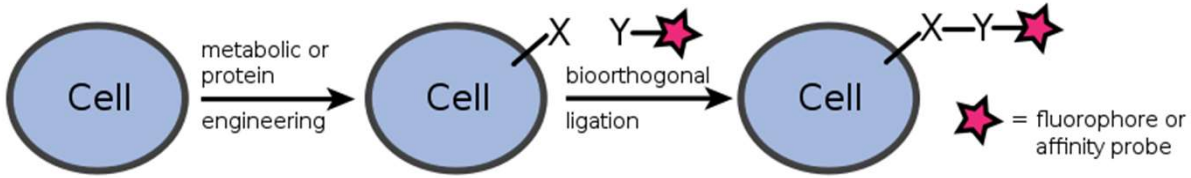
AGENDA

09:00	Introduction
09.15	Lecture 1 (Historical overview of prodrugs)
10.45	Coffee Break
11.00	Lecture 2 (Bioorthogonal prodrugs 1)
12:30	Lunch
13:30	Lecture 3 (Bioorthogonal prodrugs 2)
15:00	Coffee Break
15:30	Lecture 4 (Challenges to progress metal-activated prodrugs into the clinic)
17:00	Go to hotel
19:00	Dinner (TBC)

Bioorthogonal Prodrugs 1

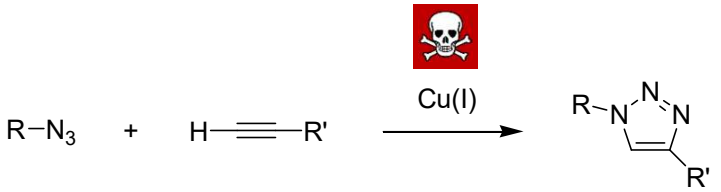
Bioorthogonal Chemistry

- ***Bioorthogonal Reactions:*** *highly selective chemical processes taking place in biological systems by non-biological reagents without interfering with the biotic components of the system. Exemplified by Bertozzi and others using metal-free ligation chemistry.*



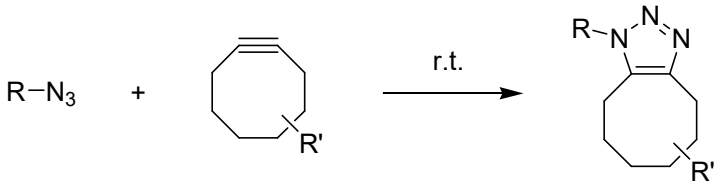
- *<u>Conditions:</u> non-biotic chemical species that efficiently and swiftly react in water at 37° C and that are chemically orthogonal to native cellular components.*

CLICK Chemistry



Cu(I)-Catalised Azide-Alkyne
[3 + 2] Cycloaddition

Toxic



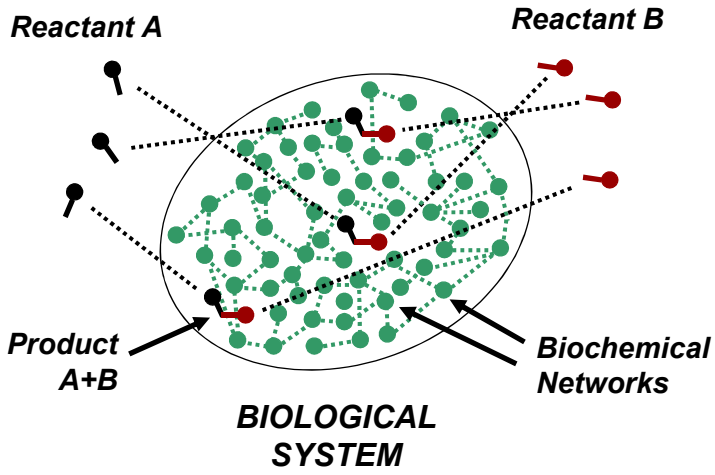
Copper-Free Azide-Alkyne
[3 + 2] Cycloaddition

SAFE

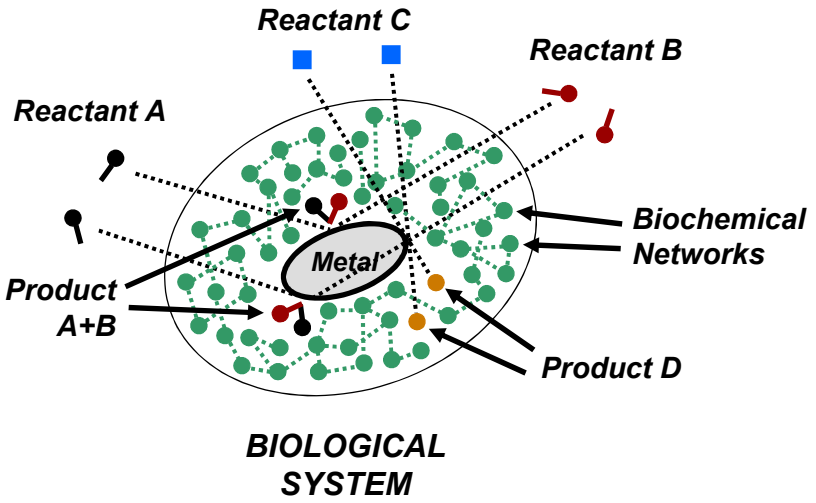
Prescher & Bertozzi, *Nat. Chem. Biol.* **2005**, *1,* 13

