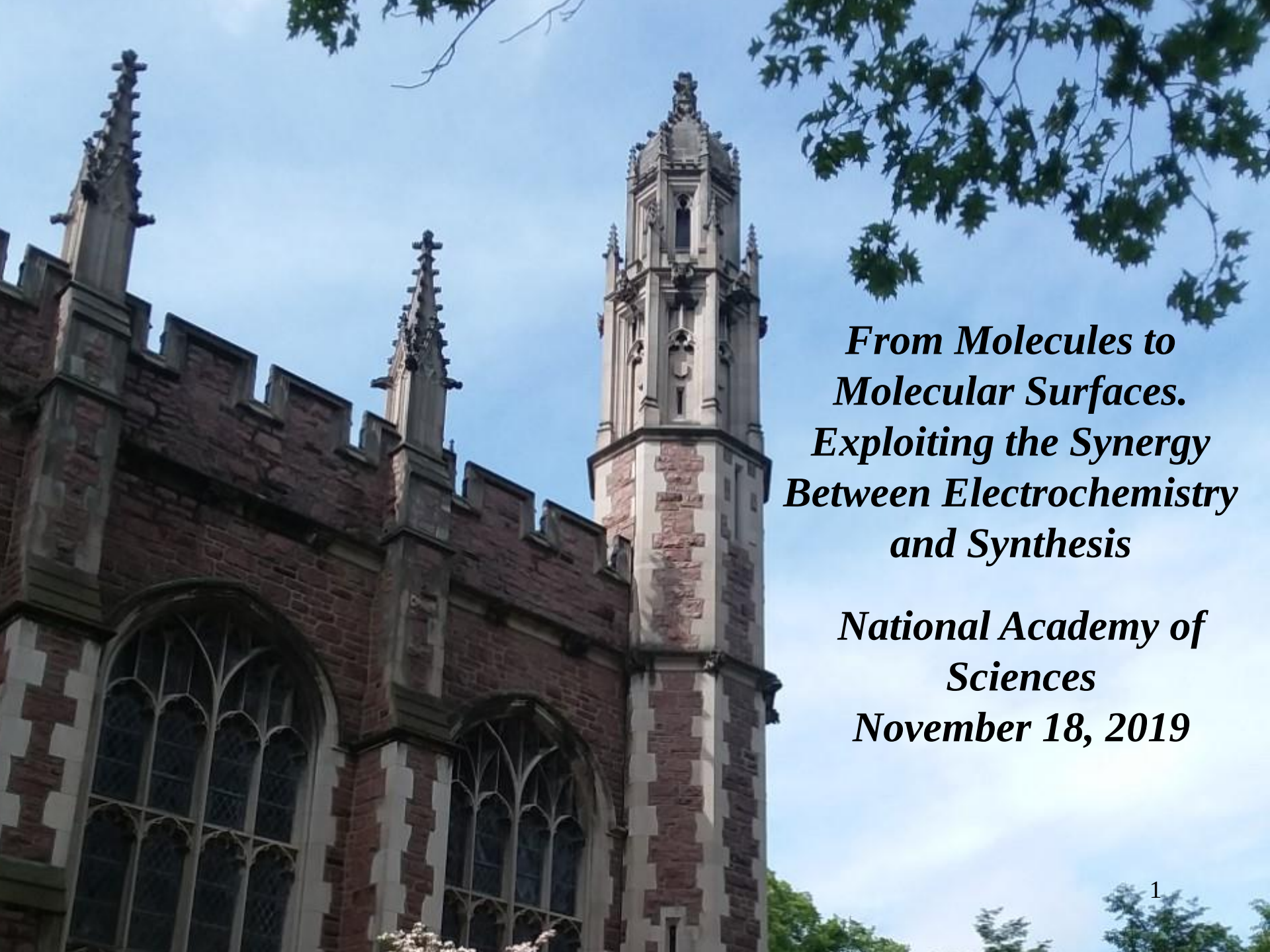
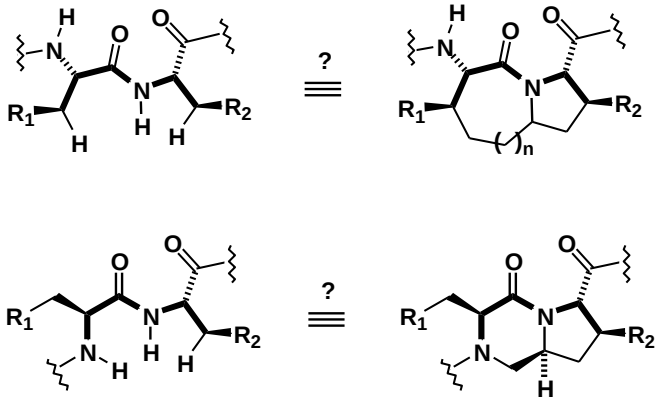


From Molecules to Molecular Surfaces. Exploiting the Synergy Between Electrochemistry and Synthesis

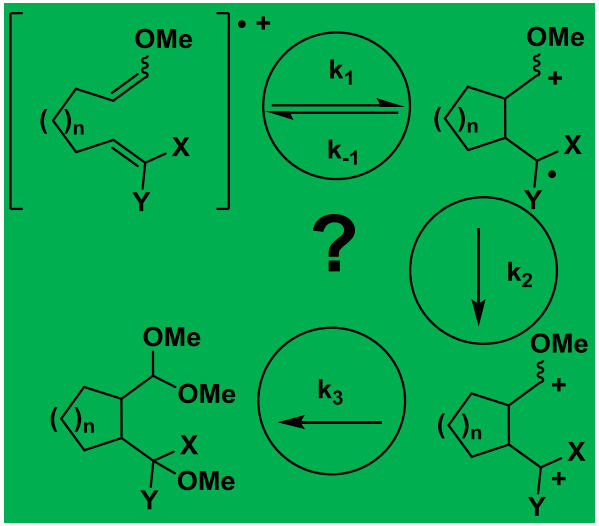
National Academy of Sciences
November 18, 2019

For today, four very short, very different vignettes that all resonate with a message of versatility and selectivity.

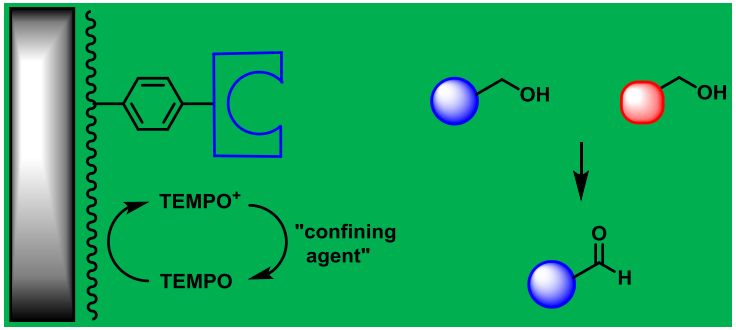
I.



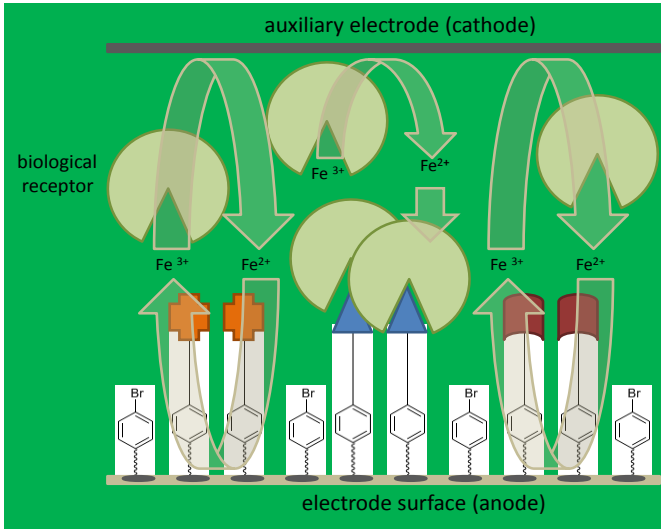
II.



IV.



III.



Manuel M. Baizer:

"…organic electrochemical synthesis has ceased to be a laboratory curiosity, a methodology to be tried when all else fails, a procedure that involves mysterious black boxes and dials and wires. The science and technology are now well developed although not mature…"

This sentiment was based on the pioneering work being done by the groups of Schäfer, Steckhan, Utley, Simonet, Shono, Torii, Tanaka, Uneyama, Osa, Weinberg, Miller, Swenton, Peters, Fry, and many others.

* From Baizer, M. M. "Electroorganic Processes Practiced in the World", *Pure and Applied Chemistry*, **1986**, *58*, 889.

A nice sentiment, but was it true?

1989: An anonymous reviewer wrote,

"This proposal has two main elements. The first is a highly interesting investigation of reactive radical cation intermediates. The second involves use of the unproven technique of organic electrochemistry, an effort that may well interfere with the PI's ability to accomplish the stated aims associated with the first."

for a proposal that was funded.

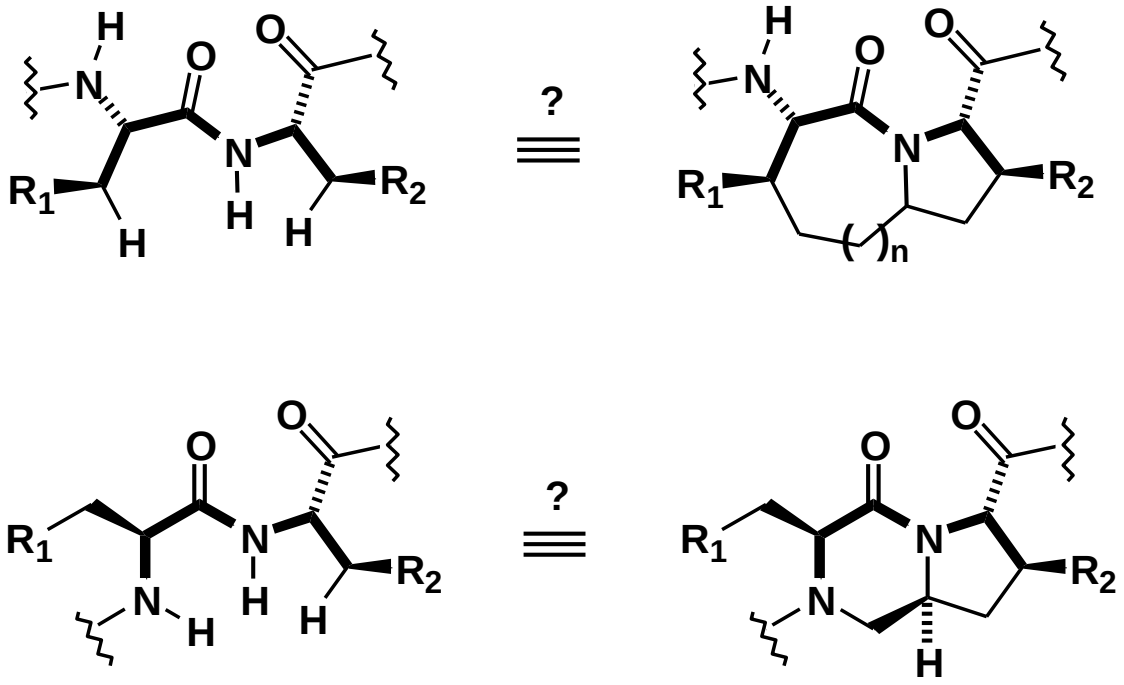
Not hard to imagine what synthetic chemists wrote when they did not like a proposal, paper, or talk. Electrochemistry was unproven, required specialized equipment, not general, and a method that would never be adopted by others.

Why this difference in opinion between this small, vibrant group of organic chemists doing electrochemistry and the larger synthetic community?

At the time, our opinion was that electrochemistry lacked the type of synthetically compelling "story" that the [2+2]-cycloaddition provided for photochemistry – a reaction that synthetic chemists wanted or needed to do that could not be done any other way.

