to the flask, and the assembly was immersed in an oil bath heated to 100 °C. The slurry was stirred at 100 °C for 48 h and then allowed to cool to room temperature. The reaction was quenched by addition of deuterium oxide (5 mL) and worked up in the usual manner. NMR integration of a VPC[24] collected sample of the product (**4a**) showed no evidence for deuterium incorporation.

Reduction of a Mixture of 2a and 3a with $LiAlH_4$ in DME-d_{10}. A 0.35-g (2.1 mmol) sample of monochlorides **2a** and **3a** (75:25), 0.441 g (11.6 mmol) of $LiAlH_4$, and 5 mL of DME-d_{10} (Merch, Sharp and Dohme Canada) were placed in a 25-mL flask equipped with a reflux condenser and a drying tube. The flask was immersed in an oil bath heated to 100 °C. The slurry was stirred at 100 °C for 50 h, cooled, quenched with water, and worked up in the usual manner. An NMR of the crude product (**4a**) showed no evidence of deuterium incorporation.

Registry No.—**1a**, 3591-42-2; **1b**, 69912-46-5; **2a**, 69912-47-6; **2b**, 69912-48-7; **2c**, 69912-49-8; **3a**, 69912-50-1; **3b**, 69979-97-1; **4a**, 2214-14-4; **4b**, 40474-25-7; **5**, 768-00-3; **6**, 16917-35-4; **7b**, 69912-51-2; chloroform, 67-66-3; lithium aluminum deuteride, 14128-54-2.

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(23) A 13 ft × 0.25 in. column packed with 20% DEGS on 80–100 mesh Chromosorb W at an oven temperature of 160 °C was used for VPC analyses.
(24) An 8 ft × 0.75 in. column packed with 20% DEGS on 45–60 mesh Chromosorb W at an oven temperature of 160 °C with a Helium flow rate of 600 mL/min was used for preparative VPC separations.
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Asymmetric Induction in the Michael Reaction

K. Hermann[1] and Hans Wynberg*

Department of Organic Chemistry, The University, Groningen, The Netherlands

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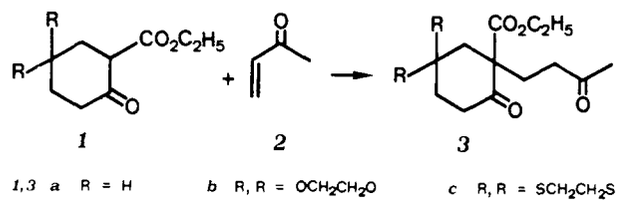
Using cinchona alkaloids (**6, 7**) and derivatives thereof as catalysts in nonpolar solvents, optically active Michael adducts were obtained when cyclohexanone derivates **1a–1c** and the indanone derivative **4** were used as donors and methyl vinyl ketone as the acceptor. The absolute configuration of the adducts was determined. The conversion of the Michael adducts to decalones of type **14a** suggests a synthetic strategy adaptable to the synthesis of chiral terpenes, steroids, and related natural products.

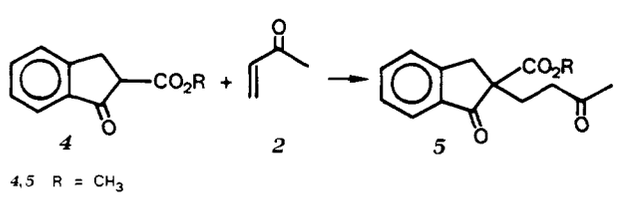
The preparation of optically active compounds by asymmetric induction in C–C bond formation is of primary importance for the synthesis of pharmacologically active compounds such as sesquiterpenes and steroids. Despite considerable efforts in this field, relatively few reactions are known which proceed in reasonable chemical and optical yields.[2-5]

Scheme I



1 2 3

1,3 a R = H b R, R = OCH_2CH_2O c R, R = SCH_2CH_2S



4 2 5

4,5 R = CH_3

The possibility of preparing optically active Michael addition products by use of a chiral basic catalyst was first reported in 1973.[6] In a brief communication from our laboratory, the use of cinchona alkaloids as catalysts in Michael reactions was described (enantiomeric excess up to 71%),[7] while more recently we showed that certain polymer-bound alkaloid derivatives are poor catalysts in reactions of this type.[8]

In the present more systematic study we disclose the results of the alkaloid-catalyzed asymmetric Michael reactions summarized in Scheme I. In addition to testing the influence of variations in the structure of the chiral catalyst, the solvent, and the reaction temperature, we focused our attention on an unambiguous determination of the enantiomeric excess and tried to settle the absolute configuration of the preferentially formed products.

Catalysts. Seven different catalysts were tested. Quinine (**6**), quinidine (**7**), and eucupine (**8**) were from commercial sources, and *O*-acetylquinine (**9**)[9] and quinine methiodide (**10**)[10] were synthesized according to known procedures. Quinine methohydroxide (**11**)[10] and quinidine methohydroxide (**12**)[10] were prepared with the aid of an ion exchange resin from the corresponding iodides and used as about 0.05 or 0.08 M solutions in ethanol (for details, see Experimental Section).

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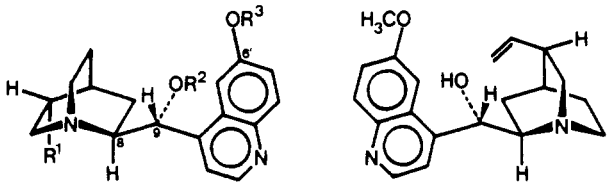
Table I. Michael Reactions of 1a–1c[a]

