JOC Article

Highly Diastereoselective Tandem Photoenolization−Hetero-Diels−Alder Cycloaddition Reactions of *o*-Tolualdehydes in the Solid State

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The (*E*)-photoenols generated in situ by photolysis of *o*-tolualdehydes **1**−**5** in the solid state react with the precursor aldehydes as dienophiles in a hetero-Diels−Alder cycloaddition fashion to afford *trans*-3-arylisochromanols in excellent yields and in a high diastereoselectivity. An examination of the reactivity of three different classes of rationally designed aldehydes shows that the tandem enolization−Diels−Alder cycloaddition occurs in the solid state efficiently for aldehydes whose (*E*)-photoenols (i) are more stable than their corresponding benzocyclobutenols and (ii) are not sterically congested. However, rapid cyclization to benzocyclobutenols is found to be the sole pathway for sterically encumbered (*E*)-enols derived from aldehydes **6**−**8**. Given that the execution of heteromolecular reactions in the solid state is a challenge, the results obtained with simple crystalline *o*-tolualdehydes are remarkable and the strategy involving in situ generation of a dienol in the crystal lattice of a dienophile to achieve hetero-Diels−Alder reaction in a highly diastereoselective manner is heretofore unprecedented. In the context of enormous interest in tandem/domino reactions in contemporary synthetic organic chemistry, the results observed with *o*-tolualdehydes exemplify successful execution of tandem reactions in the solid state.

Introduction

Prohibitive motions of the molecules in the crystalline medium exert a strict control over the reaction coordinate of a solid-state reaction.[1] Consequently, reactions in the solid state proceed largely with a high degree of regio- and/or stereoselectivity and also selectivity in terms of product profile.[1,2] In general, the occurrence of unimolecular thermal and photochemical reactions can be predicted a priori, as the molecules largely crystallize out in their lowest energy conformations; the knowledge as to the energies of various conformations can be readily had from theoretical calculations.[1b,3] On the contrary, the proximity considerations and the relative orientations between reacting partners hold sway in determining the occurrence of bi-/polymolecular reactions in the solid state.[1a,c] Insofar as homomolecular dimerizations and/or polymerization reactions are concerned, some remarkable strategies have been demonstrated in the literature, particularly with regard to the photochemical transformations.[1a,c,2d,3−5] However, engineering two dissimilar molecules into required proximity and orientations to effect hetero-bi-/polymolecular reactions in the solid state is an arduous task and is a challenge to chemists. We are aware of a few strategies, where heteromolecular reactions (thermal/photochemical) between two dissimilar molecules have been successfully demonstrated in the solid state. These strategies rely on (i) the use of container molecules,[6] (ii) exploitation of charge-transfer interactions,[7] (iii) formation of mixed crystals,[2d] and (iv)

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† Indian Institute of Technology.

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[1] (a) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433−481. (b) Scheffer, J. R.; Garcia-Garibay, M.; Nalamasu, O. *Org. Photochem.* **1987**, *8*, 249−347. (c) Venkatesan, K.; Ramamurthy, V. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH: New York, 1991; pp 133−182.

[2] (a) Ito, Y. *Synthesis* **1998**, *8*, 249−347. (b) Toda, F. *Acc. Chem. Res.* **1995**, *28*, 480−486. (c) Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203−209. (d) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025−1074.

[3] For a recent work on unimolecular carbene rearrangements in the solid state and predictions based on theoretical calculations, see: (a) Garcia-Garibay, M. A.; Shin, S. H.; Sanrame, C. N. *Tetrahedron*, **2000**, *56*, 6729−6737. (b) Garcia-Garibay, M. A. *Acc. Chem. Res.* **2003**, *36*, 491−498.

[4] (a) Moorthy, J. N.; Venkatesan, K.; Weiss, R. G. *J. Org. Chem.* **1992**, *57*, 3292−3297. (b) Jon, S. Y.; Ko, Y. H.; Park, S. H.; Kim, H.-J.; Kim, K. *Chem. Commun.* **2001**, 1938−1939. (c) Hamilton, T. D.; Papaefstathiou, G. S.; MacGillivray, L. R. *J. Am. Chem. Soc.* **2002**, *124*, 11606−11607. (d) Friscic, T.; MacGillivray, L. R. *Chem. Commun.* **2003**, 1306−1307. (e) Papaefstathiou, G. S.; Kipp, A. J.; MacGillivray, L. R. *Chem. Commun.* **2001**, 2462−2463. (f) Amirsakis, D. G.; Garcia-Garibay, M. A.; Rowan, S. J.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4256−4261. (g) Gao, X.; Friscic, T.; MacGillivray, L. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 232−236.

[5] For solid-state Diels−Alder cycloadditions, see: (a) Kishan, K. V. R.; Desiraju, G. R. *J. Org. Chem.* **1987**, *52*, 4640−4641. (b) Desiraju, G. R.; Kishan, K. V. R. *J. Am. Chem. Soc.* **1989**, *111*, 4838−4843. (c) Mikami, K.; Matsumoto, S.; Tonoi, T.; Okubo, Y.; Suenobu, T.; Fukuzumi, S. *Tetrahedron Lett.* **1998**, *39*, 3733−3736.

[6] (a) Wernick, D. L.; Yazbek, A.; Levy, J. *J. Chem. Soc., Chem. Commun.* **1990**, 956−957. (b) Mir, M.; Marquet, J.; Cayon, E. *Tetrahedron Lett.* **1992**, *46*, 7053−7056.

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application of porous organic materials,[8] which in analogy to the inorganic zeolites incorporate two dissimilar molecules in their cavities and promote reactions between them. Herein, we report an unprecedented protocol involving in situ generation of a dienol in the crystal lattice of a dienophile to achieve hetero-Diels–Alder reaction in a highly diastereoselective manner; the dienophile is a cloaked precursor of the photoenol.

