Synthesis of Chiral Molecules from Non-chiral Crystals by Controlled Reaction * at a Single Surface

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A procedure is described for performing reactions at a single face of a single crystal of organic compounds, using as examples the *cis*-dihydroxylation of tiglic and crotonic acids by osmium tetraoxide, and the dibromination of tiglic acid. For molecules whose orientation in the crystalline state is appropriate, reactions carried out in this way can produce enantiomerically enriched products from a non-chiral crystal and reagent. Enantiomeric excesses are dependent upon the crystal quality; values up to 30% have been achieved in the reactions of tiglic acid with osmium tetraoxide or bromine vapour.

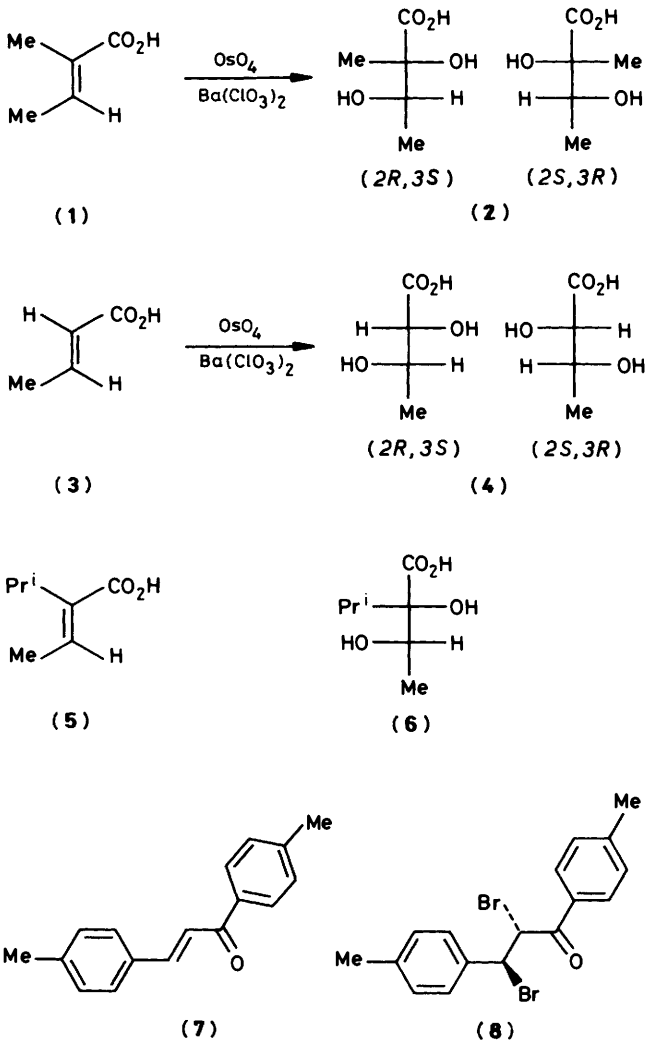
The concept that the progress of a reaction at a crystal surface can be controlled by the arrangement of molecules at that surface is now accepted.[1] Heterogeneous reactions occurring at the surface of organic crystals can exhibit selectivity of product formation which is dependent upon the crystal structure.[2]

Several years ago we specified the conditions necessary for the successful production of asymmetric molecules from non-chiral crystals and reagents by restricting reaction to a single face of the crystal.[3] It is possible to generate stereoselectively a chiral product from non-chiral reactants in this way provided that the projection of the crystal structure on to the single face in question belongs to one of the plane groups p1, p2, p3, p4, or p6, and that the molecules in the crystal are aligned in certain ways relative to the symmetry elements in the crystal.[3] In the case of an olefinic bond, for example, it is necessary that the same face (*Re* or *Si*, but not both) be aligned to the outside of the crystal at a specified face, and that the axis of the π system be approximately normal to the crystal surface.

These criteria are met by tiglic acid (**1**) in its crystalline state. Tiglic acid belongs to the space group $P\bar{1}$,[4] and its projections on to the $(\bar{2}10)$ or $(2\bar{1}0)$ faces belong to the plane group p2 (Figure). The faces of a single crystal of tiglic acid which correspond to the $(\bar{2}10)$ and $(2\bar{1}0)$ planes were identified by *X*-ray data as the small faces approximately perpendicular to the long axis of the crystal. In this way, the reactive faces of subsequent single crystals of tiglic acid could be readily identified by visual inspection of the crystal.

