ORGANIC LETTERS

2001
Vol. 3, No. 21
3253−3256

A Convenient and Asymmetric Protocol for the Synthesis of Natural Products Containing Chiral Alkyl Chains via Zr-Catalyzed Asymmetric Carboalumination of Alkenes. Synthesis of Phytol and Vitamins E and K†

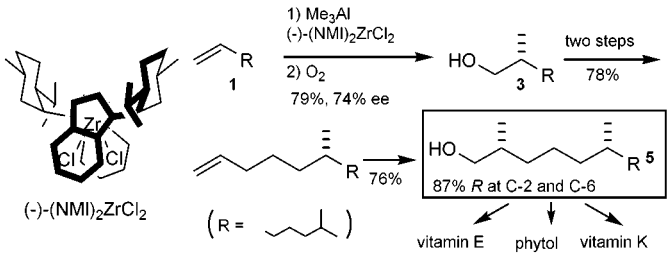
Shouquan Huo and Ei-ichi Negishi*

Herbert C. Brown Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907-1393

negishi@purdue.edu

Received June 26, 2001 *(Revised Manuscript Received September 10, 2001)*

ABSTRACT



A convenient and asymmetric protocol for the synthesis of chiral oligoisoprenoids is described. Typically, a C_{14} vitamin E side chain 5 was synthesized in 47% yield over four steps. Isomeric purity of 5 was upgraded to >99% *R* at C-2 and 97% *R* at C-6 by the statistical formation of stereoisomeric *p*-phenylenebisurethanes and their diastereomeric separation. In addition, phytol and vitamin K were synthesized in 21% and 28% overall yields, respectively, over five steps from 1.

We describe herein a novel, highly efficient, and enantioselective protocol for the synthesis of natural products containing chiral alkyl chains via the Zr-catalyzed asymmetric carboalumination of alkenes[1−3] and the Cu-catalyzed homoallylation or homopropargylation[4] of β-branched chiral alkyl iodides or sulfonates.

Of various natural products of terpenoid origin, those containing saturated and flexible chiral chains, such as vitamins E and K,[5] have presented one of the ultimate synthetic challenges from the methodological viewpoint. Highly desirable is a synthetic protocol permitting high efficiency including high product yields and high selectivity, especially high enantioselectivity,[6] while simultaneously satisfying various other requirements. One of the current benchmark syntheses is that of a C_{15} side chain of vitamins E and K reported by Noyori,[5h] which appears to satisfy the

† This paper is dedicated to Professor Herbert C. Brown, a pioneer in organometallic enantioselective synthesis, on the occasion of his 90th birthday.

(1) (a) Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc*. **1995**, *117*, 10771. (b) Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc*. **1996**, *118*, 1577.

(2) A recent report that addition of H_2O accelerates the Zr-catalyzed methylalumination is notheworthy: Wipf, P.; Ribe, S. *Org. Lett*. **2000**, *2*, 1713. See also: Wipf, P.; Ribe, S. *Org. Lett*. **2001**, *3*, 1503.

(3) For Zr-catalyzed asymmetric carbomagnesation of allylically heterosubstituted alkenes, which evidently proceeds via cyclic carbozirconation and is therefore discrete from the reaction discussed herein, see: (a) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1993**, *115*, 6697. (b) Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1262.

(4) (a) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303. (b) Fouquet, G.; Schlosser, M. *Angew. Chem., Int. Ed. Engl*. **1974**, *13*, 82. (c) Schlosser, M. *Angew. Chem., Int. Ed. Engl*. **1974**, *13*, 701.

10.1021/ol010142d CCC: $20.00
Published on Web 09/27/2001

above-mentioned requirements reasonably well. Even so, asymmetric construction of the chiral centers in the reported cases requires stereodefined allylically heterosubstituted alkenes that must be synthesized and purified for subsequent asymmetric operations.

