Urazole **6** crystallizes triclinically in the space group $P\bar{1}$ with a = 679.1 (4) pm, b = 1241.1 (8) pm, c = 632.0 (4) pm, α = 107.53 (5)°, β = 95.30 (5)°, and γ = 98.82 (5)°. The unit cell contains Z = 2 formula units; the density was calculated to be 1.466 mg m^{-3}. All atomic parameters are listed in Table III. The labeling of the atoms can be seen in Figure 2. Bond distances and bond angles are summarized in Table IV.

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Registry No. **1**, 4096-95-1; **6** (R′ = Me), 79769-95-2; **6** (R′ = Ph), 79769-96-3; **7** (R′ = Me), 79769-97-4; **7** (R′ = Ph), 79769-98-5; **8** (R′ = Me), 79769-99-6; **8** (R′ = Ph), 79770-00-6; **10**, 79770-01-7; **11**, 79770-02-8; **12**, 79770-03-9; MTAD, 13274-43-6; PTAD, 4233-33-4; tricyclo[3.2.1.0^{7,8}]oct-2-ene, 15128-95-7.

Asymmetric Synthesis of (*S*)- and (*R*)-Malic Acid from Ketene and Chloral

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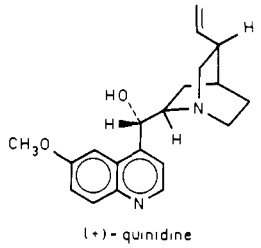
Contribution from the Department of Organic Chemistry, University of Groningen, 9747 AG Groningen, The Netherlands. *Received June 17, 1981*

Abstract: Quinidine (**5**) catalyzes the addition of ketene (**1**) to chloral (**2**) at −50 °C in toluene. The β-(trichloromethyl)-β-propiolactone **3** is formed virtually optically pure (98% enantiomeric excess). A mechanism for this reaction, accounting for the high enantiomeric excess, is proposed. Known hydrolytic procedures convert the lactone **3** to malic acid (**6**). By proper choice of catalyst both (*R*)- and (*S*)-malic acid can be obtained optically pure.

"Rarest among efficient asymmetric synthesis is carbon–carbon bond formation with the simultaneous creation of a new chiral center".[1] With this statement A. I. Meyers and co-workers introduce the subject of the asymmetric synthesis of chiral alkanoic acids. If the type of synthesis referred to in that publication[1] is rare, a further severe restriction is introduced if we limit the asymmetric syntheses to those performed with chiral catalysts only, adding a further parameter by requiring an enantiomeric excess better than 80%. Important recent examples are the (*S*)-proline catalyzed intramolecular aldol condensation[2] (ee ~95%), the chiral cobalt and copper complex catalyzed carbene addition reaction[3] (ee ~88%), and the quinine catalyzed Michael reaction[4] (ee 99%). Our successful experiences with the use of cinchona alkaloids in base-catalyzed 1,4-addition reactions led us to reexamine the base-catalyzed 2 + 2 cycloaddition reaction between ketene (**1**) and chloral (**2**) to form β-(trichloromethyl)-β-propiolactone (**3**) as reported first by Borrmann and Wegler.[5]

We have now found that by using 1–2 mol % of quinidine (**5**)

