Catalysis in Click Chemistry Reactions Controlled by Cavity Quantum Vacuum Fluctuations: The Case of endo/exo Diels-Alder Reaction

Fabijan Pavošević,1,* Robert L. Smith,1,2 and Angel Rubio1,3,4,†

1Center for Computational Quantum Physics, Flatiron Institute, 162 5th Ave., New York, 10010 NY, USA
2Department of Chemistry, Virginia Tech, Blacksburg, Virginia 24061, U.S.A.
3Max Planck Institute for the Structure and Dynamics of Matter and Center for Free-Electron Laser Science & Department of Physics, Luruper Chaussee 149, 22761 Hamburg, Germany
4Nano-Bio Spectroscopy Group and European Theoretical Spectroscopy Facility (ETSF), Universidad del País Vasco (UPV/EHU), Av. Tolosa 72, 20018 San Sebastian, Spain

Achieving control over chemical reaction’s rate and stereoselectivity realizes one of the Holy Grails in chemistry that can revolutionize chemical and pharmaceutical industries. Strong light-matter interaction in optical or nanoplasmonic cavities might provide the knob to reach such control. In this work, we demonstrate the catalytic and selectivity control of an optical cavity for two selected Diels-Alder cycloaddition reactions using the quantum electrodynamics coupled cluster (QED-CC) method. Herein, we find that by changing the molecular orientation with respect to the polarization of the cavity mode the reactions can be significantly inhibited or selectively enhanced to produce major endo or exo products on demand. This work highlights the potential of utilizing quantum vacuum fluctuations of an optical cavity to modulate the rate of Diels-Alder cycloaddition reactions and to achieve stereoselectivity in a practical and non-intrusive way. We expect that the present findings will be applicable to a larger set of relevant click chemical reactions under strong light-matter coupling conditions.

I. INTRODUCTION

Diels-Alder cycloaddition reactions [1], in which a conjugated diene and an alkene (dienophile) form a cyclohexene derivative, are one of the most iconic chemical reactions used to form carbon-carbon bonds. Due to their unique versatility, Diels–Alder cycloaddition reactions have played an essential role in virtually all fields of synthetic chemistry, such as click chemistry [2], total synthesis of certain natural products [3], biosynthesis [4], and in the synthesis of thermoplastic polymers [5]. In addition to their unrivaled synthetic significance, they also played a crucial role in the development of the famous Woodward–Hoffmann rules [6] for chemical reactivity.

A key feature of the Diels–Alder cycloaddition reaction is the ability to form two distinct endo and exo diastereomeric products when the dienophile is a substituted alkene. The endo product results from a transition state structure in which a dienophile’s substituent lies above the diene, whereas the exo product results from a transition state structure in which a dienophile’s substituent is oriented away from it (see Fig. 1A). Due to the fundamental and technological relevance of the Diels–Alder cycloaddition reactions, several techniques have been proposed to control the rate and endo/exo selectivity, such as antibody [7], enzymatic [8], or electric field [9] control.

Another path to control chemical reactions by using strong light-matter coupled hybrid states (polaritonic states) [10] has been opened recently [11–26]. Strongly coupled polaritonic states can be created by either quantum fluctuations or by external pumping in optical or nanoplasmonic cavities [27]. Inside the cavity, molecular polaritons are formed by direct coupling of the molecular complex to the cavity quantum fluctuations. Because the properties of molecular polaritons can be modulated by the strength of the light matter coupling, this technique offers a non-intrusive way to catalyze [15], inhibit [12], or even change the reaction path [14] of a given chemical reaction. Most of the experimental works for controlling chemical reactions are done in the strongly coupled vibro-polariton regime [12–14, 16, 17], however in this work our focus is on the electronic polariton effects on the chemistry as done for exciton-polaritons in driven 2D materials in cavities [28, 29]. Naturally, in order to understand and explain these experiments that operate in the exciton-polariton regime, ab initio methods in which electrons and photons are treated quantum mechanically on equal footing are required. Recent theoretical advances in which electronic structure methods and quantum electrodynamics are combined [20, 30–34] have provided a significant insight into chemical reactions inside an optical cavity where selected reactions are either enhanced, inhibited, or steered [20, 24, 35–38], however a single chemical process in which one either enhances, inhibits, or steers a chemical reaction has yet to be demonstrated.

