

transformed into the expression host B834(DE3) to yield B834(DE3)/pQE15-MRS/pREP4. Plasmid DNA from all B834(DE3)/pQE15-MRS/pREP4 cultures used for protein expression experiments was sequenced to confirm that it encoded wild-type MetRS.

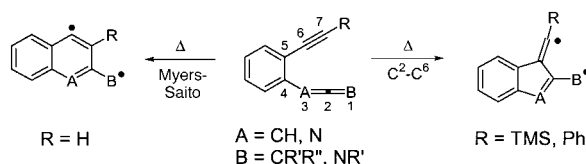
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- [21] Methionine analogues were synthesized by alkylation of diethylacetamidomalonate, as previously described.^[13]
- [22] The M9AA medium was prepared by supplementing sterile M9 medium with 60 mg mL⁻¹ of each of the amino acids, 1 mM MgSO₄, 0.2 wt % glucose, 1 mg mL⁻¹ thiamine chloride, and 1 mg mL⁻¹ calcium chloride. The antibiotics ampicillin and kanamycin were added at concentrations of 200 mg L⁻¹ and 35 mg L⁻¹, respectively.
- [23] B834(DE3)/pQE15-MRS/pREP4 cells, which overexpress MetRS, have sufficient MetRS activity to synthesize measurable levels of protein from the very low intracellular levels of methionine in the negative-control culture. Interestingly, AARS overexpression is induced by amino acid starvation in some Gram-positive bacteria, presumably to permit continued protein synthesis (D. Luo, J. Leautey, M. Grunberg-Manago, H. Putzer, *J. Bacteriol.* **1997**, 179, 2472–2478). B834(DE3)/pQE15/pREP4 cultures, which lack the increased MetRS activity, do not show background expression of protein in negative-control cultures.
- [24] ATP-PP_i exchange assays were conducted by using the methods described in ref. [15] A 50-μL aliquot of whole-cell lysate with a normalized OD₆₀₀ of 20 was prepared by one freeze–thaw cycle and added to the assay mixture to yield a final volume of 150 μL. A saturating concentration of methionine (750 μM) was used to determine the maximum exchange velocity for each cell lysate.
- [25] ¹H NMR spectra were recorded by using a Varian Inova NMR spectrometer with proton acquisition at 599.69 MHz. Spectra were recorded at 25°C overnight. A simple presaturation pulse was used for water suppression.
- [26] 1D TOCSY NMR spectra were recorded on a Varian Inova NMR spectrometer with proton acquisition at 599.69 MHz. A 1D TOCSY pulse sequence (D. Uhrin, P. N. Barlow, *J. Magn. Reson.* **1997**, 126, 248–255) with selective irradiation of the signal at δ = 5.35 (E. Kupce, J. Boyd, I. D. Campbell, *J. Magn. Reson. Ser. B.* **1995**, 106, 300–303) was used to identify which protons belonged to the spin system of that signal. The selectivity of the pulse is demonstrated in a separate, simple 1D experiment in which the selective pulse is applied alone; no other resonances are observed in the spectrum under these conditions. Observation after a mixing time of 60 ms, however, showed the protons at δ = 5.60 and 5.70, indicating that those protons are members of the same spin system (and therefore the same amino acid residue) as those corresponding to the resonance at δ = 5.35. The α-carbon and side chain β- and γ-carbon protons are also observed at chemical shift values characteristic of the free amino acid (δ = 4.3 (α-CH), 2.5 (β-CH₂), and 1.6 (δ-CH₃)).
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A Highly Efficient Triplet Analogue of a Thermal Biradical Cyclization—The Photochemical C²–C⁶ Cyclization of Enyne-Heteroallenes**

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Dedicated to Professor Harald Günther on the occasion of his 65th birthday

Cycloaromatizations of enediynes^[1] (Bergman cyclization) and enyne–allenes^[2] (Myers–Saito cyclization) have received great interest over the last decade because the resultant biradicals constitute key intermediates in the mode of action of natural enediyne antitumor antibiotics.^[3] While the above cyclizations may be regarded as electrocyclic reactions^[4] that lead to aromatic biradicals, the proper choice of substituents at the alkyne terminus (Scheme 1) has allowed us^[5] to steer the regioselectivity of thermal enyne–(hetero)allene biradical cyclizations^[6–8] away from the Myers–Saito path and instead to the C²–C⁶ path, which leads to (hetero)benzofulvene biradicals.



