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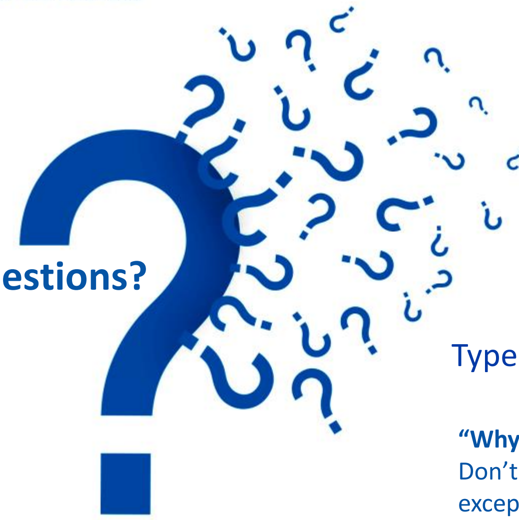

Have Questions?

Type them into questions box!

"Why am I muted?"
Don't worry. Everyone is muted except the presenter and host. Thank you and enjoy the show.

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How has ACS Webinars benefited you?

"This ACS Webinar was very informative! I'm more familiar with green chemistry than I am with developments in the pharmaceutical industry; hearing about real world applications was interesting."

https://www.acs.org/content/acs/en/acs-webinars/technology-innovation/waste-slimming.html

Fan of the Week

Charlotte Synder, MS
Green and Environmental Chemistry, George Washington University and Student Trainee, TRI Program, Environmental Protection Agency

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Recordings are an exclusive ACS member benefit and are made available to registrants via an email invitation once the recording has been edited and posted.

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http://acsoncampus.acs.org

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#HeroesofChemistry
ACS Heroes of Chemistry Award

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Heroes of Chemistry winner BMS: Carl Decicco presenting the story behind Daklinza® and Sunvepra™

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*The **ACS Heroes of Chemistry Award** is the Annual award sponsored by the American Chemical Society that recognizes talented industrial chemical scientists whose work has led to the development of successful commercialized products ingrained with chemistry for the benefit of humankind.*

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https://chemidp.acs.org

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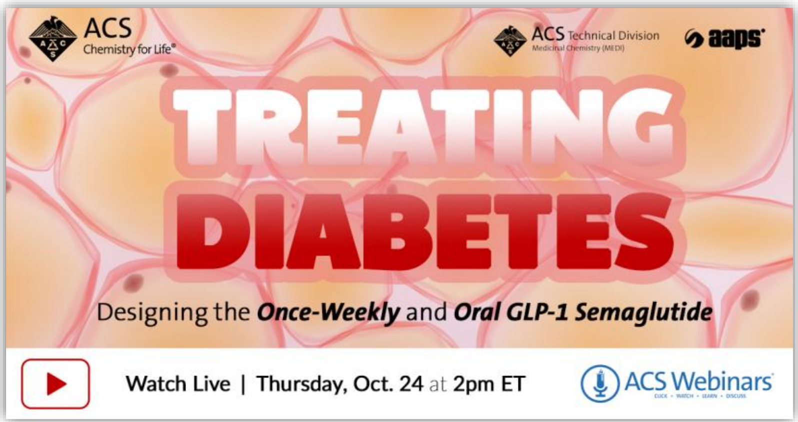
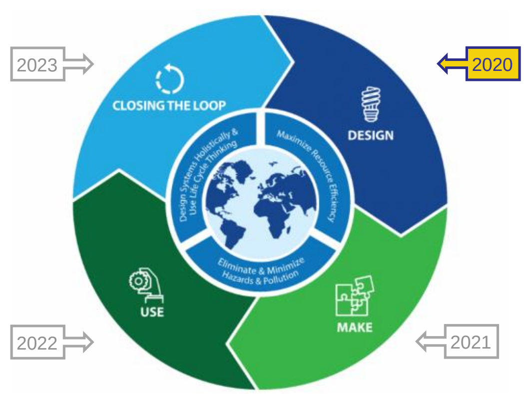


https://www.acs.org/content/acs/en/acs-webinars/drug-discovery/treating-diabetes.html

24th Annual Green Chemistry & Engineering Conference

ACS Green Chemistry Institute Chemistry for Life®

Theme: *Systems-Inspired Design*



- Symposia due by **October 4, 2019**
- Abstracts open January 4, 2020

https://www.gcande.org/call-for-symposia

ACS Green Chemistry Institute
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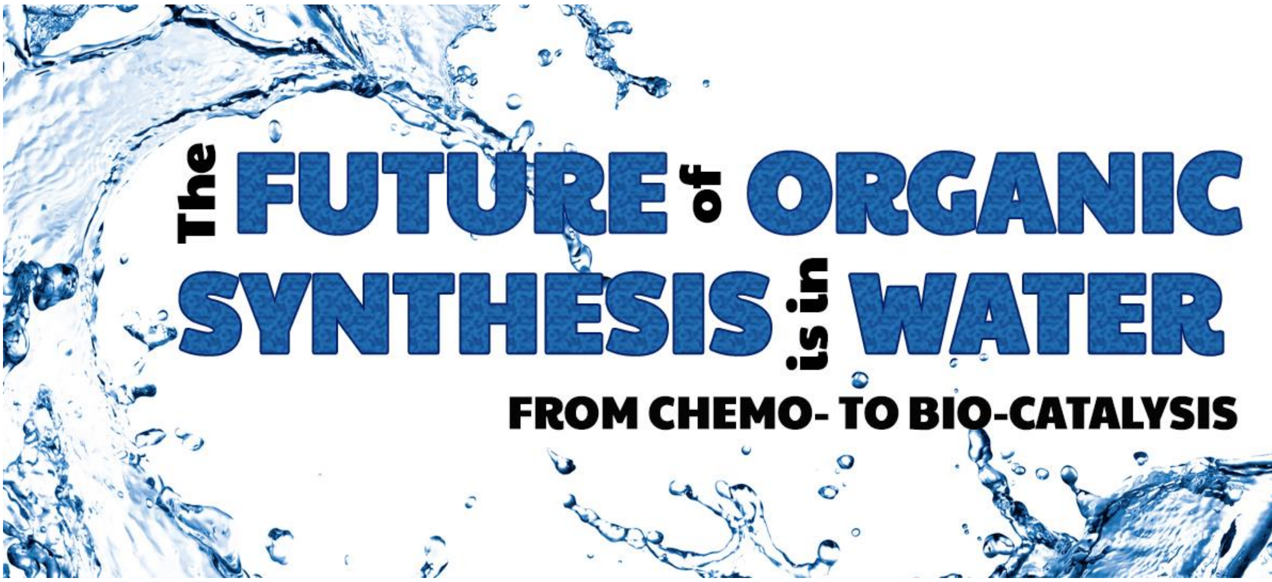

THIS ACS WEBINAR WILL BEGIN SHORTLY...

