Solid-State Racemization of 4,4′-Diamino-1,1′-binaphthyl

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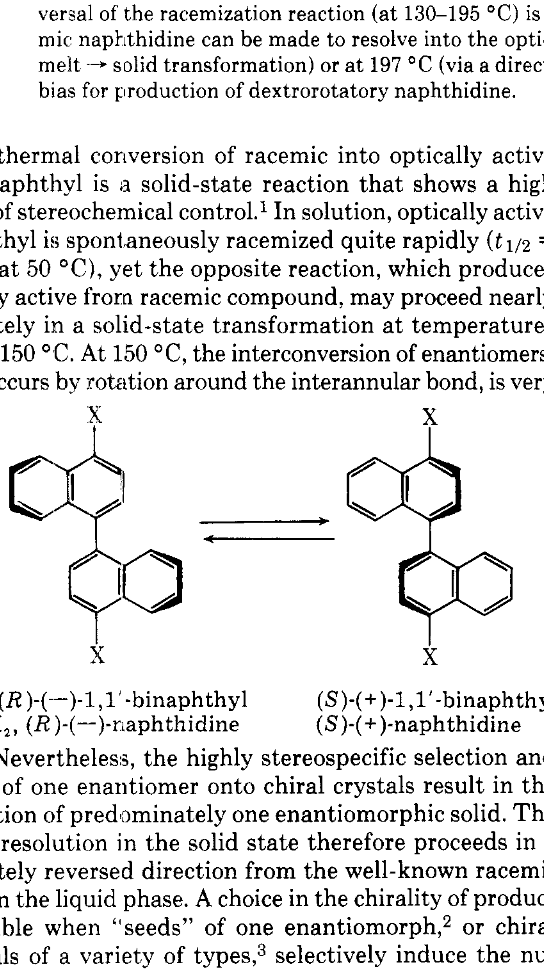
The rates of solid-state racemization of several polycrystalline samples of optically active (*S*)-(+)-4,4′-diamino-1,1′-binaphthyl (i.e., naphthidine) have been determined at 130 and 150 °C. A rapid initial reaction follows an approximate first-order relationship, but the rates are dependent on characteristics of individual samples and are increased by grinding the crystals. Racemization occurs by conversion of a eutectic crystal form to a racemic compound. The phase relationships of this polymorphic system show the racemate (mp 202 °C) to be the stable form up to the transition point of 197 °C and the eutectic form to be stable from 197 °C to its melting point of 204 °C. Reversal of the racemization reaction (at 130–195 °C) is possible simply by small variations in temperature; i.e., racemic naphthidine can be made to resolve into the optically active eutectic form by heating at 203 °C (via a solid → melt → solid transformation) or at 197 °C (via a direct solid → solid transformation). The samples showed a strong bias for production of dextrorotatory naphthidine.

The thermal conversion of racemic into optically active 1,1′-binaphthyl is a solid-state reaction that shows a high degree of stereochemical control.[1] In solution, optically active binaphthyl is spontaneously racemized quite rapidly ($t_{1/2}$ = 15 min at 50 °C), yet the opposite reaction, which produces optically active from racemic compound, may proceed nearly completely in a solid-state transformation at temperatures of 97 to 150 °C. At 150 °C, the interconversion of enantiomers, which occurs by rotation around the interannular bond, is very rapid. Nevertheless, the highly stereospecific selection and growth of one enantiomer onto chiral crystals result in the production of predominately one enantiomorphic solid. The optical resolution in the solid state therefore proceeds in a completely reversed direction from the well-known racemization in the liquid phase. A choice in the chirality of product is possible when "seeds" of one enantiomorph,[2] or chiral materials of a variety of types,[3] selectively induce the nucleation of one enantiomer.



X = H, (*R*)-(−)-1,1′-binaphthyl (*S*)-(+)-1,1′-binaphthyl
X = NH$_2$, (*R*)-(−)-naphthidine (*S*)-(+)-naphthidine

In contrast to this solid-state resolution reaction of binaphthyl, it has been briefly reported that 4,4′-diamino-1,1′-binaphthyl (i.e., naphthidine) *loses* optical activity on storage for several months ($t_{1/2}$ ~2 months at room temperature).[4] This difference in the thermal resolution of binaphthyl and the reported racemization of its 4,4′-diamino derivative prompted a more thorough investigation of the solid-state thermal reactions of neat, polycrystalline naphthidine. We report results here which allow an interpretation of the opposite reactivities of the solid states of binaphthyl and naphthidine.

