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Photoreactive Crystalline Quasiracemates

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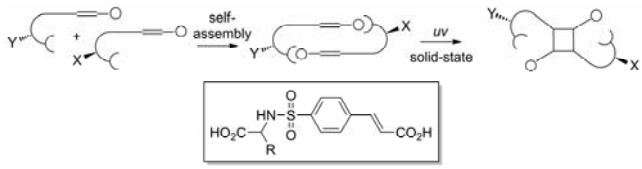
Rationally designed racemic and quasiracemic sulfonamidecinnamic acids assemble to give hydrogen-bonded dimers with coplanar alignment of neighboring olefins. The quasiracemate phase contains near inversion-related motifs with chemically distinct components forming supramolecular heterodimers that undergo asymmetric photodimerization.

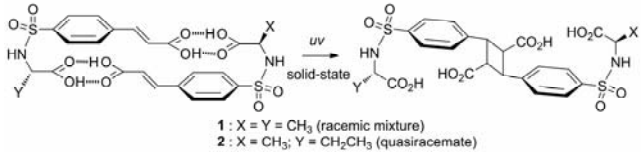
The utility of [2+2] photochemical transformations using molecular crystals continues to appeal to a wide range of disciplines that seek to understand and control the reactivity of molecular assemblies. Early success in this field can be traced to well-defined targets resulting in predetermined reactivity[1] as well as other notable examples derived from serendipitous routes[2]. The collective effort of these investigations provided contemporary developments to Schmidt and Cohen's seminal work on cinnamic acids[3] and recently paved the way for efforts that utilize the confined environments of host frameworks[4] and the directionality of molecular associations[5] for programmed reactivity. Studies that seek to align pairs of photoactive components in the solid-state have become more commonplace in the literature. Nonetheless, extending this work to the construction of reliable heteromeric assemblies[1a-b,6] or stereospecific transformations[1c,7] remains a considerable ongoing challenge for supramolecular chemists. From a design standpoint, the difficulty with directing molecules to participate in such reactions stems from the exquisite control required to implement motif asymmetry and the fundamental aspects of crystal cohesion.

Our contribution to this area combined the structural utility of 'fish hook' shaped molecular olefins and quasiracemic materials to access absolute asymmetric crystal reactions. Quasiracemates, materials consisting of equimolar portions of quasienantiomers, crystallize with near inversion symmetry that mimic the packing preferences of their racemic counterparts.[8] A recent application of the quasiracemate approach to lattice-controlled reactions involved asymmetric polymerization of mixed crystals constructed from (*R*)-phenylalanine- and (*S*)-(3-(2-thienyl)-alanine *N*-carboxyanhydrides.[9] Desymmetrization of the packing motifs *via* near inversion relationships of the components gave enantiopure isotactic polypeptides. In principal, this strategy to induce chirality by exploiting the packing preferences of quasiracemic materials should also apply to other crystal transformations such as [2+2] photodimerizations. Many examples that exhibit this reactivity pattern align with centrosymmetrically related components to give the expected topochemically derived head-to-tail products (α-truxillic acids).[3,10] Given the inversion relationships of these assemblies, we envisioned that the quasiracemic approach could present an attractive opportunity to explore and control chemical reactivity. Moreover, since quasiracemate construction involves heteromeric pairs of enantiopure compounds, the application of this general method offers promise as a facile entry point for controlling chirality of solid-state processes.

Component selection for this study followed several key criteria: isosteric molecular pairs that differed in handedness (a quasiracemate), restricted conformations that resembled molecular 'fish hooks', hydrogen-bonded dimers, and favorable olefin alignment. Although the design of these materials followed a rational plan toward predictable motifs (Scheme 1, top), identifying potential candidates that integrate each design element presented considerable challenges due to complexity and interdependence of the selection criteria. Inspiration for these reactive quasiracemic assemblies originated from previous structural investigations of diarylsulfonamides[11] and a photoreactive rigid "U" shaped naphthoic acid-derived cinnamic acid[12] where both examples displayed molecular conformations consistent with the design requirements of this study. Modifying the core sulfonamide framework of ref. 11 to include both cinnamic acid (photoreactive olefin) and amino acid (chirality) functions combined the necessary structural features to synthesize the target sulfonamidecinnamic acids (Scheme 1, bottom).