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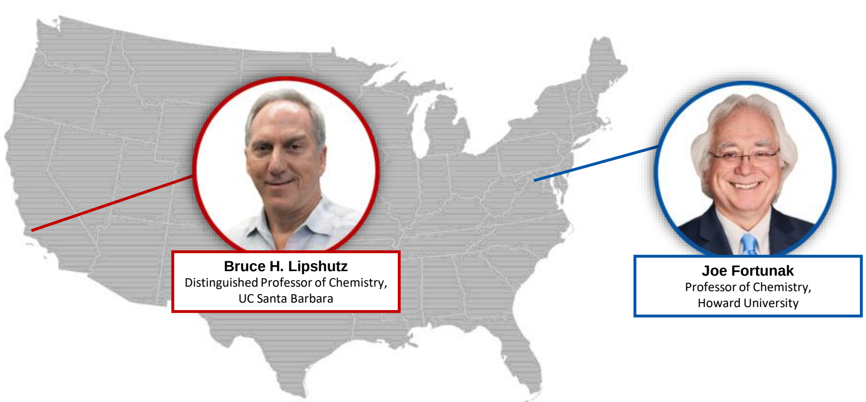
The Future of Organic Synthesis is in Water: From Chemo- to Bio-catalysis



Presentation slides are available now! The recording will be edited and posted at a later date.

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This ACS Webinar is co-produced with the ACS Green Chemistry Institute

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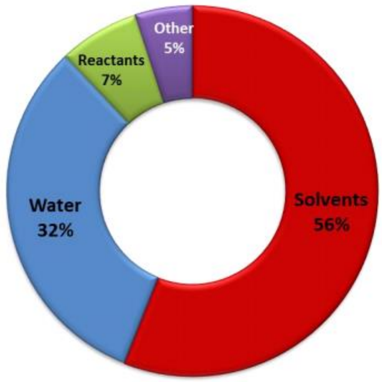
Impact of Solvents and Water within the Pharmaceutical Industry

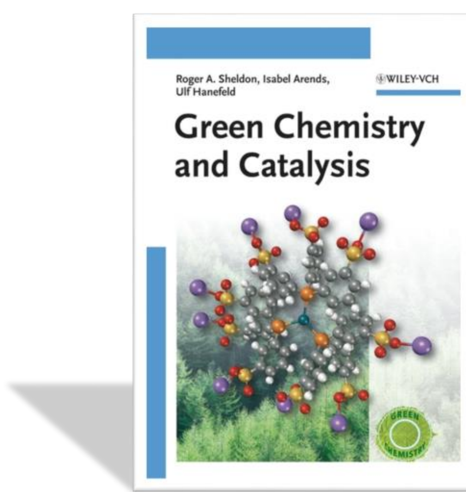


ACS Green Chemistry Institute
Pharmaceutical Roundtable

Source: 2008 ACS Green Chemistry Institute Pharmaceutical Roundtable benchmarking exercise of 10 member companies

https://www.acs.org/content/acs/en/greenchemistry/industry-roundtables/pharmaceutical.html

"The medium is the message."

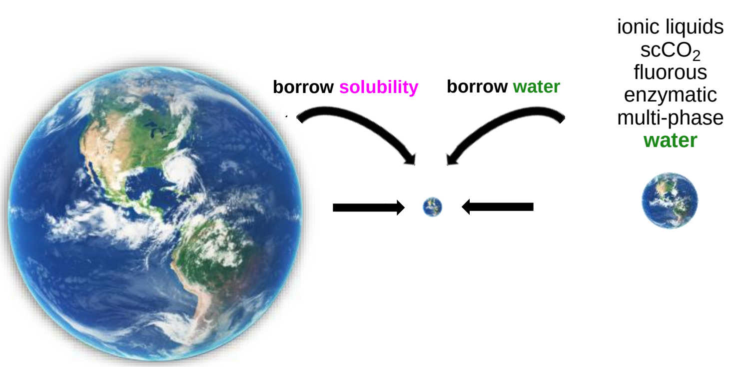


Making the switch to green chemistry...

~~Two~~ Three Worlds of Organic Chemistry

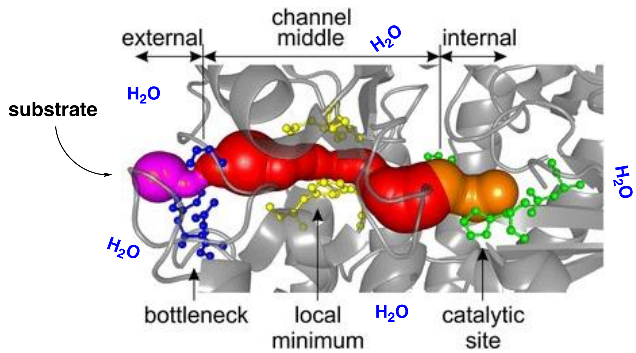
Traditional, in organic solvents

Nontraditional, in alternative media



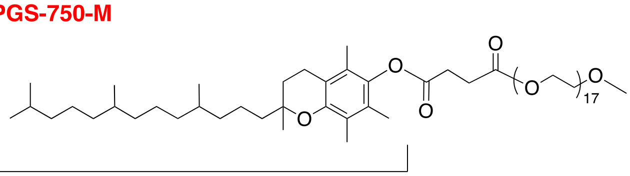
Looking Towards Nature as the Perfect Model

bio-catalysis in water; why not chemo-catalysis?



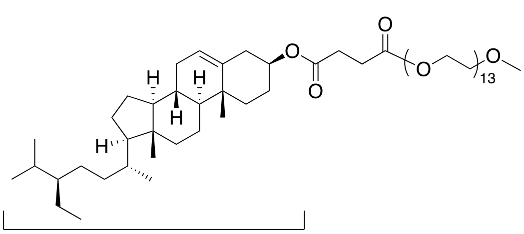
"Directed Evolution" in Micellar Catalysis: Nanomicelles as "Nanoreactors" in Water

TPGS-750-M



racemic vitamin E

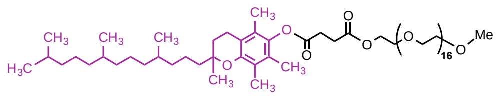
Nok

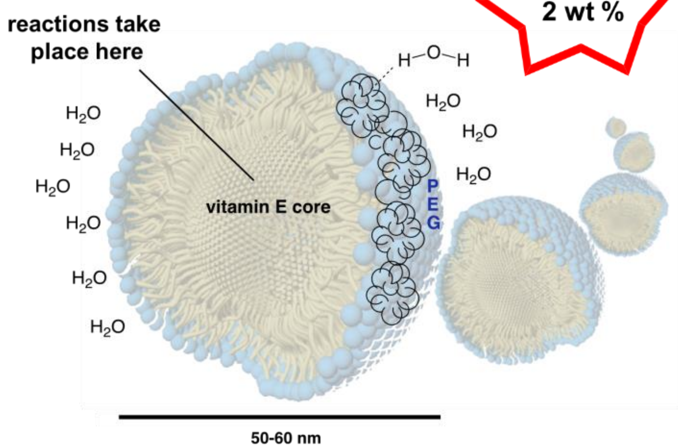


β-sitosterol

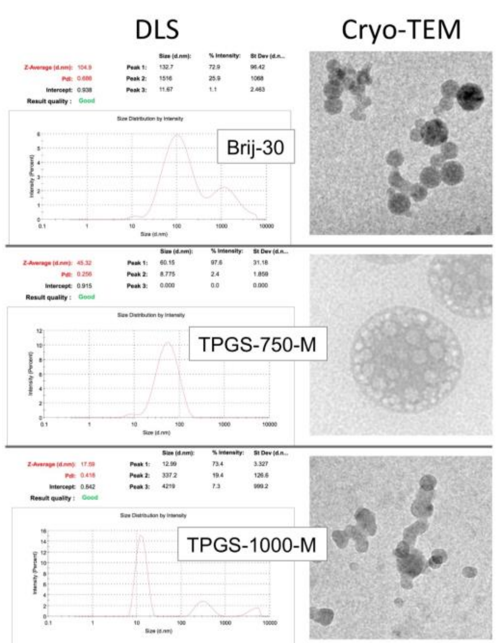
Benign by design "designer" surfactants (available from Aldrich)

