Robert R. Knowles Group Meeting
June 4th 2021

Phil Murray

PRINCETON UNIVERSITY

Fundamentals and recent applications of visible light sensitized energy transfer (E_nT) for [2+2] and [4+2] cycloaddition

- Fundamentals
  - Definitions
  - Direct substrate excitation and why sensitization
  - Mechanisms of energy transfer
  - Photocatalyst and substrate considerations
- Applications
  - Photocatalytic olefin / olefin [2+2] cycloaddition
  - Photocatalytic olefin / carbonyl and olefin / oxime [2+2] cycloaddition (Paternò-Büchi type processes)
  - Photocatalytic dearomative [2+2] and [4+2] olefin / (hetero)arene cycloaddition
  - Enantioselective photocatalytic [2+2]

Fundamentals and recent applications of visible light sensitized energy transfer

Reviews on energy transfer and sensitization:

– Energy transfer catalysis mediated by visible light: principles, applications, directions.
  Strieth-Kalthoff, F., James, M. J., Teders, M., Pitzer, L., Glorius, F., *Chem. Soc. Rev.*, **2018**, *47*, 7190–7202.
– Visible-light-induced organic photochemical reactions through energy transfer pathways.
  Zhou, Q.-Q., Zou, Y.-Q., Lu, L.-Q., Xiao, W.-J., *ACIE*, **2019**, *58*, 1586–1604.
– Triplet energy transfer photocatalysis: Unlocking the next level
  Strieth-Kalthoff, F., Glorius, F., *Chem*, **2020**, *6*, 1888–1903.

Review on [2+2] photocycloaddition in general:

– Recent advances in the synthesis of cyclobutanes by olefin [2+2] photocycloaddition reactions.
  Poplata, S., Tröster, A., Zou, Y.-Q., Bach, T., *Chem. Rev.*, **2016**, *116*, 9748–9815.

Reviews on Paternò-Büchi and aza Paternò-Büchi in general:

– The Paternò-Büchi reaction – A comprehensive review
  D'Auria, M., *Photochem. Photobiol. Sci.*, **2019**, *18*, 2297–2362.
– Synthesis of azetidines by aza Paternò-Büchi reactions.
  Richardson, A. D., Becker, M. R., Schindler, C. S., *Chem. Sci.*, **2020**, *11*, 7553–7561.

Reviews on olefin isomerization (site and *E/Z*):

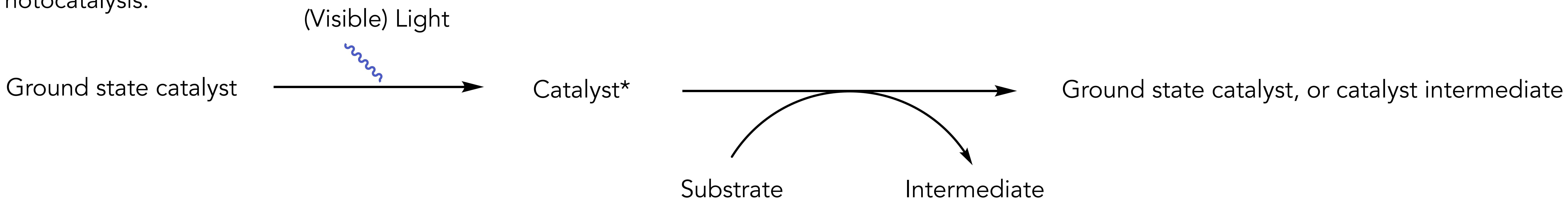
– Photocatalytic E—>Z isomerization of alkenes.
  Metternich, J. B., Gilmour, R., *Synlett*, **2016**, *27*, 2541–2552.
– Positional and geometrical isomerisation of alkenes: The pinnacle of atom economy.
  Molloy, J. J., Morack, T., Gilmour, R., *ACIE*, **2019**, *58*, 13654–13664.

Leading research groups (in no particular order):

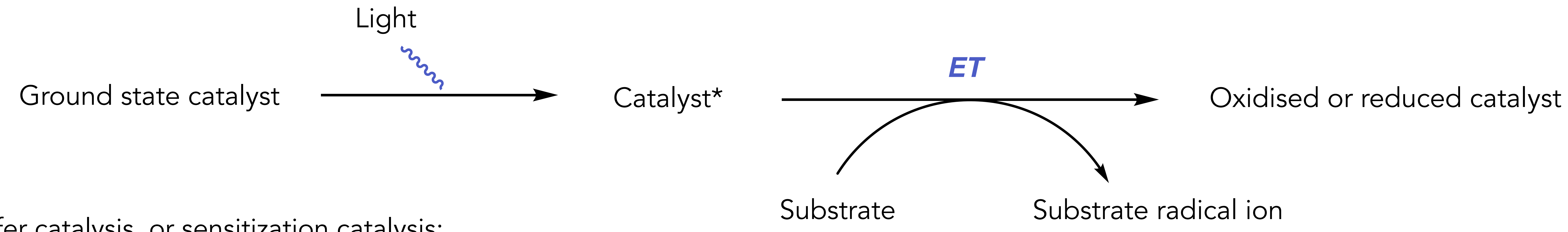
– Yoon, UW-Madison
– Oderinde, BMS Princeton
– Xiao, CCNU, Wuhan
– Houk, UCLA
– Bach, TU München
– Glorius, Münster
– Gilmore, Münster
– Schindler, UMich
– Meggers, Marburg
– Baik, KAIST Daejeon

Definitions

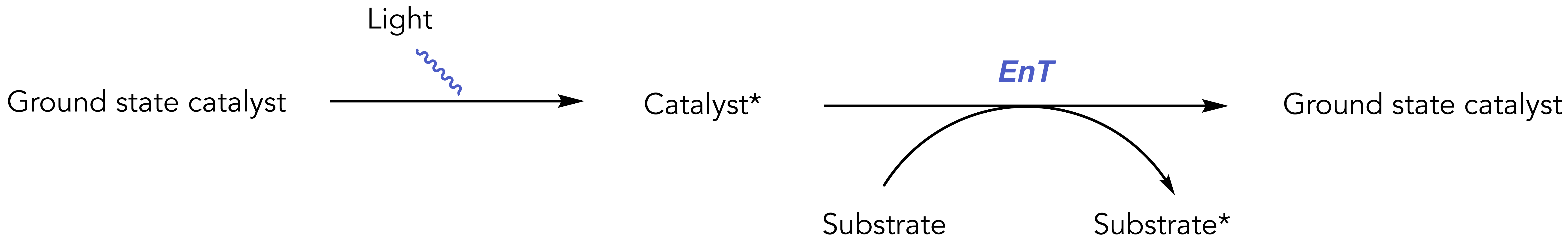
– (Visible light) Photocatalysis:



– Photoredox catalysis:

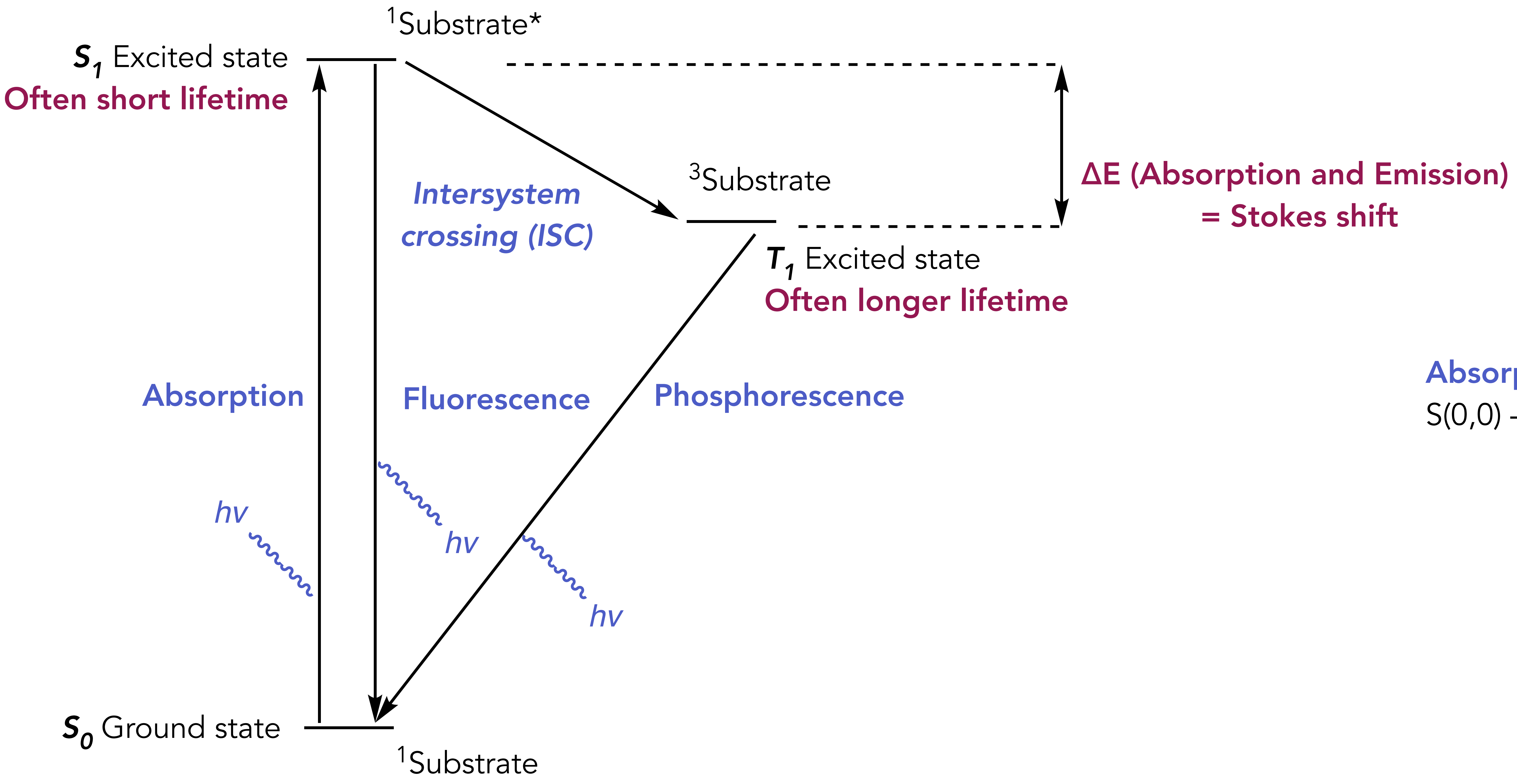


– Energy transfer catalysis, or sensitization catalysis:

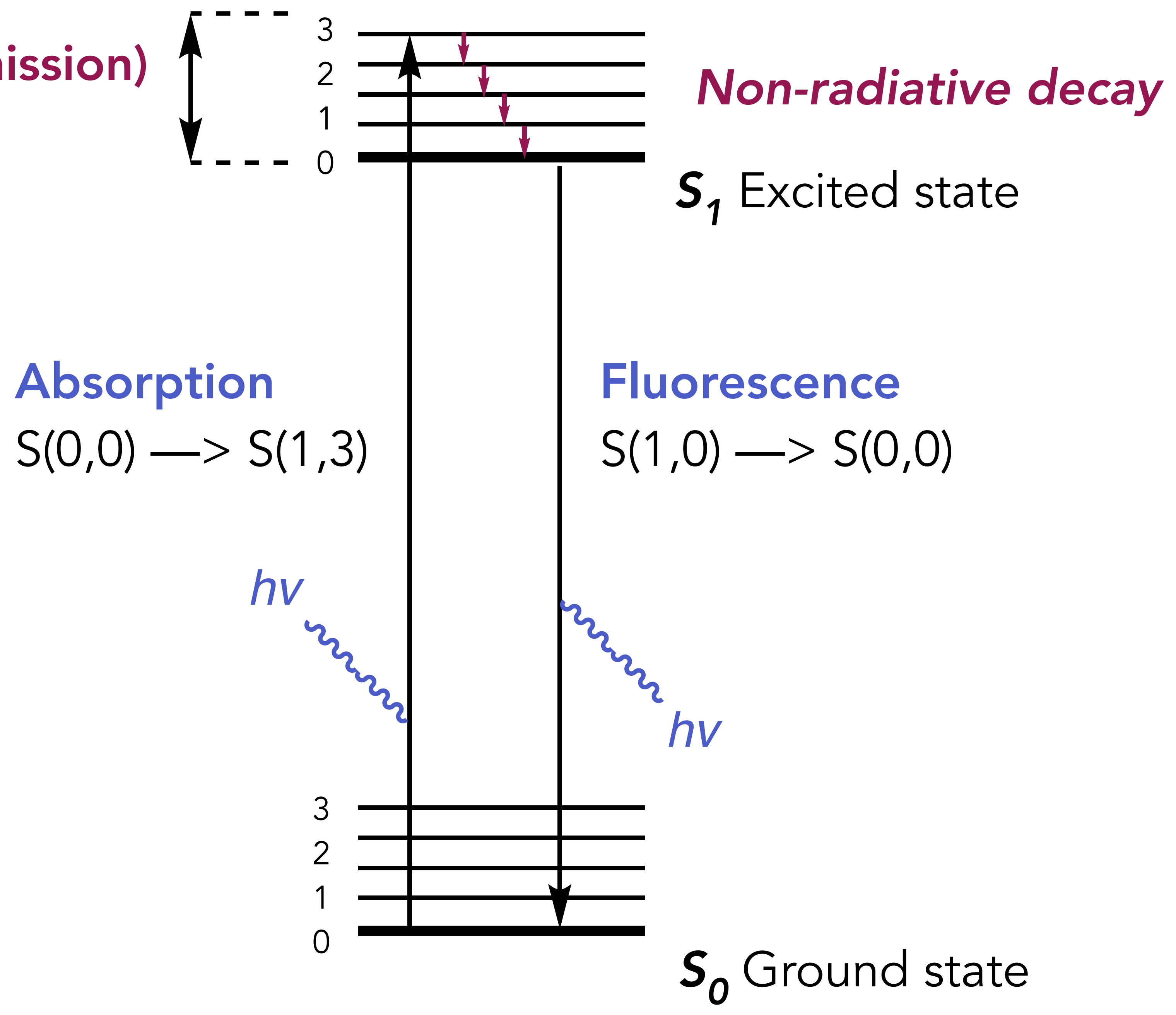


Direct substrate excitation and why sensitization

– (Simplified) Jablonski diagram for direct substrate excitation:

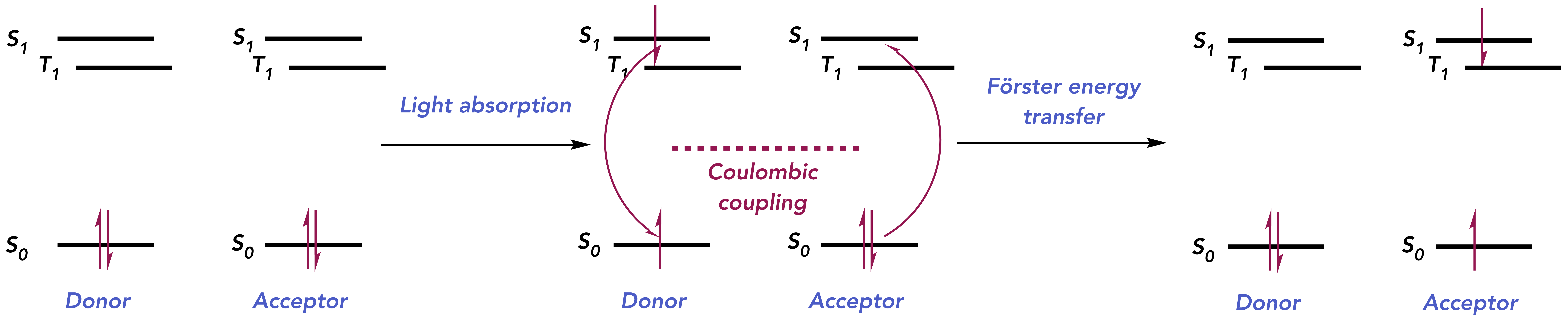


– Taking into account vibrational states:



Mechanisms of energy transfer

– Förster energy transfer mechanism (Coulombic interaction), 1948:



– Rate (k_{ET}) dependance described as:

$$k_{\mathrm{ET}} = \left(\frac{R_0}{r}\right)^6 \frac{1}{\tau_D}$$

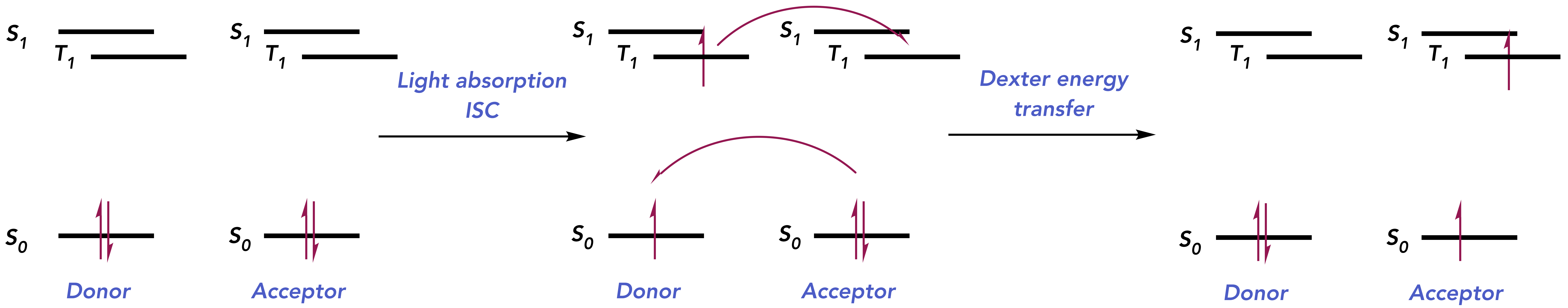
R_0 = Förster distance = distance for which energy transfer is 50% (quantum) efficient
r = Donor / Acceptor separation
τ_D = Donor fluorescence lifetime

We see that rate of EnT decreases by the inverse sixth power as distance between D and A increases.

– Longer range energy transfer, *ca.* 10 – 100 Å

Mechanisms of energy transfer

– Dexter energy transfer mechanism (exchange interaction), 1953:



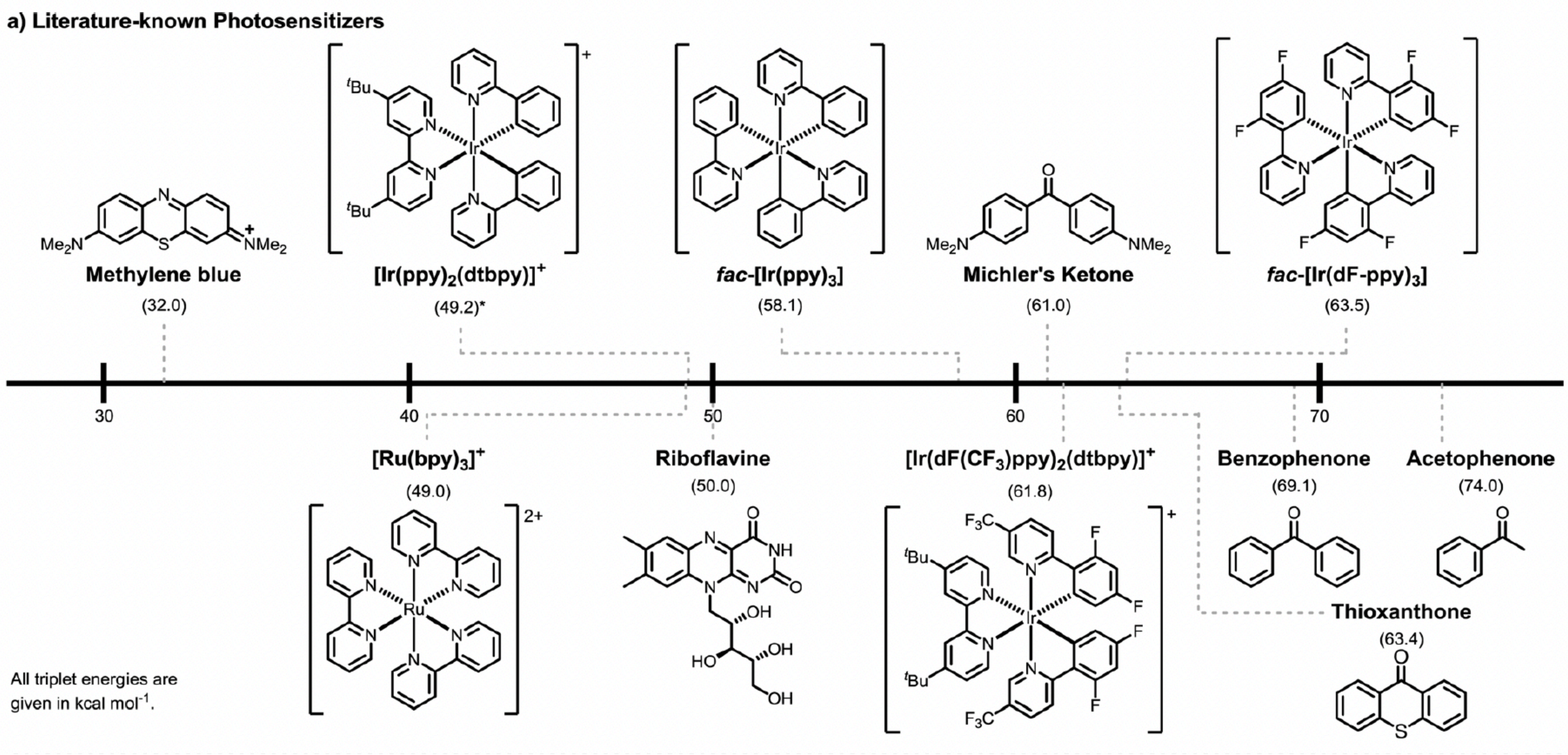
– Rate (k_{EnT}) dependance described as:

$$k_{\mathrm{EnT}} = K \cdot J \cdot \mathrm{e}^{-\frac{2R_{\mathrm{DA}}}{L}}$$

K = Specific oribital interaction parameter
J = Spectral overlap integral
R_{DA}/L = Measure of distance between donor and acceptor (catalyst and substrate in this case)

– We see that rate of EnT decreases exponentially as distance between D and A increases.
– Negligable rate at distances greater than ~2 molecular diameters
– Thus, intimate physical contact and orbital overlap is required between substrate and catalyst for EnT to occur
  – Short range energy transfer, *ca.* 5 – 30 Å

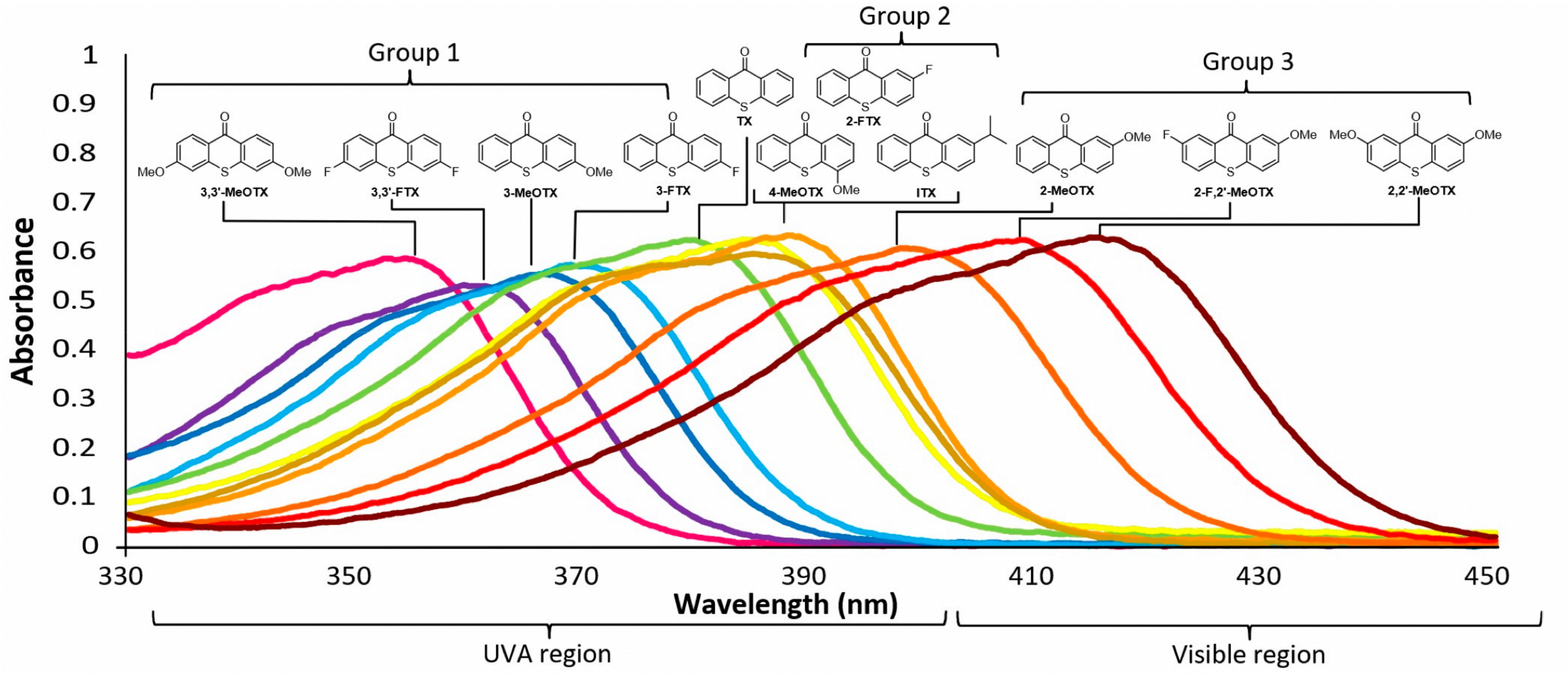
Photocatalyst considerations



Streith-Kalthoff, F., James, M. J., Teders, M., Pitzer, L., Glorius, F., *Chem. Soc. Rev.*, **2018**, *47*, 7190–7202.

Photocatalyst considerations

– State of the art in triplet photocatalyst design, Booker-Milburn and Elliot, 2020:



Elliott, L. D., Kayal, S., George, M. W., Booker-Milburn, K., *JACS*, **2020**, *142*, 14947–14956.

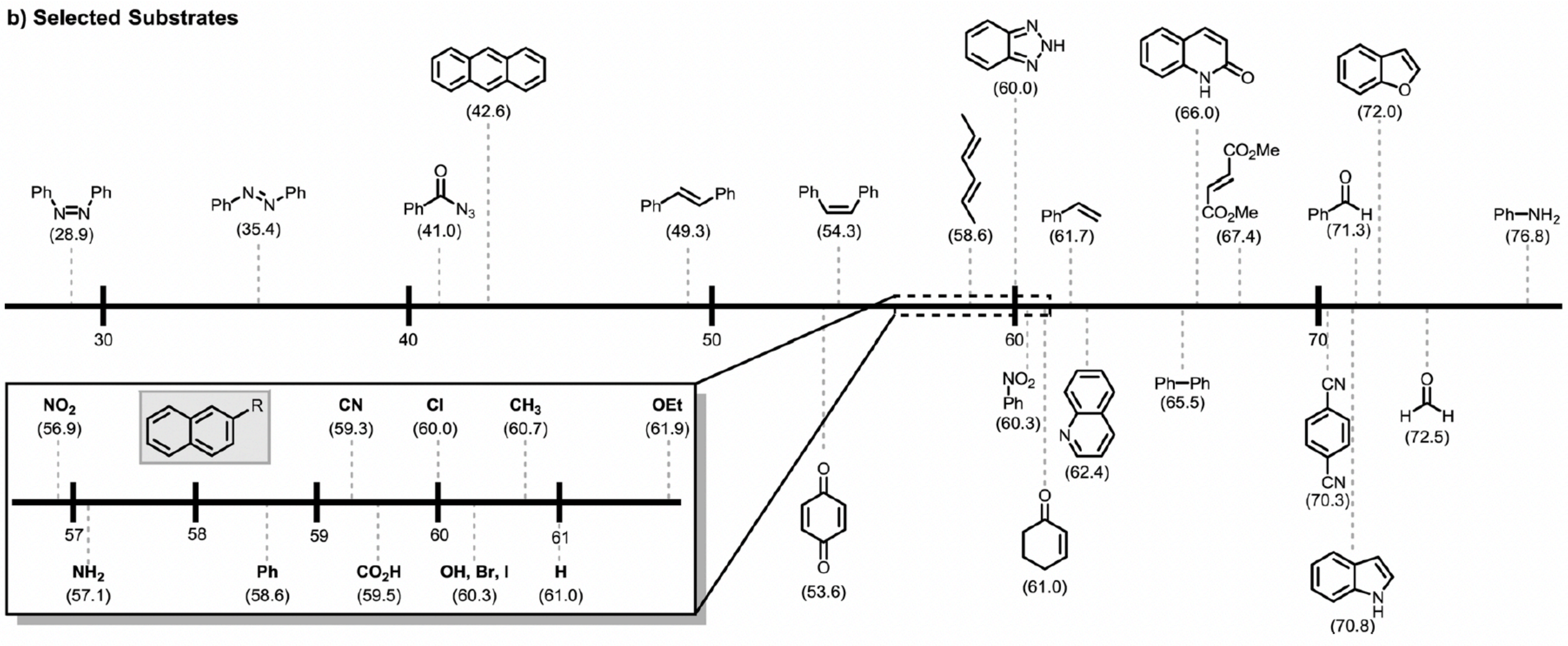
Photocatalyst considerations

– State of the art in triplet photocatalyst design, Booker-Milburn and Elliot, 2020:

entry	TX	λ_{max}[a] (nm)	$E_{T\ (Meas.)}$[d] (kJ/mol)	E_T /kcal/mol	τ_T[h]	Φ_{ISC}[i]
1	3,3′-MeOTX	354	298[e]	71.3	862 ± 40 ns	0.93
2	3,3′-FTX	362	289[e]	69.1	456 ± 25 ns	0.92
3	3-MeOTX	367	283[e]	67.7	867 ± 50 ns	>0.9
4	3-FTX	370	282[e]	67.5	520 ± 25 ns	0.83
5	TX (R/R′ = H)	380	274[e]	65.6	760 ± 30 ns	0.76[17]
6	ITX (R′ = H, R = 2-^{i}Pr)	385	266[e]	63.6	880 ± 50 ns	0.86
7	2-FTX	388	261[e]	62.4	585 ± 20 ns	0.81
8	4-MeOTX	385	263[e]	62.9	1.8 ± 0.3 μs	0.70
9	2-MeOTX	399	242[f]	57.9	1.7 ± 0.6 μs	0.83
10	2-F,2′-MeOTX	408	235[f]	56.2	1.2 ± 0.2 μs	0.62
11	2,2′-MeOTX	415	231[f]	55.3	863 ± 60 ns	0.66

Elliott, L. D., Kayal, S., George, M. W., Booker-Milburn, K., *JACS*, **2020**, *142*, 14947–14956.

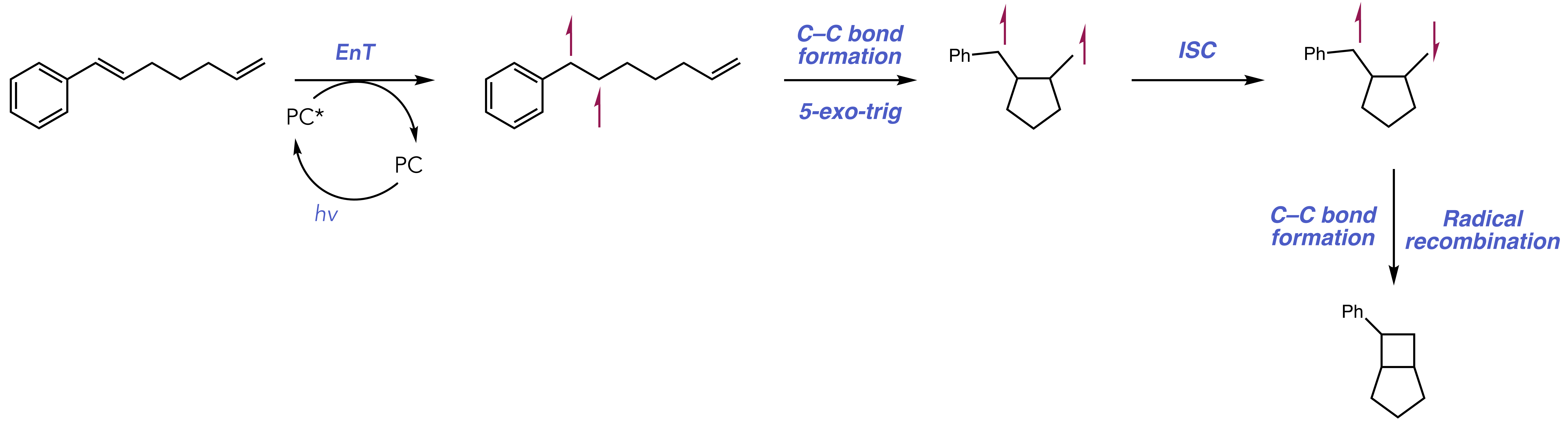
Substrate considerations



Streith-Kalthoff, F., James, M. J., Teders, M., Pitzer, L., Glorius, F., *Chem. Soc. Rev.*, **2018**, *47*, 7190–7202.

General mechanism for sensitized [2+2] photocycloaddition

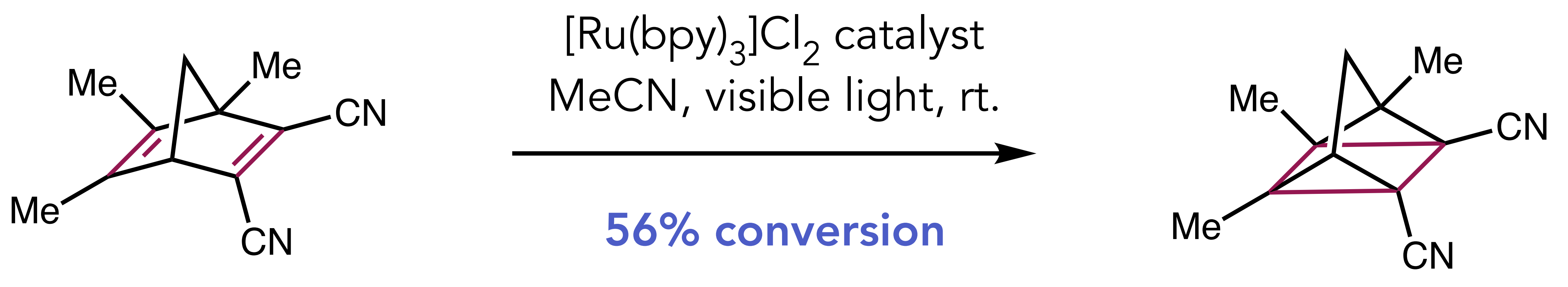
– General mechanism for sensitized olefin / olefin [2+2] photocycloaddition:



Photocatalytic olefin / olefin [2+2] cycloaddition

Photocatalytic olefin / olefin [2+2] cycloaddition

– Kutal 1989.
  – Norbornadiene / quadricyclene isomerization.
  – Investigated as a photo —> chemical energy storage system.
  – Recognised as the earliest visible light photocatalytic energy transfer process:



4 **5**

E_T = ~47–50 kcal/mol

Table I. Half-Wave Oxidation and Reduction Potentials of **4** and **5**

compound	$E_{1/2}^{ox}$, V[a]	$E_{1/2}^{red}$, V[a]
4	1.82	−1.39
5	1.76	<−2.4

[a] Measured in acetonitrile; potentials are relative to SCE.

$E_{1/2}$ *Ru(II)/Ru(I) = +0.77 V vs SCE in MeCN

Table II. Limiting Quantum Yields for Triplet-Sensitized Conversion of **4** to **5**

sensitizer	λ_{excit}, nm	ϕ_{isom}^{sen}	E_T, kcal (ϕ_T)[a]
$Ru(bpy)_3^{2+}$	546	0.06 ± 0.01[b]	47[c] (1.0)[d]
9-fluorenone	436	0.15 ± 0.01[e]	53.3[d] (0.93)[g]
biacetyl	436	0.11 ± 0.01[h]	56.3[i] (1.0)[i]
thioxanthone	405	<0.3[e]	65.5[j] (1.0)[j]

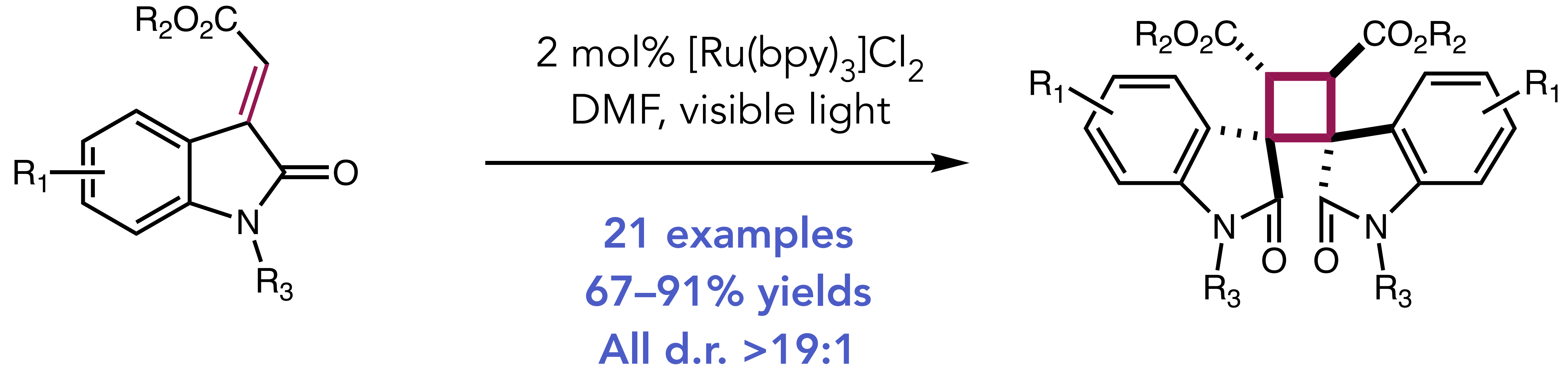
[a] Triplet-state energy (efficiency of forming triplet state). [b] Corrected for incomplete quenching of sensitizer. [c] Reference 13. [d] Reference 12. [e] Obtained from intercept of plot of ϕ^{-1} vs. $[\mathbf{4}]^{-1}$. [f] Reference 25a. [g] Reference 25b. [h] Measured under conditions of complete sensitizer quenching. [i] Reference 25d. [j] Reference 25e.

Ikezawa, H., Kutal, C., Yasufuku, K., Yamazaki, H., *JACS*, **1986**, *108*, 1589-1594.

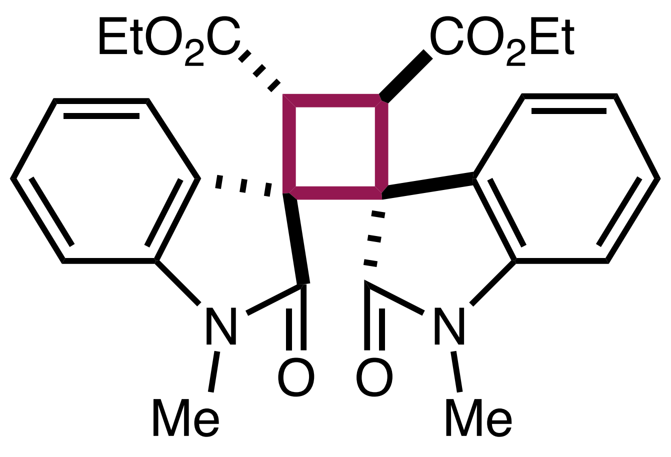
Photocatalytic olefin / olefin [2+2] cycloaddition

– Xiao 2012.

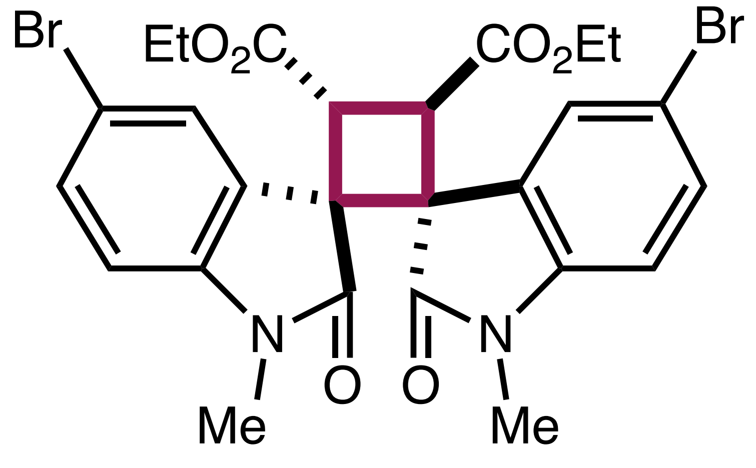
–Dimerization of 3-ylidene oxindoles via sensitized [2+2] cycloaddition:



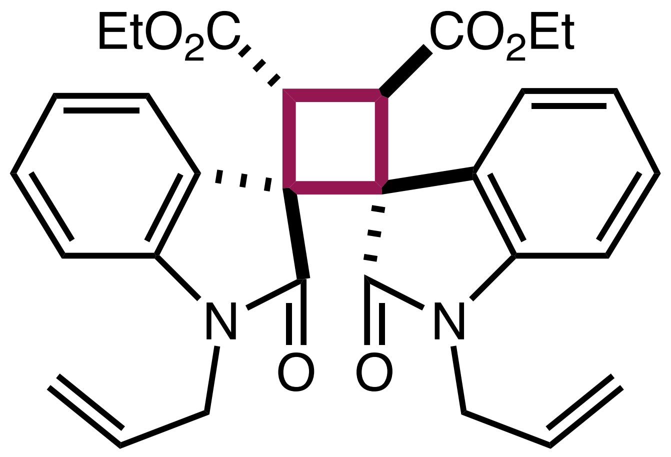
– Select examples:



83%



92%



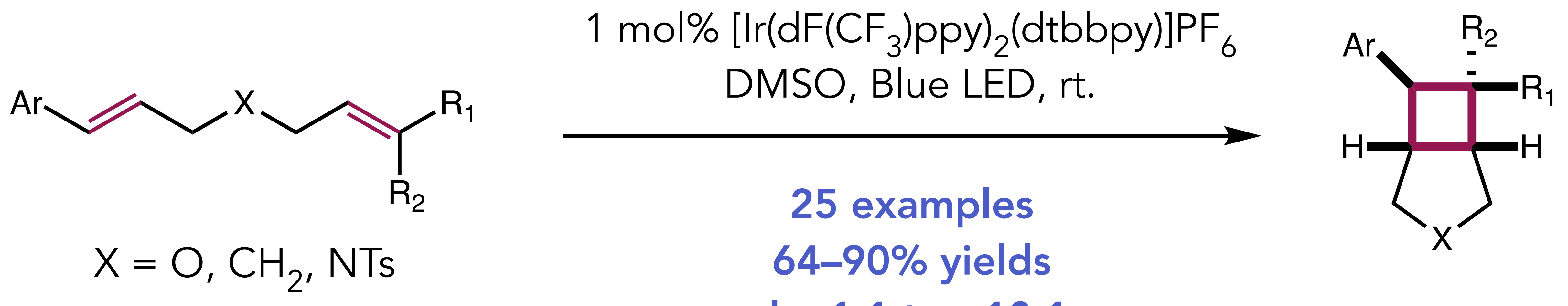
87%

Zou, Y.-Q., Duan, S.-W., Meng, X.-G., Hu, X.-Q., Gao, S., Chen, J.-R., Xiao, W.-J., *Tetrahedron*, **2012**, *68*, 6914–6919.

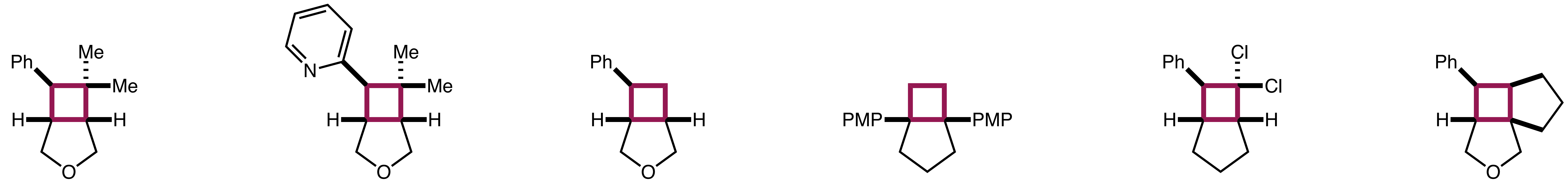
Photocatalytic olefin / olefin [2+2] cycloaddition

– Yoon 2012.

–Intramolecular [2+2] photocycloaddition of styrenes and olefins:



– Select examples:

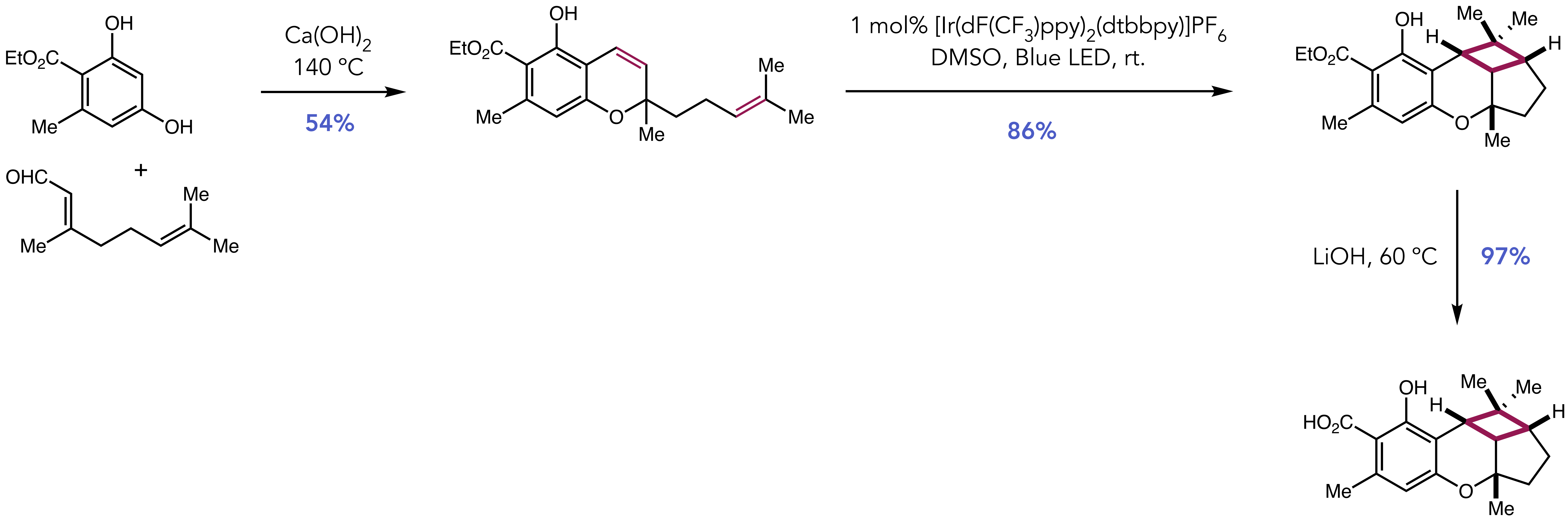


89%, d.r. >10:1 | 71%, d.r. >10:1 | 80%, d.r. 7:1 | 90%, d.r. >10:1 | 89%, d.r. >10:1 | 76%, d.r. 5:1

Lu, Z., Yoon, T. P., *ACIE*, **2012**, *51*, 10329–10332.

