

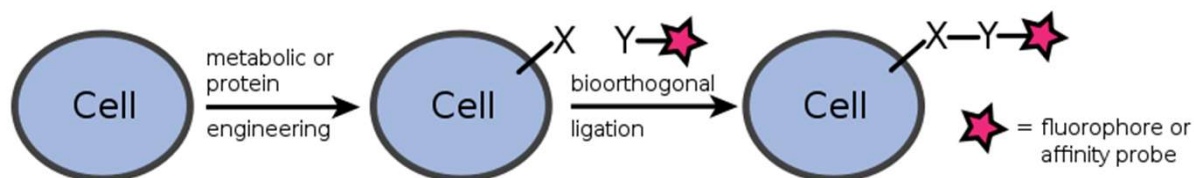
## **AGENDA**

- 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**

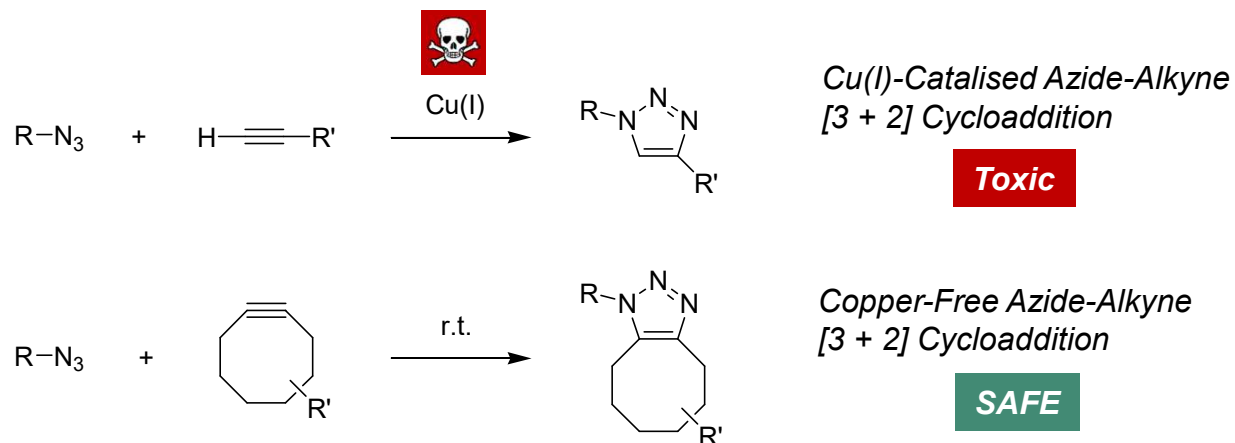
# Bioorthogonal Chemistry

- 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.



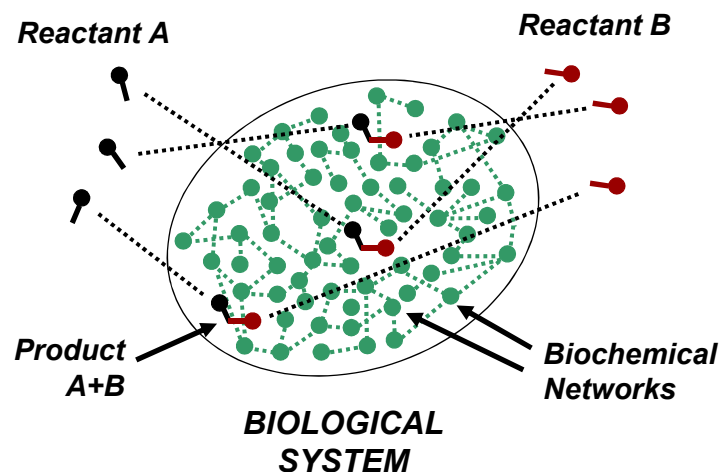
- Conditions:** non-biotic chemical species that efficiently and swiftly react in water at 37° C and that are chemically orthogonal to native cellular components.

