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Photochemically Induced Aryl Azide Rearrangement: Solution NMR Spectroscopic Identification of the Rearrangement Product

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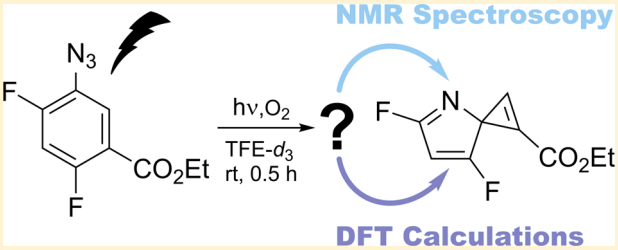
Supporting Information

ABSTRACT: Photolysis of ethyl 3-azido-4,6-difluorobenzoate at room temperature in the presence of oxygen results in the regioselective formation of ethyl 5,7-difluoro-4-azaspiro[2.4]-hepta-1,4,6-triene-1-carboxylate, presumably via the corresponding ketenimine intermediate which undergoes a photochemical four-electron electrocyclization followed by a rearrangement. The photorearrangement product was identified by multinuclear solution NMR spectroscopic techniques supported by DFT calculations.



Since their discovery one and a half centuries ago,[1] organic azides have received considerable interest in synthetic organic chemistry and have gained a plethora of applications.[2] Their photolysis and thermolysis yield a reactive nitrene by the release of molecular nitrogen. These processes were first studied by Tiemann in 1891[3] and have since then been thoroughly explored.[4] The photolysis of aryl azides has gained extensive application in lithography, polymer chemistry, surface functionalization, and synthesis of heterocycles.[5−13] Due to the smooth photoactivation and the reactivity of the formed nitrene toward a variety of functional groups, aryl azides are particularly well-suited for photoaffinity labeling of biopolymers.[2,14−19] Photoirradiation products and intermediates of aryl azides have been extensively studied.[20−28] The photolysis of aryl azide in the presence of diethylamine was first investigated by Doering and Odum.[29] Despite the wide applications of this photochemical process, only one NMR study of the ketenimine intermediate has been reported so far.[30] $^{13}C_6$-Labeled ketenimine encapsulated into hemicarcerand in CD_2Cl_2/$CDCl_3$ (6:1) solution was studied, and its lifetime was determined to be 5 h at −86 °C by ^{13}C NMR. Subsequently, the structure of the secondary photochemical rearrangement products derived from phenyl azide was elucidated by NMR.[31]

Fluorinated azidobenzoates, such as ethyl 3-azido-4,6-difluorobenzoate (**1**, Scheme 1), have been demonstrated to be useful for photoaffinity labeling.[32,33] The ester moiety provides a handle for attaching the molecule to be studied, whereas the fluorine substituents prolong the lifetime of the singlet nitrene intermediate, which can react with functional groups at the target site. Recently, we reported the formation of hemiaminals upon photolysis of aryl azides in 2,2,2-trifluoroethanol (TFE) at room temperature (rt).[34] Their structure and that of further photoproducts were established by extensive MS analyses, supported by comparison to the data of reference materials.[34,35] One of the photoproducts of **1** (Scheme 1) was found to be surprisingly stable in TFE at rt. When the photolysis was run for 2 min in the presence of oxygen (a triplet quencher),[36,37] the crude yield of the compound was increased from 4 to 20%, and the formation of other compounds was limited to traces.[35] Out of several possible alternative photoproducts, ketenimine **8**, shown in Scheme 1, was suggested as a plausible structure, however, without any spectroscopic proof. Here, the detailed solution NMR spectroscopic structure determination of the product of the photochemical transformation of **1** is reported.

To facilitate the structure elucidation, **1** was characterized by multinuclear (^1H, ^{13}C, ^{19}F, and ^{15}N) NMR, with the key experiments being ^1H,^{13}C and ^{19}F,^{13}C HMQC/HSQC; ^1H,^{13}C, ^1H,^{15}N, and ^{19}F,^{13}C HMBC; as well as ^1H,^{19}F HETCOR (Supporting Information). The data obtained (Figure 1 and Table 1) were used as a reference to identify the largest chemical shift changes, as well as the differences in 2D NMR correlations, upon conversion of **1** to ethyl 5,7-difluoro-4-azaspiro[2.4]hepta-1,4,6-triene-1-carboxylate (**6**).

