Regio- and Stereocontrol of Arene—Alkene Photocycloadditions

Reporter: Qinqin Wu

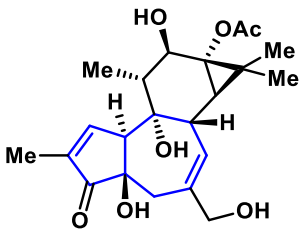
Supervisor: Prof. Ping Lu

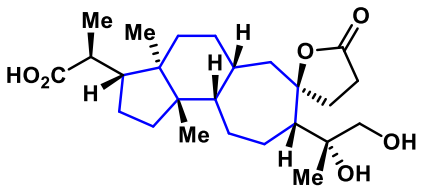
2025-3-14

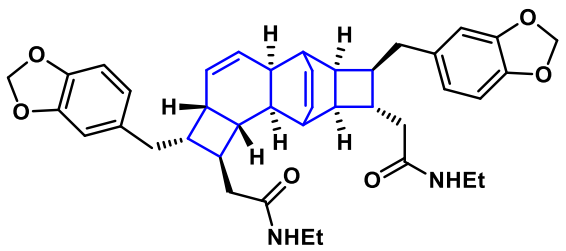
Content

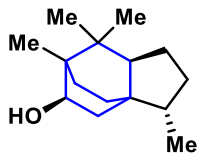
Introduction

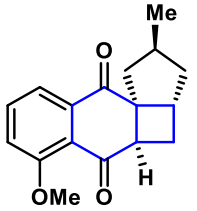
3D skeletons in natural products

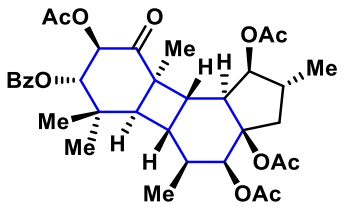

Phorbol


Lacifodilactone F

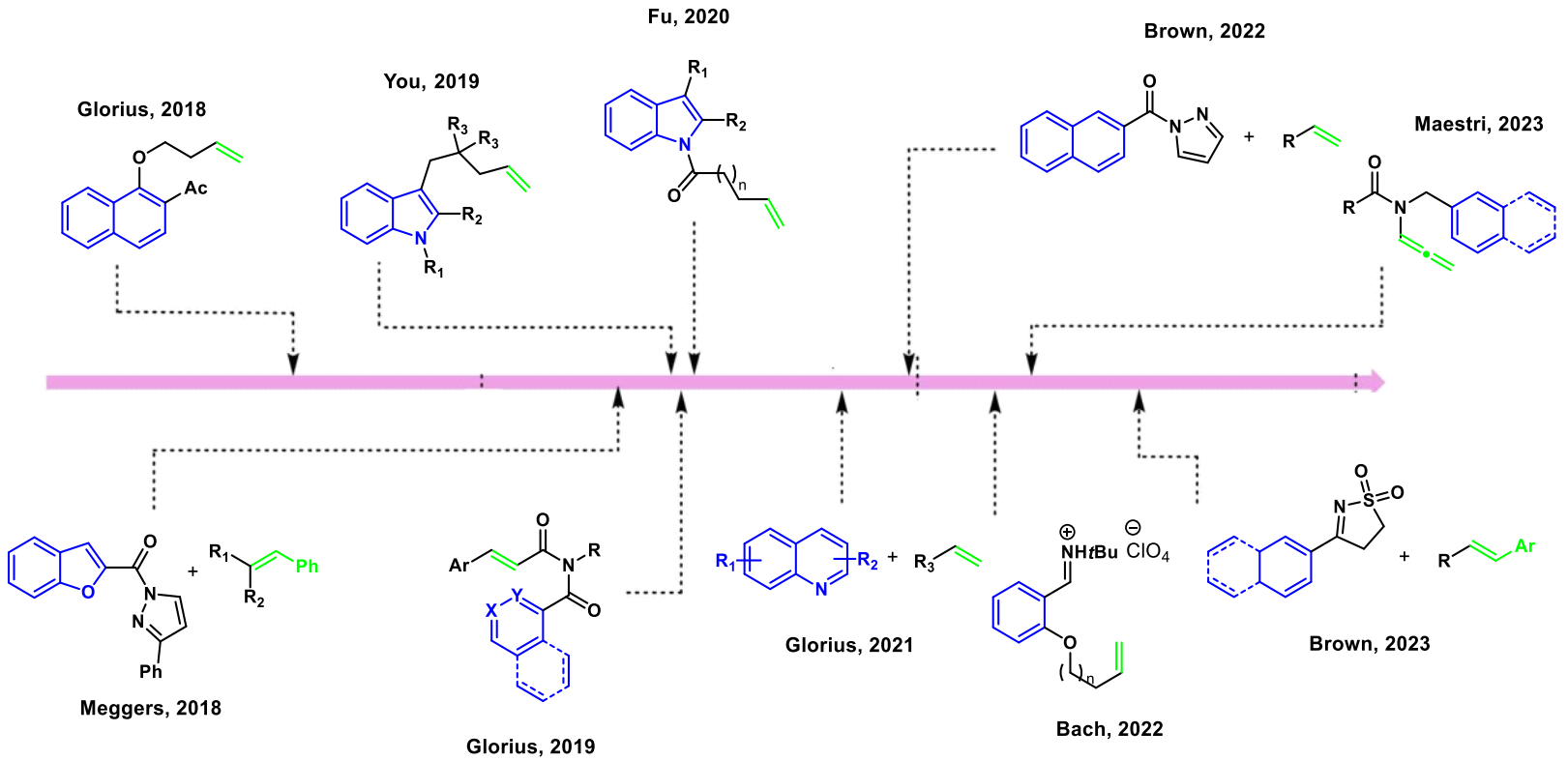

Kingianin A


Khusiol


(–)–Elecanacin


Gaditanone

Arene—Alkene Photocycloadditions

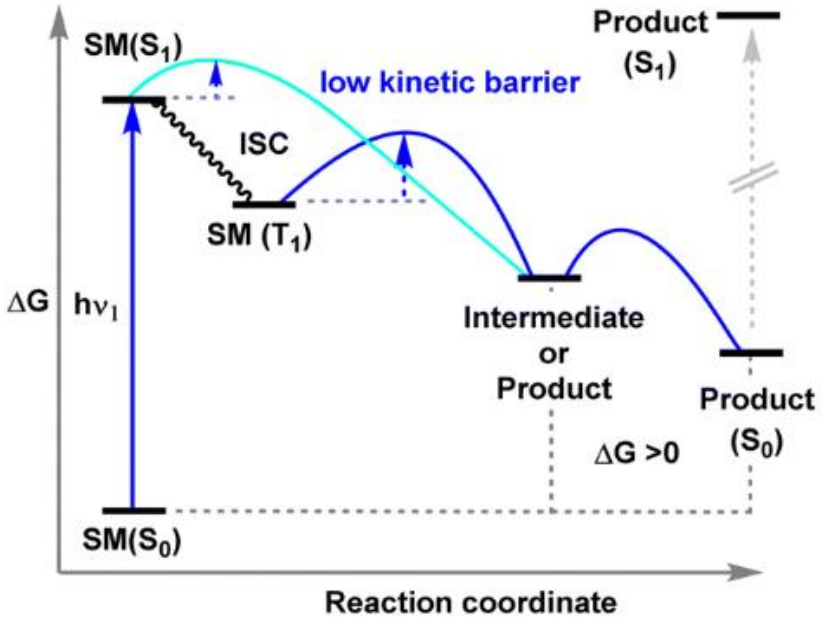


Christian G. Bochet et al, *Beilstein J. Org. Chem.* **2011**, *7*, 525–542; Biao-lin Yin et al, *Adv. Synth. Catal.* **2023**, *365*, 43–52; Frank Glorius et al, *J. Am. Chem. Soc.* **2018**, *140*, 8624−8628.

Introduction

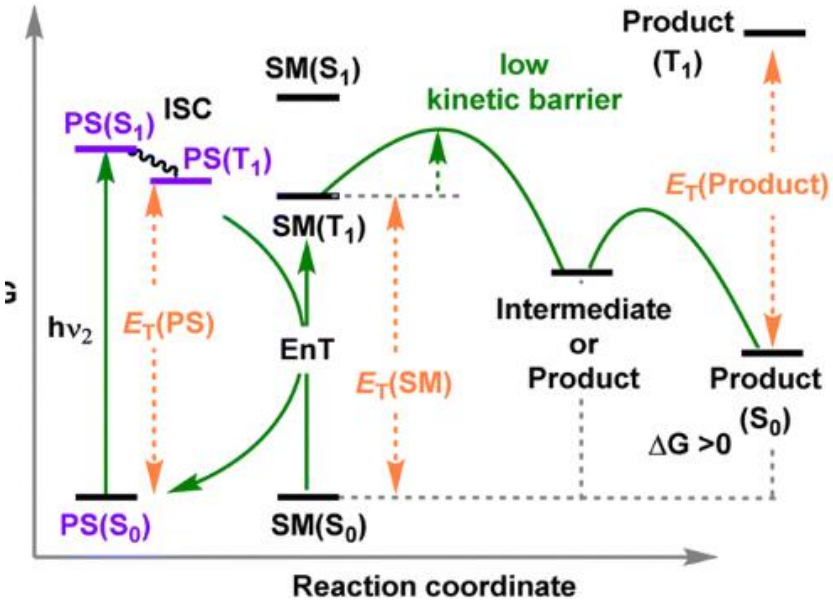
Arene–alkene cycloaddition: Two photochemical routes

A. Energy profile diagram for direct excitation process



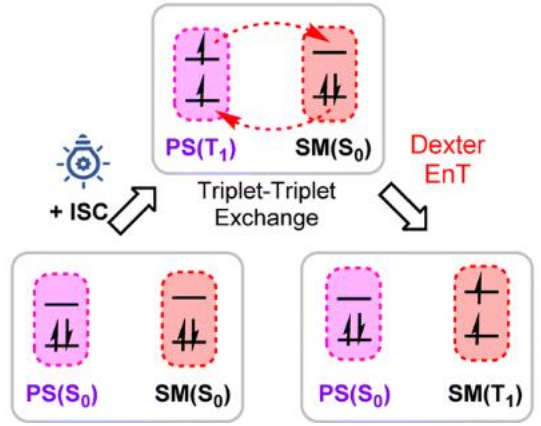
Endergonic ($\Delta G > 0$)
High energy light source
Reverse reaction prevented *via* selective excitation
Uncontrolled side reactons (low yield and selectivity)

B. Energy profile diagram for photosensitization process

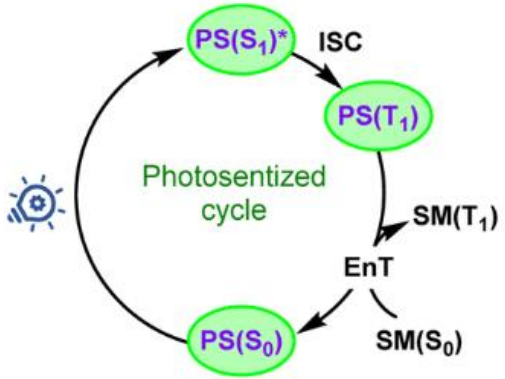


Endergonic ($\Delta G > 0$)
Mild reaction conditions using visible light
Reverse reaction prevented if $E_{\mathrm{T}}(\mathrm{TM}) \gg E_{\mathrm{T}}(\mathrm{PS})$
High yield and selectivity

C. Dexter energy transfer (EnT)



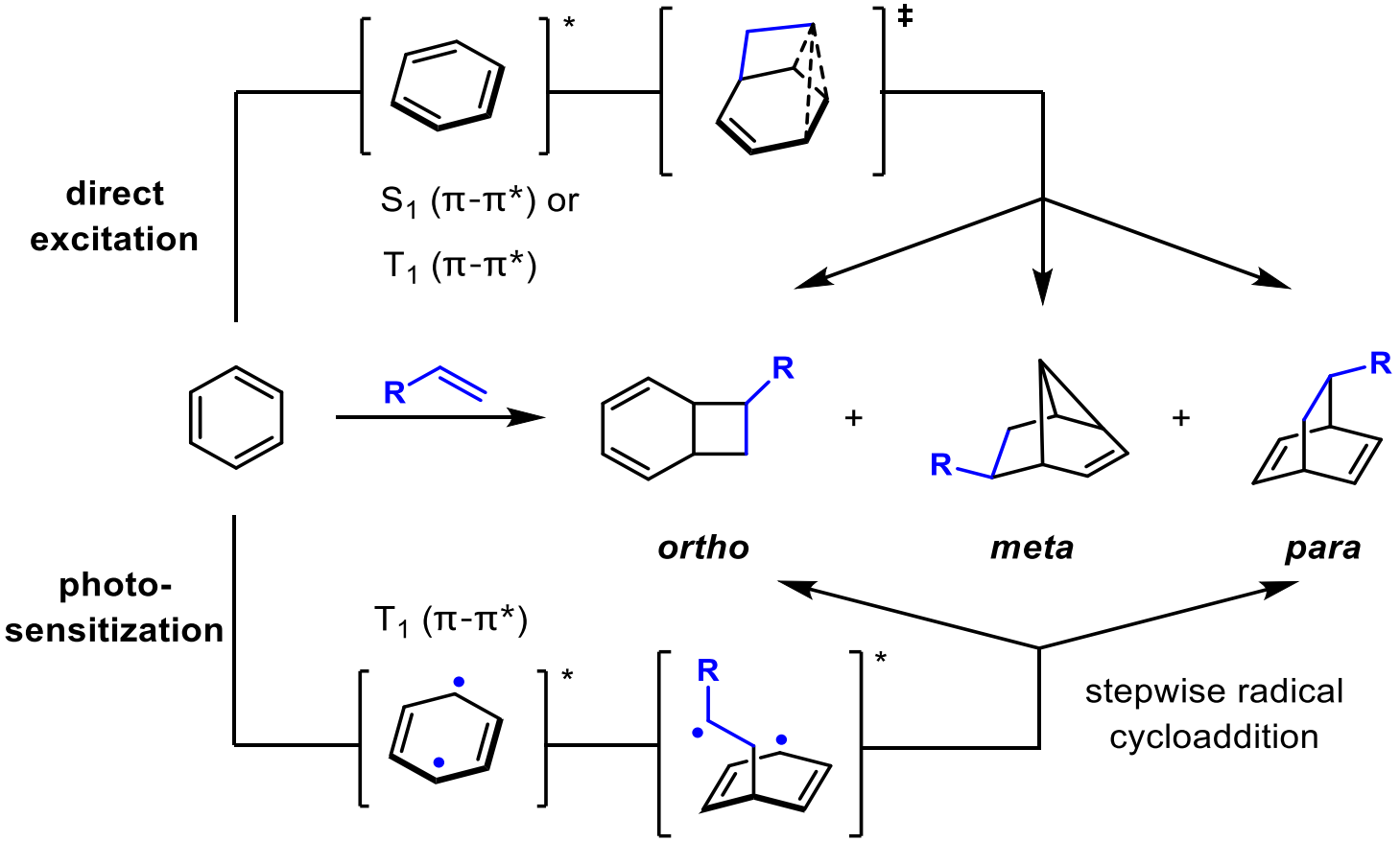
D. Simlified photocatalytic cycle



Biplab Maji et al, *Chem. Sci.*, **2023**, *14*, 12004–12025.