In this work, we demonstrate that the quantum vacuum fluctuations of a cavity can be used as a viable tool for selective control of catalysis. To achieve that goal, we extend the recently developed quantum electrodynamics coupled cluster (QED-CC) method [30–33] to investigate the effect of an optical cavity on the reaction rate and endo/exo stereoselectivity of the Diels–Alder cycloaddition reaction. The two target Diels–Alder cycloaddition

* fpavosevic@gmail.com
† angel.rubio@mpsd.mpg.de
FIG. 1. (A) The Diels–Alder cycloaddition reaction can form two different *endo* and *exo* diastereomers. These two distinct products are formed in two different paths determined by the relative orientation of the dienophile molecule. (B) Reactants for the Diels–Alder cycloaddition reactions considered in this work: cyclopentadiene (CPD), acrylonitrile (AN), and methylacrylonitrile (MeAN). (C) Schematic summary of the findings from this work. For the Diels–Alder cycloaddition between CPD and AN at room temperature, the classical reaction gives a 54:46 *endo*/*exo* product ratio, whereas the same reaction in a cavity gives 99% of *endo* or *exo* product, depending on the light mode polarization direction.

reactions considered herein are reactions of cyclopentadiene (CPD) with acrylonitrile (AN) and methylacrylonitrile (MeAN) (see Fig. 1B). As it will become clear in the remainder of this article, if the cavity mode is polarized along the forming carbon-carbon bond (corresponding to the molecular *x*-axis in Fig. 2), the cavity significantly inhibits the reaction rate, whereas the polarization of the cavity modes in the other two molecular directions catalyzes and steers the reactions to either give a major *endo* or *exo* product (Fig. 1C). The observed changes in the reactivity are due to the formation of a new light matter hybrid ground state via the quantum vacuum fluctuations. We expect our findings will further push the field of experimental and theoretical polaritonic chemistry.

II. THEORY

We begin by briefly describing the basics of the employed theoretical formalism (see Supplemental Information for more details). The interaction between quantized light and a single molecule or collection of molecules confined to a cavity with *N* cavity modes can be formally described with the Pauli-Fierz Hamiltonian [21]. Under the dipole approximation, in the length gauge [39], and in the coherent state basis [20, 21, 30], this light-matter interacting Hamiltonian (in atomic units) takes the following form:

$$\hat{H} = \hat{H}^c + \sum_{\alpha} \left( \omega_{\alpha} b_{\alpha}^{\dagger} b_{\alpha} - \sqrt{\omega_{\alpha}} \frac{1}{2} (\lambda_{\alpha} \cdot \Delta d) (b_{\alpha}^{\dagger} + b_{\alpha}) \right)$$

In this equation, $\hat{H}^c$ corresponds to the interacting electronic Hamiltonian (within the Born-Oppenheimer approximation). The second term denotes the photonic Hamiltonian for *N* cavity modes of frequency $\omega_{\alpha}$. The operators $b_{\alpha}^{\dagger} / b_{\alpha}$ are bosonic creation/annihilation operators that create/destroy a photon in cavity mode $\alpha$. The third term describes the coupling between the electronic and photonic degrees of freedom in the dipole approximation. Within this term, the $\Delta d = d - \langle d \rangle$ is the dipole fluctuation operator that describes the change of the electronic dipole moment operator with respect to its expectation value, and $\lambda_{\alpha}$ is the light-matter coupling strength of the $\alpha$-th cavity mode. The fourth term in Eq. (1) represents the dipole self energy that ensures the origin invariance of the Hamiltonian and Hamiltonian’s boundness from below [39, 40].

To describe the interaction of quantized light with a molecule, we need to solve the time-independent Schrödinger equation

$$\hat{H} |\Psi_{\text{QED-CC}}\rangle = E_{\text{QED-CC}} |\Psi_{\text{QED-CC}}\rangle,$$

where $E_{\text{QED-CC}}$ is the quantum electrodynamics coupled cluster (QED-CC) energy of a system confined to a cavity, and $|\Psi_{\text{QED-CC}}\rangle$ is the QED-CC ground state wave function ansatz [30–33] expressed as

$$|\Psi_{\text{QED-CC}}\rangle = e^{T} |0^{e}0^{ph}\rangle.$$
we use the QED-CC method in which the cluster operator is truncated to include up to single and double electronic excitations and creation of single photon, along with interactions between single electron with single photon. We refer to this method as QED-CCSD [42]. The performance of the QED-CCSD method against a more accurate but computationally costly QED-CC method is provided in the Section 2 of the Supplemental Information [43].

