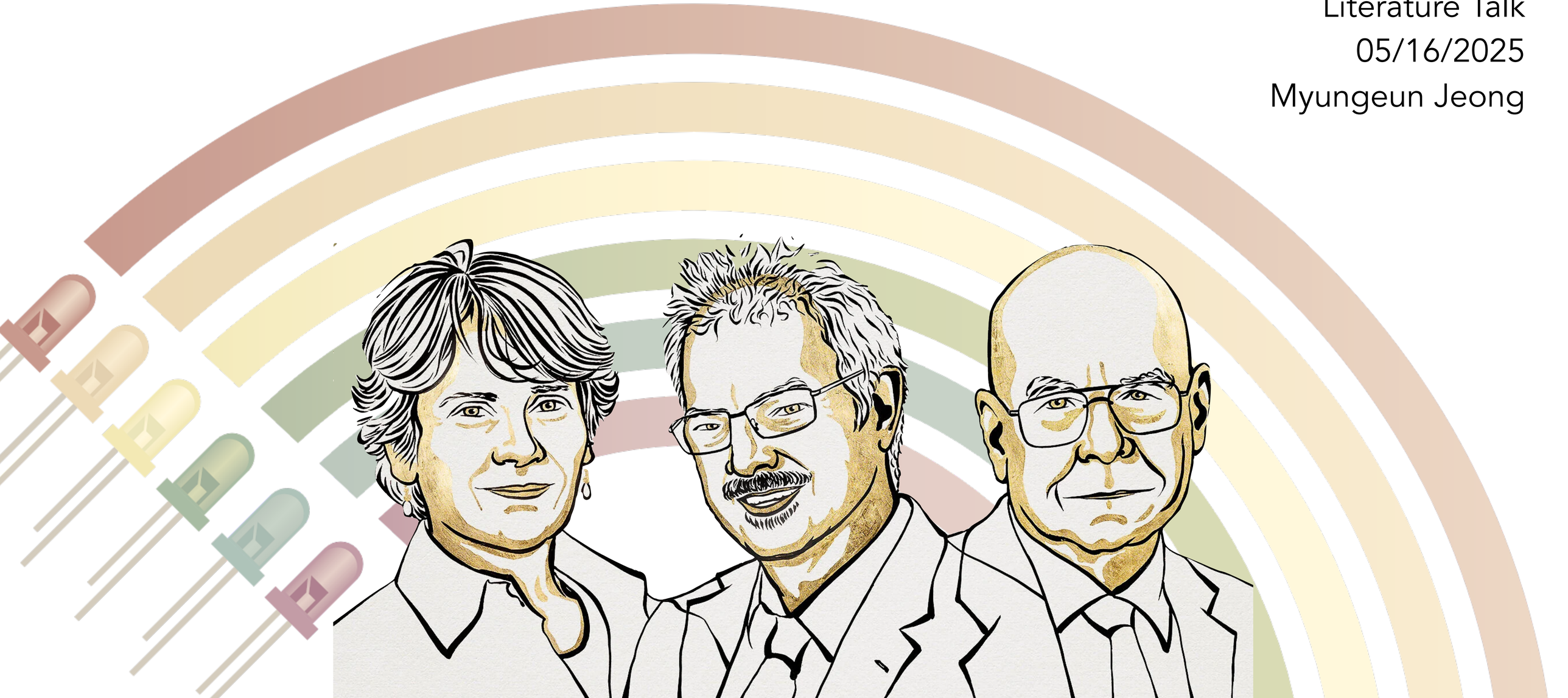
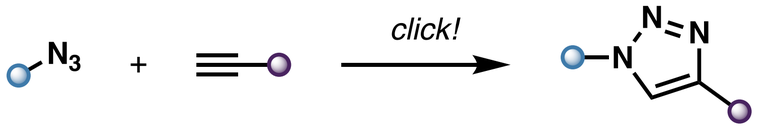
Photoclick Chemistry

Literature Talk
05/16/2025
Myungeun Jeong



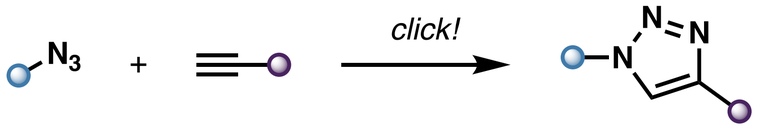
Click chemistry



"reaction sets of powerful, selective, and modular "blocks" that work reliably both small- and large-scale applications"

Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004

Click chemistry



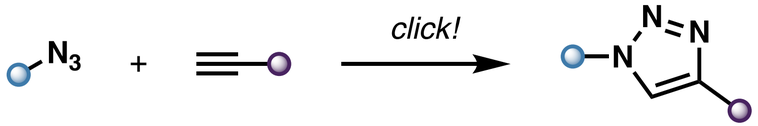
"reaction sets of powerful, selective, and modular "blocks" that work reliably both small- and large-scale applications"

must…

- be modular
- be wide in scope
- give very high yields
- generate only inoffensive byproducts (removed by nonchromatographic methods)
- be stereospecific
- have simple reaction condition (insensitive to H_2O, O_2)
- use readily available starting materials and reagents
- no solvents or benign solvents
- simple product isolation

Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004

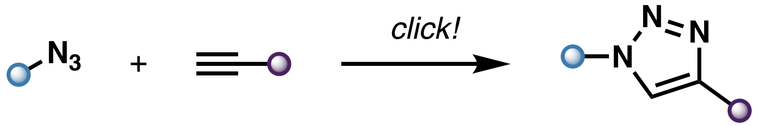
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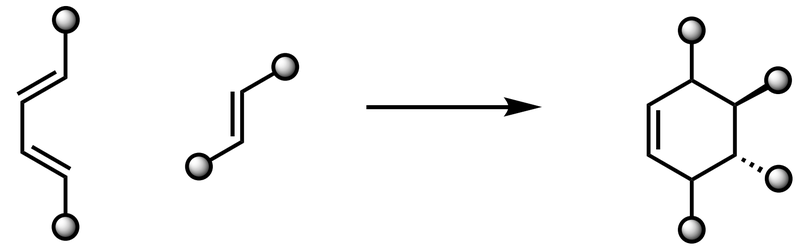
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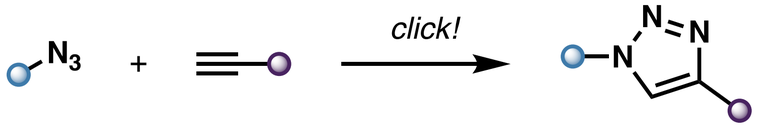
cycloadditions

1,3-dipolar cycloadditions, DAs



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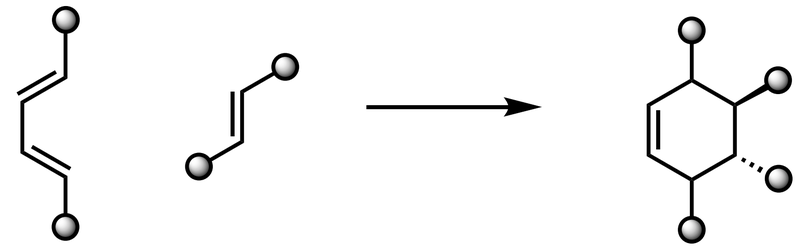
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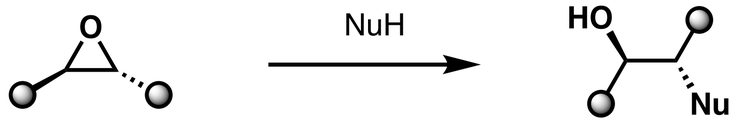
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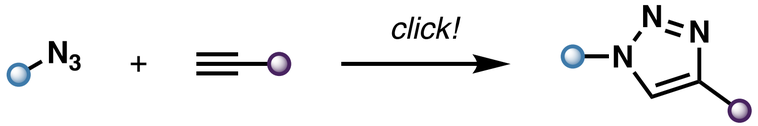
nucleophilic substitutions

ring opening of strained heterocyclic electrophiles



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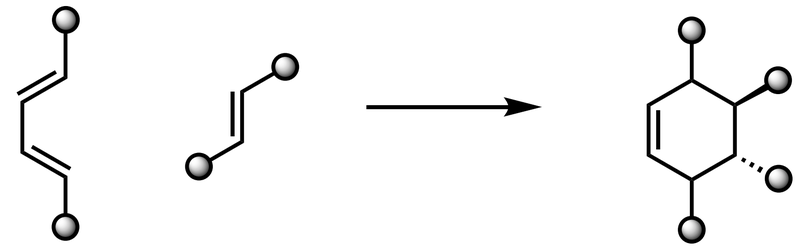
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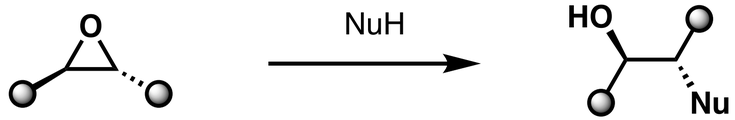
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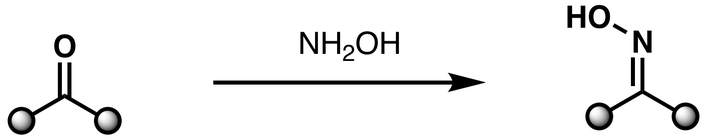
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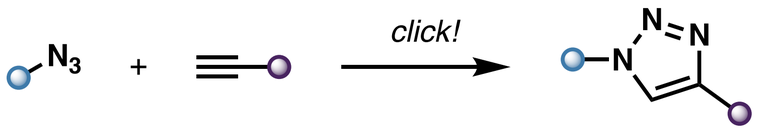
carbonyl chemistry of "non-aldol"

formation of ureas, thioureas, aromatic heterocycles, oxime ethers, hydrazones



Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004

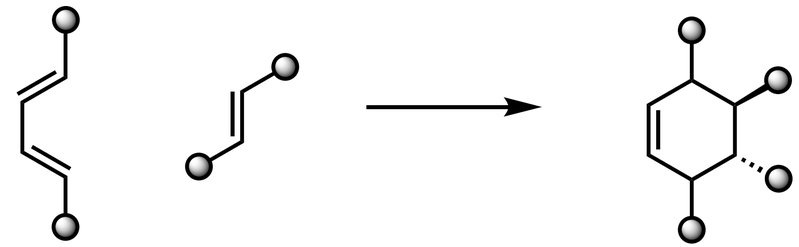
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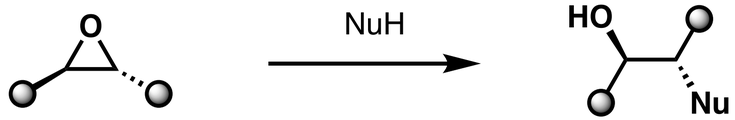
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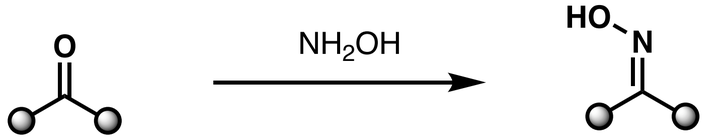
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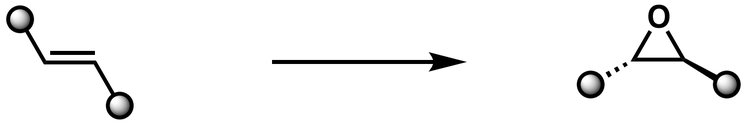
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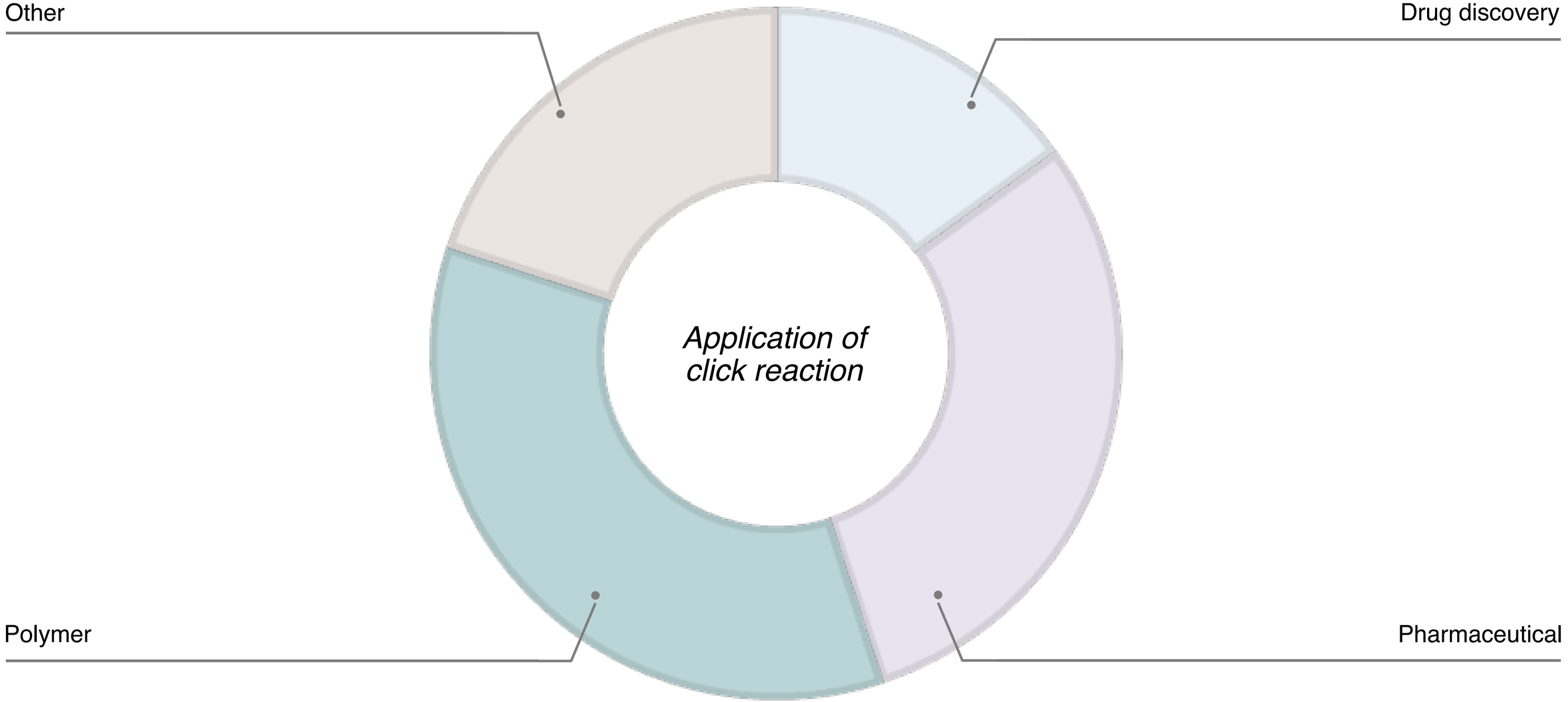
addition to C=C

epoxidation, dihydroxylation,aziridination, Michael reactions



Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004

Click chemistry



Hein, C. D.; Liu, X.; Wang, D. Pharmaceutical Research, **2008**, *25*, 2216

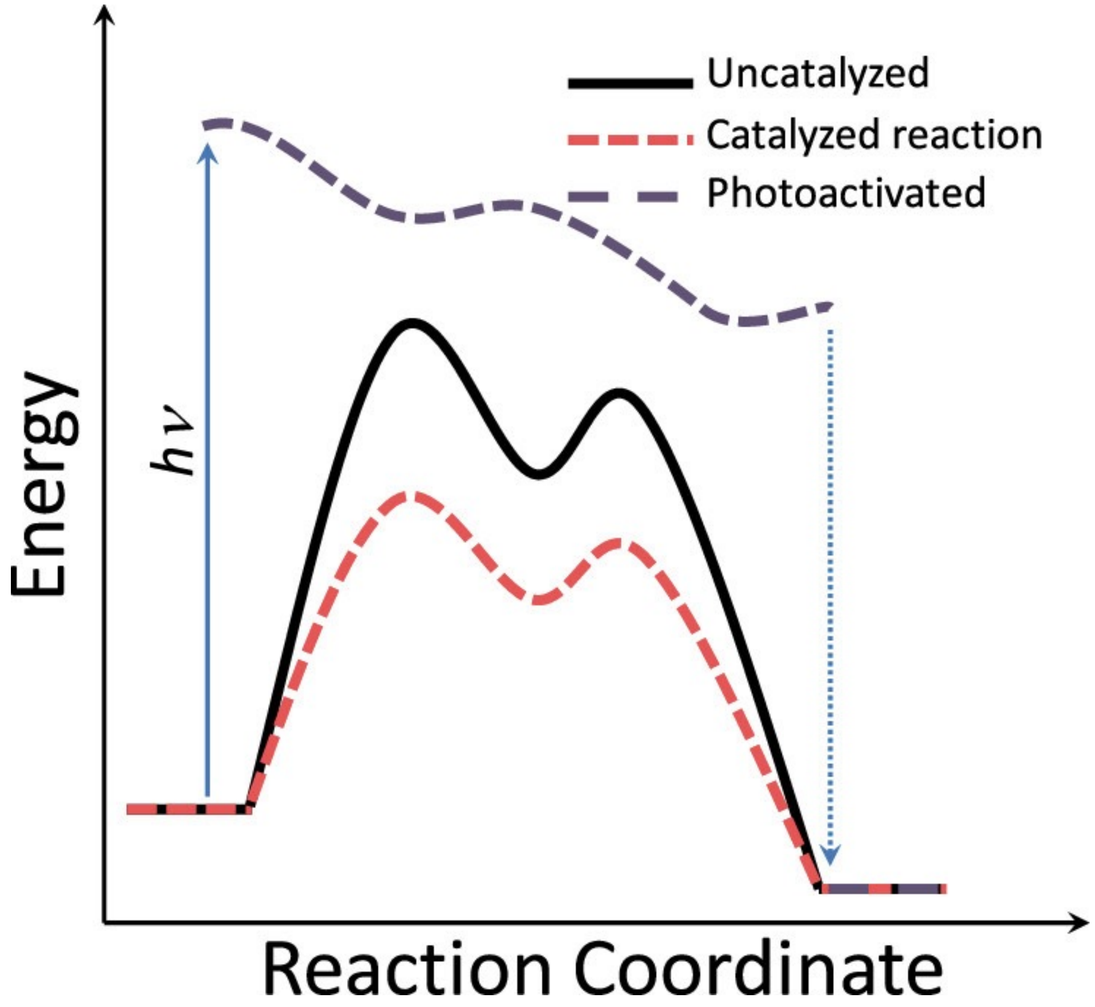
Why photoclick?

- energy efficient
  provides a alternative reaction pathway

Faribanks, B. D.; Bowman, C. N. *Chem. Rev.* **2021**, *121*, 6915

Why photoclick?

- energy efficient
  provides a alternative reaction pathway



catalyzed reaction
decreases the energy barrier

vs

photoativation reaction
excitates the energy of the absorbing species

Faribanks, B. D.; Bowman, C. N. *Chem. Rev.* **2021**, *121*, 6915

Why photoclick?

- energy efficient
  provides a alternative reaction pathway

- chemo- and regio-selective
  with a specific wavelength of the light at lower temperatures

Faribanks, B. D.; Bowman, C. N. *Chem. Rev.* **2021**, *121*, 6915

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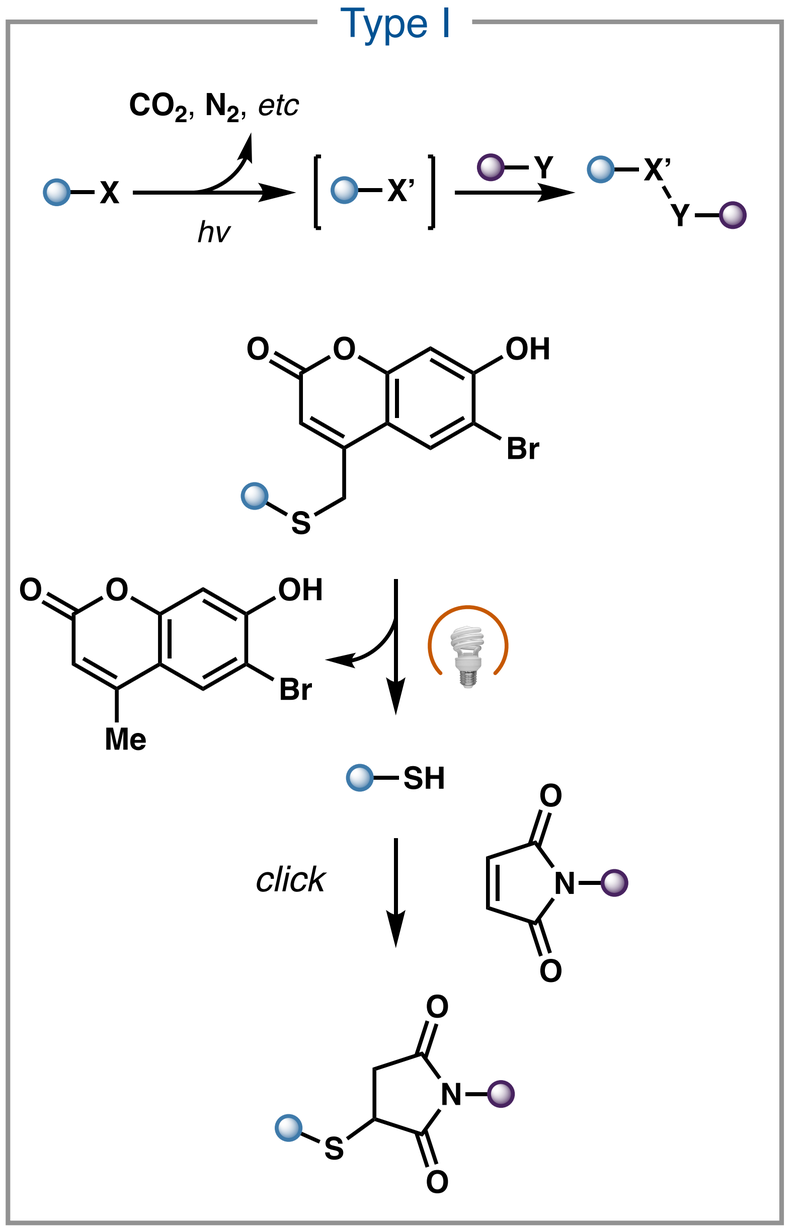
- chemo- and regio-selective
  with a specific wavelength of the light at lower temperatures

- temporal control
  control over both the initiation and termination of the reaction vs. control only over its initiation