We recently reported a novel Zr-catalyzed enantioselective carbon−carbon bond formation of simple, unactivated, terminal alkenes,[1] which represents an as yet rare example of high enantioselection of one-point binding. While the ee figures observed with alanes containing Et and higher alkyls are typically ≥90%, those observed with the singularly important methylalanes are about 75%.[7] Along with our efforts to improve the ee figures for methylalumination,[8] we were attracted by the statistical principle of enantiomeric amplification (Horeau principle)[9] through iteration of two or more asymmetric operations or combination of two or more chiral compounds. Thus, in the absence of internal chiral recognition, the overall % ee after multiple asymmetric operations (and/or synthetic combinations) may be readily predicted from the coefficients of the general mathematical expression $(a^1R + b^1S)(a^2R + b^2S)...$, where a^n and b^n are molar fractions of the *n*th *R* and *S* molecules or molecular moieties. This also indicates the maximum possible chemical yield for each stereoisomer. It is noteworthy that two and three successive and independent (lacking internal chiral recognition) enantioselective operations of 85% and 70% ee's, respectively, are sufficient to provide chiral compounds of ca. 99% ee, while permitting maximum possible chemical yields of 86.1% and 61.8%, respectively[10] (Table 1).

Table 1. Statistical Enantiomeric Amplification in Iterative Enantioselective Processes

% ee of each cycle	dimeric products		trimeric products	
	max yield (%)	% ee	max yield (%)	% ee
70	74.5	94.0	**61.8**	**98.9**
75	78.1	96.0	67.2	99.4
80	82.0	97.6	73.0	99.7
85	**86.1**	**98.8**	79.2	99.9

With this statistical principle in mind, efficient syntheses of phytol and vitamins E and K without protection−deprotection or redox manipulation shown in Scheme 1 were devised. We believe that these are the most direct and shortest syntheses of vitamin E and K side chains and phytol reported to date. The reaction of **1** with Me_3Al (1 molar equiv) and 2 mol % of (−)-$(NMI)_2ZrCl_2$[11] in CH_2Cl_2 at 23 °C[1] followed by treatment with I_2 (4 molar equiv) in Et_2O produced iodide **2** in 72% yield. Oxidation of the carboalumination product with O_2 similarly gave the corresponding alcohol **3** in 79% yield. Analysis of the ^{1}H NMR spectra of its Mosher esters obtained by using both (*R*)- and (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chlorides (MTPA) and pyridine indicated **3** to be 74% ee. Either **2** or **3** was readily converted to **4** via Cu-catalyzed coupling with 3-butenylmagnesium bromide in 93% or 78% yield, respectively, as shown in Scheme 1. Conversion of **4** into **5** was carried out in 76% yield as in the conversion of **1** into **3**.

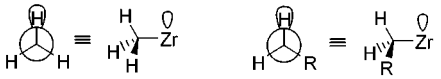
Analysis of the ^{1}H NMR spectra of the Mosher esters of **5** indicated that the second Zr-catalyzed carboalumination step to be 74% ee. It may therefore be concluded that the second carboalumination step is essentially unaffected by the first asymmetric carbon center. Although the NMR analysis mentioned above failed to directly establish the overall ee of **5**, the statistical analysis discussed above indicated that the overall ee should be 95.6%.[12] The calculated diastereomeric ratio, i.e., $(R,R + S,S)/(R,S + S,R)$, of 3.42 agreed well with the experimental value of 3.3 obtained from the relative intensities of ^{13}C NMR signals for the C atoms of the CH_3 groups bonded to the C-2 and C-6 atoms.

Noting in the literature[13] that all four diastereomers of vitamin E can be separately seen by ^{13}C NMR spectroscopy,

(5) (a) Scott. J. W.; Bizzarro, F. T.; Parrish, D. R.; Saucy, G. *Helv. Chim. Acta* **1976**, *59*, 290. (b) Chan, K. K.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497. (c) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505. (d) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1979**, 995. (e) Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* **1981**, *103*, 1864. (f) Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004. (g) Takabe, K.; Uchiyama, Y.; Okisaka, K.; Yamada, T.; Katagiri, T.; Okazaki, T.; Oketa, Y.; Kumobayashi, H.; Akutagawa, S. *Tetrahedron Lett.* **1985**, *26*, 5153. (h) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596. (i) Inoue, S.; Ikeda, H.; Sato, S.; Horie, K.; Ota, T.; Miyamoto, O.; Sato, K. *J. Org. Chem.* **1987**, *52*, 5495. (j) Takano, S.; Yoshimitsu, T.; Ogasawara, K. *Synlett* **1994**, 119.

