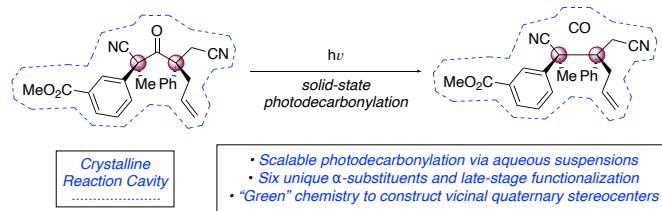


Scalable Synthesis of Vicinal Quaternary Stereocenters via the Solid-State Photodecarbonylation of a Crystalline Hexasubstituted Ketone

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ABSTRACT: We report the synthesis and stereospecific solid-state photodecarbonylation of a hexasubstituted ketone featuring six distinct α -substituents. The photoproduct of the solid-state transformation features vicinal all-carbon quaternary stereocenters. While reactions carried out in bulk powders and aqueous crystalline suspensions were complicated by secondary photochemistry of the primary photoproduct, optimal conditions provided good yields and recyclable starting material. Subsequent transformations of the α -substituents having orthogonal chemical reactivity illustrate the potential of this transformation towards constructing complex architectures.

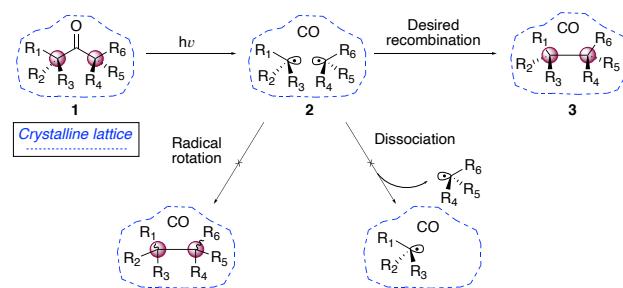
Vicinal, stereogenic, all-carbon quaternary centers (VSAQCs) embedded in the core of complex small molecules and natural products constitute a compelling, yet challenging to construct, motif in organic synthesis.¹ The inherent steric encumbrance of the two quaternary carbons hampers many conventional C–C bond-forming methodologies. While elegant solutions have been devised for the total synthesis of several natural products and related scaffolds,² a general and efficient method that meets the ideals of green chemistry³ remains a highly desirable addition to the synthetic organic toolbox. To that end, while underexplored compared to their solution-phase counterparts, photochemical reactions in crystalline solids have been known to exhibit notable advantages. Efforts in crystal engineering have spurred the design of, amongst others, precise crystalline supramolecular templates and photoswitchable moieties.^{4,5} These systems exhibit photochemical reactivities and mechanical effects not typically observed in solution, and showcase promise in altering the properties of APIs and engineering dynamic organic materials.

Our group has previously shown examples where the solid-state photodecarbonylation of crystalline ketones can be a highly selective method to access VSAQCs-containing molecules (Scheme 1a).⁶ In these transformations, hexasubstituted ketone **1** undergoes photochemical excitation and subsequent decarbonylation to furnish radical pair **2**. Restricted motion of **2** within the crystalline lattice prevents radical rotation prior to recombination to provide **3** with retention of configuration. The rigid reaction cavity also limits the number of products as compared to those observed in solution because it avoids alternative reactions arising from the dissociation of radical pair **2** to form free radicals. In this study, we address a more com-

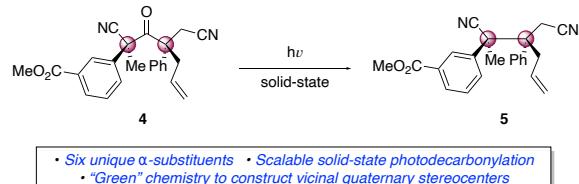
plex substrate featuring multiple orthogonal functional groups that may be viewed analogously to synthons for more complex structures.