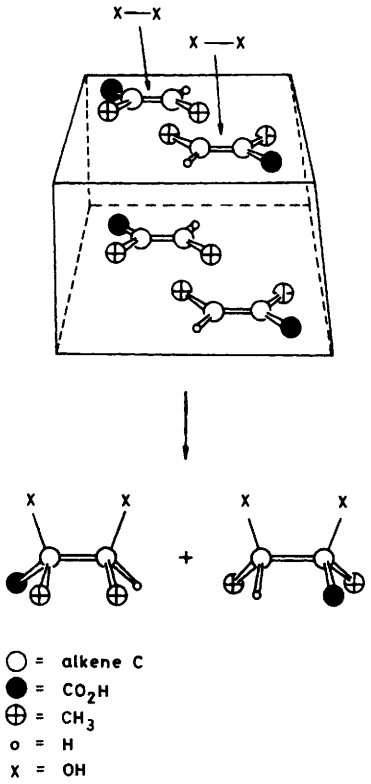
Another criterion for successful asymmetric synthesis by this method is that reactions be ideally heterogeneous surface–solution or surface–gas processes. Any reaction proceeding, for example, in solution following the dissolution of starting material could give only racemic product. Given these constraints, and in view of current interest in the stereoselective production of vicinal 1,2-diols,[5] we undertook a study of the *cis*-dihydroxylation of (**1**) by osmium tetraoxide in aqueous solution, under conditions of low temperature, where the solubility of (**1**) was minimal.

We have previously reported that the reaction of one face of a single tiglic acid crystal with osmium tetraoxide produces the *threo*-diol (**2**) in optically active form.[6] Table 1 summarizes these results. In two cases, reactions were carried out separately on the $(\bar{2}10)$ faces and $(2\bar{1}0)$ faces of a single crystal, obtained by cutting a single crystal into two halves to expose faces corresponding to the $(\bar{2}10)$ and $(2\bar{1}0)$ planes. These faces bear a mirror-image relationship to each other, and we describe them as diptychiral (having two-dimensional chirality; from the classical diptych altar piece of two complementary hinged panels). The enantiomeric excesses (e.e.) reported in Table 1 are based on ^{1}H n.m.r. analysis of the product (as its methyl ester) in the presence of Eu(hfc)$_3$ shift reagent, and are lower than those



previously reported by us.[6] The earlier values were based only on optical rotation measurements; the specific rotation of resolved (**2**) is variously reported between 3 and 6°.[7,8] The absolute configuration of the dextrarotatory isomer of (**2**) has been assigned as 2*R*,3*S*.[8]

The variation of e.e. reported in Table 1 is attributed to a variation in crystal quality. Similar variations occur in the case of bromination of (**1**) (see below). The significance of crystal defects in solid-state reactions is well documented;[9] in the present case, any reaction occurring at molecules with other

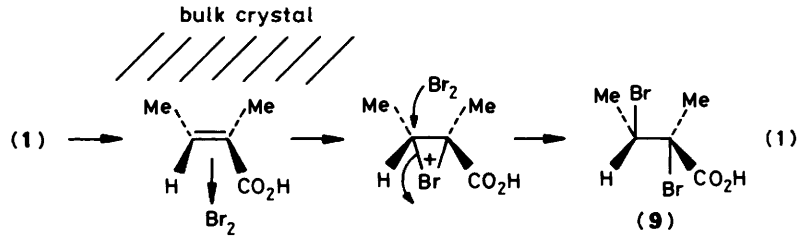


The $BaClO_3$-catalysed reaction of tiglic acid with OsO_4. The two molecules on the top plane ($\bar{2}10$) are related by a centre of symmetry. The bounding planes for this view of tiglic acid are ($\bar{2}10$), ($2\bar{1}0$), (001), (00$\bar{1}$), (100), and ($\bar{1}00$) (from ref. 6)

The addition of bromine vapour at the olefinic bond of solid unsaturated compounds has been known for many years,[13] and in one instance, enantiomerically enriched production formation has been reported.[14] Thus single crystals of 4,4′-dimethylchalcone (**7**) produce the *trans*-dibromide (**8**) in optical purities up to 22% on exposure to bromine vapour. In this instance, however, the enantiomeric enrichment is produced by virtue of the fact that (**7**) crystallizes in a chiral space group ($P2_12_12_1$).[15,16] We can now report that tiglic acid, on exposure to bromine vapour, produces the *trans*-dibromide (**9**) in high chemical yield and in optical purities up to 33% (Table 2): in the latter instance, the optical enrichment is attributed to the factors discussed in the Introduction. The stereoselectivity of bromonium ion formation is controlled by restricting the reaction to a single accessible crystal face; once stereoselectivity is established, *trans*-opening of the intermediate is regioselectively controlled by the electronic properties of the reagents, as outlined in equation (1).