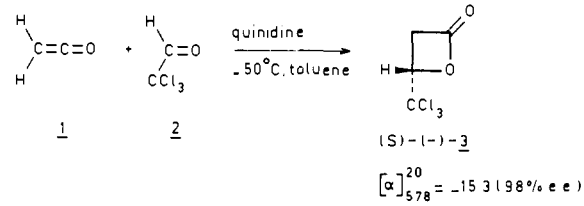


(+)-quinidine

5

in toluene at −50 °C the β-lactone **3** can be isolated in virtually quantitative chemical and optical yield (95%, Scheme I). By use of diastereomeric cinchona alkaloids (e.g., quinine) either enantiomer of the β-lactone can be obtained. The lactone **3** is readily crystallized from methylcyclohexane to complete optical purity and has an absolute rotation of $[\alpha]^{20}_{578}$ −15.6° (*c* 1, cyclohexane), mp 51–52 °C (lit. for racemic lactone mp 36–37 °C[5]). Mild acid hydrolysis of the β-lactone to the known[6] trichloromethyl hydroxy acid **4** can be used to correlate both the absolute configuration of **3** [*S*(−) and *R*(+)] and its optical purity. As check upon the reported values we prepared the diastereomeric esters of **4** using Mosher's reagent.[7] The integrated ^{19}F NMR values confirm the enantiomeric purity assignment. Careful basic hydrolysis of the trichlorohydroxy acid **4** to malic acid (**6**) by slight modification of published procedures[6] thus furnishes the natural (*S*)-(−)- and the rare (*R*)-(+)-malic acids. Under optimum conditions the optically pure malic acids can be obtained in an overall yield of 79%. This compares favorably with the elegant route of Seebach

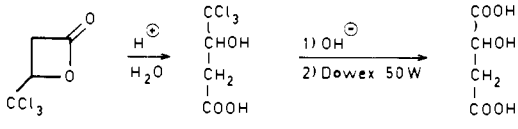
Scheme I



1 **2** (S)-(−)-**3**

$[\alpha]^{20}_{578}$ = −15.3 (98% e e)

Scheme II



3 **4** **6**

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Table I. Relationship between Absolute Configuration of the β-Lactone 3 and Configuration of Catalyst[a]

catalyst	configuration: catalyst[b]	configuration: β-lactone	ee, %
1, quinine	*S*	*R*	76
2, acetylquinine	*S*	*R*	68
3, quinidine	*R*	*S*	98
4, cinchonidine[d]	*S*	*R*	67
5, cinchonine[d]	*R*	*S*	84
6, epichlorocinchonidine[e]	*S*	*R*	65
7, deoxycinchonidine	*S*	*R*	70
8, epiquinine[e]	*S*	*R*	57
9, *N*-methylephedrine	*S*	*R*	53
10, *N,N*-dimethyl-α-phenylethylamine	*S*[c]	*S*	77
11, *N*-methylprolinol	*S*	*R*	60
12, 1,2-dimethylpyrrolidine	*R*[c]	*R*	60
13, *N,N*-dimethyl-2-amino-1-butanol	*S*	*R*	33
14, *N,N*-dimethyl-2-aminobutane	*R*[c]	*R*	15
15, brucine			68

[a] Standard conditions: 4 mol % catalyst in toluene at −50 °C. [b] Configuration of carbon atom adjacent to nitrogen atom (C_8 for entries 1–8, C_2 for entries 9 and 10). [c] Change in nomenclature because of change in substitution. [d] Experiment performed in $CHCl_3$ because of solubility problems of catalyst. [e] Chemical yields are lower in these cases (≈60%) because of intramolecular hydrogen bonding (epiquinine) and steric blocking of nitrogen by chlorine (epichlorocinchonidine) which causes reduced availability of nitrogen for catalysis.

starting from the chiral tartaric acids[8] or the (industrially viable) route of Chibata utilizing furmaric acid and immobilized fumarase.[9] Seebach's route furnishes the optically pure malic acids in an overall yield of 44% while the enzymic route of Chibata results in a mixture of products containing 80% of the *S*(-) isomer. It is self-evident that Chibata's route cannot furnish the unnatural isomer. See Scheme II.

Discussion

Only a limited number of catalytic asymmetric syntheses lend themselves to mechanistic studies. In the case of the homogeneous alkaloid catalyzed 1,4-addition of thiols to α,β-unsaturated ketones, kinetic data in addition to structural variations in substrate and catalyst were needed before a reasonable mechanism having predictive value could be proposed.[10]

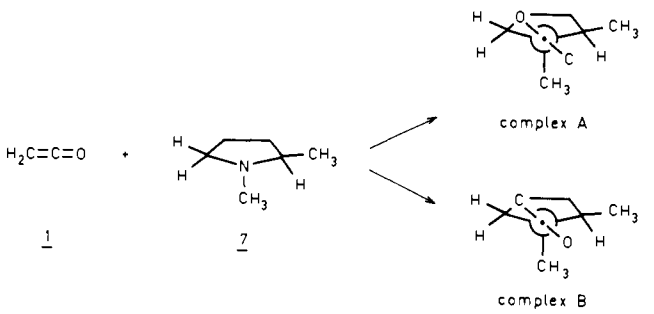
Absolutely decisive in any attempted rationalization of a catalytic asymmetric synthesis is the need for a high, or rather very high, enantioselectivity. We have used as rule of thumb that an enantiomeric excess equal or better than 50% is needed to warrant a serious mechanistic proposal since otherwise differences in the $\Delta G^{\ddagger}$ of the two diastereomeric transition states amount to less than 0.5 kcal.