Photocatalytic olefin / olefin [2+2] cycloaddition

– Yoon 2012.
  – Total synthesis of (±)-cannabiorcicycloic acid:

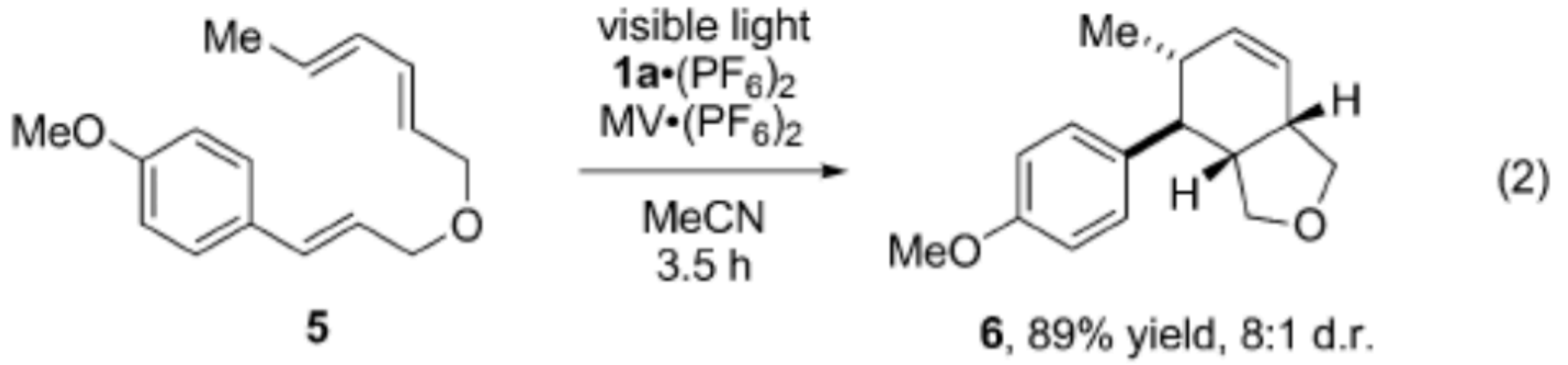


Lu, Z., Yoon, T. P., *ACIE*, **2012**, *51*, 10329–10332.

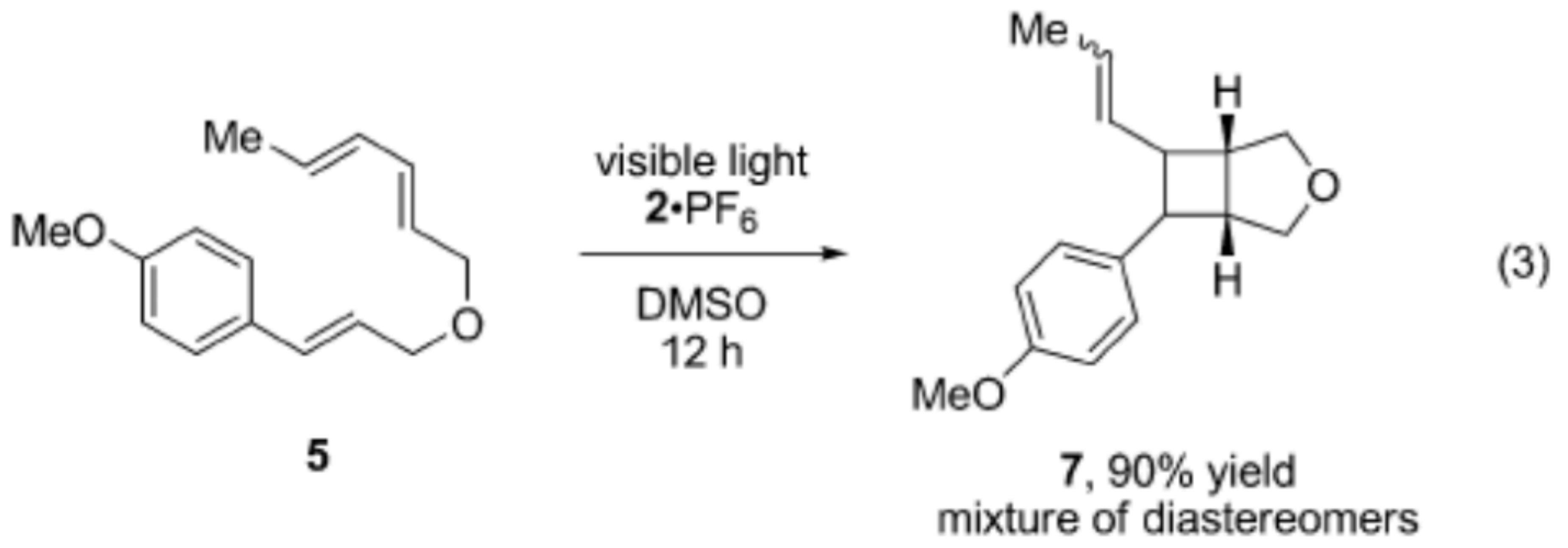
Photocatalytic olefin / olefin [2+2] cycloaddition

– Yoon 2012.
  – Switchable selectivity through partitioning between electron transfer and energy transfer pathways:

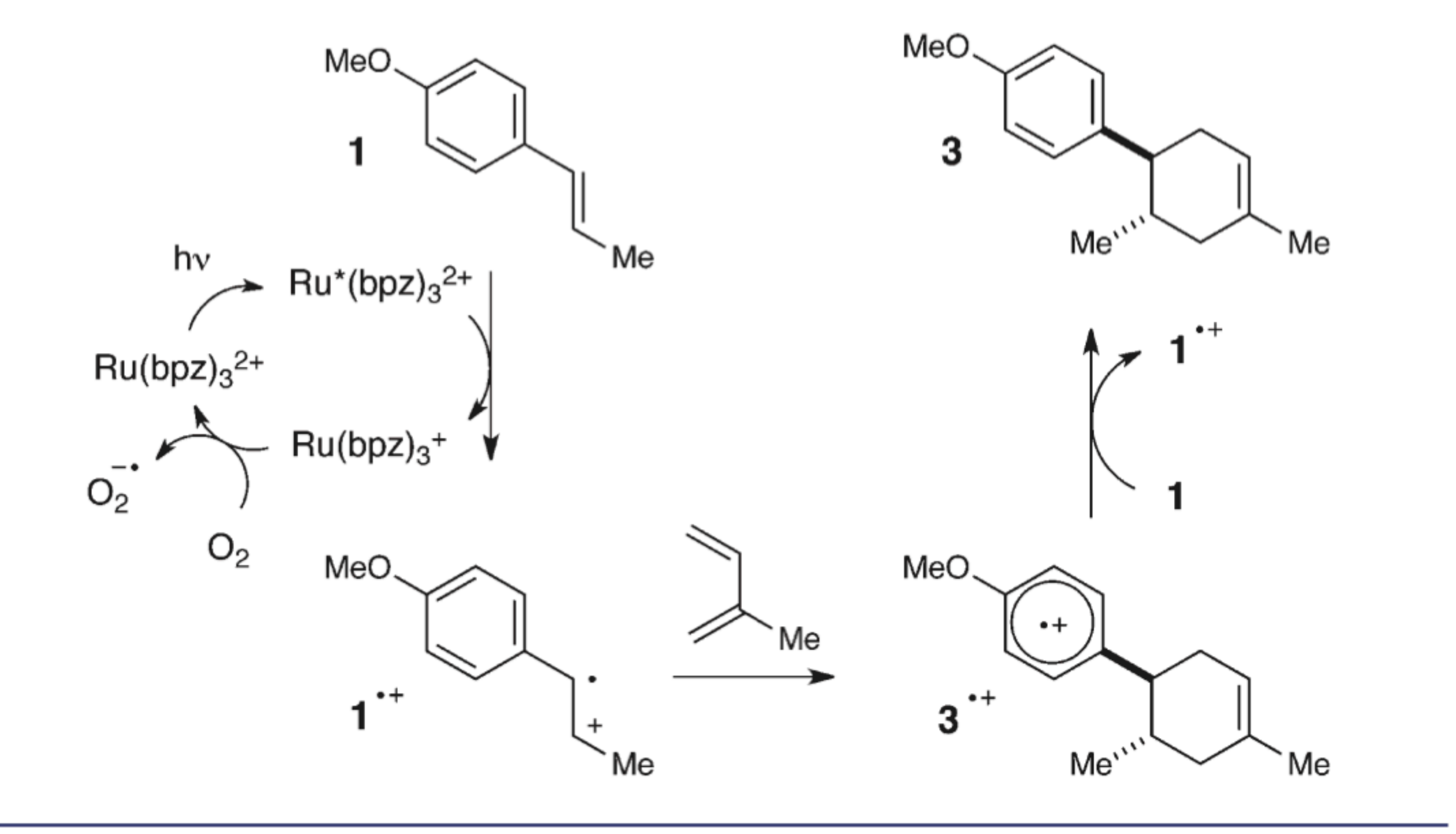
$[Ru(bpz)_3]^{2+}$:



$[Ir(dF(CF_3)ppy)_2(dtbbpy)]^+$:



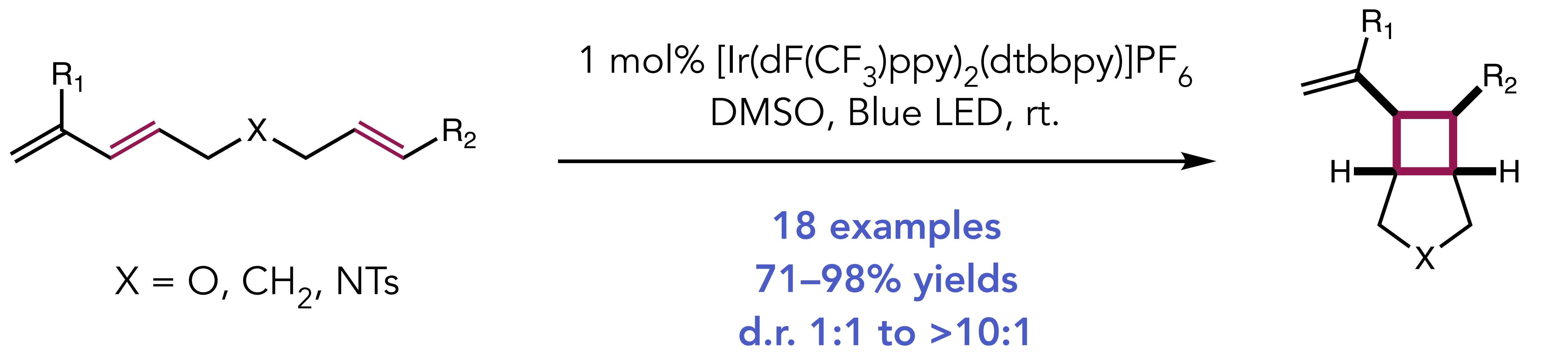
Scheme 1. Proposed Mechanism



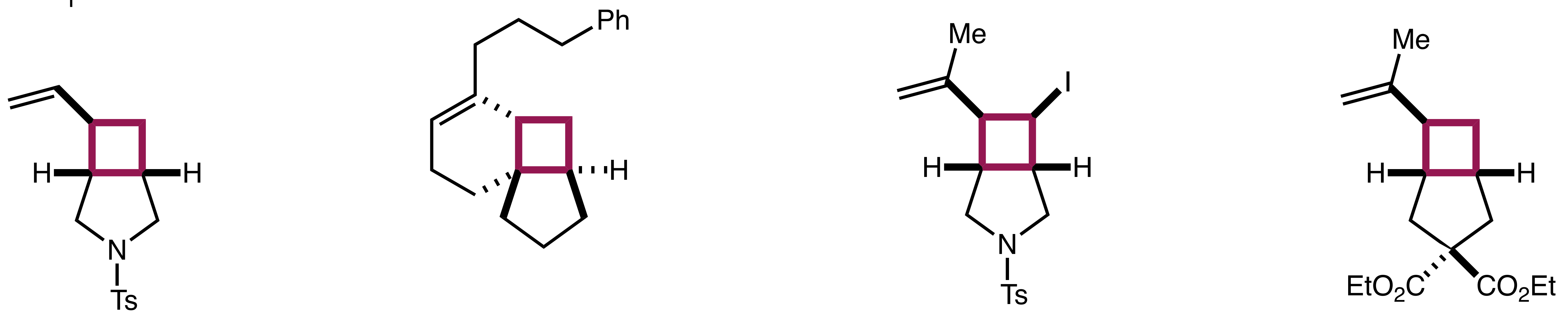
 Lu, Z., Yoon, T. P., *ACIE*, **2012**, *51*, 10329–10332. Lin, S., Ischay, M. A., Fry, C. G., Yoon, T. P., *JACS*, **2011**, *133*, 19350–19353.

Photocatalytic olefin / olefin [2+2] cycloaddition

– Yoon 2014.
  – Intramolecular [2+2] photocycloaddition of 1,3-dienes:



– Select examples:

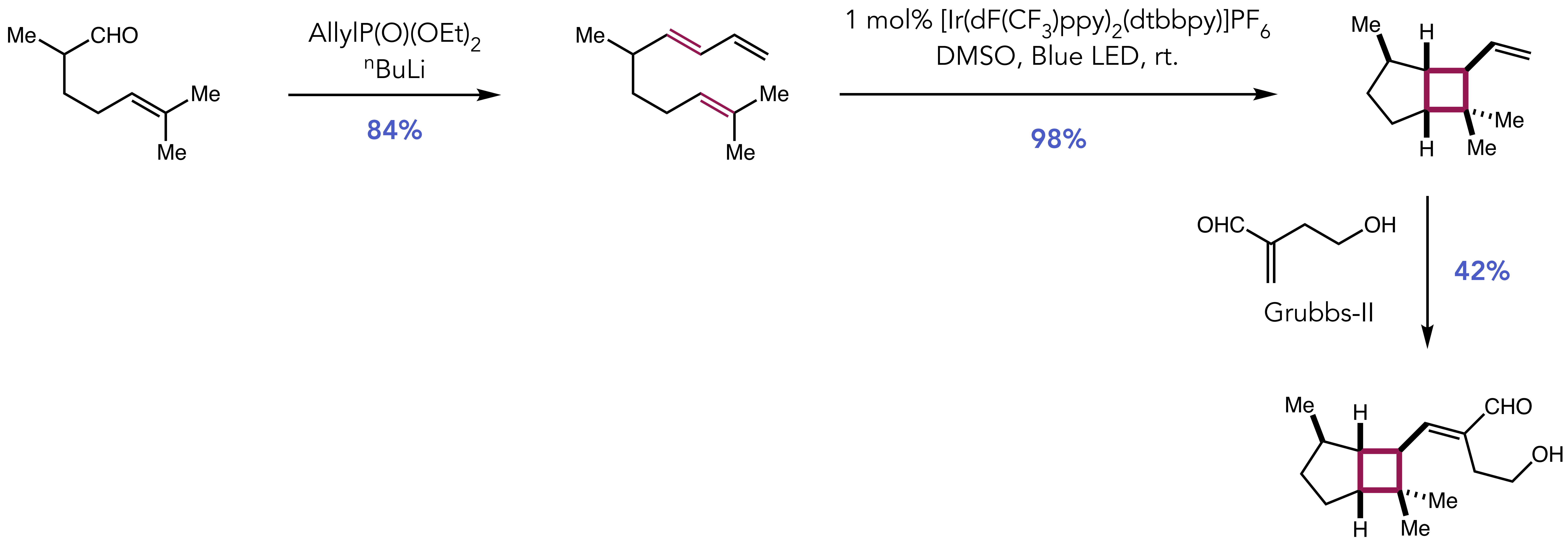


95%, d.r. 3:1 | 81%, d.r. >10:1 | 98%, d.r. 2:1 | 92%, d.r. 2:1

Hurtley, A. E., Lu, Z., Yoon, T. P., *ACIE*, **2014**, *53*, 8991–8994.

Photocatalytic olefin / olefin [2+2] cycloaddition

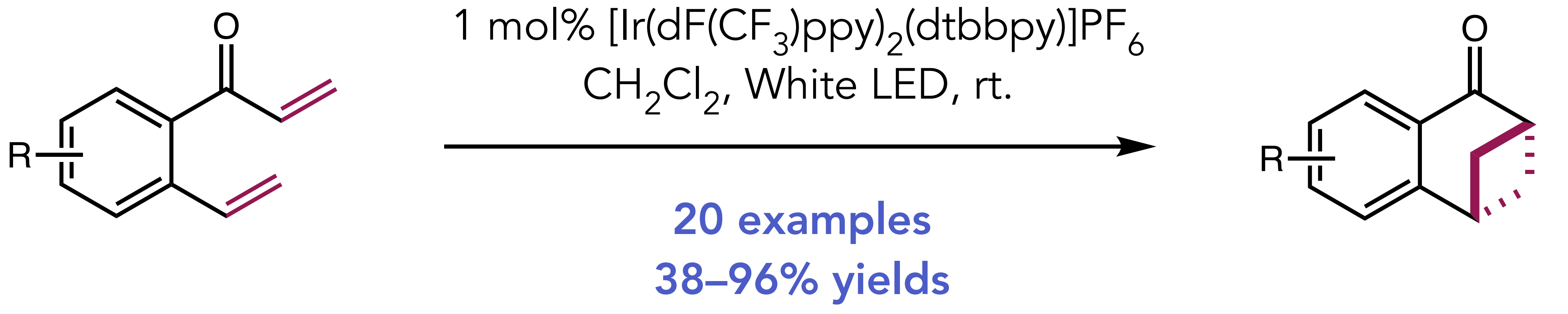
– Yoon 2014.
  – Total synthesis of (±)-epiraikovenal:



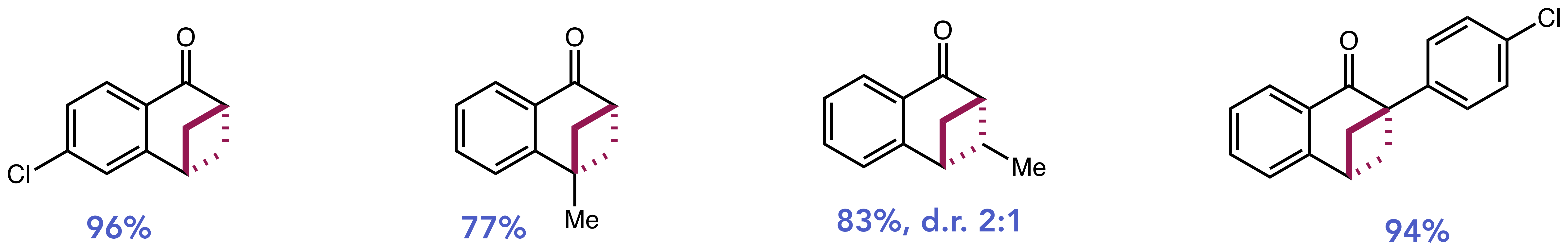
Hurtley, A. E., Lu, Z., Yoon, T. P., *ACIE*, **2014**, *53*, 8991–8994.

Photocatalytic olefin / olefin [2+2] cycloaddition

– Kwon 2017.
  – Intramolecular crossed-addition [2+2] photocycloaddition of styryl / aryl vinyl ketones:



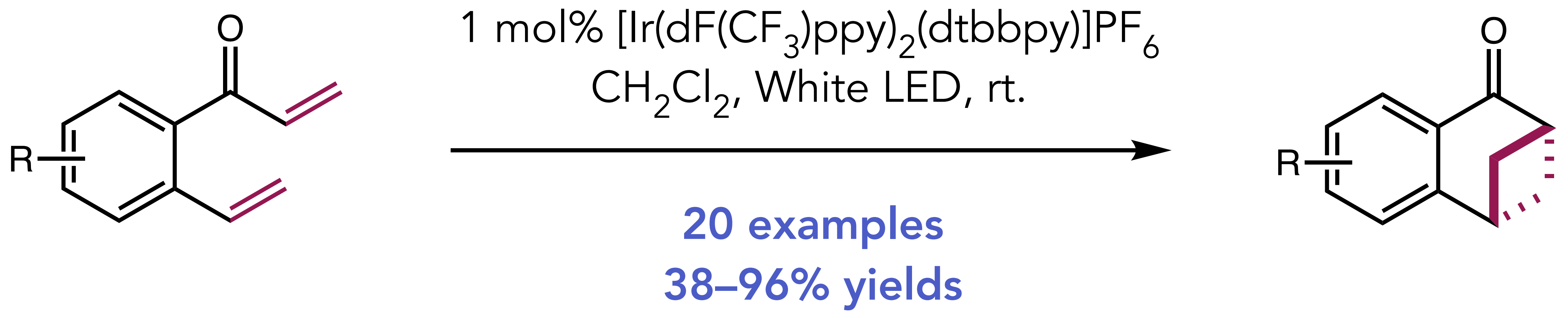
– Select examples:

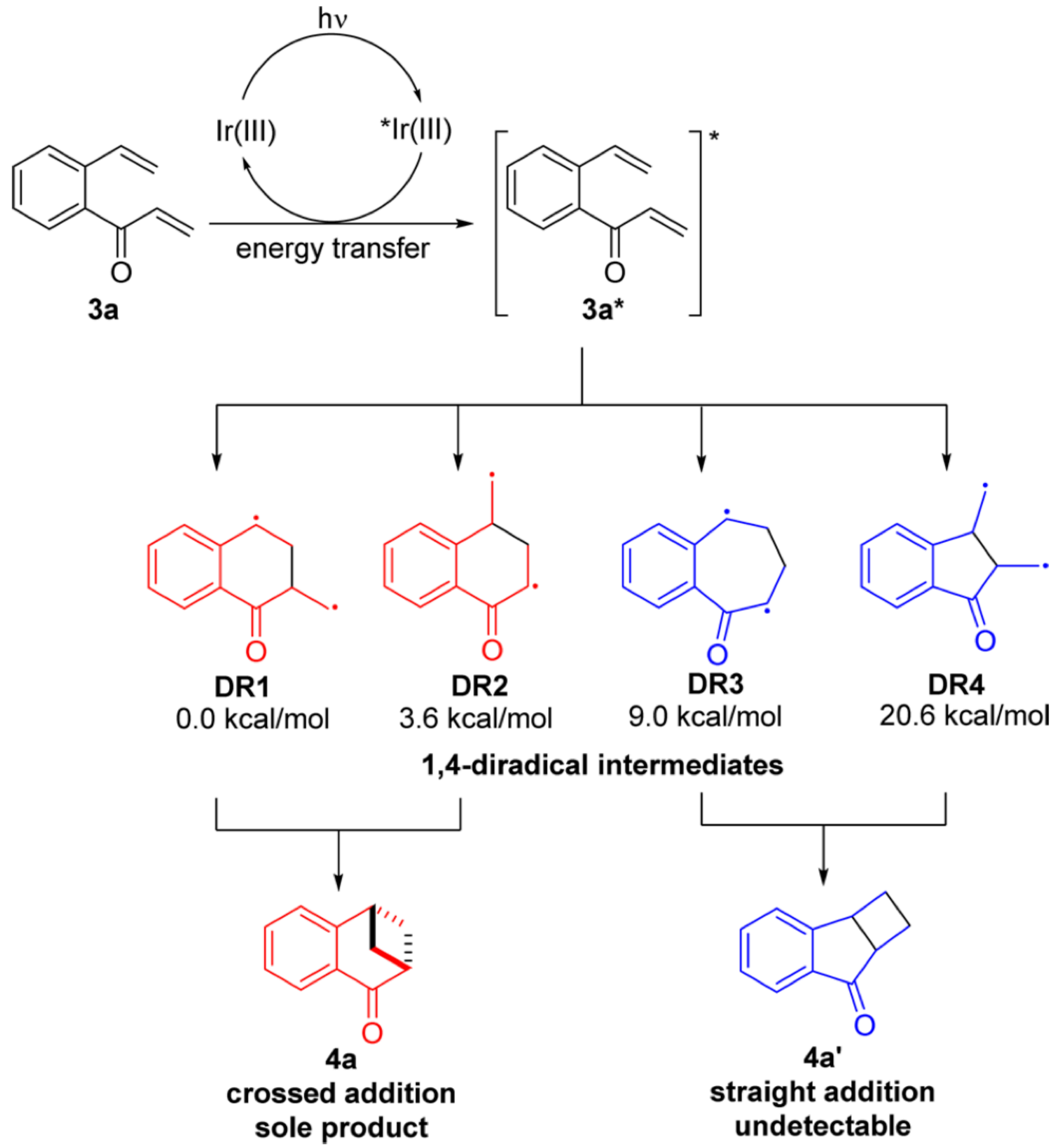


Zhao, J., Brosmer, J. L., Tang, Q., Yang, Z., Houk, K. N., Diaconescu, P. L., Kwon, O., *JACS*, **2017**, *139*, 9807–9810.

Photocatalytic olefin / olefin [2+2] cycloaddition

– Kwon 2017.
  – Intramolecular crossed-addition [2+2] photocycloaddition of styryl / aryl vinyl ketones.
  – Computational study reveals the source of crossed-addition selectivity:

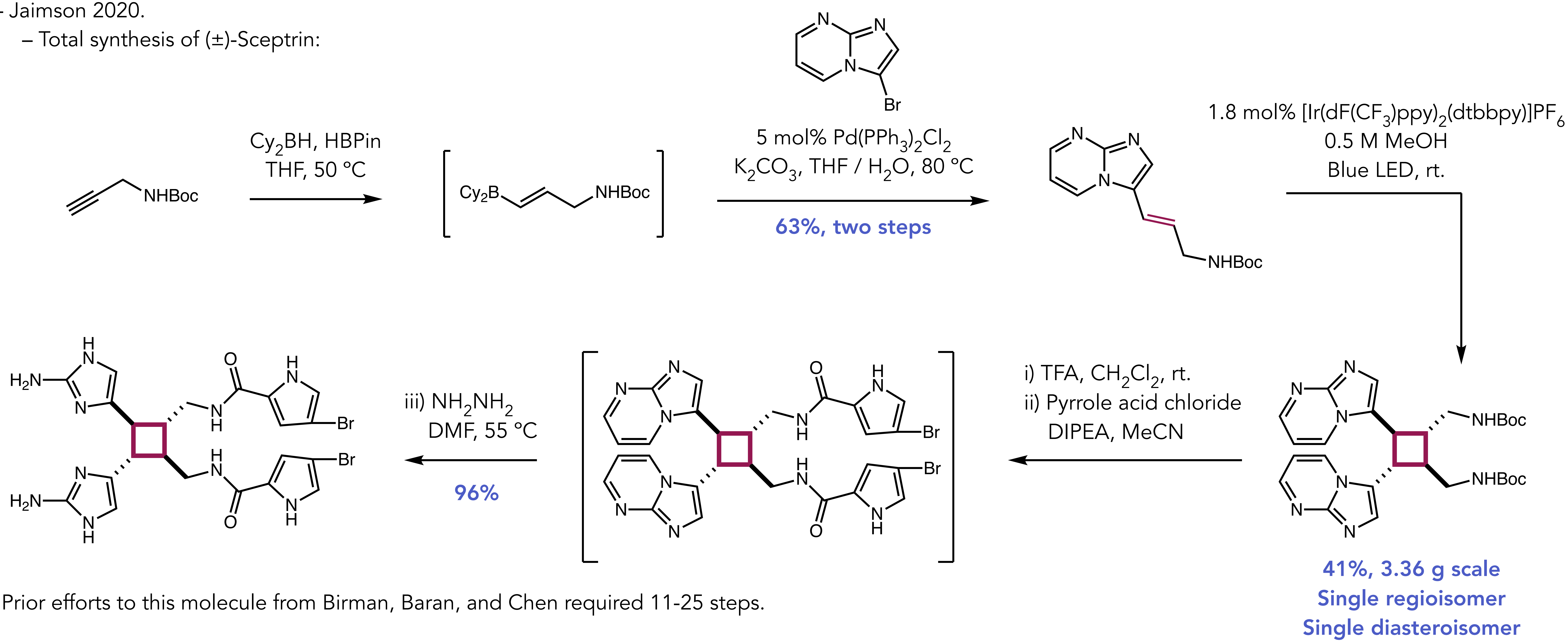




Zhao, J., Brosmer, J. L., Tang, Q., Yang, Z., Houk, K. N., Diaconescu, P. L., Kwon, O., *JACS*, **2017**, *139*, 9807–9810.

Photocatalytic olefin / olefin [2+2] cycloaddition

– Jaimson 2020.
  – Total synthesis of (±)-Sceptrin:



– Prior efforts to this molecule from Birman, Baran, and Chen required 11-25 steps.

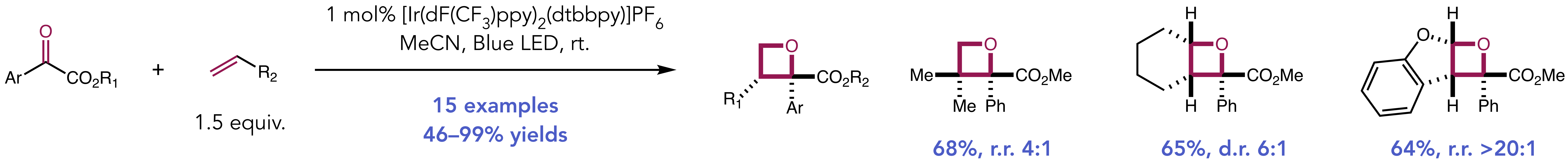
Ngyuen, L. V., Jaimson T. F., *OL*, **2020**, *22*, 6698-6702.

Photocatalytic carbonyl / olefin [2+2] cycloaddition

Photocatalytic carbonyl / olefin [2+2] cycloaddition

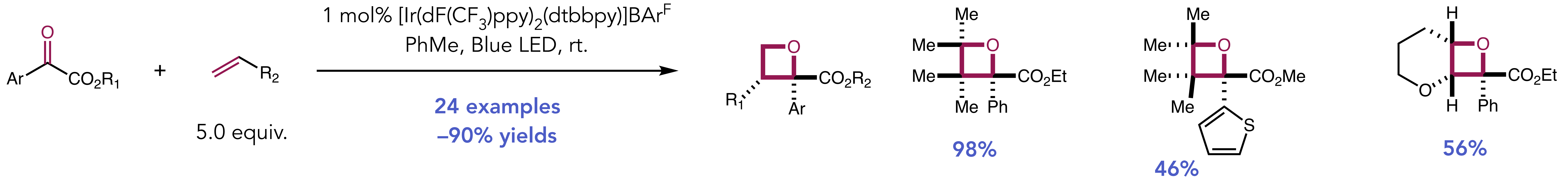
– Schindler and Yoon 2020.
  – Visible-light photosensitized Paternò-Büchi reaction of aryl glyoxalates and olefins.
  – Schindler:

– Select examples:



– Yoon:

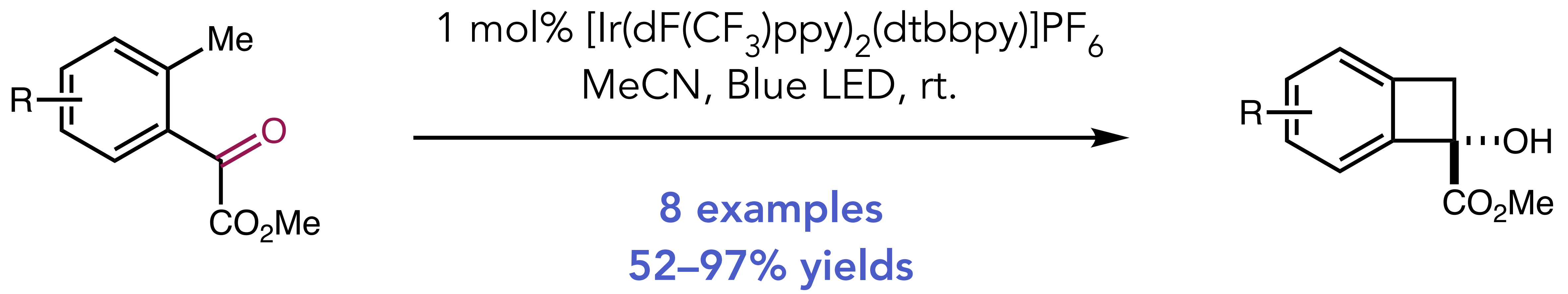
– Select examples:



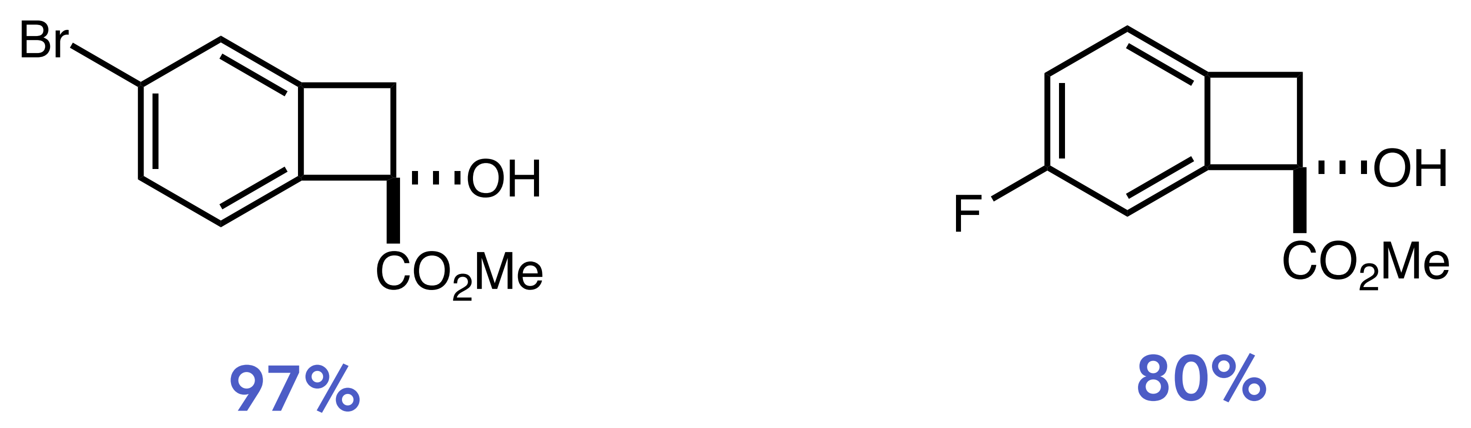
Rykaczewski, K. A., Schindler, C. S., *Org. Lett.*, **2020**, *22*, 6516–6519. Zheng, J., Dong, X., Yoon, T. P., *Org. Lett.*, **2020**, *22*, 6520–6525.

Photocatalytic carbonyl / olefin [2+2] cycloaddition

– Schindler and Yoon 2020.
  – Yoon also demonstrates Norrish type-2 energy transfer reactivity:



– Select examples:

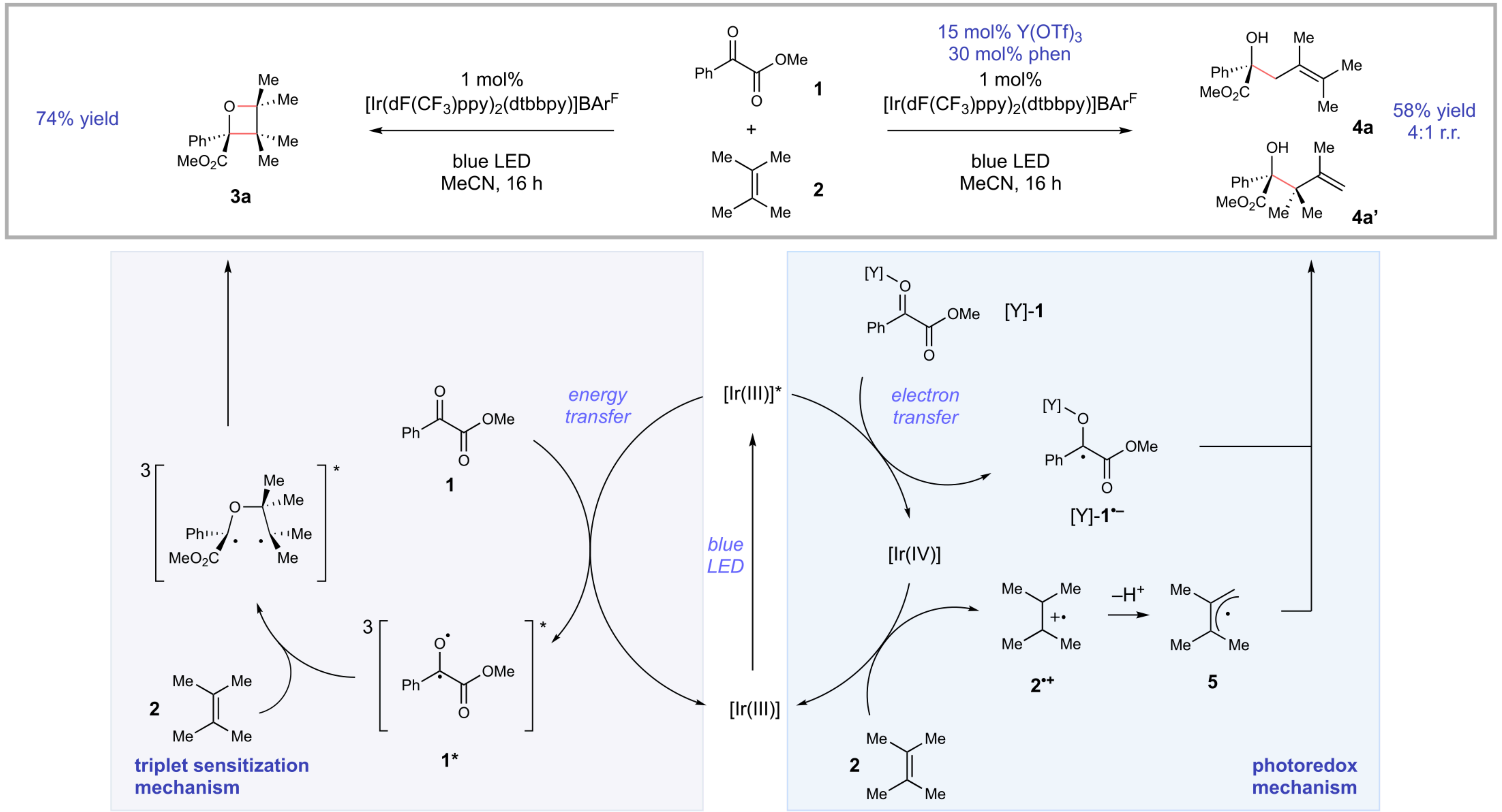


Rykaczewski, K. A., Schindler, C. S., *Org. Lett.*, **2020**, *22*, 6516–6519. Zheng, J., Dong, X., Yoon, T. P., *Org. Lett.*, **2020**, *22*, 6520–6525.

Photocatalytic carbonyl / olefin [2+2] cycloaddition

– Schindler and Yoon 2020.
  – … And partitioning between energy transfer and electron transfer reactivity:

Scheme 1. Divergent Outcomes of Triplet Sensitization and Photoredox Reactions of Benzoylformate Esters



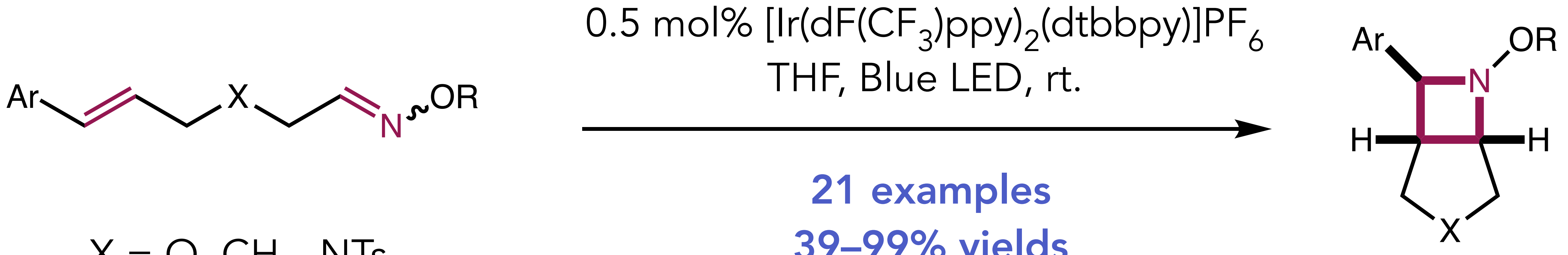
Rykaczewski, K. A., Schindler, C. S., *Org. Lett.*, **2020**, *22*, 6516–6519. Zheng, J., Dong, X., Yoon, T. P., *Org. Lett.*, **2020**, *22*, 6520–6525.

Photocatalytic oxime / olefin [2+2] cycloaddition

Photocatalytic oxime / olefin [2+2] cycloaddition

– Schindler 2019.

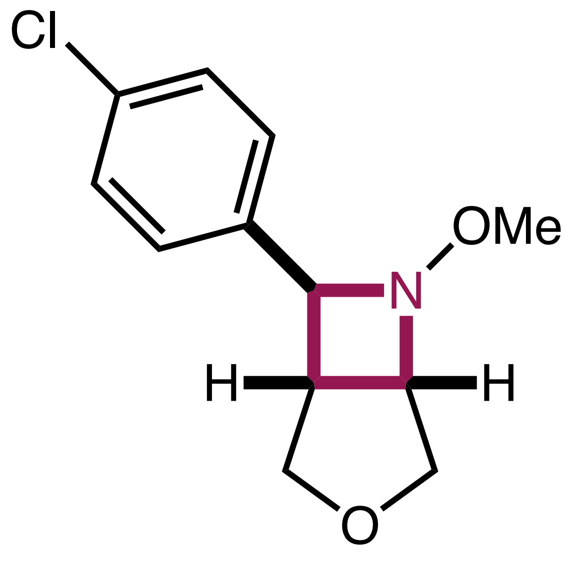
– Intramolecular oxime / olefin [2+2] photocycloaddition:



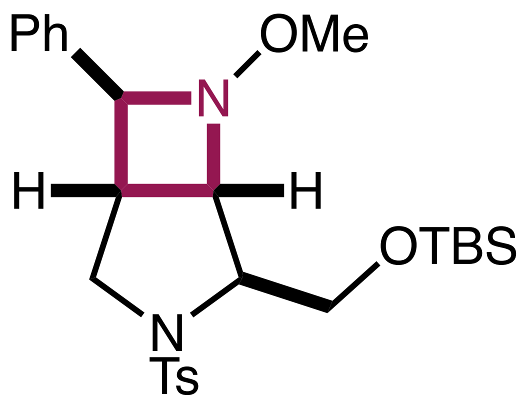
X = O, CH_2, NTs

21 examples
39–99% yields
d.r. 1.6:1 to >20:1

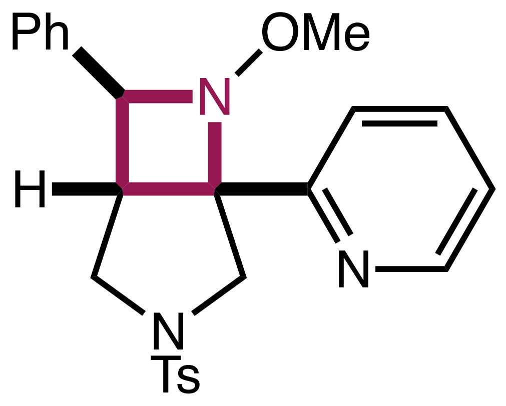
– Select examples:



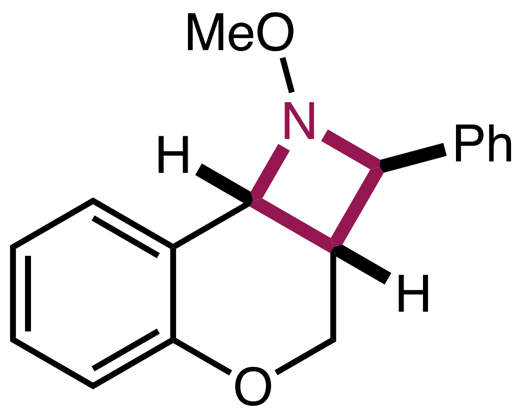
98%, d.r. >20:1



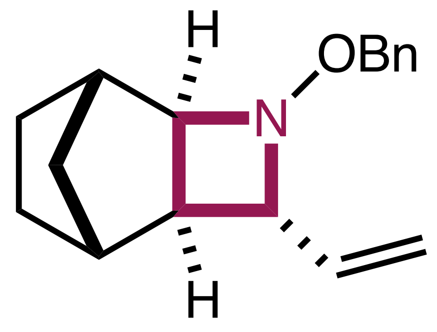
95%, d.r. 2.5:1



74%, d.r. >20:1



42%, d.r. 7:1

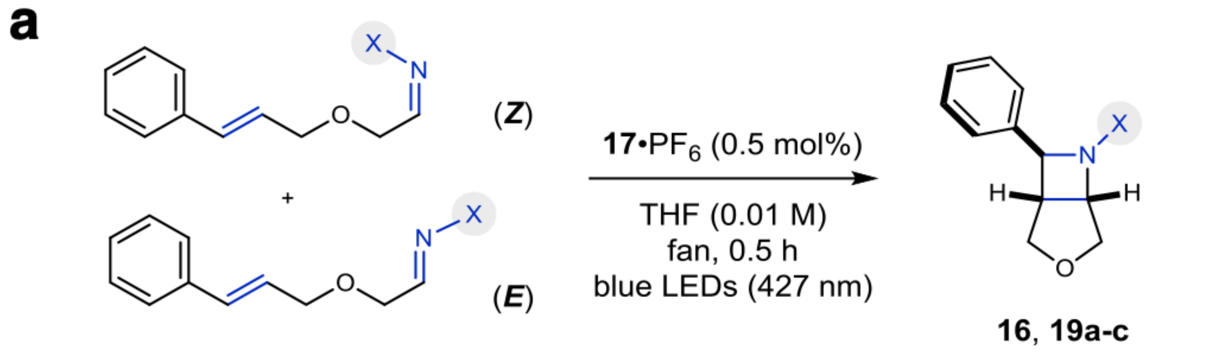


39%, d.r. >4:1
exo/endo >20:1

Becker, M. R., Richardson, A. D., Schindler, C. S., *Nat. Commun.*, **2019**, *10*, 5095.