Results and Discussion

The photoenolization and photocyclization of *o*-alkylaromatic carbonyl compounds have been well established.[9,10] The photocyclization affords benzocyclobutenols, which serve as excellent synthetic intermediates and also as masked dienols. The photoenolization leads directly to 4π-dienols,[9b,11] and is undoubtedly one of the synthetically very useful photoreactions, which continues to be exploited tremendously as a key step in the total syntheses of complex and diverse natural products.[12] The photoenols derived from *o*-alkylaromatic carbonyl compounds are also known to undergo cycloaddition with heterodienophiles to afford heterocyclic systems.[13] In the past few years, we have focused our attention on the solid-state photobehavior of *o*-alkylaromatic aldehydes,[14] which have been explored little as compared to their ketone counterparts. Our investigations have shown that the relative energy differences between (*E*)-enols (Scheme 1) and the corresponding benzocyclobutenols determine whether one observes the cyclization or the photochromism (due to photoenols) in the solid state; the (*Z*)-enols are known to be very short-lived due to rapid thermal [1,5]-sigmatropic shift, which regenerates the precursor carbonyl compounds.[15] Further, we have found that cyano-substitution,[14b] hydrogen bonding,[14d] and the presence of heteroatoms as, for example, in pyridine-3-carboxaldehydes[14d] stabilize the (*E*)-enols, while bromo-substitution and steric crowding favor cyclization. In the backdrop of this knowledge on the solid-state photobehavior of simple *o*-alkylaromatic aldehydes and on the propensity of photoenols to undergo cycloadditions, we rationally designed a set of cyano-substituted aldehydes **1**–**8** (Chart 1) to explore the possibility of trapping diastereoselectively the persistent (*E*)-photoenols generated in the solid state by the precursor aldehydes themselves in a hetero-Diels–Alder cycloaddition fashion;[16] our preference to cyano-derivatives was based on the premise that the cyano groups stabilize and thus increase the lifetimes of the dienols to permit bimolecular Diels–Alder cycloaddition reactions in competition with intramolecular cyclization to benzocyclobutenols.[17] The aldehydes **1**–**8** may be broadly classified into three categories, viz., A, B and C.

SCHEME 1

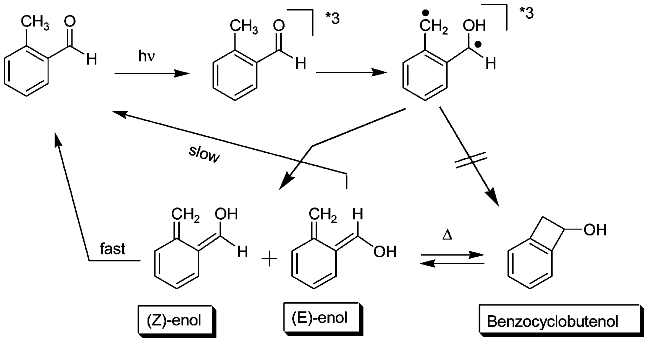
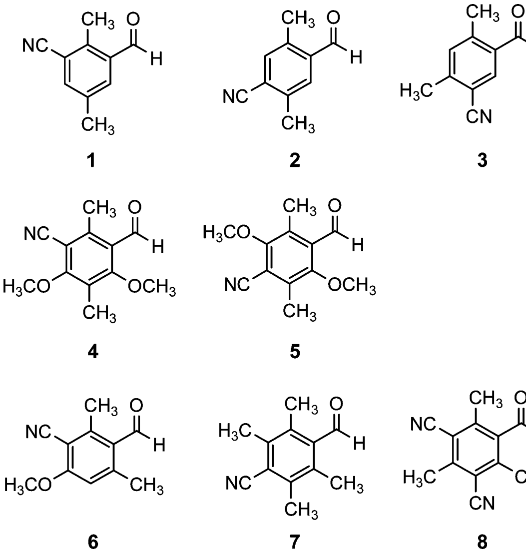


CHART 1



Category A is made up of conformationally ill-defined aldehydes (**1**–**3**) with no steric encumbrance to photoenolization. The formyl group in these aldehydes may or may not be oriented toward the *o*-methyl group in the

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(7) (a) Suzuki, T.; Fukushima, T.; Yamashita, Y.; Miyashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 2793–2803. (b) Kim, J. H.; Hubig, S. M.; Lindeman, S. V.; Kochi, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 87–95. (c) Kim, J. H.; Lindeman, S. V.; Kochi, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 4951–4959. (d) Kim, J. H.; Jaung, J. Y.; Jeong, S. H. *Opt. Mater.* **2002**, *21*, 395–400.

(8) Endo, K.; Koike, T.; Sawaki, T.; Hayashida, O.; Masuda, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4117–4122.

(9) (a) Yang, N. C.; Rivas, C. *J. Am. Chem. Soc.* **1961**, *83*, 2213. (b) Sammes, P. G. *Tetrahedron* **1976**, *32*, 405–422. (c) Wagner, P. J.; Zepp, R. G.; Liu, K.-C.; Thomas, M.; Lee, T.-J.; Turro, N. J. *J. Am. Chem. Soc.* **1976**, *98*, 8125–8134. (d) Das, P. K.; Encinas, M. V.; Small, R. D., Jr.; Scaiano, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 6965–6970.

(10) For recent examples, see: (a) Wagner, P. J.; Subrahmanyam, D.; Park, B.-S. *J. Am. Chem. Soc.* **1991**, *113*, 709–710. (b) Wagner, P. J.; Sobczak, M.; Park, B.-S. *J. Am. Chem. Soc.* **1998**, *120*, 2488–2489. (c) Gamarnik, A.; Johnson, B. A.; Garcia-Garibay, M. A. *J. Phys. Chem. A* **1998**, *102*, 5491–5498. (d) Johnson, B. A.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 8114–8115.

(11) For a recent example, see: Grosch, B.; Orlebar, C. N.; Herdtweck, E.; Massa, W.; Bach, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3693–3696.