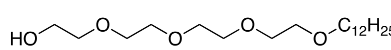
Chemistry in nanoreactors…in water @ room temperature

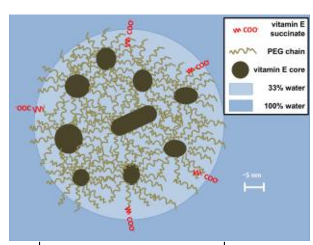


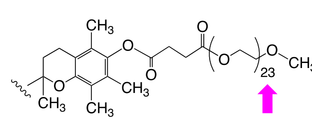


use only 2 wt %





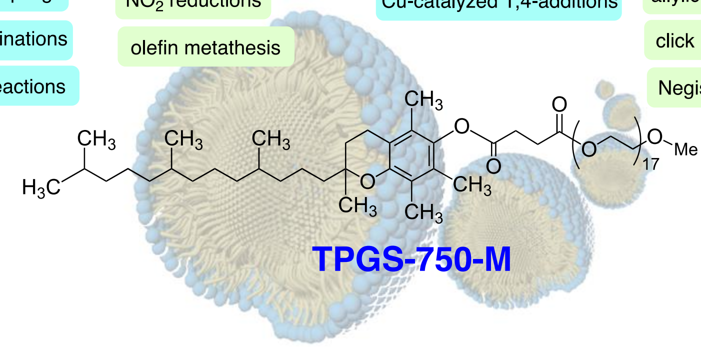




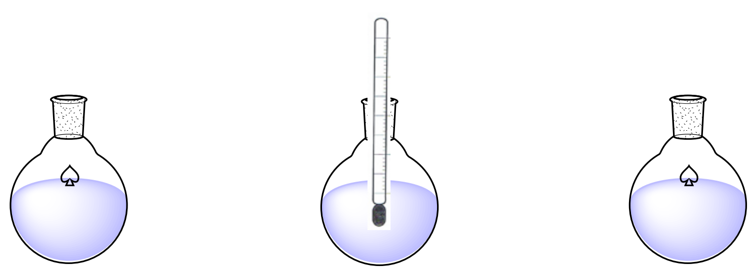
Applications of Nanomicellar Technology

chemistry in water at rt

- peptide couplings
- Stille couplings
- Heck couplings
- aryl aminations
- S_NAr reactions
- Sonogashira couplings
- Suzuki-Miyaura couplings
- NO_2 reductions
- olefin metathesis
- asymmetric CuH reactions
- allylic aminations
- Cu-catalyzed 1,4-additions
- C-H activation
- aromatic borylations
- allylic silylations
- click reactions
- Negishi couplings

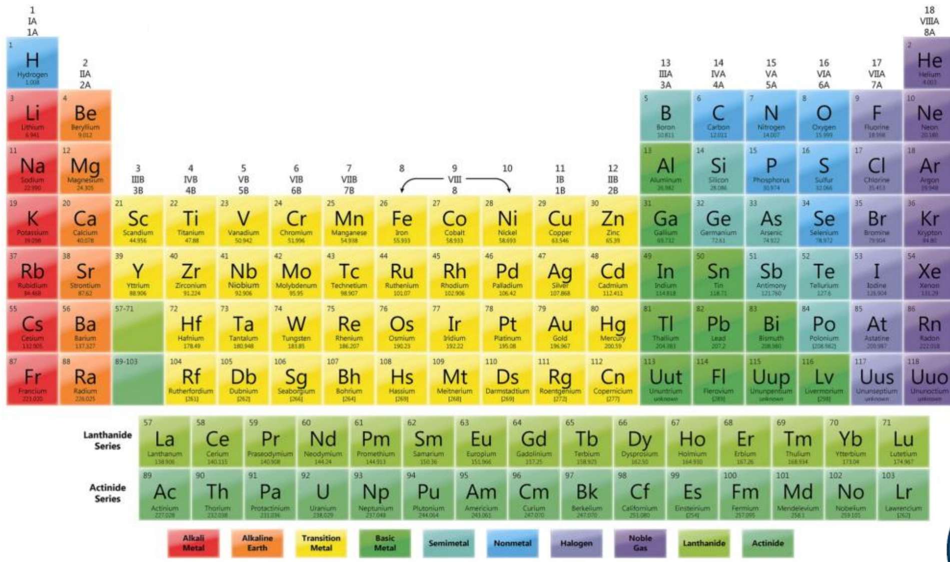


~~Three~~ One Key Reaction Parameter~~s~~ left...



~~solvent/medium~~ ~~reaction temperature~~ catalyst ?

The Periodic Table of the Elements



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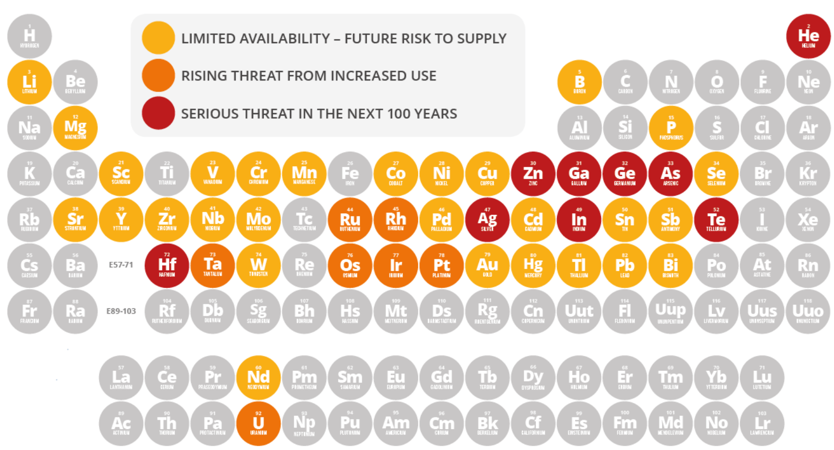
The Periodic Table of Endangered Elements



SOURCE: CHEMISTRY INNOVATION KNOWLEDGE TRANSFER NETWORK

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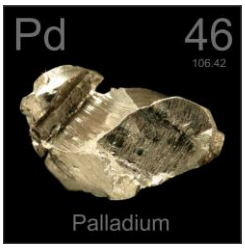
Cost of Pd over time: At what point does it become too high?



