

Literature Report



pubs.acs.org/JACS

Communication

Superfast Tetrazole–BCN Cycloaddition Reaction for Bioorthogonal Protein Labeling on Live Cells

Gangam Srikanth Kumar, Stefano Racioppi, Eva Zurek, and Qing Lin*

Reporter: Kai An
Date: 2022-01-21

About the Author



Dr. Qing Lin
Professor

Principal Investigator

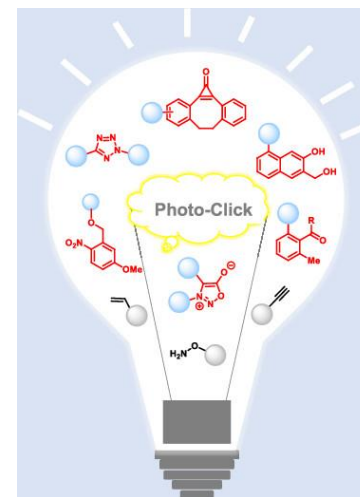
B.S., University of Science and Technology of China (1994)

M.S., University of Pittsburgh (1997)

Ph.D., Yale University (2000)

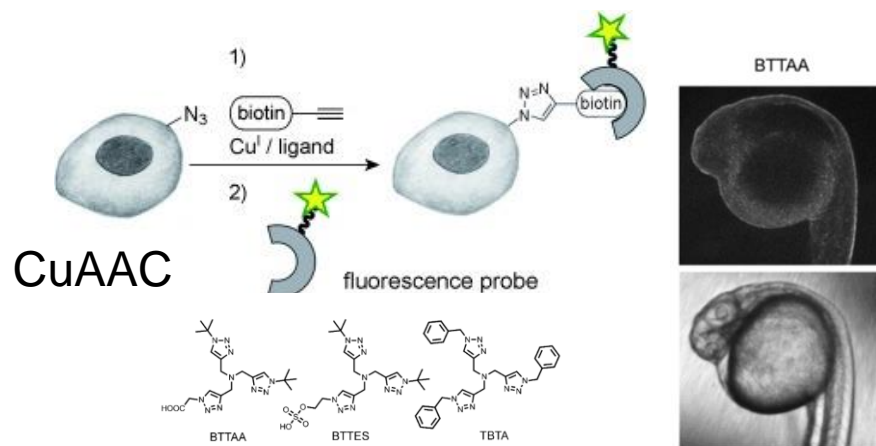
Damon Runyon Cancer Research Foundation Postdoctoral Fellow, The Scripps Research Institute, La Jolla, CA (2000-2003)

- Bioorthogonal Chemistry
- Enabling Chemistries for Peptide-Based Therapeutics
- Orthogonal Microcompartments for Biofuels Production

