



北京大学
PEKING UNIVERSITY

化学生物学与生物技术学院
School of Chemical Biology & Biotechnology



High-Throughput Discovery of New Chemical Reactions by Mass Spectrometry

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Introduction: What is High-Throughput Screening(HTS)?

Identification of one or more positive candidates
extracted from a pool of
thousands possible candidates
based on specific criteria



Introduction: What do you use HTS for?

To screen for all kind of novel biological active compounds (libraries):

- Natural products
- Combinatorial Libraries (peptides, chemicals...)
- Biological libraries

To screen MicroArrays such as:

- DNA chips
- RNA chips
- Protein chips

To discovery new chemical reactions !!!

- A method that tests pools of reactants with catalysts allows for large-scale surveying of new reactions.



Introduction: Discovery of new chemical reactions

Typical approach

Through the development of a mechanistic hypothesis

- ✓ Catalysts
- ✓ Reagents
- ✓ Reaction conditions

Limitations:

- Oversimplified
- inaccurate



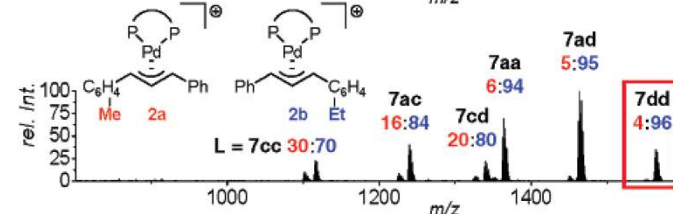
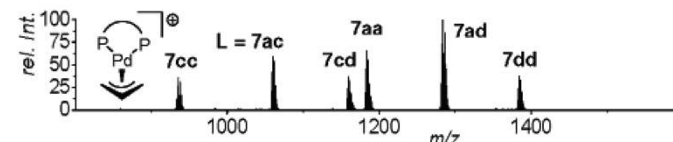
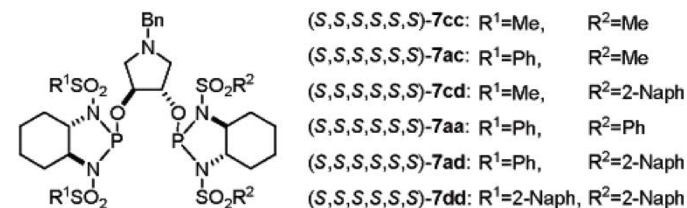
Introduction: Discovery of new chemical reactions

Preliminary high throughput screening

- ✓ the modular assembly of ligand or catalyst libraries can greatly accelerate the search for optimized structures

Limitations:

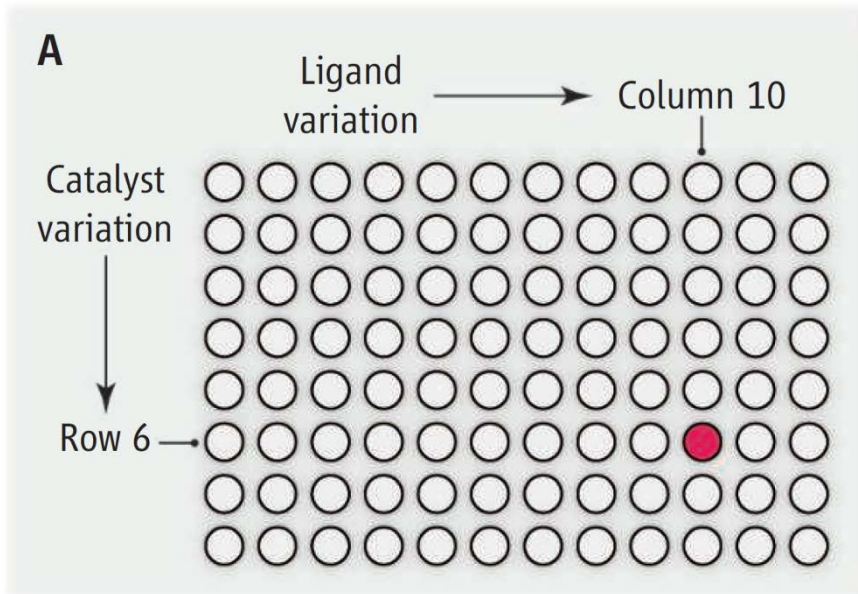
- Discovery of new catalysts or ligands that promote a specific transformation
- not allowed simultaneous examination of a wide range of both reactants and catalysts
- Require specialized techniques or expertise