Scheme 1

A: General photodecarbonylation



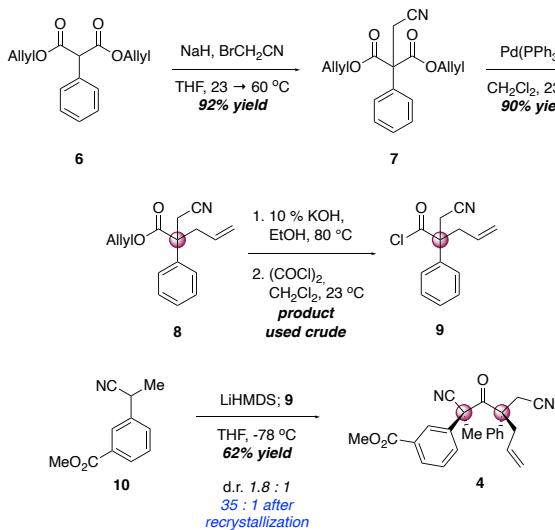
B: This work



To assess the ability of the solid-state photodecarbonylation reaction as an entry to construct complex molecules with six different functional groups, we prepared hexasubstituted ketone **4** and tested its photochemical reactivity in the crystalline solid-state (Scheme 1b). This substrate represents one of the most complex crystalline ketones studied to date, and the syn-

thetic versatility of photoproduct **5** can be explored by the selective transformations of the orthogonal functional handles. We suggest that the opportunity to readily prepare drug-like VSAQCs-containing compounds with low molecular weight and complex three-dimensional functionality may open new avenues for the medicinal chemistry community.^{7,9}

Scheme 2



Our synthetic approach to ketone **4** is depicted in Scheme 2. The synthesis commenced by cyanomethylation of malonic ester **6** under basic conditions to give the symmetric bis(allyl) ester **7** in 92% yield. This fully substituted ester was then subjected to a palladium-catalyzed Tsuji-Trost allylation to give allyl ester **8** in 90% yield, furnishing one of the requisite quaternary stereocenters present in **4**. This was followed by a two-step saponification, dehydrochlorination sequence to provide **9**, which was carried forward without further purification due to its hydrolytic lability. Acid chloride **9** was then coupled with the lithium carbanion of **10** to afford ketone **4** as a viscous oil in yields of 45–60% and a diastereomeric ratio (d.r.) of 1.8:1. Diastereomeric resolution of **4** was achieved through fractional recrystallization (see SI page S7). After subjecting the solids to three recrystallization cycles, a d.r. greater than 30:1 was achieved. The minor diastereomer **5** remained a viscous oil despite exhaustive attempts to nucleate crystallization and was therefore not a suitable candidate for a solid-state photodecarbonylation analysis.¹⁰ Single crystals of **4** obtained by slow solvent evaporation were suitable for X-ray diffraction structural elucidation. The structure was solved in the triclinic space group $P\bar{1}$ with a unit cell having the two enantiomers related by a crystallographic inversion center. The molecule adopts a conformation where the \square -cyano and \square -cyanomethyl groups are linked by bonds that are approximately aligned with plane of the carbonyl group, the two aromatic groups directed towards one side of the plane, and the methyl and allyl groups directed towards the opposite direction. The dihedral angles formed by the plane of the aromatic rings and the sigma bonds undergoing \square -cleavage are 74° (*m*-MeOCOPh-) and 50° (Ph-), which are stereoelectronically suited to exert sufficient benzylic stabilization of the incipient carbon-centered radicals (Figure 1).¹¹ The crystal structure also revealed the relative configuration of the two stereocenters to be (R,S) / (S,R) (Figure S3).

With crystalline **4** in hand, we set out to explore the photodecarbonylation of **4**. Table 1 summarizes the results in dilute solutions and in crystalline solids in the form of bulk dry powders or aqueous suspensions. Reactions carried out in dilute benzene solutions of **4** (Table 1, entry 1) resulted in full conversion within 2 h of irradiation, yielding very complex product mixtures. The recombination photoproduct **5** was isolated in a yield of 16% and d.r. of 1.8:1.¹² New vinyl group resonances between 6.5–6.0 ppm in the ¹H NMR spectrum of the crude material suggested that some of the side products arise from disproportionation reactions. Both the low chemical yield and the poor stereospecificity of **5** in solution are consistent with a mechanism that involves free radical products.

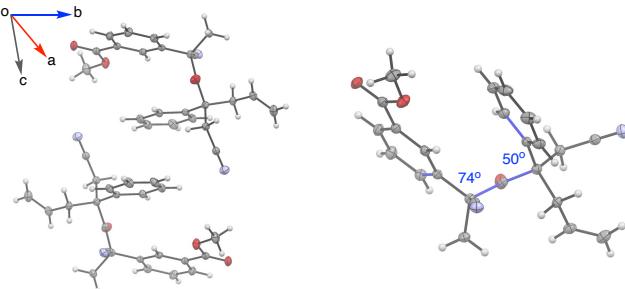


Figure 1. X-ray molecular structure of hexasubstituted ketone **4**. Left: Triclinic unit cell as viewed down the reciprocal cell axis a^* . Right: Dihedral angles of stabilizing interactions between adjacent \square -systems and breaking \square -bond (blue).

