Cocrystallization of 4-chlorostilbazole (4-Cl-sbz) with either resorcinol (res) or 4-ethylresorcinol (4-Et-res) yields three-component molecular assemblies, (res)\(_2\)(4-Cl-sbz) and (4-Et-res)\(_2\)(4-Cl-sbz), held together by two O–H···N hydrogen bonds. The olefins of each assembly conform to the distance criterion of Schmidt for [2+2] photoreaction. In the former, the olefins lie antiparallel, whereas in the latter, the olefins lie parallel. Both solids are photoactive, leading to the regiocontrolled solid-state synthesis of rctt-1,2-bis(4-pyridyl)-3,4-bis(4-chlorophenyl)cyclobutane (4-Cl-dpcb) in near or quantitative yield. The photoactivity of (res)\(_2\)(4-Cl-sbz) is attributed to the reactant undergoing a pedal-like change in conformation prior to cyclobutane formation. 

The realization that covalent bonds can form in molecular solids suggests a possibility that the solid state can be used as an environmentally friendly, or "green", solvent-free medium for conducting molecular syntheses with freedoms of the liquid phase (e.g., reliability, reactant diversity). Unfortunately, the constrained environment of the solid state owing to subtle structural demands of close packing and weak intermolecular forces has made it generally impossible to design molecules, a priori, that crystallize with certainty in position for reaction. This inability to reliably predict and, ultimately, control reactivity in molecular solids has placed severe limits on the sizes, shapes, and functionalities of targeted reactants and products, limits that are virtually nonexistent in solution.

We have introduced a flexible method for engineering [2+2] photoreactivity in the solid state that employs bifunctional molecules based on resorcinol (e.g., 5-methoxyresorcinol) in the form of linear templates that organize olefins linked to symmetrical bipyridines [e.g., trans-1,2-bis(4-pyridyl)ethylene (4,4′-bpe)] within discrete hydrogen-bonded molecular assemblies for reaction. By forcing reaction to occur within a discrete complex using relatively strong and directional forces, this approach eliminates many problems of intermolecular forces that have made such topochemical designs unreliable, the reactivity being determined by the ability of the template to preorganize the reactants in a position that conforms to Schmidt's two geometry criteria for reaction, namely, separation of <4.2 Å between double bonds and olefin alignment.

To develop a reactant library, we now turn to stilbazoles. Owing to the presence of a single hydrogen bond acceptor site, we anticipated that a single template would be required to position two stilbazoles for a regiocontrolled (i.e., head-to-head) dimerization, which, in turn, would allow us to address the reliability of the approach owing to either slippage or flipping of terminal groups of the reactants, which can lead to olefin misalignment (Scheme 1). Although misalignment occurs, we have determined that alignment can be achieved by changing the template to a homologue with functionality placed away from the reaction center (i.e., in the 4, 5, or 6 position) such that olefin alignment is a consequence of the crystal-packing demands of the new template. In addition to expanding this method to monofunctional reactants, such an ability to achieve Schmidt's alignment criterion for reaction by placing a substituent along the periphery of the template is, owing to the modularity of this method, expected to increase the synthetic flexibility of this approach.

Addition of 4-chlorostilbazole (4-Cl-sbz) (0.040 g) to resorcinol (res) (0.010 g) in a boiling aliquot of EtOH (3 mL) and chloroform (2 mL) yielded, upon slow cooling and solvent evaporation, colorless crystals of (res)\(_2\)(4-Cl-sbz) suitable for X-ray analysis (100% yield). The
formulation of (res)-2(4-Cl-sbz) was confirmed by \(^1\)H NMR spectroscopy and single-crystal X-ray diffraction.\(^{16}\)

ORTEP perspectives of (res)-2(4-Cl-sbz) are shown in Figure 1. As anticipated, similarly to 2(res)-2(4,4′-bpe),\(^{6a}\) the components of (res)-2(4-Cl-sbz) assemble to form a three-component array held together by two intermolecular O−H⋯N hydrogen bonds [O⋯N separations (Å): O(1)⋯N(1), 2.689(2); O(2)⋯N(2), 2.741(2)]. In contrast to (res)-2(4-Cl-sbz), the olefins of the “superassembly” are organized such that the reactive sites lie in close proximity, with C⋯C separations between the olefins of 3.75 (C12⋯C25) and 4.40 (C13⋯C26) Å. Unlike 2(res)-2(4,4′-bpe),\(^{6a}\) however, the olefins adopt an antiparallel orientation such that the double bonds do not conform to Schmidt’s alignment criterion for reaction.\(^{18}\) Adjacent assemblies of (res)-2(4-Cl-sbz) pack in a parallel fashion to form a 2D layered architecture, the carbon atoms of nearest-neighbor olefins being separated by 4.67 Å.

