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Unusual Temperature Dependence in the *cis*/*trans*-Oxetane Formation Discloses Competitive Syn versus Anti Attack for the Paternò−Büchi Reaction of Triplet-Excited Ketones with *cis*- and *trans*-Cyclooctenes. Conformational Control of Diastereoselectivity in the Cyclization and Cleavage of Preoxetane Diradicals

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Abstract: Toluene-d_8 solutions of *cis*- and *trans*-cyclooctene (*cis*- and *trans*-**1a**) as well as (*Z*)- and (*E*)-1-methylcyclooctene (*cis*- and *trans*-**1b**) have been irradiated at temperatures between −95 and +110 °C in the presence of benzophenone (BP) to afford mixtures of the cis- and trans-configured oxetanes **2a**,**b** and the regioisomeric **2b′**. Correspondingly, benzoquinone (BQ) gave with *cis*- and *trans*-**1a** the cycloadducts *cis*- and *trans*-**3a**. The cis/trans diastereomeric ratios of the [2 + 2]-cycloadducts **2** and **3** display a strong temperature dependence; with *cis*- and *trans*-**1a** or *cis*-**1b** as starting materials, the diastereoselectivity of the oxetane formation is high at low temperature, under preservation of the initial cyclooctene configuration. With increasing temperature, the cis diastereoselectivity decreases continuously for the *cis*-cyclooctenes; in the case of the *cis*-**1a**, the diastereoselectivity is even switched to trans (cis/trans ca. 20:80) at very high temperatures. For the strained *trans*-**1a**, the *trans*-oxetanes are strongly preferred over the entire temperature range, with only minor leakage (up to 10%) to the *cis*-oxetanes at very high temperatures. Oxetane formation is accompanied by nonthermal trans-to-cis isomerization of the cyclooctene. The methyl-substituted *trans*-**1b** constitutes an exceptional substrate; it displays cis diastereoselectivity in the [2 + 2] photocycloaddition at low temperatures for both regioisomers **2b** and **2b′**, and the trans selectivity increases at moderate temperature (cis/trans = 4:96), to decrease again at high temperature, especially for the minor regioisomer **2b′**. This complex temperature behavior of the cis/trans diastereoselectivity may be rationalized in terms of the triplet-diradical mechanism of the Paternò−Büchi reaction. We propose that the cyclooctene may be competitively attacked by the triplet-excited ketone from the higher (syn) or the less (anti) substituted side; such syn and anti trajectories have hitherto not been considered. To account for the unusual temperature behavior in the diastereoselectivity of the present [2 + 2] photocycloaddition, we suggest that temperature-dependent conformational changes of the resulting triplet preoxetane diradicals compete with their cyclization to the *cis*/*trans*-oxetane diastereomers and retro cleavage to the *cis*-cyclooctene.

Introduction

The stereoselectivity in the [2 + 2] photocycloaddition of ketones and aldehydes to olefins (Paternò−Büchi reaction)[1] presents still challenging opportunities for investigation, as attested by the intense activity in this field of research.[2] Recent developments have concentrated on the so-called *simple diastereoselectivity*[3] in the [2 + 2] photocycloaddition of unsymmetrical carbonyl partners[4] and on the *induced diastereoselectivity* by stereogenic centers either in the carbonyl partner[5] or in the olefin.[6] Unquestionably, these efforts have provided valuable methods for the stereoselective preparation of building blocks in organic synthesis.[7] Nevertheless, they have distracted

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(1) (a) Paternò, E.; Chieffi, G. *Gazz. Chim. Ital.* **1909**, *39-1*, 341. (b) Büchi, G.; Inman, C. G.; Lipinsky, E. S. *J. Am. Chem. Soc.* **1954**, *76*, 4327.

(2) (a) Griesbeck, A. G.; Fiege, M. In *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Marcel Dekker: New York, 2000; Vol. 6, p 33. (b) Fleming, S. A.; Bradford, C. L.; Gao, J. J. In *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Marcel Dekker: New York, 1997; Vol. 1, p 187. (c) Mattay, J.; Conrads, R.; Hoffmann, R. In *Houben-Weyl*, 4th ed.; Helmchen, G., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21c, p 3133. (d) Porco, J. A.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 151.

(3) Helmchen, G. In *Houben-Weyl*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21a, p 53.

(4) (a) Bach, T.; Schröder, J. *Synthesis* **2001**, 1117. (b) Abe, M.; Torii, E.; Nojima, M. *J. Org. Chem.* **2000**, *65*, 3426. (c) Griesbeck, A. G.; Buhr, S.; Fiege, M.; Schmickler, H.; Lex, J. *J. Org. Chem.* **1998**, *63*, 3847. (d) Bach, T. *Synlett* **2000**, 1699.

(5) (a) Gotthardt, H.; Lenz, W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 868. (b) Oppenländer, T.; Schönholzer, P. *Helv. Chim. Acta* **1989**, *72*, 1792. (c) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477.

(6) (a) Adam, W.; Peters, K.; Peters, E. M.; Stegmann, V. R. *J. Am. Chem. Soc.* **2000**, *122*, 2958. (b) Bach, T.; Jödicke, K.; Kather, K.; Fröhlich, R. *J. Am. Chem. Soc.* **1997**, *119*, 2437. (c) D'Auria, M.; Racioppi, R.; Romaniello, G. *Eur. J. Org. Chem.* **2000**, 3265.

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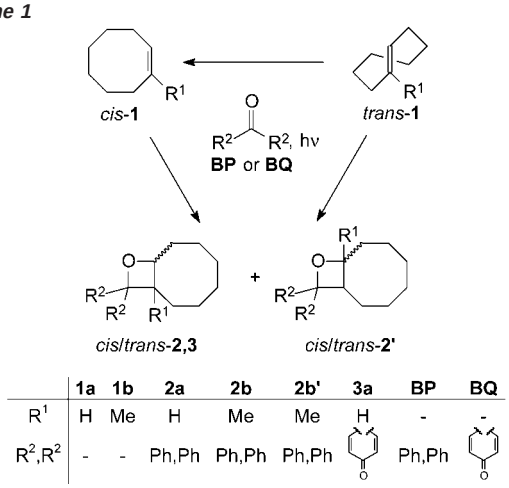
Scheme 1