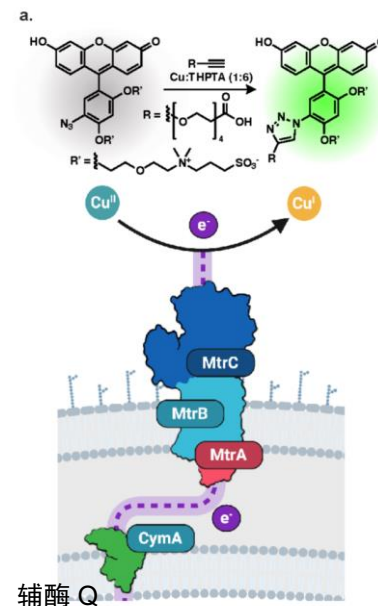


Bioorthogonal Chemistry

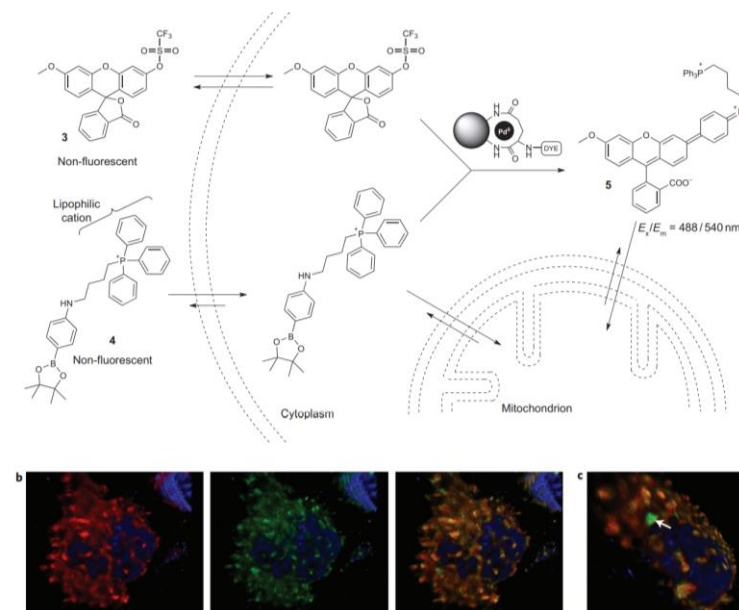
Metal-Catalyzed Bioorthogonal Reaction



Angew. Chem. Int. Ed. **2011**, 50, 8051–8056

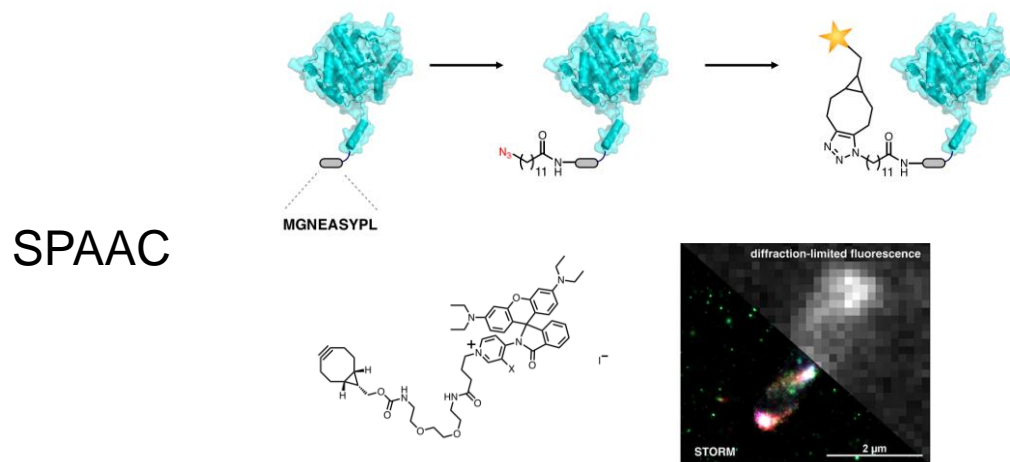


ACS Cent. Sci. **2022**



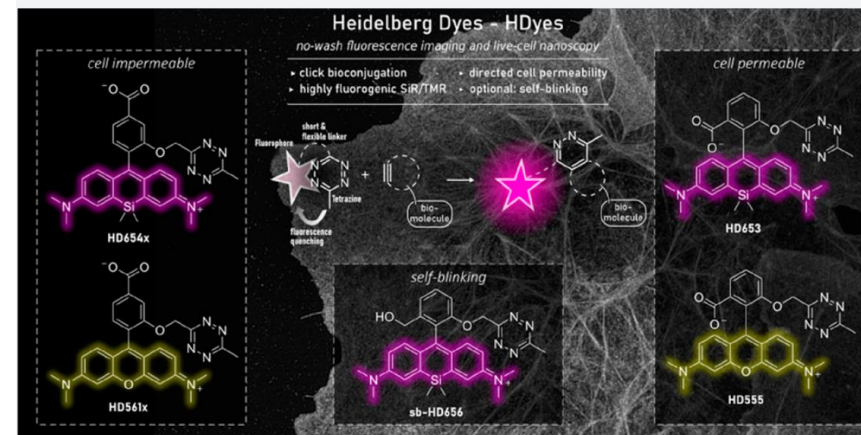