https://periodictable.com/Elements/046/index.html

The current price of palladium as of October 01, 2019 is $1,630.70 per ounce.

https://www.macrotrends.net/2542/palladium-prices-historical-chart-data

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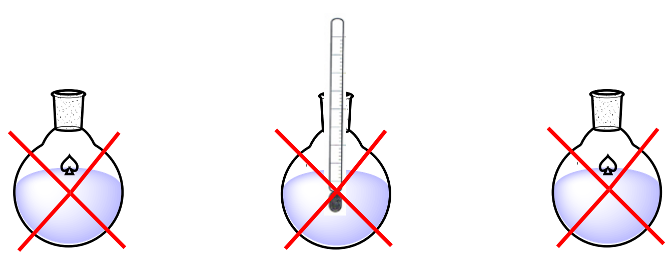
Environmentally responsible, sustainable synthetic chemistry, in route towards "zero waste"



NO organic solvent

~~reaction~~ temperature
room

practically no catalyst

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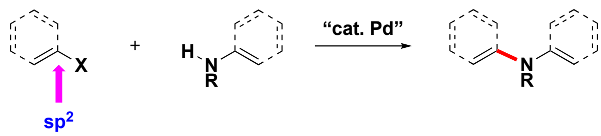
Buchwald-Hartwig aminations: From the green chemistry perspective



Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions

Paula Ruiz-Castillo and Stephen L. Buchwald*

View Author Information

Abstract

Pd-catalyzed cross-coupling reactions that form C–N bonds have become useful methods to synthesize anilines and aniline derivatives, an important class of compounds throughout chemical research. A key factor in the widespread adoption of these methods has been the continued development of reliable and versatile catalysts that function under operationally simple, user-friendly conditions. This review provides an overview of Pd-catalyzed N-arylation reactions found in both basic and applied chemical research from 2008 to the present. Selected examples of C–N cross-coupling reactions between nine classes of nitrogen-based coupling partners and (pseudo)aryl halides are described for the synthesis of heterocycles, medicinally relevant compounds, natural products, organic materials, and catalysts.

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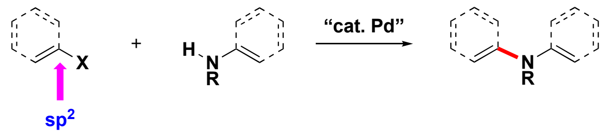
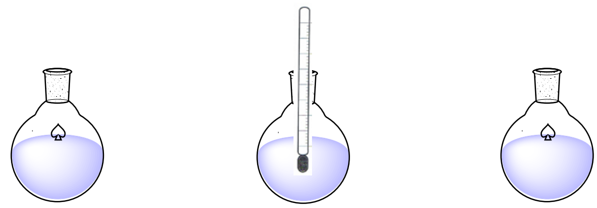
Cite this: *Chem. Rev.* 2016, 116, 19, 12564-12649
Publication Date: September 30, 2016
https://doi.org/10.1021/acs.chemrev.6b00512

https://pubs.acs.org/doi/abs/10.1021/acs.chemrev.6b00512

Buchwald-Hartwig aminations: From the green chemistry perspective





solvent/medium	reaction temperature	catalyst
toluene dioxane	reflux	2-10% Pd

The 25th Anniversary of the Buchwald–Hartwig Amination: Development, Applications, and Outlook

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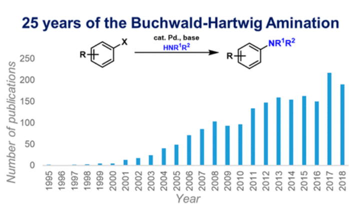
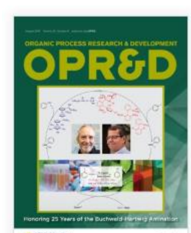


Abstract

The palladium-catalyzed cross-coupling of amines and aryl (pseudo)halides, now commonly known as the Buchwald–Hartwig amination, was first reported 25 years ago. Since the simultaneous breakthrough reports of Buchwald and Hartwig in 1995, this reaction has transformed the way synthetic chemists think about synthesizing aromatic amines. In this highlight article, a short showcasing discussion about the genesis of this reaction is provided, along with selected examples showing the impact of this transformation in synthetic chemistry in both academic and industrial settings.

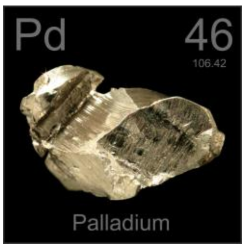


Paola A. Forero-Cortés and Alexander M. Haydl*

Cite this: *Org. Process Res. Dev.* 2019, 23, 8, 1478-1483
Publication Date: July 2, 2019
https://doi.org/10.1021/acs.oprd.9b00161

https://pubs.acs.org/doi/10.1021/acs.oprd.9b00161

Cost of Pd over time: At what point does it become too high?

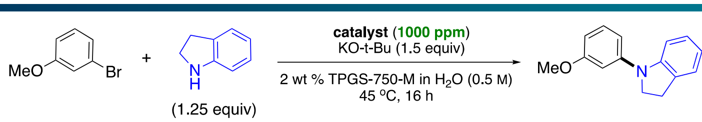


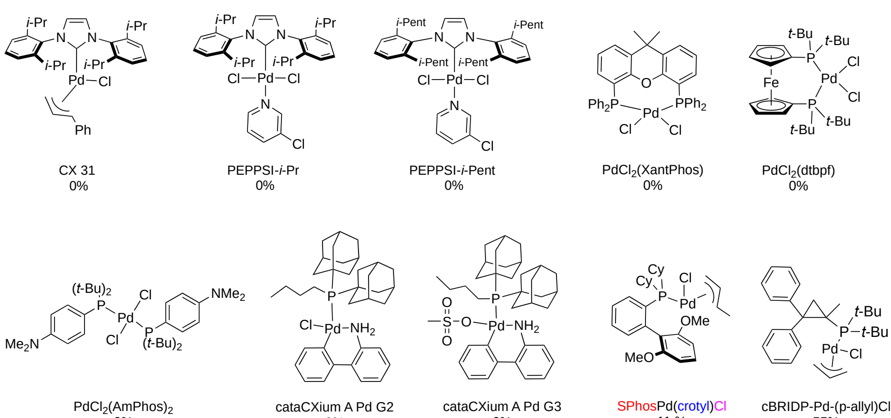
https://periodictable.com/Elements/046/index.html

The current price of palladium as of October 01, 2019 is $1,630.70 per ounce.

https://www.macrotrends.net/2542/palladium-prices-historical-chart-data

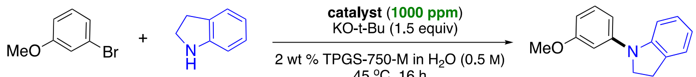
1000 ppm Pd-Catalyzed aminations in water: New catalyst

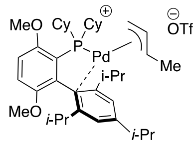




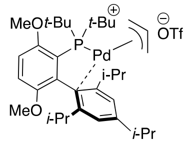
Chem. Sci. 2019

1000 ppm Pd-Catalyzed aminations in water: New catalyst

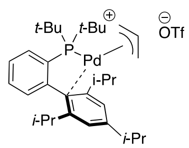




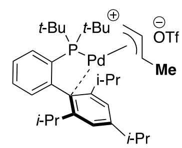
[BrettPhosPd(crotyl)]OTf (Pd-173)
79%



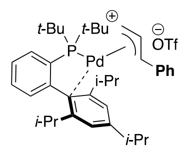
[t-BuBrettPhosPd(allyll)]OTf (Pd-175)
85%



[t-BuXPhosPd(allyl)]OTf (Pd-174)
95%



[t-BuXPhosPd(crotyl)]OTf
93%



[t-BuXPhosPd(cinnamyl)]OTf
100%

Colacot, T. J. *et. al.*, *J. Org. Chem.* **2015**, *80*, 6794.