entry	cyclohexanone derivative (mmol)	enone (mmol)	catalyst (mmol)	solvent (% C_2H_5OH)	total volume, mL	temp, °C	reaction time, h (constant rotation at 578 nm, h)	Michael adduct no.	% chemical yield	$[\alpha]^{RT}_{578}$,[b] deg	% optical purity[c] (config.)
1	**1a** (2.0)	**2** (3.1)	**11** (0.025)	CH_3CN (2)	25	+25	118[d] (–)[e]	**3a**	*d*	0	0
2	**1a** (2.1)	**2** (3.3)	**11** (0.025)	dioxane (2)	25	+25	67 (>1.5)	**3a**	99	+4.2	5 (*R*)
3	**1a** (2.1)	**2** (3.1)	**11** (0.025)	CH_2Cl_2 (2)	25	+25	43 (≤20)	**3a**	89	+6.2	8 (*R*)
4	**1a** (2.0)	**2** (3.1)	**11** (0.025)	benzene (2)	25	+25	74 (>2.5)	**3a**	99	+8.2	10 (*R*)
5	**1a** (2.0)	**2** (3.1)	**11** (0.025)	toluene (2)	25	+25	18 (>1)	**3a**	90	+8.5	10 (*R*)
6	**1a** (2.0)	**2** (3.1)	**11** (0.025)	CCl_4 (2)	25	+25	1 (¾)	**3a**	98	+13.7	17 (*R*)
7	**1a** (2.0)	**2** (3.1)	**11** (0.025)	CCl_4 (2)	25	+25	19 (¾)	**3a**	100	+13.7	17 (*R*)
8	**1a** (1.9)	**2** (3.1)	**11** (0.04)	CCl_4 (2)	25	+25	17 (–)[e]	**3a**	97	+14.6	18 (*R*)
9	**1a** (2.0)	**2** (3.1)	**11** (0.025)	CCl_4 (5)	10	+25	⅘ (⅖)	**3a**	*e*	+12.0	15 (*R*)
10	**1a** (2.0)	**2** (3.1)	**11** (0.025)	CCl_4 (2)	25	0	69 (–)[e]	**3a**	88	+17.0	21 (*R*)
11	**1a** (20)	**2** (31)	**11** (0.25)	CCl_4 (2)	250	−16	40[f] (–)[e]	**3a**	99	+17.3	21 (*R*)
12	**1a** (2.0)	**2** (3.1)	**11** (0.025)	CCl_4 (2)	25	−20	72[f] (–)[e]	**3a**	96	+17.8	22 (*R*)
13	**1a** (2.0)	**2** (3.1)	**12** (0.04)	CCl_4 (2)	25	+25	⅓ (<⅓)	**3a**	99	−7.1	9 (*S*)
14	**1b** (2.0)	**2** (3.1)	**11** (0.04)	CCl_4 (2)	25	+25	½ (1/15)	**3b**	100	+8.7	20 (*S*)
15	**1b** (2.0)	**2** (3.1)	**11** (0.04)	CCl_4 (2)	25	−21	88[f] (–)[e]	**3b**	100	+11.2	25 (*S*)
16	**1c** (2.0)	**2** (3.1)	**11** (0.04)	CCl_4 (2)	25	+25	1 (¾)	**3c**	100	+4.3	15 (*S*)
17	**1c** (2.0)	**2** (3.1)	**11** (0.04)	CCl_4 (2)	25	−20	88[f] (–)[e]	**3c**	99	+6.1	21 (*S*)

[a] For a detailed description of the performance of the experiments, see the Experimental Section. [b] Optical rotations were taken in CCl_4 (*c* 1.8–2.6). [c] Based on the calculated values for the pure enantiomers (see Table II). [d] Reaction stopped before completion; according to ^1H NMR, a 4:1 mixture of **3a** and **1a** was obtained. [e] Not determined. [f] Reaction mixture was kept at 25 °C for 1–2.5 h before workup.

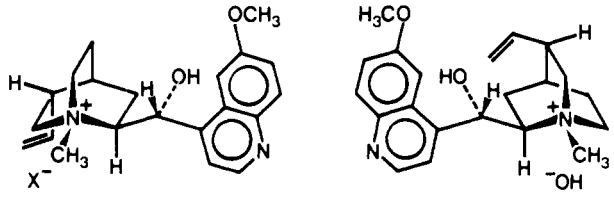


6 $R^1 = HC{=}CH_2$, $R^2 = H$, $R^3 = CH_3$

8 $R^1 = H_2CCH_3$, $R^2 = H$, $R^3 = CH_2CH_2CH(CH_3)_2$

9 $R^1 = HC{=}CH_2$, $R^2 = COCH_3$, $R^3 = CH_3$

7



10 $X^- = I^-$

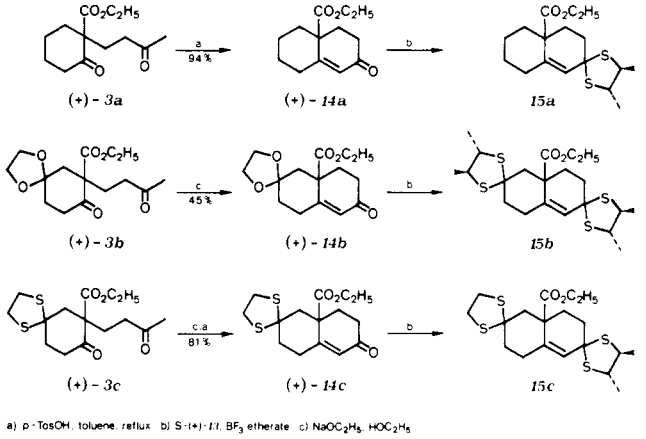
11 $X^- = HO^-$

12

Results

Michael Reactions of the Cyclohexanone Derivatives 1a–1c. In the presence of either quinine (**6**), eucupine (**8**), or sparteine, **1a**[11] did not react at all or only extremely slowly with the enone **2** to give **3a**. Since it was known that this reaction proceeds in 91% yield when benzyltrimethylammonium hydroxide (Triton B) is used as a base,[12] we tried quinine methohydroxide (**11**) as a catalyst. Table I illustrates that conditions were found which led to (+)-**3a** in almost quantitative chemical yield and optical purities up to 22% (entry 12). When quinine methohydroxide (**12**) was used in place of **11**, (−)-**3a** was formed (entry 13, Table I). As expected, **1b**[13] and the new β-keto ester **1c** did not react with **2** in the presence of quinine (**6**). Quinine methohydroxide (**11**) led to the formation of (+)-**3b** and (+)-**3c**, respectively, in quantitative chemical yields and more than 20% optical purities (entries 15 and 17, Table I). Since none of the Michael adducts **3a–3c** were known in enantiomerically pure form, the specific rotations of the pure enantiomers had to be determined. For this purpose, the new method for the determination of enantiomeric purities developed in our laboratory[14,15] was used. This method is based on the transformation of a mixture of enantiomeric ketones with (*S*)-(+)-butane-2,3-dithiol (**13**)[16] to a mixture of diastereomeric dithioacetals. The ratio of diastereomers is determined by integration of the ^1H noise-decoupled ^{13}C NMR spectrum. The reactions performed are summarized in Scheme II,[17] and Table II contains the numerical results.

