

Photochemistry

Triplet-Triplet Energy Transfer: A Simple Strategy for an Efficient Visible Light-Induced Photoclick Reaction

Youxin Fu, Georgios Alachouzos, Nadja A. Simeth, Mariangela Di Donato, Michiel F. Hilbers, Wybren Jan Buma, Wiktor Szymanski,* and Ben L. Feringa*

Abstract: Photoclick reactions combine the advantages offered by light-driven processes and classical click chemistry and have found applications ranging from surface functionalization, polymer conjugation, photocrosslinking, and protein labeling. Despite these advances, the dependency of most of the photoclick reactions on UV light poses a severe obstacle for their general implementation, as this light can be absorbed by other molecules in the system resulting in their degradation or unwanted reactivity. However, the development of a simple and efficient system to achieve bathochromically shifted photoclick transformations remains challenging. Here, we introduce triplet-triplet energy transfer as a fast and selective way to enable visible light-induced photoclick reactions. Specifically, we show that 9,10-phenanthrenequinones (**PQs**) can efficiently react with electron-rich alkenes (**ERAs**) in the presence of a catalytic amount (as little as 5 mol%) of photosensitizers. The photocycloaddition reaction can be achieved under green (530 nm) or orange (590 nm) light irradiation, representing a bathochromic shift of over 100 nm as compared to the classical **PQ-ERAs** system. Furthermore, by combining appropriate reactants, we establish an orthogonal, blue and green light-induced photoclick reaction system in which the product distribution can be precisely controlled by the choice of the color of light.

Introduction

The application of photochemical processes^[1] in the research area of click chemistry^[2–5] has led to the creation of a new class of light-triggered reactions known as photoclick chemistry.^[6,7] These transformations enable the synthesis of various molecular structures, conjugates, and polymer networks in a spatiotemporally controlled manner in complex systems.^[6,7] Photoclick chemistry has recently emerged as a promising methodology for surface functionalization,^[8–10] polymer conjugation,^[8–12] photocross-linking^[13] and protein labeling.^[14–17]

A key limitation of photoclick reactions is that they typically require ultraviolet (UV, $\lambda < 380$ nm) irradiation, as exemplified by photo-induced tetrazole-alkene cycloadditions,^[18,19] UV-light initiated thiol-ene and thiol-yne reactions,^[20,21] azide-alkyne cycloadditions,^[22] photo-induced sydnone-alkene/alkyne cycloadditions,^[23] azirine-alkene cycloaddition,^[24] and light-triggered oxime ligation reactions.^[25] However, visible light- ($\lambda = 380–700$ nm) and near-infrared (NIR) light ($\lambda = 700–2500$ nm) induced photoclick reactions are highly desirable, primarily due to Vis/NIR light's superior penetration into materials when compared to UV light.^[26–28] This unique capability facilitates non-destructive imaging and analysis of subsurface structures, providing a more profound insight into material composition and properties. Moreover, these wavelengths offer advantages in identifying molecular compositions within complex soft material devices based on organic molecules, such as polymer samples, by minimizing interference from background signals.^[29,30] Additionally, these characteristics

[*] Y. Fu, Dr. G. Alachouzos, Jun.-Prof. Dr. N. A. Simeth, Prof. Dr. W. Szymanski, Prof. Dr. B. L. Feringa
 Centre for Systems Chemistry, Stratingh Institute for Chemistry, Faculty for Science and Engineering, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands
 E-mail: w.szymanski@umcg.nl
 b.l.feringa@rug.nl

Jun.-Prof. Dr. N. A. Simeth
 Institute for Organic and Biomolecular Chemistry, Department of Chemistry, University of Göttingen, Tammannstr. 2, 37077 Göttingen, Germany

M. Di Donato
 LENS (European Laboratory for Non-Linear Spectroscopy), via N. Carrara 1, 50019 Sesto Fiorentino (FI), Italy

M. Di Donato
 ICCOM-CNR, via Madonna del Piano 10, 50019 Sesto Fiorentino (FI), Italy

M. F. Hilbers, W. J. Buma
 Van't Hoff Institute for Molecular Sciences, University of Amsterdam, Science Park 904, 1098 XH Amsterdam, The Netherlands

W. J. Buma
 Institute for Molecules and Materials, FELIX Laboratory, Radboud University, Toernooiveld 7c, 6525 ED Nijmegen, The Netherlands
 Prof. Dr. W. Szymanski

Department of Radiology, Medical Imaging Center, University of Groningen, University Medical Centre Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

© 2024 The Authors. Angewandte Chemie International Edition published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

render them suitable for applications in biological systems, where UV light can trigger undesirable responses, including cell death.^[31,32] The prevalent strategy for designing visible-light-induced photoclick systems involves extending the π -system of established click reaction substrates to shift absorption toward the red spectral region.^[33–35] Despite its common use, this approach has drawbacks, including potential loss of photoclick reactivity and reduced solubility in aqueous solutions^[34] limiting its applicability in biological systems. An alternative approach relies on multi-photon absorption processes,^[36] thereby accessing excited states using photons with lower energy, and thus enabling activation of photoclick reaction systems with visible and NIR light. However, this method requires high-intensity pulsed laser light, limiting practicality due to equipment requirements and low efficiency.^[36] Upconversion processes,^[37,38] that rely on absorbing multiple quanta of NIR light, offer another approach. Despite their promise for biological applications, challenges persist, such as low up-conversion luminescence efficiency and the need for prolonged high-power laser irradiation.

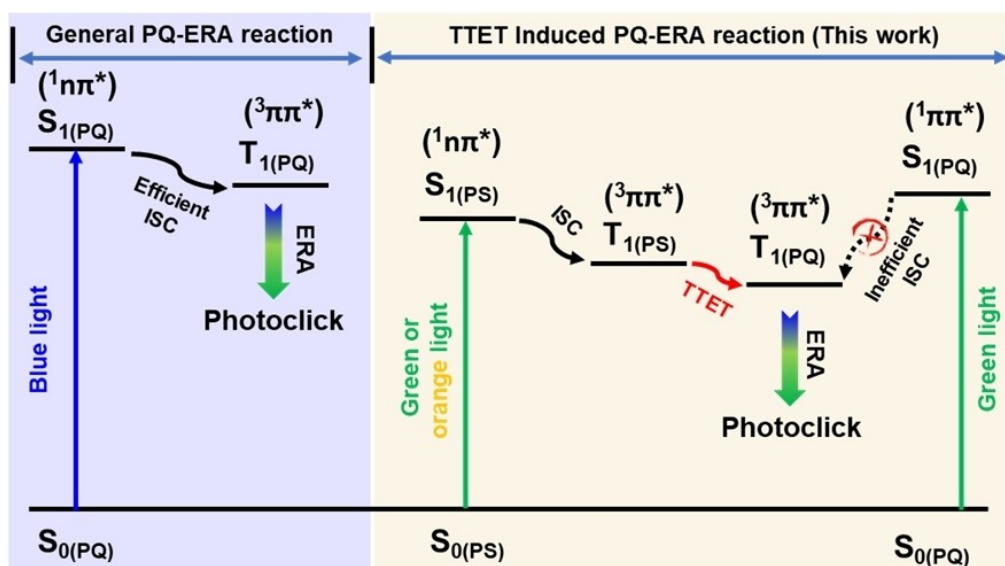
All the aforementioned strategies involve manipulation of the excitation to the singlet excited state by narrowing the $S_0 \rightarrow S_1$ gap in π -extended systems or involve multiphoton processes to excite the chromophore. However, in many photochemical transformations including photoisomerization, photocycloaddition and photoclick reactions, triplet excited states are key.^[1,6] For instance, irradiation of 9,10-phenanthrenequinones (**PQs**) with UV light populates the strongly allowed S_2 ($\pi\pi^*$) state which internally converts to the lowest excited S_1 ($n\pi^*$) singlet state.^[39–42] From this state an efficient intersystem crossing (ISC) occurs that populates the lowest excited T_1 ($\pi\pi^*$) triplet state from which a [4+2] photocycloaddition reaction with alkenes can occur (Scheme 1).^[43]

