Metal complexes catalysis in biological system

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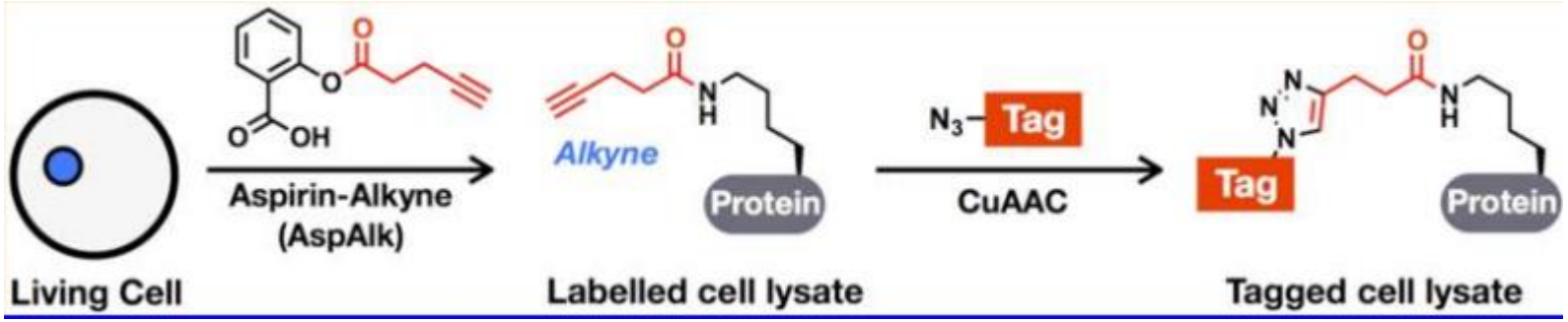
Features of modern catalysis:

New reaction/structure
Mild condition
Wide in scope
High yield (less side product)

Biological system

Copper catalysis click chemistry



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Protein PEGylation

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Self-Liganded Suzuki–Miyaura Coupling for Site-Selective Protein PEGylation**

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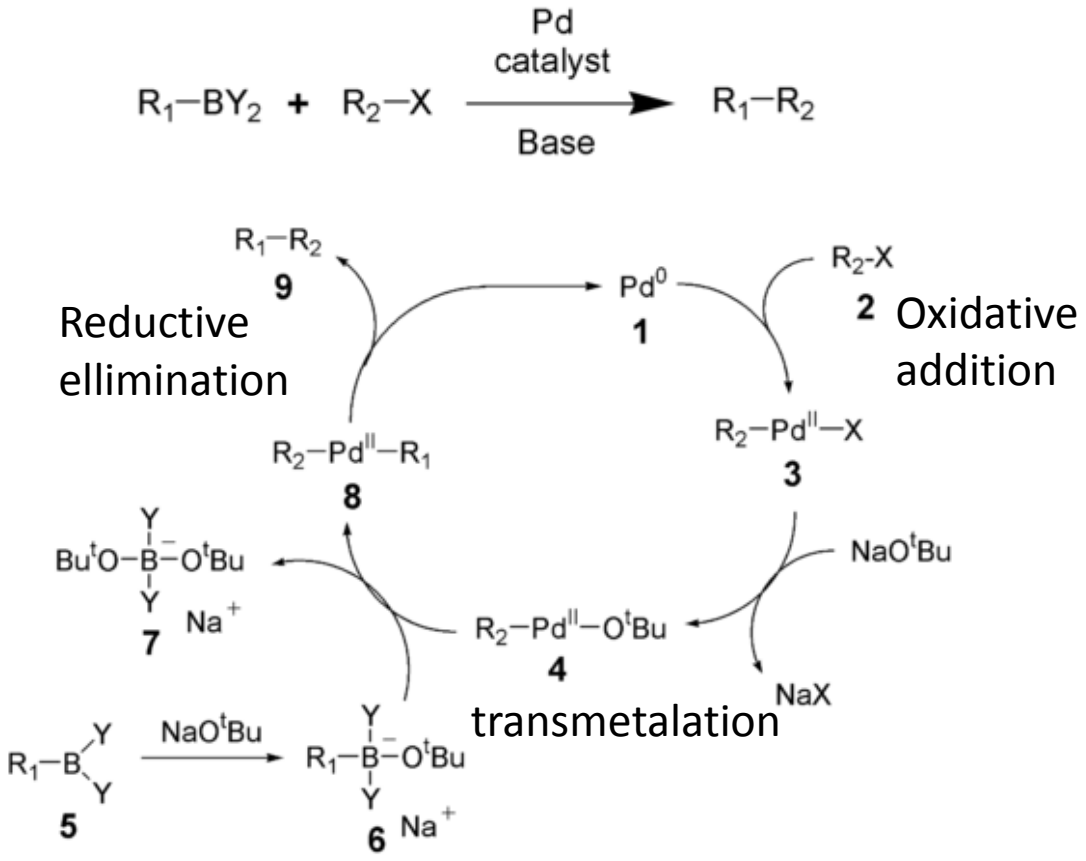
Suzuki-Miyaura coupling/ Suzuki reaction



