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Diastereomeric Discrimination in the Lifetimes of Norrish Type II Triplet 1,4-Biradicals and Stereocontrolled Partitioning of Their Reactivity (Yang Cyclization versus Type II Fragmentation)

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Abstract: The stereochemistry at C2 and C3 carbons controls the partitioning of triplet 1,4-biradicals of ketones **2** among various pathways. Differences in the major reaction pathways, for example, cyclization (*syn*) and fragmentation (*anti*), adopted by the diastereomeric 1,4-radicals of ketones **2** have permitted unprecedented diastereomeric discrimination in their lifetimes to be observed by nanosecond laser flash photolysis. From quantum yield measurements and transient lifetime data, the absolute rate constants for cyclization and fragmentation of a pair of diastereomeric triplet 1,4-biradicals have been determined for the first time.

Keywords: diastereoselectivity · ketones · photolysis · radicals

Introduction

Conformational control of reactivity of intermediates can be achieved, in principle, by restricting their mobility. This has been achieved environmentally (for example, intermolecularly) in several ways. An extreme is reaction within the neat crystalline state in which lattice forces can control the fates of intermediates generated both thermally and photochemically.[1] Usually, less specific environmental control is exerted when reactions are conducted in "container" systems, such as cyclodextrins,[2] calixarenes,[3] cucurbiturils,[4] etc.,[5] in zeolites[6] with well-defined cavities, or in liquid crystals[7] and in polymer films[8] with less well-defined and more dynamic cavities.[1d] An entirely different approach, involving intramolecularly designed control, which has been adopted by us[9] entails the imposition of steric interactions about contiguous chiral centers, such that the resulting diastereomers exhibit distinct conformational preferences; reactions in which the diastereomers exhibit differing reactivities are termed "diastereomer-differentiating".[10] This strategy has been exploited to demonstrate a remarkable diastereomeric discrimination in triplet lifetimes of a diketone.[11]

Scheme 1 is a paradigm for Norrish–Yang Type II reactions.[12] Initial γ-hydrogen abstraction from the triplet states of aromatic ketones (R^1 = phenyl) leads to a *cisoid* conformation for the 1,4-biradicals. A subsequent twisting motion about the C1–C2 bond is necessary to attain another *cisoid* conformation (shown in Scheme 1), a requisite for cyclization, in which the two singly-occupied orbitals are directed toward each other. Although the fragmentation products may derive from both *cisoid* and *transoid* conformations, the fragmentation is generally ascribed to *transoid* conformations.[12,13] While the geometries of triplet 1,4-biradicals (^{3}BR) appear to control the product profiles, there is no clear understanding until now of how they partition themselves among the various pathways shown in Scheme 1.[14] In view of this, understanding of the factors that influence the lifetimes of triplet 1,4-biradicals (τ_{BR}), which are also intermediates in reactions, such as Paterno–Büchi and enone-olefin photocycloadditions,[15] and their behavior[16] continues to be of significant contemporary interest.[17] Insofar as

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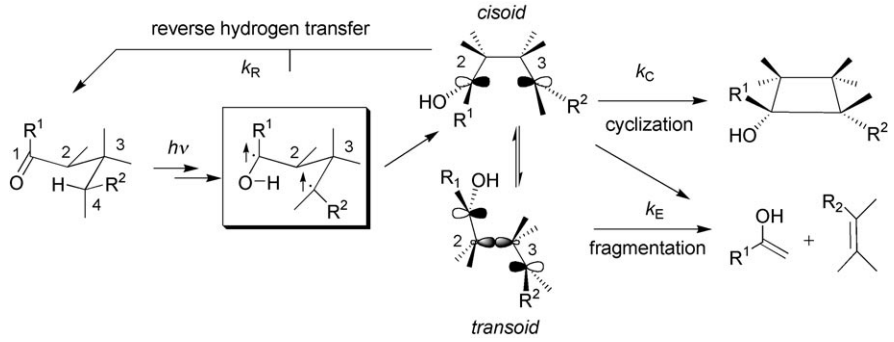
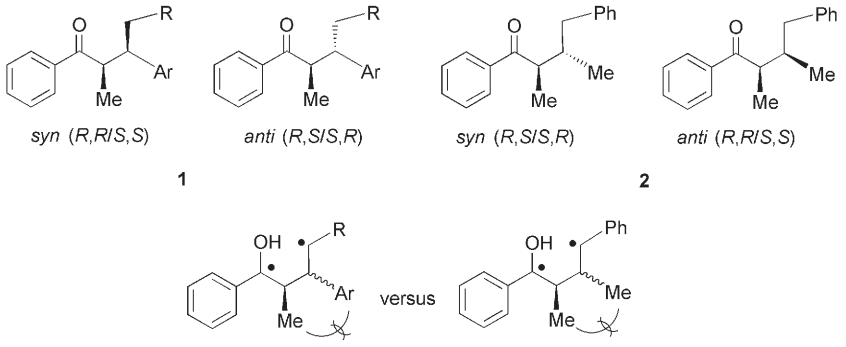