Solid-state photochemical experiments were carried out on bulk powders prepared by grinding small crystals between two microscope slides prior to irradiation (Table 1, entries 2–5). Conversion under these conditions was less efficient as compared to the solution phase. This is consistent with previous reports from our group that accumulated product can act as a filter, preventing additional reaction progress along the depth of the crystals and sometimes leading to the formation of secondary photoproducts. However, these reactions were highly selective, yielding the desired compound **5** with consistently higher retention of configuration as indicated by the d.r. = 8.0–8.6:1.¹³ While bulk-solid irradiation of **4** improved the reaction yield and stereospecificity, diminished reaction velocities with increasingly larger sample loading (>10 mg per slide) limited material throughput.¹⁴ Therefore, we decided to explore suspending the crystalline solids in water via a modified reprecipitation method as a means to scale up the photochemical reactions. We have shown that crystalline suspensions react in a more homogeneous manner, increasing the reaction velocity and conversion.^{15–19} Thus, aqueous suspensions of **4** were prepared by dissolving the ketone in a minimal amount of acetone, which was added dropwise to rapidly stirring water with sub-micellar surfactant concentrations. The reprecipitated solids were collected via filtration and confirmed to be crystalline and of the same polymorphic phase as the bulk powders (Figure S2). Treatment of the reaction vessel glass surface with a silanizing agent (Sigmacote) rendered the surface hydrophobic and helped avoid material build-up on the reactor walls. It was also found that sonication of the suspensions for five minutes after every hour of irradiation limited the adherence of reaction material to the glass surface.

Similar to the bulk powder reactions, irradiation of aqueous crystalline suspensions of **4** (Table 1, entries 6–10) exhibited higher chemoselectivity, with **5** being the only product isolated in 30–65% yields based on recovered starting material

(brsm). The diastereoselectivity observed in these cases was similar to that seen for reactions carried out on small amounts of bulk powder (d.r. = 8.0-8.7:1). We found that stopping the reaction after 4 h (Table 1, entry 7) led to the highest yields of **5** (brsm), and the recovered ketone could be readily crystallized and subjected to irradiation.

Table 1. Conversion and recombination product ratio upon irradiation of ketone **4** in various reaction media.



entry	medium	time (h)	conversion of 4 (yield of 5)	d.r. (5) ^a
1	solution ^b	2	100% (16%) ^c	1.8 : 1
2	bulk solid	1	37 (□) ^d	8.0 : 1
3	bulk solid	2	56 (□) ^d	8.6 : 1
4	bulk solid	4	79 (□) ^d	8.6 : 1
5	bulk solid	6	85 (□) ^d	8.7 : 1
6	suspension	1	<5 (trace)	□
7	suspension	4	40 (65) ^e	8.0 : 1
8	suspension	5	53 (58) ^e	8.2 : 1
9	suspension	8	81 (32) ^e	8.2 : 1
10	suspension	16	91 (30) ^e	8.6 : 1

All reactions carried out using a 450 W medium-pressure Hanovia Hg arc lamp equipped with a Pyrex filter (cutoff $\lambda > 290$ nm).

^ad.r. determined by ¹H NMR integration of □-methyl substituents in **5**. ^b0.05mmol in deuterated benzene (C_6D_6) sparged with Argon. ^cIsolated yield. ^dAnalytical scale; yields omitted. ^eYields based on recovered starting material.

