



Transitioning Organic Synthesis to a Water World.  
Faster, Better, Cheaper AND Environmentally  
Responsible Chemistry



**Bruce H. Lipshutz**

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University of California

Santa Barbara, CA 93106 USA

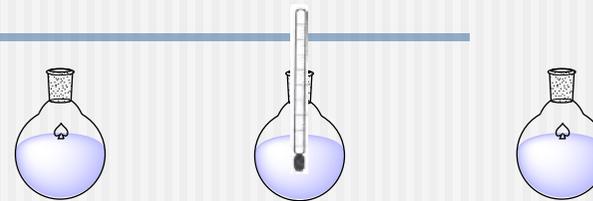
lipshutz@chem.ucsb.edu

Ischia Advanced School of Organic Chemistry

Napoli, Italy

September 23, 2018

Comparisons: **nature** vs. organic chemistry



solvent/medium

reaction temperature

catalyst

organic  
chemistry

organic  
solvents

heating/  
cooling

1-5 mol %  
(10,000-50,000 ppm)

nature

water

ambient

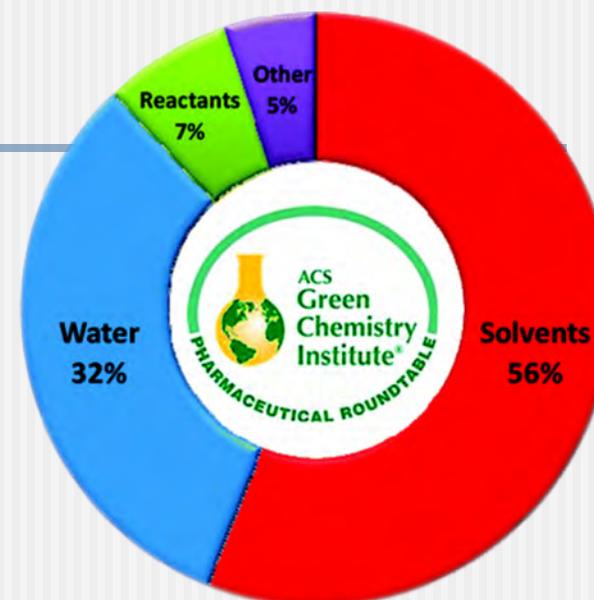
trace metals

OVERLAP:

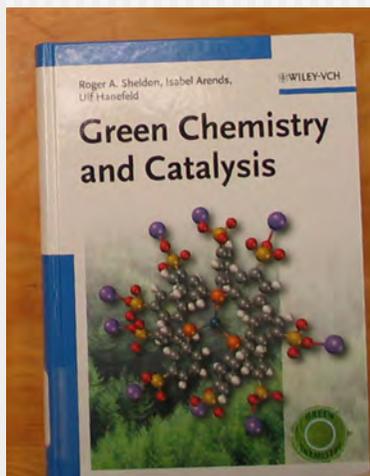
**NONE!**

*Can we make the switch?*

Making the switch to **green** chemistry...



“The medium is the message.”



## Three ~~Two~~ Worlds of Organic Chemistry

*Traditional*, in organic solvents

*Nontraditional*, in alternative media



borrow solubility

borrow water

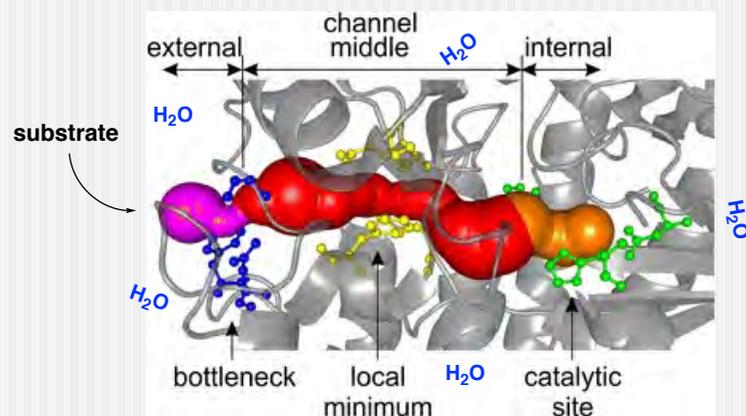
ionic liquids  
scCO<sub>2</sub>  
fluorous  
enzymatic  
multi-phase  
water



a new world with  
new rules

## Looking Towards Nature as the Perfect Model

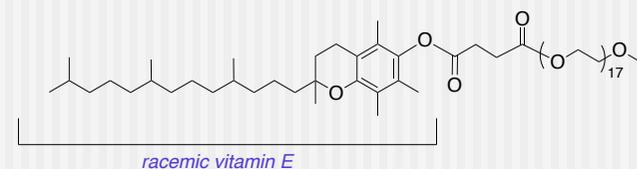
*Enzymatic Biocatalysis...in Water*



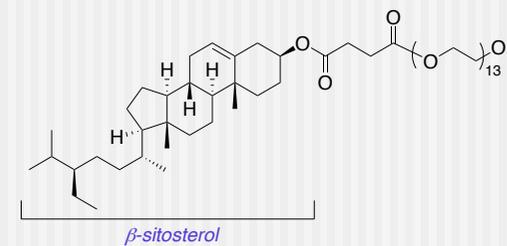
## “Directed Evolution” in Micellar Catalysis