In other photoresponsive molecules, such as photo-switches including diarylethenes,^[44–46] azobenzenes,^[47–49] and molecular motors,^[50,51] it was shown that using molecular photosensitizers with favorable absorption properties (e.g. absorbing in the visible light range) can serve as an efficient strategy to construct all-visible light controlled photo-switches via triplet-triplet energy transfer (TTET).^[52–54] However, to the best of our knowledge, employing TTET to enable the use of visible/NIR light in photoclick reactions has not yet been explored.

Here, we introduce a reliable and versatile strategy to realize efficient, triplet-sensitized, visible light-induced photoclick reactions of **PQs** with electron-rich alkenes (**ERAs**). We report that photocycloaddition reactions can be promoted by catalytic amounts of triplet photosensitizers with green (530 nm) or orange (590 nm) light while retaining its fast reaction kinetics and high chemoselectivity. Furthermore, we established an orthogonal blue and green light-induced photoclick reaction system, in which the product distribution can be precisely controlled using light of different wavelengths.

Results and Discussion

In order to establish the proper combination of **PQ** compounds and triplet sensitizers (Structures in Table 1) we investigated the substituent effect on the **PQ** properties with a variety of functional groups. Towards this goal we extended the **PQ** core with substituted phenyl moieties. Starting with 3-bromophenanthrene-9,10-dione (**PQ-Br**) and phenyl boronic acids, the Suzuki–Miyaura cross-coupling reaction allows for straightforward synthesis. Unlike direct **PQ** core modifications, palladium-mediated coupling tolerates various substrates without altering the protocol, yield-



Scheme 1. Illustration of the mechanism for the general and intermolecular TTET-induced green to orange-light induced 9,10-phenanthrenequinone (**PQ**) - electron-rich alkenes (**ERA**) photoclick reaction with a triplet photosensitizer.

ing a **PQ-Ph-R** library with satisfying product formation (30%–60% yields; for details see Supporting Information). As **PQ-ERAs** photoclick reactions occur from the lowest excited triplet state (T_1 , $^3\pi\pi^*$) of **PQ**,^[43] we hypothesized that the reaction can also be achieved by sensitizing a **PQ** compound to the T_1 state by a triplet photosensitizer with a higher T_1 energy level through a TTET process (Scheme 1). Furthermore, selecting a photosensitizer with a relatively low-lying S_1 energy level would result in longer absorption wavelengths than that of the **PQ**, allowing lower-energy photons to be used for promoting the **PQ-ERA** photoclick via TTET process.

PQ derivatives generally exhibit S_1 and T_1 states at high energies (Scheme 1), which necessitates the use of UV or blue light to initiate the **PQ-ERA** photoclick reaction. At the same time, the high energy of T_1 makes it extremely difficult to find a suitable photosensitizer to achieve green or even red light-induced **PQ-ERA** photoclick reactions by a TTET process. To overcome this obstacle, we were in search of **PQ** derivatives that have a lower-lying T_1 energy state and could be paired up with a visible-light responsive photosensitizers, which have reported values for the T_1 - S_0 energy gap.^[55] To do so, we employed Density Functional Theory (DFT) and Time-Dependent Density Functional Theory (TD-DFT) to computationally screen for **PQs** with lower-lying triplet T_1 excited states, which would undergo TTET in the presence of suitable photosensitizer.

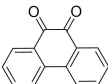
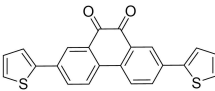
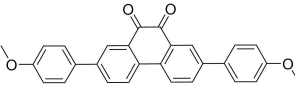
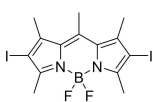
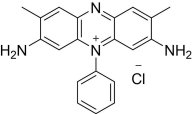
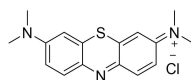
Previously, we have used TD-DFT calculations at the MN15/def2-TXVP level to model successfully various photochemical processes.^[56–61] In the present study, the same level (MN15/def2-TZVP) in combination with the Polarizable Continuum Model to take solvent effects into account has been used to calculate vertical and adiabatic excitation

energies of the relevant singlet and triplet states of **PQ** and substituted **PQs**. An overview of these results is given in Table 1. To further explore to what extent these results are dependent on the employed level and to allow for a further comparison with a recent study we performed on **PQ** and 3, 3'-substituted **PQs**, the same calculations have been performed at the M06-2X/6-31+G*/PCM(acetonitrile) level which previously showed the best quantitative agreement with the experimentally reported $^3\pi\pi^*$ - $^3n\pi^*$ energy gap in **PQ** Table S1 (see Supporting Information, section 5.2) shows that, at this level, very similar results are obtained with energies that are uniformly slightly higher than found in the MN15/def2-TZVP/PCM (acetonitrile) calculations.

As shown in Table 1, for unsubstituted **PQ** we found adiabatic excitation energies of S_1 ($n\pi^*$) and T_1 ($\pi\pi^*$) of 2.33 eV and 2.13 eV, respectively. Concluding from our previous study,^[42] photoexcitation of the strongly allowed S_2 ($\pi\pi^*$) state with an absorption maximum at 410 nm leads, after internal conversion to the S_1 ($n\pi^*$) state, to an highly efficient ISC that populates the T_1 ($\pi\pi^*$) state. Meanwhile, the adiabatic excitation energy of T_1 ($\pi\pi^*$) (2.13 eV, Table 1) is too high to populate this state from TTET common visible-light absorbing photosensitizers such as **DiIBodipy**, **Safranin O**, and **Methylene Blue** that have T_1 energies of 1.70 eV, 1.83 eV, and 1.39 eV, respectively.^[62–64]

Considering the MOs involved in the lower excited singlet and triplet states, we reasoned that 2-/2'-bifunctionalized derivatives of **PQ** might have more favorable excitation energies and therefore explored computationally for 2,2'-bis(dithiophene) (**PQ-2DiTP**) and 2,2'-bisdi-*para*-methoxyphenyl (**PQ-2DiOMe**). For both molecules the $^1n\pi^*$ state of the parent compound **PQ** is hardly affected (Table 1). Importantly, however, the $^1\pi\pi^*$ state is lowered by more

Table 1: A) Vertical and adiabatic (in parentheses) excitation energies (eV) of the $^1\pi\pi^*$ and $^1n\pi^*$ states and of the $^3\pi\pi^*$ and $^3n\pi^*$ states of **PQ**, **PQ-2DiTP** and **PQ-2DiOMe** obtained at the MN15/def2-TZVP/PCM(MeCN) level. Exp. column refers to vertical excitation energy (eV) with corresponding wavelength absorption maximum (nm) in parentheses. B) Triplet energies of photosensitizers **DiIBodipy**, **Safranin O**, and **Methylene Blue** are given in eV with absorption maximum λ_{\max} (nm) given in parentheses.