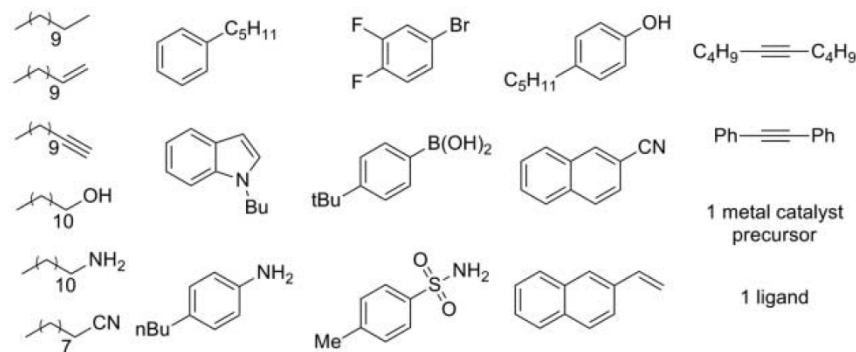


A Simple, Multidimensional Approach

A three-dimensional approach



17 organic reactants



Each well contains 17 organic reactants, 1 metal catalyst precursor and 1 ligand. The plate was sealed and heated at 100 °C for 18 hours.

Montgomery, J. *Science* **2011**, 333, 1387.

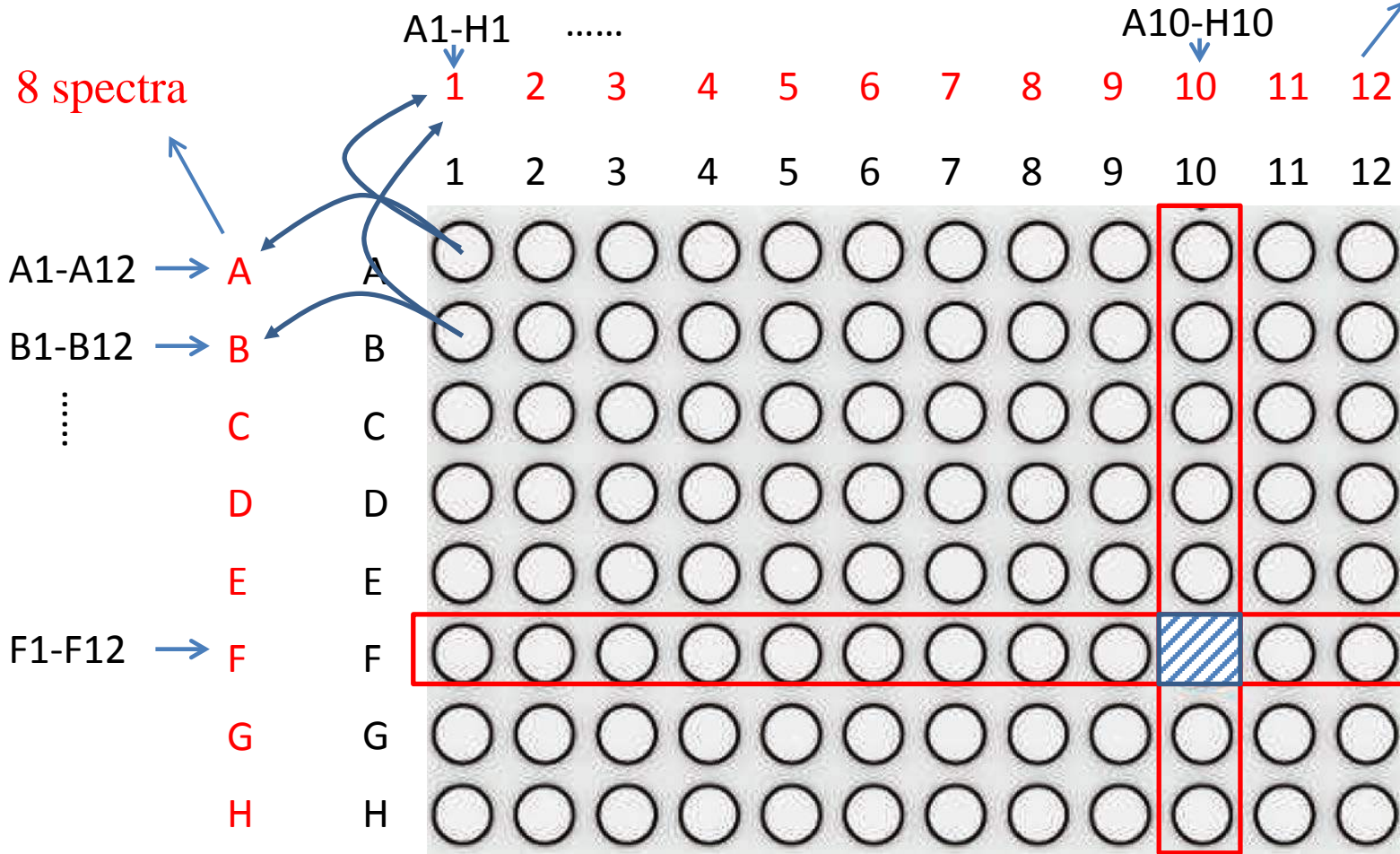
Robbins, D. W.; Hartwig, J. F. *Science* **2011**, 333, 1423.