Finally, we discuss in more detail the specifics of the cavity. The light-matter coupling strength in Eq. 1. is defined by $|\alpha|$ = $1/\sqrt{\epsilon_0 V_{\text{eff}}^\alpha}$. Here, $\epsilon_0$ is the permittivity of the vacuum and $V_{\text{eff}}^\alpha$ is the effective quantization volume [35] of a single mode cavity. Recent advances in the multi-mode cavity design [44–48] are able to realize the strong light-matter coupling strength above 0.1 a.u. and also enable the possibility of controlling the molecular orientation inside the cavity [49]. In the multi-mode cavities [44], the light-matter coupling strength can be greatly enhanced by increasing the number of cavity modes via $\lambda_{\text{eff}}^2 = \sum_n \lambda_n^2$, where $\lambda_n$ is the coupling strength of the $n$-th cavity mode. Throughout this work, we work in the strong light-matter coupling regime by considering a $|\alpha|$ = 0.1 a.u. [27, 33, 50–52].

III. RESULTS AND DISCUSSION

As first example, in Fig. 2 we show the reaction energy diagram for the Diels–Alder cycloaddition reaction between cyclopentadiene (CPD) and acrylonitrile (AN), where the left and right panels correspond to the endo and exo paths, respectively. The transition state energies (energy difference between the transition state and the reaction complex) and reaction energies (energy difference between the product and the reaction complex) along the reaction path are calculated with the CCSD method (also referred as ‘no cavity’) and the QED-CCSD method with the light mode polarized in the $x$ (green), $y$ (blue), and $z$ (red) directions (the corresponding molecular coordinate system is shown in Fig. 2). For computational details see Section 3 of the Supplemental Information. In the following, we discuss the endo:exo product ratio of the Diels–Alder cycloaddition reaction under two conditions; kinetic and thermodynamic control of the reaction. In the case of kinetically controlled reactions, the endo:exo product ratio is determined from the reaction energy barriers, whereas for thermodynamically controlled reactions the endo:exo product ratio is determined from the reaction energies. The product ratios are calculated by employing the Arrhenius equation [53] at room temperature ($T$ = 298.15 K) and are provided in Table I. The validity of the Arrhenius equation under the strong-light matter coupling regime was experimentally confirmed in the context of a closely related electrocyclic reaction [54].

As shown in Fig. 2 and Table I, the CCSD gas phase results show that the transition state energy is slightly lower along the endo path. Moreover, the computed endo:exo ratio of 54:46 for the reaction under kinetic control is in good agreement with the experimentally determined ratio of 58:42 [55], done in a liquid phase and without solvent at 298.15 K [55]. Experiments also indicate that a nonpolar solvent as well temperature [56] do not significantly affect that ratio [55]. If we perform a similar study, but where the reactants are inside an optical cavity with a fixed light matter coupling of 0.1 a.u., we found that the barrier increases by ~5.5 kcal/mol for both reaction paths if the cavity mode is polarized along the molecular $x$ direction. Such increase in the reaction barrier corresponds to decrease in reaction rate by ~10,000 times at room temperature. Because, both paths
experience nearly equal increase in the reaction barrier, the calculated endo/exo ratio changes slightly (see Table I). However, when the cavity mode is polarized in the molecular y direction, the reaction energy barrier along the endo path decreases by 3.5 kcal/mol, whereas the exo path decreases by only 0.5 kcal/mol. Therefore, the energy barrier for the endo path is lower by 3 kcal/mol relative to the exo path, resulting in 99:1 endo:exo product ratio for kinetically controlled reactions. Additionally, such a decrease in barrier increases the reaction rate along the endo path by two orders of magnitude (370 times). Lastly, for the cavity mode polarized in the molecular z direction, the reaction barrier along the endo path increases by 2.3 kcal/mol, whereas along the exo path decreases by 0.6 kcal/mol. This corresponds to a change in endo:exo ratio of 1:99 as well as in increase of the reaction rate for the preferred reaction path by ~3 times. We note that the transition state geometry does not change significantly under the strong light-matter interaction as discussed in Section 3 of the Supplemental Information.