Scheme 1. Biradical intermediates of the thermal C²–C⁷ (Myers–Saito) and C²–C⁶ cyclization reactions. TMS = Si(CH₃)₃.

As the novel C²–C⁶ cyclization currently is the focus of theoretical,^[9] DNA cleavage,^[10] and synthetic studies (for example, towards the synthesis of the kinamycin^[11] and the neocryptolepine^[12] families), it appeared important to develop a photochemical variant—as for the Bergman cyclization^[13]—which should allow a direct access to the intermediate biradicals.^[14] Herein, we now report for the first time on the photochemical reactions of enyne–carbodiimides and enyne–ketenimines constituting the first triplet analogues of a thermal biradical cyclization.

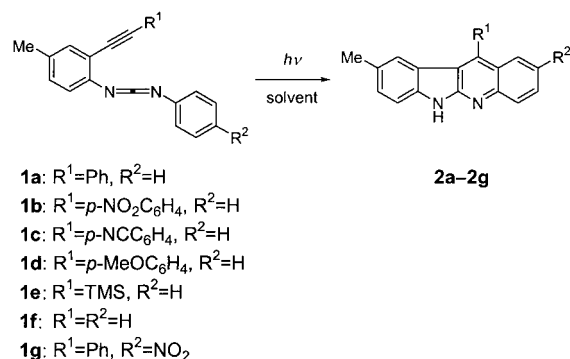
We have become aware of the photochemical cyclization when the enyne–carbodiimide **1a** partially formed indoloquinoline **2a** after prolonged exposure to sunlight (several

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[**] We would like to express our gratitude to the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the Ministerio de Educación y Ciencia (Spain) for generous support of this research.

days). Consequently, the photochemical behavior of various substituted enyne–carbodiimides **1** was examined (Scheme 2). Photolyses of degassed solutions of **1** under different



Scheme 2. Photocyclization of enyne–carbodiimides **1a–1g**.

conditions (see Tables 1 and 2) were carried out in a Rayonet RPR-100 Photochemical Reactor at four different wavelengths (254, 300, 350, and 419 nm). Conversion of the reactant was monitored by thin-layer chromatography (TLC). Depending on their solubility, indoloquinolines **2** were isolated by filtration or column chromatography.

Table 1. Photoreactivity of enyne–carbodiimides **1** under direct irradiation.^[a]

Substrate	Solvent	Wave-length λ [nm]	Reaction time [min]	Conversion of 1 [%]	Yield ^[b] of 2 [%]
1a	toluene	300	90	< 5	–
1b	<i>n</i> -hexane	419	60	100	95
1b	toluene	300	≈ 8	100	quantitative
1b	<i>n</i> -hexane	300	≈ 5	100	92
1c	toluene	300	540	100	91
1d	toluene	300	90	< 5	–
1f	toluene	300	90	< 5	–
1g	toluene	300	60	100	96

[a] $c = 4–8$ mm. [b] Yield of isolated product.

Table 2. Triplet-sensitized photoreaction of enyne–carbodiimides **1**.^[a]

Substrate	Solvent	Wave-length λ [nm]	Reaction time [min]	Conversion of 1 [%]	Yield ^[b] of 2 [%]
1a	<i>n</i> -hexane	254	360	31	19
1a	benzene	254	380	62	60
1a	toluene	254	40	100	96
1a	acetone	300	60	100	89
1d	toluene	254	120	100	93
1e	toluene	254	630	100	66 (2e), 31 (2f)
1f	toluene	254	360	100	94

[a] $c = 4–18$ mm. [b] Yield of isolated product.

When the enyne–carbodiimide is substituted by an electron-withdrawing group either at the alkyne (**1b**, **1c**) or carbodiimide (**1g**) terminus, direct irradiation at 300 nm or longer wavelengths yields >90% of **2** (Table 1). Clean conversion is also shown by the occurrence of four isosbestic points in the UV/Vis investigation (Figure 1). Moreover, all