A)	Structure of PQs	$^1\pi\pi^*$	Exp.	$^1n\pi^*$	$^3\pi\pi^*$	$^3n\pi^*$
PQ		2.99 (2.61)	3.02 (410) ^(a)	2.38 (2.33)	2.57 (2.13)	2.31 (2.26)
PQ-2DiTP		2.34 (1.99)	2.40 (516) ^(a)	2.39 (2.34)	1.96 (1.57)	2.27 (2.22)
PQ-2DiOMe		2.32 (1.98)	2.42 (513) ^(a)	2.39 (2.35)	1.95 (1.57)	2.32 (2.27)
B)	DiIBodipy	Safranin O		Methylene Blue		
Structure of Photosensitizers						
$^3\pi\pi^*$	1.70 (525) ^(b)	1.83 (522) ^(b)	1.39 (650) ^(b)			

^(a) See Supporting Information Section 4.1 Figure S20, ^(b) See Supporting Information Section 4.1 Figure S21.

than 0.6 eV including these substitutions. Such a lowering has far-reaching consequences, as it leads in the substituted compounds to a state ordering in which the $^1\pi\pi^*$ is both vertically, as well as adiabatically, the lowest excited singlet state, while the $^1n\pi^*$ state is adiabatically almost 0.4 eV (9.2 kcal/mol) higher in energy. In preliminary experiments, it was found that excitation of both **PQ-2DiTP** and **PQ-2DiOMe** gave very low photoclick reaction rates with **ERAs** when compared to unsubstituted **PQ**. The main conclusion drawn from the calculations is that the state ordering of the $^1n\pi^*$ and $^1\pi\pi^*$ state is reversed upon substitution, which provides a clear-cut explanation for the low reaction rates since El-Sayed's rules^[65] indicate that ISC from the S_1 ($\pi\pi^*$) state of the substituted **PQs** will be significantly less efficient than ISC from the S_1 ($n\pi^*$) state of unsubstituted **PQ**.

From the data in Table 1 it can be concluded that **PQ-2DiTP** and **PQ-2DiOMe** have the appropriate excited state energies for a visible light-induced, TTET-mediated **PQ-ERA** photoclick reaction: (i) their absorption maxima are at a shorter wavelength than the maxima of commonly employed photosensitizers and (ii) the triplet state energies of these commonly employed photosensitizers are such that they are either above those of the **PQ-2DiTP** and **PQ-2DiOMe** (1.57 eV) in which case an efficient photoclick reaction should occur, or below 1.57 eV, in which case the photoclick reaction is expected to be very inefficient. In the current study, three photosensitizers with a high ISC efficiency and molar extinction coefficient to ensure efficient excitation and TTET were explored. **1,3,5,7,8-Pentamethyl-2,6-diiodo Bodipy (DiIBodipy)** and **Safranin O** were selected as candidates to establish the first TTET-based **PQ-ERAs** photoclick reaction, while **Methylene Blue** was chosen as a control compound that should not enable the TTET process, since its T_1 state energy is lower compared to that of **PQs**.

The 2-/2'-bifunctionalized **PQ** derivatives **PQ-2DiTP** and **PQ-2DiOMe** were synthesized by converting 2,7-diiodophenanthrene-9,10-dione (**PQ-2DiI**) with either *para*-methoxyphenyl- or thiophene-boronic acid using a Suzuki-Miyaura cross-coupling.^[66] Employing Pd(PPh₃)₄ as a catalyst in the synthesis of **PQ-2DiR** resulted in products obtained with satisfying yields (50 % and 55 %, for **PQ-2DiTP** and **PQ-2DiOMe** respectively, Scheme S1, Supporting Information). We furthermore used **PQ-3TP**, which we have demonstrated reacts very efficiently with *N*-Boc-2,3-dihydro-1*H*-pyrrole (**PY**) under blue light excitation (Figure 3A).^[43] The synthesis of the photosensitizers was carried out according to previously published methods (for detailed information, see Supporting Information, section 1).

The occurrence of ISC, although not very efficient, for the 2-substituted **PQ** molecules was confirmed by transient absorption spectroscopy measurements (for detailed information see SI, section 4.3, Figure S37–S39). As indicated, the 2-/2'-bifunctionalized **PQ** derivatives did not perform well in the direct **PQ-ERA** reaction under 535 nm LED irradiation, even with **PY** (10 eq), the **ERA** that showed the highest reactivity in our recent studies (Figure S22, for detailed information, see Supporting Information, section 4.2).^[41] This is in line with the computational

predictions (Table 1) that ISC for **PQ-2DiTP** should be much less reduced as its lowest excited singlet state is a $\pi\pi^*$ state and not an $n\pi^*$ state.

Next, we attempted the same photoclick experiment in the presence of a photosensitizer to test the TTET process. **PQ-2DiTP** (50 μ M, 1 eq), **PY** (500 μ M, 10 eq), and **DiIBodipy** (50 μ M, 1 eq) in degassed (N₂) MeCN was irradiated with a 535 nm LED, a wavelength at which **DiIBodipy** ($\lambda_{\text{max}} = 525$ nm) features a strong absorption (molar absorptivity $\epsilon = 3.3 \times 10^4$ M⁻¹cm⁻¹, Figure S21B, Supporting Information, section 4.2). To our delight, upon monitoring the reaction by UV/Vis absorption spectroscopy (Figure 1A,B), an increase in the absorption band at 390 nm was observed, which is indicative of the fast formation of **PQ-ERA** photoclick adducts, as also confirmed by UPLC-MS measurements. The 390 nm absorption reached a plateau at ~60 s ($k_{\text{obs}}^{535} = 0.043$ s⁻¹, Figure 1C). Notably, the second-order rate constant k_2 was determined to be 87.9 M⁻¹s⁻¹ (Figure 1D), which is ~750 times faster than our recently measured value for the general **PQ-vinyl ether** reaction (**PQ-VE**, 390 nm irradiation, $k_2 = 0.117$ M⁻¹s⁻¹).^[41] This system also works at low concentrations of **PY** (from 2 eq to 8 eq), exhibiting different k_{obs}^{535} respectively (Figure S23).

