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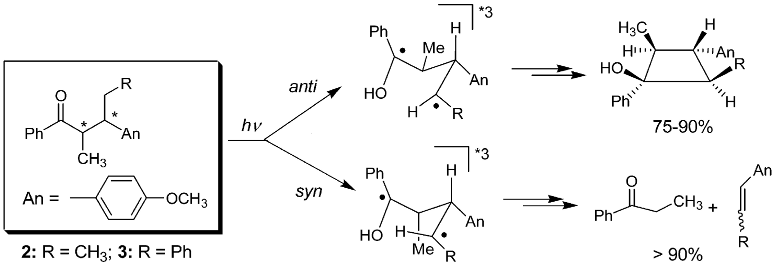

2: R = CH$_3$; **3:** R = Ph

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Diastereomer-Differentiating Photochemistry of *β*-Arylbutyrophenones: Yang Cyclization versus Type II Elimination

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Abstract: The diastereomers of ketones **2** and **3** are shown to exhibit distinct photochemical reactivities due to conformational preferences; while the anti isomers of **2** and **3** undergo efficient Yang cyclization in 75–90% yields with a remarkable diastereoselectivity (> 90%), the syn isomers predominantly undergo Norrish Type II elimination. The differences in the product profiles of the diastereomers are consistent with a mechanistic picture involving the formation of precursor diastereomeric triplet 1,4-biradicals in which the substituents at α and *β*-positions stabilize the cisoid (cyclization) or transoid (elimination) geometry. The fact that such a diastereomeric relationship does indeed ensue at the triplet-excited-state itself is demonstrated via the nanosecond laser-flash photolysis of model ketones **1**. The diastereomeric discrimination in the product profiles observed for ketones **2** and **3** as well as in the triplet lifetimes observed for ketones **1** can both be mechanistically traced back to different conformational preferences of the ground-state diastereomeric ketones and the intermediary 1,4-biradicals. Additionally, it emerges from the present study that the syn and anti diastereomers of ketones **2** and **3** represent two extremes of a broad range of widely examined butyrophenones, which lead to varying degrees of Yang photocyclization depending on the alkyl substitution pattern.

Introduction

In contrast to reactions in the solid state[1] and microheterogeneous media,[2] control of the photoreactivity of a substrate that can potentially exploit two or more reaction pathways in a homogeneous solution state is governed by conformational preferences. Conceivably, the bond rotations between two contiguous stereogenic centers of a substrate should be sufficiently restricted to permit substantial differences in conformational populations of the two diastereomers. It is precisely this strategy that has been exploited to demonstrate unprecedented diastereomeric discrimination in the triplet lifetimes of phenyl alkyl ketones.[3] It was of our interest to translate such discrimination in the triplet lifetimes into differences in the reactivity of the diastereomers of appropriately substituted photoreactive carbonyl compounds. Indeed, reactions in which SS/RR and RS/SR diastereomers exhibit differing reactivity are termed "diastereomer-differentiating".[4] The first example of a photochemical reaction wherein the two diastereomers of a substrate with two contiguous stereogenic centers, a hexa-1,5-diene, yielded two different types of products was reported by Margaretha and co-workers.[5,6] Apart from this, we are aware of only one other case of such a reaction, which involves *γ*-hydrogen abstraction (vide infra).[7,8]

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(1) (a) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433. (b) Toda, F. *Acc. Chem. Res.* **1995**, *28*, 480. (c) Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203. (d) Ito, Y. *Synthesis* **1998**, 1. (e) Garcia-Garibay, M. A. *Acc. Chem. Res.* **2003**, *36*, 491. (f) For a recent study on enantioselective Yang cyclization in the crystalline medium, see: Natarajan, A.; Mague, J. T.; Ramamurthy, V. *J. Am. Chem. Soc.* **2005**, *127*, 3568, and references therein.

(2) (a) For control of photoreactions by various microheterogeneous media, see: *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991. (b) Sivaguru, J.; Natarajan, A.; Kaanumalle, L. S.; Shailaja, J.; Uppilli, S.; Joy, A.; Ramamurthy, V. *Acc. Chem. Res.* **2003**, *36*, 509.

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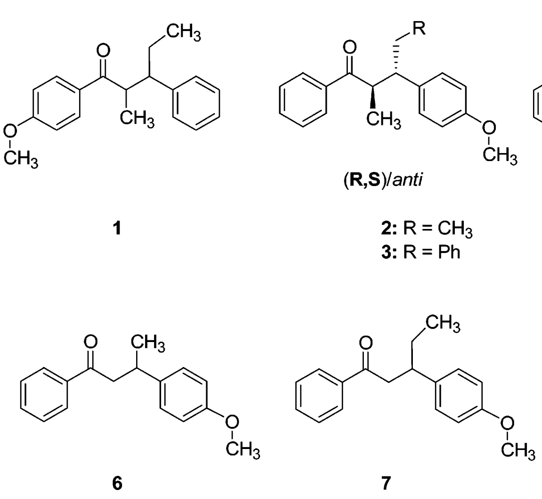
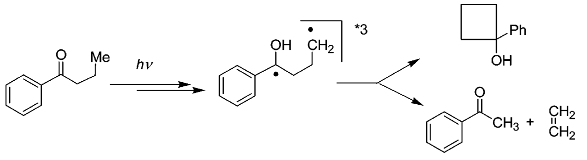
Chart 1

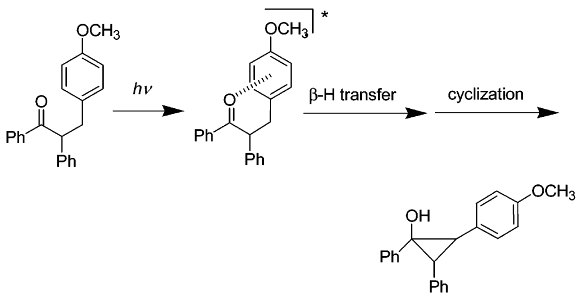


The photochemistry of butyrophenone/valerophenone is well established;[9] indeed, it is a frequently employed chemical actinometer in quantum yield measurements.[10] The early investigations by Lewis and co-workers have thoroughly established the effect of α- and β-substitution on Yang cyclization versus Norrish Type II elimination (eq 1).[11] Accordingly, α-substitution of butyrophenone increases the percentage of cyclization, while β-substitution causes only a marginal effect.

