of activation suggests that N_2 loss from **4** to give **5** is not a concerted process and probably involves a rate-determining ligand rearrangement (perhaps ring expansion with formation of a Zr–O bond) before N_2 extrusion occurs. **5** is reactive toward a number of other small molecules, and elaboration of this reaction chemistry will be the topic of a future publication.

Acknowledgment. Financial support from the National Science Foundation (CHE-8818607) and an Alfred P. Sloan Foundation Research Fellowship (1989–1991) is sincerely appreciated by G.L.H. A summer fellowship under the N.S.F. Research Experiences for Undergraduates Program (NSF 8713014) is gratefully acknowledged by C.D.S. The NMR facilities were supported in part through the University of Chicago Cancer Center Grant (NIH-CA-14599).

Supplementary Material Available: Experimental, spectroscopic (^1H, ^{13}C NMR, and IR), analytical, and crystallographic details and tables of atomic coordinates, bond angles and distances, anisotropic thermal parameters, and hydrogen atom coordinates (11 pages); table of observed and calculated structure factors (16 pages). Ordering information is given on any current masthead page.

(17) Kinetic data were obtained on **4** prepared in situ from **2** and N_2O and reflect the rate of the disappearance of **4**, which was independent of $[N_2O]$. See Supplementary Material for experimental details.

Practical Enantioselective Diels–Alder and Aldol Reactions Using a New Chiral Controller System

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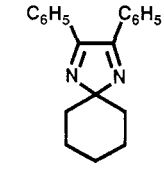
The Diels–Alder and aldol reactions are among the most useful of all synthetic processes for the construction of complex molecules, and, for this reason, they have been very extensively studied and refined. The development of enantioselective versions of these reactions, especially, has been the object of recent research in many laboratories.[1,2] Nonetheless, existing methodology is still not ideal, since there are drawbacks and limitations for all of the known procedures. Described herein is a new chiral controller system which has excellent practical potential because of the ready availability and recoverability of the chiral controllers and the high enantioselectivities which can be realized with predictable absolute configuration.

(±)-1,2-Diamino-1,2-diphenylethane (stilbenediamine, stien) has been prepared previously in six steps from ammonia and benzaldehyde[3] and efficiently resolved with tartaric acid to give both *R,R*-stein and *S,S*-stien,[3] the key ingredients of the controllers described herein. Although multigram amounts of stien can be prepared in this way, a much shorter synthesis has now been developed which provides this diamine economically and quickly on any scale. Reaction of benzil and cyclohexanone (1 equiv of each) with ammonium acetate–acetic acid at 120 °C for 1 h resulted in formation of cyclic bis-imine **1**[4] (97% yield), mp 105–106 °C, which was reduced stereospecifically with 4 equiv of lithium in 4:5 THF–liquid ammonia (0.3 M in **1**) at −78 °C for 2 h with addition of 2 equiv of ethanol in four portions to give the *trans*-imidazolidine **2** (95%). Treatment of a solution of **2** in methylene chloride successively with 2 N hydrochloric acid and aqueous base provided after removal of solvent (±)-stien (**3**), mp 81–82 °C, in 92% overall yield from **1**. After resolution[3] (tartaric acid) both the *R,R*- and *S,S*-forms of **3** (>99% optical purity) were converted to the crystalline bis-sulfonamides **4**, **5**, and **6**. Reaction of **4** in 1,2-dichloroethane at 80 °C with diisobutylaluminum hydride or trimethylaluminum (in toluene) afforded the corresponding cyclic amido aluminum alkyl, **7** or **8**. These reagents function effectively as chiral Lewis acids to catalyze a number of useful enantioselective Diels–Alder reactions.



