# **Supplementary Information**

# Divergent Construction of Cyclobutane-Fused Pentacyclic

## Scaffolds via Dearomative Photocycloaddition

Ting-Ting Song,<sup>1</sup> Fan Lin,<sup>1</sup> Shan-Tong Xu,<sup>1</sup> Bo-Chao Zhou,<sup>1,2</sup> Li-Ming Zhang,<sup>1,2</sup> Shi-Yu Guo,<sup>1</sup> Xinglong Zhang,<sup>3\*</sup> Qing-An Chen<sup>1,2,\*</sup>

<sup>1</sup>Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023,

China

<sup>2</sup>University of Chinese Academy of Sciences, Beijing 100049, China

<sup>3</sup>Department of Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong,

China

\*Corresponding author E-mail: xinglong.zhang@cuhk.edu.hk, qachen@dicp.ac.cn

#### 2.8 Density functional theory (DFT) studies

#### 2.8.1. Computational methods

Kohn-Sham density functional theory (KS-DFT) calculations were performed with *Gaussian 16* rev. B.01.<sup>7</sup> The global hybrid DFT functional M06-2X<sup>8</sup> was employed with the Karlsruhefamily double-ζ valence def2-SVP<sup>9,10</sup> basis set for all atoms to model the catalytic mechanism of the present transformation. M06-2X was chosen as it has shown good accuracy in studying radical and photochemistry of organic systems.<sup>11,12</sup> For the M06-2X/def-SVP gas phase optimized structures, single point (SP) corrections were performed using M06-2X functional and def2-TZVP<sup>9,10</sup> basis set for all atoms to improve upon the accuracy of the calculated energy. For each of these SP calculations, the implicit SMD continuum solvation model<sup>13</sup> for dimethyl sulfoxide (DMSO) solvent was used to account for the effect of solvent on the potential energy surface (PES). Minima and transition structures on the potential energy surface (PES) were confirmed using harmonic frequency analysis at the same level of theory, showing respectively zero and one imaginary frequency.

Gibbs energies were evaluated at the room temperature of 25 °C, using Grimme's scheme of quasi-RRHO treatment of vibrational entropies,<sup>14</sup> using the GoodVibes code.<sup>15</sup> Vibrational entropies of frequencies below 100 cm<sup>-1</sup> were obtained according to a free rotor description, using a smooth damping function to interpolate between the two limiting descriptions. The free energies reported in Gaussian from gas-phase optimisation were further corrected using standard concentration of 1 mol/L,<sup>16–18</sup> which were used in solvation calculations, instead of the gas-phase 1atm used by default in Gaussian program. Unless otherwise stated, the final SMD(DMSO)-M06-2X/def2-TZVP//M06-2X/def2-SVP Gibbs energies are used for discussion throughout. *All Gibbs energy values in the text and figures are quoted in kcal/mol.* 

For species with open-shell characteristics, including doublet (single radical) and triplet (diradical), we performed above-mentioned DFT methodologies using the unrestricted formalism of the Kohn-Sham theory (UKS-DFT). The eigenvalues of the spin operator **S**<sup>2</sup> after annihilation of spin contamination were checked to ensure that they comply with the

expected value of S(S+1) = 0.75 for a doublet wavefunction and S(S+1) = 2 for triplet, indicating that spin contamination is not a problem for the present methodology.

All molecular structures and spin density plots are visualized using *PyMOL*<sup>19</sup> software.

#### 2.8.2 Model reaction

Scheme S1 shows the model reaction that we used for computational studies of reaction mechanism for the present photocatalyzed cyclobutanation.



Scheme S1. Model reaction used in computational modelling.

#### 2.8.3 Conformational Considerations

The different conformers of species **4a**, **5b**, and **3[5b]**, and product **6a**, where the adamantyl group can be either axial or equatorial, were considered. The lowest energy species of each was used in the PES. We note that for the triplet **3[5b]**, the structure where adamantyl group is equatorial optimizes to one where adamantyl group is axial. The DFT optimized structures are shown in Figure S32.

