approaching that of sulfoxide 8 in examples employing Li-carbenoid 26.

A majority of methods for asymmetric synthesis rely directly on stereoinduction, viz. new stereogenic elements are introduced selectively by relay of existing stereochemical information through space across conformationally biased transition state assemblies.[1] Although stereoinduction is undoubtedly an efficient precept for synthesis, emerging stereochemistry is not completely controlled during stereoinductive events and distinct diastereoisomeric products cannot be targeted with equal facility by a given method.[2] By contrast, reagents containing preexisting stereogenic centers, which react via purely stereospecific pathways, may offer a trivial means to effect stereocontrol not reliant on stereoinduction at the point of bond formation. The allusion made here is to a stereospecific reagent control paradigm in which stereochemical information contained within the reagent is merely translated into a stereogenic feature of the product.

In pursuit of a programmable asymmetric method based firmly on a principle of stereospecific reagent control, we formulated a hypothetical chain extension process that would not be subject to the vagaries of stereoinduction. The envisioned method, stereospecific reagent controlled homologation (SRCH), calls for the stereospecific insertion of enantioenriched chiral carbenoid reagents **2** into organometallic substrates **1** via intermediate ate-complexes **3** (Scheme 1; M^1, M^2 = metal, X = nucleofugal group). 1,2-Metalate rearrangement[3] of complexes **3** would afford homologated adducts (**4**) suitable for direct subjection to

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(1) (a) *Catalytic Asymmetric Synthesis*; Ojimia, I., Ed.; Wiley: New York, 2000. (b) *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995. (c) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley: New York, 1994. (d) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(2) The common observation of matching and mismatching of substrate/reagent pairs in "double" asymmetric synthesis is a manifestation of this fundamental weakness; see: *Asymmetric Synthesis*; Procter, G., Ed.; Oxford University Press: Oxford, 1996.

(3) For recent synthetic applications of 1,2-metalate rearrangements, see: (a) Jarowicki, K.; Kocienski, P. J. *Synlett* **2005**, 167. (b) Abramovitch, A.; Varghese, J. P.; Marek, I. *Org. Lett.* **2004**, *6*, 621. (c) Pommier, A.; Stepanenko, V.; Jarowicki, K.; Kocienski, P. J. *J. Org. Chem.* **2003**, *68*, 4008. (d) Le Menez, P.; Brion, J.-D.; Lensen, N.; Chelain, E.; Pancrazi, A.; Ardisson, J. *Synthesis* **2003**, 2530. (e) Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **2000**, *41*, 6201. (f) Sidduri, A.; Rozema, M. K.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 2694 and references therein.

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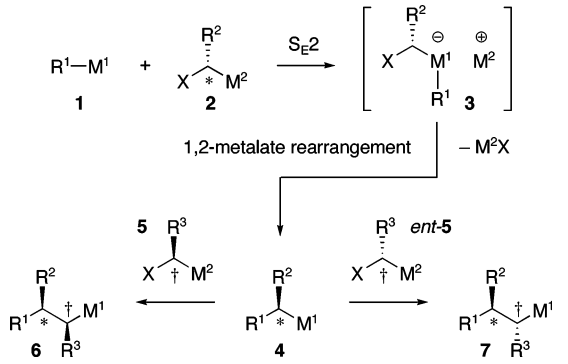
Scheme 1. Stereospecific Reagent-Controlled Homologation

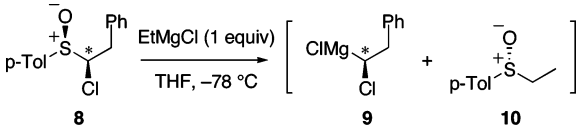


further cycles of SRCH. In this manner, iterative SRCH, if achievable, would allow for the controlled assembly of polysubstituted alkyl chains with installation of stereogenic centers being programmed at each stage of iteration by selection of the appropriate carbenoid enantiomorph. For example, in the illustrated notional sequence, either diastereoisomer **6** or **7** could be precisely targeted by choice of carbenoid reagent, **5** or *ent*-**5**.