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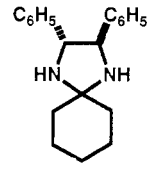

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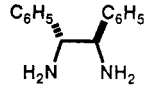

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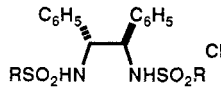
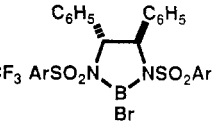


4 R=CF_3
5 R=*p*-CH_3-C_6H_4
6 R=*p*-NO_2-C_6H_4

7 R=*i*-Bu
8 R=CH_3



16 Ar=*p*-CH_3-C_6H_4
17 Ar=*p*-NO_2-C_6H_4

The first reported highly enantioselective Diels–Alder reaction with an acrylate ester involved the 8-phenylmenthol ester (ca. 95% ee with cyclopentadiene and $AlCl_3$ catalysis)[5] which was far superior to the menthyl ester (ca. 40% ee with cyclopentadiene and $SnCl_4$ catalysis).[6] Nonetheless, when (*R,R*)-**7** (0.5 equiv) was employed as catalyst in the reaction of the acrylate ester of (−)-menthol with cyclopentadiene, an 85% yield of the endo-Diels–Alder adduct **9** with de of 97% was obtained after a reaction time of 24 h at −78 °C.[7] The absolute stereochemistry and high stereoselectivity of this reaction can be easily understood in terms of the most favorable transition-state geometry represented by **10**. As expected on this basis, the corresponding reaction of (*S,S*)-**7**, cyclopentadiene, and the acrylate ester of (−)-menthol is less selective (de of 52%),[8] as is the analogous reaction with methyl acrylate (ca. 50% ee). 3-Acrylyl-1,3-oxazolidin-2-one (**11**)[1g] was found to be a much more satisfactory reactant than simple acrylate esters. Thus, reaction of **11** and cyclopentadiene

(1) For recent references on enantioselective Diels–Alder reactions, see: (a) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer Verlag: Berlin, 1986; Vol. 4, p 261; (b) *Nachr. Chem. Tech. Lab.* **1987**, *35*, 836. (c) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876. (d) Yamamoto, H.; Maruoka, K.; Furuta, K.; Ikeda, N.; Mori, A. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Sharpless, K. B., Eds.; VCH Publishers: Weinheim, 1987; p 13. (e) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310. (f) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (g) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986**, 1109. (h) Chapuis, C.; Jurczak, J. *Helv. Chim. Acta* **1987**, *70*, 436. (i) Furata, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6254.

(2) For references on enantioselective aldol methodology, see: (a) Evans, D. A. *Aldrich. Acta* **1982**, *15*, 23. (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (c) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39. (d) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (e) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (f) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 5807. (g) Brown, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031. (h) Ambler, P. W.; Davies, S. G. *Tetrahedron Lett.* **1985**, *26*, 2129. (i) Patterson, I. *Chem. Ind. (London)* **1988**, 390.

(3) Williams, O. F.; Bailar, J. C. *J. Am. Chem. Soc.* **1959**, *81*, 4464. See, also: Saigo, K.; Kubota, N.; Takebayashi, S.; Hasegawa, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 931.

(4) Weiss, M. *J. Am. Chem. Soc.* **1952**, *74*, 5193.

(5) (a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. (b) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley: New York, 1989; pp 255–264.

(6) Farmer, R. F.; Hamer, J. *J. Org. Chem.* **1966**, *31*, 2418.

(7) The absolute configuration and de of the major product were determined by $LiAlH_4$ reduction, esterification of the resulting primary alcohol with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (MTPA-Cl), and ^1H NMR analysis at 500 MHz using reference standards.

(8) In addition, the use of (*R,R*)-**8** as catalyst in place of (*R,R*)-**7** afforded **9** with somewhat lower de (85%).