New Nanomicelles as “Nanoreactors” in Water

TPGS-750-M

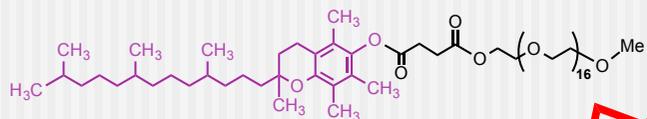


Nok

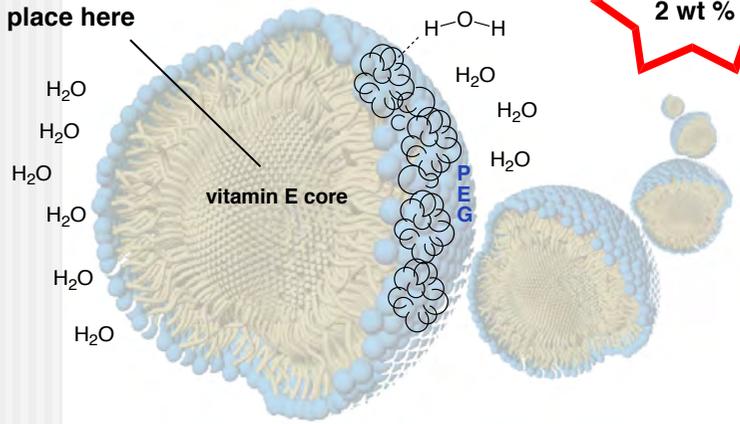


Benign by design “designer” surfactants (available from Aldrich)

## Chemistry in nanoreactors...in water @ room temperature



reactions take place here

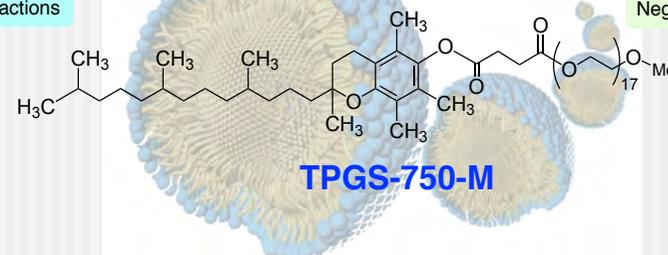


50-60 nm

## Applications of nanomicellar technology

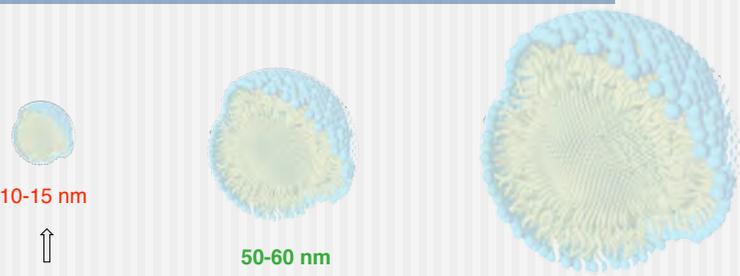
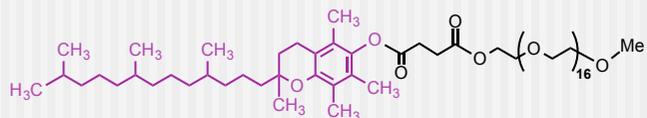
chemistry in water at RT

- |                             |                            |                            |                      |
|-----------------------------|----------------------------|----------------------------|----------------------|
| peptide couplings           | Sonogashira couplings      | asymmetric CuH reactions   | C-H activation       |
| Stille couplings            | Suzuki-Miyaura couplings   | allylic aminations         | aromatic borylations |
| Heck couplings              | NO <sub>2</sub> reductions | Cu-catalyzed 1,4-additions | allylic silylations  |
| aryl aminations             | olefin metathesis          |                            | click reactions      |
| S <sub>N</sub> Ar reactions |                            |                            | Negishi couplings    |



TPGS-750-M

## A "Goldilocks" phenomenon?



from catalogs:  
Triton X-100  
cremophore  
solutol

designer surfactants  
TPGS-750-M  
Nok

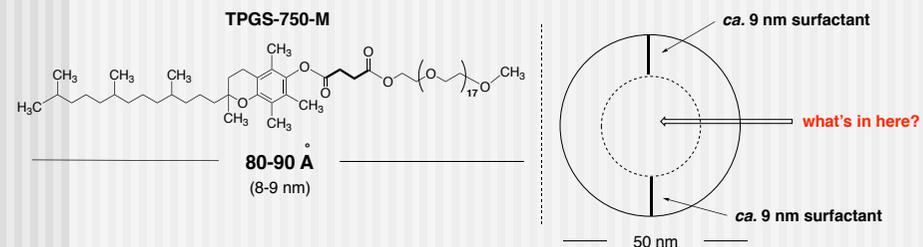
> ca. 150 nm  
too big  
heterogeneous mixtures

## Insight into TPGS-750-M: why does it work so well?

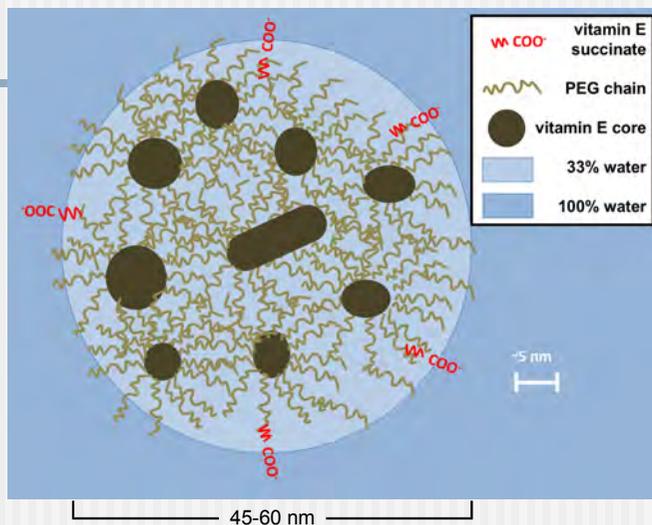


In collaboration with Prof. Martin Andersson

Problem faced:



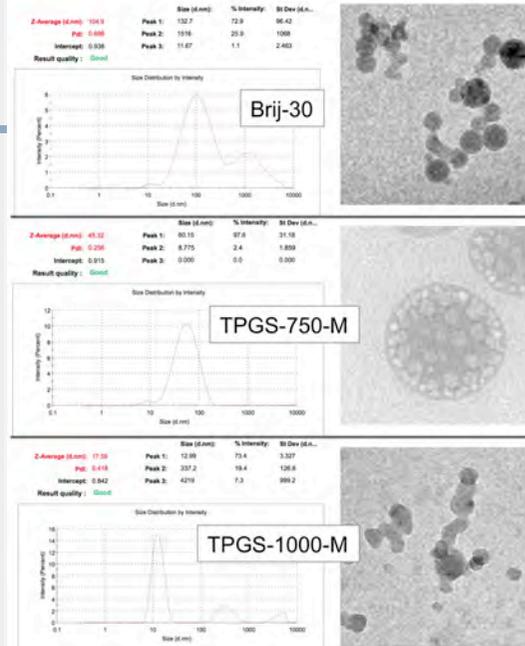
But theory says...



Andersson, M. P. *et al*, *Chem. Euro. J.* **2018**, *24*, 6778.

DLS

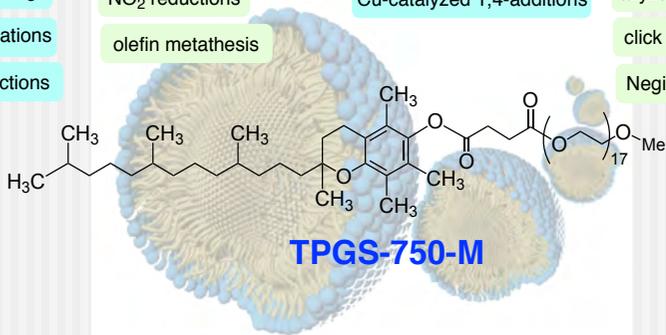
Cryo-TEM



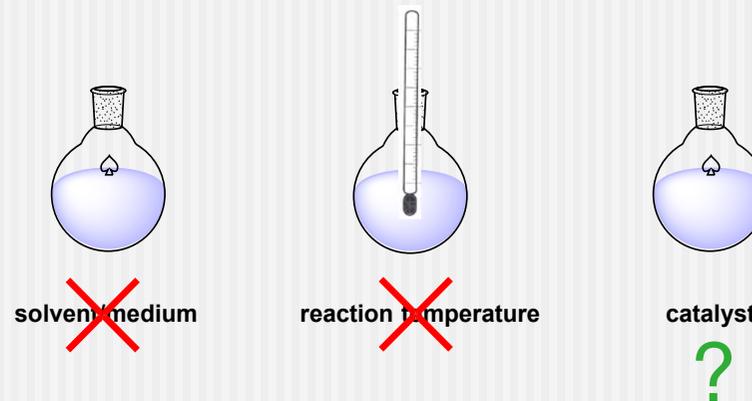
## Applications of nanomicellar technology

chemistry in water at RT

- peptide couplings
- Sonogashira couplings
- asymmetric CuH reactions
- C-H activation
- Stille couplings
- Suzuki-Miyaura couplings
- allylic aminations
- aromatic borylations
- Heck couplings
- NO<sub>2</sub> reductions
- Cu-catalyzed 1,4-additions
- allylic silylations
- aryl aminations
- olefin metathesis
- click reactions
- S<sub>N</sub>Ar reactions
- Negishi couplings



~~Three key reaction parameters~~  
 One left...



## Comparisons: nature vs. organic chemistry



solvent/medium



reaction temperature



catalyst

organic chemistry

nature

organic solvents

water

heating/cooling

ambient

1-5 mol %  
(10,000-50,000 ppm)

trace metals

### THE PERIODIC TABLE OF THE ELEMENTS

Legend:

- Alkali Metal
- Alkaline Earth
- Transition Metal
- Basic Metal
- Semimetal
- Nonmetal
- Halogen
- Noble Gas
- Lanthanide
- Actinide

## Endangered Elements

Legend:

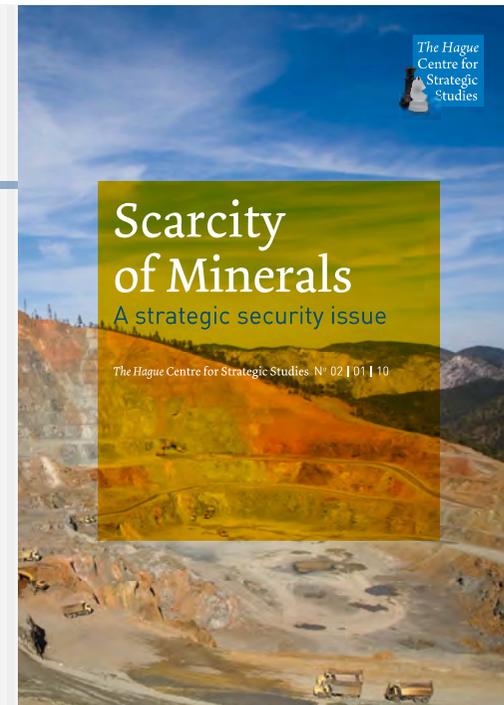
- Red:** SERIOUS THREAT IN THE NEXT 100 YEARS
- Orange:** RISING THREAT FROM INCREASED USE
- Blue:** LIMITED AVAILABILITY, FUTURE RISK TO SUPPLY