β-Phenylpropiophenone has served as a prototypal example to understand the long-recognized influence of aromatic solvents such as benzene, toluene, etc. in shortening the triplet lifetimes of ketones.[12] By nanosecond transient absorption spectroscopy, Scaiano and co-workers[13] showed that the orientation in which the β-phenyl ring is gauche to the carbonyl group leads to intramolecular charge-transfer-induced quenching.[14] This remarkable phenomenon causes the triplet lifetime, for example, of the representative β-phenylpropiophenone to be shortened by more than 2−3 orders of magnitude to ca. 1 ns. Later, Wagner and co-workers reported that photocyclization via charge transfer-promoted β-hydrogen transfer to cyclopropanol (eq 2) occurs when the β-phenyl ring is substituted with an electron-rich group such as methoxy as in β-(*p*-anisyl)-propiophenone.[15] The reaction has been suggested to proceed via the intermediacy of an intramolecular exciplex involving the β-anisyl ring and triplet-excited carbonyl group.



(eq 1)



(eq 2)

We designed ketones **2** and **3** in such a way that their two diastereomers incorporate, in their lowest energy conformations, the structural attributes necessary for the two different reaction mechanisms (cf. β- and γ-hydrogen abstraction in eq 1 and 2), and three reaction products (cyclopropanol, cyclobutanol, and cleavage products) with potentially different syn/anti stereochemistry; the spectrum of potential photoproducts should greatly facilitate the experimental detection of diastereodifferentiating photochemical effects of the racemic anti and syn diastereomers of ketones **2** and **3**. The photobehavior of ketones **1** and **4-7** (Chart 1) was investigated to gain a comprehensive understanding of the photochemical reaction pathways in this type of chromophores.

Results

Synthesis and Characterization of Ketones. The synthetic protocol followed for the preparation of ketones **1-5** is shown in Scheme 1. Accordingly, the trimethylsilyl enol ether of propiophenone, prepared from propiophenone using trimethylsilyl chloride and triethylamine in DMF,[16] was subjected to Mukaiyama aldol condensation[17] with propanaldehyde/phenyl-

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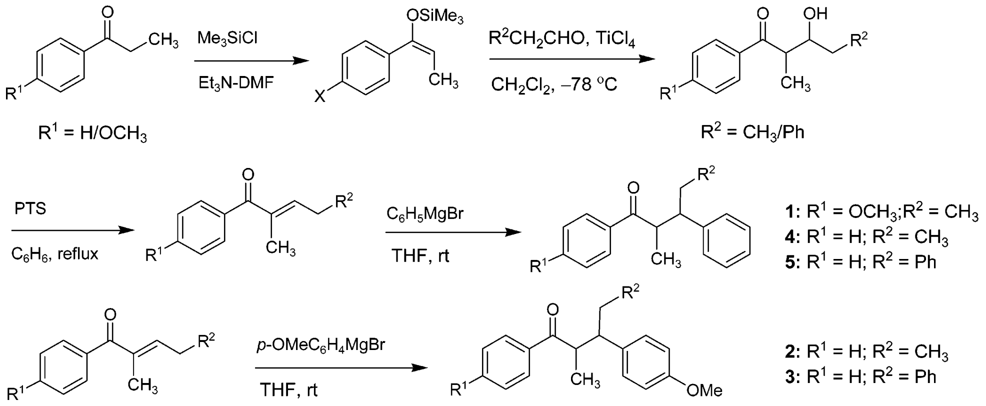
Scheme 1



acetaldehyde in the presence of TiCl$_4$ in DCM at −78 °C. The resulting aldols were dehydrated using PTS in benzene to the corresponding α,β-unsaturated ketones.[18] The 1,4-addition reaction of the latter with ArMgBr (Ar = phenyl or *p*-anisyl) yielded ketones **2**−**5** as mixtures of two diastereomers.[19] Ketones **1** were prepared in a similar manner starting from *p*-methoxypropiophenone. The ketones **6** and **7**[20] were prepared by 1,4-addition of MeMgI and EtMgI to *p*-methoxychalcone, respectively.

The diastereomers of ketones **1**−**5** were separated by silica gel column chromatography and characterized by IR, ^{1}H, and ^{13}C NMR analyses. The configurational assignment of the diastereomers was accomplished as follows. First of all, the stereochemistry for one of the diastereomers of ketone **3** was established based on a single-crystal X-ray structure determination of the crystalline isomer. The X-ray analysis revealed its stereochemistry to be 'syn' (Figure 1). The second diastereomer was assigned the 'anti' stereochemistry by default. It was recognized that the doublets in ^{1}H NMR due to α-methyl protons of anti and syn diastereomers of ketone **3** resonate very distinctly and occur at δ 0.98 and 1.37, respectively. The upfield shift in the case of anti diastereomer is due presumably to anisotropic shielding of the α-methyl protons by the β-aryl ring, which is gauche in the lowest energy conformation (vide infra). A similar difference (ca. 0.3) in the chemical shifts of the α-methyl protons was observed for the diastereomers of all other ketones, i.e., **1**, **2**, **4**, and **5**. Thus, the anti stereochemistry was assigned to that isomer for which the doublet of the α-methyl protons was found to be upfield shifted.