Advantages of using metals in vivo

BIOORTHOGONAL LIGATIONS

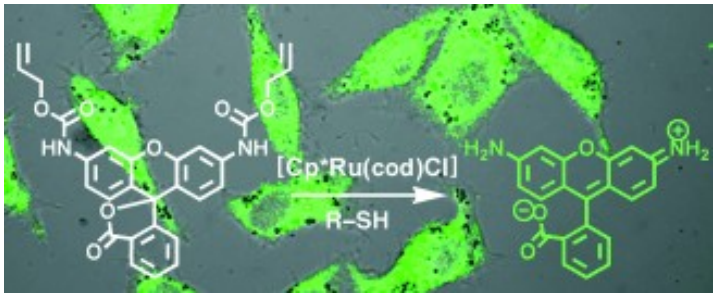


BOOM CHEMISTRY



- *Artificial chemistry and biological chemistry can take place within the same physical space while proceeding independently.*
- ***Chemical scope:*** *Many transition metals are able to catalyze highly-specific reactions in water and 37 °C. E.g. cross-coupling reactions, bond cleavage, bond rearrangement, etc.*
- ***Main problem:*** *cytotoxicity.*

Non-natural metal catalysis in cells



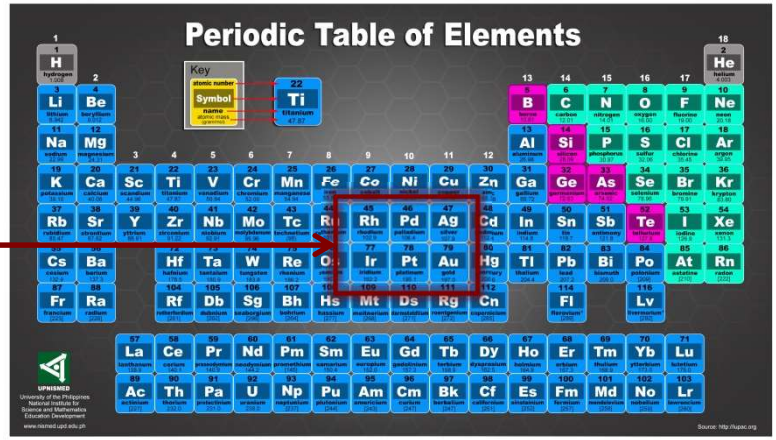
Streu & Meggers, *Angew. Chemie* **2006**, *45*, 5645

Antecedents: *Meggers developed a water-soluble ruthenium complex that rapidly entered cells and performed an allylcarbamate cleavage, while proving to be non-toxic to cells during the short duration of the experiment (minutes).*

CHALLENGE: *Reactions mediated by non-biological transition metals in living systems.* ***REQUIREMENT:*** *Elimination / control of the inherent toxicity of the metal.*

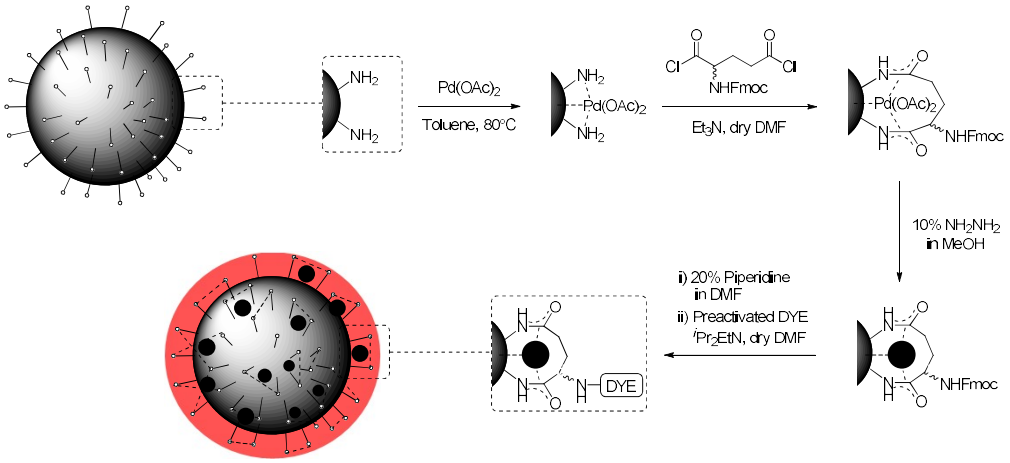
Toxicity & Mechanism:
Metals from the platinum group trigger cell death by cross-linking of DNA >>
HIGHLY TOXIC