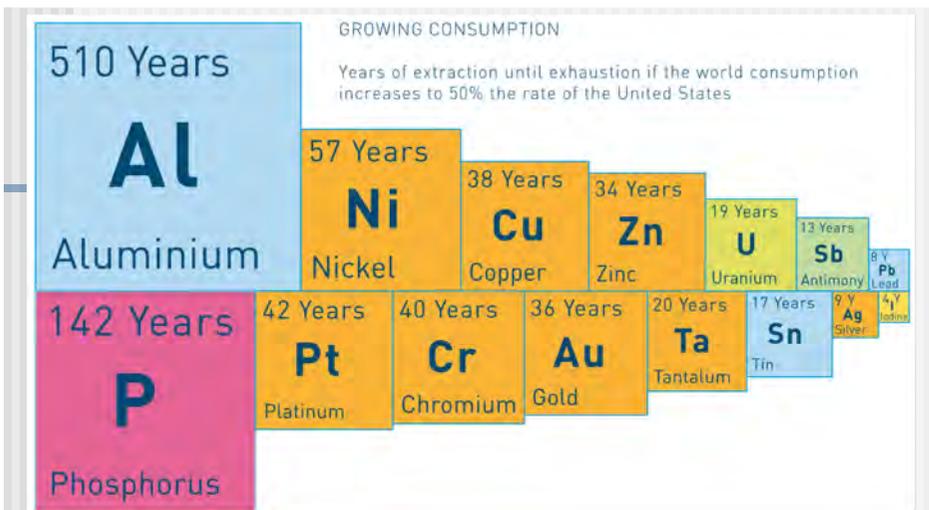
SOURCE: CHEMISTRY INNOVATION KNOWLEDGE TRANSFER NETWORK

## Scarcity of Minerals

A strategic security issue

The Hague Centre for Strategic Studies N° 02 | 01 | 10





"Let me give you some **alternative facts** on this"

(Kellyanne Conway;  
January 22, 2017)



"Truth isn't truth"

(Rudy Giuliani ;  
August 20, 2018)

## Environmentally responsible, sustainable synthetic chemistry



**NO organic solvent**

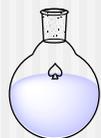


**reaction temperature  
room**



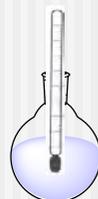
**practically no catalyst**

## Buchwald-Hartwig aminations: from the *green chemistry* perspective



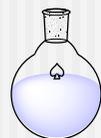
**solvent/medium**

**toluene  
dioxane**



**reaction temperature**

**reflux**



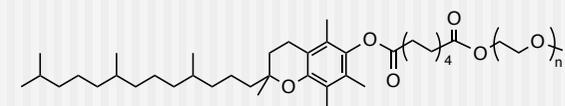
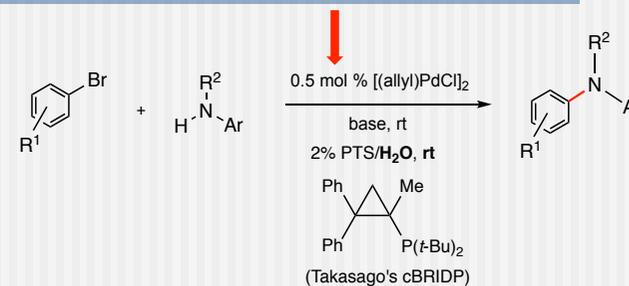
**catalyst**

**2-10% Pd**

Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564.

## Pd-Catalyzed aminations in water: earlier work

**1 mol % = 10,000 ppm**



**PTS** (commercially available)

*Adv. Syn. Catal.* **2009**, *351*, 1717.

Cite this: *Green Chem.*, 2014, 16, 4170

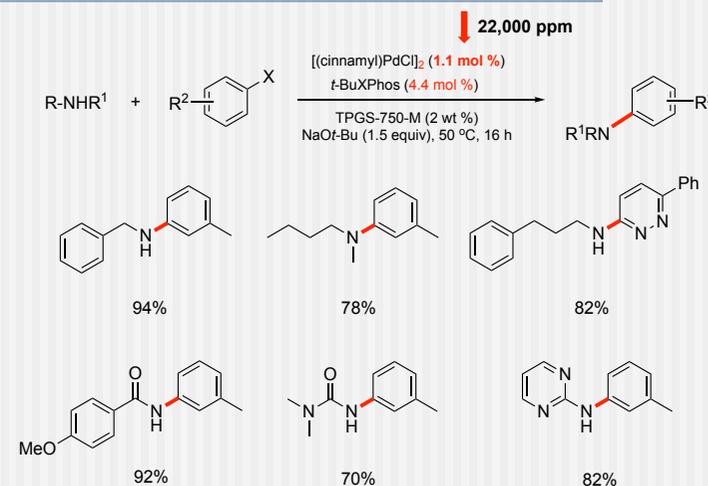
## *t*-BuXPhos: a highly efficient ligand for Buchwald–Hartwig coupling in water†