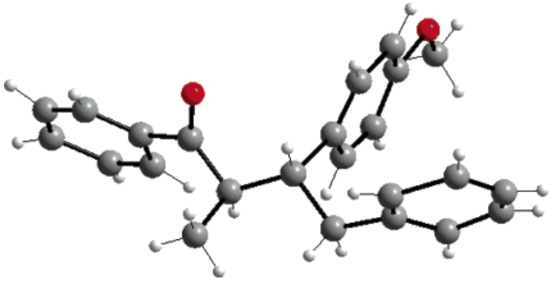


Figure 1. Molecular structure of ketone **3**-syn. Notice that the benzoyl and *p*-anisyl rings are gauche to each other, while the α-methyl and *p*-anisyl rings are anti.

Table 1. Product Composition and Disappearance Quantum Yields for Photolysis of Ketones **2** and **3**[a]

					product distribution (%)^b		
entry	ketone	solvent	conv. (%)^b	mass balance (%)^b	cyclobutanol	propiophenone + styrene/stilbene	ϕ_r^c
1	**2-*anti***	C$_6$D$_6$	95	>90	75	25	0.18
2		CD$_3$CN	60	>90	80 (71)^d	20	0.18
3	**2-*syn***	C$_6$D$_6$	100	82	e	100	0.10
4		CD$_3$CN	78	90	e	100	0.10
5	**3-*anti***	C$_6$D$_6$	57	90	85 (79)^d	15	
6		CD$_3$CN	74	>90	>90	<10	
7	**3-*syn***	C$_6$D$_6$	62	82	8^d	92	
8		CD$_3$CN	90	90	8^d	92	

[a] All the photolyses were conducted using Pyrex-filtered radiation from a 200 W high-pressure Hg-lamp at ca. 25 °C for 2−4 h. The sample (ca. 8−10 mg) contained in a deuterated solvent (ca. 0.5−0.6 mL) was purged with dry nitrogen gas for 15 min. [b] Based on ^{1}H NMR (400 MHz) analysis using methyl benzoate as an internal standard; error ± 10%. [c] Error ± 0.02. [d] Isolated yield from a preparative photolysis of ca. 0.15 g of the ketone. [e] No cyclobutanol could be isolated.

Solution-State Photolysis and Characterization of Photoproducts. The direct photolysis (high-pressure Hg lamp, $\lambda \geq$ 300 nm) of the anti diastereomers of both **2** and **3** in benzene and acetonitrile led to the formation of the corresponding cyclobutanols in high yields (ca. 75−90%) with the associated Type II elimination products, namely propiophenone and *p*-methoxy-β-methylstyrene/*p*-methoxystilbene, in low yields (eq 3; entries 1, 2, 5, and 6, Table 1). The photochemistry proceeded therefore in accordance with eq 1, and not eq 2, i.e., the formation of cyclopropanols was not observed.[21] The ^{1}H NMR monitoring of the reaction conducted in deuterated C$_6$D$_6$ and CD$_3$CN solvents for both **2**-anti and **3**-anti revealed the formation of some other minor product in less than 5%, which could not be isolated from a preparative-scale photolysis for characterization. Remarkably, only one out of eight possible diastereomers was obtained from the photolysis of the anti diastereomers of ketones **2** and **3**, suggesting thereby a high diastereoselectivity in the cyclization. The identical stereochemistry of the cyclobutanols from ketones **2**-anti and **3**-anti was established based on NOE experiments (cf. Supporting Information) and ultimately by a single-crystal X-ray crystallographic elucidation of the structure of one of the cyclobutanols, i.e., the cyclobutanol isolated from **3**-anti (**Figure 2**). Thus, in both of the cyclobutanols derived from the anti diastereomers of **2**

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(20) Moorthy, J. N.; Mal, P. *Tetrahedron Lett.* **2003**, *44*, 2493.
(21) The lack of formation of cyclopropanol (<3% detection limit) was established based on ^{1}H NMR analysis of the photolysates.

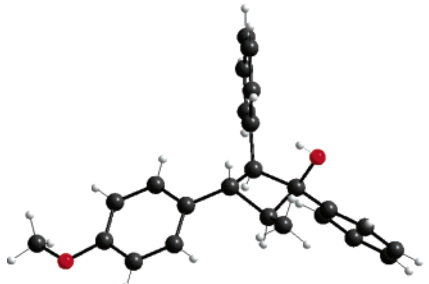
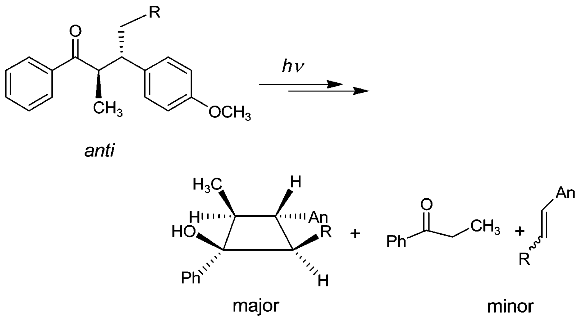