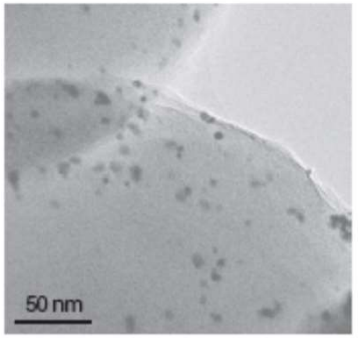
Hypothesis:
Restriction of the catalyst's freedom to enter cell nuclei will suppress its toxicity mechanism >>
HETEROGENEOUS CATALYST



Palladium chemistry in cells

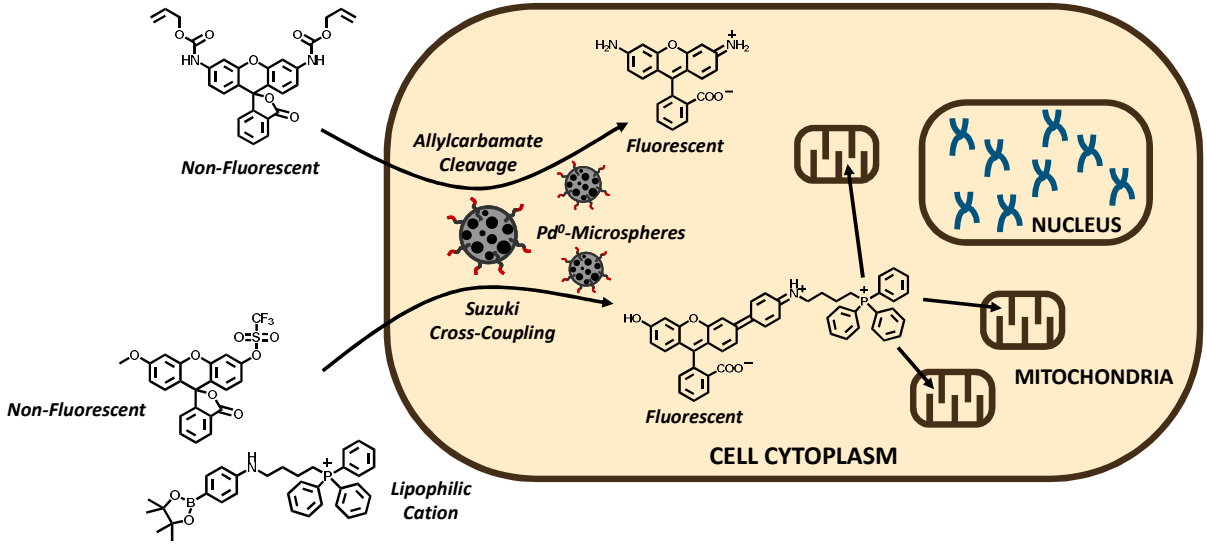
A "bio-friendly" cell-penetrating Pd^0 heterogeneous catalyst





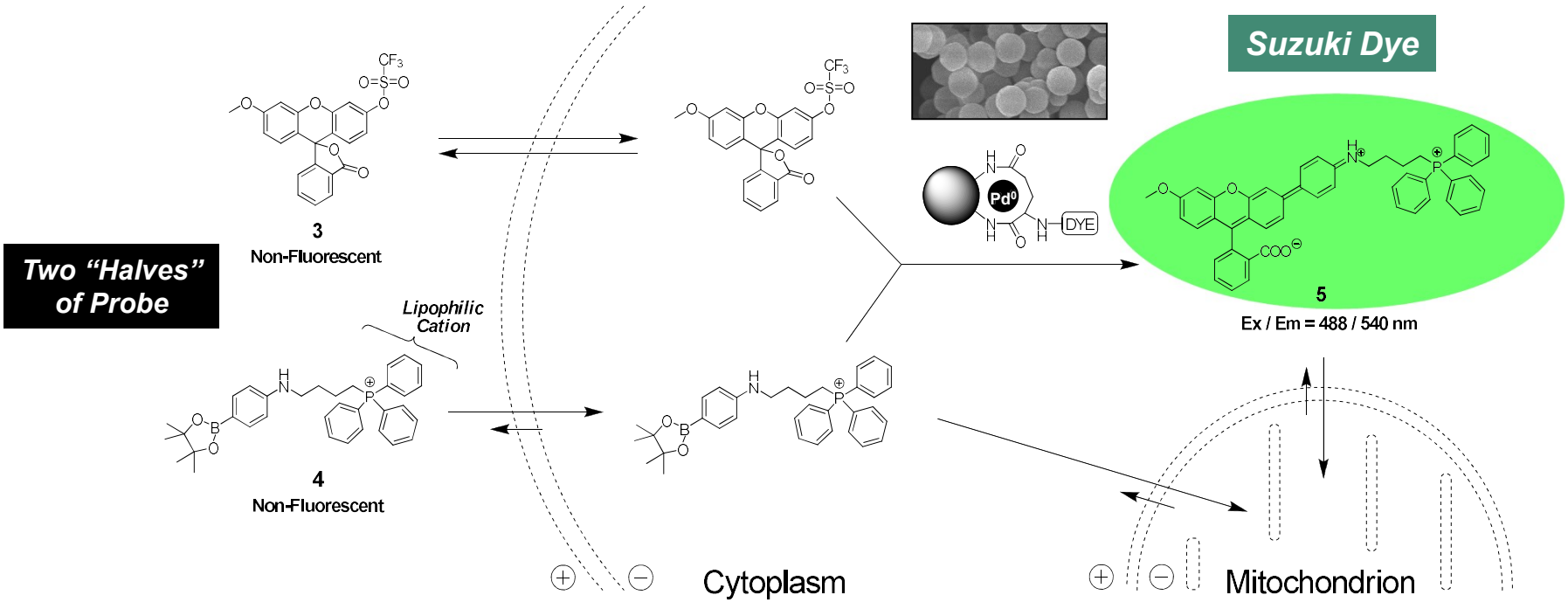
Cell penetrating microspheres that stay in the cytoplasm >> exonuclear location