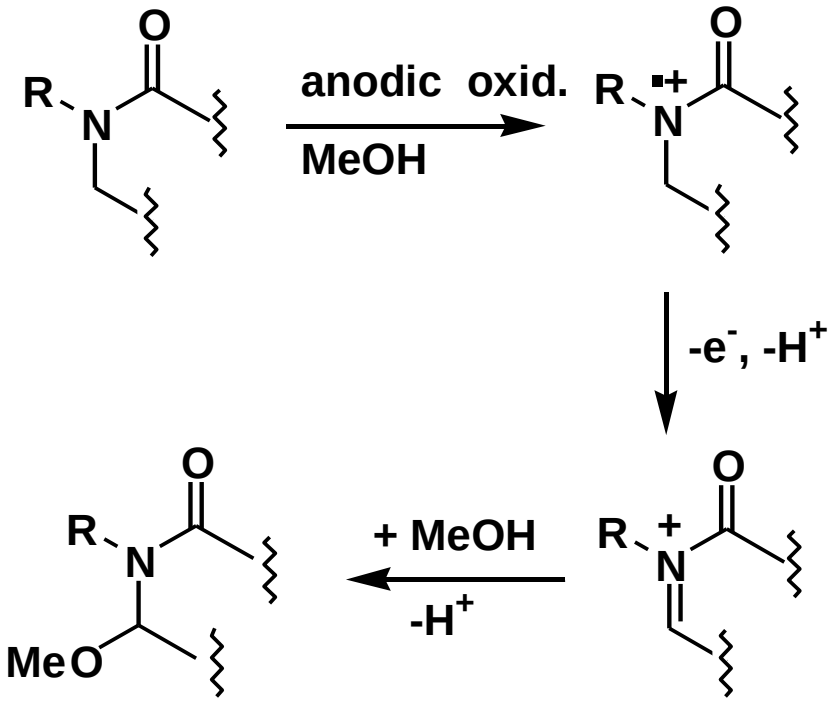
Our goal as a group became to help identify and develop that "electrochemical story".

I. Mapping the Shape of a Peptide Binding Site with Garland Marshall (WUStL Medicine):



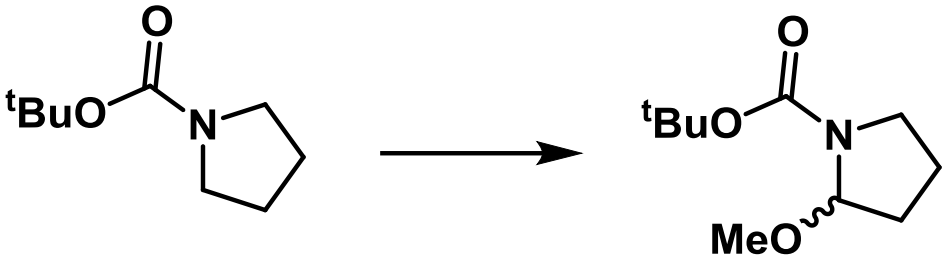
The Goal: To develop synthetic routes to lactam based peptidomimetics that will allow one to shape conformational probes.

For many such efforts, we needed a method for functionalizing an amino acid. Anodic electrochemistry looked to be an ideal solution.

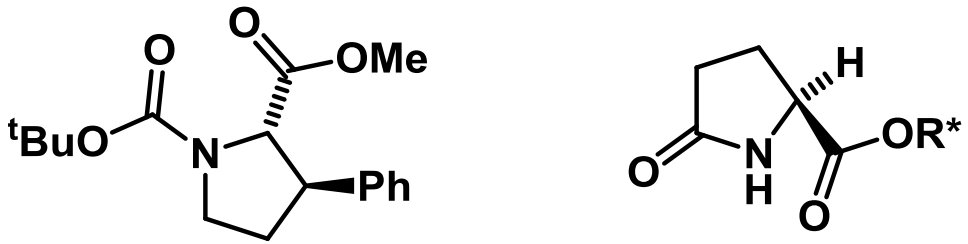


- **Well-known "Shono-oxidation" that was actually discovered by Ross, Finkelstein, and Peterson.**
- **Developed extensively by Shono, Eberson, Nyberg, Steckhan, Ban, and others.**
- **An organic synthesis preparation: Shono, T.; Matsumura, Y.; Tsubata, K. *Organic Synthesis* 1984, *63*, 26.**

Electrochemistry was the ideal tool because…



$E_{p/2}$ *ca.* + 1.95 V (Ag/AgCl) $E_{p/2}$ *ca.* + 2.15 V (Ag/AgCl)

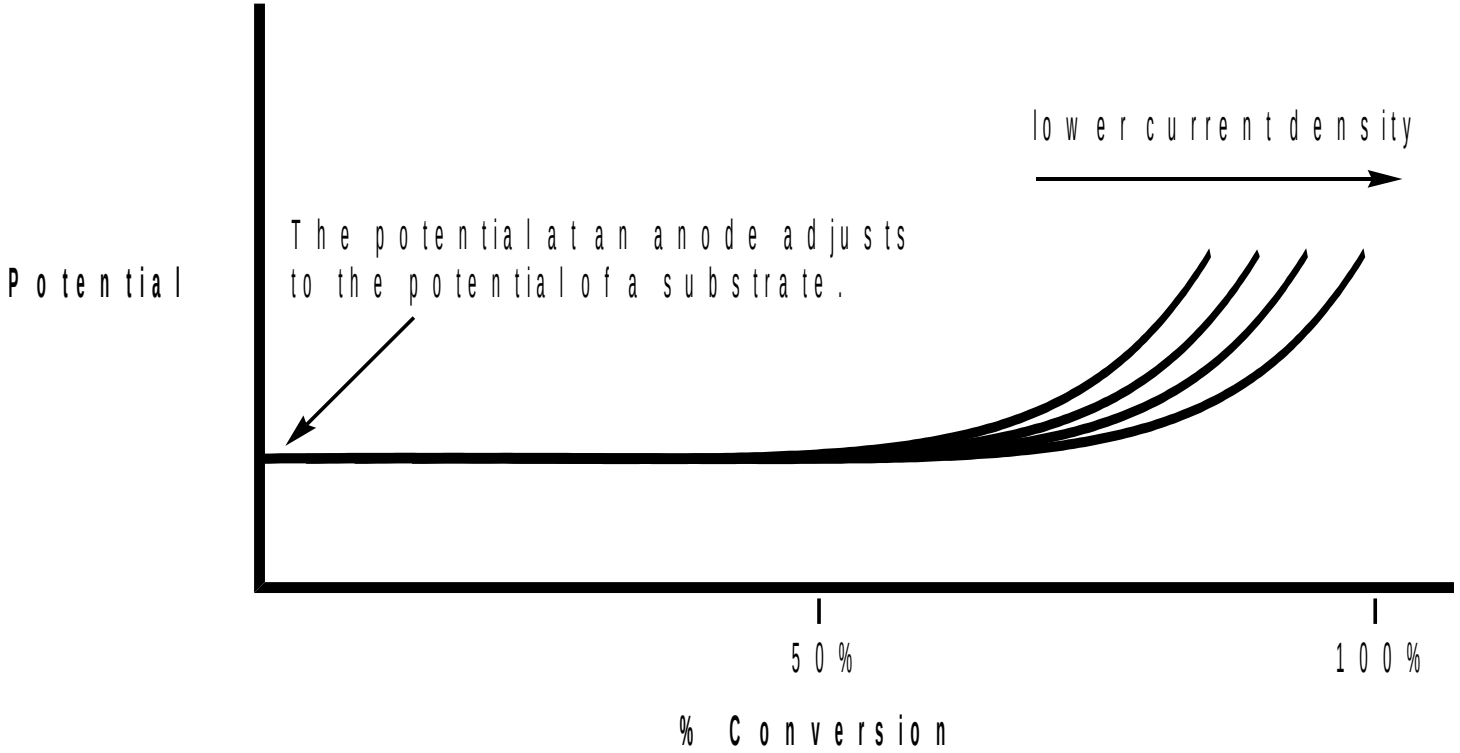


$E_{p/2}$ *ca.* + 2.1 V (Ag/AgCl) $E_{p/2}$ *ca.* + 2.3 V (Ag/AgCl)

….no single chemical oxidant can be used to accomplish the three reactions shown..

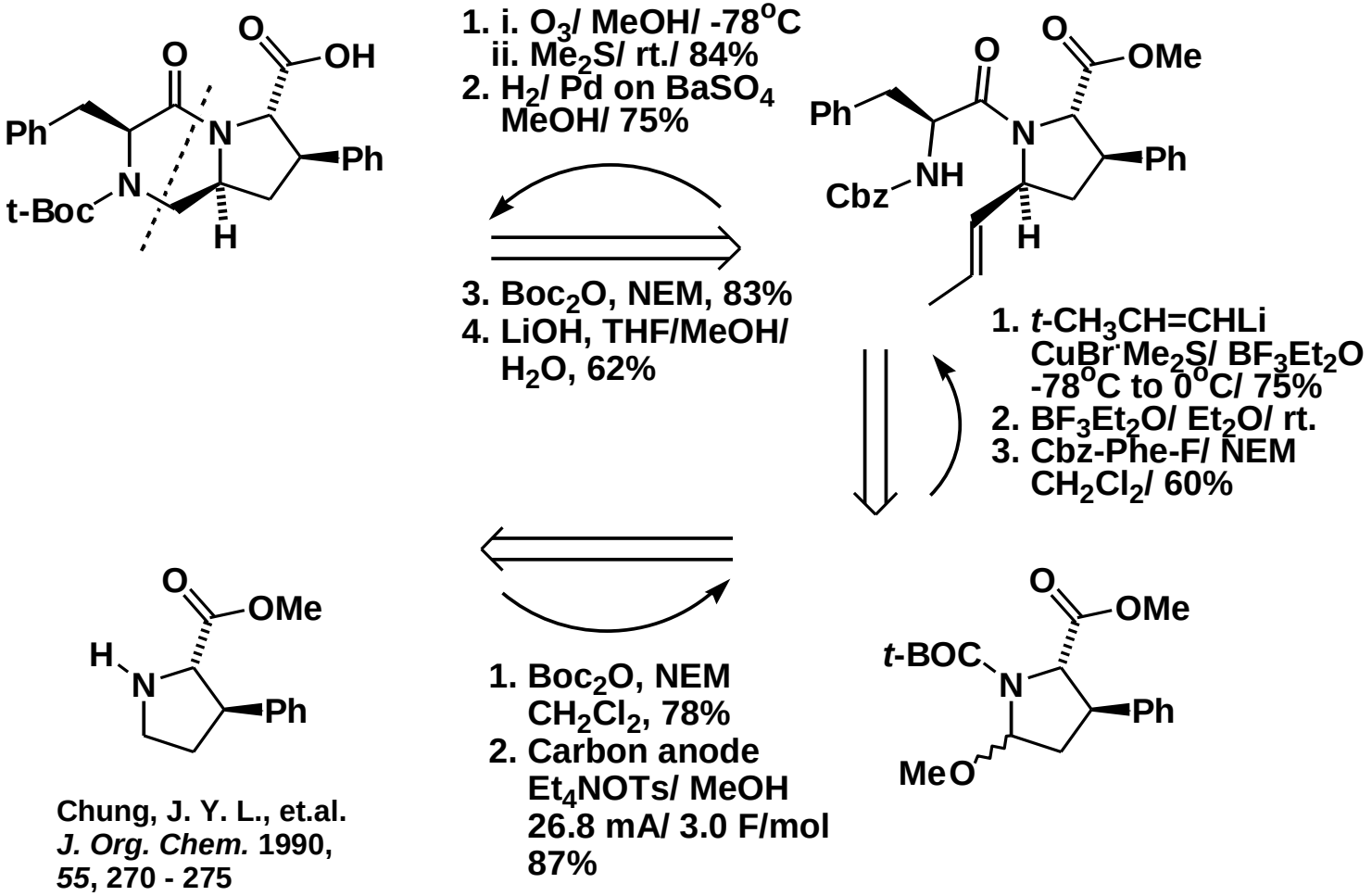
Not a problem for an electrolysis:

Potential vs. % Conversion for Varying Current Density



- **In a *constant current (galvanostatic) reaction*, the potential at the electrode will automatically vary with the nature of the substrate.**
- **Therefore, the substrate (and its oxidation potential) can be varied without any need to change the reaction conditions.**
- **We chose constant current to avoid the use of a "specialized" reference electrode with adoption by the synthetic community in mind.**

