Innovation and Sustainability in Process Chemistry

Parma, November 5th - 6th, 2024

Transition-Metal Catalysis: Quo Vadis? A Personalized Account

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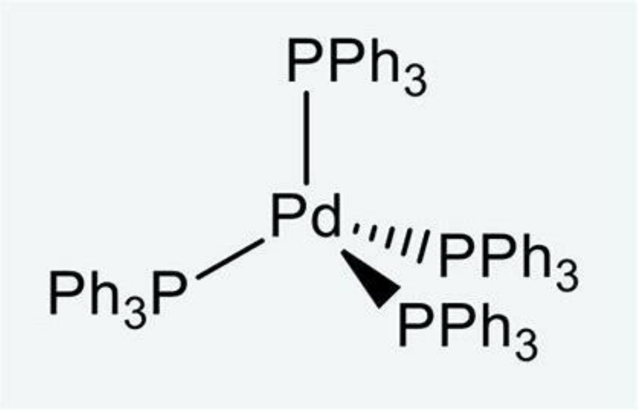
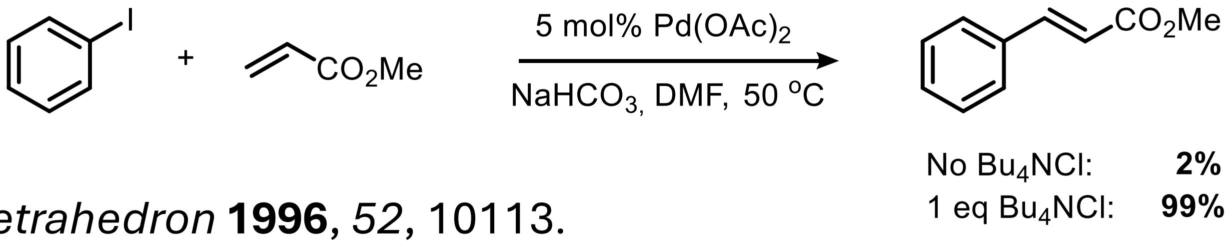
Palladium Chemistry in the 80s



Tetrakis(triphenylphosphine)palladium:

- Miyaura, N.; Yamada, K.; **Suzuki, A**. *Tetrahedron Letters* **1979**, *20*, 3437.
- Miyaura, N.; **Suzuki, A**. *Chem. Commun*. **1979**, 866.
- Milstein, D.; **Stille, J. K**. *J. Am. Chem. Soc*. **1978**, *100*, 3636.

NOTHING: Cross-coupling using ligandless Pd: **Beletskaya, I. P.** *J. Organomet. Chem*. **1983**, *250*, 551.

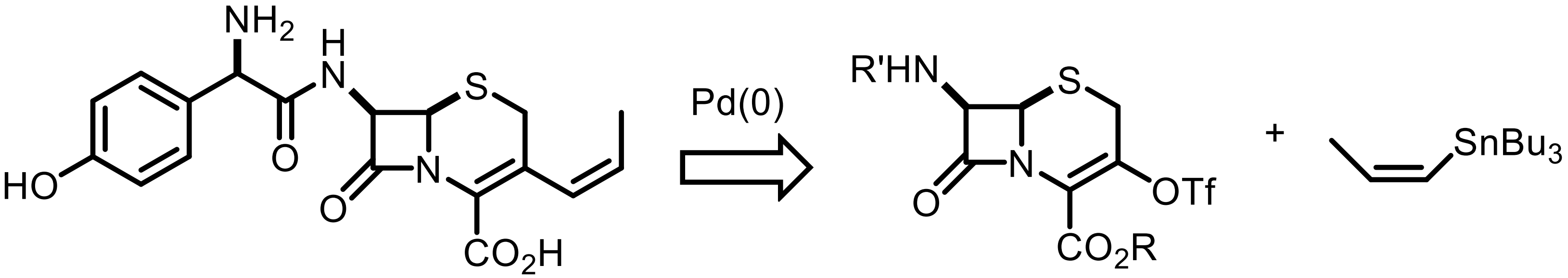


No Bu_4NCl: **2%**
1 eq Bu_4NCl: **99%**

Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

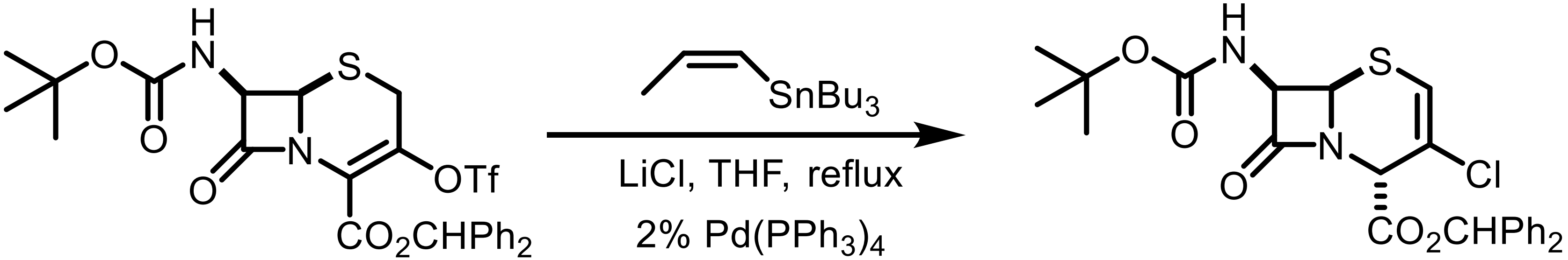
All the ligandless work puzzled me: aren't TM unstable without ligands?

My First Problem (1984)



BMY-28100 (Cefprozil), oral antibiotic

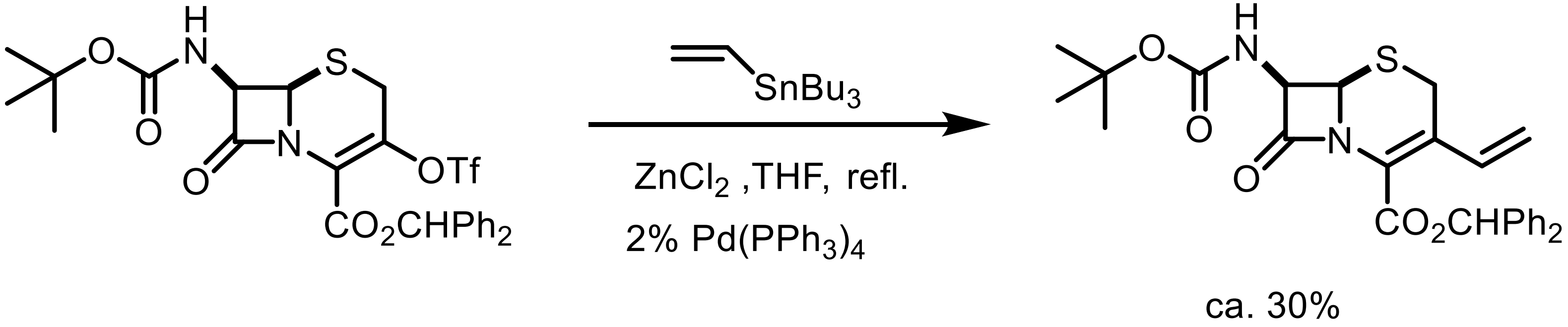
Targets: cost \$500/kg, Z selectivity >99%



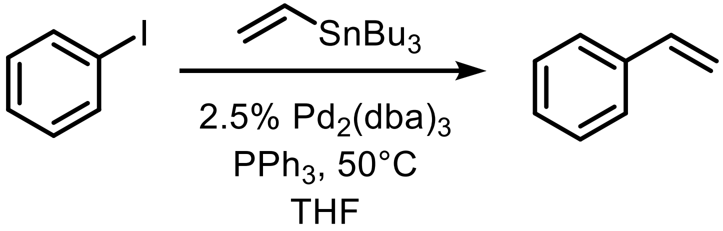
main product

Using the published Stille conditions: Scott, W. J.; Crisp, G. T.; Stille, J. K. Palladium-catalyzed coupling of vinyl triflates with organostannanes, *J. Am. Chem. Soc*. **1984**, *106*, 4630.

Solving the Problem



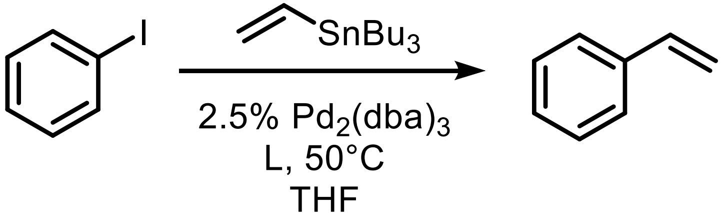
Parameter screening (Zymark robot) did not improve the yield at all.
I decided to look at the kinetics of the Stille reaction.



