cussed only the preparation of the iodides, the method could, through suitable modification in the last step, be applied to the formation of alcohols, bromides, chlorides, and odd chain length aldehydes or carboxylic acids.[13] The iodides are useful intermediates and can be used to alkylate a wide variety of substrates, e.g., malonate, to provide ready access to long-chain carboxylic acids and related compounds.

## Experimental Section[15]

**General Procedure for Metathesis of α-Olefins.** Olefin (3 mol), dried by distillation from $CaH_2$, is placed in a flame-dried, three-necked flask of at least 2-L capacity, and the flask is thoroughly flushed with argon and heated to 80 °C. Through an open side arm, with a strong flow of argon to prevent contamination with oxygen, is added 15 mmol of $WCl_6$ (preweighed under argon into sealed vials), 60 mmol of ethyl acetate (dried by percolation through silica gel), and 30 mmol of tetramethyltin. After a few minutes, vigorous evolution of ethylene begins, and the temperature of the liquid rises somewhat. At this stage foam can be a problem, and good stirring is required, as well as a condenser. After 0.5–1.0 h the foaming subsides, and analysis usually indicated about 50% conversion. If the reaction is allowed to continue, conversions of 70–80% are usually obtained after overnight heating. Alternatively, fresh batches of catalyst can be added at 1-h intervals, in which case similar conversions are obtained after 3 h. The reaction can be monitored by quenching an aliquot with concentrated $NH_4OH$, extraction with hexane, and GC analysis (5 ft × $^1/_4$ in. SE-30; 150–300 °C, 10 °C/min). After cooling to room temperature, the reaction mixture is quenched with 200 mL of concentrated $NH_4OH$, extracted with hexane, and dried over $MgSO_4$. After removal of untreated α-olefin by vacuum distillation, the crystalline residue is crystallized from acetone. Two crystallizations give essentially pure trans olefin in 30–50% yields, usually contaminated with ca. 1% of the next lower homologue. Further crystallizations of the mother liquors give varying amounts of cis/trans mixtures, usually of sufficient purity to be used in the hydrozirconation step. Alternatively, the entire crude reaction product, after removal of unreacted α-olefin, can be used in the hydrozirconation reaction.

**Hydrozirconation/Iodination, General Procedure.** Zirconocene dichloride (386 g, 1.32 mol) is dissolved in 3 L of dry THF in a flame-dried, three-necked, 5-L Morton flask fitted with a paddle stirrer, a rubber septum, and an immersion thermometer controlling a Thermo-Watch. Heat is provided by a heating mantle. After the flask is flushed with argon, Vitride (0.66 mol, 70% in toluene) is added at a moderate rate directly from the bottle via a flexible tube with needles at each end, pressure being supplied from an argon tank reduced to about 5 psig. After about 1–2 h at room temperature, olefin (0.66 mol) is added via flexible rubber tubing, and the mixture heated to 40 °C (alternatively, the olefin can be introduced with the $Cp_2ZrCl_2$). The reaction is monitored at periodic intervals by withdrawal of a small sample, quenching with iodine, and filtration through a short column of silica gel. The extent of conversion to iodide can be determined directly by $^1$HMR analysis of the crude product. When no more change occurs (1–6 days), iodine (333.5 g, 1.32 mol) is added after the reaction mixture is cooled in an ice bath. After the mixture is stirred 4 h at room temperature, the THF is distilled and replaced with hexane, which precipitates the zirconium-containing byproducts. Filtration, followed by percolation through 500 g of silica gel in a sintered-glass filter, gives the crude iodide contaminated with varying amounts of olefin. Crystallization from acetone (up to $C_{30}$) or hexane ($C_{34}$ and $C_{42}$) gave the results in Table II. Spectral data ($^1$H NMR, $^{13}$C NMR, and mass spectra) are consistent with the presence of only primary iodide and, in some instances, small amounts of the saturated hydrocarbon. The zirconocene dichloride can be recovered by treatment of the insoluble material with charcoal in chloroform, filtration, and treatment with anhydrous HCl to regenerate the dichloride.

**Registry No. 5**, 1291-32-3; **6**, 37342-97-5; 1-tridecene, 2437-56-1; 1-tetradecene, 1120-36-1; 1-pentadecene, 13360-61-7; 1-hexadecene, 629-73-2; 1-octadecene, 112-88-9; 1-docosene, 1599-67-3; (*E*)-12-tetracosene, 76665-54-8; (*E*)-13-hexacosene, 76665-55-9; (*E*)-14-octacosene, 76665-56-0; (*E*)-15-triacontene, 76665-57-1; (*E*)-17-tetratriacontene, 76665-58-2; (*E*)-21-dotetracontene, 76665-59-3; 1-iodotetracosane, 62127-55-3; 1-iodohexacosane, 52644-81-2; 1-iodooctacosane, 62154-80-7; 1-iodotriacontane, 62154-82-9; 1-iodotetratriacontane, 62154-85-2; 1-iodotetracontane, 76665-60-6; (*E*)-4-octene, 14850-23-8; 1-bromooctane, 111-83-1.

(15) Melting points were determined on a microscope equipped with a hot stage and are corrected. Infrared spectra were determined with a Perkin-Elmer Model 257 spectrometer, $^1$H NMR spectra were obtained on a Varian Model HA-100 spectrometer, $^{13}$C NMR spectra were obtained on a Varian CFT-20 spectrometer, and mass spectra were obtained on a Varian-MAT SM-1 spectrometer. α-Olefins were obtained from Aldrich or Humphreys, zirconocene dichloride from Arapahoe, tetramethytin from Aldrich, and tungsten hexachloride from Alfa-Ventron. Vitride (70% in toluene) was obtained from Hexcel Chemical Specialties.