Compound **1** was dissolved in TFE-d_3, transferred to an NMR tube, and irradiated at rt for 20 or 37 min using a 500 W mercury−xenon arc light source while bubbling O_2 through the solution. The NMR tube was then immediately inserted into an NMR spectrometer precooled to −20 °C, and the temperature

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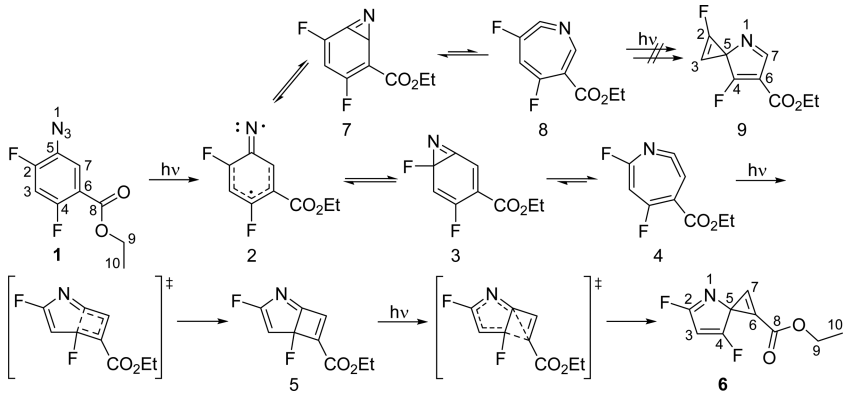
Scheme 1. Proposed Mechanism for the Formation of 6 from Photolysis of 1[31]



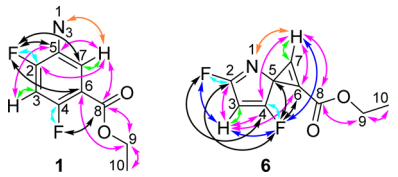


Figure 1. Two-dimensional NMR correlations for **1** and **6**. For **1**, the key correlations are presented, whereas for **6**, all correlations are presented. $^{1}H,^{13}C$ HMQC/HSQC in green; $^{1}H,^{13}C$ HMBC in magenta; $^{1}H,^{15}N$ HMBC in orange; $^{1}H,^{19}F$ HETCOR in blue; $^{19}F,^{13}C$ HSQC in cyan; and $^{19}F,^{13}C$ HMBC in black.

was kept at −20 °C while acquiring the data. Compound **6** was not isolated but was characterized in the crude reaction mixture in the presence of the educt **1** and traces of other compounds. A small amount of CD_3CN was added to facilitate the structure determination by promoting signal separation of H3 of **1** and H7 of **6**. The reaction was also successfully carried out in CD_3CN (data not shown), revealing that acidic medium is not necessary for the photochemical process to take place.

The structure determination of **6** (Figure 1 and Table 1) was initiated by analysis of the through-bond correlations of its characteristic ester carbonyl carbon C8, which is conserved throughout the photochemical transformation of **1**. This carbon was found to correlate with both H9 and H7 ($^{3}J_{CH}$ HMBC), and the $^{1}H,^{15}N$ gHMBC spectrum showed that H7 was in close proximity ($^{3}J_{NH}$) to N1. In contrast to the educt, no $^{3}J_{CF}$ (or $^{2}J_{CF}$) correlation was observed for C8, suggesting that the C4−C6 bond of **1** was disrupted in the photochemical transformation. Despite large chemical shift changes of F2 and F4, their $^{3}J_{HF}$ correlations with H3 were conserved, revealing that the C2−C3−C4 fragment was intact. The hydrogen−fluorine couplings were confirmed by ^{1}H-decoupled ^{19}F NMR experiments as well as $^{19}F,^{1}H$ HETCOR experiments with J_{HF} set to 7 and 14 Hz, respectively. No coupling was observed between F2 and H7, in contrast to the 7.3 Hz $^{4}J_{HF}$ coupling of **1**, revealing that H7 of **6** was not part of the same aromatic spin system as F2 anymore. Atoms C2−C4 and C7 were assigned by $^{1}H,^{13}C$ HMQC and $^{19}F,^{13}C$ HSQC and atoms C5 and C6 via their $^{1}H,^{13}C$ and $^{19}F,^{13}C$ HMBC correlations. The 139.0 ppm chemical shift of C6 was indicative of sp^2 hybridization. It showed through-bond correlations to F4, H3, and H7. Rupture of the C2−C5 bond was confirmed by the absence of the H7−C2 $^{3}J_{CH}$ HMBC correlation. The position of C5 in the pyrrole ring was revealed by its $^{2}J_{CF}$ correlation to F4. Further, $^{19}F,^{13}C$ long-range correlations of F4 to C2 and C6 suggested C5 to be a bridgehead carbon positioned between two aromatic rings. The 33.5 ppm chemical shift of C5 is 30 ppm more shielded