Nature Chemistry, **2011**, 3, 239-243

Bioorthogonal Reactions without Catalyst



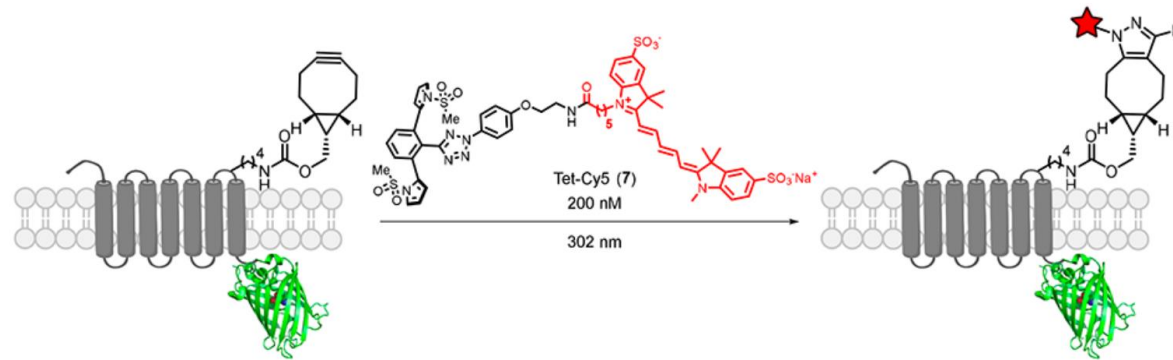
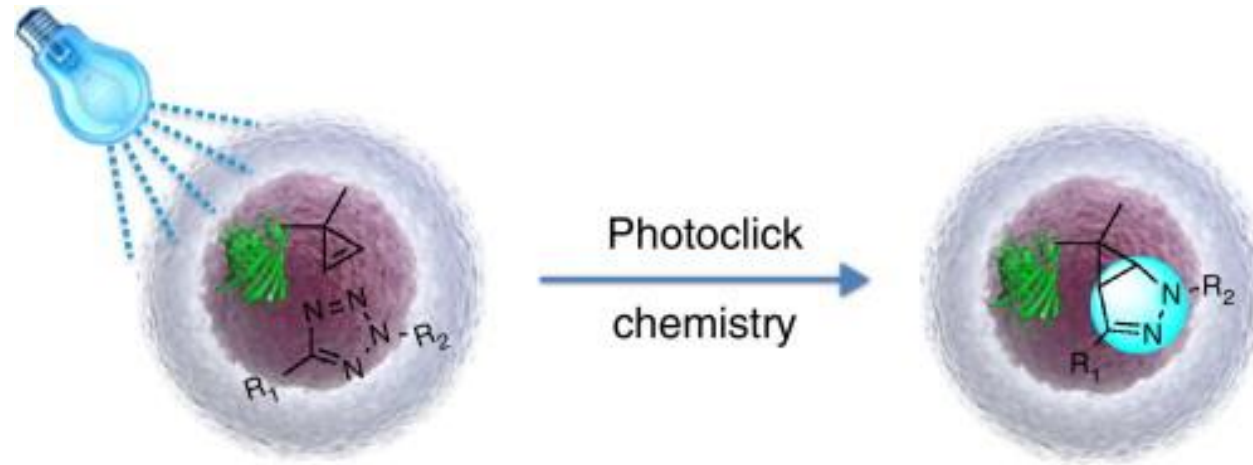
ACS Cent. Sci. **2019**, 5, 1911–1919

IEDDA



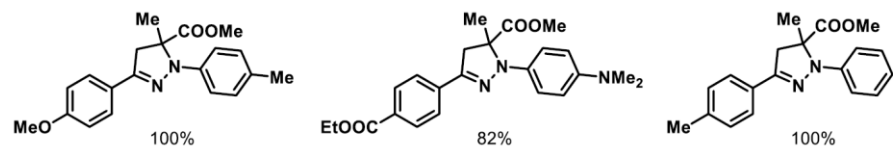
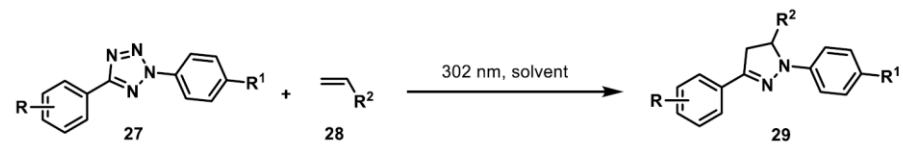
ACS Cent. Sci. **2021**, 7, 9, 1561–1571