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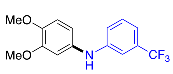
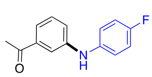
1000 ppm Pd-Catalyzed aminations in water

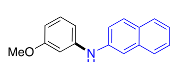
Representative examples



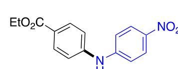
95%



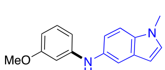
94%



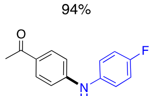
96%



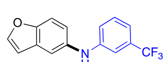
88% (rt)



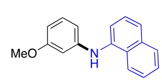
86%



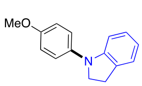
93%



71%



85%



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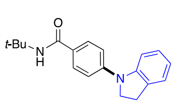

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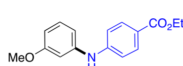
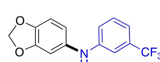
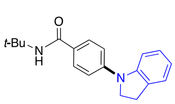


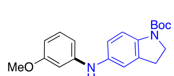
X= I, 86%, rt



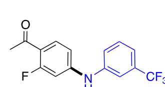
99%



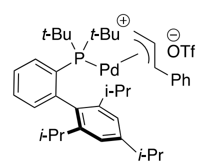
88%



85%



88%



[t-BuXPhosPd(cinnamyl)]OTf

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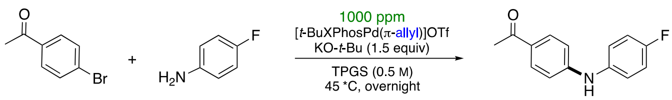
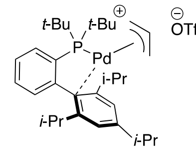
1000 ppm Pd-Catalyzed aminations in water

At gram scale



6.0 mmol (1.25 equiv) 1.37 g, 99%



[t-BuXPhosPd(allyl)]OTf
(Pd-174)

$$\text{E Factor} = \frac{\text{total organic waste (kg)}}{\text{product (kg)}} = 0.5$$

(typical pharma E Factors = 25-100)

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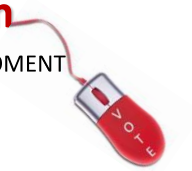
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



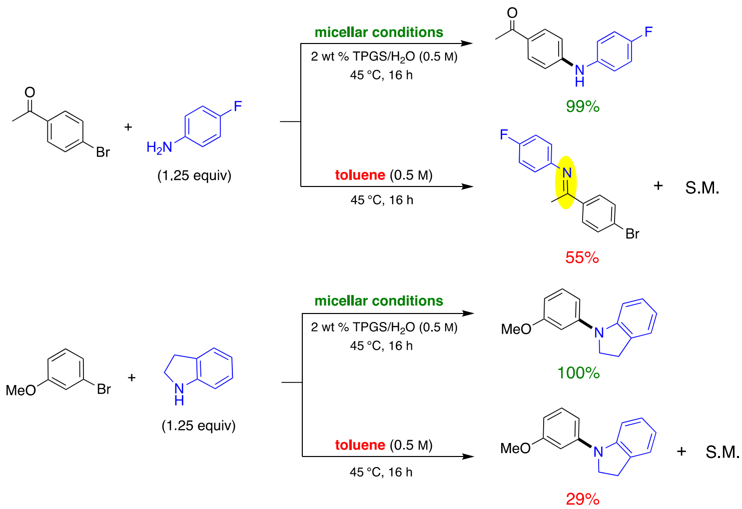
Although this amination forms the desired C-N bond virtually quantitatively using only 1000 ppm of a Pd catalyst, *from the standpoint of the student taking introductory organic chemistry*, what's confusing about this reaction shown?

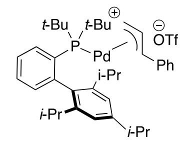
- The yield is too high
- The amine is an aniline and so, it's an unfair choice
- There is a carbonyl group in one of the reaction partners
- Additional Pd must have been added at some point along the reaction coordinate
- The cataylst formed is not the expected species and is far more active than that anticipated

** If your answer differs greatly from the choices above tell us in the chat!*

1000 ppm Pd-Catalyzed aminations in water

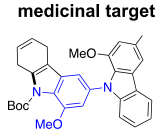
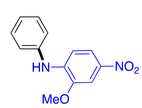
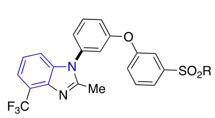
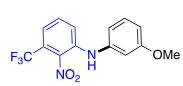
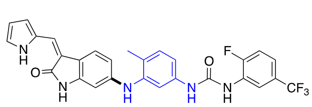
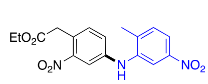
Still prefer organic solvents? Tenga cuidado



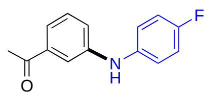


[*t*-BuXPhosPd(cinnamyl)]OTf

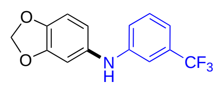
Applications to targets in pharma

medicinal target		key intermediate	literature conditions	this work
 murrastifoline B *J. Org. Chem.* **2015**, *80*, 5666	⟹		10 mol % $Pd(OAc)_2$ 10 mol % XPhos Cs_2CO_3 toluene reflux, 24 h **100%**	1000 ppm [*t*-BuXPhosPd(cinnamyl)]OTf 2 wt % TPGS-750-M/H_2O *t*-BuOK 45 °C, Ar, 16 h **89%**
 liver X receptor agonist *Bioorg. Med. Chem. Lett.* **2010**, *20*, 526	⟹		2 mol % $Pd_2(dba)_3$ 10 mol % XPhos K_2CO_3 *t*-BuOH 80-90 °C, 3 h **74%**	1000 ppm [*t*-BuXPhosPd(cinnamyl)]OTf 2 wt % TPGS-750-M/H_2O *t*-BuOK 45 °C, Ar, 16 h **72%**
 GNF5837 (TRK inhibitor) *J. Med. Chem.* **2012**, *55*, 470	⟹		2 mol % $Pd(OAc)_2$ 3 mol % XantPhos Cs_2CO_3 1,4-dioxane 110 °C, o/n **85%**	3000 ppm [*t*-BuXPhosPd(cinnamyl)]OTf 2 wt % TPGS-750-M/H_2O K_3PO_4-H_2O 35 °C, Ar, 24 h **80%**