Table 1. ^{1}H, ^{13}C, ^{19}F, and ^{15}N NMR Chemical Shifts and *J*-Couplings of Compounds 1 and 6

	1	**6**
	δ (ppm)[a]	δ (ppm)[b]
atom	multiplicity; *J* (Hz)	multiplicity; *J* (Hz)
H3	6.91	6.07
	dd; 11.1, 9.5	dd; 13.3, 1.0
H7	7.59	7.01
	dd; 8.7, 7.3	d; 3.2
H9	4.35	4.28
	q; 7.1	q; 7.2
H10	1.37	1.29
	t; 7.1	t; 7.2
C2	159.2	157.2
	dd; 260.2, 11.8	dd; 333.4, 25.1
C3	108.1	104.2
	dd; 27.3, 23.7	dd; 79.2, 33.0
C4	161.3	169.6
	dd; 261.8, 11.7	dd; 279.5, 15.9
C5	126.7	33.5
	dd; 11.4, 2.5	s
C6	116.8	139.0
	d; 7.9	d; 20.7
C7	124.9	120.0
	s	d; 3.3
C8	166.0	164.0
	d; 2.9	s
C9	64.3	65.3
	s	s
C10	14.4	14.2
	s	s
F2	−114.3	41.9
	ddd; 13.1, 9.5, 7.3	dd; 45.5, 1.0
F4	−110.6	−70.2
	ddd; 13.1, 11.1, 8.7	ddd; 45.5, 13.3, 3.2
N1	−105.9, −13.5, NA[c]	−153.7[d]

[a]TFE-d_3. ^{1}H at 500 MHz, −10 °C. ^{13}C at 101 MHz, −30 °C. ^{19}F at 470 MHz, −30 °C. [b]TFE-d_3/CD_3CN 30:1. ^{1}H at 500 MHz. ^{19}F at 470 MHz. ^{13}C NMR at 201 MHz. All at −20 °C. [c]TFE-d_3. ^{15}N NMR chemical shifts of *N*′, *N*″, and *N*‴ (NA = not acquired), respectively, from $^{1}H,^{15}N$ gHMBCAD spectra (^{15}N at 51 MHz). [d]TFE-d_3/CD_3CN 7:1. ^{15}N NMR chemical shift from $^{1}H,^{15}N$ gHMBCAD spectra (^{15}N at 51 MHz).

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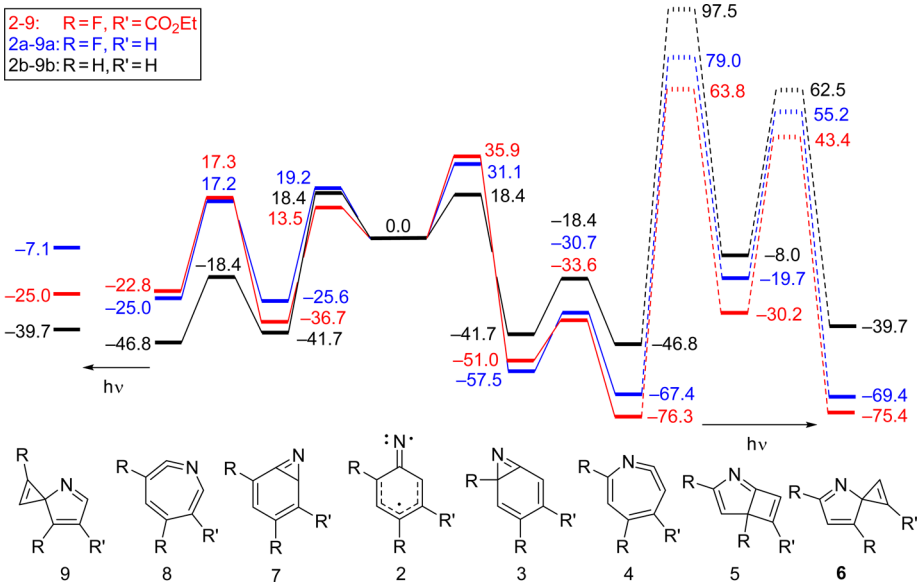
Scheme 2. Calculated Gibbs Free Energy (kJ mol^{-1}) Profiles for the Formation of 6, 6a, and 6b as Well as 9, 9a, and 9b from Diradicals 2, 2a, and 2b, Respectively[a]