4a_ax	4a_eq
∆G = -96.4	ΔG = -88.8

5a_ax	5a_eq
ΔG = -97.9	ΔG = -92.2
6a	6a_eqeq
ΔG = -147.6	ΔG = -132.6



**Figure S32.** DFT-optimized structures of different conformers of **4a** and **5b** and product **6a**. Their Gibbs energies relative are given relative to the ground state of **1a**.

For the lowest energy conformers for each structure, the adamantyl group is in the axial position. For **4a**, the adamantyl group in the axial position, **4a\_ax**, is more stable than **4a\_eq**, where the adamantyl group is in equatorial position, by 7.6 kcal/mol. Similarly, **5a\_ax** is more stable than **5a\_eq** by 5.7 kcal/mol. For the cyclobutene product, **6a**, where both adamantyl groups are axial is the most stable, more so than **6a\_eqeq**, where both adamantyl groups are equatorial, by 15.0 kcal/mol, and than **6a\_eqax**, where one adamantyl group is axial and the other equatorial, by 15.1 kcal/mol. This is consistent with the X-ray crystal structure obtained experimentally for product **6a**, where both adamantyl groups are in axial positions.

### 2.8.4 Spin densities of key intermediates

The spin density plots for key radical intermediates are shown in Figure S33. The spin density for 3[5b] indicates that the  $\beta$ -carbon has the highest radical characteristic and will attack the neutral **5b** substrate from this carbon atom.





**Figure S33.** DFT-optimized structures of key radical species and their spin density plots at an isovalue of 0.02 a.u. Mulliken spin density values are given.

#### 2.8.5 Diastereoselectivity

The diastereoselectivity outcomes of the reaction depend on the first C–C bond formation, as after the first C–C bond is formed, the second C–C bond/ring closure step occurs without possibility of stereochemical change, as the methylcarboxylate group cannot rotate due to the restriction of naphthalene scaffold.

For the head-to-head *anti* cycloaddition leading to the final product where adamantyl group and cyclobutane H atoms are *cis* (on the same side), <sup>3</sup>**[TS1]**, where the adamantyl groups are both axial (Figure S34), has the lowest in barrier, at  $\Delta G^{\ddagger} = -87.3$  kcal/mol (Figure S34). The TS where one adamantyl group is axial and the other equatorial, <sup>3</sup>**[TS1-eqax]**, is higher in barrier by 8.9 kcal/mol; the TS where both adamantyl groups are equatorial, <sup>3</sup>**[TS1-eqeq]**, is higher in barrier by 13.9 kcal/mol.

For the head-to-head *anti* cycloaddition leading to the diasteroisomer where the adamantyl group and cyclobutane H atom are *trans* (on the opposite side), <sup>3</sup>**[TS1a-eqax]**, where the adamantyl groups are in axial and equatorial position, is the lowest in barrier, at  $\Delta G^{\ddagger} = -73.6$  kcal/mol (Figure S34). The TS where both adamantyl groups are equatorial, <sup>3</sup>**[TS1a-eqeq]**, is



higher in barrier by 2.0 kcal/mol; the TS where both adamantyl groups are axial, <sup>3</sup>[TS1a-axax], is higher in barrier by 6.5 kcal/mol.





**Figure S34.** DFT-optimized structures of different conformers of first C–C bond formation transition states (TSs). Their Gibbs energies relative are given relative to the ground state of **1a**.

For the head-to-head *syn* cycloaddition leading to the diasteroisomer, **<sup>3</sup>[TS1s-eqax]**, where one adamantyl group is in axial and the other in equatorial position, is the lowest in barrier, at  $\Delta G^{\ddagger} = -81.7$  kcal/mol (Figure S34). The TS where both adamantyl groups are equatorial, **<sup>3</sup>[TS1s-eqeq]**, is higher in barrier by 10.2 kcal/mol; the TS where both adamantyl groups are axial could not be built due to steric clashes between the adamantyl groups.