(12) For recent examples, see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698. (b) Nicolaou, K. C.; Gray, D. L. F. *J. Am. Chem. Soc.* **2004**, *126*, 607–612. (c) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800–4802. (d) Nicolaou, K. C.; Gray, D. L. F.; Tae, J. *J. Am. Chem. Soc.* **2004**, *126*, 613–627.

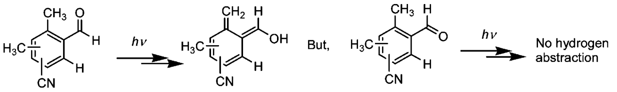
(13) (a) Griesbeck, A. G.; Stadtmuller, S. *Chem. Ber.* **1993**, *126*, 2149–2150. (b) Chino, K.; Takata, T.; Endo, T. *Synth. Commun.* **1996**, *26*, 2145–2154.

(14) (a) Moorthy, J. N.; Mal, P.; Natarajan, R.; Venugopalan, P. *Org. Lett.* **2001**, *3*, 1579–1583. (b) Moorthy, J. N.; Mal, P.; Natarajan, R.; Venugopalan, P. *J. Org. Chem.* **2001**, *66*, 7013–7019. (c) Moorthy, J. N.; Venkatakrishnan, P.; Mal, P.; Venugopalan, P. *J. Org. Chem.* **2003**, *68*, 327–331. (d) Mal, P.; Lourderaj, U.; Parveen; Venugopalan, P.; Moorthy, J. N.; Sathyamurthy, N. *J. Org. Chem.* **2003**, *68*, 3446–3453.

(15) Haag, R.; Wirz, J.; Wagner, P. J. *Helv. Chim. Acta* **1977**, *60*, 2595–2607.

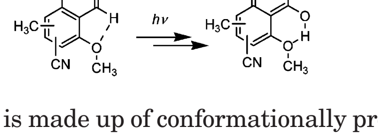
(16) This investigation was inspired by the observation of the formation of a Diels–Alder adduct in a very low yield in a preliminary study on the solid-state photochemistry of 2,6-dichloro-4-methylpyridine-3-carboxaldehyde, see: Sarkar, T. K.; Ghosh, S. K.; Moorthy, J. N.; Fang, J.-M.; Nandy, S. K.; Sathyamurthy, N.; Chakraborty, D. *Tetrahedron Lett.* **2000**, *41*, 6909–6914.

solid state. In the latter event, the γ-hydrogen abstraction, the primary photochemical event, cannot occur.



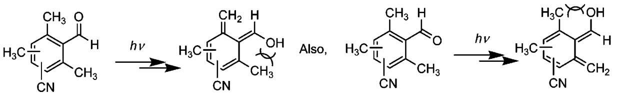
(1)

Category B is made up of conformationally predestined aldehydes (**4** and **5**), whose (*E*)-photoenols may derive additional stabilization via intramolecular O−H···O hydrogen bonding;[14a,d] the formyl oxygen in the crystals of *o*-anisaldehydes is known to orient away from the methoxy group and toward the *o*-methyl group so that the γ-hydrogen abstraction from the methyl group occurs readily upon photolysis.



(2)

Category C is made up of conformationally predestined and sterically encumbered aldehydes (**6**−**8**); in these aldehydes, the conformational preference is inconsequential, as the formyl oxygen may abstract the γ-hydrogen in both of the orientations.

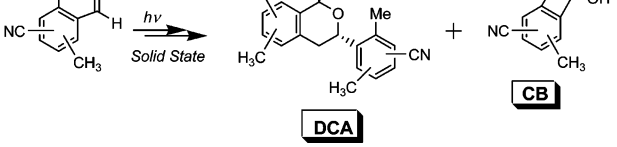


(3)

Syntheses of Aldehydes 1−8. Scheme 2 shows synthetic protocols for the preparation of aldehydes **1**−**7**. 3-Cyano-2,5-dimethylbenzaldehyde (**1**) was synthesized from the literature-known 3-bromo-2,5-dimethylbenzaldehyde[18] by cyanation with CuCN in DMF.[19] In a similar manner, 4-cyano-2,5-dimethylbenzaldehyde (**2**) was prepared from 4-bromo-2,5-dimethylbenzaldehyde.[20] Dibromination[21] of *m*-xylene followed by controlled cyanation with 1.2 equiv of CuCN led to isolation of 5-bromo-2,4-dimethylbenzonitrile. This was subjected to reduction with DIBALH, and the resulting aldehyde was cyanated to yield 5-cyano-2,4-dimethylbenzaldehyde (**3**). Dibromination of 1,3-dimethoxy-2,5-dimethylbenzene[22] with NBS in CH_3CN[23] followed by cyanation (CuCN−DMF) led to 3-bromo-4,6-dimethoxy-2,5-dimethylbenzonitrile. Reduction of this cyano compound with DIBALH and subsequent cyanation with CuCN−DMF yielded 3-cyano-4,6-dimethoxy-2,5-dimethylbenzaldehyde (**4**). A similar procedure was employed for the preparation of 4-cyano-2,5-dimethoxy-3,6-dimethylbenzaldehyde (**5**) from 1,4-dibromo-2,5-dimethoxy-3,6-dimethylbenzene.[24] Bromination of 4-methoxy-2,6-dimethylbenzonitrile[25] with 3 equiv of NBS in acetonitrile for 48 h at room temperature yielded 3-bromo-4-methoxy-2,6-dimethylbenzonitrile. This bromo derivative was first reduced with DIBALH and then subjected to cyanation to isolate 3-cyano-4-methoxy-2,6-dimethylbenzaldehyde (**6**). 4-Cyano-2,3,5,6-tetramethylbenzaldehyde (**7**) was synthesized from 1,4-dibromo-2,3,5,6-tetramethylbenzene[26] in an analogous manner. Synthesis of the 3,5-dicyano-2,4,6-trimethylbenzaldehyde (**8**) has previously been reported by us.[14b]

Solid-State Photolysis and Characterization of Photoproducts. All of the aldehydes **1**−**5** (categories A and B) were found to exhibit distinct color changes upon exposure to UV−vis radiation. While similar changes were not readily perceptible at room temperature for aldehydes **6**−**8**, exposure at low temperatures (<0 °C) did lead to a change in the color for aldehyde **8**.[14b] The UV−vis absorption spectra that characterize the color changes are typically exhibited in Figure 1 for aldehydes **1** and **4** as representative cases. Orange-yellow to brick-red color was readily observed for all of the aldehydes **1**−**5** upon brief exposure to UV radiation. The long wavelength absorption that is responsible for the observed color in all of the cases is attributed to the formation of (*E*)-enol from the respective aldehydes;[14a] as mentioned earlier, the (*Z*)-enols are notoriously labile to permit their characterization readily. Thus, the observation of (*E*)-enols is in line with the expectation that cyano groups influence their stabilities.

