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Enantiospecific Synthesis of Vicinal Stereogenic Tertiary and Quaternary Centers by Combination of Configurationally-Trapped Radical Pairs in Crystalline Solids

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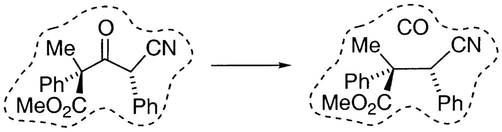
ABSTRACT



(+)-(2R,4S)-**1** (+)-(2R, 3R)-**2**

Photochemical irradiation of crystalline (2*R*,4*S*)-2-carbomethoxy-4-cyano-2,4-diphenyl-3-butanone 1 led to highly efficient decarbonylation reactions. Experiments with optically pure and racemic crystals showed that the intermediate radical pairs undergo a highly diastereo- and enantiospecific radical–radical combination that leads to the formation of two adjacent stereogenic centers in good chemical yield and with high chemical control. Reactions with chiral crystals occurred with quantitative enantiomeric yields and >95% diastereomeric yields.

We have recently shown that crystalline ketones with radical stabilizing substituents in the two α-positions can photodecarbonylate to form radical pairs in a relatively efficient and reliable manner. We have reported examples involving ketones with alkyl, phenyl,[1] carbonyl,[2] and alkoxy substituents.[3] In addition, we have observed that *radical pairs formed in crystals tend to form C−C bonds in a highly chemoselective and stereospecific manner*.[4] In this communication, we report an application of this reaction in a remarkably simple and promising method for the construction of compounds with adjacent tertiary and quaternary stereogenic centers. Our motivation for this study comes from the well-documented occurrence of natural products possessing such a structural feature and from the difficulties involved in their preparation by conventional synthetic methods.[5] In addition, we believe that challenging, solvent-free reactions may contribute to the development of the rapidly expanding field of environmentally benign chemistry.[6]

To determine the feasibility of the solid-state method, we prepared optically pure and racemic samples of (2*R*,4*S*)-2-carbomethoxy-4-cyano-2,4-diphenyl-3-butanone **1** (Scheme 1) and analyzed their photochemistry in solution and its two

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[1] (a) Choi, T.; Peterfy, K.; Khan, S. I.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 12477−12478. (b) Peterfy, K.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 4540−4541.

[2] (a) Yang, Z.; Ng, D.; Garcia-Garibay, M. A. *J. Org. Chem.* **2001**, *66*, 4468−4475. (b) Campos, L. M.; Ng, D.; Yang, Z.; Dang, H.; Martinez, H. L.; Garcia-Garibay, M. A. *J. Org. Chem.* **2002**, *67*, 3749−3754.

[3] Ng, D.; Yang, Z.; Garcia-Garibay, M. A. *Tetrahedron Lett.* **2002**, *43*, 7063−7066.

[4] Formation of radical pairs and their reactivity in crystalline solids have been previously analyzed within a primarily mechanistic context: (a) Hollingsworth, M. D.; McBride, J. M. *Adv. Photochem.* **1990**, *15*, 279−379. (b) Baretz, B.; Turro, N. J. *J. Am. Chem. Soc.* **1983**, *105*, 1309−1316.

[5] (a) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702−7703. (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

[6] (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998. (b) Poliakoff, M.; Fitzpatrick, J. M.; Farren, T. R. A., P. T. *Science* **2002**, *297*, 807−810.

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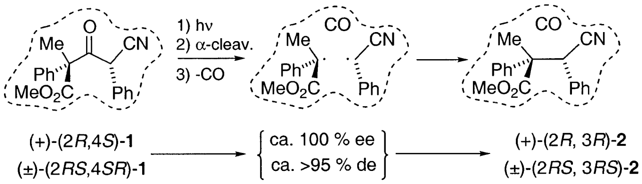
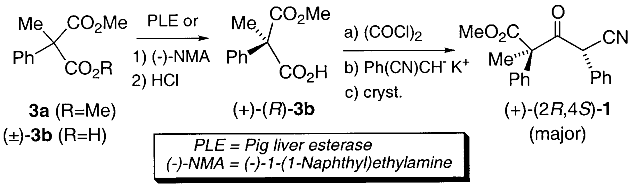
Scheme 1



enantiomorphous crystal forms.[7] A stereochemical correlation based on single-crystal X-ray diffraction analyses confirmed that the solid state reaction occurs by retention of configuration at the two configurationally trapped radical centers.