## CLICK Chemistry

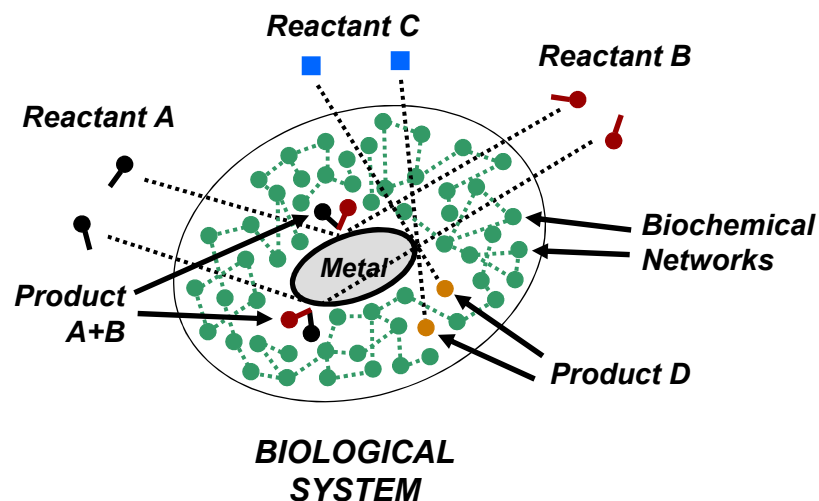


# Advantages of using metals in vivo

## BIOORTHOGONAL LIGATIONS

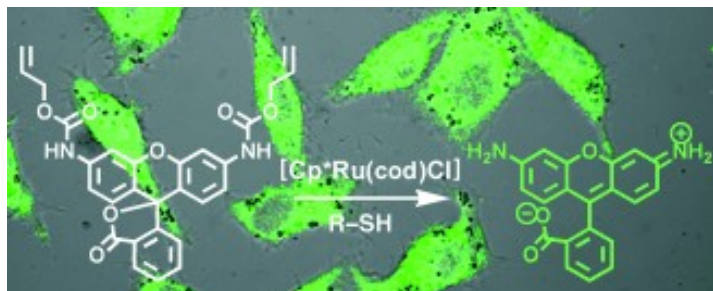


## BOOM CHEMISTRY



- *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



**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).

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

**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

# Periodic Table of Elements

1

H

Hydrogen

2

He

Helium

3

Li

Lithium

4

Be

Beryllium

5

B

Boron

6

C

Carbon

7

N

Nitrogen

8

O

Oxygen

9

F

Fluorine

10

Ne

Neon

11

Na

Sodium

12

Mg

Magnesium

13

Al

Aluminum

14

Si

Silicon

15

P

Phosphorus

16

S

Sulfur

17

Cl

Chlorine

18

Ar

Argon

19

K

Potassium

20

Ca

Calcium

21

Sc

Scandium

22

Ti

Titanium

23

V

Vanadium

24

Cr

Chromium

25

Mn

Manganese

26

Fe

Iron

27

Co

Cobalt

28

Ni

Nickel

29

Cu

Copper

30

Zn

Zinc

31

Ga

Gallium

32

Ge

Germanium

33

As

Arsenic

34

Se

Selenium

35

Br

Bromine

36

Kr

Krypton

37

Rb

Rubidium

38

Sr

Strontium

39

Y

Yttrium

40

Zr

Zirconium

41

Nb

Niobium

42

Mo

Molybdenum

43

Tc

Technetium

44

Ru

Ruthenium

45

Rh

Rhodium

46

Pd

Palladium

47

Ag

Silver

48

Cd

Cadmium

49

In

Indium

50

Sn

Sn

51

Sb

Antimony

52

Te

Tellurium

53

I

Iodine

54

Xe

Xenon

55

Cs

Cesium

56

Ba

Barium

57

La

Lanthanum

58

Ce

Cerium

59

Pr

Praseodymium

60

Nd

Neodymium

61

Pm

Promethium