Bioorthogonal Chemistry

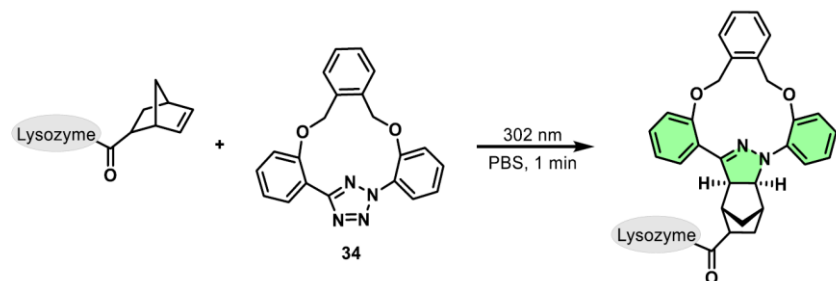


the use of light endows spatial and temporal control over the reaction

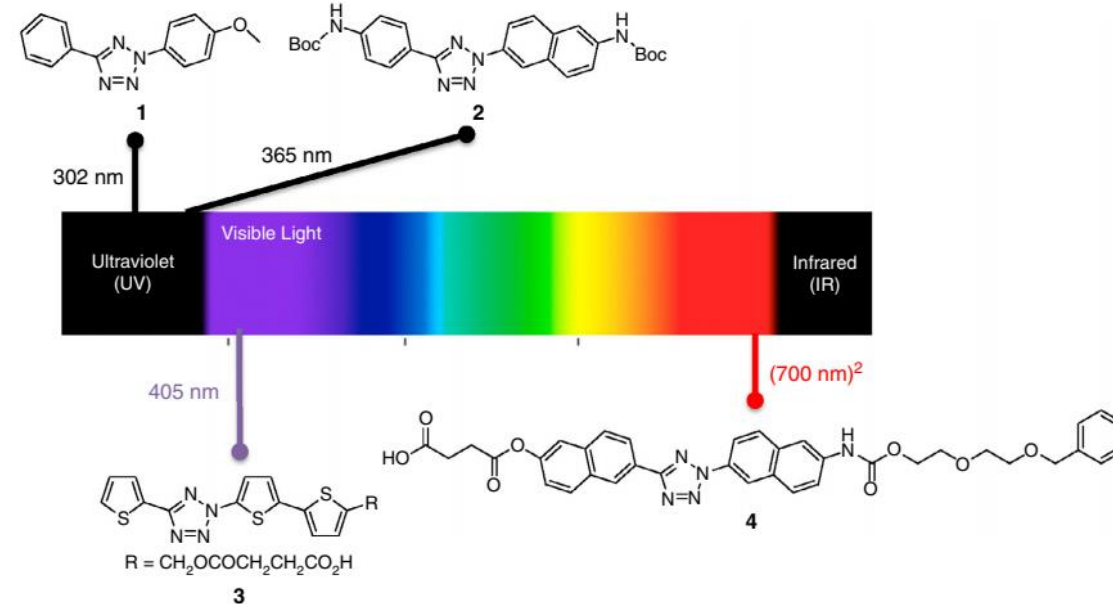
Tetrazole



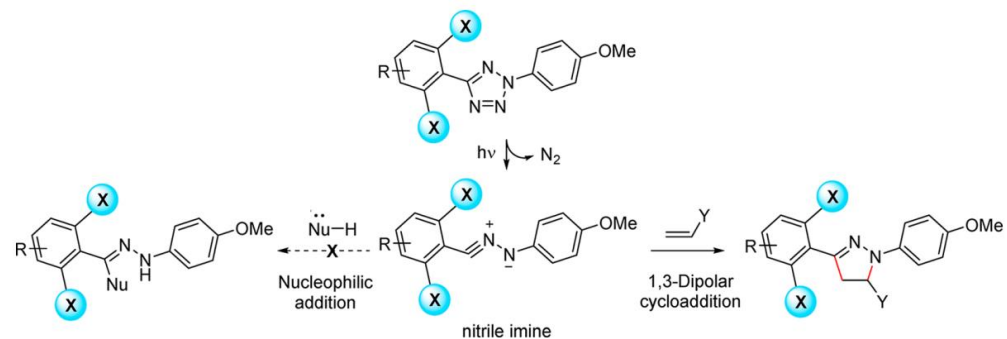
Org. Lett. **2007**, 21, 4155–4158



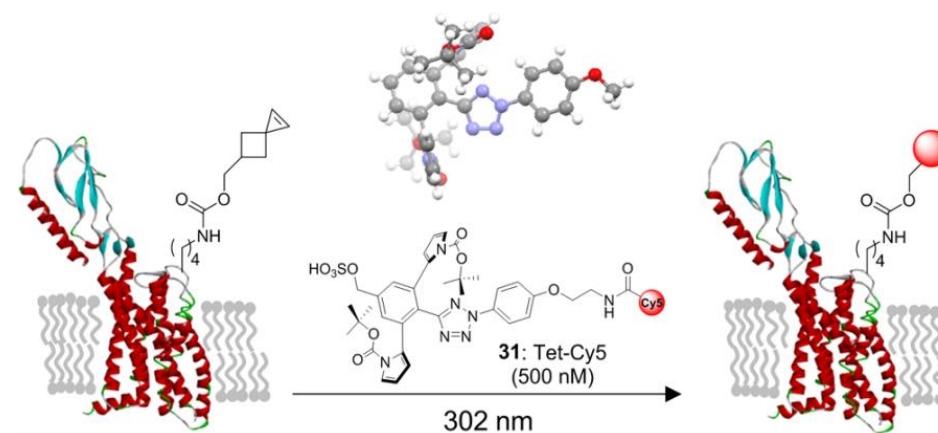
Chem. Eur. J. **2010**, 16, 13325 – 13329



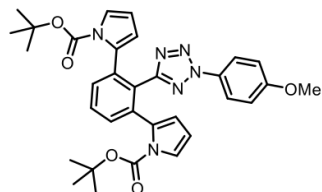
Org. Biomol. Chem., **2018**, 16, 5241–5244



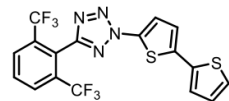
J. Am. Chem. Soc. **2018**, 140, 4860–4868



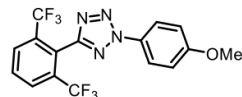
Kinetic Characterization of Sph and BCN



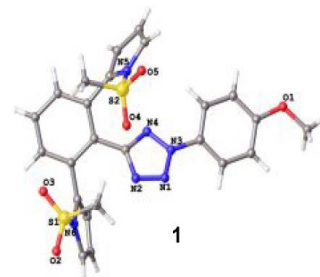
SlogP = 6.8413
LogS = -8.1467



SlogP = 6.7799
LogS = -7.8348

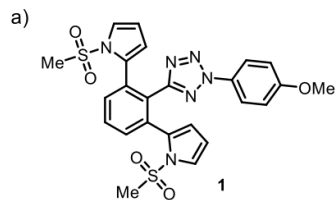


SlogP = 4.9985
LogS = -5.9025

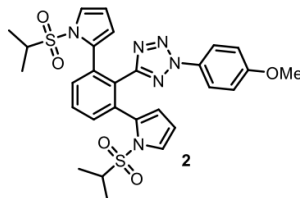


water solubility
the coplanar structure

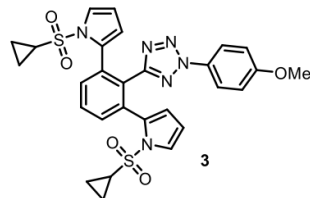
J. Am. Chem. Soc. **2018**, 140, 4860–4868



