

Investigation of *thia*-Diels–Alder Reactions by Ultrafast Transient Absorption Spectroscopy and DFT Calculations

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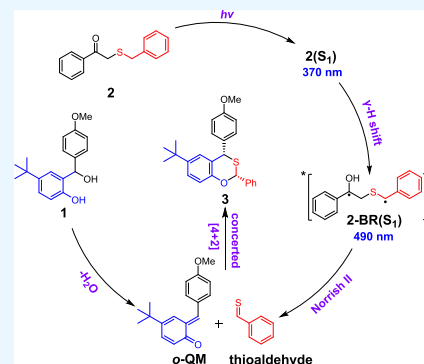


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Supporting Information

ABSTRACT: The *thia*-Diels–Alder reaction represents a versatile synthetic method for the preparation of six-membered sulfur-containing compounds. However, the mechanism of the *thia*-Diels–Alder reactions remains unclear. In this work, time-resolved spectroscopic experiments and DFT calculations demonstrate that phenacyl sulfide undergoes Norrish II cleavage to produce thioaldehyde, and ortho-hydroxy benzhydryl alcohol occurs in a dehydration reaction to generate *o*-QMs using diphenylphosphate as the catalyst. Then, the *thia*-Diels–Alder reaction takes place between thioaldehyde and *o*-QMs by an asynchronous concerted mechanism. The illustration of the *thia*-Diels–Alder reaction mechanism not only provides important support for organic synthesis and drug design but also enhances fundamental insights into reaction pathways and catalytic processes in the field of chemical synthesis.



INTRODUCTION

The *thia*-Diels–Alder reactions constitute an important class of hetero-Diels–Alder reactions and comprise a versatile synthetic method for the preparation of six-membered sulfur-containing compounds.¹ The mechanism of the hetero-Diels–Alder reaction has been a subject of critical discussion by many researchers.^{2–4} In the presented scenario, two types of mechanisms can compete within the elemental reaction: a one-step mechanism characterized by an asynchronous transition state, and a stepwise mechanism with the participation of a zwitterionic intermediate in polar reactions⁵ or a diradical in nonpolar reactions.⁶

Recently, Schneider and co-workers⁷ developed a broadly applicable one-pot process that furnishes benzo[*e*][1,3]-oxathiines in good to excellent yields and diastereo-selectivity through the *thia*-Diels–Alder reaction between ortho-quinone methides (*o*-QMs) and thioaldehyde. It is well-known that *o*-QMs and thioaldehyde are reactive intermediates.^{8,9} Currently, *o*-QMs are strongly recognized as effective methods for the synthesis of oxygen-containing heterocycles and functionally substituted phenols.^{10–13} In addition, photoinduced thioaldehydes exhibit exceptional dienophilic properties.¹⁴ Therefore, *o*-QMs are produced on-site from a dehydration reaction of ortho-hydroxy benzhydryl alcohols (like 4-(*tert*-butyl)-2-(hydroxy(4-methoxyphenyl) methyl)phenol, **1**) with diphenylphosphate (DPP, Brønsted acid) as a catalyst (the catalysis reaction is depicted in Scheme S1), and thioaldehyde is afforded by a photochemical pathway using phenacyl sulfides (like 2-(benzylthio)-1-phenylethan-1-one, **2**). The *thia*-Diels–Alder reactions between *o*-QMs and thioaldehydes containing weakly electron-donating or -withdrawing substituents proceed

successfully. To date, the reaction mechanism remains unclear, for instance, whether the concerted or stepwise reaction pathway dominates. In this work, compounds **1** and **2** were specifically chosen as target molecules (see Scheme 1) to explore the *thia*-Diels–Alder reaction mechanism. Time-resolved spectroscopy experiments of femtosecond transient absorption (fs-TA) and nanosecond transient absorption (ns-TA) were performed to detect the relative reaction intermediates. Concerted and stepwise reaction pathways were investigated by density functional theory (DFT) calculations.

RESULTS AND DISCUSSION

Steady-state absorption spectra of **1**, **2**, and DPP and the mixed solution of **1**, **2**, and DPP in DCM are shown in Figure S2. The absorption bands were detected for **1** at 280 nm, for **2** at 280 and 338 nm, for DPP at 260 nm, and for the mixed solution of **1**, **2**, and DPP at 280 and 338 nm. The steady-state photolysis experiments for **2** and the sample solution of **1**, **2**, and DPP in DCM were excited at 355 nm, and the UV–vis spectra were recorded to monitor the photolysis process as shown in Figure 1.