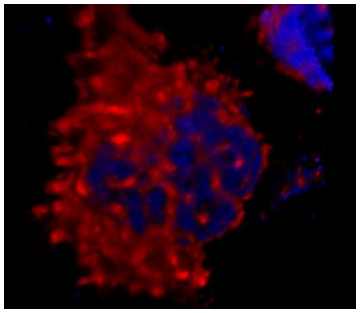
Alloc deprotection & Suzuki coupling inside cells



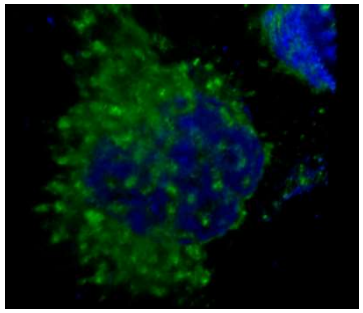
Nat Chemistry **2011**, *3*, 241-245 *Nat Protocols* **2012**, *7*, 1207-1212

Suzuki reaction inside cells

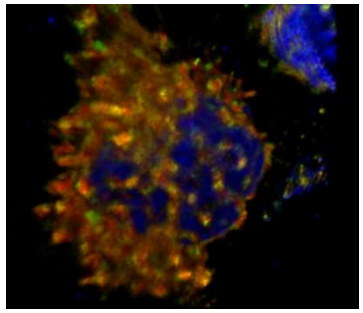




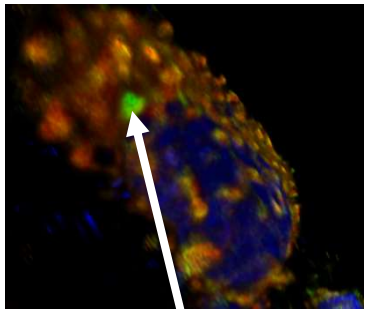
MitoTracker Far Red



Suzuki Dye



Merge



Pd^0-microsphere

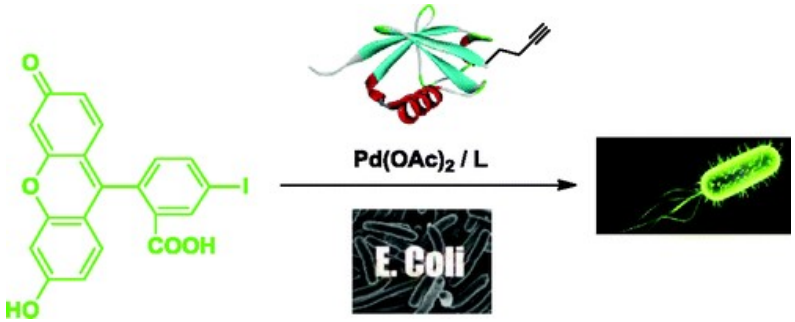
Nat Chemistry **2011**, *3*, 241-245

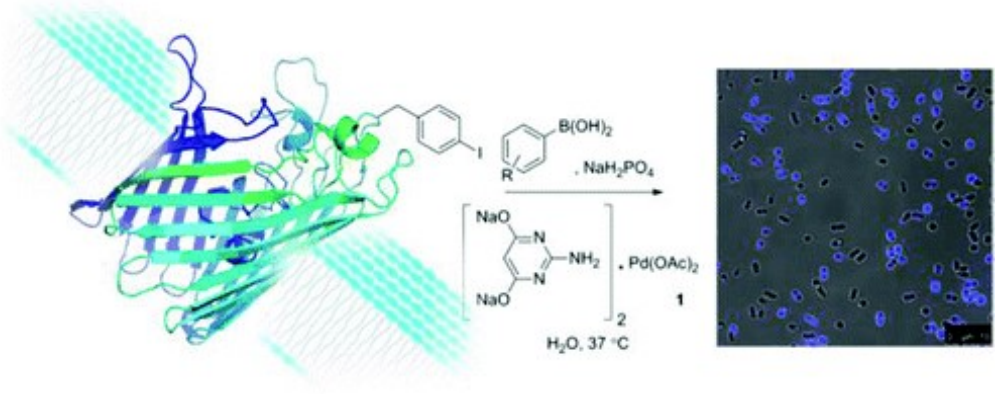
2011-2012 (Pd catalysis)