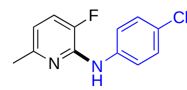
Residual Pd in the products of amination



3 ppm



4 ppm



4 ppm

Allowance: 10 ppm Pd / dose

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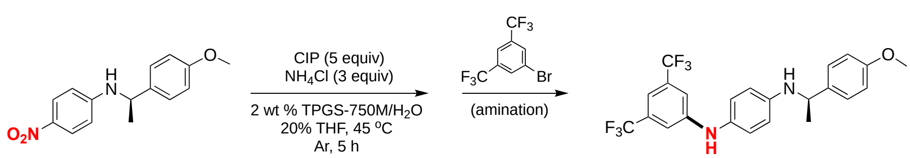
1000 ppm Pd-Catalyzed aminations in water

Tandem reactions



77%

simple filtration through Celite

CIP
carbonyl iron powder
(*Org. Lett.* **2017**, *19*, 6518)

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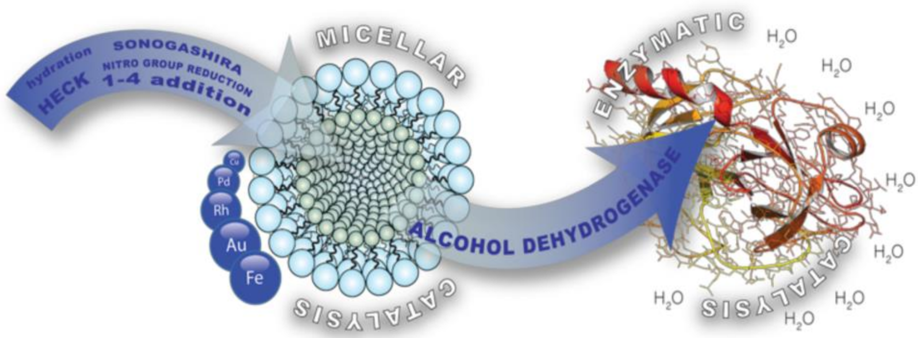
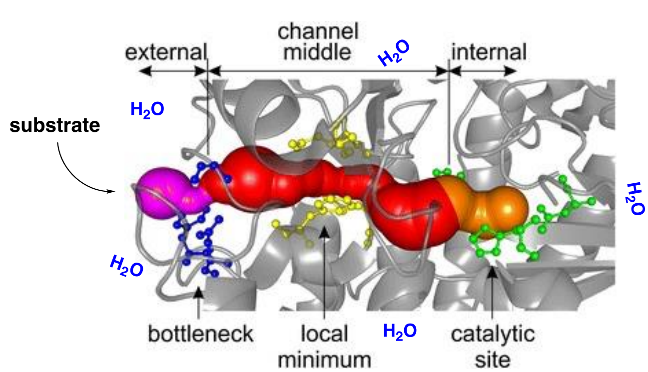
Chemo-catalysis meets bio-catalysis in water

Tandem chemo- / bio-catalyzed reactions



Looking Towards Nature as the Perfect Model

Bio-catalysis: enzymes … in water



Selection of an enzyme

Attractive Features:

low toxicity

usually performed in H_2O

mild and safe conditions

catalytic processes

reduction of waste

atom economy

Types of Enzymes:

oxidoreductases →

transferases

hydrolases

lyases

isomerases

ligases, etc.

alcohol dehydrogenase (ADH)
(from Johnson Matthey; enzyme kit)

- ADH101
- ADH105
- ADH110
- ADH112

Nat. Comm. **2019**, *10*, 2169.

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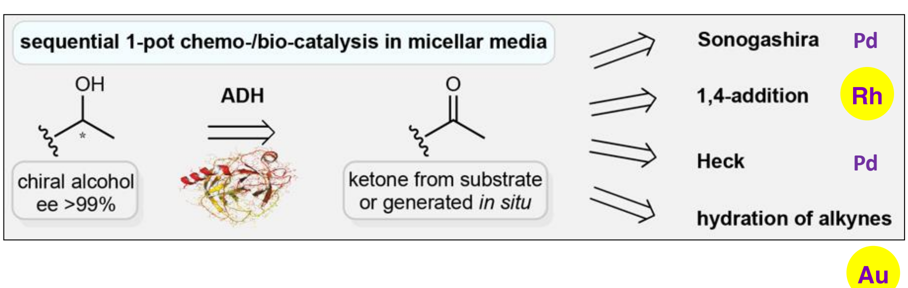
Tandem reactions in water



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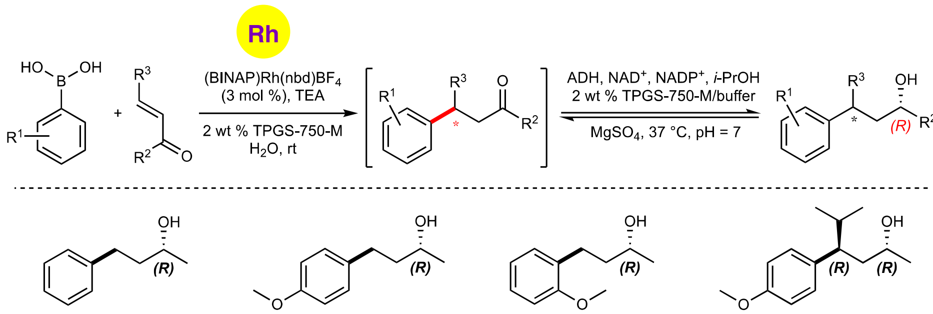
Tandem reactions in water @ rt

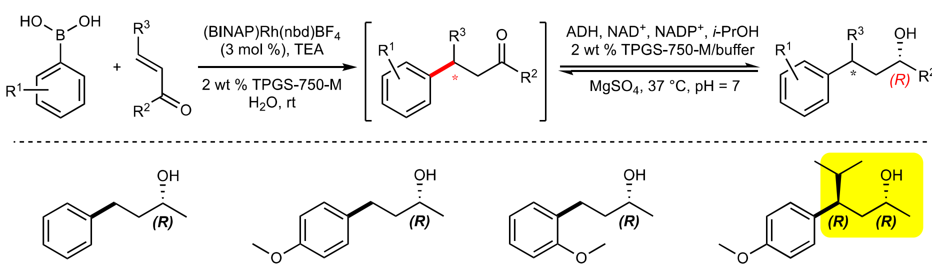
1,4-addition, then ADH



82%	88%	80%	87%
>99.8% ee	>99.9% ee	>99.9% ee	>99.9% ee
ADH101	ADH101	ADH101	>99.4% de
			(R)-BINAP/ADH110

