# Large-Scale Green Chemical Synthesis of Adjacent Quaternary Chiral Centers by Continuous Flow Photodecarbonylation of Aqueous Suspensions of Nanocrystalline Ketones

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Ⓢ Supporting Information

ABSTRACT: To demonstrate the ease of scale-up and synthetic potential of some organic solid state reactions, we report the synthesis, crystallization, and solid state photochemistry of acyclic, homochiral, hexasubstituted (+)-(2R,4S)-2-carbomethoxy-4-cyano-2,4-diphenyl-3-pentanone **1**. We demonstrate that solid state photodecarbonylation of (+)-(2R,4S)-**1** affords (+)-(2R,3R)-2-carbomethoxy-3-cyano-2,3-diphenyl-butane **2** with two adjacent stereogenic, all-carbon substituted quaternary centers, in quantitative chemical yield and 100% diastereoselectivity and enantiomeric excess. The efficient multigram photodecarbonylation of (+)-(2R,4S)-**1** as a nanocrystalline suspension in water using a continuous flow photoreactor shows that the large-scale synthesis of synthetically challenging compounds using photochemical synthesis in the solid state can be executed in a remarkably simple manner.
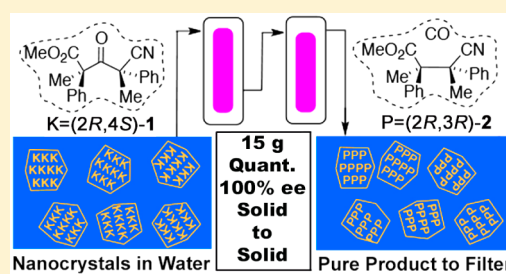
INTRODUCTION

Although photochemical reactions in crystalline solids are not as common as reactions in solution, there have been many examples reported in the literature that indicate clear advantages in the formation of structurally challenging products with a high level of selectivity and control.[1] With a potential for the solution of difficult transformations under conditions that require no organic solvents and no external reagents, solid state photochemistry fulfills some of the ideals of green chemistry,[2] especially when reactions can be carried out with sunlight.[3] A reaction that is particularly appealing from a synthetic perspective is the photodecarbonylation of crystalline hexasubstituted ketones,[4] which can cleanly and quantitatively afford compounds with adjacent quaternary stereogenic centers in one step from readily accessible starting materials, as illustrated in Scheme 1.

Over the past few years, we have analyzed the key factors that determine whether or not a particular ketone may react as desired in the crystalline state.[5] The most important requirement is the need for radical stabilizing substituents at each of the two α-carbons,[6] as they make the stepwise formation of the biradical intermediate possible even within the rigid environment of a crystalline solid. The synthetic potential of the reaction relies on the memory of chirality enforced by the crystal lattice, and on the fact that the reaction can proceed from a pure solid reactant to a pure solid product if the reaction occurs at a temperature that is below the eutectic of the two-component reactant-product phase diagram.[3,7]

Despite the promising outlook in Scheme 1, the development of solid state photochemical reactions for synthetic applications seems to have been hampered by challenges involved in their execution to ca. 100% conversion, and their scale up to grams, kilograms, and potentially larger scales. Although some exceptions are known,[8] difficulties arise from their high light absorption, which causes large single crystals and dry powders to react on the exposed surfaces while leaving the rest of the material unreacted. Attempts to reach the inner portions of a crystal or the deeper layers of a powder sample by extended illumination generally compromise the integrity of the exposed photoproduct. While tumbling powder samples could in principle help reduce problems by helping ensure a more homogeneous light exposure, most dry powders tend to cake and lump, rather than free-flow. We have shown that a promising solution to this problem is the use of crystals in the size range of ca. 200−500 nm suspended in a nondissolving fluid, which for most organic samples can be water. We and others have shown that many organic compounds can form such nanocrystalline suspensions by the solvent shift or reprecipitation method originally described by Nakanishi et al.[9] The method consists of adding a highly concentrated solution of the sample of interest in a water miscible solvent, such as acetone, into rapidly stirring or vortexing water. Suspensions prepared with low sample loading (i.e., 10−50 μg/mL) are translucent and have limited light scattering, which makes them suitable for transmission spectroscopy, including laser pump−probe methods.[10] By contrast, suspensions prepared with high loading values (i.e., >1−5 g/L) have