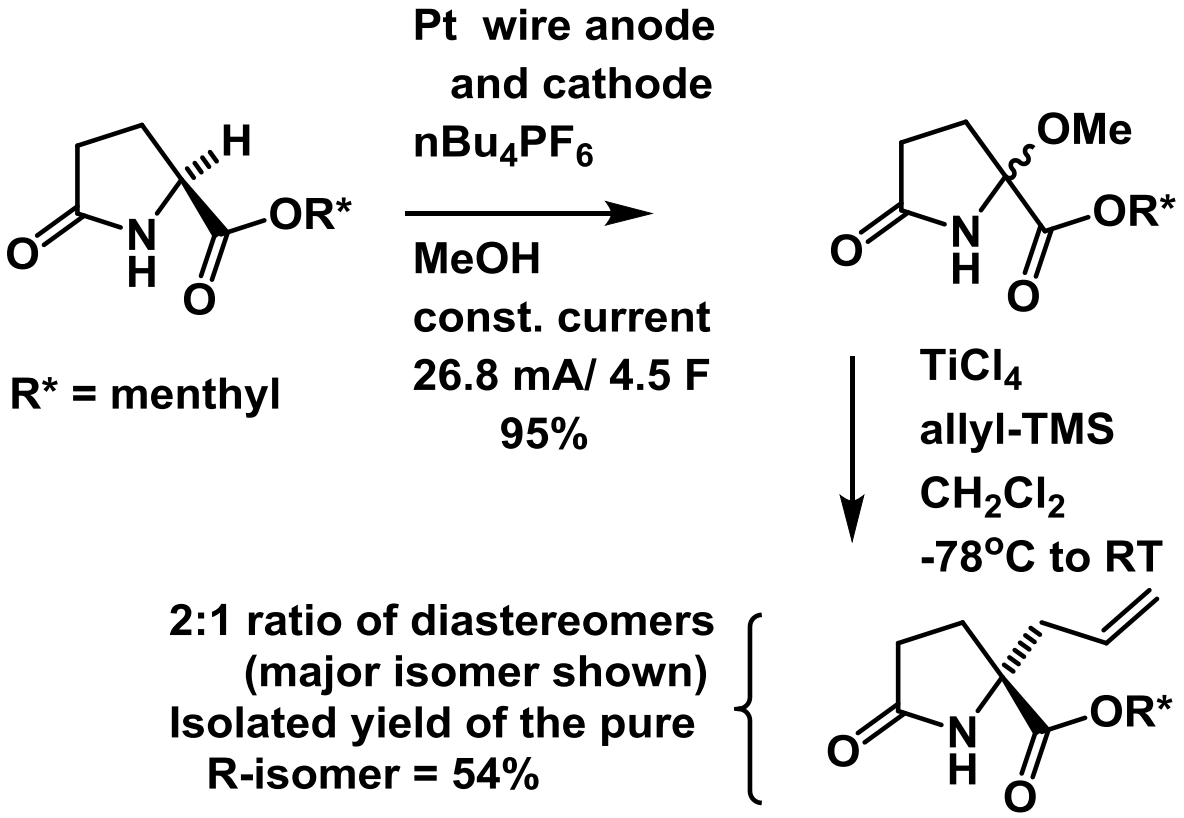
This works out nicely for amide oxidations and the synthesis of peptidomimetics:



Chung, J. Y. L., et.al. *J. Org. Chem.* 1990, *55*, 270 - 275

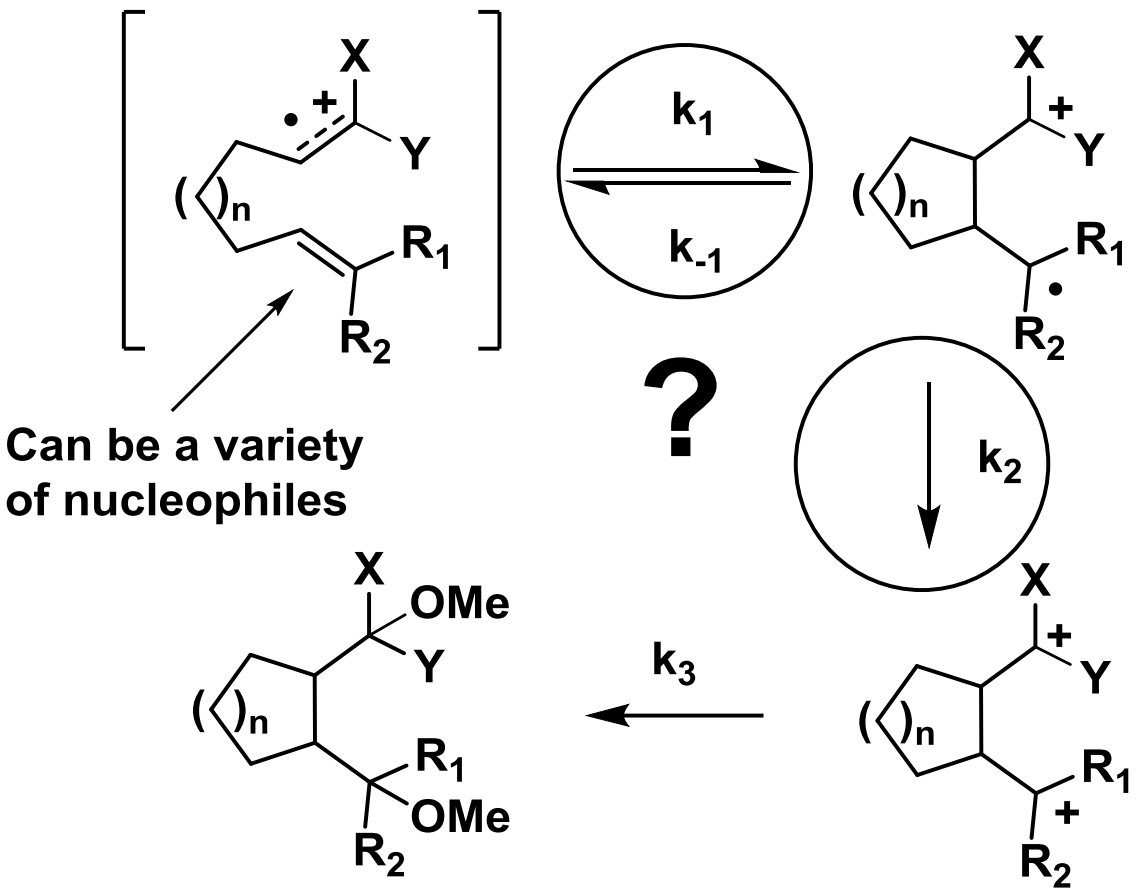
Yunsong Tong, Yvette M. Fobian, Meiye Wu, Nicholas A. Boyd, and Kevin D. Moeller. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1679-1682.

The More Challenging Secondary Amide:



- **The major product was purified by fractional crystallization from hexane.**
- **High current densities and a greasier electrolyte took advantage of the constant current electrolysis to oxidize a substrate that oxidizes slightly above the MeOH solvent.**
- Rutledge, L. D.; Moeller, K. D. *J. Org. Chem.* **1992**, *57*, 6360-6363.

With that backdrop, our second vignette :

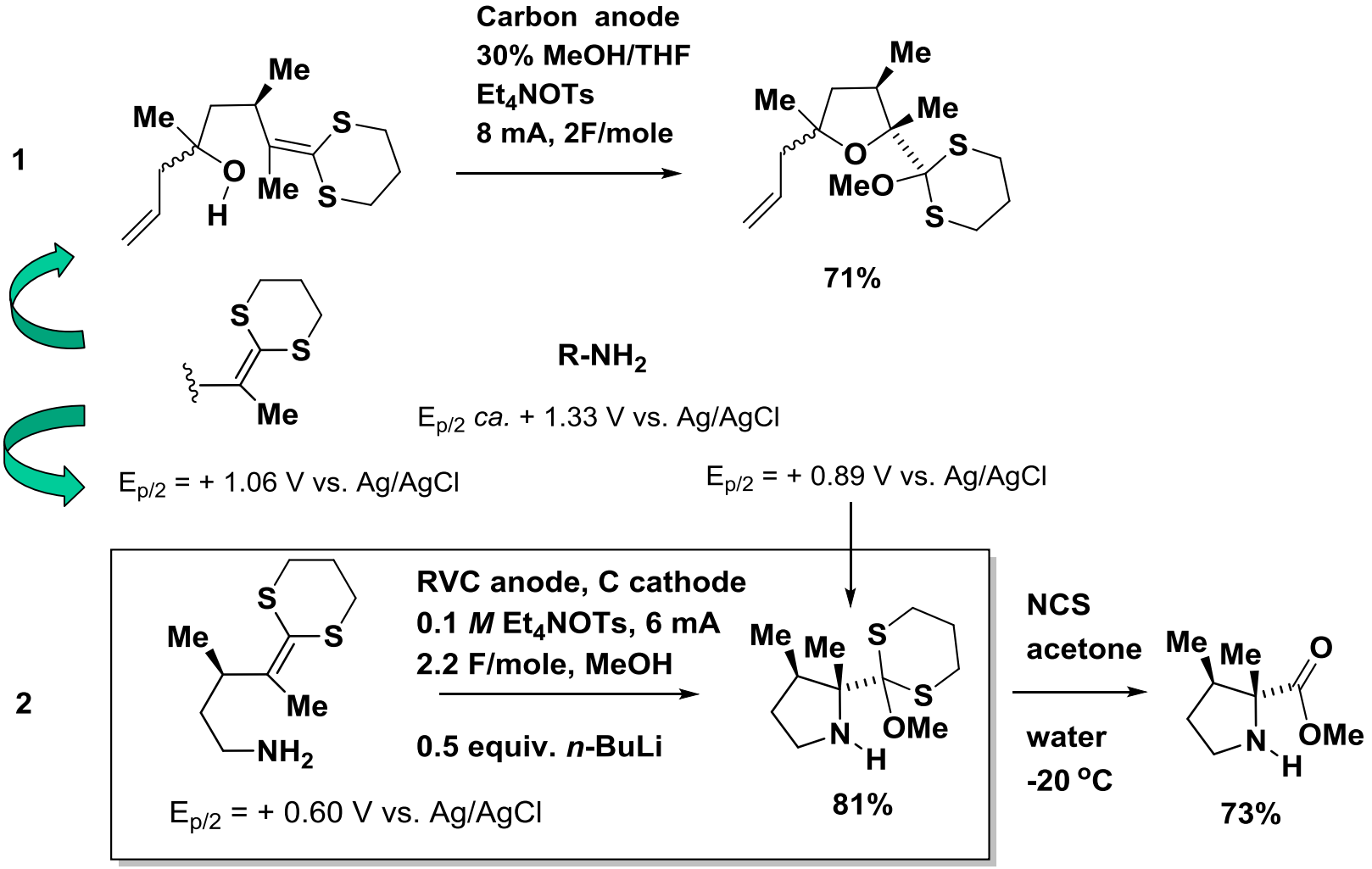


This project looks at the radical cations that are central to oxidative cyclization reactions:

1. ***For a systematic study of the intermediates we needed to do structure-activity studies.***
2. ***So, we needed a versatile method for generating radical cations from a wide variety of substrates.***

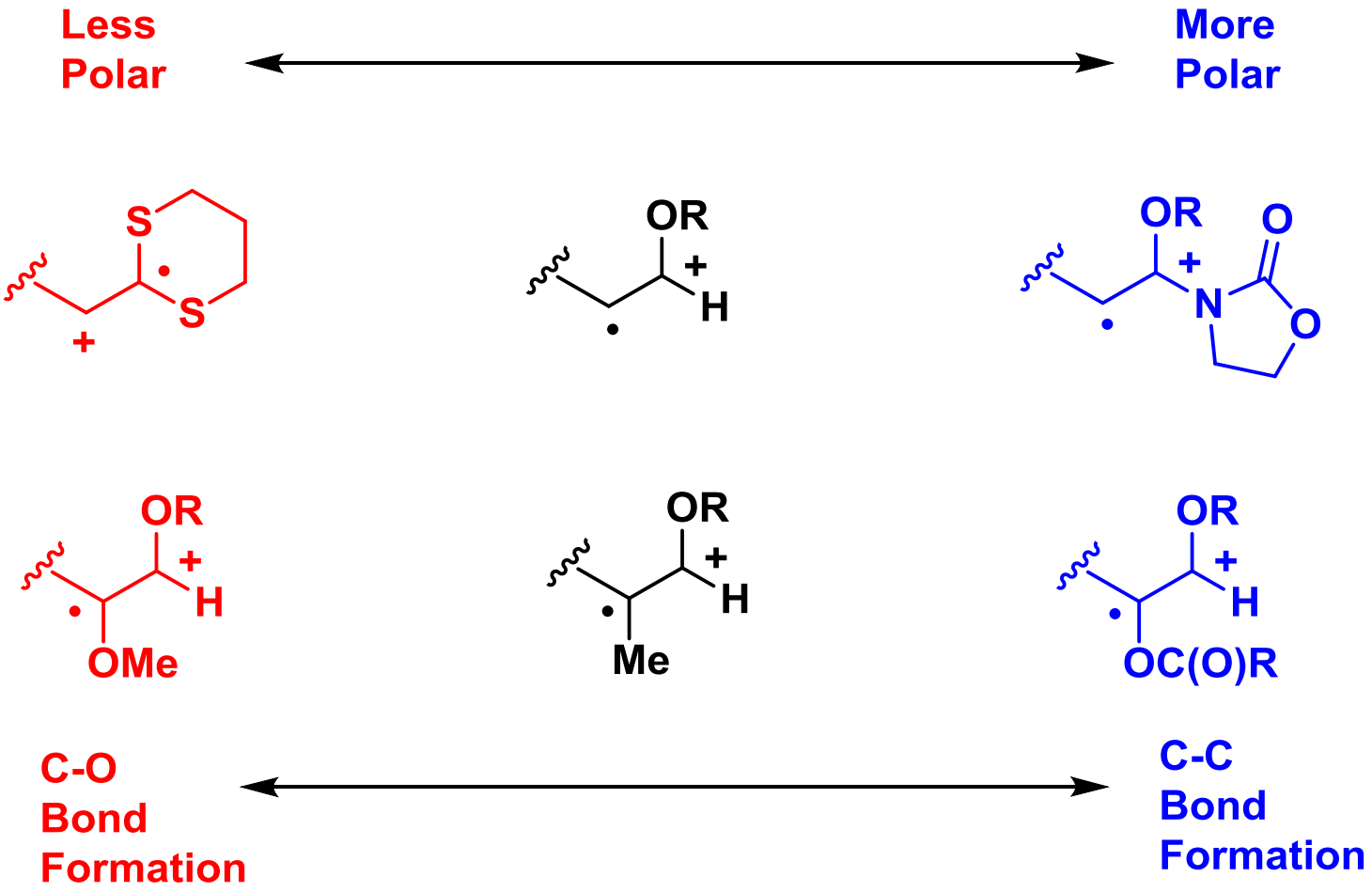
Ruozhu Feng, Jake A. Smith, Kevin D. Moeller. *Acc. Chem. Res.* **2017**, *50*, 2346-2352.