(6) The term enantioselectivity is used here to indicate the extent of preferential formation of one enantiomeric molecule or molecular moiety from a prochiral molecule or molecular moiety.

(7) Although the origin of this significant difference is not clear, the possibility that Et and higher alkyls might exert a secondary chiral induction stemming from α-agostic interaction, which is uniquely absent in the case of Me, is an attractive notion to be pursued. For a recent discussion of the effect of α-agostic interaction in alkene polymerization, see: Grubbs, R. H.; Coates, G. W. *Acc. Chem. Res.* **1996**, *29*, 85.



(8) The ee figures for methylalumination observed by Negishi[1] and Wipf[2] are as follows. Negishi-Kondakov protocol: $RCH_2CH{=}CH_2$, 70−81% ee; $ArCH{=}CH_2$, 85% ee; *c*-$C_6H_{11}CH{=}CH_2$, 65% ee. Wipf−Ribe modification: $RCH_2CH{=}CH_2$, 75−86% ee; $ArCH{=}CH_2$, 89−90% ee; *c*-$C_6H_{11}CH{=}CH_2$, 55−74% ee. Judging from these data, addition of H_2O or MAO does appear to improve the ee for methylalumination by several %. For the preparation of highly pure stereoisomers, however, either subsequent purification or further substantial improvement in ee would be needed.

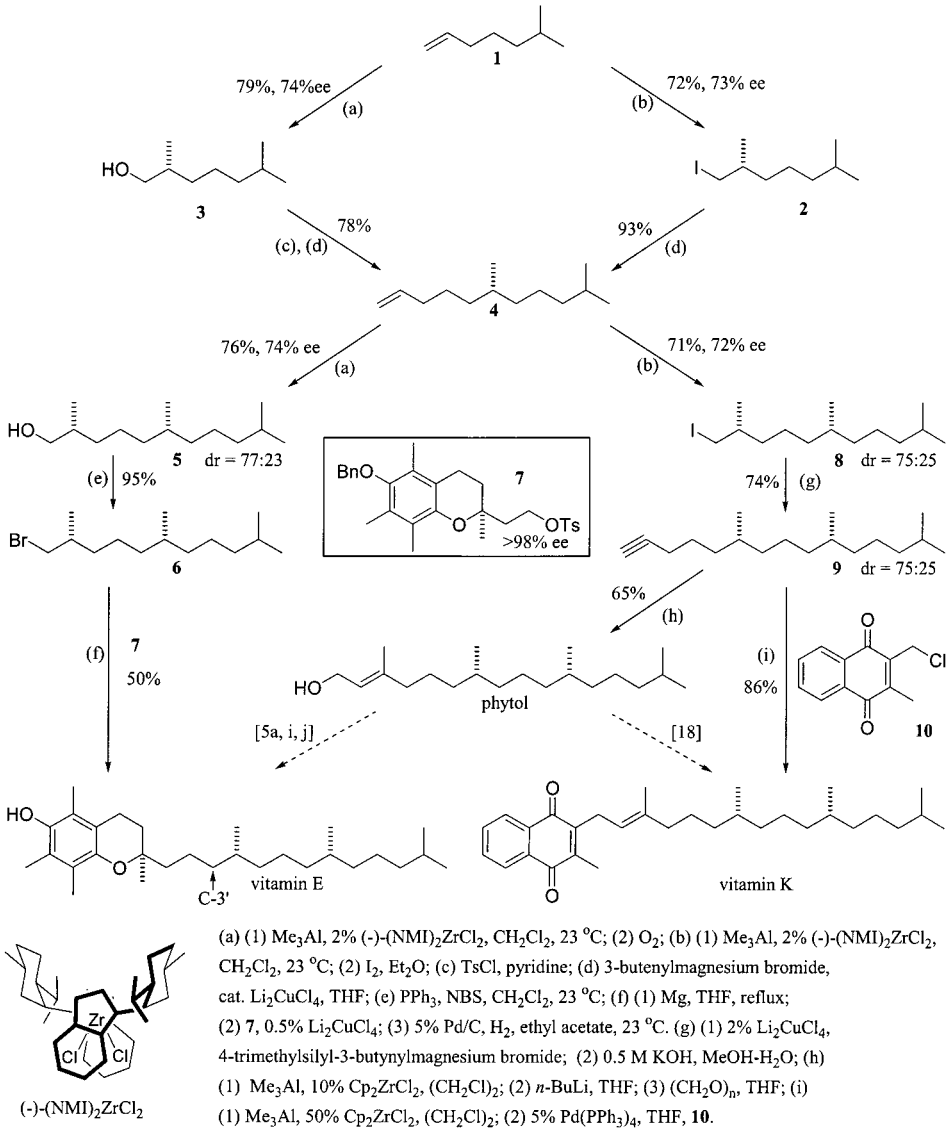
(9) For recent reviews and general discussions with pertinent references, see: (a) Rautenstrauch, V. *Bull. Soc. Chim. Fr.* **1994**, *131*, 515. (b) El Baba, S.; Sartor, K.; Poulin, J. C.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1994**, *131*, 525. For applications of the statistical asymmetric amplification−purification, see: (c) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055. (d) Toda, F.; Tanaka, K. *Chem. Latt.* **1986**, 1905. (e) Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Chem. Commun.* **1994**, 99. The references list below are several earlier and representative examples among many that explicitly discuss the statistical asymmetric amplification in synthesis: (f) Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 578. (g) Midland, M. M.; Gabriel, J. *J. Org. Chem.* **1985**, *50*, 1144. (h) Hoye, T. R.; Suhadolnik, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5312. (i) Mori, K.; Senda, S. *Tetrahedron* **1985**, *41*, 541.