Scheme 1

(2R, 4S)-**1**   (2R, 3R)-**2**
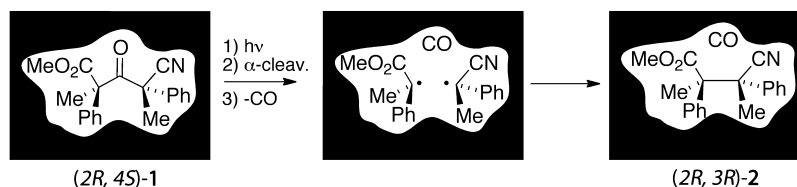
milky-white appearance and contain sufficient material to be useful for preparative reactions under conditions where all crystallites are exposed to light from a given source equally well.[11,12]

While nanocrystalline suspensions are ideal for reactions carried out in an immersion-well reactor equipped with a stirrer as all usable photons can be absorbed by the suspended nanocrystals surrounding the light source, the reaction size is limited to the reactor's volume. This was demonstrated on a 2 g batch photoreaction of nanocrystalline dicumylketone (DCK) suspended in water. We also showed that further scale-up, to a 10 g scale, could be accomplished by taking advantage of a recirculating flow system consisting of a reservoir with a pump that feeds the suspended nanocrystals into the reactor.[13] Flow conditions lead to uniform irradiation of the suspended crystals, and the extent of light-exposure from a given source can be controlled by the flow rate and reactor volume, helping address potential under- and overirradiation problems leading to low conversion or secondary photoproducts, respectively. Ideally, after the reaction is complete, the pure photoproduct can be filtered and the fluid recycled. In this paper, we describe the implementation of a nanocrystalline suspension flow method for the enantiospecific photodecarbonylation of a hexasubstituted homochiral ketone (compound (2R,4S)-**1**, Scheme 1), which is expected to generate the chiral hexasubstituted photoproduct (2R,3R)-**2** with adjacent homochiral quaternary centers.[14] We targeted 15−45 g reaction scales to show that the method has an ideal chemical performance, and that it should be scalable to the kilogram scale and further. Compound (2R,4S)-**1** was chosen to illustrate an example where the photoproduct (2R,3R)-**2** has α-ester and α-cyano substituents that can be used for subsequent derivatization. Considering the challenging structural motif that the photodecarbonylation reaction potentially addresses, as well as its simplicity and the ease of scale-up, we envision the large-scale synthesis of compounds analogous to (2R,3R)-**2** as a valuable addition to the chiral pool, which may elicit the creative endeavors of many synthetic organic chemists.

■ RESULTS AND DISCUSSION

Synthesis of (+)-(2R,4S)-1. The synthesis of optically pure hexasubstituted ketone (+)-**1** was accomplished in three steps from dimethyl 2-methyl-2 phenyl-malonate **3a**, as illustrated in Scheme 2.

Scheme 2
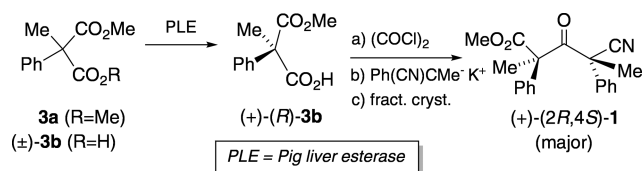
As in a previous study, the key stereogenic center in monoester (+)-(R)-**3b** was generated by enzymatic desymmetrization and hydrolysis carried out with pig liver esterase (PLE).[15,16] In the next step, acid (+)-(R)-**3b** was converted into the corresponding acyl chloride and reacted with one equivalent of the carbanion prepared from α-methylbenzylcyanide and KHMDS.[17] Purification by column chromatography followed by crystallization gave a pure dextrorotatory chiral ketone (+)-**1** in 80% yield. The minor diastereomer did not crystallize and no further purification was attempted. Samples of (±)-**1** were obtained in a similar manner from racemic (±)-**3b**. Crystals of ketone (+)-**1** were shown to have a melting point of 114−115 °C and not to include solvent of crystallization or display thermal phase transitions up to 125 °C by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Good quality single crystals of (+)-**1** were analyzed by X-ray diffraction, and the structure was solved in the chiral space group $P2_12_12_1$. Considering the known configuration of acid (+)-(R)-**3b**, we were able to assign the absolute configuration of the newly formed chiral center as S, which established the structure of the major product to be the chiral diastereomer (+)-(2R,4S)-**1**, as shown in Scheme 2 and in Figure 1. Also shown in Figure 1 are the X-ray structures of
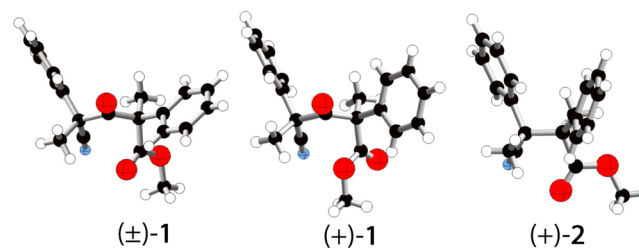