# Asymmetric Addition of Thioglycolic Acid to Nitro Olefins Catalyzed by Cinchona Alkaloids

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Thioglycolic acid (**1**) has been shown to undergo asymmetric addition to (2-nitroethenyl)benzene (**2**) in the presence of a cinchona alkaloid as a catalyst. By selection of reaction conditions, enantiomeric yields of up to 58% were obtained. Evidence is presented which supports the idea that the interaction between the carboxyl group of **1** and the active site of the catalyst (quinuclidine nitrogen) exerts a favorable effect on the extent of asymmetric induction. When methyl 7-nitrohept-6-enoate (**10**) was used as an acceptor, (*S*)-**13** was obtained in 37% ee with quinine catalyst. Also studied was the asymmetric addition of **1** to 1-methoxy-2-(2-nitroethenyl)benzene (**8**) and (2-nitro-1-propenyl)benzene (**9**).

The catalytic asymmetric addition of thiols to α,β-unsaturated compounds is a reaction that possesses a potential applicability to the synthesis of physiologically active substances having a chiral center at the α- or β-

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Table I. Asymmetric Addition of 1 to 2[a]

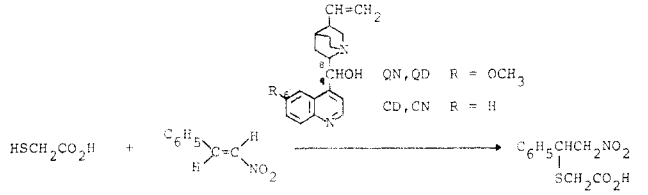
| entry | QN, mmol | QN/1, molar ratio | time, h | yield, % | $[\alpha]_D$,[b] deg | % ee[c] |
|---|---|---|---|---|---|---|
| 1 | 0.1 | 0.01 | 114 | 88[d] | −25.6 | 15 |
| 2 | 2.0 | 0.18 | 23 | 90[d] | −9.3 | 5 |
| 3 | 3.0 | 0.27 | 24 | 85[d] | +1.3 | 1 |
| 4 | 5.0 | 0.46 | 2 | 85[d] | +14.3 | 8 |
| 5 | 9.0 | 0.82 | 0.5 | 93 | +36.0 | 21 |
| 6 | 10.0 | 0.91 | 0.5 | 92 | +43.9 | 26 |
| 7 | 11.0 | 1.00 | 0.5 | 90 | +59.4 | 35 |
| 8 | 11.0 | 1.00[e] | 0.16 | 47[d] | +31.4 | 18 |
| 9 | 12.0 | 1.09 | 0.5 | 96 | +59.9 | 35 |
| 10 | 15.0 | 1.36 | 0.33 | 94 | +50.5 | 30 |

[a] Reaction conditions: 1, 11 mmol; 2, 10 mmol; toluene, 30 mL; room temperature. [b] Measured in $CHCl_3$ at 25 °C (c 1). [c] Based on $[\alpha]_D$ 170°; see text. [d] Recovering procedure for 3 from the aqueous phase was omitted. [e] QN was added to a toluene solution of 1 and 2.

position of the sulfur atom[1] and is a topic of current interest.[2] Cinchona alkaloids have been most frequently and successfully used as the chiral catalysts. However, previous investigations using alkaloid catalysts have not been extended beyond the asymmetric addition of simple thiols.

From the practical point of view the use of thiols having an additional functional group seems to be more important.[1a,b,d,e] In addition, it appeared of interest to see if the second functional group in the thiol compound could contribute to increase enantiomeric yield through its strong interaction with the active site of the catalyst molecule (quinuclidine nitrogen), although it has been recognized that salt formation at the amino group of the alkaloid usually causes lowering of optical yield[2f,h,3,4] and sometimes affects the stereochemistry.[2f,3c,d]

Accordingly, we investigated the asymmetric addition of thioglycolic acid (1) to (2-nitroethenyl)benzene (2) under




1 2 3

the influence of the cinchona alkaloids, especially quinine

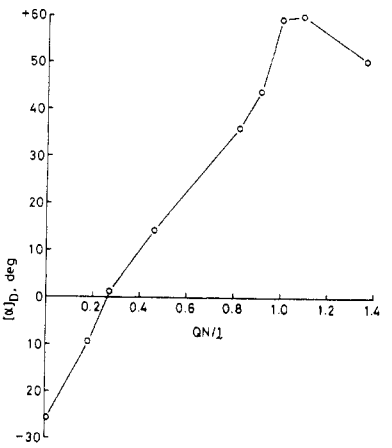
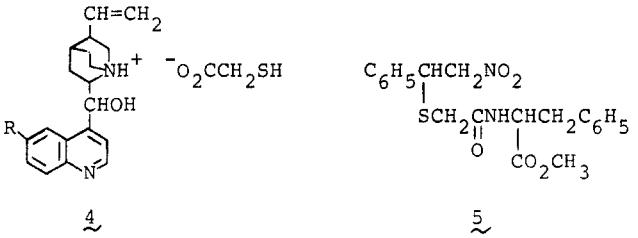



**Figure 1.** Variation in the specific rotation of the product (3) with the QN/1 ratio in the asymmetric addition of 1 to 2.

(QN). The direction and extent of asymmetric induction was found to vary depending on the catalyst/1 ratio. By selection of reaction conditions, enantiomeric yields of up to 58% were obtained. The asymmetric addition of 1 to other nitro olefins was also studied.

## Results and Discussion

**Reaction Features.** The reaction of 1 with 2 was carried out by adding a toluene solution of 2 (10 mmol) to a mixture of 1 (11 mmol) and a given amount of QN in toluene (total 30 mL) followed by stirring of the mixture at room temperature under an inert atmosphere. After the reaction was complete, the mixture was washed with dilute hydrochloric acid. Evaporative workup gave spectrally pure product, 3. When 9 mmol of QN was fed in, large quantities of QN–1 salt (4) precipitated, which dis-




4 5

appeared during the reaction, while 4 remained partly undissolved when more QN was used. In these cases a considerable amount of 3 moved to the aqueous phase during the washing procedure and was recovered by extraction with ether. The optical rotations of both samples of 3, obtained from the toluene solution and the aqueous phase, were identical. The catalyst was quantitatively recovered from the aqueous phase as $QN{\cdot}2HCl{\cdot}H_2O$. The results are summarized in Table I. The percent enantiomeric excess (ee) data of the reaction products are based on their optical rotations. Compound 3 was converted to a diastereomeric amide (5) by treating it first with oxalyl chloride and then with L-phenylalanine methyl ester.[5] The diastereomeric composition of 5 was determined by $^1H$ NMR spectroscopy with the aid of $Eu(fod)_3$. From the linear $[\alpha]_D$–% ee relationship obtained for several samples, optically pure 3 was estimated to have $[\alpha]^{25}_D$ 170° ($CHCl_3$). The same value was obtained by optical resolution of 3 with (+)-α-methylbenzylamine.