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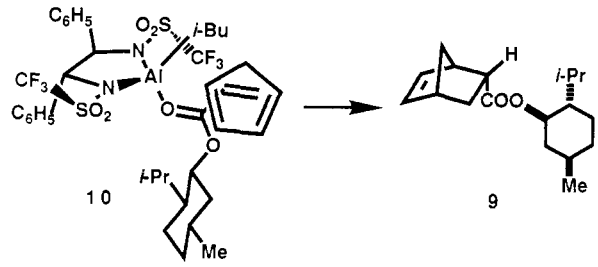
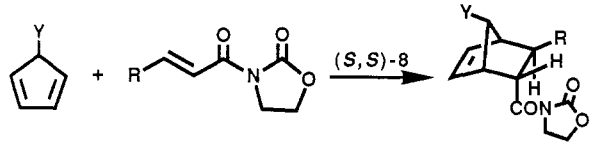


10 9

(each 0.5 M in CH_2Cl_2) in the presence of 10 mol % of (*S,S*)-**8** as catalyst at −78 °C for 10 min afforded **12** in 92% yield and

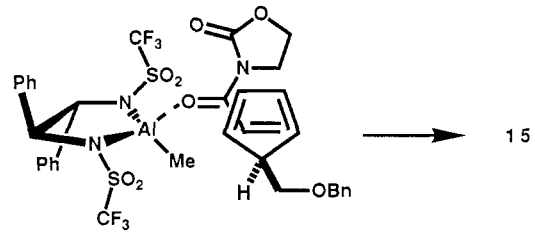


11 R=H **12** R=H, Y=H

13 R=CH_3 **14** R=CH_3, Y=H

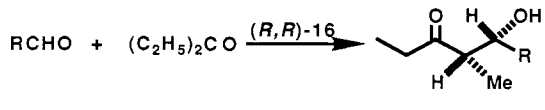
15 R=H, Y=CH_2OBn

91% ee (endo–exo ratio >50:1). At a reaction temperature of −90 °C, **12** was produced in 95% ee. The corresponding reaction of the *trans*-crotyl derivative **13** and cyclopentadiene with 20 mol % of (*S,S*)-**8** as catalyst at −78 °C for 16 h provided adduct **14** in 88% yield and 94% ee (endo–exo ratio 96:4). In each case the controller (*S,S*)-**4** was recovered in essentially quantitative yield after a simple workup. These results clearly indicate the practical value of this methodology. A further demonstration is provided by the reaction of **11** with 5-((benzyloxy)methyl)-1,3-cyclopentadiene in the presence of 0.1 equiv of (*S,S*)-**8** (−78 °C, 10 h) to form adduct **15** (94% yield) with 95% ee. This synthesis of **15**, which allows the production of optically pure prostaglandins



since a subsequent intermediate can be brought to 100% ee simply by recrystallization,[5a] is clearly of outstanding practical utility. The Harvard bicycloheptene route to prostaglandins in its current form is both enantio- and stereocontrolled through the use of new and extraordinary enzyme-like catalysts.[5b] We believe that the absolute stereopreference in the Diels–Alder reactions to form **12**, **14**, and **15** is the result of catalyst binding to acrylyl carbonyl of **11** or **13** at the lone pair anti to nitrogen, fixing the acrylyl group in the s-trans conformation, as shown below for the assembly leading to **15**.

The use of this new controller system in enantioselective aldol reactions also led to striking success. Reaction of **5** or **6** with boron tribromide (CH_2Cl_2 at 23 °C for 1 h for **5**, and $ClCH_2CH_2Cl$ at 55 °C for 3.5 h for **6**) provided the cyclic bromoborane **16** or **17**, respectively. Reaction of diethyl ketone with various aldehydes proceeded with high stereoselectivity as indicated in Table I to form syn aldol adducts **18**. In these experiments 1 equiv of



18

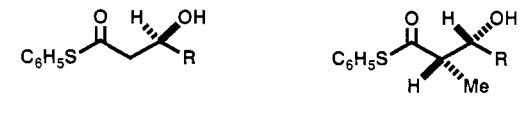
(*R,R*)-**16**, 1 equiv of the ketone, and 2 equiv of diisopropylethylamine were allowed to react in CH_2Cl_2 at −78 °C for 1 h to form a chiral boron enolate (verified by ^{11}B NMR), and then the aldehyde (0.9 to 1.0 equiv) was added and allowed to react at −78 °C for 2 h. The high efficiency of synthesis of the rice and corn weevil aggregation pheromone, sitophilure, **18** (R = C_2H_5),[9] is noteworthy. The bis-tosylamide **5** in all cases was easily recovered in high yield since hexane dissolves the aldol products but not **5** (mp 202–204 °C). We believe that this aldol methodology is superior to any other for the aldehyde–ketone reaction.