Patrick Wagner,<sup>a</sup> Maud Bollenbach,<sup>a</sup> Christelle Doebelin,<sup>a</sup> Frédéric Bihel,<sup>a</sup> Jean-Jacques Bourguignon,<sup>a</sup> Christophe Salomé<sup>\*a,b</sup> and Martine Schmitt<sup>\*a</sup>

An efficient and versatile 'green' catalytic system for the Buchwald–Hartwig cross-coupling reaction in water is reported. In an aqueous micellar medium, the combination of *t*-BuXPhos with [(cinnamyl)PdCl]<sub>2</sub> showed excellent performance for coupling arylbromides or chlorides with a large set of amines, amides, ureas and carbamates. The method is functional-group tolerant, proceeds smoothly (30 to 50 °C) and provides rapid access to the target compounds in good to excellent isolated yields. When applied to the synthesis of a known NaV1.8 modulator, this method led to a significant improvement of the E-factor in comparison with classical organic synthesis.

Received 9th May 2014,  
Accepted 1st July 2014  
DOI: 10.1039/c4gc00853g  
www.rsc.org/greenchem

## Pd-Catalyzed aminations in water: earlier work

Schmitt, M. *et al.* *Green Chem.* 2014, 16, 4170.

## Amines *via* reductive amination

*Current Organic Chemistry*, 2015, 19, 1021-1049

1021

### Recent Advances in Reductive Amination Catalysis and Its Applications

Heshmatollah Alinezhad\*, Hossein Yavari and Fatemeh Salehian

Faculty of Chemistry, University of Mazandaran, Babolsar, Iran



**Abstract:** Reductive amination is considered as the most popular and established approaches which provide rapid access to different types of amines, important intermediates for the production of natural products and organic compounds, and also synthesis of essential precursors needed for drug development in chemical and biological systems. The current review discusses the progress of reductive amination catalysis from 2008 to the latest one. Also, efficacy of different reagents including organocatalysts, asymmetric and symmetric complexes of Ir, Rh, and Ru, boron, silicon reagents for enantio-, chemo-, and diastereoselective reactions is illustrated under various reaction conditions with a focus on the yield of the obtained products. Biocatalytic reductive amination for the synthesis of chiral amines and also utility of this reaction for the development of bioactive molecules are also briefly described.

**Keywords:** Boron reagents, organocatalyst, reductive amination, silicon reagent, transfer hydrogenation, transition metal.

#### 1. INTRODUCTION

Amines and their derivatives are present in various significant naturally occurring bioactive molecules such as peptides, nucleic acids, alkaloids and so on [1]. They are known to have widespread applications as intermediates for the synthesis of bulk drugs, fertilizers, dyes, resins, explosives, fine chemicals, solvents, agrochemicals, and synthetic polymers as well as the production of detergents and pesticides. Furthermore, optically active amines have found numerous broad applications in asymmetric synthesis such as chiral auxiliaries, catalysts, and resolving agents.

Because of their significance, there are many different strategies for the synthesis of amines which include: (i) Reduction of functional groups containing nitrogen such as nitro, cyano, azide, and carboxamide derivatives; (ii) Alkylation of ammonia as well as primary or secondary amines. Alkyl halides or sulfonates could be applied as alkylating agents in these reactions; yet, commonly-encountered overalkylation of ammonia and primary amines occurs

these procedures, reductive amination is recognized as the most practical and widespread strategy in the production of various types of amines. Treatment of carbonyl compounds with ammonia and primary or secondary amines in the presence of a reductant for providing different kinds of amines is referred to as reductive amination of carbonyl compounds (Scheme 1). Reductive amination (RA) was firstly described in the early days of the twentieth century by Mignonic. Since then, it has been widely used for the preparation of different types of amines. The initial step of the reaction is the formation of addition product (carbinol amine) which, under controlled appropriate reaction conditions, loses water to offer imine or iminium ion **b**, reduction of **b** produces the amine product.

Reductive amination reaction is considered direct when carbonyl compound, amine, and suitable reducing agents are all mixed in a single one-pot operation without previous formation of the intermediates of imine or iminium salt. However, in stepwise or indirect reaction, the intermediates (imine, iminium, or enamine)

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**Keywords:** Boron reagents, organocatalyst, reductive amination, silicon reagent, transfer hydrogenation, transition metal.

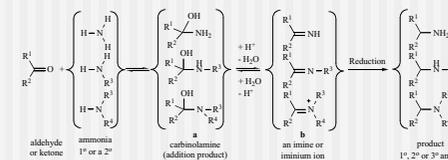
#### 1. INTRODUCTION

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these procedures, reductive amination is recognized as the most practical and widespread strategy in the production of various types of amines. Treatment of carbonyl compounds with ammonia and primary or secondary amines in the presence of a reductant for providing different kinds of amines is referred to as reductive amination of carbonyl compounds (Scheme 1). Reductive amination (RA) was firstly described in the early days of the twentieth century by Mignonic. Since then, it has been widely used for the preparation of different types of amines. The initial step of the reaction is the formation of addition product (carbinol amine) which, under controlled appropriate reaction conditions, loses water to offer imine or iminium ion **b**, reduction of **b** produces the amine product.