The reason for such selectivity is that the different orientations of the molecular dipole moment (indicated by orange arrow in Fig. 2) of the stationary structures (i.e. reaction complex, transition state, product) along the endo and exo paths dictate the direction in which coupling between light and a molecule is strongest, which ultimately leads to changes in reaction energy barriers and reaction energies. As shown in Fig. 2 (orange arrow) and in Supplemental Table II, the x component of the molecular dipole moments between the corresponding stationary structures along the endo and exo path are of roughly the same magnitude, therefore almost no discrimination is observed for either of the path. In contrast, the y component of the dipole moment for the reaction complex is ~50% larger along the endo path than along the exo path, resulting in the preference of the endo path. Similarly, the z component of the dipole moment for the reaction complex is greater along the exo path than along the endo path, leading to a preferred exo selectivity. To gain further understanding of the underlying mechanism, we have computed the individual contributions of the electronic, dipole self-energy, and dipolar coupling terms to the reaction barrier (see Section 6 of the Supplemental Information).

### Table I

|                | CPD+AN | CPD+MeAN |
|----------------|--------|----------|
|                | TS     | endo:exo| ∆E     | endo:exo |
| no cavity     | endo   | 20.8    | -29.6  | 50:50     |
|               | exo    | 20.9    | -29.6  |           |
| x direction    | endo   | 26.3    | -26.3  | 42:58     |
|               | exo    | 26.5    | -26.5  |           |
| y direction    | endo   | 17.3    | -36.7  | 99:1      |
|               | exo    | 20.4    | -33.6  |           |
| z direction    | endo   | 23.1    | -30.4  | 0:100     |
|               | exo    | 20.3    | -33.9  |           |

*aCalculated as the energy difference between the transition state and the reaction complex.
*bCalculated as the energy difference between the product and the reaction complex.
*cEndo/exo ratio for kinetically controlled reaction.
*dEndo/exo ratio for thermodynamically controlled reaction.
*eNo cavity corresponds to the conventional electronic structure CCSD result.
*fFor λy = 0.15 a.u. the computed endo/exo ratio is 88:12.
Information). When the light is polarized along the $x$ molecular direction, both the electronic and dipole self-energy terms contribute significantly to the change in the reaction barrier, whereas in the case when the light is polarized in the $y$ and $z$ molecular directions, the change in the reaction barrier is mainly due to the dipole self-energy term.

Next, we discuss the product composition under thermodynamic control (reaction energy) for the Diels–Alder cycloaddition reaction between CPD and AN. The CCSD method predicts the same reaction energy along both endo and exo paths. For thermodynamically controlled reactions, this results in equal amount of endo and exo products. For a cavity with the mode polarized in the molecular $x$ direction, both reactions become less exothermic by $\sim 3.2$ kcal/mol with a slight change of preference in favour of the exo product. The greatest effect of the cavity on the reaction energies is observed for the endo path when the cavity mode is polarized along the molecular $y$ direction, where the reaction becomes more exothermic by 7.1 kcal/mol. At the same time, the reaction along the exo path is lowered by 4.0 kcal/mol, which indicates that for thermodynamically controlled reactions, the endo:exo product ratio is 99:1. Finally, for a cavity with light polarized in the molecular $z$ direction, the reaction energy along the endo path is stabilized by 0.8 kcal/mol relative to no cavity case, whereas for the exo path the reaction energy is lower by 4.3 kcal/mol, resulting in 0:100 endo:exo product ratio.

The left panel of Fig. 3 shows the change in content of endo product for a kinetically controlled Diels–Alder cycloaddition reaction between CPD and AN as the magnitude of the cavity light-matter coupling strength is increased from 0 a.u. to 0.1 a.u., while keeping the cavity frequency constant at 1.5 eV. In the case of ideal cavity with one cavity mode (solid lines) polarized along the molecular $x$ direction, the content of endo increases by a small amount. When the cavity mode is polarized along the other two molecular directions, the content of the endo product changes rapidly, such that 90% of endo product (molecular $y$ direction) or 90% of exo (molecular $z$ direction) product is obtained for a light-matter coupling of $|\lambda| = 0.06$ a.u. The right panel of Fig. 3 shows the change in content of endo product for the same Diels–Alder cycloaddition reaction as the cavity frequency is increased from 0.5 eV to 4.0 eV, while keeping the cavity light-matter coupling strength constant at 0.1 a.u. Note that selected values of the cavity frequency are well above any molecular vibrational levels and below electronic excitations [28, 29] and the selected range was motivated by the experimentally realizable values. As shown in Fig. 3, the content of the final product shows very little dependence on the cavity frequency and no resonance effect is observed, although the effect of the cavity is the greatest at low values and slowly decreases as the cavity frequency increases. The content of endo product for the thermodynamically controlled reaction shows qualitatively similar behaviour relative to the kinetically controlled reaction as it is shown in Supplemental Fig. 2.