Introduction

Arene–alkene cycloaddition: *Meta, Para* & *Ortho* mode



Direct excitation

- High energy gap from S_0 to S_1
- *Meta* is symmetry allowed from S_1
- Slow ISC (EI-Sayed forbbidden) to T_1
- Competitive reactions of S_1 and T_1

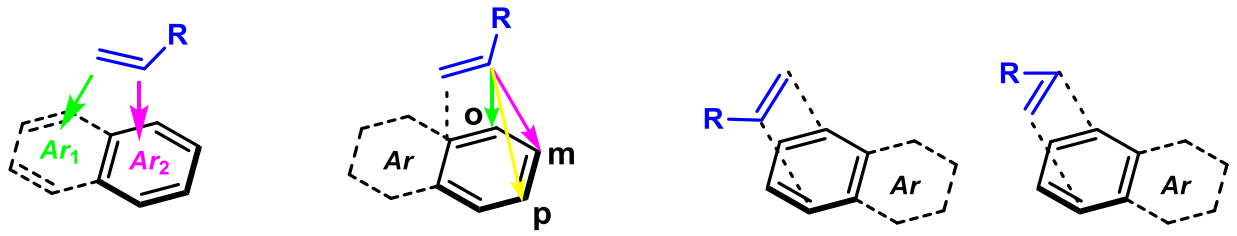
Photosensitization

- Longer wavelength for sensitizer
- Radical chemistry enables *ortho* & *para*
- Efficient Dexter energy transfer to T_1
- No S_1 reactivity

K. N. Houk, Frank Glorius, Shuming Chen, M. Kevin Brown et al, *J. Am. Chem. Soc.* **2022**, *144*, 17680−17691.

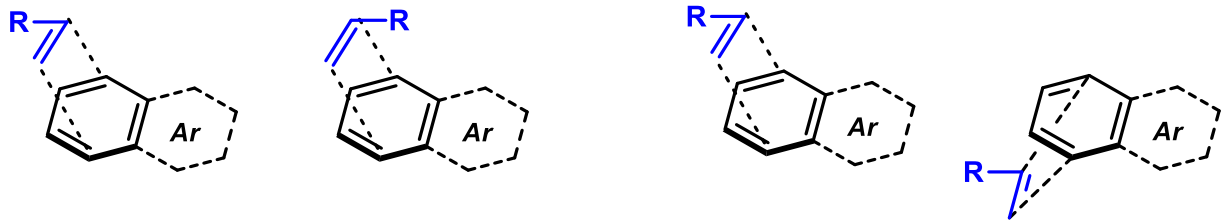
Introduction

The challenges to achieve regio- and stereoselectivity



different rings　　*ortho vs meta vs para*　　syn *vs* anti

Regioselectivity



exo *vs* endo　　*Si* face *vs Re* face

Diastereoselectivity　　**Enantioselectivity**

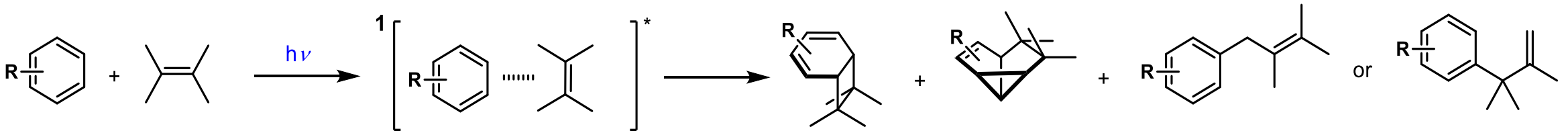
K. N. Houk, Frank Glorius, Shuming Chen, M. Kevin Brown et al, *J. Am. Chem. Soc.* **2022**, *144*, 17680−17691.

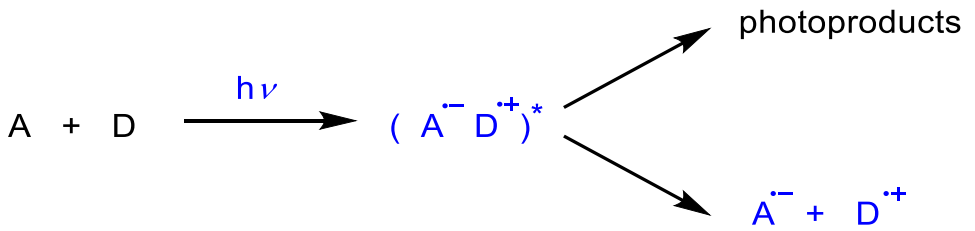
Content

Regioselectivity: Mode Selectivity (*Meta* vs *Ortho*)

Early mechanistic Investigation: an empirical rule

1. Exciplex-mechanism: an excited state intermediate of arene—alkene photoreaction





- The exciplex was confirmed by detecting long wavelength emission of itself.
- The exciplex was polar, involving **charge transfer**, which was formed by excitation of **electron donor (D)** and **acceptor (A)** molecules.
- Dissociation of the photochemically formed CIP ($A^{\bullet-}$ $D^{\bullet+}$) into free radical ions (FRI = $A^{\bullet-}$ + $D^{\bullet+}$) may be a competitive reaction to the product formation.

Jochen Mattay. *Tetrahedron* **1985**, *41*, 2393-2417.

Regioselectivity: Mode Selectivity (*Meta* vs *Ortho*)

Early mechanistic Investigation: an empirical rule

2. Mattay's rule: Rehm-Weller equation

Calculating the energy of the charge transfer of the exciplex

$$\Delta G = F[E^{ox}_{1/2}(D) - E^{red}_{1/2}(A)] - \Delta E_{\text{excit}} + \frac{e^2 N}{4\pi a \varepsilon_0}\left[\frac{1}{e} - \frac{2}{37.5}\right]$$

$$\Delta G^{\mathbf{ET}} = E^{ox}_{1/2}(D) - E^{red}_{1/2}(A) - \Delta E_{\text{excit}} + \Delta E_{\text{coul}}$$

$\Delta G^{\mathbf{ET}}$: free enthalpies of electron transfer
$E^{ox,red}_{1/2}$: oxidation (reduction) potential of the donor (acceptor) molecule. D = donor; A = acceptor
$\Delta E_{\mathbf{excit}}$: excitation energy of the chromophore
$\Delta E_{\mathbf{coul}}$: coulombic interaction energy of the radical ion

Using 1,4-dioxane as solvent:

if Arene = Acceptor

Benzene	$\Delta G^{\mathbf{ET}}_{\mathbf{1}} = E^{ox}_{1/2}(D) - 0.07$
α,α,α-Trifluorotoluene	$\Delta G^{\mathbf{ET}}_{\mathbf{1}} = E^{ox}_{1/2}(D) - 0.65$
Benzonitrile	$\Delta G^{\mathbf{ET}}_{\mathbf{1}} = E^{ox}_{1/2}(D) - 0.95$

if Arene = Donor

Benzene	$\Delta G^{\mathbf{ET}}_{\mathbf{2}} = -E^{red}_{1/2}(A) - 1.68$
α,α,α-Trifluorotoluene	$\Delta G^{\mathbf{ET}}_{\mathbf{2}} = -E^{red}_{1/2}(A) - 0.92$
Benzonitrile	$\Delta G^{\mathbf{ET}}_{\mathbf{2}} = -E^{red}_{1/2}(A) - 0.93$

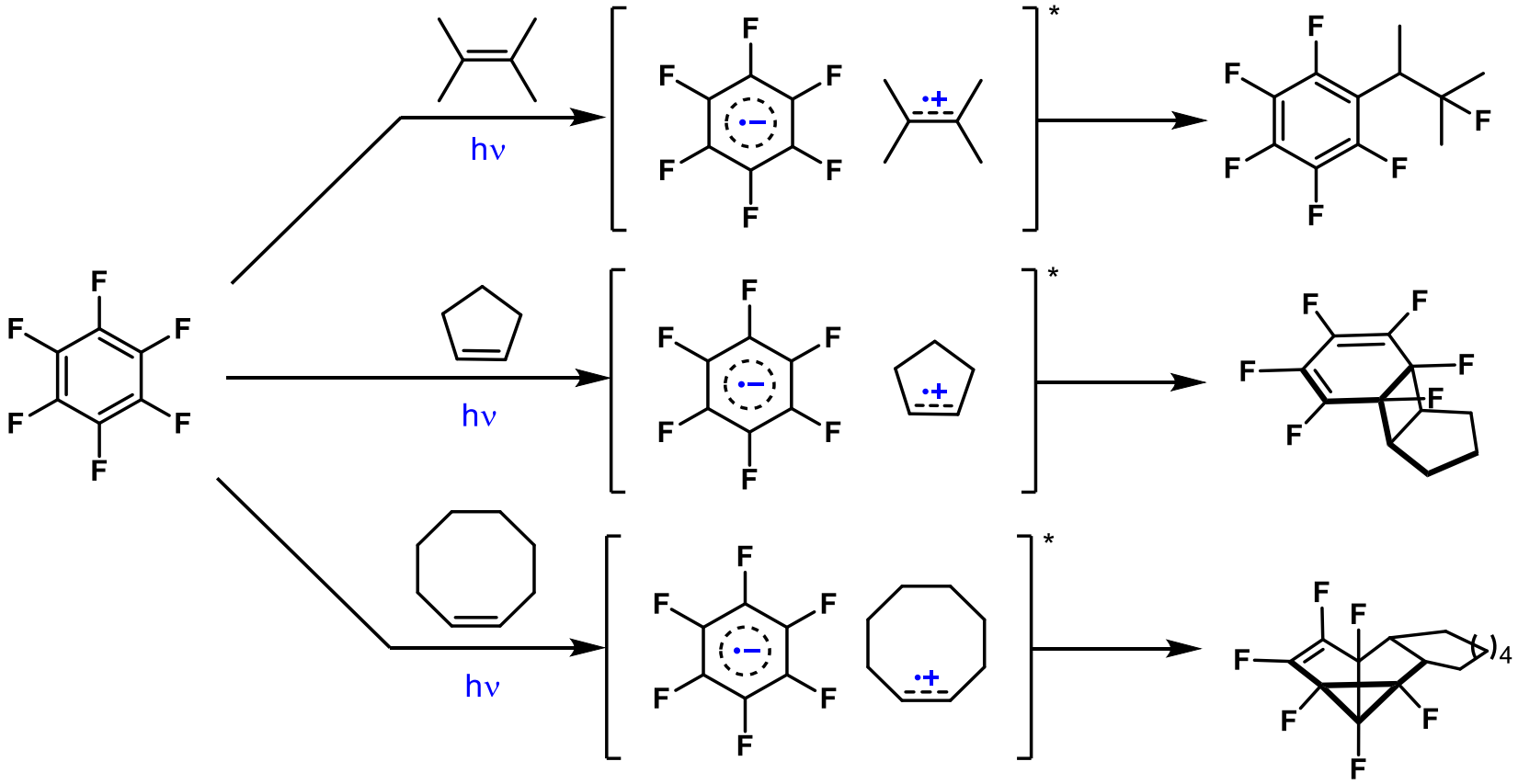
if $\Delta G^{\mathbf{ET}}_{\mathbf{1}} < \Delta G^{\mathbf{ET}}_{\mathbf{2}}$, Arene = Acceptor; if $\Delta G^{\mathbf{ET}}_{\mathbf{1}} > \Delta G^{\mathbf{ET}}_{\mathbf{2}}$, Arene = Donor.

Jochen Mattay. *Tetrahedron* **1985**, *41*, 2393-2417.

Regioselectivity: Mode Selectivity (*Meta* vs *Ortho*)

Early mechanistic Investigation: an empirical rule

Example: photoreactions of hexafluorobenzene with various olefins



Substitution $\Delta G^{ET} = -0.29$ eV

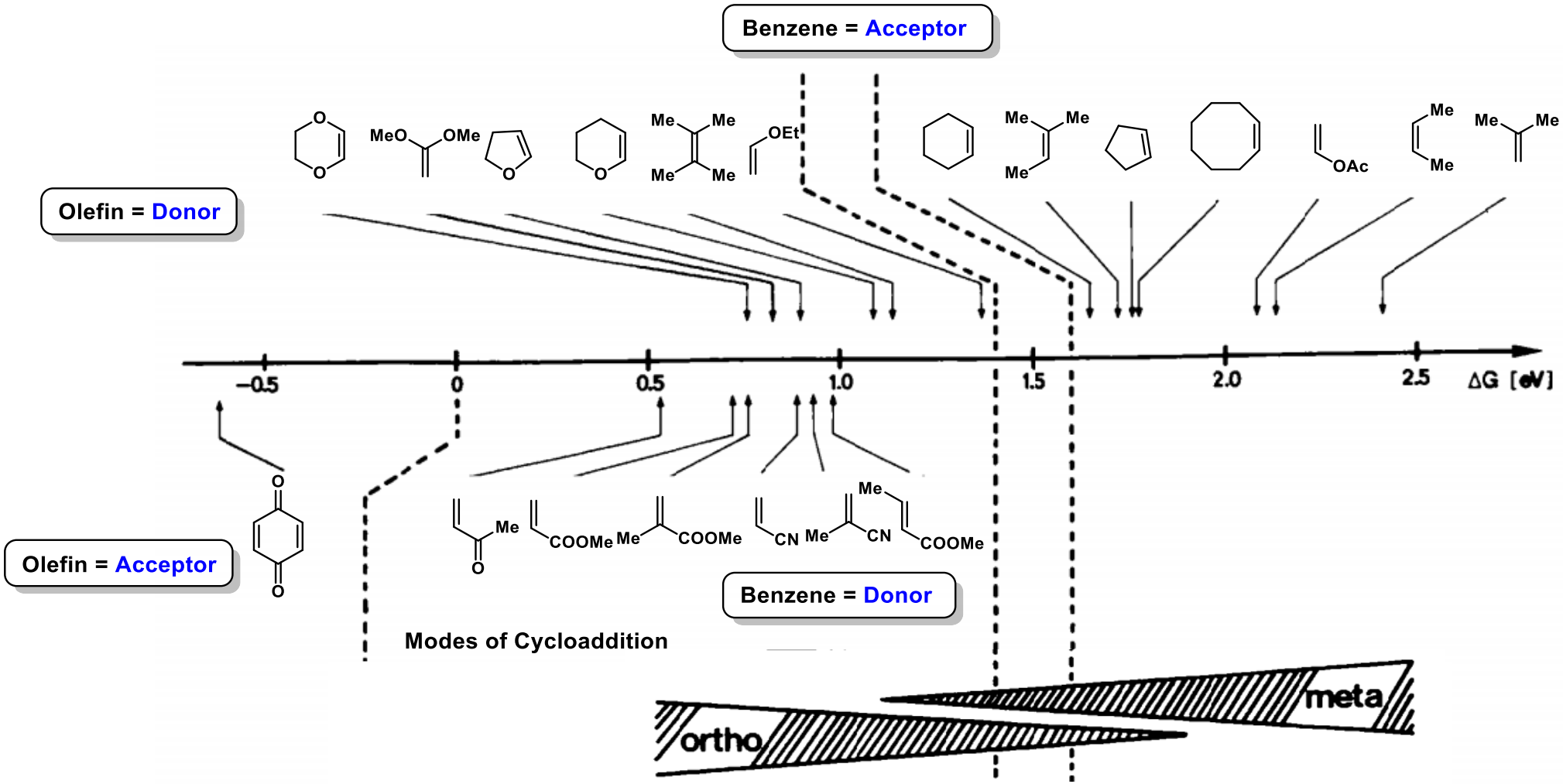
***Ortho* Addition** $\Delta G^{ET} = 0.03$ eV

***Meta* Addition** $\Delta G^{ET} = 0.35$ eV

Jochen Mattay. *Tetrahedron* **1985**, *41*, 2393-2417.

Regioselectivity: Mode Selectivity (*Meta* vs *Ortho*)

Correlation of reaction modes with ΔG^{ET} in photoreactions of benzene with olefins

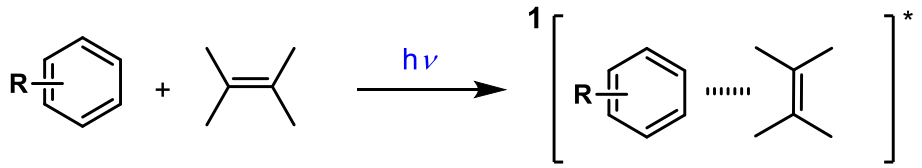


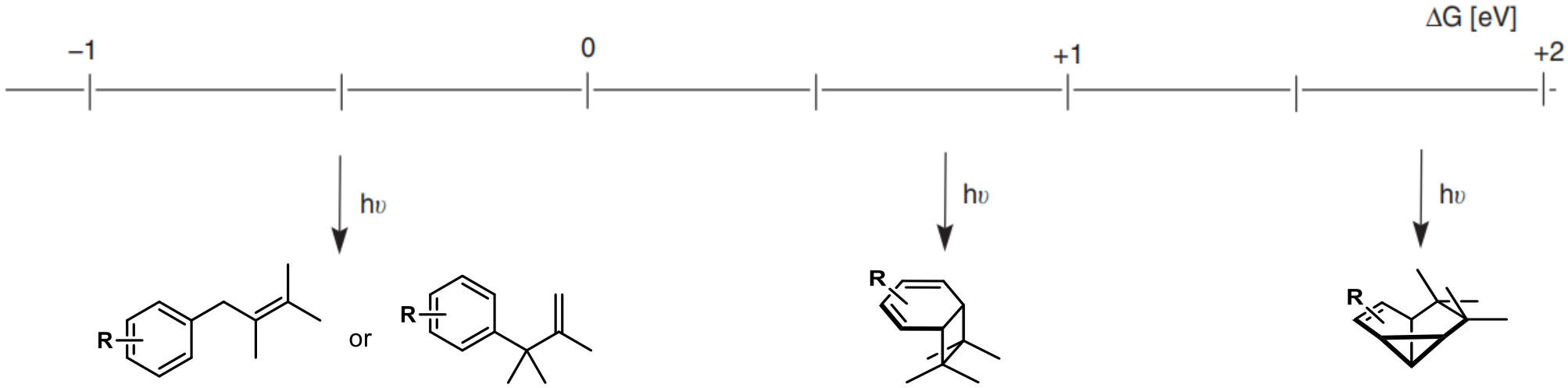
Jochen Mattay. *Tetrahedron* **1985**, *41*, 2393-2417.