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## Main-Group-Catalyzed Reductive Alkylation of Multiply Substituted Amines with Aldehydes Using H<sub>2</sub>

Yoichi Hoshimoto,<sup>\*,†,‡</sup> Takuya Kinoshita,<sup>†</sup> Sunit Hazra,<sup>†</sup> Masato Ohashi,<sup>†</sup> and Sensuke Ogoshi<sup>†,‡</sup>

<sup>†</sup>Department of Applied Chemistry, Faculty of Engineering and <sup>‡</sup>Frontier Research Base for Global Young Researchers, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

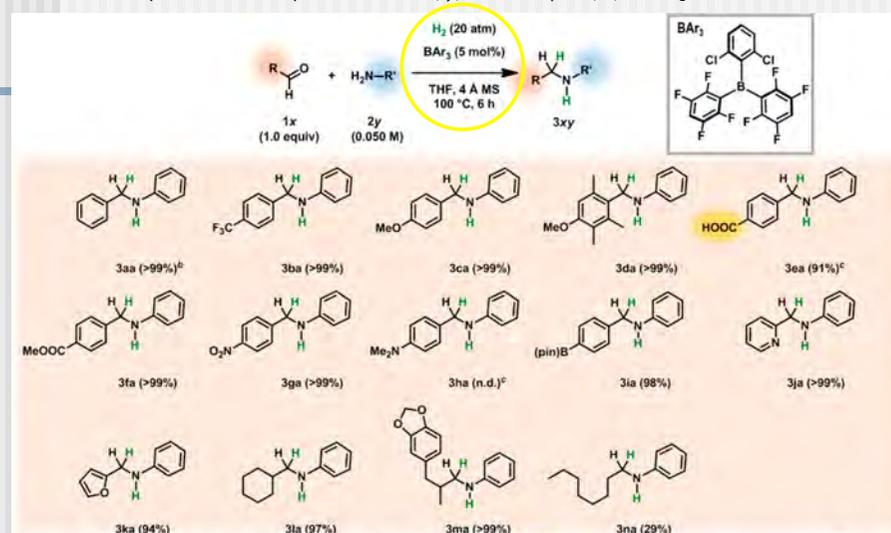
Supporting Information

**ABSTRACT:** Given the growing demand for green and sustainable chemical processes, the catalytic reductive alkylation of amines with main-group catalysts of low toxicity and molecular hydrogen as the reductant would be an ideal method to functionalize amines. However, such a process remains challenging. Herein, a novel reductive alkylation system using H<sub>2</sub> is presented, which proceeds via a tandem reaction that involves the B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub>-catalyzed formation of an imine and the subsequent hydrogenation of this imine catalyzed by a frustrated Lewis pair (FLP).

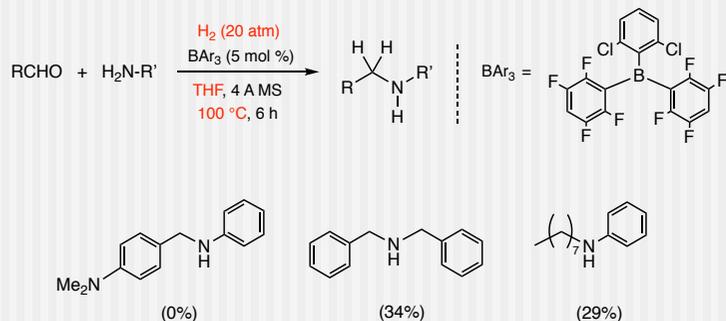


This reductive alkylation reaction generates H<sub>2</sub>O as the sole byproduct and directly functionalizes amines that bear a remarkably wide range of substituents including carboxyl, hydroxyl, additional amino, primary amide, and primary sulfonamide groups. The synthesis of isoindolinones and aminophthalic anhydrides has also been achieved by a one-pot process that consists of a combination of the present reductive alkylation with an intramolecular amidation and intramolecular dehydration reactions, respectively. The reaction showed a zeroth-order and a first-order dependence on the concentration of an imine intermediate and B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub>, respectively. In addition, the reaction progress was significantly affected by the concentration of H<sub>2</sub>. These results suggest a possible mechanism in which the heterolysis of H<sub>2</sub> is facilitated by the FLP comprising THF and B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub>.

Scheme 2. FLP-Catalyzed Reductive Alkylation of Amines (2y) with Aldehydes (1x) with H<sub>2</sub><sup>††</sup>



## Ogoshi, et al. JACS, 2018



Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub> in the FLP-catalyzed hydrogenation of carbonyl compounds.<sup>90</sup>

In the case of path A, the FLP comprising THF and **B** activates H<sub>2</sub> to afford [THF–H][H–B], and the [THF–H]<sup>+</sup> species continuously activates Im to form an iminium intermediate **Y**. A similar activation of aldehydes by [THF–H]<sup>+</sup> has been theoretically studied by Pápai and Soós et al.<sup>96</sup> Finally, a hydride transfer from [H–B]<sup>–</sup> to the iminium moiety in **Y** affords the reductively alkylated product with the concomitant regeneration of the FLP catalyst.

On the other hand, in the case of path B, the FLP comprising **Im** and **B** activates H<sub>2</sub> to afford [Im–H][H–B], which would subsequently be solvated by THF to form intermediate **Y**. This type of H<sub>2</sub> activation has been proposed for FLP-catalyzed hydrogenations in noncoordinating solvents such as toluene and CH<sub>2</sub>Cl<sub>2</sub>.<sup>90,91c</sup>

In order to clarify the reaction mechanism, detailed mechanistic studies were carried out (Figure 3). First, the reaction between **1a** and **2a** was monitored under the conditions shown in Figure 3a in order to confirm the catalysis by B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub> during the formation of imine **A**. In the presence of both 4 Å MS and B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub> (5 mol %), **A** was obtained in 83% yield within 5 min, whereas almost no reaction was observed in the absence of B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub>, most likely due to the insufficient nucleophilicity of **2a** toward **1a**.<sup>97</sup> It should be noted that the reaction was pressurized with H<sub>2</sub> within 10 min after the preparation of the THF solution of **1**, **2**, B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub>, and 4 Å MS. Thus, the B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub>-catalyzed formation of the imines should be operative under these conditions.

evaluated by varying the pressure of H<sub>2</sub> from 5 to 40 atm under the conditions shown in Figure 3f.