	1a	1b	2a	2b	2b'	3a	BP	BQ
R^1	H	Me	H	Me	Me	H	-	-
R^2,R^2	-	-	Ph,Ph	Ph,Ph	Ph,Ph	O	Ph,Ph	O

attention on the pertinent stereochemical question of whether the initial alkene geometry of cis- or trans-configured substrates is preserved in the oxetane product. Early work on the photocycloaddition of triplet-excited carbonyl compounds to acyclic cis and trans 1,2-disubstituted alkenes has shown that frequently similar or even identical mixtures of *cis*- and *trans*-oxetanes are obtained, irrespective of the configuration of the starting olefin.[8] From these stereochemical facts, the intermediacy of a common, conformationally equilibrated triplet diradical was concluded. That this stereochemical behavior is not general for the Paternò−Büchi reaction was demonstrated recently[9] by means of the highly temperature-dependent diastereoselectivity in the [2 + 2] photocycloaddition of triplet-excited benzophenone to the *cis*- and *trans*-cyclooctenes. Contrary to the stereolabeled acyclic substrates, the mechanistically informative cyclic cis/trans pair disclosed complete stereodivergence at low temperature (−95 °C), but incomplete stereoconvergence even at high temperature (+110 °C).[9] Actually, such an extreme (ΔT ca. 200 °C) temperature variation has never been examined before in the Paternò−Büchi reaction such that the observed temperature dependence of the diastereoselectivity in the oxetane formation may be a general phenomenon and not specific for the cis/trans pair of the parent cyclooctenes.

In the present study, we report the experimental data and their mechanistic rationalization for the [2 + 2] photocycloaddition of the set of cis/trans-configured cyclooctenes **1a**,**b** with benzophenone (BP) and benzoquinone (BQ) as triplet-excited ketone partners (Scheme 1).

The methyl group in the cyclooctene **1b** was chosen to explore steric effects in the conformational changes of the intermediary triplet preoxetane diradicals and their consequences on the diastereoselectivity of the oxetane products. Although additional complexity is being bargained for through the formation of the expected regioisomeric oxetanes **2** and **2′**, this choice was most fortunate since the additional methyl group revealed unprecedented mechanistic insight about the Paternò−Büchi reaction. In particular, a stereochemical feature, which

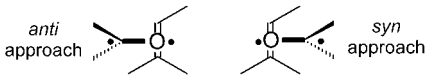


Figure 1. Alternative syn and anti approaches of a triplet-excited ketone toward an unsymmetrical alkene substrate.

has been considered only rarely so far,[10] concerns the alternative syn and anti trajectories along which the ketone and olefin partners approach (Figure 1). This mechanistic query has been presently probed by the additional methyl group in the cis/trans pair of cyclooctene **1b**. The syn approach means that the more substituted, and the anti that the less substituted, side of the cycloalkene is attacked, of which for steric reasons the anti approach should be favored to afford the respective triplet diradical intermediates. For the symmetrical parent cyclooctene **1a**, the syn and anti approaches are distinct for the C_v-symmetric cis diastereomer, but not for the C_2-symmetric trans diastereomer; thus, this set of cis/trans-configured substrates provides insufficient stereochemical data to validate whether the syn and anti approaches operate in the Paternò−Büchi reaction of this pair of cyclooctene diastereomers. In contrast, for the unsymmetrical cis/trans pair of cyclooctenes **1b**, for both diastereomers the syn and anti approaches are differentiated. Indeed, the stereochemical results presented herein for the methyl-substituted *cis/trans*-cyclooctenes **1b** suggest that the complex data are best accounted for in terms of the competitive syn and anti approaches of the cycloaddition partners. Additionally, also steric effects are exercised by the methyl substituent on the conformational changes of the triplet-diradical intermediates, which affect the stereoselectivities of their cyclization to the diastereomeric oxetane products.[11]

Results

The cyclooctenes *trans*-**1a**,[12] *cis*-**1b**, and *trans*-**1b**[13] were not commercially available and were prepared by literature-known methods. The Paternò−Büchi reactions were performed in toluene-d_8, and the product composition was assessed by ^{1}H NMR spectroscopy (200 or 600 MHz) directly on the crude product mixture. This procedure allowed for the determination of the cis/trans ratio of the cycloadducts over a large temperature range (−95 to +110 °C). Because the oxetanes *cis/trans*-**2a**, *cis/trans*-**2b**, and *cis/trans*-**2b′** are new compounds, preparative runs were conducted to attempt the separation of the complex mixtures of diastereomers and regioisomers for characterization and structural elucidation (see Supporting Information). Although the configurations of the *cis/trans*-**3a** oxetanes had been assigned in the literature,[14] ROESY spectroscopy revealed that the cis and trans isomers possess opposite configurations as claimed (see Supporting Information). The same also applies to the known[15] cis and trans cycloadducts of acetone to *cis*-**1a**, and their configurational assignment has herewith been corrected.

Analogous to the known cycloadditions of carbonyl partners with *cis*-**1a**,[14−16] the irradiation of a toluene solution of

(7) (a) Adam, W.; Stegmann, V. R. *Synthesis* **2001**, 1203. (b) Bach, T. *Synthesis* **1998**, 683.
(8) (a) Arnold, D. R.; Hinman, R. L.; Glick, A. H. *Tetrahedron Lett.* **1964**, 1425. (b) Carless, H. A. J. *Tetrahedron Lett.* **1973**, 3173. (c) Morris, T. H.; Smith, E. H.; Walsh, R. *J. Chem. Soc., Chem. Commun.* **1987**, 964.
(9) Adam, W.; Stegmann, V. R.; Weinkötz, S. *J. Am. Chem. Soc.* **2001**, *123*, 2452.
(10) Abe, M.; Fujimoto, K.; Nojima, M. *J. Am. Chem. Soc.* **2000**, *122*, 4005.
(11) Griesbeck, A. G.; Stadtmüller, S. *J. Am. Chem. Soc.* **1991**, *113*, 6923.
(12) Inoue, Y.; Tsuneishi, H.; Hakushi, T.; Tai A. In *Photochemical Key Steps in Organic Synthesis, An Experimental Course Book*; Mattay, J., Griesbeck, A. G., Eds.; VCH: Weinheim, 1994; p 207.
(13) (a) Shea, K. J.; Kim, J.-S. *J. Am. Chem. Soc.* **1992**, *114*, 3044. (b) Shea, K. J.; Kim, J.-S. *J. Am. Chem. Soc.* **1992**, *114*, 4846.
(14) Bryce-Smith, D.; Evans, E. H.; Gilbert, A.; McNeill, H. S. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1587.
(15) Sakai, Y.; Sakurai, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 215.