Three conditions require satisfaction for the concept of SRCH to be fully realized: (1) carbenoid reagents **2** must possess configurational and chemical stability under the conditions required for ate-complex formation, (2) ate-complex formation and breakdown must occur via entirely stereospecific processes, and (3) to avoid multiple insertions per cycle (leading to unwanted oligomerization), the metalate rearrangement step must occur only after any excess carbenoid reagent has suffered immolative deactivation or been otherwise consumed (i.e., greater stability for **3** vs **2**). Herein, we report that these criteria are ostensibly met where $M^1 = B(OR)_2$ and $M^2 = MgCl$ or Li and describe noniterative SRCH of boronic esters by enantioenriched α-chloroalkylmagnesium and α-chloroalkyllithium reagents.[4]

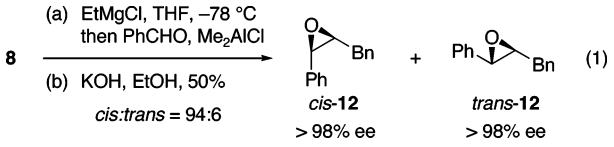
At the outset of our studies, seminal discoveries emanating from the laboratories of Matteson and Hoffmann suggested the possibility of a successful SRCH manifold with $M^1 = B(OR)_2$ and $M^2 = MgCl$. The early work of Matteson and Mah established that α-haloalkyl boronic esters experience indirect S_N2-like displacement of the α-halide atom by Grignard species via intermediate borate complexes **3** ($M^1 = B(OR)_2$, $M^2 = MgCl$).[5] Of further significance, the Hoffmann group recently reported that α-haloalkyl Grignard reagents exhibit good configurational stability (little or no racemization below −60 °C) and demonstrated that these carbenoid species can be generated in enantioenriched form by sulfoxide ligand exchange from homochiral α-chlorosulfoxides.[6] Cognizant of these results, we reasoned that addition of a configurationally stable Hoffmann-type carbenoid **2** ($M^2 = MgCl$, X = Cl) to a simple boronic ester **1** ($M^1 = B(OR)_2$) would afford essentially the same type of borate intermediate to that first encountered by Matteson and Mah, the only difference being the order of introduction of the participating carbon ligands onto boron. SRCH would therefore be a reasonable expectation providing that electrophilic substitution (S_E2) of MgCl for $B(OR)_2$ occurred stereospecifically.[7] Eager to test this hypothesis, we prepared known α-chlorosulfoxide **8** (with dr > 99:1, % ee > 98%)[8] and verified the efficacy of its sulfoxide ligand exchange reaction with EtMgCl to generate Hoffmann's carbenoid **9**. In agreement with the earlier report,[6] the exchange reaction was rapid in THF solvent at −78 °C and quenching experiments with methanol-d_4 revealed the absence of proton transfer between **9** and **10** (Scheme 2).[9] As expected given

Scheme 2. Sulfoxide Ligand Exchange from **8**



T (°C)	X (min)	11	10
–78	10	74%	91%
–50	90	64%	96%
–20	195	19%	100%

the chemical instability of **9**, the isolated yield of deuterated phenethyl chloride (**11**) diminished as time to quench and reaction temperature were increased; nevertheless, potentially adequate experimental limits for the operation of SRCH were evident. Repetition of Hoffmann's benzaldehyde trapping experiment (eq 1) confirmed the configurational stability of **9** and indicated that this species was generated from **8** with excellent enantiomeric purity (% ee > 98%).[10]



Homologation of organoboron compounds with α-chloroalkylmagnesium reagents has not been reported;[11] however, boronic ester extension with comparable LiCHRX species

(4) Presented in part at the 229th ACS National Meeting, San Diego, CA, March 13−17, 2005; Blakemore, P. R.; Vater, H. D. paper ORGN 269.