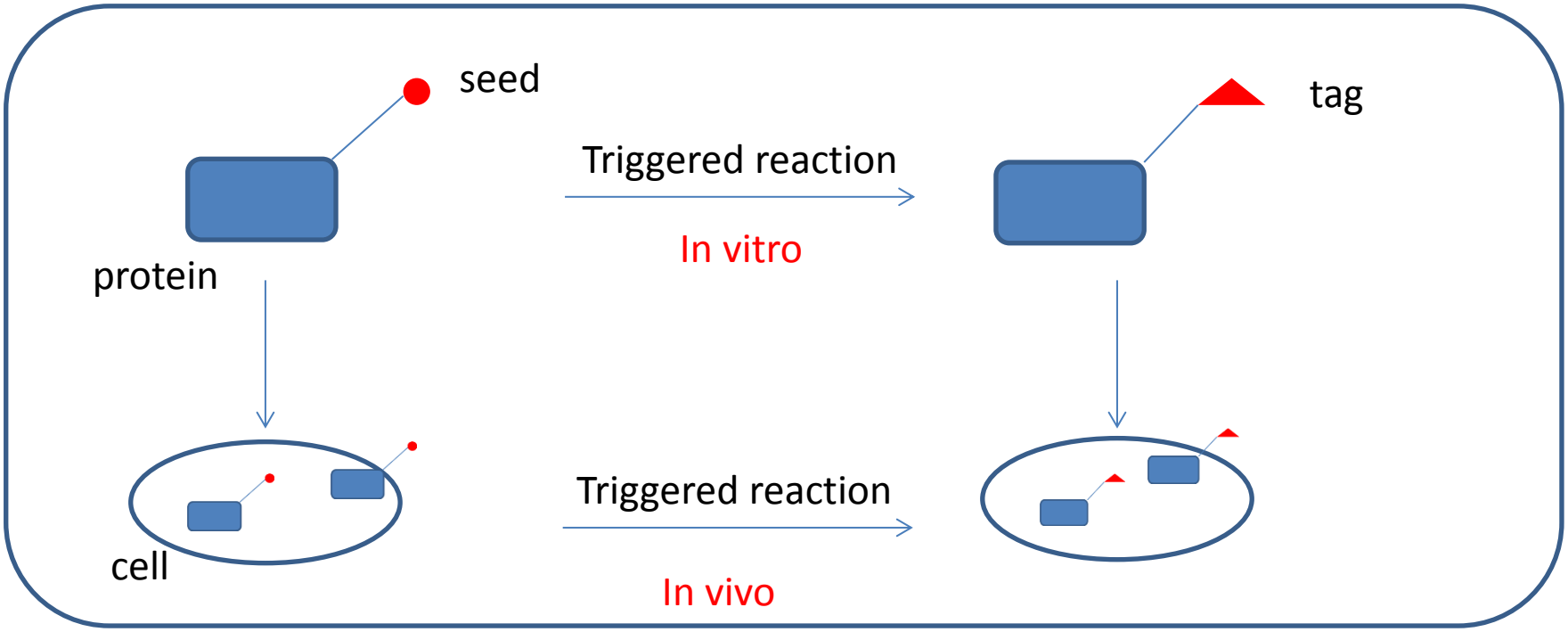
From wikipedia.org

PEGylation: PEG (polyethylene glycol) attachment

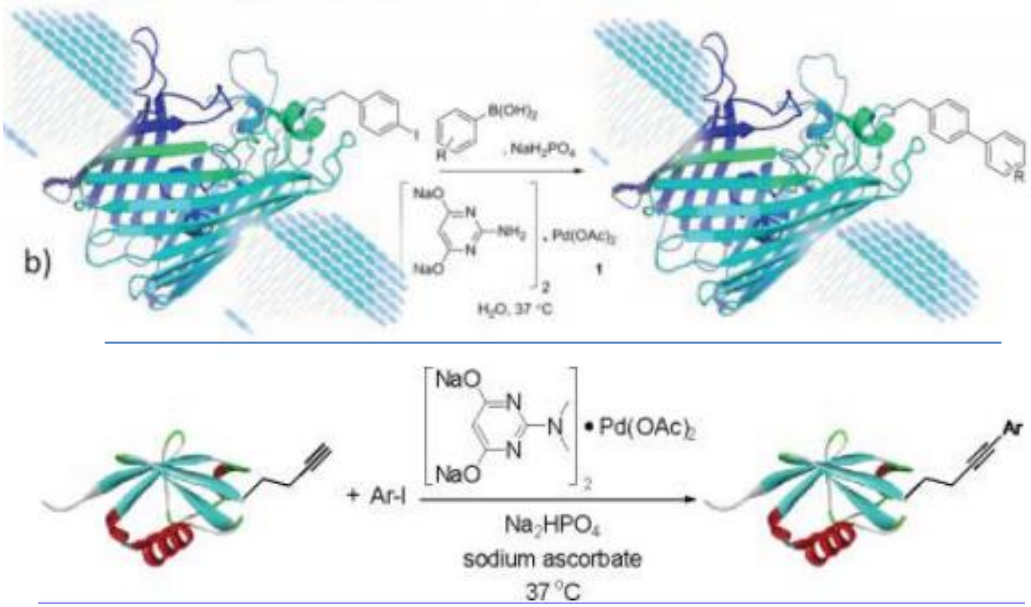
+ Enhance protein stability and pharmacokinetics
- Recognition and function problems caused by non-specific PEGylation

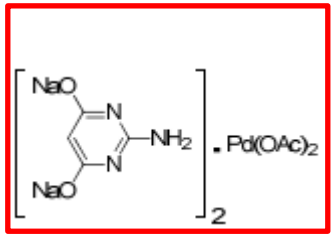