Regioselectivity: Mode Selectivity (*Meta* vs *Ortho*)

Early mechanistic Investigation: an empirical rule

Mattay's rule: an empirical correlation between selectivity and ΔG^{ET}





substitution

$\Delta G^{ET} < 0$

***ortho* addition**

$0 < \Delta G^{ET} < 1.4\ eV - 1.6\ eV$

Olefins (good electron-donor/acceptor abilities)

***meta* addition**

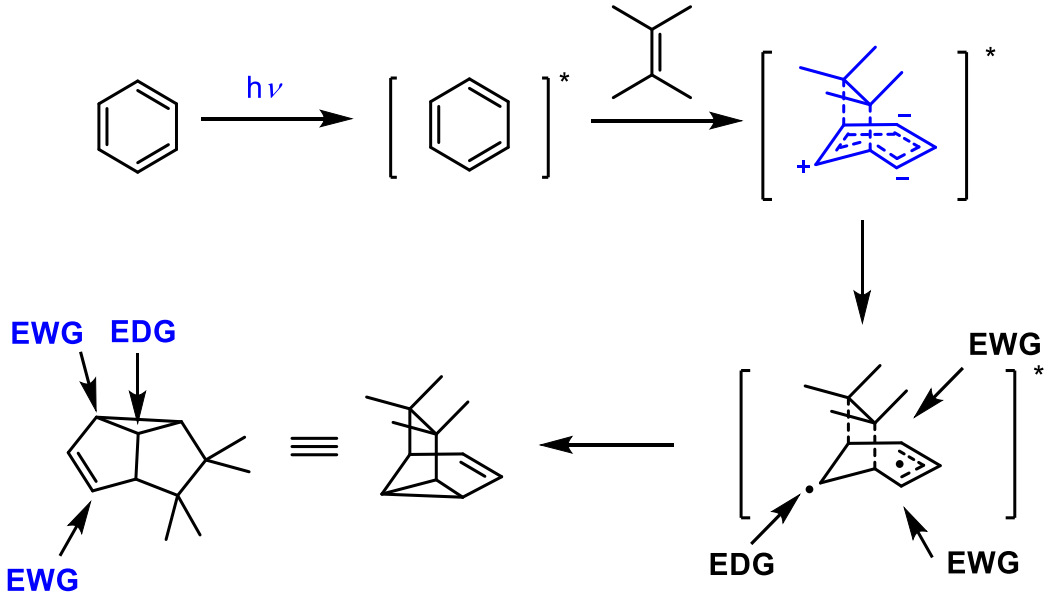
$\Delta G^{ET} > 1.4 - 1.6\ eV$

Olefins (poor electron-donor/acceptor abilities)

Jochen Mattay. *Tetrahedron* **1985**, *41*, 2393-2417.

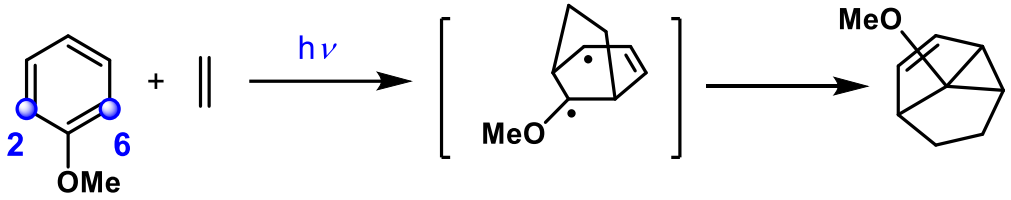
Meta-photocycloadditions: Regioselectivity & Stereoselectivity

1. Regioselectivity: different addition sites

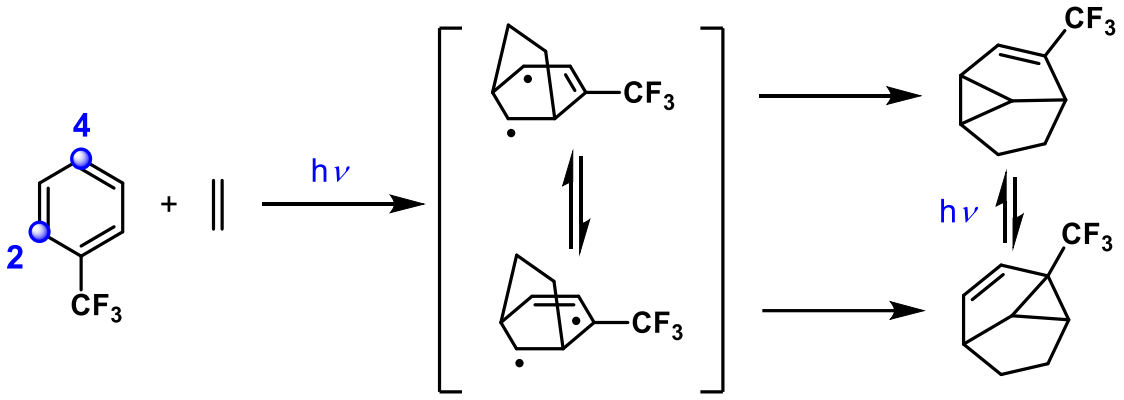


- Exciplex-like arrangement of reactants was involved.
- Electron rich aromatic ring: 2,6 addition;
  Electron poor aromatic ring: 2,4 addition.
- Recombination of the biradical created the second regioselectivity.

Electron rich aromatic ring: 2,6 addition



Electron poor aromatic ring: 2,4 addition

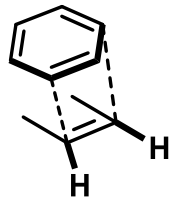


vinyl cyclopropane rearrangement

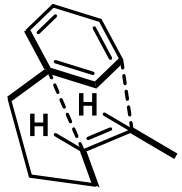
Tanja Gaich. *In Comprehensive Organic Synthesis*, 2nd ed.; Elsevier: **2014**; Vol. *5*, pp 703−731; Christian G. Bochet et al. *Chem. Rev.* **2016**, *116*, 9816-9849.

Meta-photocycloadditions: Regioselectivity & Stereoselectivity

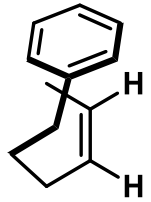
2. Stereoselectivity: *endo* vs. *exo*



Intermolecular
(exciplex model)
***endo* orientation favored**

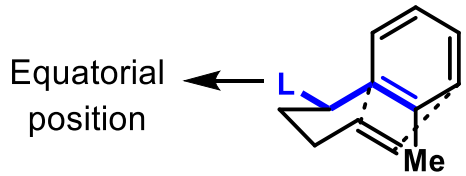


Intramolecular
(exciplex model)
***exo* orientation favored**



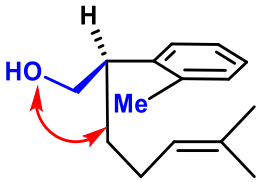
Intramolecular
(exciplex model)
***endo* orientation disfavored**

Diastereoselectivity (π-facial selectivity)

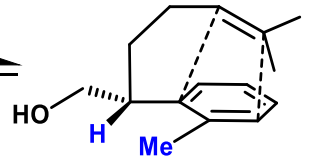


the ^{1,3}A-starin model.

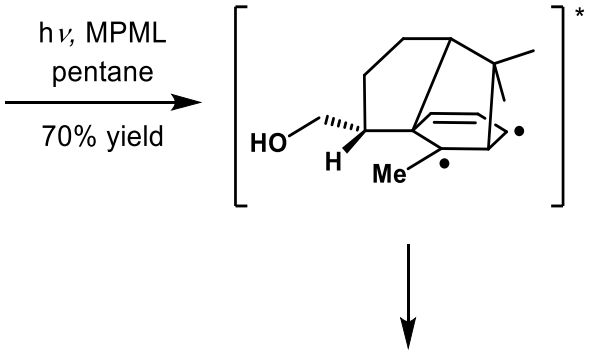
Application: Total Synthesis of (-) Penifulvin A

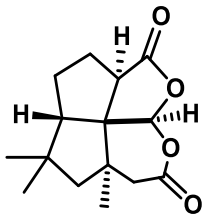


***syn*-1**

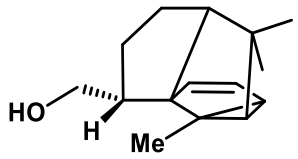


***anti*-1**





(–)-Penifulvin A
Optically pure
$[\alpha]_D^{20}$ = –127 (*c* 0.35, $CHCl_3$)



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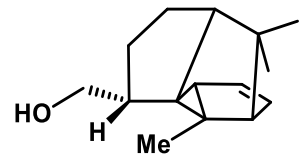

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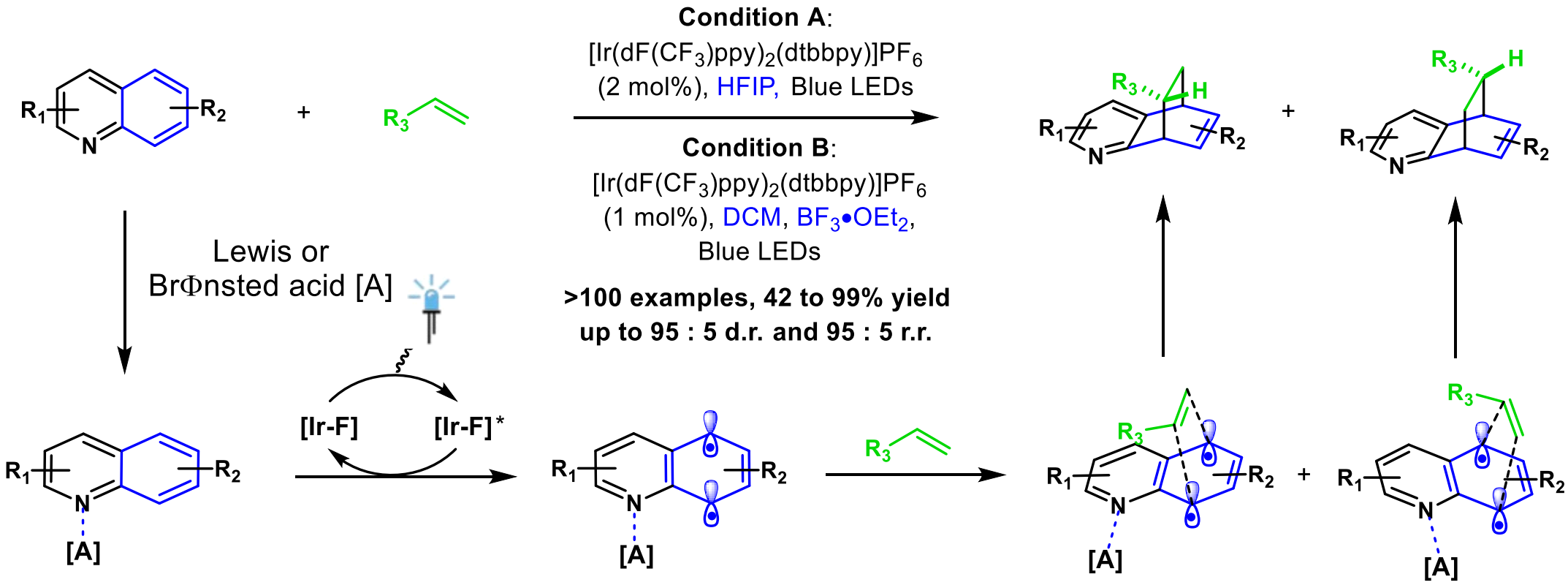
Tanja Gaich. *In Comprehensive Organic Synthesis*, 2nd ed.; Elsevier: **2014**; Vol. *5*, pp 703−731; Tanja Gaich et al. *J. Am. Chem. Soc.* **2009**, *131*, 452-453.

Content

Para-photocycloadditions : Dearomatization of Quinolines



Activated by Lewis or BrΦnsted acid

Excited by EnT process

Regio- and stereocontrol by spin density, dipole moment, SOMO→CH interaction and solvent effect

Frank Glorius et al. *Science* **2021**, *371*, 1338–1345.

Para-photocycloadditions: Mechanistic Investigations

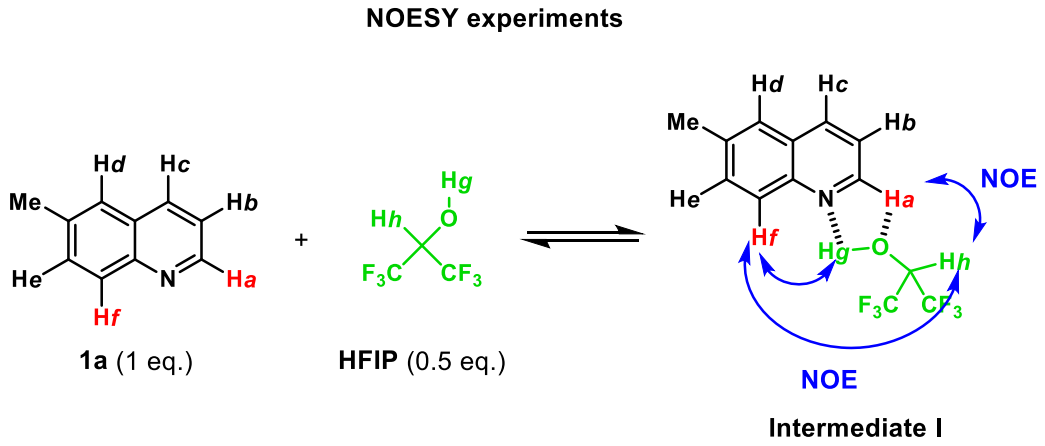
1. Probing H-bonding between HFIP and quinoline

1.1 ^{1}H NMR titration experiments: indicating complexation

1.2 NOESY experiments: intermolecular NOE observed

1.3 Job-plot analysis: indicating 1:1.5 (**1a**:HFIP) stoichiometry

1.4 UV-Vis spectra: indicating hydrogen-bonding formed



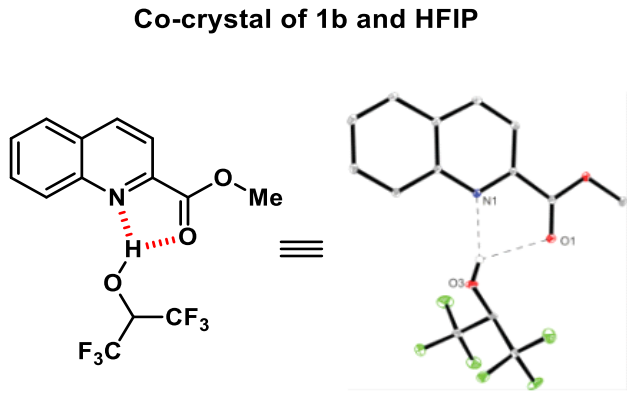
2. Probing triplet-triplet energy transfer process

2.1 Stern-Volmer luminescence quenching analysis

2.2 Control experiments with triplet quenchers

2.3 Comparison of various photosensitizers

2.4 Exclusion of the single electron transfer event

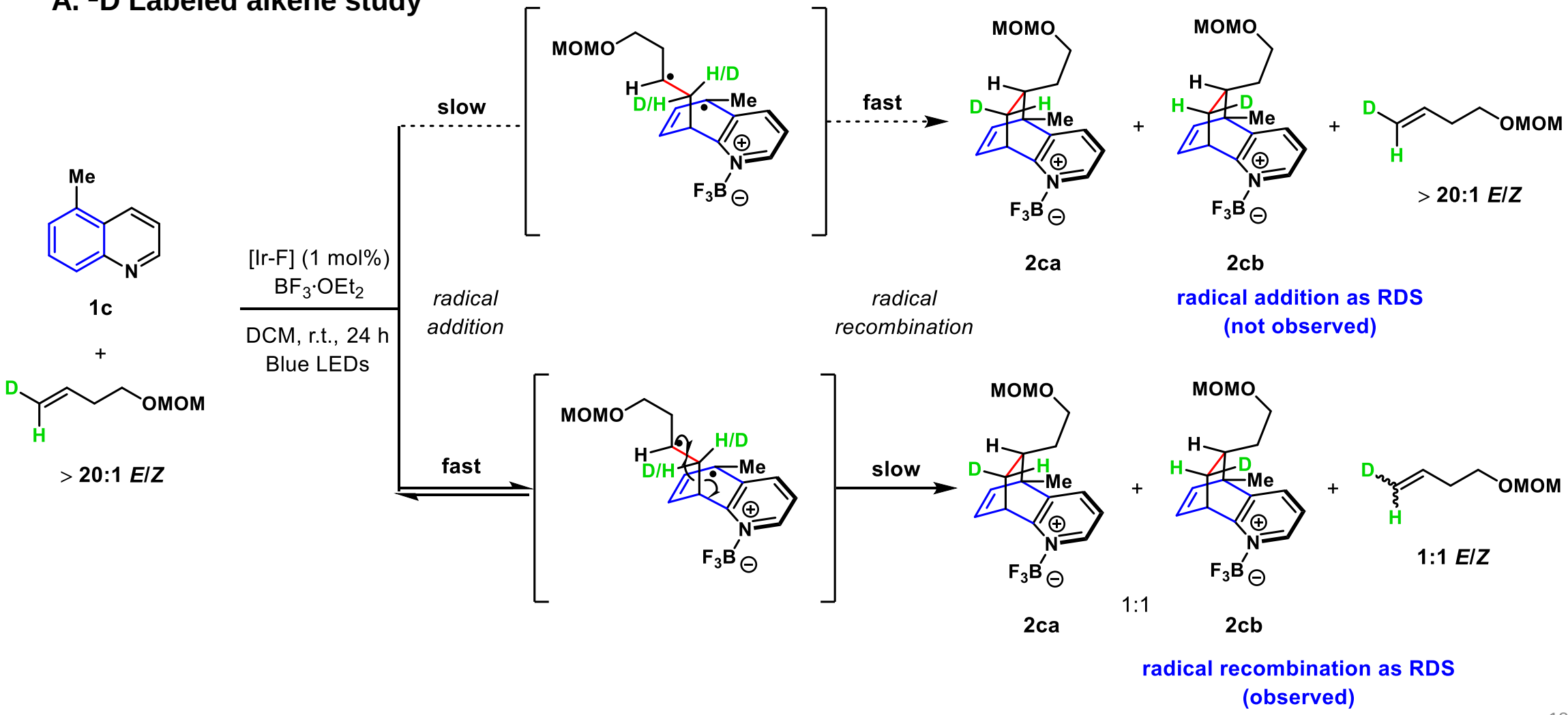


Frank Glorius et al. *Science* **2021**, *371*, 1338–1345.