- spatial control
  via spatial occlusion of light exposure

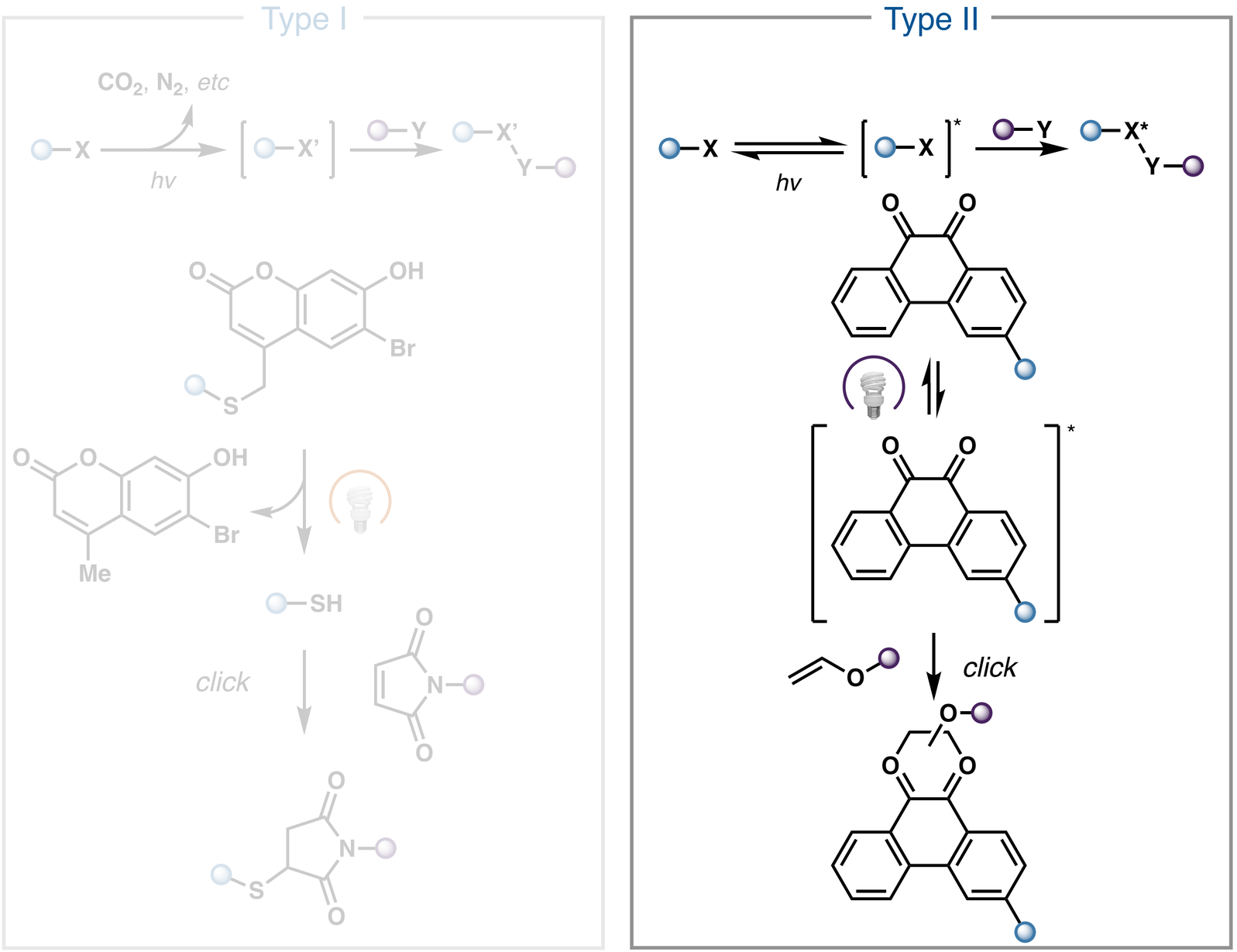
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Types of photoclick reactions



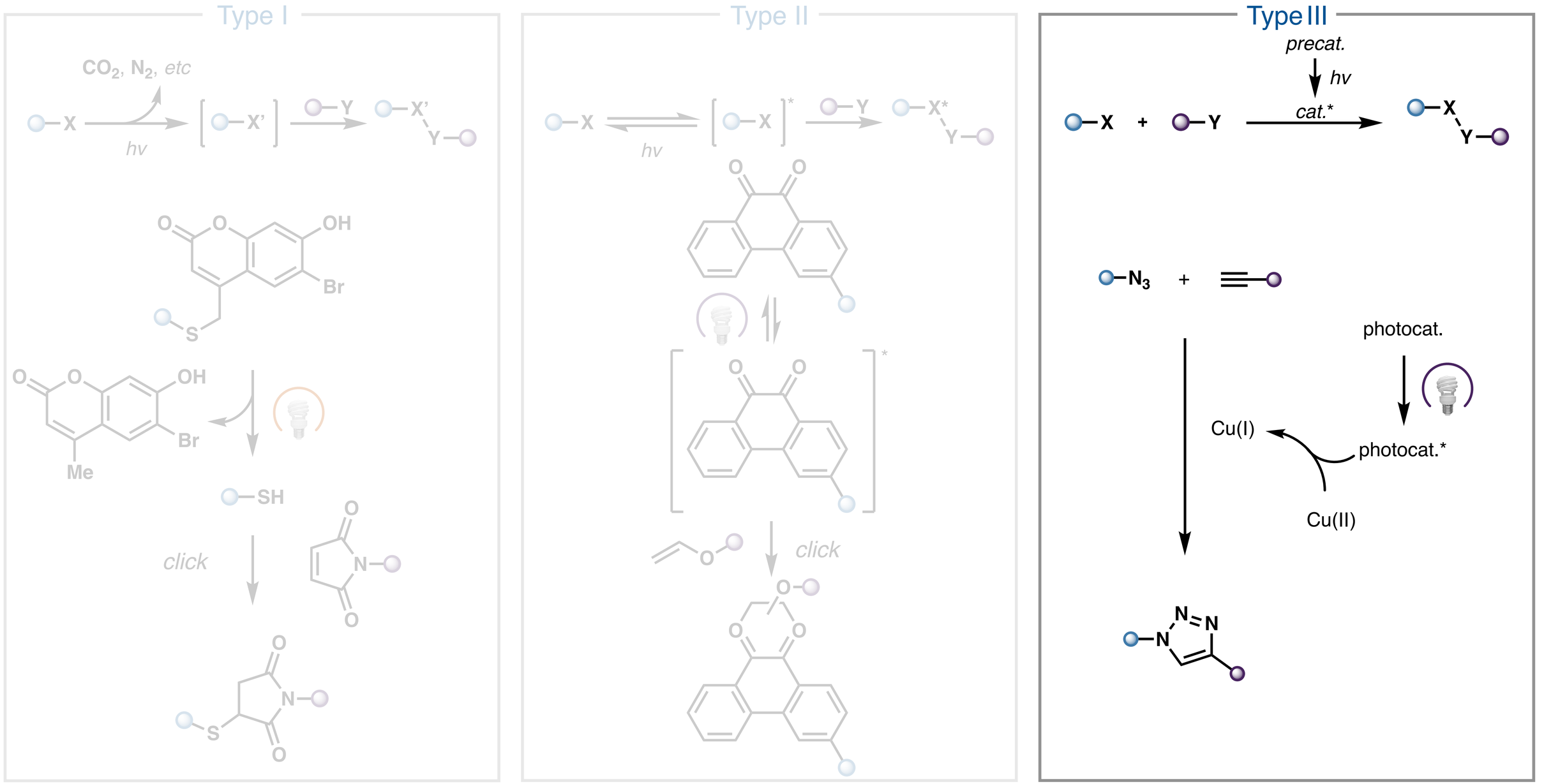
Kumar, G. S.; Lin, Q. *Chem. Rev.* **2021**, *121*, 6991

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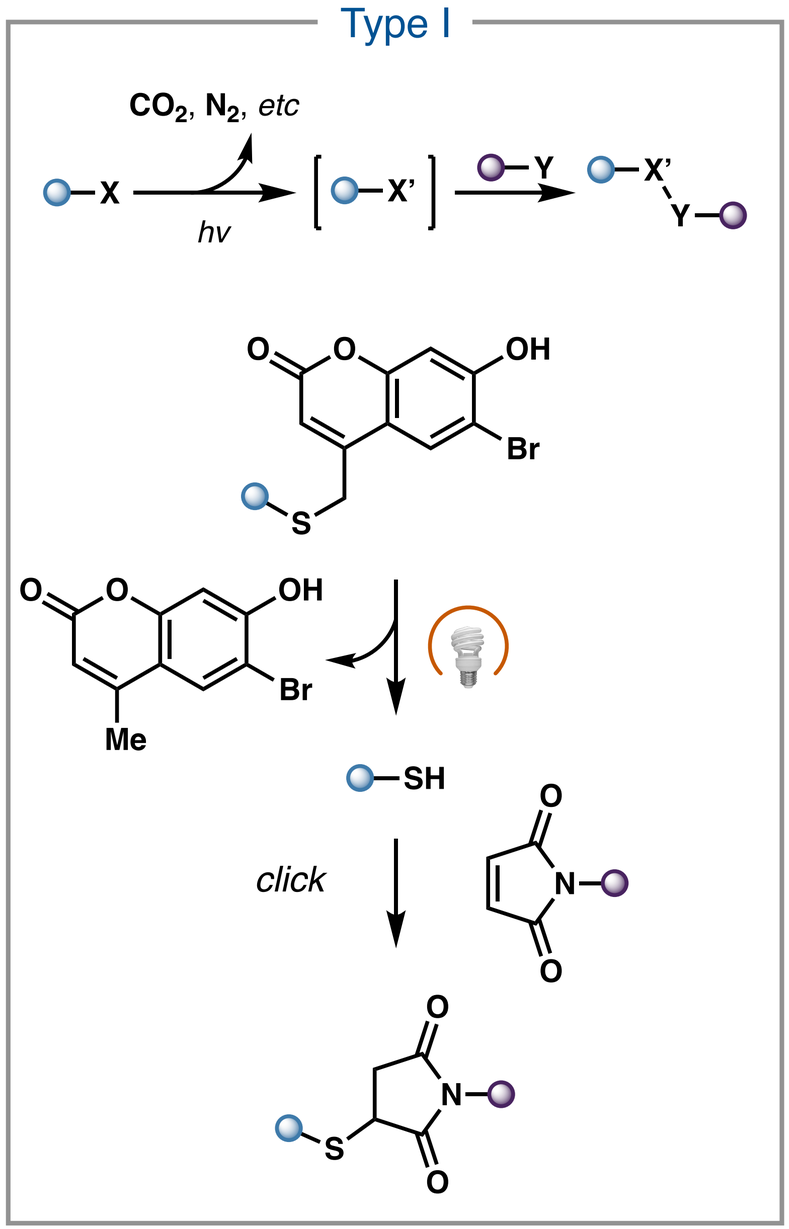
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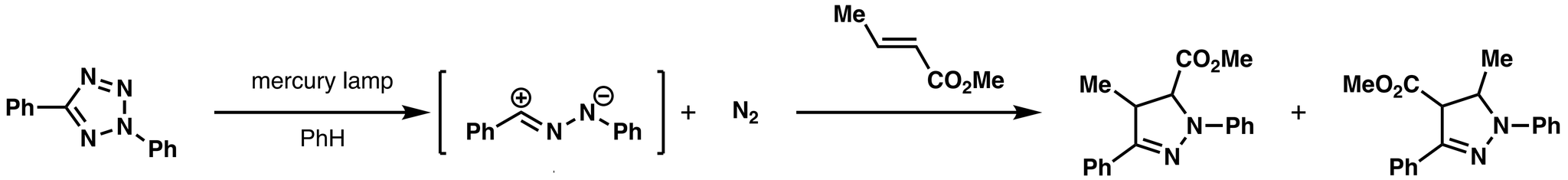


- Tetrazole-alkene cycloaddition
- Photoreleasable thiol-ene reaction
- Strain-promoted azide-alkyne cycloaddition

Kumar, G. S.; Lin, Q. *Chem. Rev.* **2021**, *121*, 6991

Nitrile imine-mediated tetrazole–alkene cycloaddition (NITEC)

- Early reports on nitrile imine-alkene cycloadditions

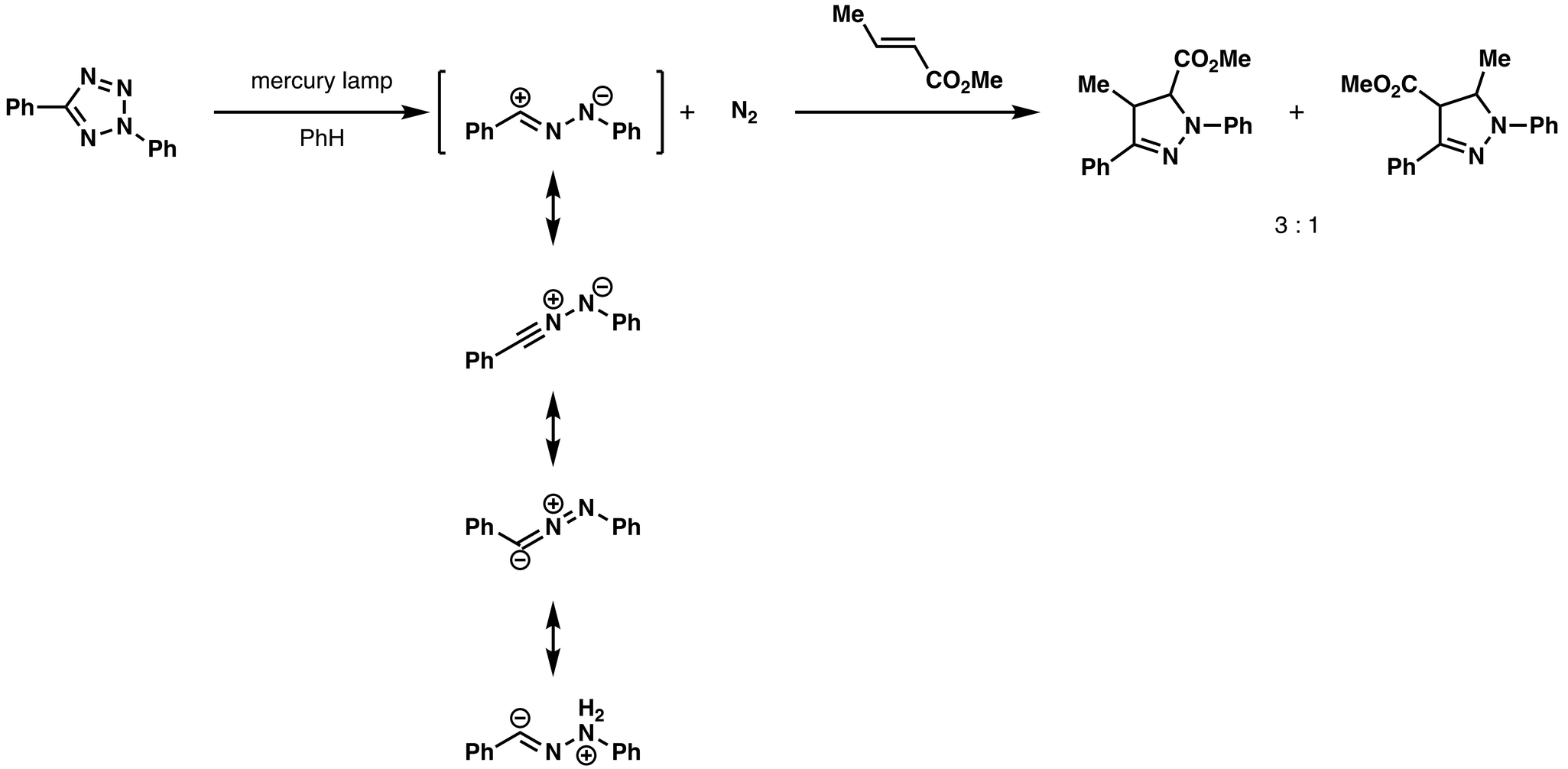


3 : 1

Hantzsch, A.; Vagt, A. *Justus Liebigs Ann. Chem.* **1901**, *314*, 339

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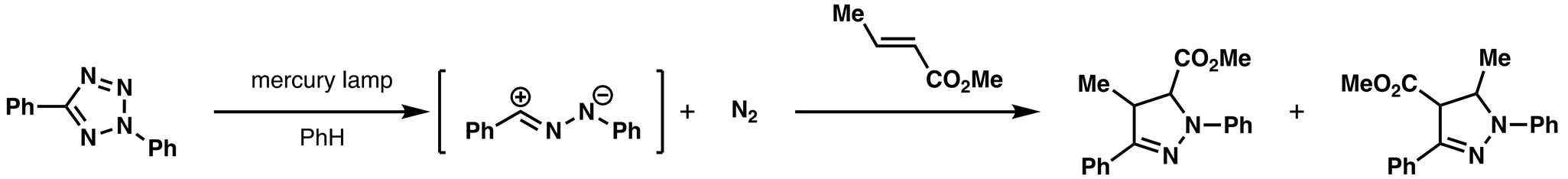
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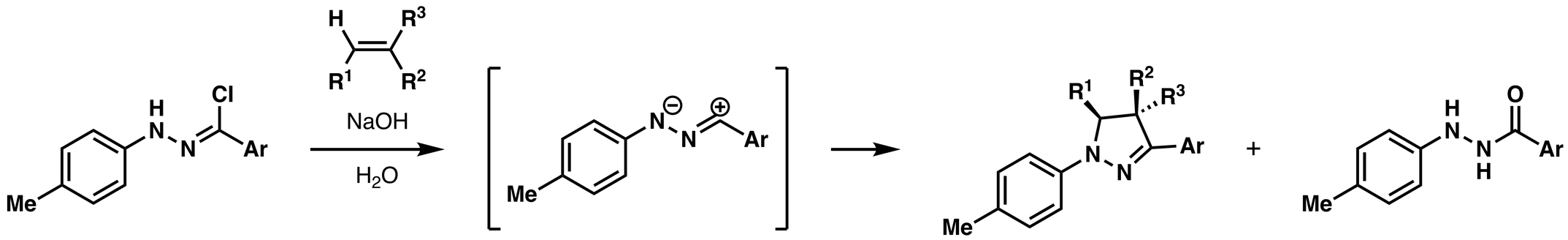


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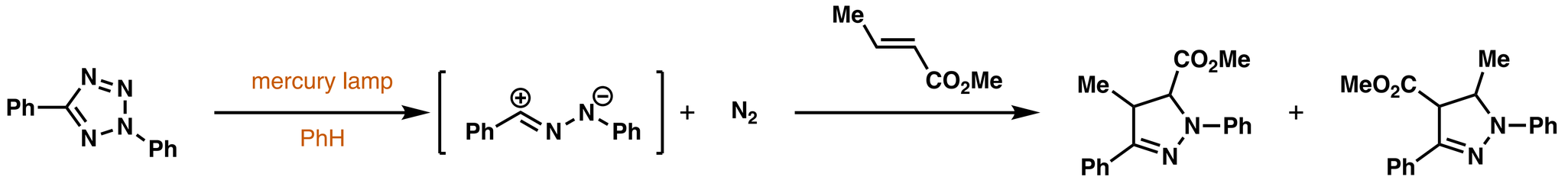


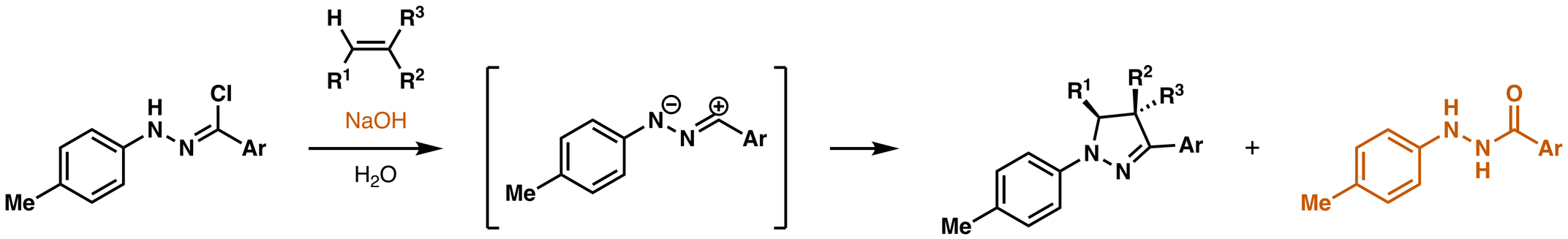


Hantzsch, A.; Vagt, A. *Justus Liebigs Ann. Chem.* **1901**, *314*, 339
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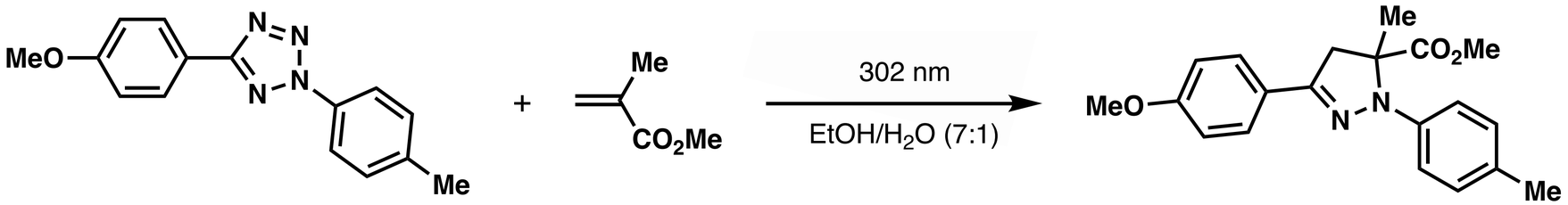




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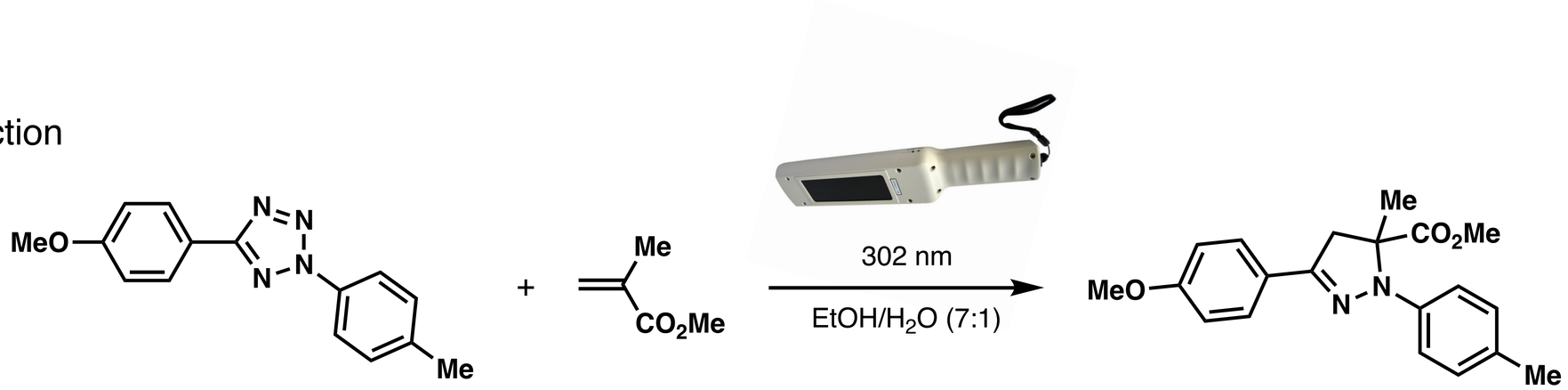
- First click reaction