A Simple, Multidimensional Approach

Analyzer: **Gas Chromatography/ESI-Mass Spectrometry**

12 spectra





A Simple, Multidimensional Approach

Advantages:

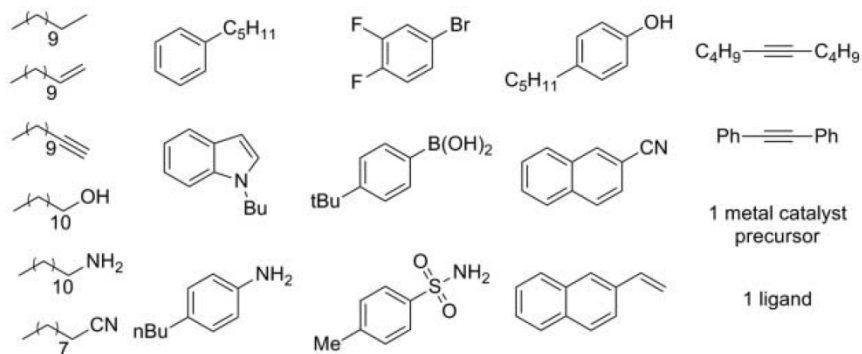
- ✓ Only 20 spectra on each 96-well plate are needed.
- ✓ More than 50'000 possible catalytic reactions were screened.(384 wells of a 16-by-24 array)
- ✓ The reactions identified in this format have the high degree of functional-group tolerance.



A Simple, Multidimensional Approach

Example:

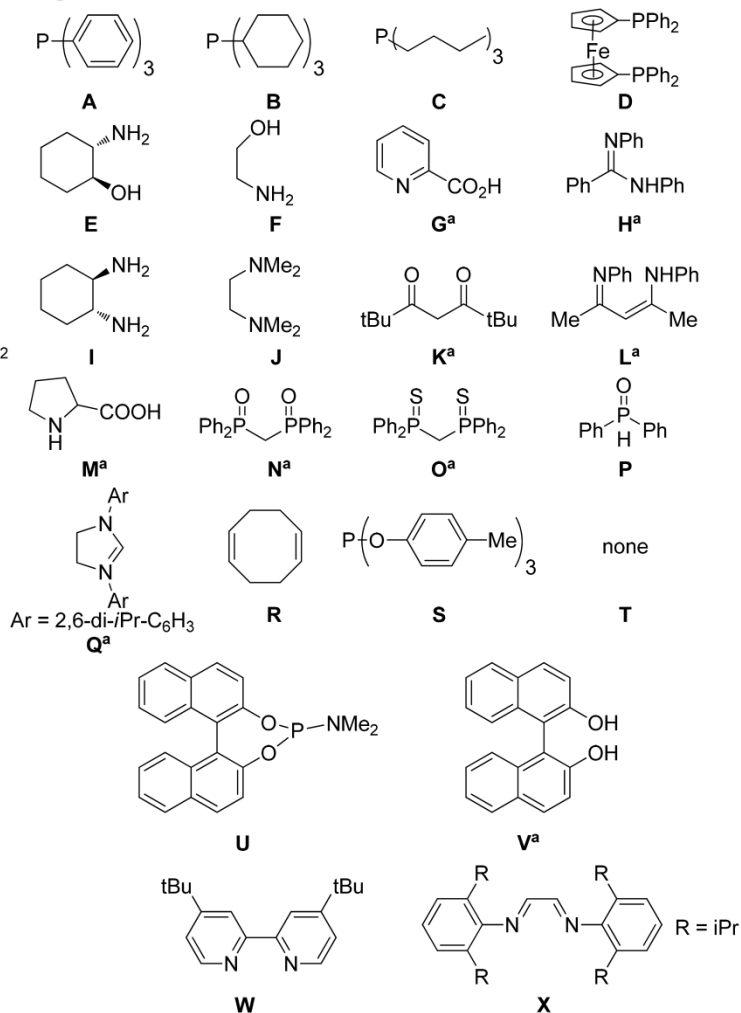
17 organic reactants



Metals

- 1) Fe(acac)₂
- 2) FeCl₃
- 3) Mo(CO)₃(EtCN)₃
- 4) MoCl₅
- 5) Mn(acac)₂
- 6) W(CO)₃(MeCN)₃
- 7) Yb(OAc)₃
- 8) Cr(CO)₃(C₆H₆)
- 9) Co(OAc)₂
- 10) Ni(cod)₂
- 11) CuCl
- 12) Cu(OAc)₂
- 13) [Ru(*p*-cymene)Cl₂]₂
- 14) AuCl
- 15) NiCl₂-dme
- 16) none

Ligands



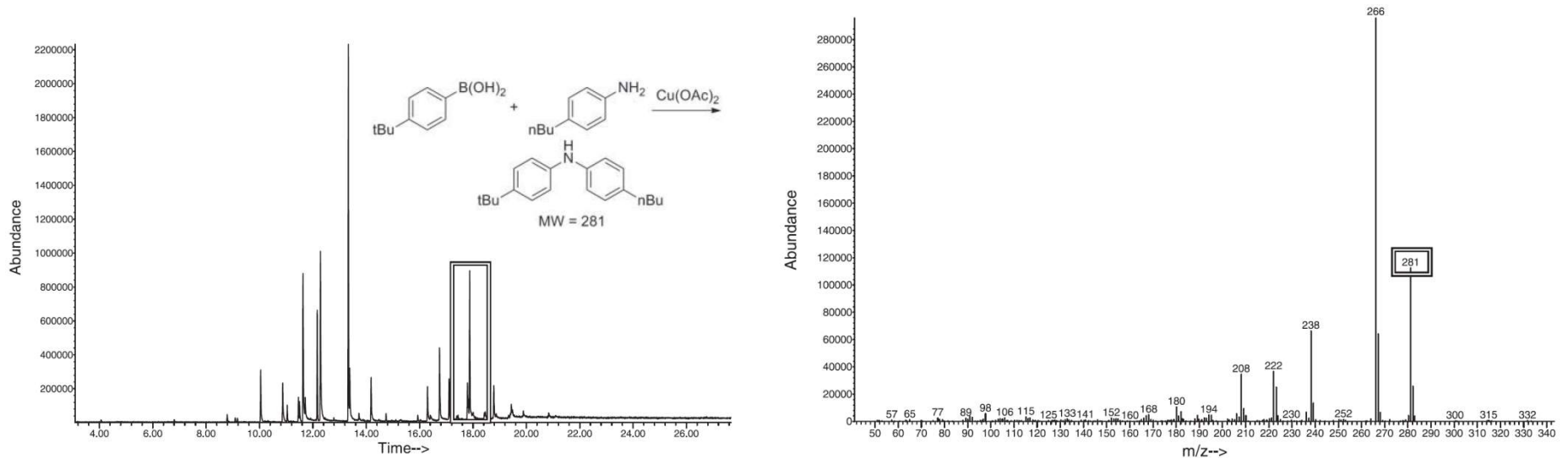
✓ First row transition metal was chosen because of its abundance and low cost.