Scheme 1. A representative mechanistic picture for Norrish–Yang Type II reactions.

the Norrish Type II reaction is concerned, its potential as applied to photorelease processes,[18] photocyclization reactions,[19] asymmetric synthesis,[20] etc. has begun to unfold only recently.

We have recently shown that different triplet lifetimes, caused by conformational preferences intrinsic to the diastereomers of α,β-disubstituted ketones, such as **1**, can lead to reactivity differences.[9,21] In this instance, rapid Yang cyclization and Norrish Type II fragmentation, accentuated by the formation of thermodynamically stable styrene/stilbene products (R = Me/Ph), precluded direct observation of the intermediary triplet 1,4-biradicals by nanosecond transient absorption spectroscopy and, hence, incontrovertible evidence for the hypothesized link between diastereomeric discrimination and biradical lifetimes. In pursuit of the latter, we designed ketones **2** based on the following rationale: 1) the ^{3}BR of **2** are bisbenzylic and hence should be relatively longer lived than those of **1** and 2) they should be less prone to fragment, further increasing the τ_{BR} of **2** with respect to those of **1** with R = Ph (in which fragmentation leads to a thermodynamically more stable alkene).

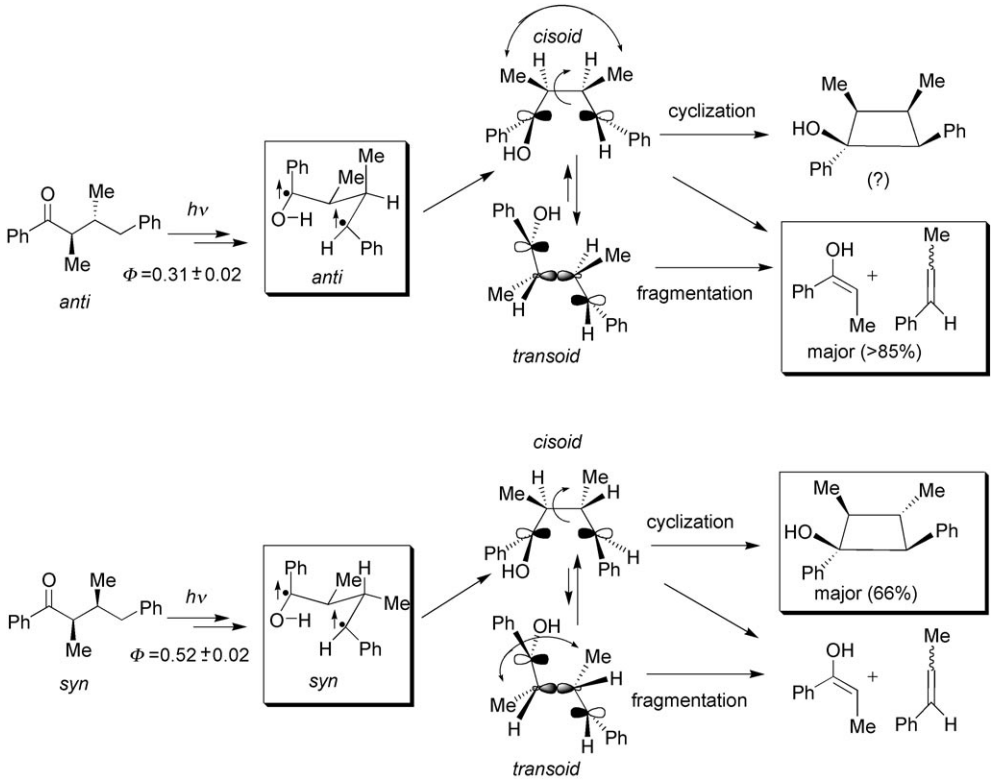


Here, we report the results of our investigation involving the unprecedented diastereomeric discrimination in τ_{BR} generated by irradiation of the diastereomeric α,β-dimethyl-γ-phenyl-butyrophenones **2** and stereocontrolled partitioning of their reactivity between Yang cyclization and Norrish Type II fragmentation.[22] Furthermore, and perhaps of even greater mechanistic importance, the absolute rate constants for the cyclization and fragmentation pathways of the diastereomeric ^{3}BR have been calculated from lifetime and quantum yield measurements. The subtle differences among the rates provide unprecedented insights into the relationships among the competing processes.

Results and Discussion

The diastereomers of ketone **2** were synthesized by 1,4-addition of MeMgI to PhCOC(CH$_3$)=CHCH$_2$Ph. Because the separation of the two diastereomers could not be achieved by silica-gel chromatography using a variety of solvent systems, an indirect route was followed. The diastereomeric mixture was first reduced with NaBH$_4$ to afford a mixture of four diastereomeric alcohols, which could be separated fractionally by TLC using diethyl ether/petroleum ether 25:75 as eluent. Gravity column chromatography of the mixture afforded three alcohols (one as a mixture), which upon oxidation yielded pure *syn* and *anti* isomers of ketone **2**. Configurational assignment of the diastereomers was based on comparisons of ^{1}H NMR spectroscopic chemical shifts of diagnostic methyl signals with those of analogous ketones reported in the literature.[9,23] Furthermore, the α-methyl carbon atoms of the *syn* and *anti* diastereomers of analogous ketones have been noted in the literature to exhibit distinct ^{13}C NMR spectroscopic chemical shifts:[24] the signal from the α-methyl carbon of the analogous *syn* diastereomer appears approximately 2–5 ppm further upfield than that of the *anti*. Thus, the ^{13}C NMR signal from the α-methyl carbon of the diastereomer of **2** assigned as *syn* based upon the ^{1}H NMR spectroscopic chemical shifts appears at 15.13 ppm, while that of the *anti* diastereomer resonates at 17.8 ppm.