Scheme II



The absolute configuration of the preferentially formed enantiomers of the Michael adducts was tentatively assigned by use of the chiroptical properties of their cyclization products (+)-**14a**–(+)-**14c** (Figures 1 and 2). It has been shown that the sign of the Cotton effect for the n → π* transition (R band) of bicyclic enones of this type depends on their conformation.[18] Inspection of Dreiding models of (+)-**14b** and (+)-**14c** suggests that the conformation II with a planar enone system is strongly favored over conformation I (nonplanar enone system). From the positive R band CD spectra of (+)-**14b** and

Table II. Determination of the Specific Rotation of the Enantiomerically Pure Michael Adducts 3a–3c

	Michael adduct		cyclization product		dithioacetal			specific rotation calcd. for enantiomerically pure Michael adduct	
					^{13}C NMR signals used for determination	%			
entry	no.	$[\alpha]^{RT}_{578}$ (c in CCl_4), deg	no.	$[\alpha]^{RT}_{578}$ (c in CCl_4), deg	no.	of ee, ppm (% ee)[a]	ee	no.	$[\alpha]^{RT}_{578}$ calcd, deg
1	(+)-**3a**	+14.6 (2.1)	(+)-**14a**	+37.4 (2.2)	**15a**	138.08/137.65 (18)	18	(+)-**3a**	+81
						61.53/60.46 (20)			
						57.08/56.64 (16)			
						38.99/38.44 (17)			
						37.97/37.35 (18)			
						35.37/34.55 (20)			
						18.22/15.43 (16)			
						17.37/16.49 (16)			
2	(+)-**3b**	+8.7 (2.0)	(+)-**14b**	+28.7 (2.4)	**15b**	57.36/56.77 (22)	20	(+)-**3b**	+44
						56.32/55.38 (18)			
						55.71/54.95 (20)			
						54.69/54.44 (20)			
						47.68/47.23 (24)			
						43.79/42.91 (22)			
						39.22/38.33 (16)			
						36.50/35.98 (18)			
3	(+)-**3c**	+6.1 (2.6)	(+)-**14c**	+16.9 (2.4)	**15c**	57.17/56.57 (24)	21	(+)-**3c**	+29
						36.35/35.61 (18)			
						18.66/16.33 (20)			
						17.92/15.28 (22)			

[a] The ^{13}C NMR spectra were measured by H. Hiemstra on a Varian XL 100 spectrometer at 25.16 MHz.

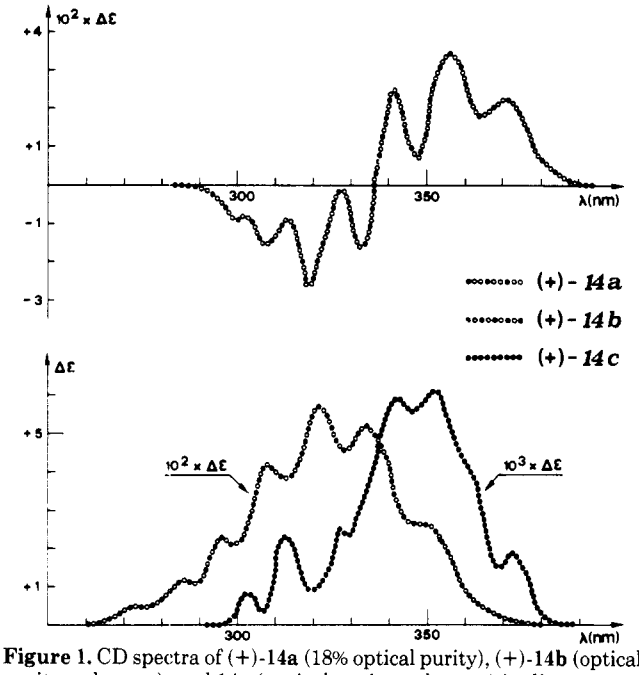
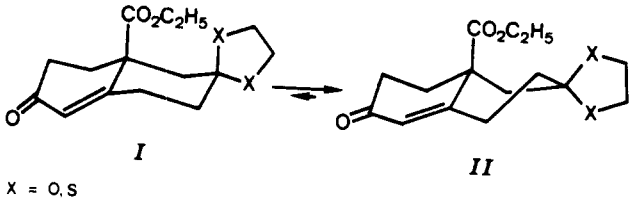


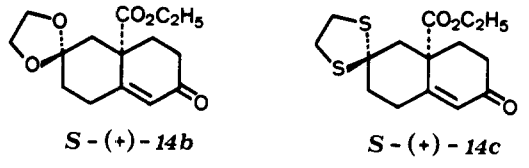
Figure 1. CD spectra of (+)-**14a** (18% optical purity), (+)-**14b** (optical purity unknown), and **14c** (optical purity unknown) in dioxane.



X = O, S

(+)-**14c** (Figure 1), the absolute configurations shown in Chart I can be deduced by application of the octant rules modified for α,β-unsaturated ketones.[18]

Chart I



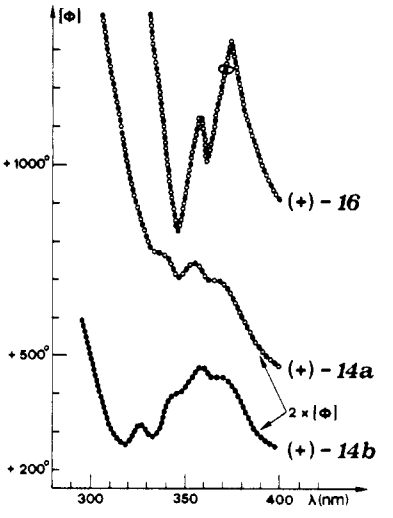
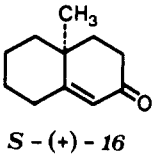
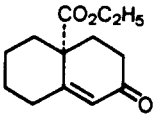


Figure 2. ORD spectra of (*S*)-(+)-**16** (reconstructed from ref 19), (+)-**14a** (18% optical purity), and (+)-**14b** (optical purity unknown in dioxane.

The CD spectrum of (+)-**14a** has negative and positive partial bands, probably due to conformational equilibria. The shape of the ORD spectra of (+)-**14a** and (+)-**14b** is similar to the shape of the ORD spectrum of (*S*)-(+)-**16**[19] (Figure 2).



S - (+) - **16**



R - (+) - **14a**

This supports the absolute configuration of (+)-**14b** deduced from the CD spectrum and leads to the suggestion that (+)-**14a** has the *R* configuration at C(4a).[20]

We therefore propose that the preferentially formed adducts in the Michael reactions catalyzed by **11** have the absolute configurations shown in Chart II.