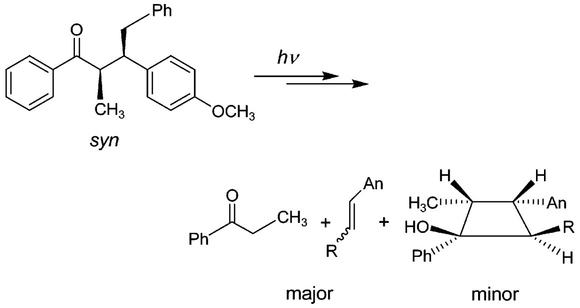
Figure 2. Molecular structure of the cyclobutanol derived from the ketone **3**-anti. Observe that the phenyl and *p*-anisyl rings at the 1,3 positions are syn as are the phenyl and methyl group at the 2,4 positions of the cyclobutane.

and **3**, the hydroxy group is syn to the α-methyl as well as the γ-methyl/phenyl groups and anti to the β-anisyl rings.



(eq 3)

In striking contrast, photolysis of the syn diastereomers of **2** and **3** led predominantly to elimination products, *viz.*, propiophenone and the olefin (*p*-methoxy-β-methylstyrene and *p*-methoxystilbene in **2**-syn and **3**-syn, respectively). The olefinic photoproducts were characterized by comparison of their spectral data with those of the authentic samples (entries 3, 4, 7, and 8, Table 1). A careful ^{1}H NMR (400 MHz) analysis provided again no indication for the formation of cyclopropanols.[21] In the case of **3**-syn, cyclobutanol was isolated in 8% yield (entries 7 and 8), and its stereochemistry, which is different from that derived from **3**-anti, was established from NOE experiments (eq 4). No perceptible change in the products was observed when the photolyses were conducted in the two different solvents, *viz.*, benzene and acetonitrile. The photochemistry of ketones **4** and **5** was found to be similar to those of **2** and **3**, as revealed from ^{1}H NMR analyses of the irradiated samples.



(eq 4)

The ketone disappearance quantum yields were representatively determined for the two diastereomers of ketone **2** for irradiation at 313 nm using valerophenone as an actinometer, $\Phi_{313\text{nm}} = 0.33$ for the formation of acetophenone in benzene[10] (Table 1). The anti diastereomer ($\phi_r = 0.18 \pm 0.02$) was found to decompose ca. 2-fold faster than that of the syn isomer ($\phi_r = 0.10 \pm 0.02$). No marked solvent dependence on the decomposition quantum yield was found for both syn and anti diastereomers in the polar (acetonitrile) and nonpolar (benzene) solvents.

Laser Flash Photolysis Studies. β-Phenyl quenching of phenyl ketones is an efficient process ($>10^9$ s^{-1}),[12−14] such that transients attributable to the triplet ketones **1**−**7** were not a priori expected to be observable in ns-time-resolved flash photolysis experiments. It has been shown, however, that the deactivation via charge-transfer-induced β-Ph quenching gets subdued when the benzoyl ring is substituted with an electron-rich group such as *para*-methoxy in ketone **1**.[13] In this case, the lowest-excited-state character of the triplet switches from n,π^* to π,π^*. Quenching does not prevail from the latter, however, but occurs instead less efficiently from the energetically proximate n,π^* state via thermal equilibration. Therefore, the triplets of methoxy-substituted β-arylpropiophenones as **1** become amenable to lifetime measurements in the nanosecond time domain. In fact, the methoxy-substituted diastereomers (2 mM) of **1** yielded strong and readily recognizable transient absorptions with a maximum at 400 nm (Figure 3). By comparison of the spectral characteristics with those of *p*-methoxy-substituted acetophenones reported in the literature[13,22] and based on quenching with oxygen, the transients were readily assigned to the ketone T−T (triplet−triplet) absorption. The lifetimes for the two diastereomers were found to be different in both methanol (460 ns for anti and 290 ns for syn) as well as in acetonitrile (100 ns for anti and 75 ns for syn), establishing a diastereomeric discrimination of this photophysical property.

The transient spectroscopy of the remaining ketones did not produce signals unequivocally attributable to the ketones triplets, presumably due to shorter triplet lifetimes as expected from β-Ph quenching of n,π^*-excited states.[12,13] No significant transient absorption was observed in ketones **4**, **5**, and **6**. In the case of the diastereomers of ketone **3**, immediate stilbene photoproduct formation ($\lambda_{\max} = 317$ nm)[23] was observed by flash photolysis, which precluded the assignment of residual intermediary transients. The transients produced from the diastereomers of the anisyl ketones **2** and **7** could not be unequivocally assigned.

AM1 Calculations. To examine the preferred conformations of ketones **1**−**5**, we calculated the energies for the gauche conformations about the C2−C3 bond for the two diastereomers of ketone **2** as representative cases; AM1 computations were performed within HyperChem.[24] The low-energy conformations were further refined by computing the energies for rotation about the C_1-C_2 as well as C_3-C_4 bonds until lowest energy was achieved in each case. The relative energies of the conformers 'a−c' for **2**-anti and those of 'd−f' for **2**-syn are given in Scheme 2. The conformers 'a' and 'd' were found to be the lowest energy ones for the **2**-anti and **2**-syn diastereomers, respectively; the conformers 'b' and 'e' are higher in energy than those of 'a' and 'd', respectively, by ca. 1.0 kcal mol^{-1}. It is noteworthy that the lowest-AM1-energy conformer 'd' corresponds to the structure actually revealed by the X-ray analysis for the case of **3**-syn (Figure 2).