(5) Matteson, D. S.; Mah, R. W. H. *J. Am. Chem. Soc.* **1963**, *85*, 2599.

(6) Hoffmann, R. W.; Nell, P. G.; Leo, R.; Harms, K. *Chem. Eur. J.* **2000**, *6*, 3359.

(7) A stereoretentive electrophilic substitution (transmetalation) reaction between an enantioenriched secondary Grignard reagent and a borate ester has been reported, see: Hoffmann, R. W.; Hölzer, B.; Knopff, O. *Org. Lett.* **2001**, *3*, 1945.

(8) Sulfoxide **8** was prepared as previously described by Hoffmann (ref 6) via a route that leads to its production as a 5:1 mixture of *syn* and *anti* diastereoisomers epimeric at the carbon stereocenter (∗). In our hands, fractional recrystallation of **8** from Et_2O was found to be superior to acetone (as reported by Hoffmann) for the purpose of obtaining this compound in an isomerically homogeneous form (single stereoisomer by chiral HPLC analysis after three recrystallation cycles).

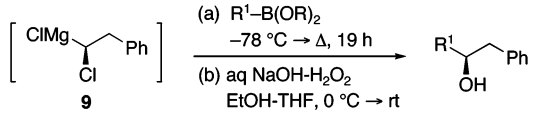
(9) In each case, no deuterium was incorporated into sulfoxide **10** and the level of deuterium incorporation in **11** was 90%; % ee for **10** and **11** was not determined.

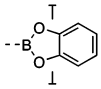
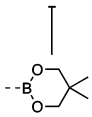
(X = halide), where R = H,[12] X,[13] and TMS,[14] is well-known and typically affords mono-homologated products in excellent yield.[15] With the expectation that Mg-carbenoid **9** would exhibit lower nucleophilicity than Li-carbenoids,[16] initial insertion studies were conducted with a strongly Lewis acidic catechol boronate (**13**) to facilitate ate-complex formation (Table 1, entries 1−4). In the first instance, Barbier-type conditions were adopted for the generation of carbenoid **9**; accordingly, EtMgCl was added to a mixture of sulfoxide **8** and boronate **13** in chilled THF solvent (entry 1). Pleasingly, after warming of the putative ate-complex to encourage a recalcitrant 1,2-metalate rearrangement,[17] *sec*-alcohol **20** was obtained with discernible enantio-enrichment (36% ee), albeit in low yield, following oxidative workup. An improvement in both yield and enantioselectivity was achieved by preforming the carbenoid prior to the introduction of boronate **13** (entry 2). Modest gains in efficacy were subsequently realized by switching to less polar reaction media (entries 3, 4). The purpose of making this change was 2-fold: first, carbanions have greater configurational stability in the absence of coordinating polar solvents,[18] and second, boronate **13** would possess a higher effective Lewis acidity in such media.

To further assess the viability of SRCH with carbenoid **9**, homologation of a series of variably *B*-substituted 1,3,2-dioxaborinanes (**14**−**19**) was next investigated (entries 5−12). Neopentyl glycol derived boronic esters, being relatively stable and easy to manipulate, offer significant practical advantages over catechol boronates; however, we held reservations that the reduced Lewis acidity of these substrates would prohibit carbenoid insertion. In the event, our fears proved groundless. Boronate **14** gave improved results as compared to its congener **13** (entries 5−7), and other non-α-branched *B*-alkyl-substituted neopentyl glycol boronates behaved similarly (entries 8 and 9). Homologation reactions from *B*-cyclohexyl- and *B*-phenyl-substituted boronates **17** and **18** were less satisfactory, however, and gave low yields of the respective carbinols, *ent*-**23** and **24**, with inferior enantiocontrol (entries 10 and 11). The same reaction failed completely for vinyl boronate **19** and gave a complex mixture of intractable products (entry 12).