Table 1. Diastereomeric Cis/Trans Ratios for the [2 + 2] Photocycloaddition of BP and BQ to the *cis*- and *trans*-Cyclooctenes **1**[a]

			diastereomeric ratios (cis/trans)[b]							
		system	1	2	3	4	5	5′	6	6′
		cyclooctene	*cis*-**1a**	*trans*-**1a**[c]	*cis*-**1a**	*trans*-**1a**[c]	*cis*-**1b**	*cis*-**1b**	*trans*-**1b**	*trans*-**1b**
		ketone	BP	BP	BQ	BQ	BP	BP	BP	BP
entry	temp (°C)	oxetane	**2a**	**2a**	**3a**	**3a**	**2b**[d]	**2b′**[d]	**2b**[e]	**2b′**[e]
1	−95		98:02				>98:02	>95:05	35:65	54:46
2	−80		88:12	04:96	92:08	<5:95	>98:02	>95:05	16:84	25:75
3	−60		76:14	03:97	81:19	<5:95	>98:02	>95:05	9:91	11:89
4	−40		59:41	01:99	70:30	<5:95	>98:02	>95:05	<2:98	04:96
5	−20		45:55	01:99	51:49	<5:95	>98:02	>95:05	<2:98	08:92
6	0		36:64	02:98	42:58	<5:95	88:12	95:05	<2:98	13:87
7	20		27:73	02:98	35:65	<5:95	77:23	90:10	<2:98	20:80
8	40		25:75	02:98	29:71[f]	<5:95[f]	64:36	87:13	<2:98	20:80
9	60		23:77	04:96	28:72[g]	<5:95[g]	57:43	83:17	<2:98	27:73
10	80		21:79	06:94	24:76	<5:95	50:50	80:20	<2:98	42:58
11	100		20:80	08:92	22:78	<5:95	45:55	77:23	5:95	51:49
12	110		20:80	10:90	21:79	<5:95	44:56	76:24	6:94	51:49

[a] For the detailed irradiation conditions, conversions, mass balances, and product distributions, cf. Supporting Information. [b] Systems 1−5′: Values determined by ^{1}H NMR spectroscopy (systems 1,2,5,5′, 600 MHz; systems 3,4, 200 MHz) in toluene-d_8 directly on the crude product mixture; error limits ±5% of the stated values. Systems 6,6′: In view of the high conversions of *trans*-**1b** (up to 64%) and extensive trans-to-cis isomerization of *trans*-**1b** during the reaction, the dr values have been corrected for the concurrent cycloaddition of *cis*-**1b**. The uncorrected values are given in Table 7 (Supporting Information). [c] In view of the trans-to-cis isomerization of *trans*-**1a** during the reaction, the conversions were kept well below 60% to minimize the concurrent photocycloaddition with *cis*-**1a**. [d] The regioisomeric ratio (**2b**:**2b′**) increased from 69:31 at −95 °C to 82:18 at +110 °C. [e] The regioisomeric ratio (**2b**:**2b′**) increased from 76:24 at −95 °C to 89:11 at +110 °C. [f] At 45 °C. [g] At 65 °C.

benzophenone (BP) and cyclooctene *cis*-**1a** afforded a mixture of the corresponding diastereomeric *cis*-**2a** and *trans*-**2a** oxetanes (Table 1).[9] The marked temperature effect on the cis/trans diastereomeric ratio (dr) of the oxetanes **2a** was, however, striking; whereas at −95 °C the *cis*-**2a** oxetane was formed in a very high (dr 98:2) cis diastereoselectivity from the *cis*-**1a** cyclooctene (Table 1, system 1, entry 1), both diastereomers were generated in about equal (dr 45:55) amounts at −20 °C (entry 5). At higher temperatures, the *trans*-**2** isomer dominated (entries 6−10) and leveled off (dr ca. 20:80) at about +80 °C (entries 10−12).

The more strained *trans*-cyclooctene (*trans*-**1a**) gave over a broad temperature range (−80 to +60 °C) nearly exclusively (98 ± 2%) within the experimental error the *trans*-**2a** oxetane (Table 1, system 2, entries 2−9). Only at temperatures above 60 °C was as much as 10% of the *cis*-**2a** isomer observed (entries 10−12). Also *cis*-cyclooctene (*cis*-**1a**) was obtained for system 2 by isomerization of *trans*-**1a** (see Supporting Information, Table 3, last column). The relative amount of *cis*-**1** increased from ca. 30% at −40 °C (Table 3, entries 2 and 3) up to ca. 70% at +110 °C (entry 11). A control experiment confirmed that thermal trans-to-cis isomerization was negligible at these temperatures. Direct or sensitized photoisomerizations of the cycloolefins were ruled out as well in view of their relatively high singlet and triplet energies.[17] To suppress parallel oxetane formation from the isomerized *cis*-**1a**, the conversions of *trans*-**1a** were kept as low as possible.

The results for the [2 + 2] photocycloaddition of BQ to *cis*- and *trans*-**1a** (Table 1, systems 3 and 4) resemble closely those of BP (Table 1, systems 1 and 2). Thus, at low temperature (−80 °C, entry 2), the *cis*-**1a** and *trans*-**1a** cyclooctenes produced the respective *cis*-**3a** and *trans*-**3a** oxetanes in a very high diastereoselectivity; that is, the initial cyclooctene configuration is preserved (*cis*-oxetane from *cis*-cyclooctene and *trans*-oxetane from *trans*-cyclooctene). With increasing temperature, the cis diastereoselectivity for *cis*-**1a** decreased drastically and, indeed, inverted to a moderate (dr ca. 20:80, entries 11 and 12, system 3) trans diastereoselectivity at temperatures above 80 °C. With the more strained *trans*-**1a** and BQ (system 4) as starting materials, the *trans*-**3a** oxetane remained to be the exclusive photoproduct over the entire temperature range of ca. 200 °C, but increased amounts of the *cis*-**1a** cyclooctene were formed (Supporting Information, Table 5).

In the [2 + 2] photocycloaddition of BP to *cis*-**1b** and *trans*-**1b**, these unsymmetrical cyclooctenes gave expectedly the regioisomeric oxetanes **2b** and **2b′**, each as a pair of cis and trans diastereomers. The **2b**:**2b′** regioisomeric ratio depends only slightly on the reaction temperature (see Supporting Information, Tables 6 and 7); the **2b** regioisomer is always the main regioisomer. Thus, the regioisomeric ratio increased from 69:31 at −95 °C to 82:18 at +110 °C for *cis*-**1b** (Table 6, entries 1 and 12) and from 76:24 at −95 °C to 89:11 at +110 °C for *trans*-**1b** (Table 7, entries 1 and 12).