Right from the start – versatility and selectivity:



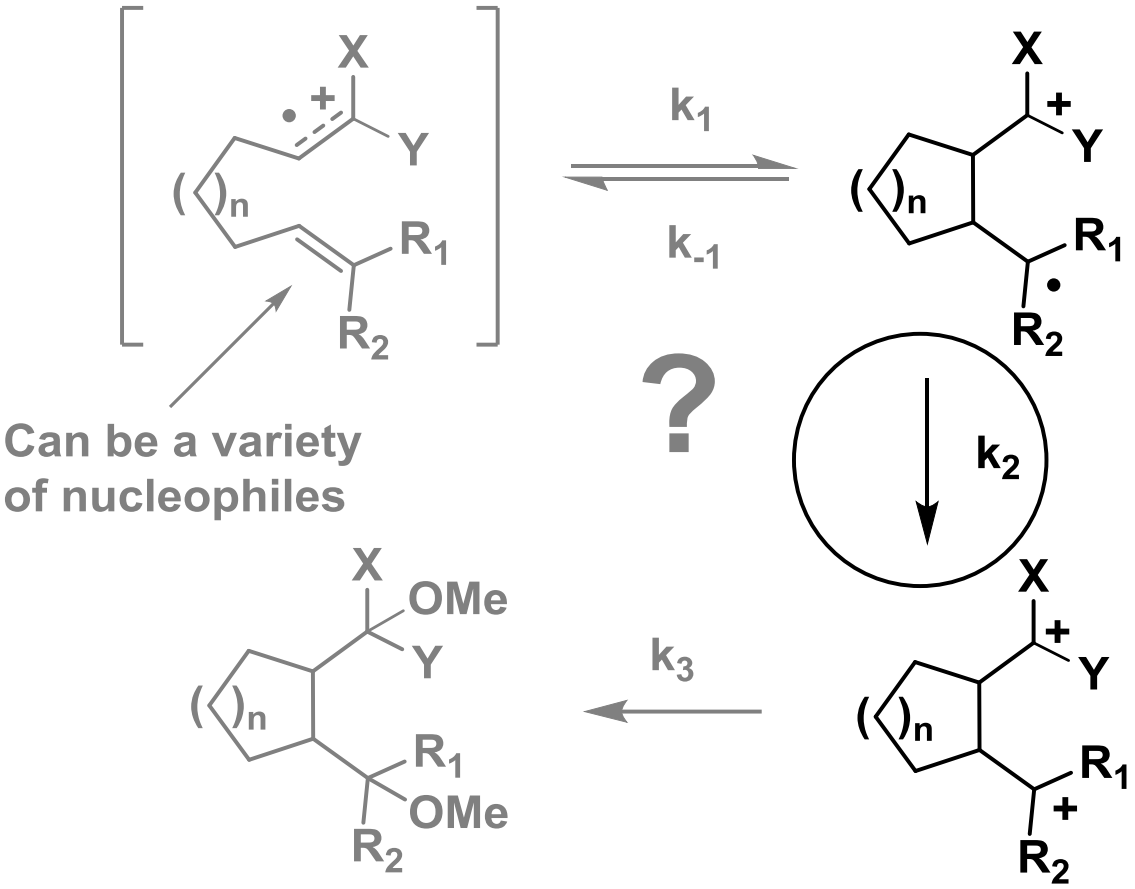
- ***The use of a chemical reagent would have failed and the approach would have been labeled as not general.***
- Liu, B.; Duan, S.; Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc*. **2002**, *124*, 10101, Hai-Chao Xu and Kevin D. Moeller *Angew. Chem. Int. Ed. Eng.* **2010**, *49*, 8004.

That versatility led to the structure activity studies:



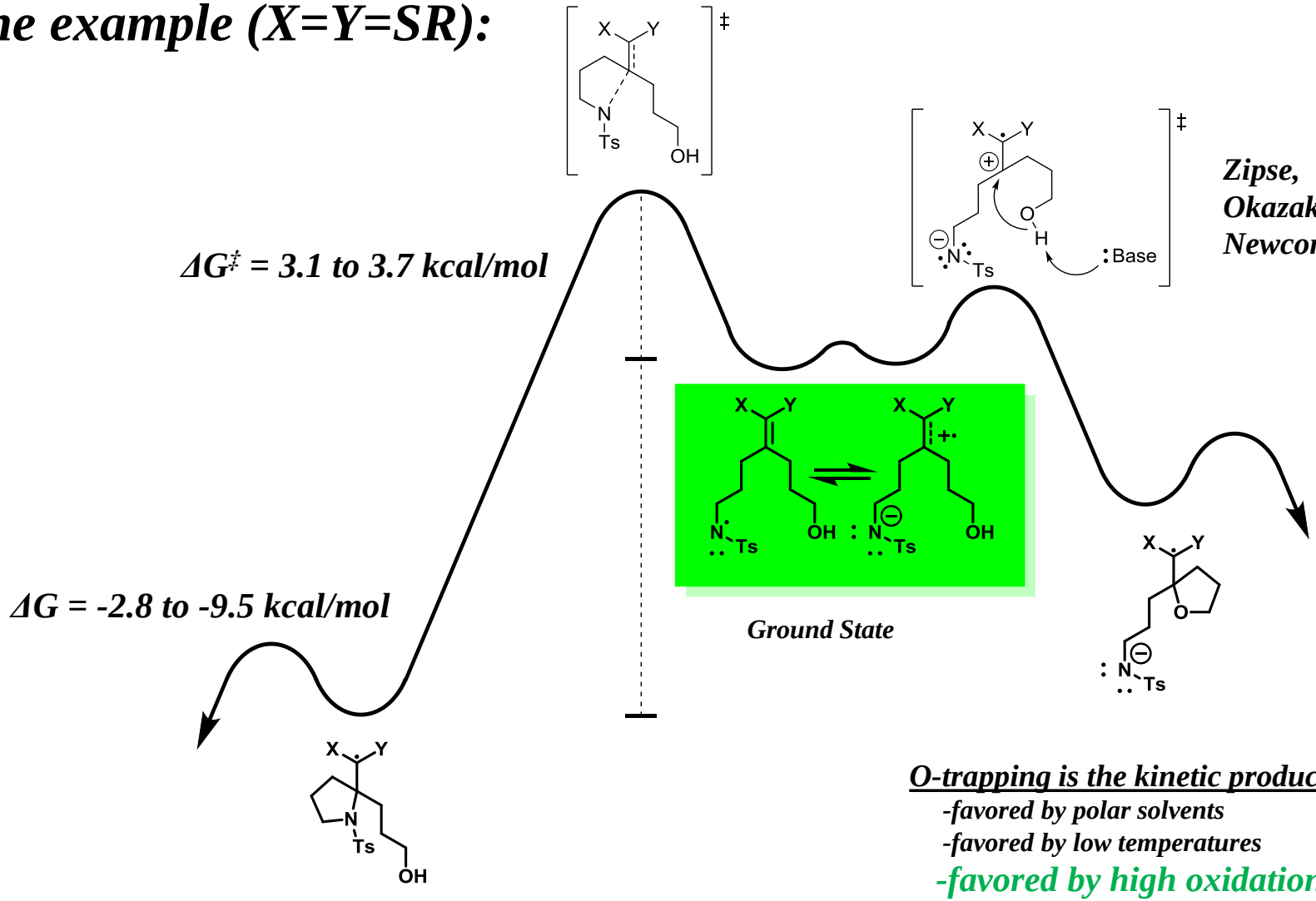
Tang, F.; Moeller, K. D. *J. Am. Chem. Soc.* 2007, *129*, 12414, Tang, F.; Moeller, K. D. *Tetrahedron* 2009, *65*, 10863. Xu, G.; Moeller, K. D. *Org. Lett.* 2010, *12*, 2590, Smith, J.; Xu, G.; Moeller, K. D. *Org. Lett.* 2013, *15*, 5818; Huang, Y.; Moeller, K. D. *Organic Letters* 2004, *6*, 4199.

One more point here. The second oxidation step is also critical:



Ruozhu Feng, Jake A. Smith, Kevin D. Moeller. *Acc. Chem. Res.* **2017**, *50*, 2346-2352.

One example (X=Y=SR):



N-trapping is the thermodynamic product

-favored by non-polar solvents

-favored by higher temperatures

-favored by low oxidation rates and a slower second oxidation

O-trapping is the kinetic product

-favored by polar solvents

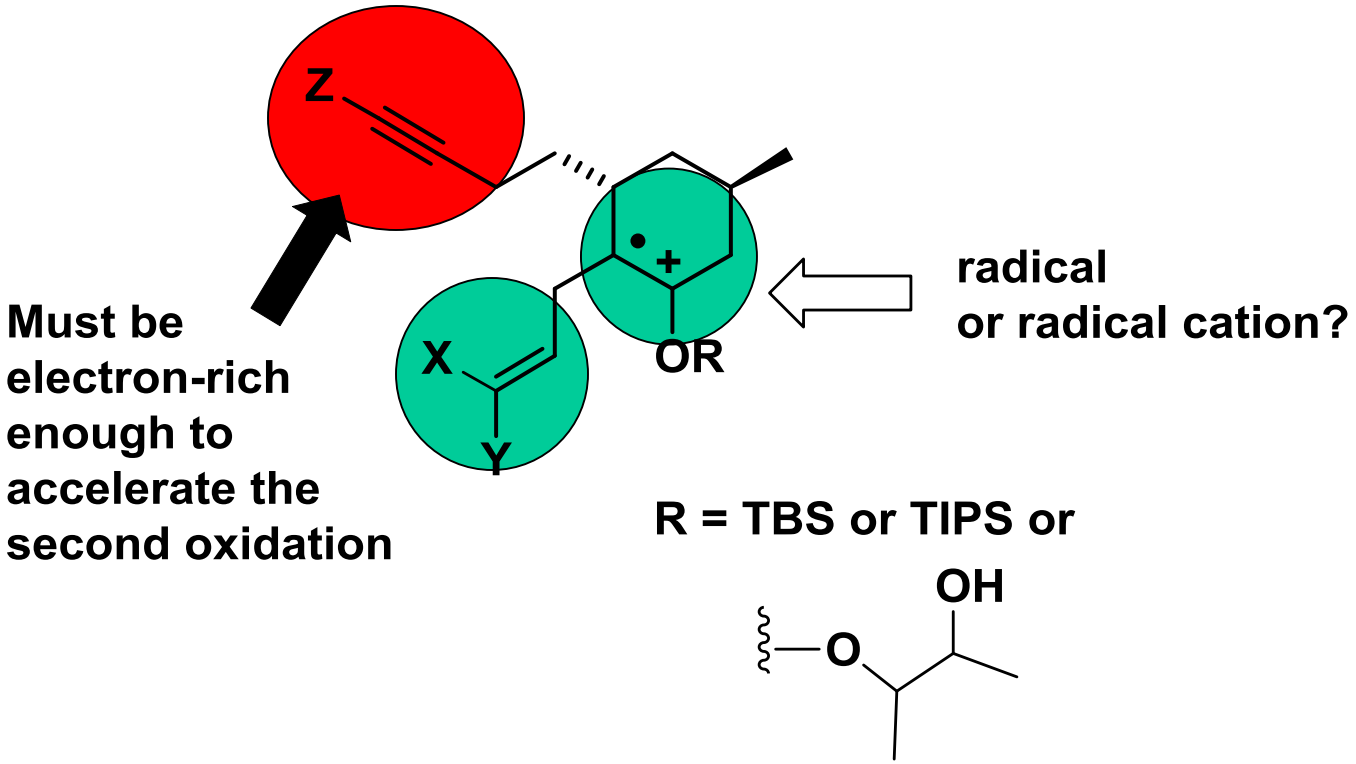
-favored by low temperatures

-favored by high oxidation rates and a fast second oxidation.