PROTEIN LABELLING
SONOGASHIRA COUPLING

J. Am. Chem. Soc., **2011**, *133*, 15316–15319

Qing Lin





PROTEIN LABELLING
SUZUKI COUPLING

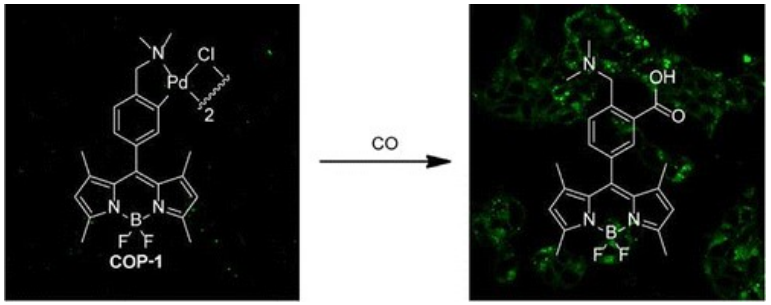
J. Am. Chem. Soc., **2012**, *134*, 800–803

Ben Davis

CARBON MONOXIDE SENSING
PALLADIUM-MEDIATED CARBOXYLATION

J. Am. Chem. Soc., **2012**, *134*, 15668–15671

Chris Chang



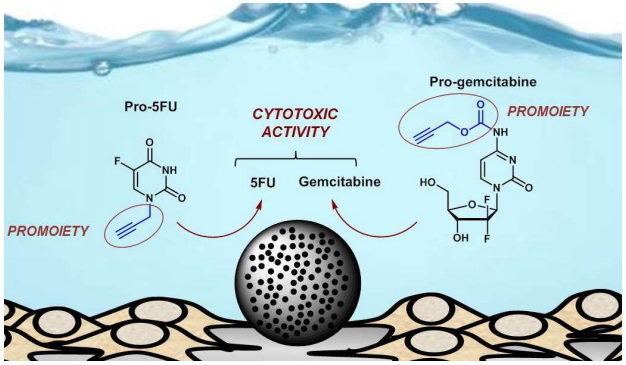
2014-2015 (uncaging chemistries)

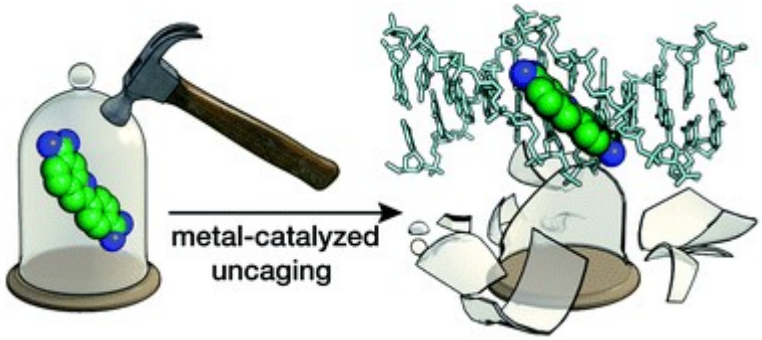
EXTRACELLULAR PRODRUG ACTIVATION -MEDCHEM-