Position-specific PEGylation:
protect while expose

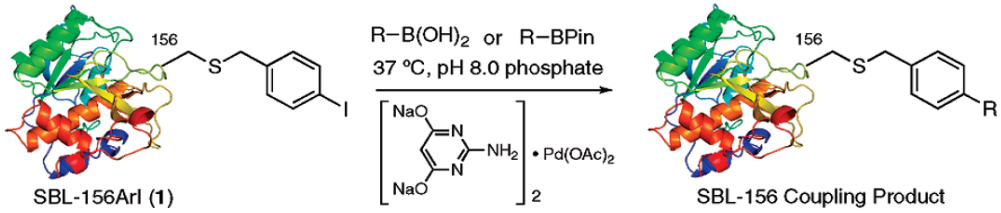
Pre-seeding protocol



Non-copper catalysis







JACS. 2012, 134 (2), pp 800–803
JACS. 2011, 133, 15316–15319
Chem. Commun. , 2011, 47, 1698-1700
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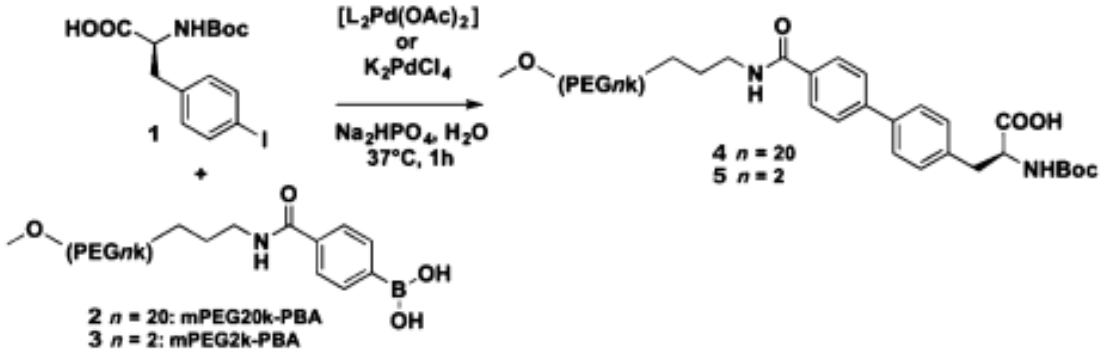