62

Sm

Samarium

63

Eu

Europium

64

Gd

Gadolinium

65

Tb

Terbium

66

Dy

Dysprosium

67

Ho

Holmium

68

Er

Erbium

69

Tm

Thulium

70

Yb

Ytterbium

71

Lu

Lutetium

72

Hf

Hafnium

73

Ta

Tantalum

74

W

Tungsten

75

Re

Rhenium

76

Os

Osmium

77

Ir

Iridium

78

Pt

Platinum

79

Au

Gold

80

Hg

Mercury

81

Tl

Thallium

82

Pb

Lead

83

Bi

Bismuth

84

Po

Polonium

85

At

Astatine

86

Rn

Radon

87

Fr

Francium

88

Ra

Radium

89

Ac

Actinium

90

Th

Thorium

91

Pa

Protactinium

92

U

Uranium

93

Np

Neptunium

94

Pu

Plutonium

95

Am

Americium

96

Cm

Curium

97

Bk

Berkelium

98

Cf

Californium

99

Es

Einsteinium

100

Fm

Fermium

101

Md

Mendelevium

102

No

Nobelium

103

Lr

Lutetium

104

Rf

Rutherfordium

105

Db

Dubnium

106

Sg

Seaborgium

107

Bh

Berkelium

108

Hs

Hassium

109

Mt

Moscovium

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Ds

Darmstadtium

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Rg

Rutherfordium

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Cn

Chlorine

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Fl

Flerovium

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Lv

Livermorium

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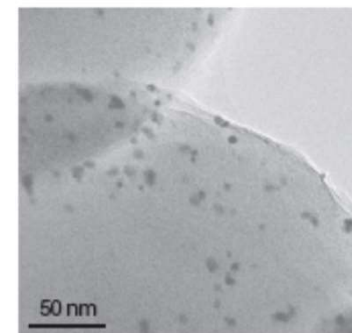
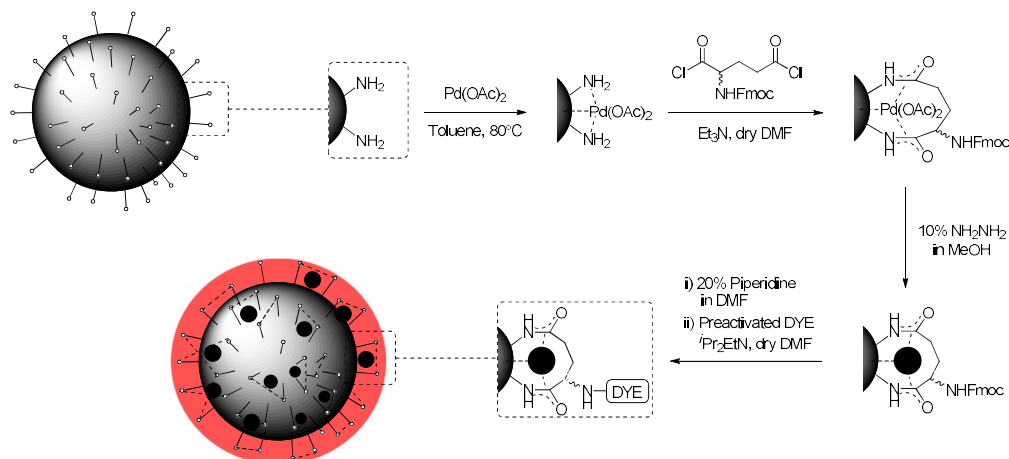
Ununoctium

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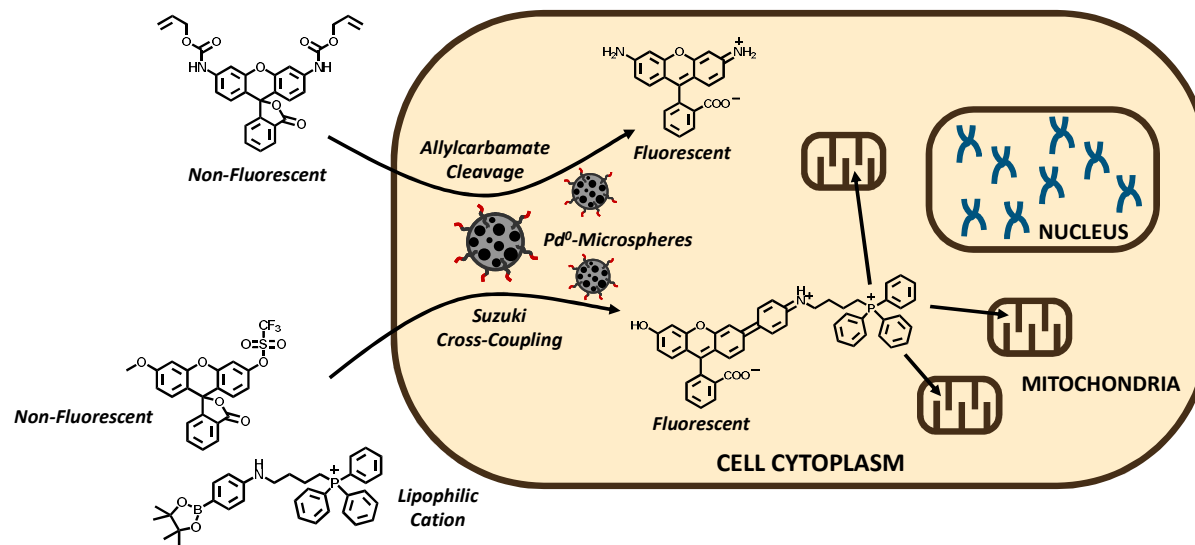
# Palladium chemistry in cells