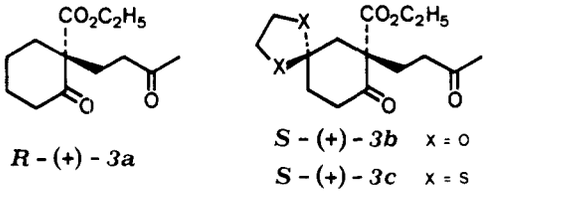
Michael Reactions of the Indanone Derivative 4. In the presence of cinchona alkaloids, the indanone derivative **4**[22]

Table III. Michael Reactions of 4[a]

entry	4, mmol	2, mmol	catalyst (mmol)	solvent (% C_2H_5OH)	total volume, mL	temp, °C	reaction time, h (constant rotation at 578 nm, h)	Michael adduct 5: % chemical yield	Michael adduct 5: $[\alpha]^{RT}_{578}$,[b]	Michael adduct 5: % optical purity[c] (config.)
1	20	31	**6** (0.21)	CCl_4 (0)	250	−21	185[d] (−)[e]	99	−58.8	76 (*S*)
2	2.0	3.1	**6** (0.02)	CCl_4 (0)	25	+25	18.5 (16.5)	98	−46.3	60 (*S*)
3	2.0	3.1	**6** (0.02)	toluene (0)	25	+25	48 (>34)	98	−40.7	53 (*S*)
4	2.0	3.1	**6** (0.02)	CCl_4 (2)	25	+25	68.5 (67)	97	−25.4	33 (*S*)
5	2.0	3.1	**8** (0.02)	CCl_4 (0)	25	+25	14 (6)	99	−46.3	60 (*S*)
6	2.2	3.7	**11** (0.02)	toluene (1)	25	+25	2/5 (1/5)	100	−11.7	15 (*S*)
7	2.0	3.1	**10** (0.02)	toluene (0)	25	+25	116 (−)[e]	100	−9.0	12 (*S*)
8	2.0	3.1	**9** (0.02)	CCl_4 (0)	25	+25	890 (−)[f]	41	+3.9	5 (*R*)
9	2.0	3.1	**9** (0.02)	CCl_4 (2)	25	+25	940 (−)[f]	53	+14.5	19 (*R*)
10	4.0	6.2	**7** (0.04)	CCl_4 (0)	50	−21	240[d] (−)[e]	100	+52.9	69 (*R*)

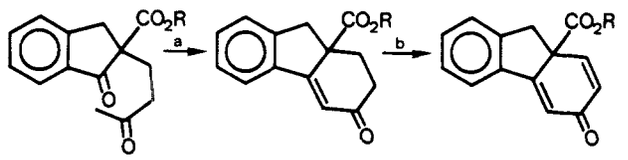
[a] For a detailed description of the performance of the experiments, see the Experimental Section. [b] Optical rotations were taken in benzene (*c* 2.0–2.8). [c] Based upon the published value, $[\alpha]^{RT}_{578}$ −77° (*c* 2, benzene), for enantiomerically pure (−)-**5**.[7] [d] Reaction mixture was kept at 25 °C before workup. [e] Not determined. [f] Reaction was stopped before reaching constant rotation.

Chart II



***R*-(+)-3a** ***S*-(+)-3b** X = O ***S*-(+)-3c** X = S

Scheme III



(−)-5 **(+)-19** **(−)-20** R = CH_3

a) $NaOCH_3$, $HOCH_3$ b) SeO_2, $(CH_3)_3COH$

readily reacts with the enone **2** to form the optically active Michael adduct **5** in good optical and chemical yields.[7] The enantiomer formed in excess depends on the choice of the catalyst: quinine (**6**) and cinchonidine produced levorotatory **5**, and cinchonine led to dextrorotatory **5**. The optical rotation of enantiomerically pure (−)-**5** was determined [$[\alpha]^{RT}_{578}$ −77° (*c* 2, benzene)[7]].

We felt that the forementioned reaction would be better suited to gain more insight into the nature of the activated complex of Michael reactions catalyzed by chiral bases than the reactions of the much less reactive cyclohexanone derivatives **1a–1c**. That this is true can be seen from the results of the Michael reactions of **4** catalyzed by cinchona alkaloids and derivatives thereoff collected in Table III. Except for the reactions catalyzed by *O*-acetylquinine (**9**) (entries 8 and 9), all reactions gave virtually quantitative chemical yields. The *S*/*R* ratios of **5** ranged from 88:12 (entry 1) to 15:85 (entry 10).

In order to determine the absolute configuration of the preferentially formed enantiomer of **5**, (−)-**5** was converted to the enone (+)-**19** and to the cross-conjugated (−)-**20** (Scheme III). The CD spectra of both (+)-**19** and (−)-**20** show a positive Cotton effect for the n → π* transition (R band) at about 360 nm (Figure 3). Inspection of Dreiding models of **19** shows that the conformation is strongly favored in which the oxygen atom and all of the carbon atoms except C(1) of the cyclohexenone ring are in the same plane. Provided that the carbomethoxy group has no dramatic influence on the Cotton

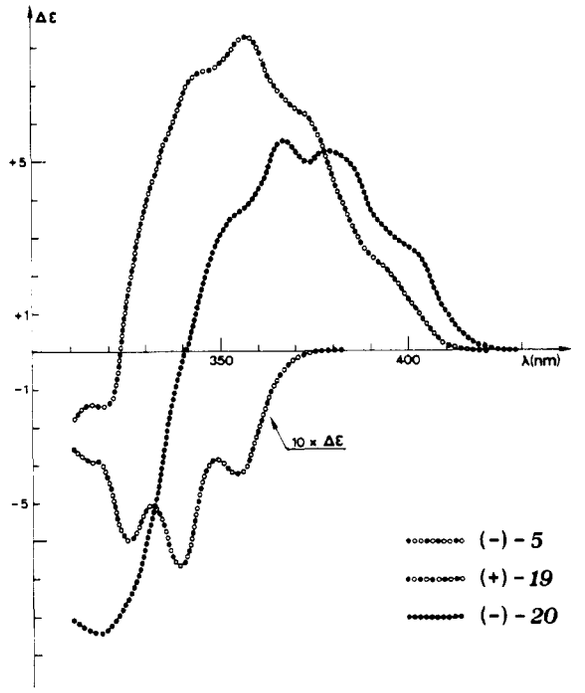


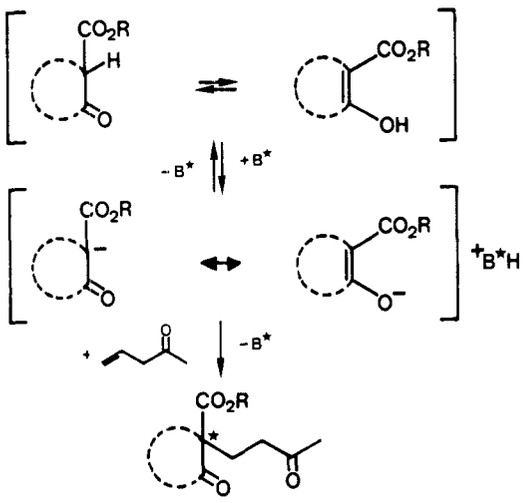
Figure 3. CD spectra of (−)-**5** (78% optical purity), (+)-**19** (optical purity unknown), and (−)-**20** (optical purity unknown) in dioxane.

effect,[20] application of Snatzke's modified octant rules[18,23] leads to the absolute configuration of (+)-**19** depicted in Figure 4. The carbomethoxy group has no influence on the chiroptical properties of **20** because it lies in the nodal plane of the octant. Here, the modified octant rules[18,23] allow an unambiguous structure assignment of (−)-**20** (see Figure 4). On the basis of this evidence, (−)-**5** has the *S* configuration at C(2).