When *cis*-**1b** was employed as substrate (Table 1, systems 5 and 5′), the cis diastereoselectivity was very high for both regioisomeric oxetanes at low temperatures (<0 °C), and diminished continuously at elevated temperature. This decrease in cis diastereoselectivity was more pronounced for the **2b** regioisomer (from >98:2 at −20 °C to 44:56 at +110 °C; entries 5 and 12) than it was for **2b′** (from >95:5 at −20 °C to 76:24 at +110 °C; entries 5 and 12); thus, the **2b′** regioisomer displays a moderate cis diastereoselectivity even at 110 °C.

For the more strained *trans*-**1b** as the olefinic reaction partner, *cis*-**1b** was formed as a major product (ca. 41−78%, see Supporting Information, Table 7), although the *trans*-**1b** cyclooctene persisted thermal trans-to-cis isomerization over the entire 200 °C temperature range. In view of the large amounts of the *cis*-**1b** formed from *trans*-**1b** during the photocycloaddition, the diastereomeric ratios of the regioisomeric oxetanes **2b** and **2b′** derived from *trans*-**1b** were corrected for the

(16) (a) Jones, G.; Khalil, Z. H.; Phan, X. T.; Chen, T. J.; Welankiwar, S. *Tetrahedron Lett.* **1981**, *22*, 3823. (b) Shigemitsu, Y.; Yamamoto, S.; Miyamoto, T.; Odaira, Y. *Tetrahedron Lett.* **1975**, 2819. (c) Bryce-Smith, D.; Evans, E. H.; Gilbert, A.; McNeill, H. S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 485.
(17) Sauers, I.; Grezza, L. A.; Staley, S. W.; Moore, J. H. *J. Am. Chem. Soc.* **1976**, *98*, 4218.

competitive simultaneous photocycloaddition between *cis*-**1b** and BP, for which the results of the *cis*-**1b** photocycloaddition were utilized (Table 1, systems 5 and 5′). Thus, only a moderate trans diastereoselectivity of 35:65 is noted for **2b** and little if any selectivity (54:46) for **2b′** at −95 °C (Table 1, systems 6 and 6′, entry 1). With rising temperature, however, for the regioisomer **2b** (system 6) the diastereoselectivity increases significantly to <2:98 in favor of the trans product, and only under considerable thermal stress (T > 80 °C) are traces (ca. 5%) of the *cis*-**2b** oxetane found for *trans*-**1b** (Table 1, system 6, entries 11 and 12). For **2b′** (system 6′), surprisingly, the trans diastereoselecitivity increases at first to a maximum value of 4:96 at −40 °C (entry 4), and then again decreases to 51:49 at +110 °C (entry 12).

This complex temperature dependence of the diastereoselectivity data (Table 1) in the Paternò−Büchi photocycloaddition for the cis- and trans-configured cyclooctenes **1a** and **1b** with benzophenone (BP) and benzoquinone (BQ) shall now be rationalized in terms of a consistent mechanism, which encompasses all these experimental facts. Because the photochemical behavior is quite similar for BQ and BP, our mechanistic analysis will focus mainly on the latter.

Mechanistic Analysis

The results in Table 1 clearly demonstrate that the configuration (cis versus trans) and substitution (R^1 = H versus R^1 = Me) of the cyclooctenes **1a**,**b** are decisive for the stereocontrol in the [2 + 2] photocycloaddition with the symmetrical carbonyl partners BP and BQ. In particular, the photocycloaddition of the two unsubstituted cyclooctenes *cis*-**1a** and *trans*-**1a** with the ketones BP and BQ (Table 1, systems 1−4), as well as the methyl-substituted *cis*-**1b** with BP (Table 1, systems 5 and 5′), follow a similar temperature dependence in the diastereoselective oxetane formation. At low temperature (below −80 °C), the diastereoselectivity is very high with preservation of the initial cis or trans configuration of the substrate, and a gradual rise of the temperature leads to a significant diminution (systems 2, 5, and 5′) or even inversion (systems 1 and 3) of the diastereoselectivity. In contrast, the *trans*-**1b** cyclooctene (systems 6 and 6′) manifests its special status in that it displays an unprecedented temperature-dependent stereochemical behavior, that much *cis*-oxetane product (extensive loss of configuration) is observed already at very low temperature (−95 °C). As the temperature is raised, the amount of *trans*-oxetanes increases and becomes essentially the exclusive cycloadduct for both regioisomers **2b** and **2b′**. Furthermore, the minor regioisomer **2b′** attains a maximum of *trans*-oxetane **2b′** at about −40 °C.

To account for the temperature dependence of the diastereoselectivity observed in these Paternò−Büchi reactions, we propose the competitive syn and anti approaches of the triplet-excited carbonyl compounds toward the olefinic substrate to afford the respective intermediary preoxetane triplet diradicals (Figure 1).[18] Their initial conformations are defined by the syn versus anti type of approach. The subsequent transformations of these diradicals through competitive conformational changes and intersystem crossing (ISC), followed by cyclization or cleavage, allow for the rationalization of the trends in the diastereoselectivity. For the intersystem-crossing (ISC) process of such triplet diradicals,[19] the orbital-orientation rule defined by Salem and Rowland applies,[20] which states that a perpendicular geometry of the 2p orbitals at the radical sites is optimal for spin−orbit coupling.

We shall first consider the cis-configured (Scheme 2) and the trans-configured (Scheme 3) cyclooctenes **1a**,**b** separately to rationalize the results mechanistically in terms of the pertinent conformational changes at the reaction center,[21] and subsequently compare the cis and trans substrates to point out similarities and differences in the form of general trends (see Mechanistic Comparison). Although in these schemes the olefin configurations are dealt with separately, the olefin substitution (R = H, Me) is presented in an integrated manner. This allows one to grasp better the complexities of the temperature-dependent substituent effects on the triplet-diradical conformations derived from the cyclooctene diastereomers. Each scheme is layed out in two major halves: The top half illustrates the attack of the triplet-excited carbonyl partner at the C-2 carbon atom of the cyclooctene, which leads to the major oxetane regioisomer when R^1 is different from H; the bottom half features the corresponding C-1 attack to afford the minor oxetane regioisomer. Of course, for the unsubstituted cyclooctenes (R^1 = H) the two halves coincide in Schemes 2 and 3, since no regioisomers are possible. The left-hand and the right-hand sides of each scheme portray the important role of the syn and the anti attacks (Figure 1) and their influence on the diastereoselectivity of the present [2 + 2] photocycloaddition.

