Enantiomeric Enrichment of Allenedicarboxylates by a Chiral Organoeuropium Reagent

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Received October 3, 1996[⊗]

Complexation of dimethyl penta-2,3-dienedioates to tris[(*R*)-(1*R**)-3-(2,2,3,3,4,4,4-heptafluoro-1-oxobutyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-onato-*O*,*O*′]europium, (+)-Eu(hfc)$_3$, enriched the (*S*)-isomer with high enantioselectivity. When a more bulky ester was used, although the enantioselectivity increased to >95% ee, considerable decomposition occurred. Among the available lanthanide shift reagents, only the europium reagent is effective in this transformation. The reaction involves interconversion of diastereomeric complexes, with enrichment of the preferred one. However, the observed decrease in the ^{1}H NMR peaks might suggest that subsequent reconstruction or reordering the higher-order complex may occur in the reaction solution.

Introduction

In the field of asymmetric induction, although great strides have been made in many types of enantioface and enantiotopic group selective reactions, progress in enantiomeric enrichment reactions (deracemization reactions[1]) has been sporadic. About a quarter of a century ago, Kagan's group studied the photochemical deracemization of methyl phenyl sulfoxide in the presence of a chiral sensitizer to recover the starting material at around 4% ee.[2] Weiss and co-workers reported the enantiomeric enrichment of penta-2,3-diene using a the sterol derivative as a sensitizer.[3] Recently, Inoue *et al.* demonstrated the application of a menthyl ester sensitizer to cyclonona-1,2-diene.[4] However, the optical induction in these photochemical reactions remained quite low. Nozaki and Noyori succeeded in the enantiomeric enrichment of (1-phenylethyl)lithium−(−)-spartein complex to yield (*R*)-phenylpropionic acid (up to 30% ee) after carboxylation.[5] In the late 1980's, two successful approaches were demonstrated. Pirkle *et al.* reported the first successful enantiomeric epimerization of amino acid derivatives with high enantiomeric excess.[6] The Merck group successfully transformed racemic benzodiazepinones, interemediates for the CCK antagonist, to their antipodes by crystallization with 10-camphorsulfonic acid.[7] However, the enantiomeric enrichment of axial-, atrop-, and other asymmetries remains a major unexplored challenge.[8]

In the course of our study of the development of novel reactivities of allenes,[9] we had examined deracemization to obtain chiral allenes. We report here the successful realization of this venture.[10]

Results and Discussion

We initially focused on three approaches. First, we tested a Lewis acid method (eq 1). Lewis acids coordinate to coordinating groups of allene substituents, such as carbonyl and nitrile, to weaken the double bond by delocalization to the Lewis acid. Racemization takes place thermally. The chiral environment of the ligands might enrich one enantiomer. We also examined a π-complex method (eq 2). An organometallic reagent might coordinate to the double bond, which racemizes during $\pi-\sigma$ coordination exchange. Silver(I) and copper(I) reagents are reportedly capable of strongly racemizing chiral allenes.[11] We expected that the use of organometallics which possess chiral ligands with appropriate structural features could lead to the enrichment of one enantiomer during racemization. Finally, we considered a betaine method with a nucleophilic reagent (eq 3). The nucleophile might attack the allene to give the betaine intermediate, which liberates the nucleophile to generate chirality by enantioselective rotation.[12] However, the latter two approaches were not very successful. Treatment of cyclonona-1,2-diene with *N*-tosyl-L-leucine cop-

[⊗] Abstract published in *Advance ACS Abstracts,* May 15, 1997.

