

Unusual Temperature-Dependent Diastereoselectivity in the [2+2] Photocycloaddition (Paternò–Büchi Reaction) of Benzophenone to *cis*- and *trans*-Cyclooctene through Conformational Control

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The stereoselectivity in the [2+2] photocycloaddition of carbonyl compounds to alkenes (Paternò–Büchi reaction) is still an issue of current interest and intensive activity.¹ In the past, the Paternò–Büchi reaction of aldehydes and ketones with *cis*-cyclooctene (*cis*-1) has been extensively investigated;² however, the corresponding *trans* isomer (*trans*-1) has not been employed. Since in numerous cycloadditions with *trans*-cyclooctene³ the *trans* configuration in the cycloadduct is preserved, it was of mechanistic import to assess whether this also applies to the triplet diradical intermediate of the Paternò–Büchi reaction between *trans*-cyclooctene and benzophenone. We report herein an unprecedented temperature-dependent diastereoselectivity in the [2+2] photocycloaddition of benzophenone with the cyclooctenes *cis*- and *trans*-1 (Scheme 1). Although the temperature dependence of the stereoselectivity in [2+2] photocycloadditions is well established⁴ and the results for the Paternò–Büchi reaction form, in fact, the basis of the *isoinversion principle*,⁵ we herewith document the unusual case that the lower-energy substrate diastereomer (*cis*-1 cyclooctene) affords with increasing temperature the higher-energy product diastereomer (*trans*-2 oxetane); the interplay of enthalpy and entropy are held responsible for this. The Paternò–Büchi reactions were performed in *d*₈-toluene, the product composition was assessed by ¹H NMR spectroscopy (600 MHz) directly on the crude product mixture. This procedure allowed the determination of the *cis/trans* ratio of the cycloadducts over a large temperature range (−95 to +110 °C).

The irradiation of the less strained *cis*-1 cycloalkene in the presence of benzophenone afforded mainly mixtures of the *cis*-2 and *trans*-2 oxetanes (cycloaddition), as is known for the *cis*-

Scheme 1

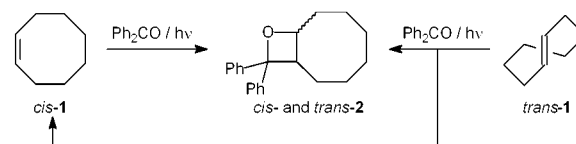


Table 1. Temperature Dependence on the Diastereoselectivity of the Oxetane Formation with *cis*-Cyclooctene (*cis*-1)

entry	temp (°C)	time (min)	<i>cis</i> -1		dr 2 ^{a,c} (<i>cis</i> : <i>trans</i>) ^d
			convn ^a (%)	mb ^{a,b} (%)	
1	−95	10	11	98	98:02
2	−80	10	19	99	88:12
3	−60	10	28	97	76:24
4	−40	10	30	97	59:41
5	−20	10	33	94	45:55
6	0	10	37	92	36:64
7	20	10	45	87	27:73
8	40	10	46	84	25:75
9	60	10	48	81	23:77
10	80	5	28	89	21:79
11	100	5	33	86	20:80
12	110	5	32	85	20:80

^a Determined by ¹H NMR spectroscopy (600 MHz) directly on the crude product mixture; error limits ±5% of the given values; sum of the aromatic signals were taken as internal standard (see Supporting Information). ^b Mass balance. ^c Diastereomeric ratio (dr) of the *cis*- and *trans*-2 oxetanes. ^d Benzpinacol (2–28%) was also formed.

Table 2. Temperature Dependence on the Diastereoselectivity of the Oxetane Formation with *trans*-Cyclooctene (*trans*-1)

entry	temp (°C)	time (min)	<i>trans</i> -1		dr 2 ^{a,c,d} (<i>cis</i> : <i>trans</i>)	product ratio ^a <i>cis</i> -1:2'
			convn ^a (%)	mb ^{a,b} (%)		
1	−80	10	22	96	04:96	35:65
2	−60	10	32	97	03:97	30:70
3	−40	10	43	95	01:99	31:69
4	−20	10	55	91	01:99	35:65
5	0	10	56	94	02:98	37:63
6	20	10	59	93	02:98	44:56
7	40	5	39	96	02:98	49:51
8	60	5	39	95	04:96	56:44
9	80	3	35	96	06:94	60:40
10	100	3	48	95	08:92	67:33
11	110	3	58	93	10:90	70:30