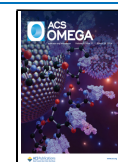
As the irradiation time increased, the typical absorption bands of **2** decreased, accompanied by the generation of a new

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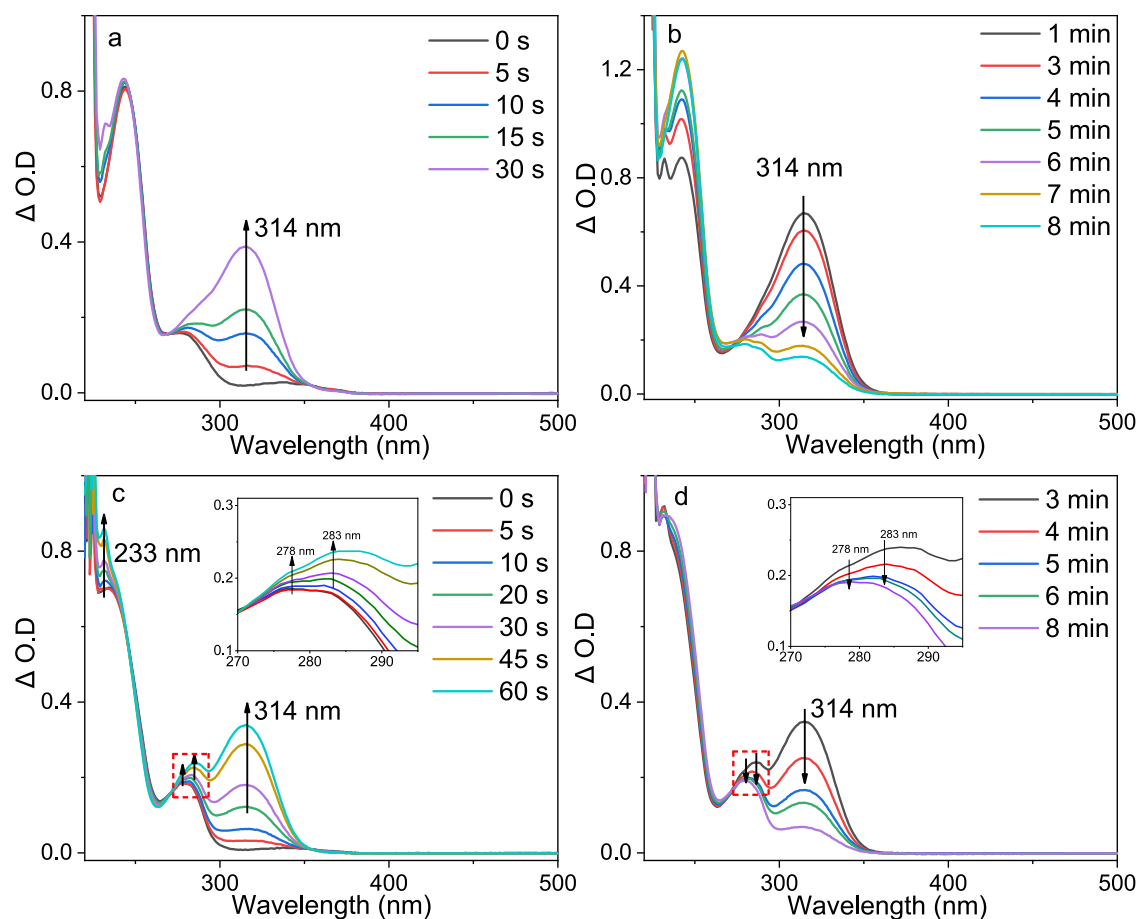
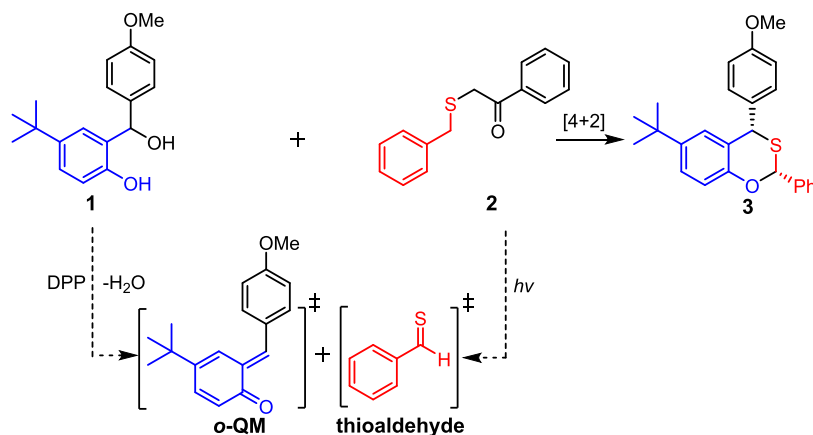
Scheme 1. Synthesis of Benzoxathiine 3 from *ortho*-Hydroxy Benzhydryl Alcohol 1 and Phenacyl Sulfide 2