Cyclization and fragmentation photoproducts accounted for >90% of consumed ketone when the diastereomers of **2** were irradiated (λ_{irrad} ca. 350 nm) at approximately 25 °C in solvents, such as chloroform, cyclohexane, etc. Whereas irradiation of the *syn* diastereomer led mostly to cyclization products (approximately 66% relative yield) with >90% diastereoselectivity as indicated by ^{1}H NMR spectroscopy, the *anti* diastereomer afforded predominantly fragmentation products (>85% relative yield, Scheme 2). The cyclobutanol (CB) from the *syn* diastereomer was isolated from a preparative-scale irradiation, characterized by



Scheme 2. Mechanistic rationalization of distinct photochemical fates observed for *syn* and *anti* diastereomers of ketone **2**.

IR and ^{1}H and ^{13}C NMR spectroscopies, and its stereochemistry was deduced from NOESY experiments (see Supporting Information).

Irradiations of both diastereomers in cyclohexane were examined in detail in view of their very different τ_{BR} in this solvent (vide infra). Thus, photoproduct distributions from approximately 0.03 M cyclohexane solutions of each diastereomer in NMR tubes under nitrogen atmospheres were determined directly by ^{1}H NMR spectroscopy using the homonuclear gated decoupling (hmg) technique. The cyclization/fragmentation product ratio was approximately 2:1 from the *syn* diastereomer and 15:85 from the *anti* (Scheme 2). The cyclobutanol shown in Scheme 2 from the *anti* isomer was detected in very low yield (approximately 6–7%), and its isolation from a preparative photolysis of approximately 1 mmol of the ketone was complicated by formation of a nearly equal amount of an inseparable second cyclobutanol derived by means of hydrogen abstraction from the β-methyl group. The major fragmentation pathway for the *anti* does not involve the "minor" ^{3}BR resulting from the abstraction of hydrogen from the β-methyl group, because β-methylstyrene (along with propiophenone) is the almost exclusively detected fragmentation alkene (Scheme 2); very little (if any) 3-phenylpropene, the olefin expected from fragmentation of the "minor" 1,4-biradical, was detectable by ^{1}H NMR spectroscopic analyses. Thus, with a maximum limit of 7% relative yield for the cyclobutanol from the "major" 1,4-biradical and 85–87% yield for fragmentation, the cyclization/fragmentation ratio is estimated to be 1:10. Furthermore, the disappearance quantum yields (Φ) for the *syn* and *anti* diastereomers upon irradiation at 313 nm in cyclohexane[25] were determined to be 0.52 ± 0.02 and 0.31 ± 0.02, respectively.