In parallel, we initiated a preliminary investigation into the biocompatibility and oxygen tolerance of this system, with detailed experimental outcomes presented in SI, section 4.2, Figures S24–26. Initially, we explored the impact of the degassing time (ranging from 5 sec to 2 min) on the rate of TTET-induced **PQ-ERA** photoclick reaction. As expected from the photochemical mechanism, we observed a reduction in the reaction rate that can be attributed to the presence of oxygen. Specifically, a two-phase kinetic behavior can be observed (Figures S24E and F), indicating a considerable delay in the formation of photoclick products. As the lag time increases with increasing amounts of oxygen, the observed delay is likely a result of the initial consumption of oxygen, leading to the generation of singlet oxygen (¹O₂) before the intended photoclick reaction occurs (for detailed information, see SI, section 4.2, Figure S24–S26; for some preliminary click reactions in the presence of water, see SI, section 4.2, Figure S27). The interaction of **PQ** and oxygen needs to be taken into account when employing the system presented here in different contexts due to the changed kinetics and ¹O₂ formation.

Using a high-power 530 nm LED (for detail information, see SI) as the light source for the **PQ-2DiTP/PY/DiIBodipy**, we determined the k_{obs}^{530} of the reaction to be 0.22 s⁻¹ (Figure S28). Furthermore, since the absorption spectrum of **DiIBodipy** tails to ~600 nm, we expected that the TTET-induced photoclick reaction would also be induced at these wavelengths. To explore this, we irradiated the **PQ-2DiTP/PY/DiIBodipy** mixture with orange (590 nm, for detailed information, see SI) light and confirmed the formation of the photoclick product ($k_{\text{obs}}^{590} = 0.036$ s⁻¹, Figure S26B,D). Importantly, direct red light (630 nm) irradiation did not result in any detectable photoclick reaction, as **DiIBodipy** absorbs virtually no light at this wavelength (Figure S29C,E).

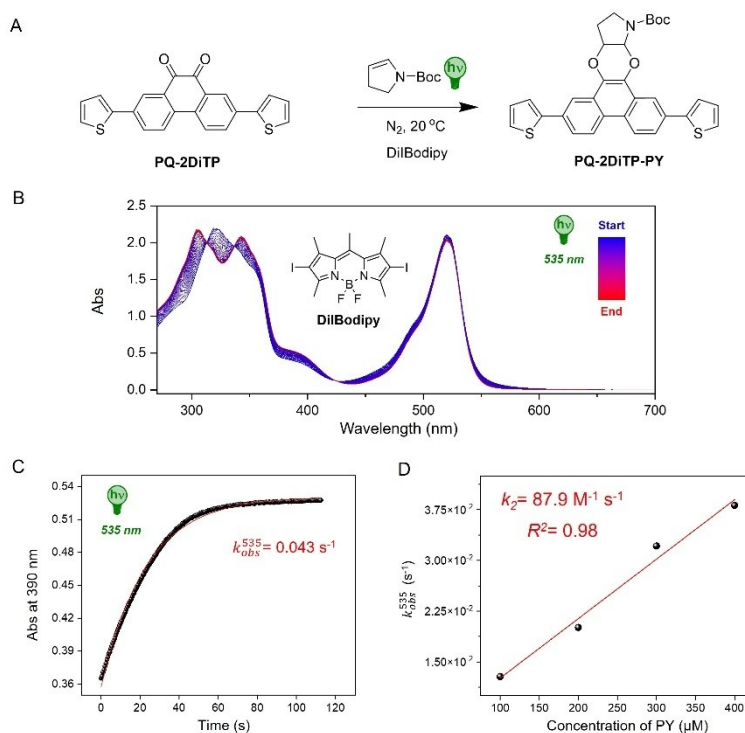


Figure 1. Kinetic analysis of TTET-initiated PQ-ERA photocycloadditions. **A)** Reaction scheme of **PQ-2DiTP** with **PY** in the presence of a photosensitizer, **B)** Time-resolved UV/Vis absorption spectra, and **C)** kinetic traces of **PQ-2DiTP/PY** reaction, 50 μM **PQ-2DiTP**, 50 μM photosensitizer (**DilBodipy**) with 500 μM of **PY** in 2.5 mL MeCN (N_2 atmosphere) was irradiated with a 535 nm LED at 20 °C. The consumption of **PQ-2DiTP** was monitored by UV/Vis absorption spectroscopy (1 cm cuvette, sample interval 1 sec). **PQ-2DiTP-PY** formation following equation: $y = (y_0 - a) e^{-k_{\text{obs}}^{535} t} + b$, to give k_{obs}^{535} . **D)** Plot of k_{obs}^{535} vs **PY** concentration. The second-order rate constant k_2 was determined to be $87.9 \text{ M}^{-1} \text{ s}^{-1}$.

Subsequently, the same TTET photoclick experiment of the **PQ-2DiTP/PY/DilBodipy** system was performed with lower photosensitizer (**DilBodipy**) loadings of 10% and 5%. At these catalytic loadings, we also observed fast photoclick reactions under green (530 nm) light irradiation ($k_{\text{obs}}^{530} = 0.078 \text{ s}^{-1}$ and 0.049 s^{-1} , respectively, Figure S30).

To further confirm the role of TTET in initiating the **PQ-ERA** photoclick reaction, control experiments were performed using **PQ-2DiTP** in combination with other photosensitizers with both matched and mismatched T_1 energy levels. First, a commercially available photosensitizer **Safranin O** with slightly higher T_1 energy levels of 1.83 eV (Table 1B) was irradiated with 535 nm light in the presence of **PQ-2DiTP/PY** in degassed MeCN. In line with our hypothesis, **Safranin O** exhibited similar TTET properties compared with **DilBodipy** in the **PQ-2DiTP/PY** system ($k_{\text{obs}}^{535} = 0.0069 \text{ s}^{-1}$, Figure S31, for detailed information see Supporting Information, section 4.2). Subsequently a control experiment was carried out with **Methylene Blue**, which has a much lower T_1 energy level (1.39 eV, Table 1B) compared to **PQ-2DiTP**. As expected, no detectable photoclick reaction took place when the **PQ-2DiTP/PY/Methylene Blue** system was excited at 630 nm (Figure S32). Altogether, these experiments provide strong evidence that our novel designed bathochromically shifted photoclick reaction system is indeed initiated by a TTET process that only takes place with well-matched T_1 energy levels.

To further verify that the photoclick product formation can indeed be traced back to a triplet energy transfer between **DilBodipy** and **PQ-2DiTP**, we studied the process using transient absorption spectroscopy at the nanosecond time scale. We monitored the change in absorbance (at 520 nm) of **DilBodipy** upon excitation at 520 nm with a nanosecond pulsed laser (Figure S37–S45, Supporting Information, section 4.4) and recorded the decay times of different samples. It was found that **DilBodipy** irradiated at 520 nm under deaerated conditions was relaxing back to the ground state in 17.9 μs (Figure S40B, Supporting Information, section 4.4). Next, the experiments were performed in the presence of varying amounts of **PQ-2DiTP** (1 to 5 eq) under a nitrogen atmosphere, showing that after the gradual addition of **PQ-2DiTP** in the dark, the triplet state lifetime decreased dramatically from 17.9 μs to 3.3 μs (Figure S37–S45, Supporting Information, section 4.4) pointing to an efficient triplet energy transfer from **DilBodipy** to **PQ-2DiTP**. The TTET rate constant (k_{TTET}) was calculated to be $4.55 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ (Figure S46), which compares favorably with literature k_{TTET} values (approximately $10^9 \text{ M}^{-1} \text{ s}^{-1}$).^[67,68]