Scheme 1 Design strategy (top) and molecular targets (bottom) for the construction of photoreactive sulfonamidecinnamic acids.



Scheme 2 Depiction of racemic and quasiracemic supramolecular assemblies engineered for [2+2] photodimerization reactions.

Sulfonamidecinnamic acids **1** and **2** were easily accessed by a cost-effective, high-throughput two-step process. While free rotation about the sulfonamide and amino acid bonds is possible, we anticipated this molecular framework would adopt the critical 'fish hook' shape, directed by carboxyl O-H···O dimer formation. When X = Y (Scheme 2), the

application of this design strategy results in racemic mixtures, whereas the use of chemically unique components (X ≠ Y), as in the case of **2** [*i.e.*, (*R*)-CH_3 and (*S*)-CH_2CH_3], create chiral assemblies capable of generating asymmetric α-truxillic acid photoproducts when irradiated.

This approach to guided assembly was initially applied to the racemic alanine derivative **1**. Colorless plate crystals of **1** were grown from an acetone solution and X-ray crystallographic assessment showed components adopting conformations with the carboxyl group of the alanine fragment positioned directly beneath the cinnamic acid group (Fig. 1, left). This compound crystallized in space group $P\bar{1}$ with each racemic pair organized into centrosymmetrically related homodimers by carboxyl···carboxyl interactions (O-H···O, 2.643 and 2.661 Å) (Fig. 1, right) that further associate with neighboring dimers *via* N-H···O=S contacts. Though the success of this discrete motif can be attributed to the cohesive and directional properties of hydrogen bonds, both chirality and molecular shape played key roles in spatial organization.

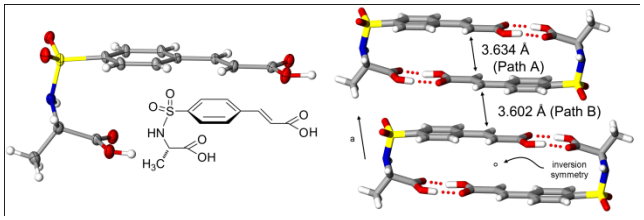


Fig. 1 Crystal structure of racemate **1** showing the 'fish hook' molecular conformation (left) and favorable alignment of homodimers and neighboring olefins (right).

Extending this work to quasiracemates involved use of a 1:1 bimolecular compound constructed from chemically unique sulfonamidecinnamic acids [**2**, X = (*R*)-CH_3 and Y = (*S*)-CH_2CH_3, Scheme 2]. Despite the distinct chemical and topological properties of the $–CH_3$ and $–CH_2CH_3$ substitutions, co-crystallization of these homochiral components resulted in single crystals with unit cell parameters and packing motifs nearly identical to those cited for racemic **1**. It is noteworthy to mention that the robust nature of the hydrogen-bonded dimers and crystalline frameworks of **1** are tolerated in quasiracemate **2** despite the imposed chemical variations. Also, unlike **1**, the supramolecular patterns observed for quasiracemate **2** are rigorously noncentrosymmetric (space group *P*1) (Fig. 2). This molecular assembly offers an unprecendent approach to the spatial control of molecular associations and, in our case, the control of chirality in solid-state transformations.