^{a–c} See Table 1. ^d In view of the *trans*-1 isomerization to *cis*-1, the conversions were kept as low as possible to minimize photocycloaddition with *cis*-1 and thereby not falsify the dr values for *trans*-1. ^e Benzpinacol (<5%) were also formed.

cyclooctene diastereomer with several carbonyl partners;² also, small amounts of benzpinacol (reduction) are formed. Striking, however, is the marked temperature effect on the *cis/trans* diastereomeric ratio (dr) of the oxetanes 2: While at −95 °C the *cis*-2 oxetane is formed nearly (dr 98:2) exclusively (Table 1, entry 1), both diastereomers are generated in about equal (dr 45:55) amounts at −20 °C (Table 1, entry 5). At elevated temperatures, the *trans*-2 isomer dominates (entries 6–10) and levels off (dr ~20:80) at ≥80 °C (entries 10–12).

The strained *trans*-cyclooctene (*trans*-1) gave over a broad temperature range (−80 up to 60 °C) the *trans*-2 oxetane nearly exclusively (98 ± 2%) within the experimental error (Table 2, entries 1–8). Only at temperatures higher than 60 °C was some (up to 10%) *cis*-2 isomer observed (entries 9–11). Also *cis*-cyclooctene (*cis*-1) was obtained as a significant isomerization product of *trans*-1. The relative amount of *cis*-1 increased from ~30% at the lower temperatures (entries 2 and 3) up to ~70% at

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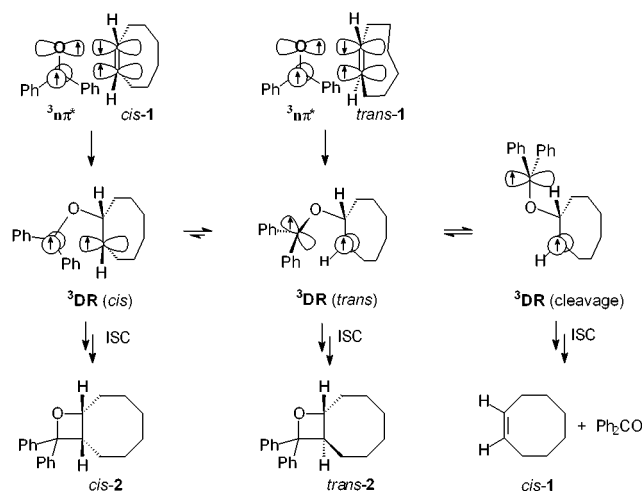
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Scheme 2



the higher temperatures (entry 11). A control experiment confirmed that the increased isomerization of *trans*-1 to *cis*-1 was not caused by the higher conversion of the *trans*-cyclooctene, since at 20 °C the ratio of the products *cis*-1 and oxetanes **2** remained constant at ~43:57 (cf. Supporting Information; Table 3, entries 1–7). Thus, the higher temperatures must be responsible for the larger extent of *trans*-to-*cis* isomerization. An additional control experiment revealed that thermal *trans*-to-*cis* isomerization is negligible under these conditions. Evidently, the *cis*-cyclooctene is produced during the temperature-dependent [2+2]-cycloaddition process, and its amount increases with temperature (Table 2).

The following unprecedented experimental facts on the [2+2] photocycloaddition of the diastereomeric cyclooctenes with benzophenone need to be rationalized in terms of a consistent mechanism: (i) The *cis*-1 cyclooctene displays a remarkable temperature dependence in that the *trans*-2 oxetane is favored with increasing temperature (Table 1); (ii) for the *trans*-1 cyclooctene the *trans* geometry is preserved in the *trans*-2 cycloadduct over a broad temperature range of 180 °C (Table 2); (iii) the extent of *trans*-to-*cis* isomerization in the cycloaddition with the *trans*-1 cyclooctene increases with temperature (Table 2).