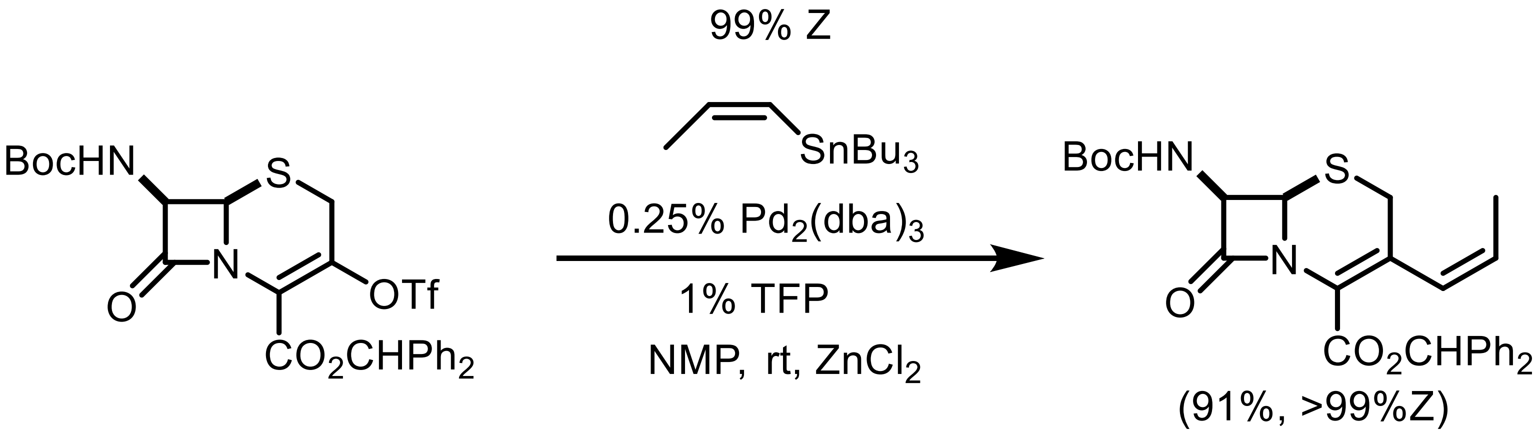
$$dP/dt = \frac{a[Cat]_0[stannane]}{b + c[PPh_3]}$$

The rate law shows that transmetalation is the rate-determining step and is inhibited by the ligand. This was a surprising result, which suggested changing the ligand. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

Problem Solved



Ligand (Pd:L=1:4)	Relative Rate
PPh_3	1
$(p\text{-}MeOC_6H_4)_3P$	0
$P(2\text{-furyl})_3$	105
$AsPh_3$	1,100



Baker, S. R.; Hauck, S. I.; Benigni, D. A.; Farina, V. *J. Org. Chem*. **1990**, *55*, 5833.

Lessons Learned

KNOW NOTHING APPROACH → **FAILURE**

KNOW SOMETHING APPROACH → **SUCCESS**

IMPORTANCE OF LIGAND TAILORING

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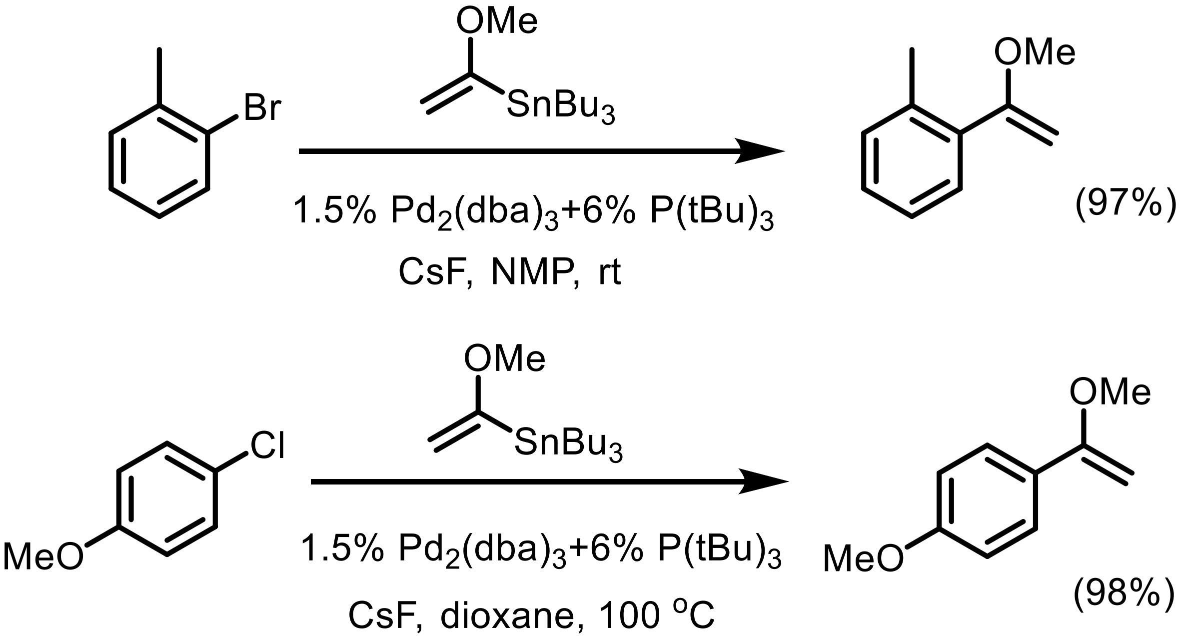
The Era of the Ligands



As a consequence of the strong L inhibition, Stille couplings are best carried out with bulky, basic phosphines. They can activate even the most unreactive aryl chlorides, and do not suffer from L inhibition, because they are usually too bulky to coordinate twice at Pd(II). **Bulky, electron-rich phosphines are the most generally useful ligands in Pd chemistry, *e.g.*, the Buchwald biaryl ligands.**

Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411.
12-Electron Pd(0)L paradigm: Colacot, T. J. et al. *Chem. Rev.* **2022**, *122*, 16983.

Ligand Screens and the HTE Hype

What came first?

1. *The need to screen catalysts, leading to screening technologies?*
2. *Screening technologies, leading to the widespread screening of catalysts and ligands?*

Ligand Screens and the HTE Hype

- The invention of lab automation originates in the biological sciences (1970s): the trigger was the need for automated sampling and diluting of biological samples for analysis.
- This technology was later adapted to HT screening assays for drug discovery.
- In the 1990s, automated technology was extended to the world of organic synthesis. Huge investments in infrastructure for the automated creation and testing of combinatorial libraries of drug-like molecules were supposed to revolutionize drug discovery.
- When these goals were not met, the automated synthesizers became a technology looking for new applications.
- Among the many possible uses, optimization of organic processes, and especially the development of catalytic reactions, was identified by vendors and quickly taken up by Big Pharma management.
- One of the early applications of sophisticated hardware and software (**Symyx**) for catalysis optimization using HTE/DOE and 96-plate technology was described by Merck (Rahway): McWilliams J. C. et al. *J. Assoc. Lab. Autom*. **2005**, *10*, 394.
- In the meantime, Symyx products evolved into the **Unchained Labs** technology line (see photo).
- Other significant players: **Mettler-Toledo, Chemspeed**.

Ligand Screens and the HTE Hype

- The value of HTE lies mostly in early development, because screens can be used to generate initial conditions to prepare a pre-developmental API with very little material and in very little time. A broad ligand screen applied to a known reaction will always yield **something that works**. However, chemists should note that:

Catalysts carry out catalysis, not ligands, not pre-catalysts.

- A recent review warns that the application of HTE to catalysis has its perils: "*the additional parameters of catalyst loading and ligand-to-metal ratio, along with generally more pronounced solvent effects, can have a significant impact on the success rate of a screen…Furthermore, the catalyst precursor identity, addition order, and aging protocol, <u>each of which is informed by mechanistic understanding of organometallic chemistry</u>, are also critical variables*". Selekman, J. A. *Ann. Rev. Chem. Biomol. Eng*. **2017**, *8*, 525.

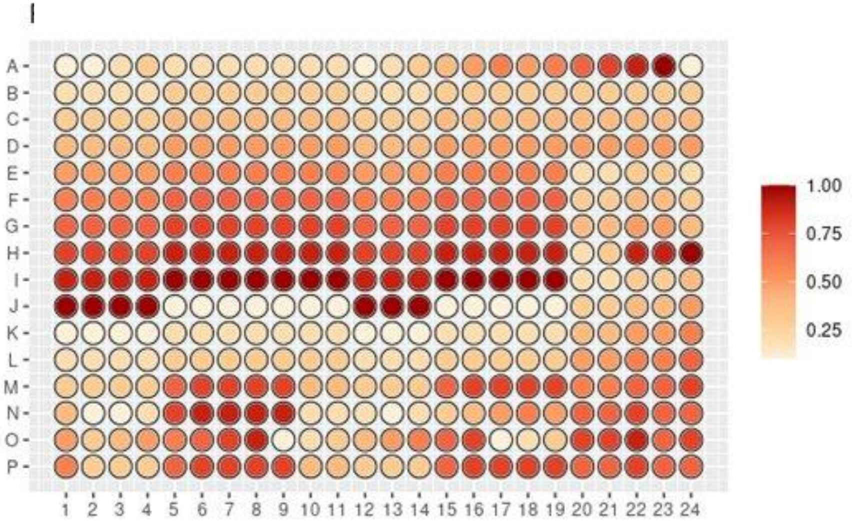
- **HTE methodology, when applied blindly and not supplemented by kinetic analysis and development work, tends to yield ineffective, poorly scalable processes. You need good chemists to drive the technology, not engineers.**

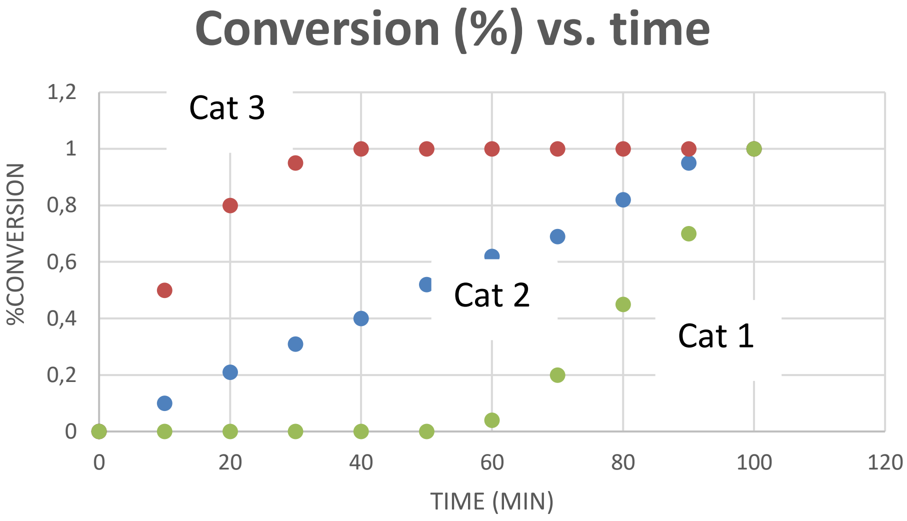
Current HTE Practices

- Palladium catalysis constitutes ca. 80% of steps described in OPRD (2017-2022).
- Pre-plated ligands used for most screen, in conjunction with a Pd source (usually palladium acetate) at high catalyst load (1-5 mol%), and a single Pd:L ratio (usually 1:2 or 1:1 for bidentate ligands).
- Yields after overnight stirring are reported, often qualitatively (color).
- This is not a recipe for finding a high-TON catalyst.
- Little attention is paid to the order of mixing of pre-catalyst, ligand and reactants.
- Little or no kinetic analysis or catalyst characterization. No knowledge of resting state of the catalyst, rate-determining step, possible off-cycle species, saturation, product inhibition.
- Synthetic chemists have embraced HTE eagerly, because it allows them to generate large amount of data by offshoring the problem to an engineer.
- This results in poorly understood, non-robust processes and is a sure recipe for scale-up problems.