Experimental Section

4,4′-Diamino-1,1′-binaphthyl. Racemic naphthidine was prepared by the method of Cohen and Oesper,[5] except that 28 g of 1-naphthylamine was used with 34 mL of concentrated hydrochloric acid and the mixture was first warmed on a steam bath to give a light purple precipitate of the amine salt. The mixture was then cooled to 0–3 °C before diazotization by the referred method and quantities given. The reduction and rearrangement of 1,1′-azonaphthalene were carried out as described,[5] and the product was crystallized by slow cooling from 3:1 ethanol–pyridine after filtering the hot solution. This naphthidine (7.1 g, 26%) was obtained as well-formed, light brown plates, mp 200–202 °C (lit.[5] mp 198–199 °C).

Naphthidine was further purified by sublimation at 2–3 mm between a bath temperature of 190 °C and an air-cooled cold finger. The crystals obtained were colorless or slightly pink leaf-like plates and were always in the racemic form (see below). The prominent infrared bands of the racemic solid, which distinguished it from the eutectic solid, are at 695, 785, 795, 892, and 1015 cm^{-1}. Other absorptions are at 760 and 837 cm^{-1}, which are both much stronger than corresponding bands from the eutectic solid.

Resolution of Naphthidine. Method A. Racemic naphthidine was resolved by the classical procedure of Theilacker and Hopp[4] using ammonium (+)-α-bromo-D-camphor-π-sulfonate to give the diastereomeric naphthidinesulfonate salt. Specific rotations for various batches were $[\alpha]^{22}_D$ 91–93 ° (lit.[4] $[\alpha]_D$ +99°) in 60% acetone–water after recrystallization from 60% ethanol. To obtain free naphthidine, the salt was suspended in a 10-fold weight of ice-cold ethanol, and dilute ammonium hydroxide was added until the solution was basic and the salt completely dissolved. Ice was then added immediately to the solution, and the free (+)-naphthidine precipitated. The product had $[\alpha]_D$ +43, 40, 41, and 40° in four batches, mp 202–204 °C (lit.[4] $[\alpha]_D$ 42 ± 1° and mp 206–207 °C). These eutectic crystals showed fewer infrared peaks than the racemate and had prominent absorption at 760 (relatively sharp), 827 (relatively weak and broad), and 1010 and 1030 cm^{-1} (both relatively weak).

Method B. "Spontaneous resolution" of previously sublimed racemic samples into eutectic crystals was carried out with ~10-mg samples in evacuated vials at 197–203 °C. (If air was present dark green or black colored material was produced which interfered with polarimetric analysis.) Eutectic crystals were produced over a period of up to 3 days. Preheating of racemic samples at 192–193 °C for up to 5 h decreased the number but increased the size (up to 7 mg) of the eutectic crystals formed at 197 °C. The contents of individual vials were dissolved completely for polarimetric analysis (see text for the results), or individual crystals were dissolved in a minimum of acetone for analysis. The highest rotations from single crystals obtained were $[\alpha]_D$ +49 ± 1° (6.95-mg crystal) and $[\alpha]_D$ −49 ± 1° (3.35-mg crystal).

Kinetic Method. The loss of optical activity in neat, polycrystalline samples of (+)-naphthidine was determined from a set of weighed samples, ~10 mg each, in 2-mL sealed vials completely immersed in a constant-temperature silicone oil bath. At an appropriate time, an individual sample was withdrawn and cooled to room temperature. Each sample was completely dissolved in acetone and transferred to a 2-mL volumetric flask which was diluted to the mark. Optical rotations were obtained at the sodium D line (5890 Å) using a Bendix type 143A automatic polarimeter with a 1-cm length cell calibrated with standard sucrose solutions.

Infrared spectra were obtained from the suspension of solid naphthidine in Nujol mulls on sodium chloride plates. Calorimetric analyses of naphthidine samples (~5 mg) were carried out by using a Perkin-Elmer Model DSC-1B differential-scanning calorimeter at a scanning rate of 10°/min.