With **PQ-2DiTP** showing promising reactivity towards **PY** in the presence of a suitable triplet sensitizer, we explored whether other synthetically accessible, **PQ** derivatives substituted at the 2-position would behave similarly. **PQ-2DiOMe** was calculated by TD-DFT to have a T_1 state energy of 1.57 eV (Table 1, ${}^3\pi\pi^*$), which also matches well with the **DilBodipy** and **Safranin O** T_1 state energies, but is

still higher than the T_1 energy of **Methylene Blue**. The photoclick reaction of **PQ-2DiOMe** with **PY** was performed in the presence of these three photosensitizers, and similar results were observed with **PQ-2DiOMe** as with **PQ-2DiTP**. Both **DiIBodipy** and **Safranin O** exhibited favorable TTET properties with k_{obs}^{530} values of 0.14 s^{-1} and 0.0274 s^{-1} , respectively (Figure 2). Beyond **PQ-2DiOMe**, we also tested a series of **PQ** derivatives and **ERAs**. To our delight, these **PQs** and **ERAs** can achieve TTET induced photoclick reaction in the presence of **DiIBodipy** (for detailed information, see SI, section 4.2, Figure S33–35). **Methylene Blue**, on the other hand, induced as expected no detectable photoclick reaction. These data suggest that our TTET strategy can indeed be applied as a general method for bathochromic shifting of the activation wavelength of **PQ-ERA** photoclick systems. Altogether, the results presented herein provide a clear picture of the complete process of the green-light-induced, TTET-initiated **PQ-ERA** reaction (Scheme 1). First, **DiIBodipy** is excited by green light ($\lambda = 535\text{ nm}$) and relaxes to the excited triplet state $^3[\text{DiIBodipy}^*]$ by ISC from the excited singlet state $^1[\text{DiIBodipy}^*]$.

Energy transfer takes place from $^3[\text{DiIBodipy}^*]$ to $^3[\text{PQ-2DiTP}^*]$ through an intermolecular TTET process, enabling the [4+2] photocycloaddition between **PQ-2DiTP** and **PY**, and yielding **PQ-2DiTP-PY**.

Recently, we have identified an intriguing opposite reactivity pattern for **PQ** compounds substituted at the 2- and 3-positions.^[41] Specifically, it was noted that **PQ-3TP** shows a high reactivity upon 420 nm light irradiation ($k_{obs}^{420} = 0.17\text{ s}^{-1}$) towards **PY**, whereas almost no reactivity was observed at 530 nm irradiation ($k_{obs}^{530} = 0.0012\text{ s}^{-1}$, Figure S36). The **PQ-2DiTP-DiIBodipy** system, in contrast, shows the opposite trend, that is, a high reactivity using 530 nm ($k_{obs}^{530} = 0.22\text{ s}^{-1}$). To exploit this effect, we combined these two individual **PQ-ERA** reactions, which are activated at two different wavelengths of light and proceed via two distinct pathways, as a starting point to establish a novel type of orthogonally reactive system. Common click reactions are known to be orthogonal, i.e., selective, in the presence of other functional groups and between different types of click reactions.^[69,70] We recently demonstrated that two individual **PQ-ERA** type of photoclick reactions can

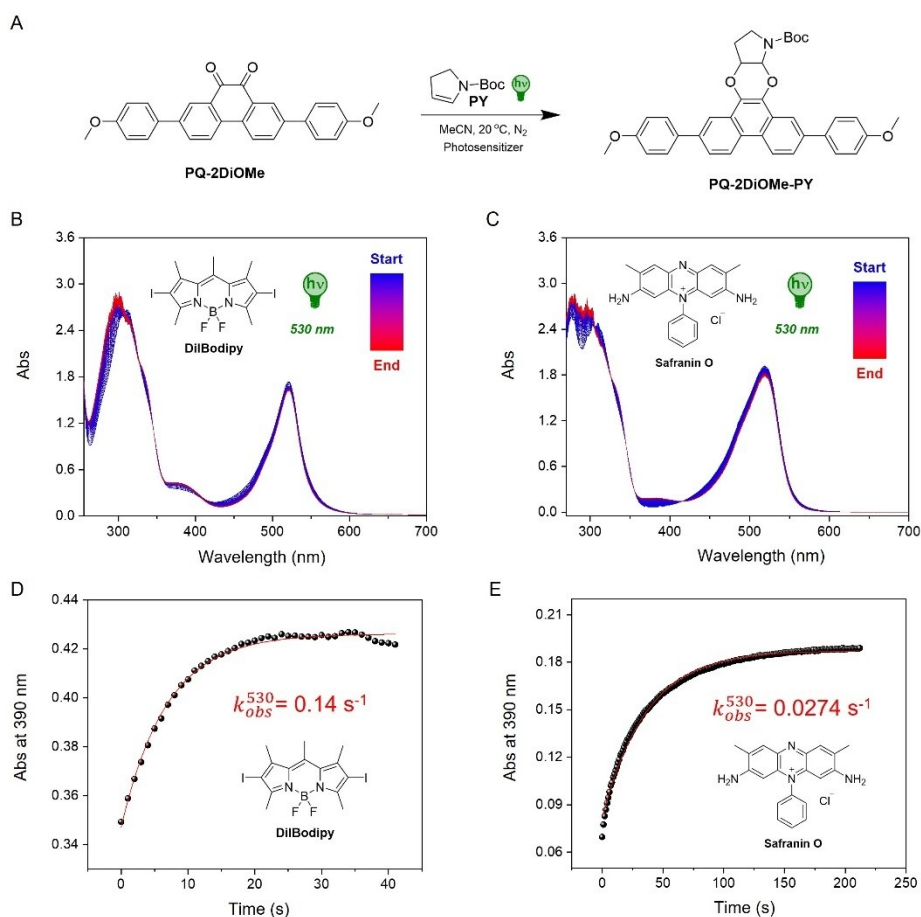


Figure 2. Kinetic analysis of TTET-initiated **PQ-2DiOMe-PY** photocycloadditions. **A)** Reaction scheme of **PQ-2DiOMe** with **PY** in the presence of a photosensitizer, **B,C)** Time-resolved UV/Vis absorption spectra of **PQ-2DiOMe/PY** reaction upon 530 nm LED irradiation, **D,E)** Kinetic traces of the photocycloaddition between $50\ \mu\text{M}$ **PQ-2DiOMe**, $500\ \mu\text{M}$ photosensitizer (**DiIBodipy** and **Safranin O**, respectively) with $500\ \mu\text{M}$ of **PY** in $2.5\ \text{mL}$ MeCN (N_2 atmosphere) irradiated with a 530 nm LED at $20\ ^\circ\text{C}$. The consumption of **PQ-2DiOMe** was monitored by UV/Vis absorption spectroscopy (1 cm cuvette, sample interval 1 sec), **PQ-2DiOMe-PY** formation following the equation: $y = (y_0 - a) e^{-k_{obs}^{530} \cdot t} + a$, to give k_{obs}^{530} .

take place in one pot under irradiation with the one single wavelength of light by choosing matching substrate couples.^[41] However, exclusively visible light to achieve orthogonality in the same class of photoclick reactions has to the best of our knowledge not been reported before. Therefore, we set out to establish a reaction system in which two different reaction pathways can be accessed in a **PQ-ERA** system using two different wavelengths of light in the low-energy regime, namely one proceeding via direct excitation of **PQ** and one via TTET.