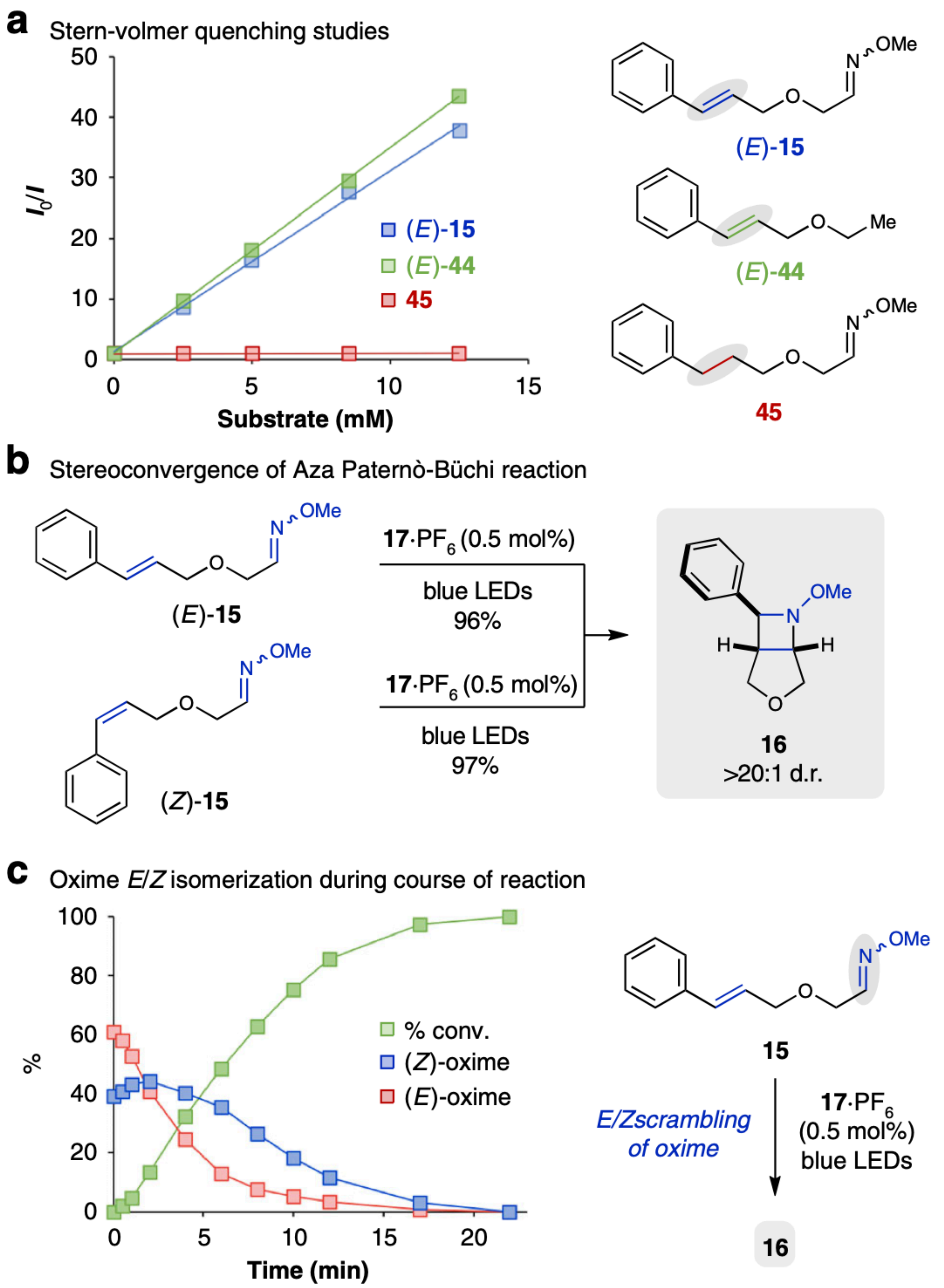
Photocatalytic oxime / olefin [2+2] cycloaddition

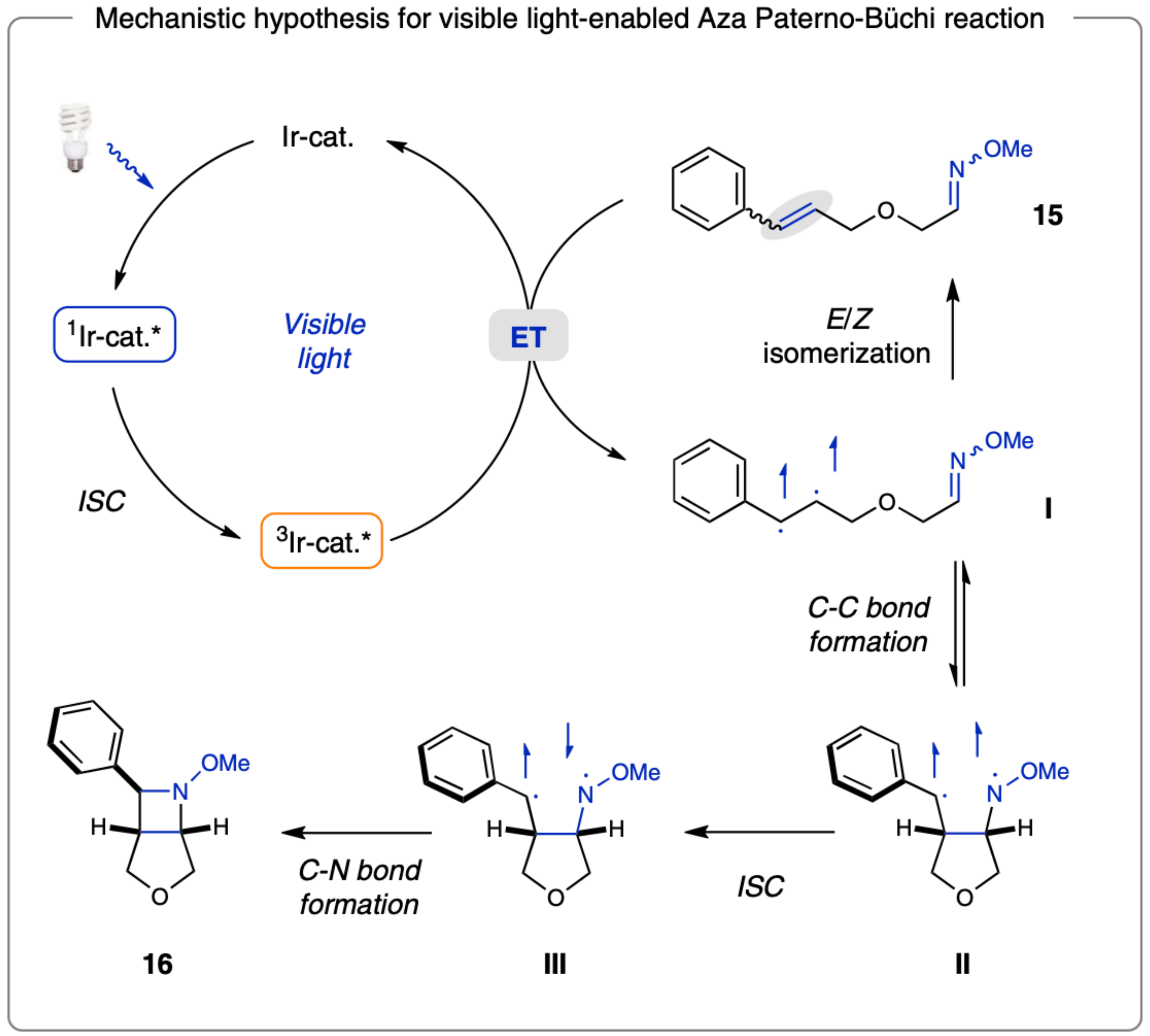
– Schindler 2019.
  – Optimization and mechanistic support:



Entry	Substrate		Z/E ratio	Yield	d.r.[a]
1	N~OMe	**15**	1:1.3	96% 91%[c]	>20:1 >20:1
2	N~OBn	**18a**	1:1.3	96% 90%[c]	16:1 20:1
3	N~OH	**18b**	1:1.1	54%	>20:1
4	N~NHBoc	**18c**	1:2.6	62%	13:1
5[b]	N~NMe_2	**18d**	0:1	0%	-

Conditions: Reactions were performed with 0.25 mmol substrate and 0.5 mol% **17•**PF_6 in THF (0.01 M) at ambient temperature under blue LED irradiation (427 nm) for 0.5 h
[a]diastereomeric ratio (d.r.) was determined by ^1H NMR from the crude reaction mixture
[b]run for 16 h
[c]reaction performed on gram scale

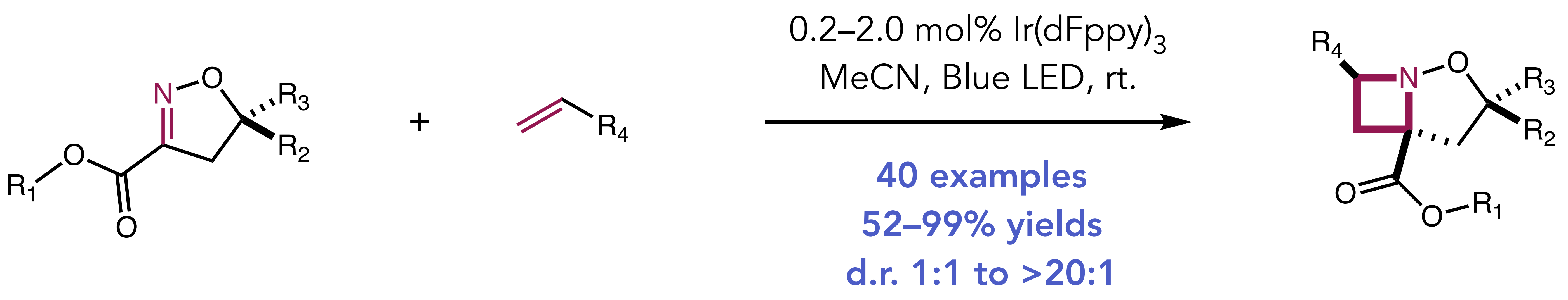




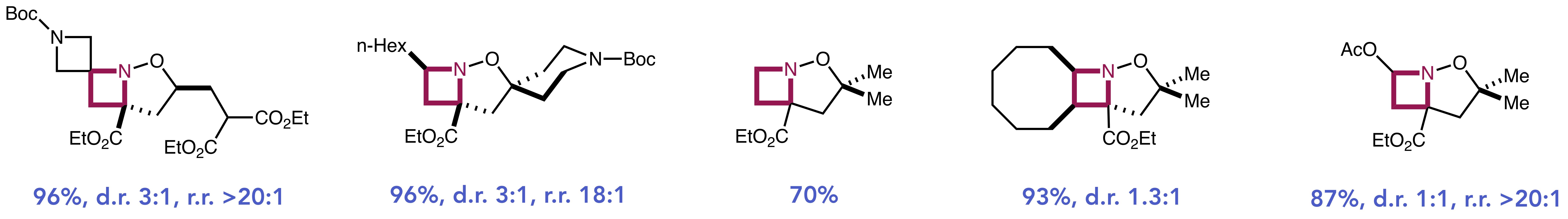
Becker, M. R., Richardson, A. D., Schindler, C. S., *Nat. Commun.*, **2019**, *10*, 5095.

Photocatalytic oxime / olefin [2+2] cycloaddition

– Schindler 2020.
  – Intermolecular [2+2] photocycloaddition between 2-isoxazoline-3-carboxylates and unactivated olefins:



– Select examples:

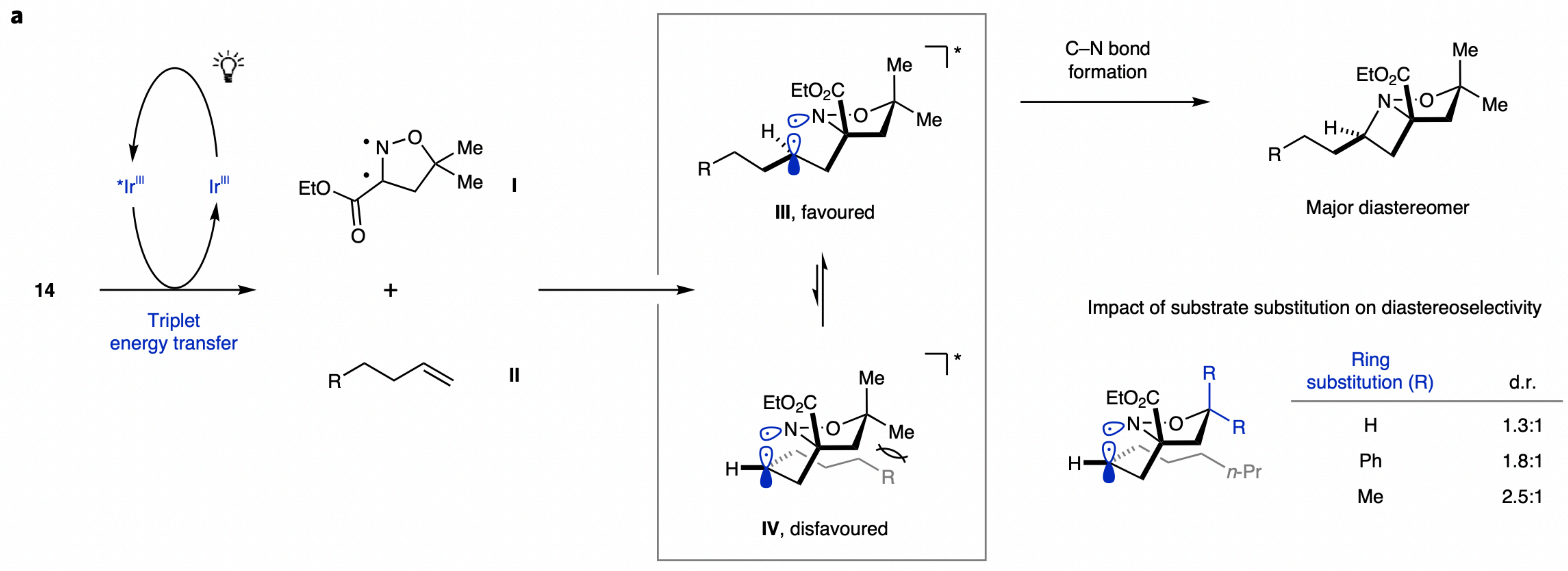


Becker, M. R., Wearing, E. R., Schindler, C. S., *Nat. Chem.*, **2020**, *12*, 898–905.

Photocatalytic oxime / olefin [2+2] cycloaddition

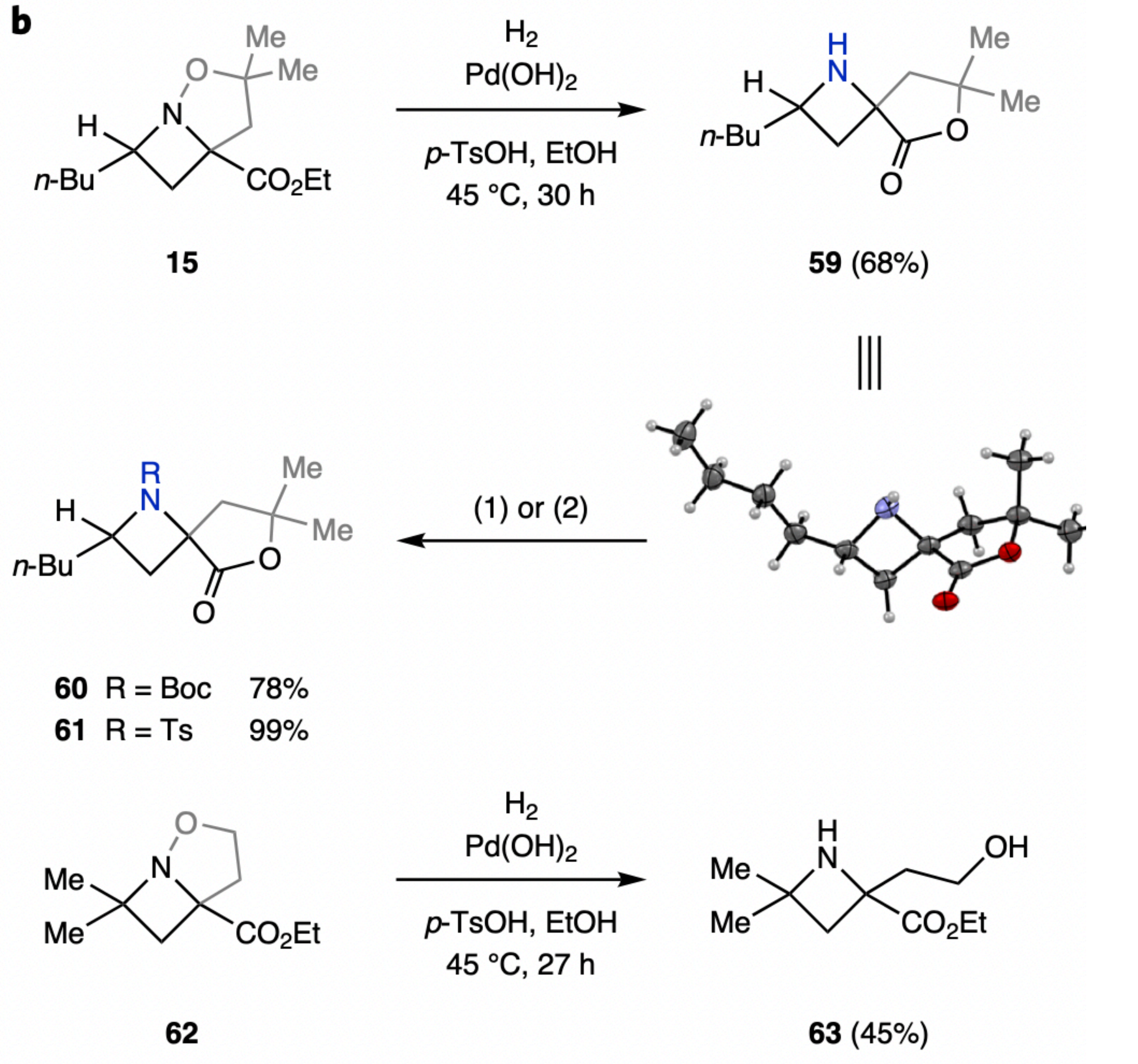
– Schindler 2020.
  – Intermolecular [2+2] photocycloaddition between 2-isoxazoline-3-carboxylates and unactivated olefins.

  – Stereochemical model:



Ring substitution (R)	d.r.
H	1.3:1
Ph	1.8:1
Me	2.5:1

– N–O cleavage:



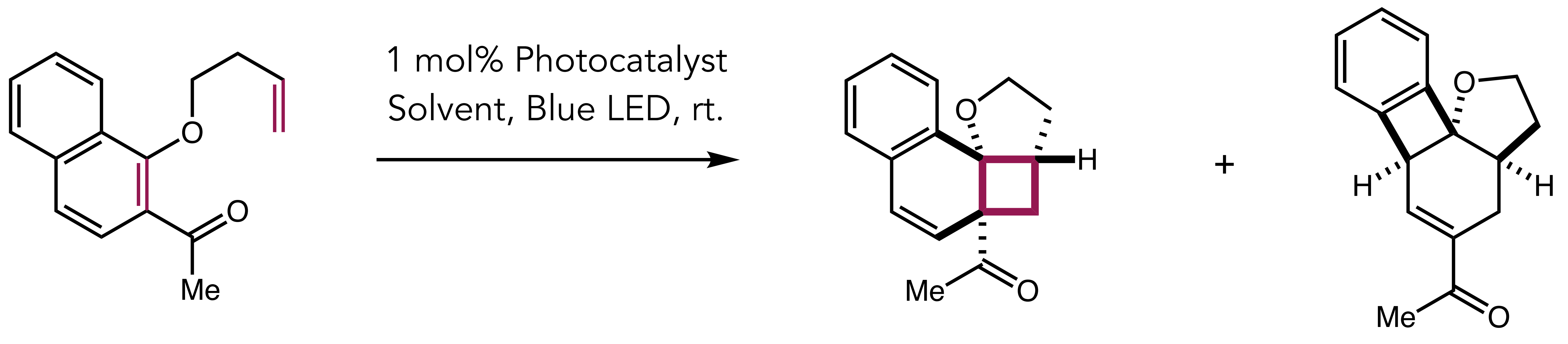
Becker, M. R., Wearing, E. R., Schindler, C. S., *Nat. Chem.*, **2020**, *12*, 898–905.

Photocatalytic dearomative [2+2] and [4+2] cycloaddition

Photocatalytic Dearomative [2+2] Cycloaddition of 1-Naphthols and Olefins

– Glorius, 2018.
  – Intramolecular 1-naphthol-tethered olefin dearomative cycloaddition:

– In optimization studies, authors note two products arising from this substrate, either of which can be selected for based on photocatalyst and solvent selection:



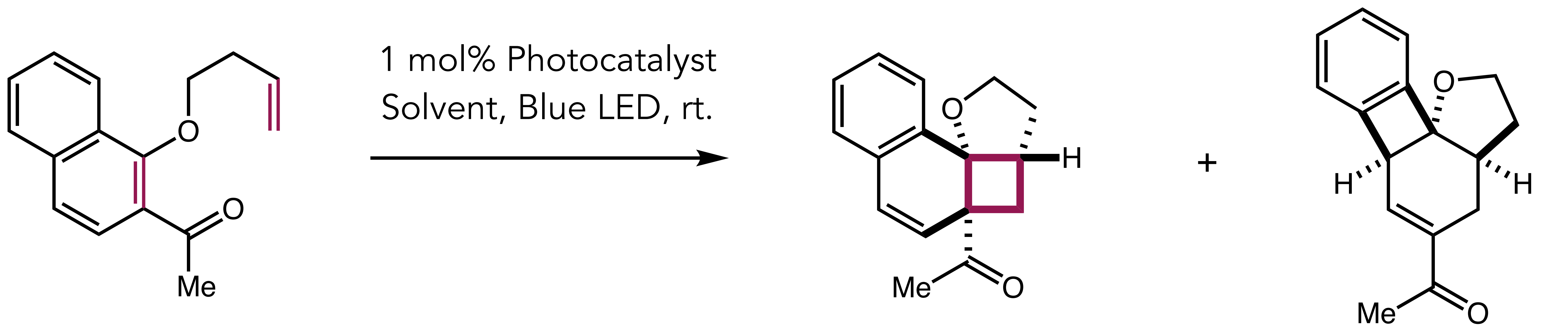
Photocatalyst	Solvent	A /%	B /%
$[Ir(ppy)_2(dtbbpy)]PF_6$	MeCN	67	30
$[Ir(ppy)_2(dtbbpy)]PF_6$	1,4-dioxane	45	53
$[Ir(ppy)_2(dtbbpy)]PF_6$	1,2-DCE	64	36
$[Ir(ppy)_2(dtbbpy)]PF_6$	**MeOH**	**93**	**7**
$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	MeCN	21	79
$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	1,2-DCE	19	81
$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$	**1,4-dioxane**	**15**	**85**

James, M. J, Schwarz J. L., Strieth-Kalthoff, F., Wibbeling B., Glorius, F., *JACS*, **2018**, *140*, 8624-8528.

Photocatalytic Dearomative [2+2] Cycloaddition of 1-Naphthols and Olefins

– Glorius, 2018.
  – Intramolecular 1-naphthol-tethered olefin dearomative cycloaddition:

– **Question**: Can you provide me with a mechanism for the appearance of the second product?



Product A

Optimal photocatalyst:
$[Ir(ppy)_2(dtbbpy)]PF_6$
PC E_T = 49.2 kcal/mol

Product B

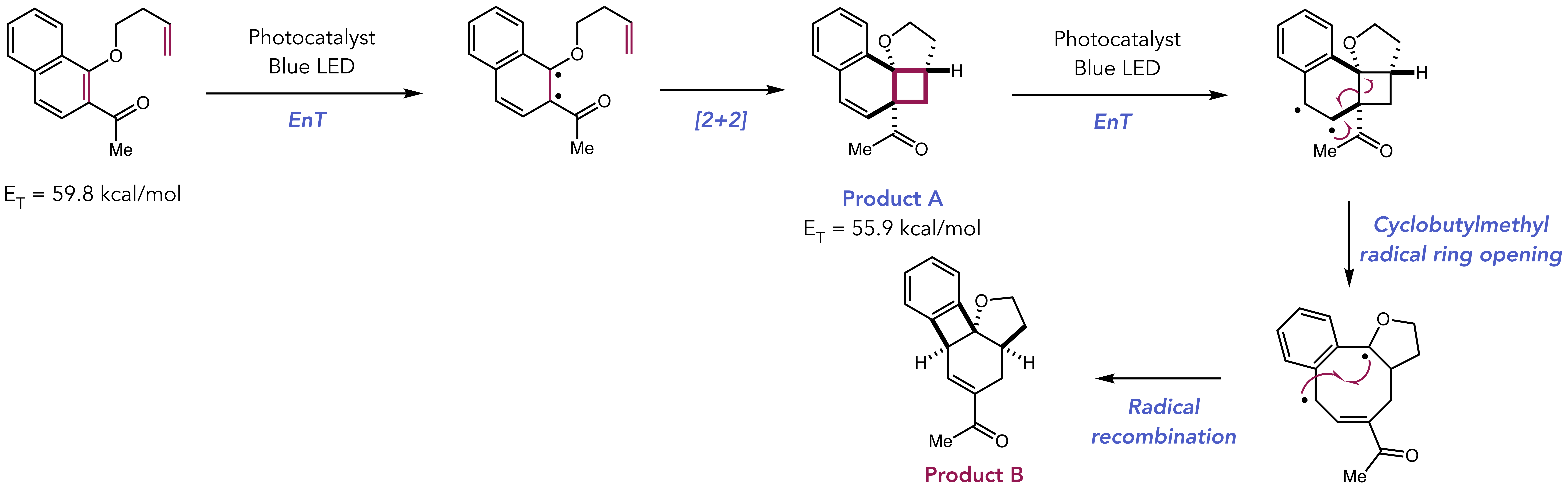
Optimal photocatalyst:
$[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$
PC E_T = 60.1 kcal/mol

James, M. J, Schwarz J. L., Strieth-Kalthoff, F., Wibbeling B., Glorius, F., *JACS*, **2018**, *140*, 8624-8528.

Photocatalytic Dearomative [2+2] Cycloaddition of 1-Naphthols and Olefins

– Glorius, 2018.
  – Intramolecular 1-naphthol-tethered olefin dearomative cycloaddition:

– **Answer**: Sequential sensitized [2+2] cycloaddition, sensitized cyclobutylmethyl ring opening / recombination

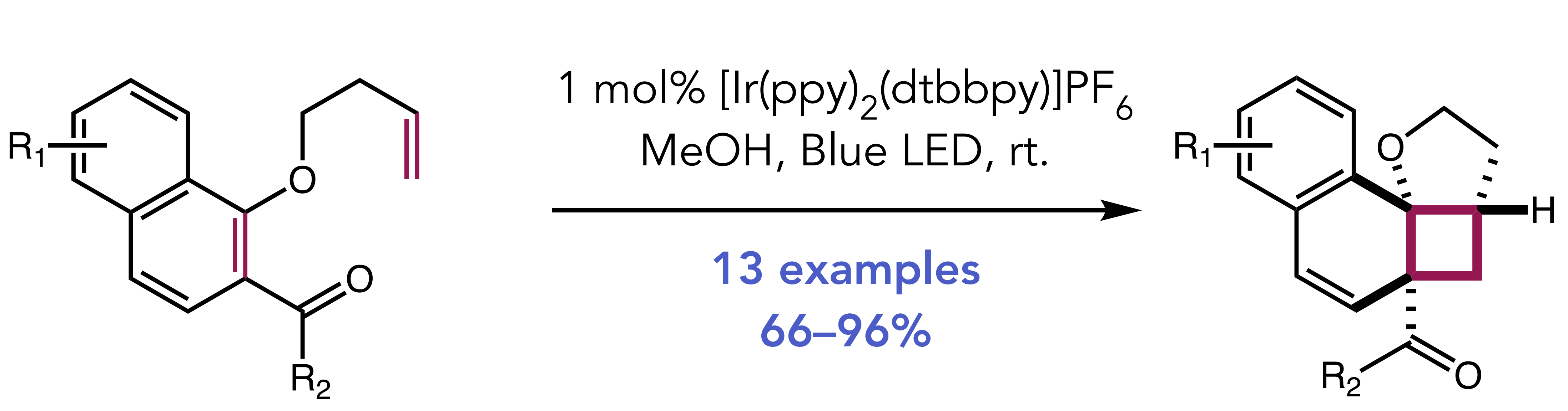


James, M. J, Schwarz J. L., Strieth-Kalthoff, F., Wibbeling B., Glorius, F., *JACS*, **2018**, *140*, 8624-8528.

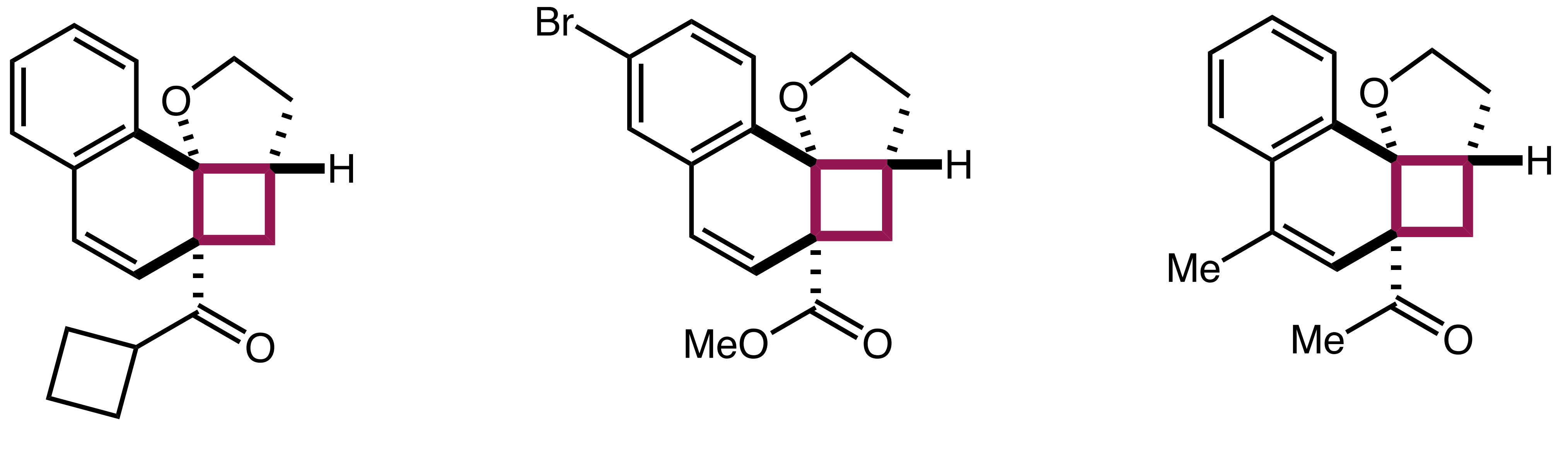
Photocatalytic Dearomative [2+2] Cycloaddition of 1-Naphthols and Olefins

– Glorius, 2018.

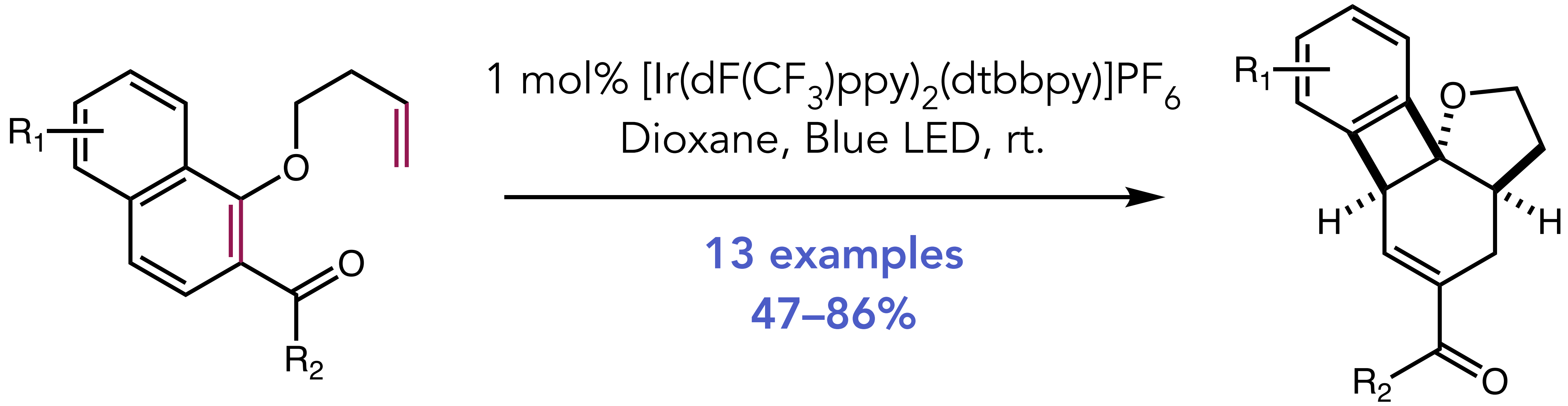
  – Intramolecular 1-naphthol-tethered olefin dearomative cycloaddition:



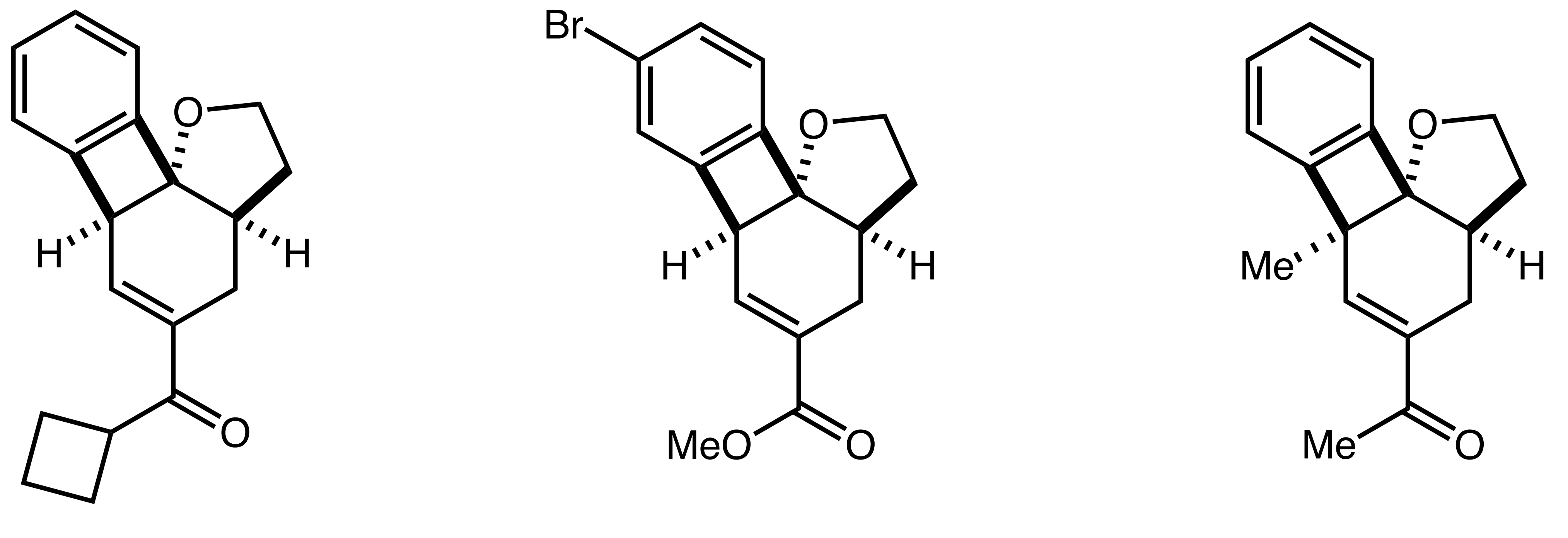
– Select examples:



79% 77% 76%



– Select examples:



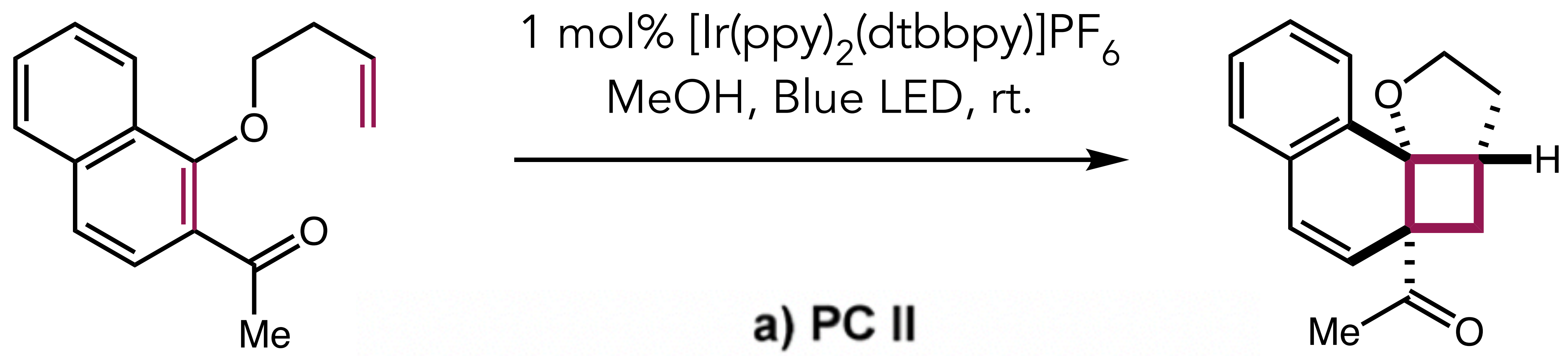
72% 83% 63%

James, M. J, Schwarz J. L., Strieth-Kalthoff, F., Wibbeling B., Glorius, F., *JACS*, **2018**, *140*, 8624-8528.

Photocatalytic Dearomative [2+2] Cycloaddition of 1-Naphthols and Olefins

- Glorius, 2018.
  - Intramolecular 1-naphthol-tethered olefin dearomative cycloaddition.

- Stern Volmer and reaction timecourse studies reveal source of reaction selectivity:

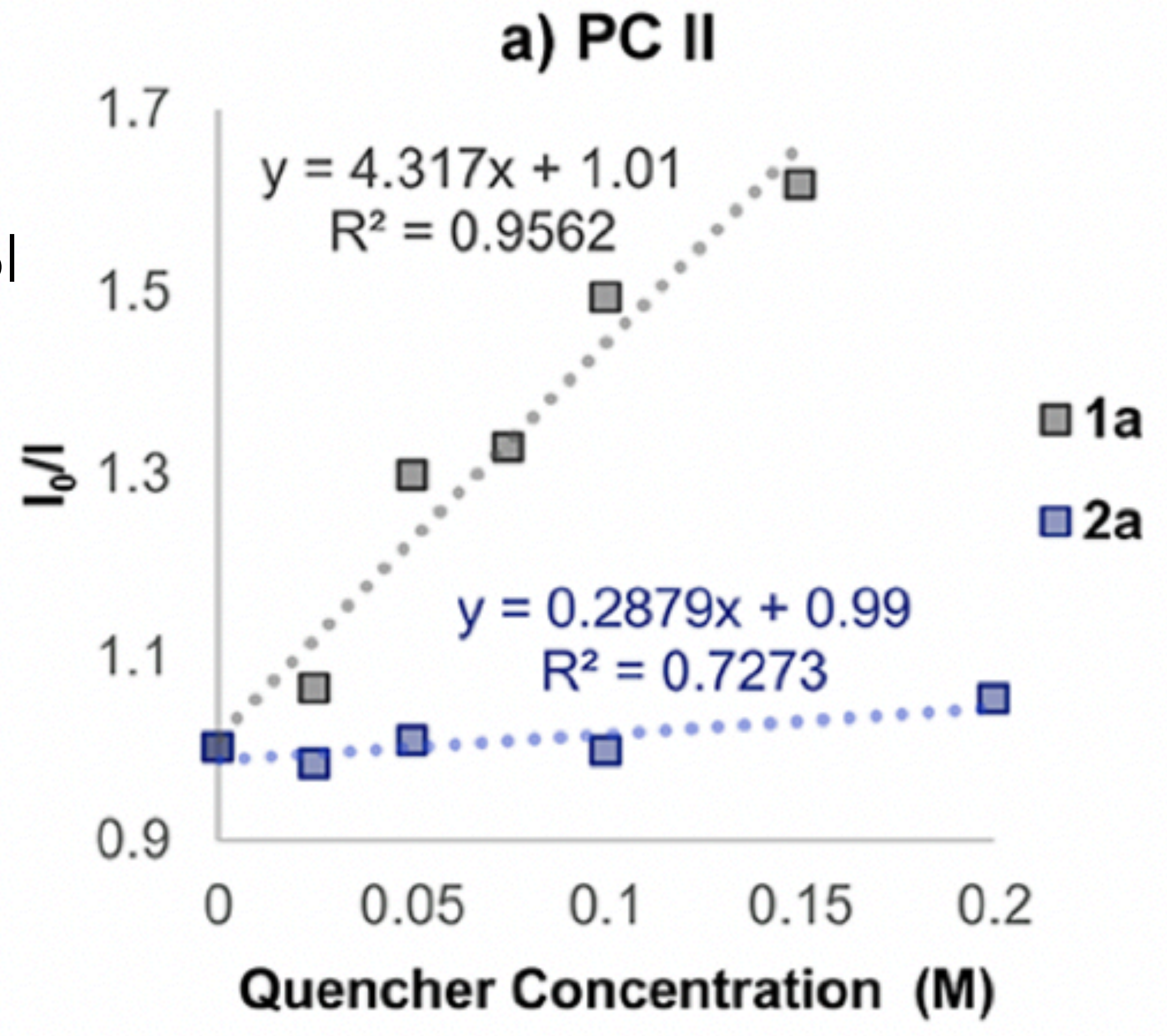


1a

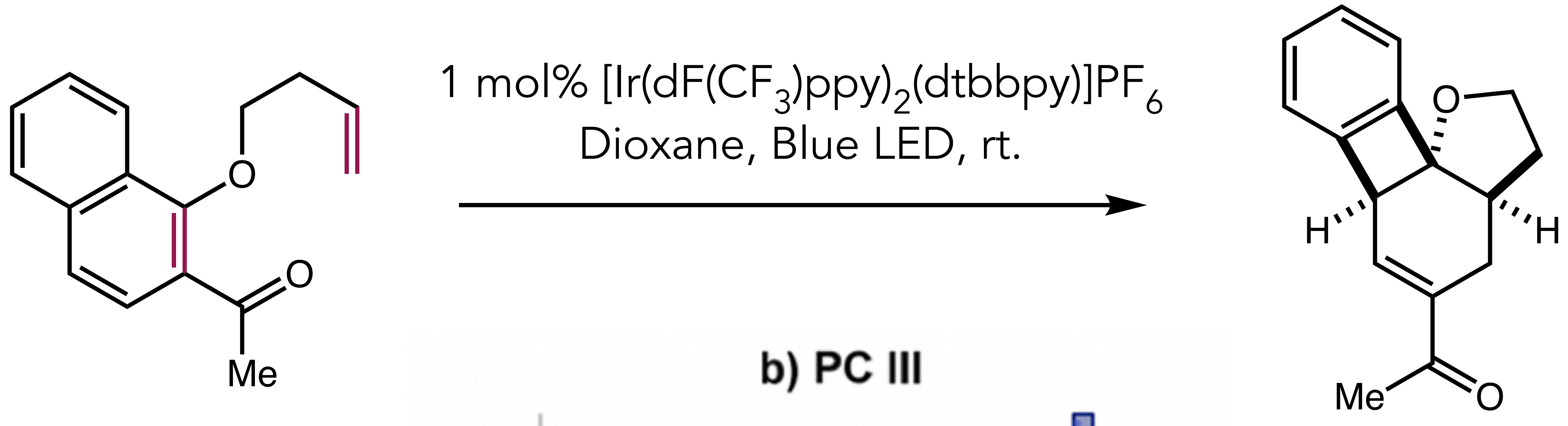
E_T = 59.8 kcal/mol

2a

E_T = 55.9 kcal/mol

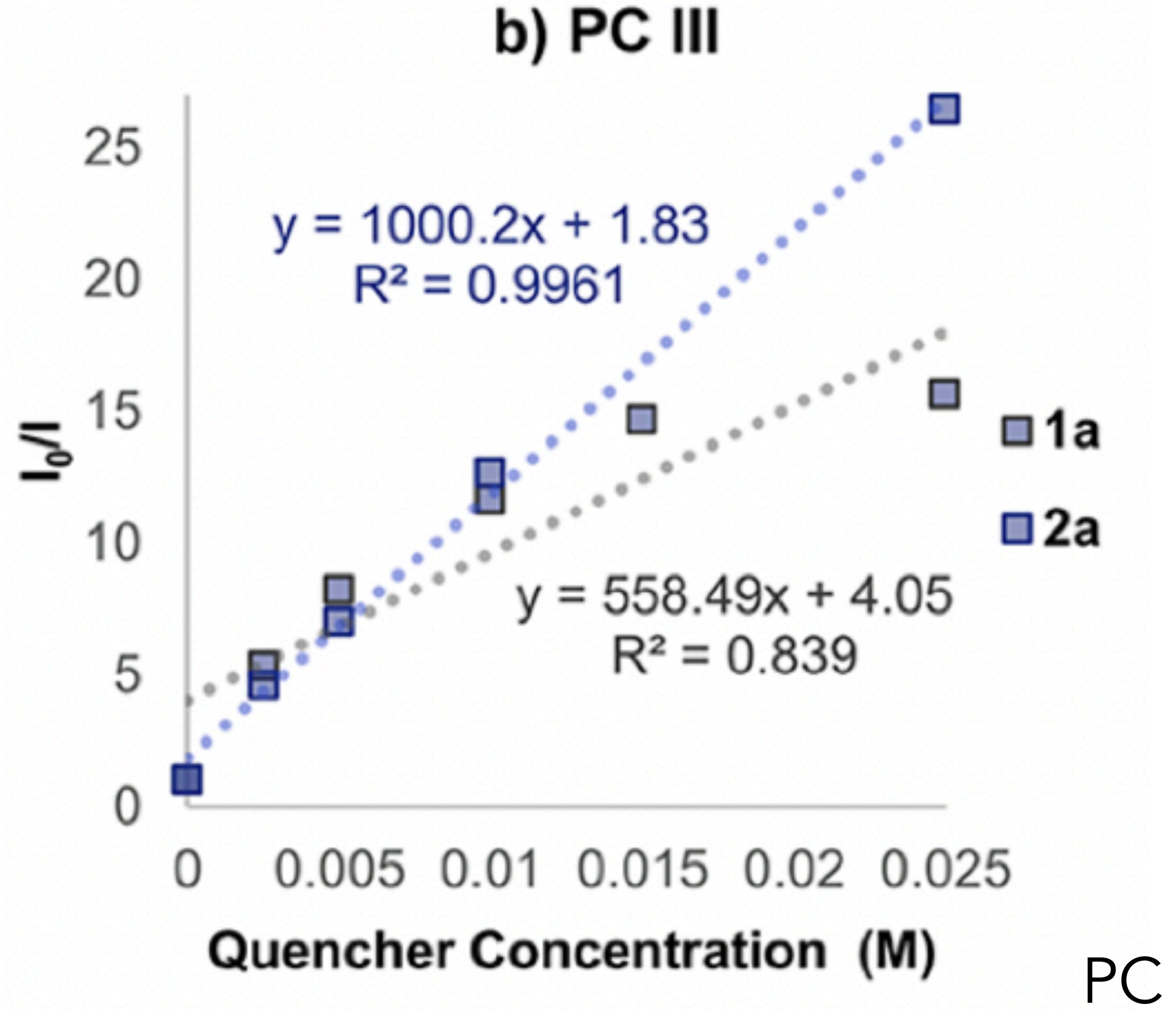


PC E_T = 49.2 kcal/mol



1a

3a



PC E_T = 60.1 kcal/mol

James, M. J, Schwarz J. L., Strieth-Kalthoff, F., Wibbeling B., Glorius, F., *JACS*, **2018**, *140*, 8624-8528.