The formation of the *trans*-dibromide (**9**) as the sole product of gaseous bromine addition to a solid olefin was established by comparison of the product so obtained with that produced by solution bromination; the respective samples were identical in all respects. *trans*-Bromination at a crystal surface requires that the initially formed bromonium ion dissociate from the surface to the extent that it can be attacked from the rear by molecular bromine. This view is consistent with the known mechanism of olefin bromination, where the reaction is second order in bromine,[17] and has a precedent in other solid-state brominations.[14–16]

Bromine vapour is capable of diffusing into tiglic acid crystals, as evidenced by the reaction in which access of bromine was limited to a nominally unreactive 'side' of the tiglic acid crystal (see Table 2), in which racemic product was slowly formed. The direct vapour-phase reaction of tiglic acid with bromine can also occur. These two factors, combined with less



than the desired alignment would lead to a reduction in stereospecificity and hence lower e.e. of product. We envisage that, as the reaction proceeds, successive layers of crystal surface are exposed to the reagent to form, in turn, product which is removed into solution. Thus the presence of defects such as screw dislocations could lead to reaction at molecules with undesirable orientations.

Crotonic acid (**3**), whose *X*-ray structure (space group $C2/c$, plane group p2 in projection down the *b* axis)[10] shows that the π bond is aligned approximately parallel to the '*b*' axis, is also a suitable substrate for asymmetric synthesis using our technique. Reaction of a single crystal of (**3**) with osmium tetraoxide gave (−)-2,3-dihydroxybutanoic acid (**4**), in an e.e. of 23%. It was our intention to submit 2-isopropylcrotonic acid (**5**) to the asymmetric dihydroxylation procedure in order to produce trachelanthic acid (**6**), the acid portion of several pyrrolizidine alkaloid esters;[11] to this end (**5**) was prepared and its crystal structure determined.[12] Unfortunately, the molecules are aligned in the crystal in such a way that stereoselective addition to *Re* or *Si* face of the alkene at a single crystal face would not be expected to occur.[3,12]

than perfect crystal quality, can explain the low enantiomeric excesses listed in Table 2.

We have attempted the reaction of solid tiglic acid with chlorine, hydrogen chloride, or hydrogen bromide, all in the gaseous state, but in none of the above cases was any product formation observed.

The concept of a relationship between the crystal packing of an organic compound and the regiochemistry of its reactions is not new,[2] nor is the observation of chiral induction in the presence of a chiral crystal or packing arrangement. However, the phenomenon described herein, that of chiral induction by selecting for reaction only a single face of a non-chiral crystal, has potentially greater application, since it can in theory be applied to over 80% of solid organic molecules.[3] Recent developments in organic crystal chemistry such as the ability to extend growth of a crystal in a specific, desired direction,[18] promise further developments in this area.

Experimental

Materials.—All materials were commercial reagent grade unless otherwise stated. Single crystals of tiglic acid, crotonic

Table 1. Treatment of tiglic acid with osmium tetraoxide–barium chlorate $Ba(ClO_3)_2 \cdot H_2O$

Tiglic acid crystal (g)	$Ba(ClO_3)_2 \cdot H_2O$ (g)	OsO_4 (mg)	Product (g)	Product $[\alpha]_D^{20}$ (°)	Product e.e. (by n.m.r.)
0.37*	0.27	2	0.12	+1.84	30
0.37*	0.27	2	0.11	−1.88	30
0.35†	0.25	2	0.18	+0.84	16
0.35†	0.25	2	0.2	−0.9	16
1.6	1.35	8	0.64	+0.87	16
0.8	0.72	5	0.45	+0.9	16
0.42	0.32	2	0.1	+0.68	10

* and † are enantiomeric pairs produced by reactions at diptychiral (mirror) faces from the same crystal (see text).

Table 2. Treatment of tiglic acid with bromine vapour

Tiglic acid crystal (g)	Isolated product (g)	Reaction time (h)	$[\alpha]^{20}$ ($CHCl_3$) (°)	E.e. (by n.m.r.)	Conditions of reaction
0.3*	0.41	0.33	+5.24	30	Normal
0.3*	0.3	0.33	−2.6	13	Normal
0.5	0.52	0.33	+5.4	33	In dark
0.05†	0.033	24	0	0	In gas phase
0.6	0.64	4	0	0	On crystal side

* See footnote to Table 1. † In gas phase.

acid, and 2-isopropylcrotonic acid were grown from acetone solution by slow evaporation of the solvent over 5—6 days.

Methods.—The analytical methods used in this study have been described elsewhere.[19]

Reaction Procedures.—(a) *Protection of crystal faces against reaction.* Large single crystals of the appropriate acid were coated with quick-setting epoxy glue (in the case of subsequent reaction with OsO_4) or candle wax (in the case of subsequent reaction with Br_2, Cl_2, HCl, or HBr), omitting the reactive face. The location of the reactive face was determined by crystal morphology once this had been related to the packing arrangements of the crystal by *X*-ray crystallography.[3,6]

(b) *Reactions with osmium tetraoxide–barium chlorate.* Reactions were carried out in a flat-bottomed flask using a stirred, ice-cold aqueous solution of reagents. The coated crystal was placed in the solution in such a position that it did not come into direct contact with the magnetic stirring bar. At the end of the reaction the empty epoxy shell was removed and the solution worked up as described below.