Wang, X. S.; Liu,W. S. R. *Chem. Commun.* **2014**, *50*, 3176

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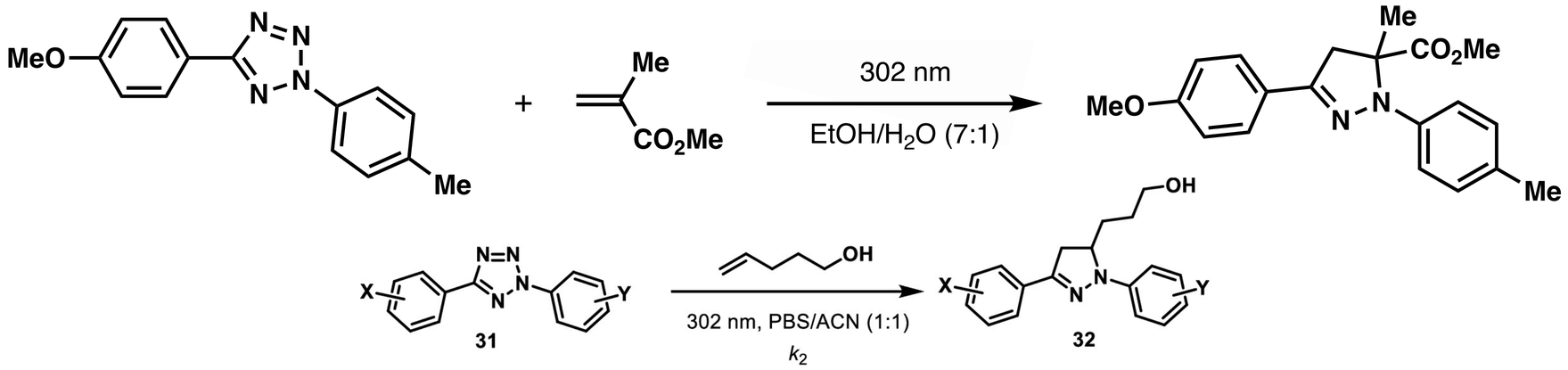
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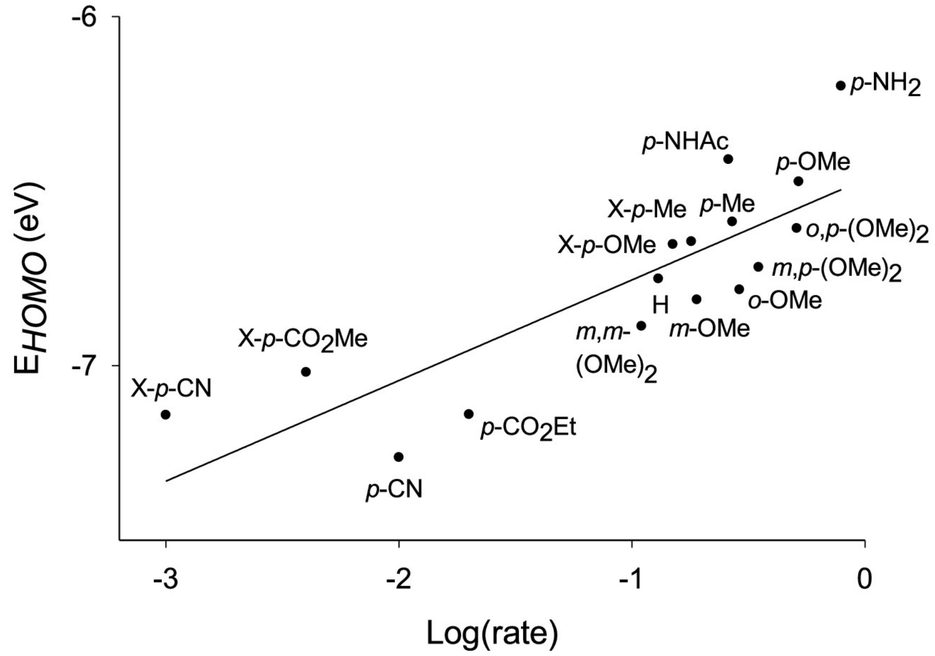


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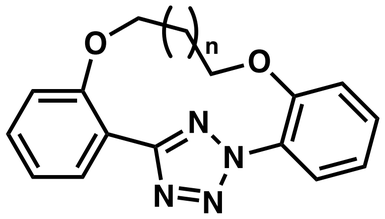




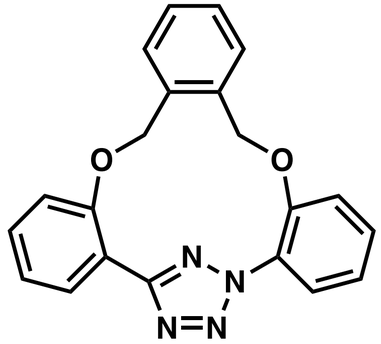
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Nitrile imine-mediated tetrazole–alkene cycloaddition (NITEC)

- Bioorthogonal tetrazole-alkene cycloaddition with strained macrocyclic tetrazoles



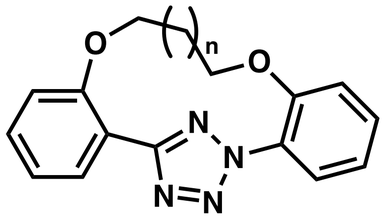
n=1, 2, 3, 4



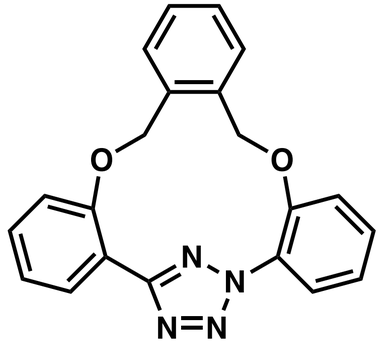
Yu, Z.; Lin, Q. *Chem. -Eur. J.* **2010**, *16*, 13325

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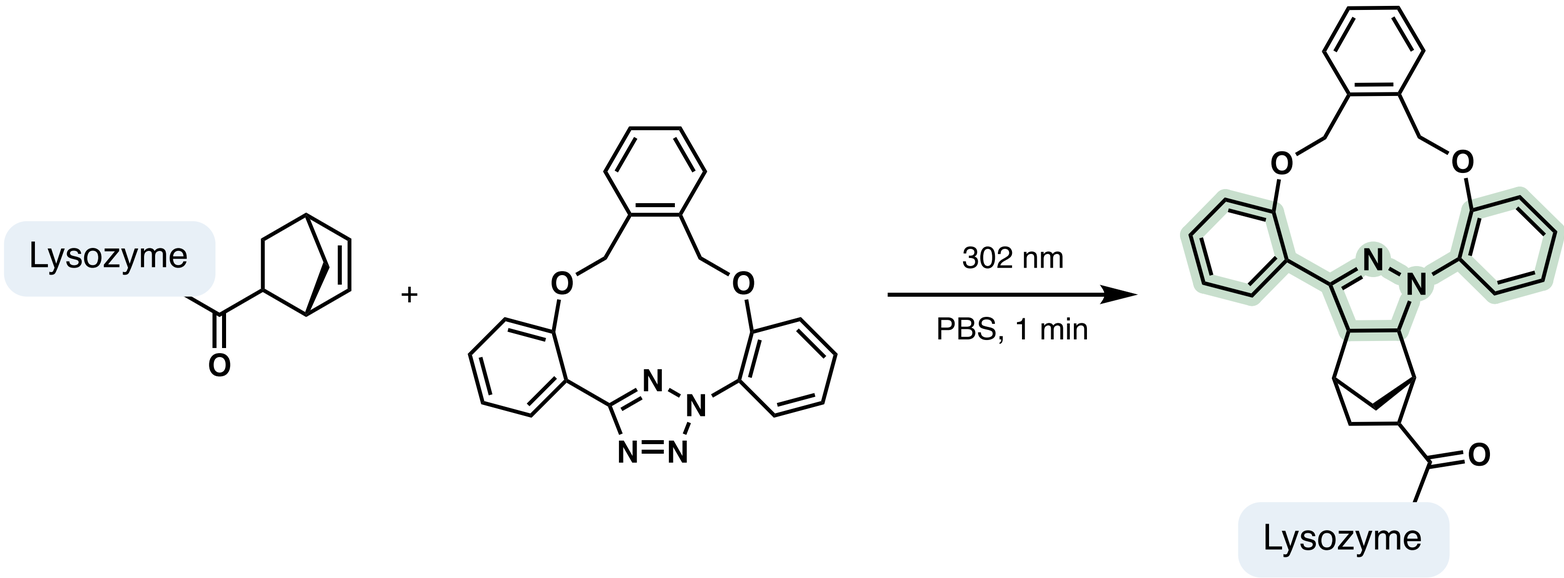
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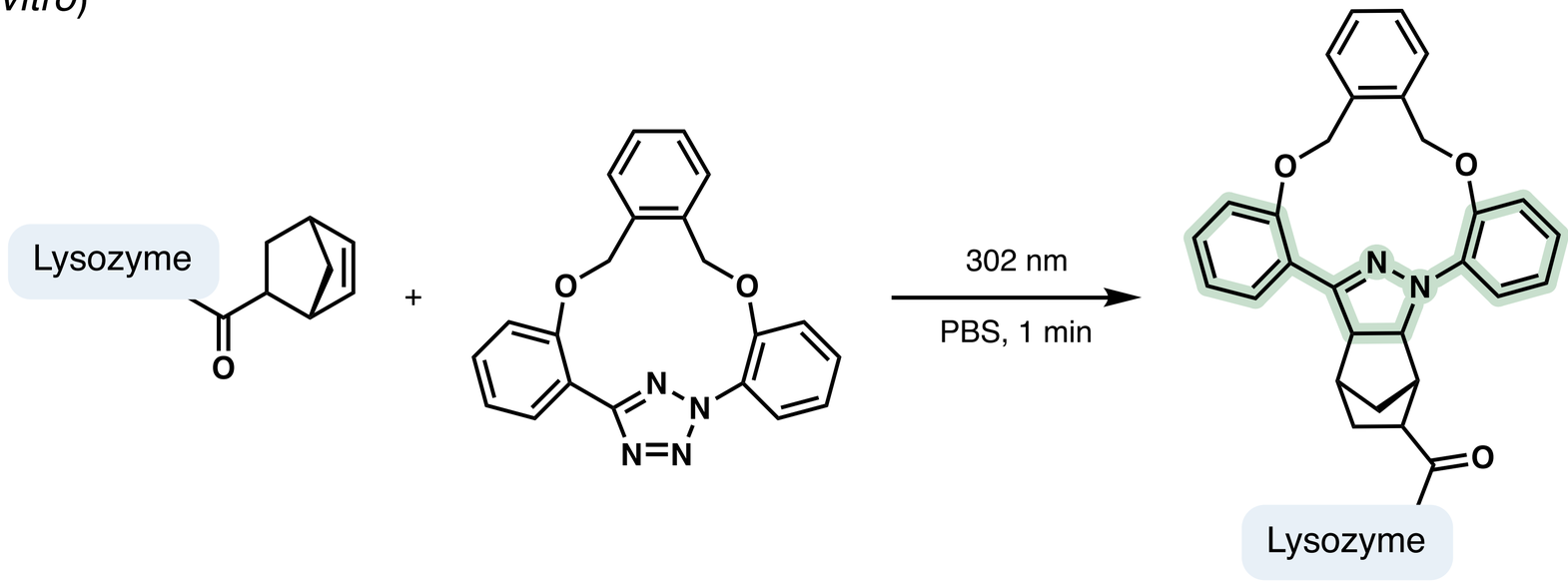
- Protein labeling (*in vitro*)

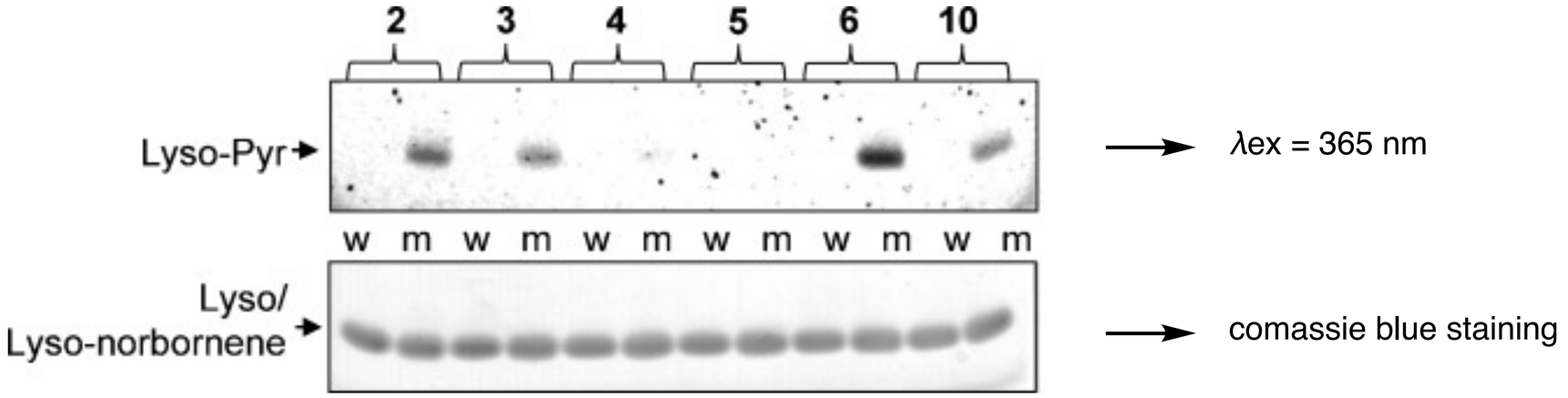


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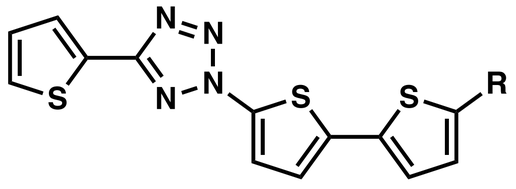




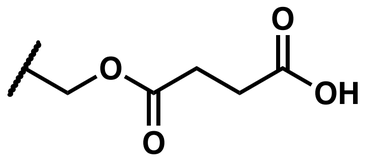
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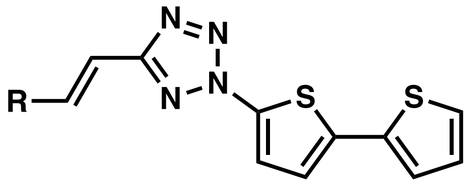
- Bioorthogonal tetrazole-alkene cycloaddition under visible light with elongated conjugation



R=H,

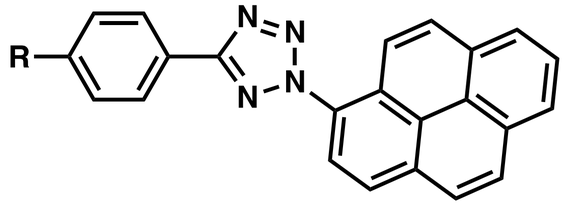


405 nm



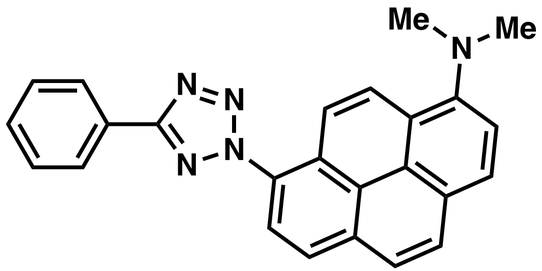
R = Aryl, elongated aryl

405 nm



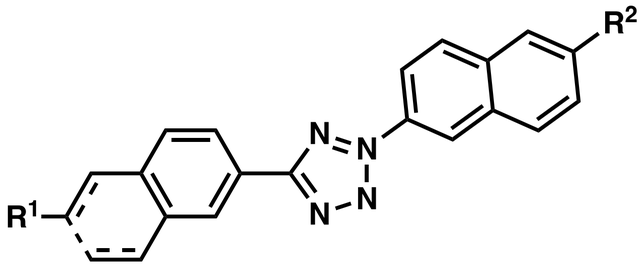
R = Aryl, elongated aryl

410-420 nm



R = Aryl, elongated aryl

320-515 nm

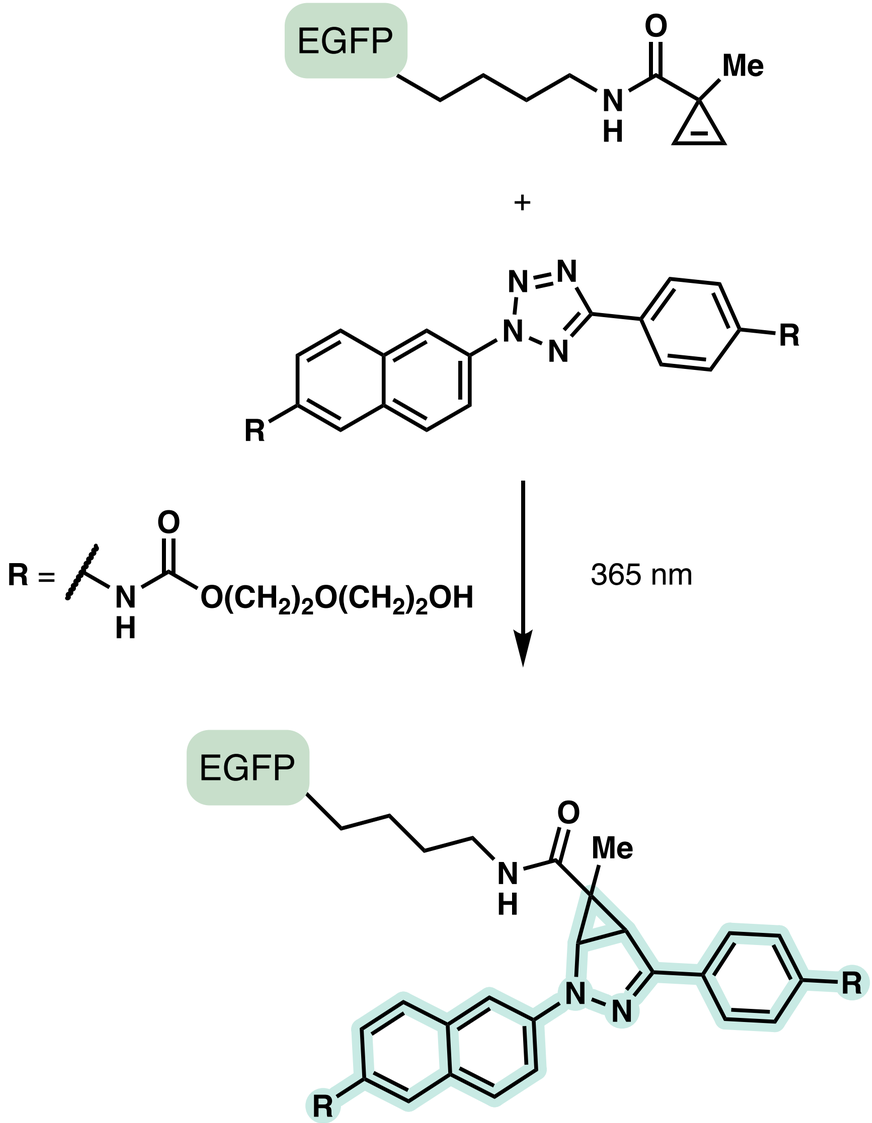


700 nm

Kumar, G. S.; Lin, Q. *Chem. Rev.* **2021**, *121*, 6991

Nitrile imine-mediated tetrazole–alkene cycloaddition (NITEC)

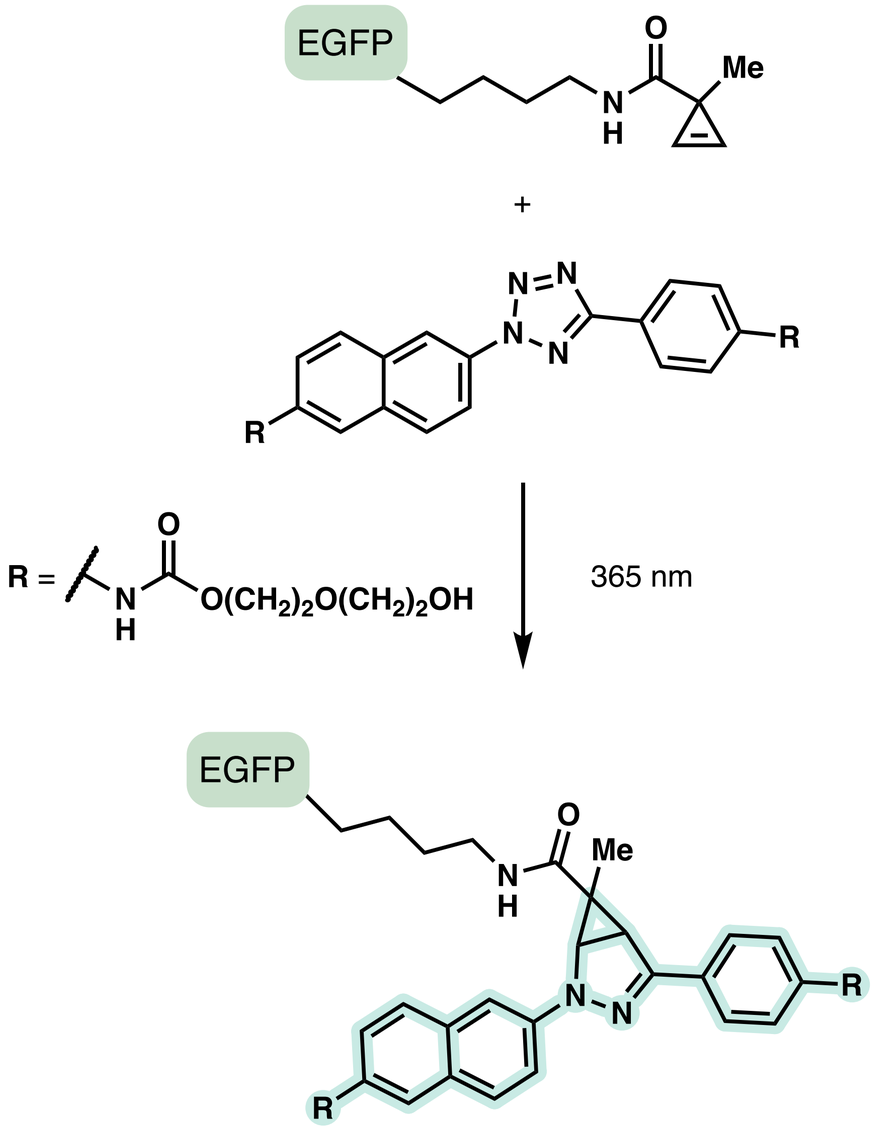
- Biological application to human embryonic mammalian cells (*in vivo*)

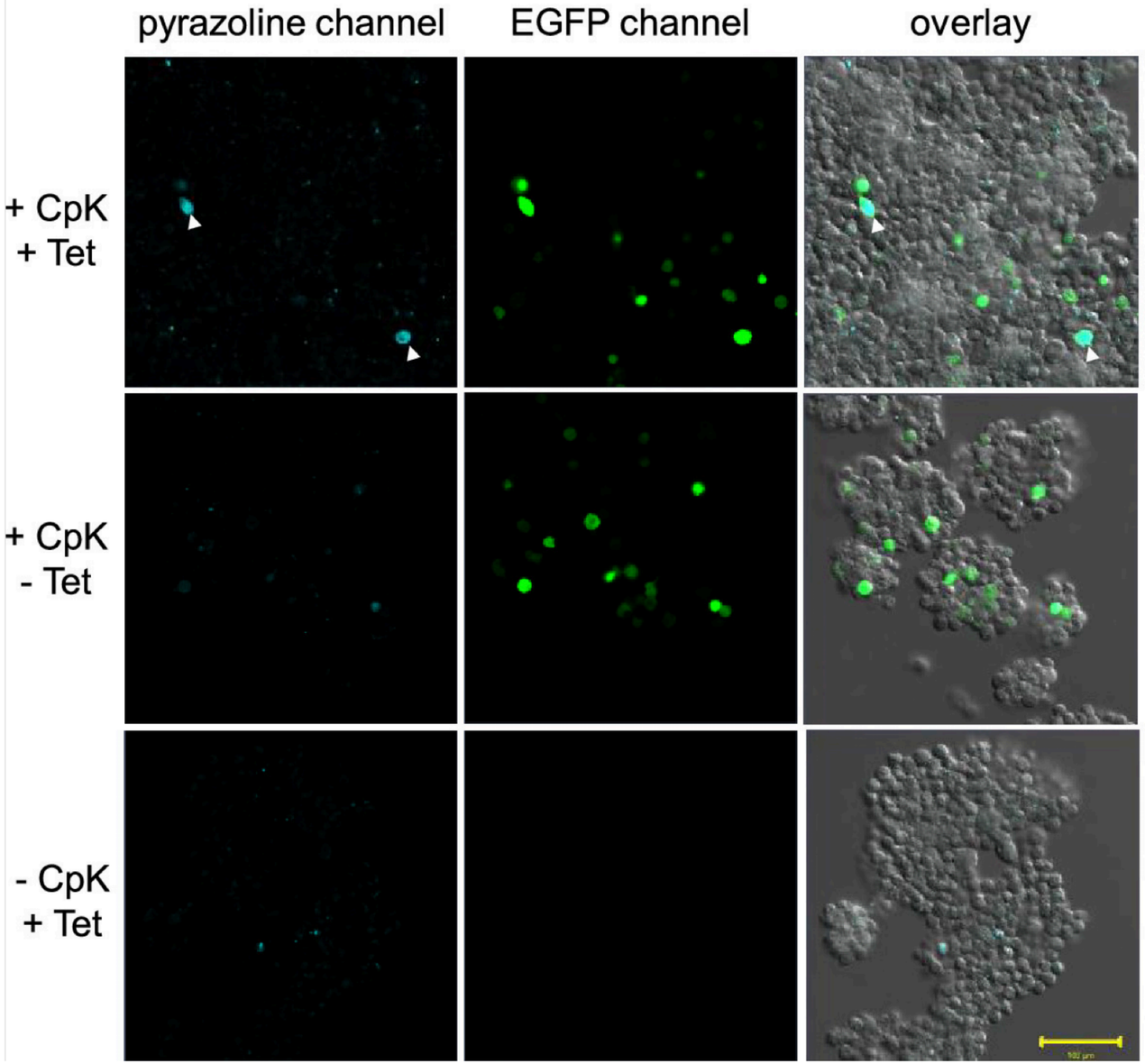


Yu, Z.; Lin, Q. *Angew. Chem. Int. Ed.* **2012**, *51*, 10600

Nitrile imine-mediated tetrazole–alkene cycloaddition (NITEC)