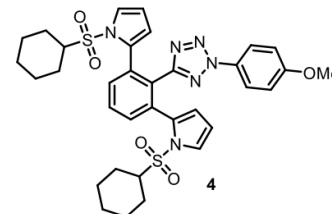
SlogP = 2.8903
LogS = -5.7004



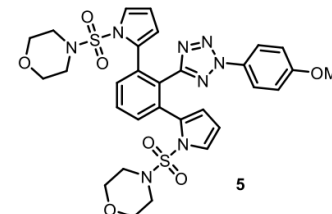
SlogP = 4.4475
LogS = -7.0092



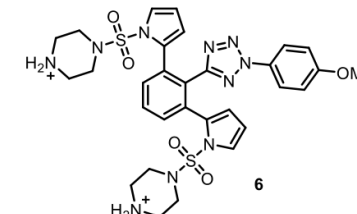
SlogP = 3.9555
LogS = -6.8051



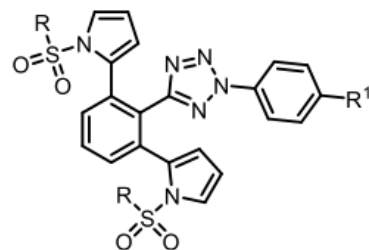
SlogP = 6.2961
LogS = -8.6426



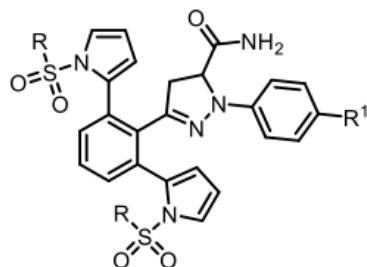
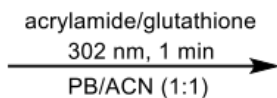
SlogP = 3.9619
LogS = -7.5970