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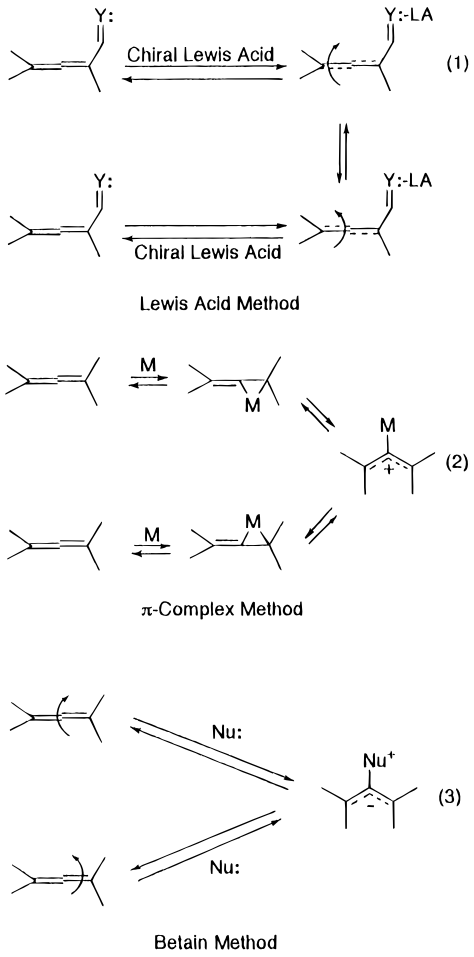
S0022-3263(96)01870-1 CCC: $14.00



per(II) salt gave only 9% ee.[13] We also tested a variety of chiral bidentate ligands. However, the enantioselectivities remained quite low regardless of the conditions. A diastereomeric excess of only 28% was obtained by epimerization[14] of di-(*l*)-menthyl penta-2,3-dienedioate[15] by treatment with triphenyl phosphite, which led to considerable decomposition. Therefore, we concentrated our investigation on the first method. After screening a series of chiral organometallics, we noted that tris[(*R*)-(1*R**)-3-(2,2,3,3,4,4,4-heptafluoro-1-oxobutyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-onato-*O*,*O*′]europium, (+)-Eu(hfc)$_3$, known as a NMR shift reagent, is very effective for this transformation.[16]

Racemic dimethyl pentadiene-2,3-dioate (**1a**)[17] was treated with (+)-Eu(hfc)$_3$ in chloroform-*d*. Two sets of diastereomeric peaks of the same intensity were observed. The methoxyl peaks appeared at 6.2 ppm with a difference ($\Delta\delta$) of 0.06 ppm when 1.0 mol equiv of (+)-Eu(hfc)$_3$ was used. The diastereomeric peak at the higher field came to be the major peak. After 9 days, the enantiomeric ratio was maximized to 89:11 (78% ee) with only slight decomposition.

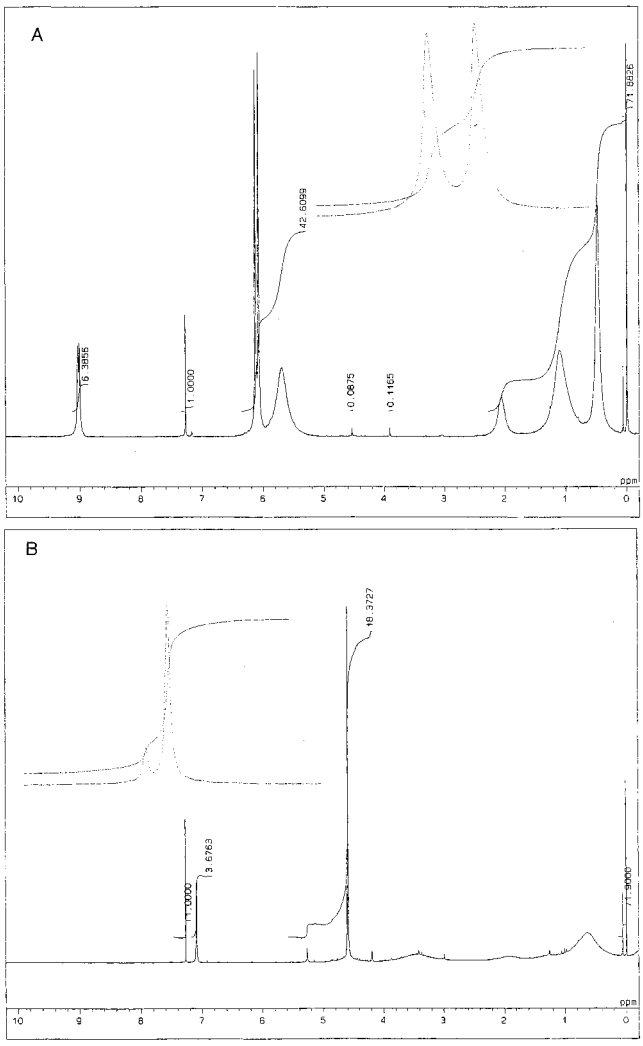
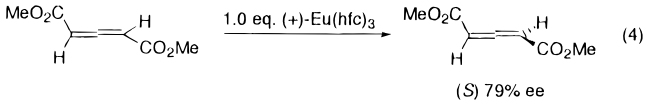


Figure 1. ^{1}H NMR spectra at 20 °C in $CDCl_3$. A: Just after racemic dimethyl 2,3-pentadienediate (**1a**) and (+)-Eu(hfc)$_3$ were mixed. B: After stored in the dark for 9 days.