Laser flash photolyses (XeCl excimer laser, 308 nm and 10 ns pulses of 80 mJ energy) of solutions of the diastereomers of **2** in a number of solvents led to transient absorption spectra, such as those in Figure 1. The transient spectra are virtually identical in position and shape, as expected. Each has the attributes of a benzylic/ketyl radical:[26] a strong absorption (OD ca. 0.05–0.10) at 310–320 nm and a weak, broad absorption with a shoulder in the region around 400–470 nm. Also, the absorption was efficiently quenched by oxygen, and the decay times of the transients are similar to those reported for a 1,4-biradical from γ-phenylbutyrophenone in MeOH (146 ± 19 ns) and in a low polarity solvent, such as heptane (55 ± 8 ns).[27] Based upon these observations, the transient absorptions in Figure 1 are attributed to ^{3}BR from the diastereomers of **2**.[28]

The decays monitored at 320 and 420–440 nm were clearly monoexponential and had the same decay constants. The lifetimes thus determined for the diastereomeric ^{3}BR of **2** in a variety of solvents are collected in Table 1. Small differences in the lifetimes for the diastereomeric biradicals were observed in a number of polar and low-polarity protic and aprotic solvents. However, an unprecedented discrimination in the τ_{BR} was found in cyclohexane, a relatively viscous and low-polarity solvent.[29] In at least six independent determinations, the τ_{BR} from the two diastereomers reproducibly ex-

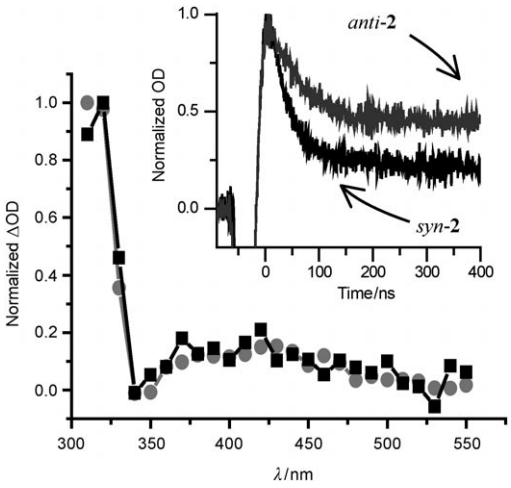


Figure 1. Transient absorption spectra attributed to ^{3}BR derived from *syn*-**2** (■) and *anti*-**2** (●) in cyclohexane after a pulse delay time of 35 and 65 ns, respectively. Inset shows the decay profiles monitored at 320 nm (slow for *anti* and fast for *syn*) of the diastereomeric ^{3}BR; the relatively higher OD after the decay of the biradical in the case of the *anti* diastereomer is unquestionably due to stronger absorbance of the derived fragmentation photoproducts.

Table 1. Lifetimes of ^{3}BR (ns) derived from the diastereomers of **2**.[a,b]

Entry	Solvent	*syn*-**2**	*anti*-**2**
1	acetonitrile	134	142
2	benzene	65	71
3	methanol	158	161
4	chloroform	59	59
5	*n*-hexane	47	50
6	cyclohexane	46	61
7	*t*BuOH/ethylene glycol 3:2	173	194
8	benzene/water 95:5	74	93

[a] Monitoring wavelength = 320 nm. [b] Error = ± 5 %.

hibited a lifetime difference of 15 ns, representing approximately 30 % of the average. A similar trend, albeit less pronounced, was observed in two mixed solvent systems, *t*BuOH/ethylene glycol 3:2 and benzene/water 95:5. More specifically, the τ_{BR} from the *syn* diastereomer (which decays to cyclobutanol as the major product) were consistently shorter than those from the *anti* (which fragments principally).