Where determined (entries 9 and 10),[19] the stereochemical outcome of insertion was consistent with a stereoretentive S_E2 reaction between boronate and carbenoid followed by 1,2-nucleophilic rearrangement from the resulting metalate-complex with inversion of configuration at the migratory terminus (and as illustrated in Scheme 1). It is reasonable to conclude that homologation of other substrates took the same stereochemical course. The erosion in enantiomeric excess observed in proceeding from sulfoxide **8** to carbinols **20**−**24** is attributed to partial racemization of Mg-carbenoid **9** prior to its capture by the boronic ester. The fact that a significant lowering in both yield and ee resulted upon the introduction of branching elements about the boron atom is consistent with this hypothesis: increased steric hindrance

Table 1. Homologation of Boronic Esters with (*R*)-1-Chloro-2-phenylethylmagnesium Chloride (**9**)[a]



entry	boronic ester #	R¹	---B(OR)₂	solvent	isolated carbinol #	% yield	% ee[b]
1[c]	**13**	Ph(CH₂)₂		THF	**20**	11	36
2	**13**	Ph(CH₂)₂		THF	**20**	31	68
3	**13**	Ph(CH₂)₂		CH_2Cl_2	**20**	40	71
4	**13**	Ph(CH₂)₂		PhMe	**20**	44	76
5	**14**	Ph(CH₂)₂		CH_2Cl_2	**20**	49	82
6	**14**	Ph(CH₂)₂		PhMe	**20**	48	82
7[d]	**14**	Ph(CH₂)₂		PhMe	*ent*-**20**	52	–75
8[e]	**15**	Me		PhMe	**21**	56	n/d
9	**16**	*n*-Bu		PhMe	**22**	40	70
10[d]	**17**	*c*-hex		PhMe	*ent*-**23**	9	–60
11	**18**	Ph		PhMe	**24**	13	59
12	**19**	(*E*)-PhCH=CH		PhMe	**25**	0	n/a

[a] Carbenoid **9** formed by addition of EtMgCl (2 equiv, 1.8 M in THF) to sulfoxide **8** (2 equiv, dr > 99:1, % ee > 98%) in the indicated solvent (0.2 M) at −78 °C; the mixture was allowed to stir for 30 min before addition of boronate (1 equiv). [b] Determined by HPLC analysis; absolute configuration established for **22** and *ent*-**23** only. [c] EtMgCl (2 equiv) added to a mixture of **8** (1 equiv, dr (∗) = 92:8) and **13** (1 equiv). [d] From sulfoxide *ent*-**8** (*ent*-**9**). [e] Product contaminated by sulfoxide **8**, yield based on ^{1}H NMR analysis.

(10) % ee for epoxides *cis*-**12** and *trans*-**12** was determined by HPLC analysis. Hoffmann and co-workers reported 69% overall yield for a closely related transformation employing EtMgBr in place of EtMgCl and found *cis*:*trans* = 88:12 and % ee (*cis*-**12**) = 93 ± 3% (see ref 6). Diastereoselectivity in this type of addition has been studied in detail; see: Schulze, V.; Nell, P. G.; Burton, A.; Hoffmann, R. W. *J. Org. Chem.* **2003**, *68*, 4546.

(11) Satoh and co-workers have investigated many other aspects of the chemistry of α-halo Grignard species. For recent work, with leading references, see: (a) Satoh, T.; Ogino, Y.; Ando, K. *Tetrahedron* **2005**, *61*, 10262. (b) Miyashita, K.; Satoh, T. *Tetrahedron* **2005**, *61*, 5067. (c) Satoh, T.; Musashi, J.; Kondo, A. *Tetrahedron Lett.* **2005**, *46*, 599. (d) Satoh, T.; Kondo, A.; Musashi, J. *Tetrahedron* **2004**, *60*, 5453.