Campbell, J. M.; Xu, H.; Moeller, K. D. *J. Am. Chem. Soc.* **2012**, *134*, 18338.

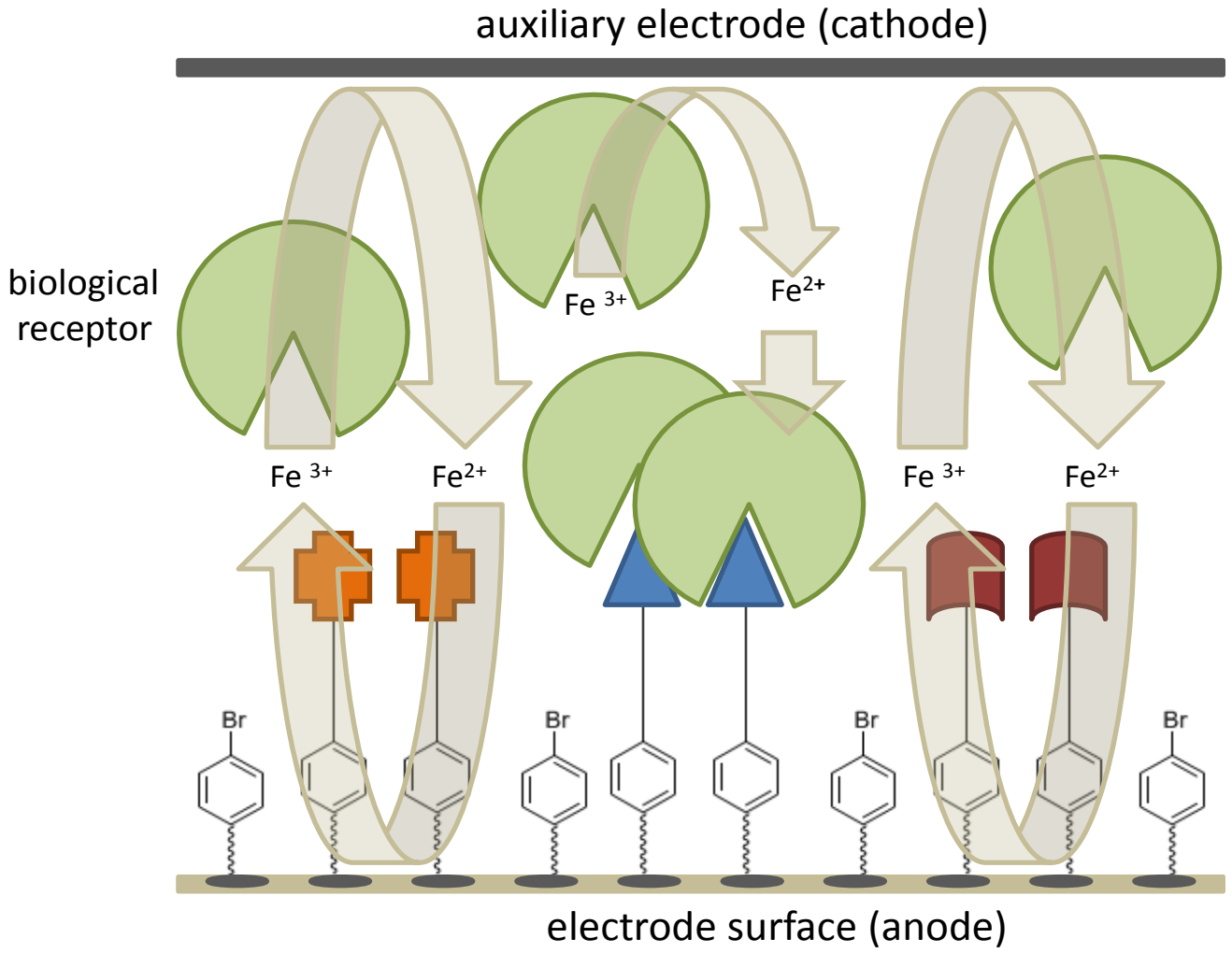
DFT: UB3LYP/6-31G(d)

Synthetically, this is very important:



It looks like the second oxidation step provides the key to success. Using electrochemistry, we can control the rate of that second oxidation step.

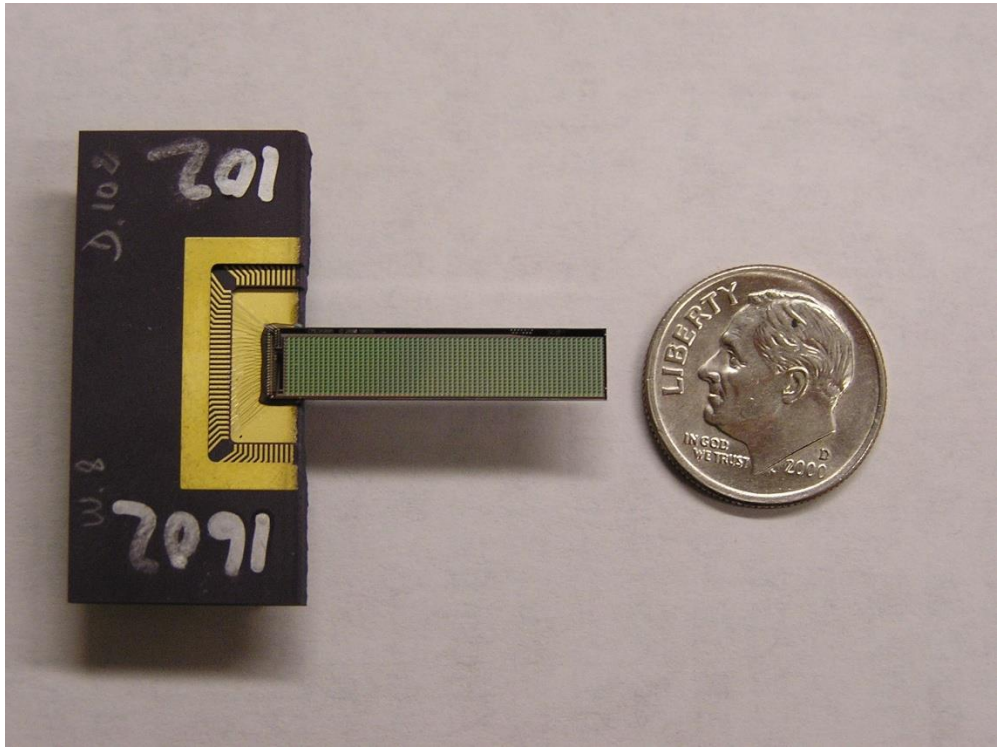
The third vignette and a new total synthesis challenge:

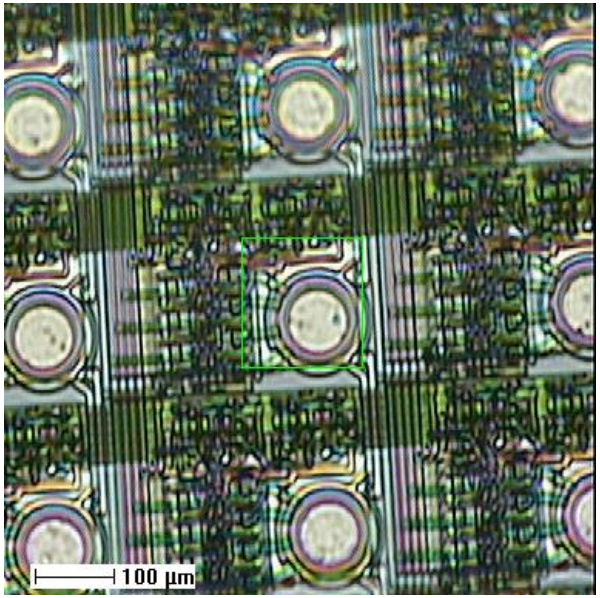


- ***The construction of molecular libraries that are addressable in real-time?***

- ***Electrochemical biosensor: Murata, M. et. al. BioorgMed. Chem. Lett. 2004, 14, 137.***

The problem…..

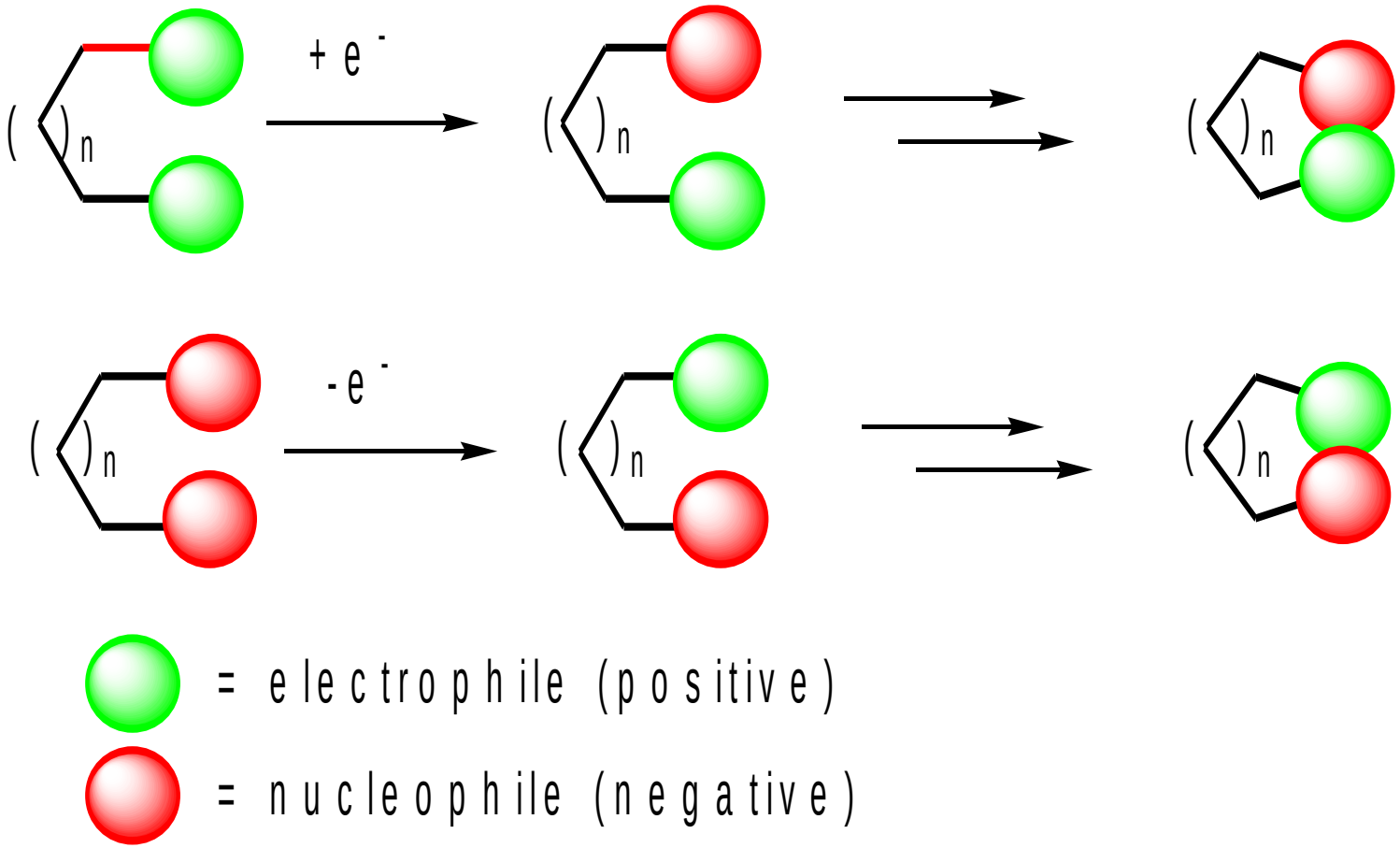




…..We need to synthesize complex molecular surfaces have each unique member of library proximal to a unique set of individually addressable electrodes, even when an array has 12,544 microelectrodes/ cm^2?