To determine the enantiomeric excess more precisely, we attempted to resolve 2,3-pentadienedioates by HPLC with a chiral column Daisel Chiralsel-OD or Regis Whelk-O-1, but the compounds failed to separate. We also attempted to isolate the recovered allenes. However, the europium reagent was very difficult to remove. Washing with a 2.5% EGTA slurry was not sufficient.[18] Purification by two courses of column chromatography on silica gel was required to obtain the pure product. However, a severe deterioration in enantiomeric excess occurred. The observed enantiomeric ratio was 20% ee by ^{1}H NMR analyses with (+)-Eu(hfc)$_3$, which had an optical rotation of $[\alpha]^{20}_D = 29.4$ (*c*, 0.408, methanol). This was in good agreement with the value calculated using the equation proposed by Runge.[19] The optical rotation of enantiopure

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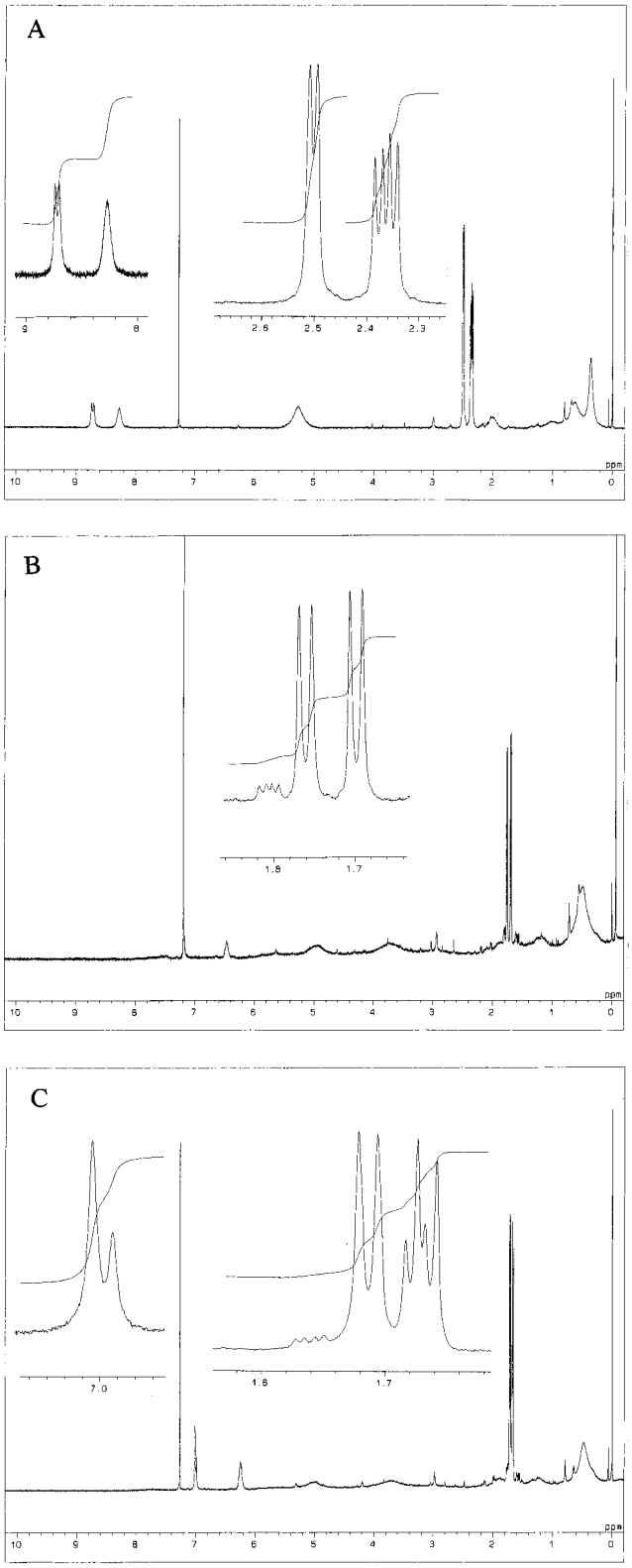