Compound **1** was obtained in enantiomerically pure and racemic forms from 2-methyl-2-phenyl malonic acid monomethyl ester **3b** (Scheme 2). Samples of (+)-(*R*)-**3b** were prepared from the meso diester **3a**[8] by enzymatic desymmetrization with pig liver esterase (90% ee)[9] or by resolution of acid (±)-**3b** with (−)-1-(1-naphthyl)ethylamine.[10] Acid (+)-**3b** was converted into the corresponding acyl chloride, which was reacted with the anion of benzyl cyanide to give ketone (2*R*,4*S*)-**1** and its diastereomer (2*R*,4*R*)-**1a** (not shown) in 85% isolated yield in a 4:1 ratio. Pure samples of (+)-(2*R*,4*S*)-**1** {$[\alpha]_D = 120°$ (*c* 0.73, $CHCl_3$)} were obtained by crystallization from hexane and diethyl ether (4:1 v/v). Thin needles of the optically pure ketone had a melting point of 66−68 °C. An identical procedure starting with racemic (±)-**3b** led to racemic crystals of (±)-(2*RS*,4*SR*)-**1**,[11] which have a melting point of 97−100 °C.

Scheme 2



Photochemical experiments with oxygen-free 0.1 M benzene solutions of (+)-(2*R*,4*S*)-**1** and (±)-(2*RS*,4*SR*)-**1** using a Hanovia lamp with a Pyrex filter ($\lambda > 300$ nm) at 298 K led to complex product mixtures (Figure 1, bottom). In contrast, crystals of (+)-(2*R*,4*S*)-**1** and (±)-(2*RS*,4*SR*)-**1** (ca. 50 mg) irradiated under similar conditions resulted in a very clean reaction with formation of a major photoproduct in 40−60% conversion and >95% selectivity (Figure 1, top). The product was later shown to be (+)-(2*R*,3*R*)-**2** and (±)-(2*RS*,3*RS*)-**2** from the optically pure and racemic crystals, respectively.

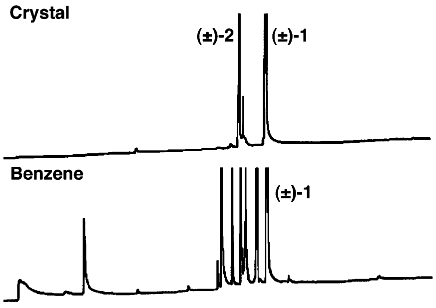


Figure 1. Gas chromatograph obtained after ca. 40% conversion upon photolysis of (±)-(2*RS*,4*SR*)-**1** in benzene solutions (bottom) and in crystals (top). Results of experiments carried out with (+)-(2*R*,4*S*)-**1** were essentially identical.

The relative configurations of (+)-(2*R*,4*S*)-**1** and (±)-(2*RS*,4*SR*)-**1** were established by single-crystal X-ray diffraction analyses (Figure 2). Enantiomerically pure (+)-(2*R*,4*S*)-**1** crystallizes in the hexagonal space group $P6_5$ with six ketones and one disordered hexane molecule