Discussion

We will limit our discussion almost entirely to the Michael reactions of the indanone derivative **4**, although the difference in reactivity between **4** and the cyclohexanone derivatives **1a–1c** seems to be striking. In light of the fact that 2-carbethoxycyclopentanone is not only a stronger acid than 2-carbethoxycyclohexanone but that the corresponding five-membered enolate also is reacting much faster with methyl iodide than the six-membered one,[24] this difference is easily understood. In addition, both types of reactions gave comparable optical yields when similar conditions were used

Scheme IV



(entry 5 in Table I and entry 6 in Table III).

The kinetics of the reaction between 2-carbethoxycyclohexanone (**1a**) and the enone **2** catalyzed by alkoxide ions have been studied.[25] In analogy to these results and in accordance with our own findings, we assume that the reversible formation of the enolate is followed by an irreversible alkylation (Scheme IV).

From Table III, several conclusions concerning the role of the chiral catalyst can be drawn. (1) The spatial arrangement of the substituents at C(8) and C(9) is mainly responsible for the stereochemistry of the Michael adduct. Quinine (**6**, 8*S*,9*R*) and the diastereomeric quinidine (**7**, 8*R*,9*S*) led to the preferential formation of (*S*)-(−)-**5** (entry 1) and (*R*)-(+)-**5** (entry 10), respectively, in similar optical purity. (2) The hydroxyl group at C(9) is crucial for the success of the reaction. Its acetylation not only caused a strong decrease in reaction velocity, but the optical purity of **5** was also lowered (compare entries 2 and 8). (3) The role of the aromatic part of the catalysts is not clear. Introduction of a bulkier substituent at C(6′) had no influence on the asymmetric induction (compare entries 2 and 5); when the quinuclidine nitrogen was blocked as in **10**, the quinoline nitrogen was basic enough to secure a reaction, but the reaction velocity and the asymmetric induction were lower (entry 7).

In addition to the influence of the chiral catalyst, the influence of the temperature and the solvent must be considered. When the reaction temperature was lowered, the enantiomeric excess increased (entries 8 and 12 in Table I, entries 1 and 2 in Table III). Addition of as little as 2% of ethanol to CCl_4 almost halved the optical purity and slowed down the reaction velocity (entries 2 and 4 in Table III). Unfortunately, the reactions of the cyclohexanone derivatives **1a–1c** with the enone **2** catalyzed by the methohydroxides **11** and **12** had to be performed in the presence of a small amount of ethanol; omission of ethanol led to heterogenous mixtures and no or at least very slow reactions. Additional information came from the reactions of **1a**: in acetonitrile–2% ethanol, a slow reaction with no asymmetric induction was observed; the reaction in CCl_4–2% ethanol was fast and gave 17% asymmetric induction (entries 1 and 6 in Table I).

An apolar solvent obviously favors the formation of a tight ion pair of the protonated catalyst and the enolate ion. The hydroxyl group of the catalyst probably forms a hydrogen bond with the enone, bringing it into position and activating the system toward 1,4-addition and the preferential formation of one enantiomer.

Addition of ethanol would result in at least a partial destruction of the hydrogen bonds.

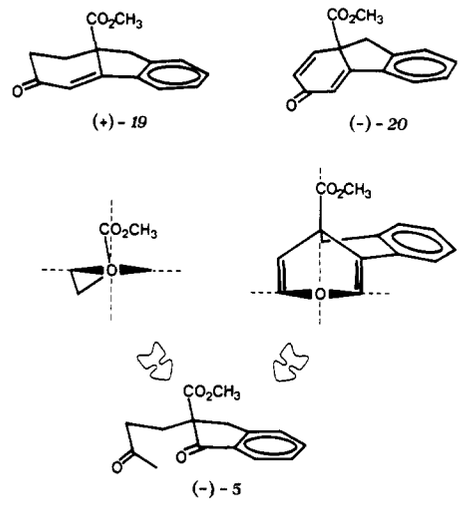


Figure 4. Structure determination of (−)-**5**. Stereo formulas of (+)-**19** and (−)-**20** with corresponding octant projections.

Further speculations seem to be premature. We do not yet know exactly which parts of the catalysts play a role in the asymmetric induction, and the preferred conformations of the cinchona alkaloids and their derivatives are unknown too.[26] Our efforts to change the asymmetric induction by the introduction of a bulky group in the 4 position of **1a** gave also a negative result; the optical purities of the Michael adducts of **1b** and **1c** were almost the same as the optical purity of the adduct of **1a** (entries 8, 14, and 16, Table I). Finally, we would like to stress the point that nitrogen-containing bases of natural origin are of moderate strength. Therefore, they are of limited use as bases in asymmetric synthesis. To our knowledge, the methohydroxides **11** and **12**, being much stronger bases, have not been used in asymmetric reactions before.[29] Their utilization in other asymmetric reaction certainly merits investigation.

Experimental Section

Instrumentation. Melting points were determined on a Mettler FP 2 melting point apparatus. All melting and boiling points are uncorrected. The temperatures cited for short-path distillations refer to the maximum temperature attained by the air chamber during the distillation. Optical rotations were measured at room temperature (RT) on a Perkin-Elmer 241 polarimeter with 1-dm cells. UV spectra were measured on a Beckman 24 spectrophotometer and IR spectra on an Unicam II spectrophotometer. ^1H NMR spectra were recorded at either 60 (Varian A-60 spectrometer) or 100 MHz (Varian XL-100 spectrometer) as indicated; chemical shifts are reported in δ units (ppm) relative to Me_4Si (δ 0). ORD and CD spectra were measured on a Cary 60 recording spectropolarimeter with a Cary 6002 CD accessory.

Solvents. All solvents used for Michael reactions were dried according to standard procedures and kept over molecular sieves.