All results presented so far assumed an ideal (lossless) cavity. In order to approximately account for the real cavity losses, we translate the openness of the cavity into a broadening of the cavity mode in which the photon mode is broadened by explicitly including multiple discrete photon modes close in energy to the fundamental frequency of the cavity mode [57]. In this approximated treatment of a lossy cavity, the mode’s width is controlled by the dissipation constant of the mirrors (a zero value of the dissipation constant corresponds to the previous lossless cavity results). This approach has been used in different contexts in quantum optics and recently within the realm of molecules coupled to a cavity in Ref [57]. As shown in Fig. 3 (dotted lines), the cavity losses with a dissipation constant of 1 eV show only minor impact on the content of the endo product as the cavity coupling strength (left panel) and cavity frequency (right panel) increases. We found in our calculations (see Section 7 of the Supplemental Information) that cavity losses have only minor impact on the reaction diagram for the investigated reaction.

As second example, we investigate the Diels–Alder cycloaddition reaction between cyclopentadiene (CPD) and methy lacrylonitrile (MeAN) in a cavity. Figure 4 shows the reaction energy diagram for the endo (left panel) and exo (right panel) paths. The CCSD results (no cavity) are given in black, whereas the QED-CCSD results with the cavity mode polarized along the molecular $x$, $y$, and $z$ directions are given in green, blue, and red, respectively.

As shown in Fig. 4 and Table 1, the reaction energy barrier calculated with the CCSD method for the endo path is higher by 1.5 kcal/mol relative to the exo path. Therefore, unlike the previous reaction where the endo was the major product, the calculated endo:exo product ratio for kinetically controlled reaction is 7:93. The calculated ratio is in qualitatively good agreement with the experimentally determined ratio of 12:88 [55], done in a liquid phase and without solvent at 298.15 K [55]. The greatest effect of the cavity on the reaction barrier is observed when the cavity mode is polarized along the molecular $x$ direction. In that event, the reaction barrier is increased by $\sim 5.3$ kcal/mol, which results in the decrease in reaction rate by roughly 8,000 times at room temperature for kinetically controlled reaction. Additionally, the ratio of the products changes slightly relative to the no cavity case. When the cavity mode is polarized in the molecular $y$ direction the reaction barrier along the endo path is lowered by 2.1 kcal/mol, whereas along the exo path it is lowered by only 0.7 kcal/mol. Under these conditions, the calculated endo:exo ratio is 46:54. As a result, the reaction rate along the endo path is increased by 35 times, whereas the reaction rate along the exo path is increased by only 3 times. We note (Table 1) that when the cavity strength reaches $\lambda_{\nu} = 0.15$ a.u, the endo:exo product ratio is completely inverted in favor of endo product. In the event when the cavity mode is polarized in the molecular $z$ direction, the barrier in-
creases/decreases along the endo/exo paths, leading to formation of the endo:exo products ratio of 1:99.

Next, we discuss the cavity effect on the thermodynamically controlled reaction between CPD and MeAN. The CCSD method predicts that the exo product is thermodynamically more stable than its endo counterpart where the calculated endo:exo ratio is 30:70. If now the cavity mode is polarized in the molecular $x$ direction, the reaction along both paths becomes less exothermic while preserving the ratio between endo and exo products. In the case the cavity mode is polarized along the molecular $y$ direction, the effect is more pronounced along the endo path than along the exo path. This results in a ratio (88:12) where the endo product is more favorable. Lastly, for the cavity with light polarized along the molecular $z$ direction, the endo:exo reaction ratio is 1:99 for thermodynamically controlled reactions.