Results and Discussion

Rates of Racemization. Several different individual batches of optically active (+)-naphthidine, mp 202–204 °C,

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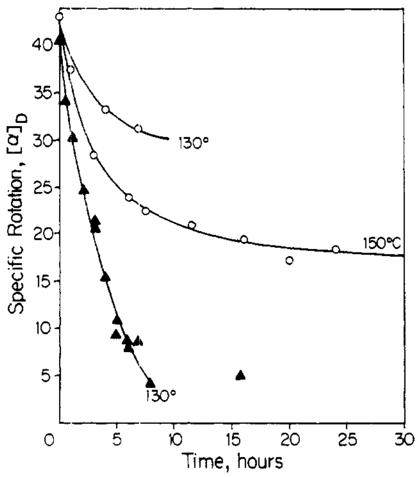

Figure 1. Loss of specific rotations in samples of (+)-naphthidine heated at 130 and 150 °C: ○, preparation 1; ▲, preparation 2.

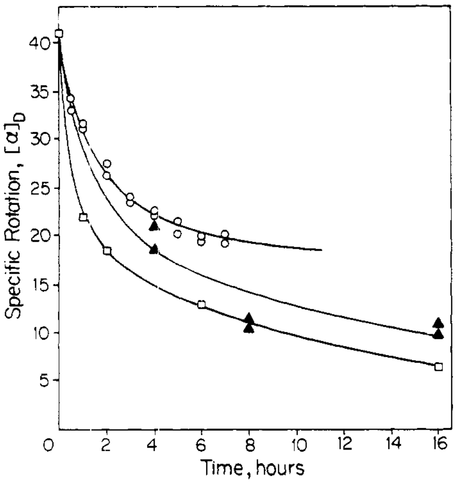

Figure 2. Loss of specific rotations in samples of (+)-naphthidine (preparation 3) heated at 130 °C: ○, initial preparation; ▲, ground samples; □, more highly ground samples.

were heated at constant temperatures of 150 or 130 °C and samples were periodically analyzed to determine loss of optical activity. In each case the initial specific rotations rapidly dropped, but some optical activity persisted for much longer times of heating; e.g., in one sample rotation dropped to 50% in 6 h at 130°, but 30% of the original activity was present after 220 h. Although individual samples from a single preparation racemized in a fairly smooth manner in the initial part of the racemization, a great variation in rate was obtained from different batches. This is shown in Figure 1, which shows the decrease in specific rotation for two different batches of (+)-naphthidine at 130 and 150 °C. Sample 1 racemized slowly at 130 °C, and its rate at 150 °C was still slower than that of another sample (2) at 130 °C.

The wide variation of observed rates for various preparations of (+)-naphthidine points up the great sensitivity of solid-state reaction kinetics to the previous history of the sample.[6] The rapid initial reaction shown in Figure 1 is opposite to the much more commonly observed induction periods followed by rapid acceleration for a solid-state reaction. The polycrystalline state of the sample, in which growth of the racemic product can immediately occur over a relatively large surface area, may be reflected in the observed initial rapid reaction. Consistent with this is that further division of the crystallites of the sample by grinding resulted in more rapid reaction to a greater extent (as shown in Figure 2 for a third preparation of (+)-naphthidine).

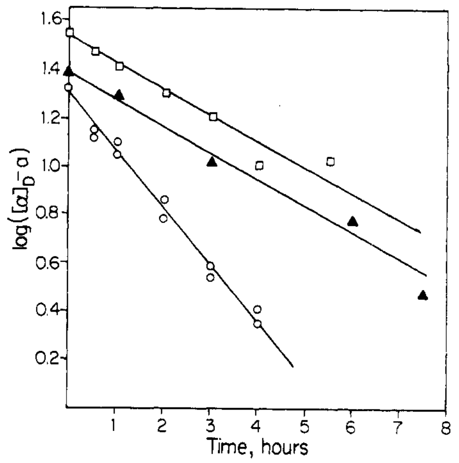

Figure 3. First order plots for racemization of (+)-naphthidine. The specific rotation at the end of the initially fast reaction, α, has been subtracted from the rotation at various times, $[\alpha]_D$: ○, sample 1, α = 18° at 150 °C; ▲, sample 2, α = 5° at 130 °C; □, sample 3, α = 20° at 130 °C.