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

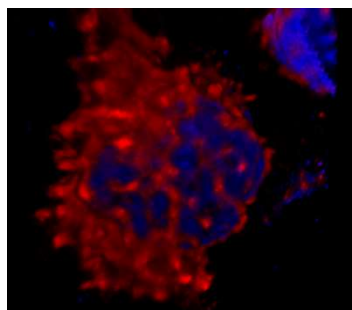
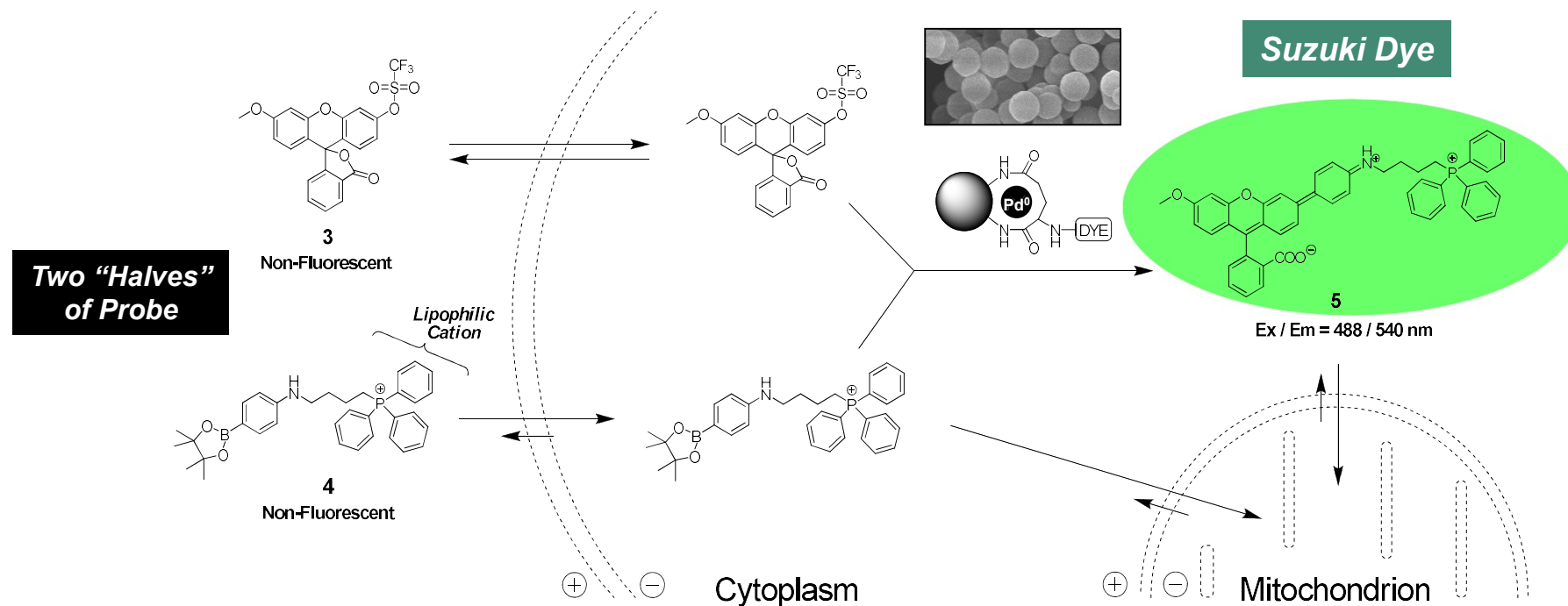


Cell penetrating microspheres that stay in the cytoplasm >> exonuclear location

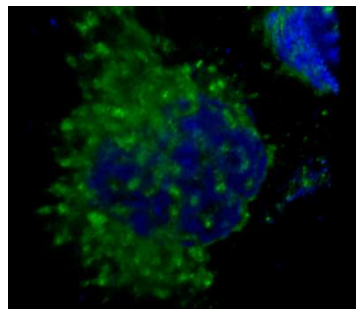
**Alloc  
deprotection  
&  
Suzuki  
coupling  
inside cells**