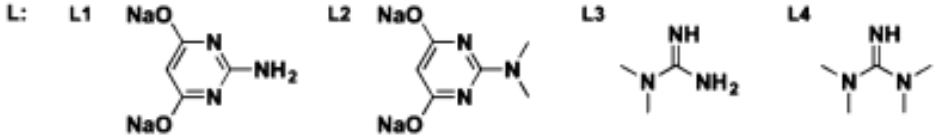

Entry	PEG [kDa]	L	PEG [equiv]	Pd loading [mol%]	Yield [%][a]
1	20	**L1**	1.5	5	0
2	20	**L2**	1.5	5	68
3	20	**L3**	1.5	5	63
4	20	**L4**	1.5	5	69
5	20	**L4**	1.5	20	64
6	20	**L4**	3	20	90
7	2	**L1**	3	5	2
8	2	**L2**	3	5	92
9	2	**L3**	3	5	85
10	2	**L4**	3	5	93
11	20	–[b]	3	20	92
12	2	–[b]	3	5	93

[a] Yields determined by ^{1}H NMR spectroscopy. [b] K_2PdCl_4 was used as the palladium source.

L1 not working
Samaller PEG favored
[catalyst] favored
[PEG] favored
No ligand favored

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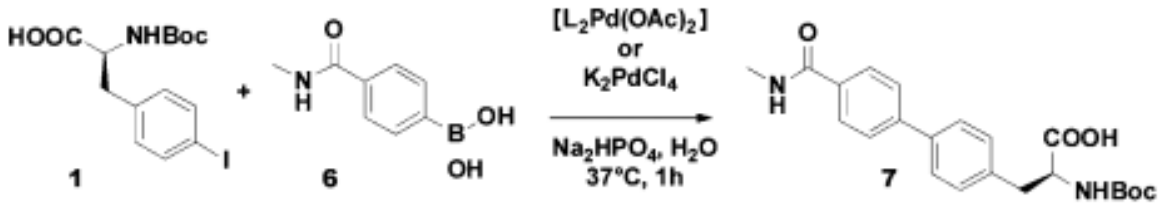
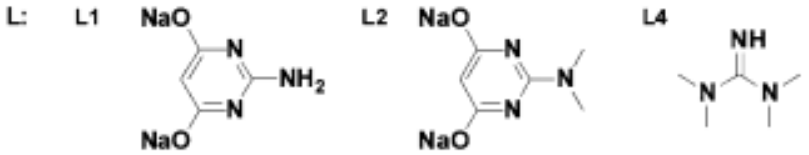