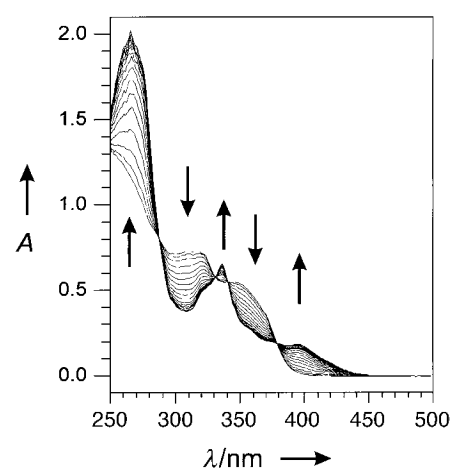


Figure 1. Spectral changes during photolysis of **1b** ($50 \mu\text{M}$ in *n*-hexane) at 350 nm. Between the consecutively recorded spectra, the irradiation time was 3 seconds; complete photocyclization was achieved within 50 seconds.

other systems can also be efficiently cyclized at shorter wavelengths when irradiation is carried out in a solvent that can act as a triplet photosensitizer (triplet energy^[15] $E_T = 83 \text{ kcal mol}^{-1}$ (toluene), 84 kcal mol^{-1} (benzene), 82 kcal mol^{-1} (acetone); Table 2).

The above observations provide some evidence for a triplet cyclization. To further strengthen our mechanistic assignment, the photochemical cyclization of **1a** was effected in presence of triplet sensitizers of varying E_T in hexane (Table 3). While strong sensitizers ($E_T > 60 \text{ kcal mol}^{-1}$) work very well, the

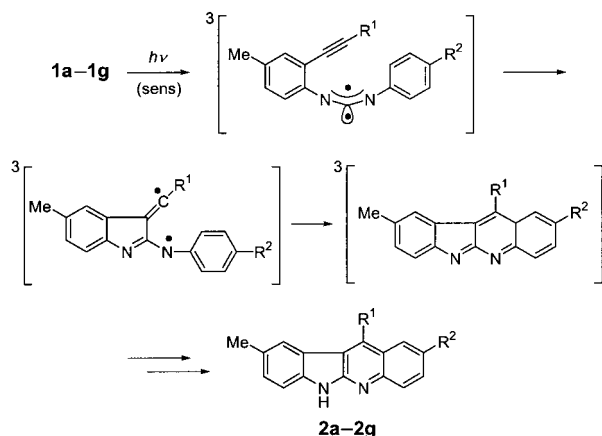
Table 3. Triplet-sensitized photoreaction of enyne–carbodiimide **1a** in *n*-hexane.^[a]

Sensitizer	E_T ^[b] [kcal mol ⁻¹]	Wave-length λ [nm]	Re-action time [min]	Conver-sion of 1a [%]	Yield ^[c] of 2a [%]
acetophenone ^[d]	74	350	60	100	88
acetophenone ^[e]	74	350	360	94	85
acetophenone ^[d]	74	300	40	100	90
benzophenone ^[f]	69	350	25	100	83
naphthalene ^[f]	61	254	60	100	81
diacetyl ^[f]	57	254	60	20	15
benzil ^[f, g]	54	254	60	< 5	–
no sensitizer	0	254	60	< 5	–

[a] $c = 5–11$ mm. [b] Triplet energy.^[15] [c] Yield of isolated product. [d] *n*-Hexane/acetophenone = 10/1. [e] 1 equiv (based on **1a**). [f] 20 equiv (based on **1a**). [g] Not completely soluble.

efficiency of the cyclization with benzil as a sensitizer ($E_T = 54 \text{ kcal mol}^{-1}$) is close to zero, as it is without sensitizer. Moreover, a triplet quencher is expected to interfere with any triplet cyclization. Indeed, photochemical cyclization of **1a** in toluene as well as in *n*-hexane could be completely suppressed in the presence of 1,4-diphenyl-1,3-butadiene, a triplet quencher with $E_T = 42 \text{ kcal mol}^{-1}$.^[15]

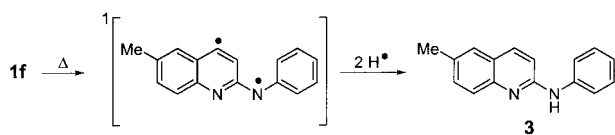
The mechanistic tests above clearly indicate that cyclization is taking place via triplet intermediates. Hence, we favor the following mechanistic proposal (Scheme 3) that is additionally supported by several independent facts: 1) allenes^[16] and heteroallenes^[17] are readily excited to the triplet state; 2) PM3



Scheme 3. Proposed mechanism for the triplet-sensitized cyclization of **1a–1g**. (sens) = sensitizer.