Table I. Reaction of Aldehydes with the Enolate from Diethyl Ketone and Bromoborane (*R,R*)-**16**

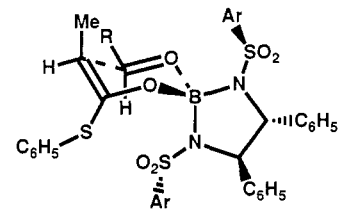
RCHO	% yield of **18**	syn:anti[a]	% ee[b]	$[\alpha]_D^{23}$[c] (deg)
C_6H_5CHO	95	94.3:5.7	97	−20.2
$(CH_3)_2CHCHO$	85	98:2	95	−31.9
C_2H_5	91	>98:2	>98	+28.8

[a] Determined by 300 MHz ^1H NMR analysis. [b] Determined by 500 MHz ^1H NMR analysis of the corresponding MTPA ester, see: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. [c] Rotations measured in benzene (*c* = 1), see: (a) Enders, D.; Lohray, B. B. *Angew. Chem.* **1988**, *100*, 594. (b) Mori, K.; Yoshimura, T.; Sugai, T. *Ann. Chem.* **1988**, 899.

Aldol reactions between aldehydes and an acetate ester were also demonstrated to proceed with good enantioselectivity, in contrast to almost any other known process. Thus, reaction of 1 equiv of (*R,R*)-bromoborane **16**, 1 equiv of phenyl thioacetate, and 1.5 equiv of triethylamine at −78 °C for 10 min and 23 °C for 1 h produced a boron enolate (from ^{11}B NMR analysis) which upon treatment with benzaldehyde or isobutyraldehyde at −90 °C for 2 h gave **19**, R = C_6H_5, in 84% yield and 91% ee or **19**, R = *i*-Pr, in 82% yield and 83% ee.[10] The phenylthio ester of propionic acid could be converted to a chiral boron enolate with (*R,R*)-bromoborane **17** (but not the less Lewis acidic **16**) in CH_2Cl_2 at −45 °C with use of 2 equiv of diisopropylethylamine. Further reaction of this species with benzaldehyde or isobutyraldehyde provided **20**, R = C_6H_5, in 70% yield and 95% ee (syn:anti : 98.3:1.7) or **20**, R = *i*-Pr, in 72% yield and 97% ee (syn:anti = 94.5:5.5), respectively.



19 **20**



21

The stereochemistry of the predominating aldol adducts, as for the Diels–Alder reactions, follows from the assumption that the phenyl groups of the stien ligand force the vicinal *N*-sulfonyl substituents to occupy the opposite face of the five-membered ring to which they are attached. The optimum stereoelectronic and steric arrangement of the favored transition state for formation of aldol product is then **21**, which leads to the observed major products **20**.[12]

(9) Schmuff, N. R.; Phillips, J. K.; Burkholder, W. E.; Fales, H. M.; Chen, C.-W.; Roller, P. P.; Ma, M. *Tetrahedron Lett.* **1984**, *25*, 1533.

(10) Absolute configurations were determined by conversion of **19** to the previously described[2b] β-hydroxy acids (4 equiv of H_2O_2 and 2 equiv of LiOH in 3:1 THF–H_2O at 0 °C for 4 h); ee values were determined by 500 MHz ^1H NMR measurements of the MTPA esters.

(11) For literature, see: (a) Hirama, M.; Garvey, D. S.; Lu, L. D. L.; Masamune, S. *Tetrahedron Lett.* **1979**, 3937. (b) Heathcock, C. H.; White, C. T.; Morrison. J. J.; Van Derveer, D. *J. Org. Chem.* **1981**, *46*, 1296. (c) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. References 11a and 11b refer to the free β-hydroxy acids which were obtained as indicated in ref 10.

(12) This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health.