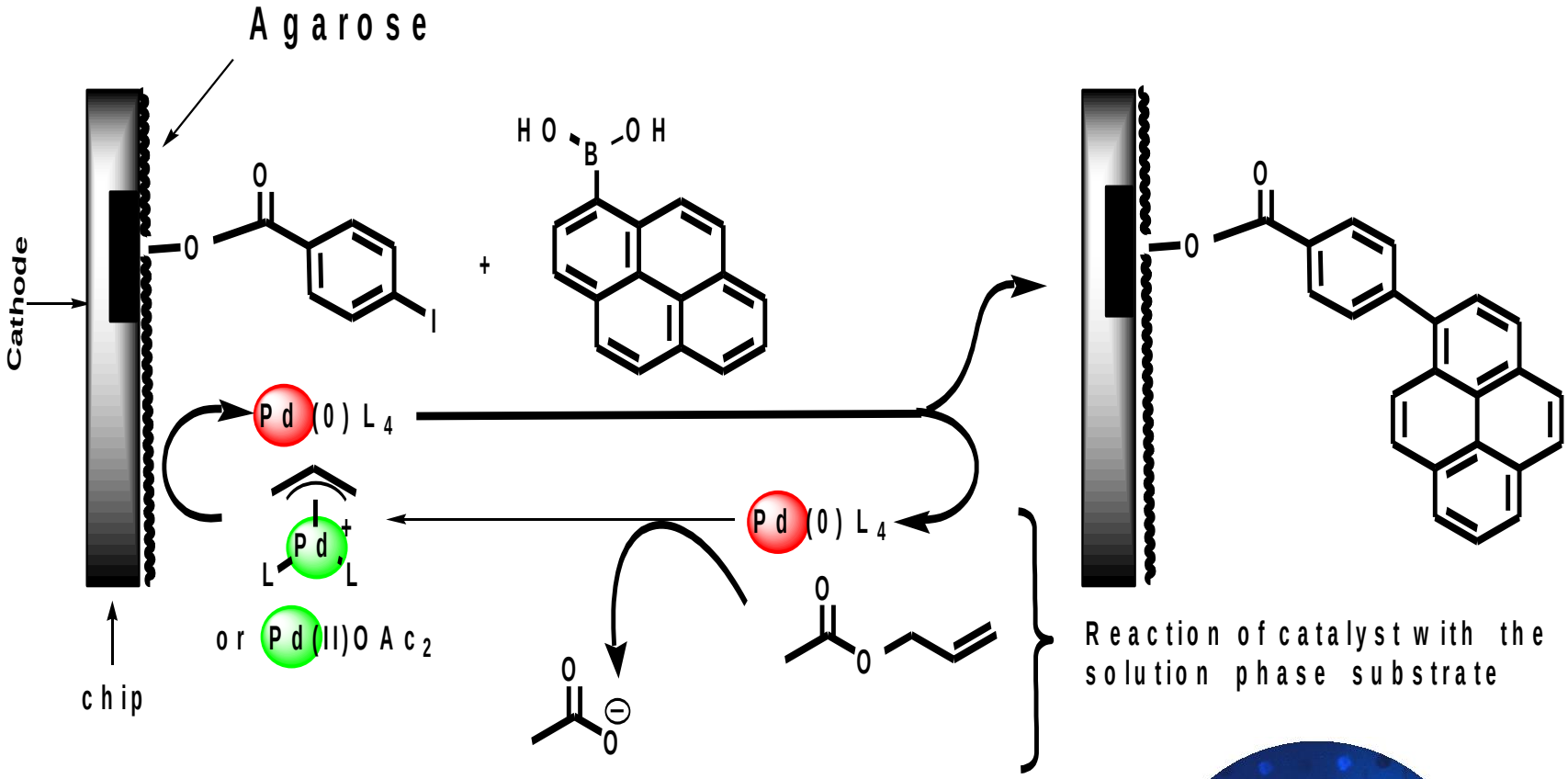
The only handle is the electrode itself, but…

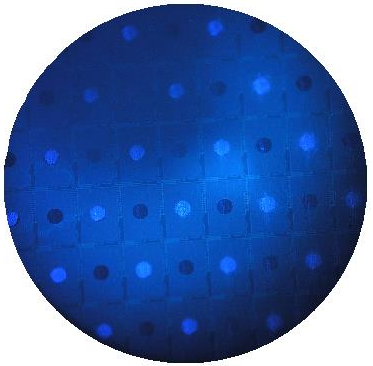
….fortunately we know what electrodes do:



….umpolung chemistry!

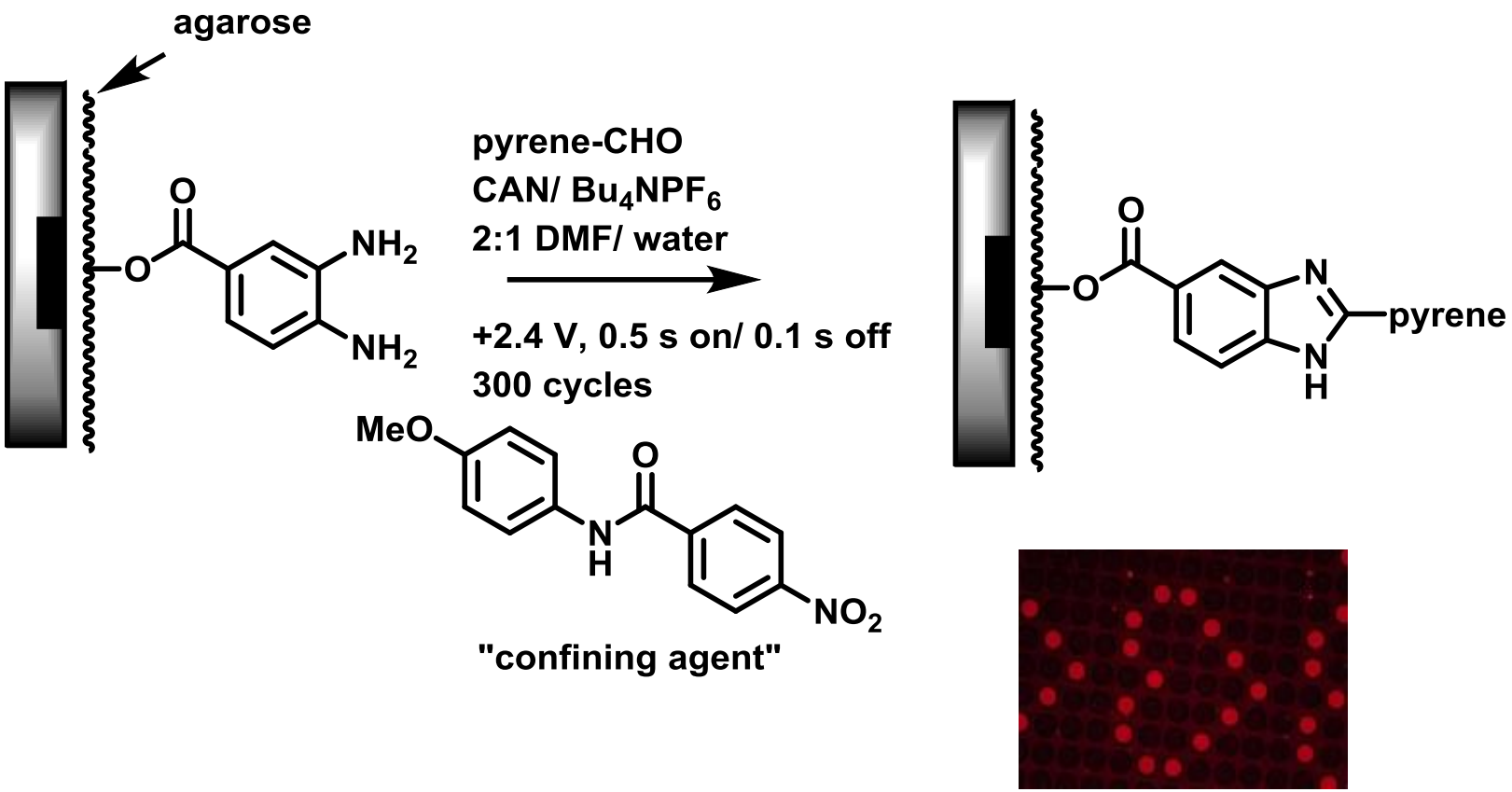
An example with a reduction...





- Libo Hu, Karl Maurer, Kevin D. Moeller. *Org. Lett.* **2009**, *11*, 1273.

….and one with an oxidation.



Bichlien H. Nguyen, David Kesselring, Eden Tesfu, and Kevin D. Moeller
Langmuir **2014**, *30*, 2280.

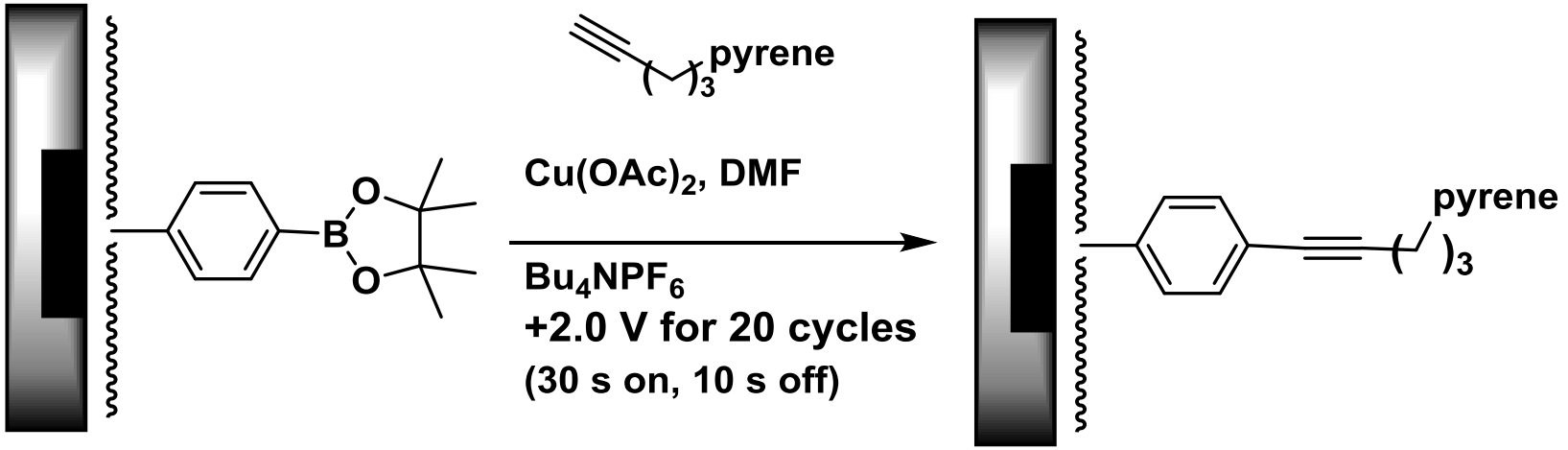
The approach is general.