(10) See Table 1 compiled by using the mathematical expression: $(a^1R + b^1S)(a^2R + b^2S)\ (a^3R + b^3S)$.

(11) This compound was originally synthesized by G. Erker and coworkers: Erker, G.; Aulbach, M.; Knickmeier, M.; Wingbermühle, D.; Krüger, C.; Nolte, M.; Werner, S. *J. Am. Chem. Soc.* **1993**, *115*, 4590.

(12) Compound **3** of 74% ee = $0.87R + 0.13S$ and compound **5** of 74% ee at C-2 = $0.87R + 0.13S$ gives the following statistical expression $(0.87R + 0.13S)^2 = 0.7569R,R + 0.0169S,S + 0.1131R,S + 0.1131S,R$. The statistically predicted overall % ee of **5** = ((0.7569−0.0169)/(0.7569 + 0.0169)) × 100 = 95.6%. The diastereomeric ratio of **5** = (0.7569 + 0.0169)/(2 × 0.1131) = 3.42.

Scheme 1



(a) (1) Me_3Al, 2% (-)-$(NMI)_2ZrCl_2$, CH_2Cl_2, 23 °C; (2) O_2; (b) (1) Me_3Al, 2% (-)-$(NMI)_2ZrCl_2$, CH_2Cl_2, 23 °C; (2) I_2, Et_2O; (c) TsCl, pyridine; (d) 3-butenylmagnesium bromide, cat. Li_2CuCl_4, THF; (e) PPh_3, NBS, CH_2Cl_2, 23 °C; (f) (1) Mg, THF, reflux; (2) **7**, 0.5% Li_2CuCl_4; (3) 5% Pd/C, H_2, ethyl acetate, 23 °C. (g) (1) 2% Li_2CuCl_4, 4-trimethylsilyl-3-butynylmagnesium bromide; (2) 0.5 M KOH, MeOH-H_2O; (h) (1) Me_3Al, 10% Cp_2ZrCl_2, $(CH_2Cl)_2$; (2) *n*-BuLi, THF; (3) $(CH_2O)_n$, THF; (i) (1) Me_3Al, 50% Cp_2ZrCl_2, $(CH_2Cl)_2$; (2) 5% $Pd(PPh_3)_4$, THF, **10**.