All these results demonstrate that (i) B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub> is involved in both catalytic cycles of the present tandem processes and (ii) the rate-limiting heterolytic cleavage of H<sub>2</sub> would be mediated by the FLP comprising THF and B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub>, given that the reaction rate depends on the H<sub>2</sub> pressure. Path A in Figure 2 is likely to occur for the reaction of **1a**, **2a**, and H<sub>2</sub> in the presence of B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub> in THF.

### CONCLUSION

In summary, a novel reductive alkylation system has been developed for the direct functionalization of amines that bear a remarkably wide range of functional groups, which include carboxyl, hydroxyl, and additional amino groups. Thus, a variety of amino acids (or their derivatives) were alkylated in good to excellent yield. The reaction proceeds via tandem processes comprising the B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub>-catalyzed formation of imines and their subsequent hydrogenation catalyzed by a frustrated Lewis pair (FLP). The results of our mechanistic studies support the proposed mechanism: (i) the formation of the imine is significantly accelerated in the presence of B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub> and MS and (ii) the rate-limiting heterolytic cleavage of H<sub>2</sub> should be mediated by the FLP comprising THF and B(2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>)(p-HC<sub>6</sub>F<sub>4</sub>)<sub>2</sub>. Moreover, H<sub>2</sub> was used as the reductant, which generates H<sub>2</sub>O as the sole byproduct. In their entirety, the aforementioned results demonstrate that the present catalytic system represents an environmentally benign, atom-efficient, and practical route to functionalize multiply substituted amines.

## ppm metal catalysis... Suzuki-Miyaura couplings

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Journal of Medicinal Chemistry

Perspective  
pubs.acs.org/jmc

### Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone?

Miniperspective

Dean G. Brown<sup>1</sup>\* and Jonas Boström<sup>2</sup>

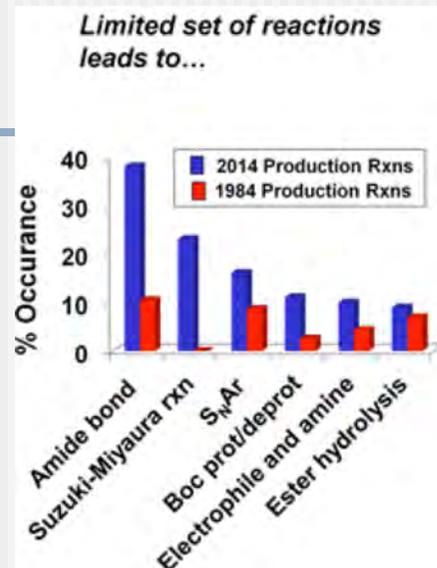
<sup>1</sup>AstraZeneca Neurosciences, IMED Biotech Unit, AstraZeneca R&D Boston, 141 Portland Street, Cambridge, Massachusetts 02139, United States  
<sup>2</sup>CVMD Innovative Medicines, IMED Biotech Unit, AstraZeneca, Mölndal SE-431 83, Sweden

Supporting Information

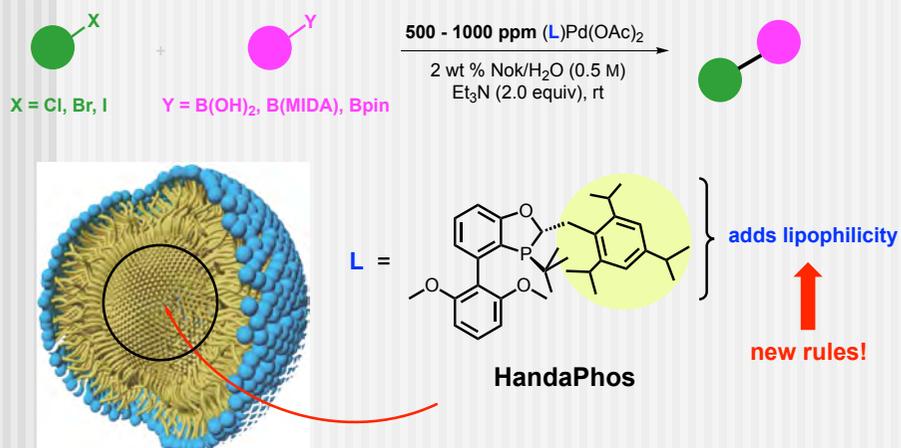
**ABSTRACT:** An analysis of chemical reactions used in current medicinal chemistry (2014), three decades ago (1984), and in natural product total synthesis has been conducted. The analysis revealed that of the current most frequently used synthetic reactions, none were discovered within the past 20 years and only two in the 1980s and 1990s (Suzuki–Miyaura and Buchwald–Hartwig). This suggests an inherent high bar of impact for new synthetic reactions in drug discovery. The most frequently used reactions were amide bond formation, Suzuki–Miyaura coupling, and  $S_NAr$  reactions, most likely due to commercial availability of reagents, high chemoselectivity, and a pressure on delivery. We show that these practices result in overpopulation of certain types of molecular shapes in drug discovery. The most frequently used reactions were amide bond formation, Suzuki–Miyaura coupling, and  $S_NAr$  reactions, most likely due to commercial availability of reagents, high chemoselectivity, and a pressure on delivery. We show that these practices result in overpopulation of certain types of molecular shapes in drug discovery. The most frequently used reactions were amide bond formation, Suzuki–Miyaura coupling, and  $S_NAr$  reactions, most likely due to commercial availability of reagents, high chemoselectivity, and a pressure on delivery. We show that these practices result in overpopulation of certain types of molecular shapes in drug discovery.