Note that for each TS above, a constrained CREST conformational sampling was performed, however, regardless of which TS structure, whether from *anti* or *syn* addition, used as input for CREST, the lowest energy conformers converged to <sup>3</sup>[TS1].

#### 2.8.6 Regioselectivity

For the regioselectivity studies, we consider only the head-to-tail addition where the triplet species **{}^{3}[5b]** attacks from the  $\beta$ -carbon to the  $\alpha$ -carbon of the C=C bond on singlet substate **5b** in an *anti* fashion, as the corresponding head-to-head addition TS where the  $\beta$ -carbon of **{}^{3}[5b]** attacks the  $\beta$ -carbon of C=C bond of substate **5b** via **{}^{3}[TS1]** has the lowest activation barrier (Figure S34). We only consider the attack from the  $\beta$ -carbon of **{}^{3}[5b]** since there is a

larger spin characteristic on this carbon (1.022, Figure S33) than that on the  $\alpha$ -carbon (0.741, Figure S33).

The DFT-optimized structure for this TS, termed **<sup>3</sup>[TS1r]** is shown in Figure S35, which is 8.9 kcal/mol higher than **<sup>3</sup>[TS1]**. The head-to-tail regioisomeric TS, **<sup>3</sup>[TS1r]**, is higher in barrier likely due to the out-of-phase spin density interactions as shown by the spin density plots.



Figure S35. DFT-optimized structures and the spin density plots of the lowest energy conformers of the first C–C bond formation from head-to-head, <sup>3</sup>[TS1], vs head-to-tail, <sup>3</sup>[TS1r], cycloaddition. Their Gibbs energies relative are given relative to the ground state of 1a.

#### 2.8.7 Ring closure

After the triplet species **IV** undergoes intersystem crossing (ISC) to the singlet state, the cyclization step is expected to be barrierless, as the direct geometry optimization of the intermediate yields the ring-closed cyclobutane product, indicating a negligible barrier for the ring closure step.

#### 2.8.8 Mechanism of crossed [2+2] reaction in O<sub>2</sub>



Figure S36. Gibbs energy profile for the formation of product 20 in the presence of O<sub>2</sub>.



Figure S37. Conversion of species VII to 20 under either acid or base catalysis.

#### 2.8.9 DFT-optimized structures and absolute energies

Geometries of all optimized structures (in.*xyz* format with their associated gas-phase energy in Hartrees) are included in a separate folder named *DFT\_optimized\_structures* with an associated readme.txt file. All these data have been uploaded to zenodo.org (DOI: 10.5281/zenodo.14523339).

Absolute values (in Hartrees) for SCF energy, zero-point vibrational energy (ZPE), enthalpy and quasi-harmonic Gibbs free energy (at 25 °C/298.15 K) for optimized structures are given below. Single point correction energy values are also included.

Structure	E/au	ZPE/au	H/au	T.S/au	qh-G/au	SP
1a_singlet	-613.058904	0.192951	-612.85381	0.047072	-612.899773	-613.7532659
1a_triplet	-612.956566	0.188585	-612.75525	0.049767	-612.80346	-613.6503076
I	-613.070994	0.188804	-612.86983	0.047828	-612.916704	-613.837302
II	-613.606715	0.201667	-613.39229	0.049538	-613.440122	-614.3054668
111	-389.589716	0.231254	-389.35056	0.036294	-389.386859	-390.0200269
4a_ax	-1003.314422	0.440084	-1002.8544	0.063422	-1002.915454	-1004.434669
4a_eq	-1003.298756	0.4397	-1002.8391	0.06363	-1002.900455	-1004.421804