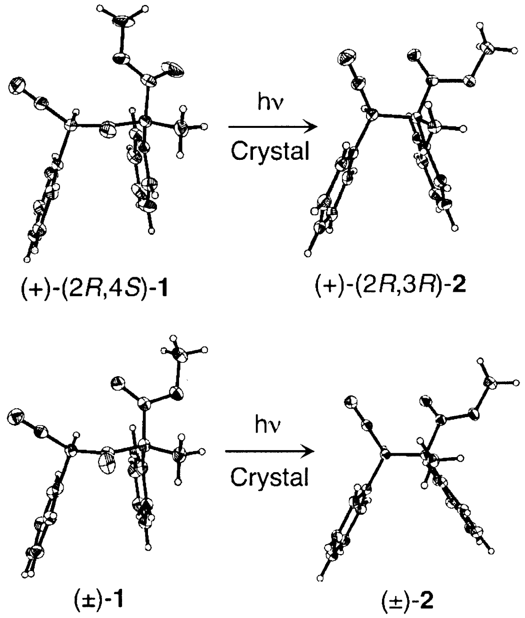


Figure 2. ORTEP diagrams of (top) (+)-(2*R*,4*S*)-**1** and its solid-state product (+)-(2*R*,3*R*)-**2** and (bottom) ORTEP diagrams of (±)-(2*RS*,4*SR*)-**1** and the racemic solid-state photoproduct (±)-(2*RS*,3*RS*)-**2**. The X-ray structures of (+)- and (±)-**2** were obtained after dissolving crystals of reacted **1**. From the racemic crystals, only the (2*R*,4*S*)-**1** and (2*R*,3*R*)-**2** enantiomers are illustrated.

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(7) For an excellent monograph describing the crystallization of chiral molecules, please see: Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; John Wiley & Sons: New York, 1981.

(8) Canet, J. L.; Louis, F. A.; Salaun, J. *J. Org. Chem.* **1992**, *57*, 3463−73.

(9) Toone, E. J.; Jones, B. *Tetrahedron: Asymmetry* **1991**, *2*, 1041−1052.

(10) Optically enriched samples of (+)-**3b** were obtained by crystallization of (±)-**3b** with (−)-1-(1-naphthyl)ethylamine in Et_2O (50% ee). These crystallized as optically pure (+)-(2*R*,4*S*)-**1** after the reaction sequence in Scheme 2.

(11) Optically pure and racemic forms of diastereomers are named as recommended by: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; Chapter 5, pp 117−124.

per unit cell.[12] The racemic compound crystallizes in the space group $P2_1/c$ with four molecules per unit cell and no solvent of crystallization.[13] The absolute configuration of (+)-(2*R*,4*S*)-**1** was assigned from the known configuration of (+)-(*R*)-**3b**, which is determined by the enantioselectivity of the enzymatic hydrolysis.[9]

As illustrated in Figure 2, the structure of ketone (2*R*,4*S*)-**1** is very similar in the two enantiomorphous (i.e., enantiomerically pure and racemic) crystal forms.[7] It is characterized by a conformation where the 2-methyl and 4-cyano substituents are approximately eclipsed with the ketone carbonyl and the phenyl groups adopt a staggered orientation. The main difference between the two molecular structures is the orientation of the carboxylate ester groups. The ester carbonyl points toward the cyano substituent in the racemic crystals and in the opposite direction in the optically pure modification.[14]

Assuming that double inversion in the crystal lattice is extremely unlikely, the optical purity of (+)-(2*R*,3*R*)-**2** is determined by the optical purity of crystalline (+)-(2*R*,4*S*)-**1**, which is expected to be 100% in its enantiomorphous phase. An $[\alpha]_D = 128°$ (*c* 1, EtOAc) determined for (+)-(2*R*,3*R*)-**2** is of the same sign as those of the ketone precursor (+)-(2*R*,4*S*)-**1** and the acid ester (+)-**3b**. A >95% de determined by GLC for optically active and racemic samples (Figure 1, top trace) indicates a very small amount of inversion at either one of the two stereogenic centers. A small stereochemical loss may be due to reaction occurring at the crystal surface or at defect sites. X-ray structural elucidation of (+)-(2*R*,3*R*)-**2** (mp = 78−79 °C)[15] and (±)-(2*RS*,3*RS*)-**2** (mp = 99−101 °C)[16] confirmed the expected stereospecificity of the bond-forming reaction. The simple visualization of the reaction illustrated in Scheme 1 is borne out from the X-ray structures shown in Figure 2. The spatial orientation of the substituents at C2 and C4 in ketone **1** is maintained at stereocenters C2 and C3 in product **2**. Notably, the orientation of the ester group in crystals of (+)-(2*R*,4*S*)-**1** is different than that observed in crystals of (+)-(2*R*,3*R*)-**2** (Figure 2, top). However, for reactions in crystals, it is well-known that changes in size and shape must be relatively small.[17] Therefore, it is likely that (+)-(2*R*,3*R*)-**2** is originally formed with the ester carbonyl in a conformation similar to that of the starting material and that it only changes after the reacted sample is dissolved and recrystallized. Very small conformational differences can be appreciated for the structure of compound **2** in its two crystal forms.