(±)-**1**   (+)-**1**   (+)-**2**

Figure 1. Molecular structures in the two enantiomorphous crystals of ketone **1**, racemic (left) and optically pure (middle), and the enatiomerically pure solid state photoproduct (+)-**2**. Their corresponding space groups are $C2/c$, $P2_12_12_1$, and $P2_1$ and their detailed information is included in the Supporting Information as crystallographic information files (cif).

the racemic ketone, (±)-**1** (mp 92−94 °C), which was solved in the space group $C2/c$, and the X-ray structure of the chiral photoproduct (+)-**2** that will be discussed below. It can be readily appreciated that the molecular structure in the two crystal forms display a very similar conformation, with some changes in the torsion angles of the two phenyls and carbomethoxy groups.

The molecular structures of (+)-(2R,4S)-**1** and (±)-**1** are characterized by a conformation where the (C5) methyl group attached to C4 is roughly aligned with the carbonyl C═O bond, while the (C1) methyl group attached to C2 points in the opposite direction. While ester carbonyl of (+)-(2R,4S)-**1** points away from the ketone, the corresponding carbonyl in (±)-**1** points in the same direction. The phenyl groups at C4

adopt an orientation where the C4-Ph bond is nearly orthogonal to the plane of the carbonyl, while the direction of the phenyl group at the C2 is roughly aligned with the direction of the C=O bond. The conformations of the two phenyl rings are such that their mean planes make dihedral angles with the α-bond that are nearly orthogonal, as required for their π-orbitals to delocalize the benzylic radicals that form as a result of the α-cleavage and decarbonylation reactions.[18] The π-bonds of the ester carbonyl and cyano groups are also well disposed for the stabilization of the intermediate radical centers.

Nanocrystals of Ketone (+)-(2R,4S)-1. The preparation of nanocrystals of (+)-**1** was explored by the "reprecipitation" method[19] using THF and acetone as good solvents. Only samples prepared from acetone and water, either alone or with sodium dodecyl sulfate (SDS) with concentrations 10−15 times below its critical micelle concentration were shown to be effective. It was shown that flowing nanocrystalline suspension had a tendency to stick to the (Pyrex) glass surfaces of the corresponding containers. This could be overcome by treatment of the polar glass surface with a commercially available silanizing agent (Sigmacote), which renders the glass surface hydrophobic allowing the nanocrystalline suspensions to free flow. This was a particularly important consideration during photochemical scale-up as aggregates that stick to the glass surface block the light from reaching the nanocrystals flow. Nanocrystals of (+)-**1** were generally characterized by dynamic light scattering (DLS) and sometimes by scanning electron microscopy, which revealed an average sample size centered in the range of ca. 420 nm. The identity of their crystalline phase was established by comparing their FT-IR and powder X-ray diffraction data (PXRD) from precipitated and filtered samples with those of samples obtained with powders prepared by gentle crushing of larger single crystals (Figure 2).
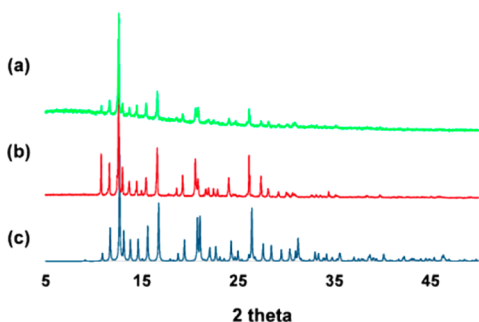

Figure 2. Powder X-ray diffraction PXRD pattern of (a) nanocrystals of chiral ketone (+)-**1**, (b) powder obtained from single crystal of (+)-**1**, and (c) PXRD pattern calculated from the single crystal structure of (+)-**1**.