Continued irradiation of the aldehydes **1**−**5** was found to result in clean products as monitored by 400-MHz ^{1}H NMR spectroscopy of the irradiated samples at regular intervals. Figure 2 shows a typical spectral profile for **2** with increasing duration of irradiation (350 nm, Luzchem photoreactor) of the crystalline samples dispersed in a test tube under a N_2 gas atmosphere. As can be seen from ^{1}H NMR spectra, the signals corresponding to the formyl and methyl hydrogens disappear gradually with concomitant appearance of the signals due to protons of the products. Most gratifyingly, the uncomplicated ^{1}H NMR spectra revealed diagnostic signals in the region of ca. δ 5.0−6.5, which immediately suggested the formation of the Diels−Alder cycloadducts (DCAs), viz., 1-isochromanols (eq 4). With the exception of aldehyde **5**, the ^{1}H NMR analyses of the irradiated samples of aldehydes **1**−**4** at different time intervals (at different conversions) clearly indicated the formation of only one Diels−Alder



(4)

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(17) Semiempirical AM1 calculations are known to predict reliably the enthalpy of thermal conversion of (*E*)-enols to benzocyclobutenols, see: ref 14b and the references therein. These calculations for aldehydes **1**−**3** and **6**−**8** show that the stability of the (*E*)-enol in each case is comparable to the corresponding benzocyclobutenol. In **3** and **5**, the (*E*)-enol is much more stabilized relative to the benzocyclobutenol due to the intramolecular O−H···O hydrogen bond involving the methoxy oxygen and the hydrogen of the hydroxy group of the dienol (see category B).

(18) Mitchell, R. H.; Zhang, L. *J. Org. Chem.* **1999**, *64*, 7140−7152.

(19) Friedman, L.; Shechter, H. *J. Org. Chem.* **1961**, *26*, 2522−2524.

(20) Brizius, G.; Pschirer, N. G.; Steffen, W.; Stitzer, K.; zur Loye, H.-C.; Bunz, U. H. F. *J. Am. Chem. Soc.* **2000**, *122*, 12435−12440.

(21) Ashton, P. R.; Girreser, U.; Giuffrida, D.; Kohnke, F. H.; Mathias, J. P.; Raymo, F. M.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J. *J. Am. Chem. Soc*. **1993**, *115*, 5422−5429.

(22) Azzena, U.; Denurra, T.; Melloni, G.; Piroddi, A. M. *J. Org. Chem*. **1990**, *55*, 5386−5390.

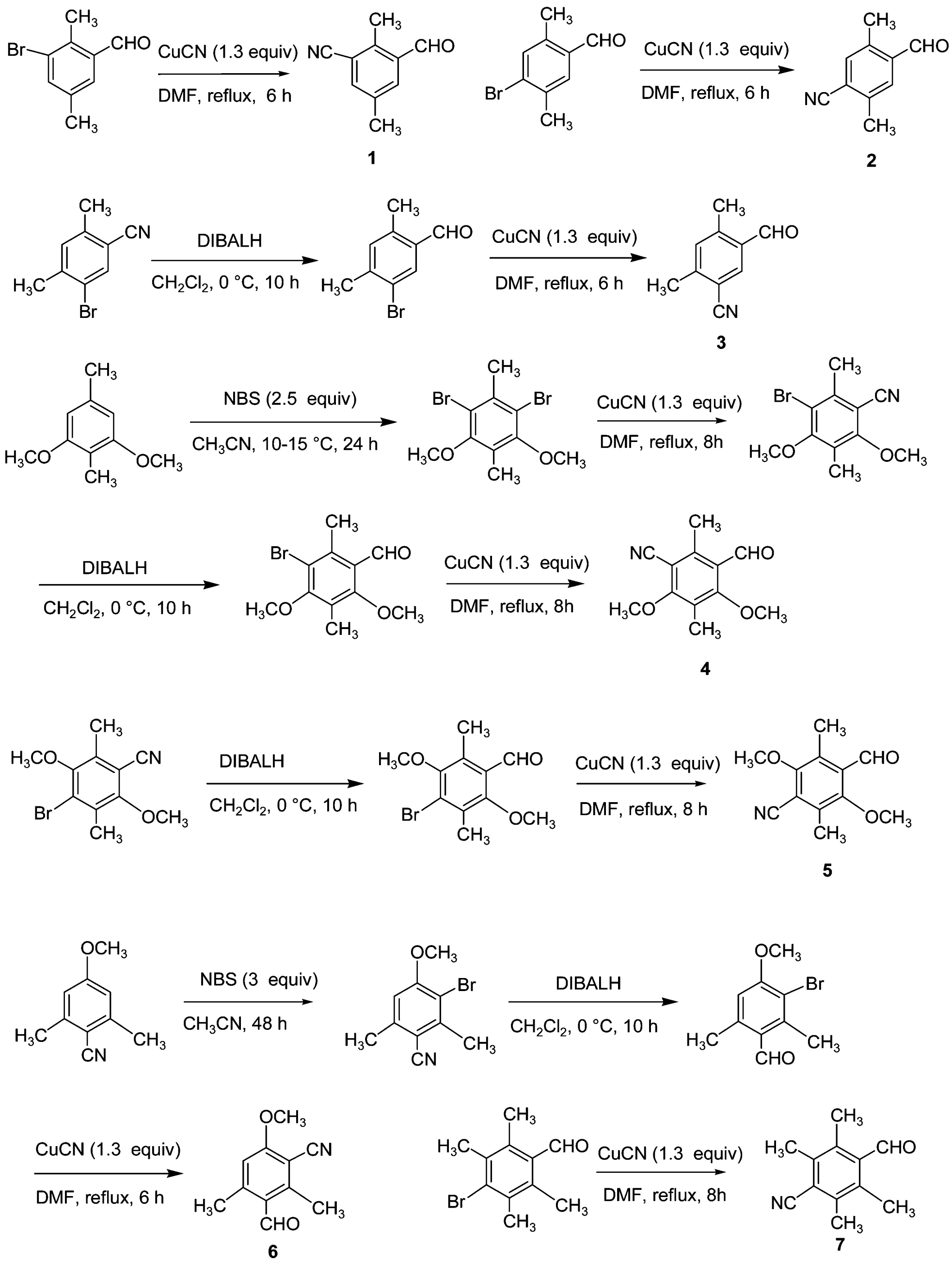
(23) Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328−5331.