Farina, V. *Org. Process Res. Dev*. **2023**, *27*, 831-846.

Big Data, Missing Data or Junk Data?



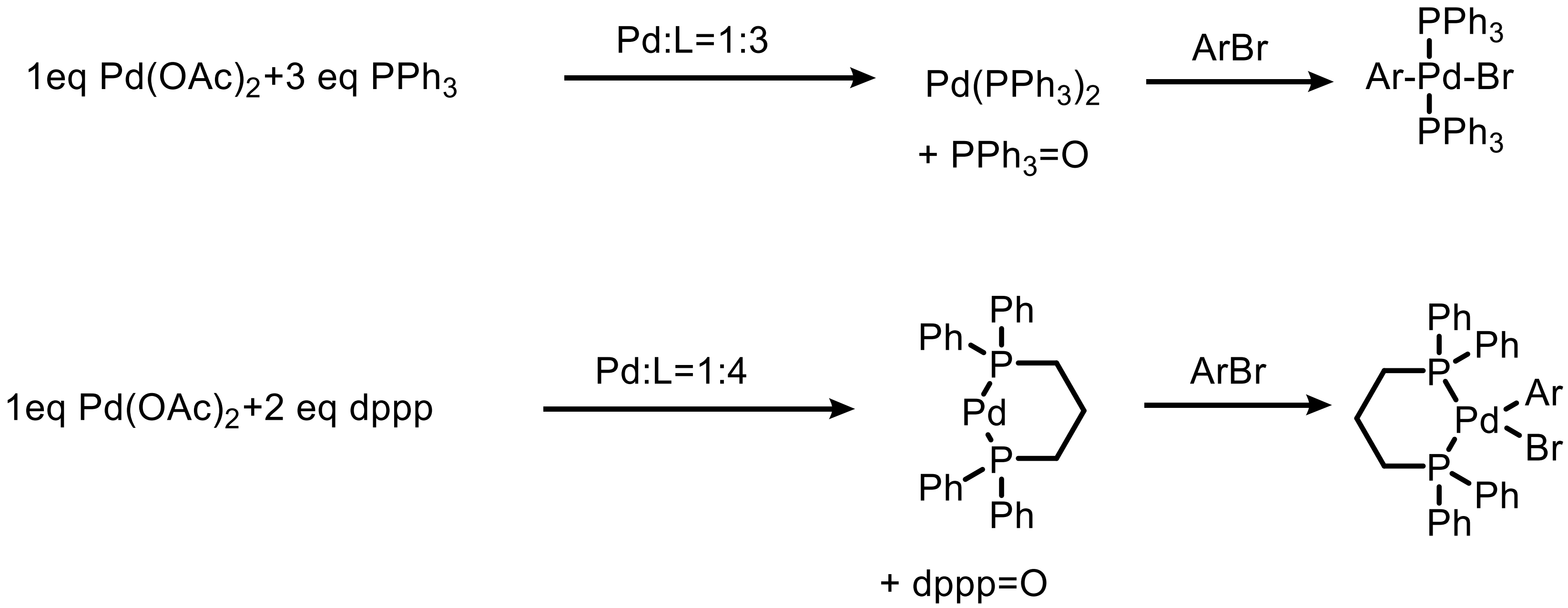


The “big data“ in these plates only shows what works and what does not under the specific conditions. **This information is flawed by the lack of knowledge of the active catalyst**. If the experiments are not well designed, this is junk data!

The “big data“ associated with each conversion curve, if interrogated, yields information about catalyst activation, decomposition, RDS, resting state, order in catalyst, off-cycle species, step reversibility etc. **This precious information is lost in current HTE screens.**

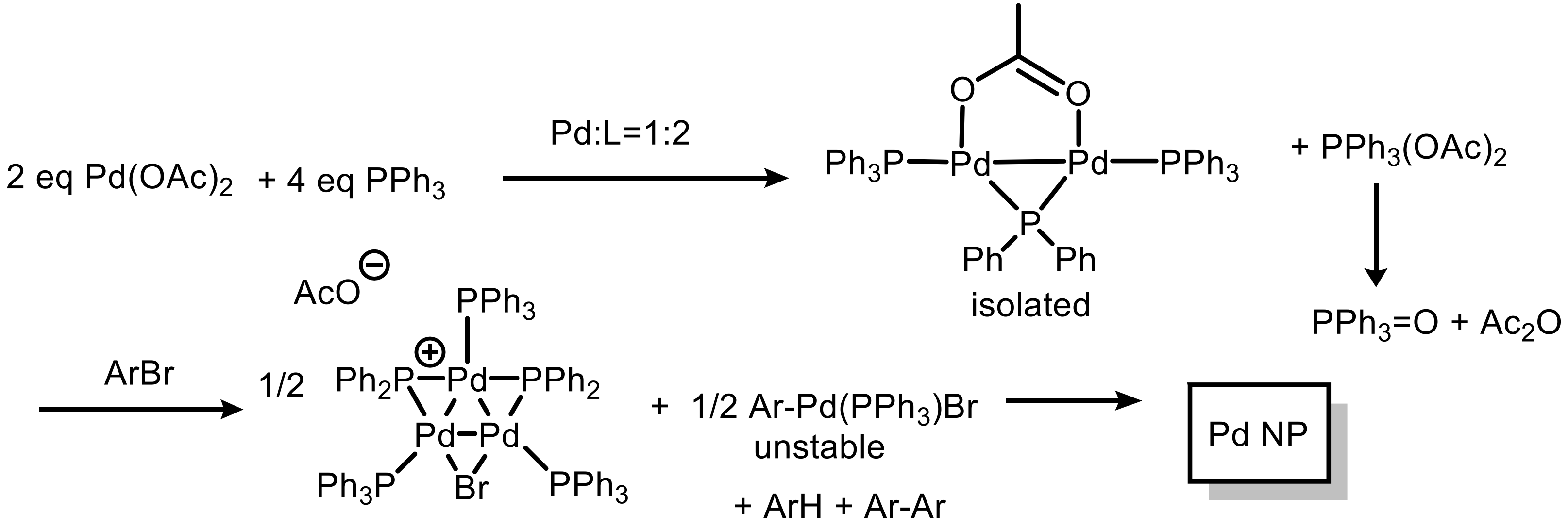
Why Junk Data: $Pd(OAc)_2$ Activation

The active species depends closely on the Pd:L ratio.



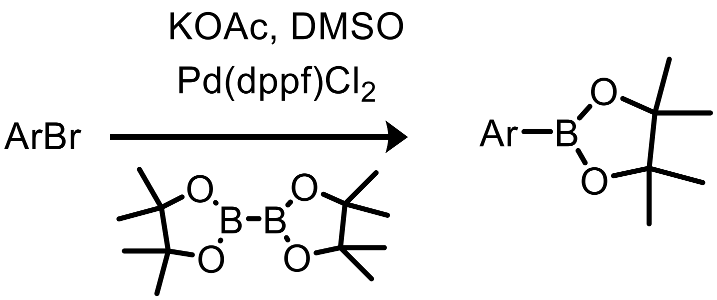
PPh_3: Amatore, C; Jutand, A. *Organometallics* **1992**, *11*, 3009. **Dppp**: Amatore, C.; Jutand, A. *Organometallics* **2001**, *20*, 3241. **$Pd(OAc)_2$-phosphine complexes are intrinsically unstable** and form a phosphine oxide at rt. Thus, attention must be paid at how the reagents are mixed and the time elapsed between charging operations, especially if some reagents are also Pd(II) reducing agents, such as diboron cpds. and most ArM, RM species.