Nat. Commun. **2014**, *5*, 3277

J. Med. Chem. **2014**, *57*, 5395

OUR LAB





Chem. Sci. **2014**, *5*, 1901

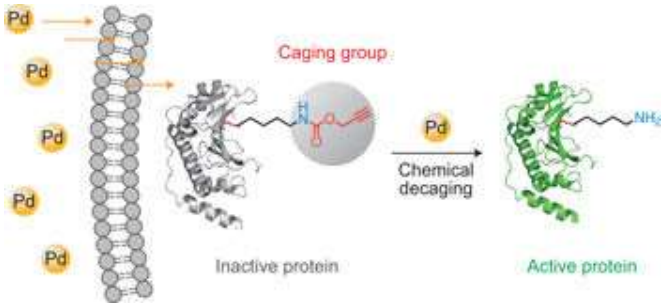
J. L. Mascareñas

INTRACELLULAR PROBE ACTIVATION -CHEMICAL BIOLOGY-

INTRACELLULAR PROTEIN ACTIVATION -CHEMICAL BIOLOGY-

Nat. Chem. ***2014***, *6, 352*

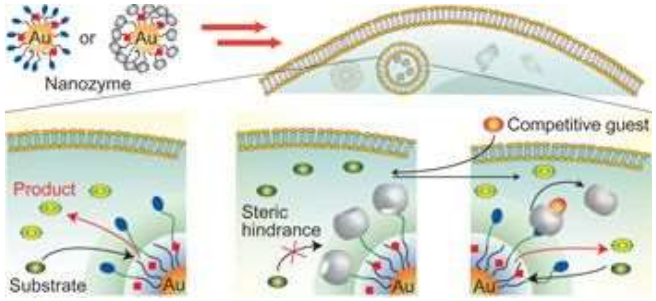
Peng Chen



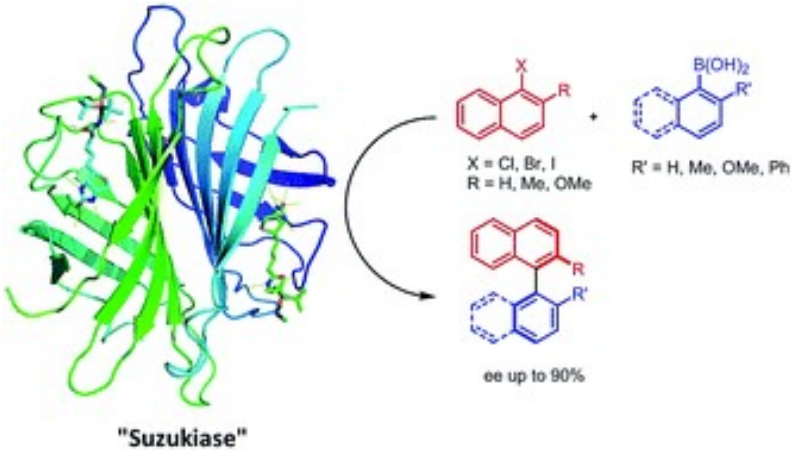
SUPRAMOLECULAR REGULATION OF CATALYSIS -CHEMICAL BIOLOGY & MEDCHEM-

Nat. Chem. ***2015***, *7, 597*

Vince Rotello

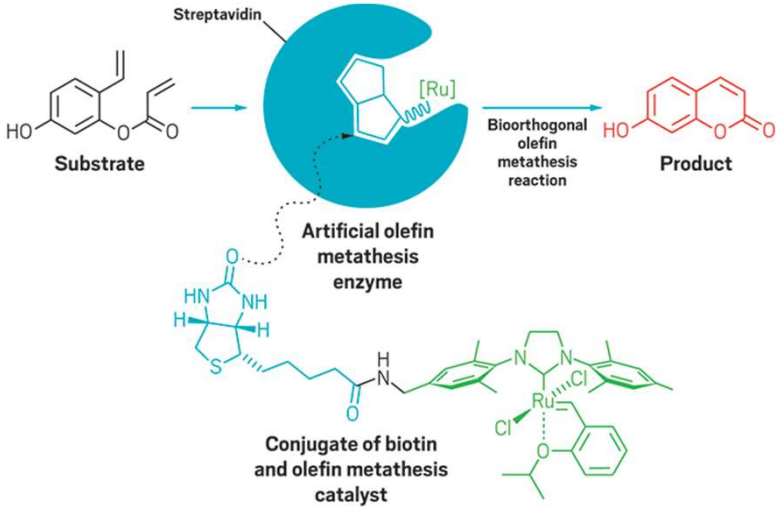


2016 (metalloenzymes)



Chem. Sci. **2016**, *7, 673*
T. Ward

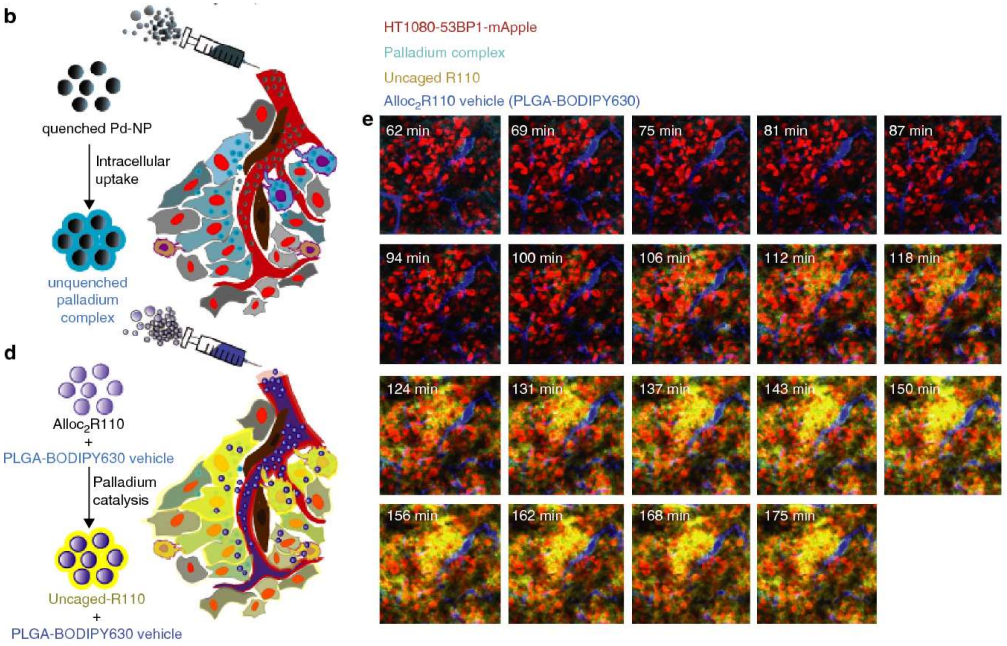
DESIGN OF A SUZUKIASE -CHEMICAL BIOLOGY-