The reaction rate was sensitive to the QN/1 ratio; when the QN/1 ratio was 0.01, the reaction was quite sluggish,

(1) (a) I. T. Harrison, R. J. K. Taylor, and J. H. Fried, *Tetrahedron Lett.*, 1165 (1975); (b) M. Winn, R. K. Razdan, H. C. Dalzell, and J. R. Krei, German Offen. 2 441 206; *Chem. Abstr.*, **83**, 79220 (1975); (c) M. A. Ondetti, B. Rubin, and D. W. Cushman, *Science*, **196**, 441 (1977); (d) M. Marx, F. Marti, J. Reisdorff, R. Sandmeier, and S. Clark, *J. Am. Chem. Soc.*, **99**, 6754 (1977); (e) J. Vasilevskis, J. A. Gualtieri, S. D. Hutchings, R. C. West, J. W. Scott, D. R. Parrish, F. F. Bizzarro, and G. F. Field, *ibid.*, **100**, 7423 (1978).

(2) (a) K. Yamaguchi and Y. Minoura, *Chem. Ind. (London)*, 478 (1975); (b) H. Pracejus, F.-W. Wilcke, and K. Hanemann, *J. Prakt. Chem.*, **319**, 219 (1977); (c) R. Helder, R. Arends, W. Bolt, H. Hiemstra, and H. Wynberg, *Tetrahedron Lett.*, 2181 (1977); (d) S. Inoue and Y. Kawano, *Makromol. Chem.*, **180**, 1405 (1979), and previous papers; (e) N. Kobayashi and K. Iwai, *J. Am. Chem. Soc.*, **100**, 7071 (1978); (f) N. Kobayashi and K. Iwai, *Macromolecules*, **13**, 31 (1980); (g) N. Kobayashi and K. Iwai, *J. Polymn. Sci., Polym. Lett. Ed.*, **18**, 417 (1980); (h) N. Kobayashi and K. Iwai, *Tetrahedron Lett.*, **21**, 2167 (1980).

(3) (a) G. Berti and A. Marsili, *Tetrahedron*, **22**, 2977 (1966); (b) K. Hermann and H. Wynberg, *J. Org. Chem.*, **44**, 2238 (1979); (c) N. Kobayashi and K. Iwai, *J. Polym. Sci., Polym. Chem. Ed.*, **18**, 923 (1980); (d) N. Kobayashi and K. Iwai, *Polym. J.*, **13**, 263 (1981).

(4) N(1)-Quaternized cinchona alkaloids have been successfully used as the chiral phase-transfer catalysts. See, for example: R. Helder, J. C. Hummelen, P. W. P. M. Laane, J. S. Wiering, and H. Wynberg, *Tetrahedron Lett.*, 1831 (1976); S. Colonna and R. Fornasier, *J. Chem. Soc., Perkin Trans. 1*, 371 (1978); S. Juliá, A. Ginebreda, and J. Guixer, *J. Chem. Soc., Chem. Commun.*, 742 (1978).

(5) We thank M. Kakutani for a gift of L-phenylalanine methyl ester hydrochloride.

Table II. Effect of Catalyst on Asymmetric Addition of 1 to 2[a]

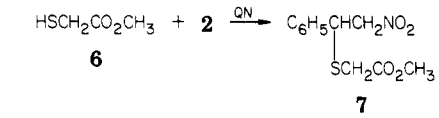
| catalyst | time, min | yield, % | $[\alpha]_D$,[b] deg | % ee[c] |
|---|---|---|---|---|
| QN | 30 | 96 | +59.9 | 35 |
| QD | 15 | 80[d] | −50.2 | 30 |
| CD | 15 | 78[d] | +3.8 | 2 |
| CN | 10 | 80[d] | −12.9 | 8 |

[a] Reaction conditions: 1, 11 mmol; 2, 10 mmol; catalyst, 12 mmol; toluene, 30 mL; room temperature. [b] Measured in $CHCl_3$ at 25 °C (c 1). [c] Based on $[\alpha]_D$ 170°; see text. [d] Recovering procedure for 3 from the aqueous phase was omitted.

while it was complete within 30 min when the QN/1 ratio was greater than 0.81. The most important observation from Table I is that the optical rotation of 3 changed dramatically on changing the amount of QN catalyst. At a QN/1 ratio of 0.01 the specific rotation of 3 was −25.6° (entry 1), and it dropped to −9.3° at a QN/1 ratio of 0.18 (entry 2). At a QN/1 ratio of 0.27 the (+) enantiomer predominated slightly (entry 3), and the optical rotation increased up to +59.9° (entry 9) and then decreased with increasing QN/1 ratio. This behavior is even more apparent from Figure 1. The best result was obtained with the QN/1 ratio of 1.09.

The order of addition also affected the asymmetric induction. When the addition was altered, QN being added to a mixture of 1 and 2, the enantiomeric yield decreased from 35% to 18% (compare entry 7 with entry 8).