(12) (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687. (b) Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631. (c) Wallace, R. H.; Zong, K. K. *Tetrahedron Lett.* **1992**, *33*, 6941. (d) Soundararajan, R.; Li, G.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 8957.

(13) Diastereoselective homologation of boronic esters with $LiCHX_2$ species (X = Cl, Br) has been extensively studied by Matteson and co-workers and constitutes an important method for substrate controlled asymmetric chain extension. For reviews, see: (a) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555. (b) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535. For recent applications, see: (c) Hiscox, W. C.; Matteson, D. S. *J. Organomet. Chem.* **2000**, *614*−*615*, 314. (d) Davoli, P.; Spaggiari, A.; Castagnetti, L.; Prati, F. *Org. Biomol. Chem.* **2004**, *2*, 38.

(14) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 230.

(15) Multiple insertions with $LiCH_2X$ species have been encountered, see: Ren, L.; Crudden, C. M. *Chem. Commun.* **2000**, 721.

(16) α-Haloalkylmetal reagents are relatively poor nucleophiles and in many of their characteristic reactions are best considered as electrophilic species, see: Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697.

(17) Homologated carbinol products were only successfully obtained from Mg-carbenoid **9** when the reaction mixture was either briefly heated or else allowed an excessive time at ambient temperature (= 12 h), prior to quenching with aq $NaOH/H_2O_2$.

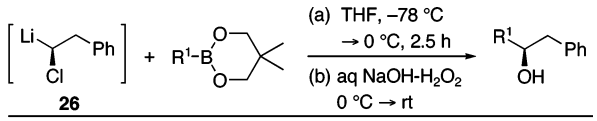
(18) For discussion of this topic as it relates to organolithiums, see ref 22.

(19) Absolute configuration for carbinol **22** was determined by ^{1}H NMR analysis of its derived MTPA-ester according to Mosher's method: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. To establish absolute configuration for *ent*-**23**, an authentic sample of its antipode was prepared by enantioselective reduction of benzyl cyclohexyl ketone with (*S*)-methyl-CBS-oxazaborolidine according to Corey's method: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. See Supporting Information for details.

would impede ate-complex formation and afford the sensitive carbenoid intermediate the opportunity for racemization and chemical decomposition.

In their first report describing the synthesis of (racemic) α-halo Grignard reagents by sulfoxide ligand exchange, Satoh and Takano had also demonstrated the generation of analogous Li-carbenoids by addition of alkyllithiums to the same α-halosulfoxide precursors.[20] With remaining stocks of homochiral sulfoxide **8** in hand, we therefore elected to briefly explore an alternative SRCH manifold with $M^1 = B(OR)_2$ and $M^2 = Li$; however, since α-haloalkyllithiums are more chemically labile and less configurationally stable than α-haloalkylmagnesium halides,[21,22] we were doubtful of a successful outcome according to this new scheme. Indeed, initial attempts to homologate boronic ester **14** by a modification of our earlier protocol involving substitution of *n*-BuLi for EtMgCl during sulfoxide ligand exchange met with failure (Table 2, entry 1). Mindful of the distinct possibility that the putative carbenoid in this case (**26**) had decomposed prior to the introduction of the boronate,[23] we returned to Barbier conditions with welcome results. Thus, addition of *n*-BuLi to a *mixture* of boronate **14** and sulfoxide **8** in THF solvent at −78 °C gave, after warming to 0 °C and the usual oxidative workup, the expected carbinol product (**20**) in a remarkable 96% ee and 70% yield (entry 2).[24] The high stereochemical fidelity observed in proceeding from sulfoxide **8** (>98% ee) to alcohol **20** (96% ee) provides compelling evidence that all of the fundamental steps involved in this process are essentially stereospecific. To our further delight, the same protocol as applied to *B*-cyclohexyl-substituted boronate **17** also gave highly impressive results, although again, the presence of chain branching in this case seemingly had the effect of lowering enantiomeric excess (entry 3). As may be expected, the carbinol products obtained via insertion of Li-carbenoid **26** (Table 2) were produced in the same enantiomeric series as those generated earlier from sulfoxide **8** via the insertion of Mg-carbenoid **9** (Table 1).