Photochemical Studies. The photochemistry of ketones (+)-**1** and (±)-**1** was investigated in dilute (ca. 0.1 M) benzene solutions, as dry polycrystalline powders, and as nanocrystalline suspensions in water at ambient temperature. As summarized in Table 1, reactions were carried out with a medium pressure 400 W Hanovia Hg arc lamp using a Pyrex filter to select light with wavelengths λ > 290 nm. Analysis of the crude reaction mixtures from both optically pure and racemic samples in solution gave similar complex mixtures (Table 1, entries 1 and 2) with no less than ten products from radical combination,

Table 1. Conversion and Product Ratio Obtained upon Excitation of Ketone 1[a]

entry	medium	% conversion	% yield of 1[b]	dr[c] (% ee)[e]
1	(±)-**1** Solution[d]	100	18	1.3:1 (0)
2	(+)-**1** Solution[d]	100	18	1.3:1 (77)[e]
3	(+)-**1** Nanocrystalline Suspension	100	100	100:0 (100)[f]
4	(±)-**1** Dry solid	90	91	10:1 (0)
5	(+)-**1** Dry solid	62	96	24:1 (100)[f]

[a]Determined by GC and ¹H NMR. [b]Combination vs disproportionation products ratio. [c]Diastereomeric ratio. [d]Reaction in ca. 0.1 M benzene. [e]Enantiomeric excess of (+)-**2** established by ¹H NMR using the chiral shift reagent (+)-Eu(tfc)₃ in benzene-d_6. [f]Obtained as a pure crystalline phase.

disproportionation and polymerization reactions detected by GC−MS and ¹H NMR (Figure 3).

As illustrated in Figure 3 (top) and Scheme 3, analysis by GC−MS and ¹H NMR of samples reacted in solution revealed signals consistent with the products formed from two different tertiary free radicals. These include four radical combination products from homocoupling reactions as mixtures of *meso*- and *d,l*-diastereomers, two more radical combination products from heterocoupling reactions in the form of two racemic diastereomers, and four disproportionation products, including highly reactive acrylates prone to polymerization reactions, which further increase the complexity of the product mixture. Surprisingly we found that the photolysis in benzene of the homochiral ketone (+)-**1** afforded compound (+)-**2** in a modest 18% yield but with ca. 77% enantiomeric excess (Table 1, entry 2), as opposed to the expected racemic mixture associated with a free radical process. This result is in agreement with a previous report by our group, where the photodecarbonylation in solution of (*R*, *S*)-, (*R*, *R*)-, and (*S*, *S*)-bis-(*N*-methyl-phenylpyrrolidinonyl)-ketones occurs with remarkably high memory of chirality (ca. 80% ee).[20] By contrast, as shown in entry 3 in Table 1 and depicted in the bottom frame in Figure 3, reactions carried out with nanocrystalline suspensions of (+)-**1** were extremely clean and efficient, giving only the desired stereospecific recombination product, which was thoroughly characterized by spectroscopic methods and by single crystal X-ray diffraction. A comparison of the key aromatic, methoxy, and methyl regions in the ¹H NMR spectra of the crude reaction mixtures obtained in solution (Figure 3, top) and in the suspended nanocrystals (Figure 3, bottom) are a striking illustration of the reaction control exerted by the crystalline solid state.

Notably, reactions carried out with dry powders between two microscope slides or in a shallow bed on a Petri dish were not nearly as efficient or as selective, as indicated in entries 4 and 5 of Table 1. We infer that the heterogeneity of light exposure and sample heating result in some melting, such that some reaction control is lost leading to the formation of small amounts of disproportionation products and a small loss of diastereoselectivity.