- Biological application to human embryonic mammalian cells (*in vivo*)

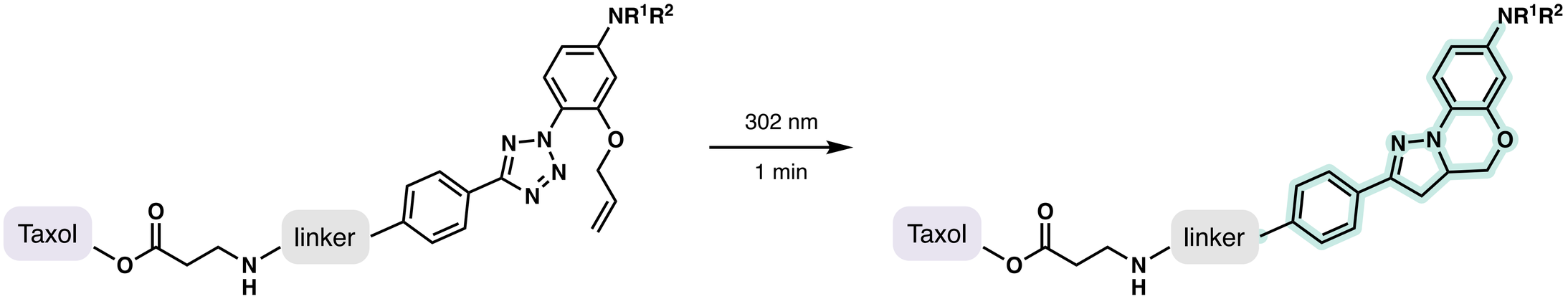


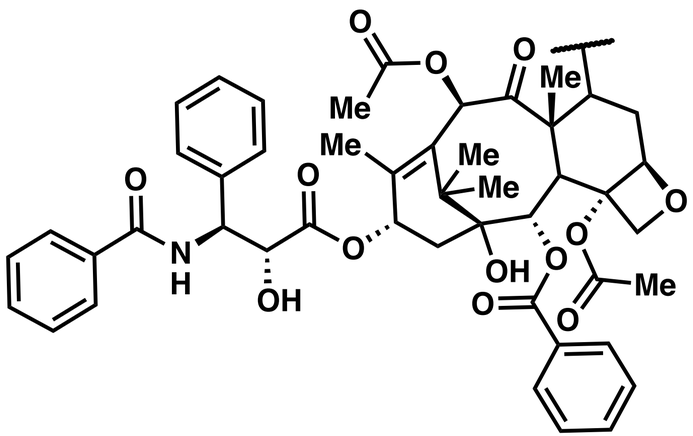


Yu, Z.; Lin, Q. *Angew. Chem. Int. Ed.* **2012**, *51*, 10600

Nitrile imine-mediated tetrazole–alkene cycloaddition (NITEC)

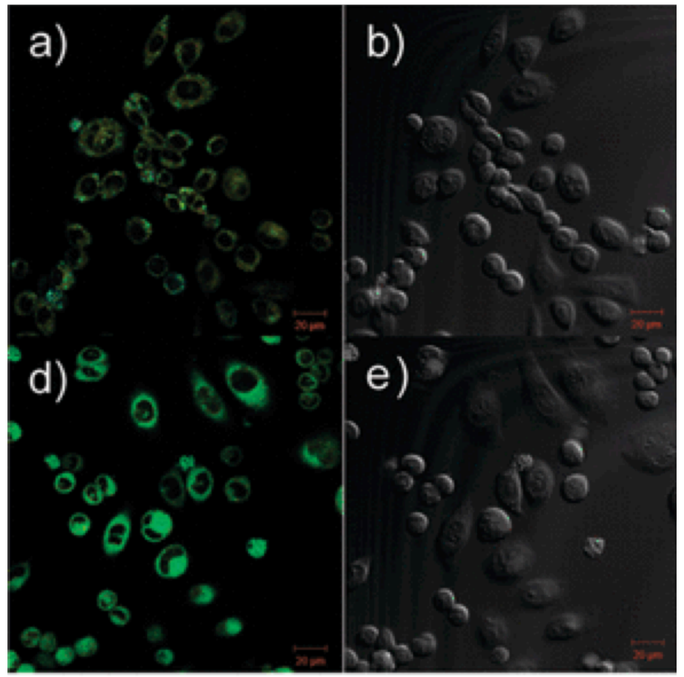
- Chemosensor (fluorescent probes *in situ* for cytosolic microtubules)





=

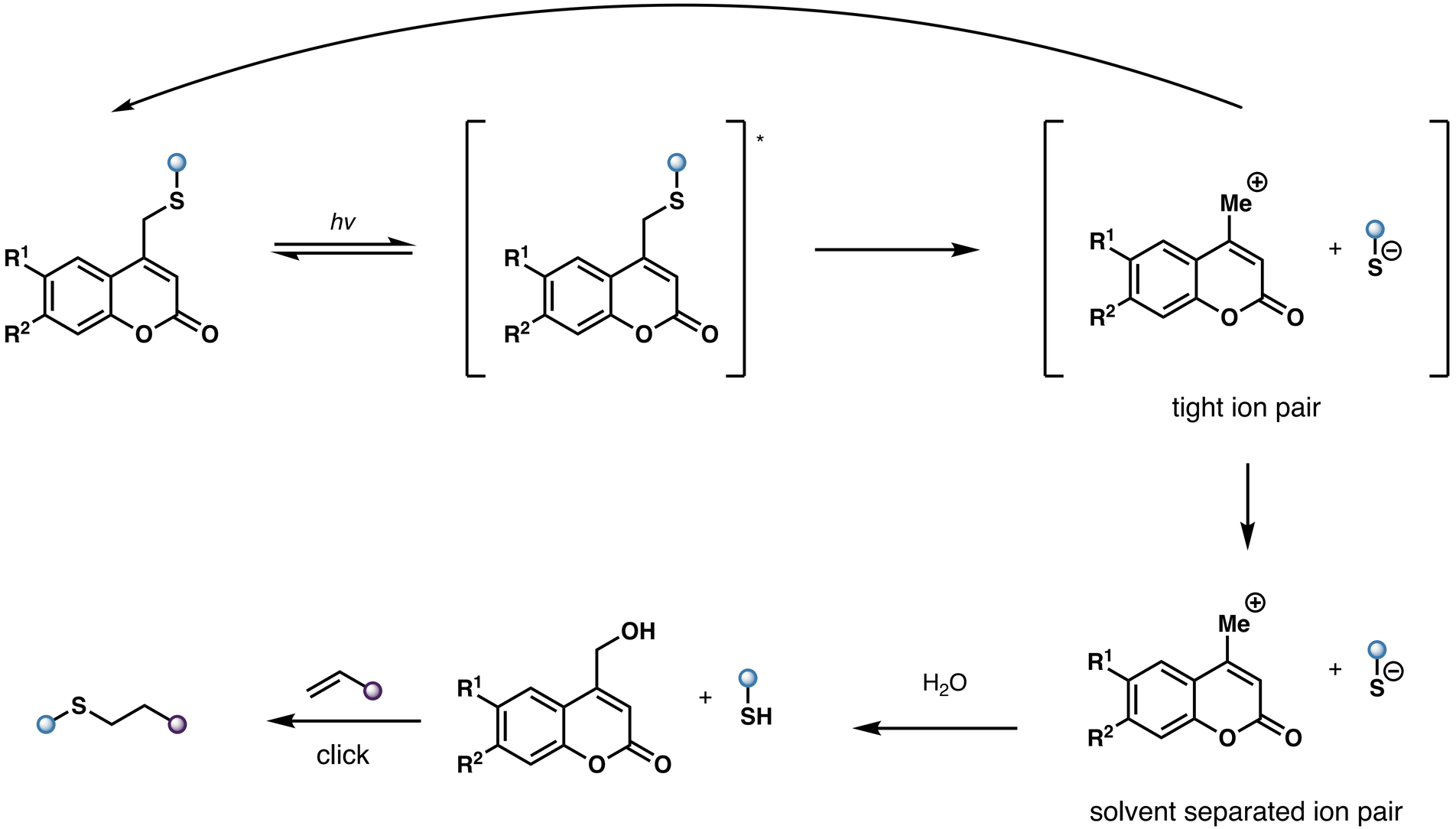
Taxol



Yu, Z.; Lin, Q. *J. Am. Chem. Soc.* **2011**, *133*, 11912

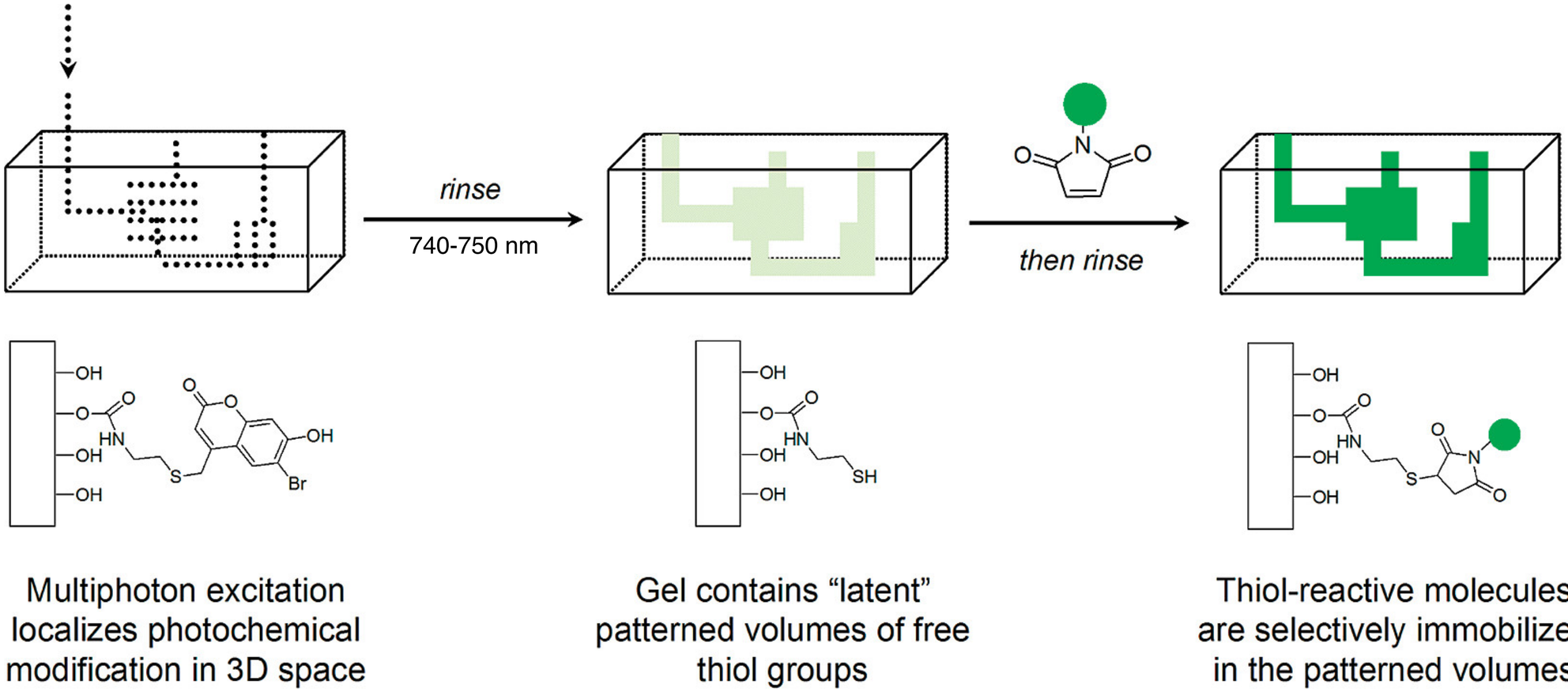
Photoreleasable thiol-ene reaction

- General mechanism



Photoreleasable thiol-ene reaction

- Photochemical patterning of hydrogels



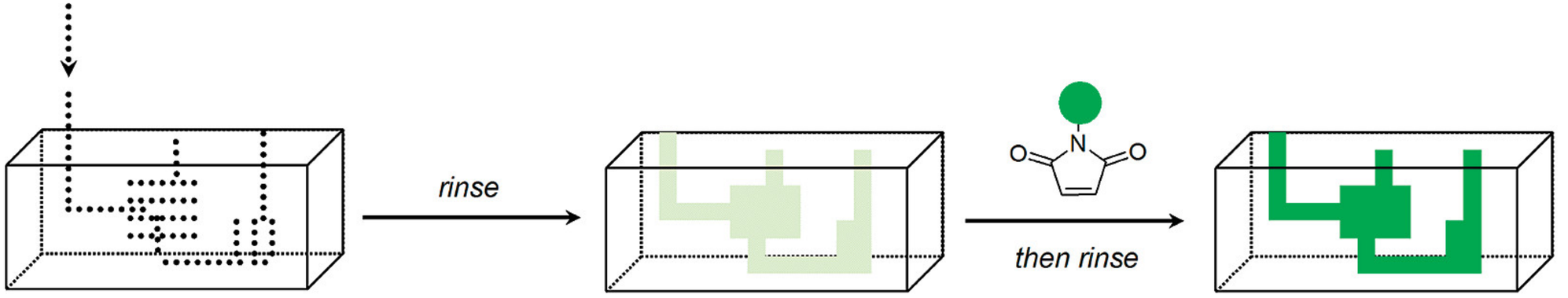
Multiphoton excitation localizes photochemical modification in 3D space

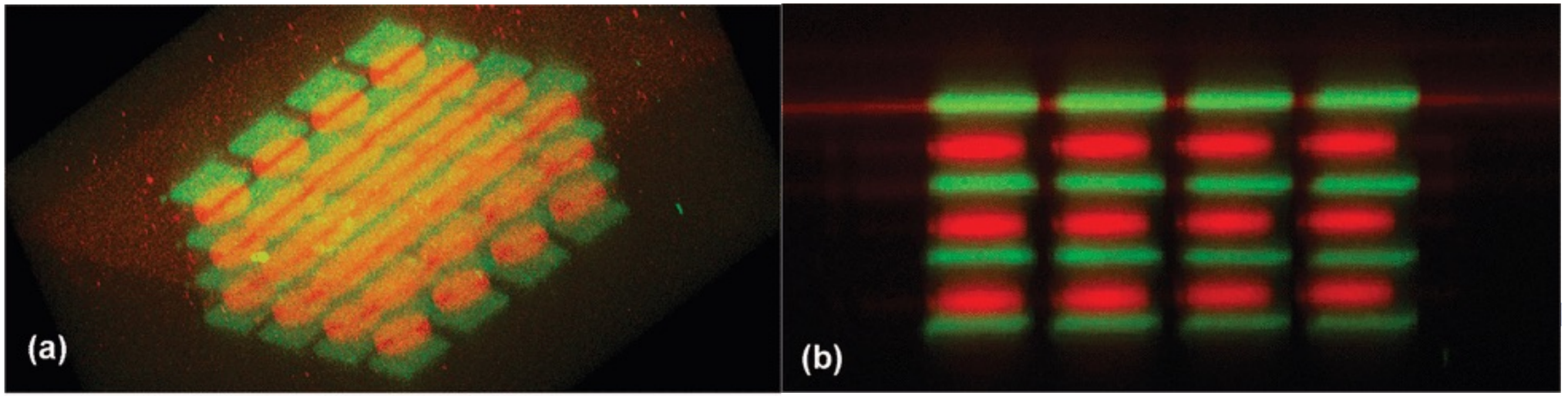
Gel contains “latent” patterned volumes of free thiol groups

Thiol-reactive molecules are selectively immobilized in the patterned volumes

Wosnick, J., H.; Soichet, M. S. *Chem. Mater.* **2008**, *20*, 55

Photoreleasable thiol-ene reaction

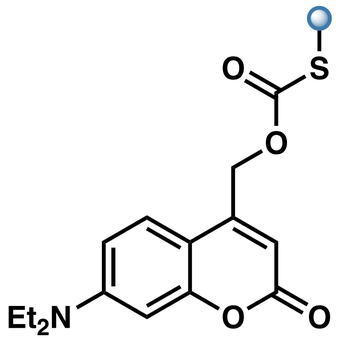




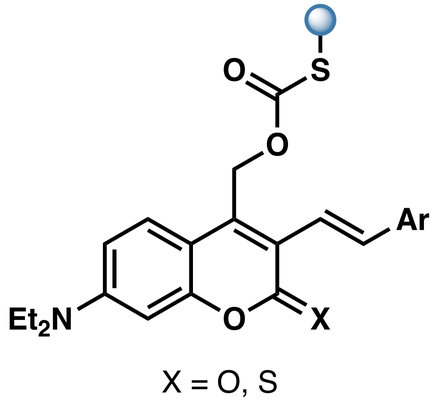
Wosnick, J., H.; Soichet, M. S. *Chem. Mater.* **2008**, *20*, 55

Photoreleasable thiol-ene reaction

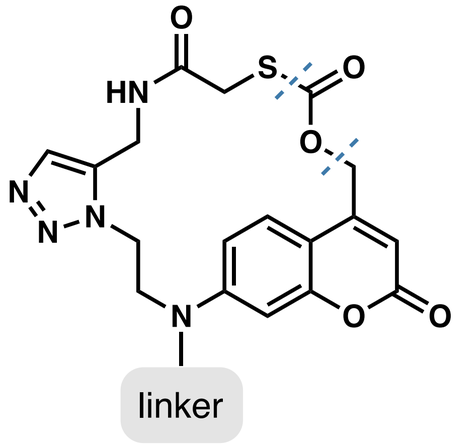
- Other coumarin based photoreleasable protecting group



420 nm



405-450 nm

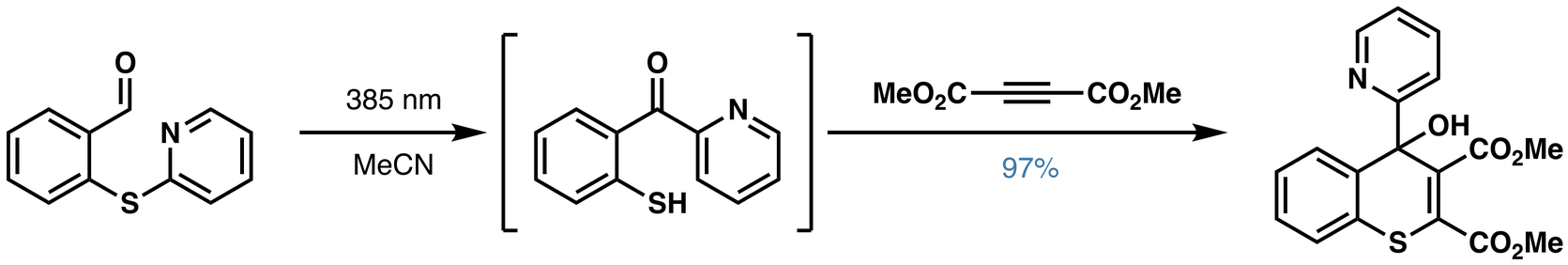


405 nm

Liu, Z; Zhu, L. *Chem. Commun.* **2014**, *50*, 1256
Liu, Z; Zhu, L. *Adv. Mater.* **2014**, *26*, 3912
Lin, Q; Zhu, L. Angew. Chem. Int. Ed. **2018**, *57*, 3772

Photoreleasable thiol-ene reaction

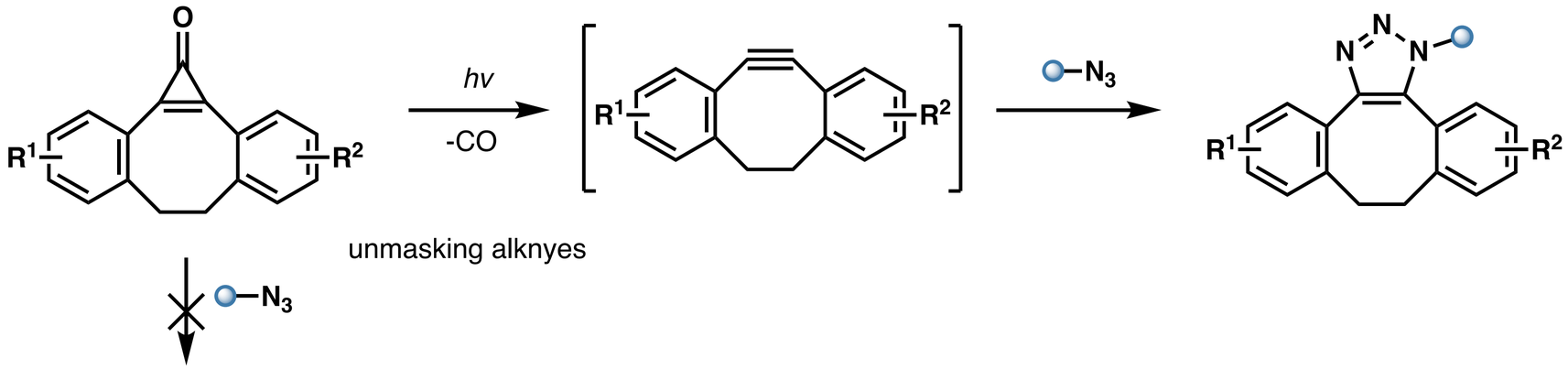
- Photorearrangement



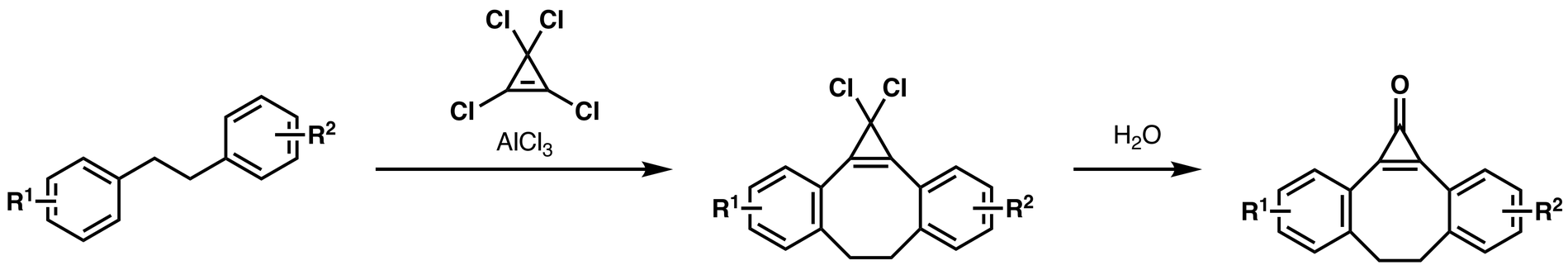
Rodrigues, L. L.; Kowollik, C. *J. Am. Chem. Soc.* **2021**, *143*, 7292

Strain-promoted azide-alkyne cycloaddition (SPAAC)