DIRECTED EVOLUTION TO CREATE A METATHASE -CHEMICAL BIOLOGY & MEDCHEM-

Nature ***2016****, 537, 661*
T. Ward

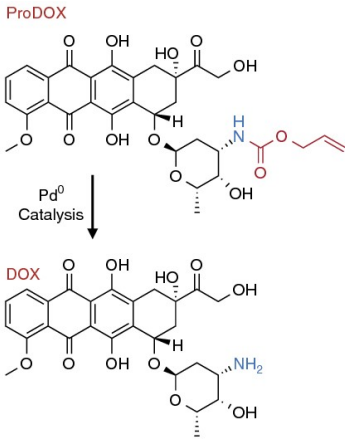
2017 (in vivo PoC)

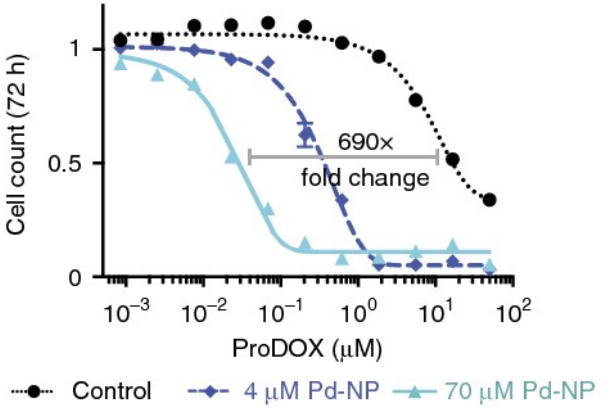


PALLADIUM NANOPARTICLES -CANCER THERAPY-

Nat. Commun. **2017**, *8, 15906*

R. Weisledder

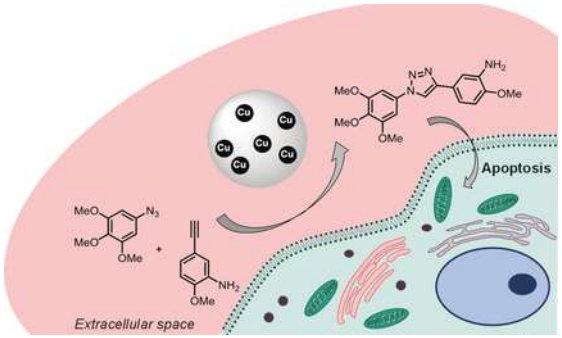


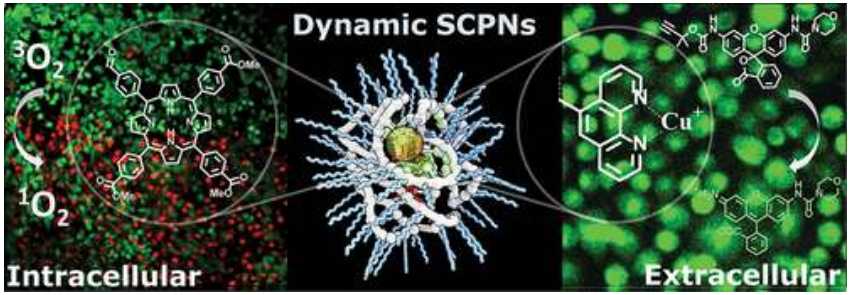


2016 & 2018 (Cu catalysis)