Photocatalytic Dearomative [2+2] Cycloaddition of 1-Naphthols and Olefins

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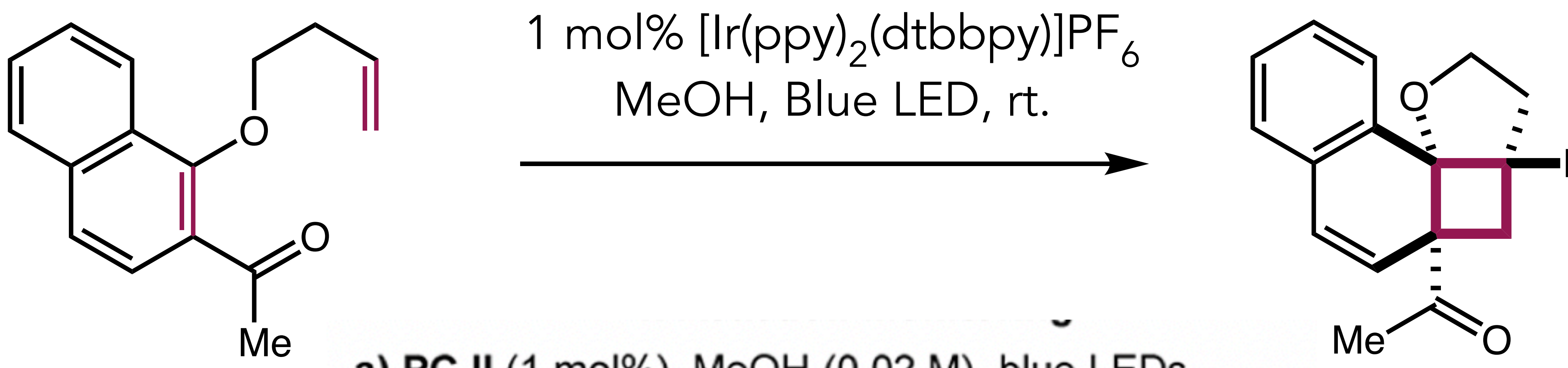
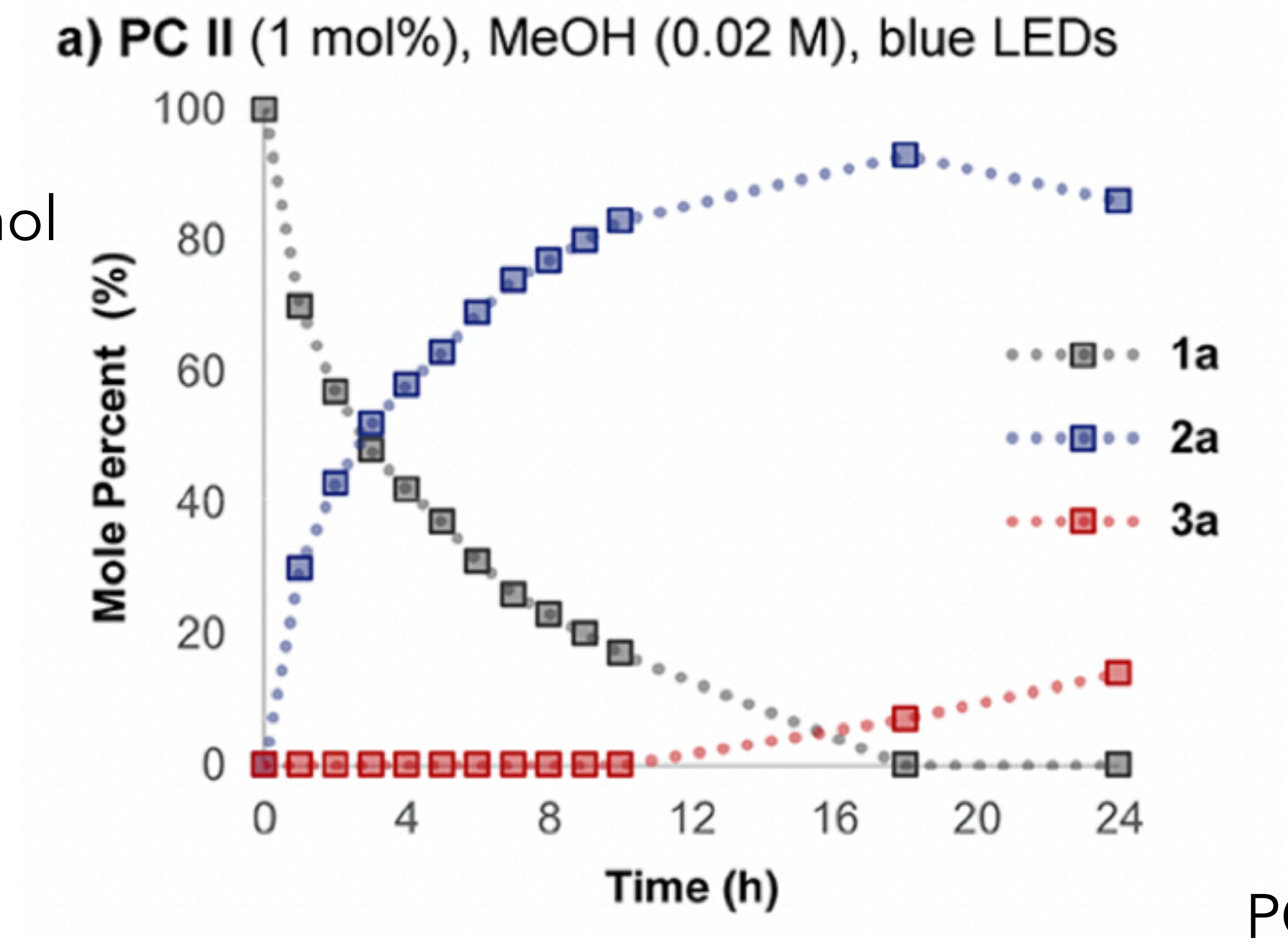
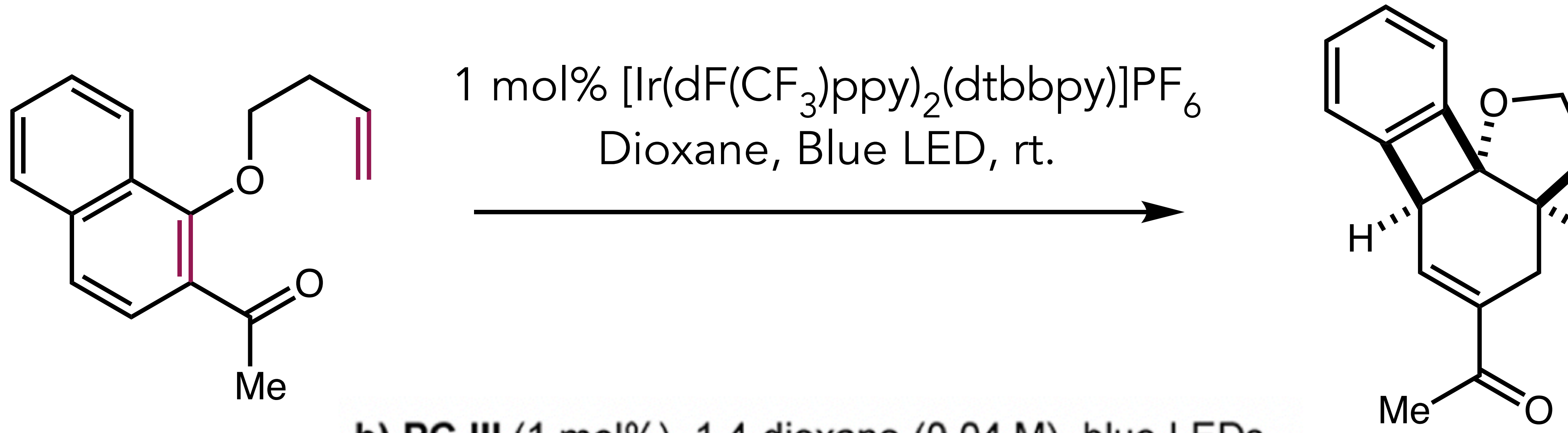


1a
E_T = 59.8 kcal/mol

2a
E_T = 55.9 kcal/mol

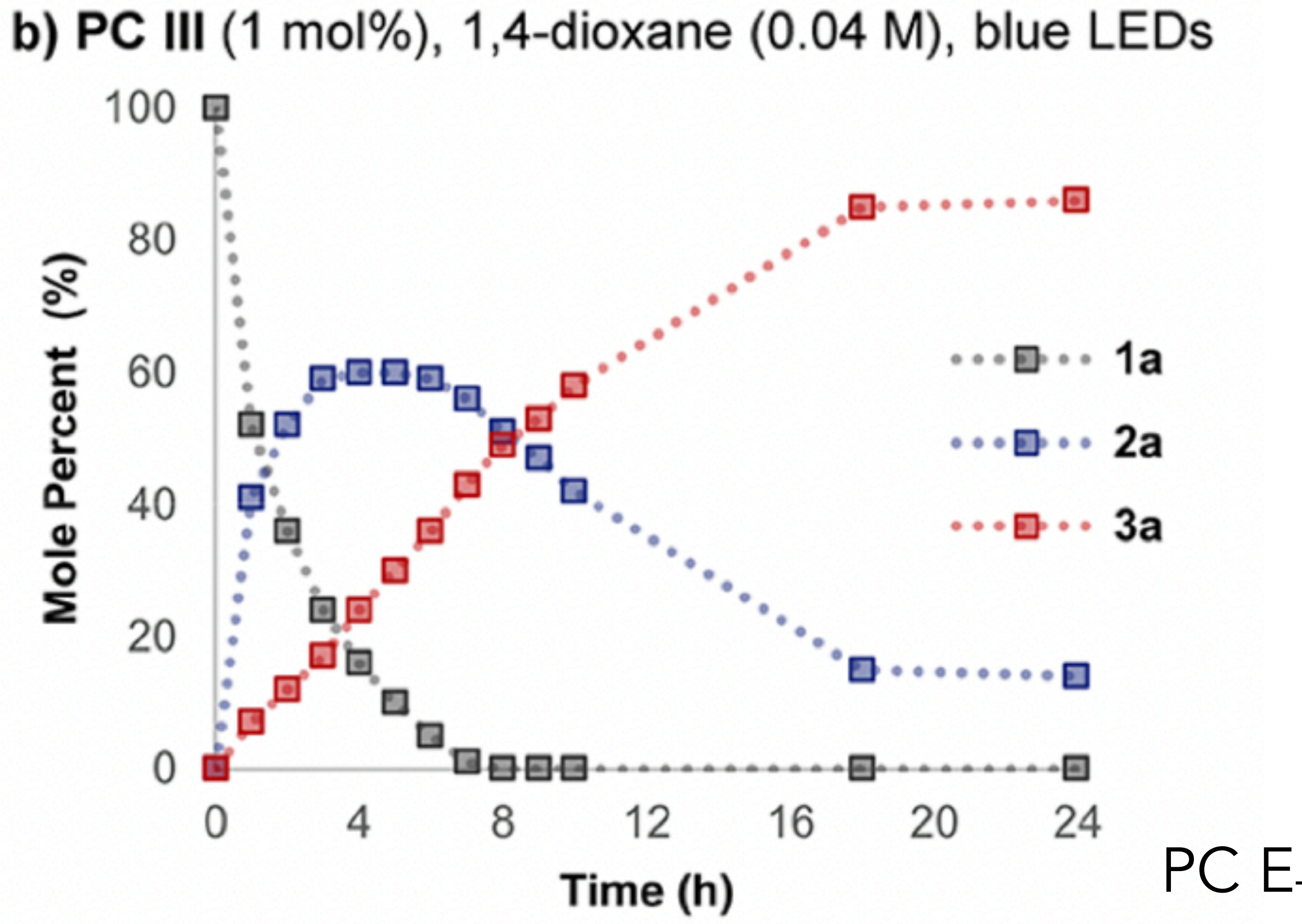


PC E_T = 49.2 kcal/mol



1a

3a

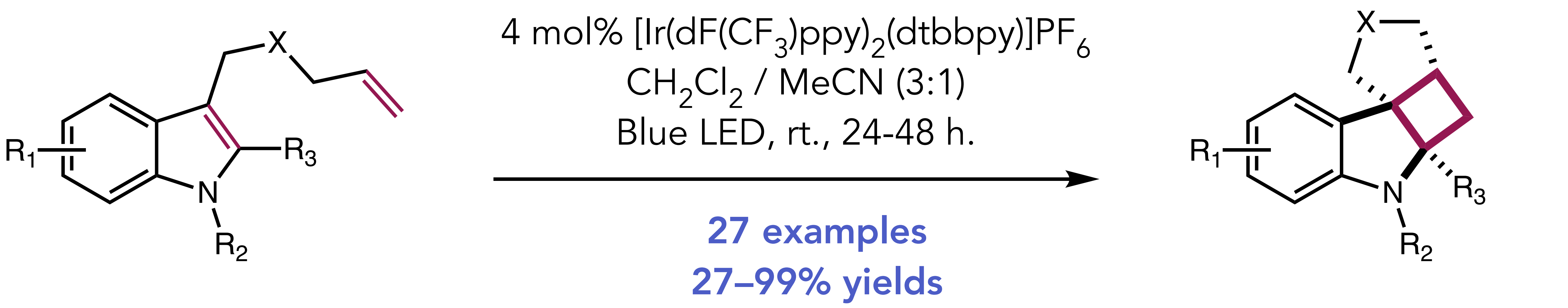


PC E_T = 60.1 kcal/mol

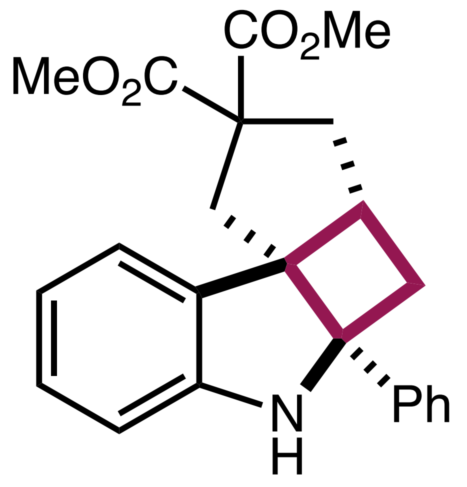
James, M. J, Schwarz J. L., Strieth-Kalthoff, F., Wibbeling B., Glorius, F., *JACS*, **2018**, *140*, 8624-8528.

Photocatalytic Dearomative [2+2] Cycloaddition of Indoles and Olefins

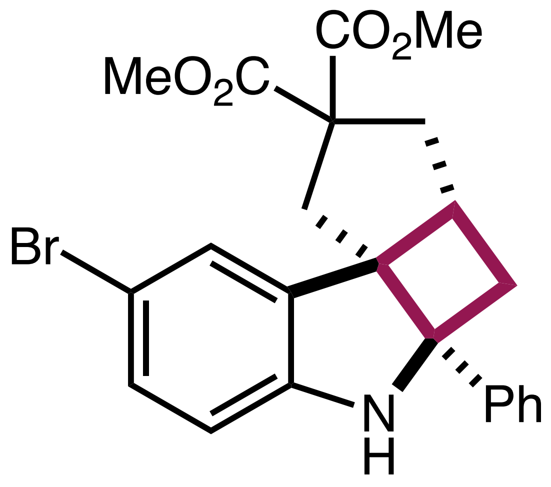
– Zheng and You, 2019.
  – Intramolecular indole C3-tethered olefin dearomative cycloaddition:



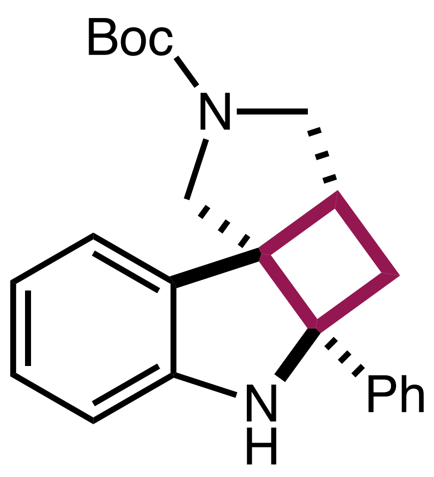
– Select examples:



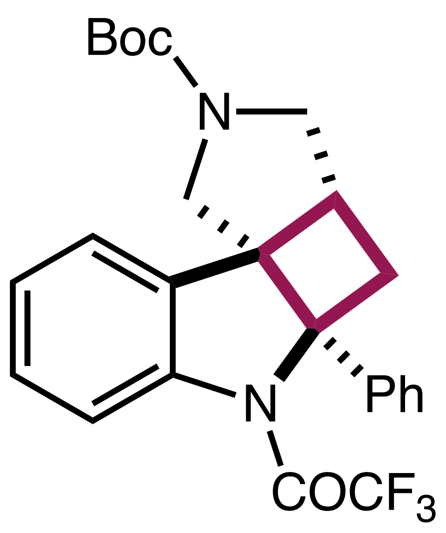
95%



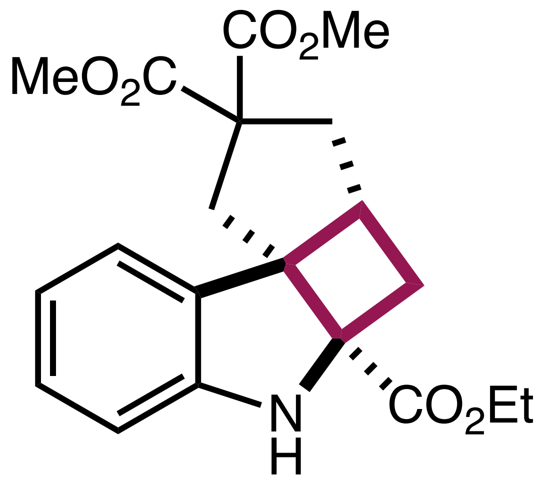
91%



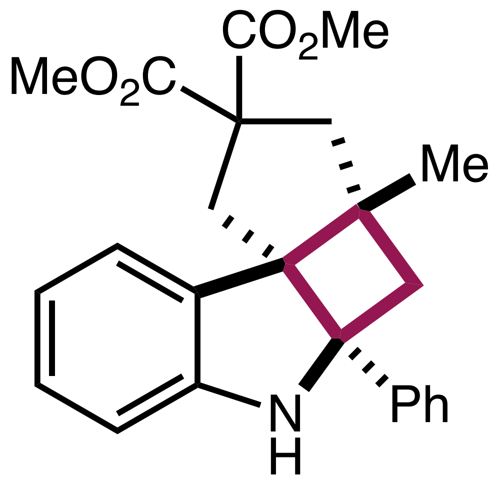
66%



98%



81%

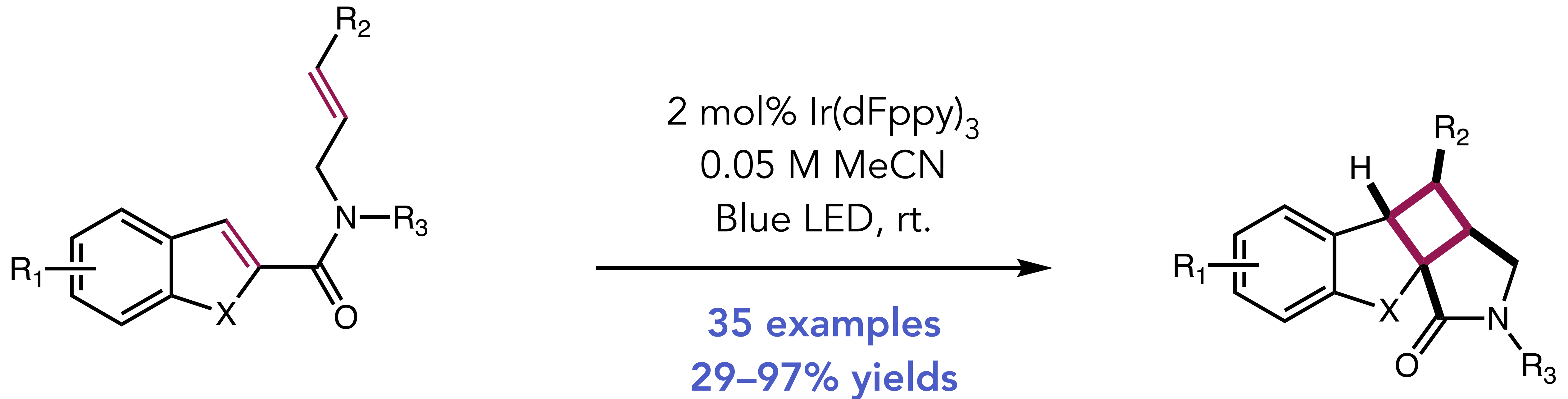


50%

Zhu, M., Zheng C., Zhang X., You S.-L., *JACS*, **2019**, *141*, 2636-2644.

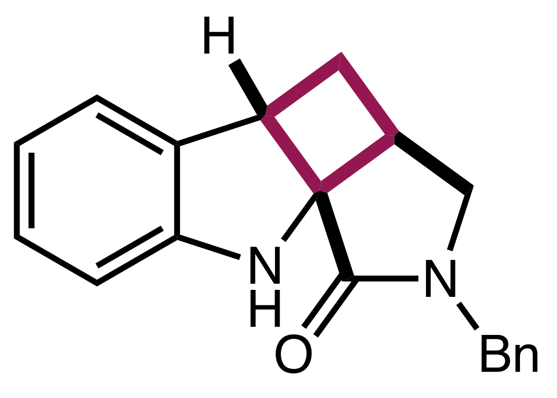
Photocatalytic Dearomative [2+2] Cycloaddition of Indoles and Olefins

– Oderinde and Dhar, 2020.
  – Intramolecular indole C2-tethered olefin dearomative cycloaddition:

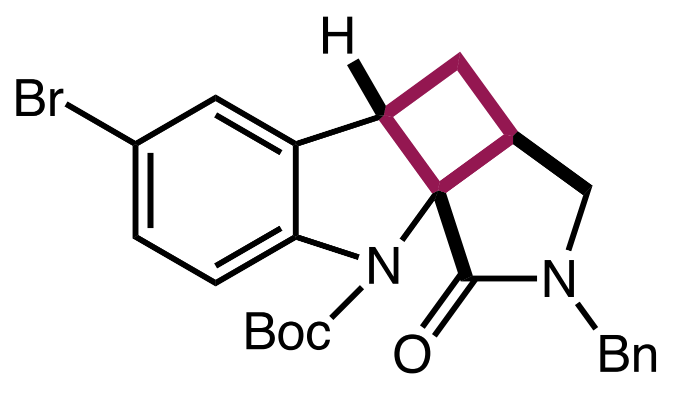


X = NBn, NH, O, S, CH

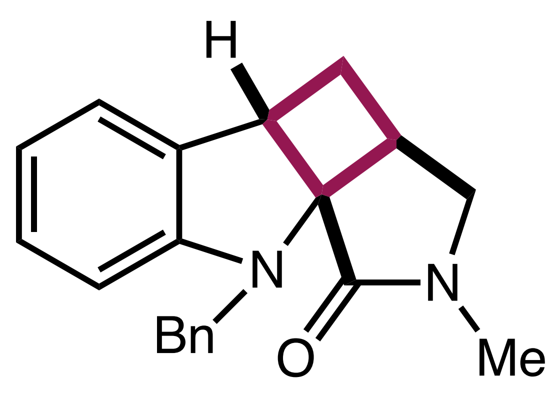
– Select examples:



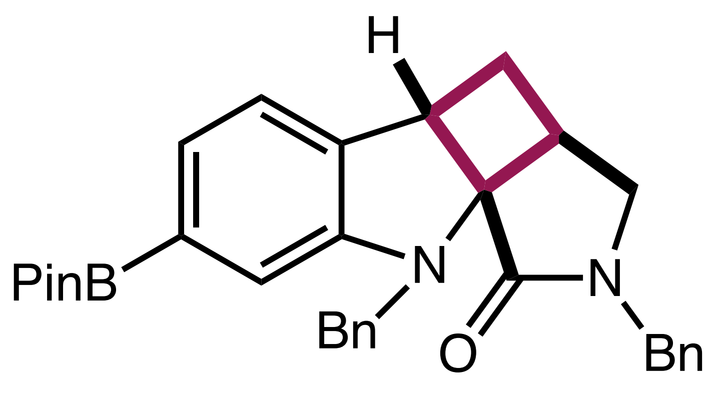
97%



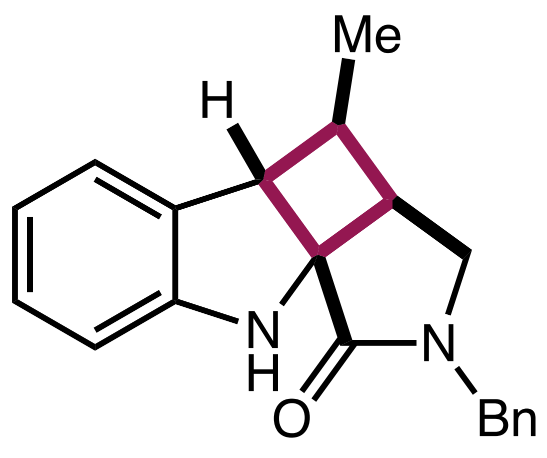
97%



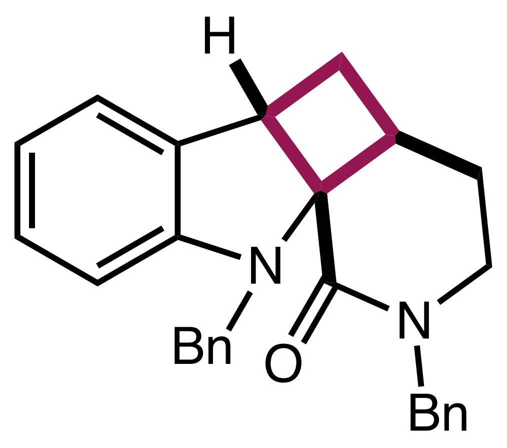
85%



82%



95%

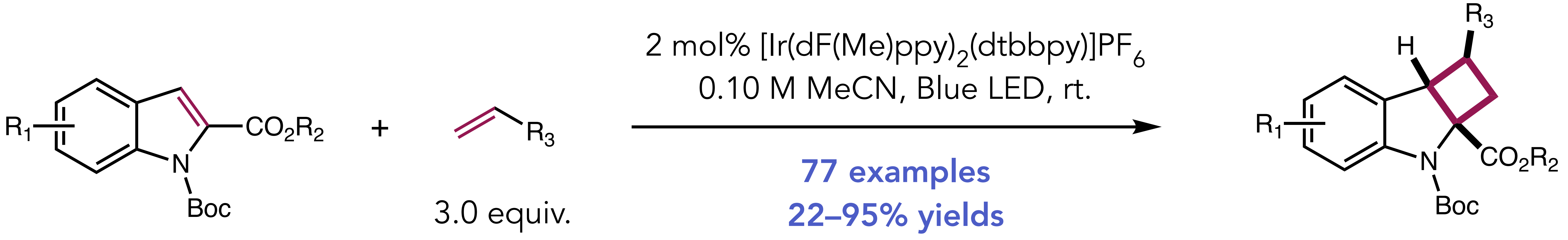


95%

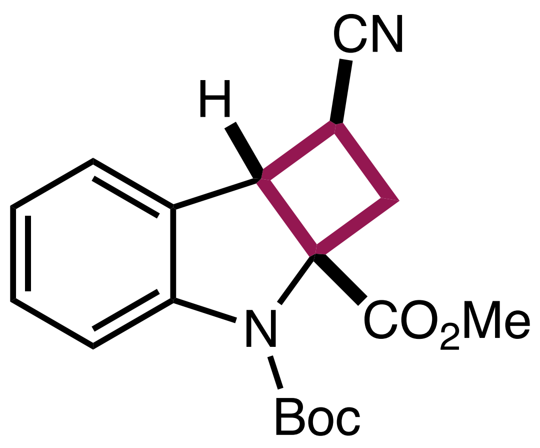
Oderinde, M. S. and co-workers, *JACS*, **2020**, *142*, 3094-3103.

Photocatalytic Dearomative [2+2] Cycloaddition of Indoles and Olefins

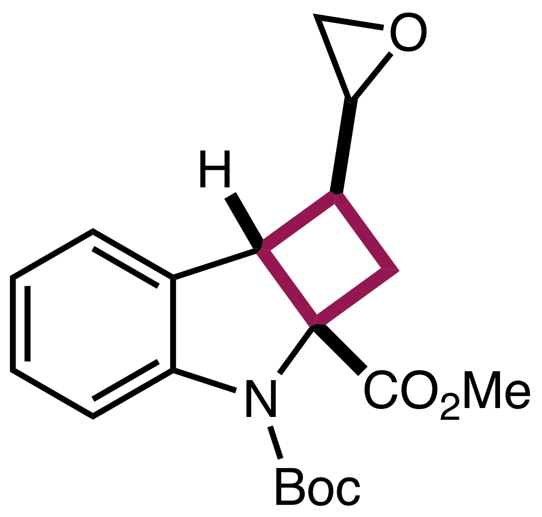
– Oderinde, 2021.
  – Extension to intermolecular indole / olefin dearomative cycloaddition:



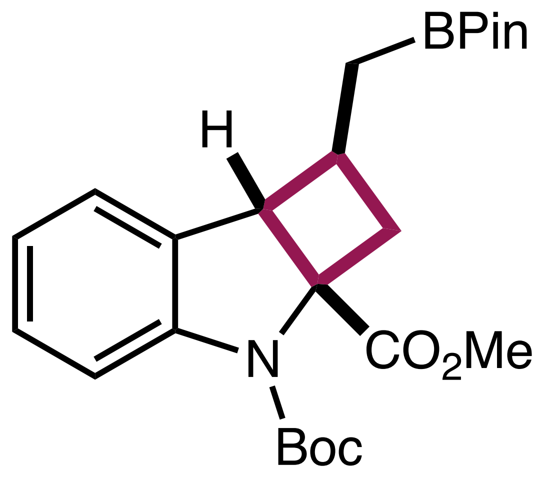
– Select examples:



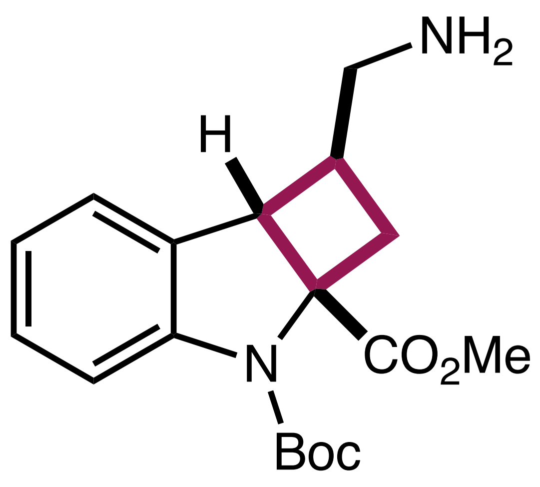
90%, d.r. 1:1



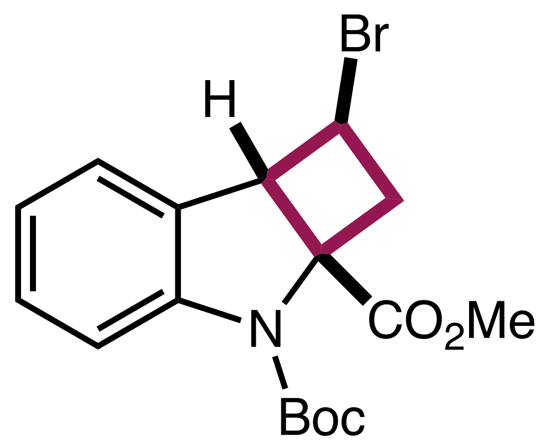
87%, d.r. 7:1



75%, d.r. 8:1



62%, d.r. 6:1

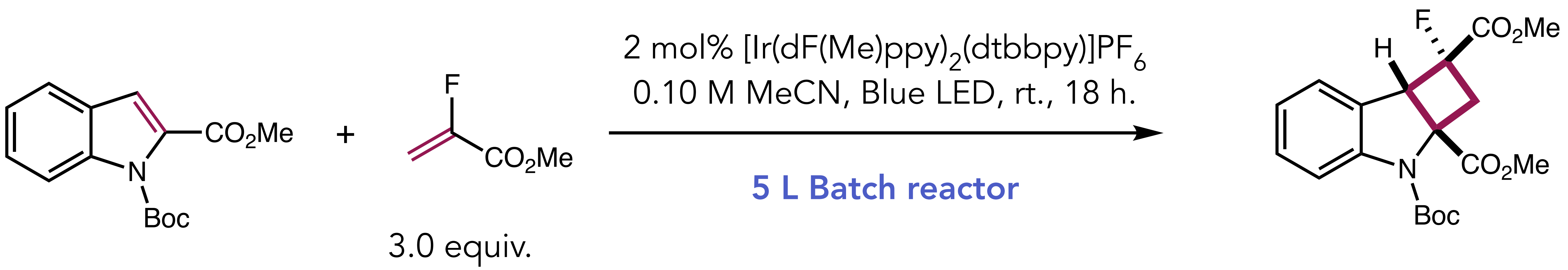


90%, d.r. 6:1

Oderinde, M. S. and co-workers, *JOC*, **2021**, *86*, 1730-1747.

Photocatalytic Dearomative [2+2] Cycloaddition of Indoles and Olefins

– Oderinde, 2021.
  – Extension to intermolecular indole / olefin dearomative cycloaddition:
  – Scale up:



100 g

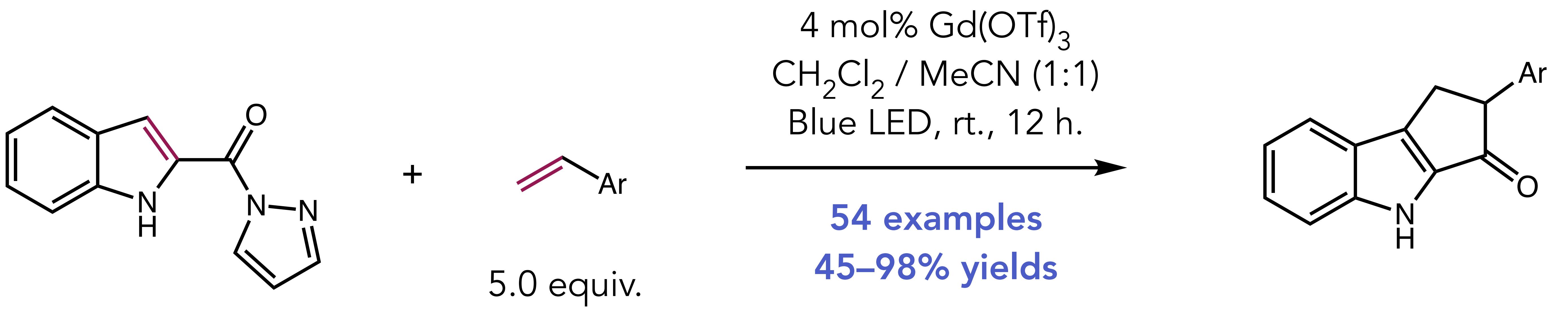
107 g
78 % yield
d.r. >20:1

Oderinde, M. S. and co-workers, *JOC*, **2021**, *86*, 1730-1747.

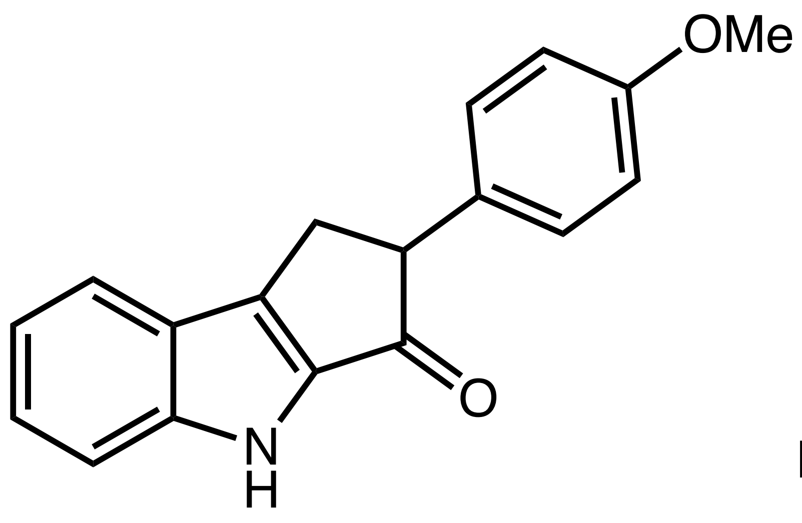
Photocatalytic [2+2] Cycloaddition of Indoles and Olefins with ring expansion

– Glorius, 2020.

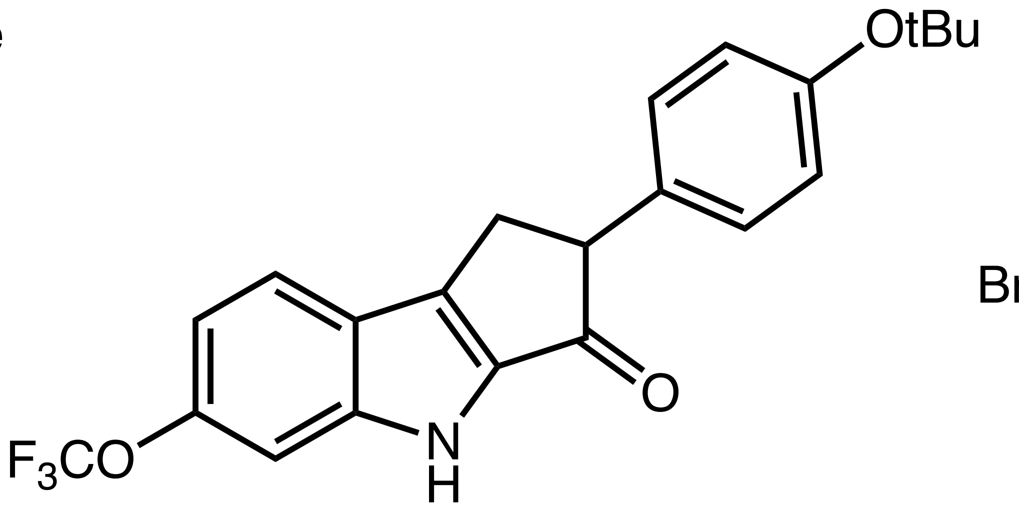
– A rare example of Gd-photocatalysis for energy transfer:



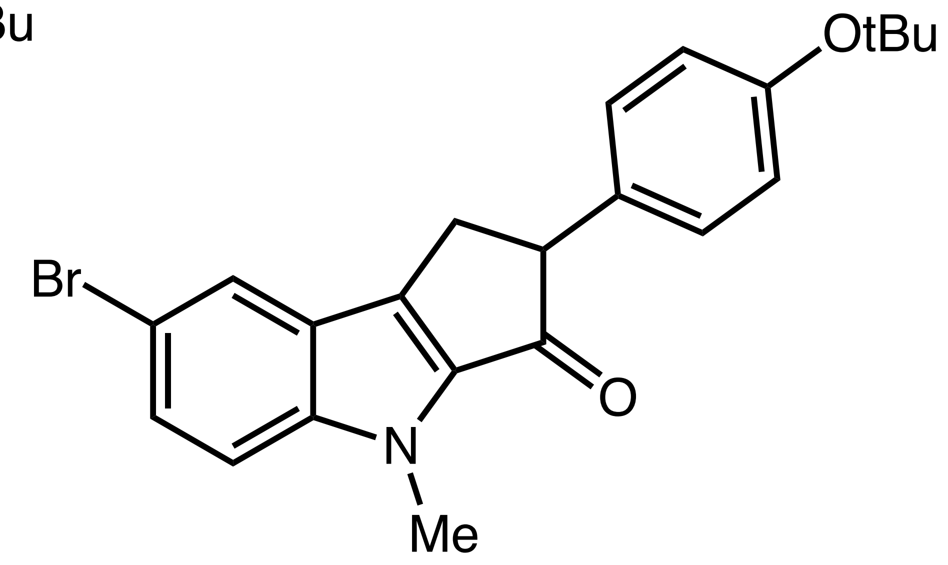
– Select examples:



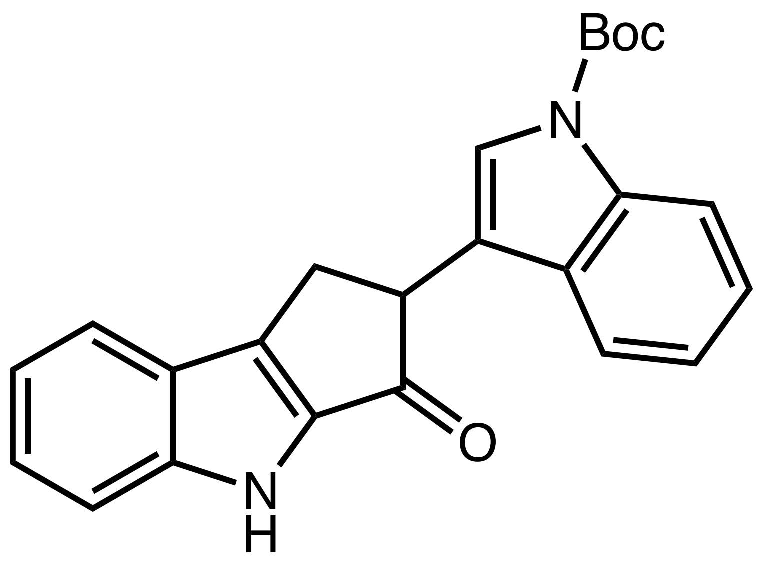
84%, >95:5 r.r.



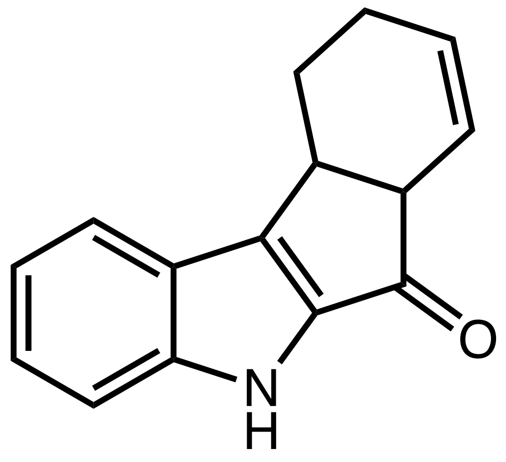
89%, 92:8 r.r.



97%, >95:1 r.r.



57%, >95:5 r.r.

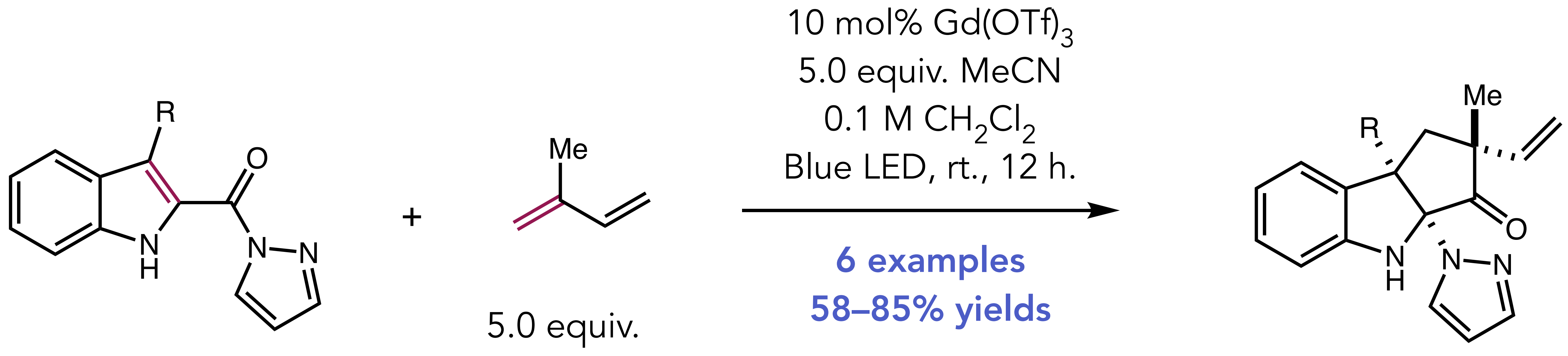


45%, 80:20 r.r.