Although the olefins of (res)-2(4-Cl-sbz) do not conform to Schmidt’s alignment criterion for [2+2] photoreaction, the stilbazoles are photoactive. UV irradiation of a powdered crystalline sample of (res)-2(4-Cl-sbz) (Hg lamp, 350 nm) for a period of 7 h produced a product consistent with a regiospecific dimerization that produces rctt-1,2-bis(4-pyridyl)-3,4-bis(4-chlorophenyl)cyclobutane (4-Cl-dpcb), as determined by \(^1\)H NMR spectroscopy, in quantitative yield. Crystallization of a portion (0.005 g) of the reacted material from a solution of EtOH (3 mL) and chloroform (2 mL) yielded single crystals of (res)-(4-Cl-dpcb), with confirmation of the structure of the product by X-ray analysis.\(^{19}\) As shown in Figure 2, the photoproduct assembles with the linear template by way of O−H⋯N forces [O⋯N separations (Å): O(1)⋯N(1), 2.690(4); O(2)⋯N(2), 2.745(4)] to form a discrete four-component array where a hydroxyl group of the template, in contrast to 2(res)-(rctt-tetraakis(4-pyridyl)cyclobutane),\(^{5a}\) adopts a divergent conformation along the periphery of the molecule. We attribute the generation of 4-Cl-dpcb to the reactant undergoing a pedal-like change in conformation in the solid,\(^{11−13}\) which enables the double bonds to adopt a parallel orientation and form the cyclobutane ring.

The observation that the double bonds of the discrete assembly (res)-2(4-Cl-sbz) do not conform to Schmidt’s geometry criteria for reaction prompted us to employ an alternative strategy to achieve olefin alignment. Although the olefins of (res)-2(4-Cl-sbz) are photoactive, we reasoned that such an approach would be useful for achieving reaction involving olefins of a discrete assembly that might be misaligned and photostable.\(^{13}\) To achieve olefin alignment, we turned to modifying the shape of the template by the addition of a substituent in a position away from the reaction center.\(^{20}\) We anticipated that such a change to the shape of the template would alter the crystal-packing environment of the assembly, and therefore of the reactant, which, owing to specific packing demands of the template,\(^{14}\) could then result in olefin alignment.\(^{13}\) Moreover, although an ability to successfully predict solid-state packing remains elusive,\(^{21}\) such switching of the template would, in effect, exploit unpredictable consequences of crystal packing, enabling this modular approach to increase the likelihood of achieving Schmidt’s alignment criterion for a [2+2] reaction.\(^{1}\)

Addition of 4-chlorostilbazole (0.031 g) to 4-ethylresorcinc (4-Et-res) (0.010 g) in a boiling aliquot of EtOH (3 mL) and chloroform (2 mL) yielded, upon slow cooling and solvent evaporation, colorless crystals of (4-Et-res)-2(4-Cl-sbz) suitable for X-ray analysis (100% yield). The formulation of (4-Et-res)-2(4-Cl-sbz) was confirmed by \(^1\)H NMR spectroscopy and single-crystal X-ray diffraction.\(^{22}\)

ORTEP perspectives of (4-Et-res)-2(4-Cl-sbz) are shown in Figure 3. Similarly to (res)-2(4-Cl-sbz), the components of (4-Et-res)-2(4-Cl-sbz) form a discrete three-component array held together by two O−H⋯N hydrogen bonds [O⋯N separations (Å): O(1)⋯N(1), 2.752(4); O(2)⋯N(2), 2.707(4)]. In this arrangement, the olefins of (4-Et-res)-2(4-Cl-sbz) conform to Schmidt’s distance criterion for photoreaction, the olefin C⋯C separations being 4.00 (C14⋯C27) and 3.84 (C15⋯C28) Å. In contrast to (res)-2(4-Cl-sbz), however, the olefins of the complex are aligned such that adjacent assemblies form a 2D herringbone motif,\(^{23}\) the carbon atoms of nearest-neighbor olefins being separated by 4.79 and 4.93 Å. Indeed, UV irradiation of a powdered crystalline sample of (4-Et-res)-2(4-Cl-sbz) produced the targeted product, 4-Cl-dpcb, in near-quantitative yield, as confirmed by \(^1\)H NMR spectroscopy. Thus, placement of the alkyl group along the periphery of the template in the 4-position has resulted in a change in packing of the
reactants, which, in turn, has induced olefin alignment. Moreover, because a virtually limitless number of such resorcinol derivatives are accessible,23 such observations suggest that such switching of the template can be exploited as a general means of achieving alignment of double bonds using this approach.6 From a synthetic perspective, this observation is important because such an ability to achieve olefin alignment is expected to increase the synthetic flexibility of this method, providing alternative supramolecular24 pathways to targeted molecular products.25