The ^{3}BR may decay by three possible unimolecular pathways, denoted by k_C, k_E, and k_R in Scheme 1, which involve intersystem crossing.[12,15] As mentioned earlier, there is still no clear understanding of how biradical structure affects its partitioning among the three pathways,[14] although certain structural features of biradical reactivity are established.[12,13] We have recently shown that the diastereomer-differentiating photochemical reactions of **1** can be rationalized based on 1) stereocontrolled stabilization of the geometry (*cisoid*/*transoid*) of the ^{3}BR and 2) the premise that cyclization will be observed only if a ^{3}BR assumes a *cisoid* geometry while *fragmentation* occurs predominantly from the *transoid* geometry.[9]

We apply similar considerations to **2** as well (Scheme 2, double arrows signal steric congestion). The steric interactions between the α,β-dimethyl substituents should cause conformational preferences of the ketones such that their respective ^{3}BR, generated subsequent to photolysis, are also similarly influenced. Furthermore, steric repulsions between the C2 and C3 methyl substituents must disfavor the attainment of a *cisoid* conformation of the *anti* ^{3}BR; the conformational preference and the source of most reactivity should be from the *transoid* conformation. The opposite conformational preference (and source of reaction) is predicted by the same steric arguments for the *syn* ^{3}BR; the *cisoid* conformation must be favored energetically. Thus, the observed predominant fragmentation from the *anti* diastereomer and high cyclization yields from the *syn* diastereoisomer are in accord with expectations based on simple arguments for stereochemical preferences of the diastereomers of **2** and their 1,4-biradicals. Although the *cisoid* conformer may, in principle, lead to fragmentation, it is less likely because of the stringent stereoelectronic requirements,[13] involving the overlap of the singly-occupied orbitals at C1 and C4 with the C2–C3 sigma orbitals and the steric crowding that this geometry entails.

Inherent to the stereocontrolled partitioning of the diastereomeric biradical reactivity discussed above is the possibility to observe differential rates for their decay. The two τ_{BR}, especially in cyclohexane, demonstrate that their very different chemical fates (for example, predominantly fragmentation or cyclization) occur at distinctly different rates; although the observed differences in the τ_{BR} are small such a discrimination has not been heretofore scrutinized. By using a simplified form of the mechanism in Schemes 1 and 2, in which k_E refers to fragmentation from both the *transoid* and *cisoid* ^{3}BR precursors, the experimentally-determined ^{3}BR decay rate constants and absolute rate constants for each of the reactive pathways followed by the diastereomeric triplet 1,4-biradicals can be calculated from disappearance quantum yields and the relative cyclization and fragmentation photoproduct yields.

As the triplet states of phenyl alkyl ketones and the triplet 1,4-biradicals are formed with unit efficiency,[12,13] the quantum yields for fragmentation (Φ_E) and cyclization (Φ_C) are given by: $\Phi_E = \frac{k_E}{k_E+k_C+k_R}$ and $\Phi_C = \frac{k_C}{k_E+k_C+k_R}$ in which k_E, k_C, and k_R are the rate constants for fragmentation, cyclization, and reversion of the ^{3}BR to **2**, respectively. Accordingly, $k_E = \frac{\Phi_E}{\tau_{BR}}$ and $k_C = \frac{\Phi_C}{\tau_{BR}}$.

Based on the relative product ratios for the two diastereomers, the total quantum yield for ketone disappearance ($\Phi_E + \Phi_C$), the decay constants in cyclohexane ($1/\tau_{BR}$), and the absolute rate constants for cyclization and fragmentation of the diastereomeric ^{3}BR are calculated to be: $k_C^{anti} = 0.46 \times 10^6\ s^{-1}$, $k_E^{anti} = 4.6 \times 10^6\ s^{-1}$[30] and $k_C^{syn} = 7.5 \times 10^6\ s^{-1}$, $k_E^{syn} = 3.8 \times 10^6\ s^{-1}$. As $1/\tau_{BR} - (k_C + k_E) = k_R$, its values are calculated to be $11.5 \times 10^6\ s^{-1}$ (*anti*) and $11.3 \times 10^6\ s^{-1}$ (*syn*). Clearly, the difference in the overall quantum yields for consumption of the two diastereomers of **2** is governed by their rates of cyclization; the values of k_E and k_R are nearly the same for the two diastereomers! These data demonstrate the importance of diastereocontrol over the conformations of the 1,4-biradicals.