To establish the orthogonal behavior, a batch reaction system was designed employing different wavelengths of light in a defined sequence (see Figure 3A). For this, **PQ-2DiTP** (50 μM , 1 eq), **PQ-3TP** (1 eq), **PY** (10 eq), and **DiIBodipy** (0.5 eq) were combined in MeCN (N_2 atmosphere) and irradiated with 530 nm (green light) and 420 nm (blue light) LEDs, respectively, at a fixed distance for different time intervals (0 sec, 10 sec, 20 sec, 30 sec, 40 sec, 50 sec, and 60 sec, for detailed information see SI, section 1 and 4.5, Figure S47–S59). The samples were then analyzed by HPLC to follow the conversion over time. Under green light irradiation, **PQ-2DiTP** was consumed quickly (Figure 3B, blue line, 50 μM to 10 μM), while increasing amounts of the desired product, **PQ-2DiTP-PY**, was observed (Figure 3B, red line, 0 μM to 40 μM) within a period of 60 sec irradiation. Meanwhile, the concentration of **PQ-3TP** remained mostly unaffected and only minor

amounts of the undesired photoclick product, **PQ-3TP-PY**, was observed (less than 7 μM). Upon treatment with blue light, we found the opposite trend (Figure 3C): now **PQ-3TP** was consumed quickly, while the amount of **PQ-2DiTP** decreased only slightly.

These experiments show that the TTET system presented here has distinctive advantages compared to other orthogonal photoclick systems. We were able to achieve unprecedented selective transformations in the same photoclick reaction class using only visible light, combined with ultrafast reaction rates. The transformation can reach full conversion with both blue and green light stimuli within 60 sec (2.5 mL of a 50 μM solution), surpassing previous reports.^[69,70] Moreover, the sole reliance on visible light, in contrast to UV-dependent methods, alleviates concerns about compound degradation and promotes more efficient energy transfer. We foresee a broad applicability of our method for precise material construction, photo-crosslinking, modifications of biological macromolecules in the future.

Conclusion

In summary, we report here for the first time the use of TTET process as a promising alternative for achieving red-shifted photoclick activation by leveraging the low-lying

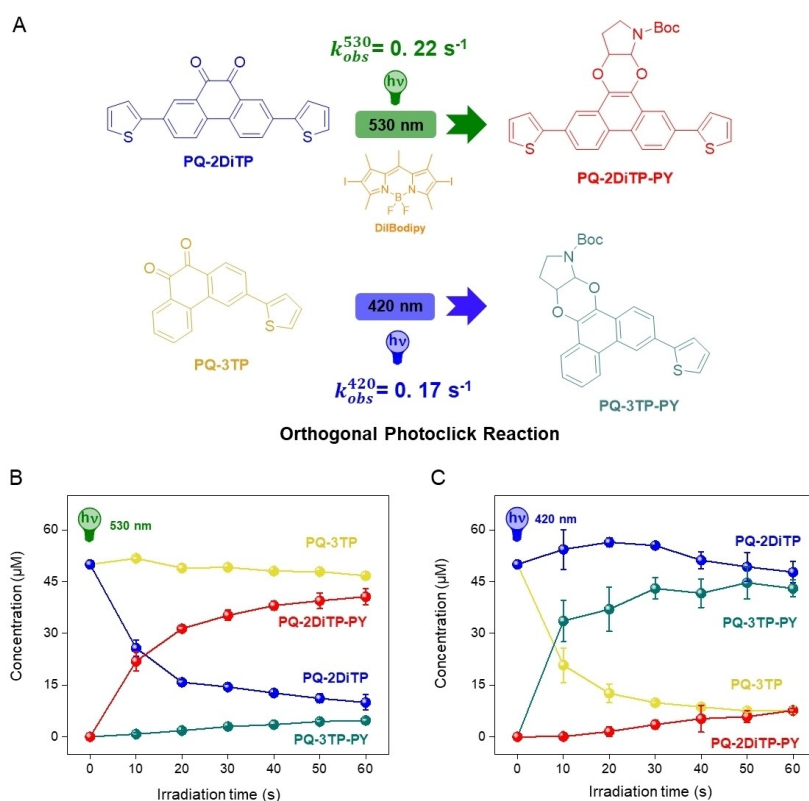


Figure 3. Overview of the orthogonal photoclick reaction system. **A)** Comparison of the first-order rate constants (k_{obs} , s^{-1}) for **PQ-ERA** photocycloaddition. **B,C)** HPLC quantitative analysis of **PQ-2DiTP**, **PQ-3TP**, **PY**, and **DiIBodipy** orthogonal photoclick reaction with 530 nm and 420 nm LED irradiation, respectively.

excited triplet state, which offers distinct advantages when compared with π system extension, multi-photon absorption processes, and UCNP approach. This approach proves effective in systems relying on the triplet state, eliminating the need for intricate structural modifications. Importantly, the TTET system operates efficiently without the need of these expensive instruments (such as pulsed lasers), showcasing its practical utility in diverse applications. The fast and efficient (k_2 up to $87.9 \text{ M}^{-1} \text{ s}^{-1}$) TTET-based **PQ-ERA** photoclick reaction can be performed in the presence of catalytic amounts (5 mol %) of the photosensitizer. An in-depth computational analysis supported by transient spectroscopy allowed for a full picture of the processes involved and provided strong support for the interpretation of our experimental results. By defining the best combination of reactants, a dual wavelength (blue and green) visible-light-induced orthogonal photoclick reaction system was established that can selectively generate the desired products in the presence of competing reactions. This wavelength-orthogonality within the same type of click reaction is in striking contrast to the reactivity of classical click reactions. However, there are still challenges remaining, including oxygen sensitivity and limited water solubility of **PQ** compounds. To enhance water solubility, we are currently exploring the use of water-soluble groups on **PQs**, **ERAs**, and photosensitizers. Oxygen sensitivity can be likely reduced or even circumvented by incorporating triplet-sensitized photoclick systems into confined environments like polymer films, micelles, or nano-channels.^[49] Exploring innovative assemblies within such confined spaces is crucial for unlocking the full potential of our strategy. We envision that this novel, ultrafast, triplet sensitized **PQ-ERA** photoclick reaction will provide a solid basis and highly effective methodology to be used in a wide range of applications, such as materials surface photo-patterning and photochemical crosslinking. This involves incorporating functional groups essential for the selected **PQ-ERA** photoclick reaction into molecules designated for crosslinking. Polymers equipped with pendant **PQ** groups and photosensitizers can engage in TTET-induced **PQ-ERA** photoclick reactions with another polymer featuring **ERAs** modified as its side chain. By exposing these materials to the specific wavelength necessary for the photoclick reaction, light-triggered click chemistry is initiated, leading to the formation of covalent bonds between functional groups resulting in material crosslinking. In polymers, this process creates a network structure, thereby enhancing mechanical properties.