Figure 2. ^{1}H NMR spectra at 20 °C in $CDCl_3$. A: Just after racemic diisopropyl 2,3-pentadienedioate (**1c**) and (+)-Eu(hfc)$_3$ were mixed. B: After stored in the dark for 9 days. C: After additional racemic **1c** added to the sample B. See Experimental Section for the details.

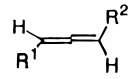
dimethyl (*S*)-penta-2,3-dienedioate ((*S*)-**1a**) was calculated to be $[\alpha]_D = 173$ in methanol. Therefore, the absolute configuration of the recovered dimethyl diester was considered to be (*S*).

The reaction rate was greatly affected by temperature. At 40 °C, severe decomposition occurred within 2 days, while the reaction proceeded very slowly at 10 °C. Therefore, further experiments were performed at 20 °C.

Table 1. Enantiomeric Enrichment of Allenecarboxylates

allene	Lewis acid	equiv	solvent	ee/%
1a	(+)-Eu(hfc)$_3$	0.3	$CDCl_3$	19
		0.5		41
		0.8		64
		1.0		79
		1.2		82
		1.5		63[a]
		1.0	C_6D_6	65
			C_6D_{12}	b
	(+)-Pr(hfc)$_3$		$CDCl_3$	b
	(+)-Er(hfc)$_3$			b
	(+)-Yb(hfc)$_3$			b
1b	(+)-Eu(hfc)$_3$			94[c]
1c				>95[c]
2				0
3				0

[a] The diastereomeric peaks were not in good separation. [b] See text. [c] See Experimental Section.



1a $R^1 = R^2 = CO_2Me$
1b $R^1 = R^2 = CO_2Et$
1c $R^1 = R^2 = CO_2iPr$
2 $R^1 = CO_2Me$, $R^2 = Me$
3 $R^1 = CO_2Me$, $R^2 = Ph$

Enantiomeric purity was enhanced when more bulky diethyl and diisopropyl diesters were used. Enantiomeric selectivity was enhanced by use of diethyl and diisopropyl ester, **1b** and **1c**. However, these reagents were more labile under these conditions and considerable decomposition occurred. In the case of diisopropyl diester, the complexof **1c** with (+)-Eu(hfc)$_3$ was transformed into almost a diastereomerically pure form (Figure 2). However, the enantiomeric excess fell to 51% after addition of the racemate. This corresponded to a recovery of 47%. Highly efficient kinetic resolution was acheived along with enantiomeric enrichment.

We expected that diastereodifferentiation might be enhanced using a readily available chiral source. However, up to 10% de was obtained using both enantiomers of menthol. No complexation was observed with more bulky di-8-phenylmenthyl diester due to severe steric constraints, based on the lack of a downfield shift in the ^{1}H NMR spectra. Methyl 4-phenyl-2,3-butadienoate (**2**) and methyl 2,3-pentadienoate (**3**)[20] were also inert to Eu(hfc)$_3$.

Among the solvents used for NMR analyses, benzene-d_6 was slightly less effective, and considerable decomposition occurred in cyclohexane-d_{12} after 3 days at 20 °C.

The other NMR shift reagents available[21] were ineffective. (+)-Pr(hfc)$_3$ and (+)-Yb(hfc)$_3$ were inert even when heated to 100 °C and totally decomposed at 120 °C. Severe decomposition occurred with (+)-Er(hfc)$_3$ even at −20 °C. Lanthanide elements are believed to have similar reactivities and are known for lanthanide contraction. Greater steric interaction with the ligand, and hence increased enantiomeric selectivity, was expected