- General reactivity



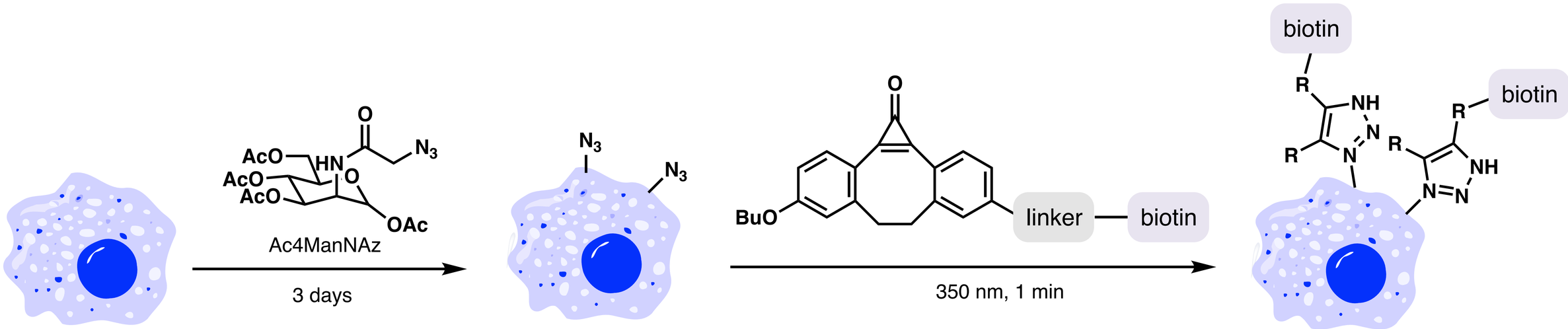
- Synthesis of cyclopropenones



Poloukhtin, A. A.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 15769

Strain-protmoted azide-alkyne cycloaddition (SPAAC)

- Visualization of glycoconjugates of cells



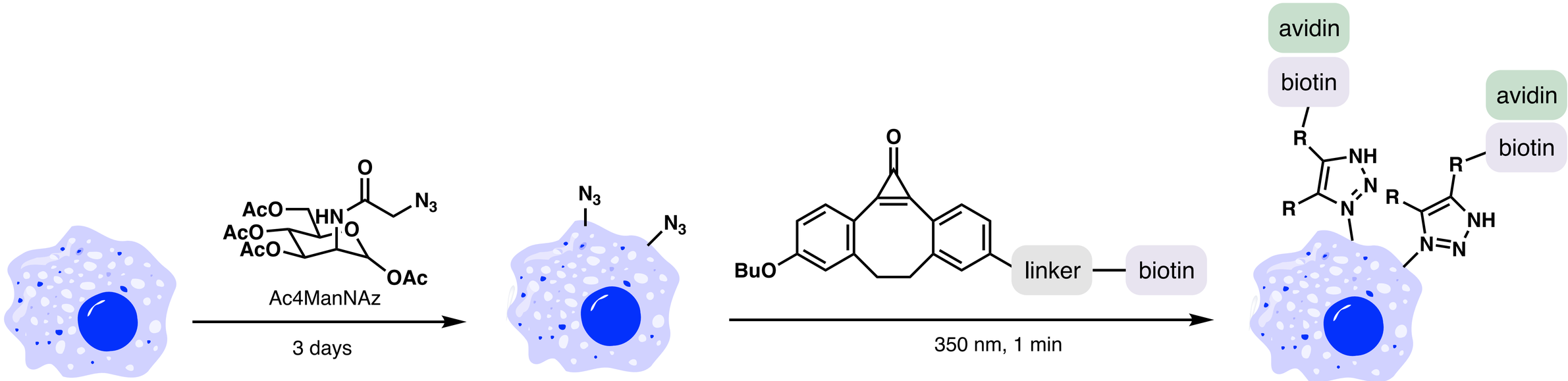
Chinese hamster ovary (CHO) cells

CHO cells with azido-cell surface

Poloukhtin, A. A.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 15769

Strain-protmoted azide-alkyne cycloaddition (SPAAC)

- Visualization of glycoconjugates of cells



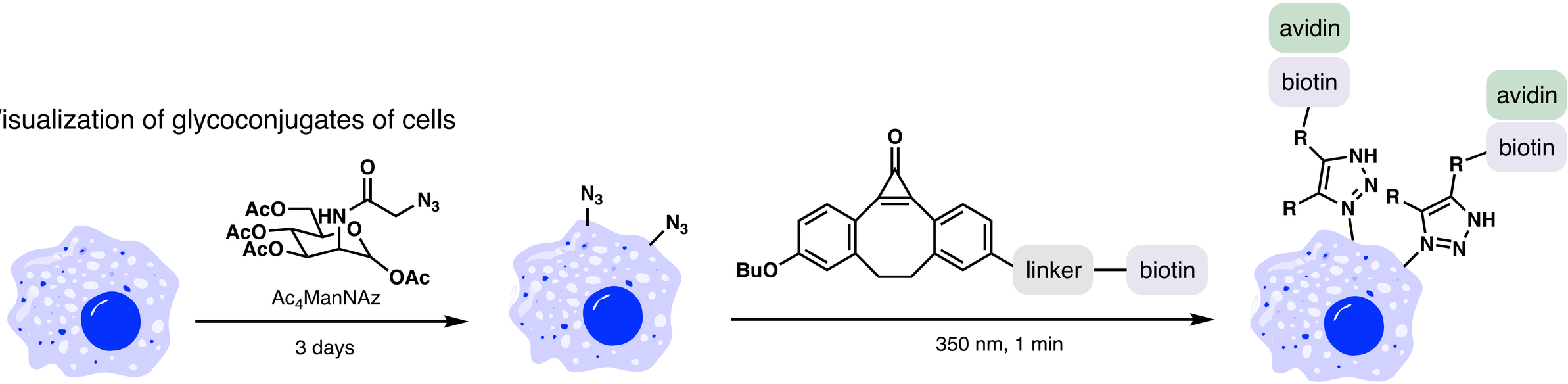
Chinese hamster ovary (CHO) cells

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Poloukhtin, A. A.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 15769

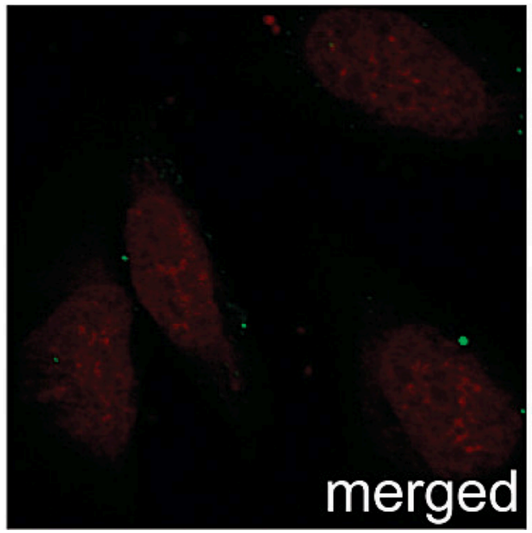
Strain-protmoted azide-alkyne cycloaddition (SPAAC)

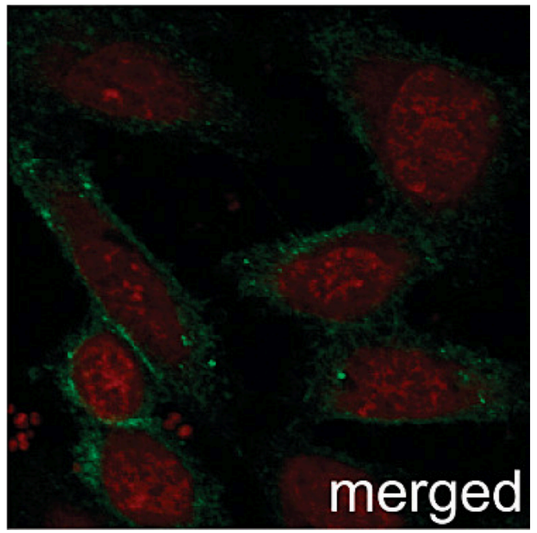
- Visualization of glycoconjugates of cells



Chinese hamster ovary (CHO) cells

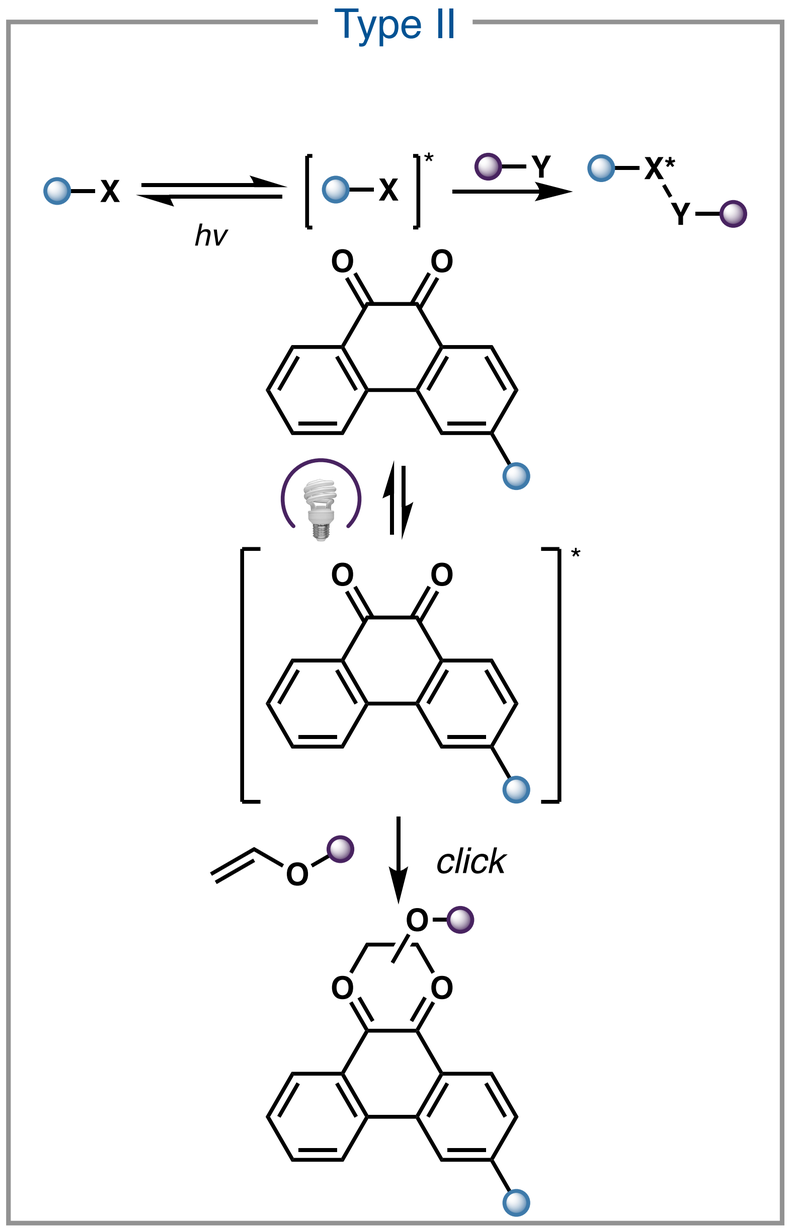
CHO cells with azido-cell surface





Poloukhtin, A. A.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 15769

Types of photoclick reactions

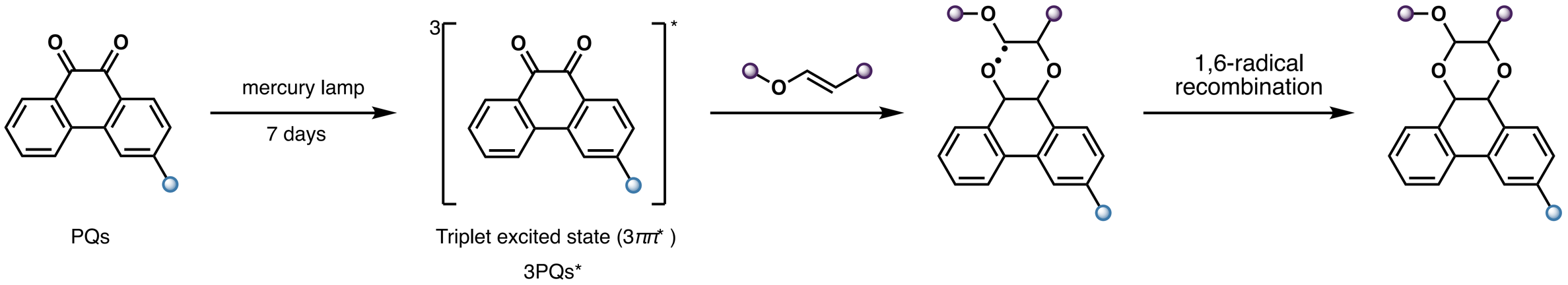


- Cycloaddition of phenathrenequinone
- ligations of o-quinodimethanes

Kumar, G. S.; Lin, Q. *Chem. Rev.* **2021**, *121*, 6991

Phenanthrenequinone-electron rich alkene (PQ-ERA) photocyclization

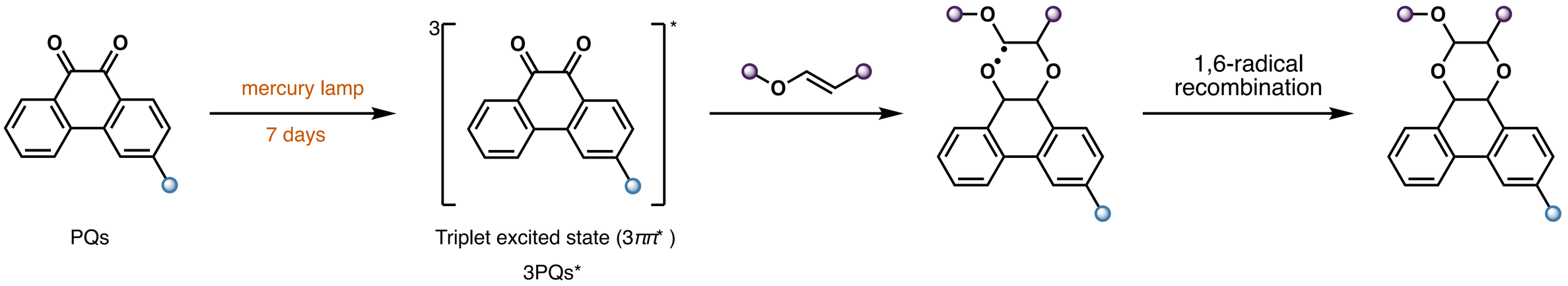
- Early reports on PQ-ERA



Schonberg, A.; Mustafa, A. *Nature* **1944**, *153*, 195
Schonberg, A.; Mustafa, A. *J. Chem. Soc.* **1944**, *387*, 1944

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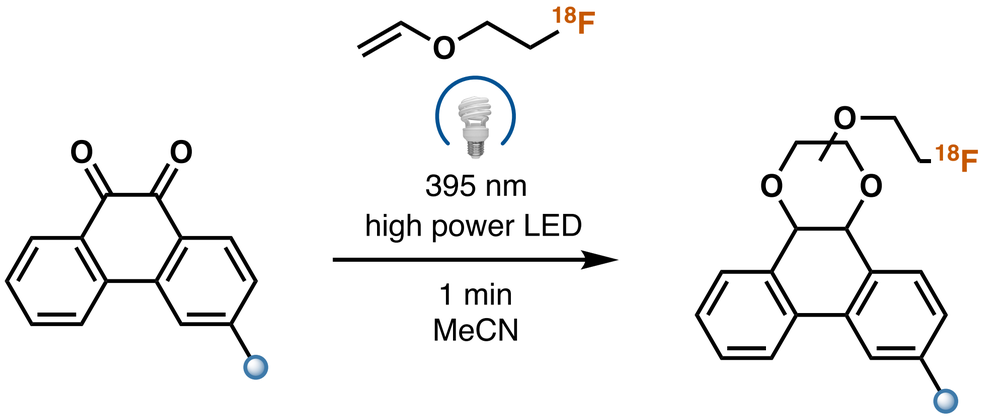
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Schonberg, A.; Mustafa, A. *Nature* **1944**, *153*, 195
Schonberg, A.; Mustafa, A. *J. Chem. Soc.* **1944**, *387*, 1944

Phenanthrenequinone-electron rich alkene (PQ-ERA) photocyclization

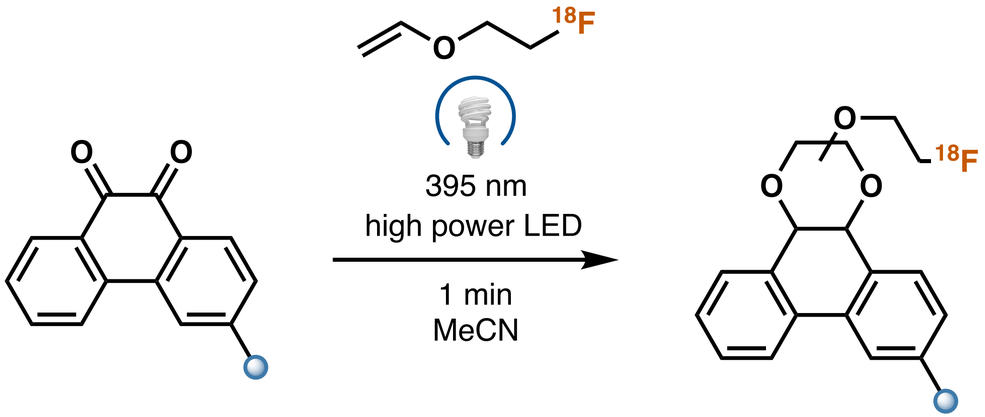
- Isotopic labeling on the tracer for PET(Poistron Emission Tomography)

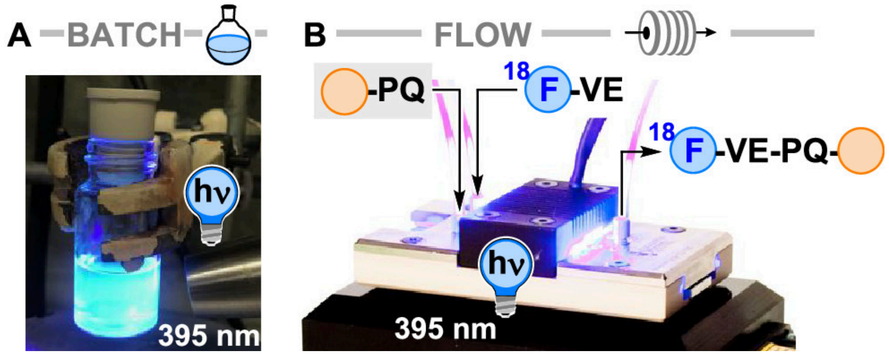


Fu, Y.; Feringa, B. L. *J. Am. Chem. Soc.* **2021**, *143*, 10041

Phenanthrenequinone-electron rich alkene (PQ-ERA) photocyclization

- Isotopic labeling on the tracer for PET(Poistron Emission Tomography)

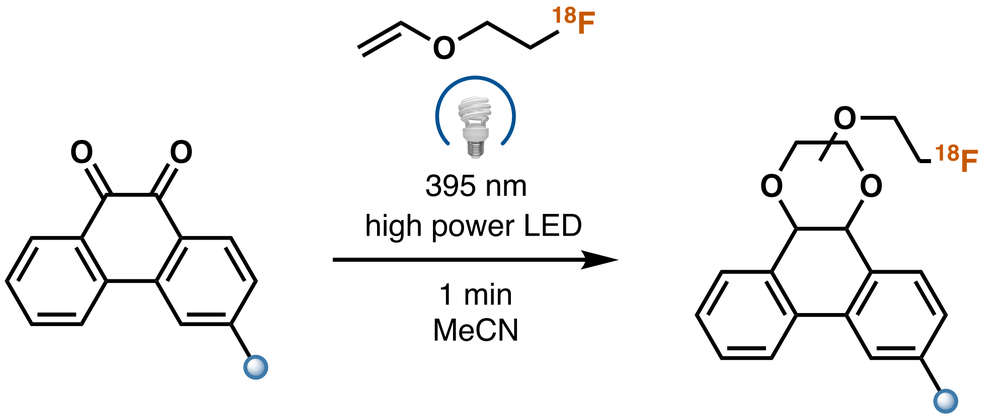


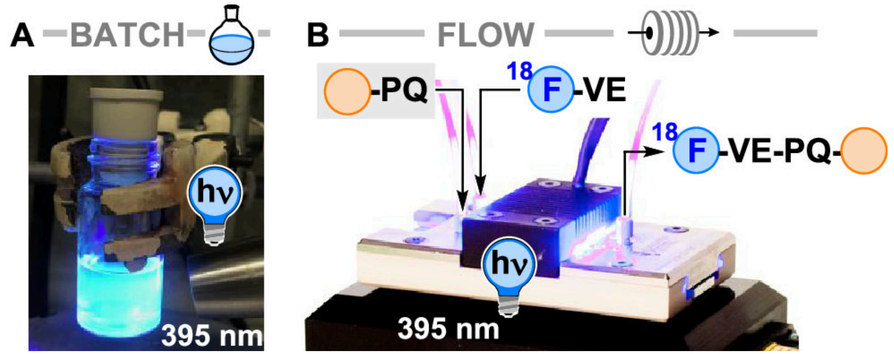


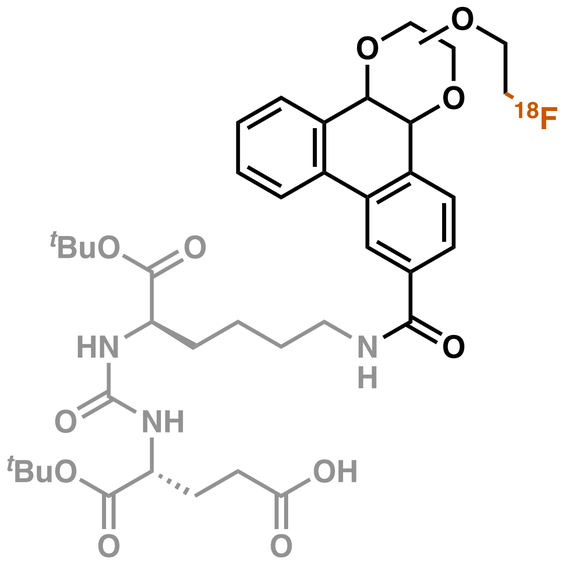
Fu, Y.; Feringa, B. L. *J. Am. Chem. Soc.* **2021**, *143*, 10041

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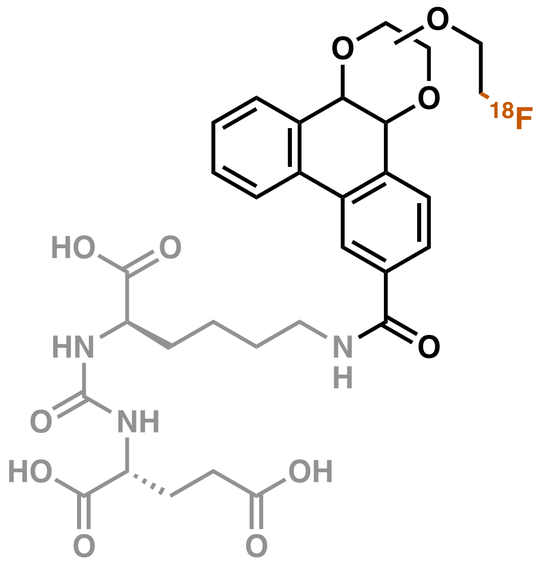
- Isotopic labeling on the tracer for PET(Poistron Emission Tomography)