Substrates. Commercial 3-buten-2-one (**2**) was distilled at reduced pressure and stabilized by addition of about 0.1% of hydroquinone. Published procedures were used for the synthesis of ethyl 2-oxocyclohexanecarboxylate (**1a**),[11] ethyl 8-oxo-1,4-dioxaspiro[4.5]decane-7-carboxylate (**1b**),[30] and methyl 2,3-dihydro-1-oxo-1*H*-indene-2-carboxylate (**4**).[22,31]

Ethyl 8-Oxo-1,4-dithiaspiro[4.5]decane-7-carboxylate (1c). To a stirred solution of 23.1 g (0.10 mol) of diethyl 4-oxoheptanedioate in 15 mL of 1,2-ethanedithiol cooled to 0 °C was added 16 mL of BF_3 etherate. After the mixture was stirred for 30 min, the ice bath was removed and the solution was left at room temperature for 18 h. A 300-mL amount of 10% aqueous NaOH and 100 mL of toluene were then added, the organic layer was separated, and the aqueous layer was extracted twice with 100 mL of toluene. The combined extracts were washed with three portions of 100 mL of H_2O and evaporated. Distillation (150 °C at 0.05 mm) of the residue gave 26.5 g (86%) of diethyl 1,3-dithiolane-2,2-dipropanoate (**21**). Analytically pure **21** was obtained by short-path distillation (150 °C at 0.05 mm): IR (neat) 2995, 2945, 1738, 1453, and 1180 cm^{-1}; NMR (60 MHz, CCl_4) δ 4.07

(q, 4, J = 7 Hz), 3.26 (s, 4), 1.95–2.72 (m, 8), and 1.24 (t, 6, J = 7 Hz). Anal. Calcd for $C_{13}H_{22}O_4S_2$: C, 50.95; H, 7.24; S, 20.92. Found: C, 50.85; H, 7.26; S, 20.81.

To a stirred solution of 18.8 g (0.06 mol) of **21** in 100 mL of dry ether was added 2.64 g (about 0.06 mol) of a 55–60% NaH suspension in oil. The mixture was warmed briefly. A vigorous reaction ensued. After 10 min, 100 mL of ether was added and the mixture was left at room temperature for 2.5 days. Careful addition of 10 mL of acetic acid followed by 25 mL of H_2O dissolved all of the solid material. The organic layer was separated and washed twice with saturated aqueous $NaHCO_3$ and three times with H_2O. The oil which remained after evaporation of the ether was distilled (160 °C at 0.01 mm) to yield 10.0 g (63%) of **1c** as a viscous oil which solidified (mp 46–51 °C) on addition of ethanol. An analytical sample was prepared by short-path distillation (160 °C at 0.01 mm): mp 47–50 °C; IR (neat) 2950, weak absorptions at 1742, 1720 (keto ester), strong absorptions at 1660, 1620 (enol), 1290, and 1220 cm^{-1}; H NMR (100 MHz, CCl_4) of enolized **1c** (about 90% by comparison of the integration of the triplets displayed by the ester groups) δ 12.12 (s, 1), 4.19 (q, 2, J = 7 Hz), 3.30 (br s, 4), 2.79 (br s, 2), 2.3–2.6 (m, 2), 2.0–2.2 (m, 2), and 1.30 (t, 3, J = 7 Hz); signals at δ 3.36 (s, 4) and 1.26 (t, 3, J = 7 Hz) can be assigned to **1c**. Anal. Calcd for $C_{11}H_{16}O_3S_2$: C, 50.74; H, 6.20; S, 24.63. Found: C, 51.00; H, 6.20; S, 24.58.

Chiral Catalysts. Quinine (**6**) was purified according to the method of Thron and Discherl:[32] mp 175–177 °C; $[\alpha]^{RT}_D$ −167° (c 2.0, C_2H_5OH) (lit.[33a] −169°). Commercial samples of quinidine (**7**) and eucupine (**8**) were used without further purification. **7**: mp 171–172 °C; $[\alpha]^{RT}_D$ +239° (c 1.0, C_2H_5OH) (lit.[33b] +258°). **8**: mp 152–154 °C (lit.[33c] 152 °C); $[\alpha]^{RT}_D$ −98° (c 0.1, toluene). The procedure of Pettit and Gupta[9] was used for the synthesis of *O*-acetylquinine (**9**): mp 117–119 °C; $[\alpha]^{RT}_D$ −54.2° (c 1.4, CH_3OH) (lit.[9] −32°).[34] Quinine methiodide (**10**) and quinidine methiodide (**22**), synthesized according to Major and Finkelstein,[10] were recrystallized from H_2O. **10** had mp 229 °C dec (lit.[27] 226 °C), and **22** had mp 236–237 °C dec (lit.[33b] 248 °C). Quinine methohydroxide (**11**)[10] and quinidine methohydroxide (**12**)[10] were synthesized in the same way. A 10-g amount of Amberlite IRA-401, after being washed with 500 mL each of 1 N aqueous NaOH, H_2O, 1 N hydrochloric acid, H_2O, C_2H_5OH, and H_2O, was conditioned with 10 g of NaOH dissolved in 225 mL of H_2O, followed by 250 mL each of H_2O and dry C_2H_5OH. A 2.0-mmol amount of **10** (or **22**) dissolved in 250 mL of dry C_2H_5OH was applied on the column and eluted. An additional 250 mL of C_2H_5OH was used to wash the column. The eluates were collected under N_2 or Ar, concentrated below 25 °C under reduced pressure, and diluted with dry C_2H_5OH to 25.0 mL. The concentrations of alcoholic solutions of **11** and **12** were determined by titration with 0.0107 m hydrochloric acid: 0.08 M for **11** and 0.01 M for **12**. (The concentration of **12** was too high, probably due to some decomposition of the ion exchange resin. We therefore assumed the concentration of **12** to be about 0.08 M.) The ^1H NMR spectrum (100 MHz, CD_3OD) of **11** exhibited, besides the signals of the quinuclidine ring, the typical patterns of the substituted quinoline ring and the vinyl group, with signals at δ 6.12 (br s, 1), 3.96 (s, 3), and 3.40 (s, 3).

General Procedure for Michael Reactions. (See also Tables I and III for conditions and results.) Reactions at 25 °C were done in volumetric flasks kept in a thermostated bath. A solution of the α-keto ester (about 2 mL of solvent less than required) was brought to reaction temperature, the vinyl ketone and the catalyst were then added, and the flask was filled with solvent to the mark. After being thoroughly mixed, part of the reaction mixture was placed in a thermostated polarimeter cell and the reaction was followed polarimetrically at 578 nm whenever possible. After the time indicated in the tables, the reaction mixture was filtered through 8 g of silica. An additional 100 mL of ethyl acetate was used to elute all of the products. The residue obtained after concentration of the eluates was further purified by short-path distillation (120–180 °C at 0.1–0.001 mm). Reactions at temperatures below 25 °C were performed in a similar way but not followed polarimetrically.