These findings show that the salt formation between QN and 1 exerts a pronounced effect on the reaction rate and stereochemistry. In order to obtain further insight into the nature of the reaction, we carried out additional experiments. A mixture of 4, prepared independently, and 2 in toluene was stirred at 0 °C for 8 h and then at room temperature for 16 h to afford (+)-3 in 34% chemical yield and 0.5% ee. When the reaction was conducted in $CHCl_3$ in which 4 was soluble, (+)-3 was obtained in 91% chemical yield and 17% ee. Furthermore, the reaction of 2 with methyl thioglycolate 6, that does not form a salt with QN,



6 7

proceeded rapidly even at a QN/6 ratio of 0.01 and gave (+)-7 in 14% ee.[6] (+)-7 was also formed at a QN/6 ratio of 1.09 but in a decreased enantiomeric yield (7%). It is to be noted that higher enantiomeric yield was obtained with 1 which can strongly interact with the catalytic site through its carboxyl group.

From these results the asymmetric addition of 1 to 2 in the presence of QN may be explained as follows. There is an equilibrium (1 + QN ⇌ 4) which must lie far to the right. The salt 4 could be a poor catalyst, giving the (−) enantiomer of 3 predominantly. On the other hand, free QN catalyzes the reaction quite well, giving (+)-3 in excess. The apparent stereochemistry, therefore, would depend on the amount of free QN in the system relative to that of 4. The higher chemical and enantiomeric yields obtained in the reaction of 4 with 2 in $CHCl_3$ as compared with that in toluene are in accord with the increased amount of free QN in the homogeneous system.

**Effect of Catalyst.** Table II shows the effect of catalyst on asymmetric induction. The catalyst/1 ratio was kept

(6) The enantiomeric excess of 6 was determined by the chemical correlation with 3. See the Experimental Section.

Table III. Effect of Temperature on the Asymmetric Addition of 1 to 2[a]

| temp,[e] °C | time, h | yield,[b] % | $[\alpha]_D$,[c] deg | % ee[d] |
|---|---|---|---|---|
| −78 | 30 | 19 | +29.3 | 17 |
| −20 | 3 | 91 | +73.2 | 43 |
| 0 | 0.5 | 91 | +97.5 | 57 |
| rt | 0.25 | 86 | +99.0 | 58 |
| +70 | 1.5 | 75 | +1.7 | 1 |

[a] Reaction conditions: 1, 11 mmol; 2, 10 mmol; QN, 12 mmol; toluene, 210 mL. [b] Recovering procedure for 3 from the aqueous phase was omitted. [c] Measured in $CHCl_3$ at 25 °C (c 1). [d] Based on $[\alpha]_D$ 170°; see text. [e] rt = room temperature.

at 1.09. QN and cinchonidine (CD) having C(8)-*S*,C(9)-*R* erythro configurations gave (+)-3 in excess, while quinidine (QD) and cinchonine (CN) with opposite *R*,*S* erythro arrangements gave (−)-3 in excess. Thus the stereochemistry is said to be controlled by the configurations at C(8) and C(9) in the alkaloid, as is generally observed in the asymmetric reactions under the influence of cinchona alkaloids or their derivatives.[7,8] The order of enantioselectivity QN, QD ≫ CN, CD reflects the effect of a methoxy substituent at C(6′) on the extent of asymmetric induction.

**Effect of Concentration.** Dilution of the reaction system resulted in an increase in the enantiomeric yield. When the amount of toluene was increased from 30 to 210 mL, with the QN/1 ratio being kept at 1.09, the enantiomeric yield increased from 35% to 58%.[9] Further twofold dilution did not cause any increase in the percent enantiomeric excess. Additional advantages of dilution are ease of stirring and ease of workup; the system became homogeneous during the reaction, and most of the 3 remained in the organic phase after it was washed with dilute hydrochloric acid. Thus, conditions of 11 mol of 1, a QN/1 ratio of 1.09, and 210 mL of toluene were used in the remainder of this study.

**Effect of Temperature.** There are wide variations in the extent of asymmetric induction with temperature (Table III). The best results were obtained between 0 °C and room temperature, and either raising or lowering the temperature caused a decrease in the percent enantiomeric excess.[10] Although the sudden decrease in the percent enantiomeric excess at 70 °C is difficult to account for, the decreased values at low temperature may be ascribed, at least in part, to the decreased solubility of 4.

The reaction rate increased with increasing temperature from −78 °C to room temperature. At 70 °C the reaction proceeded homogeneously, but the rate was decreased again. We have no explanation for this phenomenon as yet. However, it is advantageous that the reaction proceeds best at ambient temperature with respect to both rate and enantioselectivity.

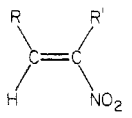
**Asymmetric Addition of 1 to Other Nitro Olefins.** Essentially the same conditions were applied to the reactions of 1 with nitro olefins 8–10. The results are summarized in Table IV. With every nitro olefin as the acceptor, QN and QD gave products with opposite optical rotations. The adducts 11 and 12 were converted to the corresponding methyl esters, 14 and 15. Attempts to

(7) See, for example: L. Meurling, *Chem. Scr.*, 7, 90 (1975); ref 2b, f–g and 3a,c.

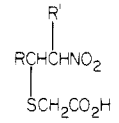
(8) Very recently reaction systems where the stereochemistry is controlled by the configuration at C(3) were disclosed (see ref 2h and 3d).

(9) When the order of addition was altered, 1 being added to a mixture of 2 and QN, the enantiomeric yield decreased from 58% to 32%.

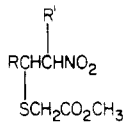
(10) Analogous temperature effects have been observed in some asymmetric reactions catalyzed by acrylonitrile–cinchona alkaloid copolymers (see ref 2f,h).



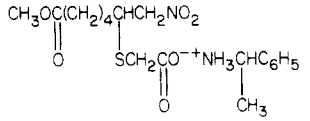
8, R = 2-$CH_3OC_6H_4$; R′ = H
9, R = $C_6H_5$; R′ = $CH_3$
10, R = $CH_3OCO(CH_2)_4$; R′ = H



11, R = 2-$CH_3OC_6H_4$; R′ = H
12, R = $C_6H_5$; R′ = $CH_3$
13, R = $CH_3OCO(CH_2)_4$; R = H



14, R = 2-$CH_3OC_6H_4$; R′ = H
15, R = $C_6H_5$; R′ = $CH_3$



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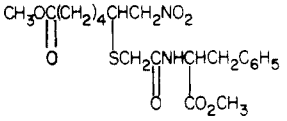
determine the optical purity of these esters by NMR spectroscopy using $Eu(TFC)_3$ were unsuccessful. Therefore, nothing definite can be said about the extent of asymmetric induction in these cases, although the magnitude of $[\alpha]_D$ suggests a considerable stereoselectivity.