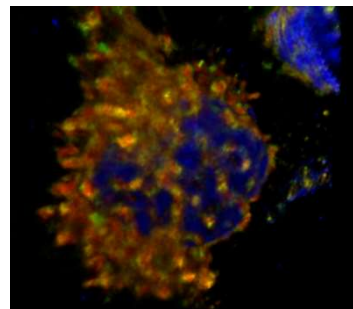
# Suzuki reaction inside cells



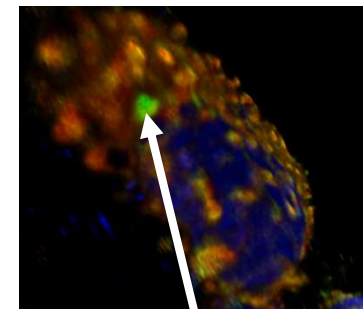
MitoTracker Far Red



Suzuki Dye



Merge



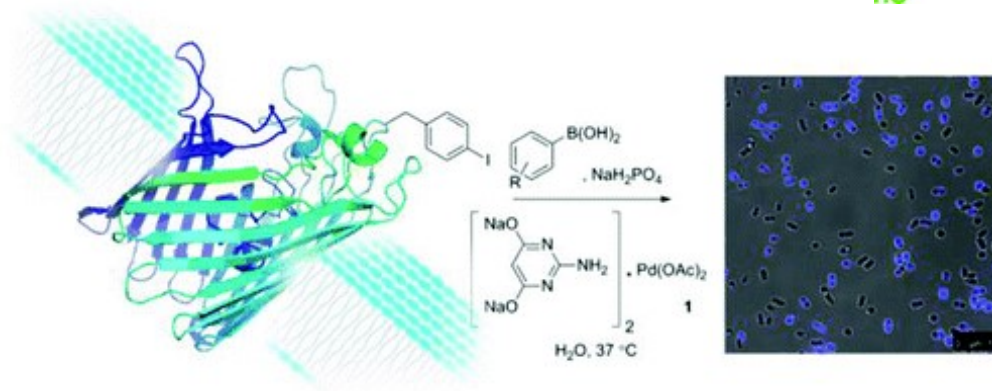
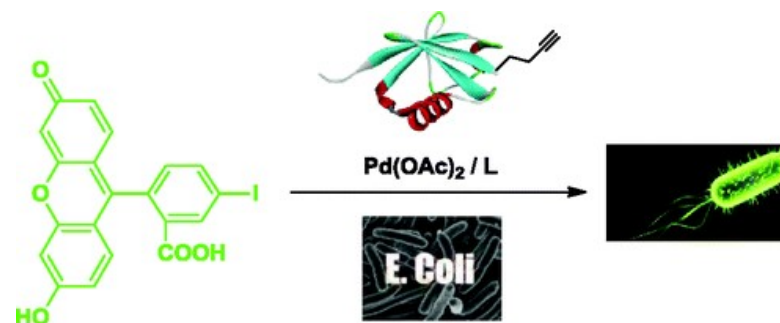
Pd<sup>0</sup>-microsphere

# 2011-2012 (Pd catalysis)

## PROTEIN LABELLING SONOGASHIRA COUPLING

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

Qing Lin



## PROTEIN LABELLING SUZUKI COUPLING

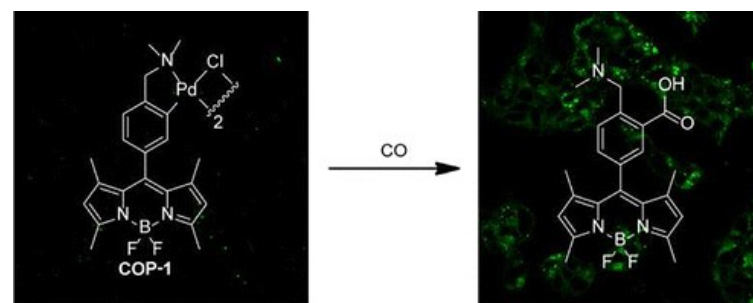
*J. Am. Chem. Soc.*, **2012**, 134, 800–803

Ben Davis

## CARBON MONOXIDE SENSING PALLADIUM-MEDIATED CARBOXYLATION

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

Chris Chang

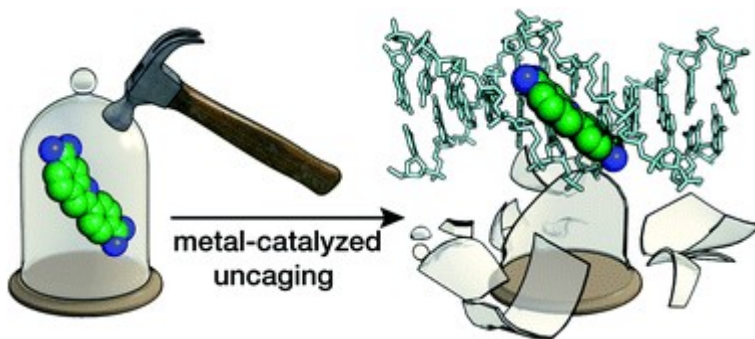
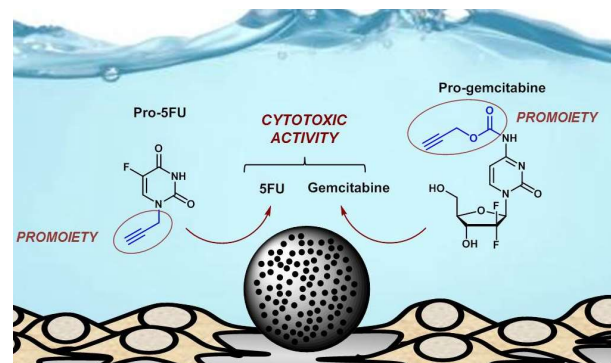