The detailed mechanism in terms of the competitive syn and anti approaches for the cycloadditions of the triplet-excited benzophenone (BP) to the cis-configured cyclooctenes *cis*-**1a**,**b** is shown in Scheme 2, and applies also for benzoquinone (BQ). In the C-2 attack (Scheme 2, top) from the syn (left) as well as the anti (right) side, the initial conformations of the resulting triplet-diradical conformers **A** and **B** reflect the cis configuration of the olefin **1**. Therefore, from these conformations the *cis*-oxetanes are produced after intersystem crossing (ISC) to the singlet state and subsequent ring closure. However, on closer inspection of the intervening triplet-diradical conformations **A** and **B** in Scheme 2, unfavorable gauche interactions become apparent due to the initially cis-configured eight-membered ring, which may induce CC-bond rotation to the **C** and **D** conformers to avoid this steric strain. Whereas for the syn approach also

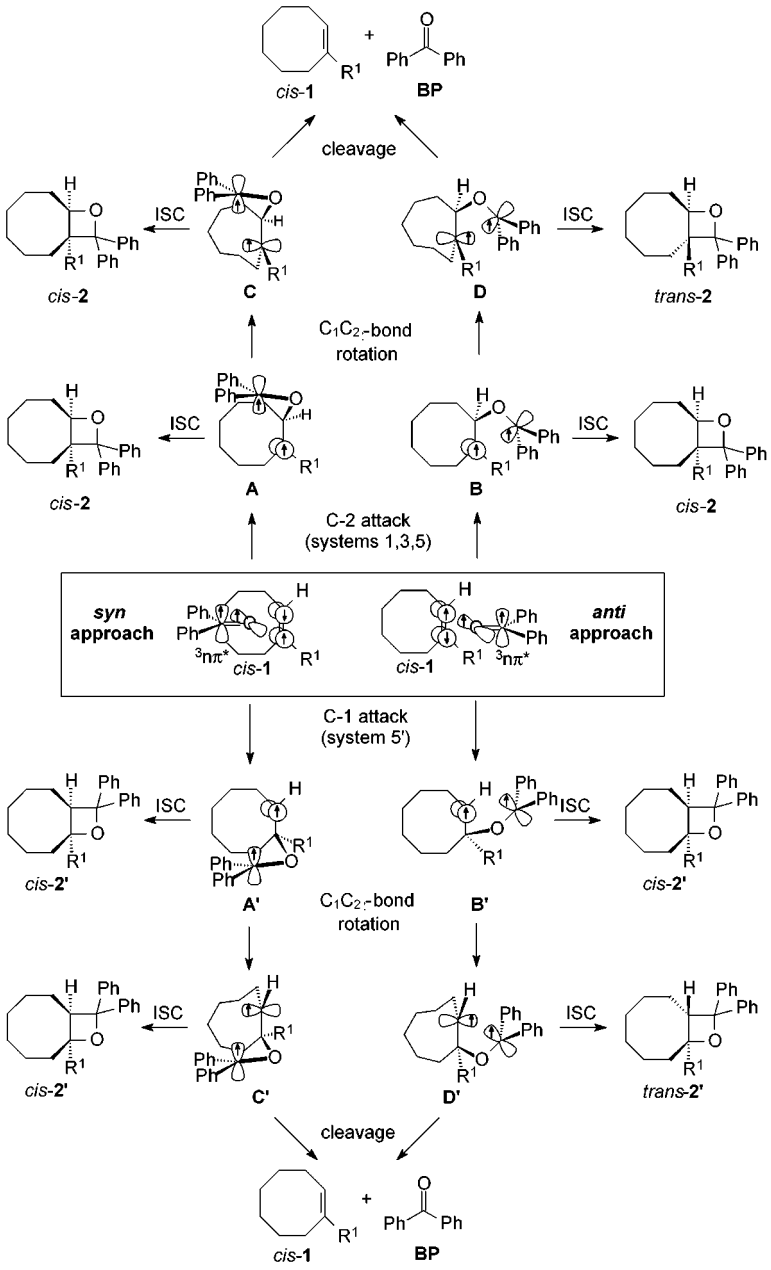
(18) (a) Freilich, S. C.; Peters, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 3819. (b) Freilich, S. C.; Peters, K. S. *J. Am. Chem. Soc.* **1981**, *103*, 6255.

(19) Griesbeck, A. G.; Mauder, H.; Stadtmüller, S. *Acc. Chem. Res.* **1994**, *27*, 70.

(20) Salem, L.; Rowland, C. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 92.

(21) The following clarifications need to be made about our conformational analysis: We have conducted PM3-UHF calculations on the triplet-diradical intermediates, but the flexibility of the eight-membered ring allows the CH_2 units of the cyclooctyl ring to be arranged in numerous essentially isoenergetic (all within less than 0.5 kcal/mol) conformations such that no definite energy minima may be reliably computed. However, this also implies that these conformational changes do not contribute significantly to the energetics of the overall cycloaddition process and, expectedly, do not provide any mechanistically useful information. In view of this difficulty, by inspection of molecular models, we have in our analysis concentrated on the conformational details in the direct vicinity of the reaction center, defined by the two olefinic carbon atoms involved in the cycloaddition, rather than on the periphery of the cyclooctyl ring system. Our intentions are more clearly illustrated in the detailed structures of Figure 2, in which the remaining six CH_2 units of the eight-membered ring have been intentionally left out, and attention has been focused on the conformational features with their steric implications of the two CH_2 substituents at the reaction center. For simplicity, since Schemes 2 and 3 are already quite complex, we have drawn the remaining cyclooctyl ring as planar structures with no conformational preferences. On the basis of our computational results and inspection of models, we contend that the conformational changes of the remaining cyclooctyl ring do not significantly influence our mechanistic conclusions.