CLICK CHEMISTRY OUTSIDE CELLS -CHEMICAL BIOLOGY & MEDCHEM-

Angew. Chemie ***2016****, 55, 15662*
M. Bradley



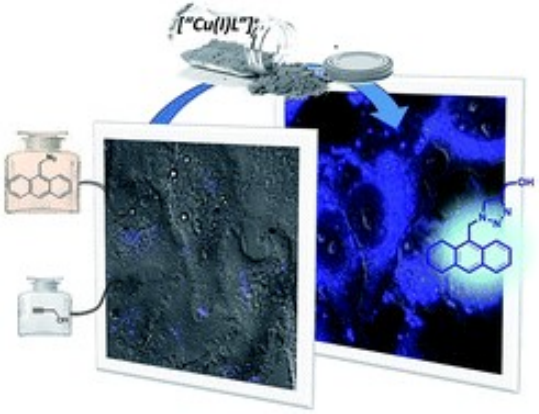


JACS **2018***, 140, 3423*
Albertazzi & Palmans

COPPER MEDIATED UNCAGING CHEMISTRY IN CELLS -CHEMICAL BIOLOGY-

CLICK CHEMISTRY IN CELLS -CHEMICAL BIOLOGY-

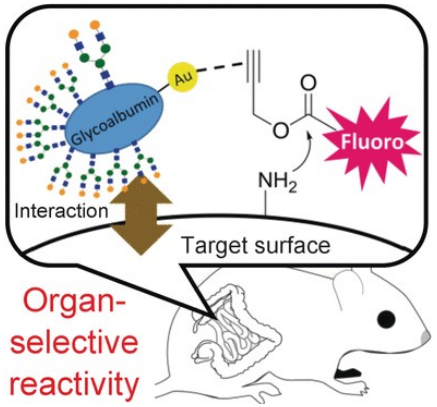
Chem. Sci. ***2018****, 9, 1947*
Mascarenas

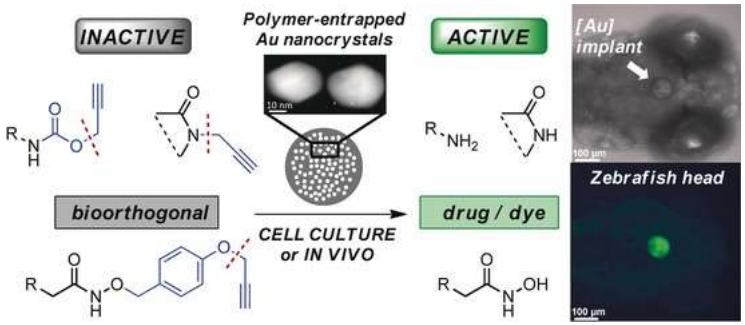


2017 & 2018 (Au catalysis)

GOLD(III)-CATALISED CROSS-COUPLING IN VIVO -CHEMICAL BIOLOGY -

Angew. Chemie ***2017****, 56, 3579*
Tanaka



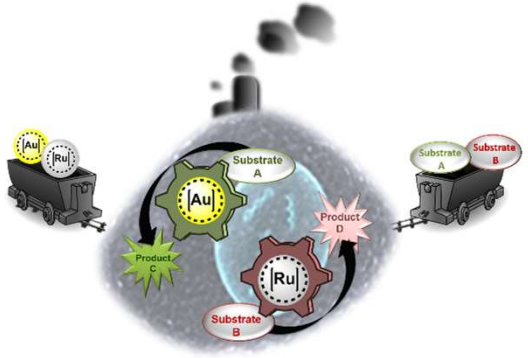


Angew. Chemie **2017***, 56, 12548*
OUR LAB

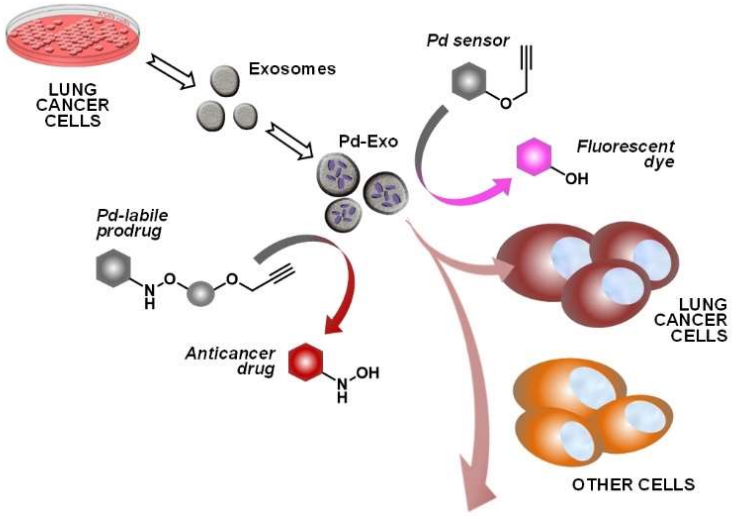
GOLD(0)-MEDIATED UNCAGING CHEMISTRY -MED. CHEM-

GOLD(I)-CATALISED CYCLIZATION IN CELLS -CHEMICAL BIOLOGY-

Nat. Commun. ***2018****, 9, 1913*
Mascarenas



2019 (last 'new' strategies)



TARGETED PALLADIUM-MEDIATED PRODRUG ACTIVATION

-MEDCHEM & THERAPY-

Nat. Catalysis **2019**, 10.1038/s41929-019-0333-4

OUR LAB

RING-CLOSING METATHESIS TO UNCAGE PRODRUGS

-CHEMICAL BIOLOGY & MEDCHEM-

JACS ***2019****, 10.1021/jacs.9b07193*
T. Ward