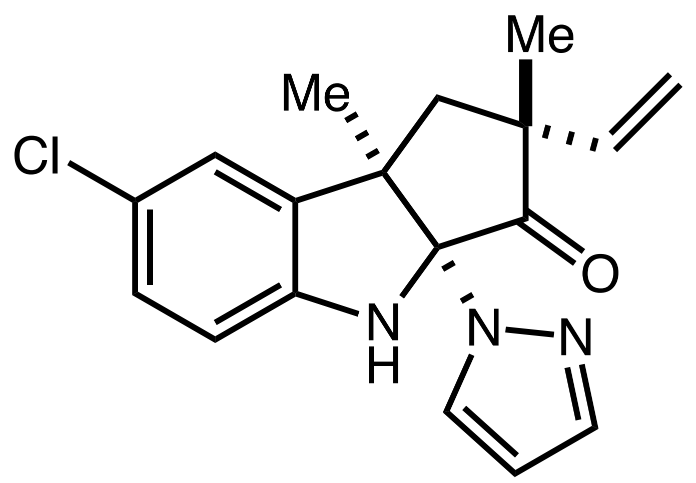
Ma, J., Schäfers, F., Daniliuc, C., Bergander, K., Strassert, C. A., Glorius, F., *ACIE*, **2020**, *59*, 9639-9645.

Photocatalytic [2+2] Cycloaddition of Indoles and Olefins with ring expansion

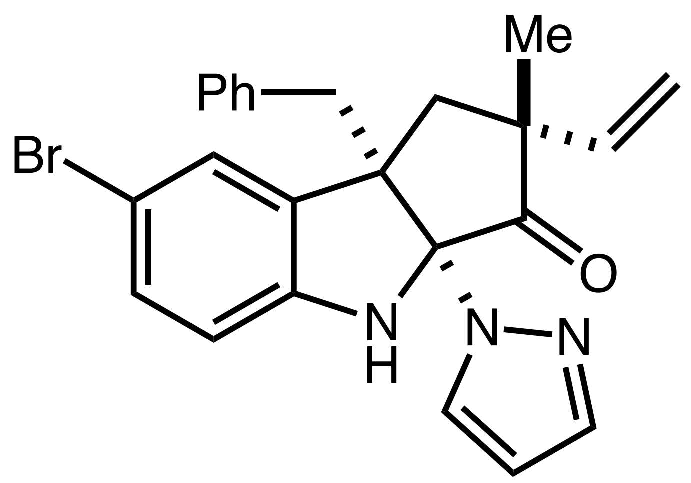
– Glorius, 2020.
  – Dearomatization in 3-substituted indoles with isoprene:



– Select examples:



70%, d.r. 3:1

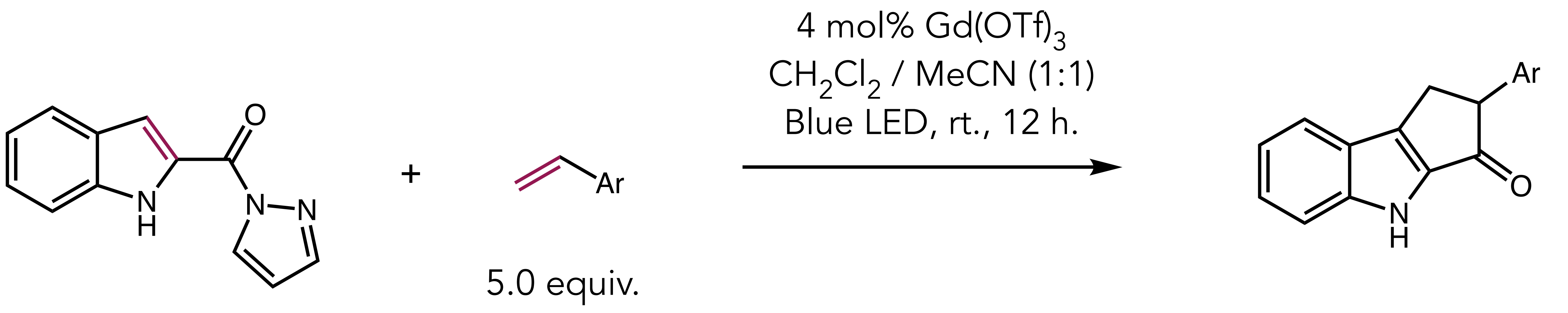


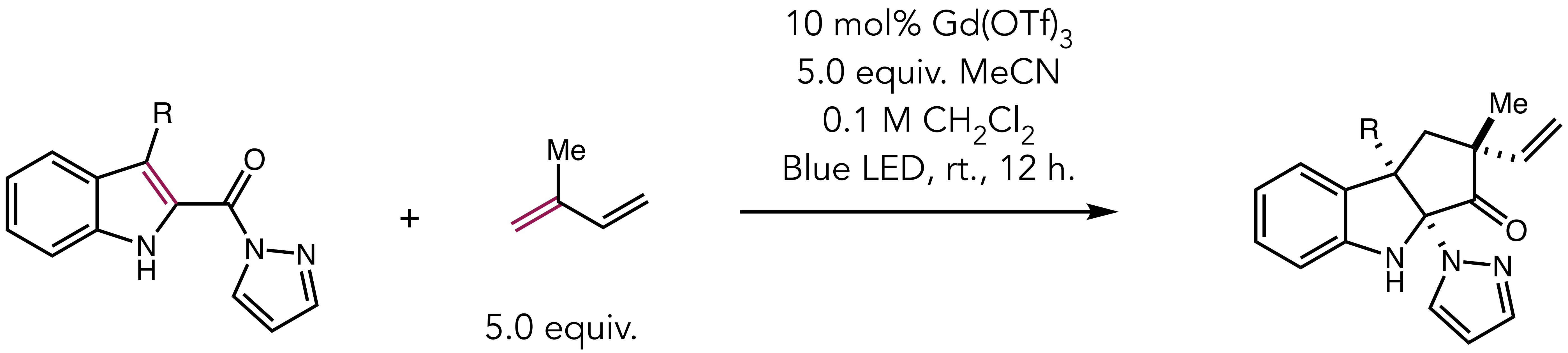
76%, d.r. 3:1

Ma, J., Schäfers, F., Daniliuc, C., Bergander, K., Strassert, C. A., Glorius, F., *ACIE*, **2020**, *59*, 9639-9645.

Photocatalytic [2+2] Cycloaddition of Indoles and Olefins with ring expansion

– Glorius, 2020.
  – A rare example of Gd-photocatalysis for energy transfer:





– **Question**: Can you provide me with a mechanism for these transformations?

Ma, J., Schäfers, F., Daniliuc, C., Bergander, K., Strassert, C. A., Glorius, F., *ACIE*, **2020**, *59*, 9639-9645.

Photocatalytic [2+2] Cycloaddition of Indoles and Olefins with ring expansion

– Glorius, 2020.
  – Proposed mechanism of transformation:

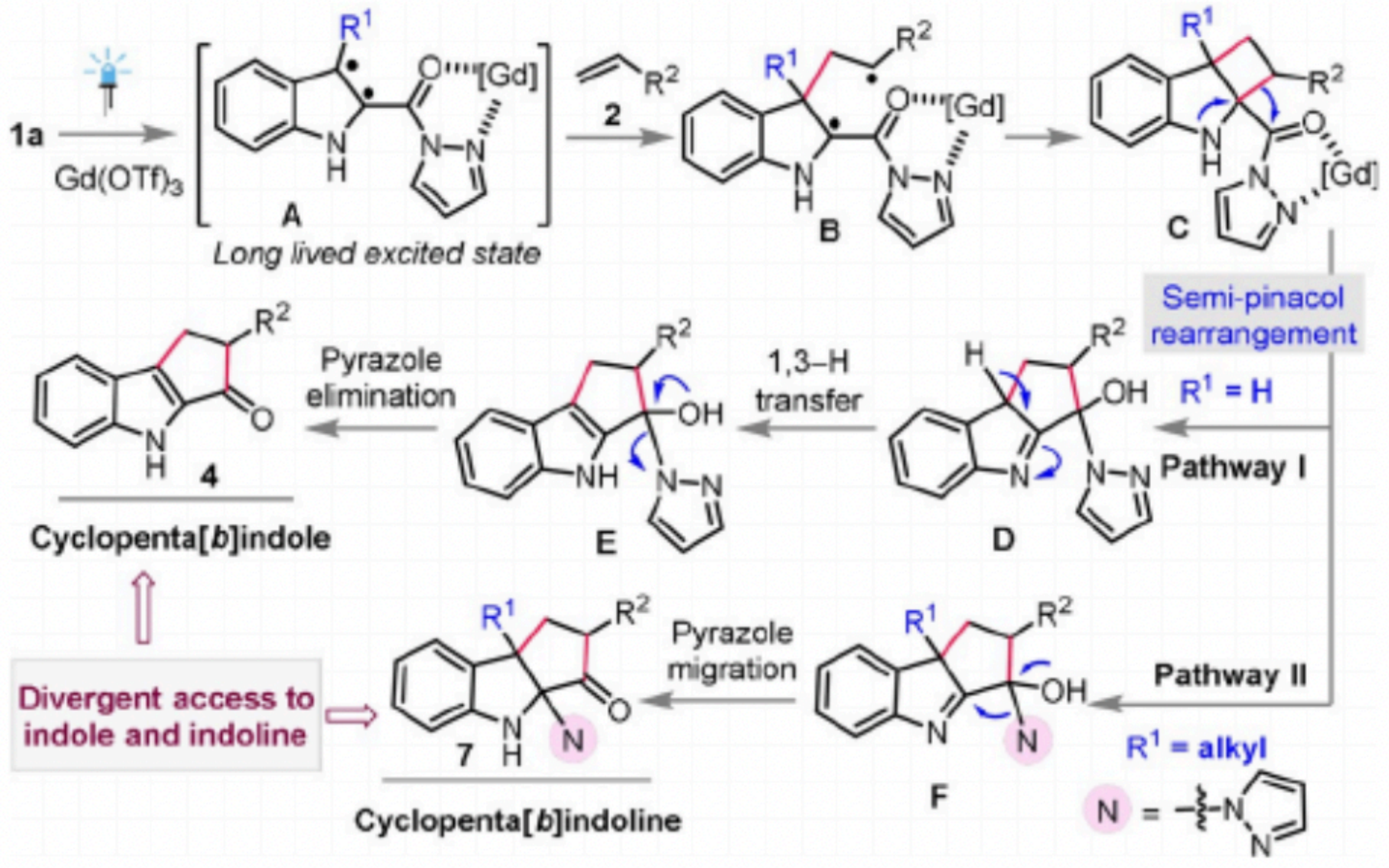
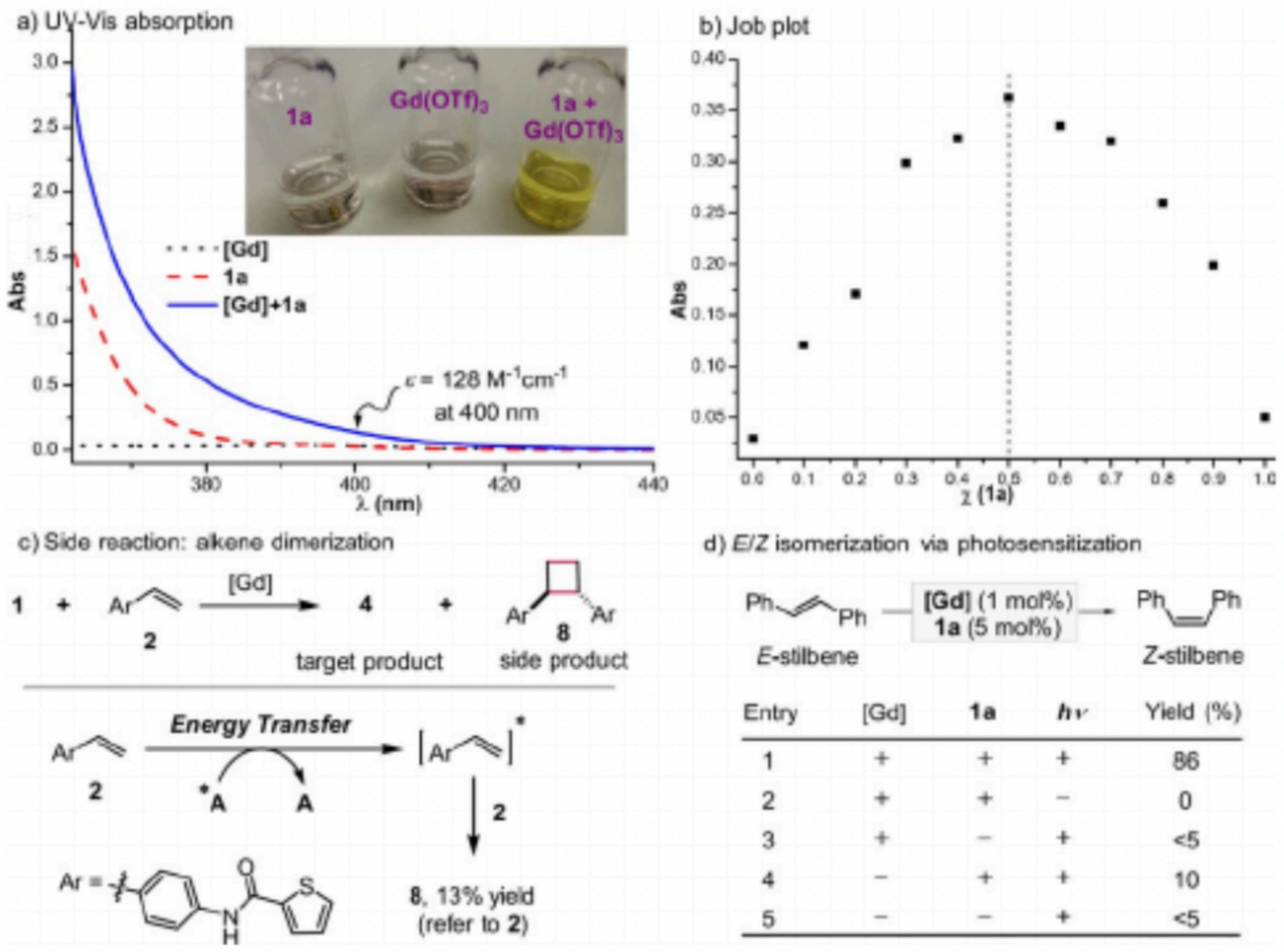


Figure 4. Proposed divergent reaction pathways following [2+2] photo-cycloaddition/ring-expansion sequence.

Ma, J., Schäfers, F., Daniliuc, C., Bergander, K., Strassert, C. A., Glorius, F., *ACIE*, **2020**, *59*, 9639-9645.

Photocatalytic [2+2] Cycloaddition of Indoles and Olefins with ring expansion

- Glorius, 2020.
  - Mechanistic support:



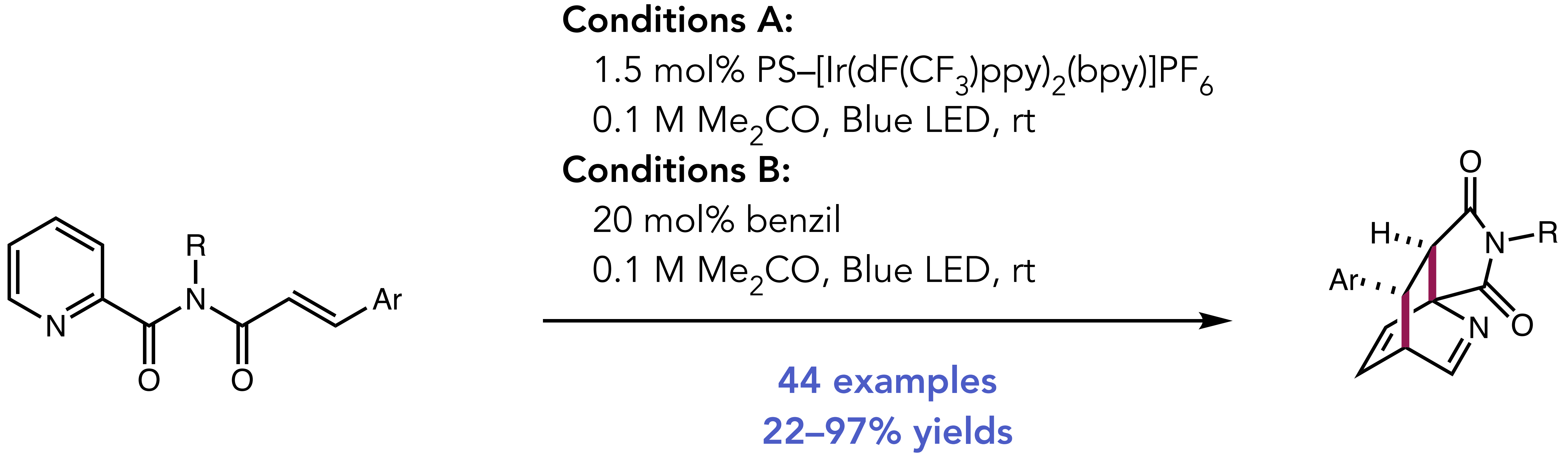
Entry	[Gd]	1a	hν	Yield (%)
1	+	+	+	86
2	+	+	–	0
3	+	–	+	<5
4	–	+	+	10
5	–	–	+	<5

Figure 5. a) UV/Vis absorption spectra of **1a**/[Gd] (1:1, 1.0 mM) in CH_3CN. b) Job plot analysis (absorbance as a function of χ, that is, the molar fraction of **1a**). c) Isolation of a side product **8** as an indicator for intermediate **A**. d) Probing the intermediate **A** through the photosensitized isomerization.

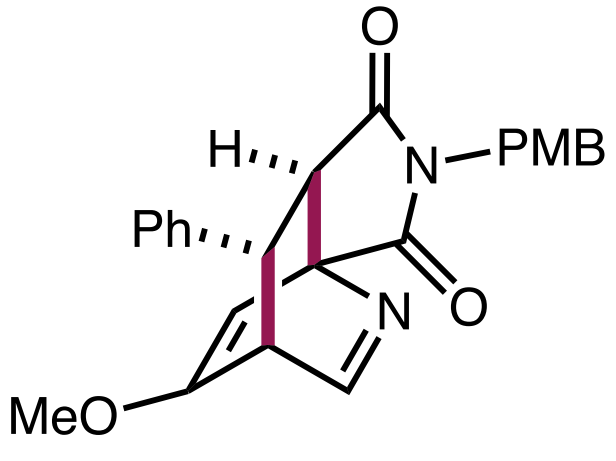
Ma, J., Schäfers, F., Daniliuc, C., Bergander, K., Strassert, C. A., Glorius, F., *ACIE*, **2020**, *59*, 9639-9645.

Photocatalytic Dearomative via [4+2] Cycloaddition in pyridines and quinolines

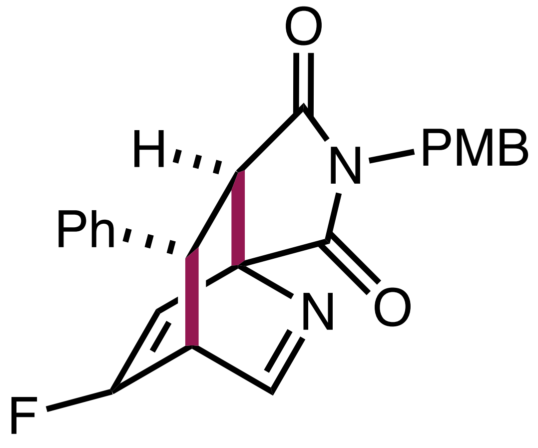
– Glorius, 2019.
  – Intramolecular [4+2] cycloaddition of C2-tethered pyridine olefins:



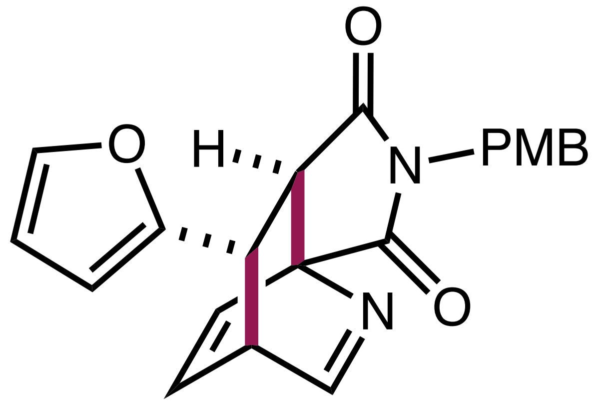
– Select examples:



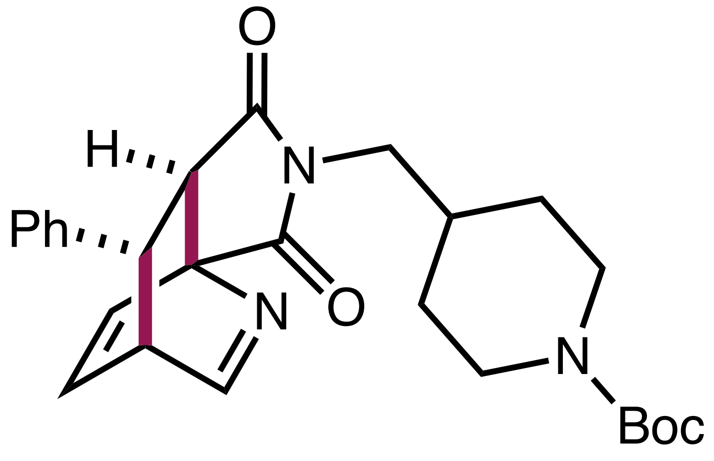
94%, d.r. 3.5:1



71%, d.r. 1.2:1



97%, d.r. 2:1



86%, d.r. 3.4:1

Ma, J., Strieth-Kalthoff, F., Dalton, T., Freitag, M., Luca Schwarz, J., Bergander, K., Daniliuc, C., Glorius, F., *Chem*, **2019**, *5*, 2854-2864.

Photocatalytic Dearomative via [4+2] Cycloaddition in pyridines and quinolines

- Glorius, 2019.
  - Interesting use of a recyclable polymer supported photocatalyst:

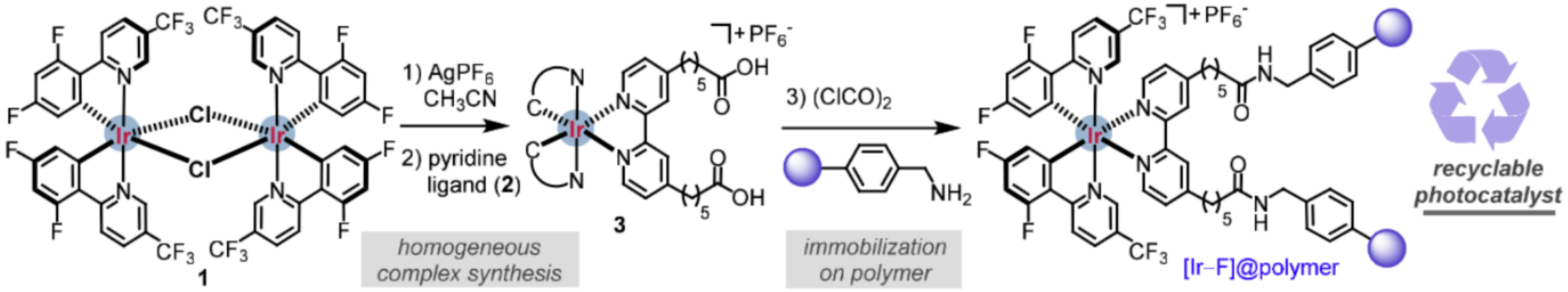
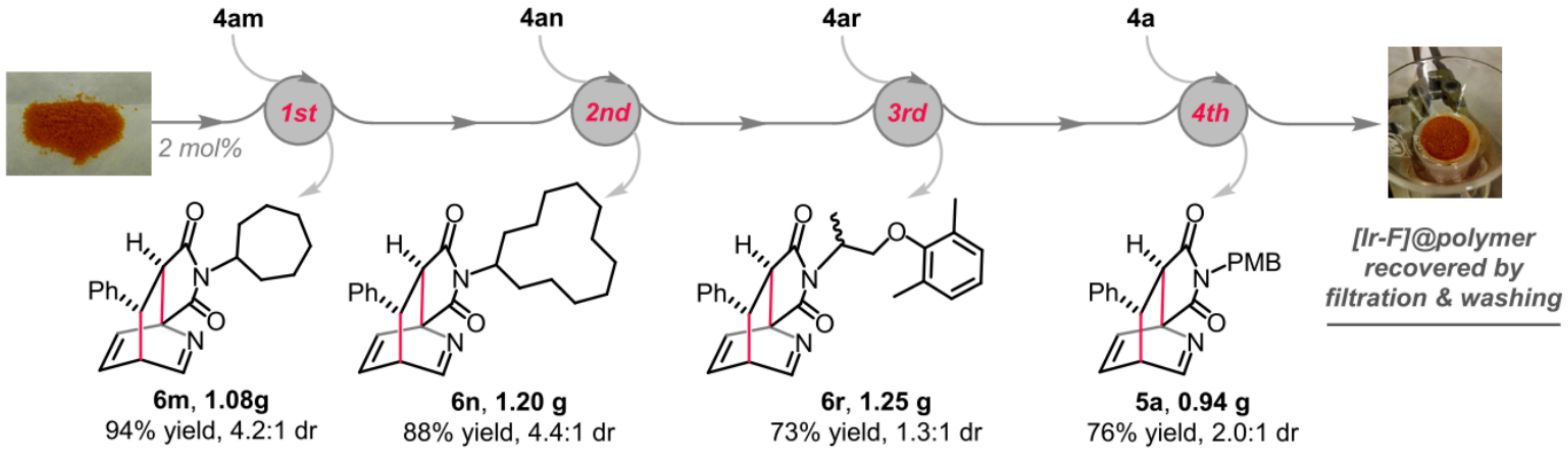


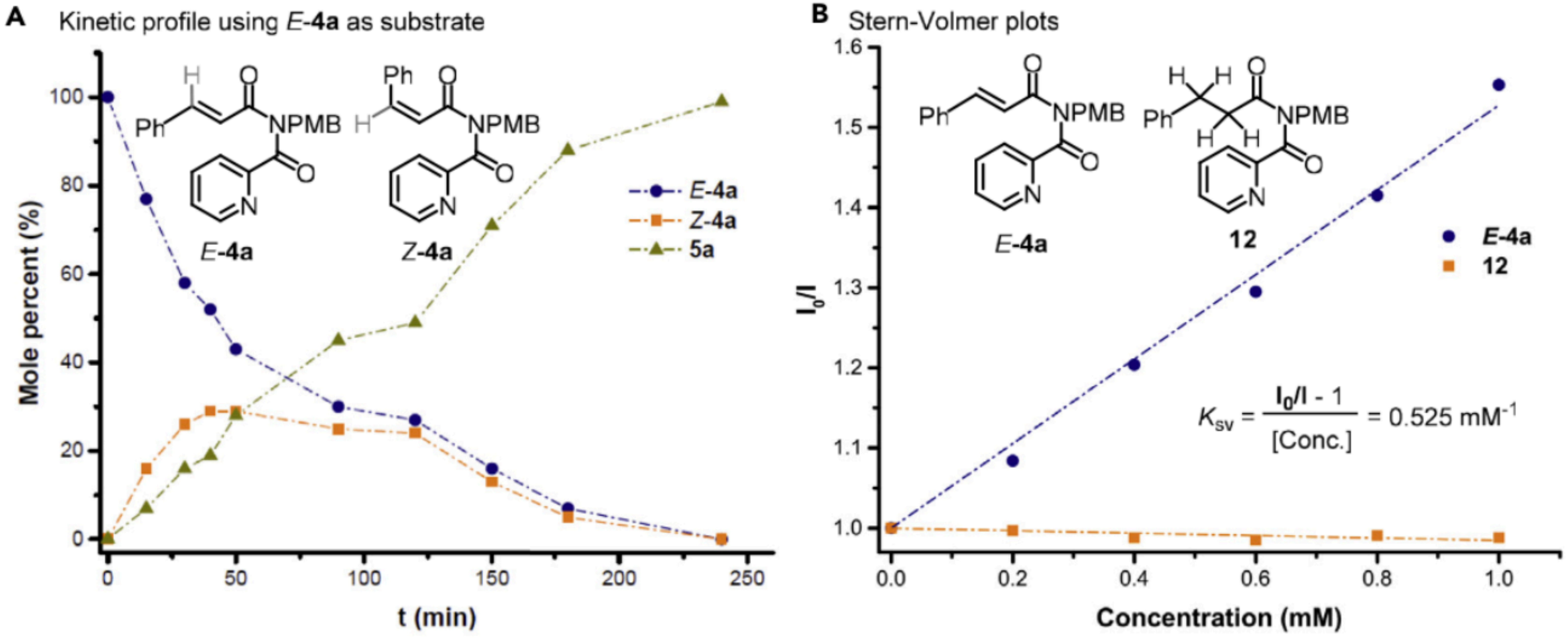
Figure 2. Synthesis of an Immobilized Iridium Photocatalyst

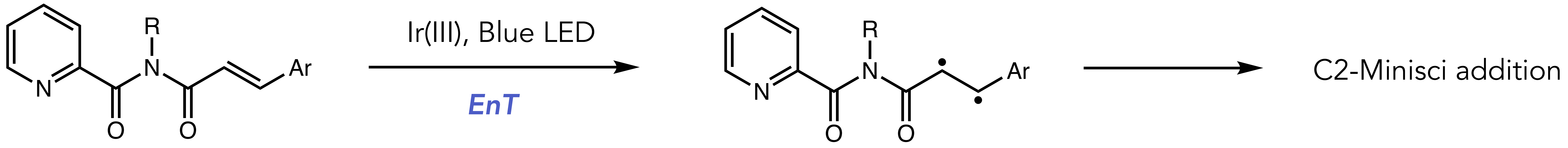


Ma, J., Strieth-Kalthoff, F., Dalton, T., Freitag, M., Luca Schwarz, J., Bergander, K., Daniliuc, C., Glorius, F., *Chem*, **2019**, *5*, 2854-2864.

Photocatalytic Dearomative via [4+2] Cycloaddition in pyridines and quinolines

– Glorius, 2019.
  –Mechanistic support:



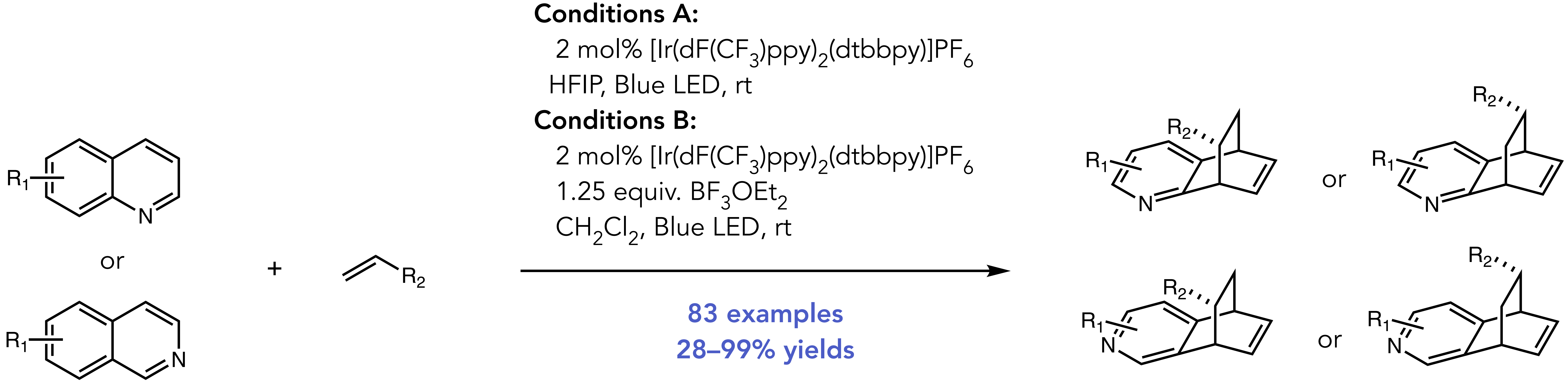


Ma, J., Strieth-Kalthoff, F., Dalton, T., Freitag, M., Luca Schwarz, J., Bergander, K., Daniliuc, C., Glorius, F., *Chem*, **2019**, *5*, 2854-2864.

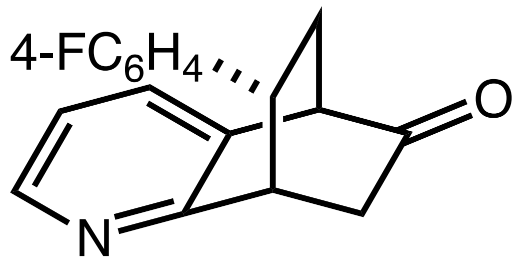
Photocatalytic Dearomative via [4+2] Cycloaddition in pyridines and quinolines

– Glorius, Houk, Brown, 2021.

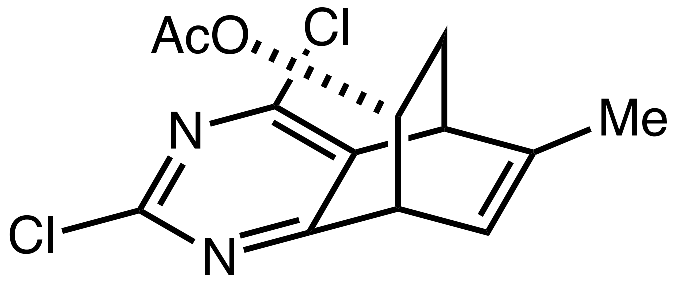
–Photocatalytic dearomative intermolecular [4+2] cycloaddition between quinolines or isoquinolines and olefins:



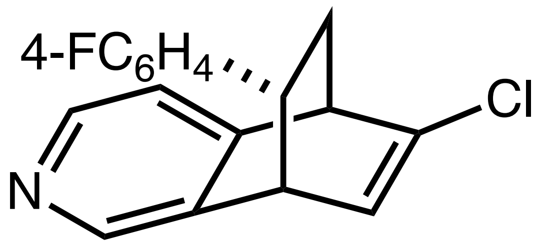
– Select examples:



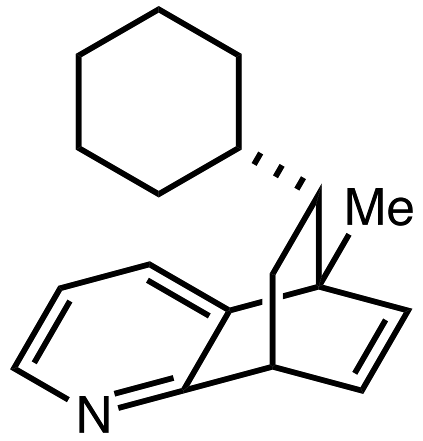
64%, r.r. >19:1, d.r. 4:1



67%, r.r. 94:6, d.r. >19:1



40%, r.r. 9:1, d.r. >19:1

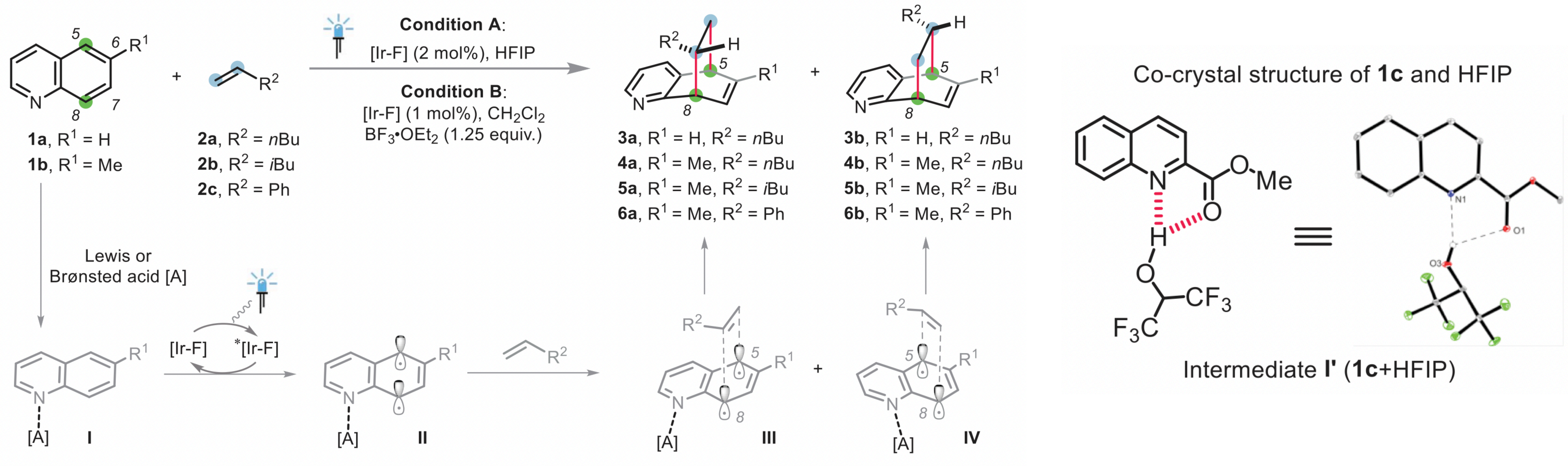


46%, r.r. >19:1, d.r. 94:6

Ma, J., Chen, S., Bellotti, P., Guo, R., Schäfer, F., Heusler, A., Zhang, X., Daniliuc, C., Brown, K. M., Houk, K. N., Glorius, F., *Science*, **2021**, *371*, 1338-1345.

Photocatalytic Dearomative via [4+2] Cycloaddition in pyridines and quinolines

– Glorius, Houk, Brown, 2021.
    –Photocatalytic dearomative intermolecular [4+2] cycloaddition between quinolines or isoquinolines and olefins:

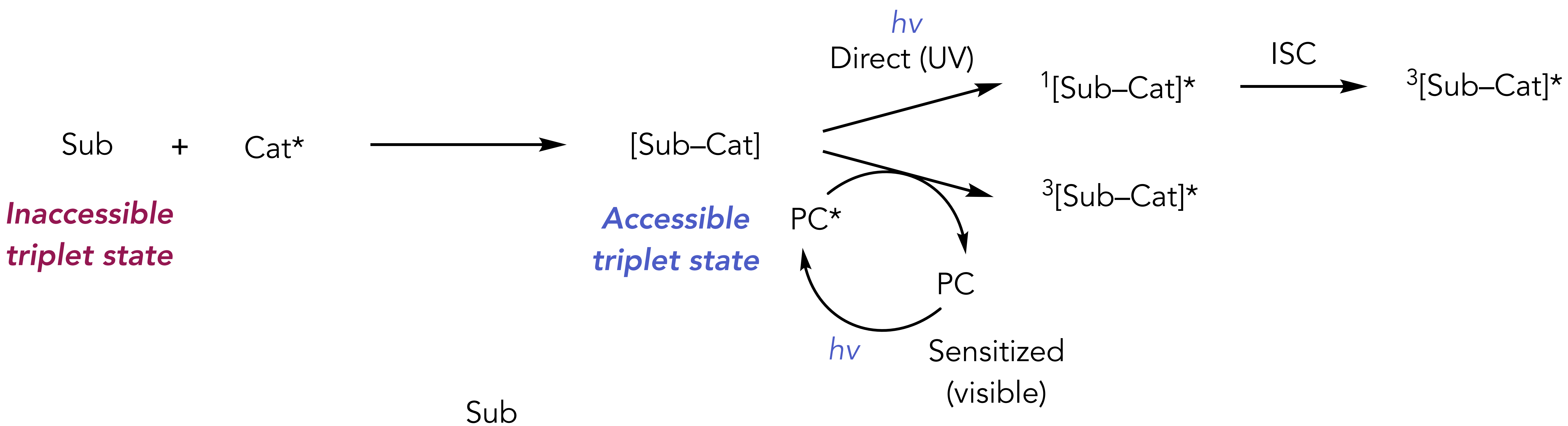


Ma, J., Chen, S., Bellotti, P., Guo, R., Schäfer, F., Heusler, A., Zhang, X., Daniliuc, C., Brown, K. M., Houk, K. N., Glorius, F., *Science*, **2021**, *371*, 1338-1345.