Scheme 2



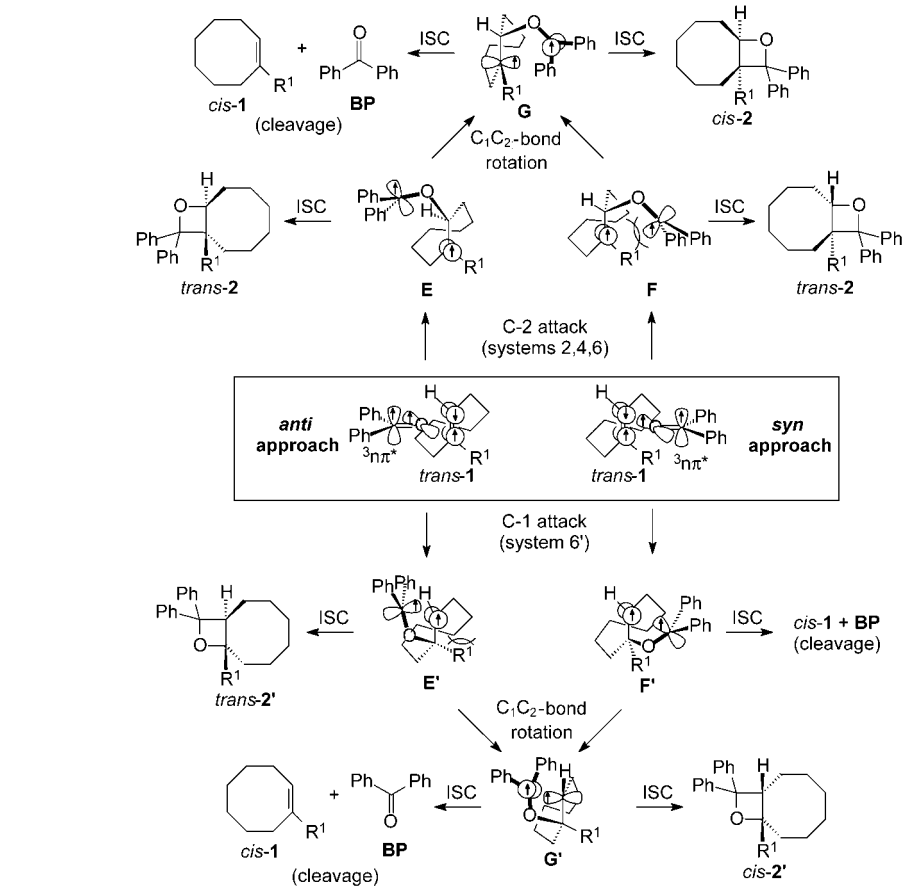
14

cis-oxetanes should be produced from the **C** conformer, the **D** conformer in the anti approach opens up the only channel for the formation of the *trans*-oxetane. For the parent *cis*-**1a** as starting cyclooctene, **D** should be the most favored conformer, because of minimized steric repulsions at the reaction center (gauche interactions) and between the cyclooctyl ring and the benzophenone group (annular interactions). Consequently, large amounts of *trans*-oxetanes are produced, especially at temperatures above 0 °C (Table 1, systems 1 and 3).

When R^1 is a methyl group, conformer **D** suffers from an additional steric repulsion due to the interaction between the methyl substituent and the benzophenone group as compared to when R^1 is a hydrogen atom (Figure 2). As a consequence, the *trans*-**2b** oxetane is formed to a lesser extent from *cis*-**1b** (Table 1, system 5) than is *trans*-**2a** from *cis*-**1a** (Table 1, system 1) even at high temperatures. The fact that the proportion of *trans*-oxetane continuously increases with rising temperature is attributed to the activation barrier for the CC-bond rotation in the conformational change from **B** to **D**, such that at elevated temperatures more of the **D** conformer is populated, and thereby more *trans*-**2b** oxetane results. Thus, the *cis*-oxetanes constitute the products of the initially generated higher-energy **A** and **B** diradical conformers, while the *trans*-oxetanes are formed from the higher-energy intermediate **D** that results from the conformational change **B** to **D**. Besides oxetane formation, also diradical cleavage back to the starting materials should take place.[18] Although in Scheme 2 this cleavage is specified only for **C** and **D**, the other conformations **A** and **B** may also pursue this cleavage pathway.

For the formation of the minor regioisomer **2b′**, the C-1 attack (Scheme 2, bottom) has to be considered, for which also the syn (left) and the anti (right) approaches operate. For both

Scheme 3



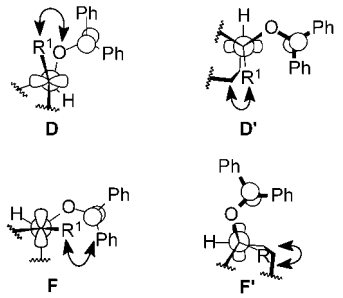


Figure 2. Structural details for steric interactions in the conformer pairs **D**, **D′** and **F**, **F′**.

approaches, again the initial conformers **A′** and **B′** reflect the cis configuration of the starting olefin, which is expressed in the high cis diastereoselectivity at low temperature (Table 1, system 5′, entries 1−6). With rising temperature, however, the diminution in the cis diastereoselectivity is not as pronounced as for the major regioisomer **2b** (Table 1, system 5′) and the oxetanes derived from the parent cyclooctene *cis*-**1a** (systems 1 and 3). This finding may be explained by the transannular interactions in the **D′** conformer, which are caused by the methyl substituent at the newly generated sp^3 carbon atom (Figure 2). In contrast, for the **D** conformer of the major regioisomer (Scheme 2, top right), the methyl substituent is bound to the radical-bearing sp^2 carbon atom and points away from the eight-membered ring. Therefore, such transannular interactions are absent in conformer **D** versus **D′**, and more of the oxetane *trans*-**2b** is formed from the cyclooctene *cis*-**1b** than from *trans*-**2b′**, as is especially evident at higher temperatures, for example, already at 0 °C (Table 1, systems 5 and 5′, entry 6).

The mechanistic scenario for the more complex but also more informative *trans*-cyclooctenes **1a** and **1b** (two regioisomers) is exhibited in Scheme 3, in conception quite analogous to the *cis*-cyclooctene substrates of Scheme 2. However, for the C_2-symmetric *trans*-cyclooctene (*trans*-**1a**), both sides of the CC double bond are equivalent, and, hence, the differentiation between the syn and the anti approaches does not apply; of course, for the methyl-substituted derivative *trans*-**1b** it does. Nevertheless, as already expressed, it is more effective and instructive to cover both trans-configured substrates in one common scheme to allow better comparison.

The syn and anti approaches are displayed in the top half in Scheme 3 for the C-2 attack and in the bottom half for the regioisomeric C-1 attack. Because for the C_2-symmetric parent *trans*-cyclooctene **1a** the syn and anti approaches are identical, all that needs to be considered for this substrate is the left part of Scheme 3. Of the C-1 and C-2 attacks, for steric reasons the latter one should be more important. Thus, we only analyze the *trans*-**1a** → **E** → **G** → *trans/cis*-**2a** trajectory, which simplifies the mechanistic analysis considerably. Once the triplet-excited carbonyl partner (BP or BQ) has attacked, the initially resulting conformer **E** has released part of the strain energy[13] of *trans*-cyclooctene by rehybridization. This partially relaxed **E** conformation is well-suited for the ring closure to the corresponding *trans*-oxetane products, by far the dominant diastereomer of the photocycloaddition (Table 1, systems 2 and 4). For the formation of the corresponding cis-configured photoadducts, the conformational change of **E** to **G** needs to be performed, which encounters unfavorable gauche interactions between the CH_2 groups of the eight-membered ring at the

reaction center, and such conformational change should be suppressed. Expectedly, the *cis*-oxetanes are only observed to a minor extent (system 2), if at all (system 4), at high temperatures (Table 1).