Para-photocycloadditions: Mechanistic Investigations

3. Probing regio- and stereocontrol for the reaction: Selectivity-determining step

A. ^{2}D Labeled alkene study

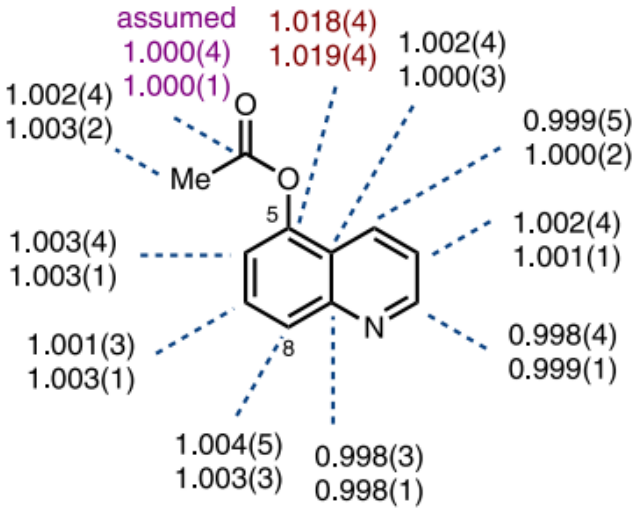


K. N. Houk, Frank Glorius, Shuming Chen, M. Kevin Brown et al, *J. Am. Chem. Soc.* **2022**, *144*, 17680−17691.

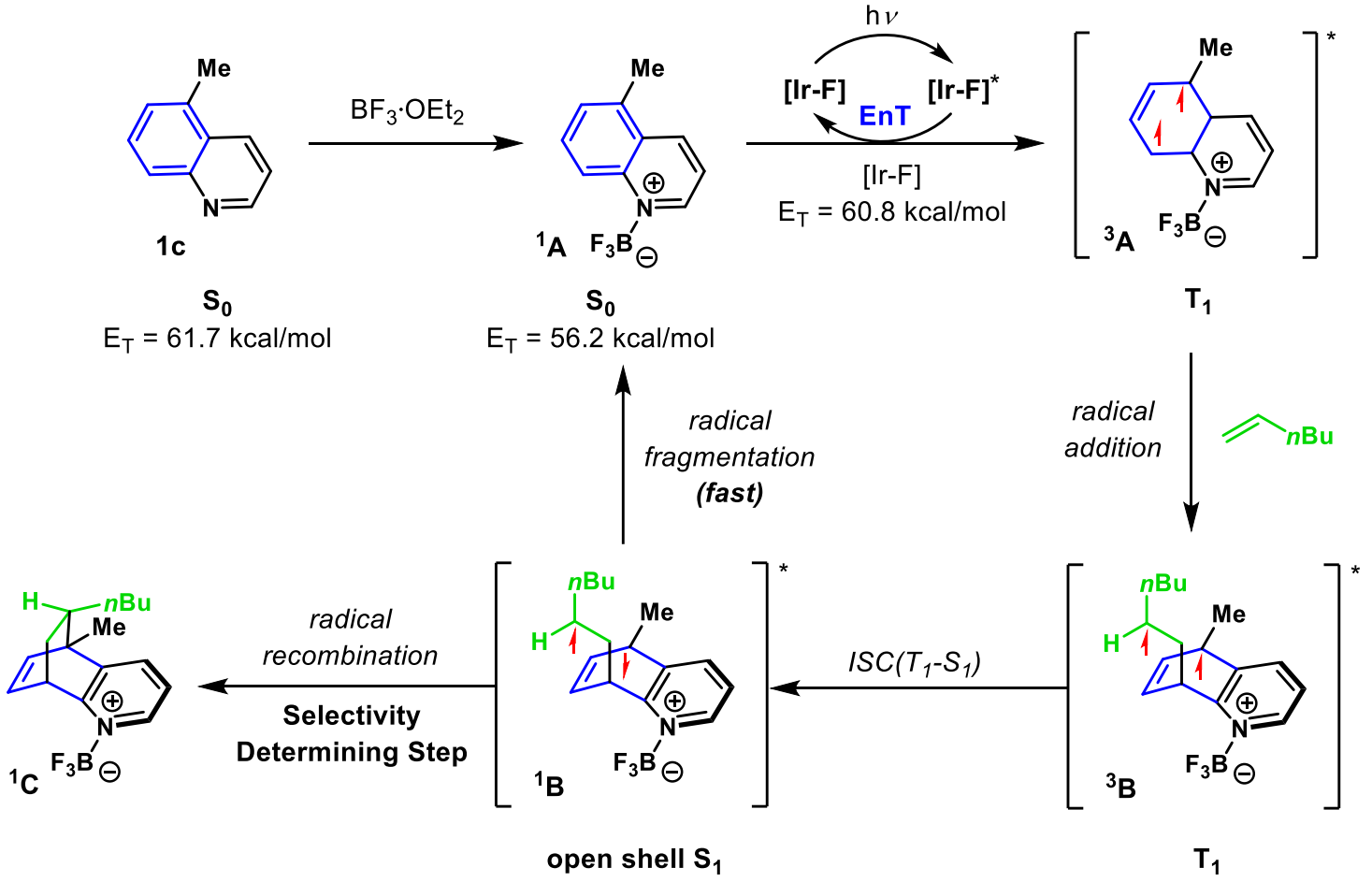
Para-photocycloadditions: Mechanistic Investigations

3. Probing regio- and stereocontrol for the reaction: Selectivity-determining step

B. ^{13}C-KIE study



C. Propoesd mechanism



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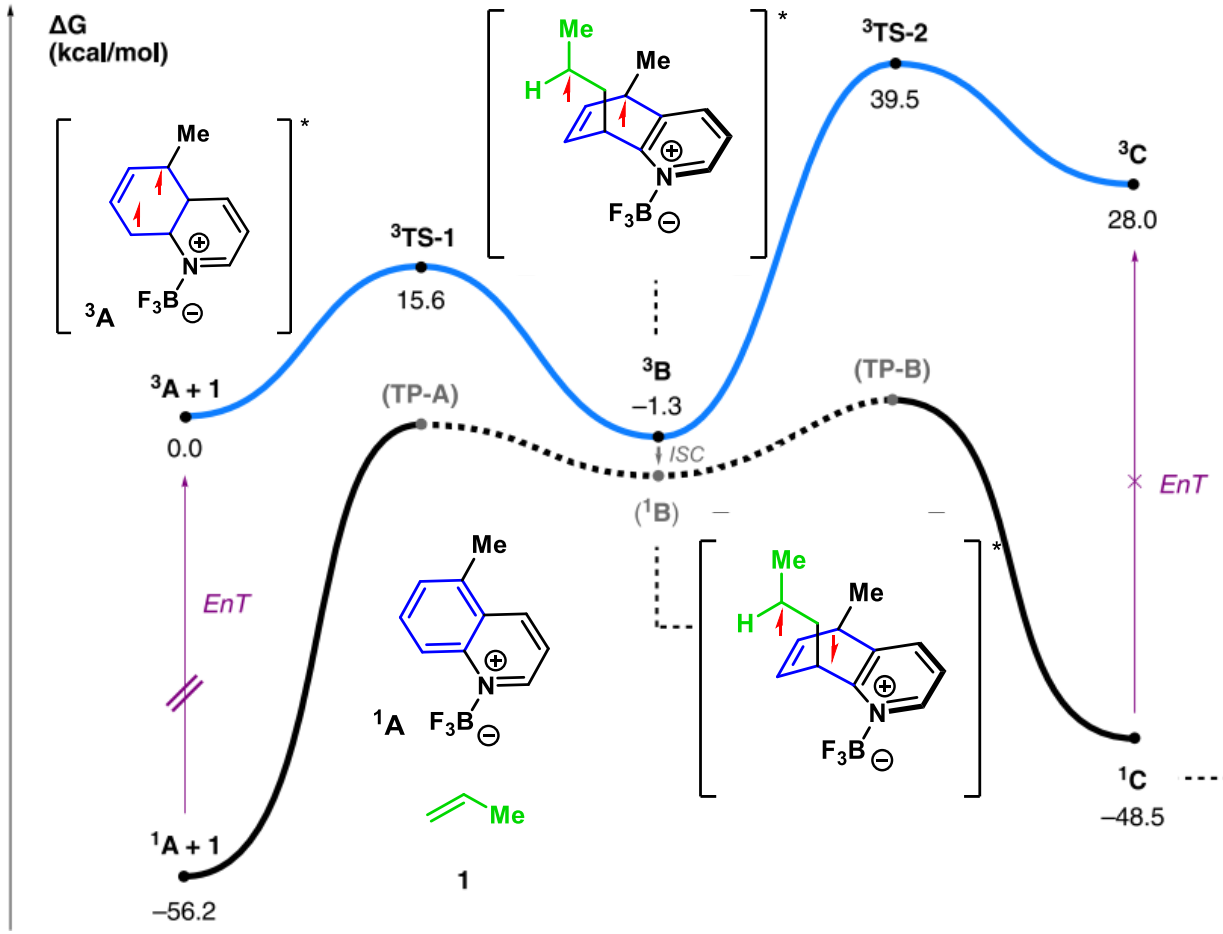
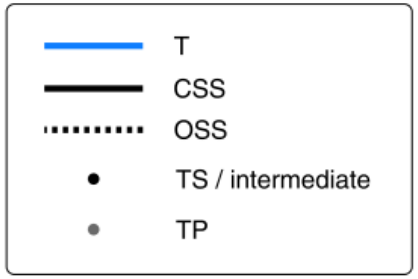
Para-photocycloadditions: Mechanistic Investigations

3. Probing regio- and stereocontrol for the reaction: Selectivity-determining step

D. DFT Calculation



Triplet (T)
Open-shell singlet (OSS)
Closed-shell singlet (CSS)



Chemo- and diastereoselectivities of the reaction are controlled by the rate of ISC from ^{3}B to ^{1}B, as well as the energies of the OSS to CSS TPs.

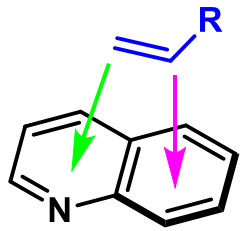
K. N. Houk, Frank Glorius, Shuming Chen, M. Kevin Brown et al, *J. Am. Chem. Soc.* **2022**, *144*, 17680−17691.

Para-photocycloadditions: Mechanistic Investigations

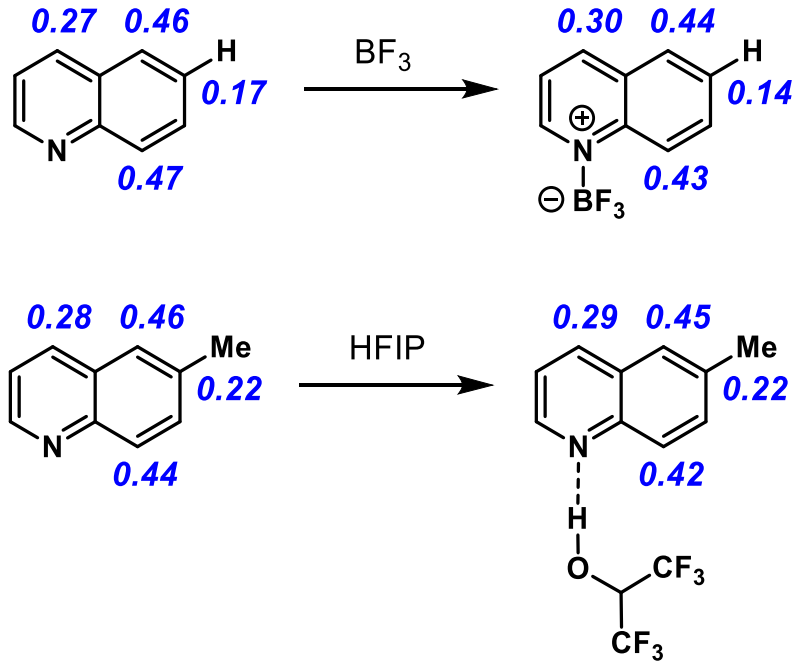
3. Probing regio- and stereocontrol for the reaction: pyridine moiety or benzene moiety?

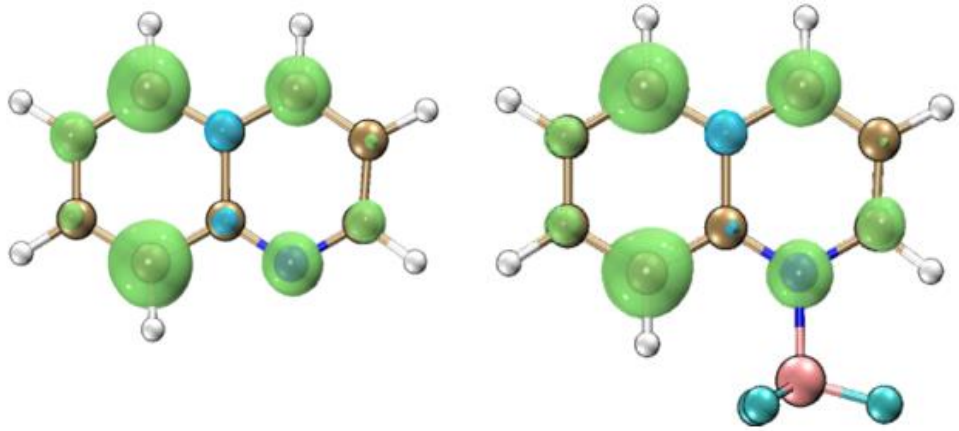
Spin Densities: higher on the benzene moiety