Conclusion

We have shown that the partitioning of the ^{3}BR between cyclization (*cisoid*) and fragmentation (*transoid*) pathways can be controlled by means of steric interactions built around substituents at C2 and C3 of ketone **2**. The two diastereomeric ^{3}BR derived from irradiation of **2** collapse by distinct pathways—cyclization, fragmentation and return to **2**—that can be discriminated kinetically to correlate structure and reactivity with unprecedented detail. To the best of our knowledge, these are the first absolute rate constant determinations for cyclization and fragmentation of a pair of diastereomeric triplet 1,4-biradicals. These results offer extremely detailed insights into the motions that triplet 1,4-biradicals must undergo to decay to singlet ground-state products. Clearly, other substitution patterns will expand our knowledge of the motions of 1,4-biradicals.

Experimental Section

Preparation of α,β-dimethyl-γ-phenylbutyrophenones 2: The required precursor α,β-unsaturated ketone, namely 1,4-diphenyl-2-methyl-2-butenone, was prepared according to the procedure already reported by us.[9] Methyl iodide (10.09 g, 71.16 mmol) was added to the Mg turnings (1.7 g, 71.16 mmol) suspended in dry ether (50 mL) followed by a catalytic amount of iodine. The reaction mixture was stirred at room temperature until the Mg turnings disappeared. The Grignard reagent was added to a solution of cuprous iodide (6.77 g, 35.58 mmol) in THF (25 mL) at −40 °C through a cannula. The resulting heterogeneous mixture was stirred at −40 °C for 2 h. After this time, 1,4-diphenyl-2-methyl-2-butenone (2.8 g, 11.86 mmol) in THF (25 mL) was added to this mixture at the same temperature and stirred for 2 h. Subsequently, the reaction mixture was warmed up and stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc. The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, and the solvent removed in vacuo. The crude compound was purified by silica gel column chromatography (2.5% EtOAc/petroleum ether), yielding the diastereomeric mixture (*syn* and *anti*) in approximately 32% yield.

$NaBH_4$ reduction of the mixture of diastereomers of 2 and reoxidation of separated alcohols: To the mixture of diastereomers (0.930 g, 3.69 mmol) in EtOH (40 mL) was added $NaBH_4$ (0.084 g, 2.21 mmol). After refluxing for 2 h, the reaction mixture was quenched with 10% aqueous HCl (10 mL) and the volume was reduced to approximately 20 mL. The resultant mixture was extracted with EtOAc and the organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude diastereomeric mixture of the alcohols, isolated in near quantitative yields (>96%) was purified by silica gel column chromatography (diethyl ether/petroleum ether 6:94) to obtain three fractions of alcohols. PCC (pyridinium chlorochromate) oxidation of each alcohol led to pure *syn* and *anti* diastereomers as revealed by ^{1}H NMR spectroscopy in a quantitative yield.

anti-**2**: Colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.91$ (d, $J =$ 5.4 Hz, 2H; arom. H), 7.56 (t, $J = 5.3$ Hz, 1H; arom. H), 7.46 (t, $J =$ 5.7 Hz, 2H; arom. H), 7.13–7.22 (m, 3H; arom. H), 7.04 (d, $J = 5.7$ Hz, 2H; arom. H), 3.42–3.49 (m, 1H; CH), 2.82–2.89 (m, 1H; CH), 2.16–2.27 (m, 2H; CH_2), 1.26 (d, $J = 5.1$ Hz, 3H; CH_3), 0.86 (d, $J = 4.5$ Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 204.6$ (PhCO), 140.9 (C_{ar}), 137.5 (C_{ar}), 132.9 ($C_{ar}H$), 129.2 ($C_{ar}H$), 128.7 ($C_{ar}H$), 128.3 ($C_{ar}H$), 128.26 ($C_{ar}H$), 126.0 ($C_{ar}H$), 45.9 (CH), 39.2 (CH_2), 38.0 (CH), 17.8 (CH_3), 13.8 (CH_3); IR (neat): $\tilde{\nu} = 1680$ cm^{-1}.

