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Communication

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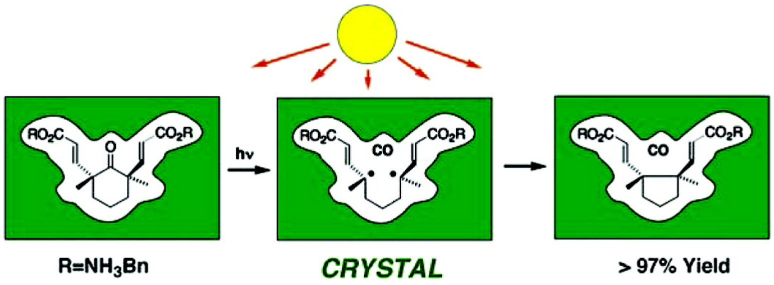

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Green Chemistry Strategies Using Crystal-to-Crystal Photoreactions: Stereoselective Synthesis and Decarbonylation of *trans*-α,α′-Dialkenoylcyclohexanones

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Although photochemical crystal-to-crystal reactions have been documented since the early nineteenth century,[1] most examples have been discovered by serendipity. It is only recently, and greatly motivated by the development of green chemistry,[2] that chemists have begun systematic studies of synthetically promising crystal-to-crystal reactions.[3] In a perfect setting, pure crystalline compounds would be activated to break and make bonds in a predictable manner. Multigram quantities of readily accessible crystalline reactants would be transformed into value-added crystalline products, perhaps by sunlight, with no need of external reagents or purification. Naturally, to reach this stage one must identify suitable reactions, develop mechanistic models to establish their generality, and ascertain the experimental feasibility of the method. With that in mind, we have recently explored the photodecarbonylation[4] of crystalline ketones as a model with far-reaching potential. The reaction is suited to address one of the most important challenges in organic synthesis: the construction of adjacent stereogenic quaternary centers (Scheme 1).[5,6]

The overall process may start with simple ketones and take advantage of several synthetic strategies to attach up to six α-substituents (R_1−R_6) in a stereoselective manner.[5,7] We have shown that a robust crystal lattice is needed to ensure that the stereochemistry of the reactant is transferred efficiently to the product and that the reaction relies on the high energy content of the ketone n,π^* excited state (ca. 80 kcal/mol) and on the effects of the α-substituents, which lower the bond dissociation energies of the two α-bonds.[4] Notably, taking acetone as a standard and assuming that bond cleavages in crystals must be thermoneutral or exothermic, we proposed that substituents with radical-stabilizing energies (RSE) greater than ca. 12−15 kcal/mol should enable the solid-state reaction.[4,8] In fact, several crystalline ketones with secondary, tertiary, and quaternary α-carbons bearing phenyl,[9] carbonyl,[8] and dialkoxy groups[10] support this model. Thus, recognizing the potential of α-akenyl-cyclohexanones as precursors of prostaglandins and other interesting structures, we decided to investigate the solid-state reactivity of a model structure. Although thermochemical values[11] suggest that crystals of these compounds should be highly reactive (RSE ≥ 18 kcal/mol),[12] solution studies have shown that β,γ-unsaturation often leads to concurrent 1,3-acyl shifts, oxa-di-π-methane rearrangements, intramolecular oxetane formation, and γ-hydrogen abstraction.[13] For that reason, it was important to determine whether the crystalline media could control the chemo- and stereoselectivity of the reaction, and whether the reaction may be carried out under environmentally benign conditions.

Searching for an efficient and simple preparation of bis-β,γ-unsaturated ketones, we decided test an extension of the conjugate addition of *tert*-butyl-substituted imines to acetylenic esters reported by Ito et al.[14] Although we found that alkyl propiolates fail to produce a double Michael adduct, presumably due to the steric demands of the second conjugate addition,[15] this was not the case when 2,6-dimethyl-cyclohexanone *iso*-butyl imine (**1**) was submitted to the reaction (Scheme 2). Although small amounts of *cis*-alkenoyl isomers were detected in the crude ^{1}H NMR spectrum, imine hydrolysis followed by equilibration of the ketone with 1 equiv of Bu_3P[16] yielded the *trans*-alkenoyl cyclohexanone isomers *trans*-**2** and *cis*-**2** in ca. 85 and 15% yields, respectively.

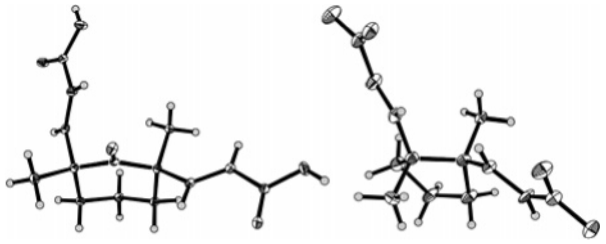
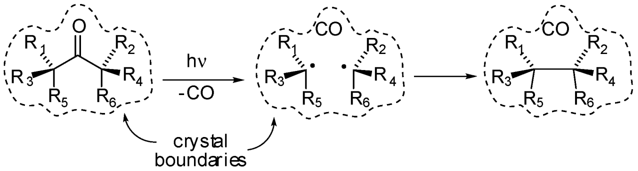
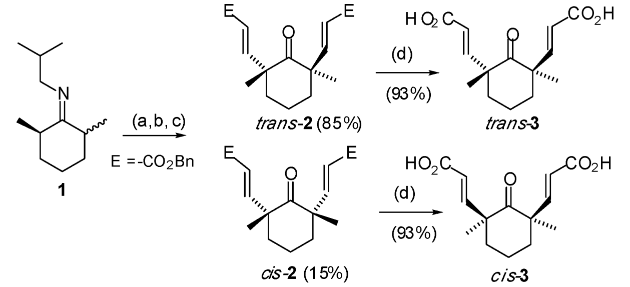


Figure 1. Single-crystal X-ray diffraction-derived ORTEP diagrams of cyclohexanone diacid *trans*-**3** (left) and cyclopentane diacid *trans*-**6**.[17]

Scheme 1



Scheme 2 [a]



[a] Conditions: (a) Benzyl propiolate 6 h, 80 °C. (b) $HCl_{(aq)}$, MeOH, reflux 3 h. (c) Bu_3P, toluene, reflux 12 h. (d) BBr_3 (3 equiv); NH_4Cl (aq).