Supplementary Material Available: Experimental and spectral data (mp, IR, ^{1}H NMR, and MS) for **3–6** and (*S,S*)-enantiomers of **7** and **8** and spectral data for **15** (R_f, IR, and ^{1}H NMR) and for **1** (mp, R_f, and ^{1}H NMR) (5 pages). Ordering information is given on any current masthead page.

A Practical and Efficient Method for Enantioselective Allylation of Aldehydes

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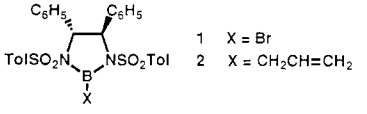
The enantioselective addition of allyl groups to the carbonyl function of aldehydes to form chiral secondary homoallylic alcohols is a highly useful synthetic operation for multistep synthesis since the resulting adducts serve as precursors of β-hydroxy and γ-hydroxy carboxylic acid derivatives.[1] Subsequent to early studies on the use of allylic boranes in this reaction by Hoffmann,[2] many groups have made important contributions to the steady improvement in this methodology.[1,3] Nonetheless, each of the published approaches suffers from major disadvantages, for example, because of destruction of expensive chiral reagents or the reliance on impractical reagents or intermediates. Described herein is a new method which is believed to be superior to earlier procedures, especially for work on larger scale. The process utilizes the readily available and easily recoverable (*R,R*)- or (*S,S*)-1,2-diamino-1,2-diphenylethane (stien) controller group, which is also the subject of the preceding communication.[4]

Reaction of the bis-*p*-toluenesulfonyl derivative of (*R,R*)-stien[4] in dry CH_2Cl_2 with 1 equiv of BBr_3, at 0 °C or below initially and then at 20 °C for 40 min, afforded, after removal of solvent and HBr under reduced pressure, the bromoborane **1** (CAUTION: moisture sensitive). Treatment of a solution of **1** in dry CH_2Cl_2 at 0 °C initially and at 23 °C for 2 h with allyltributyltin resulted in generation of the chiral allylborane **2**. Reaction of **2** in CH_2Cl_2



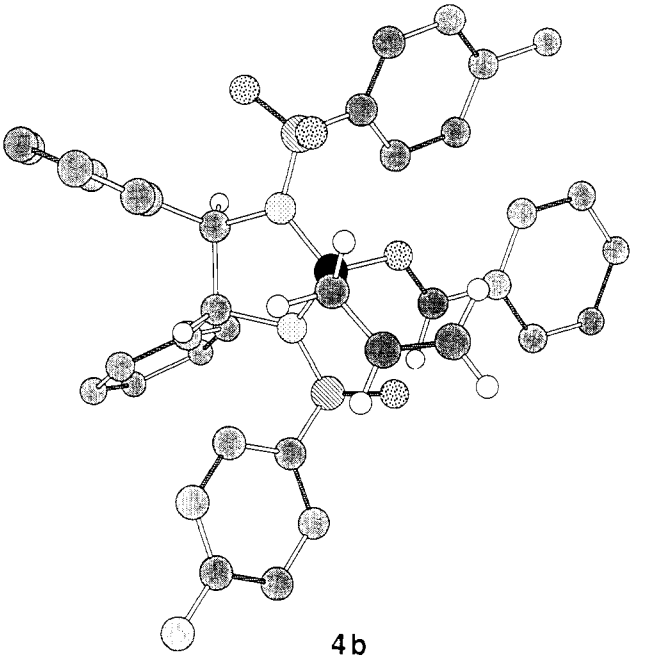
1 X = Br
2 X = $CH_2CH{=}CH_2$

or toluene solution at −78 °C with a variety of aldehydes (0.9 equiv) produced the corresponding homoallylic alcohols **3** in the optical purities indicated in Table I. The product **3** was isolated in >90% yield and ca. 97% purity by addition of aqueous pH 7 buffer, removal of CH_2Cl_2, addition of ether to precipitate the bis-*p*-toluenesulfonamide of (*R,R*)-stien, filtration, removal of tin halide (by washing the ethereal filtrate with 50% aqueous potassium fluoride), and removal of solvent. Final purification of **3** can be effected by silica gel chromatography or distillation, depending on scale. In each case enantiomeric excess (ee) values were determined by 500 MHz ^{1}H NMR analysis of the (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetate (MTPA) ester,[5] and absolute configuration was established by measurement of optical rotation and comparison with literature data.[6]