syn-**2**: Colorless viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.69$ (d, $J =$ 5.4 Hz, 2H; arom. H), 7.50 (t, $J = 5.6$ Hz, 1H; arom. H), 7.37 (t, $J =$ 5.7 Hz, 2H; arom. H), 7.17–7.33 (m, 5H; arom. H), 3.36–3.42 (m, 1H; CH), 2.61–2.68 (m, 1H; CH), 2.50–2.56 (m, 1H; CH), 2.22–2.31 (m, 1H; CH), 1.15 (d, 3H, $J = 5.1$ Hz; CH_3), 0.83 (d, 3H, $J = 5.1$ Hz; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 204.1$ (PhCO), 140.8 (C_{ar}), 136.7 (C_{ar}), 132.8 ($C_{ar}H$), 129.3 ($C_{ar}H$), 128.6 ($C_{ar}H$), 128.4 ($C_{ar}H$), 128.3 ($C_{ar}H$), 126.2 ($C_{ar}H$), 43.4 (CH), 41.8 (CH_2), 37.4 (CH), 15.1 (CH_3), 10.8 (CH_3); IR (neat): $\tilde{\nu} = 1680$ cm^{-1}.

Photolysis procedure: Solutions of a diastereomer of ketone **2** (approximately 6–8 mg) in 0.6 mL of $CDCl_3$ in NMR tubes were purged with nitrogen gas and irradiated in a Luzchem photoreactor fitted with 350 nm lamps. Disappearance of the ketone was monitored periodically by ^{1}H NMR spectroscopic analyses. To quantify yields of products, a small amount of methyl benzoate was added to each tube as an internal standard.

The cyclobutanol product from the *syn* diastereomer (*syn*-CB-**2**) was isolated by irradiating the ketone (approximatley 150 mg) in chloroform (100 mL). The photolysate was monitored periodically by TLC analysis for disappearance of the ketone. After complete conversion, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc/hexane 20:80).

syn-CB-**2**: Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.20$–7.45 (m, 10H; arom. H), 3.39 (d, $J = 7.5$ Hz, 1H; CH), 2.51–2.53 (m, 1H; CH), 2.18–2.20 (m, 1H; CH), 1.23 (d, $J = 5.1$ Hz, 3H; CH_3), 1.13 (d, $J = 5.1$ Hz, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.3$ (C_{ar}), 137.4 (C_{ar}), 128.6 (x2) ($C_{ar}H$), 128.5 ($C_{ar}H$), 128.4 ($C_{ar}H$), 127.0 ($C_{ar}H$), 125.2 ($C_{ar}H$), 78.8 (C_{al}), 56.3 (CH), 46.7 (CH), 37.3 (CH), 18.8 (CH_3), 11.2 (CH_3); IR (neat): $\tilde{\nu} = 3364$ cm^{-1} (br), 2926 cm^{-1}.

Determination of quantum yields: The quantum yields were determined by using valerophenone as an actinometer ($\Phi_{313nm} = 0.33$ for the formation of acetophenone).[25] For quantum yield measurements, a solution of a diastereomer of **2** in cyclohexane (approximatley 0.04 M) and a small amount of methyl benzoate as an internal standard were irradiated (313 nm) by using a high-pressure Hg lamp (Applied Photophysics) equipped with a monochromator. Conversion of the ketones was limited to 15–16% and analyses were performed by gas chromatography.

Laser flash photolyses: Experiments were carried out with an LKS.60/S nanosecond laser flash photolysis spectrometer (Applied Photophysics) with a GSI Lumonics Pulsemaster PM-846 excimer laser running on XeCl for excitation (308 nm, approximatley 80 mJ pulse energy, 10 ns pulse width). The transient data were recorded with a 54830B 600 MHz Infinium oscilloscope (Agilent Technologies) and processed with the instrument-supplied software. Transient spectra were recorded in a step-scan mode in 10 nm intervals. Transient decay traces were recorded near the transient absorption maxima at approximately 320 and 450 nm. Samples (approximately 3 mL) were prepared in fused long-neck quartz cuvettes to allow bubbling with dry nitrogen gas for 15 min to remove oxygen. The optical densities of all samples were adjusted to 0.4 ± 0.1 at 308 nm by using a Cary50 UV spectrophotometer (Varian).

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