[a]Each compound number represents all analogues; e.g., **2** represents **2**, **2a**, and **2b**. Dashed lines refer to transition states that are not actually passed because the respective reaction steps proceed by optical rather than thermal activation.

than the spirocarbon of 4-azaspiro[2.4]hepta-1,4,6-triene[31] and 15−18 ppm more shielded than the spirocarbons of a series of spiro[2.4]hepta-1,4,6-trienes reported by Dürr et al.[38] On the basis of published reaction routes of analogous substances, the 4-azaspiro[2.4]hepta-1,4,6-triene structure shown in Scheme 1 was proposed for **6**.[31] In addition to the NMR data, the structure was supported by its molecular weight (199.16 Da) matching that determined by Sydnes et al. in 2009 (*m*/*z* 200 [M + H]$^+$, ESI-Q-TOF-MS).[35] Structure **9** (Scheme 1) was evaluated as a possible alternative for **6**[31] but omitted based on the lack of $^3J_{CF}$ correlations between F4−C7 and F4−C8. Moreover, the 41.9 ppm ^{19}F chemical shift of F2 is incompatible with structure **9**, in which it would be expected to be significantly more shielded. This shift is, however, similar to those observed for the fluorine of compounds containing analogous CF═N fragments to **6**, such as the *Z*- and *E*-isomers of PhCF═N*t*Bu (39.0 versus 37.0 ppm).[39] Neither is the 13.3 Hz scalar coupling of H3 and F4 nor the 3.2 Hz coupling of H7 and F4 compatible with the structure of **9**.

As a complement to the experimental data, density functional theory (DFT) was used to calculate the energy profiles for the proposed reaction paths leading to **6** and **9** (Scheme 2; see the Supporting Information for computational details). Standard DFT provides reliable energy profiles only for reactions with thermal activation, that is, the paths from 2 to 4 and 2 to 8. For illustration, the fictitious reaction path from **4** to **6** was calculated. The calculation shows that the activation energies for the formation of **5** and **9** are substantially higher than those for the formation of **3**, **4**, **7**, and **8**, confirming the assumption that the formation of **5** and **6** requires optical activation. Furthermore, the formation of **7** ($\Delta G^{\#}$ = 13.5 kJ mol^{-1}) is strongly kinetically favored over that of **3** ($\Delta G^{\#}$ = 35.9 kJ mol^{-1}), whereas the formation of **3** is thermodynamically favored (ΔG_r = −51.0 kJ mol^{-1}) over that of **7** (ΔG_r = −36.7 kJ mol^{-1}). The formation of **4** from **3** is both kinetically and thermodynamically more favorable than that of **8** from **7** ($\Delta G^{\#}$ = 17.4 kJ mol^{-1}, ΔG_r = −25.3 kJ mol^{-1} for **3** and **4**, $\Delta G^{\#}$ = 54.0 kJ mol^{-1}, ΔG_r = 13.9 kJ mol^{-1} for **7** and **8**; **4** is 53.5 kJ mol^{-1} lower in *G* than **8**). Finally, the product **6** is 50.4 kJ mol^{-1} lower in energy than its hypothetical counterpart **9**. Thus, formation of **4** and **6** is more favorable than that of **8** and **9**, respectively, in agreement with the conclusions from the NMR studies.