(24) Staab, H. A.; Rebafka, W. *Chem. Ber.* **1977**, *110*, 3333−3350.

(25) Dell'Erba, C.; Sancassan, F.; Novi, M.; Petrillo, G.; Mugnoli, A.; Spinelli, D.; Consigilo, G.; Gatti, P. *J. Org. Chem.* **1988**, *53*, 3564−3568.

(26) Sawatzky, H.; Wright, G. F. *Can. J. Chem.* **1958**, *36*, 1555−1569.

SCHEME 2. Synthesis of Aldehydes 1−7



cycloadduct.[27] In the former though, the Diels−Alder adduct was found to be accompanied by benzocyclobutenol, as monitored by ^{1}H NMR spectroscopy. Most remarkably, only one of the two diastereomeric lactols was observed predominantly in all cases, with the presence of the other diastereomer being hardly traceable. The trans stereochemistry between the aryl and hydroxyl groups of the lactols derived from **1** and **2** was established by NOE experiments and also by comparison of the spectral characteristics with analogous lactols reported in the literature.[13] A similar stereochemistry was inferred for the lactols derived from other aldehydes **3**−**5** by comparison of the ^{1}H NMR spectral characteristics. In contrast, all of the three sterically encumbered aldehydes **6**−**8** were found to undergo efficient cyclization to the corresponding cyclobutenols (eq 4); we have previously shown that the latter indeed derive from the precursor (*E*)-photoenols via thermal conrotatory closure.[14b] The isolated yields of the Diels−Alder cycloadducts from aldehydes **1**−**3** (category A) were 70−90% from a preparative photolysis employing ca. 100−150 mg of the aldehyde in each case (Table 1). While one of the dimethoxy-cyano aldehydes, i.e., **4**, yielded exclusively the DCA adduct (from 400-MHz ^{1}H NMR spectroscopy), **5** was found to afford the cyclobutenol (CB) in addition to

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(27) For comparison, the solution-state photolysis of **1** and **2** was found to yield, as monitored by ^{1}H NMR spectroscopy, the Diels−Alder adduct with trans stereochemistry as a major product in each case, which was accompanied by a variety of other products. It has been shown that solution-state photolysis of *o*-tolualdehyde leads to products resulting from intermolecular photoreductions, see: (a) Findlay, D. M.; Tchir, M. F. *J. Chem. Soc.*, *Chem. Commun.* **1974**, 514−515. (b) Arnold, B. J.; Mellows, S. M.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc.*, *Perkin Trans. 1* **1974**, 401−409.

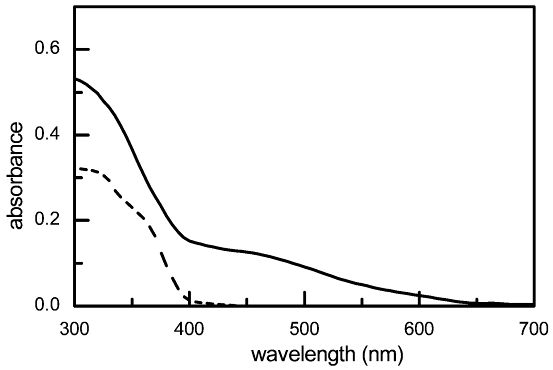


FIGURE 1. The solid-state absorption spectra of aldehydes **1** and **4** before (- - -) and after (—) brief exposure to UV radiation (λ ca. 350 nm).