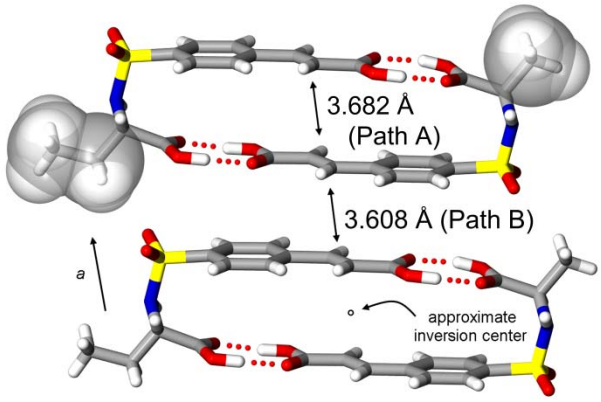


Fig. 2 Crystal structure of quasiracemate **2** showing the chiral alignment of heterodimers, spatial variation of CH_3 and CH_2CH_3 groups, and close stacking of neighboring olefins.

The novel molecular recognition profile of these systems is well suited to investigate photodimerization reactions in crystals. Figs. 1 (right) and 2 show the hydrogen-bonded homodimer of **1** and heterodimer of **2** organized with parallel alignment of neighboring cinnamic acid olefin groups (Path A). The distance between the centers of adjacent C=C bonds [**1**, 3.634 Å; **2**, 3.682 Å] was within Schmidt's 4.2 Å threshold for reactivity[3], thus indicating the topochemical feasibility of conducting photoreactions with these systems. While the close proximity of olefinic groups offered a reasonable mode for cyclobutane formation another plausible path exists. In addition to favorable separation of intra-dimer olefins (Path A), similar short C=C···C=C contacts existed between these discrete motifs *via* Path B. This raised the question of whether the UV initiated reaction will proceed by a single reaction path. If not, how would this affect reaction outcomes? For **1**, both Paths A and B yield identical racemic photoproducts, but invoking the analogous contacts with quasiracemate **2** would give two distinct compounds, both homochiral, but diasteriomerically related.

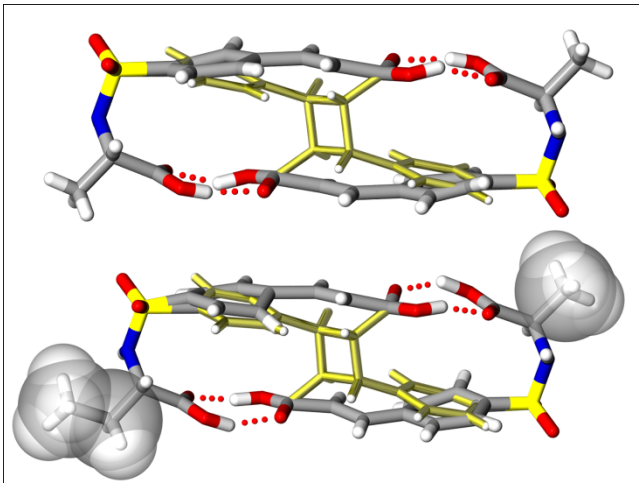


Fig. 3 Crystal structure projection of racemate **1** (top, 72% conversion) and quasiracemate **2** (bottom, 61% conversion) obtained after UV irradiation for 26 hours.

Single-crystal-to-single-crystal transformations were

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performed on crystals of **1** and **2** *via* the UV tail-irradiation technique[5b,13] using a 200W Xe(Hg) arc lamp equipped with a 360nm optical edge filter [**1**, λ_{max} = 280nm]. During UV exposure, crystal color and morphology remained intact providing an opportunity to investigate reaction outcomes by X-ray crystal analysis. Periodic X-ray data collection of **1** and **2** showed photodimerization occurred exclusively by the intra-dimer route (Path A) in reasonable yields [26 hr: 72% (**1**) and 61% (**2**)] (Fig. 3). Unutilized Path B, determined by inspection of ΔF density maps of crystal structure electron density, was somewhat surprising since the distance between inter-dimer olefins is slightly less than Path A. One explanation for the observed selectivity may relate to the degree of π-orbital overlap of the reacting centers. Intra-dimer C=C bond slip distance is considerably less [1.01 Å (**1**) and 1.16 Å (**2**)] than those observed for the inter-dimer contact [1.49 Å (**1**) and 1.59 Å (**2**)]. This supports the idea that geometry, not just distance, controls the outcome of chemical transformations in molecular crystals.[3a,14]