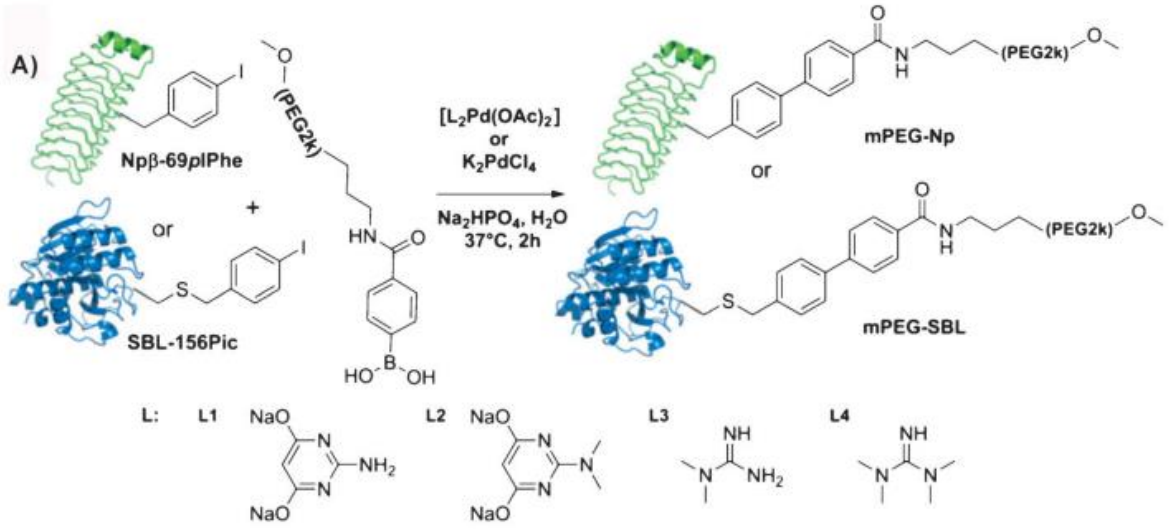


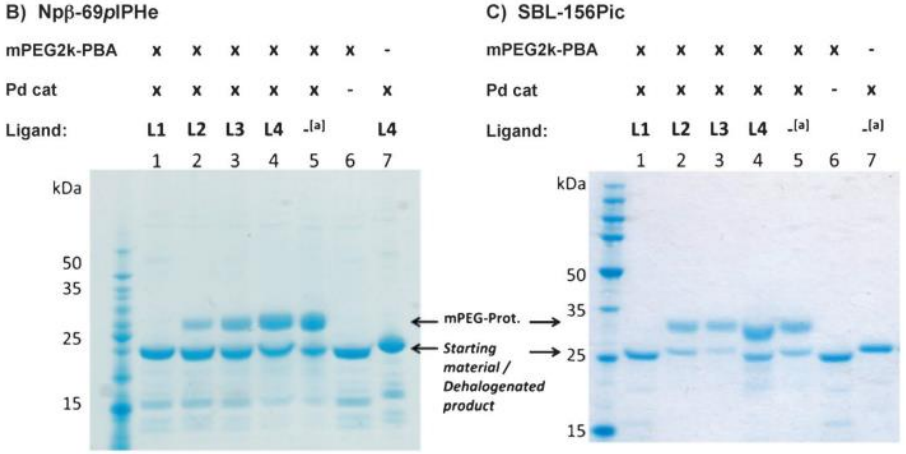
Entry	L	Yield [%][b]
1	**L1**	34
2	**L2**	>95
3	**L4**	93
4	–[c]	20
5	mPEG 2000[c]	86
6	mPEG 2000, Δ[c,d]	>95

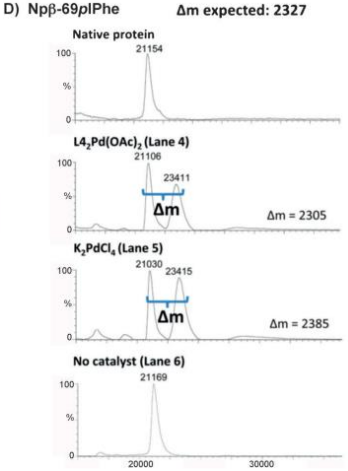
[a] Reaction conditions: **6** (3 equiv)/Boc*p*IPhe, Pd (5 mol%), 1 h, 37°C. [b] Yields determined by ^{1}H NMR spectroscopy. [c] K_2PdCl_4 was used as the palladium source. [d] mPEG2000 pre-incubated with K_2PdCl_4 at 37°C for 15 min.