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(23) Roberts, J. C.; Pincock, J. A. *J. Org. Chem.* **2004**, *69*, 4279.
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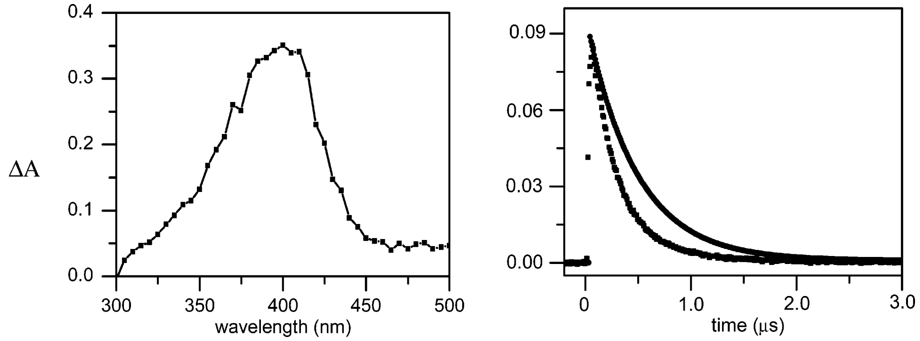
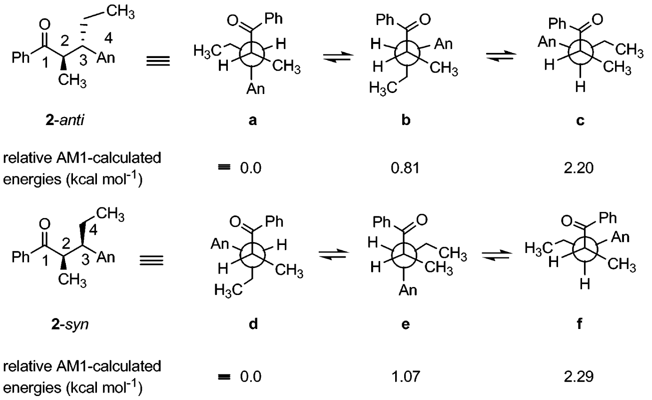


Figure 3. The T−T absorption spectrum of **1**-syn diastereomer in MeOH recorded with a 200-ns delay (left) and the triplet decay traces of **1**-anti (upper trace) and **1**-syn (lower trace) in MeOH (right). The T−T absorption spectrum for **1**-anti was similar.

Scheme 2



Discussion

As mentioned at the outset, our objective in investigating the photochemistry of ketones **2** and **3** was to expand the well-established diastereodifferentiation in a *photophysical* property (variation in triplet lifetimes) of ketones with two contiguous stereogenic centers to actual *photoreactivity* (different products). The lifetimes observed for the diastereomers of ketone **1** and the photochemical results recorded in Table **1** for the diastereomers of ketones **2** and **3** clearly attest to disparate pathways of triplet deactivation and reactivity of the syn and anti diastereomers. Insofar as the reactivity is concerned, the anti isomers undergo efficient photocyclization with a remarkable stereoselectivity as established from NMR and X-ray crystallographic analyses, while the syn counterparts undergo elimination predominantly. To rationalize the observed stereodifferentiation in triplet lifetimes as well as reactivity, we shall assume, as a starting point, that the conformations ‘a’ and ‘d’ in Scheme 2 are the most stable ones for **2**-anti and **2**-syn, which indeed is borne out by both AM1 calculations as well as X-ray structural investigations (only for **3**-syn). Of course, the same conformational preferences are assumed to prevail for ketones **1** and **3**−**5** as well. As will be seen later, these conformational preferences are entirely consistent with the observed diastereodifferentiation of the photophysical property (for ketone **1** as a model) as well as the photoreactivity.

Mechanistic Background and Diastereodifferentiation in the Triplet Lifetimes. Our mechanistic interpretations in terms of conformational preferences are independent, in a first approximation, of the spin multiplicity of the reactive intermediates. The photochemistry of alkyl phenyl ketones is well understood.[25] Due to rapid intersystem crossing, the triplet-excited n,π^* state is normally responsible for product formation. Thus, the origin for diastereodifferentiation of triplet lifetimes observed for ketones **1** should be sought from the differences in the reactivities of the triplet states. The triplet lifetimes of β-aryl substituted alkyl aryl ketones with n,π^* lowest excited states are known to be short (<1 ns) as a consequence of β-Ph quenching.[12−14] This was confirmed by the absence of the characteristic triplet ketone absorption in all cases but ketone **1**, which has a less reactive π,π^*-excited state.

The diastereomeric triplet-excited ketones **2**−**5** undergo two distinct reaction pathways, namely β-Ph quenching and γ-H abstraction. The rate of β-Ph quenching can become as fast as 10^9 s^{-1},[13] while γ-hydrogen abstraction ($k_{\gamma\text{-H}} > 10^8$ s^{-1}) is certainly competitive.[25] The conformational distributions are essential to understand the relative contribution of each pathway for the different diastereomers. We concentrate here on the situation for ketones **2**, but assume implicitly a similar scenario for ketones **3**−**5**.