Figure 1. UV-vis absorption spectra of (a, b) 2 and (c, d) the mixture solution of 1, 2, and DPP in DCM recorded at different irradiation times upon 355 nm light.

signal at 314 nm. For the photoexcitation of the mixed solution of 1, 2, and DPP in DCM, observation of absorbances at 233, 278, and 283 nm suggested formation of photoproduct 3.⁷ This result is further supported by mass spectrometry, where the protonated molecular ion signal of 3 was detected (Figure S3). Additionally, compound 3 was not probed by mass spectrometry in photolysis experiments on the mixed solution of 1 and 2, suggesting that DPP is essentially required for the generation of the photoproduct. It was reported that phenacyl sulfides could undergo a Norrish II reaction to produce thioaldehydes and alcohols.¹⁵ Therefore, it is assumed that the

newly formed band is the signal of the photoproduct acetophenone through a Norrish type II reaction for 2. The UV-vis spectrum of acetophenone appeared at 242, 277, and 314 nm (Figure S4), further verifying that the absorption band at 314 nm corresponds to acetophenone.

Time-resolved spectroscopic experiments were carried out to detect the intermediates produced during the photoreaction. Figure 2 displays the fs-TA spectra of 2 in DCM. During the early times, the species appearing at 370 nm was ascribed to the singlet state of 2 (denoted as 2(S₁)), which then converted to a new species appearing at 490 nm and then decayed from

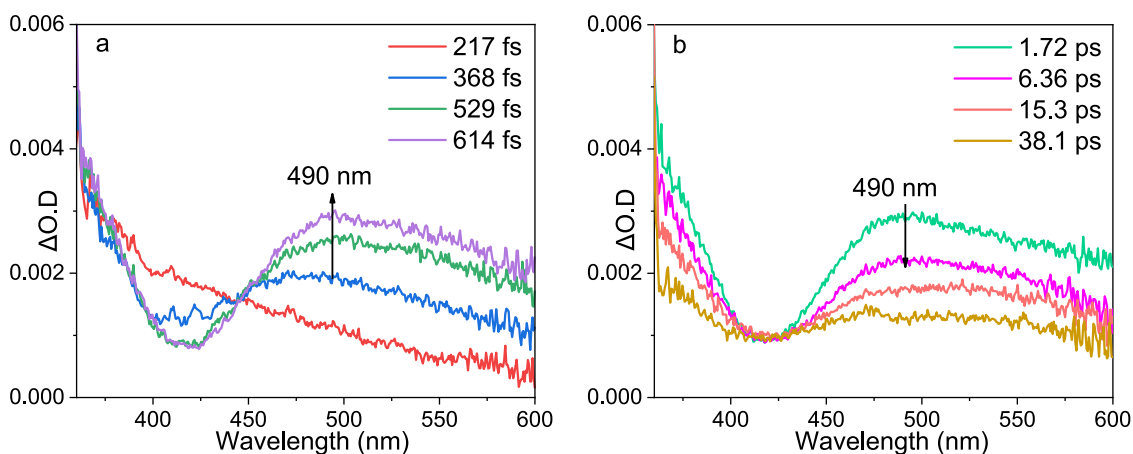


Figure 2. fs-TA results of (a, b) **2** in DCM ($\lambda_{\text{ex}} = 355$ nm).