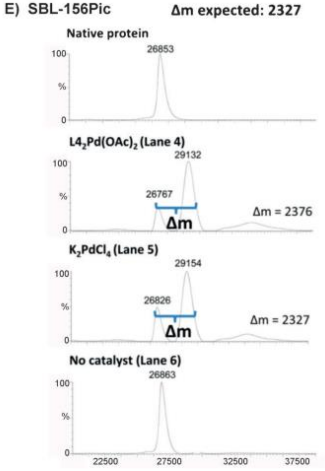
PEG dependency

Catalysis on protein









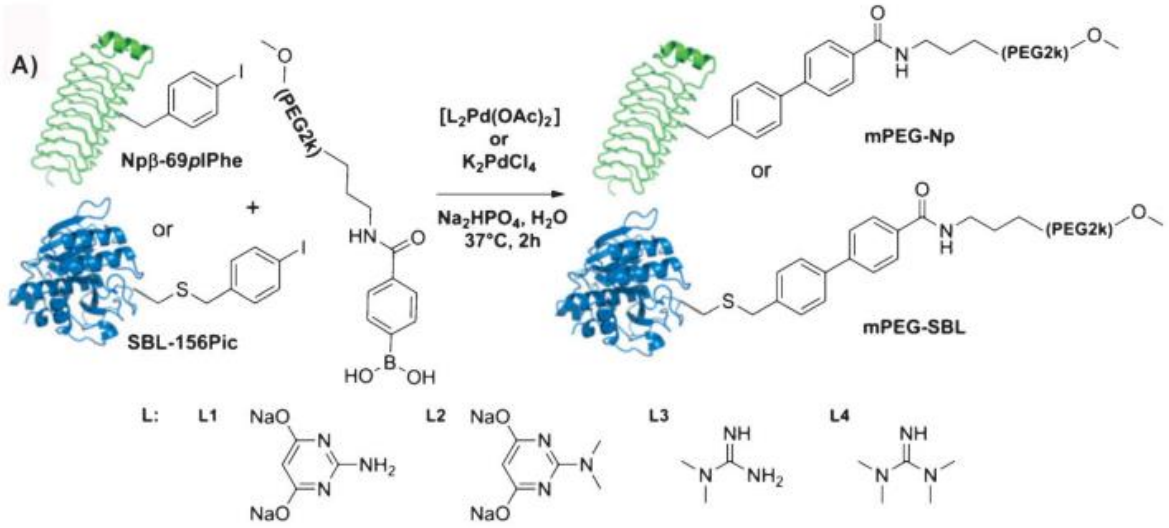
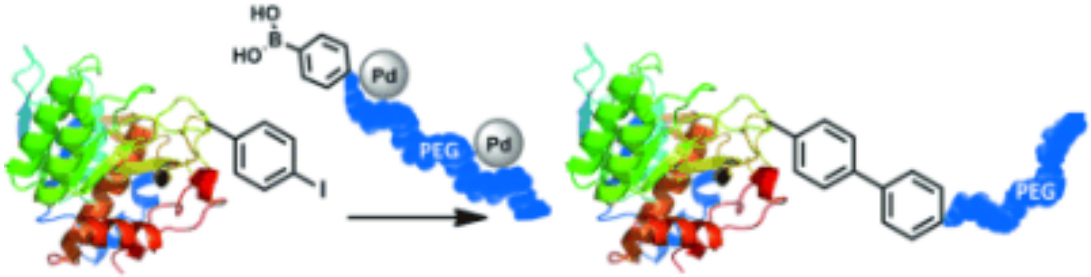


Table 3: Yield of the Suzuki–Miyaura PEGylation of Npβ-69*p*IPhe and SBL-156Pic with mPEG2k-PBA, as determined by gel densitometry.

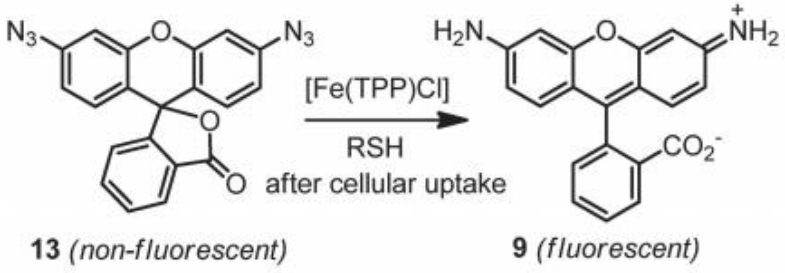
Npβ-69*p*IPhe		SBL-156Pic	
ligand	yield [%]	ligand	yield [%]
L1	0	**L1**	0
L2	25	**L2**	70
L3	40	**L3**	80
L4	55	**L4**	70
_[a]	60	_[a]	70