Examination of Table I is revealing. Several facts stand out immediately: (a) tertiary amines with (entries 1 and 3) or without (entries 2, 10, and 15) β-hydroxy groups give comparable induction; (b) flexible (entry 10), completely rigid (entry 15), or slightly flexible (entry 1) catalysts all give virtually identical ee's (77, 68, and 76%); (c) the chirality of the product is predictable on the basis of knowledge of the chirality of the carbon adjacent to the tertiary amine function of the catalyst (see note *c*, Table I, for the exception). In sharp contrast to the base-catalyzed 1,4-addition studied previously, the presence or absence of a hydroxy group (β to the amine) in the catalyst is irrelevant. In the Michael-type addition the OH group served two functions; by hydrogen bonding to the carbonyl group of the cyclohexenone the latter Michael acceptor is both activated toward nucleophilic addition as well as kept in its (proper) orientation.

Since ketene undoubtedly rapidly acylates any free hydroxyl group present, its role in our catalyst is, at most, a general steric one. Experiments with acetylquinine (entry 2, Table I) confirm this conclusion. Together with observation a, items b and c can now be used to propose two mechanisms. In one, chloral complexes with the tertiary amine; in the other it is the ketene–amine complex which is formed first in a rapid preequilibrium reaction.

Although the recent work of Herndon, Schilling, and Roth[11] would make the chloral–amine complex reasonable, we still reject it for the following reasons: we have not been able to observe chloral–amine complexation by ^{13}C NMR under the conditions which allowed Roth to see the dipolar ion formed by complexation of Dabco[12] and trifluoroacetophenone (which of course does not necessarily imply the chloral–amine complex does not exist); models indicate that chloral (and certainly bromal) cannot approach the nitrogen of the quinuclidine system in quinine or quinidine to form a tight complex (as is expected on the basis of the high ee's found in the reaction) in which the chirality around the carbonyl carbon of chloral is already fixed.

The second mechanism is based on the formation of a ketene–amine complex. For simplicity's sake we will use 1,2-dimethylpyrrolidine (**7**) in our mechanistic arguments. The assumption is made that 1,2-dimethylpyrrolidine at −50 °C is present in its most favorable trans conformation. Complexation of 1,2-dimethylpyrrolidine with ketene can give rise to two different complexes, A and B. The configuration of the product in the



reaction of the complex with chloral then is determined by the manner in which the trichloromethyl group of chloral recognizes the structure (i.e., the chirality) of the tertiary amine. Models make clear that the trichloromethyl group faces two steric barriers, in both complex A and B: the methyl group attached to the chiral center (complex A) and the methylene of the ring (complex B). The least sterically hindered path in the models leads, in both complex A and B, unequivocally to the absolute configuration found experimentally. A choice between the two complexes cannot be made on the basis of the present evidence. The ketene–chloral reaction is a $_s2_\pi + _s2_\pi$ thermally forbidden cycloaddition reaction. If the reaction proceeds stepwise, two sequences are feasible: namely, C–C bond formation proceeds or follows C–O bond formation. This question too must remain unanswered at this time.

The proposed mechanism suggests that the chiral center adjacent to the tertiary nitrogen determines the chirality of the product. This holds for the catalysts employed thus far (Table I). A striking feature of the results listed in Table I is that by using exceedingly simple catalysts such as 1,2-dimethylpyrrolidine or *N,N*-dimethyl-α-phenylethylamine, high ee's (successively 60 and 77%) can be achieved in the reaction of ketene and chloral.