1.72 to 38.1 ps. A previous study on dibenzoylmethane compounds unraveled the intramolecular transfer of γ -hydrogen to oxygen to form the 1,4-diradical.¹⁶ Thus, the new species observed for **2** in fs-TA was tentatively attributed to the 1,4-diradical (labeled as **2-BR**(S_1)). The above assignments were further confirmed by TD-DFT calculations, where the simulated UV-vis spectra of **2**(S_1) and **2-BR**(S_1) resembled the corresponding fs-TA spectra recorded at 217 fs and 15.3 ps, respectively (Figures S5 and S6). Furthermore, DFT calculations reveal that **2**(S_1) overcame a reaction barrier of 5.82 kcal mol⁻¹ to undergo an intramolecular hydrogen shift by generating a biradical species. Ns-TA performed under analogous experimental conditions appeared at 314 nm (Figure 3), which is consistent with the photolysis test by

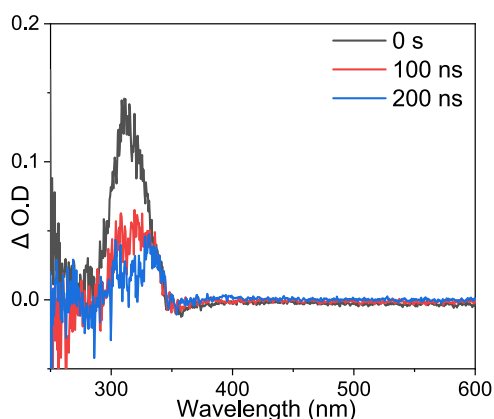


Figure 3. ns-TA spectra of **2** in DCM ($\lambda_{\text{ex}} = 355$ nm).

detecting acetophenone. Combining the above experimental and calculation results, a plausible reaction mechanism of **2** is depicted in Scheme 2. Irradiation of **2** leads to the S_1 state, which undergoes intramolecular transfer of γ -hydrogen to oxygen to form **2-BR**(S_1). Thereafter, the C–S bond cleaved to form acetophenone and benzothialdehyde.

Figure 4 displays fs-TA spectra of the mixed solution of **1**, **2**, and **DPP** in DCM under 355 nm irradiation, where only **2** could be excited. The profile of Figure 4 is almost identical to that recorded for **2**, and the signals of **2**(S_1) and **2-BR**(S_1) were detected. That is, the intermediate formed from **2** did not react with **1** or **DPP** on the fs-TA detection time scale. Furthermore, the ns-TA spectral profile of the mixed solution

of **1**, **2**, and **DPP** is identical to the one recorded for **2** (Figure S7). Therefore, the cycloaddition reaction is highly likely to be a concerted reaction, as shown in Scheme 3.

To explore the detailed *thia*-Diels–Alder process between *o*-QM and benzothialdehyde, DFT calculations were conducted. As reported, the coordination between **DPP** and benzothialdehyde is complicated due to their low capability of forming hydrogen bonds.⁷ Therefore, **DPP** is not involved in the cycloaddition reaction and is not considered in the DFT calculations. The potential energy surface profile for the concerted pathway was simulated (Figure 5). The reaction barrier is 11.63 kcal mol⁻¹, and the process is exothermic by 21.86 kcal mol⁻¹. Note that the energy barrier of the reaction is lower than that of the hetero-Diels–Alder reactions occurring between *aza*-ortho-quinone methide and 4-bromobenzaldehyde.¹⁷ Comparing the C–S and C–O bond lengths between the transition state and the product, it is suggested that the concerted reaction involves an asynchronous mechanism,¹⁸ where the C–O bond formation occurs faster than that of the C–S bond. In addition, stepwise reaction pathways were studied, in which a diradical intermediate is involved, whether a C–S bond or a C–O bond forms first, followed by diradical coupling to produce **3** (Scheme S3). However, we could only optimize the intermediates where the C–S bond or C–O bond formed (Figure S8) while failing to locate the corresponding transition states. Considering the above analysis, we tend to conclude that the *thia*-Diels–Alder reaction occurs via a concerted reaction pathway at this stage.