Table 2. Homologation of Boronic Esters with (*S*)-1-Chloro-2-phenylethyllithium (**26**)



entry	boronic ester #	boronic ester R^1	carbenoid generation[a]	isolated carbinol #	% yield	% ee[b]
1	**14**	$Ph(CH_2)_2$	pre-form	**20**	0	n/a
2	**14**	$Ph(CH_2)_2$	Barbier	**20**	70	96
3	**17**	*c*-hex	Barbier	**23**	86	87

[a] preform = carbenoid **26** formed by addition of *n*-BuLi (2 equiv, 1.5 M in hexanes) to sulfoxide **8** (2 equiv, dr > 99:1, % ee > 98%) in THF at −78 °C; the mixture was allowed to stir for 10 min before addition of boronate (1 equiv). Barbier = *n*-BuLi (2 equiv, 1.5 M in hexanes) added to a mixture of sulfoxide **8** (2 equiv, dr > 99:1, % ee > 98%) and boronate (1 equiv) in THF at −78 °C. [b] Determined by HPLC analysis.

In summary, asymmetric homologation of boronic esters by enantioenriched main-group chiral carbenoids has been demonstrated for the first time. Realization of this process with a Mg-carbenoid (**9**) was predicated on the work of Hoffmann and Matteson; however, the fact that greater success was ultimately achieved with a Li-carbenoid (**26**) was unexpected and is likely to prove highly significant for the further development of SRCH. Studies to extend and improve on the results reported herein are in progress, as are allied efforts directed at the realization of alternative M^1/M^2 manifolds for SRCH. Details of this work will be reported in due course.

Acknowledgment. The Engineering and Physical Sciences Research Council, U.K. (GR/R91922/01) are thanked for financial support of this work. Mr. James Titchmarsh and Ms. Jacqui Colley are gratefully acknowledged for performing HPLC analyses.

Supporting Information Available: Full experimental procedures, ^{1}H NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Satoh, T.; Takano, K. *Tetrahedron* **1996**, *52*, 2349.

(21) Hoffmann and co-workers have demonstrated that α-bromoalkyllithiums are configurationally stable for short periods of time at −110 °C. See: (a) Hoffmann, R. W.; Ruhland, T.; Bewersdorf, M. *J. Chem. Soc., Chem. Commun.* **1991**, 195. (b) Hoffmann, R. W.; Bewersdorf, M. *Chem. Ber.* **1991**, *124*, 1249. (c) Hoffmann, R. W.; Julius, M.; Chemla, F.; Ruhland, T.; Frenzen, G. *Tetrahedron* **1994**, *50*, 6049.

(22) For reviews concerning the configurational stability of organolithium species, see: (a) *Organolithiums: Selectivity for Synthesis*; Clayden, J., Ed.; Pergamon: New York, 2002. (b) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 716.

(23) Carbenoid **26** presumably decomposed via *β*-hydrogen insertion and dimerization pathways; see: *Carbene Chemistry*; Kirmse, W., Ed.; Academic Press: New York, 1971.

(24) The expected exchange product from this reaction, butyl *p*-tolyl sulfoxide, was also isolated (53% based on **8**), as were phenethyl chloride (10% based on **8**) and recovered chlorosulfoxide **8** (23%). The latter exhibited significant epimerization (dr (*syn*:*anti*) = 48:52), believed to be the result of deprotonation by BuLi followed by poorly diastereoselective reprotonation upon quench. Satoh and Takano reported that alkyllithium-mediated ligand exchange from sulfoxide substrates possessing acidic α-hydrogen atoms is complicated by competing deprotonation. See ref 20.