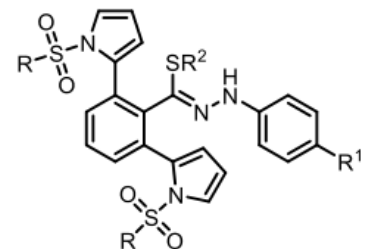
SlogP = 1.0555
LogS = -6.7560



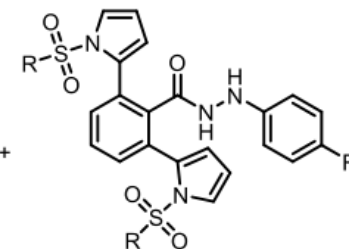
1-6



cycloadduct A



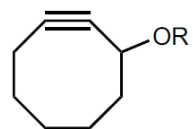
GSH adduct B



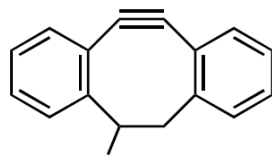
H₂O adduct C

90%

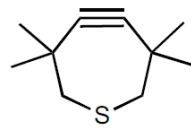
Cyclooctynes



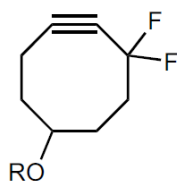
OCT



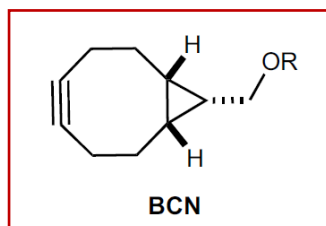
DIBO



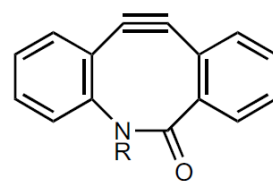
TMTH



DIFO

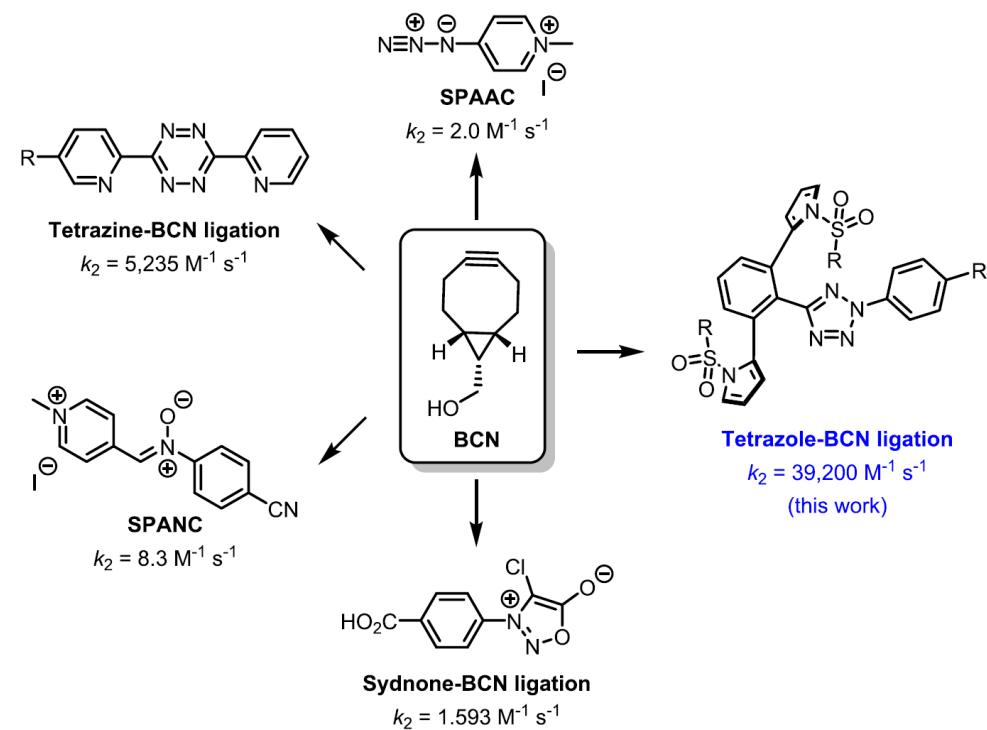


BCN

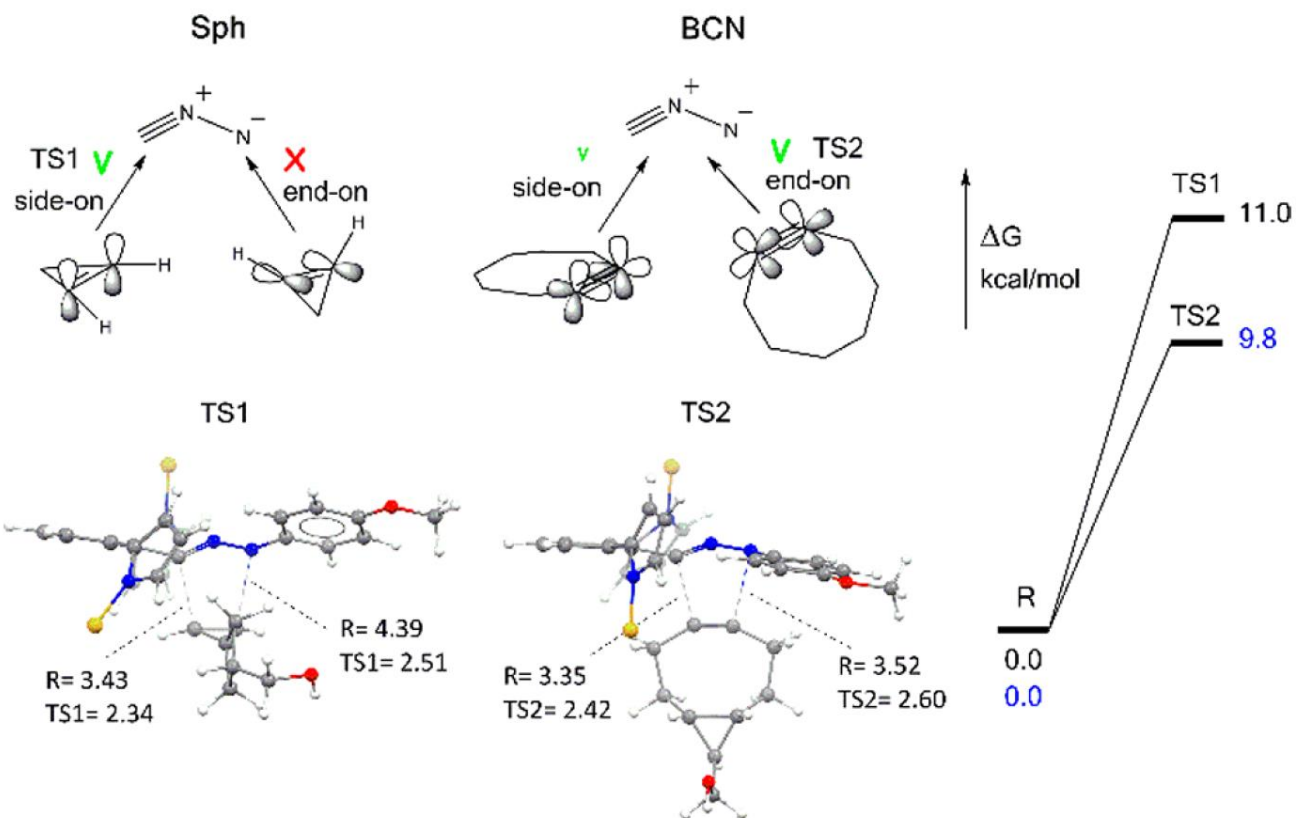
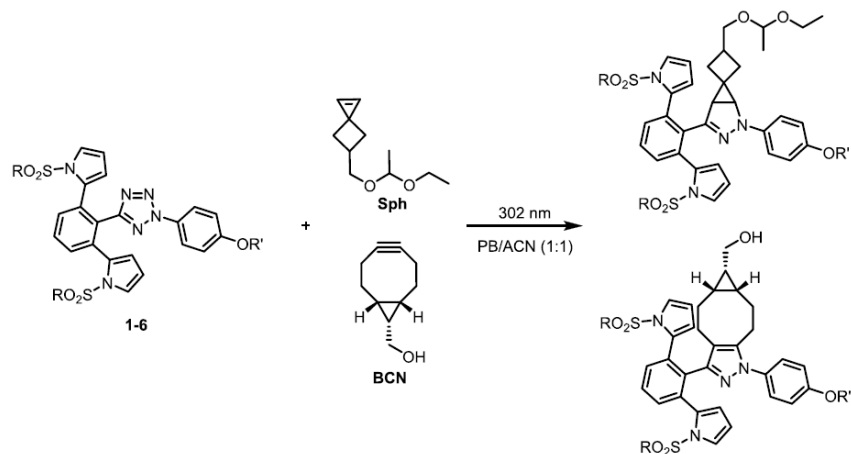