Experimental Section

The chemical purity of the commercially available cinchona alkaloids was determined by ^{13}C NMR. All proved to be >97% pure. Quinidine was purified from its dihydro base by a known procedure.[13] Samples of acetylquinine, epichlorocinchonidine, and deoxycinchonidine were kindly provided by Dr. H. Hiemstra. *N*-Methylephedrine and *N,N*-dimethyl-α-phenylethylamine were prepared from ephedrine and α-phe-

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nylethylamine, respectively, by methylation with formaldehyde. *N*-Methylprolinol, 1,2-dimethylpyrrolidine, *N,N*-dimethyl-2-aminobutanol, and *N,N*-dimethyl-2-aminobutane were prepared by known procedures[14] from L-proline and 2-amino-1-butanol. All catalysts used were dried prior to use. Solvents used (toluene, $CHCl_3$) were dried and distilled over P_2O_5 and stored over molecular sieves. Chloral was distilled [bp 96 °C (765 mmHg)] under N_2 and stored at −25 °C. Ketene was prepared by pyrolysis of acetone vapors in an apparatus described by Williams and Hurd.[15] Residual acetone vapors were removed as thoroughly as possible by cooling the vapors to −40 °C (ketene bp −42 °C). No further purification of the ketene was performed. With the equipment used, after 0.75–1 h about 0.01 mol of ketene is formed, as was established by leading ketene through an aniline solution and isolating the acetanilide formed. All chloral–ketene addition reactions were performed under an inert atmosphere of dried nitrogen.

(*S*)-β-(Trichloromethyl)-β-Propiolactone (3). In a three-necked round-bottom flask (100 mL) equipped with a thermometer, a ketene inlet under the surface of the toluene, and a dropping funnel was dissolved 83 mg (0.25 mmol) of purified quinidine in 50 mL of toluene. The solution was cooled to −50 °C. Ketene was bubbled through the solution with magnetic stirring while 1.47 g (0.01 mol) of anhydrous chloral in 20 mL of toluene was added dropwise during 0.75–1 h. Excess of ketene should be avoided in order to minimize formation of diketene. After the reaction was complete, the mixture was warmed to room temperature and transferred to a separatory funnel. The catalyst was removed by repeated (2×) washing with 4 N HCl. The toluene layer was washed with saturated NaCl solution and dried over $MgSO_4$. After removing $MgSO_4$ by filtration, the toluene was removed under reduced pressure. The residue was purified by bulb to bulb distillation: 120 °C (0.5 mmHg), yield 1.67 g (89%); $[\alpha]^{20}_{578}$ −15.3° (*c* 1, cyclohexane) corresponding to an ee of 98%; NMR 3.7 (2 H, m), 5.0 ppm (1 H, t).

Optically Pure (*R*)- and (*S*)-β-(Trichloromethyl)-β-propiolactone. Lactone **3** (18 g) (ee 95%) was dissolved in 41 mL of methylcyclohexane by warming. The solution was filtered and allowed to cool to room temperature. After filtration and washing with a little cool methylcyclohexane, 15.5 g of (*S*)-lactone product could be isolated (85% recovery), $[\alpha]^{20}_{578}$ −15.6° (*c* 1, cyclohexane), mp 51–52 °C. The specific rotation did not change after another crystallization. The same procedure starting with 19.7 g of lactone **3** (72% ee) from 110 mL of methylcyclohexane yielded 12.8 g (*R*)-lactone (65% recovery), $[\alpha]^{20}_{578}$ 15.4° (*c* 1, cyclohexane), mp 51–52 °C. Again the rotation did not change after another crystallization. Racemic lactone **3** has mp 36–37 °C.[15]

4,4,4-Trichloro-3-hydroxybutanoic Acid (4). Lactone **3** (9.7 g), mp 51–52 °C, $[\alpha]^{20}_{578}$ −15.6° (*c* 1, cyclohexane), was suspended in 150 mL of 4 N HCl and heated under reflux for 3 h. The water/HCl was removed by distillation under reduced pressure, furnishing 11.24 g (100%) of acid after drying; $[\alpha]^{20}_{546}$ +26.1° (*c* 1, acetone).