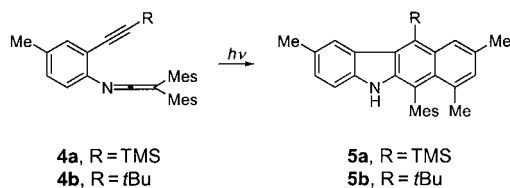
calculations^[18] indicate that the triplet diazabenzofulvene biradical is more stable than the singlet species,^[19] and 3) the regioselective 5-*exo-dig* cyclization of triplet biradicals is well established.^[20]

Furthermore, a strong argument for a triplet cyclization can be derived from the clean photochemical transformation **1f** → **2f** (94 %, Table 2). An intermediate singlet biradical can definitely be ruled out for this reaction, since under pure thermal conditions, i.e. via singlet biradical intermediates, **1f** forms aminoquinoline **3** along the Myers–Saito pathway (Scheme 4).^[6b]



Scheme 4. Thermal cyclization of **1f**.^[6b]

To establish the photocyclization as a general route to triplet heterobenzofulvene biradicals we have additionally subjected the stable enyne–ketenimines **4a** and **4b** to the conditions applied above (Scheme 5, Table 4). Notably, the cyclization can equally be effected but the yields of **5**^[21] are reduced due to formation of polymeric material.



Scheme 5. Photocyclization of enyne–ketenimines **4a** and **4b**. Mes = 2,4,6-(CH₃)₃C₆H₂.

Table 4. Irradiation of enyne–ketenimines **4a** and **4b**.^[a]

Substrate	Solvent	Wave-length λ [nm]	Reaction time [min]	Conversion of 4 [%]	Yield ^[b] of 5 [%]
4a	toluene	254	270	100	50 ^[c]
4a	<i>n</i> -hexane	254	360	54	14 ^[c]
4b	toluene	254	300	100	62 ^[c]

[a] *c* = 6–8 mm. [b] Yield of isolated product. [c] Besides **5**, only polymeric material was obtained.

In conclusion, we have found two remarkably efficient photocyclizations of enyne–carbodiimides and enyne–ketenimines. As evidence for triplet intermediates in the Bergman case is rather poor,^[13b] the above cyclizations constitute the first unequivocal triplet analogues of thermal biradical cyclizations. Because of the very good yields and the high 5-*exo-dig* regioselectivity, these cyclizations not only contrast the Myers–Saito pathway (see R¹ = H in **1f**) but also open the way for photoactive prodrugs towards the neocryptolepine^[12] family. Moreover, while the lack of a photochemical Myers–Saito cyclization still precludes a time-resolved study of the Myers–Saito biradical, the present triplet photoreaction appears to be ideal for flash photolysis or matrix isolation^[22] and for characterizing (hetero)benzofulvene biradicals. A mechanistic study along this line will be reported in due course.

Experimental Section

Photolysis of 1a in toluene: A solution of **1a** (23.0 mg, 74.5 μmol) in degassed toluene (13 mL, *c* = 5.7 mm) was placed in a quartz flask under a nitrogen atmosphere and irradiated with 16 lamps for 40 minutes (Rayonet RPR-100 photochemical reactor lamp, 253.7 nm, water cooling to 20 ± 5 °C). Reaction control by TLC showed the complete disappearance of **1a**. The solution was concentrated in vacuo and the remaining residue was purified by column chromatography (silica gel, *n*-hexane/ethyl acetate 3/1), to yield **2a** as a yellow solid (22.0 mg, 71.3 μmol, 96 %) that was recrystallized from ethanol.

2a: Yellow prisms; m.p. 242.5–243.5 °C (ethanol); ¹H (600 MHz, CDCl₃): δ = 2.28 (s, 3H), 6.84 (s, 1H), 7.17 (d, ³J(H,H) = 7.9 Hz, 1H), 7.39 (d, ³J(H,H) = 7.9 Hz, 1H), 7.39 (dd, ³J(H,H) = 8.4, 6.3 Hz, 1H), 7.53–7.55 (m, 2H), 7.65–7.70 (m, 3H), 7.74 (dd, ³J(H,H) = 8.3, 6.3 Hz, 1H), 7.76 (d, ³J(H,H) = 8.4 Hz, 1H), 8.26 (d, ³J(H,H) = 8.3 Hz, 1H), 12.29 (br. s, 1H; NH); ¹³C (50 MHz, CDCl₃): δ = 21.39, 110.54, 116.81, 121.24, 122.94, 123.30, 123.76, 126.36, 126.61, 128.61, 128.97 (2 signals), 129.12, 129.24, 129.40, 136.46, 139.43, 142.98, 145.68, 153.20; IR (KBr): $\tilde{\nu}$ = 3440, 3145, 3056, 2916, 2853, 1600, 1485, 1442, 1382, 1355, 1294, 1250, 1230, 1150, 1128, 1071, 799, 756, 702 cm^{−1}; elemental analysis calculated for C₂₂H₁₆N₂: C 85.69, H 5.23, N 9.08; found: C 85.27, H 5.50, N 9.44.