Properties of the New Michael Adducts. Ethyl 8-Oxo-7-(3-oxobutyl)-1,4-dioxaspiro[4.5]decane-7-carboxylate (3b). An analytical sample was prepared by short-path distillation (130 °C at 0.001 mm): IR (neat) 2995, 1725, 1718, 1450, 1375, and 1040 cm^{-1}; NMR (60 MHz, CCl_4) δ 4.15 (q, 2, J = 7 Hz), 3.94 (br s, 4), 1.5–3.2 (m, 10), 2.07 (s, 3), and 1.29 (t, 3, J = 7 Hz). Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.02; H, 7.47.

Ethyl 8-Oxo-7-(3-oxobutyl)-1,4-dithiaspiro[4.5]decane-7-carboxylate (3c). An analytical sample was prepared by recrystallization from C_2H_5OH: mp 64–66 °C; $[\alpha]^{RT}_{578}$ +1.2° (c 2.0, CCl_4); IR (neat) 2995, 1725, 1718, 1440, 1378, 1224, 1110, and 1030 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 4.12 (q, 1, J = 7 Hz), 4.11 (q, 1, J = 7 Hz), 3.2–3.4 (m, 4), 1.5–3.1 (m, 10), 2.01 (s, 3), and 1.26 (t, 3, J = 7 Hz). Anal. Calcd for $C_{15}H_{22}O_4S_2$: C, 54.52; H, 6.71; S, 19.40. Found: C, 54.34; H, 6.63; S, 19.12.

Cyclization of the Michael Adducts 3a–3c. Ethyl 3,4,5,6,7,8-Hexahydro-2-oxo-4a(2*H*)-naphthalenecarboxylate (14a). A solution of 1.77 g (7.4 mmol) of **3a**, $[\alpha]^{RT}_{578}$ +14.6° (c 2.1, CCl_4), and 75 mg (0.4 mmol) of p-toluenesulfonic acid in 100 mL of toluene was heated at reflux in a flask equipped with a Dean-Stark trap. After 22 h, the reaction mixture was cooled, washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution, and concentrated at reduced pressure. Short-path distillation (130 °C at 0.1 mm) yielded 1.54 g (94%) of the known[12] enone **14a** as a colorless oil, $[\alpha]^{RT}_{578}$ +37.4° (c 2.2, CCl_4).

Ethyl 4′,6′,7′,8′-Tetrahydro-6′-oxospiro[1,3-dioxolane-2,2′-(1′*H*)-naphthalene]-8′a(3′*H*)-carboxylate (14b). To a solution of 595 mg (2.0 mmol) of **3b**, $[\alpha]^{RT}_{578}$ +8.70° (c 2.0, CCl_4), in 3 mL of dry C_2H_5OH, cooled to 0 °C, was slowly added a solution of $NaOC_2H_5$, freshly prepared from 48 mg (2.10 mmol) of Na and 2.5 mL of dry C_2H_5OH. The reaction mixture was stirred for 2 h at 25 °C, cooled again to 0 °C, and acidified by 0.20 mL (3.5 mmol) of acetic acid. The yellow solution was diluted with 50 mL of toluene and evaporated almost to dryness at reduced pressure. The residue was dissolved in 50 mL of toluene and 25 mL of H_2O. The organic phase was washed with saturated aqueous $NaHCO_3$ solution and H_2O. Concentration of the organic phase at reduced pressure gave a yellow oil which yielded 238 mg (43%) of spectroscopically pure **14b** after two short-path distillations (150 °C at 0.03 mm), $[\alpha]^{RT}_{578}$ +28.7° (c 2.4, CCl_4). **14b** solidified on standing. An analytical sample was prepared by recrystallization from C_2H_5OH and short-path distillation (130 °C at 0.005 mm): mp 72–74 °C; IR (neat) 2995, 1725, 1680, 1630, and 1460 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 5.95 (d, 1, J = 2 Hz), 4.22 (q, 1, J = 7 Hz), 4.18 (q, 1, J = 7 Hz), 3.8–4.1 (m, 4), 1.4–3.1 (m, 10), and 1.26 (t, 3, J = 7 Hz). Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.01; H, 7.34.

Ethyl 4′,6′,7′,8′-Tetrahydro-6′-oxospiro[1,3-dithiolane-2,2′-(1′*H*)-naphthalene]-8′a(3′*H*)-carboxylate (14c). The cyclization procedure outlined for **3a** was followed using 655 mg (1.98 mmol) of **3c**, $[\alpha]^{RT}_{578}$ +6.1° (c 2.6, CCl_4), and 25 mg of p-toluenesulfonic acid in 100 mL of toluene. A 596-mg amount (96%) of **14c**, $[\alpha]^{RT}_{578}$ +16.9° (c 2.4, CCl_4), was obtained after short-path distillation (185 °C at 0.05 mm) as a viscous oil which slowly solidified. An analytical sample was prepared by recrystallization from C_2H_5OH followed by short-path distillation (155 °C at 0.01 mm): mp 85–87 °C; IR (Nujol) 1708, 1672, and 1638 cm^{-1}; NMR (60 MHz, CCl_4) δ 5.82 (d, 1, J = 1.5 Hz), 4.18 (q, 2, J = 7 Hz), 3.2–3.5 (br s, 4), 1.7–3.2 (m, 10), and 1.30 (t, 3, J = 7 Hz). Anal. Calcd for $C_{15}H_{20}O_3S_2$: C, 57.66; H, 6.45; S, 20.52. Found: C, 57.47; H, 6.52; S, 20.50.

Illustrative Procedure for the Preparation of Dithioacetals 15a–15c. To a cooled solution of 312 mg (1.0 mmol) of **14c** in 187 mg (1.5 mmol) of (*S*)-(+)-butane-2,3-dithiol (**13**)[15,16] was added 0.60 mL of BF_3 etherate with stirring. After 2 h at room temperature, 10 mL of ether was added and the mixture was washed with 10% aqueous NaOH solution and H_2O. The organic phase yielded, after concentration at reduced pressure and drying at 0.001 mm, 421 mg (100%) of **15c** as an oil which was used without further purification for the determination of the enantiomeric excess (see Table II). (The IR spectrum of neat **15c** showed the complete absence of the α,β-unsaturated carbonyl group at 1672 cm^{-1}.)