CONCLUSIONS

In this work, time-resolved transient absorption spectroscopy coupled with DFT calculations was performed to unravel the cycloaddition reaction mechanism between *o*-QMs and thioaldehydes. With the help of transient absorption spectroscopy, irradiation of **2** leads to the S_1 state, which undergoes intramolecular transfer of γ -hydrogen to oxygen to form **2-BR**(S_1). Thereafter, benzothialdehyde is formed by the C–S bond cleavage. On the other hand, the transient absorption result of the mixed solution of **1**, **2**, and **DPP** is identical to that recorded for **2**, suggesting that the cycloaddition reaction follows a concerted pathway. This is confirmed by DFT calculations, where the *thia*-Diels–Alder reaction of *o*-QM and thioaldehyde occurs by an asynchronous concerted mechanism with a reaction barrier of 11.63 kcal mol⁻¹. Understanding the cycloaddition reaction mechanism contributes significantly to

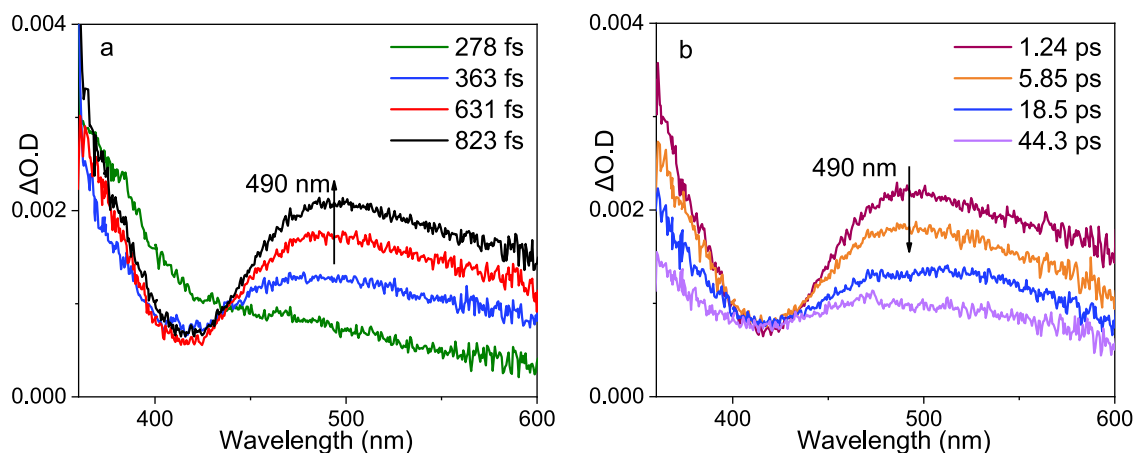
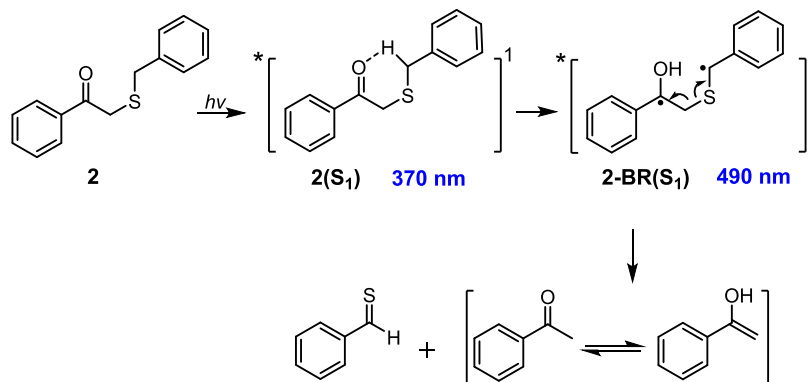
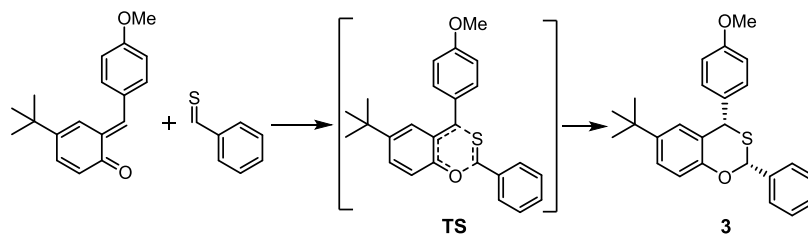
Scheme 2. Norrish II Reaction Mechanism of **2** in DCM

Figure 4. fs-TA of a mixed solution of (a, b) **1** and **2** with DPP in DCM ($\lambda_{\text{ex}} = 355$ nm).