In this report, we have expanded a template approach for controlling reactivity in the solid state to monofunctional reactants, and we have demonstrated the ability of this method to achieve Schmidt’s alignment criterion for solid-state reaction by placing a substituent along the periphery of the template.12,13,14 With a library of reactants nonmerging, experiments are underway to apply this method to the targeted solvent-free synthesis of complex mono- and bifunctional products (e.g., nanostructures). Owing to the increasing reliability of this method, the deliberate solvent-free design of such targets should be feasible, so that access to molecules, and materials, less accessible using more traditional approaches can be realized.

Acknowledgment

We are grateful to the National Science Foundation (CAREER Award, L.R.M., DMR-0133138), the Natural Sciences and Engineering Research Council of Canada (research grant, L.R.M.; doctoral scholarship, J.L.R.), and the University of Iowa for support of the work. Acknowledgment is also made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (research grant, L.R.M.).

Supporting Information Available: Crystallographic reports and tables of positional and thermal parameters, bond lengths and angles, and 2H NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

Literature Cited

(11) Using a conceptually similar approach, phthalic acid has been employed to organize trans-cinnamamide within an infinite ribbon assembly such that the olefins adopt an antiparallel orientation and react to produce a photodimer in 13% yield. See: Ohba, S.; Hosomi, H.; Ito, Y. In Situ X-Ray Observation of Pedal-like Conformational Change and Dimerization of Trans-Cinnamamide in Cocrysists with Phthalic Acid. J. Am. Chem. Soc. 2001, 123, 6349.
(13) Orientation of the double bond of stilbene and derivatives is sensitive to crystal environment. This suggests that olefins of a discrete assembly similar to the hydrogen-bonded arrays described here can readily adopt either an parallel or antiparallel orientation in the solid state (see: Galli, S.; Mercandelli, P.; Sironi, A. Molecular Mechanics in Crystalline Media: The Case of (E)-Stilbenes. J. Am. Chem. Soc. 1999, 121, 3767), being either photostable or photoactive.
(15) 4-Chlorostylobenzene was prepared by an aldol-type reaction involving 4-picolinamide with 4-chlorobenzaldehyde.
(16) Crystal data for (res)-(2/4-CI-sbz): crystal size 0.20 × 0.25 × 0.40 mm, triclinic, space group P1, a = 9.926(1) Å, b = 10.203(1) Å, c = 13.865(1) Å, α = 105.433(3)°, β = 97.863(1)°, γ = 92.481(1)°, V = 1336.01(1) Å3, 2θ = 45°, Mo Kα radiation (λ = 0.7107 Å) for Z = 2 and R = 0.028.
An examination of the X-ray data reveals that electron density associated with a conformer that corresponds to parallel alignment of the olefins is not present.

Crystal data for (res)-(4-Cl-dpcb): crystal size 0.25 x 0.25 x 0.30 mm, monoclinic, space group C2/c, a = 38.240(4) Å, b = 9.463(1) Å, c = 14.971(1) Å, β = 98.193(3)°, V = 5362.3(9) Å³, 2θ = 45°, Mo Kα radiation (λ = 0.71070 Å) for Z = 2 and R = 0.060.

The 4, 5, or 6 position places the substituent in a location away from the active site of the template.


Crystal data for (4-Et-res)-2(4-Cl-sbz): crystal size 0.25 x 0.40 mm, monoclinic, space group P21/n, a = 8.572(1) Å, b = 36.722(2) Å, c = 9.739(1) Å, β = 108.457(1)°, V = 2908.1(3) Å³, 2θ = 45°, Mo Kα radiation (λ = 0.71070 Å) for Z = 2 and R = 0.056.


The significance of this observation in the context of targeted solid-state synthesis has not been discussed.

Received for review September 17, 2001
Revised manuscript received January 23, 2002
Accepted January 24, 2002
IE010775W