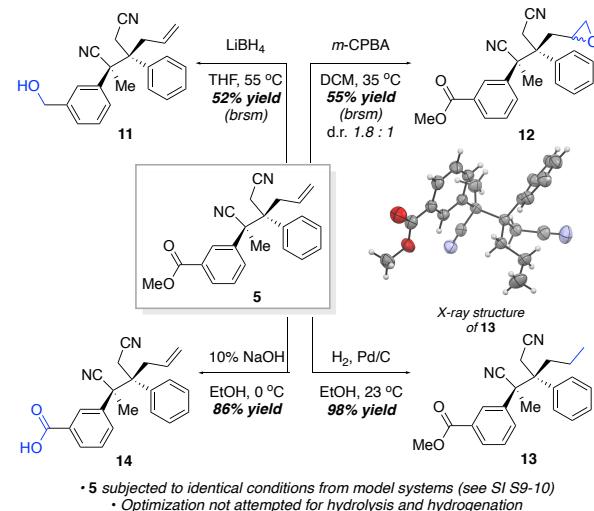
Notably, greater conversion of **4** as suspended crystals resulted in yields of **5** that were unexpectedly low (Table 1, entries 8-10).²⁰ We hypothesized that the observed loss of chemical yield at high conversion was indicative of secondary photochemical decomposition of **5**. To test this hypothesis, we conducted a control experiment (not shown) in which pure **5** was irradiated. As expected, an unidentifiable yellow material was observed after 2 h, suggesting **5** may decompose during irradiation. Despite the limitations of this particular substrate, photodecarbonylation reactions in crystalline suspensions could be carried out on scales as large as 300 milligrams.

After optimizing the solid-state photodecarbonylation reaction, we set out to explore the synthetic versatility of photoproduct **5**. Scheme 3 shows optimized reaction conditions first carried out on model compounds and subsequently applied to **5**. Treating **5** with LiBH₄ at 55 °C proved to be selective for methyl benzoate reduction, providing alcohol **11** in 52% yield (brsm). The use of other reducing agents such as LiAlH₄ or DIBAL-H resulted in complex product mixtures and significant decomposition. Epoxidation with *m*-CPBA gave **12** as a mixture of diastereomers with a d.r. ≈ 1.7:1 after 18 h at 35 °C. Hydrogenation of the terminal alkene using palladium on activated carbon gave **13** in 98% yield, and saponification afforded the corresponding acid **14**, though cold temperature was necessary to avoid decomposition. Single-crystal X-ray dif-

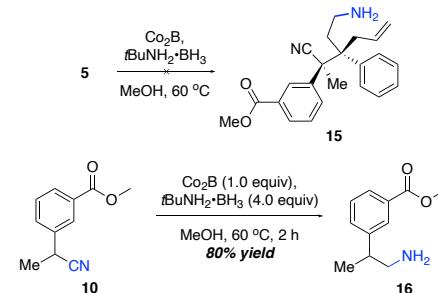
fraction unambiguously determined the structure and relative stereochemistry of **13** (Figure S4). Interestingly, when **5** was treated with nitrile-selective reducing conditions, neither **15** nor any other identifiable reduced products were observed, and only starting material was recovered from the reaction mixture. This reactivity contrasts with the efficient reduction of model nitrile **10** to furnish the primary amine **16** (Scheme 3b).²¹ While these transformations demonstrate some of the versatility of **5**, we note that some of the challenges faced (i.e. the failed conversion to **15**) were likely due to the dense steric encumbrance of the VSAQCs motif.

Scheme 3

A: Synthetic diversification of photoproduct **5**



B: Attempted selective nitrile reduction of **5**



In conclusion, we illustrate the relatively simple preparation of compounds containing vicinal, all-carbon substituted quaternary stereocenters by taking advantage of the solid-state photodecarbonylation of a diastereomerically pure crystalline ketone with six different □-substituents. We have shown that photochemical reactions in crystals proceed with highly improved chemo- and stereo-selectivity, and can be easily carried out in synthetically useful scales by taking advantage of aqueous crystalline suspensions. Transformations of the orthogonal functional groups in the photoproduct demonstrate some of the challenges and potential for the synthetic elaboration of three-dimensionally complex structures. While the yield and stereoretention for the photodecarbonylation of this particular crystalline starting material were modest,²² this report showcases the continued development of a promising green methodology for the stereospecific construction of vicinal quaternary carbons.

ASSOCIATED CONTENT

Supporting Information

Synthesis and spectroscopic characterization of compounds **4–14** and **16–19**, and select crystal parameters of compounds **4** and **13** (please see supporting information). Single X-ray crystal structures of compounds **4** and **13** deposited as CCDC 2033984 (**4**) and 2033983 (**13**) (CIF). The Supporting Information is available free of charge on the ACS Publications website.

ACKNOWLEDGMENTS

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