Pd(II)	**TEMPO**	**Cu(II)**	**H_2**
Ru(VII)	**DDQ**	**Os(VIII)**	**Pd(0)**
Sc(III)	**H^+**	**Ce(IV)**	**Cu(I)**

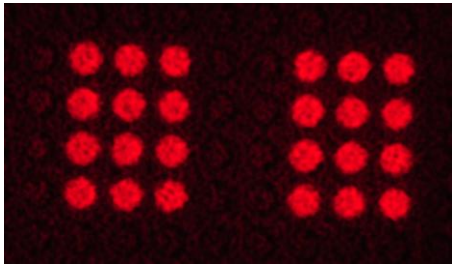
vitamin $B_{12}^{\bullet -}$

- ***All of the reagents shown can be employed site-selectively on an array.***
- ***In each case, the potential of the selected electrode in the array automatically adjusts to the potential needed for the oxidation or reduction.***

One example with a point:

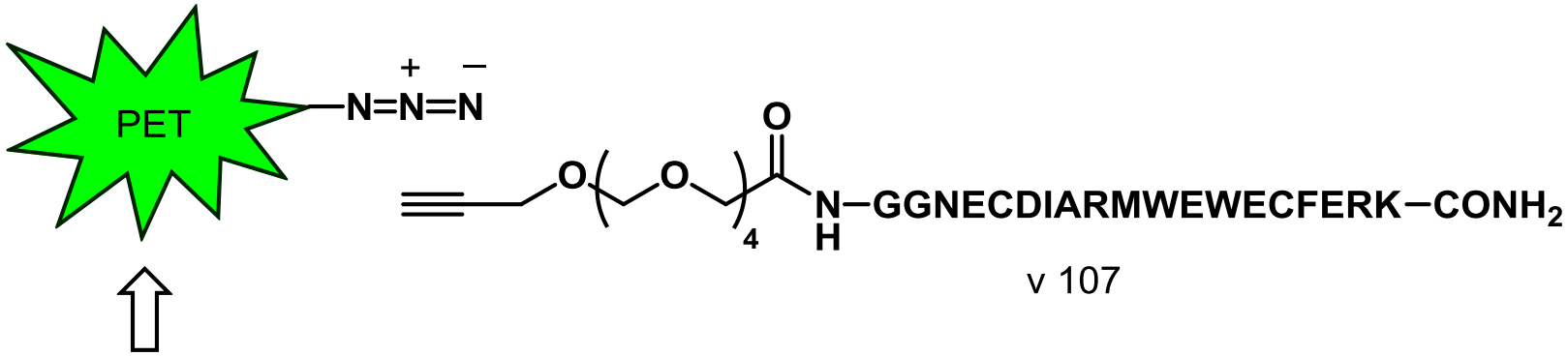


- *A Chan-Lam type coupling.*
- *As always, the key is controlling the relative rates of reactive intermediates at the electrode surface.*



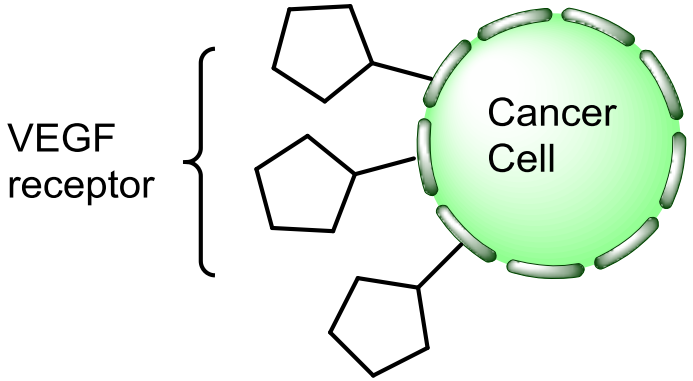
For an "instructional review" of the overall approach see: Graaf, M. D.; Moeller, K. D. Langmuir 2015, 31, 7697-7706.

New synthetic chemistry means new opportunities for biology:



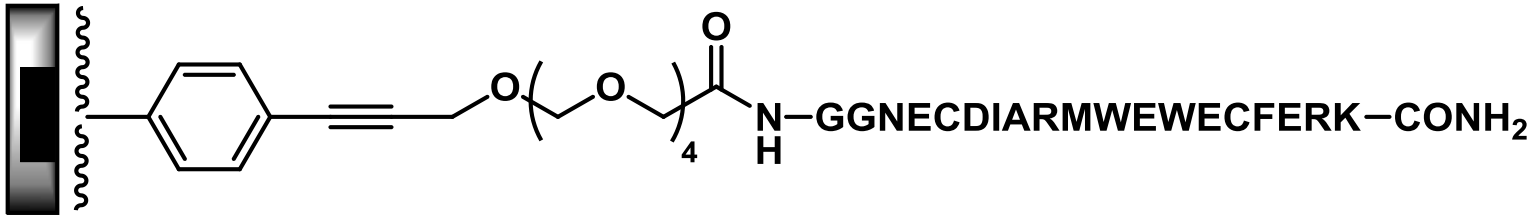
v 107

An imaging agent that can be "clicked" onto a targeting group.

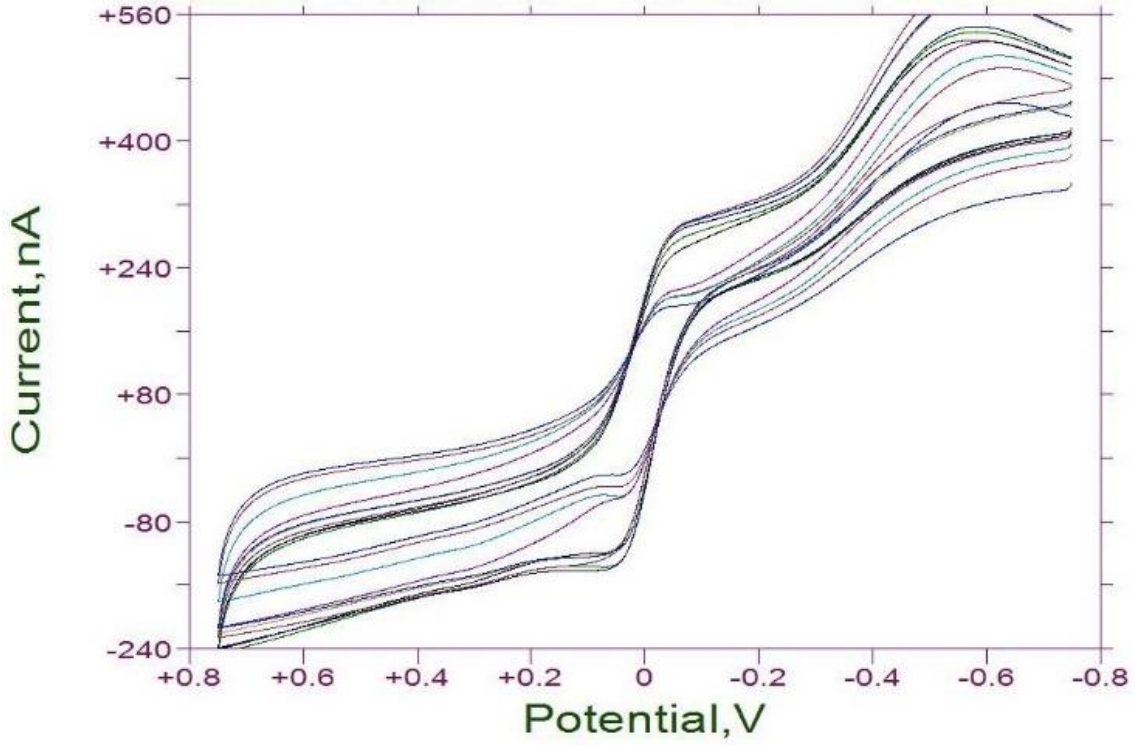


- VEGF (Vascular Endotheliel Growth Factor) is an important target for imaging cancer cells. It is expressed when the cells implant in tissue
- The v107 peptide is a know targeting group for VEGF, but it binds weakly.
- ***Optimizing the imaging agent means optimizing the v107/ VEGF interaction. However, the interaction is hard to monitor….***

The modified v107 peptide is already perfectly functionalized for placement on an array:

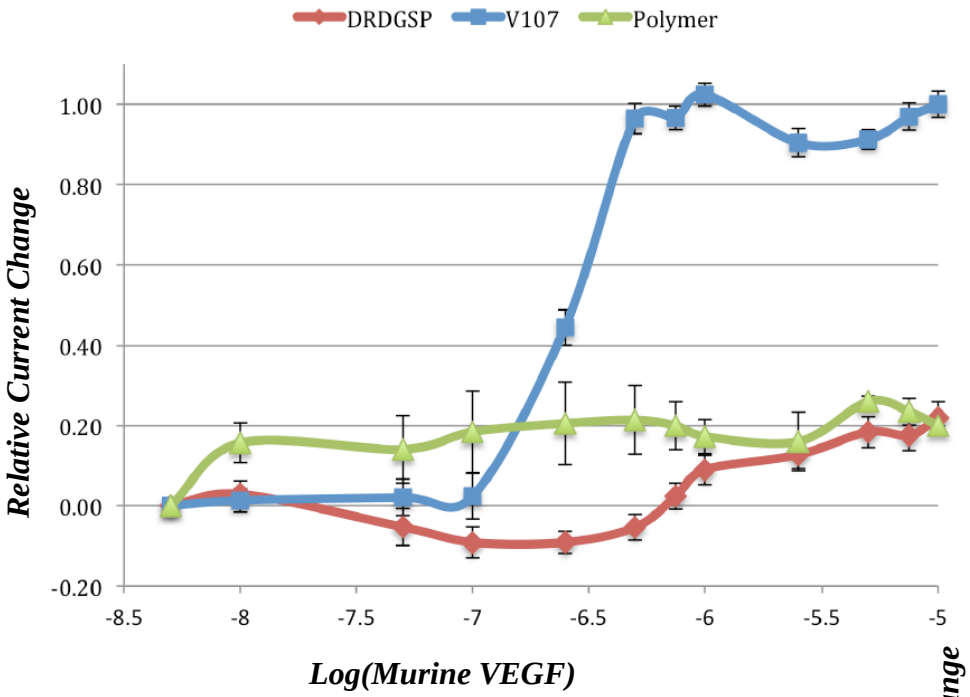


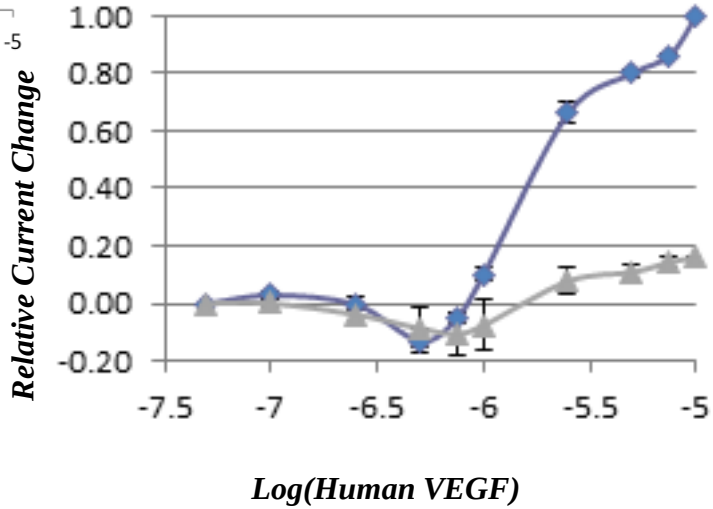
- Add ferrocene carboxylic acid and varying amounts of the receptor, and then monitor the current associated with the redox mediator.



Graaf, M. D.; Marquez, B. V.; Yeh, N.; Lapi, S. E.; Moeller, K. D. *ACS Chem. Bio.* **2016**, *11,* 2829-2837.

Showing the viability of murine VEGF as a mimic for the human protein:





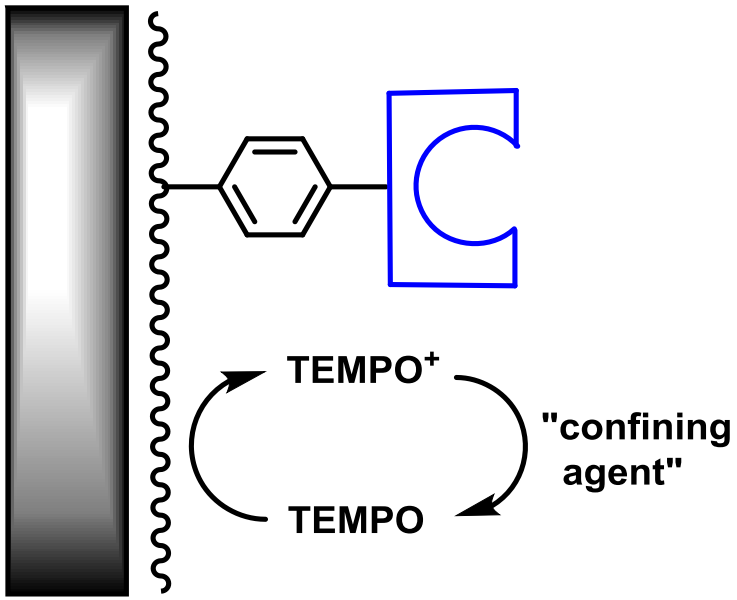
The arrays can be used to probe affinities using the far cheaper murine VEGF

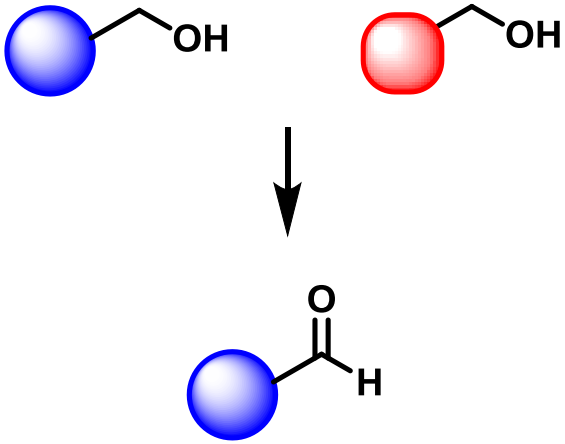
Where we are:

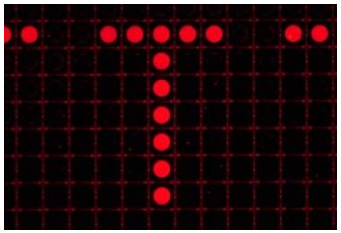
- ***We can place molecules at any given site on an array and in so doing synthesize complex, addressable molecular surfaces.***
- ***We can control the concentration of those molecules.***
- ***We can build stable surfaces for synthesis and then convert them into tunable surfaces for signaling experiments.***
- ***We can use the functionalized surface to probe biological interactions in "real-time".***
- ***We can recover molecules from any electrode in an array so that that can be characterized, a situation that affords an unprecedented level of quality control for an addressable molecular library.***

- ***The conclusion: Our ability to conduct electrosynthetic methods on a microelectrode array is dramatically expanding the utility of the devices as tools for probing molecular interactions.***

One final vignette and a lesson from the arrays:



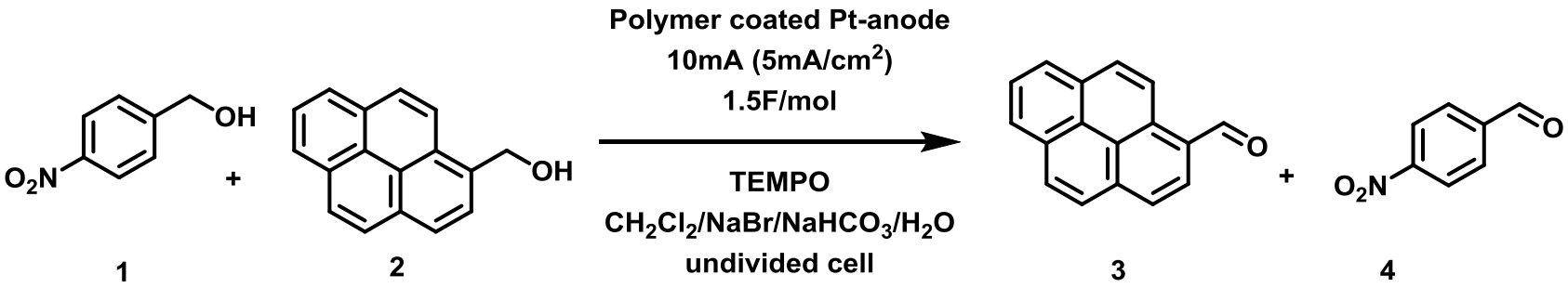




The reaction has been confined to selected electrodes on an array.

- **On the arrays, we confine reagents to within 25 microns of their origin.**
- **Can we use this to induce selectivity into a preparative reaction?**

The test reaction?



Sugar confining agent

1	**1 equiv.**	**0.5 mmol**	**77 mg**
2	1 equiv.	0.5 mmol	116 mg
TEMPO	0.1 equiv.	0.05 mmol	8 mg
Methyl-α-D-glucopyranoside (confining agent)	10 equiv.	5 mmol	971 mg
solution	10 mL DCM 5 mL 25% NaBr solution saturated with $NaHCO_3$		

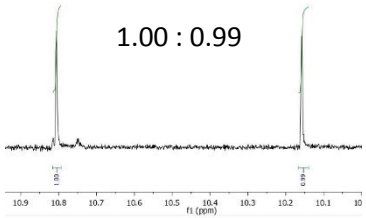
- ***A classic competition study.***

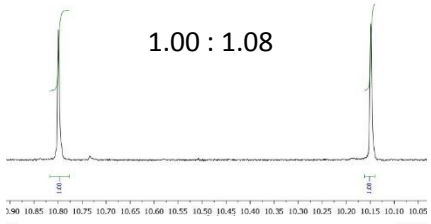
The result:

Trial 1 **Trial 2**

20 mA/cm^2

Pt

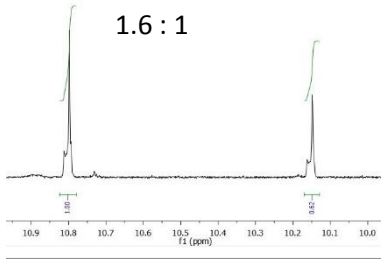


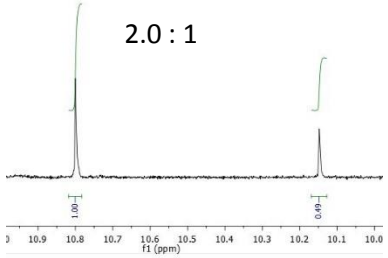


5 mA/cm^2

polymer

Pt





A surface-based molecular recognition event can alter the course of the reaction.

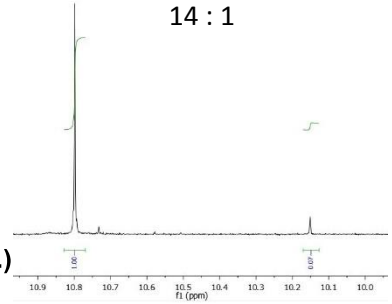
5 mA/cm^2

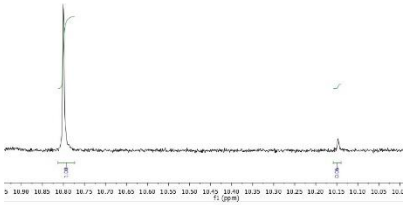
polymer

Pt

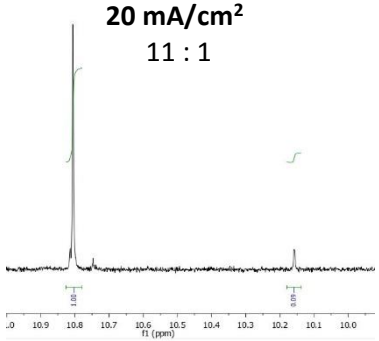
\+

Methyl-a-D-glucopyranoside (10 eq.)

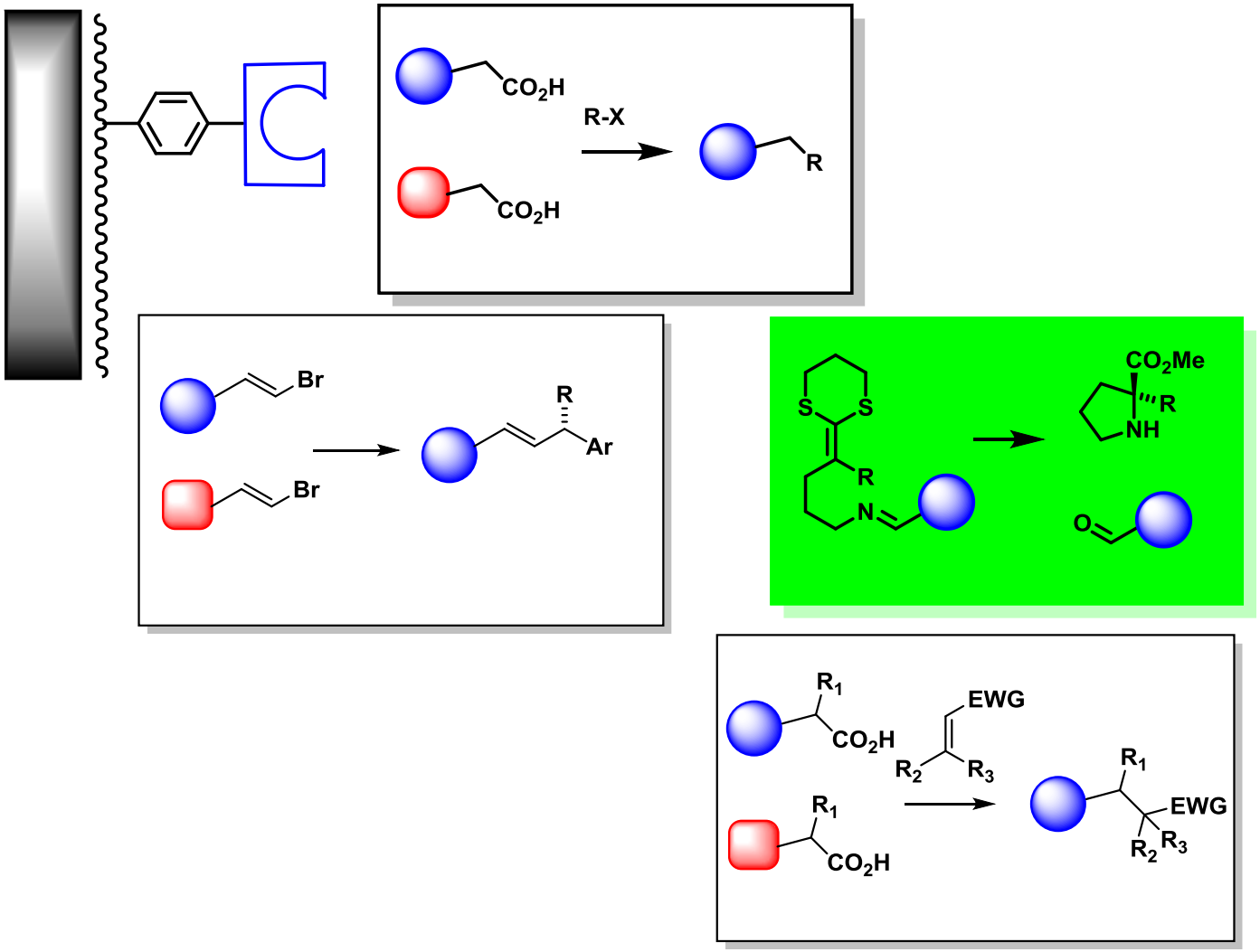




20 mA/cm^2



A general method for selectivity?



A story for another time…...

So in the four vingettes highlighted, we have used electrochemistry to…

- ***….oxidize a variety of molecules ranging in potential from +0.6 V to +2.3 V vs. Ag/AgCl with selectivities as small as 150 mV (an effort that would require 11 selective chemical oxidants that all utilized the reaction conditions).***
- ***….recycle 13 (and counting) different chemical reagents and catalysts and confine those reagents to specific sites on an array,***
- ***….monitor binding interactions between small molecules and biological targets in "real-time",***
- ***….and provide a proof of principle experiment for a new avenue to selectivity.***

In all of these efforts, electrochemistry has not been a separate "main element". It has been and remains the essential tool for each investigation.

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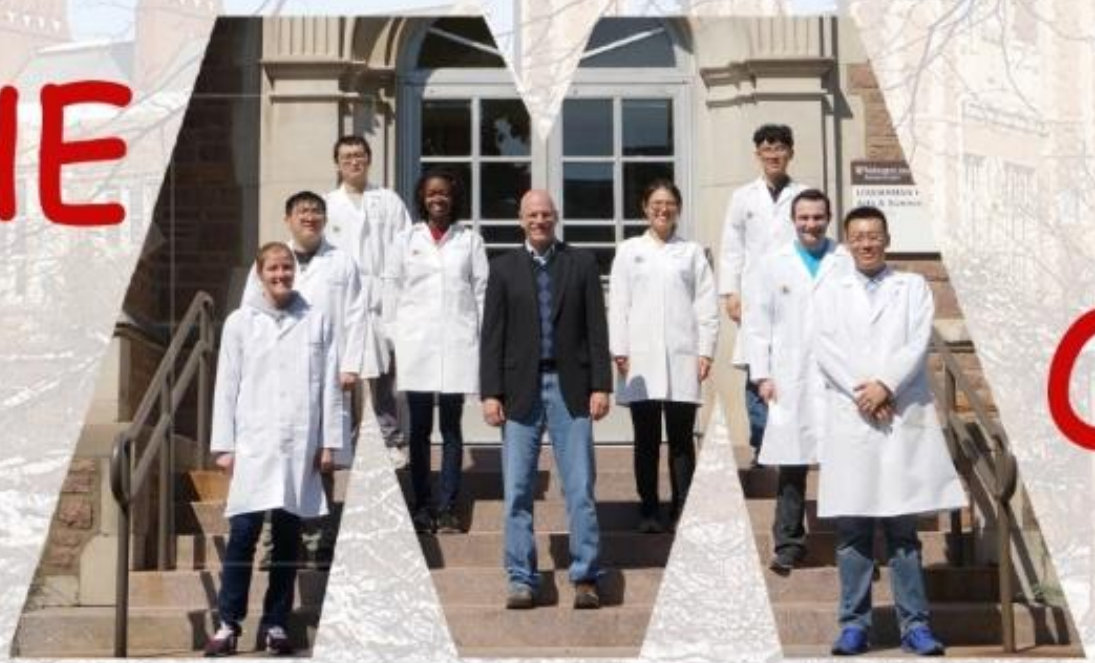

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