Regioselectivity I



benzene vs pyridine
benzene



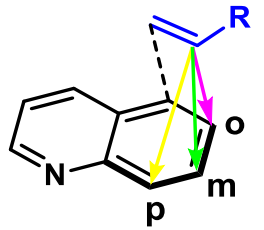


K. N. Houk, Frank Glorius, Shuming Chen, M. Kevin Brown et al, *J. Am. Chem. Soc.* **2022**, *144*, 17680−17691.

Para-photocycloadditions: Mechanistic Investigations

3. Probing regio- and stereocontrol for the reaction: *ortho* or *para* addition?

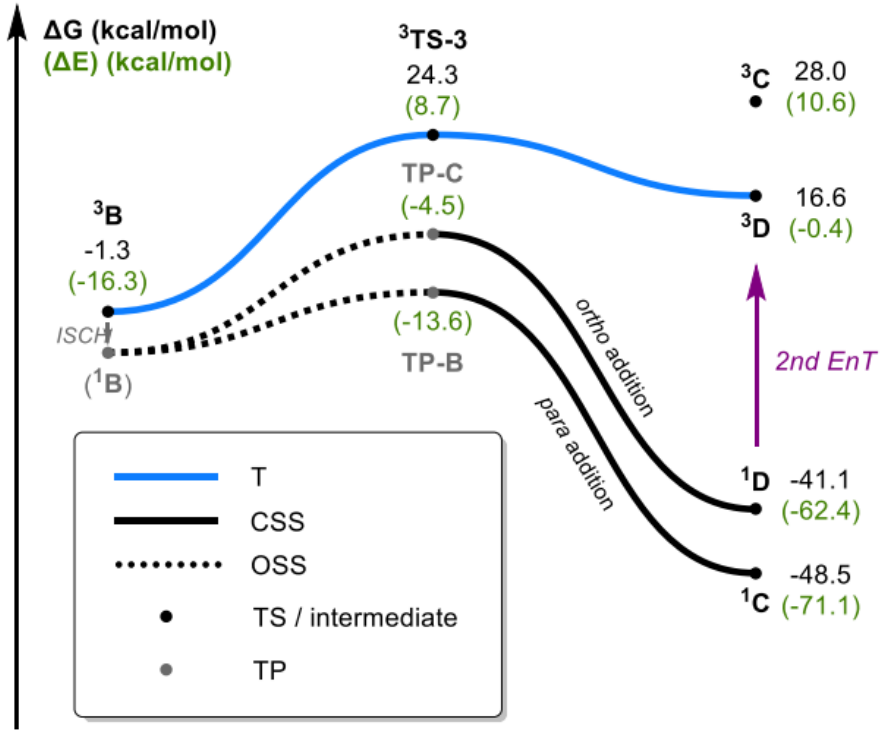
Regioselectivity II

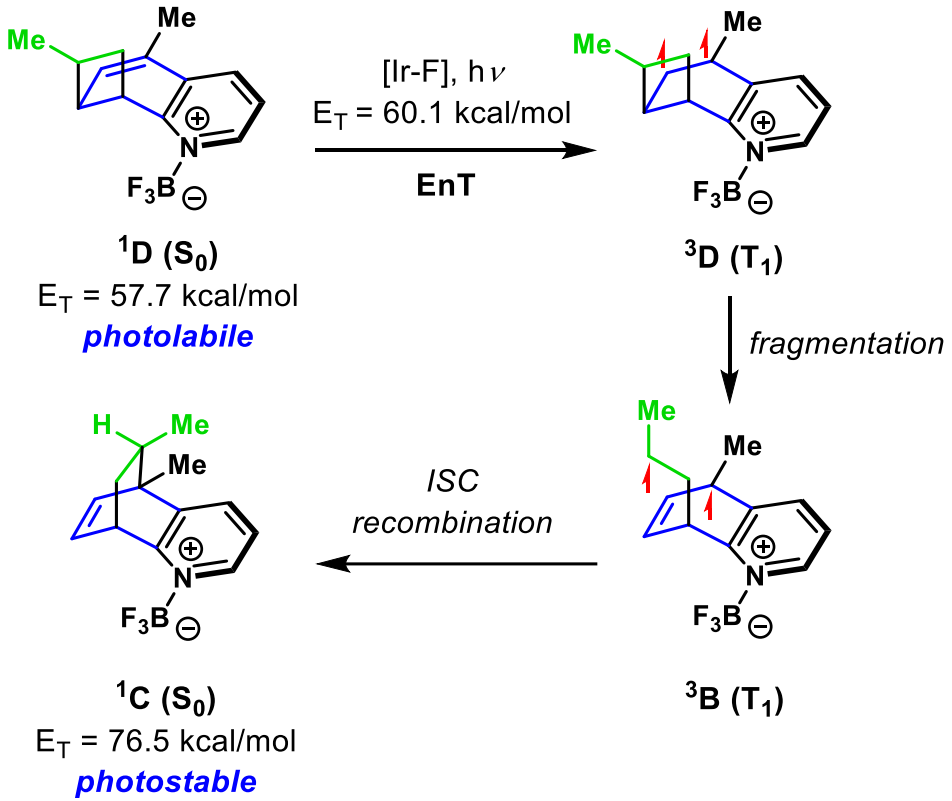


ortho vs meta vs para

para

Calculated energy diagram for *ortho* vs. *para* product formation





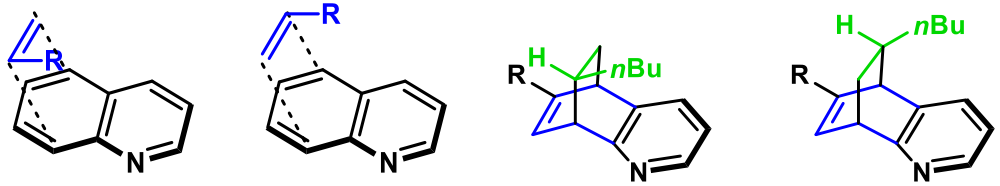
- The formation of the para cycloadduct is likely kinetically favorable for this substrate.
- The photostability of ortho and para products is different.

K. N. Houk, Frank Glorius, Shuming Chen, M. Kevin Brown et al, *J. Am. Chem. Soc.* **2022**, *144*, 17680−17691.

Para-photocycloadditions: Mechanistic Investigations

3. Probing regio- and stereocontrol for the reaction: *syn* or *anti* addition?

Regioselectivity III

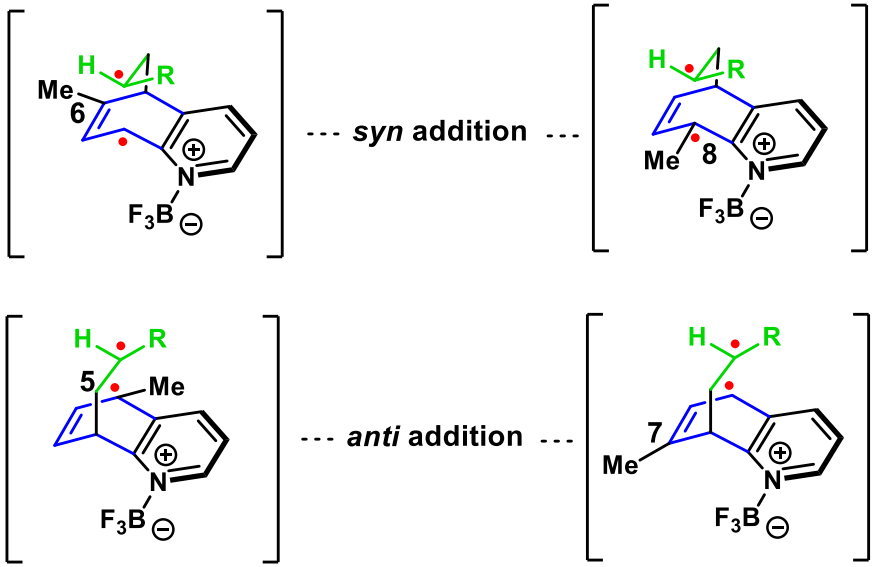


syn *vs* anti

substrate & solvent control

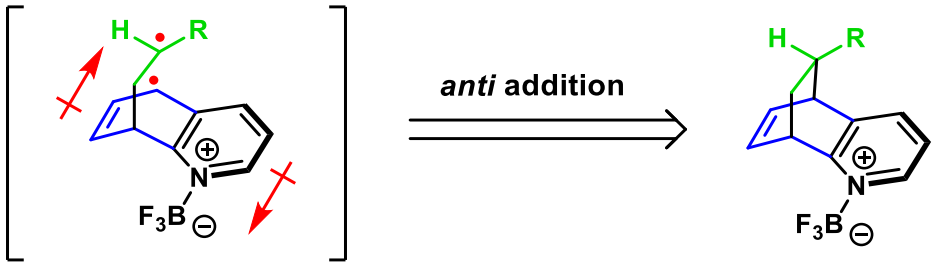
***syn* product** ***anti* product**

A. Substitution-controlled



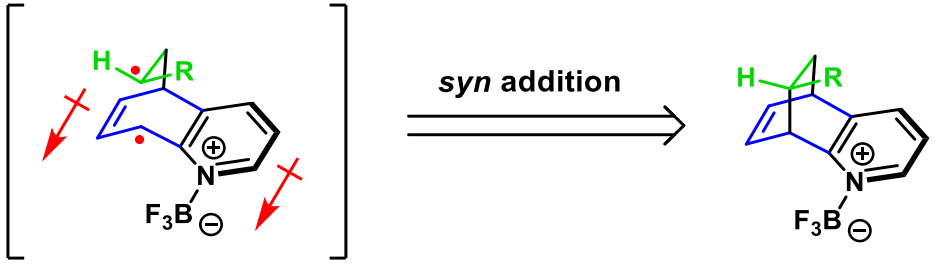
radical stabilized by hyperconjugation

B. Solvent-controlled



ρ_{calc} = 7.0 Debye
R = Me

smaller dipole intermediate stabilized by low polarity solvent



ρ_{calc} = 8.2 Debye
R = Me

larger dipole intermediate stabilized by high polarity solvent

Stability of the biradical intermediates:

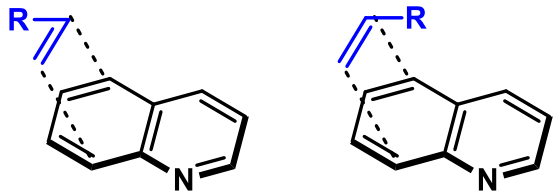
- Substitution-controlled: hyperconjugation.
- Solvent-controlled: dipole moment.

K. N. Houk, Frank Glorius, Shuming Chen, M. Kevin Brown et al, *J. Am. Chem. Soc.* **2022**, *144*, 17680−17691.

Para-photocycloadditions: Mechanistic Investigations

3. Probing regio- and stereocontrol for the reaction: endo or exo diastereoselectivity?

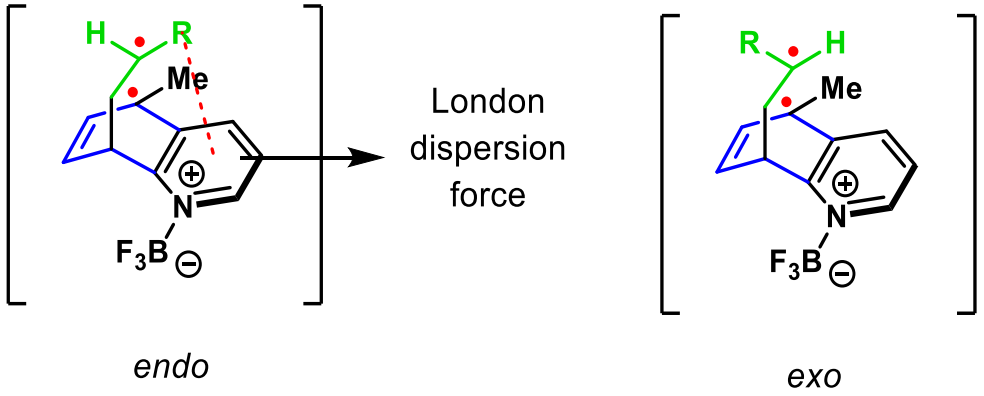
Diastereoselectivity



exo vs endo

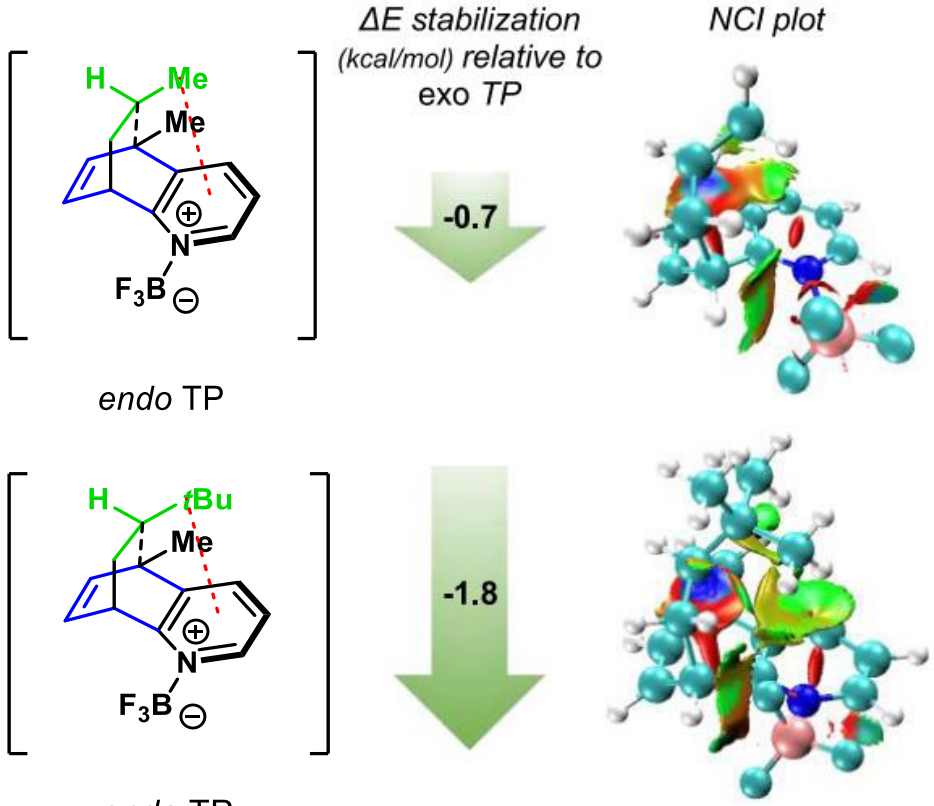
endo

A. London dispersion force



endo *exo*

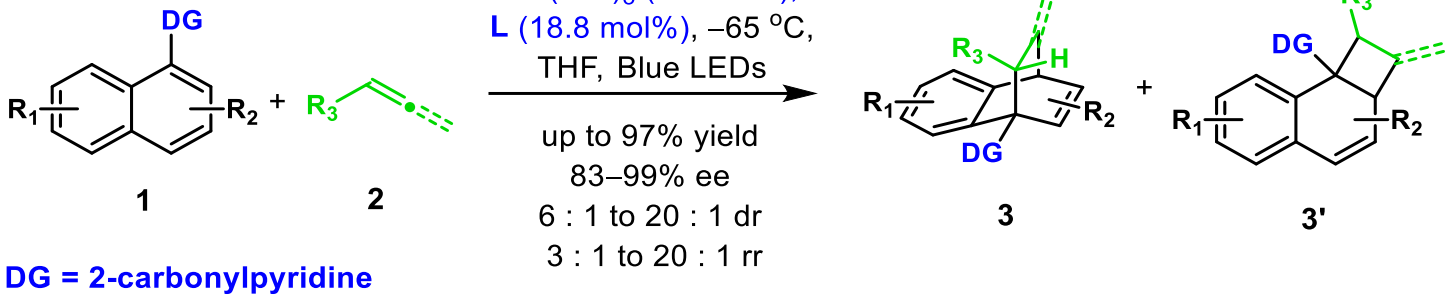
B. Computational investigation of dispersion effects

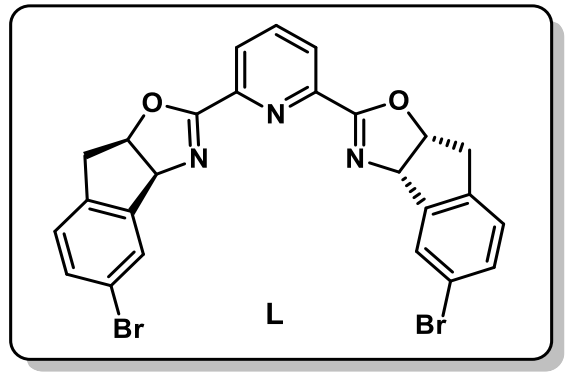


London dispersion has the effect of steering diastereoselectivity toward the endo product isomer.

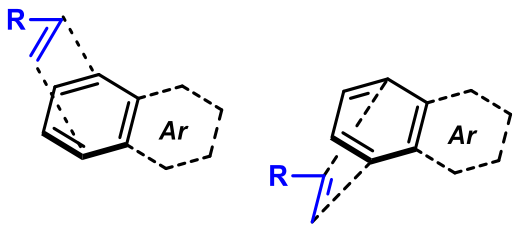
K. N. Houk, Frank Glorius, Shuming Chen, M. Kevin Brown et al, *J. Am. Chem. Soc.* **2022**, *144*, 17680−17691.