In order to obtain some insight into the influence of the substituent pattern on the selectivity of the reaction, the same calculations were performed for **2a**−**9a**, in which the ethyl ester moiety is replaced by a hydrogen atom, and **2b**−**9b**, in which the two fluorine atoms are replaced by hydrogen atoms (**6b** and **9b**, and the corresponding reaction paths, are identical). The energy profile of **2a**−**9a** shows the same qualitative features as those of **2**−**9**. The ethyl ester substituent provides a slight preferential stabilization of **4** over **8**, whereas it reduces the energy difference between the two 4-azaspiro[2.4]hepta-1,4,6-trienes from 62.3 kJ mol^{-1} (cf. **6a** and **9a**) to 50.4 kJ mol^{-1} (cf. **6** and **9**), respectively. Our findings are in line with those in references 24 and 40 for the ring expansion of different fluorinated phenylnitrenes. TS2−3 (acronym for transition state between geometries 2 and 3) and TS2a−3a are destabilized by the electrostatic and possibly steric repulsion between the approaching nitrogen and the *ortho*-fluorine, with NAP charges for N of −0.35, −0.36, and −0.29 for TS2−3, TS2a−3a, and TS2b−3b (Figure S1) and for F of −0.27 and −0.28 for TS2−3 and TS2a−3a, respectively. Conversely, **3** and **3a** are stabilized relative to **7** and **7a** mainly by a delocalization from the C═N π orbital into the C−N σ^* orbital,[40] with NBO-PT2 energies of 119.3 (**3**) and 121.5 (**3a**) kJ mol^{-1}, as compared to 49.2, 49.7, and 48.4 kJ mol^{-1} for **7**, **7a**, and **7b** (=**3b**), respectively. The stabilization of **4** over **8** can be ascribed to the C═C double bond in the ketenimine group.[24] The *ipso*-carbon donates charge to the neighboring nitrogen and carries a positive NAP charge in all compounds (**4**, 0.44; **4a**, 0.42; **4b** = **8b**, 0.42; **8**, 0.29; **8b**, 0.26). The *ortho*-carbon carries a negative charge in **4** (−0.37), **4a** (−0.40), and **4b** = **8b** (−0.45) but donates charge to the *ortho*-fluorine and carries a positive charge in **8** (0.23) and **8b** (0.22). The repulsion

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between the two carbons and the weakening of the C=C bond due to charge depletion destabilize **8** and **8a** relative to **4** and **4a**. Interestingly, the C=C bond length is elongated by less than 0.01 Å in **8** and **8a** compared to **4** and **4a**. Both nitrogen and fluorine are σ acceptors and π donors, thus the electron-withdrawing effect in **8** and **8a** is supposed to affect the σ rather than the π bond in the first instance.

It should be noted that the DFT description of the low-spin diradical **2** is challenging, and thus, the uncertainty for its calculated energy is larger than that for the remaining compounds. However, this uncertainty does not affect the conclusions on relative energies for the two reaction paths that were investigated.

The photolysis of **1** under O_2 bubbling at rt in TFE-d_3 yielded **6**. This photoproduct is presumed to be formed by an initial two-step ring expansion of singlet nitrene **2** to ketenimine **4** via benzazirine intermediate **3** (Scheme 1). In the next step, ketenimine **4** is likely converted to anti-Bredt imine **5** by photochemical four-electron electrocyclization, which further rearranges to **6** under irradiation conditions.[31] In agreement with previous studies of mono-*ortho*-fluoro-substituted phenylnitrenes,[24,33,40−42] at high temperature, cyclization toward the fluorine-substituted *ortho*-carbon C2 of **2**, giving benzazirine **3**, is favored over cyclization toward the unsubstituted *ortho*-carbon C7 which leads to benzazirine **7**. At lower temperatures, the opposite selectivity is expected. This is explained by the higher barrier but more stable product of the conversion of **2** to **3** compared to that of **2** to **7** and the more stable **4** compared to **8**. Hence, in addition to the properties and the arrangement of the substituents, the irradiation conditions have critical influence on the yields of these regioisomers.[43,44] Although the origin for the regioselectivity is not fully explained, these results are of analytical and preparative importance. The experimentally determined chemical shifts and coupling constants are foreseen to be useful as reference values. By further optimization of reaction conditions and by the use of flow chemistry techniques, for example, multisubstituted 4-azaspiro[2.4]hepta-1,4,6-triene-type heterocycles, such as **6**, may be efficiently prepared and trapped.

EXPERIMENTAL SECTION

General Information. Ethyl 3-azido-4,6-difluorobenzoate (**1**) was prepared according to our previously reported method.[34] NMR spectra were recorded at −30, −20, or −10 °C on a spectrometer equipped with an HFX probe (^{1}H at 500 MHz, ^{13}C at 101 MHz, ^{19}F at 470 MHz, and ^{15}N at 51 MHz) or at −20 °C on a spectrometer equipped with an TXO cryoprobe (^{13}C at 201 MHz). Chemical shifts (δ) are reported in parts per million and referenced indirectly to tetramethylsilane (TMS) via the solvent residual signal. ^{1}H, ^{13}C, and ^{19}F NMR chemical shifts were referenced indirectly to TMS via TFE-d_3 (3.88, 126.3, and −77.72 ppm, respectively). ^{15}N NMR chemical shifts were referenced indirectly to TMS via CD_3CN (−137.6 ppm). The two-dimensional NMR experiments utilized in the structural elucidation were ^{1}H,^{13}C ASAPHMQC/gHSQCAD; ^{1}H,^{13}C gHMBCAD; ^{1}H,^{15}N gHMBCAD; ^{1}H,^{19}F HETCOR; ^{19}F,^{13}C gHSQCAD; and ^{19}F,^{13}C gHMBCAD.