Received: January 13, 2000 [Z14531]

Revised: March 16, 2000

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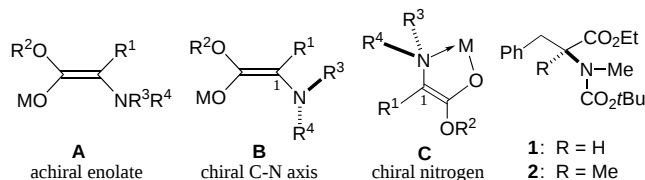
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A Chiral Nonracemic Enolate with Dynamic Axial Chirality: Direct Asymmetric α -Methylation of α -Amino Acid Derivatives**

Takeo Kawabata,* Hideo Suzuki, Yosikazu Nagae, and Kaoru Fuji

The structure of enolates was long believed to be achiral because all four substituents are on the same plane as the enolate double bond. For example, enolates generated from

α -amino acid derivatives are seemingly achiral when substituents R^1 – R^4 are achiral (**A**). However, we proposed that some enolate structures are intrinsically chiral.^[1–3] As shown in **B** an enolate with axial chirality along the C1–N axis is expected if R^3 is different from R^4 . An enolate with a chiral nitrogen atom is shown in **C**, where tight coordination of the



nitrogen atom to a metal cation creates a stereogenic nitrogen atom.^[4] Racemization of these chiral enolates takes place so readily through simple C1–N bond rotation that the chirality is not static, but dynamic. These enolates can exist in chiral nonracemic forms for a limited time at low temperatures. We describe here experimental evidence for a chiral nonracemic enolate with dynamic axial chirality, as exemplified in **B**. Asymmetric α -methylation of various α -amino acid derivatives can occur in a highly enantioselective manner through the intrinsically chiral enolate intermediate.^[5–7]

We have previously reported that phenylalanine derivative **1** undergoes asymmetric α -methylation by treatment with lithium 2,2,6,6-tetramethylpiperide followed by methyl iodide to give **2** in 82% *ee* and 40% yield.^[2] This is the second example of the retention of chiral information of optically active α -amino acid derivatives during their α -alkylation. The first one was reported by Seebach and Wasmuth.^[6a] Although the transformation of **1** into **2** was noteworthy in that asymmetric induction was realized without using any external chiral sources, such as chiral auxiliaries or chiral ligands, there were significant drawbacks: 1) low chemical yield, 2) low generality of asymmetric induction among α -amino acids, and 3) difficulty in removing the *N*-methyl protective group. The mechanism of the novel asymmetric induction was ambiguous. We further examined the present strategy in order to develop a more efficient process and to elucidate the mechanism. We anticipated that the choice of R^3 and R^4 in **B** or **C** would have the key role for the asymmetric induction, so we screened the substituents at the nitrogen atom of phenylalanine. We found that substrates possessing *t*-butoxycarbonyl (Boc) and methoxymethyl (MOM) groups at the nitrogen atom gave satisfactory results. Treatment of *N*-Boc-*N*-MOM-phenylalanine derivative **3** with potassium hexamethyldisilazide (KHMDs) in toluene:THF (4:1) at -78°C for 30 min followed by methyl iodide afforded α -methylated product **4** in 96% yield and 81% *ee* (Table 1, entry 1).^[8] Similarly, α -methylation of histidine derivative **5** gave **6** in 83% yield and 93% *ee* (entry 2). The α -amino acid derivatives **7**, **9**, and **11** with aromatic side chains, as well as those with aliphatic side chains, **13** and **15**, gave α -methylated products **8**, **10**, **12**, **14**, and **16**, respectively, in 78–95% yields and *ee* values of 76–87% by a similar treatment (entries 3–7). Removal of the protective groups of **4**, **8**, **14**, and **16** was readily accomplished in one step by treatment with 6M

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[**] This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 706: Dynamic Control of Stereochemistry) from the Ministry of Education (Monbusho), Japan.

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