Malic Acid. To a solution of 2.12 g (10 mmol) of 4,4,4-trichloro-3-hydroxybutanoic acid, $[\alpha]^{20}$ + 26.1 (*c* 1, acetone), in 15 mL of water was added dropwise at 0 °C a solution of 2.2 g of NaOH (55 mmol) in 15 mL of water. The solution was stirred, with the exclusion of carbon dioxide, for 24 h at 20 °C. The solution was passed through a Dowex 50W column (3-cm diameter, 20-cm length, 150 g of Dowex 50W-X8). The resulting solution was evaporated to dryness. The residue was dissolved in 1 mL of water and filtered to remove the fumaric acid formed during the hydrolysis (about 5%). After evaporation of the solvent and drying under vacuum, 1.14 g of malic acid could be obtained, $[\alpha]^{20}_D$ −28.4° (*c* 5.5, pyridine) (lit. $[\alpha]^{20}_D$ −28.6° (*c* 5.5, pyridine).[16]

Acknowledgment. The cooperation and advice both on the mechanism of the reaction and the ^{13}C NMR work by Professor I. Agranat, Jerusalem University, Jerusalem, Israel is gratefully acknowledged.

Registry No. 1, 463-51-4; **2**, 75-87-6; (*S*)-**3**, 16493-62-2; (*R*)-**3**, 16493-63-3; (*S*)-**6**, 97-67-6; (*R*)-**6**, 636-61-3; quinine, 130-95-0; acetylquinine, 18797-86-9; quinidine, 56-54-2; cinchonidine, 485-71-2; cinchonine, 118-10-5; epichlorocinchonidine, 79769-63-4; deoxycinchonidine, 5808-37-7; epiquinine, 572-60-1; *N*-methylephedrine, 552-79-4; (*S*)-*N,N*-dimethyl-α-phenylethylamine, 17279-31-1; (*S*)-*N*-methylprolinol, 34381-71-0; (*R*)-1,2-dimethylpyrrolidine, 40170-49-8; (*S*)-*N,N*-dimethyl-2-amino-1-butanol, 79769-64-5; (*R*)-*N,N*-dimethyl-2-aminobutane, 40916-66-3; brucine, 357-57-3.

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(16) The Aldrich-Europe Catalog Handbook of Fine Chemicals, 1981–1982. The original reference [*Beilstein* **1921**, *3*, 419. Walder, P. *Ber.* **1899**, *32*, 2859: $[\alpha]_D^{18}$ 38.0° (*c* 5, pyridine)] is misleading. The rotation cited by Aldrich $[\alpha]_D^{20}$ 28.6° (*c* 5.5, pyridine) is correct, checked by ourselves.

Reaction of Cyclohexane and Cyclohexyl Radicals with Atomic and Molecular Oxygen

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Contribution from the Division of Atmospheric Environment, The National Institute for Environmental Studies, P.O. Tsukuba-gakuen, Ibaraki 305, Japan. *Received July 7, 1981*

Abstract: The reaction of oxygen atoms with cyclohexane in a fast-flow system was studied with a photoionization mass spectrometer. Cyclohexyl radicals formed by the initial hydrogen abstraction were detected directly. The subsequent reaction of the cyclohexyl radicals with atomic oxygen proceeds by both hydrogen abstraction (52%) and an oxygen atom addition reaction (48%). The product in the hydrogen abstraction reaction was cyclohexene. Most of the products in the oxygen atom addition reaction resulted from ring cleavage of the vibrationally hot cyclohexyloxy radicals. (The yield of cyclohexanone was just 3%.) Competition experiments show that cyclohexyl radicals react $(5.0 \pm 1.3) \times 10^{-2}$ times as fast with O_2 as with $O(^3P)$. In the presence of an excess of O_2 both cyclohexene and cyclohexanone are observed but in decreased yields—cyclohexene (25%) and cyclohexanone (2%). These results could be explained by the reaction of oxygen atoms with cyclohexylperoxy radicals produced by the recombination of cyclohexyl radicals with O_2.

When alkyl radicals react with oxygen atoms, two typical processes are conceivable: (1) formation of olefins by hydrogen abstraction; (2) formation of aldehydes or ketones by oxygen atom addition. For example, the reaction of the *tert*-butyl radicals[1] with atomic oxygen forms isobutene (80%) and acetone (20%). In the case of the cycloalkyl radicals, formation of cycloalkene and cycloalkanone are expected by analogy. However, since four hydrogen atoms in the cycloalkyl radical can be abstracted to form cycloalkene as compared to nine equivalent hydrogen atoms in the *tert*-butyl radical to produce isobutene, the branching ratios to produce cycloalkene and cycloalkanone are expected to be different from the case of the *tert*-butyl radical. Further, ring

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