Limited set of reactions leads to... narrowly populated chemical shape space

Brown, D. G.; Bostrom, J. *J. Med. Chem.* **2016**, *59*, 4443.



## Pd-catalyzed Suzuki-Miyaura couplings: with Pd at ppm levels



*Angew. Chem., Int. Ed.* **2016**, *55*, 4914.

## ACS Catalysis

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### 2-Aminobiphenyl Palladacycles: The "Most Powerful" Precatalysts in C–C and C–Heteroatom Cross-Couplings

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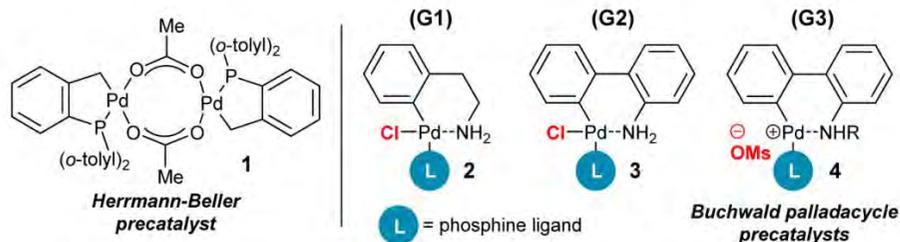
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**ABSTRACT:** New approaches to the Pd-catalysis employing palladacycle precatalysts have been recently developed. Breakthroughs in this area using 2-aminobiphenyl palladacycle precatalysts are highlighted. High reactivity and selectivity are achieved for the C–C and C–heteroatom bond formation under mild reaction conditions.

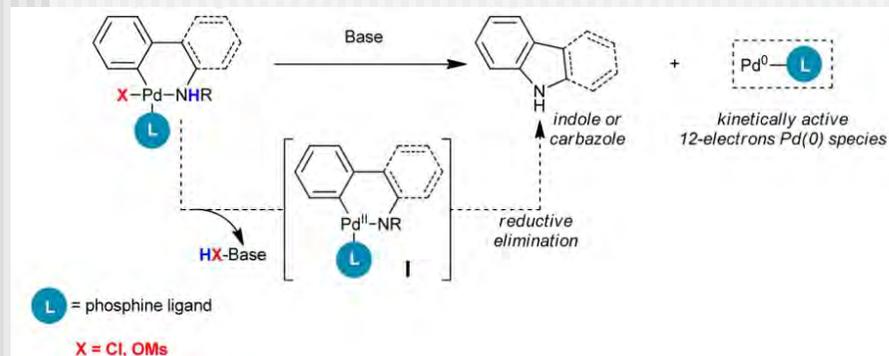
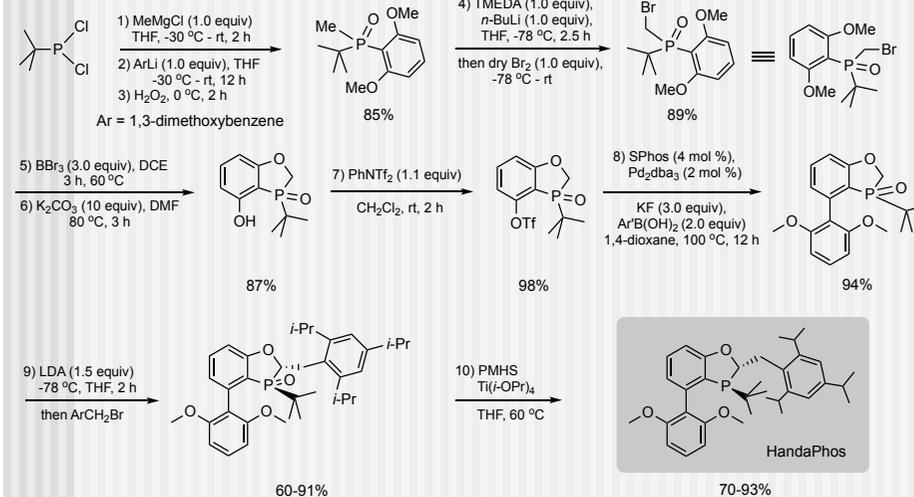


**KEYWORDS:** catalysis, palladacycles, precatalysts, C–C and C–heteroatom bonds formation, cross-couplings

*ACS Catalysis* **2015**, *5*, 1386.



## Preparation of HandaPhos



## When Does Organic Chemistry Follow Nature's Lead and "Make the Switch"?

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**ABSTRACT:** The case is made for transitioning organic chemistry from a developed discipline that remains highly dependent upon organic solvents to one that will be sustainable, based on water as the reaction medium. Processes in hand that today achieve the same bond constructions characteristic of traditional organic synthesis, but can be accomplished under environmentally responsible conditions, are discussed as representative of the potential that lies ahead.