Of special interest is the reaction of **1** with **10**, because the product **13** is useful as a synthetic intermediate to biotin. Field and co-workers have synthesized *d*-biotin starting from the *S* enantiomer of **13** prepared by optical resolution.[1e] To establish the relationship between the absolute configuration and rotational sign of **13**, we prepared a sample of **13** rich in *S* enantiomer according to the method of Field.[1e] Racemic **13** was treated with (+)-α-methylbenzylamine in ethyl acetate and the mixture diluted with ether. The solid salt **16** formed was recrystallized from ethyl acetate and treated with 5% aqueous $KHSO_4$ to give free **13** with $[\alpha]_D$ −8.3° (*c* 1.042, benzene). Thus the configuration of (−)-**13** was determined as *S*. The enantiomeric excess of **13** was determined by NMR by using $Eu(fod)_3$ on the amide **17**, prepared by treating **13**



17

with oxalyl chloride followed by condensation with L-phenylalanine methyl ester. Table IV shows that with QN catalyst the desired *S* enantiomer was obtained in 37% ee. This degree of asymmetric induction is reasonably high and offers the promise of a chiral synthesis of this important class of compounds.

## Conclusions

We have (1) achieved the asymmetric addition of **1** to **2** in good enantiomeric yield by using a cinchona alkaloid as a catalyst, (2) demonstrated the effect of salt formation between **1** and the catalyst on the asymmetric induction, and (3) broadened the area of asymmetric thiol addition.

## Experimental Section

Melting points were determined on a Yanaco MP micro melting point apparatus. All melting points are uncorrected. Optical rotations were measured at 25 °C on a Union PM-201 automatic digital polarimeter. $^1H$ NMR spectra were recorded on a Varian EM-390 spectrometer. Infrared (IR) spectra were obtained by using a Hitachi EPI-G3 grating infrared spectrophotometer.

TLC analysis was performed with Merck, DC-Alufolien (Kieselgel 60 $F_{254}$) sheets. Column chromatography was performed with Wako Pure Chemical Industries, Ltd., Wakogel C-200 (silica gel).

Cinchona alkaloids and (+)-α-methylbenzylamine were commercial reagents and were used without further purification. Thioglycolic acid (**1**) and methyl thioglycolate (**6**) were obtained commercially and distilled before use. Published procedures were used for the synthesis of (2-nitroethenyl)benzene (**2**)[11] and (2-nitro-1-propenyl)benzene (**9**).[12] 1-Methoxy-2-(2-nitroethenyl)-benzene (**8**) was prepared in a similar manner as **2**; mp 44-44.5 °C (EtOH) (lit.[13] mp 50 °C). Methyl 7-nitrohept-6-enoate (**10**) was synthesized by starting from ε-caprolactone. The lactone was opened with MeOH[14] and oxidized with pyridinium chlorochromate[15] to furnish the corresponding ester aldehyde, which in turn was condensed with nitromethane[16] and then acetylated.[16] Deacetylation with aqueous $NaHCO_3$[1d] gave **10**: bp 100 °C (0.2 mm).

All asymmetric reactions were carried out under an atomosphere of nitrogen.

**General Procedure for Asymmetric Addition of 1 to 2.** (See also Tables I–III for conditions and results.) QN and **1** (11 mmol) were mixed in toluene. If the whole system solidified, the solid was crushed to facilitate stirring. To the stirred mixture was added a toluene solution of **2** (10 mmol), and the mixture was stirred at the indicated temperature. The reaction was followed by observing the reduction of the yellow color due to **2** and by TLC (benzene). After the time indicated in the tables, the reaction mixture was extracted three times with 20-mL portions of dilute (0.1–1 N) hydrochloric acid, washed with water, and dried over anhydrous $MgSO_4$. Evaporation of toluene gave spectrally homogeneous **3** as a white solid. If necessary, the combined extracts and washings were extracted with ether. On evaporation of the aqueous solution to dryness, QN was recovered quantitatively as QN·2HCl·$H_2O$. Its IR spectrum was in good agreement with that of an authentic sample. The ether solution was washed with 0.1 N NaOH and then with water, dried, and concentrated to give a varying amount of **3**, depending on the reaction conditions. The optical rotations of both samples of **3** agreed nicely.

**Properties of 3.** An analytical sample was prepared by recrystallization from hexane–ether: mp 72–72.5 °C (lit.[17] mp 71 °C); IR (KBr disk) 1700, 1510, 1380, 1315, 1219, 700 $cm^{-1}$; NMR ($CDCl_3$) δ 3.15 (d, *J* = 2 Hz, 2 H), 4.83 (s, 3 H), 7.35 (s, 5 H), 11.36 (s, 1 H). Anal. Calcd for $C_{10}H_{11}NO_4S$: C, 49.78; H, 4.60; N, 5.81; S, 13.29. Found: C, 49.96; H, 4.59; N, 5.78; S, 13.31.