# 2014-2015 (uncaging chemistries)

## EXTRACELLULAR PRODRUG ACTIVATION -MEDCHEM-

*Nat. Commun.* **2014**, 5, 3277  
*J. Med. Chem.* **2014**, 57, 5395  
**OUR LAB**

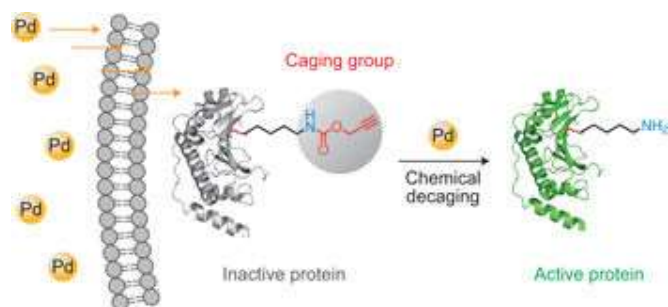


*Chem. Sci.* **2014**, 5, 1901  
 J. L. Mascareñas

## INTRACELLULAR PROBE ACTIVATION -CHEMICAL BIOLOGY-

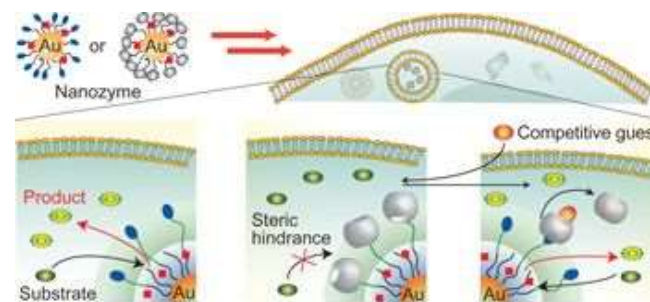
## INTRACELLULAR PROTEIN ACTIVATION -CHEMICAL BIOLOGY-

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

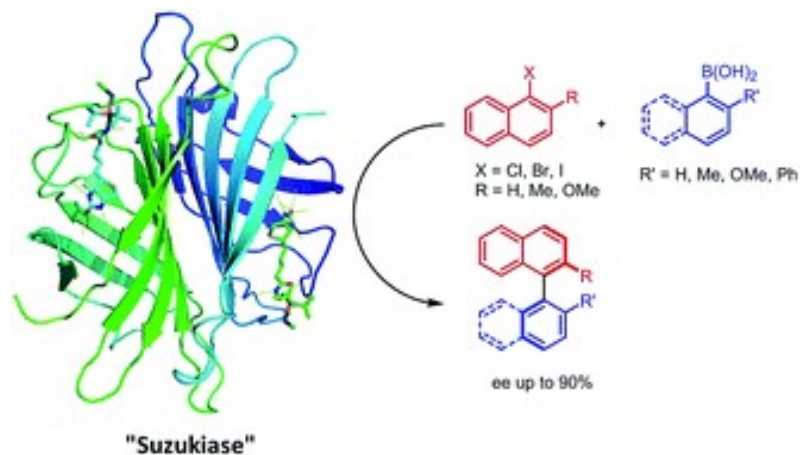