(c) *Reactions with halogen or hydrogen halide vapour.* Reactions were performed in a 250 ml desiccator filled with the reactant vapour. In the case of bromine this was achieved by placing 1—2 ml of liquid bromine in the base of the desiccator. The coated crystal was suspended (by a thread embedded in the coating) from the roof of the desiccator in such a way that the open (reactive) face hung downwards. Product was collected in a small glass dish located on the desiccator plate directly beneath the crystal.

Treatment of solid tiglic acid with osmium tetraoxide–barium chlorate. Details of multiple runs are summarized in Table 1. Typically, a single crystal of tiglic acid (0.8 g), coated as described above, was reacted with a solution of barium chlorate monohydrate (0.72 g) and osmium tetraoxide (5 mg) in water (40 ml). The resulting solution was extracted with benzene (2 × 10 ml) and the aqueous layer then concentrated *in vacuo* below 5 °C to *ca.* 10 ml. It was then saturated with sodium chloride and continuously extracted with ether for 24 h. The etheral layer was then dried and evaporated to give *threo*-2,3-dihydroxy-2-methylbutanoic acid (0.45 g) as a thick oil. All spectral data were in agreement with those published.[7,20] Optical rotation measurements were performed directly on this sample $[\alpha]^{20}$ + 0.9° (*c* = 35%, H_2O). For analysis by ^1H n.m.r. chiral shift reagent, the diol was converted into its methyl ester by treatment with diazomethane in ether, δ (CCl_4) 1.15 [3 H, d, $CH_3CH(OH)$], 1.25 [3 H, s, $C(CH_3)(OH)$], 3.25 (br, OH, exchanges D_2O), 3.80 (3 H, s, CO_2CH_3), and 3.81 [1 H, m, $CH_3CH(OH)$].

Treatment of solid tiglic acid with bromine vapour. Results are summarized in Table 2. The product was collected as described above and analysed directly, m.p. 86—88 °C (lit.,[21] 82—88 °C), $[\alpha]^{20}$ determined in $CHCl_3$ and presented in Table 2, δ(CCl_4) 1.9 (3 H, d, CH_3CH), 2.0 [3 H, s, $CH_3C(Br)COH$], and 4.80 (1 H, q, CH_3CH). The dibromide was converted into its methyl ester by treatment with diazomethane prior to ^1H n.m.r. analysis by chiral shift reagent.

Reaction of tiglic acid vapour with bromine vapour. A 500 ml flask was filled with tiglic acid vapour using a vacuum line for transfer, and then 1 mol equiv. bromine vapour added. Over a period of 24 h the flask walls became coated with 2,3-dibromo-2-methylbutyric acid, m.p. 82—84 °C, identical in all respects with the sample prepared as described above.

Solution preparation of 2,3-dibromo-2-methylbutyric acid. (a) In carbon tetrachloride. Using the conditions described,[21] conversion of tiglic acid into the dibromide at room temperature took 7 days for completion. The product was identical with that above.

(b) With lithium bromide in water. Bromine (3 g) was added to a stirred solution of tiglic acid (1 g) and lithium bromide (2 g) in water (15 ml) at room temperature. The mixture was stirred for 20 min and then filtered to give the dibromide (2.15 g, m.p. 86—88 °C), identical with that described above.

Treatment of solid crotonic acid with osmium tetraoxide–barium perchlorate. A single crystal of crotonic acid (0.21 g) was reacted as described above with osmium tetraoxide (2 mg) and barium chlorate (0.3 g) in water (5 ml) at 0—5 °C. Work-up as described above gave 2,3-dihydroxybutanoic acid (0.11 g; oil) which was converted into its methyl ester as described above. The latter gave δ 2.1 [3 H, d, $CH_3CH(OH)$], 3.3 (br, 2 × OH),

4.1 (3 H, s, CO_2CH_3), and 4.5—6.0 (2 H, m, 2 × C*H*OH), e.e. by n.m.r., 23%, $[\alpha]^{20}$ −3.5° (*c* = 2.0, H_2O), $[\alpha]_D^{25}$ (resolved material) −17.75°.[22]

2-*Isopropylcrotonic acid.* This was synthesized from ethyl acetoacetate and isopropyl bromide by the published procedure.[23,24] The product, m.p. 54—55 °C, showed δ 1.24 (6 H, d, isopropyl CH_3), 1.82 (3 H, d, C*H*$_3$CH=), 2.85 (1 H, isopropyl H), and 6.85 (1 H, q, CH_3C*H*). The *X*-ray crystal structure has been described.[12]

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