For ketone **2**-anti, the most stable conformation ‘a’ is destined for γ-hydrogen abstraction, while β-phenyl quenching can only occur from the higher energy conformers ‘b’ and ‘c’. Indeed, this accounts readily for the substantial quantum yield (ca. 20%) for photoproduct formation from **2**-anti. In contrast, **2**-syn is destined, in its lowest energy conformation ‘d’, to undergo deactivation via β-phenyl quenching, while the γ-hydrogen abstraction can occur only from the proximate higher energy conformer ‘e’. This accounts immediately for the much lower quantum yield for photoproduct formation measured for **2**-syn (ca. 10%). Further, since the rate of β-Ph quenching is presumed to be intrinsically faster than γ-H abstraction (see above), one expects a shorter lifetime for the triplet state in which the preferred conformation is set up for β-Ph quenching, i.e., for the syn diastereomer. This expectation could not be verified for ketones **2** or **3** as a consequence of very short triplet lifetimes, but is nicely met for the less reactive model compounds **1** (see Results), for which the triplet state of syn (290 ns in MeOH) is indeed significantly shorter lived than that for anti (460 ns in MeOH).

Diastereomer-Differentiating Photoreactivity. The triplet-excited ketones have to pass through a chairlike transition state to achieve efficient γ-hydrogen abstraction,[26] which leads to triplet 1,4-biradicals; the geometrical criteria for this process have been extensively investigated by Scheffer and co-workers for solid-state photolysis.[27] There are three possible ways by which the triplet 1,4-biradicals might decay (cf. Schemes 3 and

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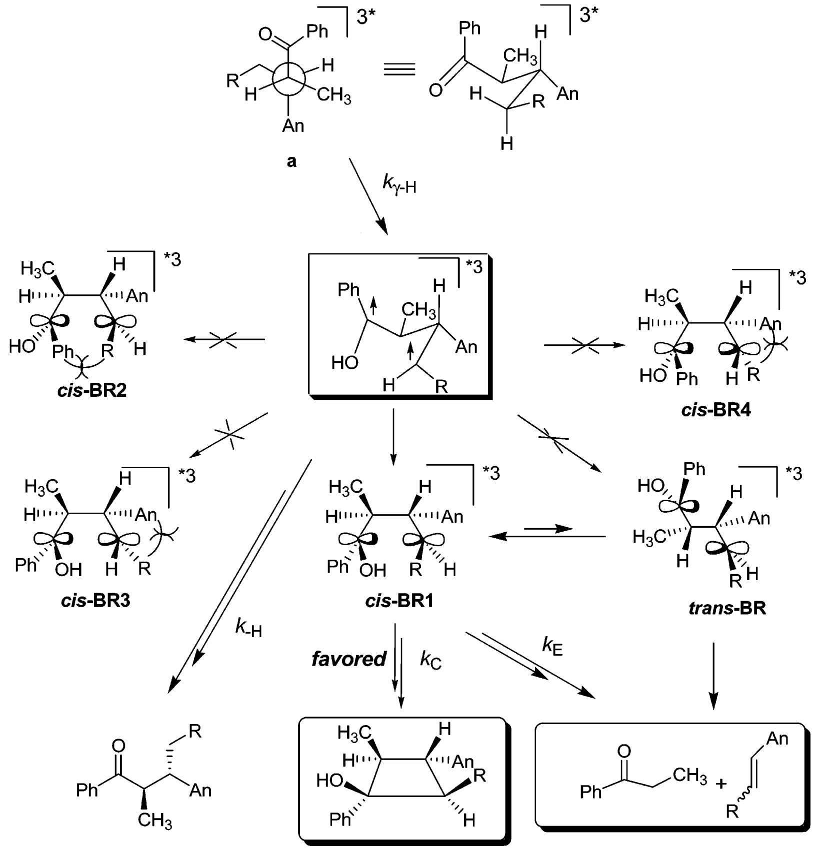
(25) (a) Wagner, P. J. *Acc. Chem. Res.* **1971**, *4*, 168. (b) Wagner, P. J.; Park, B.-S. In *Organic Photochemistry*; Pawda. A., Ed.; Marcel Dekker: New York, 1991; Vol 11, Chapter 4.

Scheme 3



4): (i) reverse hydrogen transfer may occur to regenerate the ground-state ketone, (ii) cleavage of the central C2−C3 bond may lead to an alkene and an enol, and (iii) the radicals may combine at C1 and C4 positions to afford Yang cyclization products, namely cyclobutanols. All of these three processes are necessarily accompanied by a triplet−singlet intersystem crossing (isc), concerning which two schools of thought exist. The first due to Wagner and co-workers considers the triplet 1,4-biradical partitioning as being controlled by kinetic barriers such that isc accompanies the product formation.[25b] The second due originally to Scaiano views intersystem crossing as controlling the behavior of the 1,4-biradical.[28] Accordingly, the singlet biradical is assumed to react immediately in the conformation in which it is born, and the geometry of this conformation, which may be vastly different from the ones thought to favor reverse hydrogen transfer, cyclization and cleavage, is considered to be the favorable one for isc. This mechanism has been expanded by Griesbeck and co-workers in a variety of photocyclizations.[29] Although certain structural features for biradical reactivity are well established, such as the requirement of good overlap during the cleavage between the C2−C3 bond and the singly occupied orbitals at C1 and C4, there is still no clear-cut understanding as to how the biradical structure affects partitioning among the three processes discussed above. Indeed, recent work by Scheffer and co-workers on bi- and tricyclic ketones in the solid state has shown that the geometry of the 1,4-biradical does influence its partitioning, but that the full understanding of its behavior requires also consideration of the magnitude of strain associated with cyclization.[30]