1 min
flow reaction
52%



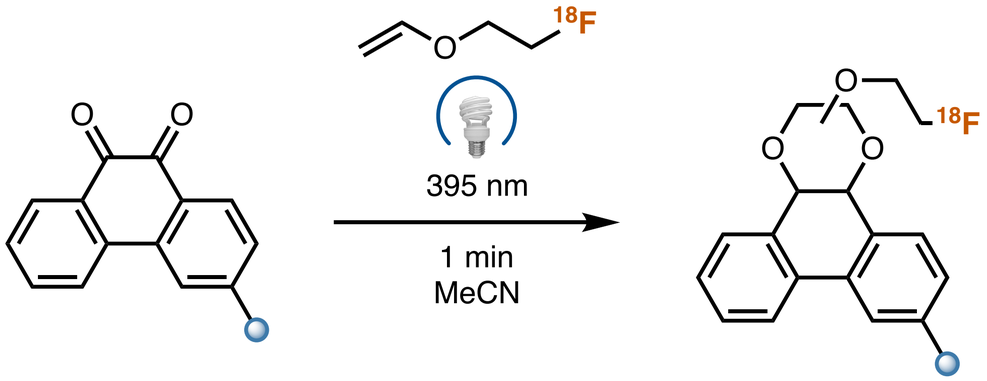
1 min
flow reaction
18%

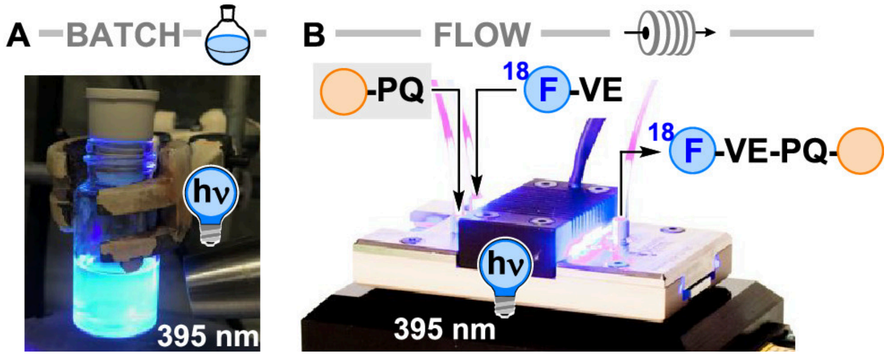
Prostate-specific membrane antigen (PSMA), a biomarker of prostate cancer, binding motifs

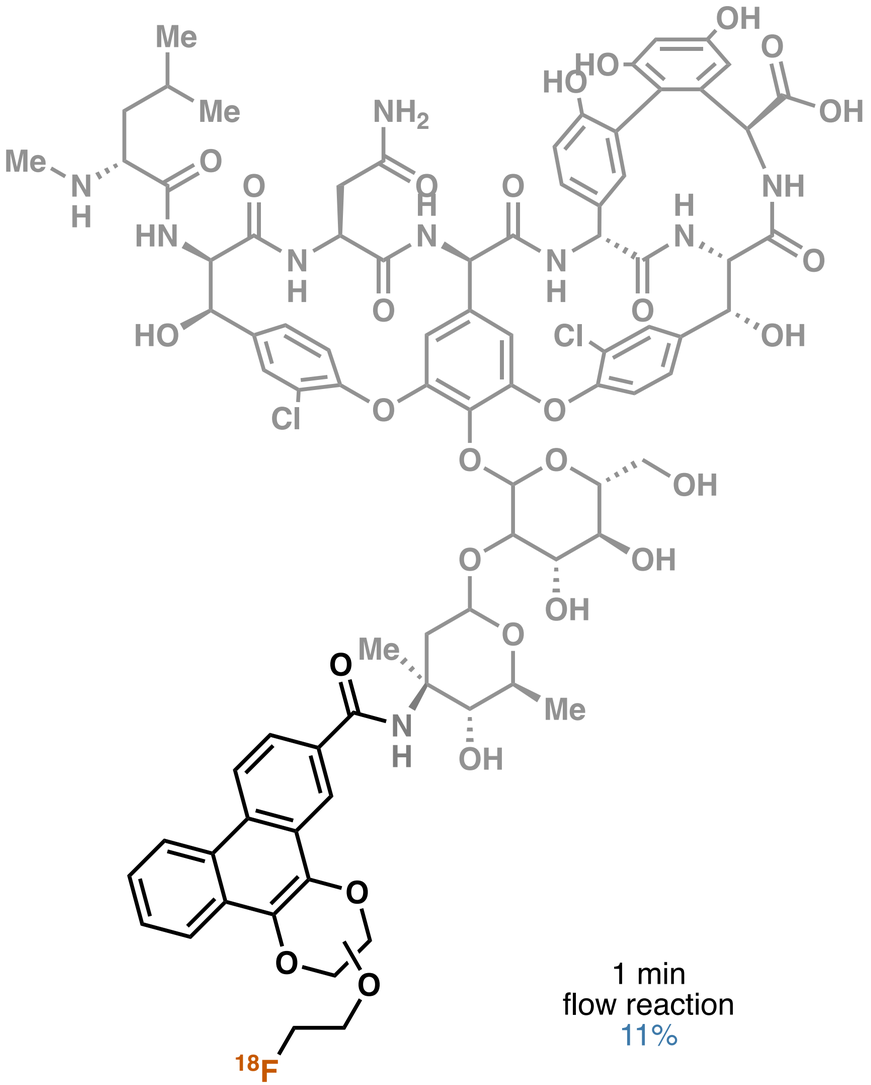
Fu, Y.; Feringa, B. L. *J. Am. Chem. Soc.* **2021**, *143*, 10041

Phenanthrenequinone-electron rich alkene (PQ-ERA) photocyclization

- Isotopic labeling on the tracer for PET(Poistron Emission Tomography)





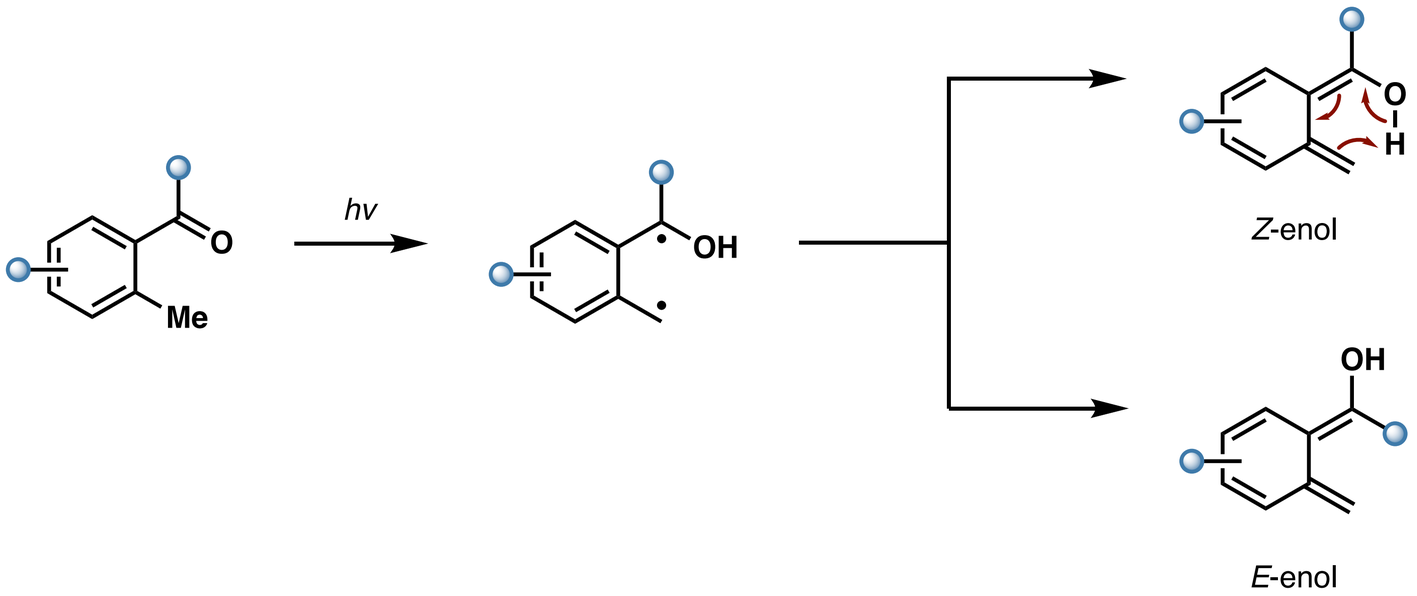


Fu, Y.; Feringa, B. L. *J. Am. Chem. Soc.* **2021**, *143*, 10041

Detecting bacterial infections

Ligation of o-quinodimethanes

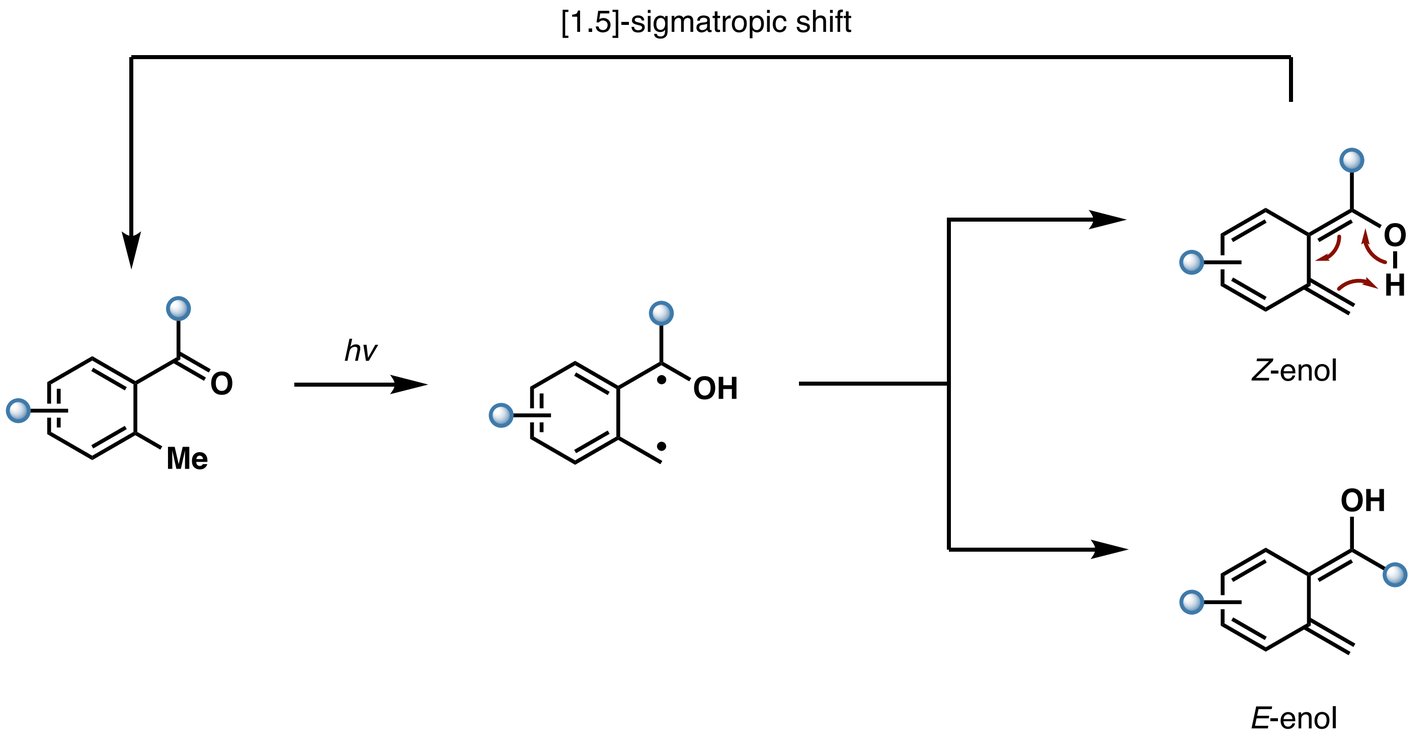
- Light-induced Diels-Alder reactions



Gruendling, T.; Kowollik, C. *Macromol. Rapid Commun.* **2011**, *32*, 807

Ligation of o-quinodimethanes

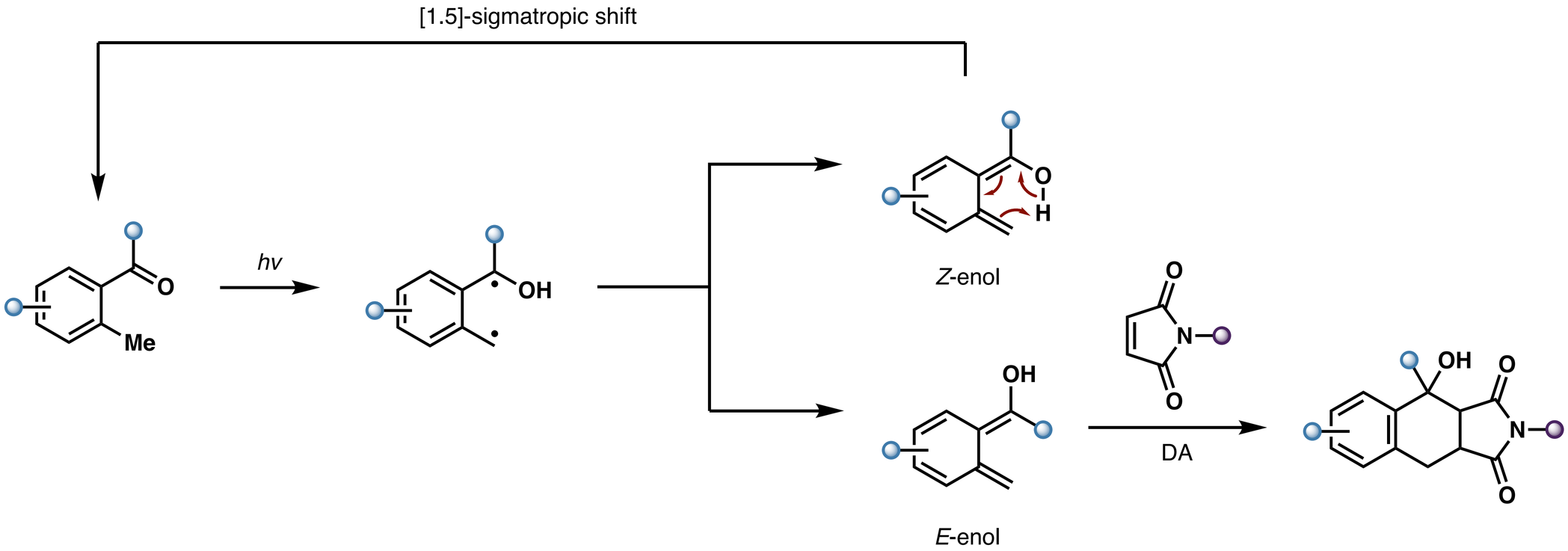
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Gruendling, T.; Kowollik, C. *Macromol. Rapid Commun.* **2011**, *32*, 807

Ligation of o-quinodimethanes

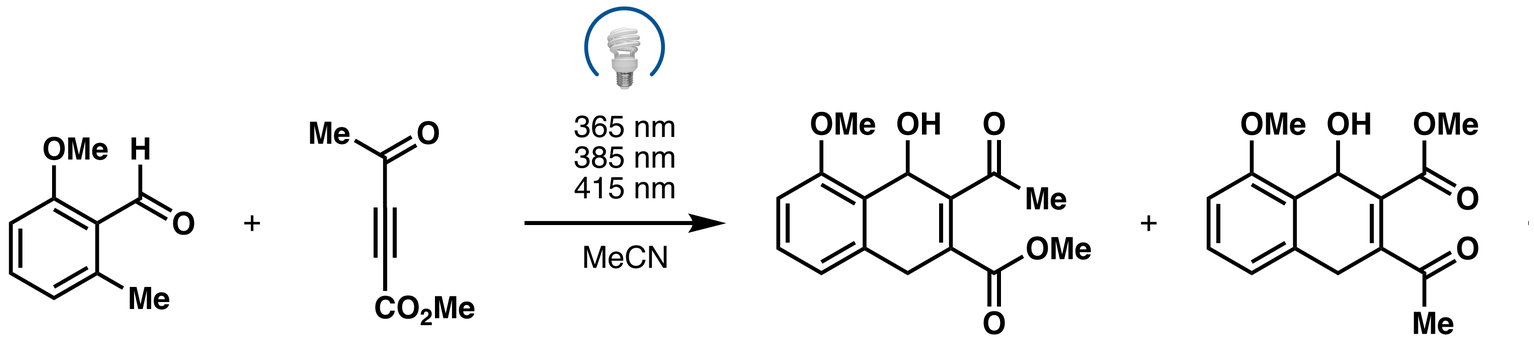
- Light-induced Diels-Alder reactions



Gruendling, T.; Kowollik, C. *Macromol. Rapid Commun.* **2011**, *32*, 807

Ligation of o-quinodimethanes

- Gated Fluorescence from the DA

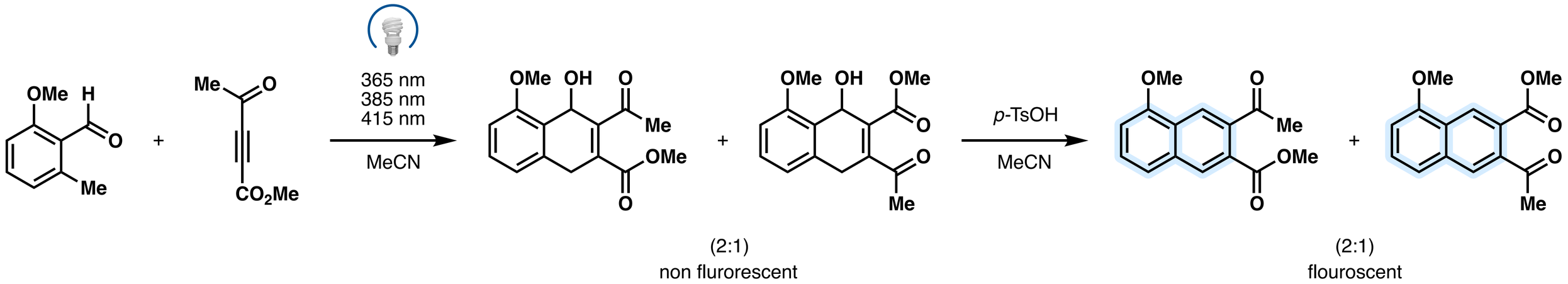


(2:1)
non flurorescent

Feist, F.; Kowollik, C. *J. Am. Chem. Soc.* **2020**, *142*, 7744
Villabona, M. C.; Kowollik, C. *Org. Lett.* **2021**, *23*, 2405

Ligation of o-quinodimethanes

- Gated Fluorescence from the DA



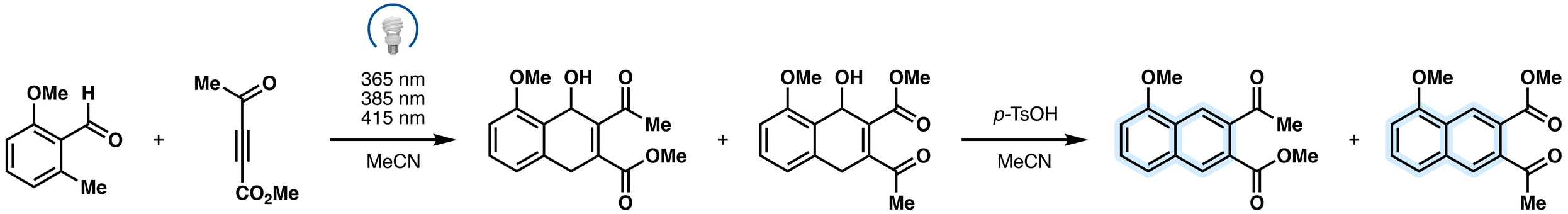
(2:1)
non flurorescent

(2:1)
flouroscent

Feist, F.; Kowollik, C. *J. Am. Chem. Soc.* **2020**, *142*, 7744
Villabona, M. C.; Kowollik, C. *Org. Lett.* **2021**, *23*, 2405

Ligation of o-quinodimethanes

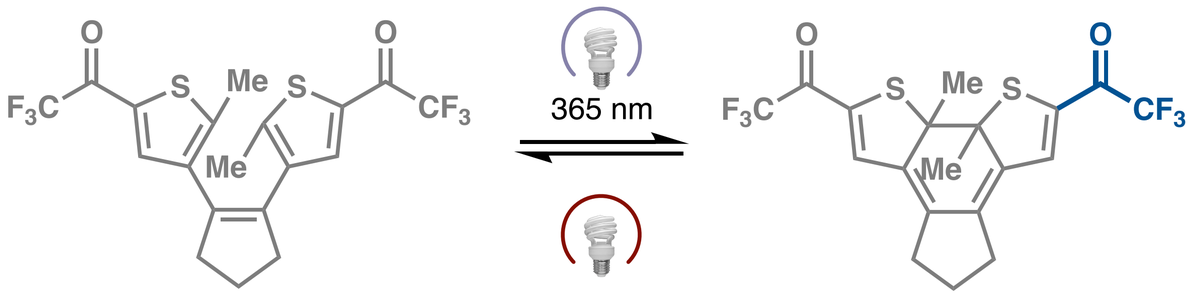
- Gated Fluorescence from the DA



(2:1)
non flurorescent

(2:1)
flouroscent

- Dual-wavelength *oxo*-DA



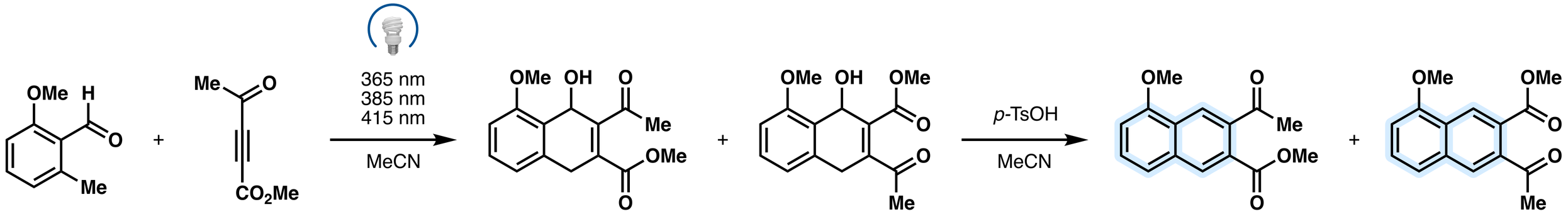
inactive dienophile

active dienophile

Feist, F.; Kowollik, C. *J. Am. Chem. Soc.* **2020**, *142*, 7744
Villabona, M. C.; Kowollik, C. *Org. Lett.* **2021**, *23*, 2405