## SUPRAMOLECULAR REGULATION OF CATALYSIS -CHEMICAL BIOLOGY & MEDCHEM-

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



# 2016 (metalloenzymes)

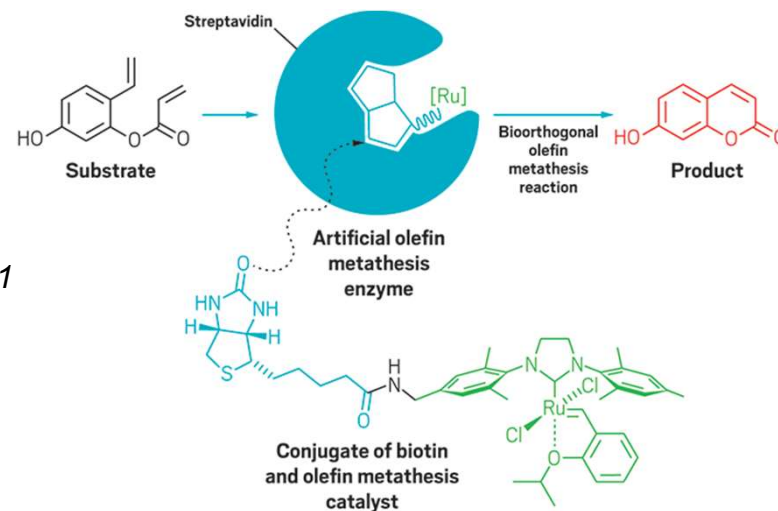


*Chem. Sci.* **2016**, 7, 673  
T. Ward

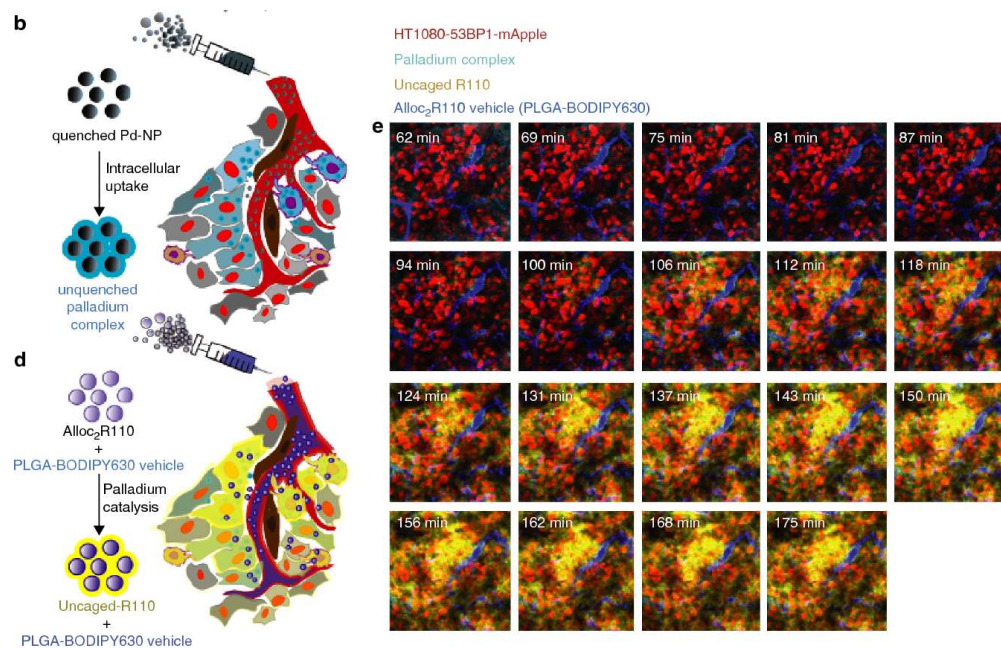
**DESIGN OF A  
SUZUKIASE  
-CHEMICAL BIOLOGY-**

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

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



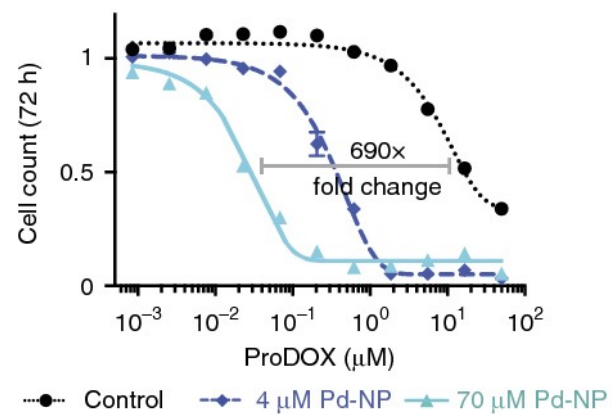
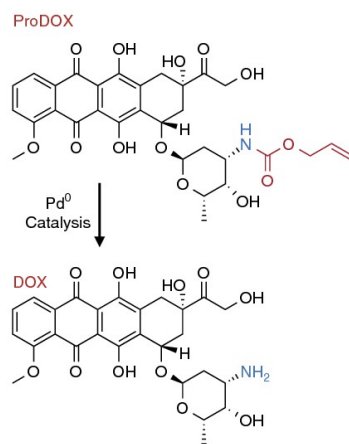
# 2017 (in vivo PoC)