In the context of the presently observed diastereomer-dependent product distributions (cyclization being preferred for anti, and elimination for syn, cf. Table 1), it is important to realize that the 1,4-biradicals derived from ketones **2** and **3** are also diastereomeric in nature, such that the outcome of a diastereodifferentiating photoreaction can also be determined at this stage. In fact, Griesbeck and co-workers have recently examined the diastereodifferentiating photochemistry of α-amido- and α-methoxycarbonyl-β-methylvalerophonones,[6] and have rationalized their results also on the basis of the stability and spin−orbit coupling efficiencies in the intermediary 1,4-biradicals. The specific reasons are not directly transferable to the 1,4-biradicals derived from ketones **2** and **3** studied herein, since, e.g., no intramolecular hydrogen bonding applies, but β-aryl quenching needs to be mechanistically considered. In other words, consideration of conformational preferences should be pivotal to understanding the diastereodifferentiating behavior of the 1,4-biradicals. Our premise to rationalize the results constitutes the following: cyclization would be observed *only if* the 1,4-biradical assumes the *cisoid* geometry, while C2−C3 cleavage may occur predominantly from the *transoid* geometry; of course, competitive cleavage, which is driven by the stereoelectronic requirement of the overlap of the orbitals of

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(26) Dorigo, A. E.; McCarrick, M. A.; Loncharich, R. J.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 7508.

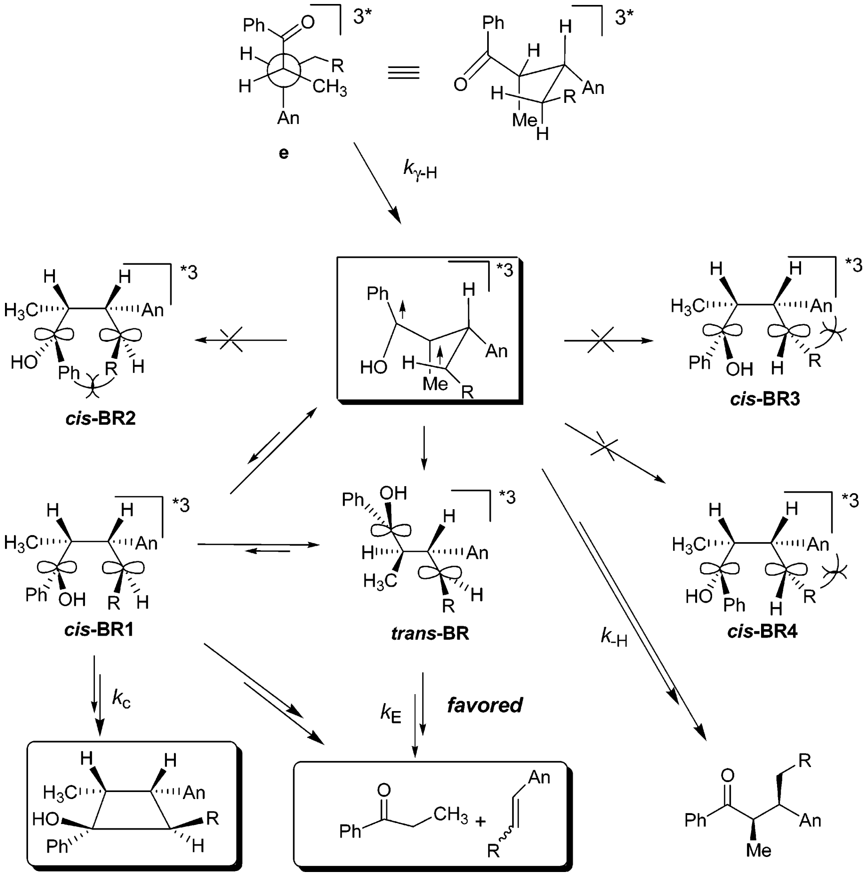
(27) Ihmels, H.; Scheffer, J. R. *Tetrahedron* **1999**, *55*, 885.

(28) Scaiano, J. C. *Tetrahedron* **1982**, *38*, 819.

(29) Griesbeck, A. G.; Fiege, M. In *Molecular and Supramolecular Photochemistry*, Vol 6; Ramamurthy, V.; Schanze, K. S. Eds; Marcel Dekker. New York; 1999; p 33.

(30) Braga, D.; Chen, S.; Filson, H.; Maini, L.; Netherton, M. R.; Patrick, B. O.; Scheffer, J. R.; Scott, C.; Xia, W. *J. Am. Chem. Soc.* **2004**, *126*, 3511.

Scheme 4



the breaking bond with singly occupied p-orbitals, cannot be ruled out in the *cisoid* geometry.

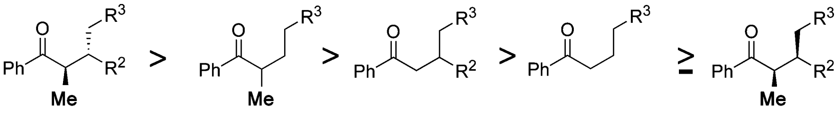
Let us consider ketone **2** as a representative case. The lowest-energy conformations that undergo γ-hydrogen abstraction as a primary photochemical event to yield the diastereodifferentiating photochemical outcome are ‘a’ and ‘e’ for the anti and syn diastereomers, respectively. Scheme 3 shows the consequences of triplet-excited conformer ‘a’ derived from the anti isomer. In this instance, the triplet 1,4-biradical, generated after γ-hydrogen abstraction via six-membered cyclic transition state, is likely to exist in the most stable cisoid conformation, i.e., *cis*-BR1, due to the anti relationship between C2-methyl and C3-aryl substituents. This biradical may undergo cyclization predominantly after intersystem crossing such that the stereochemistry about C1 and C4 carbons of the cyclobutanols is controlled by nonbonded interactions as the two ends of the biradical begin to bond. While the formation of elimination products is, in principle, possible from *trans*-BR, it is unlikely that the latter is populated due to steric repulsions between the *cis*-related C2-methyl and C3-aryl substituents in this conformation (Scheme 3). Thus, this mechanistic picture accounts for the formation of cyclobutanol in a highly diastereoselective manner as well as its stereochemistry.