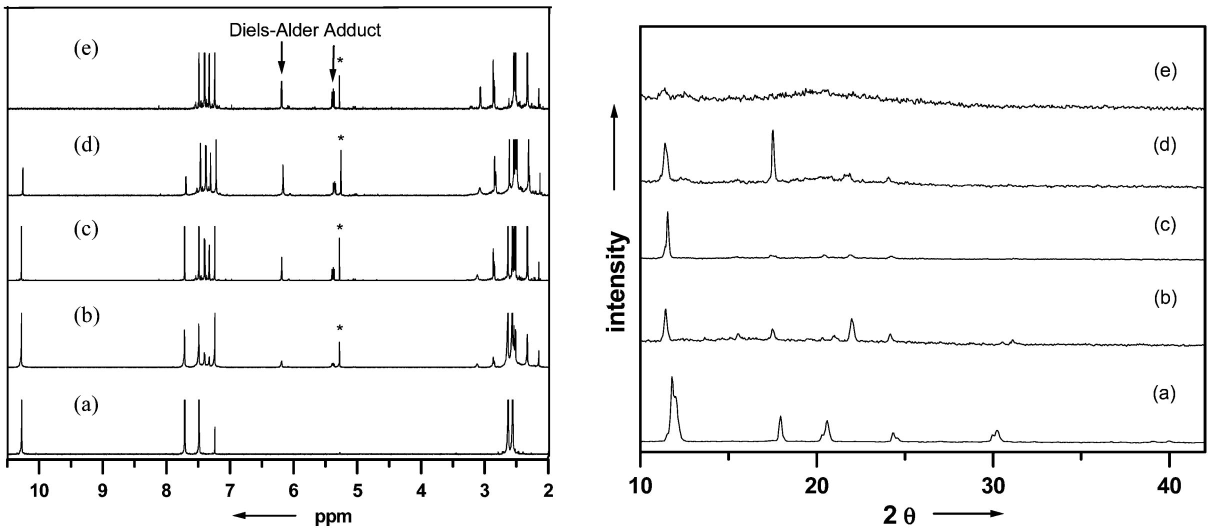


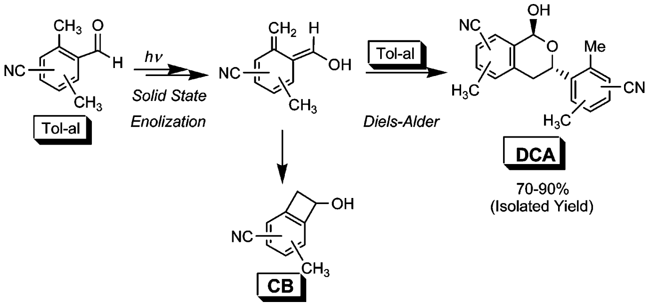
FIGURE 2. Powder XRD and ^{1}H NMR monitoring of the tandem reaction of aldehyde **2** in the solid state with increasing durations of irradiation: (a) 0 h; (b) 3.5 h, conversion 33%; (c) 7.0 h, conversion 50%; (d) 12.0 h, conversion 82%; (e) 20.0 h, conversion ~100%.

TABLE 1. Results of Photolysis of Aldehydes 1−8 in the Solid State[a,b]

aldehyde	duration of *hν* (h)	conv[c] (%)	DCA[d]	CB[d]
1	10	79	71	<5
2	10	82	90	
3	60	95	82	
4	12	100[e]	>90	
5	60	>80[f]	38	32
6	19	85		88[g]
7	60	90		89
8	24	100[h]		90

[a] The photolyses were carried out in a Luzchem photoreactor fitted with UV lamps (λ = 350 nm). [b] The irradiations were carried out on ca. 100 mg scale, unless otherwise mentioned. [c] Based on the recovered starting material. [d] Unless otherwise mentioned, isolated yields of the products. DCA = Diels−Alder cycloadducts; CB = cyclobutenols (cf. eq 4). [e] From 400-MHz ^{1}H NMR spectroscopy. [f] The DCA and CB were isolated as an inseparable mixture. The relative ratios of DCA and CB were obtained from the integrals of the characteristic signals in the ^{1}H NMR spectrum of the mixture. [g] Regioisomeric mixture, see text. [h] From ref 14b.

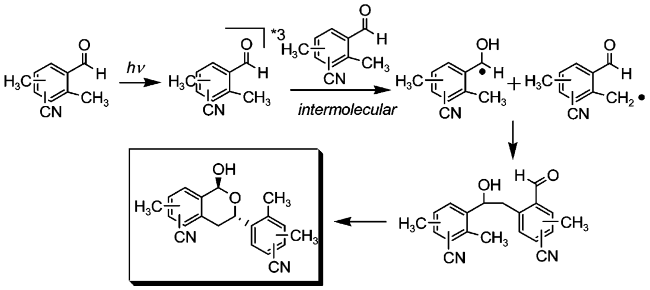
SCHEME 3



the Diels−Alder cycloadduct. The two products were isolated as an inseparable mixture and their relative ratio (55:45 for DCA:CB) was deduced from the integrals of the characteristic signals in the ^{1}H NMR spectrum of the mixture. All of the sterically hindered aldehydes **6**−**8** (category C) yielded the benzocyclobutenols in excellent yields (88−100%). In the case of **6**, an inseparable regioisomeric mixture of benzocyclobutenols was isolated.

Mechanistic Rationalizations. The formation of bimolecular Diels−Alder adducts (DCAs) may, in principle, occur by either of the two following mechanisms: First, the photoenolization via *intramolecular* γ-hydrogen abstraction from the *o*-methyl group by the triplet-excited formyl oxygen followed by trapping of the persistent (*E*)-enol with the precursor aldehyde in a hetero-Diels−Alder cycloaddition fashion may lead to DCA (Scheme 3).[9,10] Second, the *intermolecular* hydrogen abstraction by the

SCHEME 4



triplet-excited carbonyl from the *o*-methyl group of a neighboring aldehyde and subsequent coupling of the resulting radicals may lead to a hydroxy aldehyde, which may lactonize (Scheme 4).[28]

To rationalize the observed photochemical results in the light of crystal packing, the X-ray crystal structures of one aldehyde each of the two categories A and B, i.e., **2** and **5,** were determined; the X-ray crystal structure of **8** (category C) has previously been reported.[14b] In Figure 3 are exhibited the molecular structures of **2** and **5**; the oxygen and nitrogen atoms of CHO and CN groups are disordered in both cases with an occupancy factor of 0.5 for each. In both cases, the orientation of the formyl oxygen is ideally suited for γ-hydrogen abstraction from the *o*-methyl groups, a prerequisite for photochemical reactivity, to afford *o*-xylylenols.[29] Thus, the structural studies show that the photoenolization may proceed strictly in a *topochemical* fashion in both cases; we believe that the formyl oxygen orients toward the *o*-methyl group in the crystals of **1**, **3**, and **4** as well, otherwise the color due to the formation of photoenols would not be observed. The topochemical formation of photoenols (as revealed by structural analysis) in conjunction with UV−vis spectral characterization of the (*E*)-photoenols attest to the fact that the formation of Diels−Alder cycloadducts occurs via the trapping of dienols, generated in situ, by the precursor aldehydes in their respective crystal lattices (Scheme 3). Figure 4 shows the crystal packing diagrams for aldehydes **2** and **5**. Both of the aldehydes crystallize with about a 4.0 Å short *a*-axis corresponding to plane-to-plane aromatic stacking. From the crystal packing analysis, it is not readily explicable as to how the DCA adducts with anti stereochemistry may result after photoenolization. The fact that the Diels−Alder reaction between translationally related molecules along the *a*-axis does not occur is suggested by the anti stereochemistry observed with the bimolecular adducts. The contact distances between the reaction sites of the molecules in the *bc*-plane are very large (>6.0 Å), and this necessitates large-scale motions in the crystal lattice to afford the product with anti stereochemistry.