We determined that photoreaction of the nanocrystalline suspension of (+)-(2*R*,4*S*)-**1** gives the corresponding stereospecific recombination product (+)-(2*R*,3*R*)-**2**. The identity of (+)-(2*R*,3*R*)-**2** was first confirmed by FT-IR, ¹H and ¹³C NMR, and mass spectrometry. The IR spectrum showed the characteristic frequencies of the ester at 1240 and 1729 cm⁻¹, and the absence of the C=O stretching vibration of the
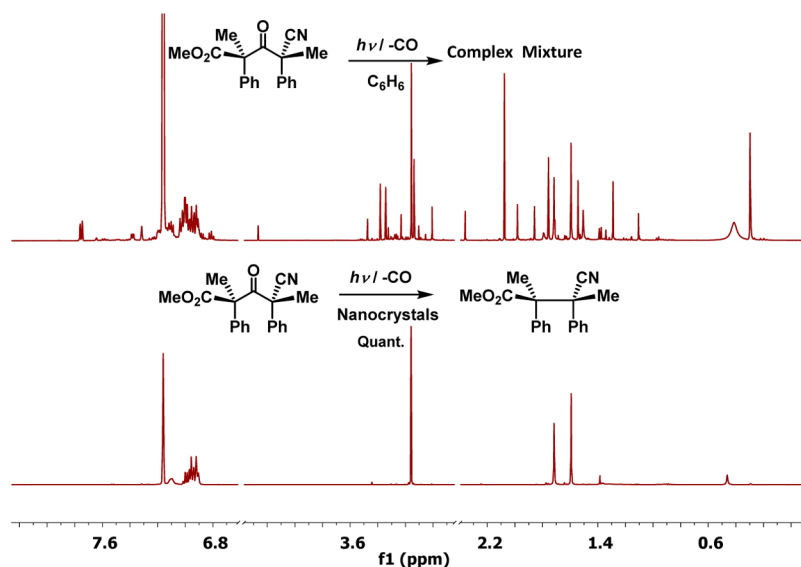
Figure 3. Aromatic (ca. 7.7−6.5 ppm), methoxy (ca. 3.75−2.75 ppm), and methyl group (ca. 2.25−1.25 ppm) sections of the ¹H NMR spectra measured with crude reaction mixtures from ketone (+)-**1** in benzene solution (top) and in a nanocrystalline suspension (bottom).
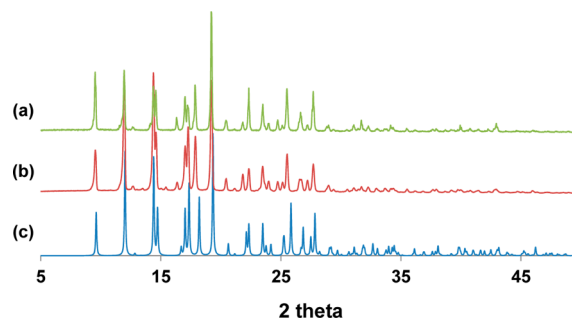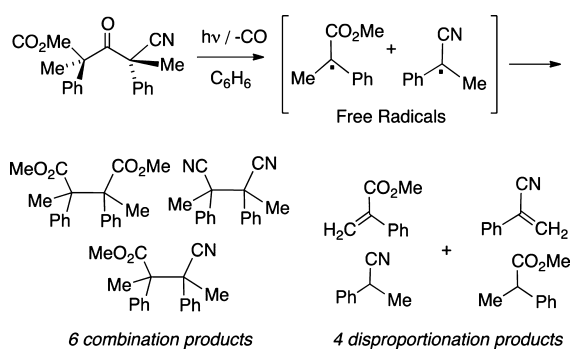
Scheme 3

Figure 4. Comparison of the experimental PXRD pattern of the product (+)-**2** using samples obtained from (a) powdered single crystals grown from acetone-diethyl ether; (b) filtered nanocrystals of the "as formed" photoproduct obtained from the solid-state photo-reaction, and (c) calculated from the single crystal structure of (+)-**2**.