**Determination of Enantiomeric Excess of 3.** Chemically pure samples of **3** with a different specific rotation were prepared by fractional recrystallization from hexane–ether. Each sample (2 mmol) was converted to acid chloride by treating it with oxalyl chloride (5 mmol). The acid chloride was dissolved in ethyl acetate (10 mL) and added dropwise to a stirred mixture of L-phenylalanine methyl ester hydrochloride (2 mmol), triethylamine (4 mmol), and ethyl acetate (20 mL) below −5 °C. After the addition was complete, stirring was continued for 15 min under cooling for 1 h at room temperature and 1 h at 40 °C. The mixture was washed with water, dried, concentrated, and passed through a short column of silica gel by using 1:1 hexane–ethyl acetate to afford *N*-[[[(2-nitro-1-phenylethyl)thio]methyl]carbonyl]-L-phenylalanine methyl ester (**5**) as a white solid. Addition of $Eu(fod)_3$ (60 mol %) to **5** dissolved in $CDCl_3$ gave rise to two separated singlets for the ester methyl group. From integration ratio of these peaks the enantiomeric excess was calculated [% ee ($[\alpha]_D$ of **3**)]: 89 (+151.6°), 70 (+122.0°), 35 (+59.3°). On the basis of this relationship the $[\alpha]^{25}_D$ ($CHCl_3$) value of optically pure **3** was estimated at 170°. This value was supported by optical resolution study of **3**. A sample of (+)-**3** was treated with (+)-α-methylbenzylamine in ethyl acetate and then diluted with ether. After several recrystallizations from ethyl acetate, the salt exhibited the maximum rotation, $[\alpha]^{25}_D$ +97.0° (*c* 1.044, MeOH),

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Table IV. Asymmetric Addition of 1 to 8-10[a]

| nitro olefin | catalyst | time, min | product | yield,[b] % | $[\alpha]_D$, deg | % ee (config) |
|---|---|---|---|---|---|---|
| 8 | QN | 20 | 11 | 83[c] | +65.3[d] | |
| | QD | 20 | 11 | 93[c] | −71.3[d] | |
| 9 | QN | 180 | 12 | 96[c] | +86.6[d] | |
| | QD | 120 | 12 | 96[c] | −96.5[d] | |
| 10 | QN | 30 | 13 | 82 | −3.8[e] | 37[f] (S) |
| | QD | 30 | 13 | 81 | +4.0[e] | 39[f] (R) |

[a] Reaction conditions: 1, 6 mmol; nitro olefin, 5 mmol; catalyst, 6 mmol; toluene, 105 mL; stirring at rrom temperature. [b] After purification by column chromatography. [c] Recovering procedure of the product from the aqueous phase was omitted. [d] Measured in $CHCl_3$ at 25 °C (c 1). [e] Measured in benzene at 25 °C (c 1). [f] The enantiomeric excess was determined by use of a NMR shift reagent; see text.

which corresponds to 3 with $[\alpha]^{25}_D$ +170° ($CHCl_3$). The percent enantiomeric excess values of the reaction products listed in Tables I–III are based on their optical rotations.

**Properties of 5.** An analytical sample was prepared by recrystallization from benzene–hexane: mp 128–129.5 °C (when prepared from 3 with $[\alpha]_D$ +151.6°); IR (KBr disk) 3320, 1732, 1660, 1559, 701 $cm^{-1}$; NMR ($CDCl_3$) δ 2.95–3.20 (m, 4 H), 3.72 (s, 3 H), 4.35–4.92 (m, 4 H), 6.70–6.92 (br d, $J$ = 8 Hz, 1 H), 7.03–7.40 (m, 10 H). Anal. Calcd for $C_{20}H_{22}N_2O_5S$: C, 59.69; H, 5.51; N, 6.96; S, 7.97. Found: C, 59.70; H, 5.45; N, 6.93; S, 8.10.

**Preparation of QN–1 Salt (4).** To a stirred solution of 0.92 g (10 mmol) of 1 in 30 mL of $CH_2Cl_2$ cooled to 0 °C was added 3.24 g (10 mmol) of QN. Stirring was continued for 15 min. Evaporation of the solvent followed by recrystallization of the residue from toluene gave 3.44 g of 4 as a white crystal. Elemental analysis of this salt revealed that it contains $^1/_2H_2O$ per molecule: yield 81%; mp 133–144 °C; IR (KBr disk) 2720, 1620, 1591, 1510, 1381, 1362, 1240, 1097, 1031 $cm^{-1}$. Anal. Calcd for $C_{22}H_{28}N_2O_4S \cdot {}^1/_2H_2O$: C, 62.09; H, 6.87, N, 6.58; S, 7.35. Found: C, 62.09; H, 6.89; N, 6.54; S, 7.48.

**Reaction of 4 with 2.** A typical procedure is as follows. A solution of 0.75 g (5 mmol) of 2 was added to a mixture of 2.29 g (5.4 mmol) of 4 and 100 mL of toluene cooled with an ice–water bath. The mixture was stirred for 8 h at 0 °C and then 16 h at room temperature. The salt remained partly undissolved, and TLC (benzene) indicated the presence of unreacted 2. The mixture was extracted three times with 20-mL portions of 1 N HCl, washed with water, dried over anhydrous $MgSO_4$, and concentrated. From the residual oily material was isolated 0.41 g (34%) of 3 by column chromatography (benzene and then ethyl acetate): $[\alpha]_D$ +0.8° (c 0.998, $CHCl_3$); 0.5% ee.

**Asymmetric Addition of 6 to 2.** A typical procedure is as follows. To a stirred solution of 1.17 g (11 mmol) of 6 and 32.4 mg (0.1 mmol) of QN in 25 mL of toluene was added a solution of 1.49 g (10 mmol) of 2 in 5 mL of toluene, and the resulting solution was stirred for 30 min at room temperature. Workup of the rection mixture as above, except that 0.1 N HCl was used, followed by column chromatography (benzene) yielded 2.33 g (91%) of 7 as a colorless liquid:[17] $[\alpha]_D$ +20.4° (c 1.031, $CHCl_3$); 14% ee; IR (neat) 1740, 1560, 1443, 1381, 1308, 1290, 1160, 1135, 1008, 702 $cm^{-1}$; NMR ($CDCl_3$) δ 3.09 (d, $J$ = 2 Hz, 2 H), 3.67 (s, 3 H), 4.80 (s, 3 H), 7.34 (s, 5 H). Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49; S, 12.56. Found: C, 51.94; H, 5.08; N, 5.51; S, 12.50. The enantiomeric excess of 7 was determined by the chemical correlation with 3. Methylation of 3 ($[\alpha]_D$ +11.4°) with diazomethane gave the corresponding methyl ester 7, $[\alpha]_D$ +9.6° (c 1.022, $CHCl_3$). IR and NMR spectra of this ester were identical with those described above. From the $[\alpha]_D(3)$–$[\alpha]_D(7)$ relationship, optically pure 7 was estimated to have $[\alpha]^{25}_D$ 143° ($CHCl_3$).