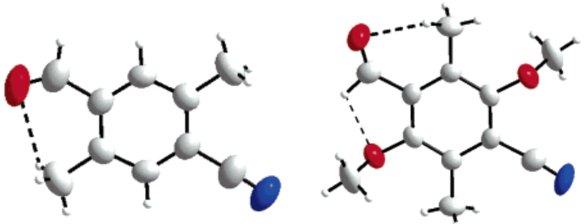


FIGURE 3. The X-ray molecular structures of the aldehydes **2** and **5**. Note that the oxygen and nitrogen atoms of CHO and CN groups are disordered in both cases with an occupancy factor of 0.5 for each. The hydrogens that may be abstracted by the formyl oxygens after photoexcitation are shown by a thick broken line.

The formation of (*E*)-enols via the initially generated triplet-excited *twisted* biradical[10c] necessitates a conformational change, which must be permitted in the crystal lattices of the aldehydes. Besides, the bimolecular trapping of the dienol by a dienophile can result in further reorganization of atomic positions. As a result, one may anticipate that the occurrence of a tandem reaction could disrupt the crystal lattice. Figure 2 shows the powder XRD profile typically recorded for aldehyde **2** with increasing conversions. As can be seen from the powder X-ray diffraction patterns, the crystallinity is conserved up to ca. 50% conversion of the aldehyde, which suggests that the crystal lattice in the aldehydes is tolerant to large-scale motions to afford the adducts with anti stereochemistry. However, with a further increase in the conversion, the crystallinity is gradually lost. The sample becomes entirely amorphous at 100% conversion. The product formation at low conversions is evidently controlled by crystal lattice forces; indeed, the photolysis of the amorphous sample of **2** obtained from quenching of the melt led to observation of a substantial amount of the acid (ca. 30%) in addition to the DCA adduct under N_2 atmosphere, which suggests that the mobility of O_2 in the crystals is restricted for oxidation.[30] The efficient formation selectively of the same product at high conversions, in the absence of any lattice effects, is remarkable and must be construed as resulting from a highly efficient reaction proceeding under solvent-free conditions with astounding selectivity.[31] This also suggests that the longer lifetimes of the (*E*)-enols cause the bimolecular reaction to be more efficient, while the thermal intramolecular cyclization to benzocyclobutenols becomes disfavored due to lesser stability of the cyclobutenols relative to the corresponding (*E*)-enols.[32] A reason for the observed exo selectivity of the Diels−Alder cycloaddition should be traceable to steric factors in the transition state for endo cycloaddition. Notably, even the solution-state

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[28] Intermolecular hydrogen abstractions from the methyl groups attached to the arene rings are known. For example, the solid-state photolysis of 4,4′-dimethylbenzophenones is known to yield intermolecular coupling products arising from hydrogen abstraction from the methyl groups, see: Ito, Y.; Matsuura, T.; Tabata, K.; Ji-Ben, M.; Fukuyama, K.; Sasaki, M.; Okada, S. *Tetrahedron* **1987**, *43*, 1307−1312.

[29] The calculated geometrical parameters for hydrogen abstraction in both cases fall in good agreement with the values generally observed, see: Ihmels, H.; Scheffer, J. R. *Tetrahedron* **1999**, *55*, 885−907.

[30] In a similar manner, the photolysis of the amorphous powder of the aldehyde **1** yielded anti DCA adduct together with small amounts of syn adduct as well as the acid, as monitored by 400-MHz spectroscopy.

[31] The irradiation carried out typically for aldehydes **1** and **2** in melt (ca. 130 °C) led predominantly to the corresponding acids even under O_2-excluded conditions. It appears that aldehydes undergo facile oxidation at high temperatures even with trace amounts of O_2 present.

[32] The competitive formation of benzocyclobutenol in the case of **5** may be a result of a smaller reaction cavity (see: Weiss, R. G.; Ramamurthy, V.; Hammond, G. S. *Acc. Chem. Res.* **1993**, *26*, 530−536) in the crystal lattice, which causes the bimolecular trapping reaction to occur rather sluggishly. The calculated densities (from X-ray studies) of the crystals of **2** (1.215 g/cm^3) and **5** (1.301 g/cm^3) suggest that the molecules in the latter are more tightly packed.

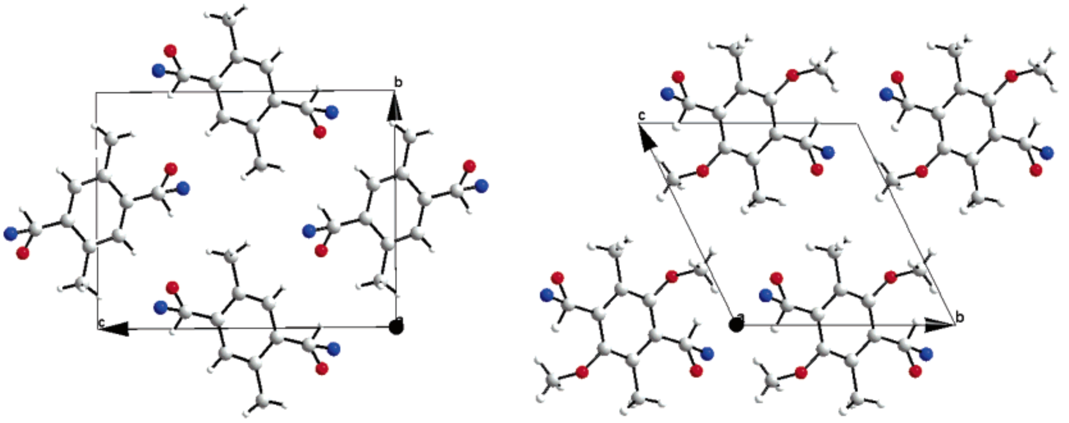

FIGURE 4. The crystal packing diagrams of aldehydes **2** (left) and **5** (right) viewed down the short (ca. 4.0 Å) *a*-axis. The blue and red atoms correspond to disordered positions of nitrogen and oxygen atoms of the CHO and CN groups with an occupancy factor of 0.5 for each.