In conclusion, this report demonstrates an unprecedented approach to regio- and stereocontrolled [2+2] photodimerization reactions in molecular crystals. Such work is based on rationally designed chiral sulfonamide cinnamic acids that readily form robust supramolecular dimers *via* the complementary features of non-bonded contacts and molecular shape. Construction of these hydrogen-bonded dimers using racemic or quasiracemic molecular pairs effectively aligns reactive centers to give cyclobutane photoproducts in 61-72% yield. In the case of quasiracemate **2,** the asymmetric crystalline environment translates to enantiopure reaction products.

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Notes and references

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† Electronic Supplementary Information (ESI) available: detailed description of synthesis, ^{1}H-NMR, and ^{13}C-NMR analyses. See DOI: 10.1039/b000000x/

‡ Crystallographic data: **1 (unreacted):** $C_{12}H_{13}NO_6S$, M = 229.3, T = 100(2)K, triclinic, $P\bar{1}$, a = 7.2052(2), b = 8.2040(2), c = 11.3088(3) Å, α = 91.461(1), β = 92.761(1), γ = 90.699(1) º, V = 667.43(3) Å^3, Z = 2, D_c = 1.489 g cm^{-3}, refls collected = 13877, unique = 2380, (R_{int} = 0.0372), final R indicies [I >2σ]: $R1$ = 0.0447, $wR2$ = 0.1091, $GooF$ = 1.103. **1 (reacted):** $C_{12}H_{13}NO_6S$, M = 229.3, T = 296(2)K, triclinic, $P\bar{1}$, a = 7.1475(1), b = 8.1722(1), c = 11.5458(2) Å, α = 91.920(1), β = 93.863(1), γ = 94.634(1) º, V = 670.153(17) Å^3, Z = 2, D_c = 1.483 g cm^{-3}, refls collected = 13739, unique = 2379, (R_{int} = 0.0372), final R indicies [I >2σ]: $R1$ = 0.0449, $wR2$ = 0.1205, $GooF$ = 1.048. **2 (unreacted):** $C_{25}H_{28}N_2O_{12}S_{12}$, M = 612.6, T = 100(2)K, triclinic, $P1$, a = 7.3133(3), b = 8.2316(3), c = 11.5670(4) Å, α = 88.171(3), β = 84.518(3), γ = 86.427(4) º, V = 691.57(5) Å^3, Z = 1, D_c = 1.471 g cm^{-3}, refls collected = 6649, unique = 3209, (R_{int} = 0.0277), final R indicies [I >2σ]: $R1$ = 0.0415, $wR2$ = 0.1047, $GooF$ = 1.038. **2 (reacted):** $C_{25}H_{28}N_2O_{12}S_{12}$, M = 612.6, T = 296(2)K, triclinic, $P1$, a = 7.2486(2), b = 8.1094(2), c = 11.8857(3) Å, α = 89.015(2), β = 82.881(2), γ = 83.670(3) º, V = 689.05(3) Å^3, Z = 1, D_c = 1.476 g cm^{-3}, refls collected = 7005, unique = 4837, (R_{int} = 0.0157), final R indicies [I >2σ]: $R1$ = 0.0434, $wR2$ = 0.0945, $GooF$ = 1.016.

X-ray diffraction data were collected on a Bruker APEX-II [**1**(unreacted/reacted), **2**(unreacted), CuKα radiation: λ=1.54178 Å] and P4 CCD [**2**(reacted), MoKα radiation: λ=0.71073 Å] diffractometers. Empirical absorption corrections were applied using SADABS.[15] Structures solved by direct methods and refined by full-matrix least-squares analysis on F^2 using SHELX.[16] Non-hydrogen atoms corresponding to reactant (six phenyl and two olefin C atoms) and product (six phenyl and two cyclobutane C atoms) were located on successive ΔF density maps. Percent conversion was estimated by refinement of the occupacy factors of each phase with the sum constrained to 1.0. CCDC 782795-782798 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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