Similar to the *cis*-**1a** case, also for *trans*-**1a** the reaction is reversible due to diradical cleavage (Scheme 2). Indeed, for *trans*-**1a** this reversibility has been verified by the experimentally observed trans-to-cis isomerization of the cyclooctene *trans*-**1a** (see Supporting Information, Tables 3 and 5). In contrast, not even traces of *trans*-**1a** have been observed for *cis*-**1a** as substrate. Because *trans*-**1a** cyclooctene possesses ca. 10 kcal/mol[13] more ring strain than does the *cis*-**1a** diastereomer, formation of the *cis*-**1a** rather than *trans*-**1a** cyclooctene is expected during this diradical cleavage.

For the [2 + 2] photocycloaddition of benzophenone (BP) to (*E*)-1-methylcyclooctene (*trans*-**1b**), that is, systems 6 and 6′, the mechanistic analysis is more involved since the two regioisomeric oxetanes **2b** and **2b′** display distinct temperature behavior in their formation and need to be treated separately for better clarity. In view of its mechanistic significance (Table 1), we recall that in the photocycloaddition of the cyclooctene *trans*-**1b** with the ketone partner BP, for the major regioisomeric oxetane product **2b** (system 6) the trans diastereomer *trans*-**2b** continually increases throughout the temperature range from −95 to +80 °C (entries 1−10), with a slight if at all statistically significant falloff at ≥100 °C (entries 11 and 12). On the contrary, for the minor regioisomer oxetane **2b′** (system 6′), the cis/trans ratio starts out with a slight preference for the *cis*-**2b′** diastereomer at −95 °C (entry 1), inverts to a maximum value in favor of the *trans*-**2b′** product at −40 °C (entry 4), to decrease again to about equal amounts of the two diastereomers at about +100 °C (entry 11). To emphasize this important difference in the temperature dependence for the minor regioisomeric oxetane **2b′**, an Eyring plot of the cis/trans oxetane ratio is given in Figure 2 (see Supporting Information). Also, the major regioisomer **2b** (system 6) displays an inversion in diastereoselectivity at about +100 °C (Table 1, entry 11), but the variation is too small over the temperature range from −40 °C to +80 °C to allow a statistically significant correlation and is, therefore, not considered.

For the *trans*-**1b** cyclooctene, once the triplet-excited BP has attacked at the C-2 position by either the anti or syn approach, the initial conformers **E** and **F** may lead directly to the *trans*-**2b** oxetanes. This is quite feasible for the conformer **E** because the methyl substituent at the radical site points away, both from the cyclooctane ring and the benzophenone group, but for the **F** conformer, this methyl substituent evidently encumbers ring closure for severe steric reasons (Figure 2). Thus, for the diradical conformer **F** initially generated in the syn approach (Scheme 3, right), such steric compression is partly relieved by CC-bond rotation to afford conformer **G**. This is apparently favored even at low temperature, since large amounts of *cis*-**2b** oxetane are obtained below −40 °C (Table 1, system 6, entries 1−3). For the anti approach (Scheme 3, left), initially the **E** conformer is produced, which is less prone to attain the **G** conformer through CC-bond rotation, because the benzophenone group in the diradical must slide past the methyl substituent. Additionally, steric interactions between the benzophenone group and the cyclooctane ring, as well as methyl substituent, are built up. From our experimental results (Table 1, system 6) we may conclude that the considerable (ca. 35%) amount of the minor *cis*-**2b** oxetane product formed at low temperatures, at −95 °C (entry 1), derives from the syn approach through the **F** diradical conformer by way of **G** (Scheme 3, right). In contrast, the main diastereomer *trans*-**2b** stems primarily from the anti approach through the **E** diradical conformer (Scheme 3, left). At higher temperatures, the anti approach may play a more significant role, and since CC-bond rotation for the **E** to **G** conformational change is enhanced, some *cis*-oxetane product may arise in this way.

To explain the temperature-dependent diastereoselectivity of the minor oxetane regioisomer **2b′**, a similar argumentation applies. At the low temperature of −95 °C, large (ca. 54%) amounts of the *cis*-**2b′** oxetane (Table 1, system 6′, entry 1) are formed through the syn approach (Scheme 3, right). In this case, the initially resulting diradical conformer **F′** is so severely sterically impeded toward *trans*-oxetane formation by transannular interactions (Figure 2) that rather CC-bond rotation takes place to the **G′** conformer. The latter readily cyclizes to the *cis*-**2b′** oxetane product and is observed as slightly preferred diastereomer (entry 1).

Through the anti approach (Scheme 3, left), at low temperatures only *trans*-**2b′** should be formed by way of conformer **E′**. Apparently, temperatures higher than −40 °C promote the CC-bond rotation from **E′** to **G′** by surpassing more effectively the activation barrier, and, therefore, continuously increasing amounts of *cis*-**2b′** are formed from the **G′** conformer with rising temperature (Table 1, system 6′, entries 4−12). Thus, this unusual temperature dependence for system 6′ comes from the competition between the syn and the anti approaches. The higher proportion of the *cis*-oxetane at high temperature for system 6′ as compared to that of system 6 may be explained by the transannular interactions of the sp^3-bonded methyl group in the **E′** conformer (Scheme 3), which is absent for the sp^2-bonded methyl group in **E**. Therefore, CC-bond rotation is much more prone for the **E′**/**G′** conformer pair than for **E**/**G**, as is evidenced by the larger amounts of the *cis*-oxetane product for the **E′**/**G′** pair over the entire temperature range from −95 to +110 °C (Table 1, systems 6 and 6′).