photolysis is found to afford selectively the exo addition product in addition to a variety of other products.[27]

Why do aldehydes **6**−**8** of category C undergo cyclization efficiently? As mentioned at the outset, the (*E*)-enols derived from these aldehydes are highly sterically encumbered. Indeed, it is known that the steric hindrance in dienols promotes cyclization.[33] Evidently, the dienols do not survive long enough to be trapped intermolecularly. It is noteworthy that even stabilization of the dienols through dicyano substitution has no effect on diverting the unimolecular reactivity. As mentioned earlier, we have previously shown that the dicyano aldehyde **8** does produce the colored dienols when photolysis is carried out at low temperature.[14b] However, the thermal activation at room temperature is high enough to enforce cyclization and obviate UV−vis spectral detection of the former. It is precisely for this reason that simple *o*-alkyl aromatic ketones do not readily lend themselves to the phenomenon of photochromism based on photoenolization being observed in the solid state. The fleeting existence of the photoenols in these cases, due to steric factors that promote cyclization, presumably prevents any bimolecular chemistry from being competitively observed. This is a clear illustration of how the photochemistry of *o*-alkyl aromatic aldehydes can be at so much of a variance with that of the analogous ketones.

Conclusions

We have shown that the (*E*)-enols generated in the solid state by the photolysis of crystalline *o*-alkyl aromatic aldehydes (cloaked dienols) react with the precursor aldehydes within the crystal lattice in a hetero-Diels−Alder cycloaddition fashion to afford *trans*-3-arylisochromanols in excellent isolated yields with a high diastereoselectivity. An examination of the reactivity of three different classes of aldehydes shows that the tandem enolization−Diels−Alder cycloaddition occurs efficiently for aldehydes whose (i) photoenols are more stable relative to their benzocyclobutenols and (ii) are not sterically congested. However, rapid cyclization to benzocyclobutenols is found to be the predominant pathway for sterically encumbered (*E*)-enols derived from aldehydes such as **6**−**8**. Given that the execution of heteromolecular reactions in the solid state is a challenge, the strategy involving the in situ generation of a dienol in the crystal lattice of a dienophile so that the Diels−Alder reaction occurs readily is conceptually different from those that rely on host−guest chemistry, charge-transfer complexation, and mixed crystal formation. Further, from the point of view of enormous interest in tandem/cascade/domino[34] reactions in the contemporary organic synthesis, the results reported herein exemplify successful execution of tandem reactions in the solid state.

Experimental Section

The details of synthesis and characterization data for all of the aldehydes **1**−**7** and the photoproducts have been provided in the Supporting Information.

Photolysis Procedure and Characterization of Products. The gently ground crystalline sample of an aldehyde was dispersed in a Pyrex test tube and subjected to photolysis, under N_2 gas, in a Luzchem reactor fitted with 350-nm lamps. The sample was kept rotated over a turntable during the photolysis. The irradiated samples were analyzed at regular intervals by ^{1}H NMR spectroscopy by dissolving the photolysate in either $CDCl_3$ or DMSO-d_6. In preparative scale photolysis, ca. 100 mg of each of the aldehydes was irradiated for the durations specified in Table 1, and the reaction mixture was subjected to column chromatography on neutral alumina (eluent: 25% EtOAc in petroleum ether) to isolate the pure products. The characterization data are given below for two representative cases.

1-DCA: Colorless powder, mp 210 °C dec; IR (KBr) 3315, 2926, 2226 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.340 (s, 3H), 2.344 (s, 3H), 2.51 (s, 3H), 2.95−3.05 (m, 2H), 5.37 (dd, 1H, $J_1 = 8.5$ Hz, $J_2 = 5.8$ Hz), 5.97 (d, 1H, $J = 6.1$ Hz), 7.14 (d, 1H, $J = 5.9$ Hz), 7.45 (s, 1H), 7.59 (s, 1H), 7.63 (s, 1H), 7.67 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 16.6, 20.3, 20.4, 31.8, 64.2, 90.8, 111.2, 112.7, 117.5, 118.6, 132.2, 132.4, 132.8, 133.1, 134.6, 136.3, 136.8, 137.0, 137.2, 140.5. FAB-MS 319 (M + H), 301, 287, 279, 214, 179, 157.

7-CB: Colorless solid, mp 154−156 °C; IR (KBr) 3263, 2923, 2214 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19 (s, 3H), 2.29 (s, 3H), 2.40 (s, 3H), 2.89 (d, 1H, $J = 14.2$ Hz), 3.48 (dd, 1H, $J_1 = 14.3$ Hz, $J_2 = 4.4$ Hz), 5.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz)

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[33] (a) Matsuura, T.; Kitaura, Y. *Tetrahedron Lett.* **1967**, *8*, 3309−3310. (b) Kitaura, Y.; Matsuura, T. *Tetrahedron* **1971**, *27*, 1597−1606.

[34] (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167−176.

δ 13.9, 15.7, 17.9, 40.0, 69.6, 113.9, 118.0, 130.1, 134.8, 138.1, 140.6, 150.3.

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Supporting Information Available: The synthesis of all aldehydes **1**−**7**, characterization data for all of the (i) intermediates, (ii) aldehydes **1**−**7,** and (iii) photoproducts, and crystallographic data for aldehydes **2** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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