As was the case for our first reaction, the composition of the endo product for kinetically and thermodynamically controlled reaction changes slowly as the cavity coupling strength increases, however this change is rapid when the cavity mode is polarized along the molecular $y$ and $z$ directions (for more details see Section 4 of the Supplemental Information). The driving force responsible for this selectivity is the polarization of the cavity mode and its coupling to the molecular dipole moment (see the dipole moment direction in Fig. 4 and Section 5 of the Supplemental Information). We also find that the content of the endo product for this reaction under kinetic and thermodynamic control does not reasonably depend on the cavity frequency (see Supplemental Information). Lastly, the calculations indicate that the cavity losses show only minor impact on the reaction energy diagram for the investigated reaction (see Supplemental Table 4).

IV. SUMMARY AND CONCLUSION

In this work, we have demonstrated that an optical cavity modifies the chemical reaction of prototypical Diels–Alder cycloaddition reactions of cyclopentadiene (CPD) with acrylonitrile (AN) and methyacrylonitrile (MeAN) for both perfect and lossy cavities. Our theoretical study suggests that all the effects of the cavity observed in here are due to cavity quantum fluctuations (we are not driving the cavity by adding photons in the cavity mode). The selected Diels–Alder reactions provide an ideal platform in which one either enhances, inhibits, or controls the stereoselectivity of the products in a controlled manner for the very same reaction. We show that a cavity with the mode polarized along the forming carbon–carbon bonds increases the reaction barrier by more than 5 kcal/mol for both investigated reactions without significantly impacting the endo/exo product ratio. Such increase of the reaction barrier corresponds to decrease in reaction rate roughly by four orders of magnitude at room temperature. A cavity with modes polarized along the molecular $y$ and $z$ directions (in the plane of the CPD ring) catalyzes both reactions along the endo and exo paths, respectively. For kinetically controlled reactions and in the case of the first reaction this corresponds to a selective production of endo or exo as a major product. In the case of the second reaction, a cavity with the mode polarized along the molecular $y$-direction gives nearly equal composition of the endo and exo products, whereas the $z$-direction oriented cavity mode gives major exo product. In addition to the reaction energy barrier, we show that the cavity also has a significant impact on the reaction energy. Therefore for the thermodynamically controlled reactions, major endo and major exo product is obtained with $y$ or $z$ oriented fields, respectively, in
both reactions. We also note that inclusion of triple electronic excitations as well as its interactions to the photonic degrees of freedom are also possible, and it would improve the overall quantitative accuracy of the calculated reaction barriers and reaction energies as well as the effect of the cavity, but at a significantly higher cost. However, we believe that that our findings are robust with respect to those improvements in the description of electron correlation effects in the molecule and electron-photon interactions beyond the single cavity mode used here, and would not change the main trends discussed in the present work. Finally, we show that for the investigated reactions the cavity losses do not impact the reaction dynamics in appreciable manner.

This work highlights the possibility to experimentally realize the control of the endo/endo stereoselectivity of Diels–Alder cycloaddition reactions. In order to achieve this experimentally, the reacting molecules must be oriented relative to the light polarization direction. Although this is not trivial to achieve, a similar control was already experimentally achieved through bottom-up nanoassembly [49] and in the context of electrostatic catalysis of a Diels–Alder reaction [58]. Moreover, the external static fields can also be used to align the molecules inside the cavity [59]. Although the present study have focused on a single-molecule reaction inside a cavity, it represents the necessary starting point for exploiting other effects such as collectivity [25, 38], because the observed changes in chemical reactivity and selectivity can only be enhanced in the large collective limit if the cavity is able to modify the energy landscape of a single-molecule reaction. Another importance of our work is that it represents the first computational study of cavity enhancement in click chemistry reactions. Because the click chemistry reactions are one of the most powerful tools in drug discovery, chemical biology, and proteomic applications [2], we believe that this work will further stimulate theoretical investigations and experiments of other click chemical reactions under the strong light-matter regime.

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AUTHOR CONTRIBUTIONS

F.P. and A.R. conceived the project. F.P. proposed the investigated applications, oversaw the project, wrote the code, prepared the figures, and wrote the first draft. R.S. and F.P. obtained and evaluated the data. All authors participated in analyzing and discussing the results, and editing the manuscript.

Data availability

All data that support the findings in this paper is available in the manuscript or the supplemental information.

Code availability

The code used for obtaining the numerical results is available from the corresponding author or in Ref. 33.

Competing interests

The authors declare no competing interests.

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See Section 1 of the Supplemental Information for more details on the method and extensions of it to include higher order electronic and photonic interactions.

The level of accuracy is adequate to support the conclusions about catalytic control of the Diels–Alder reaction discussed in this work.

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