**Asymmetric Addition of 1 to 8.** A typical procedure is as follows. To a mixture of 0.55 g (6 mmol) of 1 and 1.94 g (6 mmol) of QN in 90 mL of toluene was added a solution of 0.90 g (5 mmol) of 8 in 15 mL of toluene. The mixture was stirred for 20 min at room temperature. During this period the system became homogeneous. The reaction mixture was extracted with 1 N HCl, washed with water, dried, and concentrated. The residual yellow liquid was submitted to column chromatography (benzene and then 8:2 benzene–ethyl acetate) to give 1.13 g (83%) of 11: $[\alpha]_D$ +65.3° (c 1.046, $CHCl_3$); IR (neat) 1717, 1557, 1500, 1380, 1300, 1259, 1026, 760 $cm^{-1}$; NMR ($CDCl_3$) δ 3.20 (s, 2 H), 3.81 (s, 3 H), 4.78–5.16 (m, 3 H), 6.80–7.40 (m, 4 H). Methylation of this sample with diazomethane followed by column chromatography (10:3 hexane–ethyl acetate) gave the corresponding methyl ester, 14, as a slightly yellow oil: $[\alpha]_D$ +64.3° (c 1.035, $CHCl_3$); IR (neat) 1740, 1558, 1500, 1471, 1444, 1381, 1298, 1258, 1027, 760 $cm^{-1}$; NMR ($CDCl_3$) δ 3.18 (s, 2 H), 3.64 (s, 3 H), 3.82 (s, 3 H), 4.75–5.12 (m, 3 H), 6.78–7.37 (m, 4 H). Anal. Calcd for $C_{12}H_{15}NO_5S$: C, 50.52; H, 5.30; N, 4.91; S, 11.24. Found: C, 50.57; H, 5.36; N, 4.81; S, 11.25. An attempt to determine the enantiomeric excess of 14 by NMR by using $Eu(TFC)_3$ was unsuccessful.

**Asymmetric Addition of 1 to 9.** A typical procedure is as follows. To a solution of 0.55 g (6 mmol) of 1 in 90 mL of toluene was added 1.94 g (6 mmol) of QD. To this was added a solution of 0.82 g (5 mmol) of 9 in 15 mL of toluene, and the resulting mixture was stirred at room temperature for 2 h, during which time the system became homogeneous. The reaction mixture was worked up as above and submitted to column chromatography (8:2 benzene–ethyl acetate) to yield 1.22 g (96%) of 12 as an orange oil: $[\alpha]_D$ −96.5° (c 1.032, $CHCl_3$); IR (neat) 1715, 1557, 1456, 1392, 1361, 1300, 755, 702 $cm^{-1}$; NMR ($CDCl_3$) δ 1.38 and 1.77 (2 d, $J$ = 7 Hz, 3 H), 3.03 (d, $J$ = 3 Hz, 2 H), 4.42–4.58 (m, 1 H), 4.80–5.05 (m, 1 H), 7.31 (s, 5 H), 9.35 (br s, 1 H). Methylation of this sample with diazomethane followed by column chromatography (10:3 hexane–ethyl acetate) gave the corresponding methyl ester, 15, as a slightly yellow oil: $[\alpha]_D$ −97.4° (c 1.087, $CHCl_3$); IR (neat) 1740, 1555, 1457, 1390, 1362, 1295, 1010, 750, 705 $cm^{-1}$; NMR ($CDCl_3$) δ 1.35 and 1.72 (2 d, $J$ = 7 Hz, 3 H), 3.01 (d, $J$ = 3 Hz, 2 H), 3.60 (s, 3 H), 4.38–4.55 (m, 1 H), 4.70–5.05 (m, 1 H), 7.30 (s, 5 H). Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20; S, 11.91. Found: C, 53.63; H, 5.58; N, 5.13; S, 12.00. An attempt to determine the optical purity of 15 by NMR by using $Eu(TFC)_3$ was unsuccessful.

**Asymmetric Addition of 1 to 10.** A typical procedure is as follows. To a mixture of 0.55 g (6 mmol) of 1 and 1.94 g (6 mmol) of QN in 90 mL of toluene was added 0.94 g (5 mmol) of 10. The mixture was stirred at room temperature. After 30 min the reaction mixture was extracted with 1 N HCl, washed with water, and dried. The combined extracts and aqueous washings were extracted with ether. The ether solution was washed with 0.1 N NaOH and then with water and dried. Concentration of the combined organic solutions followed by column chromatography (7:4 hexane–ethyl acetate) gave 1.14 g (82%) of 13 as a yellow oil: $[\alpha]_D$ −3.8° (c 1.022, benzene); IR (neat) 2940, 1722, 1542, 1435, 1375, 1200 $cm^{-1}$; NMR ($CDCl_3$) δ 1.40–1.90 (m, 6 H), 2.20–2.50 (m, 2 H), 3.33 (d, $J$ = 1 Hz, 2 H), 3.33–3.67 (m, 1 H), 3.68 (s, 3 H), 4.36–4.80 (m, 2 H), 9.78 (s, 1 H). Anal. Calcd for $C_{10}H_{17}NO_6S$: N, 5.01; S, 11.48. Found: N, 4.81; S, 11.38. For the conversion of this sample to 17, essentially the same procedure was applied as described for the synthesis of 5. Column chromatography (6:4 hexane–ethyl acetate) of the crude product gave 17 as a semisolid: IR (neat) 3280, 2940, 1740, 1660, 1555, 1445, 1380, 750, 705 $cm^{-1}$; NMR ($CDCl_3$) δ 1.15–1.80 (m, 6 H), 2.12–2.40 (m, 2 H), 2.95–3.45 (m, 5 H), 3.64 (s, 3 H), 3.72 (s, 3 H), 4.30–4.50 (m, 2 H), 4.65–4.95 (m, 1 H), 6.72–7.00 (br s, 1 H), 7.00–7.40 (m, 5 H). Anal. Calcd for $C_{20}H_{28}N_2O_7S$: N, 6.36; S, 7.28. Found: N, 6.10; S, 7.24. Addition of $Eu(fod)_3$ (60 mol %) to 17 dissolved in $CDCl_3$ gave rise to two separated singlets for the methoxy group (possibly of the phenylalanine part). From the integration ratio of these peaks the enantiomeric excess was calculated as 37%.