Para-photocycloadditions: Enantioselectivity

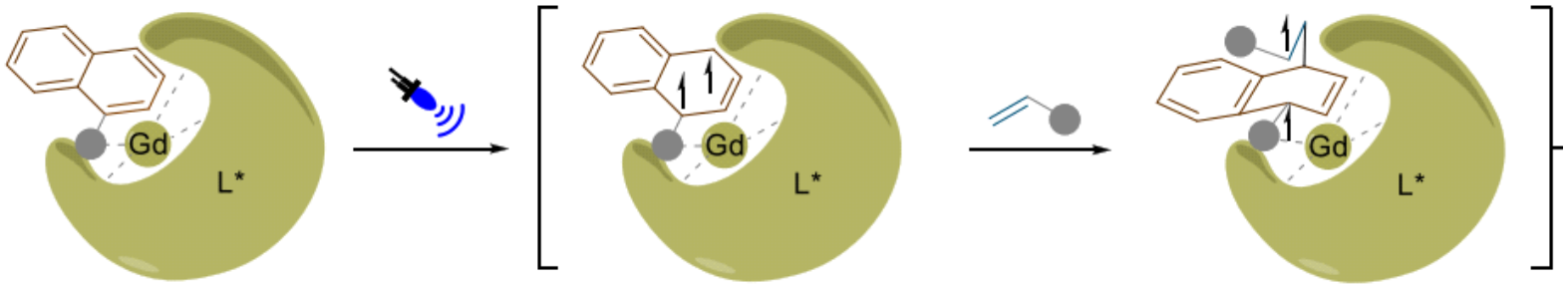




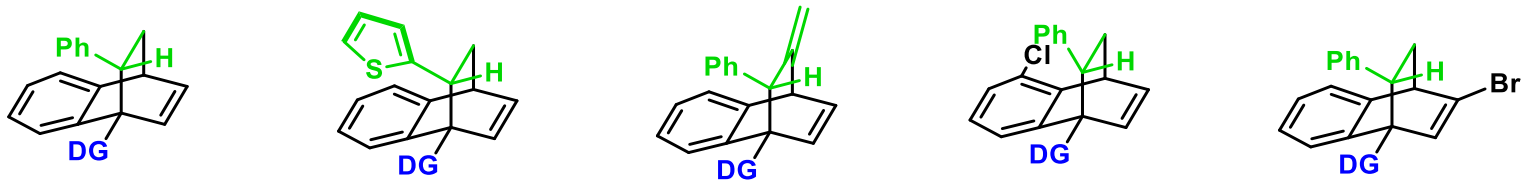
Enantioselectivity



Si face *vs Re* face



Selected examples:



3a, 91% yield
3a:**3a'** = >20:1
>20:1 dr, >99% ee

3b, 75% yield
3b:**3b'** = >20:1
20:1 dr, 94% ee

3c, 61% yield
3c:**3c'** = >20:1
>20:1 dr, 93% ee

3d, 96% yield
3d:**3d'** = >20:1
>20:1 dr, 95% ee

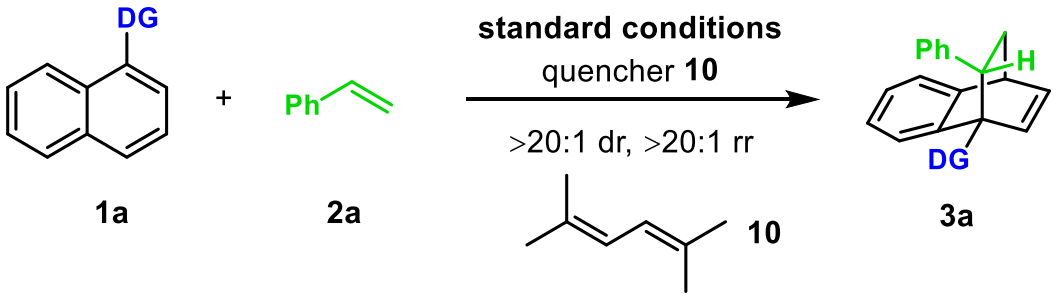
3e, 54% yield
3e:**3e'** = 10:1
6:1 dr, 90% ee

Shu-Li You et al. *J. Am. Chem. Soc.* **2024**, *146*, 16982−16989.

Para-photocycloadditions: Enantioselectivity

Mechanistic Investigations:

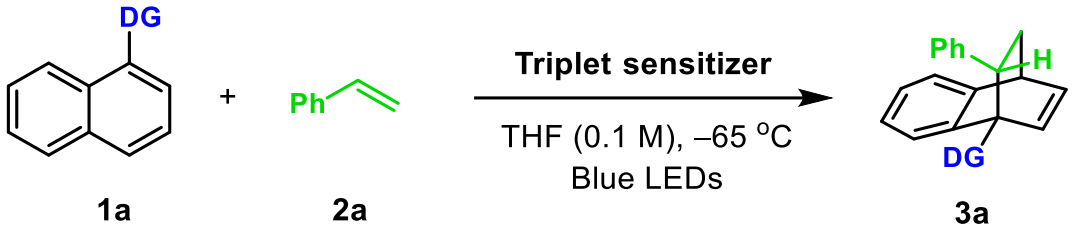
A. Quenching experiments



1a 2a 3a

entry	quencher	NMR yield (%)	ee (%)
1	O_2 (1 atm)	26	96
2	**10** (100 mol %)	5	96
3	**10** (50 mol %)	10	97
4	**10** (20 mol %)	26	95
5	**10** (10 mol %)	46	95

B. Racemic reactions using triplet sensitizers



1a 2a 3a

entry	triplet sensitizer, E_T	NMR yield (%)	dr	rr
1	benzil (40 mol%), ~54 kcal/mol	17	1.1:1	5.7:1
2	$[Ir(ppy)_2(dtbbpy)]PF_6$ (2 mol%) 49.2 kcal/mol	23	1.9:1	3.1:1
3	$[Ir(dFCF_3ppy)_2(dtbbpy)]PF_6$ (2 mol%) 61.8 kcal/mol	54	1.8:1	3.8:1

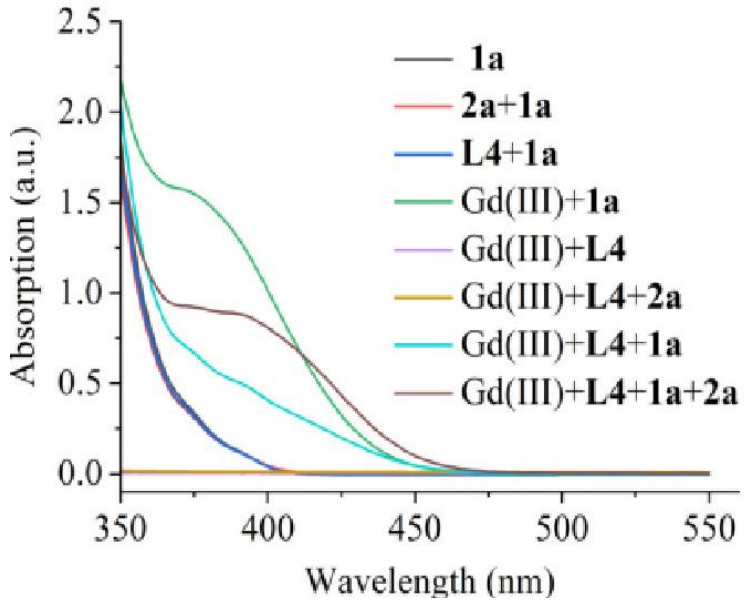
- EnT process was confirmed by quenching experiments involving a triplet-state complex derived from Gd(III)/PyBox.
- The activity and selectivity of the reaction decreased in the presence of triplet sensitizers.

Shu-Li You et al. *J. Am. Chem. Soc.* **2024**, *146*, 16982−16989.

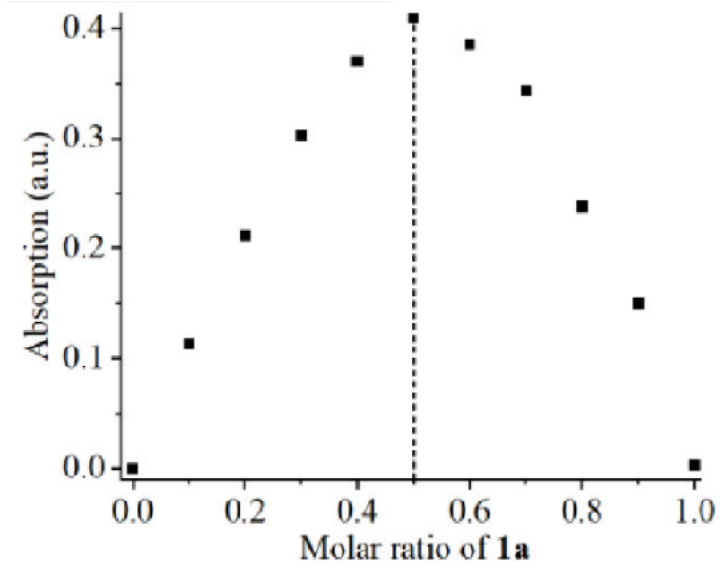
Para-photocycloadditions: Enantioselectivity

Mechanistic Investigations:

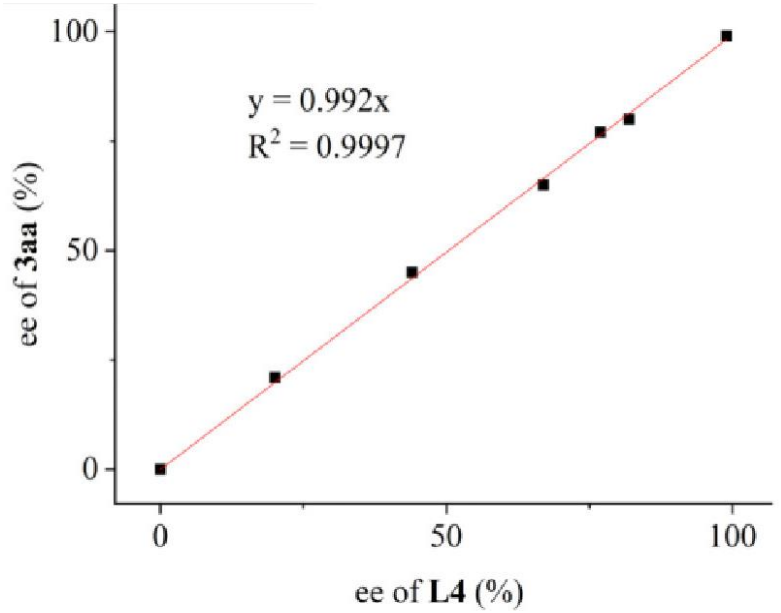
C. UV-Vis-absorption spectroscopy



D. Job's plot at λ = 448 nm



E. Nonlinear effect study

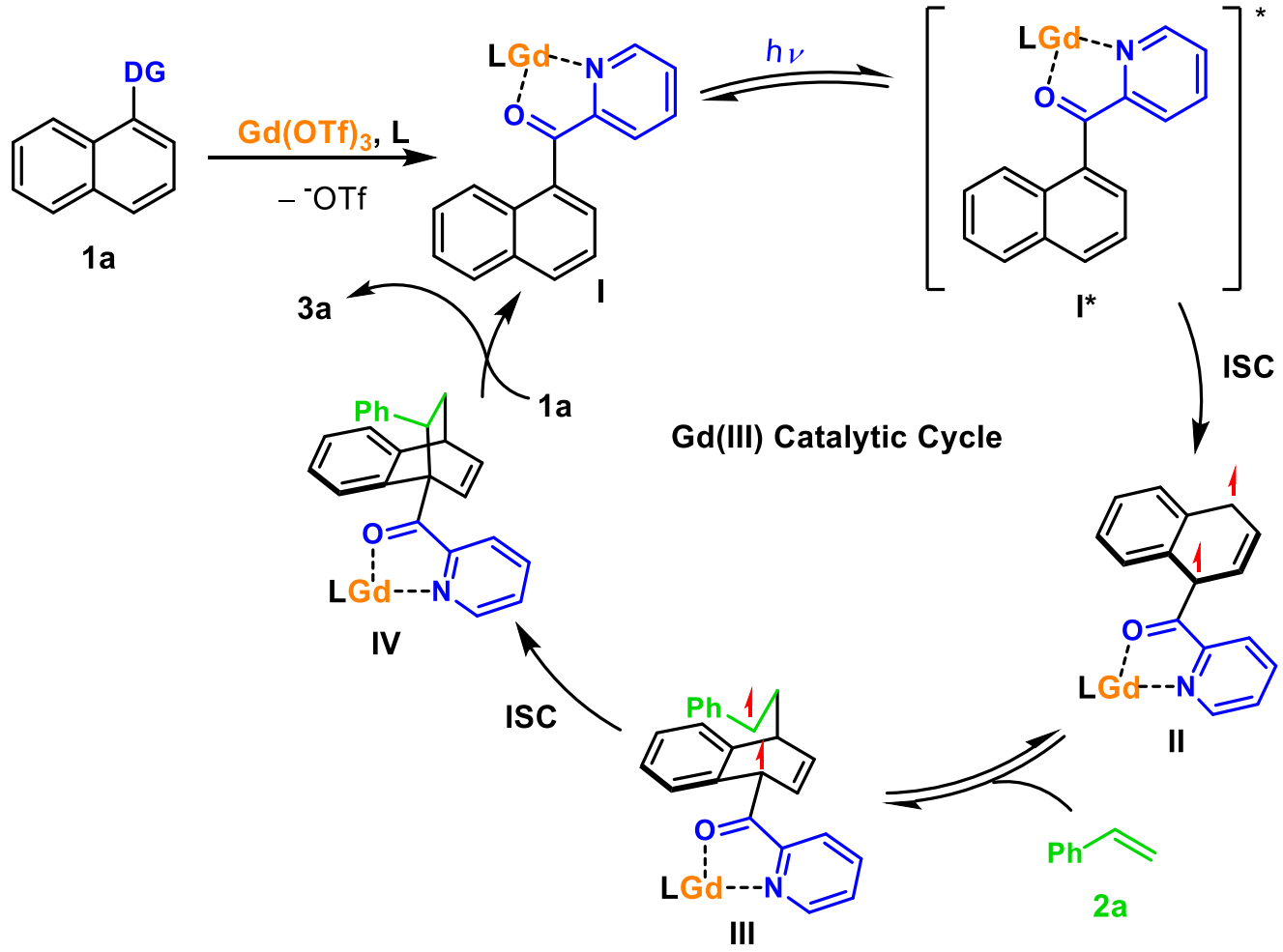


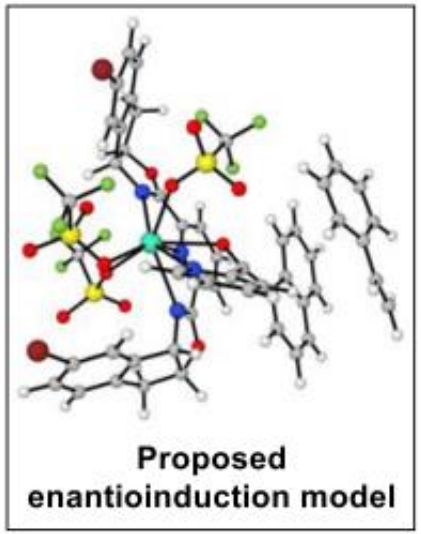
- The coordination between the catalyst and substrate was in a 1:1 molar ratio.
- One ligand molecule was involved in each enantio-determining transition state.

Shu-Li You et al. *J. Am. Chem. Soc.* **2024**, *146*, 16982−16989.

Para-photocycloadditions: Enantioselectivity

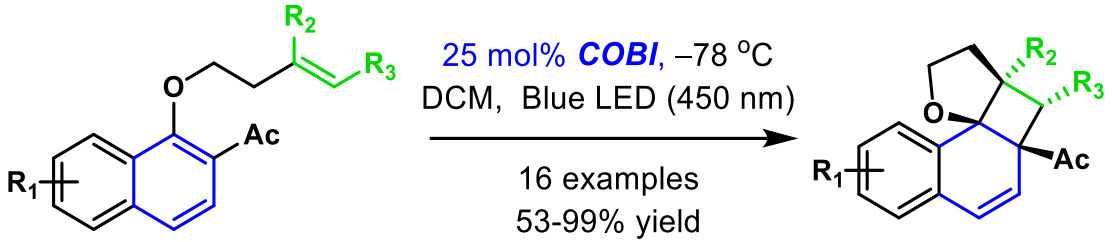
Mechanistic Investigations: Propoesd mechanism

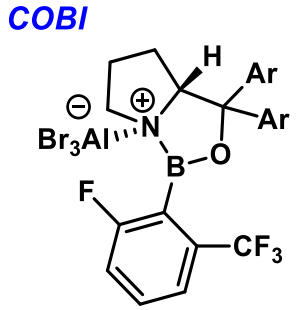




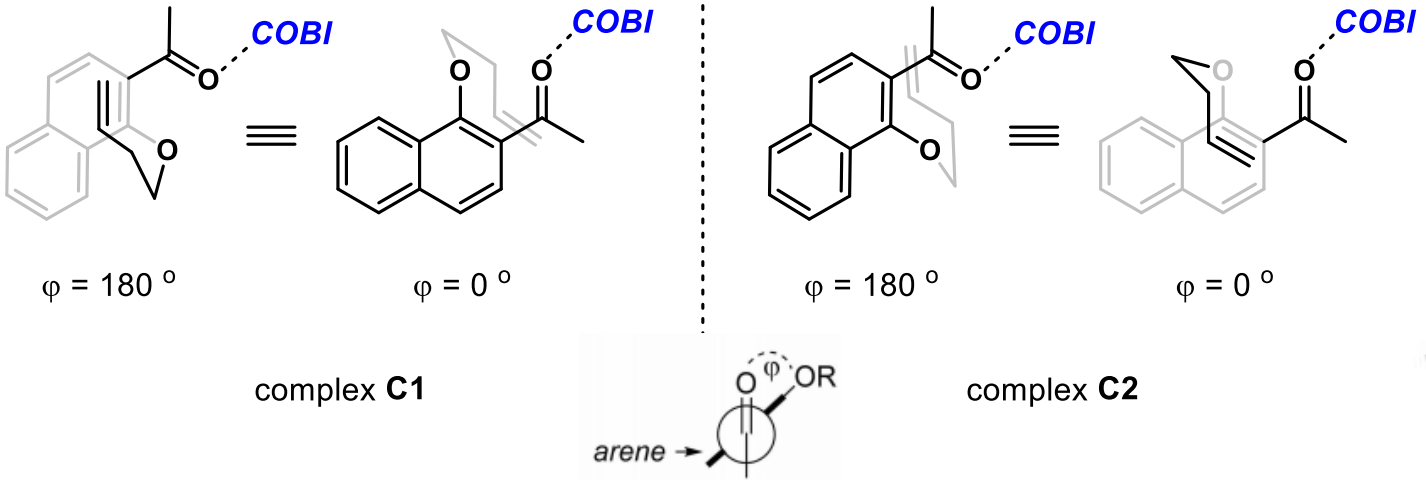
Shu-Li You et al. *J. Am. Chem. Soc.* **2024**, *146*, 16982−16989.