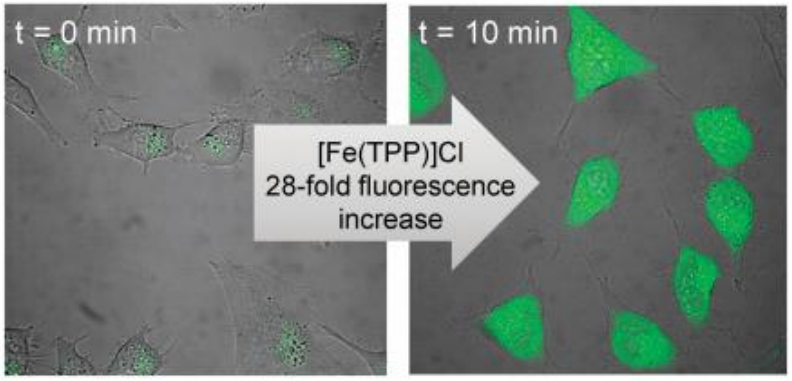
[a] K_2PdCl_4 was used as the palladium source.

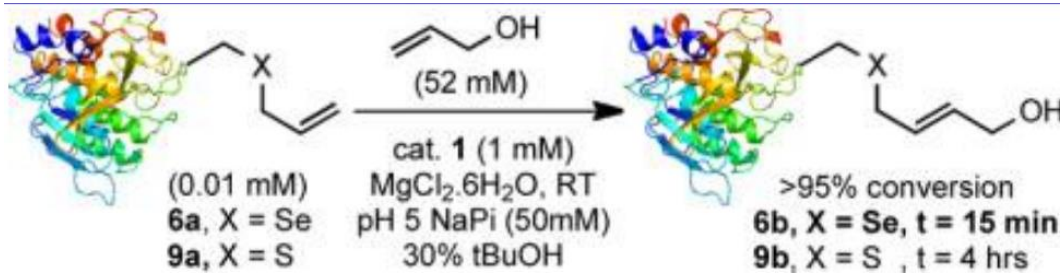


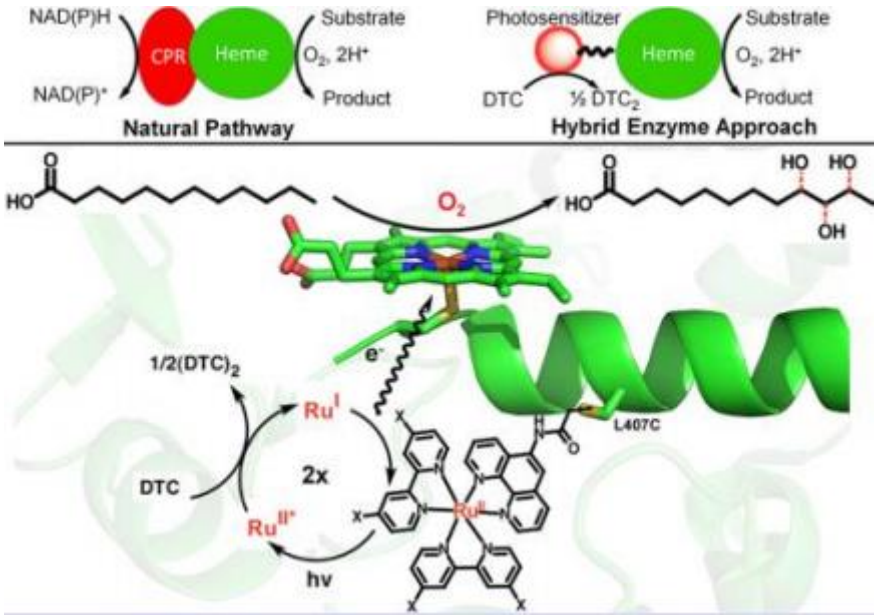
Summary

1. First ligandless metal catalysis on protein
2. Discovery PEG dependency of metal catalyst
3. C-C bond for PEGylation better than other method like disulfination
4. Site-specific PEGylation with previous seeding









Expand the vision to biosystem

Using chemical tools and methods to explore biology

JACS. ASAP
JACS. 2013, 135, 12156−12159
ChemBioChem. 2012, 13, 1116–1120

THANKS !