BARAC

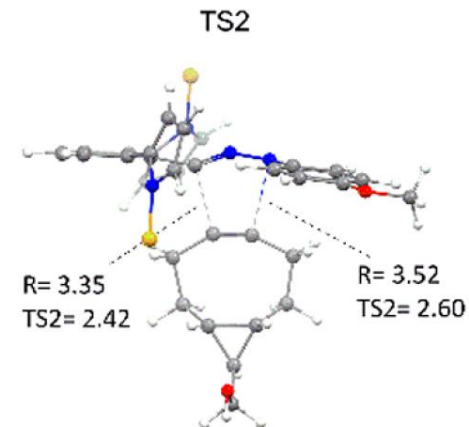
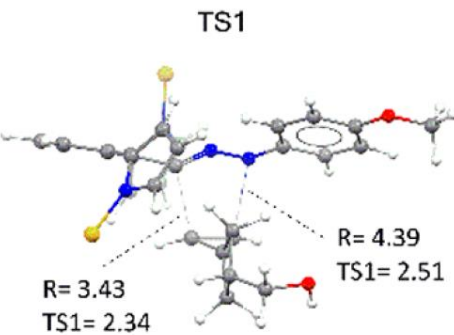
- Copper-free catalysis with rates as fast as $k_2 = 10^2 \text{ M}^{-1} \text{ s}^{-1}$ with nitrene dipolarophiles
- Dipoles include azides, nitrones, diazo compounds and nitrile imines
- Bioorthogonal dipoles tuned for ease of incorporation and reactivity
- Dipolarophiles commonly used are cyclooctynes
- Modifications to cycloalkynes made to speed up reaction rates: fluorination, heterocycles, benzannulation, seven-membered rings, cyclopropanation and fluorogenic variations for cycloalkynes
- Used in live-cell applications



Kinetic Characterization of Sph and BCN



tetrazole	k_2 ($M^{-1} s^{-1}$)		k_{BCN}/k_{Sph}
	Sph	BCN	
1	2321 ± 76	39200 ± 4600	17
2	1398 ± 98	20800 ± 2600	15
3	1247 ± 25	21000 ± 3200	17
4	687 ± 37	11400 ± 1400	17
5	1023 ± 59	17700 ± 2100	17
6	925 ± 79	14500 ± 990	16



Bioorthogonal fluorescent labeling via tetrazole-BCN ligation.