Acknowledgements

We thank Renze Sneep (University of Groningen) for his help with the HRMS measurements. We gratefully acknowledge the generous financial support from the Horizon 2020 Framework Program (ERC Advanced Investigator Grant No. 694345 to BLF), the Ministry of Education, Culture and Science of the Netherlands (Gravitation Program No. 024.001.035 to BLF), and the European Molecular Biology

Organization (EMBO LTF-232-2020 Postdoctoral Fellowship to GA). This research was supported by NWO domain TTW and Stryker European Operations Ltd. MDD gratefully acknowledge support from the European Union's Horizon 2020 research and innovation program under grant agreement n. 871124 Laserlab-Europe.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Triplet-Triplet Energy Transfer • Photoclick • Photochemistry • Phenanthrenequinone • Orthogonality

- [1] M. Montalti, A. Credi, L. Prodi, M. T. Gandolfi, *Handbook of Photochemistry*, CRC Press 2006.
- [2] C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064.
- [3] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; *Angew. Chem.* **2002**, *114*, 2708–2711.
- [4] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; *Angew. Chem.* **2001**, *113*, 2056–2075.
- [5] N. J. Agard, J. A. Prescher, C. R. Bertozzi, *J. Am. Chem. Soc.* **2004**, *126*, 15046–15047.
- [6] B. D. Fairbanks, L. J. Macdougall, S. Mavila, J. Sinha, B. E. Kirkpatrick, K. S. Anseth, C. N. Bowman, *Chem. Rev.* **2021**, *121*, 6915–6990.
- [7] G. S. Kumar, Q. Lin, *Chem. Rev.* **2021**, *121*, 6991–7031.
- [8] S. Arumugam, S. V. Orski, J. Locklin, V. V. Popik, *J. Am. Chem. Soc.* **2012**, *134*, 179–182.
- [9] S. Arumugam, V. V. Popik, *J. Am. Chem. Soc.* **2012**, *134*, 8408–8411.
- [10] C. Xie, W. Sun, H. Lu, A. Kretzschmann, J. Liu, M. Wagner, H.-J. Butt, X. Deng, S. Wu, *Nat. Commun.* **2018**, *9*, 3842.
- [11] E. Blasco, M. Wegener, C. Barner-Kowollik, *Adv. Mater.* **2017**, *29*, 1604005.
- [12] D. Fong, A. Lang, K. Li, A. Adronov, *Macromolecules* **2020**, *53*, 1760–1766.
- [13] V. X. Truong, J. Bachmann, A. Unterreiner, J. P. Blinco, C. Barner-Kowollik, *Angew. Chem. Int. Ed.* **2022**, *61*, e202113076; *Angew. Chem.* **2022**, *134*, e2021130.
- [14] K. Lang, L. Davis, S. Wallace, M. Mahesh, D. J. Cox, M. L. Blackman, J. M. Fox, J. W. Chin, *J. Am. Chem. Soc.* **2012**, *134*, 10317–10320.
- [15] P. An, T. M. Lewandowski, T. G. Erbay, P. Liu, Q. Lin, *J. Am. Chem. Soc.* **2018**, *140*, 4860–4868.
- [16] C. Wang, H. Zhang, T. Zhang, X. Zou, H. Wang, J. E. Rosenberger, R. Vannam, W. S. Trout, J. B. Grimm, L. D. Lavis, C. Thorpe, X. Jia, Z. Li, J. M. Fox, *J. Am. Chem. Soc.* **2021**, *143*, 10793–10803.
- [17] G. S. Kumar, S. Racioppi, E. Zurek, Q. Lin, *J. Am. Chem. Soc.* **2022**, *144*, 57–62.
- [18] W. Song, Y. Wang, J. Qu, Q. Lin, *J. Am. Chem. Soc.* **2008**, *130*, 9654–9655.