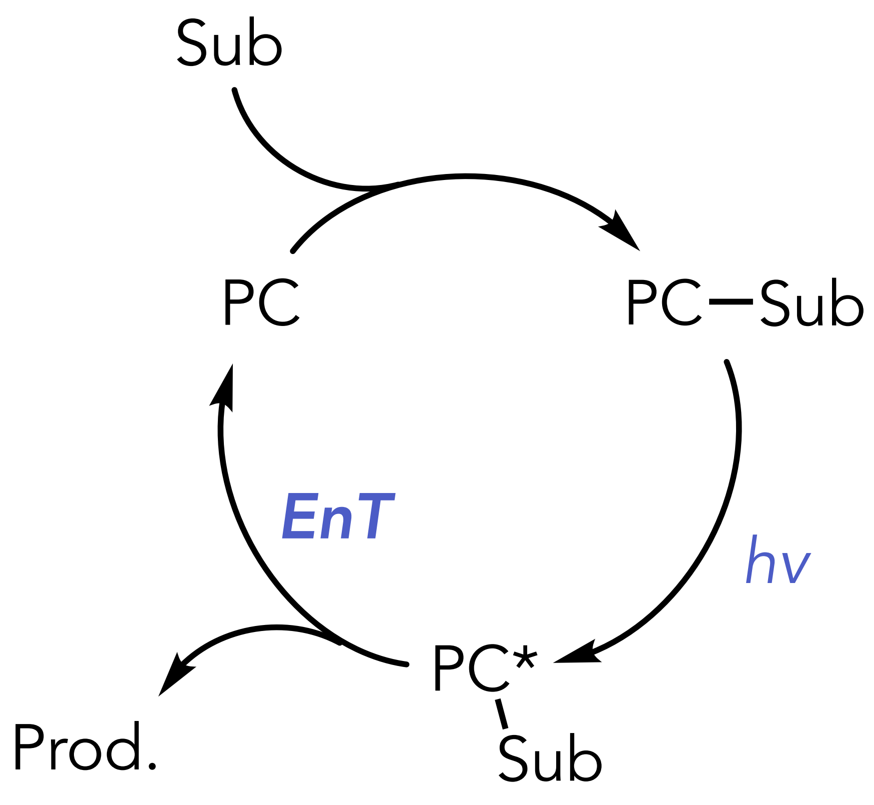
Photocatalytic Asymmetric [2+2] Cycloaddition

Photocatalytic Asymmetric [2+2] Cycloaddition

– Different modes of enantioinduction have thus far been explored.
  – 1. Coordination / Complexation induced triplet state energy lowering:

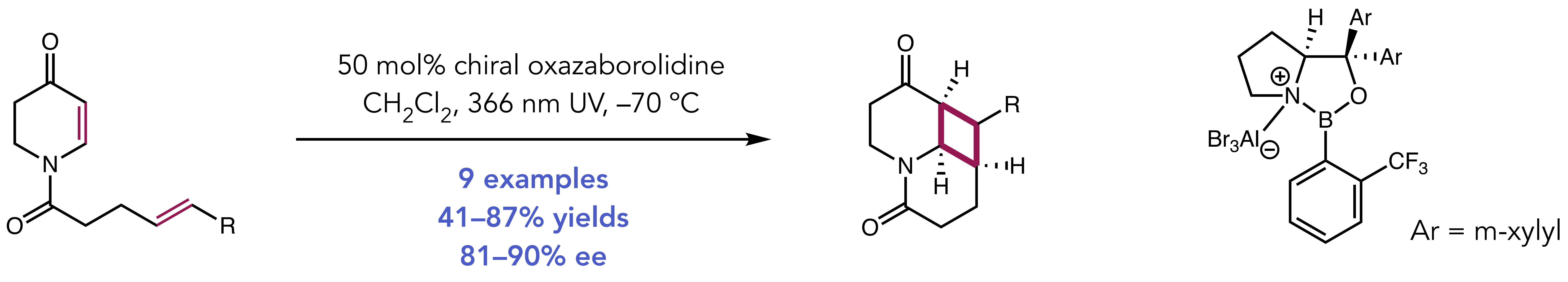


  – 2. Chiral photocatalyst with recognition motif for substrate:

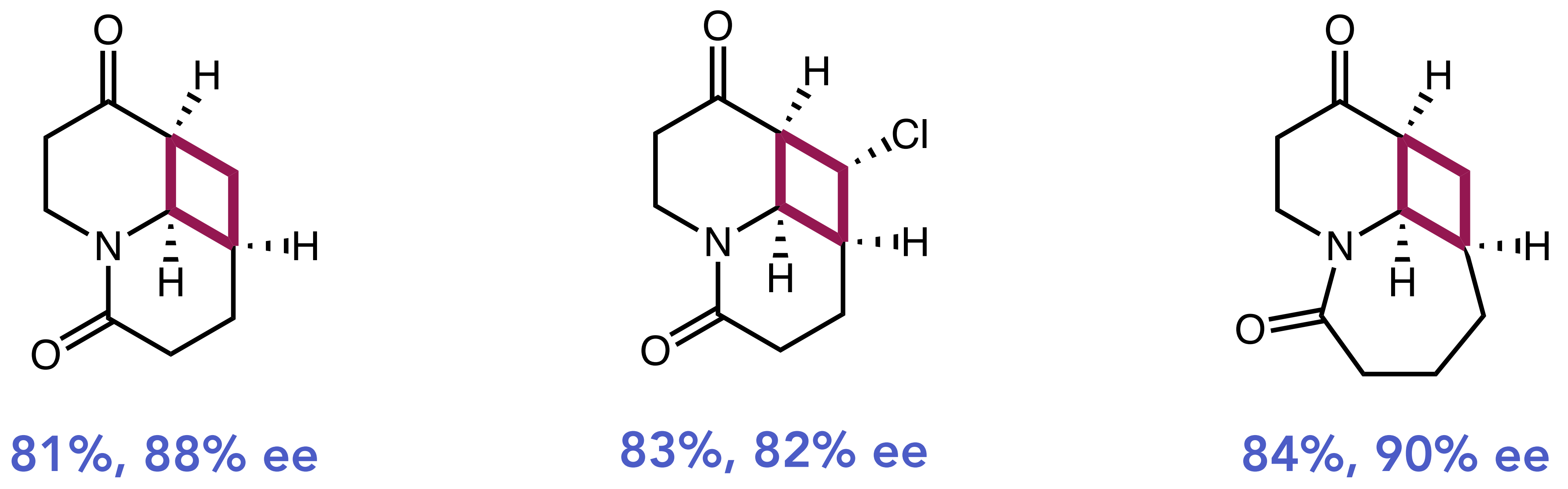


Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

– Bach, 2013.
  – A chiral Lewis acid promotes triplet state energy lowering in a UV-light mediated intramolecular [2+2] cycloaddition:



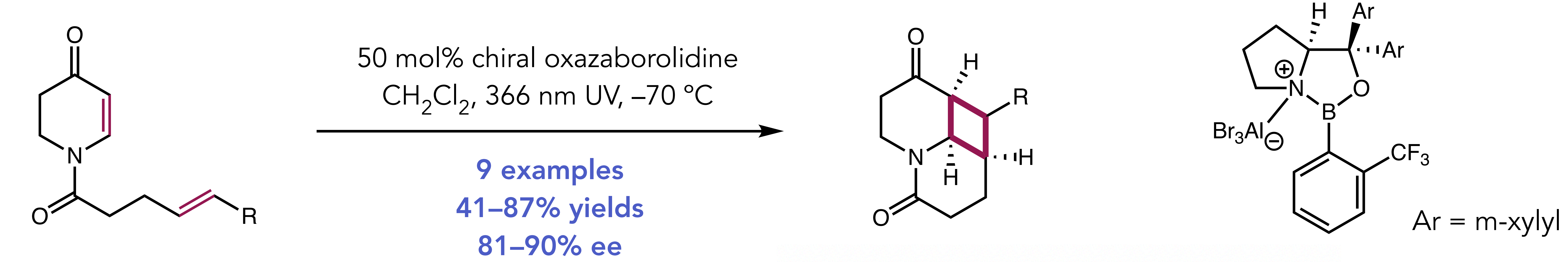
– Select examples:



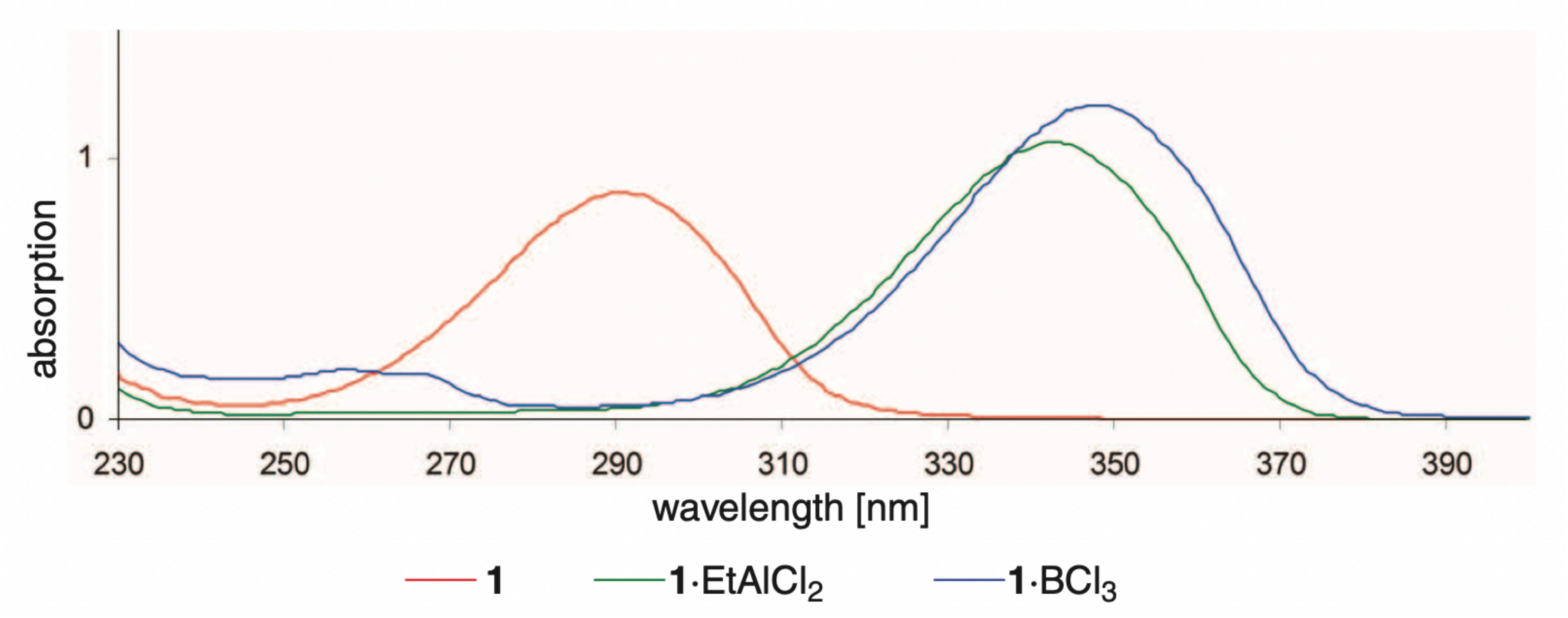
Brimioulle, R., Bach, T., *Science*, **2013**, *342*, 840–843.

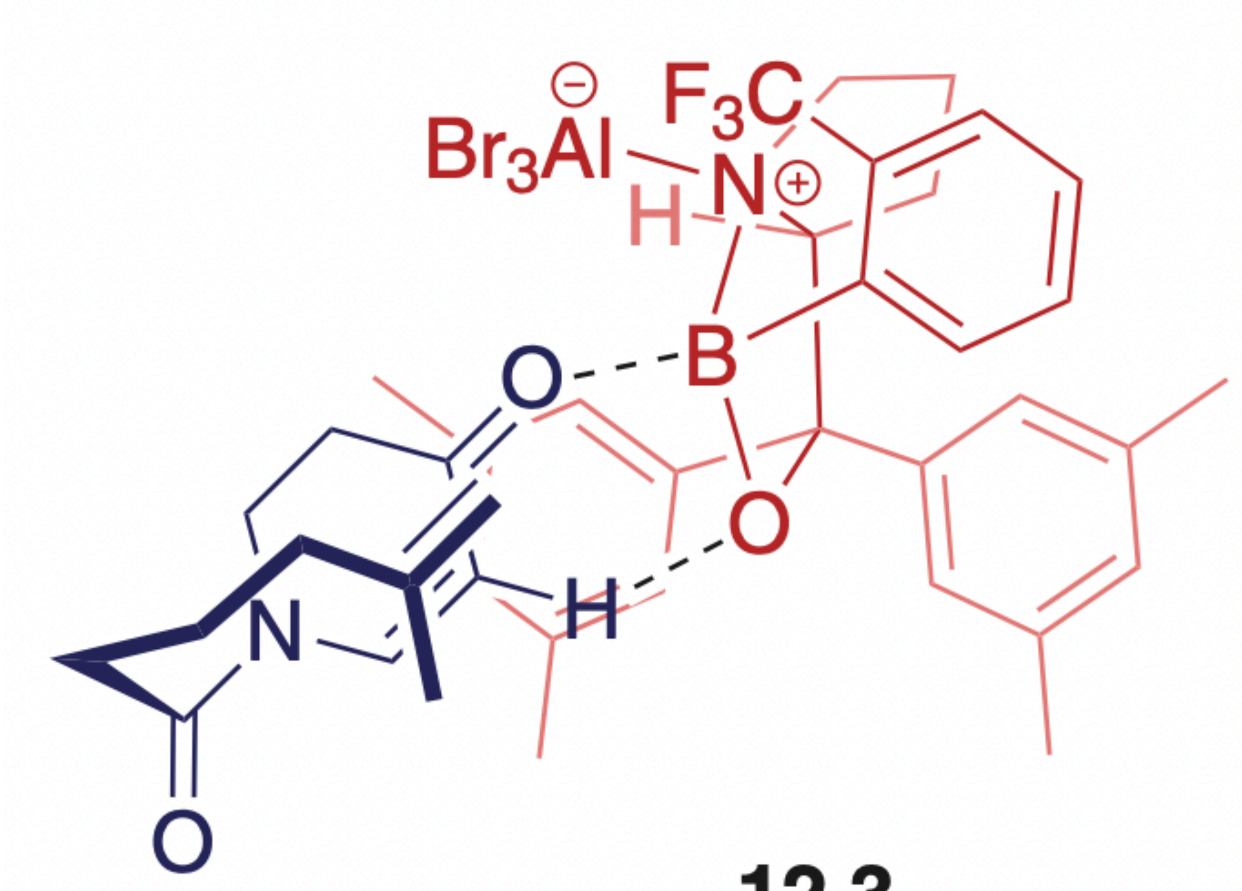
Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

– Bach, 2013.
  – A chiral Lewis acid promotes triplet state energy lowering in a UV-light mediated intramolecular [2+2] cycloaddition:



– Bathochromic shift upon Lewis acid / substrate coordination:



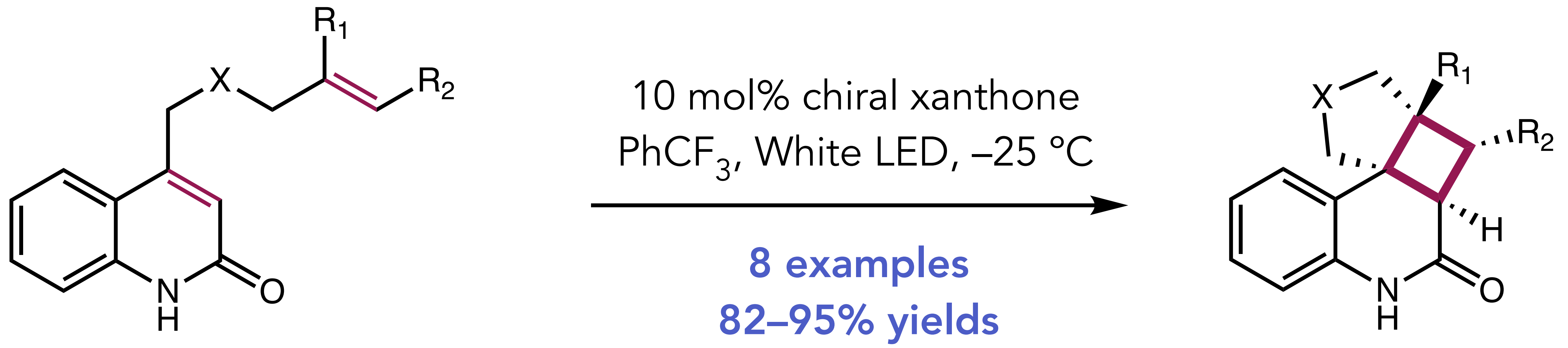


12·3

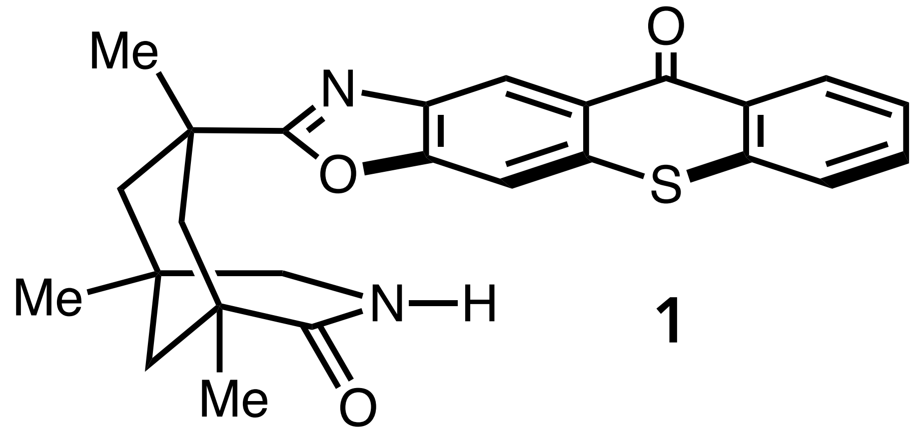
Brimioulle, R., Bach, T., *Science*, **2013**, *342*, 840–843.

Photocatalytic Asymmetric [2+2] Cycloaddition of Quinolinones and Olefins

– Bach, 2014.
  – A xanthone sensitizer incorprating a hydrogen bond recognition motif allows for visible-light driven (>400 nm) enantioselective [2+2]:

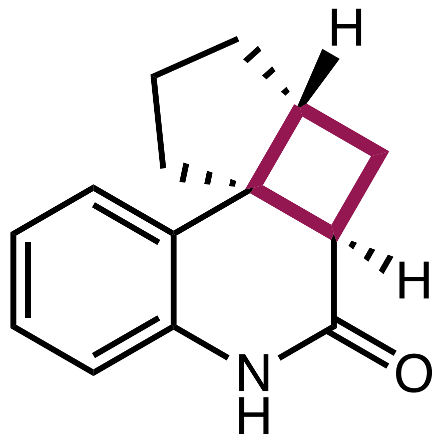


X = CH_2, O, NTs

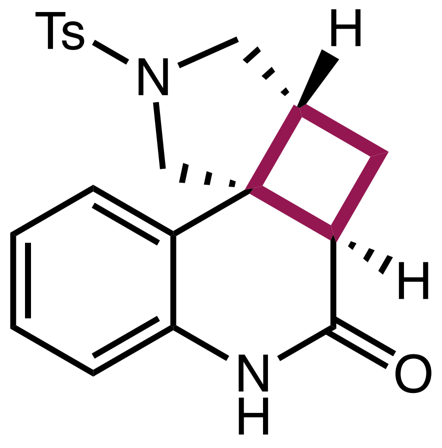


1

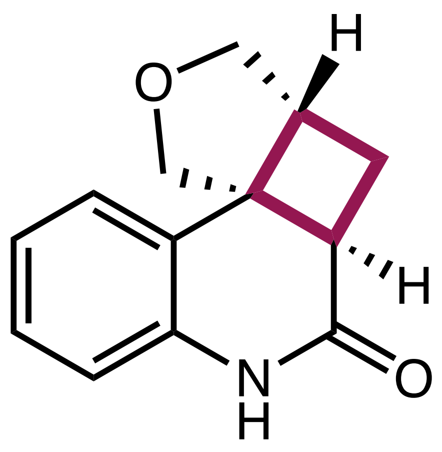
– Select examples:



86%, 92% ee



79%, 88% ee



95%, 87% ee

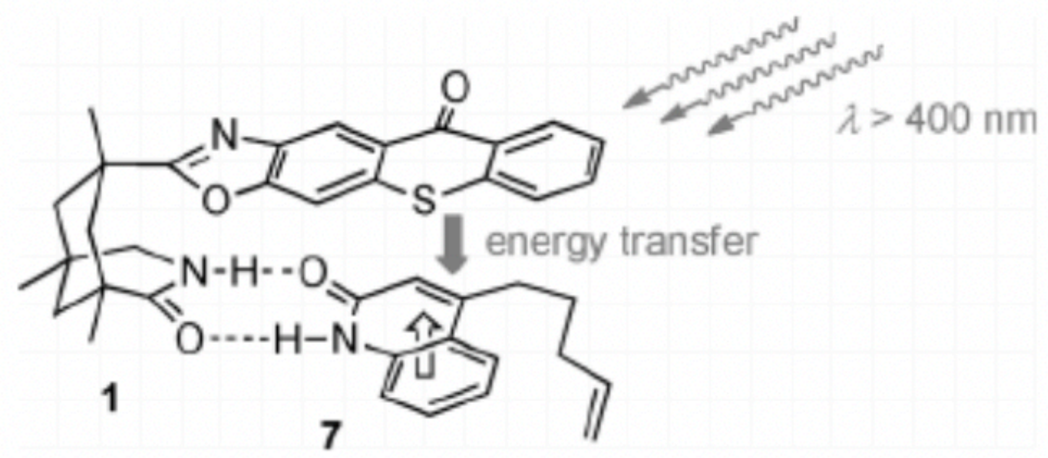


Figure 3. Mechanistic model for sensitization and enantioface differentiation in the complex **1·7**. The unshaded arrow indicates the approach of the tethered alkene onto the excited quinolone double bond.

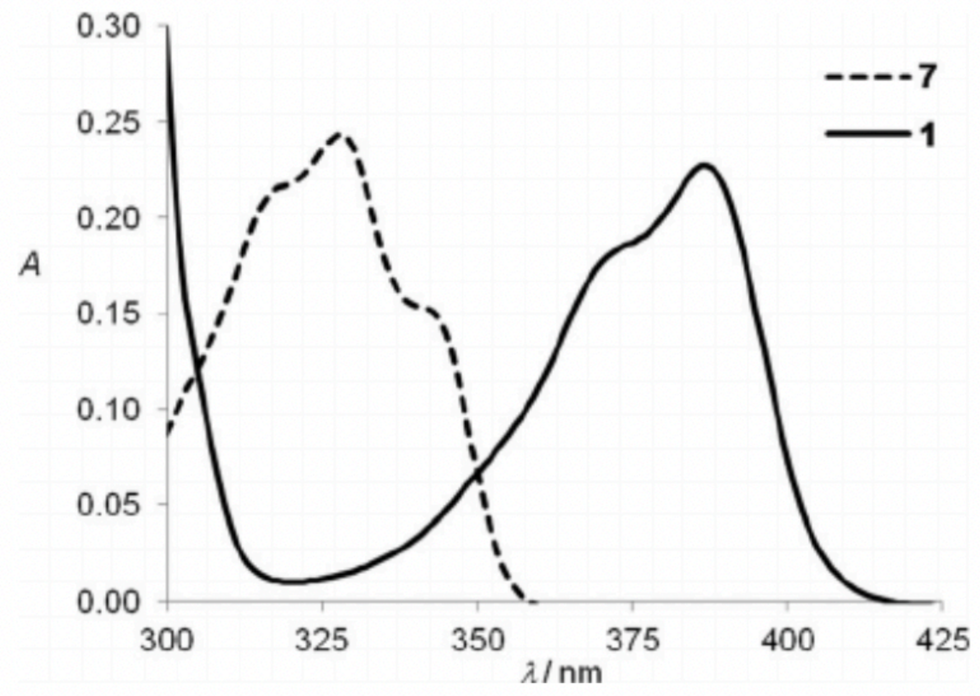
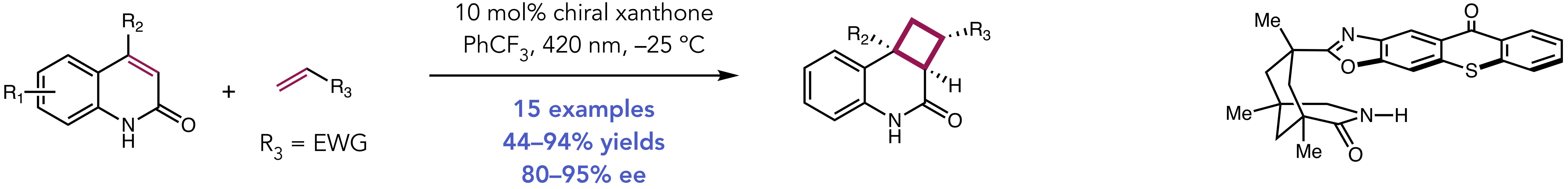


Figure 1. UV/Vis spectra of **1** (c = 0.5 mM) and **7** (c = 0.5 mM) in trifluorotoluene ($PhCF_3$).

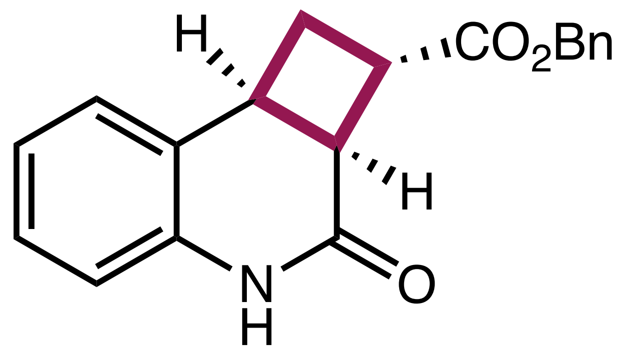
Alonson, R., Bach, T., *ACIE*, **2014**, *53*, 4368–4371.

Photocatalytic Asymmetric [2+2] Cycloaddition of Quinolinones and Olefins

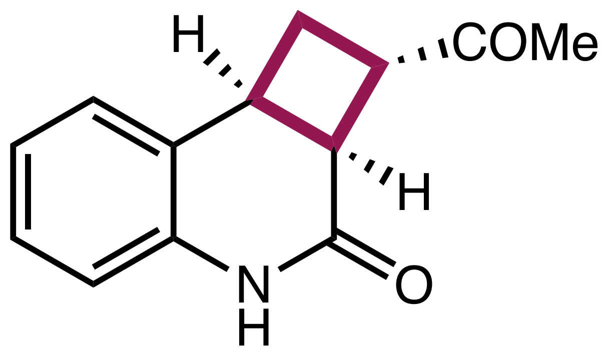
– Bach, 2016.
  – Extension to an intermolecular regime:



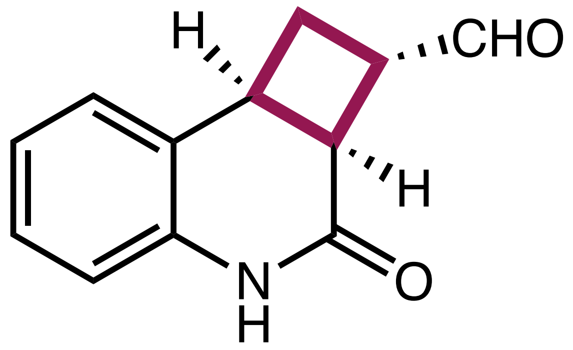
– Select examples:



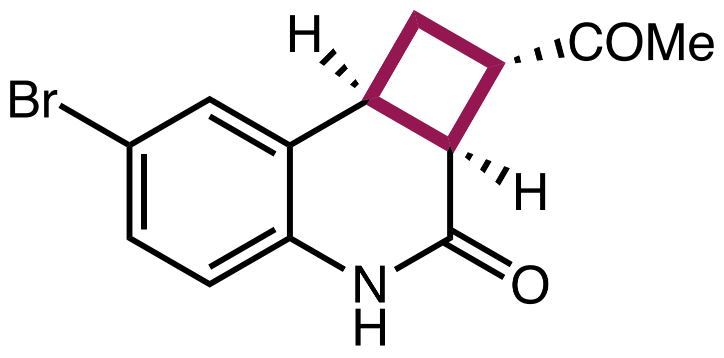
79%, 80% ee



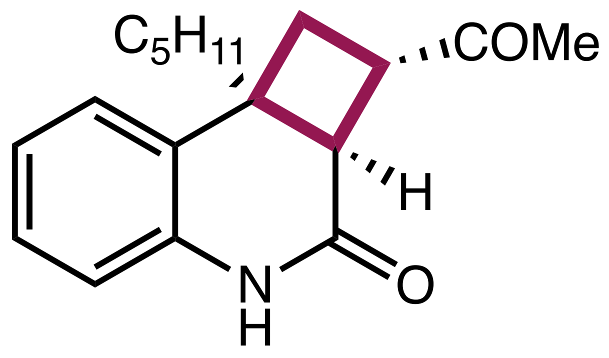
80%, 91% ee



44%, 91% ee



59%, 94% ee

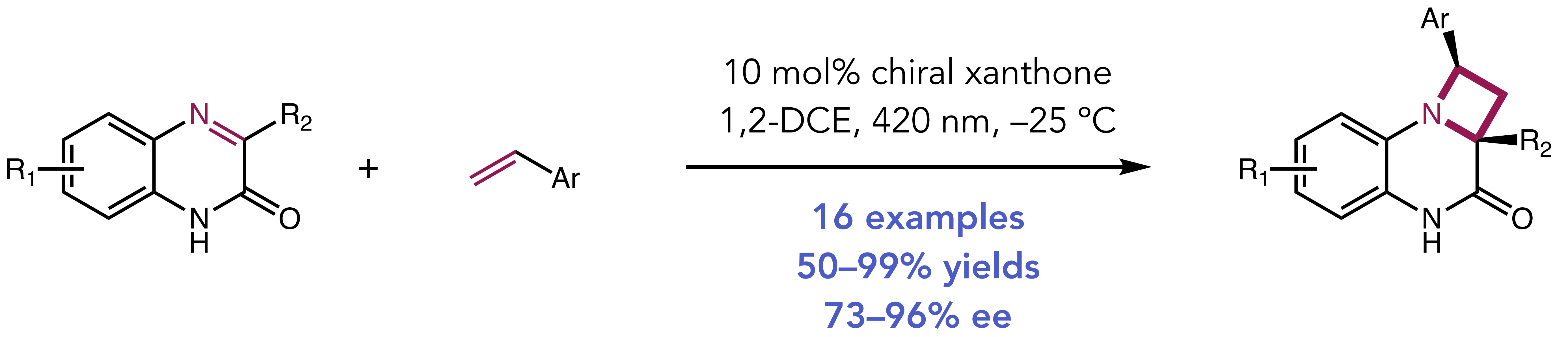


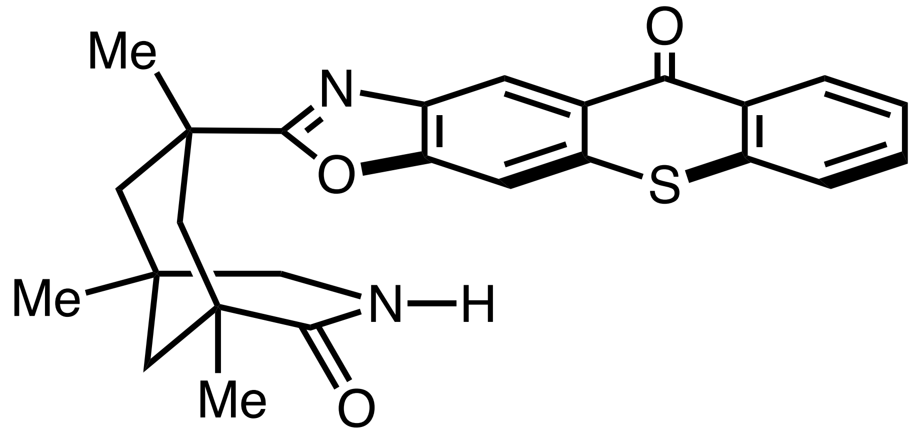
94%, 94% ee

Tröster, A., Alonso, R., Bauer, A., Bach, T., *JACS*, **2016**, *138*, 7808–7811.

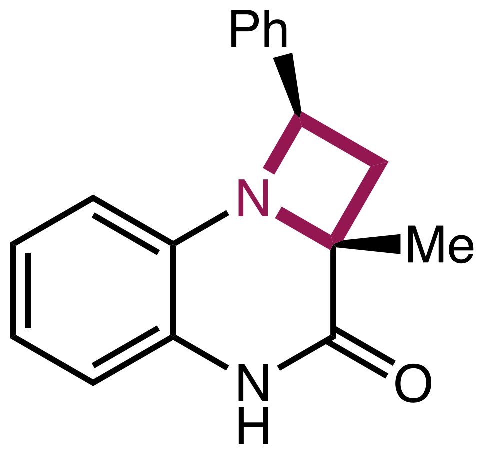
Photocatalytic Asymmetric [2+2] Cycloaddition of Quinoxalinone and Olefins

– Bach, 2021.
  – First enantioselective visible-light photocatalytic intermolecular [2+2] cycloaddition for azetidine synthesis. Use of the same hydrogen-bond recognition xanthone sensitizer:

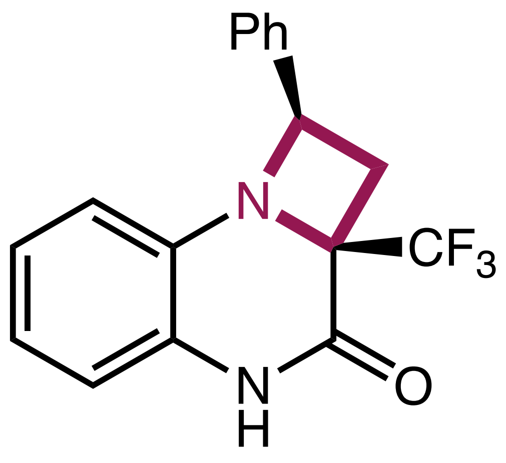




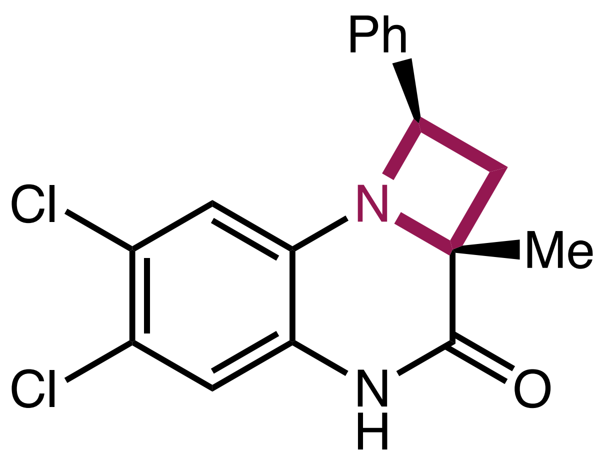
– Select examples:



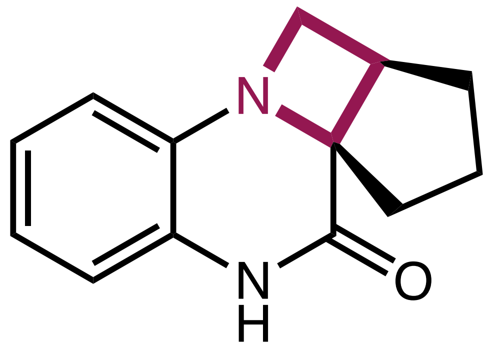
99%, 94% ee



99%, 89% ee



50%, 96% ee

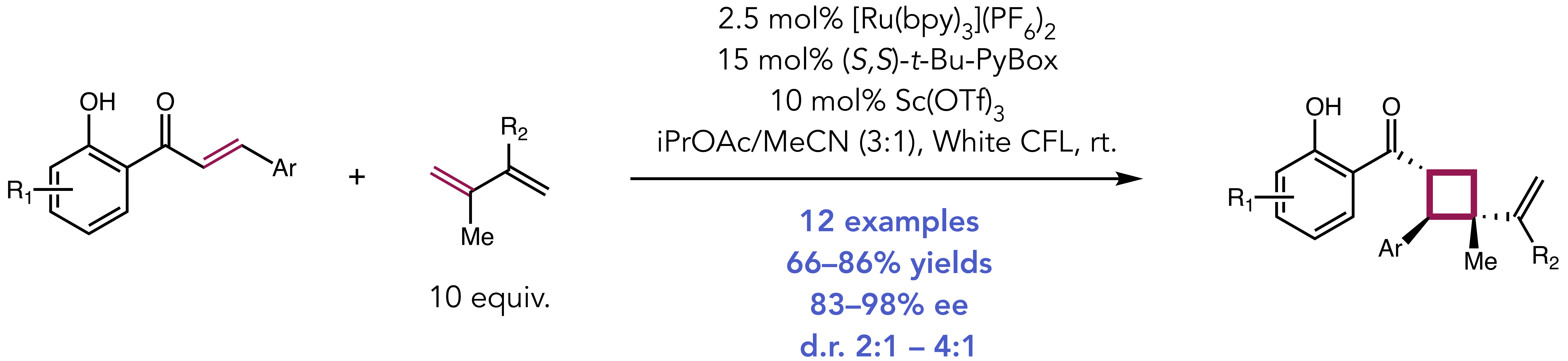


90%, 73% ee

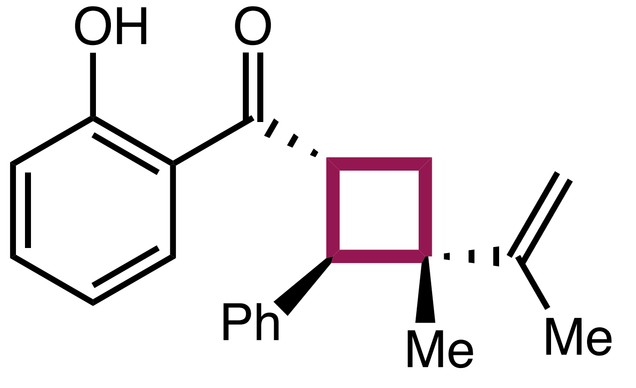
Li, X., Groβkopf, J., Jandl, C., Bach, T., *ACIE*, **2021**, *60*, 2684–2688.

Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

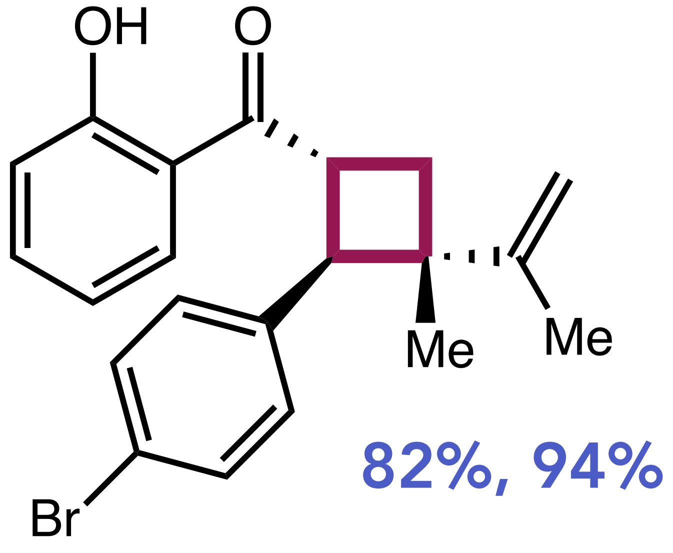
– Yoon, 2016.
  – Enantioselective intermolecular [2+2] cycloaddition enabled by substrate triplet state energy lowering catalysis:



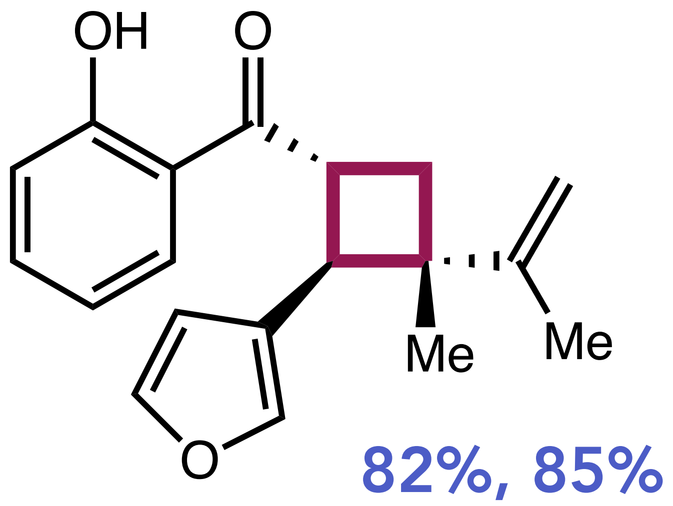
– Select examples:



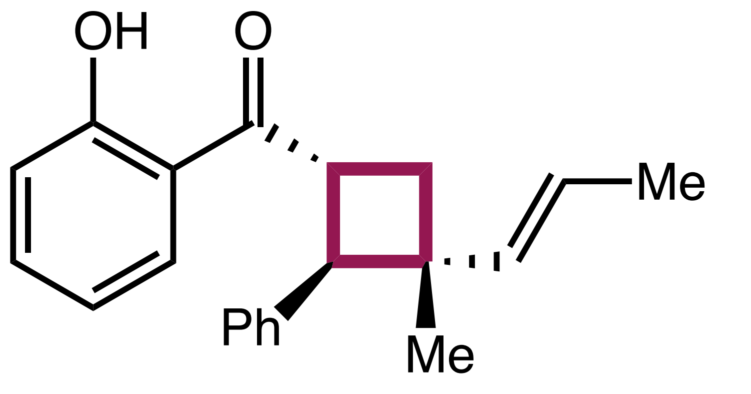
84%, 93% ee, d.r. 3:1



82%, 94% ee, d.r. 3:1



82%, 85% ee, d.r. 4:1



84%, 92% ee, d.r. 2:1

Blum, T. R., Miller, Z. D., Bates, D. M., Guzei, I. A., Yoon, T. P., *Science*, **2016**, *354*, 1391–1395.

Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

- Yoon, 2016.
  - Enantioselective intermolecular [2+2] cycloaddition enabled by substrate triplet state energy lowering catalysis:

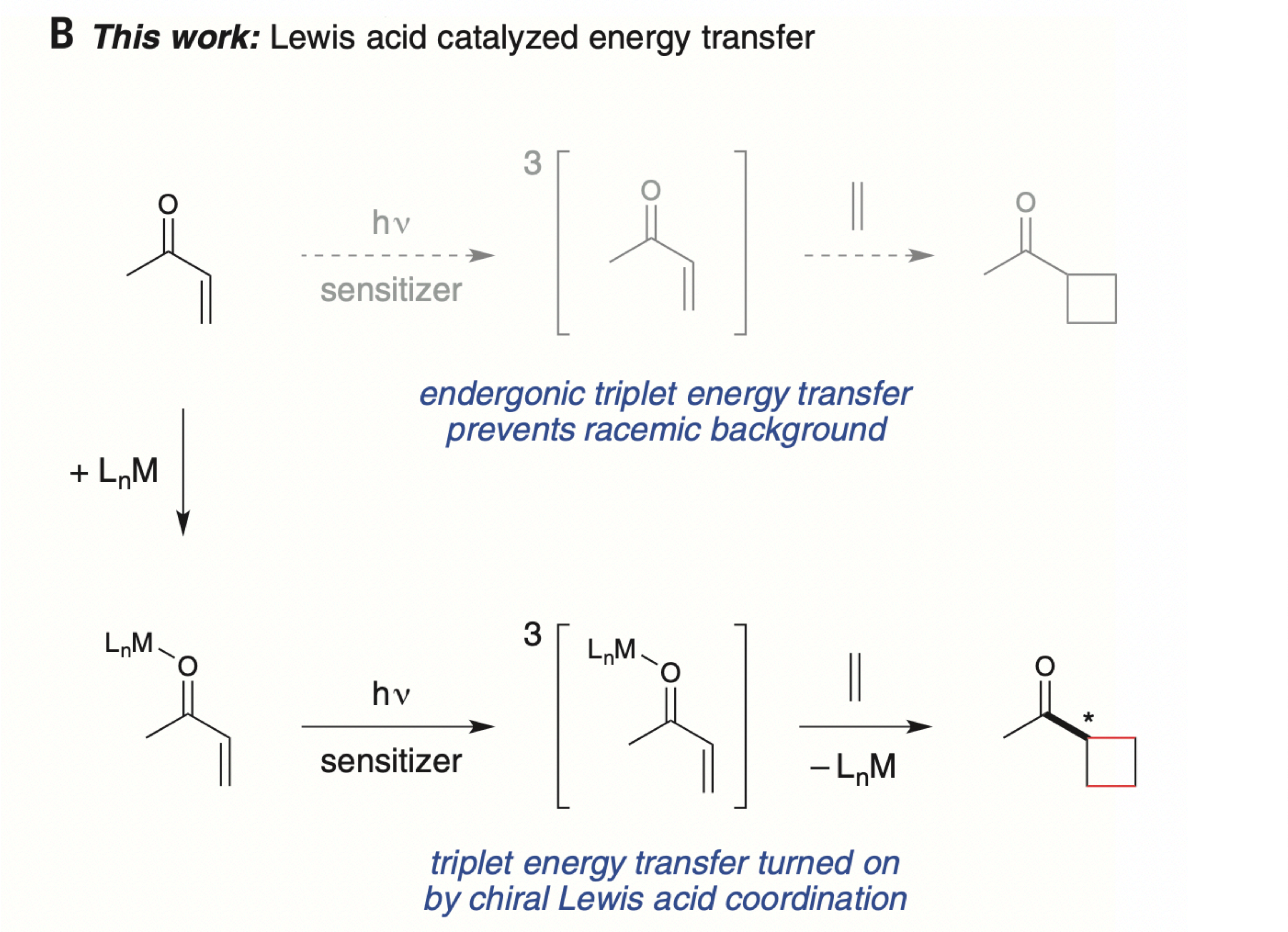
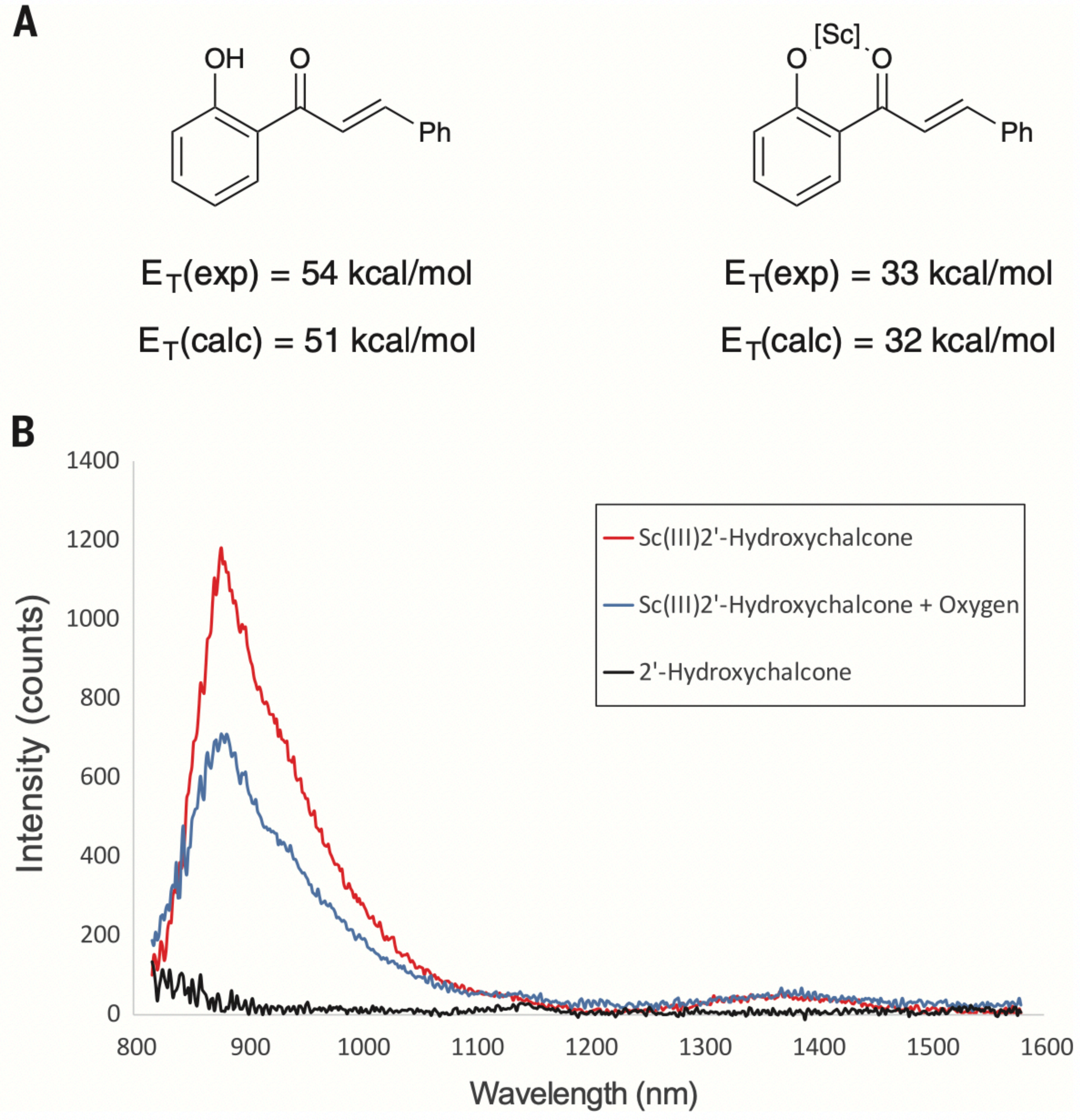


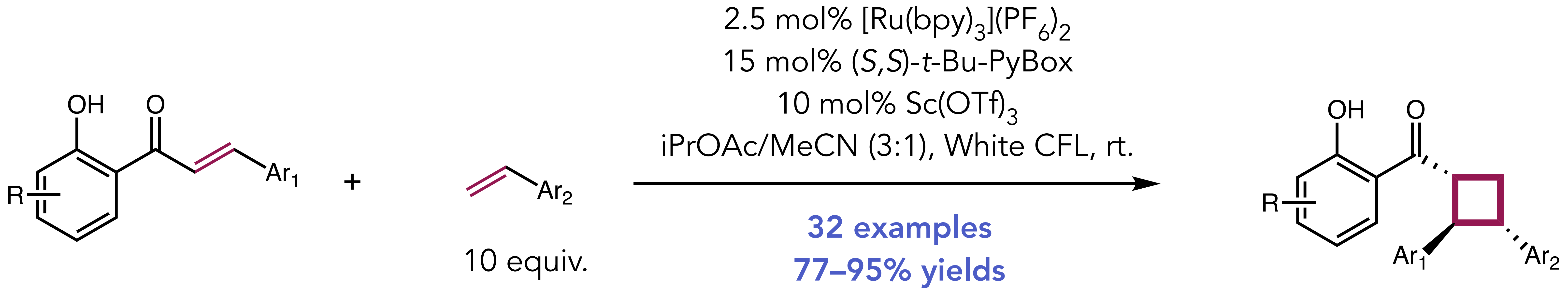
Fig. 4. Computational and experimental evidence for a Lewis acid–promoted decrease in triplet energy (E_T). (**A**) Experimental (exp) and calculated (calc) S_0–T_1 gaps for 2′-hydroxychalcone **2** and its Sc(III) complex. (**B**) Experimental near-IR emission data for 2′-hydroxychalcone **2** in the absence (black) and presence (red) of $Sc(OTf)_3$. The emission is partially quenched in the presence of oxygen (blue).