we decided to use the optically pure *R* isomer (≥99% *R*) of a chroman derivative **7**[5a] in Scheme 1 obtained via resolution as a reagent for determining the overall ee of **5**. To this end, **5** was converted into **6** in 95% yield and then into vitamin E in 50% yield by the reported procedure,[5b] as shown in Scheme 1. Assuming that the final cross-coupling step is essentially statistical, the *R*,*R*,*R*:*R*,*S*,*S*:(*R*,*R*,*S* + *R*,*S*,*R*) ratio for vitamin E may be calculated to be 75.7:1.7:(11.3 + 11.3). ^{13}C NMR analysis of the C-3′ signals indicated the experimental ratio to be 75.2:1.2:(10.3 + 13.3), which is in excellent agreement with the calculated ratio, strongly suggesting that the cross-coupling step producing vitamin E must indeed be essentially statistical. Furthermore, the above-indicated *R*,*R*,*R* to *R*,*S*,*S* ratio of vitamin E observed experimentally permits determination of the overall ee of **5** to be 96.7%,[14] which once again is in excellent agreement with the statistically predicted value of 95.6% (vide supra). Although the % ee of the final product, i.e., vitamin E, was not experimentally determined in this experiment,[15] it now seems very safe to predict that the statistical cross-coupling (vide supra) of **6** (96.7% ee) with **7** (≥98% ee) must have produced vitamin E of >99.9% ee. It should also be noted that the observation of the highest field signal of the four signals for the C-3′ atom as the major one, to which the *R*,*R*,*R* (and *S*,*S*,*S*) isomers were previously assigned,[13] further confirms the assignment of the *R* and *R*,*R* configurations to **2**−**4** and **5** (or **6**), respectively.

Having established the feasibility of efficiently synthesizing flexible chiral compounds such as **5** and **6** in high ee, we then turned our attention to no less challenging issue of

(13) Bremser, W.; Vogel, F. G. M. *Org. Magn. Reson.* **1980**, *14*, 155.

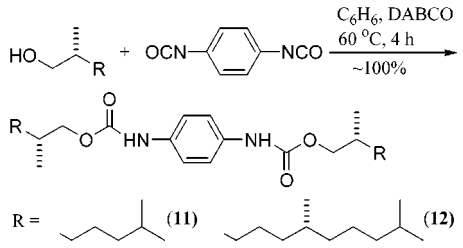
(14) The experimental overall % ee of **5** = ((75.21 − 1.25)/(75.21 + 1.25)) × 100 = 96.7%.

(15) It has been reported that a combination of capillary GLC and HPLC using a chiral column distinguishes all eight stereoisomers of vitamin E: Vecchi, M.; Walther, W.; Glinz, E.; Netscher, T.; Schmid, R.; Lalonde, M.; Vetter, W. *Helv. Chim. Acta* **1990**, *73*, 782.

stereoisomeric separation for isolation of the desired single stereoisomer. In addition to the classical resolution technique requiring pure *chiral* reagents, we were also attracted by the feasibility of using bi- and multifunctional *achiral* reagents for statistical enantiomeric or asymmetric amplification.[9c−e] This has been reported only in a few papers since Horeau's original publication in 1973.[9c] Furthermore, the substrates have been restricted to relatively rigid secondary and tertiary alcohols in which the chiral center is at the HO-bearing C atom.

Treatment of **3** (74% ee) with *p*-phenylene diisocyanate (PPDI) in a 2:1 molar ratio in benzene in the presence of 2% DABCO at 60 °C over 4 h produced the corresponding bisurethane (**11**) in quantitative yield as a crystalline compound, which could be readily recrystallized from MeOH (Scheme 2). After four cycles of recrystallization requiring

Scheme 2



<1 day, the crystals recovered in 43% were treated with NaOEt in EtOH under reflux for 0.5 h to give a 95% yield of **3**, which was 93% ee by Mosher ester analysis. Prompted by these initial results, we then subjected **5**, which was 87% *R* and 13% *S*, i.e., 74% ee, at both C-2 and C-6, to the treatment with PPDI and recrystallization from MeOH. To our delight, the bisurethane readily crystallized, and its recrystallization from MeOH required only 0.5−1 h for each cycle. We also learned that the progress of asymmetric enrichment could be readily checked by monitoring the ratios of diastereomeric bisurethane by ^{13}C NMR spectroscopy. After nine cycles of recrystallization, reductive cleavage of the urethane with $LiAlH_4$ in THF at 50 °C for 1 h in 98% yield provided **5** ($[\alpha]^{23}_D$ +9.21; lit. max value +9.36[5a]), which was recovered in 33% overall yield, as compared with the statistically estimated maximum recovery of 57.3%.[16] On the basis of a reasonable assumption that the formation of the bisurethane **12** is statistical, the desired *R,R,R,R* isomer is predicted to be 99.9% ee.[17] The Mosher ester analysis indicated that the stereoisomeric purity at C-2 to be well over 99%. Furthermore, the stereoisomeric purity at C-6 was also determined to be 97% (or 94% ee at C-6) by ^{13}C NMR analysis of the C-12 and C-13 signals. Thus, the C_{14} chain moiety of vitamins E and K as well as of phytol, i.e., **5**, has been synthesized in 97% overall isomeric purity, providing the first example of separation−purification of primary alcohols resorting to statistical asymmetric amplification.