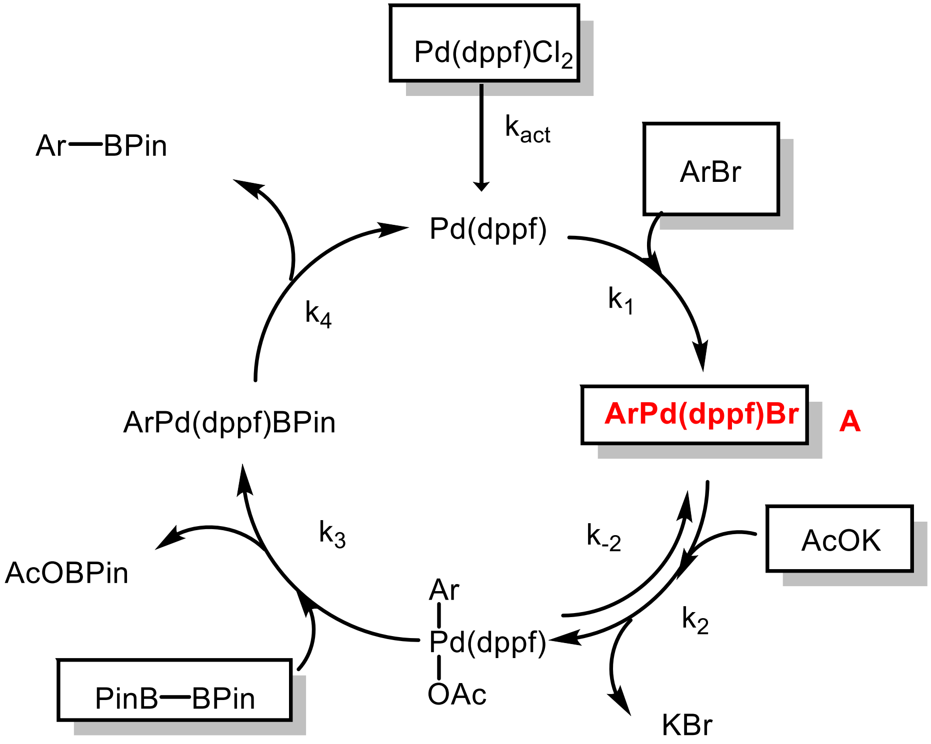
Why Junk Data: $Pd(OAc)_2$ Activation



- Scott, N. W. J. et al. *Chem. Sci.* **2019**, *10*, 7898; Scott, N. W. J. et al. *Organometallics* **2021**, *40*, 2995. After oxidative addition, the catalyst is a mixture of Pd nanoparticles and a Pd cluster having its own specific reactivity in cross-coupling.
- Pd(I) dimers with XPhos: Wagschal, S. et al. *Chem. Eur. J.* **2019**, *25*, 6980-6987.
- $Pd(OAc)_2$ and $P(tBu)_3$ form palladacycles: Henderson, W. H. et al. *Organometallics* **2011**, *30*, 5038-5044.
- SPhos undergoes *o*-palladation: Montgomery, M. et al. *Dalton Trans.* **2019**, *48*, 3539-3542.
- **All this literature is systematically ignored in HTE work. The catalyst is almost never characterized or studied before it is implemented in scale-up.**

Example: Miyaura Borylation





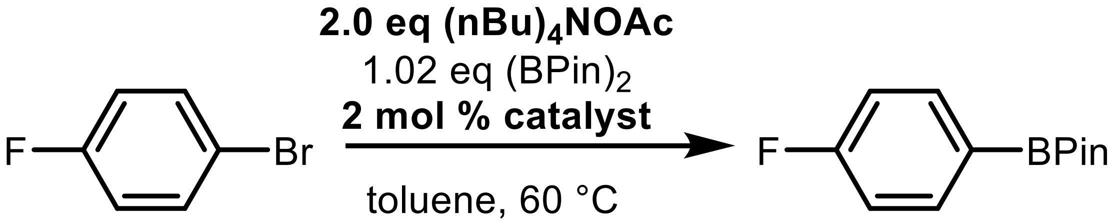
Hugely popular reaction, but mechanistically not understood. Miyaura's proposal is just a scheme. **Note: precatalyst activation is not explained!**

Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem*. **1995**, *60*, 7508.

If the mechanism is correct, one can use in-cycle species **A** as catalyst.

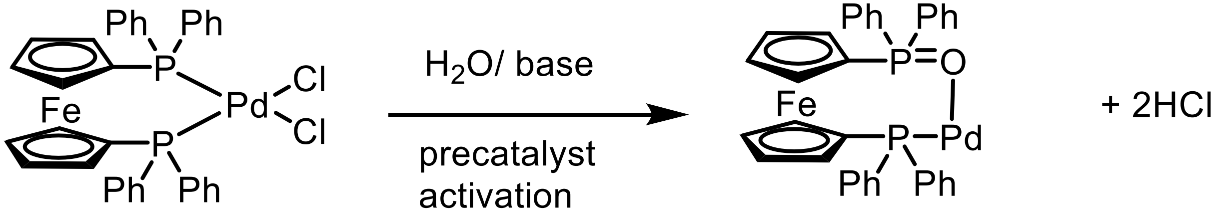
We found that the transmetalation is L-dissociative, and **A** is not an intermediate in the catalytic cycle. See: Barroso, S. et al. *J. Org. Chem*. **2021**, 86, 103.

Example: Miyaura Borylation



2.0 eq $(nBu)_4NOAc$
1.02 eq $(BPin)_2$
2 mol % catalyst
toluene, 60 °C

(pre)-catalyst:	
***p*-F-C_6H_4Pd(dppf)Br (A)**	no reaction
Pd(dppf)Cl_2	>98% conv.
Pd(dppf)Cl_2 + dppf (1:1)	no reaction
$Pd_2(dba)_3$ + dppf=O (1:1)	>98% conv.



H_2O/ base

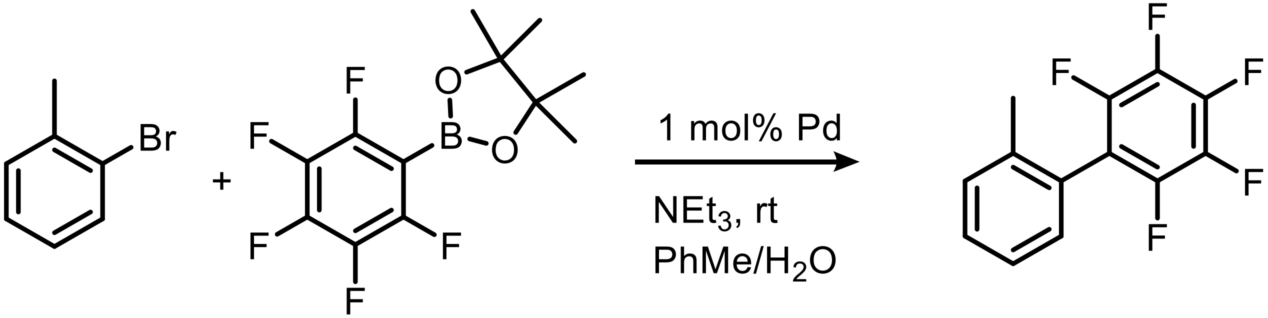
precatalyst activation

P, P bidentate (tight)

P,O bidentate (loose)

Kinetics show the active intermediate in the cycle has a P/O ligand which is poorly chelating, whereas the P/P ligand is an inhibitor. A screen at different Pd:L ratios would have helped. **In a ligand database for borylation, a clueless chemist would insert dppf among the ligands that "work". It does NOT!**

It is NOT All About the Ligand!

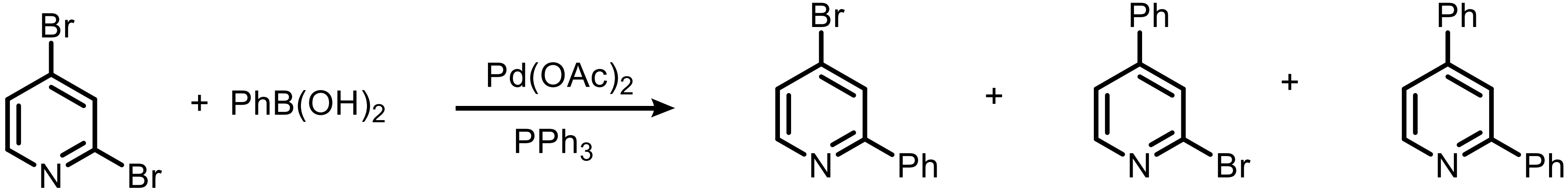


This is challenging coupling because under the basic conditions the boronate undergoes a deborylation reaction, and the authors did not want to use an excess of the reactant. Here **the success of the reaction depends on the mode and rate of catalyst activation.**

Timsina, Y. N.; Xu, G.; Colacot, T. J. *ACS Catal.* **2023,** *13*, 8106.

Catalyst [L = $(tBu)_3P$]	***In Situ* Coupling Yield**
p-$CF_3C_6H_4$-Pd(L)Cl	58
p-$CF_3C_6H_4$-Pd(L)Br	99
p-$CF_3C_6H_4$-Pd(L)I	33
$Pd(OAc)_2$:L =1:1	3
PdL_2	2
$[PdL(\mu\text{-}Br)]_2$	5
Buchwald G2L	6
Buchwald G4L	26

It is NOT All About the Ligand



major with Pd:L=1:3 or 1:4

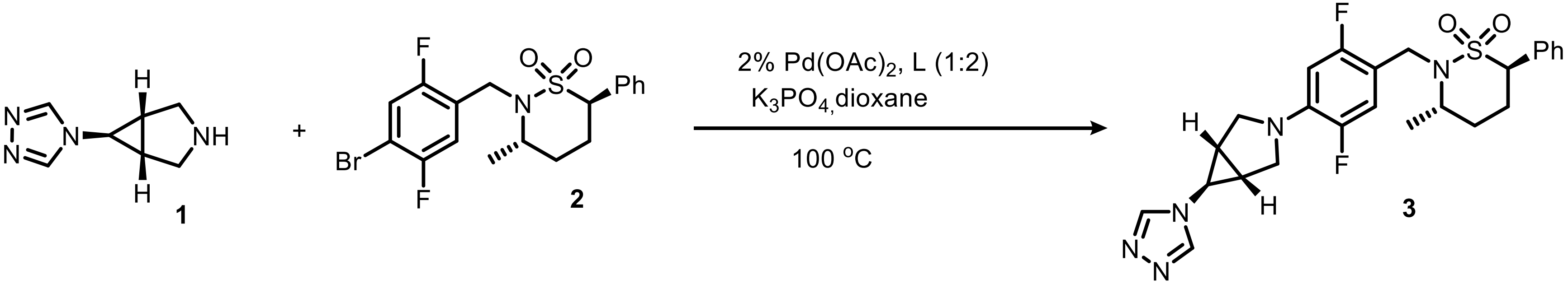
major with Pd:L=1:2

minor

A typical screen using only one ratio of Pd:L would not uncover this dichotomy. **Different Pd:L ratios give different catalysts!** Most screens would typically focus on optimizing the ligand without paying attention to the activation mechanism. Thus, important information is lost in most screens currently run in the Pharma industry.