Blum, T. R., Miller, Z. D., Bates, D. M., Guzei, I. A., Yoon, T. P., *Science*, **2016**, *354*, 1391–1395.

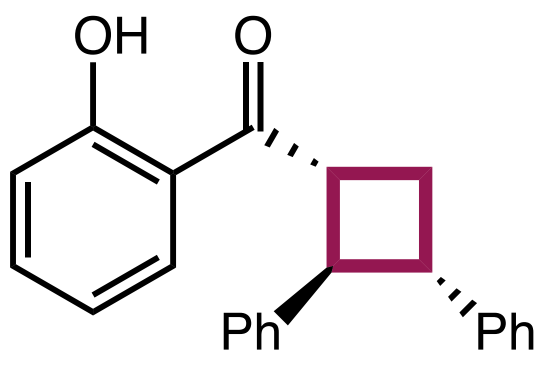
Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

– Yoon, 2017.
  – Extension to styrene substrates in enantioselective [2+2] photocycloaddition:

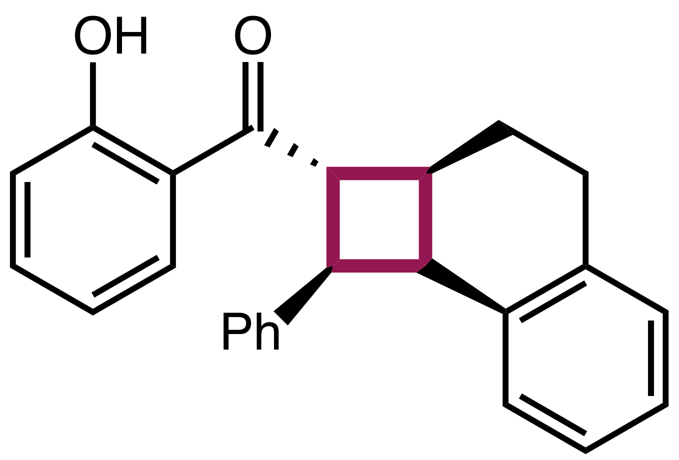


32 examples
77–95% yields
85–>99% ee
d.r. 1:1 – >10:1

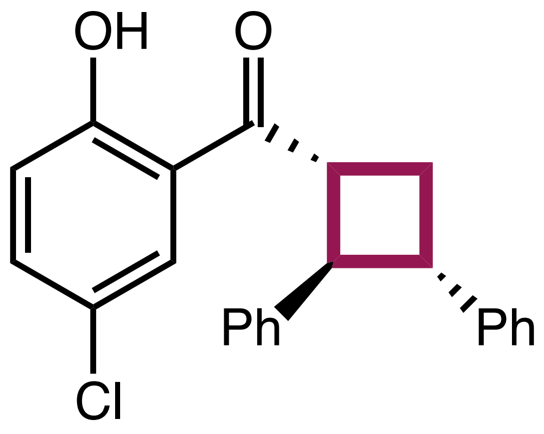
– Select examples:



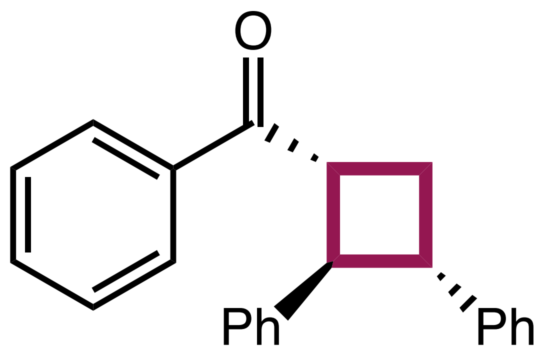
88%, >99% ee, d.r. 2:1



94%, 96% ee, d.r. >10:1



94%, 96% ee, d.r. 2:1

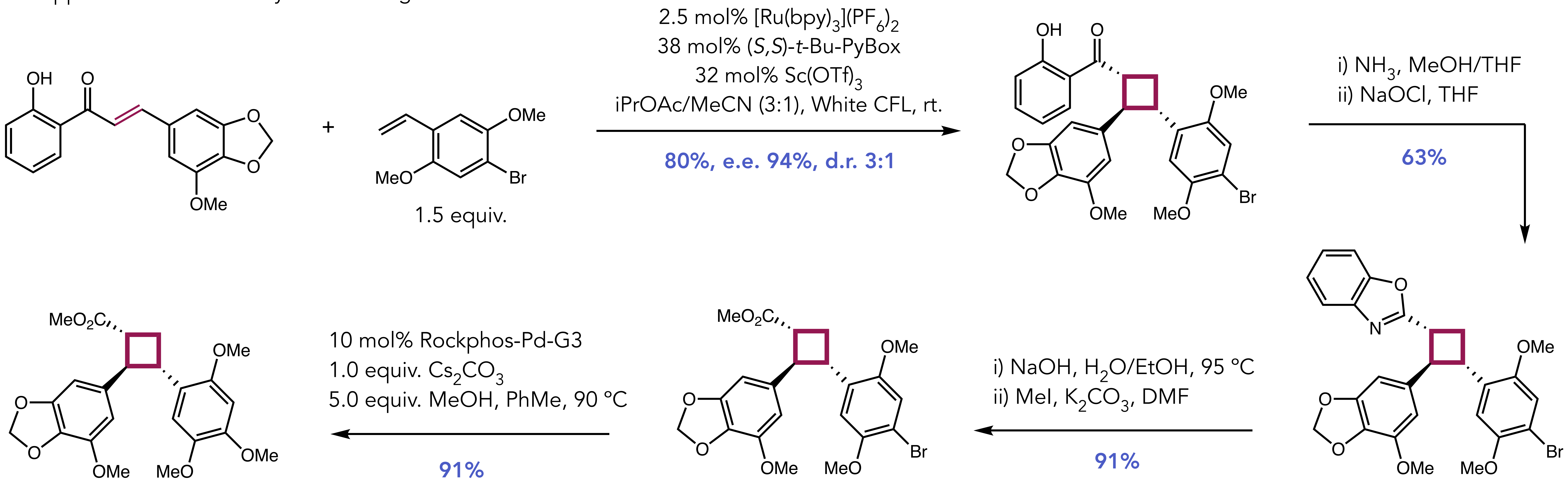


18%, 17% ee, d.r. 2:1

Miller, Z. D., Lee, B. J., Yoon, T. P., *ACIE*, **2017**, *56*, 11891–11895.

Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

– Yoon, 2017.
  – Application to the total synthesis norlignan:

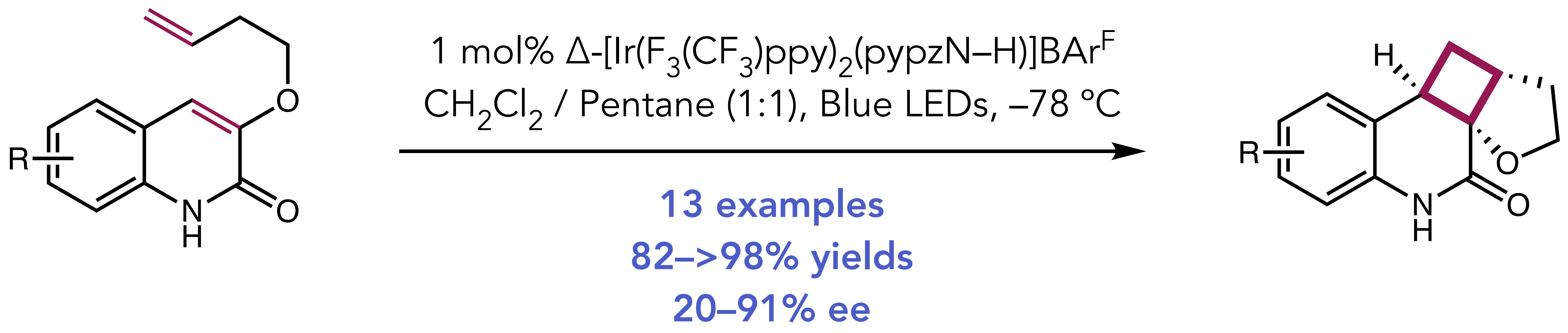


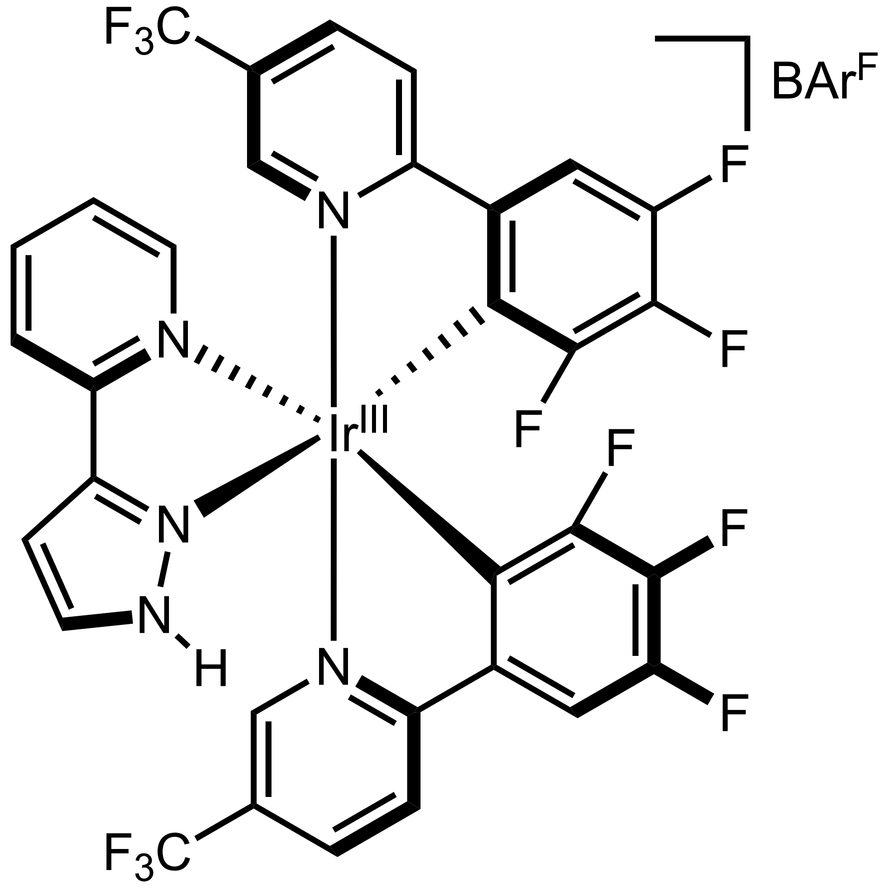
Miller, Z. D., Lee, B. J., Yoon, T. P., *ACIE*, **2017**, *56*, 11891–11895.

Photocatalytic Asymmetric [2+2] Cycloaddition of Quinolinones and Olefins

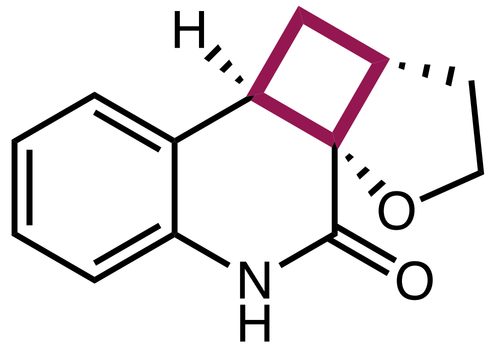
– Yoon and Baik, 2017.

– A chiral Ir photocatalyst with a hydrogen-bonding motif induces asymmetry in an intramolecular [2+2]:

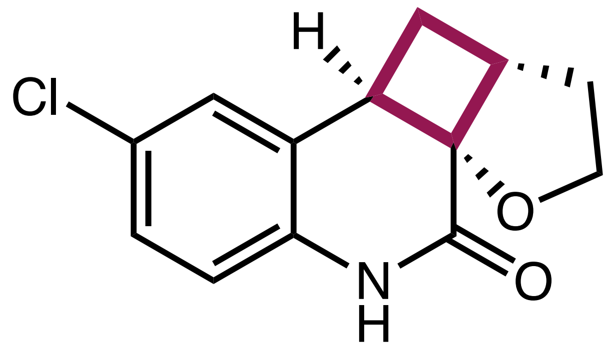




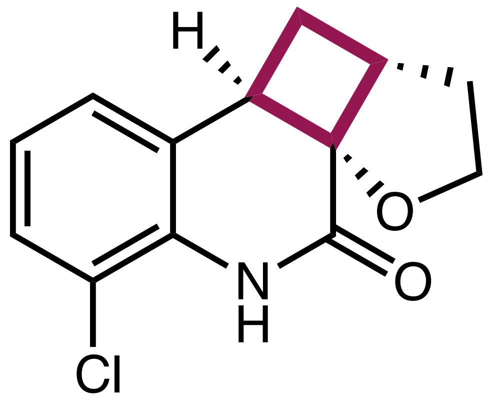
– Select examples:



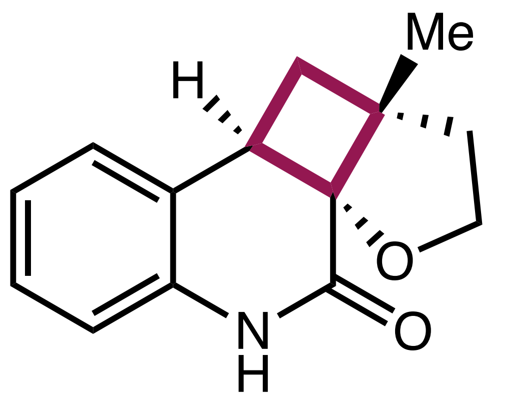
>98%, 91% ee



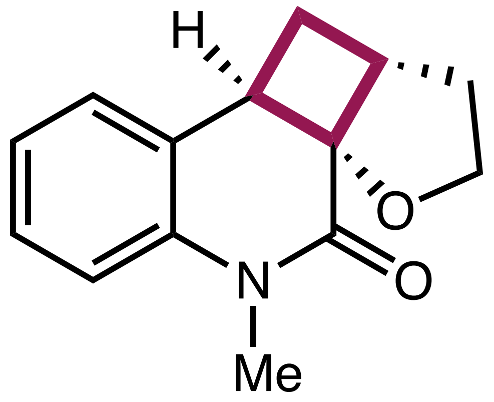
93%, 90% ee



98%, 20% ee



86%, 68% ee

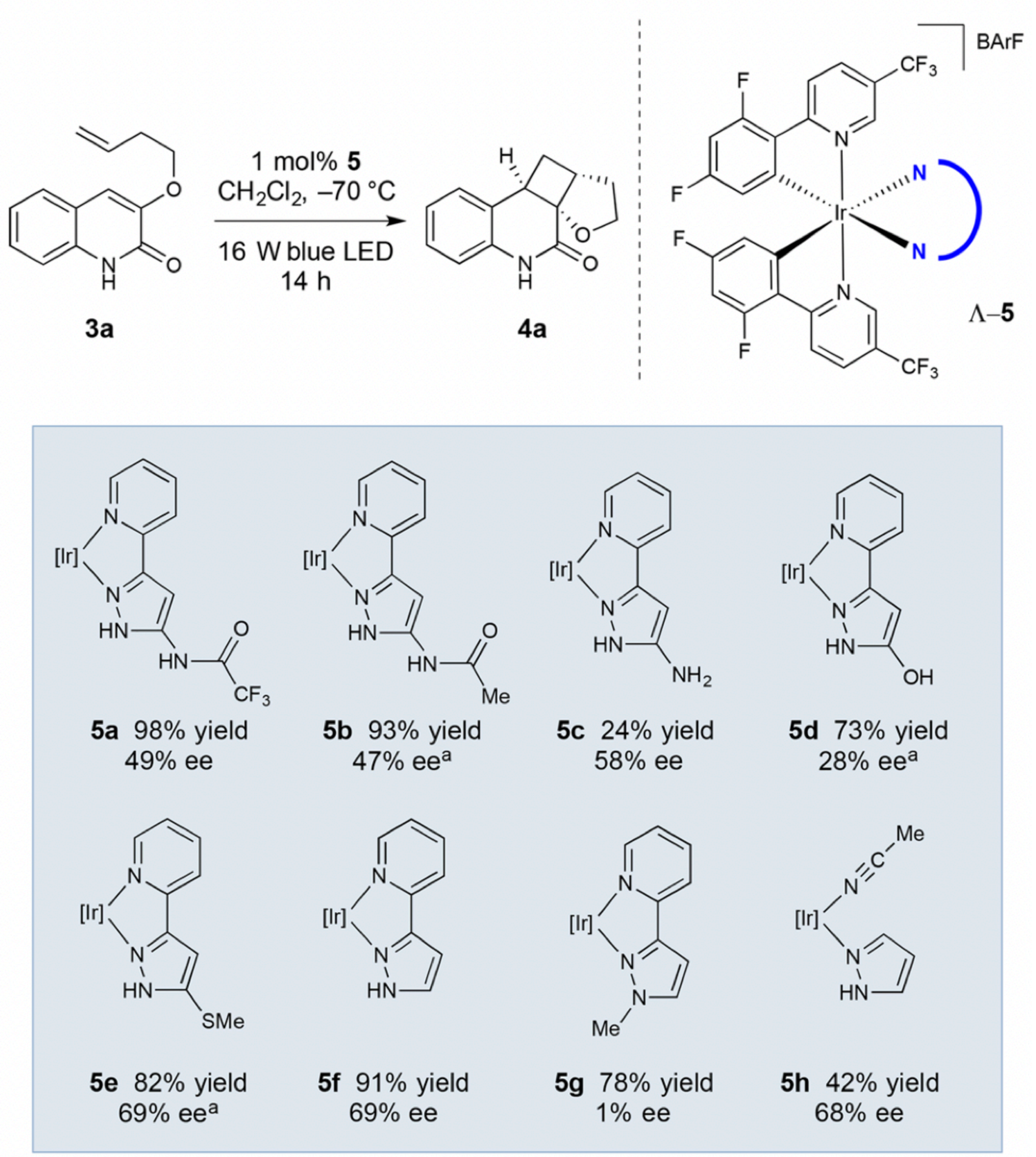


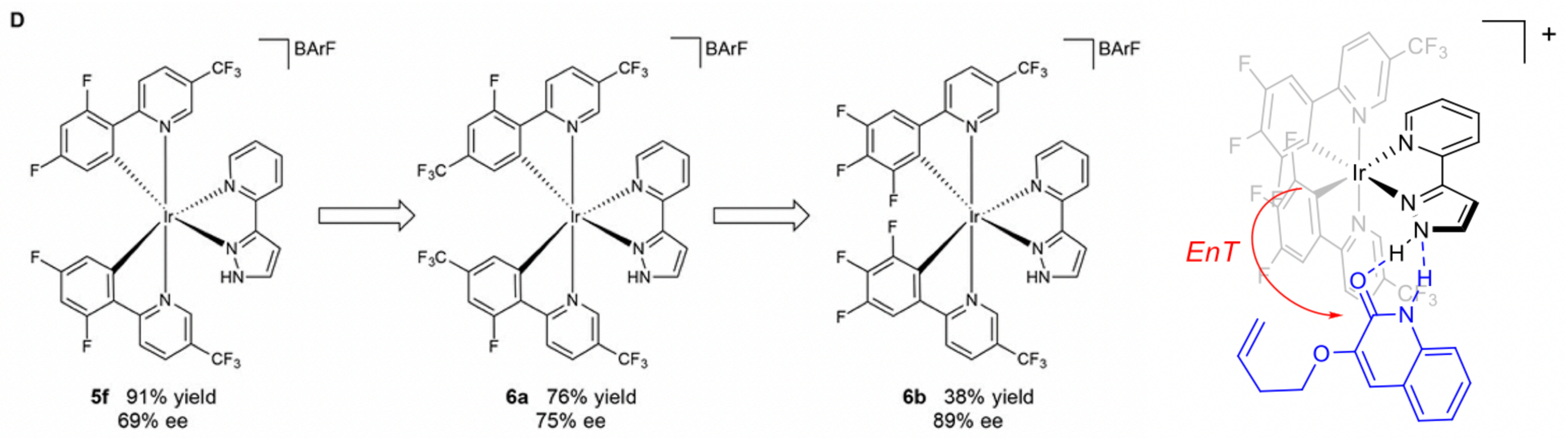
98%, 3% ee

Skubi, K. L., Kidd, J. B., Jung, H., Guzei, I. A., Baik, M.-H., Yoon, T. P., *JACS*, **2017**, *139*, 17186–17192.

Photocatalytic Asymmetric [2+2] Cycloaddition of Quinolinones and Olefins

– Yoon and Baik, 2017.
  – A chiral Ir photocatalyst with a hydrogen-bonding motif induces asymmetry in an intramolecular [2+2]:
  – Photocatalyst optimization:

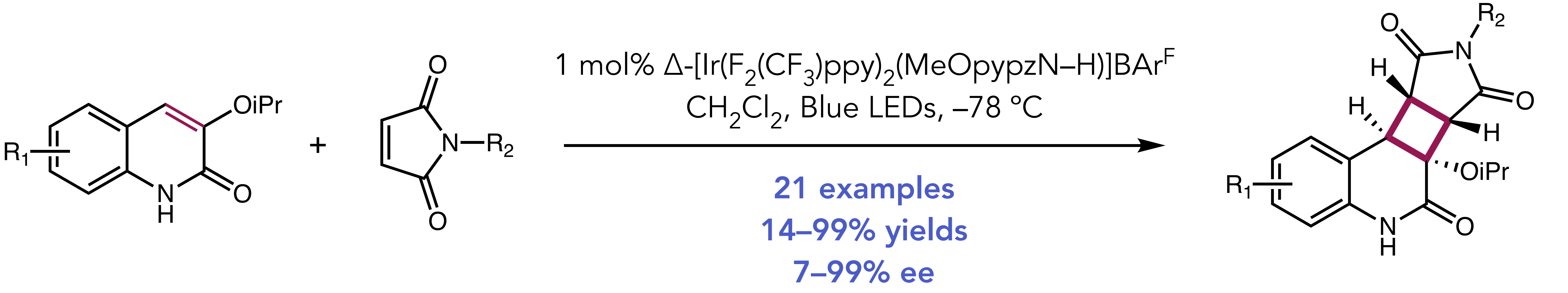


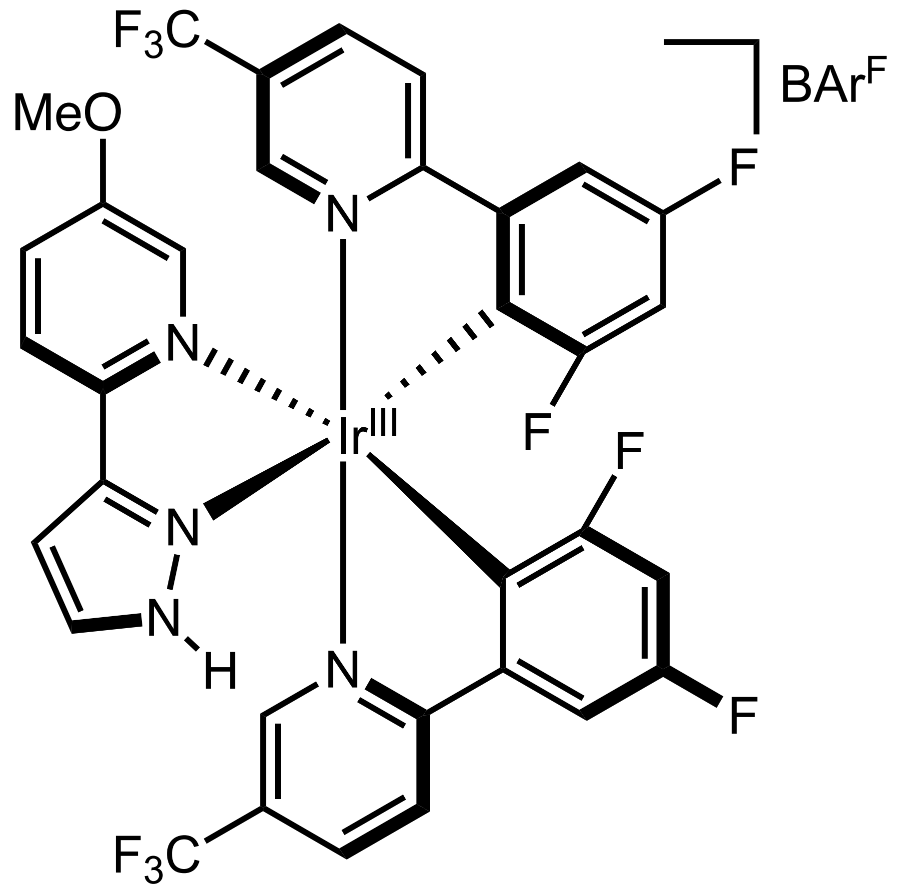


Skubi, K. L., Kidd, J. B., Jung, H., Guzei, I. A., Baik, M.-H., Yoon, T. P., *JACS*, **2017**, *139*, 17186–17192.

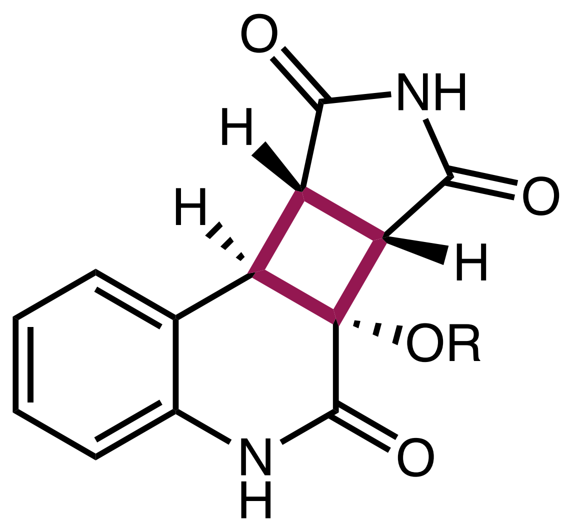
Photocatalytic Asymmetric [2+2] Cycloaddition of Quinolinones and Maleimide

- Yoon and Baik, 2019.
  - A later publication from these groups explored intermolecular asymmetric [2+2] cycloaddition between quinolinones and maleimide.
  - This work revealved an enecpected order of events in energy transfer leading to optically enriched products.

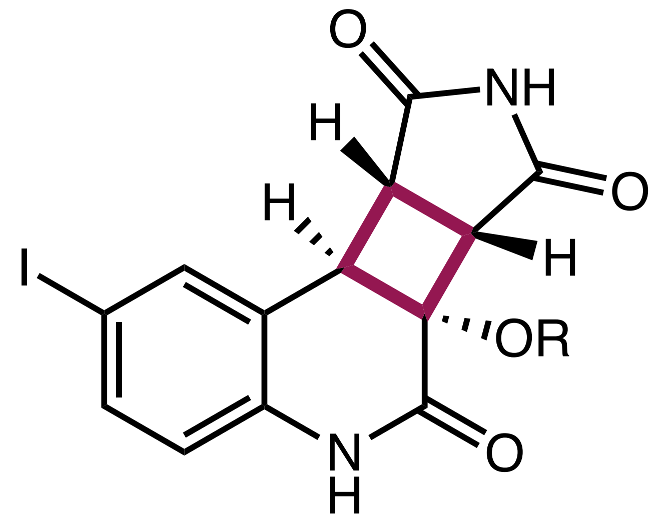




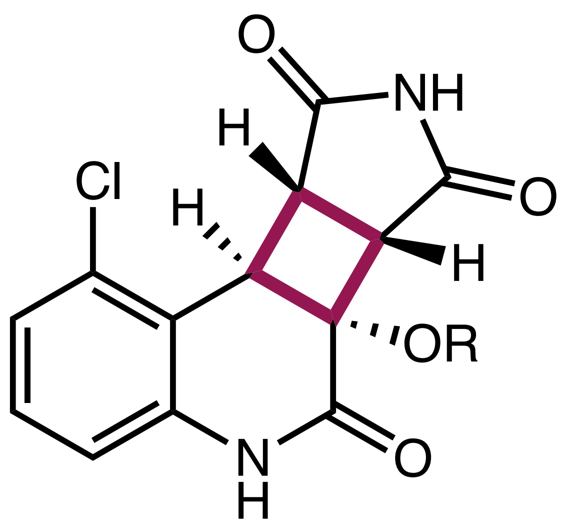
- Select examples:



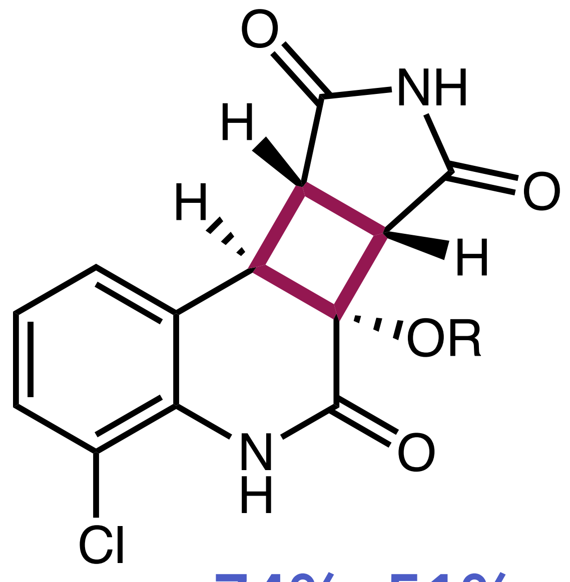
R = iPr
82%, 97% ee
R = nBu
14%, 7% ee
R = Me
30%, 70% ee



67%, 99% ee



99%, 99% ee, d.r. 6:1



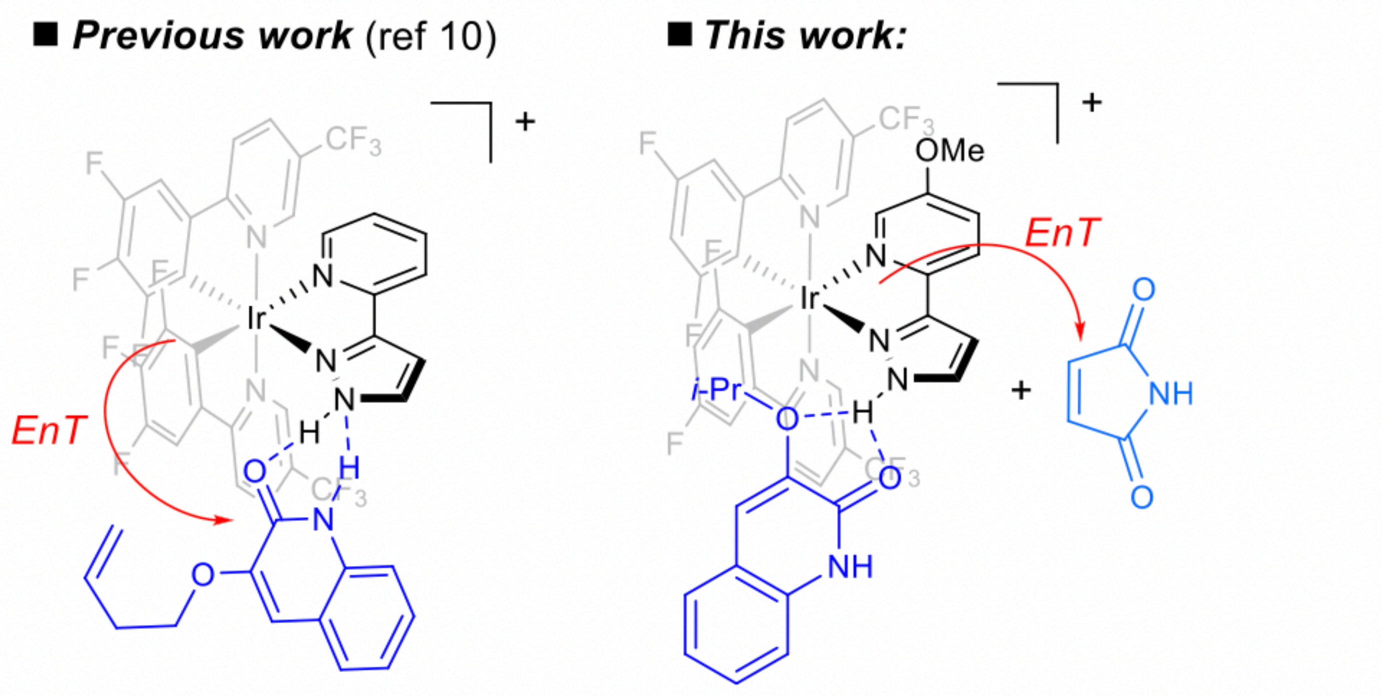
74%, 51% ee

Zheng, J., Swords, W. B., Jung, H., Skubi, K. L., Kidd, J. B., Meyer, G. J., Baik, M.-H., Yoon, T. P., *JACS*, **2019**, *141*, 13625-13634.

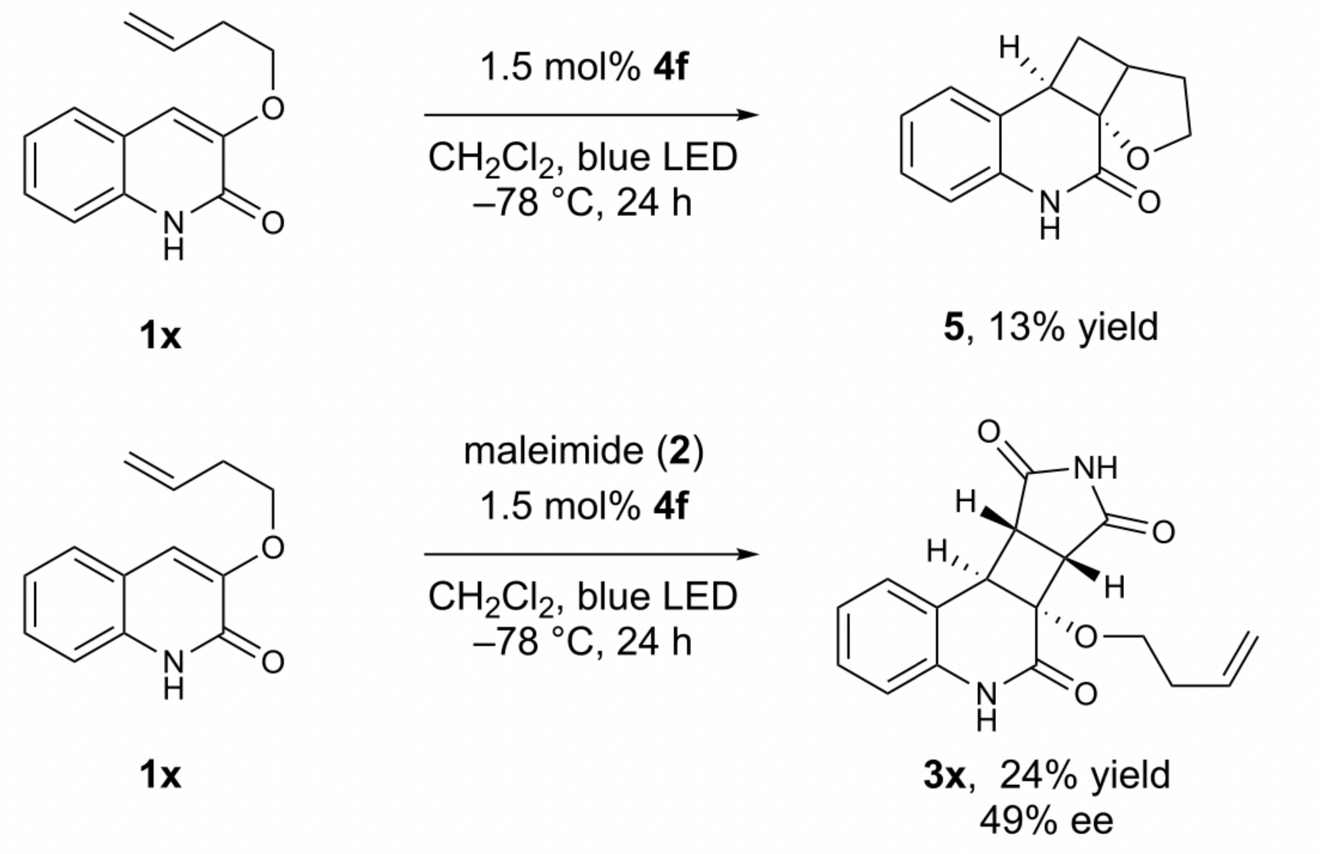
Photocatalytic Asymmetric [2+2] Cycloaddition of Quinolinones and Maleimide

– Yoon and Baik, 2019.
  – A later publication from these groups explored intermolecular asymmetric [2+2] cycloaddition between quinolinones and maleimide.
  – This work revealved an enecpected order of events in energy transfer leading to optically enriched products.

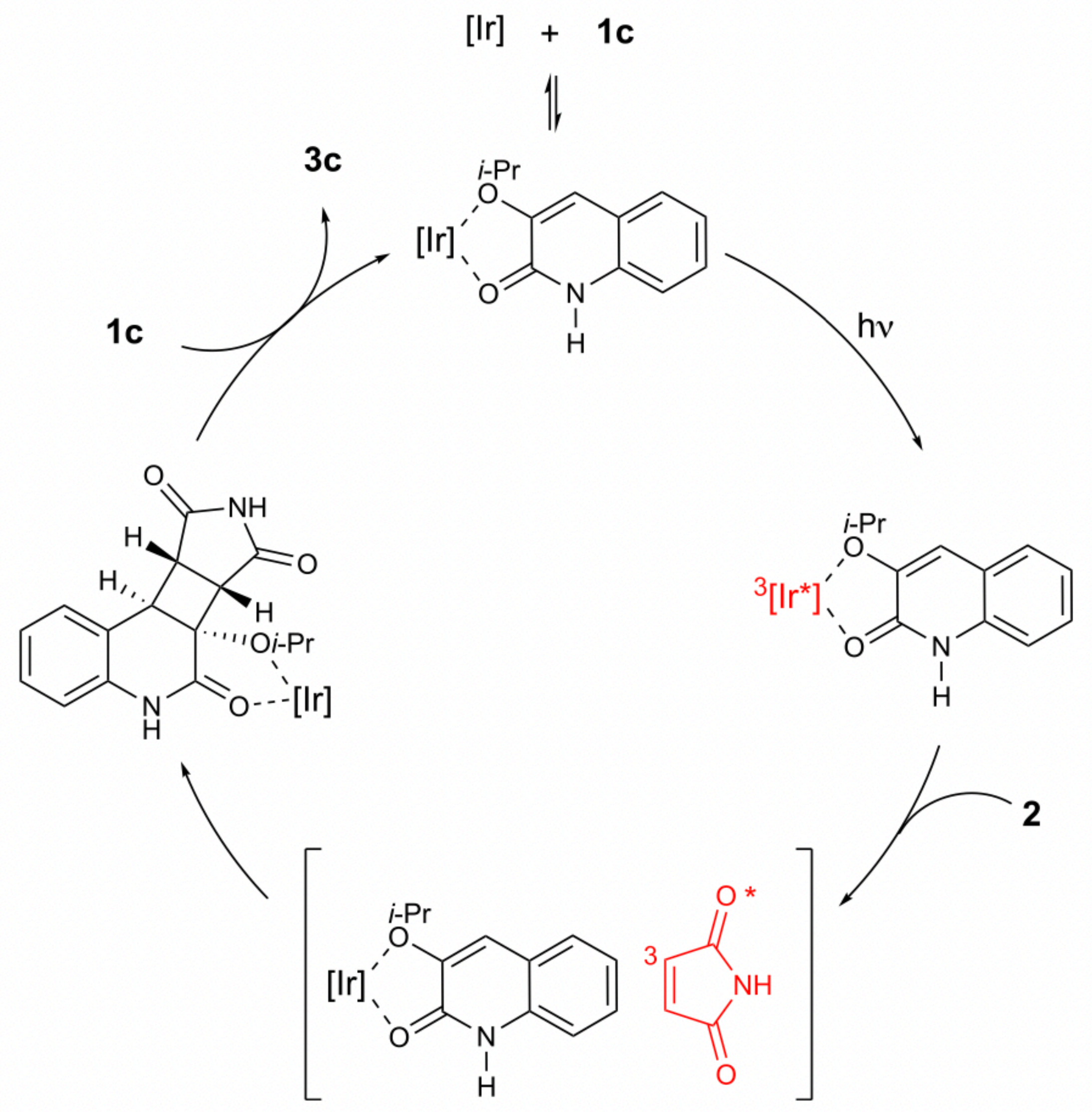
Scheme 1. *Intra*molecular vs *Inter*molecular Enantioselective [2 + 2] Photoreactions Using Enantiopure Chiral Ir Sensitizers



Scheme 2. Control Experiments Show That Intermolecular Cycloaddition of 1x with Maleimide Outcompetes Intramolecular Cyclization



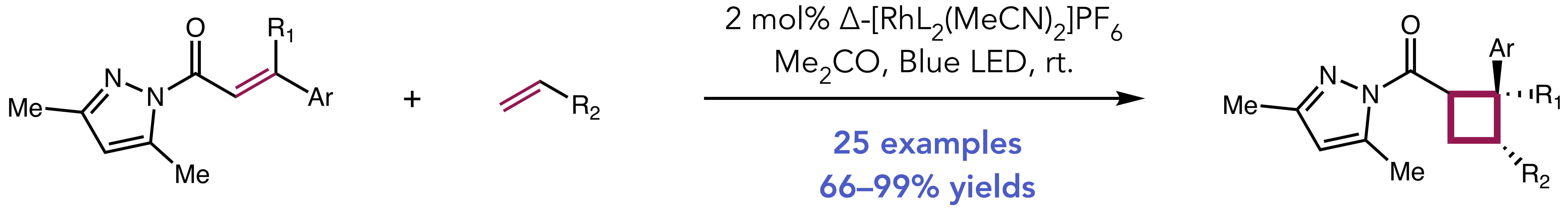
Scheme 4. Proposed Mechanism for Enantioselective Intermolecular [2 + 2] Photocycloaddition



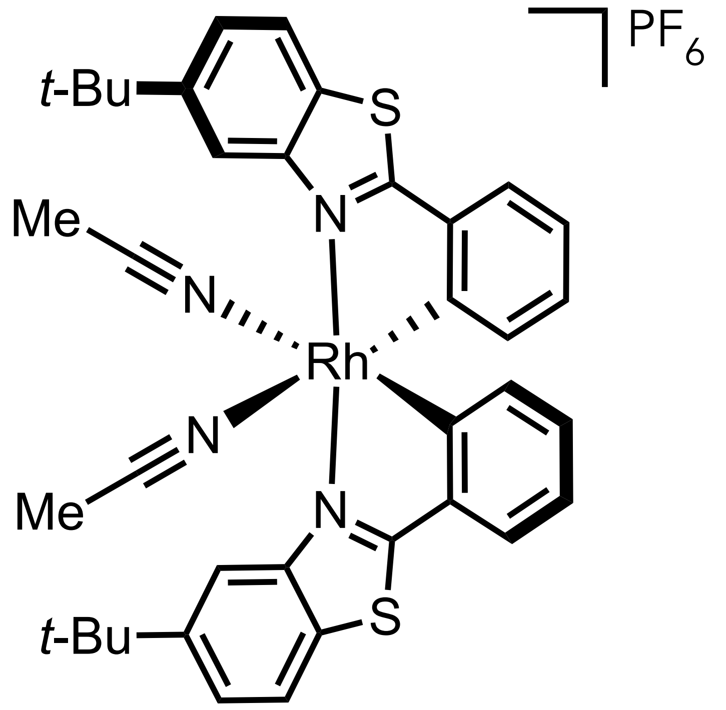
Zheng, J., Swords, W. B., Jung, H., Skubi, K. L., Kidd, J. B., Meyer, G. J., Baik, M.-H., Yoon, T. P., *JACS*, **2019**, *141*, 13625-13634.

Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

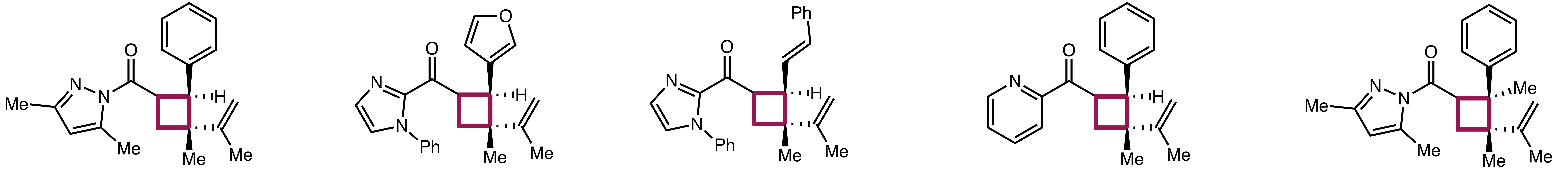
– Meggers, 2017.
  – Chiral-at-Rh complex coordination to a 2-acrolyl imidazole / pyrazole allows for enantioselective intermolecular [2+2]:



25 examples
66–99% yields
88–99% ee
d.r. 6:1 – >20:1



– Select examples with 2,3-dimethylbutadiene:



93%, 96% ee, d.r. 10:1 | **72%, 99% ee, d.r. 9:1** | **84%, 96% ee, d.r. 6:1** | **72%, 95% ee, d.r. 8:1** | **95%, 99% ee, d.r. >20:1**

Huang, X., Quinn, T. R., Harms, K., Webster, R. D., Zhang, L., Wiest, O., Meggers, E., *JACS*, **2017**, *139*, 9120–9123.

Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

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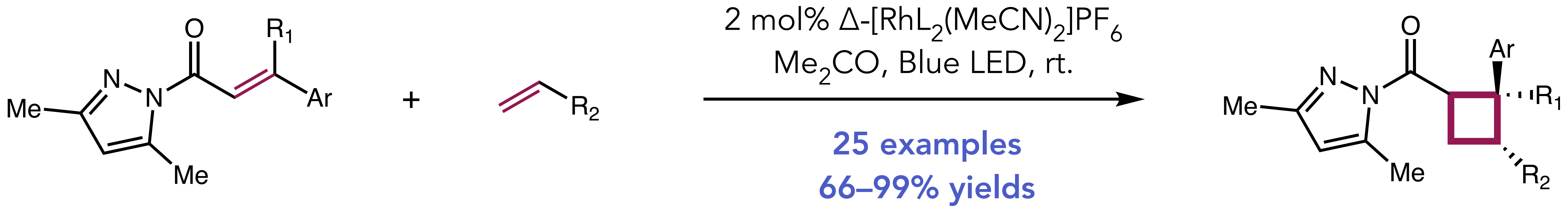
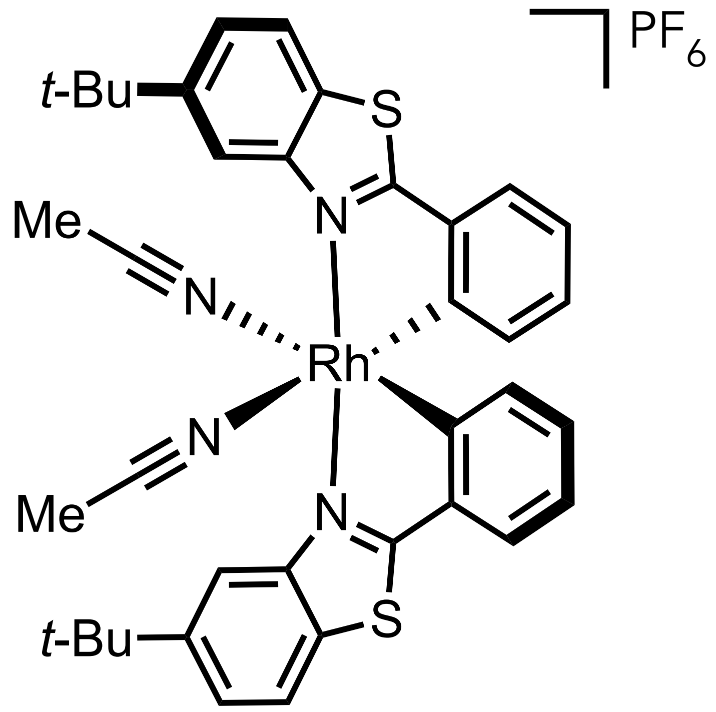
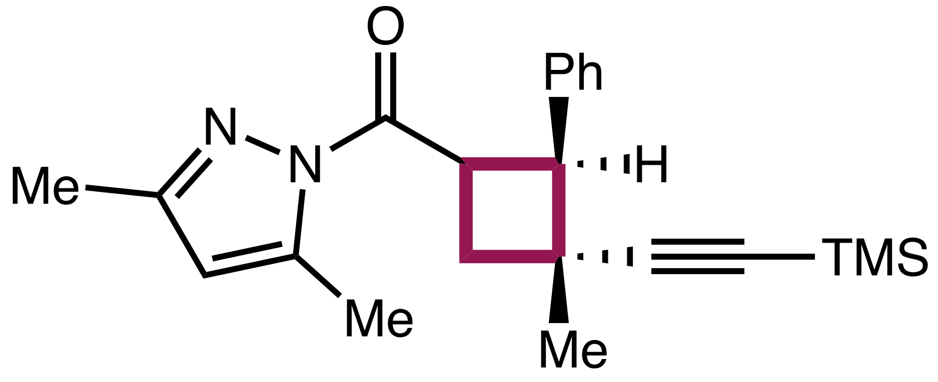
  - Chiral-at-Rh complex coordination to a 2-acrolyl imidazole / pyrazole allows for enantioselective intermolecular [2+2]:



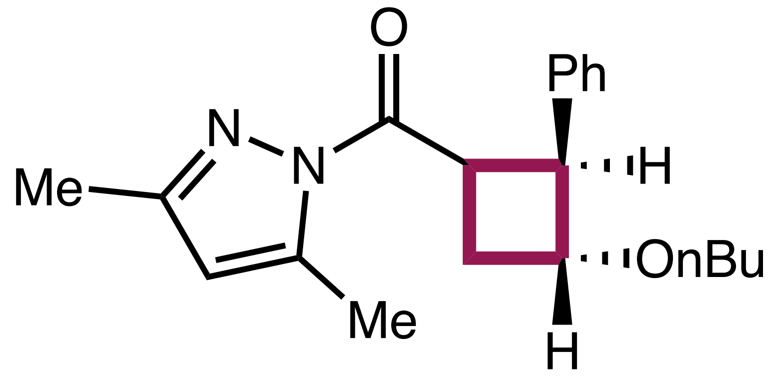
25 examples
66–99% yields
88–99% ee
d.r. 6:1 – >20:1



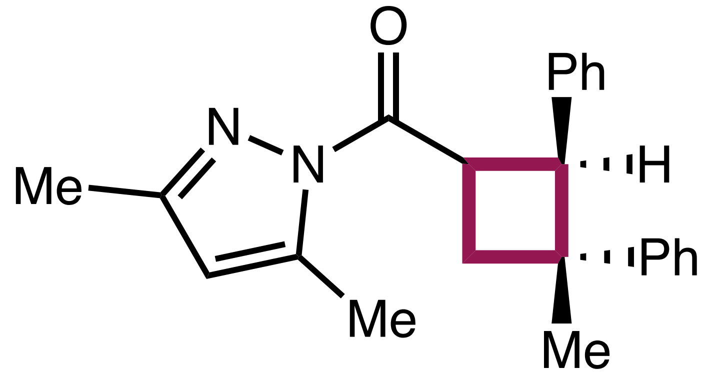
- Select examples with other olefins:



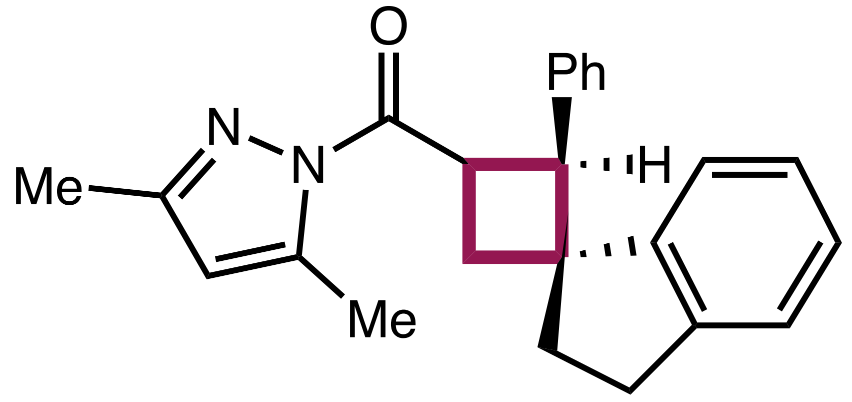
66%, 97% ee, d.r. 9:1



97%, 99% ee, d.r. 6:1



94%, 99% ee, d.r. >20:1

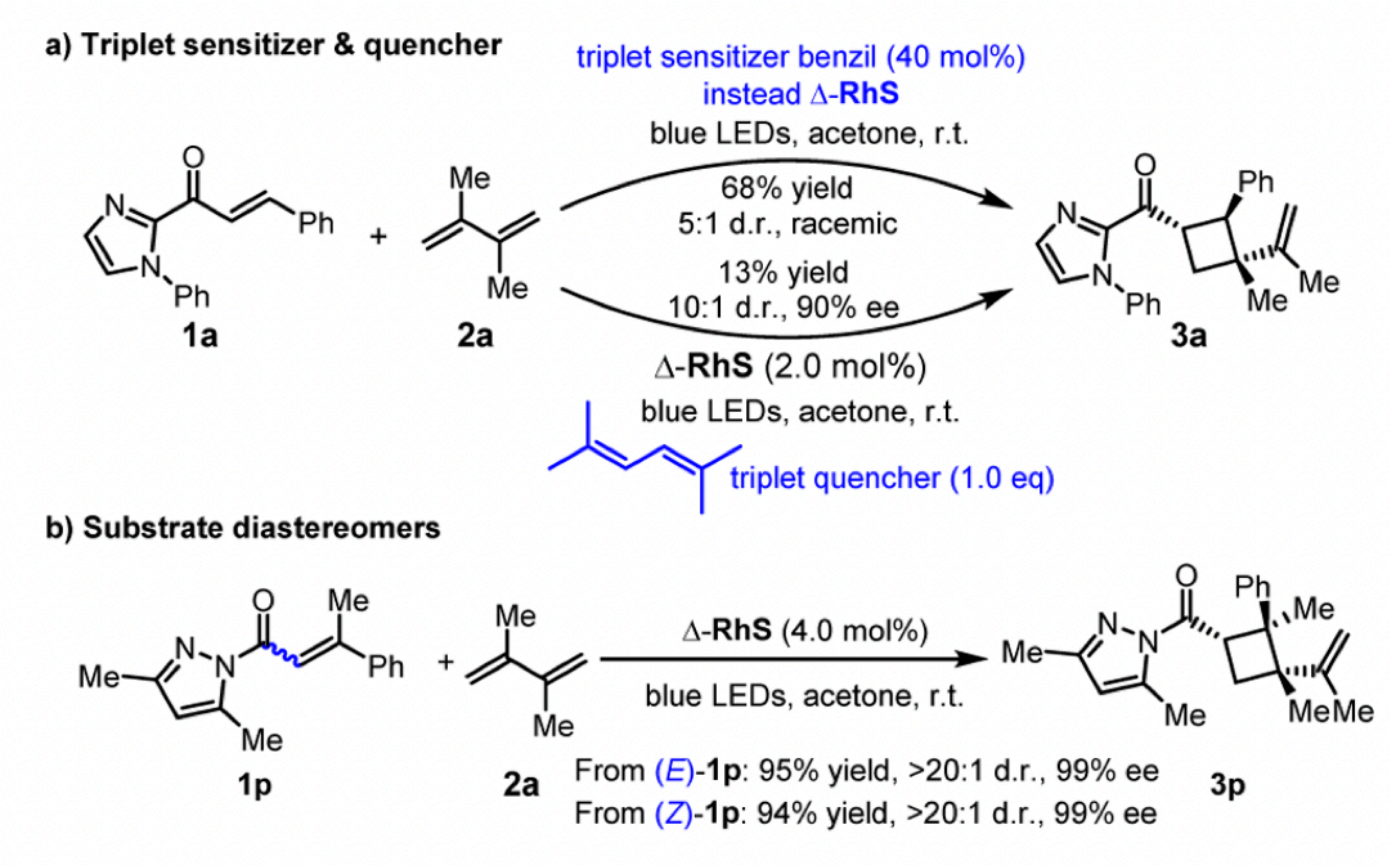


96%, 99% ee, d.r. >20:1

Huang, X., Quinn, T. R., Harms, K., Webster, R. D., Zhang, L., Wiest, O., Meggers, E., *JACS*, **2017**, *139*, 9120–9123.

Photocatalytic Asymmetric [2+2] Cycloaddition of Enones and Olefins

- Meggers, 2017.
  - Mechanistic support:



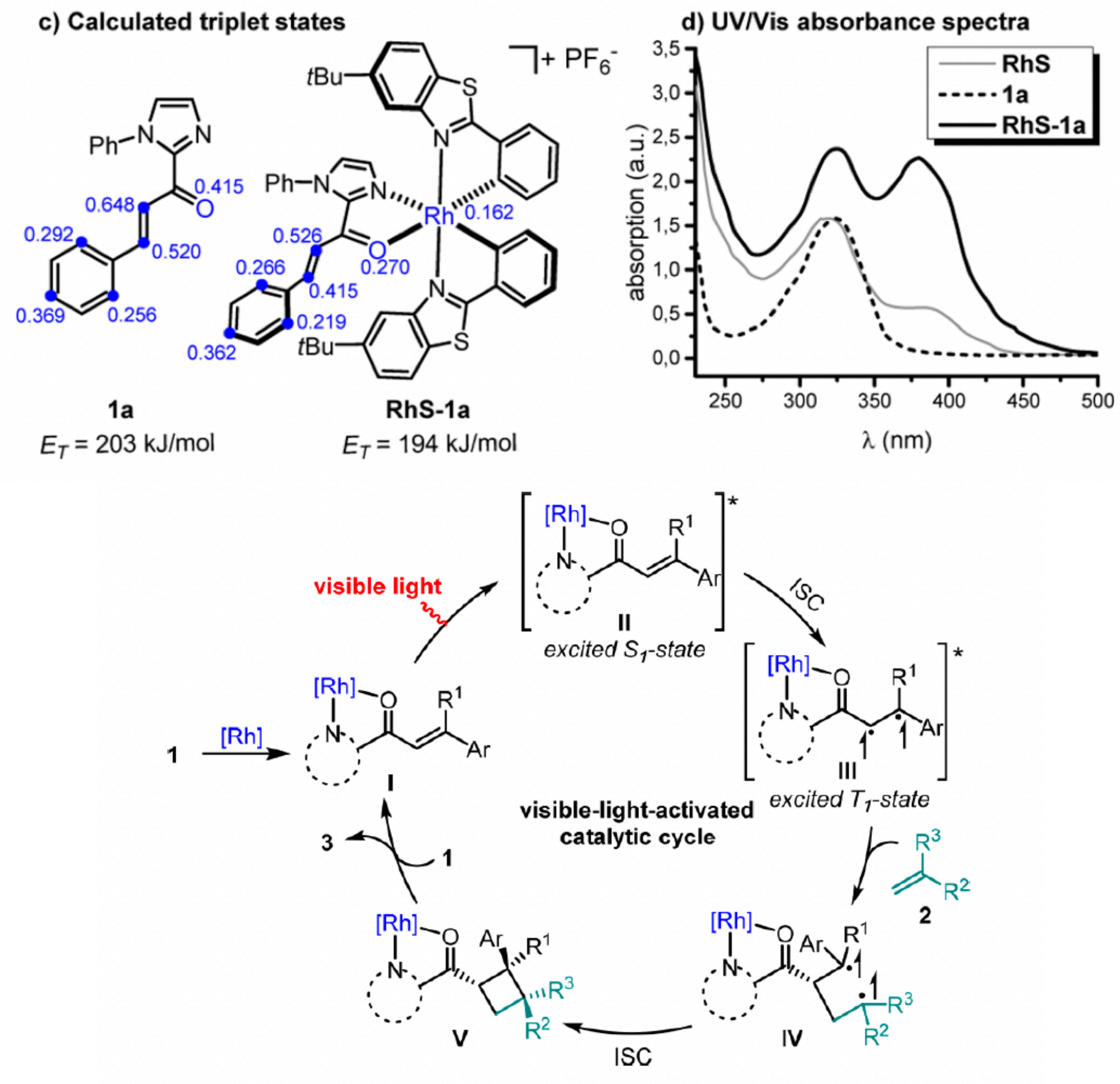
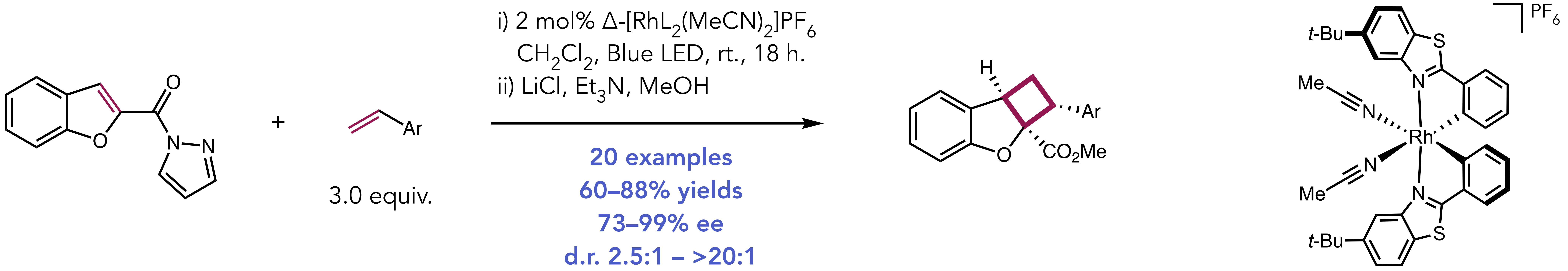


Figure 4. Proposed mechanism. ISC = intersystem crossing.

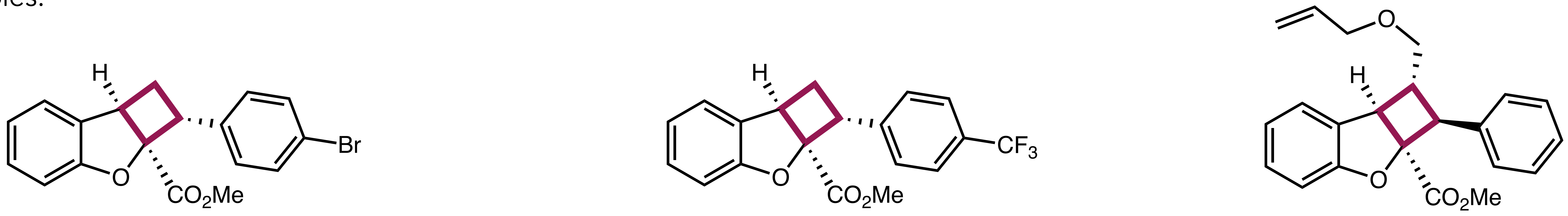
Huang, X., Quinn, T. R., Harms, K., Webster, R. D., Zhang, L., Wiest, O., Meggers, E., *JACS*, **2017**, *139*, 9120–9123.

Photocatalytic Asymmetric Dearomative [2+2] Cycloaddition of Benzofurans and Olefins

– Meggers and Baik, 2018.
 – Chiral at Rh coordination to a 2-acylpyrazole benzofuran produces a photoactive complex:



– Select examples:



76%, 98% ee, 12.1:1 d.r., 11.8:1 r.r

74%, 96% ee, 11.1:1 d.r., 9.1:1 r.r

91%, 99% ee

Hu, N., Jung, H., Zheng, Y., Lee, J.; Zhang, L., Ullah, Z., Xie, X., Harms, K., Baik, M.-H., Meggers, E., *ACIE*, **2018**, *57*, 6242-6246.

Photocatalytic Asymmetric Dearomative [2+2] Cycloaddition of Benzofurans and Olefins

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  - Chiral at Rh coordination to a 2-acylpyrazole benzofuran produces a photoactive complex:

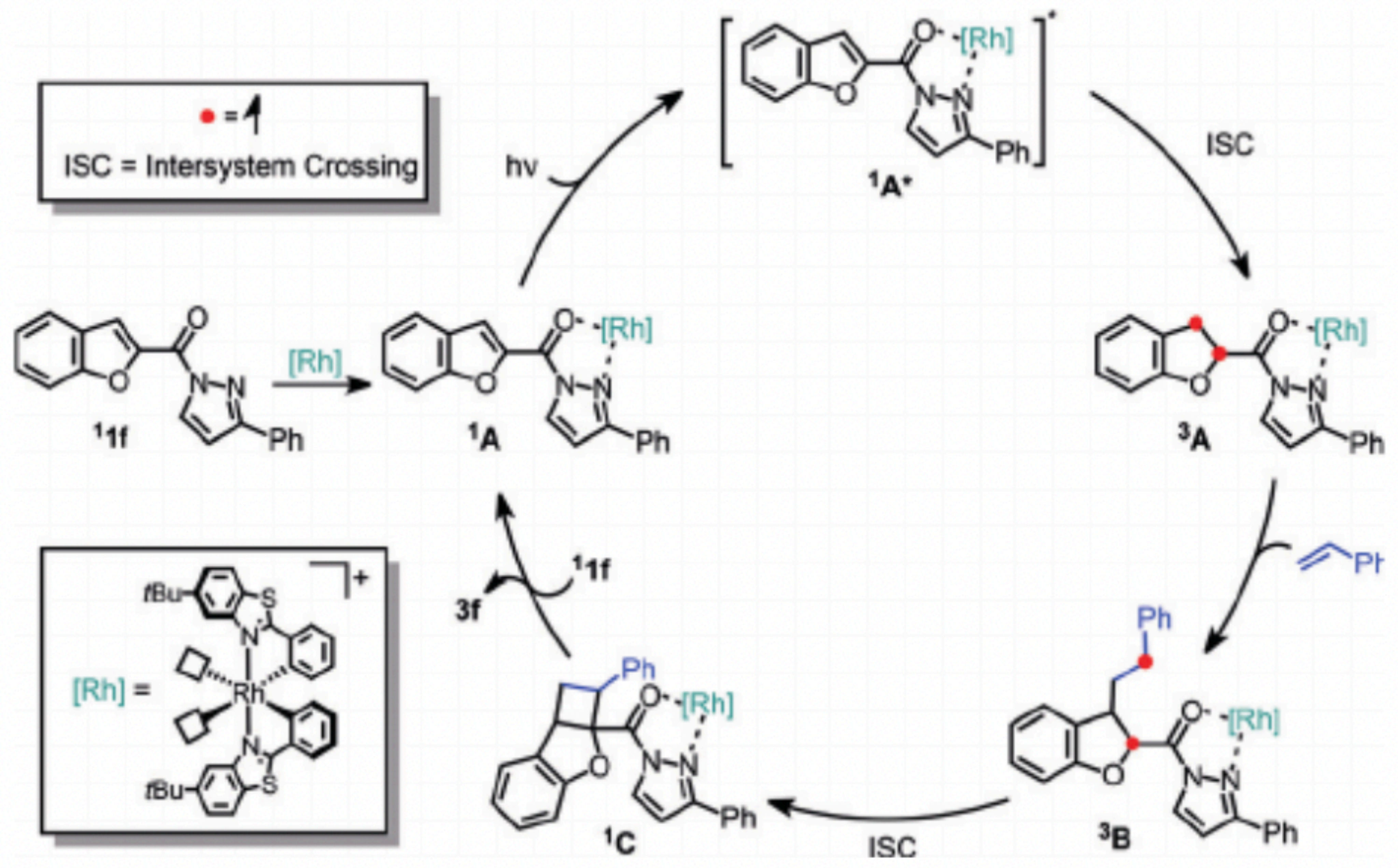

Figure 3. Proposed catalytic cycle.

Hu, N., Jung, H., Zheng, Y., Lee, J.; Zhang, L., Ullah, Z., Xie, X., Harms, K., Baik, M.-H., Meggers, E., *ACIE*, **2018**, *57*, 6242-6246.

Photocatalytic Asymmetric Dearomative [2+2] Cycloaddition of Benzofurans and Olefins

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  – Chiral at Rh coordination to a 2-acylpyrazole benzofuran produces a photoactive complex:

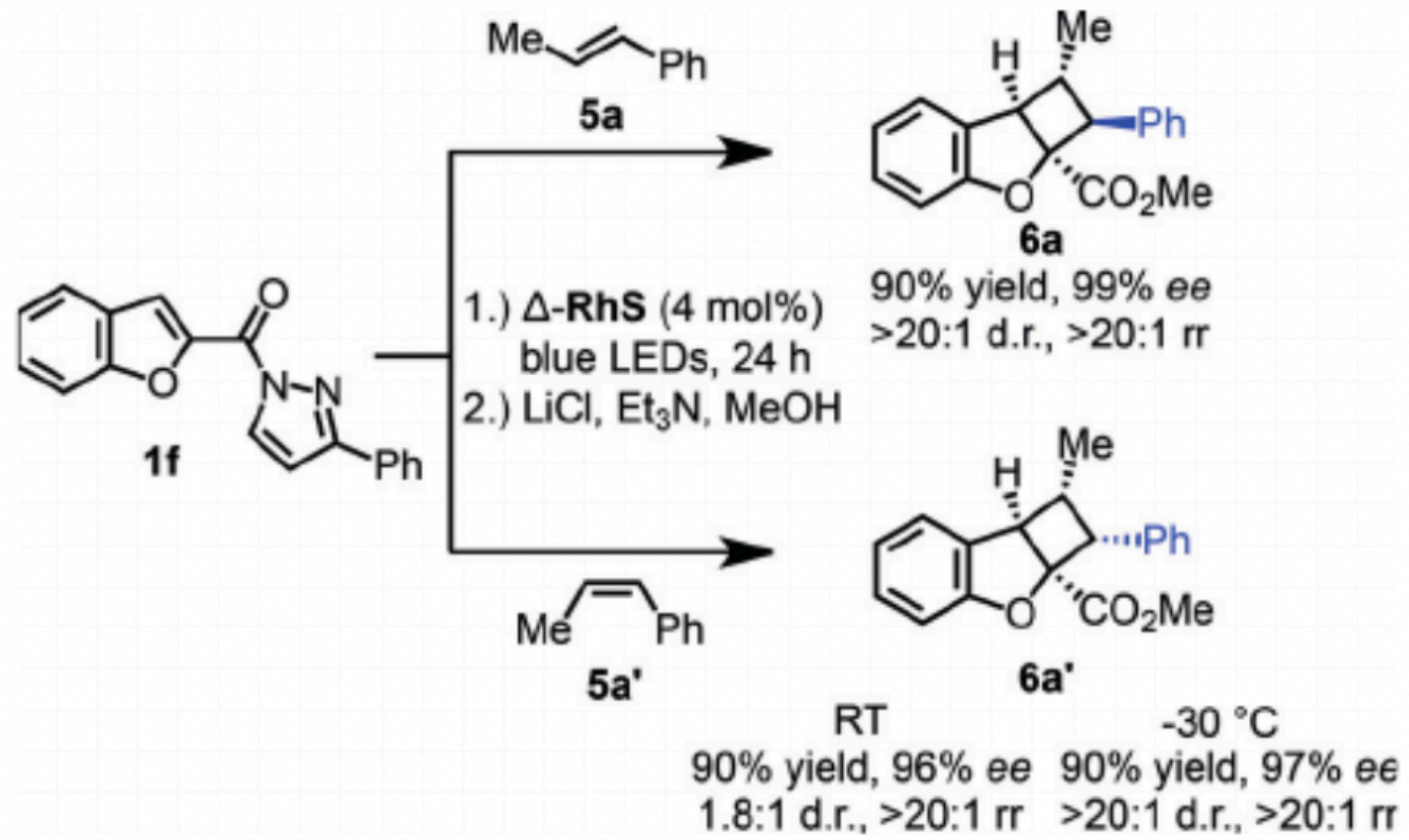
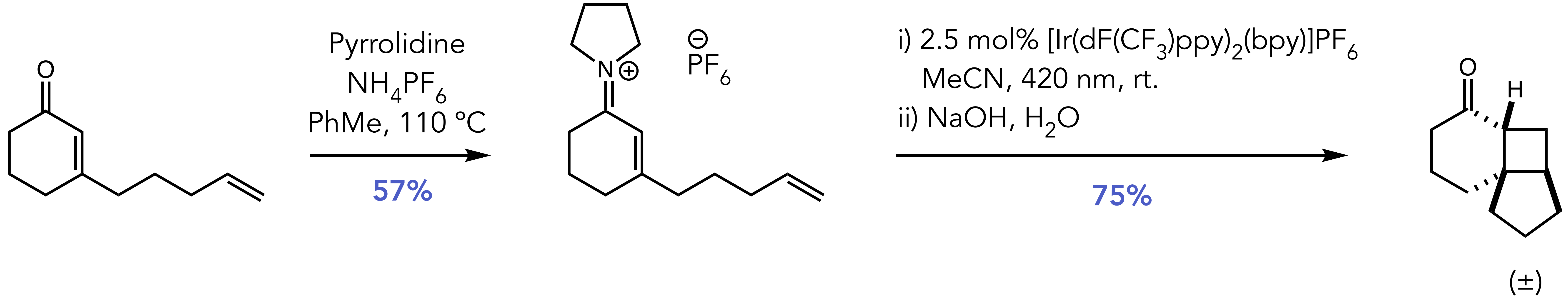


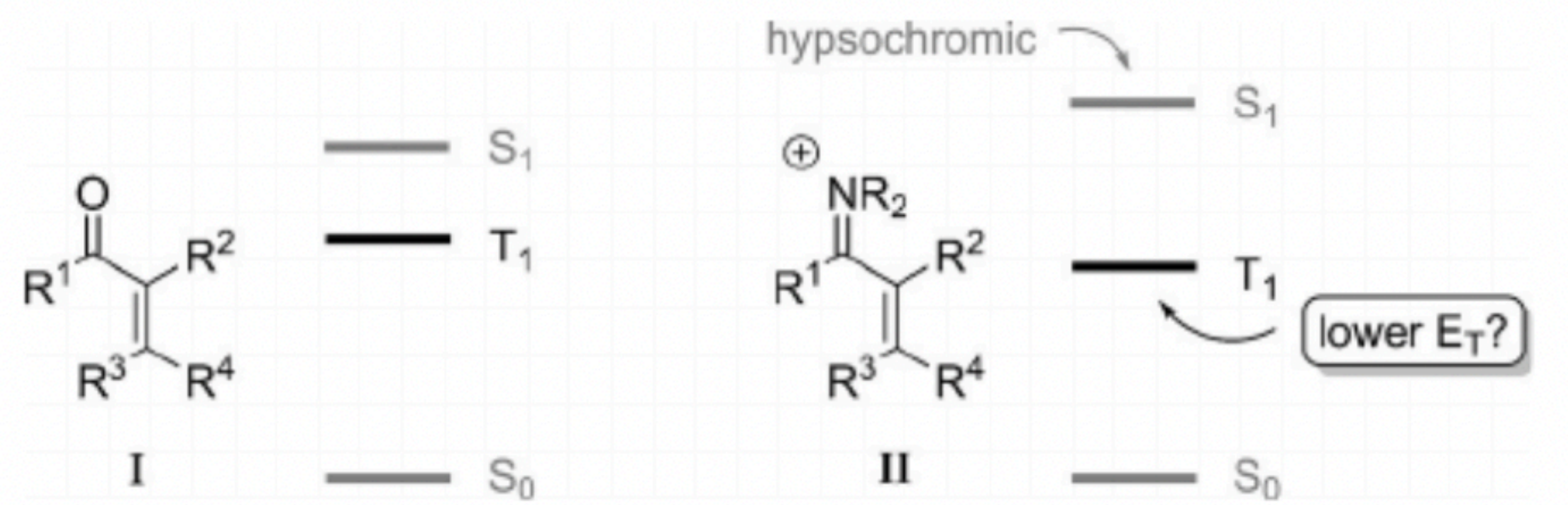
Figure 5. Asymmetric dearomatization with (*E*)- and (*Z*)-β-methylstyrene. For the reaction at −30°C, 5 W blue LEDs were employed (see the Supporting Information for the setup) and reaction time was 60 h. The absolute configuration of a derivative of **6a** was determined by X-ray crystallography. The relative configuration of its diastereoisomer **6a'** was determined by NMR studies.

Hu, N., Jung, H., Zheng, Y., Lee, J.; Zhang, L., Ullah, Z., Xie, X., Harms, K., Baik, M.-H., Meggers, E., *ACIE*, **2018**, *57*, 6242-6246.

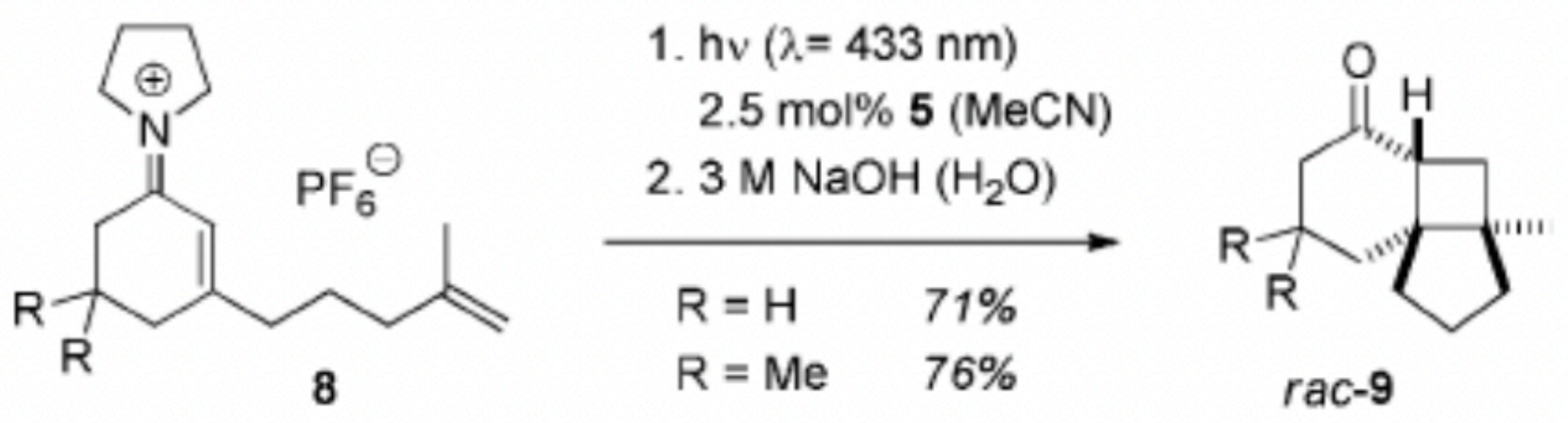
Photocatalytic Asymmetric [2+2] Cycloaddition of eneiminium ions and olefins

– Bach 2018 and Bach, Wenger 2020
  – Iminium ions of unsaturated carbonyl compounds lead to triplet state energy lowering and therafter asymmetric [2+2] photocycloaddition:





Scheme 1. Schematic energy diagram for the singlet (S) and triplet (T) states of α,β-unsaturated carbonyl compounds **I** and the respective eniminium ions **II**.

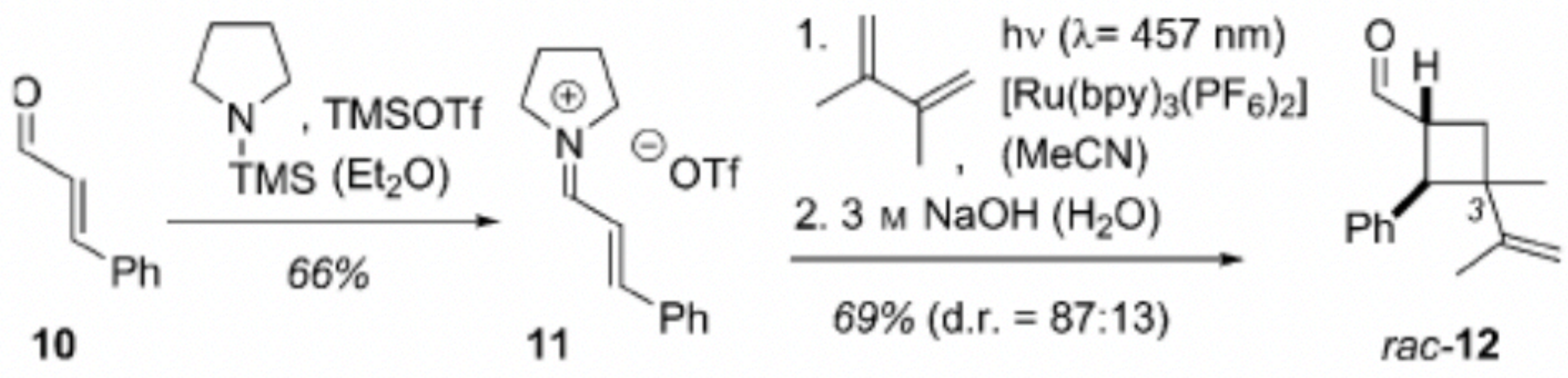


Scheme 3. Intramolecular iridium-catalyzed [2+2] photocycloaddition of eniminium ions **8**.

Hörmann, F. M., Chung, T. S., Rodriguez, E., Jakob, M, Bach, T., *ACIE*, **2018**, *57*, 827–831. Hörmann, F. M., Kerzig, C., Chung, T. S., Bauer, A., Wenger, O. S., Bach, T., *ACIE*, **2020**, *59*, 9659–9668.

Photocatalytic Asymmetric [2+2] Cycloaddition of eneiminium ions and olefins

– Bach 2018 and Bach, Wenger 2020
  – Iminium ions of unsaturated carbonyl compounds lead to triplet state energy lowering and therafter asymmetric [2+2] photocycloaddition:



Scheme 4. Formation of eniminium ion **11** and its ruthenium-catalyzed [2+2] photocycloaddition to 2,3-dimethylbutadiene (d.r. = diastereomeric ratio).

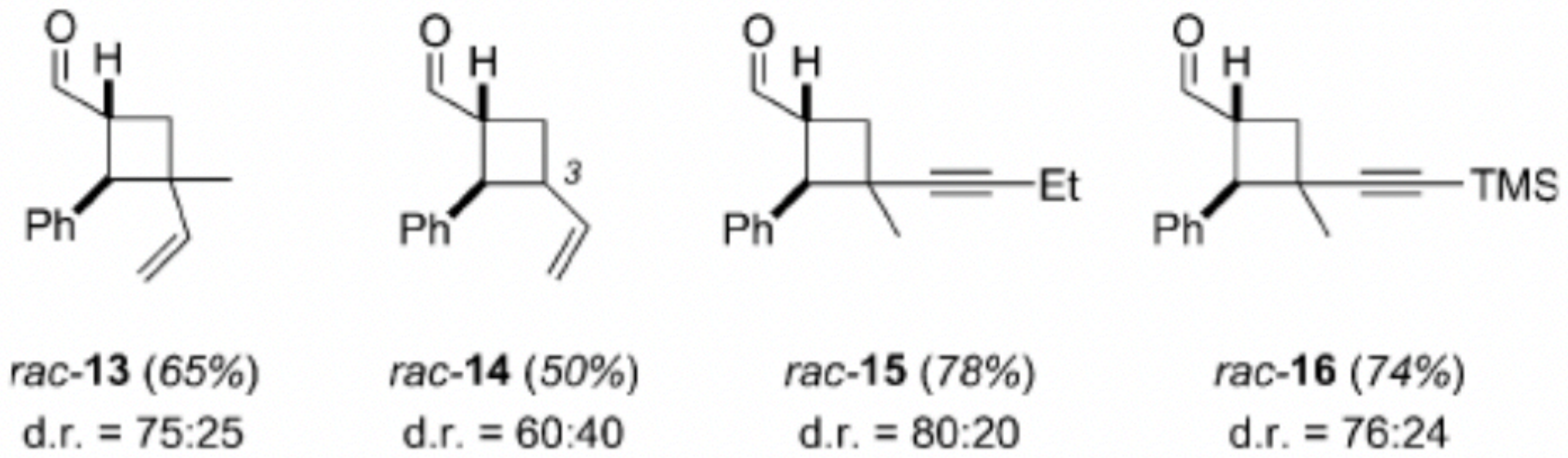


Figure 2. [2+2] Photocycloaddition products obtained by the reaction of eniminium ion **11** with different olefins ($\lambda = 457$ nm, catalyst: 2.5 mol% $Ru(bpy)_3(PF_6)_2$ in MeCN).

Hörmann, F. M., Chung, T. S., Rodriguez, E., Jakob, M, Bach, T., *ACIE*, **2018**, *57*, 827–831. Hörmann, F. M., Kerzig, C., Chung, T. S., Bauer, A., Wenger, O. S., Bach, T., *ACIE*, **2020**, *59*, 9659–9668.

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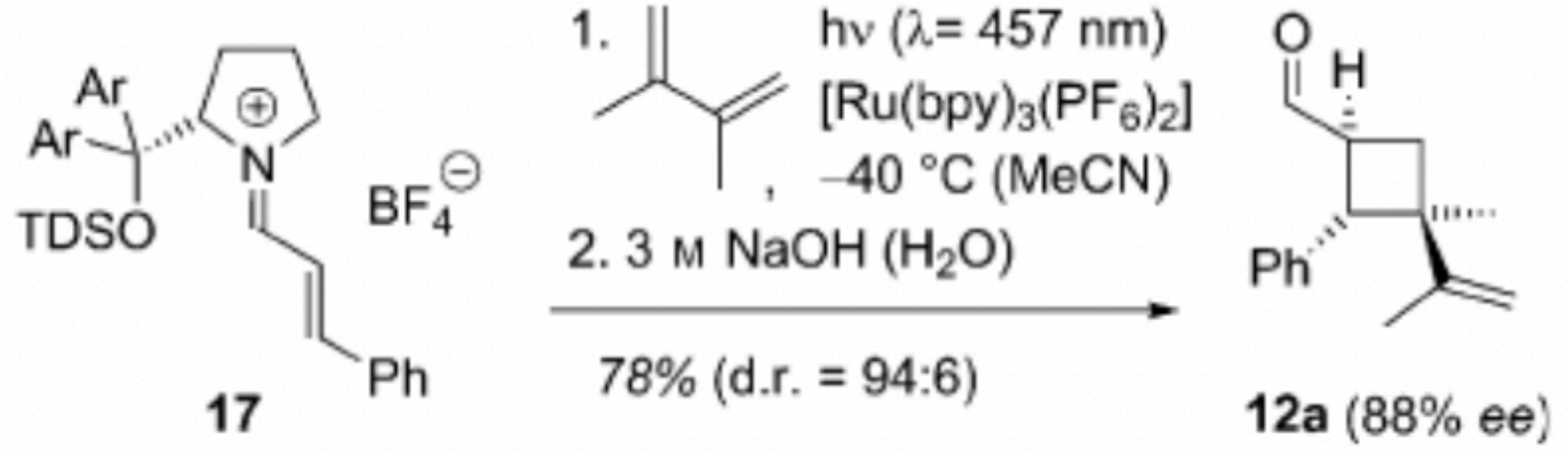
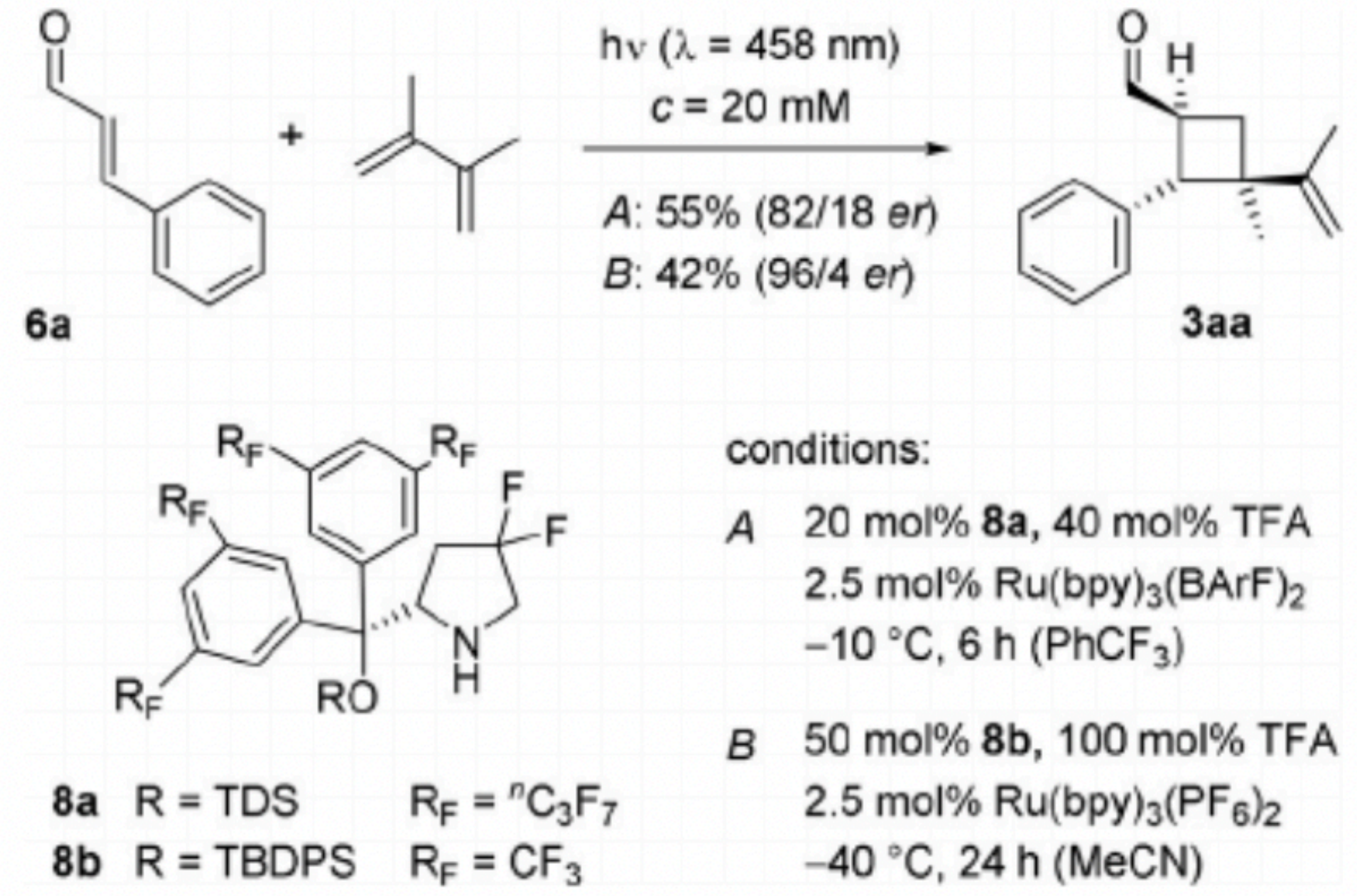
  – Iminium ions of unsaturated carbonyl compounds lead to triplet state energy lowering and therafter asymmetric [2+2] photocycloaddition:



Scheme 5. Enantioselective ruthenium-catalyzed [2+2] photocycloaddition of eniminium ion **17** (Ar = 3,5-bis(trifluoromethyl)phenyl; TDS = *tert*-hexyldimethylsilyl) to cyclobutane **12a**.



Scheme 8. Formation of enantioenriched compound **3aa** from cinnamic aldehyde (**6a**) under catalytic conditions.

Hörmann, F. M., Chung, T. S., Rodriguez, E., Jakob, M, Bach, T., *ACIE*, **2018**, *57*, 827–831. Hörmann, F. M., Kerzig, C., Chung, T. S., Bauer, A., Wenger, O. S., Bach, T., *ACIE*, **2020**, *59*, 9659–9668.

Summary

– Photosensitization, or energy transfer catalysis promotes a broad range of different modes of [2+2] and [4+2] cycloadddition.

– Olefins, carbonyls, oximes, and arenes have been shown to undergo sensitization.

– Two general modes of inducing enantiocontrol in photocatalytic [2+2] have thus far been explored:
  – Triplet state energy lowering in the presence of a chiral catalyst
  – Chiral photocatalyst coordination to a substarte prior to energy transfer

– Current limitations in the methodology involve accessing substrates with higher triplet state energies.
  – This may soon be lifted with the recent development of a family of near-UV absorbing high triplet energy xanthone dyes.

– Other types of energy transfer processes can be promoted:
  – Alkene isomerization
  – Bond homolysis processes for *N*- and *C*-centered radical generation, for example