Ligation of o-quinodimethanes

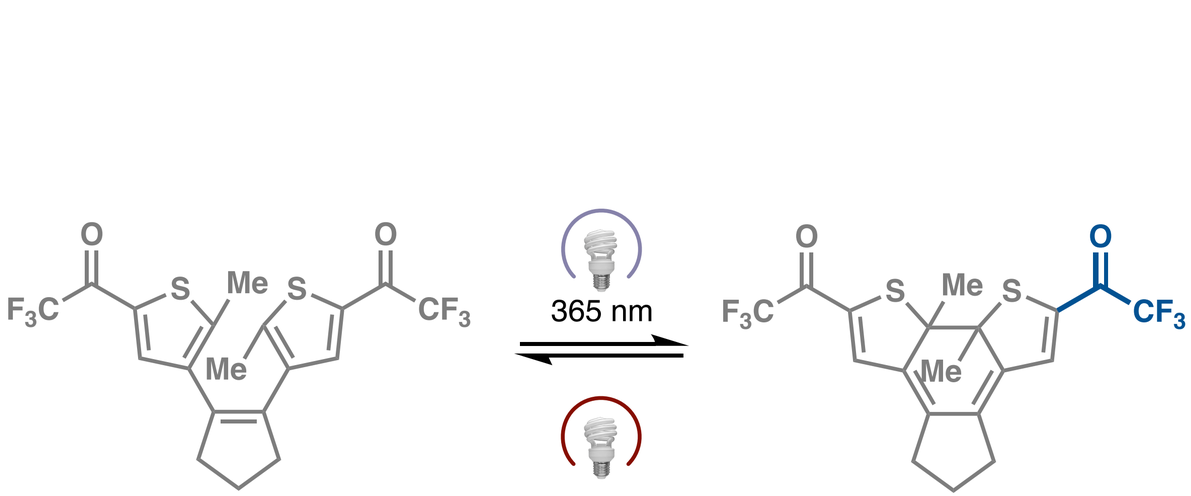
- Gated Fluorescence from the DA



(2:1)
non flurorescent

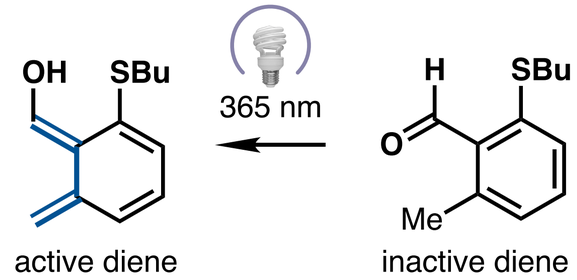
(2:1)
flouroscent

- Dual-wavelength *oxo*-DA



inactive dienophile

active dienophile



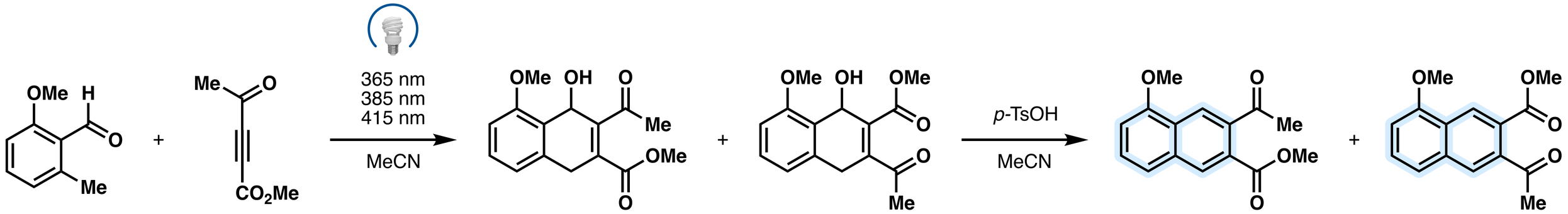
active diene

inactive diene

Feist, F.; Kowollik, C. *J. Am. Chem. Soc.* **2020**, *142*, 7744
Villabona, M. C.; Kowollik, C. *Org. Lett.* **2021**, *23*, 2405

Ligation of o-quinodimethanes

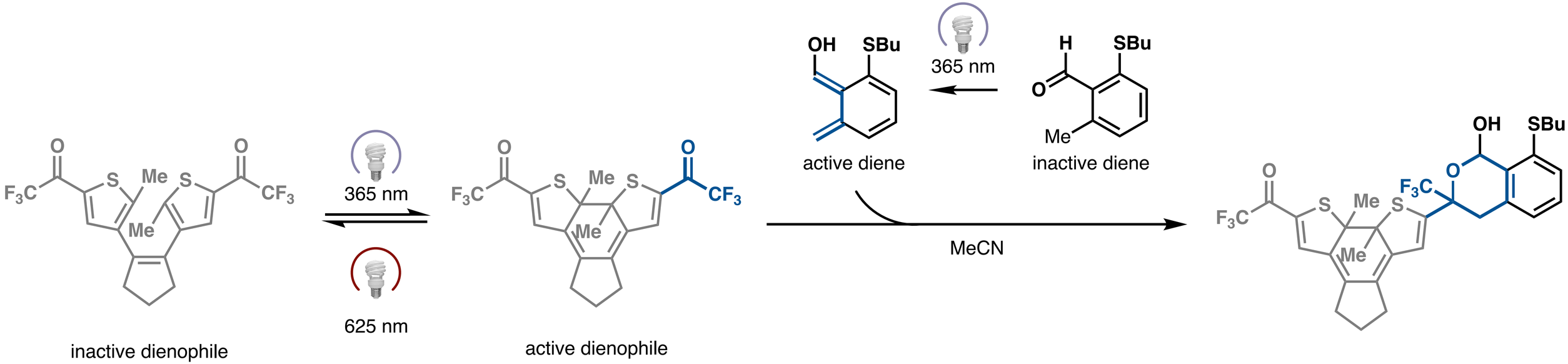
- Gated Fluorescence from the DA



(2:1)
non flurorescent

(2:1)
flouroscent

- Dual-wavelength *oxo*-DA



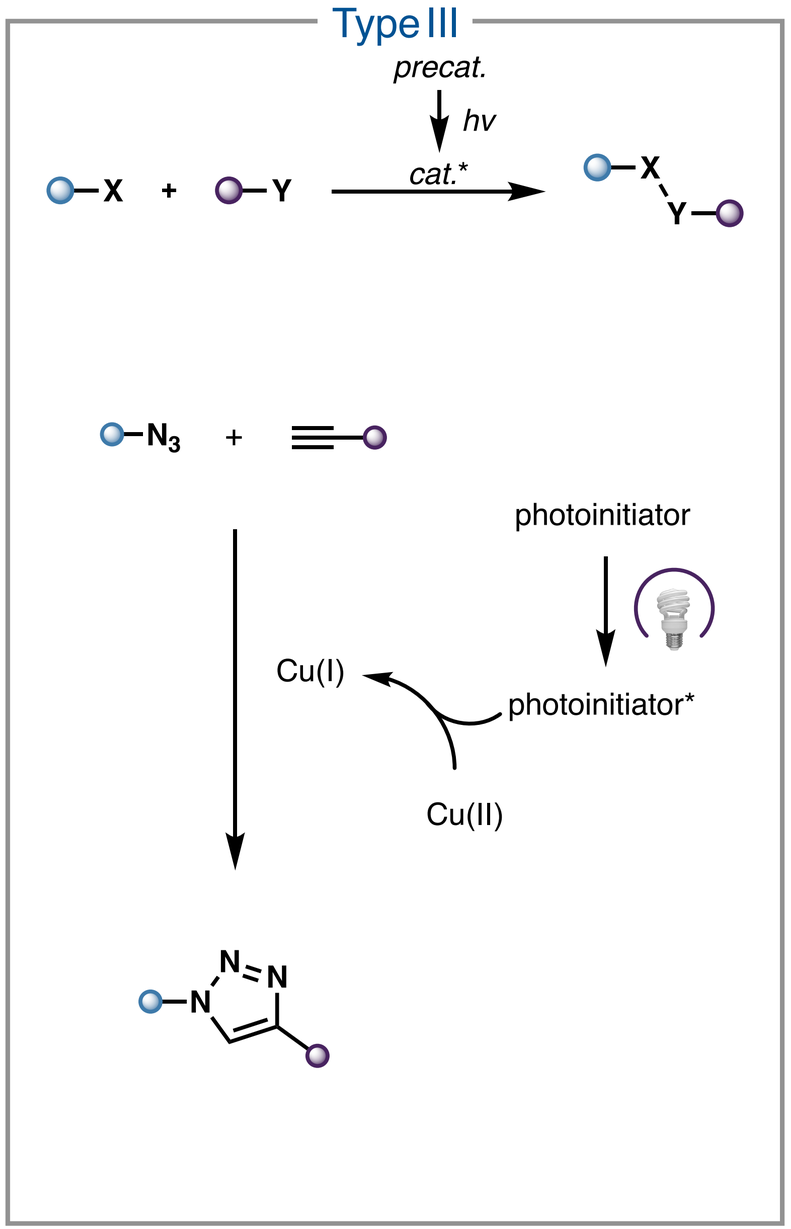
inactive dienophile

active dienophile

Feist, F.; Kowollik, C. *J. Am. Chem. Soc.* **2020**, *142*, 7744
Villabona, M. C.; Kowollik, C. *Org. Lett.* **2021**, *23*, 2405

Types of photoclick reactions

- Photo–catalyzed CuAAC
- Photo-catalyzed SPAAC



Kumar, G. S.; Lin, Q. *Chem. Rev.* **2021**, *121*, 6991

Photo Copper Azide-Alkyne Cycloaddition (CuAAC)

- Reduction of copper via photochemistry

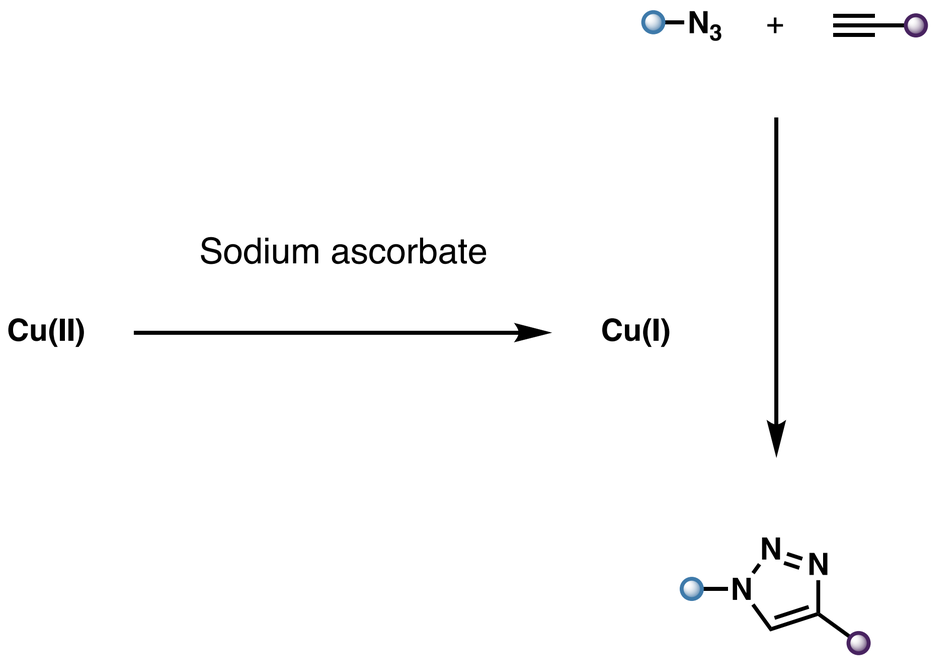


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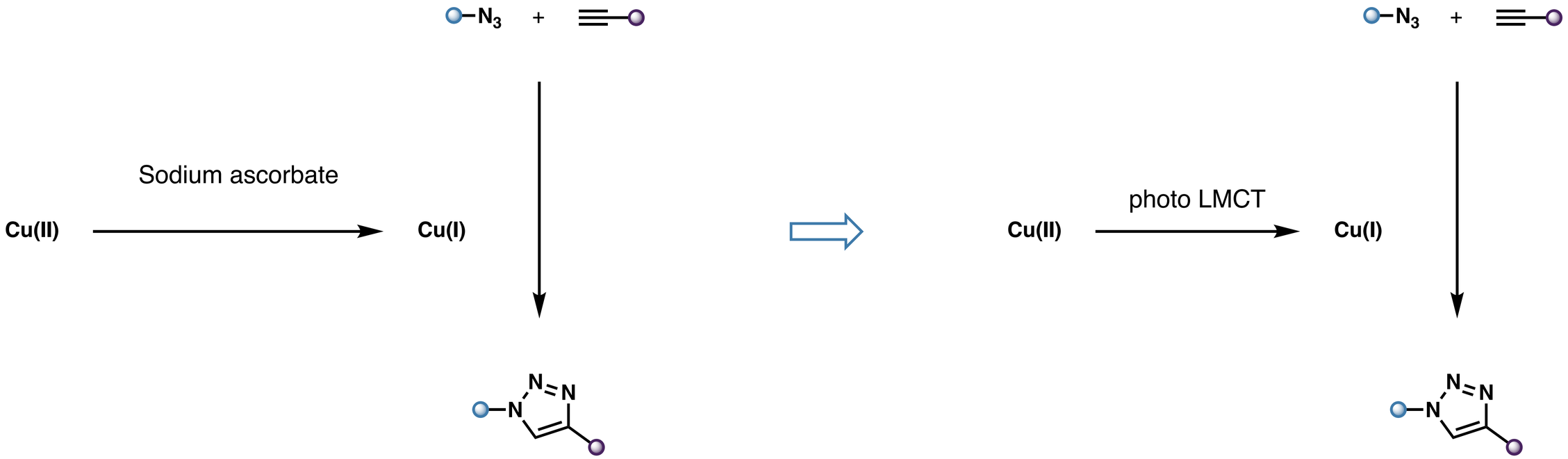


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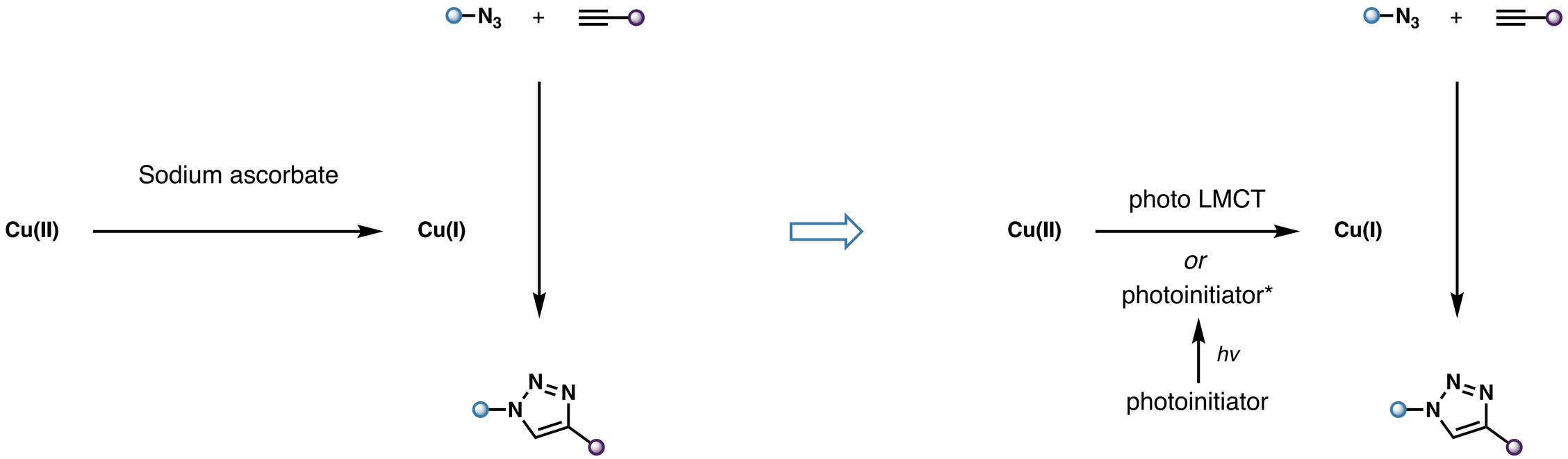
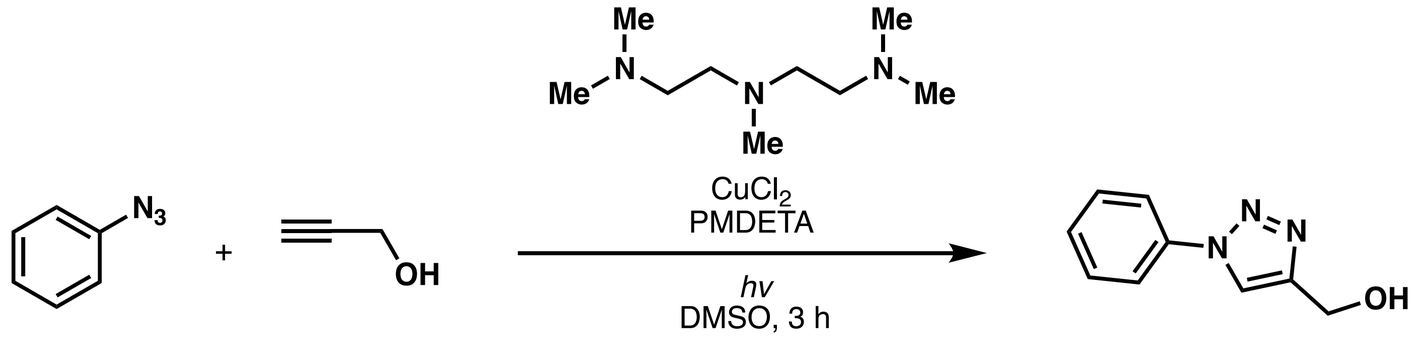


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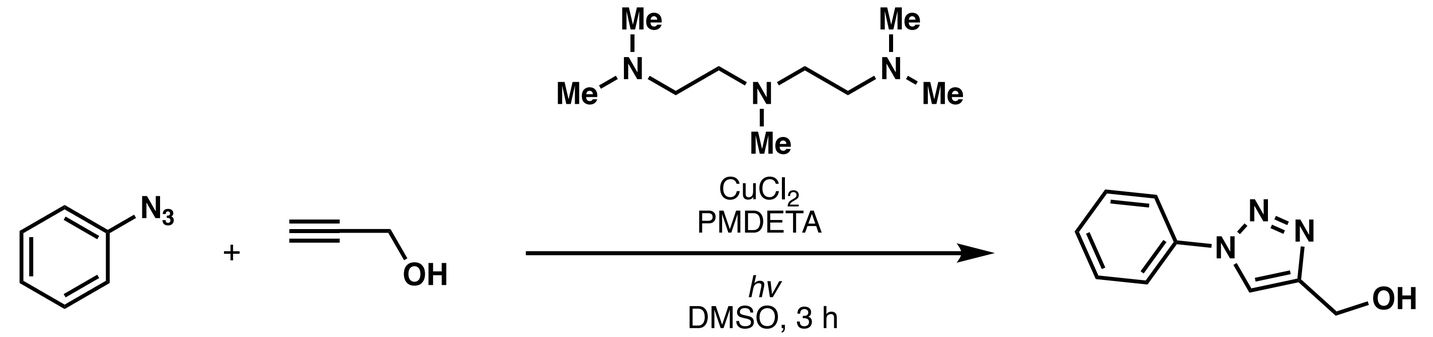
- Direct photoreduction of copper

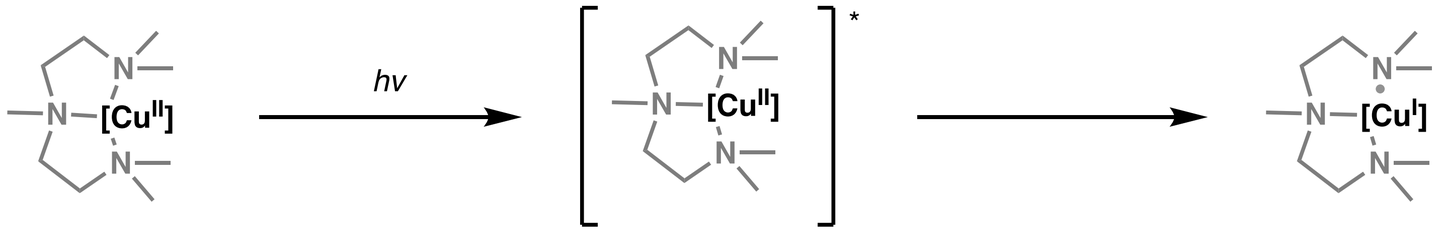


Yagci, Y.; Tasdelen, M. A. *Tetrahedreon Letters* **2020**, *51*, 6945

Photo Copper Azide-Alkyne Cycloaddition (CuAAC)

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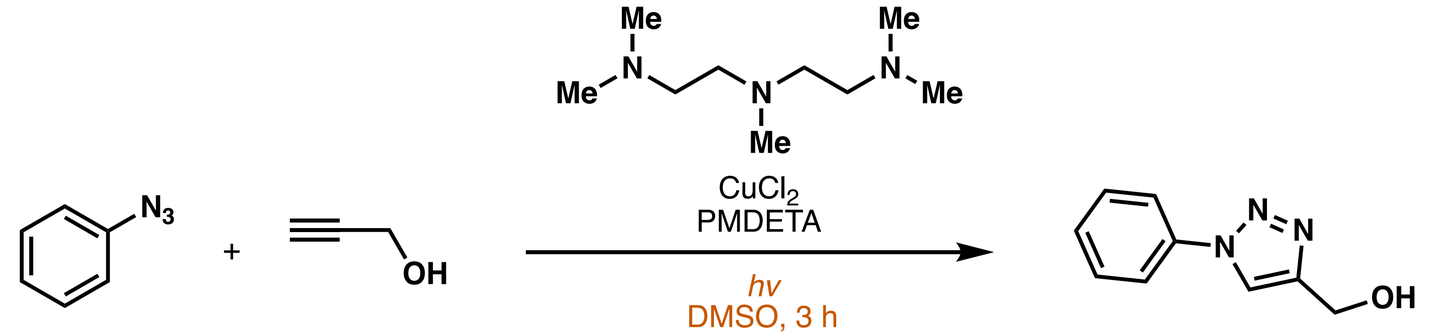


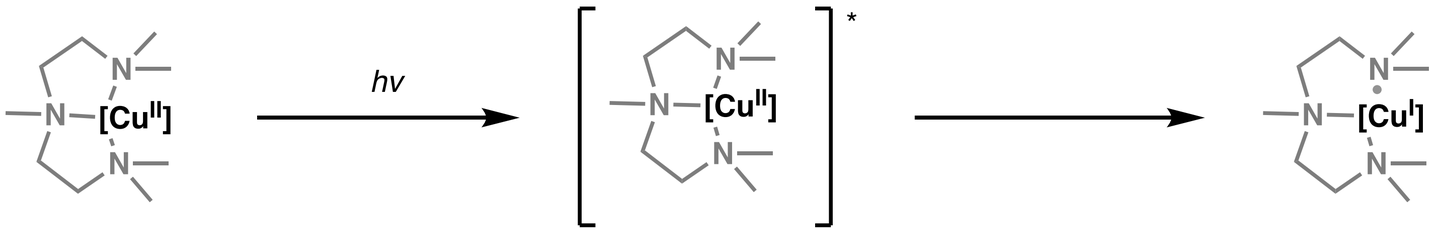


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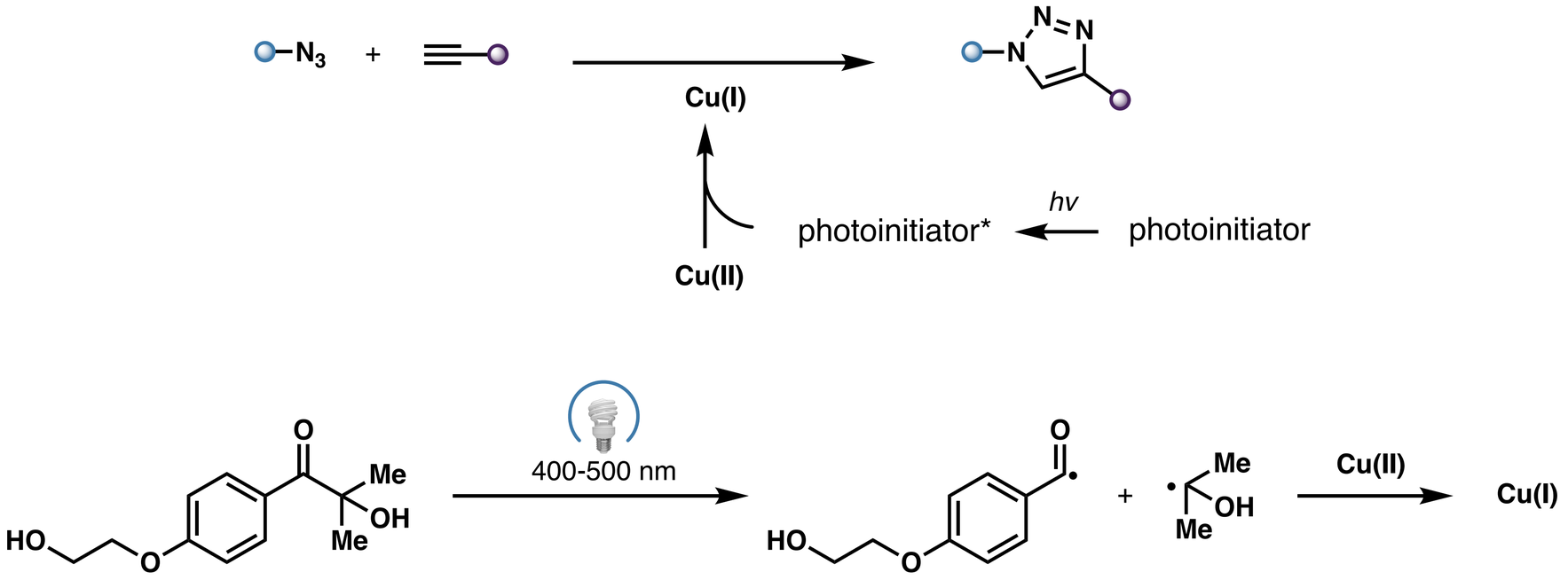