Structure Determination of (−)-Methyl 2,3-Dihydro-1-oxo-2-(3-oxobutyl)-1*H*-indene-2-carboxylate [(−)-5]. Methyl 1,2,9,9a-Tetrahydro-3-oxo-3*H*-fluorene-9a-carboxylate (19). A suspension of 3.02 g (11.6 mmol) of (−)-**5**, $[\alpha]^{RT}_{578}$ −58.8° (c 2.1, benzene), in 60 mL of dry CH_3OH cooled to 0 °C was treated dropwise with a solution of $NaOCH_3$, freshly prepared by adding 7 mL of dry CH_3OH to 290 mg (12.6 mmol) of Na. After addition was complete, the reaction mixture was warmed to room temperature and stirring was continued for 2.5 h. Addition of 1.2 mL of acetic acid and 200 mL of toluene followed by concentration at reduced pressure and washing a toluene solution of the residue with H_2O, 0.1 N aqueous NaOH solution, and H_2O furnished, after concentration of the organic phase, a yellow oil which contained only about 30% of the desired product **19** (^1H NMR analysis). Repetition of the aforementioned procedure with 230 mg (10 mmol) of Na and 22 h of reaction time gave, after fractional recrystallization of the crude reaction product from CCl_4, two crops of colorless crystals, namely, 980 mg of **19**, $[\alpha]^{RT}_{578}$ +41° (c 2.1, benzene), and 236 mg of **19**, $[\alpha]^{RT}_{578}$ +313° (c 2.0, benzene), in 43% total yield. The second crop, further purified by short-path distillation (120 °C at 0.005 mm), was used for the oxidation to **20** and the UV and CD measurements. Two recrystallizations from CCl_4 of the first crop provided an analytically pure sample of **19**: mp 126–127

°C; IR (Nujol) 1720, 1660, and 1638 cm^{-1}; UV (dioxane) λ_{max} 307 nm (ϵ 15 400), 289 (18 400), and 229 (10 300); NMR (100 MHz, $CDCl_3$) δ 7.2–7.7 (m, 4), 6.38 (s, 1), 3.62 (s, 3), 3.32 (AB q, 2, J = 16 Hz, $\Delta\nu_{AB}$ = 54 Hz), and 2.0–2.9 (ABCD m, 4). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.38; H, 5.78.

Methyl 9,9a-Dihydro-3-oxo-3*H*-fluorene-9a-carboxylate (20). A solution of 160 mg (0.66 mmol) of (+)-**19**, $[\alpha]^{RT}_{578}$ +313° (*c* 2.0, benzene), and 181 mg (1.63 mmol) of SeO_2 in 14.1 g of *tert*-butyl alcohol was refluxed for 43 h. Evaporation of the *tert*-butyl alcohol at reduced pressure, filtration of the residue through 15 g of neutral Al_2O_3 with toluene, and short-path distillation (160 °C at 0.02 mm) of the eluate yielded 89 mg of impure **20**, $[\alpha]^{RT}_{578}$ −191° (*c* 1.8, benzene). Analytically pure **20** (52 mg, 33%) was obtained by recrystallization from hexane followed by short-path distillation (125 °C at 0.001 mm): mp 106–124 °C; $[\alpha]^{RT}_{578}$ −238° (*c* 0.5, benzene); IR (Nujol) 1730, 1660, 1638, and 1605 cm^{-1}; UV (dioxane) λ_{max} 314 nm (ϵ 15 000) and 247 (13 600); NMR (60 MHz, $CDCl_3$) δ 7.3–7.8 (m, 4), 6.3–7.2 (ABC m, 3), 3.60 (s, 3), and 3.48 (AB q, 2, J = 16 Hz, $\Delta\nu_{AB}$ = 49 Hz). Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.04. Found: C, 74.69; H, 5.04.

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Registry No.—**1a**, 1655-07-8; **1b**, 14160-65-7; **1c**, 69881-56-7; **2**, 78-94-4; (*R*)-(+)-**3a**, 69881-57-8; (*S*)-(−)-**3a**, 69881-58-9; **3b**, 69881-59-0; **3c**, 69881-60-3; **4**, 22955-77-7; (*R*)-**5**, 69881-61-4; (*S*)-**5**, 69881-62-5; **6**, 130-95-0; **7**, 56-54-2; **8**, 1301-42-4; **9**, 18797-86-9; **10**, 69881-63-6; **11**, 69881-64-7; **12**, 69927-28-2; **13**, 69307-86-4; **14a**, 68235-49-4; **14b**, 69881-65-8; **14c**, 69927-37-3; **15a**, 69979-91-5; **15b**, 69881-66-9; **15c**, 69881-67-0; **19**, 69881-68-1; **20**, 69881-69-2; **21**, 69881-70-5; **22**, 42982-87-6; diethyl 4-oxoheptanedioate, 6317-49-3.

References and Notes

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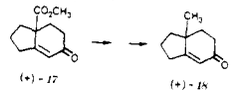

(+)-17 (+)-18

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Reaction of 2,2,4,4-Tetramethylpentane-3-thione *S*-Oxide (Di-*tert*-butylsulfine) with Grignard Reagents

Atsuyoshi Ohno,* Misao Uohama, Kaoru Nakamura, and Shinzaburo Oka

Institute for Chemical Research, Kyoto University, Uji, Kyoto-Fu 611, Japan

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The reaction of 2,2,4,4-tetramethylpentane-3-thione *S*-oxide with RCH_2MgX gives a thiirane, whereas the reaction with R_2CHMgX affords a sulfide. The reaction with 1,1-dimethylethylmagnesium chloride results in the formation of 2,2,4,4-tetramethylpentane-3-thione. The reactions are interpreted in terms of competitive nucleophilic attack and one-electron-transfer processes: a Grignard reagent from a primary alkylmagnesium halide prefers the nucleophilic attack, whereas a *tert*-alkylmagnesium halide prefers the electron transfer. A *sec*-alkylmagnesium halide is between them in behavior.

Sulfines belong to a class of heterocumulenes and are available by several syntheses.[1,2] Since sulfines have three potentially reactive centers (carbon, sulfur, and oxygen), we can expect a variety of reactions with them. Reactions of aromatic sulfines with dienes,[3] 1,3-dipoles,[4–7] and nucleophiles[8] give sulfoxides. Aryl arylthiosulfines[9] and aryl arylsulfonylsulfines[10] behave similarly. On the other hand, substitution on the sulfinyl carbon is known for chlorosulfines.[9a,11]

Sulfines have also been the subject of interest from the viewpoint of theoretical calculations.[12–17] van Lierop and his co-workers have proposed, based on the ab initio INDO calculations on sulfine and halogenated sulfines, that regardless of the substituent(s) the charges on sulfur and oxygen were almost constant, keeping the S–O grouping as a whole almost neutral.

To extend our understanding on the chemistry of sulfines, it is desirable to study their reactions systematically. The reactions of aliphatic sulfines have been especially ignored,

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