Regarding the reaction mechanism, it is well-known[18] that decarbonylation proceeds in a stepwise manner by sequential α-cleavage and decarbonylation.[2] With experimental[1,2a,3] and computational[2b] evidence gathered in our group, we have suggested some general guidelines to "engineer reactions in crystals".[1−3] Our observations indicate that photodecarbonylation in the solid state is enabled by substituents that lower the bond dissociation energy of the two α-bonds by more than ca. 12 kcal/mol as compared to that of acetone (BDE-[Me−COMe] = 81.1 kcal/mol).[19] This suggestion arises from a known relation between reaction efficiencies and heats of reaction first proposed by Fisher and Paul.[20] α-Cleavage and decarbonylation in ketone **1** are enabled by phenyl, carbomethoxy, and cyano groups. On the basis of extensive literature data,[19] one may expect that phenyl, ester, and methyl groups at C2 will lower the α-bond dissociation energy by ca. 25 kcal/mol with respect to that of acetone. Similarly, phenyl and cyano substituents at C4 are expected to weaken the other α-bond by ca. 23 kcal/mol, which is also well in excess of the suggested value. Not surprisingly, compound **1** reacts in crystals with apparent efficiencies that compete with those observed in solution reactions.

Knowing that accumulation of the product depresses the melting point of the pure starting material, it is advantageous to document the nature of the (ideally) two-component system so that a suitable photolysis temperature is selected.[21] Differential scanning calorimetric (DSC) analyses of (±)-(2*RS*,4*SR*)-**1** before reaction and after ca. 45% conversion indicate that a solid phase is preserved below ca. 30−40 °C and that reaction proceeds by a phase separation mechanism (Figure 3).[21] The melting transition of pure (±)-(2*RS*,4*SR*)-**1** at 97 °C broadens and shifts to lower temperatures as the product accumulates in crystals of the reactant phase. That phase separation occurs in this reaction is deduced by the observation of a broad peak at about 60 °C, which corresponds to the formation of a eutectic mixture. This result suggests that high reaction yields with maintained selectivity may be attained by controlling the temperature

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[12] (+)-(2*R*,4*S*)-**1**: $C_{19}H_{17}NO_3$, MW = 307.34, space group $P6_5$, a = 19.154(3) Å, Å, b = 19.154(3) Å, c = 8.393(2) Å, $\alpha = \beta = 90°$, γ = 120°, V = 2666.5(9) Å^3, Z = 6, ρ_{calcd} = 1.156 Mg/m^3, $F(000)$ = 978, λ = 0.71073 Å, μ(Mo Kα) = 0.080 mm^{-1}, T = 100(2) K, crystal size = 0.60 × 0.10 × 0.10 mm^3. Of the 15 993 reflections collected (2.72° ≤ θ ≤ 28.29°), 4062 [R(int) = 0.0297] were independent reflections; max/min residual electron density 357 and −176 e nm^{-3}, R_1 = 0.0369 [$I > 2\sigma(I)$] and wR_2 = 0.0874 (all data).

[13] (±)-(2*R*,4*S*)-**1**: $C_{19}H_{17}NO_3$, MW = 307.34, space group $P2_1$/c, a = 12.238(3) Å, b = 9.468(2) Å, c = 13.810(4) Å, β = 97.769(5)°, V = 1585.6(7) Å3, Z = 4, ρ_{calcd} = 1.287 Mg/m^3, $F(000)$ = 648, λ = 0.71073 Å, μ(Mo Kα) = 0.087 mm-1, T = 100(2) K, crystal size = 0.4 × 0.3 × 0.3 mm^3. Of the 9819 reflections collected (1.68° ≤ θ ≤ 28.26°), 3760 [R(int) = 0.0298] were independent reflections; max/min residual electron density 327 and −189 e nm^{-3}, R_1 = 0.0371 [$I > 2\sigma(I)$] and wR_2 = 0.1030 (all data).

[14] Calculated (AM1) dipole moments are 5.92 and 3.53 D for structures in racemic and optically active crystals, respectively. However, only the chiral crystals are macroscopically polar.