**Determination of the Configuration of 13.** A racemic sample of 13 was prepared by stirring a mixture of 1.47 g (16 mmol) of 1, 2.81 g (15 mmol) of 10, 1.79 g (16 mmol) of triethylenediamine, and 100 mL of toluene for 1 h at room temperature under an

atmosphere of nitrogen. Workup of the reaction mixture followed by column chromatography (7:4 hexane–ethyl acetate) gave 2.86 g (68%) of racemic **13**. To a solution of 2.51 g (9 mmol) of racemic **13** in 10 mL of ethyl acetate was added 1.10 g (9.1 mmol) of (+)-α-methylbenzylamine, and the resulting solution was stirred for 10 min at room temperature. After addition of 100 mL of ether, the mixture was cooled with a dry ice/acetone bath. The precipitates were collected, washed with ether, and dried to give 3.33 g (93%) of the salt **16**. Recrystallization of this salt (2.44 g) from ethyl acetate gave 0.46 g of crystals, which were, according to Field,[1e] mainly composed of (*S*)-**13**. Treatment of the crystals with a mixture of 30 mL of 5% aqueous $KHSO_4$ and 30 mL of ethyl acetate for 10 min gave, after workup, 0.28 g of **13** with $[\alpha]_D$ −8.3° (*c* 1.042, benzene). Therefore, (−)-**13** was concluded to have an *S* configuration. From the mother liquor of recrystallization was recovered 1.21 g of **13** with $[\alpha]_D$ +2.1° (*c* 1.045, benzene) by treating it with 20 mL of 5% aqueous $KHSO_4$ for 10 min.

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**Registry No.** **1**, 68-11-1; **2**, 102-96-5; (+)-**3**, 76665-77-5; (−)-**3**, 76665-78-6; (+)-**3** acid chloride, 76665-79-7; (−)-**3** acid chloride, 76665-80-0; **4**, 76741-87-2; **5** (isomer 1), 76665-81-1; **5** (isomer 2), 76665-82-2; **6**, 2365-48-2; (+)-**7**, 76665-83-3; **8**, 3316-24-3; **9**, 705-60-2; **10**, 61379-36-0; (+)-**11**, 76665-84-4; (−)-**11**, 76665-85-5; **12**, 76665-86-6; (±)-**13**, 61379-25-7; (*R*)-**13**, 61379-30-4; (*S*)-**13**, 69088-64-8; (+)-**14**, 76665-87-7; **15**, 76665-88-8; (*S*)-**16**, 69088-65-9; **17** (isomer 1), 76665-89-9; **17** (isomer 2), 76665-90-2; L-phenylalanine methyl ester HCl, 7524-50-7.

# 1-Thio-Substituted Cyclopropylphosphonium Salts: Reagents for Pentannulation Reactions

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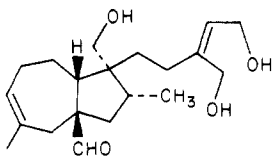
The preparation and pentannulation reactions of 1-(phenylthio)-, 1-(methylthio)- and 1-(isopropylthio)-cyclopropylphosphonium fluoborates are described. As part of a synthetic approach to portulal, a plant-growth regulator, 2-(carbomethoxy)-4-methylcyclohept-4-en-1-one is converted to its bicyclo[5.3.0]decenone derivative. This annulation reaction illustrates the synthetic application and limitations of the 1-thio-substituted cyclopropylphosphonium reagents.

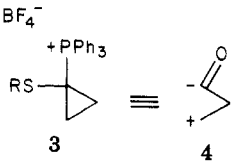
In conjunction with the synthesis of hydroazulene natural products such as portulal,[1] **1**, we have been interested




**1**

in the efficient annulation of cyclopentanone ring systems that bear a functionalized carbon atom at the bridgehead position. Methodology for the one-step annulation of β-keto esters[2] to cyclopentanone precursors was lacking prior to our study. Ring-fused cyclopentanones **2** can be valuable precursors for further elaboration to natural products by α-alkylation and/or geminal functionalization as outlined in Scheme I.

Our design of a three-carbon synthon of structure **3** that is equivalent to a cyclopropane zwitterion **4** was based on (1) the facile ring opening of activated cyclopropanes by nucleophiles[3] and (2) an umpolung reactivity[4] for an incipient acyl anion equivalent.




In a preliminary report,[5] we have described 1-(phenylthio)cyclopropylphosphonium fluoborate as an efficient pentannulation reagent. In one step, reagent **3** (R = Ph) reacts with enolates of β-keto esters to form 1-(phenylthio)cyclopentenes in good to high yield. The vinyl sulfide products were then hydrolyzed to the β-carboxycyclopentanones with hydrochloric acid (Scheme II). Since none of the milder mercury-catalyzed methods for hydrolysis of vinyl sulfides[6] were effective and only HCl hydrolysis of aryl vinyl sulfides worked in our hands, we sought new reagents of **3** in which R was an alkyl group. Alkyl vinyl sulfides are usually hydrolyzed to ketones under milder conditions.

In this report, we describe the preparation of 1-methylthio (**3b**) and 1-isopropylthio (**3c**) derivatives of **3**

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