The stereochemical relation of the methyl groups in *trans*-**2** and *cis*-**2** was established by single-crystal X-ray diffraction analysis of diacids *trans*-**3** (mp = 192−193 °C, Figure 1a) and *cis*-**3** (mp = 237−239 °C) obtained by removal of the benzyl group with BBr_3 (Scheme 2).

Solution photolyses of diesters *trans*-**2** and *cis*-**2** and diacids *trans*-**3** and *cis*-**3**, in dilute methanol-d_4 solutions (2 mg/mL), gave complex mixtures of products showing multiple vinyl hydrogens and methyl signals in their ^{1}H NMR spectra. In contrast, small-

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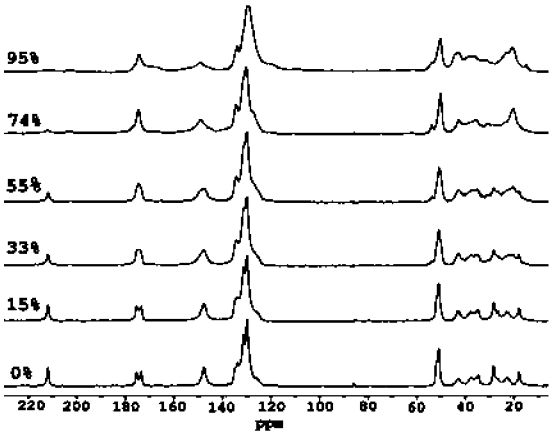
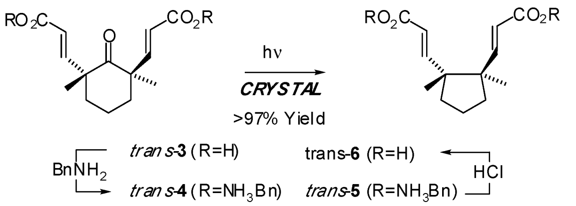


Figure 2. Collection of ^{13}C-CPMAS NMR spectra of *trans*-**4** at various degrees of conversion. The ketone peak at 212 ppm disappears as the reaction proceeds.

Scheme 3



scale photolyses of stereoisomerically pure samples of **2** and **3** in the crystalline state at 25 °C each yielded a single photoproduct at low conversion values (<20%), but a loss of selectivity due to partial melting was observed at higher conversion. Since Scheffer has shown that ionic crystals tend to be very robust in solid-state reactions,[3c] the quaternary ammonium salt *trans*-**4** (mp = 187−189 °C) obtained by addition of 2 equiv of benzylamine to *trans*-**3** was investigated in detail (Scheme 3). As expected, photolyses carried out with ca. 25 mg samples at 25 °C showed the formation of a single product in >97% yield, which was later shown to be the cyclopentane derivative *trans*-**5**. Dissolution and acidification of *trans*-**5** yielded the crystalline diacid *trans*-**6**, which was suitable for X-ray diffraction analysis[17] (Figure 1). Notably, the *trans*-dimethyl and *trans*-alkene configurations of the reactant were preserved in the structure of the product.

Microscopic observations of reacted samples of *trans*-**4** under polarized light revealed that crystals remain birefringent at all conversion values, as expected for a reaction that proceeds in a crystal-to-crystal manner. Differential scanning calorimetric[18] analysis of partially reacted samples revealed a eutectic temperature of 45 °C, indicating that reactions may be carried out at ambient temperature (ca. 20−25 °C) without the occurrence of liquid phases. Accordingly, analysis by ^{13}C CPMAS NMR as a function of irradiation time showed a smooth progression from 0 to 95% conversion (Figure 2). Searching for improved conditions, we discovered that microcrystals obtained from a rapidly cooled supersaturated acetone solution were ideal for large-scale reactions. A suspension of carboxylate microcrystals (1.5 g) in 100 mL of *n*-hexane irradiated with a medium-pressure Hg lamp using a Pyrex jacket ($\lambda \geq 290$ nm) proceeded to >97% conversion in 12 h, and the nearly pure photoproduct was simply collected by filtration. Qualitative experiments with 25 mg samples using sunlight resulted in quantitative reaction within 2 h.[19]

In conclusion, the combined effects of the α-alkenoyl and α-methyl groups in *trans*-**4** enable the photodecarbonylation of crystalline ketones by forming stabilized allyl radical intermediates. Following the loss of CO, the 1,5-biradicals react with chemoselectivity and stereospecificity that rival those observed in enzymatic processes. Notably, the use of ionic crystals results in a remarkable improvement in the efficiency of the solid-state reaction, and photolysis with suspended microcrystals and using sunlight hint at promising methods to scale-up these reactions into the multigram scale. Put together, these results and observations highlight the potential of crystal-to-crystal reaction strategies for the development of green chemistry.

Supporting Information Available: Photochemical procedures, synthesis of compounds **1**−**4**, analytical data for all compounds, and CIF files for *trans*-**2** and *trans*-**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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