Tandem reactions in water @ rt

1,4-addition, then ADH



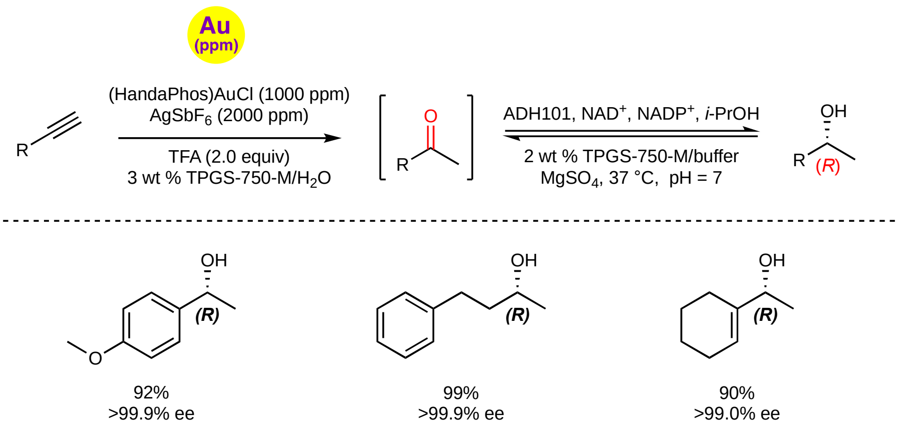
82%	88%	80%	87%
>99.8% ee	>99.9% ee	>99.9% ee	>99.9% ee
ADH101	ADH101	ADH101	>99.4% de
			(R)-BINAP/ADH110

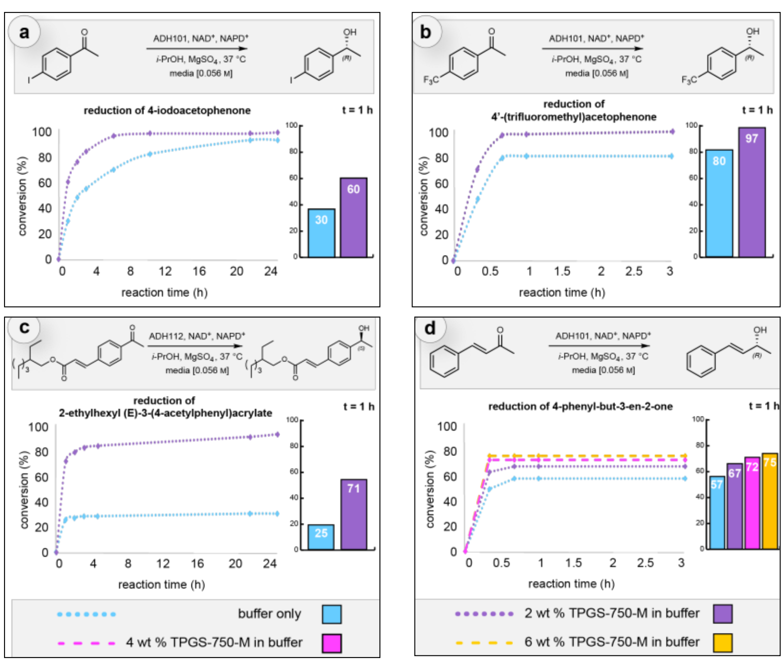
1st stereocenter: ligand-controlled
2nd stereocenter: enzyme-controlled

implication: access to all 4 enantiomers

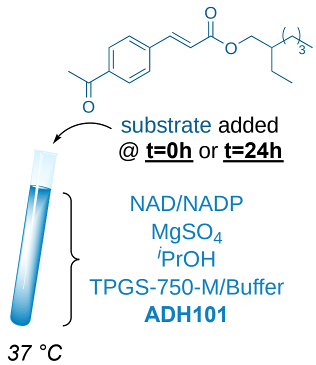
Tandem reactions in water @ rt

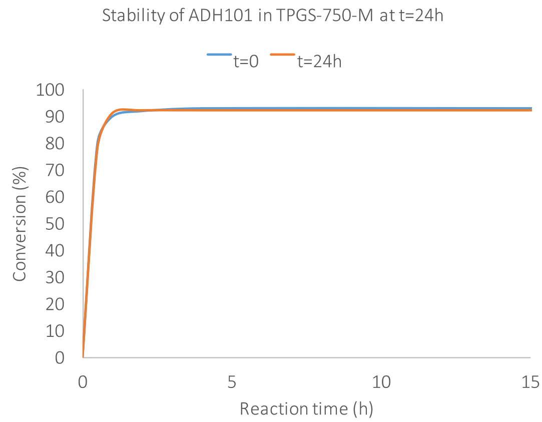
Alkyne hydration, then ADH



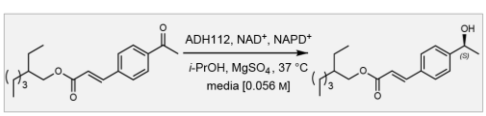


Stability of enzymes in the presence of TPGS-750-M

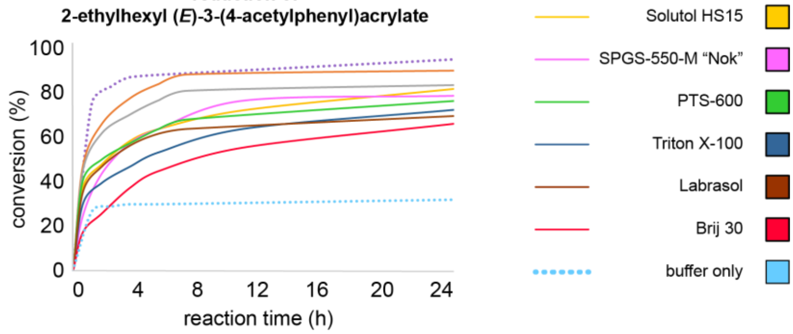




Comparisons: Surfactants



reduction of
2-ethylhexyl (*E*)-3-(4-acetylphenyl)acrylate



Reaction with TPGS-750-M present is fastest.

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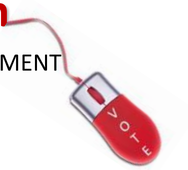
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

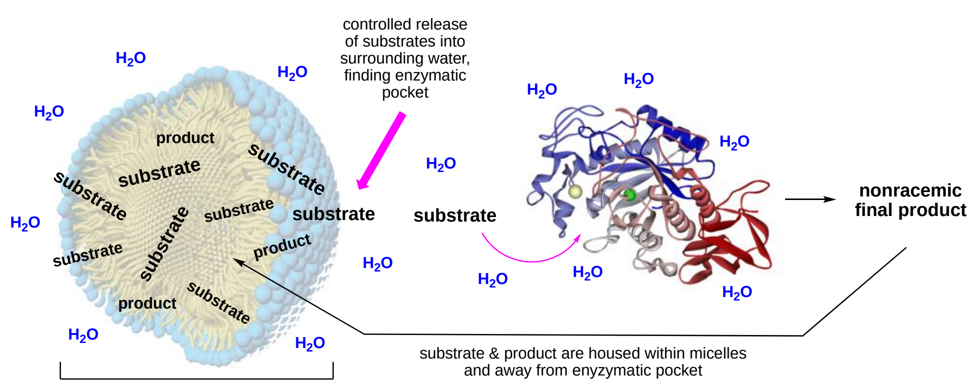


How can just the presence of a surfactant and its derived nanomicelles in the aqueous reaction medium lead to higher levels of enzymatic conversion and hence, greater yields of the desired product?