The racemization rate up to the point where it almost stops (with a slow and erratic reaction thereafter) seems best described as a first-order reaction (see Figure 3). Preparations 2 and 3 gave essentially the same rate constant at 130 °C, even though the loss of optical activity slowed down at different fractions of the reaction. The more finely divided parts of the sample may follow a first-order equation, as is observed for some finely crushed inorganic powders,[7] while the second, slow, and widely variable part of the racemization may arise from differing amounts of larger crystals in the various batches. It should be noted that the incomplete racemization over much longer times of heating was not due to production of any nonracemizable products. Once dissolved, kinetic samples previously heated for long periods of time in the solid state racemized like normal naphthidine in solution. The great sensitivity of the rate and extent of racemization of the sample condition made any kinetic study on available polycrystalline samples less feasible, and they were not pursued further.

Mechanism of Racemization. The observed solid-state racemization might, in principle, arise simply from a conversion of a sample consisting only of enantiomorphic crystals of one configuration into an equal mixture of the two enantiomeric crystals (i.e., the production of a eutectic mixture). The driving force for racemization would then be only the greater entropy of the mixture and would be similar to the driving force for spontaneous racemizations in solutions. However, a free-energy change for ideal mixing in a solution amounts only to 580 cal/mol at 150 °C and would be even smaller in the less complete mixture of larger aggregates (crystallites) of the two enantiomers in a solid-eutectic system. The rigidity of molecules present in a crystallite would tend to kinetically prevent such a small free-energy decrease from coming into operation in a solid-state racemization. The result is that most optically active materials are optically stable indefinitely in the solid state even if a simple process (like the bond rotation in naphthidine) is possible for the racemization in the freer state of a solution. For example, no racemization of a 2,2′-disubstituted biphenyl compound occurred during heating at 100 °C for 55 days, even though, in solution, the half-life is 2 h at this temperature.[8]

A greater driving force for a solid-state conversion is possible if the racemization involves conversion to a structurally different (not just enantiomeric) product, i.e., the production of a racemic compound. Racemic naphthidine and optically active naphthidine do indeed have different crystal structures, as shown by the marked differences in their solid-state infrared spectra (especially in the 670–900 and 1000–1060 cm^{-1} regions).

In addition to differences in IR spectra, the transformation of a eutectic to a racemic form of naphthidine may be seen by changes in a (+)-naphthidine sample during differential-scanning calorimetry. A sample previously heated at 130 °C until it was 85% racemized showed endotherms for low-melting naphthidine (196–200 °C) which dominated the previously major endotherm (202–204 °C) shown by fully resolved naphthidine. Correspondingly, the IR spectrum of the heated sample showed development of the bands due to the racemic form. The naphthidine phase system is therefore one in which two polymorphic forms exist, a eutectic form (which may be optically active) and an inactive racemic form. The observed racemization on storage is accounted for in that the racemic form is more stable at room temperature and, from the kinetic data shown in Figures 1 and 2, up to at least 150 °C.

Phase Relationship of Naphthidine Polymorphs. A more thorough understanding of thermal racemization requires knowledge of the phase diagram of the two forms of naphthidine. In such a polymorphic system, two possibilities for relative stabilities exist.[9] Either the racemate is more stable than the eutectic form at all temperatures up to the melting point (a monotropic system) or it is stable up to a certain solid-to-solid transition temperature at which the eutectic solid becomes more stable (a so-called enantiotropic system). The first possibility must be excluded since the DSC results definitely showed that racemic naphthidine has a slightly lower melting point than the optically active eutectic form. A narrow range of temperature therefore exists in which the relative stabilities of the phases are racemate < melt < eutectic solid, and the eutectic solid is therefore stable with respect to the racemic solid, at least within that range. The solid-to-solid transition point for a change of racemic to eutectic forms must lie below 202 °C (the melting point of the racemate); the results of Figure 1 show that it lies above 150 °C. In order to refine this temperature range and determine the transition point, pairs of samples, one racemate and the other eutectic naphthidine, were heated at constant temperatures under vacuum for several hours. Up to 195 °C, the racemic sample remained unchanged (except for a slight yellowing) over a 1-week period, while after 24 h eutectic samples showed development of the IR bands of the racemic form. At 197 °C, however, the situation is reversed; eutectic crystals grow from racemate within 24 h, while a sample of eutectic crystals showed no change in its IR spectrum over 64 h. The temperature of the solid-state transformation of the two crystal forms must therefore be ~195–197 °C, and the phase diagram is correspondingly shown in Figure 4.