Scheme 3. Concerted Pathways for *thia*-Diels-Alder Reaction

synthesizing compounds with specific structures, laying the groundwork for drug design and synthesis.

EXPERIMENTAL SECTION

Compounds **1** and **2** were synthesized following the procedures detailed in the literature,^{19,20} and the synthesis routes are shown in Scheme S2. For characterization of the samples prepared, see the ¹H NMR spectra displayed in Figure S1.

Steady-state photolysis experiments were performed in a photochemical reactor PRP-100 (Rayonet, 355 nm). Absorption spectra were recorded on a UV-1700 spectrophotometer (Shimadzu).

fs-TA tests were performed using a regenerative amplified Ti:sapphire laser system and an automated data acquisition system. The probe pulse was obtained by using approximately 5% of the amplified 800 nm output from the laser system to generate a white-light continuum (330–800 nm) in a CaF₂ crystal. The instrument response function was determined to

be about 150 fs. For the present experiments, the sample solutions were excited by a 355 nm pump beam (the third harmonic of the fundamental 800 nm from the regenerative amplifier). A 40 mL sample solution with an optical density of around 0.8 at 355 nm was flowed through a 2 mm path-length cuvette throughout the data acquisition. ns-TA experiments were recorded on an LP980 laser flash photolysis spectrometer (Edinburgh Instruments, U.K.).

DFT, which incorporates dynamical and, more roughly, nondynamical electron correlation, has proven to be a reliable approach for studying Diels–Alder reactions.^{21–23} The M062X²⁴ functional has been found to be more accurate than the other functionals in terms of the free energy of cycloaddition reactions.²⁵ Thus, DFT calculations employing the M062X method with a 6-311G** basis set were carried out to determine the optimized geometries using the Bery analytical gradient²⁶ optimization method and electronic absorption spectra of the potential intermediate species. The frequency computations were performed to verify that the

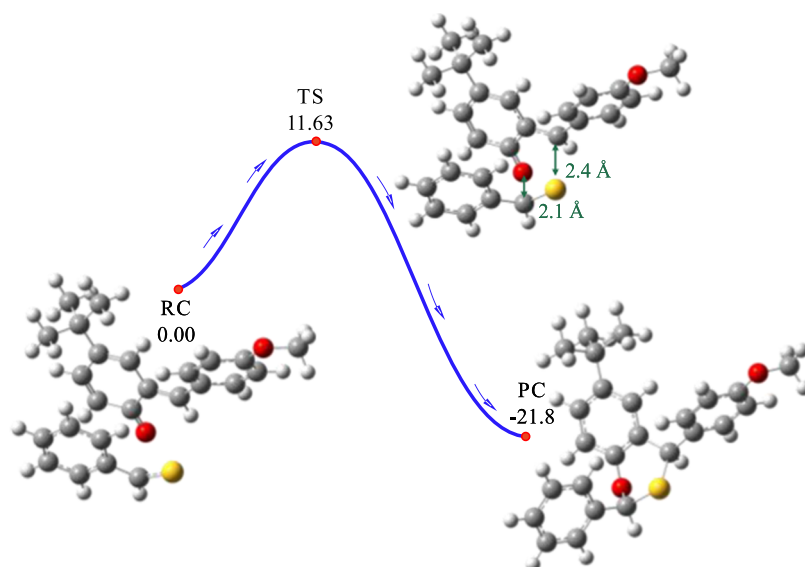


Figure 5. Reactive energy profile obtained from M062X/6-311G** calculations for the concerted reaction of *thia*-Diels–Alder in DCM (energy in kcal mol⁻¹).

transition state (TS) has only one imaginary frequency. The intrinsic reaction coordinate (IRC)²⁷ paths were calculated to check the energy profiles connecting each TS to the two associated minima of the reactant complexes (RCs) and product complexes (PCs) using the second-order Gonzalez–Schlegel integration method. Solvent effects of dichloromethane (DCM) were considered through full optimizations using the solvation model based on density (SMD) as developed by Truhlar and co-workers in the framework of the self-consistent reaction field (SCRF).^{28,29} All calculations were carried out with the Gaussian 09 suite of programs.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.4c00235>.

Synthesis route and ¹H NMR of **1** and **2**, ns-TA obtained under varying conditions, DFT calculations using M062X/6-311G** for the possible transient species, and the Cartesian coordinates and energies for all calculated structures discussed in the text (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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