Scheme 4 shows the consequences of the reactivity of the triplet-excited syn diastereomer in the conformation ‘e’. In contrast to the previous case, the 1,4-biradical generated after γ-hydrogen abstraction would be destabilized in the cisoid-conformation due to steric repulsion between C2-methyl and C3-aryl groups. It may, therefore, undergo reaction from the most stable transoid-conformation, i.e., *trans*-BR, in which the steric repulsions are minimum. This accounts directly for the observed predominant elimination. Importantly, the isolation in small yield (8%) of the cyclobutanol with a syn stereochemistry between C2-methyl and C3-anisyl substituents from **3**-syn (entries 9 and 10, Table 1) is suggestive of a minor reactivity from the *cis*-BR1 biradical as well, which is also fully consistent with this mechanistic picture.

Clearly, the origin of the diastereomer-differentiating photoreactivity of ketones **2**−**5** is traceable to the geometries of the triplet 1,4-biradicals. In the anti diastereomers, the stabilization of the triplet 1,4-biradical in the cisoid conformation leads predominantly to cyclization (Scheme 3), while the destabilization of the triplet 1,4-biradical derived from the syn diastereomers due to steric repulsions between the C2 and C3 substituents in the cisoid conformation promotes elimination via the more stable transoid conformation, i.e., *trans*-BR (Scheme 4). The diastereomeric discrimination observed in the deactivation of the triplets of the diastereomers of **1** need not necessarily be related to the photochemical outcome of ketones **2** and **3**. However, it is the unique design of ketones with a rational selection of substituents at α and β positions that renders the diastereodifferentiation observable in triplet lifetimes as well as product profiles.

Dependence of Photocyclization Propensity on the Substitution Pattern and Stereochemistry. In addition to the clear manifestation of diastereodifferentiation, the present study has afforded valuable data on photoproduct distributions (cyclization versus elimination) for additional alkyl aryl ketones, which can now be compared with literature data in an effort to reach more general conclusions. Incidentally, it is the influence of both

Scheme 5



R^1 = **Me**	>75	43	31	22	<10
R^1 = H	-	29	15	10	-

substituents at α and β-positions (as in ketones **2** and **3**) that has been least examined in the otherwise exhaustively investigated butyropheonones, which are prototype substrates for Norrish Type II reaction.[11,25] For example, Lewis and coworkers[11] showed long ago that the behavior of 1,4-biradical intermediates is highly sensitive to the position and number of substituents. The cyclization yields for butyrophenones and valerophenones with varying substitutions in a solvent such as benzene are known.[11,31] Including the present results for the diastereomers **2** and **3**, the general dependence of the propensity for photocyclization (% yields) on the alkyl substitution pattern follows, therefore, the general order in Scheme 5.

It follows from Scheme 5 that the degree of alkylation is very important in promoting cyclization over elimination. However, and this also constitutes an additional important conclusion from the present results, the diastereochemistry of the ketones is even more important! Solely switching the diastereochemistry from anti to syn allows principally a variation over the entire range of alkylation degree from one extreme reactivity pattern to the other. Since the fate of the reaction, as demonstrated herein, depends ultimately on the diastereomeric 1,4-biradicals, conformational preferences at the biradical stage appear to be very critical for determining cyclization versus elimination. It transpires from the present study that the cisoid geometry crucial for cyclization is best achieved via α,β-disubstitution with anti stereochemistry.

Conclusions

We have examined the possibility of diastereomer-differentiating photoreactivity in a rationally designed set of β-aryl ketones. The diastereomers of ketones **2** and **3** are shown to exhibit distinct photochemical reactivities due to conformational preferences; while the anti isomers of **2** and **3** undergo efficient Yang cyclization in 75−90% yields with a remarkable diastereoselectivity (>90%), the syn isomers undergo Norrish Type II elimination predominantly. The differences in the product profiles of the diastereomers are consistent with a mechanistic picture involving the formation of precursor diastereomeric triplet 1,4-biradicals in which the substituents at the α- and β-positions stabilize the cisoid (cyclization) or transoid (elimination) geometry. The fact that such a diastereomeric relationship does also ensue at the triplet-excited-state itself is demonstrated via the nanosecond laser-flash photolysis of the diastereomers of model ketone **1**. Thus, the diastereomeric discrimination in the product profiles of ketones **2** and **3** and in the triplet lifetimes of ketone **1** can both be linked to conformational differences as imposed by the different relative stereochemistry. Additionally, it emerges from the present study that the syn and anti diastereomers of ketones **2** and **3** represent two extremes of a broad range of widely examined butyrophenones, which lead to varying degrees of Norrish Type II photocyclization depending on the extent as well as the pattern of alkyl substitution.

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Supporting Information Available: Experimental details of synthesis and photolysis of ketones, characterization details of photoproducts (figures showing the NOE interactions), description of laser-flash photolysis studies, and X-ray crystal structure determination details for **3**-syn and **3**-anti-CB. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) In general, α-substitution has been found to promote cyclization, while β-substitution has only a marginal effect, see ref 11. We have recently shown that the photolysis of β-anisyl ketone **7**, which lacks an α-methyl group, yields, in contrast to the presently studied ketones **2**−**5**, a highly *solvent-dependent* mixture of two diastereomeric cyclobutanols in 30−40% yields, see ref 20.