The solid states of naphthidine present an enantiotropic system in which each solid form has a range of true stability. The racemate is stable from below room temperature to 197 °C and metastable up to 202 °C, where it converts to melt. The eutectic form is the stable phase over the narrow range from 197 °C to ~204 °C, where an optically pure eutectic sample would melt and racemize. Below 197 °C, optically active naphthidine is metastable with respect to racemate and is thermally converted with accompanying racemization in a direct solid-to-solid-state reaction to the racemic form.

Except for the individual temperatures of transitions, the phase diagram of Figure 4 for naphthidine takes a form identical with that of binaphthyl.[1] The opposite characters of the solid-state reactions (i.e., racemization with naphthidine and resolution with binaphthyl) arise from the different ranges of temperature in which racemic and eutectic phases are stable. Above ~100 °C in a region where the rates of solid-state reactions of these organic solids are rapid enough to be noticeable, the eutectic form of binaphthyl is the stable state; with naphthidine (except for a narrow region of stable eutectic solid at 197–204 °C) the racemic form is the more stable state.

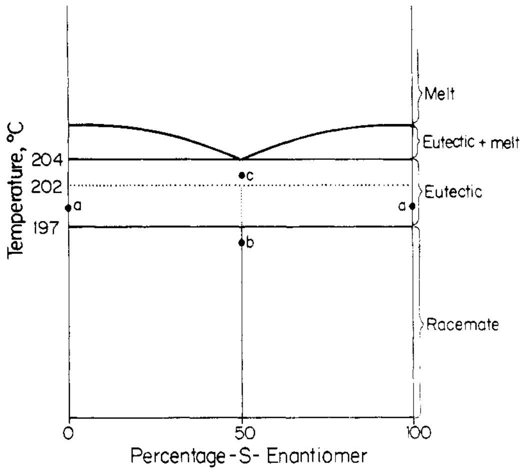

Figure 4. Phase diagram of the naphthidine system. The melting point of the racemic compound is 202 °C, of the eutectic form 204 °C, and the solid-to-solid-state transition temperature is 197 °C.

This pair of compounds (X = H and X = NH_2) thus provides an interesting contrast in stereochemical results (resolution vs. racemization) which, nevertheless, both arise from the same basic property, i.e., the highly stereospecific character of solid-state reactions. Clearly the difference lies in the presence or absence of the 4,4′-diamino groups on the binaphthyl system, which serve to shift the ranges of solid-state stabilities. The detailed crystal structure of naphthidine is not known,[10] and, in any case, a crystallographically based explanation of relative stabilities of polymorphic phases does not seem possible as yet.

Control of Racemization vs. Resolution. Although such stereospecific reactions in the organic solid state can therefore not be predicted on the basis of molecular structure, they can be utilized once the phase relationships are known. If, as shown below, seed crystals to promote growth of the other phase are present, the stereospecific character can be reversed simply by a variation of temperature by a few degrees. Eutectic naphthidine is stable and produced at 198 °C (points a on Figure 4) and racemic naphthidine is stable and produced at, say, 195 °C (point b on Figure 4). The existence of a temperature range at which the eutectic solid is the thermodynamically stable state suggests that optically active samples of this eutectic form may be produced by thermal treatment alone. This would be similar to the spontaneous solid-state resolution of binaphthyl.[1,2]

To investigate this possibility, 17 weighed samples of ordinarily prepared racemic naphthidine were heated to just above the melting point (point c on Figure 4). The naphthidine melted rapidly and then slowly crystallized. After ~5 hours at 203 °C, the samples were cooled, dissolved completely, and analyzed to give specific rotations of $[\alpha]_D$ +40, +16, +30, +14, +42, +9, +25, +31, +17, −2, +18, +36, +36, +24, +33, +32, and +30°. The samples had certainly resolved, some to nearly 100% optical purity ($[\alpha]_D$ ±49°). They also showed an interesting bias for production of the dextrorotatory enantiomer. (Had the bias been *absent*, the chance of obtaining the observed 16 dextrorotatory samples out of 17 trys would be only 1 in 7710.)[3] The racemic preparation had apparently picked up adventitious seed of the (+) enantiomer of naphthidine, which is the one predominate in our laboratory since it was previously produced by classical resolution procedures (see Experimental Section). The growth of these seeds present in the naphthidine melt accounts for the strongly biased results.