For the synthesis of (*R,R*)-phytol, which is a widely used key intermediate for the synthesis of both vitamin E[5a,i,j] and vitamin K,[18] the methylalumination product obtained from **4** was converted to iodide **8**. After its Cu-catalyzed cross-coupling with $Me_3SiC{\equiv}C(CH_2)_2MgBr$ and desilylation with methanolic KOH to give **9**, its methylalumination with $Me_3Al-Cp_2ZrCl_2$ followed by evaporation of the volatiles, ate complexation with *n*-BuLi, and treatment with $(CH_2O)_n$ in THF[19] afforded ≥99% (*E*)-phytol in 65% yield, the yield based on **1** over five steps being 21%. In fact, vitamin K was preparable more directly by alkenylation with alkenylalanes[20] of a naphthoquinone derivative **10**[21] in 86% yield (28% over five steps).

In summary, the preliminary results reported above have established the feasibility of developing an efficient protocol with minimal or no protection−deprotection and redox manipulations for the synthesis of phytol and vitamins E and K, which promises to be applicable to many other related syntheses. It has been demonstrated that the statistical asymmetric amplification principle permits the synthesis of flexible primary alcohols of high stereoisomeric purity containing two or more asymmetric carbon atoms even if each stereogeneric process is of modest stereoselectivity. Not only synthetic iteration or combination but also stereoisomeric purification based on statistical asymmetric amplification can be exploited in their syntheses. At the same time, however, the results point to the desirability of further improving the enantioselectivity in each stereogeneric synthetic step for higher practical synthetic values. Our efforts along this line are in progress.

Acknowledgment. We thank the National Science Foundation (CHE-0080795), the National Institutes of Health (GM 36792), and Purdue University for supports of this research. We also thank Albemarle, Boulder Chemical, and Johnson-Matthey for assistances in the procurement of Al, Zr, and Pd compounds, respectively. Information on the analysis of vitamin E provided by Drs. D. Burdick, T. Netscher, A. Rüttimann, and R. Schmid of Hoffmann-La Roche (Basel) is thankfully acknowledged. We also acknowledge Professors H. Kagan, R. Noyori, and D. Seebach for useful suggestions and information.

Supporting Information Available: Experimental procedures, spectroscopic data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010142D

(16) The maximum yield can be predicted from the following expression: $(0.87R + 0.13S)^4$, i.e, $(0.87^4 + 0.13^4) \times 100 = 57.3$.

(17) The statistically predicted overall % ee = $((0.87^4 - 0.13^4)/(0.87^4 + 0.13^4)) \times 100 = 99.9\%$.

(18) (a) Tso, H.; Chen, Y. *J. Chem. Res. Synop.* **1995**, 104. (b) Schmid, R.; Antoulas, S.; Rüttimann, A.; Schmid, M.; Vecchi, M.; Weiser, H. *Helv. Chim. Acta* **1990**, *73*, 1276. (c) Rüttimann, A. *Chimia* **1986**, *40*, 290 and references therein.

(19) Okukado, N.; Negishi, E. *Tetrahedron Lett.* **1978**, *19*, 2357.

(20) (a) Matsushita, H.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 2882. (b) Negishi, E.; Matsushita, H.; Okukado, N. *Tetrahedron Lett.* **1981**, *22*, 2715.

(21) Lipshutz, B. H.; Kim, S.; Mollard, P.; Stevens, K. L. *Tetrahedron* **1998**, *54*, 1241.