[15] (+)-(2*R*,4*S*)-**2**: $C_{18}H_{17}NO_2$, MW = 279.33, space group $P2_1$, a = 8.4096(6) Å, b = 9.4818(7) Å, c = 9.3272(6) Å, β = 96.9610(10)°, V = 738.25(9) Å^3, Z = 2, ρ_{calcd} = 1.257 Mg/m^3, $F(000)$ = 296, λ = 0.71073 Å, μ(Mo Kα) = 0.082 mm^{-1}, T = 100(2) K, crystal size = 0.50 × 0.40 × 0.33 mm^3. Of the 6629 reflections collected (2.20° ≤ θ ≤ 28.27°), 3454 [R(int) = 0.0132] were independent reflections; max/min residual electron density 272 and −150 e nm^{-3}, R_1 = 0.0284 [$I > 2\sigma(I)$] and wR_2 = 0.0680 (all data).

[16] (±)-(2*RS*,3*RS*)-**2**: $C_{18}H_{17}NO_2$, MW = 279.33, space group $P2_1/n$, a = 11.1764(16) Å, b = 9.0080(13) Å, c = 15.168(2) Å, β = 98.844(2), V = 1508.9(4) Å^3, Z = 4, ρ_{calcd} = 1.230 Mg/m^3, $F(000)$ = 592, λ = 0.71073 Å, μ(Mo Kα) = 0.080 mm^{-1}, T = 100(2) K, crystal size = 0.40 × 0.35 × 0.25 mm^3. Of the 9649 reflections collected (2.12° ≤ θ ≤ 28.30°), 3568 [R(int) = 0.0170] were independent reflections; max/min residual electron density 360 and −190 e nm^{-3}, R_1 = 0.0345 [$I > 2\sigma(I)$] and wR_2 = 0.0875 (all data).

[17] Cohen, M. D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 386−393.

[18] Weiss, D. *Org. Photochem*; Padwa, A., Ed.; Marcel Deker: New York, 1981; Vol. 5, pp 347−420.

[19] Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, FL, 2003.

[20] Fisher, H.; Paul, H. *Acc. Chem. Res.* **1987**, *20*, 200−206.

[21] Keating, A. E.; Garcia-Garibay, M. A. *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Schanze, K., Eds.; Marcel Dekker: New York, 1998; Vol. 2, pp 195−248.

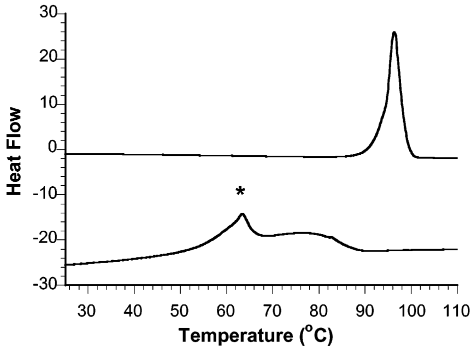

Figure 3. Differential scanning calorimetric (DSC) analysis of (±)-(2*RS*,4*SR*)-**1** before photolysis (top) and after 45% conversion (bottom). The eutectic transition is marked with an asterisk (*) in the bottom thermogram.

of the reaction well below the eutectic point. While the presence of solvent in crystals of (+)-(2*R*,4*S*)-**1** makes the phase diagram more complex and high conversions difficult, suitable crystals may be obtained from other solvents or from the melt, by hydrolysis of the ester to form the carboxylic acid, or by forming higher-melting carboxylate salts,[22] alternatives that will be investigated.

In conclusion, we have shown that photodecarbonylation of crystalline ketones with radical-stabilizing α-substituents provides a promising strategy for the diastereo- and enantiospecific construction of adjacent stereogenic quaternary and tertiary centers. The method used for the synthesis of **1** can be easily modified to prepare a large number of analogues, which may be used to obtain building blocks for the synthesis of more complex molecules. The generality of this procedure and applications in total synthesis will be reported in forthcoming publications.

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Supporting Information Available: X-ray diffraction data for racemic and optically pure crystals of compounds **1** and **2** (CIF files) and experimental procedures for the preparation of **3a**, **1**, **3b**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[22] Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203−209.