The presence of such seeds was further indicated when racemic naphthidine was heated to 215–220 °C, which is well above the melting point of both forms of naphthidine. This destroyed all seed crystals, and when the samples were returned to 203 °C no crystallization occurred over long periods of time. With further cooling (to 175 °C) crystallization occurred, but the samples were completely optically inactive and in the racemic form. Naphthidine melt has a great tendency to supercool, and spontaneous nucleation apparently does not occur in the range of temperature above 197 °C, where the optically active eutectic form is stable. Thus, in contrast to the demonstrated[2] spontaneous production of optical activity in binaphthyl, naphthidine cannot be made to resolve in a truly spontaneous way. Only a bias arising from inadvertent seeding may be amplified by growth of the eutectic form at 203 °C.

Some further variations of experiments arising from knowledge of the phase relationships given in Figure 4 are possible. Above 197 °C and below the melting point of 202 °C, samples of racemic naphthidine should undergo a direct solid-to-solid-state resolution reaction. Eleven samples of racemic preparation were heated to 197 °C, where only the eutectic form is stable. At this temperature the racemization observed up to 195 °C is reversed, resolution occurred, and after 65 h the samples showed rotations of $[\alpha]_D$ +13, −5.5, +25, +26, +29, +32, +39, +36, −3.0, +27, and +20°. Again a bias toward the (+) enantiomer is caused by the presence of adventitious seeds of the eutectic form. If such seeds are annealed out by heating samples at 192 °C for over 5 h (or melted out by heating to 215 °C and solidifying at 175 °C) and the samples then held at 197 °C, no production of optically active samples, nor even the growth of any eutectic crystals, was observed. The spontaneous nucleation of the eutectic form apparently does not occur in solid naphthidine. Also, as mentioned above, it does not occur in supercooled naphthidine melt in the 197–204 °C range.

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Registry No.—(*S*)-(+)-Naphthidine, 18531-98-1; (±)-naphthidine, 64282-15-1; (*R*)-(−)-naphthidine, 64235-43-4.

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Synthesis and Epoxidation Kinetics of Some Fused-Ring Cyclopropenes

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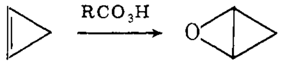
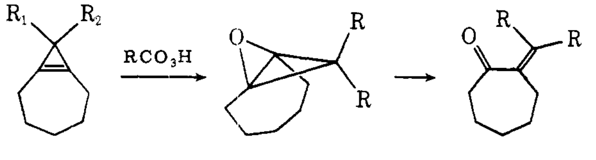
A series of 8,8-disubstituted bicyclo[5.1.0]oct-1(7)-enes was prepared. Measured relative rates of epoxidation were obtained for these allylically substituted fused-ring cyclopropenes. An attempt to fit the partial rate constants of epoxidation to a simple linear free energy dependence revealed a moderate backside interaction of the allylic cyclopropene substituents with the cycloheptane ring.

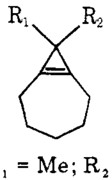
For many years we[4] have been attempting to delineate the details of cyclopropene epoxidations, since the expected initial product is an oxabicyclobutane. Oxabicyclobutanes have been postulated as unstable intermediates in many different reactions.[5] They are also interesting theoretical molecules due to a potential antiaromatic interaction of the cyclopropane ring with the neighboring nonbonded electrons on the oxygen atom. Such an interaction mimics the electronic π-type resonance in the yet to be synthesized oxirenes.[6]



Our previous work[4] has studied the epoxidation kinetics and products using simple cyclopropenes. In this work, we sought to epoxidize cyclopropenes that are fused to a seven-membered ring. Not only are the resulting intermediate oxabicyclobutanes unique and novel propellanes,[6b] but we also hoped to establish a quantitative linear free-energy relationship between the epoxidation rate constants and the steric substituent constants of the cyclopropene allylic substituents.



The desired cyclopropenes are compounds **1a–d**. These four compounds form two relevant series. The first series, **1a**, **1b**, and **1c**, can be used to probe the steric reaction constant with respect to allylic substituents of different size. The compounds in the second series, **1a**, **1b**, and **1d**, all have R_1 = Me with increasing steric bulk for R_2.



1a, R_1 = Me; R_2 = Me
1b, R_1 = Me; R_2 = Et
1c, R_1 = Et; R_2 = Et
1d, R_1 = Me; R_2 = *i*-Pr

Results

All four cyclopropenes were prepared by irradiation of the tosylhydrazone salts of their corresponding ketones, **2a–d**.