The above mechanistic analysis makes evident the important role that the **E**/**E′** to **G**/**G′** (anti approach) versus **F**/**F′** to **G**/**G′** (syn approach) conformational changes play in the temperature dependence of the cis/trans ratio of oxetane product during the triplet-diradical cyclization, but also the competitive cleavage of the **E**/**E′** and **F**/**F′** diradical conformers must be considered.[22] This is necessary since major amounts of *cis*-cyclooctene **1b** are produced in the photocycloaddition with the *trans*-cyclooctene substrate (Table 7, cf. Supporting Information). Such reversibility should influence the cis/trans diastereoselectivity on account of preferential cleavage of a particular diradical conformer. Thus, due to the more intense steric interactions, the diradical conformers **F** and **F′** derived from the syn approach are expected to undergo the cleavage more efficiently than do the **E** and **E′** conformers from the anti approach. Because such diradical cleavage should become more pronounced at higher temperatures, as witnessed by the enhanced formation of *cis*-**1b** (Table 7, cf. Supporting Information), the syn approach

(22) Andrew, D.; Weedon, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 5647; in this work, the reversible formation of the diradicals generated in the photocycloaddition of ketones to enones has been experimentally established by trapping experiments.

becomes less important for the oxetane formation. Initially, the amounts of *cis*-**2b** and *cis*-**2b′** oxetanes decrease with rising temperature (Table 1, systems 6,6′, entries 1−4), and progressively more trans product is formed. At temperatures higher than −40 °C, the diradical conformers **F** and **F′** derived from the syn approach suffer mainly cleavage, and, thus, the anti approach dominates. Because on further increase of temperature CC-bond rotation is promoted in the relevant **E** and **E′** to the respective **G** and **G′** conformers, the formation of the cis-configured oxetanes is enhanced again, such that the diastereoselectivity traverses through a maximum. Consequently, the composite steric effects of the methyl group on the syn versus anti approaches, on the conformational changes in the resulting triplet diradicals, and on the cyclization versus cleavage of the latter allow one to account for the complex temperature dependence of the diastereoselectivity in the cycloaddition of system 6 and 6′.

Mechanistic Comparison

So far we have analyzed the temperature-dependent oxetane cis/trans diastereoselectivities in Table 1 individually for the cis-configured (Scheme 2) and for the trans-configured (Scheme 3) cyclooctenes **1a**,**b**, which has disclosed some unprecedented stereochemical features on the Paternò−Büchi photocycloaddition. In this closing section we shall compare the cis with the trans configurations of the symmetrical (**1a**) and unsymmetrical (**1b**) cyclooctenes and from the similarities and differences in the temperature-dependent oxetane cis/trans ratios conclude some general mechanistic trends about the generation and transformation of the triplet preoxetane diradicals. The choice of the set of cyclooctenes **1a**,**b** has been most fortunate, since the complexity and diversity of the diastereoselectivity data in Table 1 has not only allowed one to sense steric effects exercised by the methyl group on the conformational changes in the intervening triplet diradical, but also to recognize the hitherto unknown competitive syn and anti approaches of the cycloaddition partners. Such stereochemical control in the Paternò−Büchi reaction is unprecedented for the simpler acyclic substrates.[2]

Comparison of the cis/trans oxetane ratios for the parent cyclooctenes *cis,trans*-**1a** with BP shows the common feature that at low temperature the initial cyclooctene geometry is essentially completely preserved for both isomers. Whereas the diastereoselectivity for the *cis*-**1a** cylcooctene extensively inverts on raising the temperature, with the *trans*-**2a** oxetane as the main cycloadduct, for the *trans*-**1a** cyclooctene there is only a slight diminution in the cis/trans oxetane ratio. For BQ a similar trend applies, except that even at high temperature the cis/trans oxetane ratio remains constant, with a high preference for the trans product. The fact that over the entire temperature range (ΔT ca. 200 °C) there is no common point reached at which the cis/trans oxetane ratio is the same for both diastereomers of the parent cyclooctene **1a** is mechanistically significant. Thus, incomplete equilibration is observed for the triplet diradical conformers initially generated from the separate cyclooctene **1a** isomers. This stereochemical behavior of the parent cyclooctenes **1a** contrasts that observed for diastereomeric acyclic alkenes, which usually display similar cis/trans oxetane ratios,[8a,b] or even only one common oxetane diastereomer from both alkene isomers.[8c] Evidently, the initial triplet diradical conformer generated from *trans*-**1a** cylcooctene is energy-wise preferred, and a relatively high activation barrier must be overcome during the conformational equilibration; this is not achieved for *trans*-**1a** even at the high temperatures employed herein. Instead, alternative reaction channels of the triplet diradicals prevail, such as more rapid cyclization to the oxetanes and cleavage to the starting material.

The unsymmetrical cyclooctene **1b** diastereomeric pair constitutes the disparate set not only when compared to the parent cylcooctene **1a**, but also when the *cis*-**1b** and *trans*-**1b** diastereomers are compared within the set. Actually, for both regioisomeric oxetanes **2b** and **2b′** derived from the unsymmetrical *cis*-**1b** cyclooctene, the general trend in the cis/trans oxetane ratios is quite similar to that observed for the parent *cis*-**1a** cyclooctene. Thus, at low temperature, the initial cyclooctene geometry in *cis*-**1b** is completely preserved in the oxetane *cis*-**2b**. A raise in temperature lowers the diastereoselectivity, but not as pronounced as for the parent *cis*-**1a** cyclooctene. Here the steric effects of the methyl group (the gauche and transannular interactions in the triplet diradicals presented in Scheme 2) come into play and additionally impede the conformational changes in the triplet diradicals, such that proportionally less *trans*-**2b** and *trans*-**2b′** oxetanes are generated from *cis*-**1b** as compared to *trans*-**2a** from *cis*-**1a**.

The exceptional substrate is the methyl-substituted *trans*-cyclooctene **1b**, which exhibits no common features whatsoever in the temperature dependence of the cis/trans oxetane ratio, when compared to the set of diastereomeric parent cyclooctenes **1a** and even with its *cis*-**1b** isomer. In sharp contrast, a diastereoselectivity is observed for the formation of both regioisomeric **2b** and **2b′** oxetanes at low temperatures, a maximum in favor of the trans cycloadduct is obtained at intermediate temperatures, and finally the diastereoselectivity decreases again at higher temperatures. This unusual trend is particularly pronounced for the **2b′** regioisomer. It is precisely this unprecedented temperature-dependent diastereoselectivity of the **2b′** oxetane regioisomer which has led to the recognition of the novel syn and anti approaches in the cycloaddition process and allows one to explain the divergent data in Table 1, as illustrated in Schemes 2 and 3. These trajectories also apply to the C_v-symmetric *cis*-**1a** diastereomer, and may as well operate for appropriate acyclic substrates, but the latter needs yet to be tested.

In summary, the temperature-dependent stereodifferentiation between the *cis*- and *trans*-oxetane products, generated from cis- and trans-configured symmetrical (**1a**) and unsymmetrical (**1b**) cyclooctenes, derives from the combination of the following steric effects: on the competitive syn and anti approaches of the cycloaddition partners, on the conformational changes of the intermediary triplet diradicals, and on the competitive cyclization versus cleavage of the diradicals.

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Supporting Information Available: Experimental section (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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