starting ketone at 1760 cm⁻¹. The absolute configuration was established by correlating the single crystal X-ray diffraction structures of (+)-(2R,4S)-**1** and (+)-(2R,3R)-**2**, which confirms the retention in the adjacent carbons (Figure 1).[21] Thermal analyses of the starting material and the reactant by DSC showed melting transitions at 114−115 °C for (+)-**1** and 153 °C for the photoproduct (+)-**2**, suggesting that the reaction proceeds entirely in the solid state. Notably, as in many other cases reported in the literature,[7] the powder X-ray diffraction (PXRD) pattern of the as-formed solid-state photoproduct (+)-**2** is nearly identical to the one obtained from ground single crystals of the same compound, and the one calculated from the single crystal grown from acetone-diethyl ether (Figure 4). Considering that the reactant and product phase are crystallo-graphically very different, the formation of the stable product phase along reaction progress is consistent with a reconstructive phase transition mechanism.[4,7]

To determine the efficiency of the solid state photoreaction, we measured its quantum yield using dicumyl ketone (DCK) as a nanocrystalline actinometer, which was previously established to have a quantum yield $\Phi_{DCK} = 0.2$.[11] Experiments were carried out by mixing two independently prepared nanocrystal-line suspensions of DCK and (+)-**1**, making sure that their absorbances have similar values and are optically dense. Optical densities were established with an immersion probe and irradiation was carried out with an immersed 2.9 W pen light

source emitting at a wavelength of 302 nm. Under these conditions, the quantum yield (Φ_1) of (+)-**1** is given by,

$$\Phi_1 = N_1 \Phi_{DCK} OD_{DCK} / N_{DCK} OD_1$$

where N_1 and N_{DCK} are the number of moles of (+)-**1** and DCK reacted after a certain time, OD_1 and OD_{DCK} are the optical densities of (+)-**1** and DCK, respectively, and $\Phi_{DCK} = 0.2$. The relative number of moles of each ketone that reacted up to a given time was determined by ¹H NMR with the help of an external standard. Duplicate experiments resulted in a value $\Phi_1 = 0.29$ (± 0.05), which is consistent with the additional carbomethoxy and cyano radical stabilizing substituents in the case of ketone (+)-**1**, which are expected to make the two bond cleavage reactions more exothermic, faster, and efficient when compared to the effect of the methyl groups in DCK.

Scale-Up of the Photodecarbonylation Reaction in a Continuous Flow Reactor. The use of photochemistry in industrial-scale synthesis has been limited to relatively simple cases, such as the free radical Toray process[22] for the synthesis of caprolactam, which proceeds by irradiation of cyclohexane with NOCl and HCl and is carried out in dedicated plants producing >100 000 tons per year. While applications for the photochemical synthesis of more complex molecules with

stoichiometric amounts of photons is unlikely to require such a large volumes, the production of at least a few tons per year would be essential for the production of pharmaceuticals and some consumer products. On average, for every 1000 kg of material needed one should be able to prepare ca. 2.74 kg per day or ca. 114.2 g of the desired product per hour. It seems reasonable to assume that the scale-up of photochemical reactions up to this level should be entirely feasible by using either batch or flow reactors.[7] With the enantiospecific synthesis of molecules with adjacent stereogenic centers as a test,[23] and recognizing its potential in the development of green chemistry strategies,[2,3] we decided to investigate scale-up procedures using a continuous flow system.[24] We explored the use of one or two photoreactors (connected in series) equipped with 450 W medium pressure Hg arc lamps (Figure 5). To prepare the nanocrystalline suspensions in large
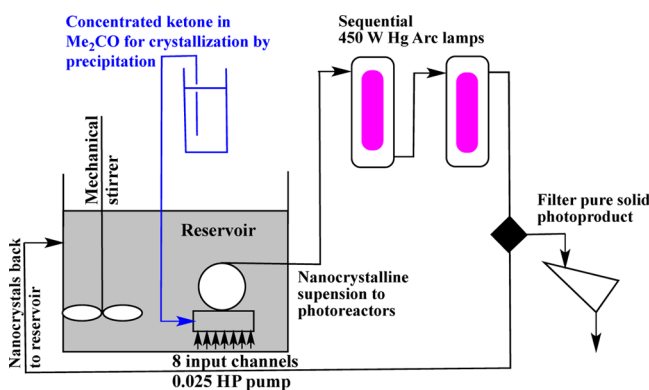

Figure 5. Diagram of the apparatus used for the photodecarbonylation reaction of nanocrystalline suspensions in a continuous flow systems with sequential water-cooled photochemical immersion reactors, each housing a 450 W medium pressure Hg arc lamp.

amounts, we implemented the use of a 0.025 HP submersible pump with 8 input channels and a premixing chamber that generates and sustains a vortex before delivering the resulting suspension into an exit channel toward the UV lamp(s). One of the input channels in the pump was connected to a smaller container where the starting material was dissolved in acetone (shown in blue in Figure 5). The other seven channels collected Millipore water from the large reservoir where the pump was submerged (illustrated with black arrows at the bottom of the pump). The nanocrystals formed upon mixing the acetone solution with the water were directed from the pump output to the photochemical reactor(s) and were circulated back to the reservoir for multiple cycles until the reaction was completed and the product collected by filtration.