- [19] Z. Li, L. Qian, L. Li, J. C. Bernhammer, H. V. Huynh, J. S. Lee, S. Q. Yao, *Angew. Chem. Int. Ed.* **2016**, *55*, 2002–2006; *Angew. Chem.* **2016**, *128*, 2042–2046.
- [20] C. E. Hoyle, C. N. Bowman, *Angew. Chem. Int. Ed.* **2010**, *49*, 1540–1573; *Angew. Chem.* **2010**, *122*, 1584–1617.
- [21] A. R. Davis, J. A. Maegerlein, K. R. Carter, *J. Am. Chem. Soc.* **2011**, *133*, 20546–20551.
- [22] A. A. Poloukhine, N. E. Mbu, M. A. Wolfert, G.-J. Boons, V. V. Popik, *J. Am. Chem. Soc.* **2009**, *131*, 15769–15776.
- [23] L. Zhang, X. Zhang, Z. Yao, S. Jiang, J. Deng, B. Li, Z. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 7390–7394.
- [24] R. K. V. Lim, Q. Lin, *Chem. Commun.* **2010**, *46*, 7993–7995.
- [25] T. Pauloehr, G. Delaitre, M. Bruns, M. Meißler, H. G. Börner, M. Bastmeyer, C. Barner-Kowollik, *Angew. Chem. Int. Ed.* **2012**, *51*, 9181–9184; *Angew. Chem.* **2012**, *124*, 9316–9319.
- [26] D. Bléger, S. Hecht, *Angew. Chem. Int. Ed.* **2015**, *54*, 11338–11349; *Angew. Chem.* **2015**, *127*, 11494–11506.
- [27] J. Moreno, M. Gerecke, L. Grubert, S. A. Kovalenko, S. Hecht, *Angew. Chem. Int. Ed.* **2016**, *55*, 1544–1547; *Angew. Chem.* **2016**, *128*, 1569–1573.
- [28] K. Klaue, W. Han, P. Liesfeld, F. Berger, Y. Garmshausen, S. Hecht, *J. Am. Chem. Soc.* **2020**, *142*, 11857–11864.
- [29] K. Kuntze, J. Viljakka, M. Virkki, C. Y. Huang, S. Hecht, A. Priimagi, *Chem. Sci.* **2023**, *14*, 2482–2488.
- [30] M. Wegener, M. J. Hansen, A. J. M. Driessen, W. Szymanski, B. L. Feringa, *J. Am. Chem. Soc.* **2017**, *139*, 17979–17986.
- [31] R. Weinstain, T. Slanina, D. Kand, P. Klán, *Chem. Rev.* **2020**, *120*, 13135–13272.
- [32] W. Szymański, J. M. Beierle, H. A. V. Kistemaker, W. A. Velema, B. L. Feringa, *Chem. Rev.* **2013**, *113*, 6114–6178.
- [33] P. An, Z. Yu, Q. Lin, *Chem. Commun.* **2013**, *49*, 9920–9922.
- [34] P. Lederhose, K. N. R. Wüst, C. Barner-Kowollik, J. P. Blinco, *Chem. Commun.* **2016**, *52*, 5928–5931.
- [35] D. Kodura, L. L. Rodrigues, S. L. Walden, A. S. Goldmann, H. Frisch, C. Barner-Kowollik, *J. Am. Chem. Soc.* **2022**, *144*, 6343–6348.
- [36] Z. Yu, T. Y. Ohulchanskyy, P. An, P. N. Prasad, Q. Lin, *J. Am. Chem. Soc.* **2013**, *135*, 16766–16769.
- [37] P. Lederhose, Z. Chen, R. Müller, J. P. Blinco, S. Wu, C. Barner-Kowollik, *Angew. Chem. Int. Ed.* **2016**, *55*, 12195–12199; *Angew. Chem.* **2016**, *128*, 12382–12386.
- [38] Y. Wu, J. Zheng, D. Xing, T. Zhang, *Nanoscale* **2020**, *12*, 10361–10368.
- [39] Y. L. Chow, T. C. Joseph, *Chem. Commun.* **1968**, 604.
- [40] L. Wang, Y.-C. Huang, Y. Liu, H.-K. Fun, Y. Zhang, J.-H. Xu, *J. Org. Chem.* **2010**, *75*, 7757–7768.
- [41] Y. Fu, N. A. Simeth, R. Toyoda, R. Brilmayer, W. Szymanski, B. L. Feringa, *Angew. Chem. Int. Ed.* **2023**, *62*, e202218203; *Angew. Chem.* **2023**, *135*, e202218203.
- [42] Y. Fu, H. Helbert, N. A. Simeth, S. Crespi, G. B. Spoelstra, J. M. van Dijk, M. van Oosten, L. R. Nazario, D. van der Born, G. Luurtsema, W. Szymanski, P. H. Elsinga, B. L. Feringa, *J. Am. Chem. Soc.* **2021**, *143*, 10041–10047.
- [43] Y. Fu, G. Alachouzos, N. A. Simeth, M. Di Donato, M. F. Hilbers, W. J. Buma, W. Szymanski, B. L. Feringa, *Chem. Sci.* **2023**, *14*, 7465–7474.
- [44] S. Fredrich, R. Göstl, M. Herder, L. Grubert, S. Hecht, *Angew. Chem. Int. Ed.* **2016**, *55*, 1208–1212; *Angew. Chem.* **2016**, *128*, 1226–1230.
- [45] Z. Zhang, J. Zhang, B. Wu, X. Li, Y. Chen, J. Huang, L. Zhu, H. Tian, *Adv. Opt. Mater.* **2018**, *6*, 1700847.
- [46] Z. Zhang, W. Wang, P. Jin, J. Xue, L. Sun, J. Huang, J. Zhang, H. Tian, *Nat. Commun.* **2019**, *10*, 4232.
- [47] P. Bortolus, S. Monti, *J. Phys. Chem.* **1979**, *83*, 648–652.
- [48] J. Isokuoritti, K. Kuntze, M. Virkki, Z. Ahmed, E. Vuorimaa-Laukkanen, M. A. Filatov, A. Turshatov, T. Laaksonen, A. Priimagi, N. A. Durandin, *Chem. Sci.* **2021**, *12*, 7504–7509.
- [49] J. Gemen, J. R. Church, T. P. Ruoko, N. Durandin, M. J. Bialek, M. Weißenfels, M. Feller, M. Kazes, M. Odaybat, V. A. Borin, R. Kalepu, Y. Diskin-Posner, D. Oron, M. J. Fuchter, A. Priimagi, I. Schapiro, R. Klajn, *Science* **2023**, *381*, 1357–1363.
- [50] A. Cnossen, L. Hou, M. M. Pollard, P. V. Wesenhagen, W. R. Browne, B. L. Feringa, *J. Am. Chem. Soc.* **2012**, *134*, 17613–17619.
- [51] W. Danowski, F. Castiglioni, A. S. Sardjan, S. Krause, L. Pfeifer, D. Roke, A. Comotti, W. R. Browne, B. L. Feringa, *J. Am. Chem. Soc.* **2020**, *142*, 9048–9056.
- [52] L. Hou, R. Ringström, A. B. Maurer, M. Abrahamsson, J. Andréasson, B. Albinsson, *J. Am. Chem. Soc.* **2022**, *144*, 17758–17762.
- [53] L. Hou, W. Larsson, S. Hecht, J. Andréasson, B. Albinsson, *J. Mater. Chem. C* **2022**, *10*, 15833–15842.
- [54] W. Zhao, T. S. Cheung, N. Jiang, W. Huang, J. W. Y. Lam, X. Zhang, Z. He, B. Z. Tang, *Nat. Commun.* **2019**, *10*, 1595.
- [55] J. Zhao, W. Wu, J. Sun, S. Guo, *Chem. Soc. Rev.* **2013**, *42*, 5323–5351.
- [56] A. M. Schulte, G. Alachouzos, W. Szymański, B. L. Feringa, *J. Am. Chem. Soc.* **2022**, *144*, 12421–12430.
- [57] G. Alachouzos, A. M. Schulte, A. Mondal, W. Szymanski, B. L. Feringa, *Angew. Chem. Int. Ed.* **2022**, *61*, e202201308; *Angew. Chem.* **2022**, *134*, e202201308.
- [58] S. van Vliet, G. Alachouzos, F. de Vries, L. Pfeifer, B. L. Feringa, *Chem. Sci.* **2022**, *13*, 9713–9718.
- [59] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.
- [60] J. Zheng, X. Xu, D. G. Truhlar, *Theor. Chem. Acc.* **2011**, *128*, 295–305.
- [61] H. S. Yu, X. He, S. L. Li, D. G. Truhlar, *Chem. Sci.* **2016**, *7*, 5032–5051.
- [62] B. Köksoy, E. N. Kaya, F. Hacivelioglu, S. Yeşilot, M. Durmuş, *Dyes Pigment.* **2017**, *140*, 384–391.
- [63] A. Ibrahim, B. El Fouhaili, A. C. Yong, C. Ley, X. Allonas, C. Carré, *Can. J. Chem.* **2015**, *93*, 1345–1353.
- [64] R. I. Patel, A. Sharma, S. Sharma, A. Sharma, *Org. Chem. Front.* **2021**, *8*, 1694–1718.
- [65] S. K. Lower, M. A. El-Sayed, *Chem. Rev.* **1966**, *66*, 199–241.
- [66] N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437–3440.
- [67] W. Lv, Y. Li, F. Li, X. Lan, Y. Zhang, L. Du, Q. Zhao, D. L. Phillips, W. Wang, *J. Am. Chem. Soc.* **2019**, *141*, 17482–17486.
- [68] X. Cui, J. Zhao, Y. Zhou, J. Ma, Y. Zhao, *J. Am. Chem. Soc.* **2014**, *136*, 9256–9259.
- [69] P. W. Kamm, L. L. Rodrigues, S. L. Walden, J. P. Blinco, A.-N. Unterreiner, C. Barner-Kowollik, *Chem. Sci.* **2022**, *13*, 531–535.
- [70] I. M. Irshadeen, S. L. Walden, M. Wegener, V. X. Truong, H. Frisch, J. P. Blinco, C. Barner-Kowollik, *J. Am. Chem. Soc.* **2021**, *143*, 21113–21126.

Manuscript received: December 14, 2023

Accepted manuscript online: March 21, 2024

Version of record online: April 12, 2024