Scott, N. W. J. et al. *J. Am. Chem. Soc*. **2021**, *143*, 9682.

Example of Ligand Confusion



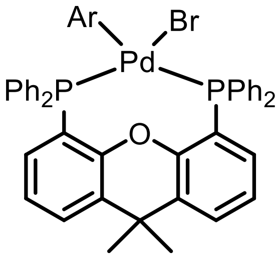
Sirois, L. A. et al. *Org. Process Res. Dev.* **2020**, *24*, 567.

Upon screening **300 conditions** using the infamous Pd(OAc)$_2$ precatalyst, a **ligand** is selected, **XantPhos,** as best yielding. Under the screening conditions, the catalyst is, very likely, **B**.

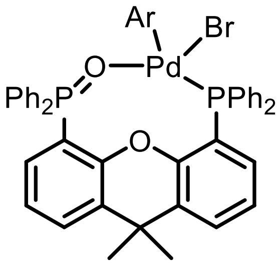
In the final process, they select a **G2 Buchwald pre-catalyst**, which forms **A**. Therefore, the ligand selected in the screen may not be the one chosen for the scale-up!

In an attempt to distinguish between **A** and **B**, they run kinetics with Pd(OAc)$_2$ and XantPhos monoxide, which does not work because it leads to **C**. However, the authors think they have excluded **B** as a catalytic species!

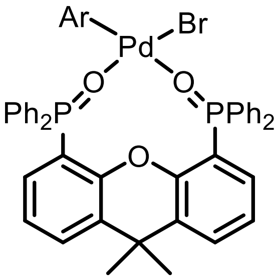
A

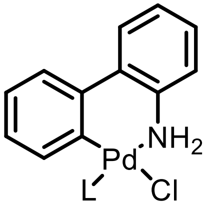


B



C

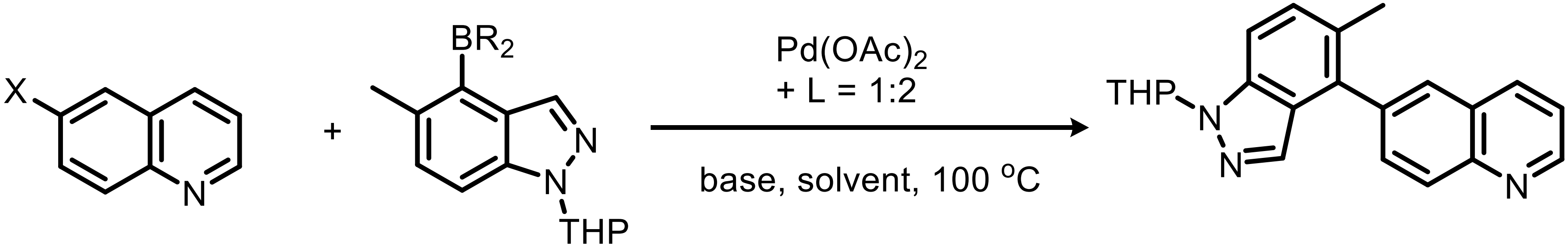




G2

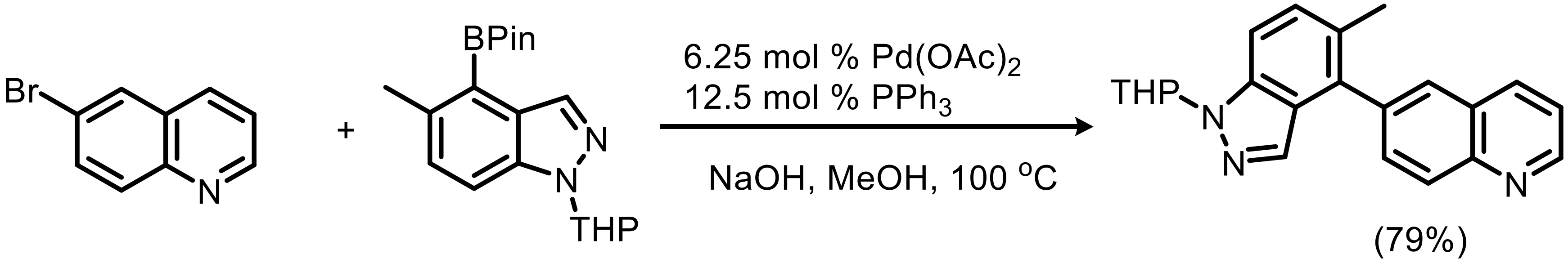
Focus on Automation Technology

Recent example of miniaturization: Pfizer chemists and engineers have described a HT flow system capable of handling **5,760 reactions** in 3 days, including analysis. This was applied to a "difficult" Suzuki coupling reaction, screening all combinations of 7 leaving groups, 4 nucleophiles, 12 ligands, 8 bases and 4 solvent systems. The best conditions were scaled successfully in flow (residence time = 1 min).



Perera, D. et al. (Pfizer) *Science* **2018,** *359*, 429.

Final Results



Screening several ligands only with Pd(OAc)$_2$ pre-catalyst + 2 equiv. L is a methodological error. The selected catalytic system is intrinsically ill-defined and likely unstable.

Difficult to believe one needed >5,000 experiments on such a well-known reaction to arrive at such an inefficient, ill-defined, unstable catalytic system!

This example, while technologically impressive, does not solve any problems: if we want to start solving chemical problems, a competent chemist must be involved in these studies!

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Catalysis in Flow: Ask ChatGPT

CLAIMED ADVANTAGES OF FLOW CHEMISTRY ACCORDING TO CHATGPT

Efficiency: Continuous operation leads to higher throughput and productivity, especially for large-scale production.	X
Safety: Improved safety due to better control of reaction conditions and smaller reactor volumes.	V
Optimization: Easier to optimize and automate processes, allowing for precise control over reaction parameters.	X
Environmental Impact: Reduced waste and more efficient use of reagents.	X
Heat and Mass Transfer: Enhanced heat and mass transfer rates due to smaller reactor dimensions, improving reaction efficiency and selectivity.	X

The Flow Fanfare

Angewandte Chemie
International Edition

GDCh
A Journal of the German Chemical Society

Essay

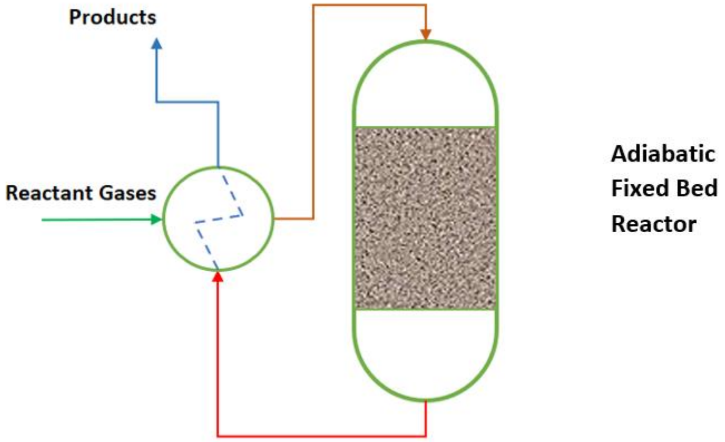
The Flow's the Thing...Or Is It? Assessing the Merits of Homogeneous Reactions in Flask and Flow

Fernando E. Valera, Michela Quaranta, Antonio Moran Dr., John Blacker Prof., Alan Armstrong Prof., João T. Cabral Dr., Donna G. Blackmond Prof.

First published: 23 March 2010 **https://doi.org/10.1002/anie.200906095**

Except for safety considerations, none of these "advantages" are real, at least for homogeneous reactions. **Mass transfer is no different in flow**, and heat can be efficiently controlled by **semi-batch processing**. The highest potential for flow in catalysis is in the development of heterogeneous reactions!

The Hype of the Reusable Catalyst



- Fixed bed flow reactors are widely used in the chemical industry.
- In the field of complex catalysis (fine chemicals and pharmaceuticals), this technique has not found much utility, yet countless reviews announce an impending revolution. Is this likely to really happen any time soon?

“*Innovation in catalysis for fine chemicals is coming in the form of new-generation solid catalysts* ***replacing both conventional homogeneous and heterogeneous catalysts****, and new organic process technology with conversions under* ***continuous flow replacing chemical processes in batch****. This wave of innovation is due to reshape both manufacturing at fine chemical and pharmaceutical companies and catalyst development and production at catalysis companies, enabling also the industrial uptake of electrocatalysis and photocatalysis which for more than a century have remained confined to a few industrial processes.*”

Ciriminna, R.; Pagliaro, M.; Luque, R. *Green Energy & Environment* **2021**, 6, 161e166.

What Do We Place in the Bed?

IMMOBILIZED HOMOGENEOUS CATALYSTS

- Because homogeneous catalysts decompose readily, it makes little sense to immobilize them, unless the immobilization process minimizes decomposition. However, immobilization strategies do not start with an analysis of the decomposition pathways of a homogeneous catalyst: they assume the catalyst is still intact in solution, and we need an easy way to recover and recycle it. This is a fallacy. For a critique of the field, see:

Hübner, S.; De Vries, J. G.; Farina, V. *Adv. Synth. Catal*. **2016,** *358*, 3.