To test the apparatus and establish the method, we carried out a reaction with 45 g of the readily available dicumyl ketone (DCK). A total suspension loading of 6.7 g/L was prepared in the above flow system using an 8 L reservoir with 5 L of water containing submicellar SDS and two photoreactors that have a total volume of 1.7 L[25] (Figure 5). The total irradiation time was 21 h for a conversion of 96%, which corresponds to the formation of the product at an apparent reaction velocity of 2.1 g per hour. The reaction of 43.2 g of starting material (0.135 mol) with a quantum yield of reaction $\Phi = 0.2$, required the use of 0.68 einstein (1 einstein = 1 mol of photons). If one assumes that the light used for this reaction is at $\lambda = 300$ nm (339.3 kJ/einstein), the reaction requires an energy use of 267.4 kJ, for a

power usage of only ca. 1.8 W per lamp. While this is a low efficiency process in agreement with the fact that arc lamps emit light at all wavelengths, one would expect a greater energy efficiency using sources with a more suitable energy output, such as UV light emitting diodes.

Experiments carried out with the significantly more valuable chiral ketone (+)-**1** were carried out at scales of 2, 4, and 15 g with some variations in suspension loading. Nanocrystalline suspensions were prepared with Millipore water containing submicellar sodium dodecyl sulfate (SDS). Suspended solids of (+)-**1** were used in the range of 0.6 up to 4 g/L with the submersible pump flowing the suspension from the reservoir into the water-cooled photochemical reactor until the reaction was complete. Although apparent reaction velocities for product formation depend on the setup used and extent of reaction, observed values were in the range ca. 0.4 g/h per UV lamp. By contrast, a reaction carried out with dry powders at a much smaller scale (e.g., 40 mg) proceeded to completion with an apparent reaction velocity of 0.0014 g/h per UV lamp, which is a factor of ca. 286 slower. At the end of the flow reactions, nanocrystals of product (+)-**2** were collected with a cellulose filter (11 μm nominal retention size) and dried. Analyses by ^{1}H NMR, GC, and TLC of the flow reactions revealed no byproducts.

■ CONCLUSIONS

We demonstrated that the enantiospecific photodecarbonylation of nanocrystalline hexasubstituted ketones may be easily scaled to multigram quantities by taking advantage of a stop flow reactor to produce compounds with adjacent stereogenic quaternary centers in near 100% yield, with quantitative diastereoselectivity and enantiomeric excess, and with no need for extraction, removal of reagents, or purification. With reactions carried out at scales of 2, 4, 15 g of ketone (+)-**1** and 45 g in the case of dicumylketone, we were able to determine that aqueous nanocrystalline suspensions with loading of 5 g/L prepared by the reprecipitation method, and the use of a flow system with sequential 450 W photochemical reactors, provide the means to carry out reaction with apparent velocities of ca. 0.5−1.0 g/h per reactor. We propose that the scale-up of reactions that transform readily accessible crystalline reactants into crystalline solids of highly desirable but otherwise challenging structures will provide a valuable additional tools and methods for the development of green chemical synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthesis and characterization of ketones ($\pm$)-**1** and (+)-**1** as well as of their corresponding photoproducts, ($\pm$)-**2** and (+)-**2**, respectively. Detailed procedures for photochemical reactions in solution and in the solid state, including detailed procedures for the generation of nanocrystalline suspensions and their use in photochemical flow reactors. Crystallographic information files (cif) of ($\pm$)-**1**, (+)-**1**, and (+)-**2**. A detailed description of the method used to determine quantum yields in the solid state. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(25) A detailed description of the dimensions of the batch and continuous flow photoreactor is included in the Supporting Information section.