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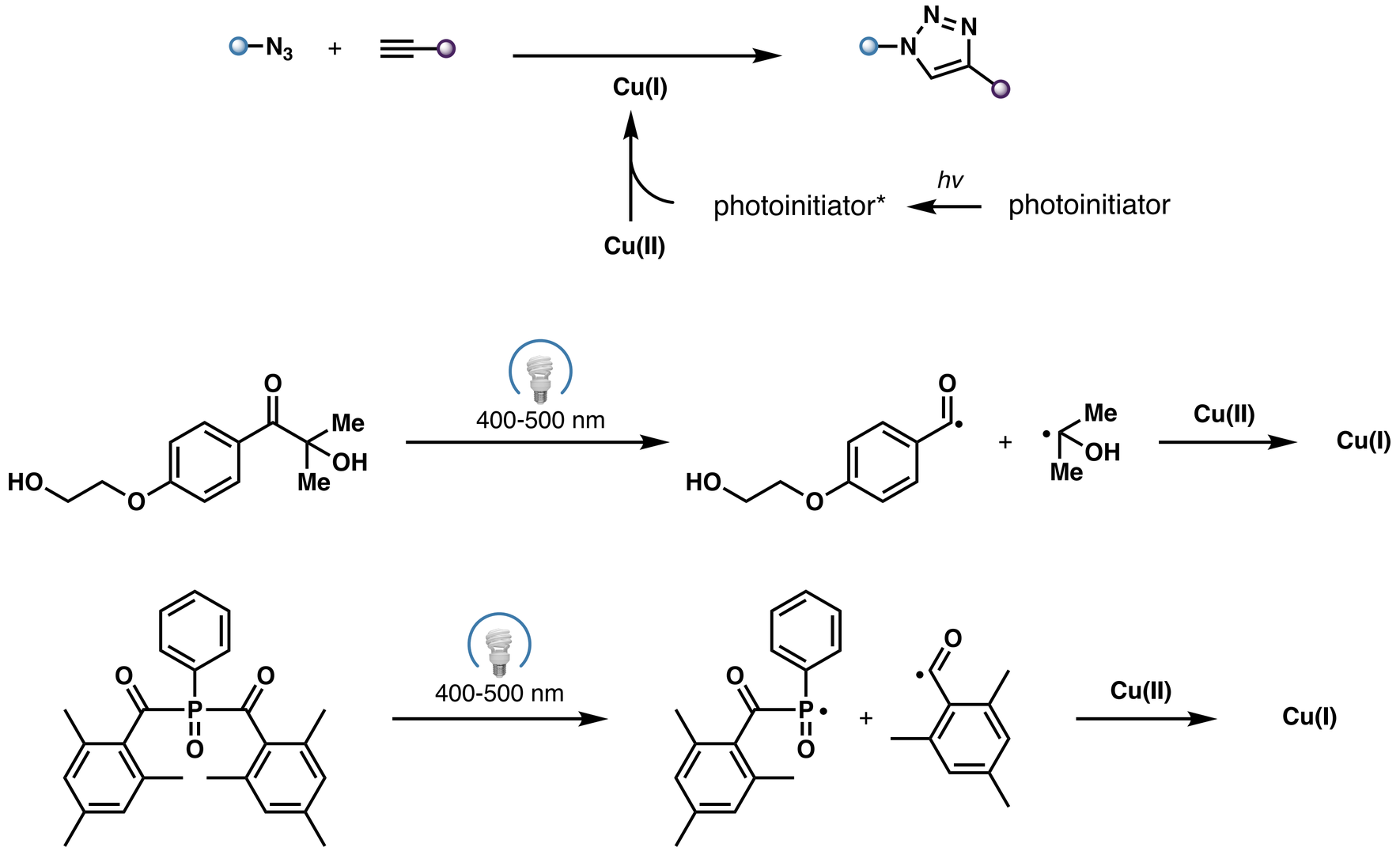
- Indirect photoreduction of copper



Adzima, B.; Bowman, C. N. *Nat. Chem.* **2011**, *3*, 256

Photo Copper Azide-Alkyne Cycloaddition (CuAAC)

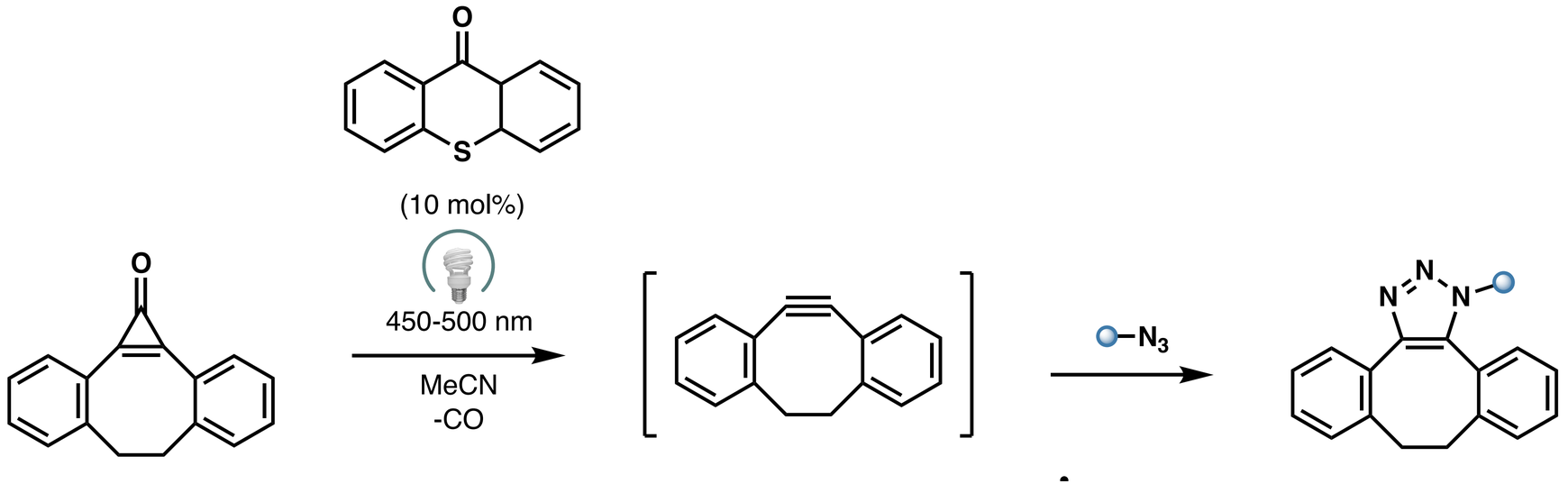
- Indirect photoreduction of copper



Adzima, B.; Bowman, C. N. *Nat. Chem.* **2011**, *3*, 256

Copper free Azide-Alkyne Cycloaddition

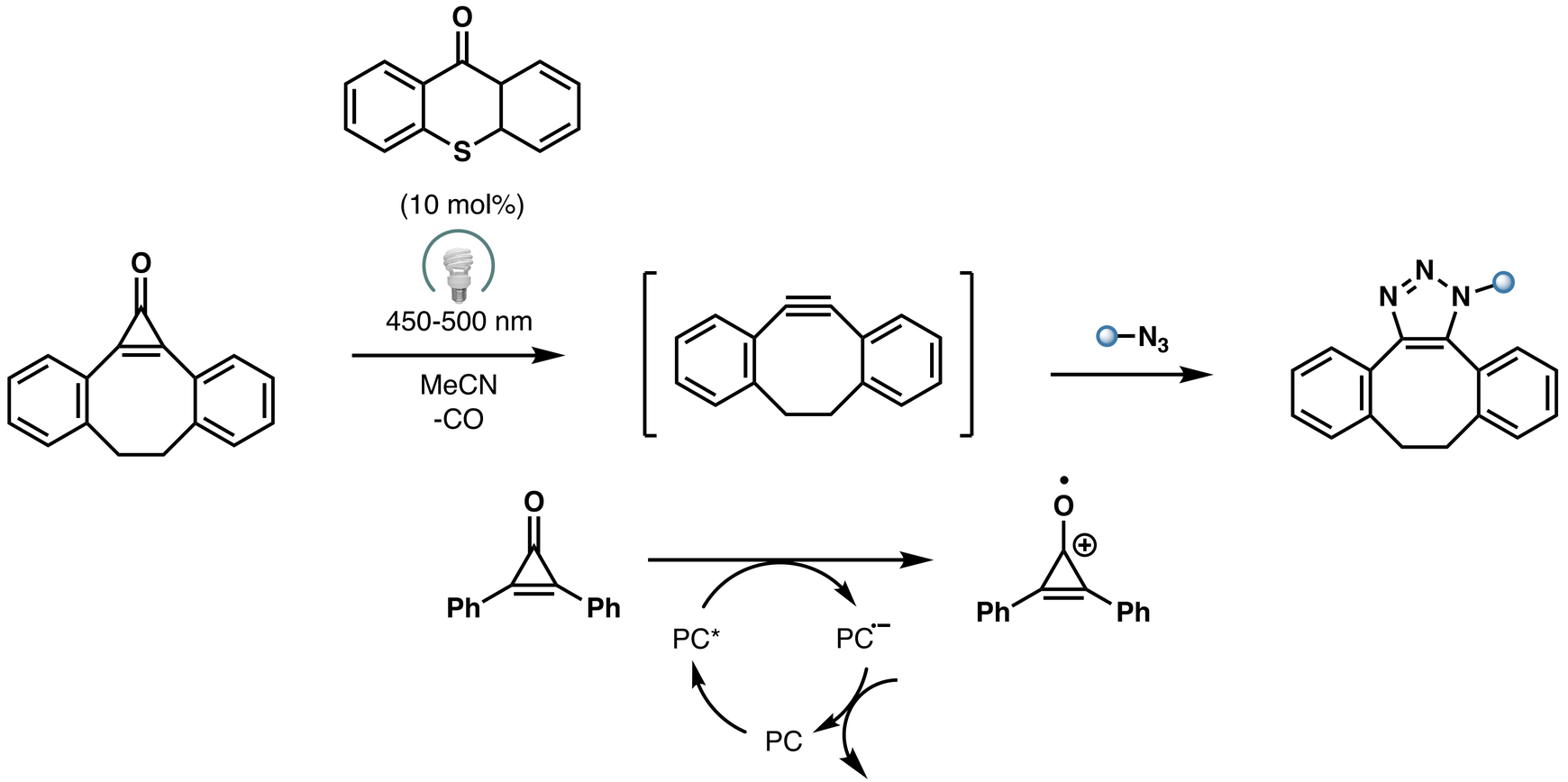
- Photocatalyzed SPAAC



Mishiro, K.; Kunishima, M. *Org. Lett.* **2019**, *21*, 4101

Copper free Azide-Alkyne Cycloaddition

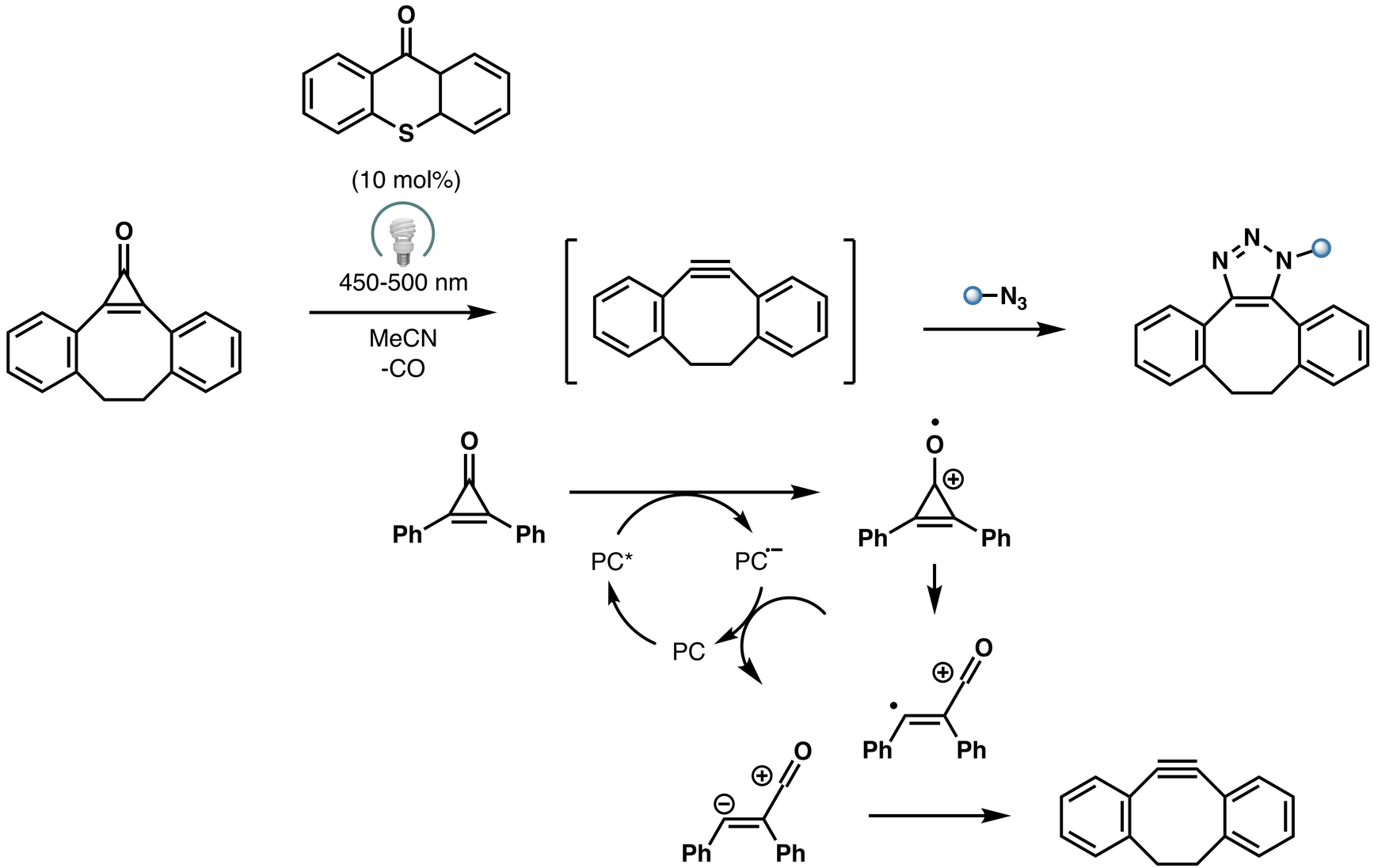
- Photocatalyzed SPAAC



Mishiro, K.; Kunishima, M. *Org. Lett.* **2019**, *21*, 4101

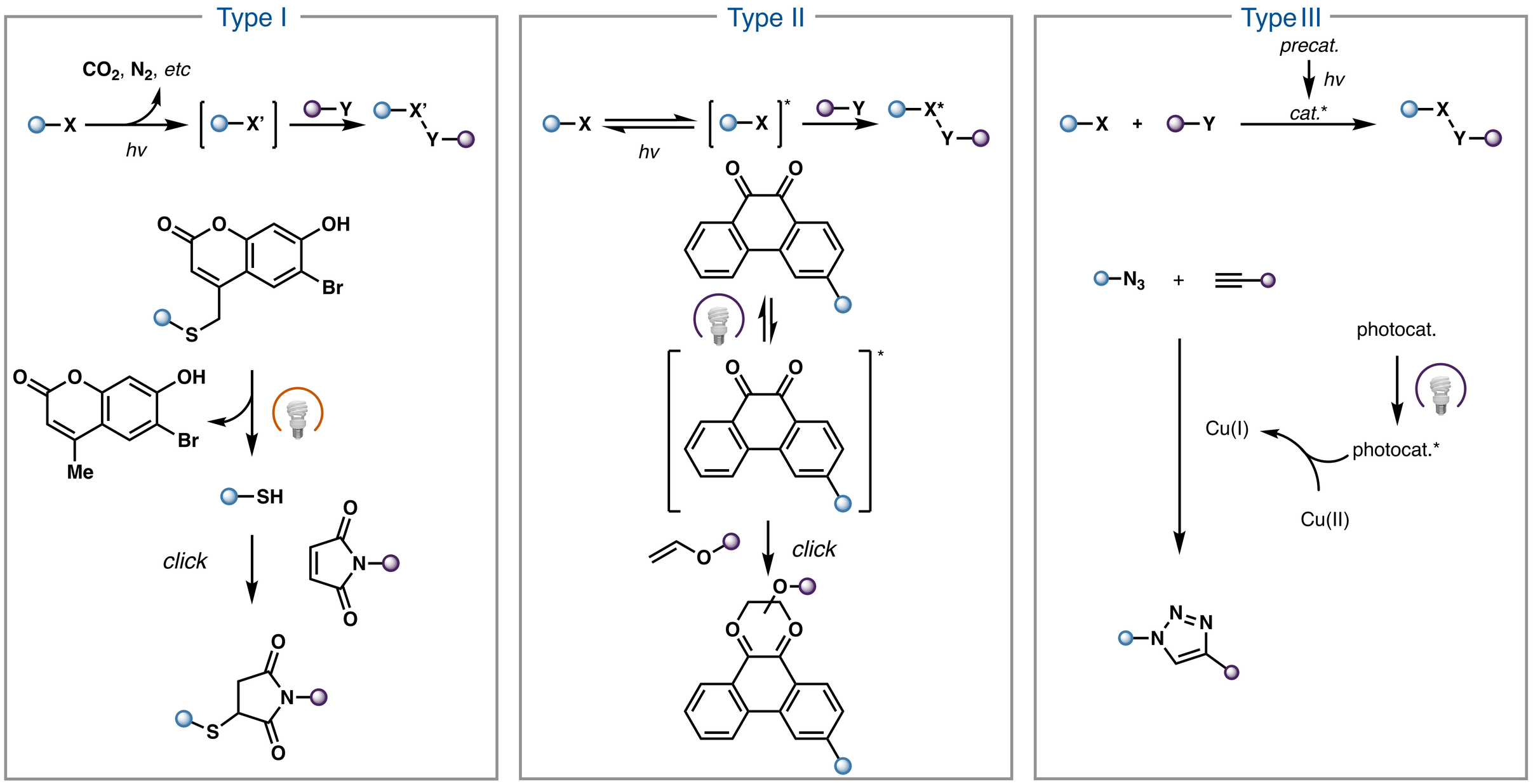
Copper free Azide-Alkyne Cycloaddition

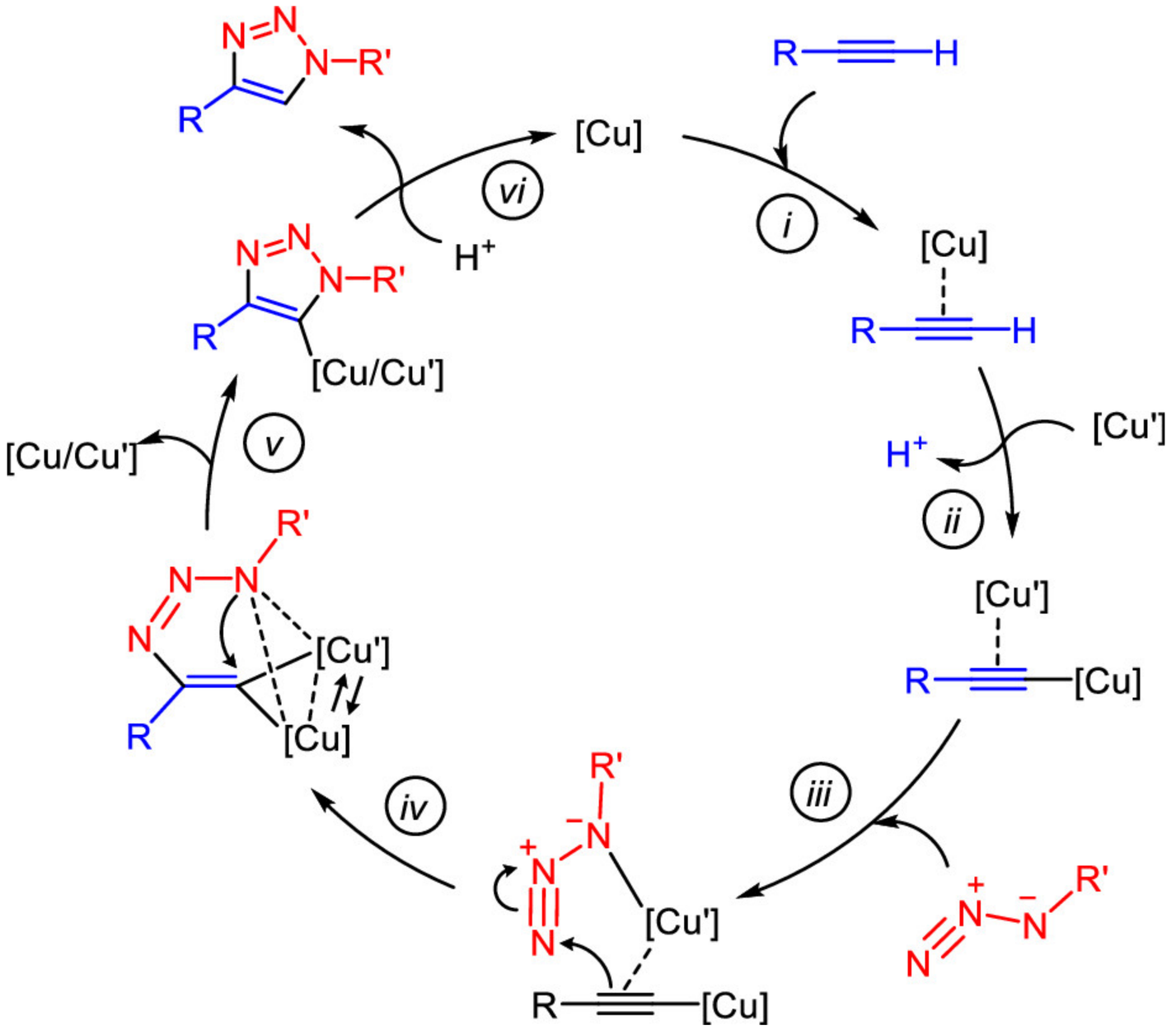
- Photocatalyzed SPAAC



Mishiro, K.; Kunishima, M. *Org. Lett.* **2019**, *21*, 4101

At a glance


Type I
CO_2, N_2, *etc*
X
X'
Y
X'
Y
hv
OH
Br
S
OH
Br
Me
SH
click
N
O
O
O
N
S
O
O
Type II
X
X
*
Y
X*
Y
hv
O
O
*
O
click
O
O
O
Type III
precat.
hv
*cat.**
X
+
Y
X
Y
N_3
+
photocat.
photocat.*
Cu(I)
Cu(II)
N
N
N


R
H
[Cu]
i
[Cu]
R
H
H+
[Cu']
ii
[Cu']
R
[Cu]
iii
R'
N
N
N
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R
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iv
R'
N
N
N
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N
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vi
H+
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R'
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N
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N
R'
R