5b_ax	-1003.317981	0.440255	-1002.8578	0.063705	-1002.918992	-1004.43697
5b_eq	-1003.307919	0.440344	-1002.8475	0.063965	-1002.909129	-1004.427786
5b_triplet	-1003.221262	0.436257	-1002.7643	0.066807	-1002.828175	-1004.33915
INT1_triplet	-2006.567514	0.878702	-2005.648	0.11099	-2005.750612	-2008.789608
TS1_triplet	-2006.564045	0.879075	-2005.6451	0.107797	-2005.745554	-2008.785718
INT2_triplet	-2006.610508	0.883086	-2005.6877	0.107855	-2005.787975	-2008.829926
TS1_triplet_eqeq	-2006.540815	0.879435	-2005.6215	0.106711	-2005.721796	-2008.764314
TS1_triplet_eqax	-2006.550304	0.879653	-2005.6309	0.106779	-2005.730908	-2008.772395
TS1a_triplet_eqax	-2006.53477	0.878344	-2005.6162	0.10901	-2005.717767	-2008.762443
TS1a_triplet_axax	-2006.526491	0.878792	-2005.6077	0.107964	-2005.708374	-2008.75316
TS1a_triplet_eqeq	-2006.528676	0.878599	-2005.6098	0.109138	-2005.711541	-2008.759386
TS1s_triplet_eqeq	-2006.536931	0.878752	-2005.6181	0.106898	-2005.718657	-2008.760235
TS1s_triplet_eqax	-2006.551529	0.878673	-2005.6328	0.107762	-2005.73363	-2008.776249
TS1r_triplet	-2006.54835	0.877891	-2005.6302	0.108684	-2005.731448	-2008.769894
6a	-2006.674814	0.886048	-2005.7499	0.1029	-2005.846771	-2008.891372
6a_eqeq	-2006.645356	0.885956	-2005.7202	0.105194	-2005.818427	-2008.866295
6a_eqax	-2006.653327	0.886289	-2005.7289	0.102293	-2005.824814	-2008.867738
H₂O	-76.323214	0.021589	-76.297846	0.019066	-76.316911	-76.43406553
O <sub>2</sub> _singlet	-150.082951	0.004141	-150.0755	0.019179	-150.094683	-150.280371
O <sub>2</sub> _triplet	-150.14314	0.004164	-150.13567	0.020216	-150.155886	-150.339069
peroxide_radical	-150.719392	0.014652	-150.70095	0.022903	-150.723849	-150.923549
K <sub>2</sub> CO <sub>3</sub>	-1463.336757	0.017321	-1463.3118	0.037736	-1463.348915	-1463.815091
VI	-1002.689372	0.42748	-1002.2421	0.064226	-1002.303755	-1003.806195
VII'	-1152.852234	0.436684	-1152.3934	0.070078	-1152.460068	-1154.16397
VII	-1153.492079	0.448717	-1153.0209	0.070177	-1153.087557	-1154.804433
RCT_base	-2616.840977	0.467434	-2616.3427	0.091358	-2616.427311	-2618.631058
TS_base	-2616.815818	0.460312	-2616.3248	0.089933	-2616.408733	-2618.594726
PRD_base	-2616.815818	0.460308	-2616.3248	0.089942	-2616.408742	-2618.594726
RCT_acid	-2017.544288	0.48195	-2017.0345	0.082209	-2017.112017	-2019.250888
TS_acid	-2017.430756	0.473056	-2016.9304	0.081313	-2017.007031	-2019.135736
PRD_acid	-2017.633358	0.47786	-2017.1263	0.085036	-2017.206348	-2019.326959
20_singlet	-1077.256216	0.421547	-1076.814	0.065692	-1076.876915	-1078.467249

#### 3. Supplementary References

#### Full reference Gaussian 16:

Gaussian 16, Revision B.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2016**.

(1) Miller, D. C.; Ganley, J. M.; Musacchio, A. J.; Sherwood, T. C.; Ewing, W. R.; Knowles, R. R. Anti-Markovnikov Hydroamination of Unactivated Alkenes with Primary Alkyl Amines. *J. Am. Chem. Soc.* **2019**, *141*, 16590–16594.