(20) Preparation of allenecarboxylates: Lang, R. W.; Hansen, H.-J. In *Organic Syntheses*; John Wiley and Sons, Inc.: New York, 1990; Collect Vol. VII, pp 232−235.
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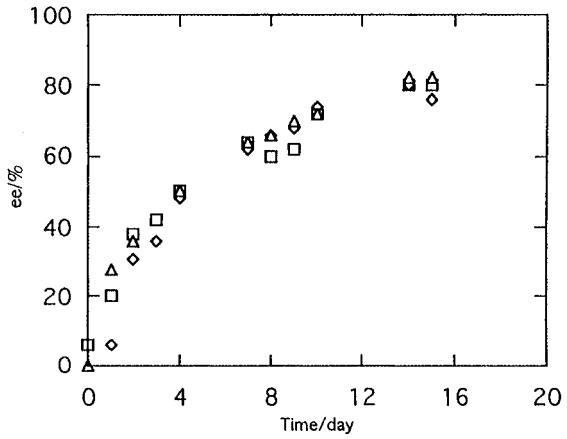
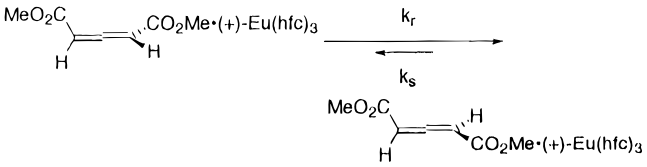


Figure 3. Time dependence of the enantiomeric excess using 1.0 equiv of (+)-Eu(hfc)$_3$: (◇) 5 mg; (△) 7 mg; (□) 10 mg of dimethyl 2,3-pentadienedioate.

with smaller ionic radii, but this phenomenon was not observed in this case. Table 1 summarizes the results.

Reaction Mechanism

Initially, we considered the participation of higher-order complexes. However, the enantiomeric excess reached ca. 80% regardless of the concentration. The change in enantiomeric excess could be described by the equation, which was derived by a first-order approximation of the interconversion of the enantiomers:



$$D_t[S\text{-Eu}] = -k_s[S\text{-Eu}] + k_r[R\text{-Eu}]$$

$$[S\text{-Eu}]_{t=0} = [R\text{-Eu}]_{t=0} = C/2$$

$$k_s[S\text{-Eu}]_{t=\infty} = k_r[R\text{-Eu}]_{t=\infty}$$

$$k_r = Kk_s$$

To obtain:

$$\text{ee} = (2[S\text{-Eu}]\text{-}1)/C = \{(K-1)/(K+1)\}\{1 - \exp(-(K+1)k_s t)\},\ \text{ee}_{\text{equilibrium}} = (K-1)/(K+1)$$

where [*R*-Eu], [*S*-Eu]: concentrations of the complexes of the (*R*)- and (*S*)-isomers, respectively, with the europium reagent; *C*: total concentration of the complex; k_s and k_r: the rate of the conversion from the (*S*)- to the (*R*)-isomer and *vice versa*; *K*: the rate ratio k_r/k_s; *t*: time. The kinetic parameters $\text{ee}_{\text{equilibrium}} = 79\%$, $K = 8.4$, $k_r = 2.8 \times 10^{-2}$ day^{-1} were obtained when 7.0 mg of **1a** was used ($\chi^2 = 85$). Thus, (+)-Eu(hfc)$_3$ prefers to complex to the (*S*)-isomer of **1a** by ca. 5.4 kJ mol^{-1} (1.3 kcal/mol) at 20 °C.

However, decrease in the peaks in the ^{1}H NMR spectrum of dimethyl 2,3-pentadienedioate was obvious. We examined enantiomeric enrichment in the presence of *tert*-butylcyclohexane as an internal standard. After 6 days, the sample was almost enantiomerically pure with ca. 14% of a byproduct, based on the ^{1}H NMR spectra. The enantiomeric excess after addition of the racemate clearly showed that no consumption of the diester, other than formation of a small amount of byproduct, occurred during enantiomerization. We also noted that the peak strength in the ^{1}H NMR spectrum of **1a** was enhanced much more than expected after addition of the racemate. Thus we concluded that enrichment occurred via equilibrium of the 1:1 complex of the allene diester and Eu(hfc)$_3$ and that reconstruction or reordering of the higher-order complex should then proceed in the reaction solution.

Conclusion

We have demonstrated the successful enantiomeric enrichment of allenedicarboxylates **1** by complexation with (+)-Eu(hfc)$_3$ with high optical purity. Further studies using this method are currently underway.