Table I. Reaction of Aldehydes with Chiral Allylborane **2**, (*R,R*)-Form, at −78 °C To Give Homoallylic Alcohols **3**

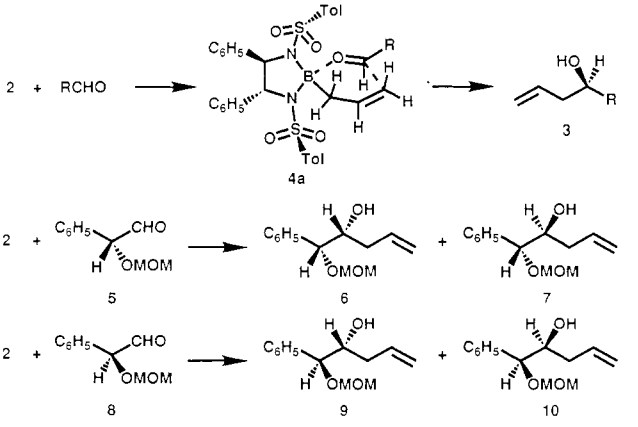
R of RCHO	solvent	% ee of **3**	abs config
C_6H_5	CH_2Cl_2	94	*R*
C_6H_5	toluene	95	*R*
(*E*)-$C_6H_5CH{=}CH$	CH_2Cl_2	98	*R*
(*E*)-$C_6H_5CH{=}CH$	toluene	97	*R*
c-C_6H_{11}	CH_2Cl_2	93	*R*
c-C_6H_{11}	toluene	97	*R*
n-C_5H_{11}	CH_2Cl_2	90	*S*
n-C_5H_{11}	toluene	95	*S*

The observed preference for absolute configuration **3** for the homoallylic alcohols from the (*R,R*)-allylborane reagent **2** was predicted on the basis of a chair-like transition state with optimum stereoelectronics and minimum steric repulsion between appendages on the five-membered ring, the optimum arrangement being as depicted in line drawing **4a** and three-dimensional representation **4b**.



4b

High and predictable diastereoselectivity was also observed in the allylation of chiral aldehydes by reagent **2**. Thus aldehyde **5** was converted by reaction at −78 °C for 2 h with (*R,R*)-**2** in 80% yield principally to **6** (ratios **6**:**7** of 25.3:1 in CH_2Cl_2 and 20.2:1 in toluene), whereas its enantiomer, **8**, was transformed mainly into **9** (ratios **9**:**10** of 39:1 in CH_2Cl_2 and 51.6:1 in toluene).[7]



(1) For recent elegant applications, see: (a) Roush, W. R.; Palkowitz, A. D. *J. Am. Chem. Soc.* **1987**, *109*, 953. (b) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316. (c) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294.

(2) Hoffmann, R. W.; Schrott, U.; Herold, T. *Chem. Ber.* **1981**, *114*, 359. Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555.

(3) (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (c) Garcia, J.; Kim, B. M.; Masamune, S. *J. Org. Chem.* **1987**, *52*, 4831. (d) Reetz, M. T.; Zierke, T. *Chem. Ind. (London)* **1988**, 663. (e) Reetz, M. T. *Pure Appl. Chem.* **1988**, *60*, 1607. (f) Roder, H.; Helmchen, G.; Peters, E.-M.; Peters, K.; Schnering, H.-G. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 898. (g) Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.

(4) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, preceding communication in this issue.

(5) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(6) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Minowa, N.; Mukaiyama, T. *Bull. Soc. Chem. Jpn.* **1987**, *60*, 3697. (c) Tamao, K.; Kanatani, R.; Kumada, M. *Tetrahedron Lett.* **1984**, *25*, 1913.

0002-7863/89/1511-5495$01.50/0