LIGANDLESS HETEROGENEOUS METALS

- These catalysts operate through leaching. "*We anticipate that the insights provided by these studies will eventually lead to effective mitigation strategies against catalyst leaching, which will greatly enhance the sustainability of catalytic processes that are implemented under continuous flow*." The fact that no catalysis is observed without leaching does not seem to lead to the realization that leaching is necessary!

Hii, M. et al. *Catalysis Today* **2018**, *308*, 64.

Homogeneous or Heterogeneous?

The literature invariably proposes incorrect criteria for distinguishing homogeneous from heterogeneous catalysis.

- **Maitlis filtration test: the lack of reaction of the filtrate obtained under the actual reaction conditions.**

Not a decisive test. The filtration test is not useful because of the possible decomposition of active catalysts and the further evolution of the filtrate. Filtration pore sizes vary widely.

- **Quantitative analysis of the actual values of Pd leached in solution.**

This is wrong. The amount of Pd actually leached says nothing about what the active species is. A very small amount leached may lead to a lot of catalysis, whereas massive amount of leaching may result in no catalysis.

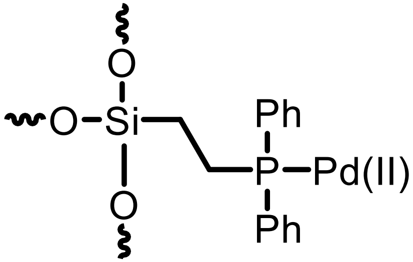
- **Assessment of the catalyst activity in further recycles.**

This is wrong. The ability to isolate a large percentage of active pre-catalyst complex following catalysis has no direct bearing on the evidence for the catalytic species. Recycles do not yield useful information on the catalyst’s identity.

Key paper: Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A: Chem.* **2003**, *198*, 317.

Homogeneous or Heterogeneous?

There are solid Pd catalysts on the market which are claimed to be really heterogeneous and recyclable. One of the more popular sources is SiliaCat®: SiliaCat - Heterogeneous Catalysts (silicycle.com)



Example: SiliaCat DPP-Pd.

Cross-couplings: Lemay, M. et al. *Top. Catal*. **2010**, *53*, 1059.
Miyaura borylation: Pandarus, V. et al. *ChemCatChem* **2014**, *6*, 1340.

Highlights of the papers:

- These catalysts are patented and the structure is not clear. The diarylphosphine structure and the Pd(II) nature of the pre-catalyst would immediately suggest a Pd NP mechanism.
- Filtration tests suggest catalysis is heterogeneous.
- Kinetics not done: no sigmoidal curve seen, but no early monitoring was done. Catalyst not characterized. No TEM, no Hg poisoning data.
- Reproducibility of rates is poor.
- Very low leaching per run (1-5 ppm).
- Recycle is possible by filtration. Drop in kinetic activity seen after a few recycles.

MY CONCLUSION: these catalysts clearly work by leaching Pd nanoparticles.

Homogeneous or Heterogeneous?

The literature claims many cases of true heterogeneous catalysis in Pd-catalyzed couplings, but careful examination of the data allows for a measure of skepticism.

- Jones, C. W. et al. *Adv. Synth. Catal*. **2006**, *348*, 609. It draws a clear conclusion: *No heterogeneous Pd catalyst promoting complex reactions, like Heck or C-C coupling chemistry, proceeds by surface mechanism. They all proceed by leached Pd nanoparticles (NP).*

- Biffis, A. et al. *Chem. Rev.* **2018**, *118*, 2249. An excellent review on Pd NP systems draws similar conclusions: aryl halides react at defect atoms on surfaces and extract the atoms into the solution. The rest of the cycle occurs in solution and at the end the Pd particle may be redeposited on the surface. *Low level of detected leaching leads to incorrect assumptions.*

- *Fixed-bed reactor will drop steadily in catalytic power, making flow operations problematic. This does not stop chemists from using Pd chemistry in flow.* Review: Patel, I. S. et al. *Org. Process Res. Dev.* **2024**, *28*, 3464.

High-TON Ligandless Catalysis

The field of ill-defined catalysts is advancing toward a better definition of these systems: "Deep Learning reveals the extraordinary activity of single Pd/C particles". Eremin, D. B.; Ananikov, V. P. Et al. *J. Am. Chem. Soc*. **2022**, *144*, 6071-6079. Combining nanomanipulation techniques inside a field-emission scanning electron microscope with neural network analysis, kinetic properties of individual NP can be analyzed, and TON estimated.

TON and TOF of different NP from Pd/C in a standard Suzuki coupling.

Entry NP	Number Pd atoms	TON	TOF (h^{-1})
1	527	8.2×10^8	3.4×10^7
2	1727	2.6×10^8	1.1×10^7
3	2,815	1.8×10^8	7.7×10^6
4	4,663	1.1×10^8	4.5×10^6
5	2,302	3.6×10^7	1.5×10^6

Virtually ALL very high-TON Pd catalysts known to us operate via NP: Farina, V. *Adv. Synth. Cat*. **2004**, *346*, 1553.

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- Is artificial intelligence the solution?
- What next?

Catalysis in Pharma is NOT GREEN

	Metal	GWP in Kg e-CO_2	Crustal abundance (ppm)	Annual production (MT)
Noble metals	Rhodium	35,800	0.001	30
	Iridium	8,860	0.001	7
	Palladium	3,880	0.015	210
	Ruthenium	2,110	0.001	30
Base metals	Nickel	6.5	84	2,700,000
	Copper	2.8	60	21,000,000
	Cobalt	8.3	25	170,000
	Iron	1.5	56,300	1,150,000,000

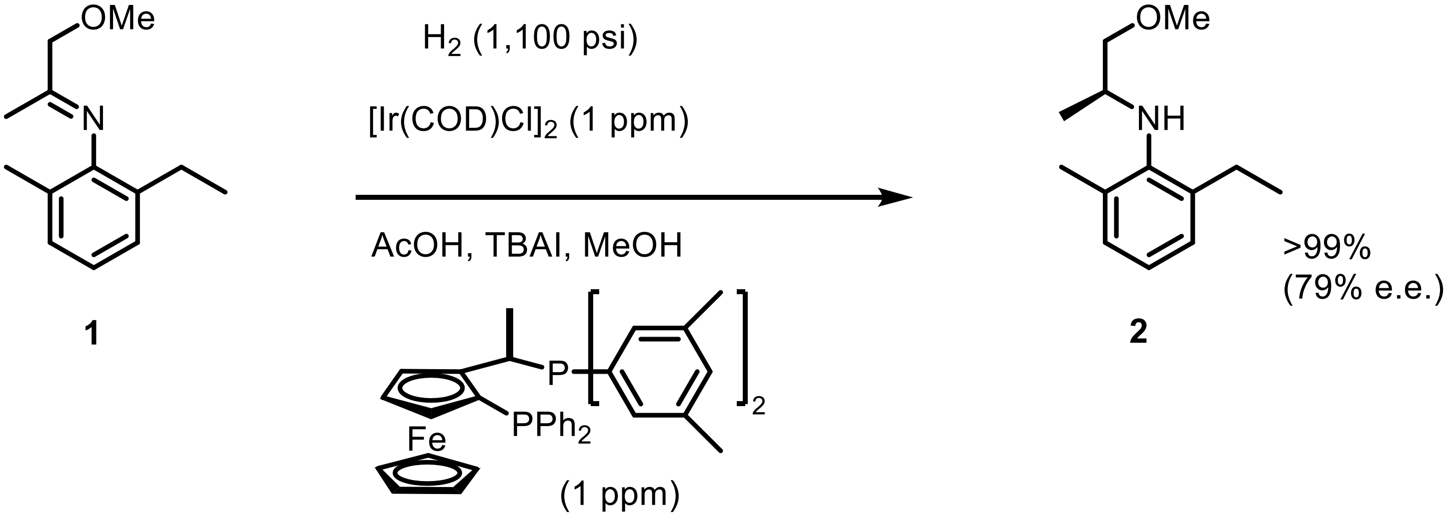
Global Warming Potential: CO_2 produced (Kg) to extract 1 Kg metal. Other liabilities of second/third row metals are *high cumulative energy demand (CED) for their extraction, terrestrial acidification, freshwater eutrophication*. *Reserves of many second/third row metals (Pd, Rh, Ir) may be depleted in 50 years.* Reviews: J. D. Hayler, et al. *Organometallics* **2019**, *38*, 36; Zhao, H. et al. *ACS Catal*. **2024**, *14*, 9708.

Catalysis in Pharma is NOT GREEN

SURVEY OF ALL TM-CATALYZED REACTION IN: *Org. Process Res. Dev*. **2017-2022**

- Percentage of papers (2017-2022) in which **base metals** were used in the catalyst: 7.3%. **Over 90% of the applications employ highly expensive, unsustainable metal catalysts.**
- Cases in which the desirable target of TON = 10^3 was reached: 0**.** Average: 80.
- Number of cases in OPRD where "green solvents" were used (renewables like cyrene, γ-valerolactone, Me-THF, or non-conventional ones, like $scCO_2$, DES, Ionic liquids, micellar catalysis in water etc.): 0.
- Cases in which a supported homogeneous or recyclable catalyst found application in a pharmaceutical process: 0.
- **Yet, entire journals are devoted to these topics. Dozens of reviews, special issues, conferences and awards extol new, more sustainable manufacturing approaches.**

Green Catalysis is Possible!