(2) You, Y.; Park, S. Y. Inter-Ligand Energy Transfer and Related Emission Change in the Cyclometalated Heteroleptic Iridium Complex: Facile and Efficient Color Tuning over the Whole Visible Range by the Ancillary Ligand Structure. *J. Am. Chem. Soc.* **2005**, *127*, 12438–12439.

(3) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A.; Malliaras, G. G.; Bernhard, S. Single-Layer Electroluminescent Devices and Photoinduced Hydrogen Production from an Ionic Iridium(III) Complex. *Chem. Mater.* **2005**, *17*, 5712–5719.

(4) Huang, H.; Li, X.; Yu, C.; Zhang, Y.; Mariano, P. S.; Wang, W. Visible-Light-Promoted Nickel- and Organic-Dye-Cocatalyzed Formylation Reaction of Aryl Halides and Triflates and Vinyl Bromides with Diethoxyacetic Acid as a Formyl Equivalent. *Angew. Chem. Int. Ed.* **2017**, *56*, 1500–1505.

(5) Speckmeier, E.; Fischer, T. G.; Zeitler, K. A Toolbox Approach to Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor–Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018**, *140*, 15353–15365.

(6) Guo, W.; Ding, H.; Gu, C.; Liu, Y.; Jiang, X.; Su, B.; Shao, Y. Potential-Resolved Multicolor Electrochemiluminescence for Multiplex Immunoassay in a Single Sample. *J. Am. Chem. Soc.* **2018**, *140*, 15904–15915.

(7) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; et al. Gaussian 16, Revision B.01. **2016**.

(8) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Function. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

(9) Weigend, F.; Ahlrichs, R. Balanced Basis Sets of Split Valence, Triple Zeta Valence and Quadruple Zeta Valence Quality for H to Rn: Design and Assessment of Accuracy. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305.

(10) Weigend, F. Accurate Coulomb-Fitting Basis Sets for H to Rn. *Phys. Chem. Chem. Phys.* **2006**, *8*, 1057–1065.

(11) Zhang, X.; Paton, R. S. Stereoretention in Styrene Heterodimerisation Promoted by One-Electron Oxidants. *Chem. Sci.* **2020**, *11*, 9309–9324.

(12) Liu, D.; Tu, T.; Zhang, T.; Nie, G.; Liao, T.; Ren, S.-C.; Zhang, X.; Chi, Y. R. Photocatalytic Direct Para-Selective C-H Amination of Benzyl Alcohols: Selectivity Independent of Side Substituents. *Angew. Chem. Int. Ed.* **2024**, *63*, e202407293.

(13) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

(14) Grimme, S. Supramolecular Binding Thermodynamics by Dispersion-Corrected Density Functional Theory. *Chem. Eur. J.* **2012**, *18*, 9955–9964.

(15) Luchini, G.; Alegre-Requena, J. V.; Funes-Ardoiz, I.; Paton, R. S. GoodVibes: Automated Thermochemistry for Heterogeneous Computational Chemistry Data. *F1000Research* **2020**, *9*, 291.

(16) Bryantsev, V. S.; Diallo, M. S.; Goddard Iii, W. A.; Goddard, W. A. Calculation of Solvation Free Energies of Charged Solutes Using Mixed Cluster/Continuum Models. *J. Phys. Chem. B* **2008**, *112*, 9709–9719.

(17) Boyle, B. T.; Levy, J. N.; de Lescure, L.; Paton, R. S.; McNally, A. Halogenation of the 3-Position of Pyridines through Zincke Imine Intermediates. *Science* **2022**, *378*, 773–779.

(18) Darù, A.; Hu, X.; Harvey, J. N. Iron-Catalyzed Reductive Coupling of Alkyl lodides with Alkynes to Yield *cis*-Olefins: Mechanistic Insights from Computation. *ACS Omega* **2020**, *5*, 1586–1594.

(19) Schrödinger, L. The PyMOL Molecular Graphics Development Component, Version 1.8; **2015**.