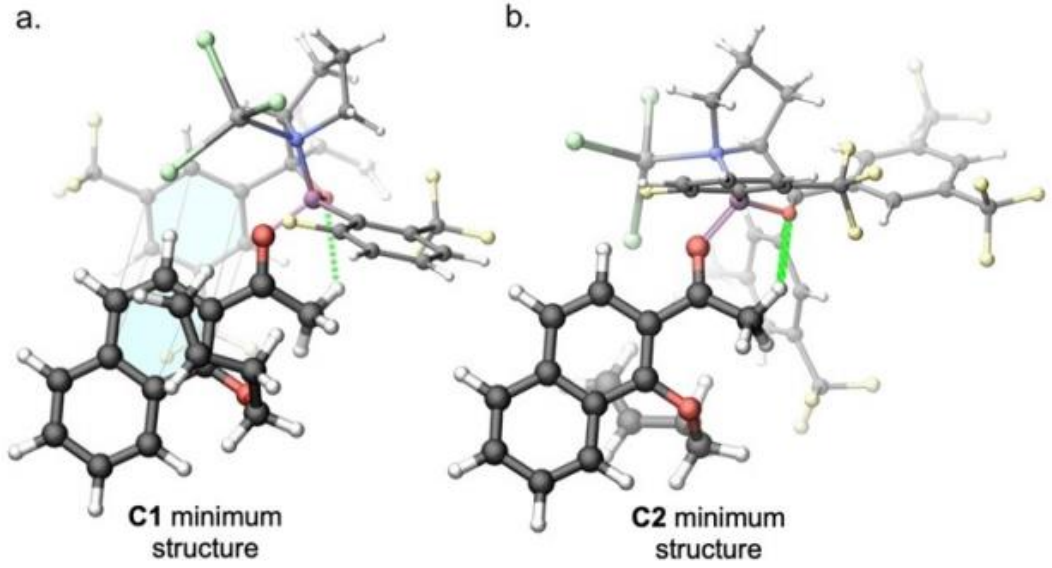
Ortho-photocycloadditions: Enantioselectivity





COBI coordination model:





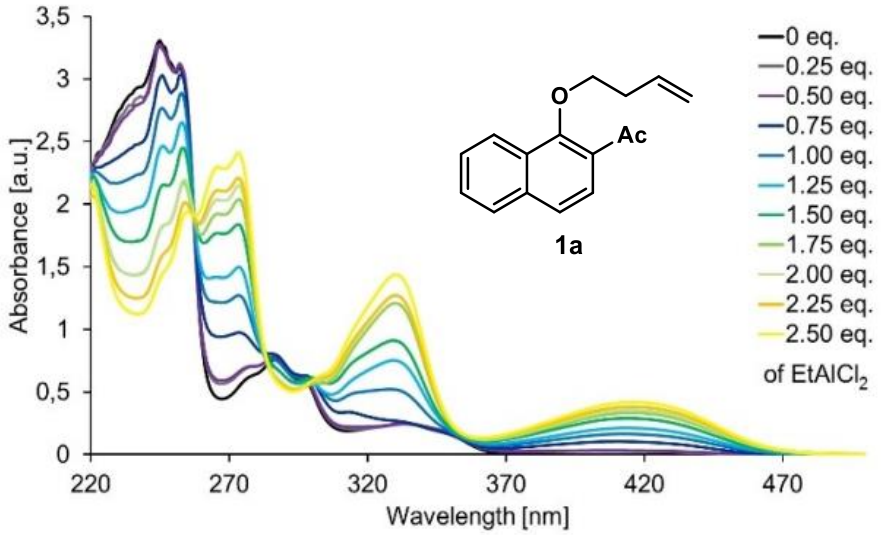
Methyl group of the acetyl substituent is involved in a favorable hydrogen bonding interaction, which in concert with π-stacking directs the attack of the internal olefin to the *Si* face of the naphthalene core.

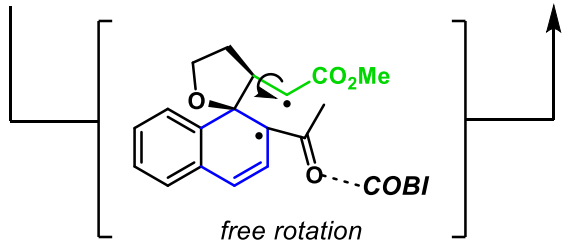
Ping Lu, Thorsten Bach et al. *Angew. Chem. Int. Ed.* **2024**, *63*, 6969–6972.

Ortho-photocycloadditions: Enantioselectivity

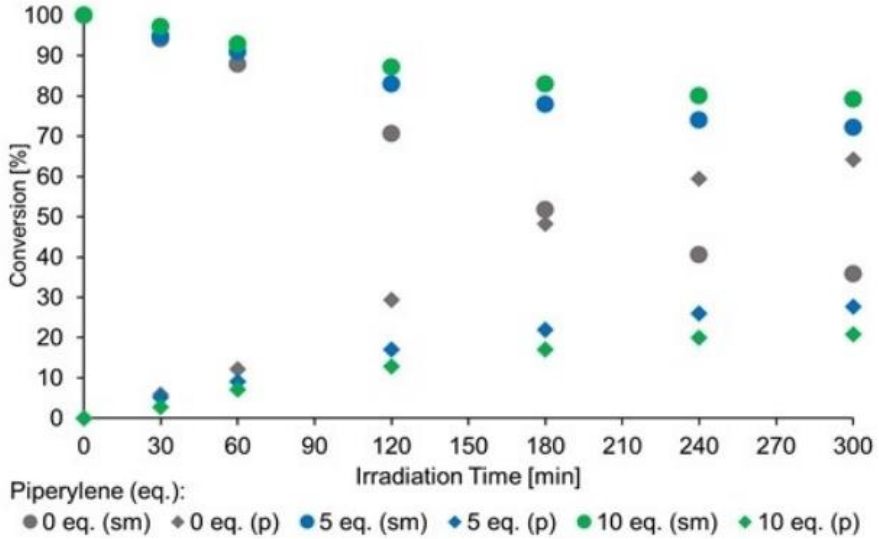
Mechanistic Investigations:

A. UV/Vis spectrum of 1a with $EtAlCl_2$ in DCM





B. Quenching experiments (1,3-pentadiene as triplet quencher)

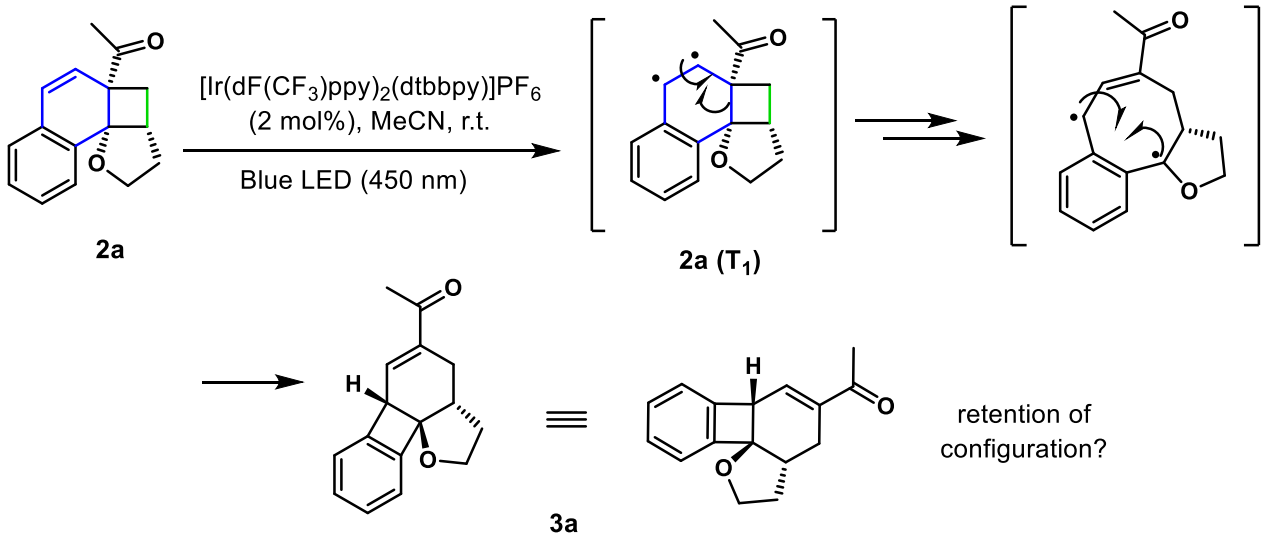


- Lewis acid coordination leads to a significant bathochromic shift of the absorption.
- EnT process was confirmed by quenching experiments and a stereoconvergent reaction course of substrate with (*E*)- or (*Z*)-olefin.

Ping Lu, Thorsten Bach et al. *Angew. Chem. Int. Ed.* **2024**, *63*, 6969–6972.

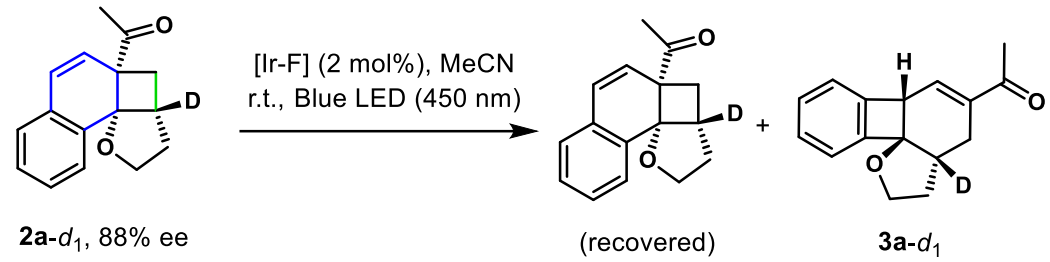
Ortho-photocycloadditions: Enantioselectivity

Skeletal rearrangement of *ortho* product:

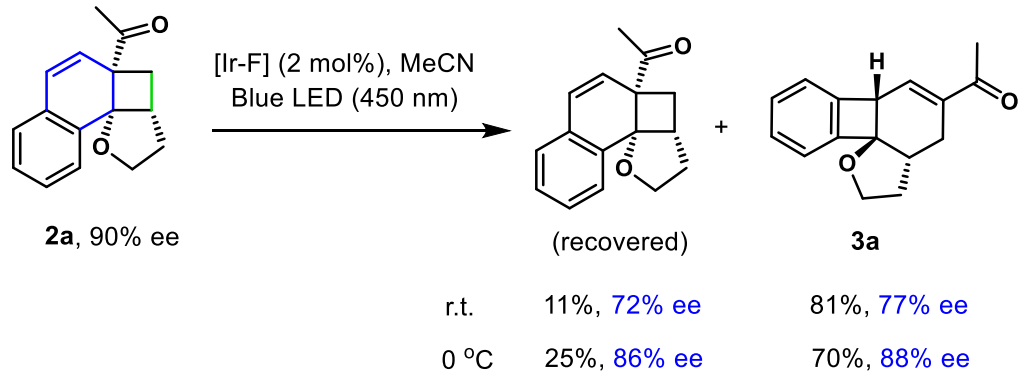


- The enantiomeric purity diminished upon skeletal rearrangement, indicating *ortho* cycloaddition was reversible, which could be suppressed at lower temperature

A. Deuteration study



B. Temperature effect

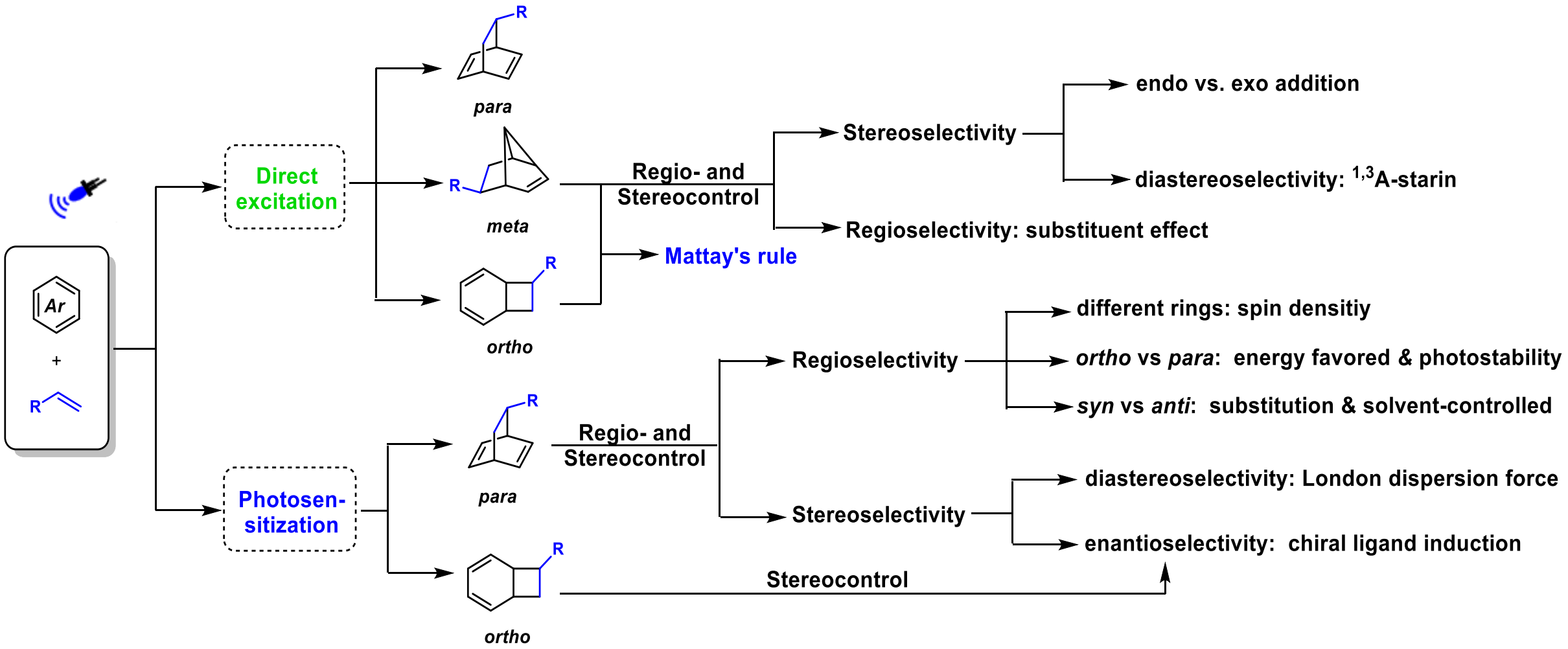


Ping Lu, Thorsten Bach et al. *Angew. Chem. Int. Ed.* **2024**, *63*, 6969–6972.