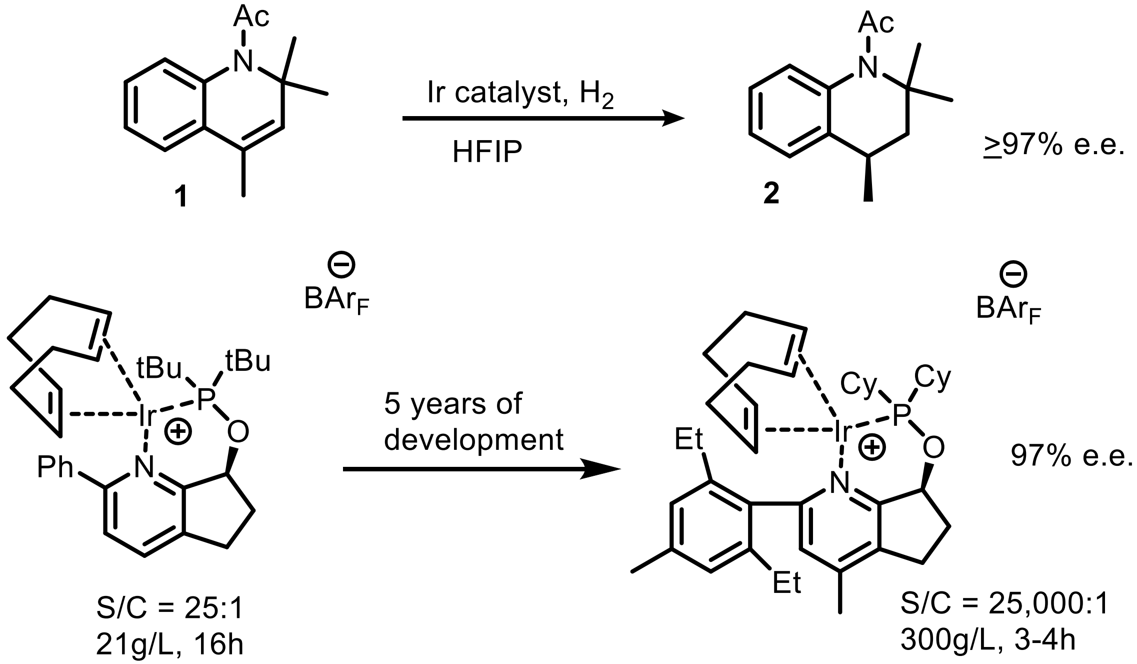
1

2

Target **2,** (S)-Metolachlor, is the active ingredient of Syngenta‘s herbicide Dual-Magnum®, and is produced using the above process with a volume of >10,000 tons/year. The TON is 7 x 10^6, and was reached after 14 years of patient and stepwise development.

Blaser, H-U.; Pugin, B.; Spindler, F.; Thommen, M. *Acc. Chem. Res.* **2007,** *40*, 1240.

Green Catalysis is Possible!



Target **2** is an intermediate toward an important agricultural product, hence TON for a precious catalyst must be >10,000. The work was a five-year collaboration between **Bayer AG** and **Solvias, LIKAT, BUSS**. Schotes, C.; Müller, S. *ACS Sustainable Chem. Eng.* **2022**, 10, 13244.

These timelines are too long for Big Pharma and the costs too high for generic manufacturers. A big problem is how to create incentives and speed up high-TON catalyst development at Big Pharma.

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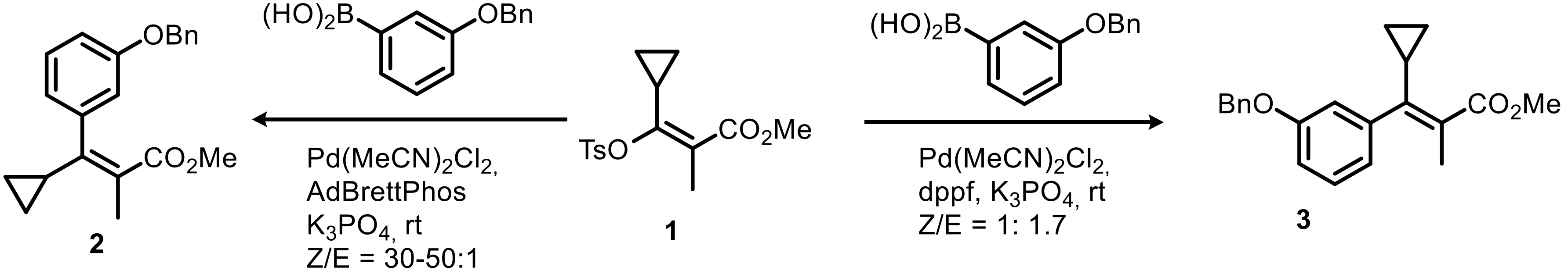
The Future: Artificial Intelligence?

- Machine Learning (ML) can supplement HTE. Drawing from the literature, ML can select conditions for a screen, analyze data and propose conditions for the next series of experiments, eventually arriving at the optimum conditions, all without human intervention.

- So far, applications have been limited to very simple problems, which could easily be solved by single experiments. **To make a mark, the field must start solving real problems**.

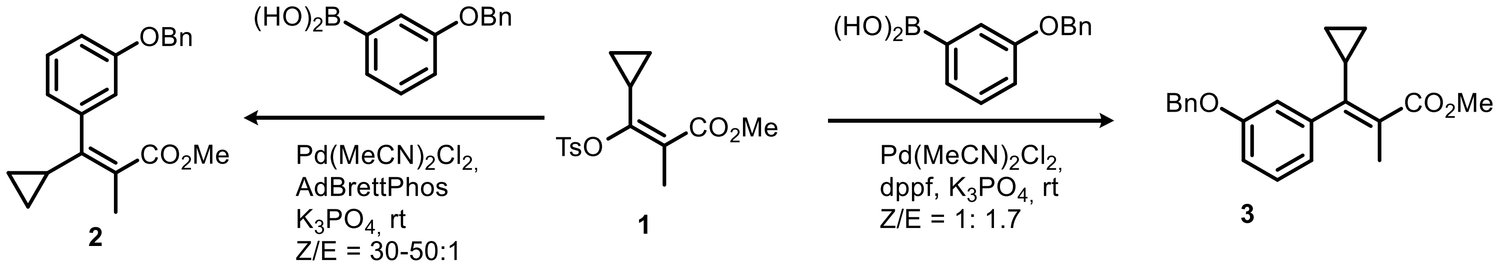
Artificial Intelligence: Example



- AI is used to analyze the results with many ligands and a single precatalyst, hoping to identify the ligand features that lead to a retentive process (**3**) as opposed to inversion (**2**). The study, after 2 x 192 automated experiments, achieves a 74% yield of **2**+**3** in Z/E ratio of 1:2.6, a small improvement vs. the original 1:1.7.
- From a practical standpoint, the result is not useful, as no process chemist would scale up this reaction.
- The authors claim: "*optimization of reaction conditions could lead to even improved yields of **3**, but that was not the focus of the current study*".
- To demonstrate the validity of an approach, problems have to be solved. In this case, little progress was achieved after much effort. The problem, a very modest one in my opinion, remains unsolved.

Christensen, M. *et al.* Data-science driven autonomous process optimization. *Nature Commun. Chem.* **2021**, *4*, 112.

The Future: Artificial Intelligence?



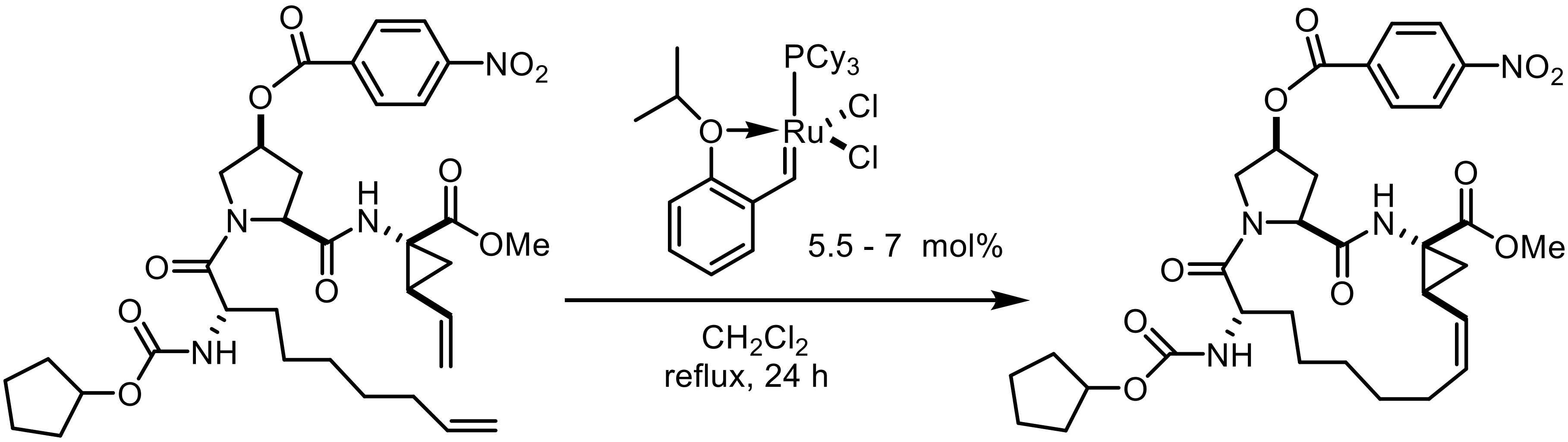
Oxidative addition, transmetalation and reductive elimination typically occur with **retention of configuration** at sp^2 C. Thus, isomerization must take place somewhere and this step can perhaps be controlled if the mechanism is understood. What is promoting the isomerization, and can such reaction be independently studied in order to minimize it? **This involves the study of consecutive reaction kinetics.**

Look for literature precedents: are there examples of cross-coupling reactions in which lack of complete retention is observed? Is there any suggested mechanism which could account for this problem?