Experimental Section

^{1}H NMR spectra were recorded on a JEOL GMX-270 and an alpha-400 spectrometers. Diisopropyl 2,3-pentadienedioate (**1c**) was prepared in a manner similar to that for dimethyl and diethyl diesters.[17]

General Procedure for Enantiomeric Enrichment. In an NMR tube (5 mm diameter) under argon, penta-2,3-dienedioate **1** and chiral organolanthanide reagent were dissolved in $CDCl_3$ (0.70 mL). The resulting sample was wrapped with aluminum foil and stored in an air-conditioned room at 20 °C for 9 days. The enantiomeric ratio was determined by ^{1}H NMR using integration of the methoxyl peak.

Enantiomerization of Dimethyl Penta-2,3-dienedioate 1a with (+)-Eu(hfc)$_3$ on a Larger Scale. In a Schlenk tube under argon, **1a** (0.14 g, 0.84 mmol) and (+)-Eu(hfc)$_3$ (1.0 g, 0.84 mmol) were diluted in $CDCl_3$ (3.0 mL). The resulting yellow solution was stored in the dark for 9 days at 20 °C. Purification by two courses of column chromatography on silica gel (eluant: hexane−ether, 5:1) gave the pure recovered diester (92 mg 67%). The enantiomeric excess was determined by ^{1}H NMR with (+)-Eu(hfc)$_3$ (14.0 mg of recovered **1a** with 84.0 mg of (+)-Eu(hfc)$_3$). The sample used to examine the optical rotation was prepared with 20.4 mg of **1a** in 5.00 mL of methanol. $\alpha^{20}_D = +0.011°$ (10 mm cell path): $[\alpha]^{20}_D = +29.4$ (c, 0.408).

Enantiomerization of Diethyl Penta-2,3-dienedioate (1b) with (+)-Eu(hfc)$_3$. A sample prepared from diethyl penta-2,3-dienedioate (**1b**) (4.9 mg, 0.027 mmol) and (+)-Eu(hfc)$_3$ (32 mg, 0.027 mmol) was stocked in the dark for 9 days. Determination of the enantiomeric ratio was not satisfactory at this stage due to severe overlapping of signals, but was estimated by signal strength of the peaks. After the addition of racemic **1b** (3.3 mg), the ratio fell to 21% ee, which corresponds to a recovery of 33%.

Enantiomerization of Diisopropyl Penta-2,3-dienedioate (1c) with (+)-Eu(hfc)$_3$. A sample prepared from diisopropyl penta-2,3-dienedioate (**1c**) (5.5 mg, 0.026 mmol) and (+)-Eu(hfc)$_3$ (30 mg, 0.026 mmol) was stocked in the dark for 9 days. Determination of the enantiomeric ratio failed at this stage due to the high enantiomeric excess (>95% ee). After the addition of racemic **1c** (2.2 mg), the observed ratio fell down to 51% ee, which corresponds to a recovery of 47%.

Enantiomerization of Dimethyl Penta-2,3-dienedioate (1a) with (+)-Eu(hfc)$_3$ in the Presence of *tert*-Butylcyclohexane as a Internal Standard. In a Schlenk tube under argon were diluted dimethyl penta-2,3-dienedioate (**1a**) (30 mg), *tert*-butylcyclohexane (19 mg), and (+)-Eu(hfc)$_3$ (0.33 g) in $CDCl_3$ (to 4.5 mL). Some of this solution was subjected to ^{1}H NMR analysis. The integration ratio of the peaks of the olefinic proton and methyl groups of the allene, and t-Bu of *tert*-butylcyclohexane was 30:95:100. After 6 days at 20 °C, the ratio was 3:13:100. The methoxyl peak at 4.91 ppm was

accompanied by a signal from a byproduct (4.88 ppm), which was considered to be a mixture of almost enantiomerically pure **1a** and a byproduct (86:14). Racemic **1a** (10 mg) was added to 2.5 mL of the resulting solution, which showed 62% ee by ^{1}H NMR analysis. Thus, we ascertained that the product was almost enantiomerically pure. The integration ratio at this stage was 18:65:100.

Supporting Information Available: ^{1}H NMR of the reaction solutions (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO961870V