General Procedure for the Synthesis of Ethyl 5,7-Difluoro-4-azaspiro[2.4]hepta-1,4,6-triene-1-carboxylate (6). Ethyl 3-azido-4,6-difluorobenzoate (**1**) was dissolved in TFE-d_3 and irradiated at rt in an NMR tube using a 500 W mercury−xenon arc lamp (see above for irradiation time) with oxygen bubbling through the solution according to our previously reported method.[35] The reaction mixture was diluted with CD_3CN, and the resulting TFE-d_3/CD_3CN solution containing **1** and ethyl 5,7-difluoro-4-azaspiro[2.4]hepta-1,4,6-triene-1-carboxylate (**6**) was then immediately used for NMR analysis at −20 °C. Thus, **6** was not isolated but characterized by NMR spectroscopy in solution using the crude reaction mixture also containing **1** (**1**/**6** 95:5) and traces of other compound(s).

NMR Sample 1 (37 min, TFE-d_3/CD_3CN 7:1). The 37 min sample was prepared according to the general procedure described above using **1** (60 mg, 0.264 mmol) in TFE-d_3 (500 μL). After 17 min of irradiation, 170 μL of the sample (i.e., one-third) was withdrawn. The remaining part of the sample was irradiated for an additional 20 min (37 min in total) and then diluted with CD_3CN (47 μL). The 37 min sample was immediately used for NMR analysis.

NMR Sample 2 (20 min, TFE-d_3/CD_3CN 30:1). The sample was prepared according to the general procedure described above using **1** (67 mg, 0.295 mmol) in TFE-d_3 (600 μL). After 20 min of irradiation, the mixture was diluted with CD_3CN (20 μL). The 20 min sample was immediately used for NMR analysis.

Computational Methods. All computations were performed with DFT using the M06 exchange and correlation functional by Truhlar et al. and Jensen's polarization-consistent pc-2 basis set.[45,46] Geometries were optimized for the gas phase, and vibration frequencies were calculated to characterize the equilibrium geometries as well as to determine zero-point and thermochemical corrections. For the optimized geometries, single-point calculations were performed using the polarizable continuum model to account for solvent effects using TFE as the solvent.[47,48] For each of the molecules **2**−**9**, both conformations of the ethyl ester group were considered. A natural bond orbital (NBO)[49,50] analysis was performed for selected compounds to determine natural atomic population (NAP) charges and second-order perturbation (NBO-PT2) stabilization energies.

The Gibbs free energies for the molecules in solutions were then calculated approximately as $G(\text{solv}) \approx E_e(\text{solv}) + G(\text{gas}) - E_e(\text{gas})$, where E_e is the pure electronic energy (without zero-point corrections). The approximate values for G(solv) are given in Table S1 in the Supporting Information. For each of the molecules **2**−**9**, the conformer with the lower G(solv) was used for the investigation of the reaction energetics (denoted in Table S1 in the Supporting Information).

The singlet states of nitrene **2** and its analogues **2a** and **2b** (Scheme 2) have open-shell character and cannot be described properly with standard DFT. Therefore, we calculated the energies of these states by the extrapolation method suggested by Cramer and Ziegler.[51,52] For this purpose, we performed spin-unrestricted (U) DFT calculations for the triplet states of **2**, **2a**, and **2b** and permuted-orbital (PO)-UDFT calculations for the respective singlet states and approximated the open-shell singlet (OSS) energy as $E(\text{OSS}) \approx 2E(\text{singlet, PO-UDFT}) - E(\text{triplet, UDFT})$, analogously for the Gibbs free energy.[53] The extrapolated values are given in Table S2 in the Supporting Information. All calculations were performed with the Gaussian09 package.[54]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02555.

NMR spectra of compounds **1** and **6**, computational data (PDF)

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Notes

The authors declare no competing financial interest.

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