Lots of precedents. Lu, G. P. at al. *Chem. Commun*. **2012**, *48,* 8661; A. Krasovskiy, A. et al. *Org. Lett*. **2011,** *13*, 3818; Lu, K. R. et al. *J. Org. Chem*. **2012**, *77*, 3700; Farina, V. et al. *Tetrahedron Lett*. **1991**, *32*, 4243; Brady, K. A. et al. *J. Organomet. Chem*. **1981**, *206*, 299; Zargarian, D. et al. *Organometallics* **1991**, *10*, 2914; **1993**, *12*, 712.

Artificial Intelligence must be given the correct instructions on how to solve a problem. This may require better Human Intuition (HI). **This is not a difficult problem.**

Artificial vs. Human Intelligence



1a **2a**

Concentr. INRF16	**HPLC (*in situ*) yield of INRF12**
0.01 M	92%
0.03 M	65%
0.05 M	55%
0.10 M	40%

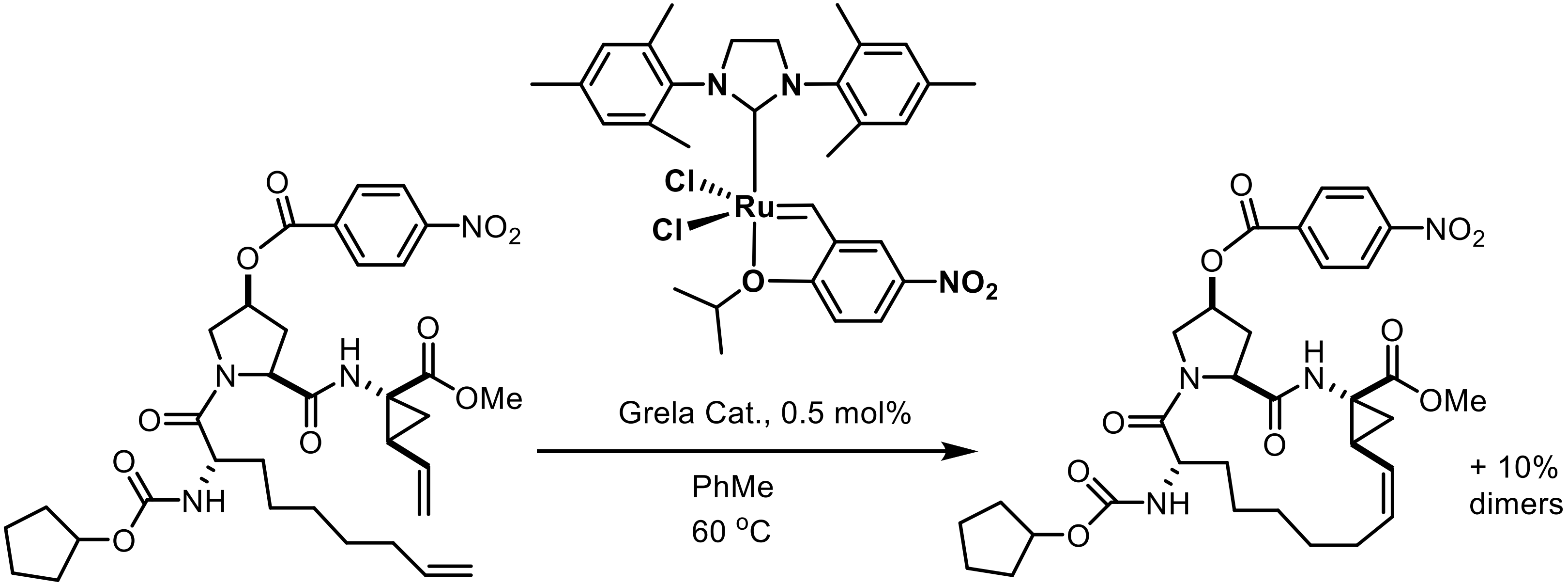
For *kinetically controlled reactions*:

$$\mathbf{EM=k_{intra}/k_{inter}}$$

The **EM** has the dimension of concentration.

In this case, EM_{kin} is 0.066M

Changing Catalyst?



1a (10 mM)

2a, 85%

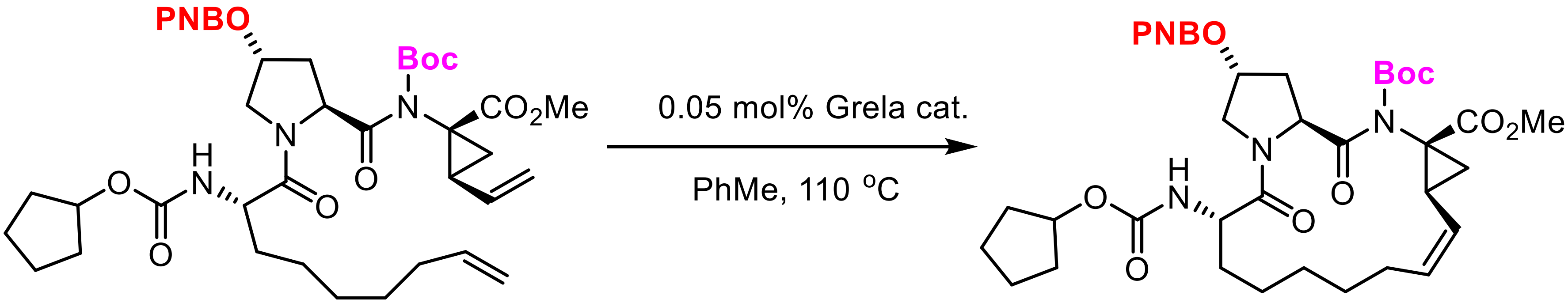
With 2nd GEN catalysts, the reaction is thermodynamically controlled!

For *thermodynamically controlled reactions*: $\mathbf{EM_{therm}=K_{(eq)intra}/K_{(eq)inter}}$

The **EM** has again the dimension of concentration. In this case, EM_{therm} is 0.045M Thus, under thermodynamic conditions the reaction is more efficient but must be run even more diluted to guarantee a good yield.

Could one apply AI to this problem? How? We had to use HI (Human Intuition)

Changing the Substrate



1b, 200 mM

2b (93%)

EM$_{therm}$ for N-H P1 at 60 °C: **0.045M**

EM$_{therm}$ for N-Boc P1 at 60 °C: **0.83M**

EM$_{therm}$ for N-Boc P1 at 110 °C: **1.78M**

Overall improvement in EM : 40-fold

Reaction is run at 0.2M concentration: Other substrates also work: N-Ac as well as N-Boc, N-Bn like N-H.: Shu, C.; Farina, V. et al. *Org. Lett*. **2008**, *10*, 1303.

AI will have made an impact when it can solve these sorts of problems!

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What Next?

- Current paradigms (HTE) are focused on noble metal catalysts: these can be "efficient" in some cases (hydrogenations, olefin metathesis) but are hardly ever efficient for Pd-catalyzed chemistry (80% of TM catalysis in Pharma).

- **Computer-assisted synthesis** and HTE seem to enjoy the highest priority in the Pharma industry. This approach will not lead to the development of high-turnover (hence **efficient/green**) catalysts.

- Neither catalyst immobilization nor flow chemistry or recycling are addressing the problem. Farina, V. *Adv. Synth. Cat*. **2004**, *346*, 1553: all the high-TON ($>10^6$) palladium catalysts, whether initially homogeneous or heterogeneous, work through NP, *i.e*., **heterogeneous soluble catalysts**. **This area is probably the best prospect for high-TON Pd catalysis.**

- We also need to abandon petroleum-derived organic solvents and embrace alternative reaction media, *e.g.,* water. See: Lipshutz, B. H. et al. *Chem. Sci*. **2023**, *14*, 6399, and references therein. These catalysts are stabilized NP.

What Next?

Lu, L.; Corma, A. Metal Catalysts for Heterogeneous Catalysis: From Single Atoms to Nanoclusters and Nanoparticles. *Chem. Rev*. **2018**, *118*, 4981.

Du, Y.; Sheng, H.; Astruc, D.; Zhu, M. Atomically Precise Noble Metal Nanoclusters as Efficient Catalysts: A Bridge Between Structure and Properties. *Chem. Rev.* **2020**, *120*, 526.

"Recently, researchers have developed a variety of well-controlled methods to synthesize atomically precise metal nanoclusters (NCs). NCs have shown high catalytic activity and unique selectivity in many catalytic reactions, which are related to their ultrasmall size, abundant unsaturated active sites, and unique electronic structure different from that of traditional nanoparticles (NPs)."

New generations of nanoparticles and nanoclusters enjoy considerable stability and can be prepared reproducibly. This is a hot field.

Earth-Abundant Metal Catalysis

We need to invent new catalysts based on abundant metals and slowly abandon our cherished Pd, Ru, Rh, Ir paradigms. This is hard because we have no solid mechanistic foundations in EAM catalysis. **It will be a huge challenge.**

Academia/government MUST lead this effort and industry must cooperate. The collaboration Princeton University-BMS is an important initiative to implement base-metal catalysis in the pilot plant. Low TON is still a major problem.

Perspective: Chirik, P., Engle, K. M.; Simmons, E. M.; Wisniewski, S. R. "Collaboration as a Key to Advance Capabilities for Earth-Abundant Metal (EAM) Catalysis". *Org. Process Res. Dev*. **2023**, *27*, 1160.

"***The advancement of EAM catalysis in the past decade has been remarkable**. As a field, we are just starting to break the ice on fundamental understanding of these underexplored modes of catalysis, and the future is very bright. Discovering new reactivity of EAMs to impact the way in which complex molecules are assembled is only one promising future for EAMs.*"

Acknowledgments

Bristol-Myers Squibb

Boehringer
Ingelheim

janssen
PHARMACEUTICAL COMPANIES
OF Johnson&Johnson

Farinachem Consulting GmbH

THANK YOU FOR YOUR ATTENTION