## PALLADIUM NANOPARTICLES -CANCER THERAPY-

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

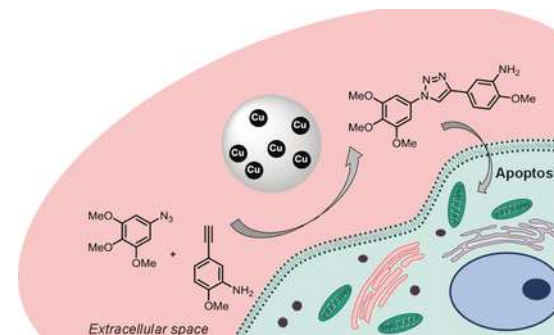
R. Weisleder



# 2016 & 2018 (Cu catalysis)

CLICK CHEMISTRY  
OUTSIDE CELLS  
-CHEMICAL BIOLOGY  
& MEDCHEM-

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

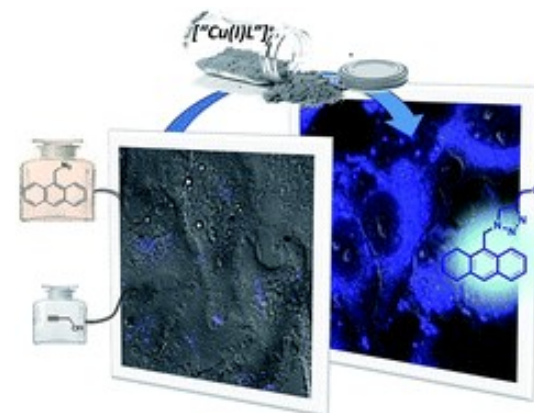


*JACS* **2018**, 140, 3423  
Albertazzi & Palmans

COPPER MEDIATED  
UNCAGING CHEMISTRY  
IN CELLS  
-CHEMICAL BIOLOGY-

CLICK CHEMISTRY IN CELLS  
-CHEMICAL BIOLOGY-

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

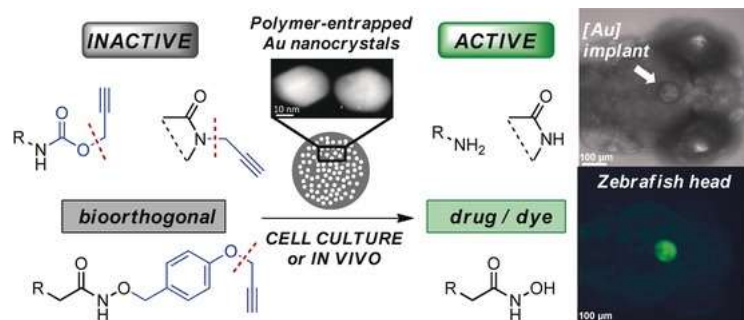
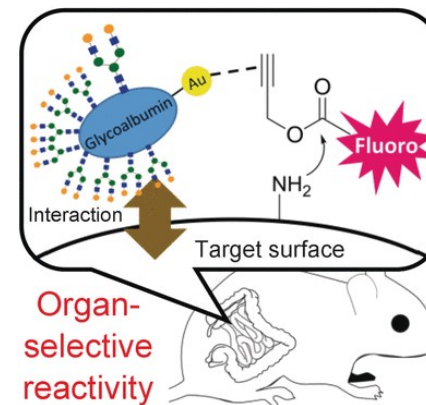




# 2017 & 2018 (Au catalysis)

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

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

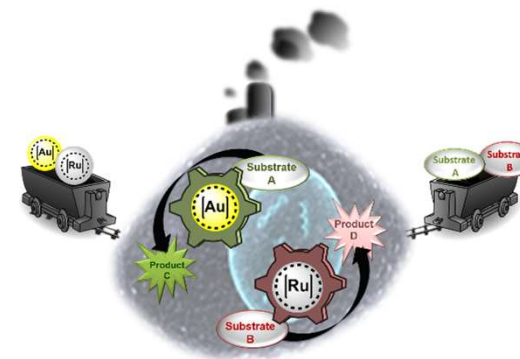


*Angew. Chemie* **2017**, 56, 12548  
**OUR LAB**

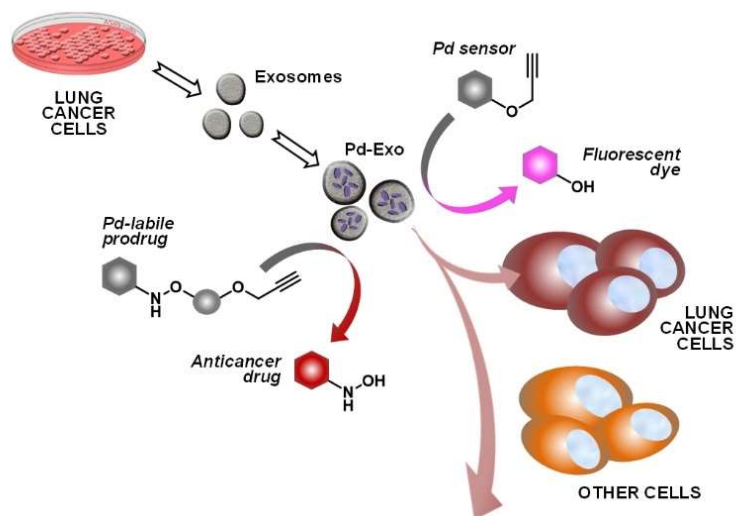
## GOLD(0)-MEDIATED UNCAGING CHEMISTRY -MED. CHEM-

## 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

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## RING-CLOSING METATHESIS TO UNCAGE PRODRUGS

-CHEMICAL BIOLOGY & MEDCHEM-

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

T. Ward