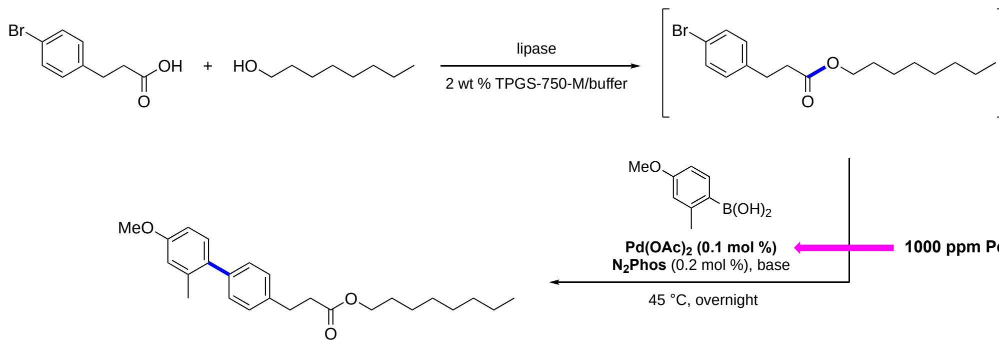
- By widening the entrance of the enzymatic cavity
- By inhibiting re-entry of the initial product
- By providing alternative housing for educts and products
- Via non-covalent bonding to enzyme, thereby changing its size and shape
- None of the above, explaination remains a mystery

** If your answer differs greatly from the choices above tell us in the chat!*

It's in the water: Just add TPGS

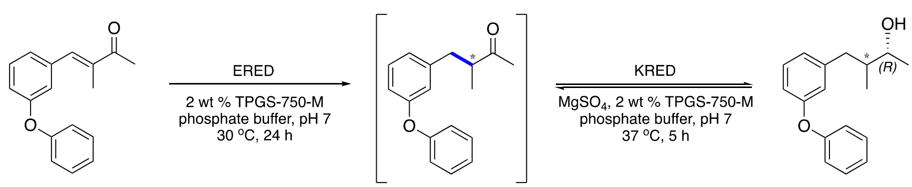


Tandem bio-/chemo-catalysis

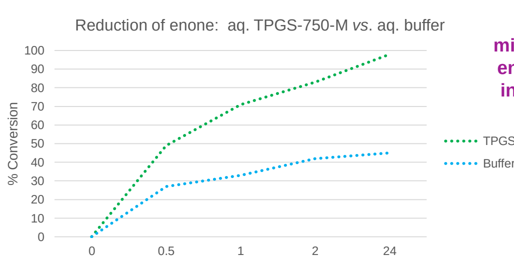


82%

Tandem bio-/bio-catalysis



82%



minimizing enzymatic inhibition

Summary, Conclusions, and a look forward…

Traditional,
in organic solvents

Nontraditional,
in alternative media

new world with
new rules for
doing synthesis,
faster, better, cheaper
&
environmentally responsibly

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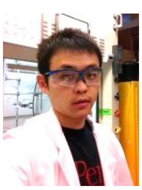
Acknowledgements



Dr. Yitao Zhang
(aminations)

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Nnamdi Akporji

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Sigma-Aldrich/Millipore/Sigma (Tom Colacot, David Klick, Subir Ghorai)

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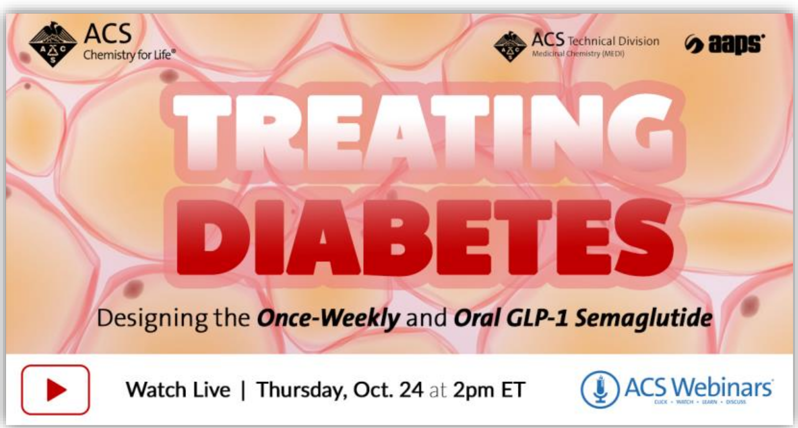

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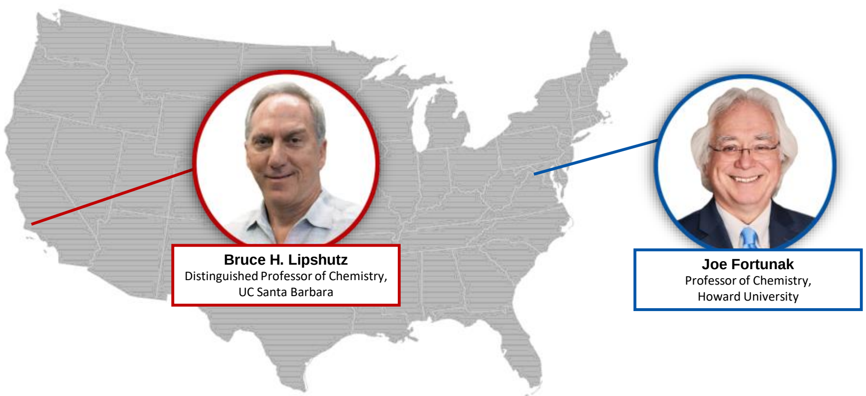

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Fan of the Week

Charlotte Synder, MS
Green and Environmental Chemistry, George Washington University and Student Trainee, TRI Program, Environmental Protection Agency

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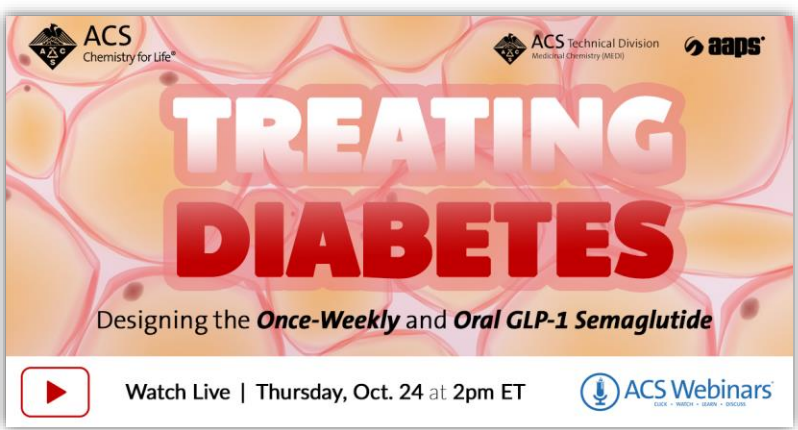

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