Content

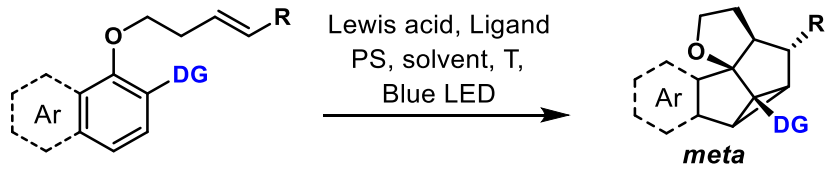
Summary and Outlook

Regio- and Stereocontrol of Arene—Alkene Photocycloadditions



Summary and Outlook

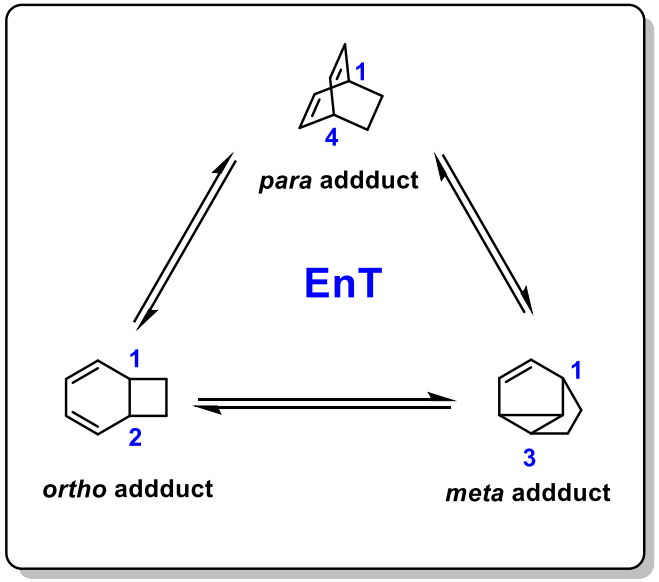
Asymmetric transformations of *meta* mode



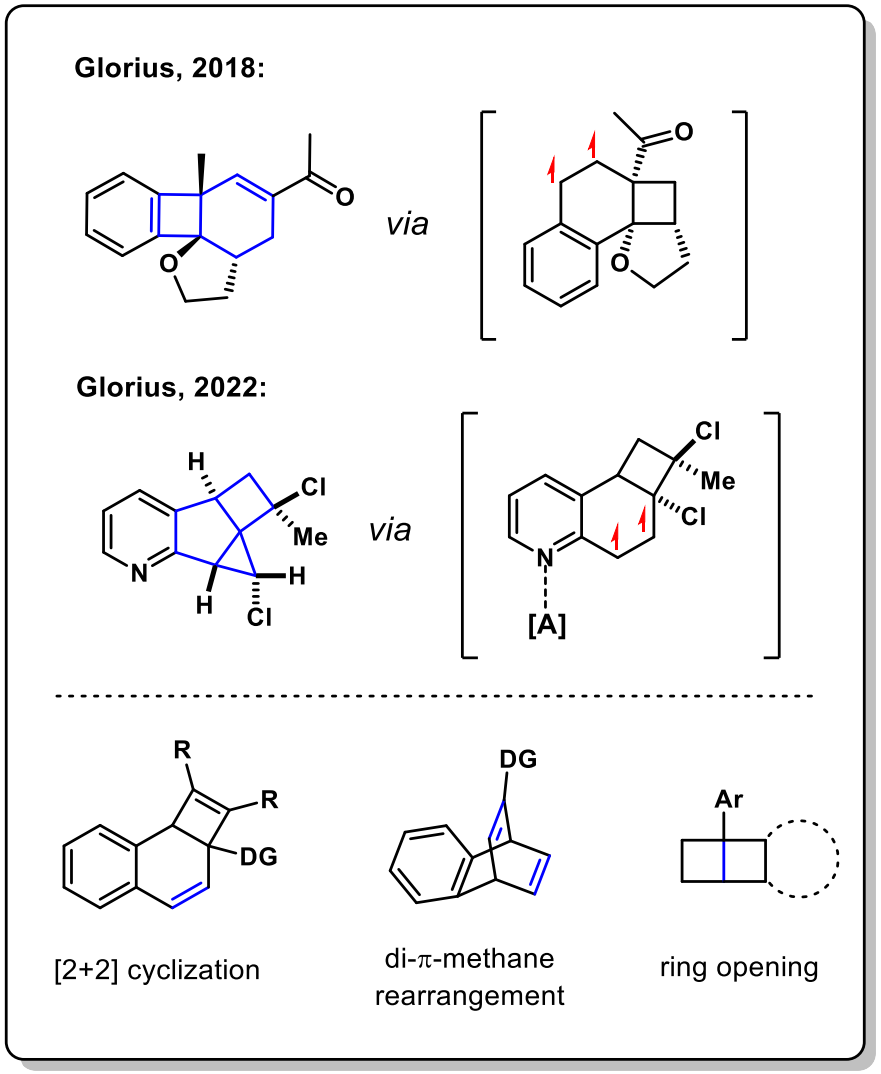
LA = $Sc(OTf)_3$, $Ni(OTf)_2$, $Ga(OTf)_3$, $Gd(OTf)_3$, $Yb(OTf)_2$, $Zr(OTf)_4$, $ZrCl_4$, $BF_3{\cdot}OEt_2$, $AlBr_3$, (Salen)Al(III), ATPH, etc.

Chiral Ligand = Box, bpy, imine, Jacobsen's ligand etc.

Mechanical insights of three modes



Utilizing photolabile intermediates for reaction design



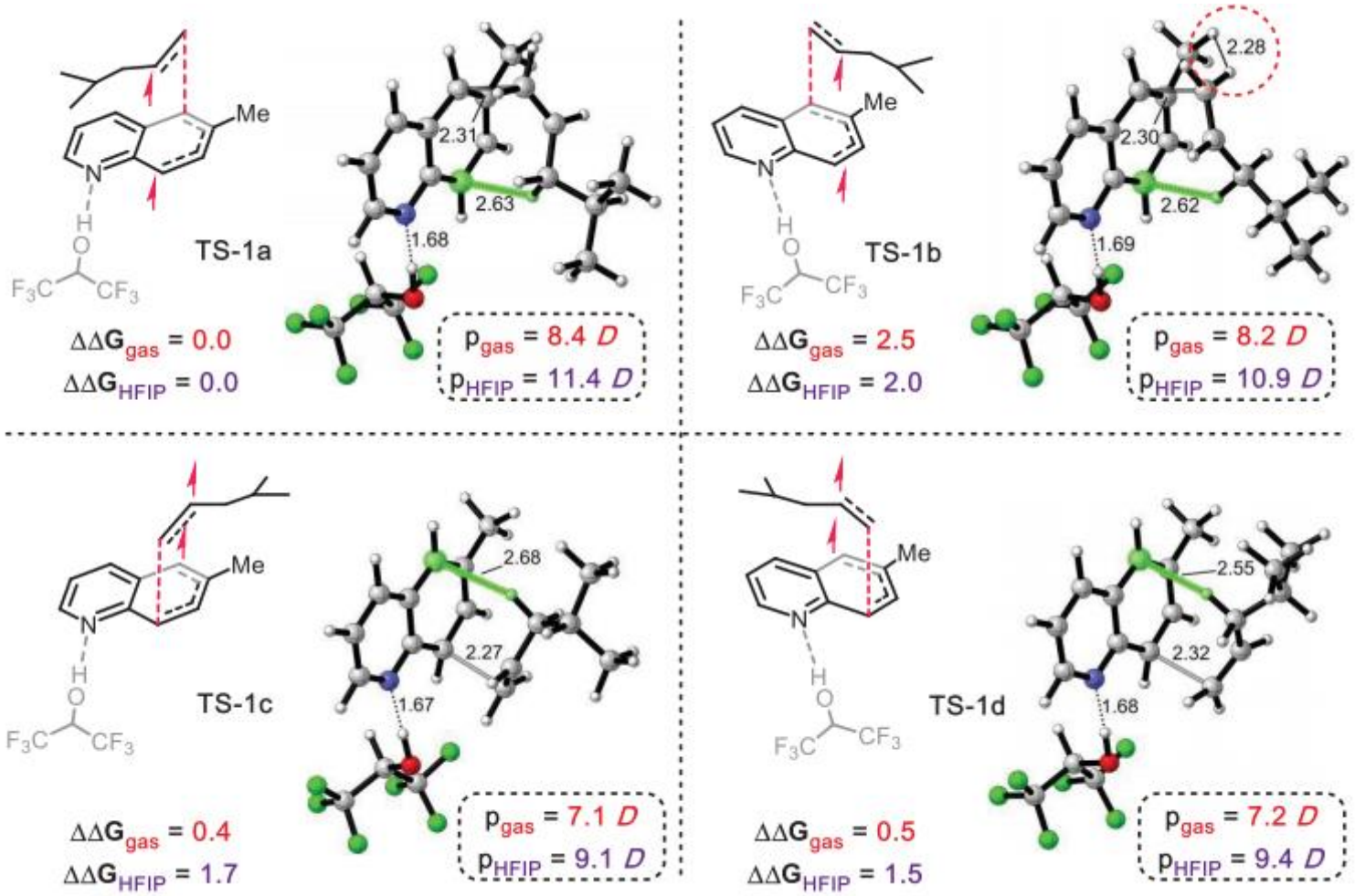
Frank Glorius et al. *J. Am. Chem. Soc.* **2018**, *140*, 8624−8628; Frank Glorius et al. *Nature Catal.* **2022**, *5*, 405-413.

Thanks for your attention

Appendix: *Para*-photocycloadditions

DFT Calculations for the [4 + 2] DAC reaction between triplet 1b and 2b

C–C-forming TS geometries, energies, dipole moments

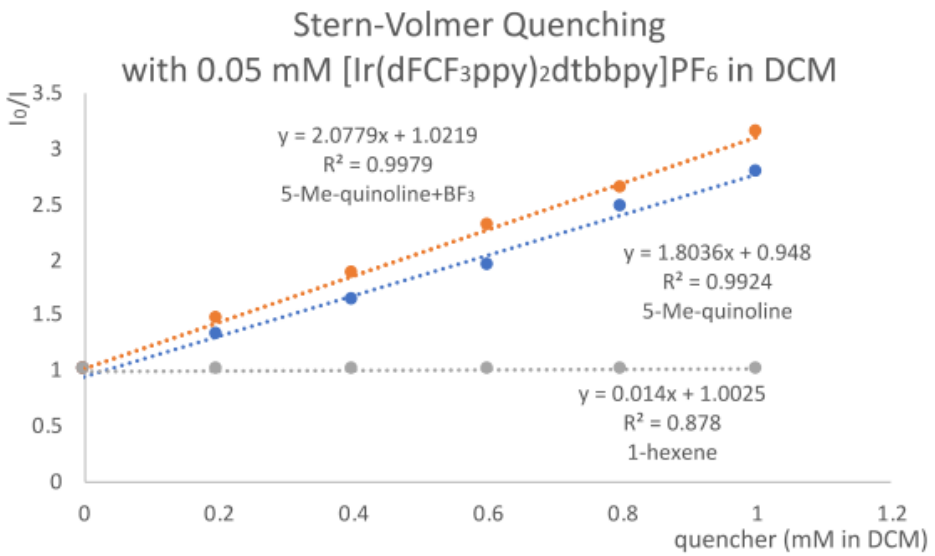


Frank Glorius et al. *Science* **2021**, *371*, 1338–1345.

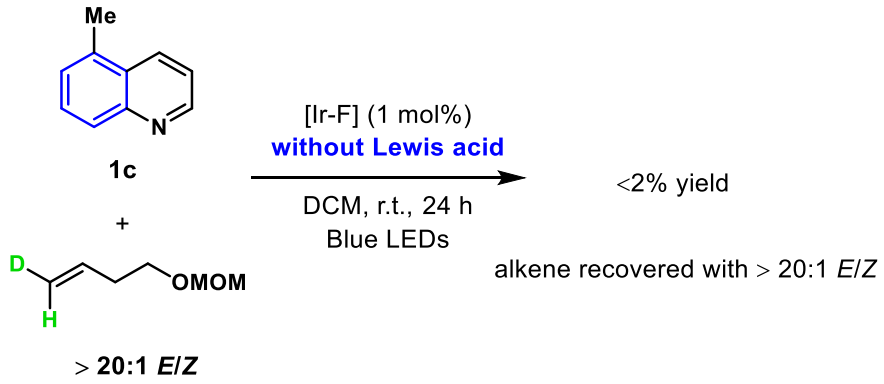
Appendix: *Para*-photocycloadditions

Probing regio- and stereocontrol for the reaction: Roles of Lewis acid and Brønsted acid

A. Stern-Volmer experiment

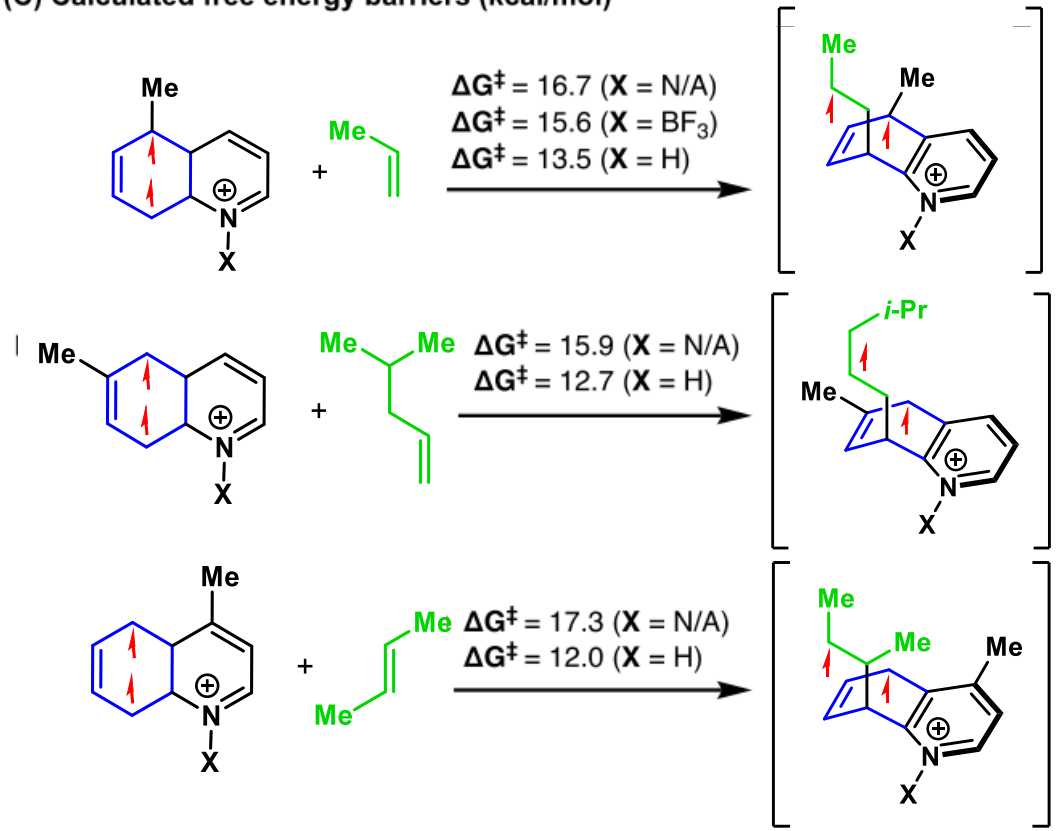


B. Deuterium-labeled alkene



Quinoline is sensitized, but radical addition to alkene does not occur

(C) Calculated free energy barriers (kcal/mol)



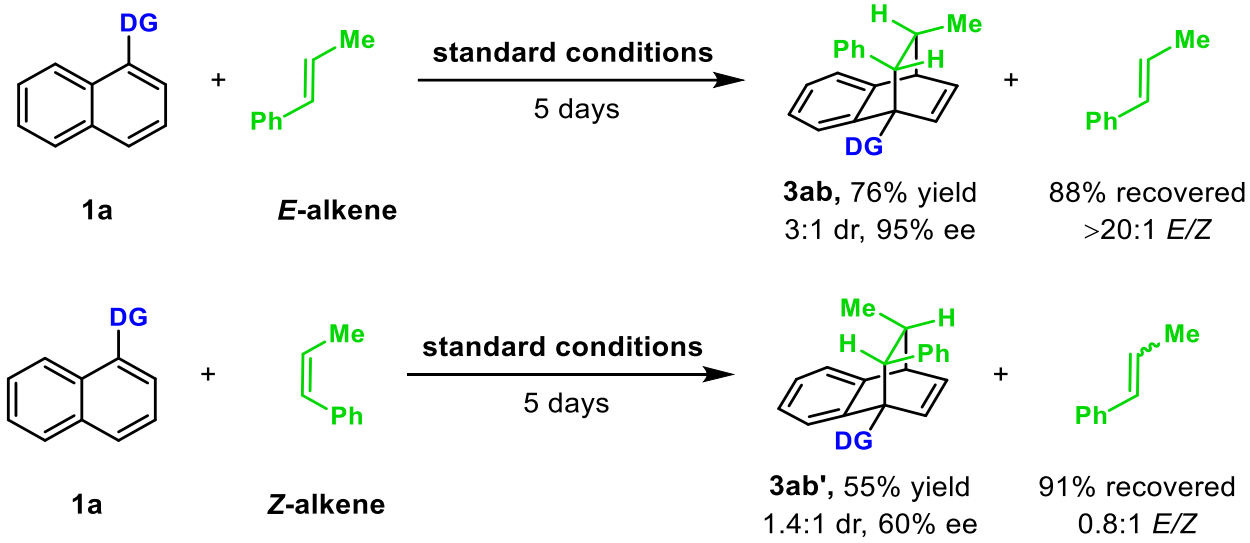
- Facilitating energy transfer by lowering E_T.
- Accelerating the radical addition step by increasing the electrophilicity of the quinoline substrate.

M. Kevin Brown et al. *J. Am. Chem. Soc.* **2022**, *144*, 17680-17691.

Appendix: *Para*-photocycloadditions

Mechanistic Investigations of asymmetric *para*-photocycloadditions

Reactions of 1a with (*E*)- or (*Z*)-alkene



Shu-Li You et al. *J. Am. Chem. Soc.* **2024**, *146*, 16982−16989.