On the basis of the generally accepted mechanism⁶ for the Paternò–Büchi reaction, a triplet diradical (^3DR) is formed during the attack of the triplet-excited benzophenone on the double bond (Scheme 2). If the same triplet diradical (^3DR) were generated from the *cis*- and *trans*-cyclooctenes, the diastereomeric oxetanes **2** should be formed in similar *cis/trans* ratios and not be dependent on temperature, which disagrees with the experimental results (Tables 1 and 2).

The pronounced temperature dependence provides a plausible mechanistic clue in terms of reversible conformations for the ^3DR intermediate. We propose the two ground-state conformers $^3\text{DR}(\text{cis})$ or $^3\text{DR}(\text{trans})$, formed in the initial step from the *cis*-1 or *trans*-1 cyclooctenes (Scheme 2). The perpendicular orientation of the 2p orbitals at the radical sites allows fast intersystem crossing,⁶ and subsequent cyclization affords the *cis*-2 and the *trans*-2 oxetanes. Although such intermediary triplet 1,4-diradicals (^3DR) are expected to be relatively short-lived (1–5 ns),^{6,8} the interconversion between $^3\text{DR}(\text{cis})$ and $^3\text{DR}(\text{trans})$ may be

kinetically hindered and, thus, depend on temperature. The temperature effect should be reflected in the *cis/trans* ratio of the cycloadducts **2**, especially when a temperature range of ca. 200 °C is employed (Tables 1 and 2). The fact that the *trans*-2 cycloadduct increases with temperature for the *cis*-1 substrate (Table 1), but is essentially the exclusive temperature-invariant product for the *trans*-1 cycloalkene (Table 2), implies that the conformer $^3\text{DR}(\text{trans})$ is of lower enthalpy than $^3\text{DR}(\text{cis})$. The eclipsed interactions in the cyclooctyl ring and the unfavorable orientation of the phenyl ring in the conformer $^3\text{DR}(\text{cis})$ are absent in $^3\text{DR}(\text{trans})$. ISC to the singlet 1,4-diradical is an irreversible process, and once it has occurred, immediate formation of the oxetane ring is expected, such that the preferred conformation of the ^3DR intermediate is reflected in the product configuration.⁹

Therefore, after intersystem crossing (ISC), the *trans*-2 cycloadduct is the preferred photoproduct at higher temperatures (≥ -20 °C) for *cis*-1 and at all temperatures for *trans*-1.

Not only enthalpy but also entropy plays a role in these temperature-dependent diastereoselectivity trends, as witnessed by the nonlinear Eyring plot (cf. Figure 1, Supporting Information) for the *cis*-1/Ph₂CO cycloaddition (unfortunately, the variation of the *dr* values for the *trans*-1 is too small to allow a reliable correlation). An inversion temperature of 293 K is obtained, which substantiates the reversibility of the triplet diradical ^3DR and that entropy effects are also important.⁵

It remains to explain the formation of the large amounts of *cis*-1 from *trans*-1 in the photoreaction of the latter, which depends also on temperature. We propose the third conformer $^3\text{DR}(\text{cleavage})$ in Scheme 2, for which the radical centers assume an *antiperiplanar* arrangement. Once intersystem crossing (ISC) has taken place, this conformer is destined to cleave into the starting materials, because the distance between the spin-bearing 2p orbitals is too large to form the final CC bond.⁹ Since *trans*-1 is by ~10 kcal/mol more strained than the *cis*-1 diastereomer,¹⁰ the latter is the preferred product of diradical cleavage for the $^3\text{DR}(\text{cleavage})$ conformer. The temperature effect (Table 2) derives from the competition between bond rotation and intersystem crossing in the $^3\text{DR}(\text{trans})$ conformer.

In summary, the temperature effect observed in the present [2+2] photocycloaddition is remarkable, if not unique, since the lower-energy substrate diastereomer, namely *cis*-1 cyclooctene, affords with increasing temperature the higher-energy product, namely the *trans*-2 oxetane. In contrast, the more strained *trans*-1 cyclooctene preserves its *trans* configuration in the cycloadduct **2** over a temperature range of more than 150 °C. The thermodynamic preference of the $^3\text{DR}(\text{trans})$ conformer, combined with the kinetically controlled conversion of the $^3\text{DR}(\text{cis})$ into the $^3\text{DR}(\text{trans})$ conformer, account for the present results.

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

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