✓ More than 50'000 possible catalytic reactions



A Simple, Multidimensional Approach

Example: positive control

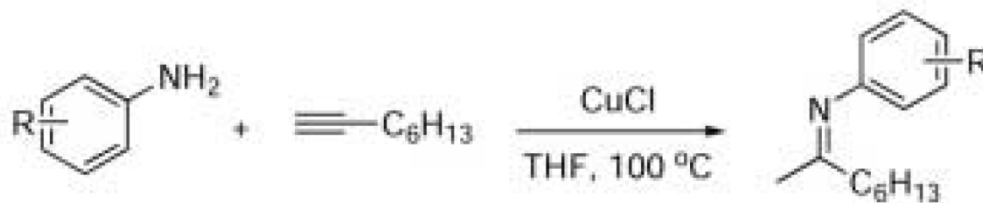


Positive-control experiments showed that discrete transition metal-catalyzed reactions can be identified from a pool of substrates that could undergo thousands of possible binary reactions.



A Simple, Multidimensional Approach

Example: reaction selected from HTS



| Entry | R | Catalyst Loading | Yield [*] |
|-------|----------------------|------------------|--------------------|
| 1 | 4-nBu | 10 mol% | 57% |
| 2 | 4-OH | 25 mol% | 80% |
| 3 | 4-CN | 25 mol% | 51% |
| 4 | 4-CO ₂ Me | 25 mol% | 68% |
| 5 | 3-Br | 25 mol% | 84% |
| 6 | 4-acetyl | 25 mol% | 60% |
| 7 | 2,6-di-isopropyl | 25 mol% | 70% |

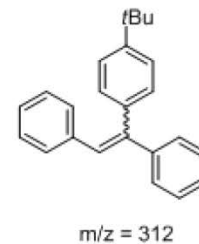
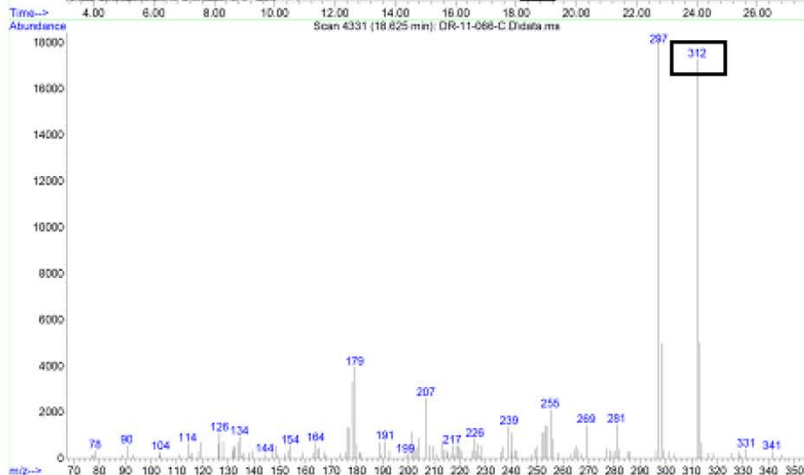
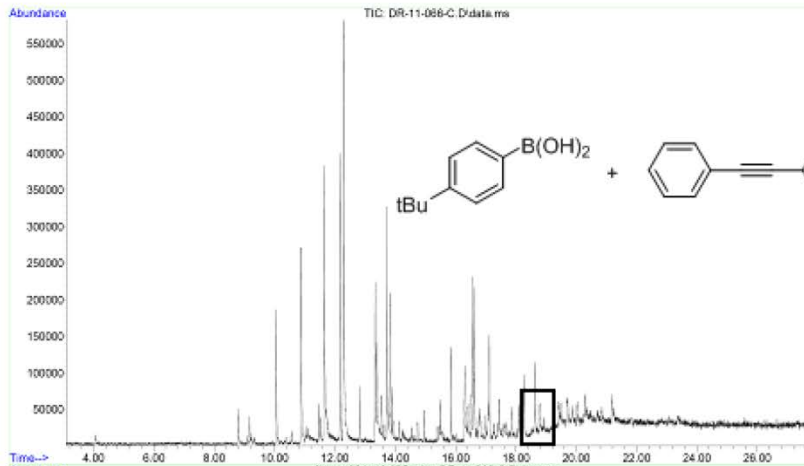
* Yield determined by using gas chromatography with 1,3,5-trimethoxybenzene as an internal standard after hydrolysis with 1 M HCl at room temperature to 2-octanone

- ✓ Represents a rare hydro-amination of an alkyne catalyzed by the first-row metal.
- ✓ Tolerates an array of potentially reactive functional groups



A Simple, Multidimensional Approach

Example: reaction selected from HTS

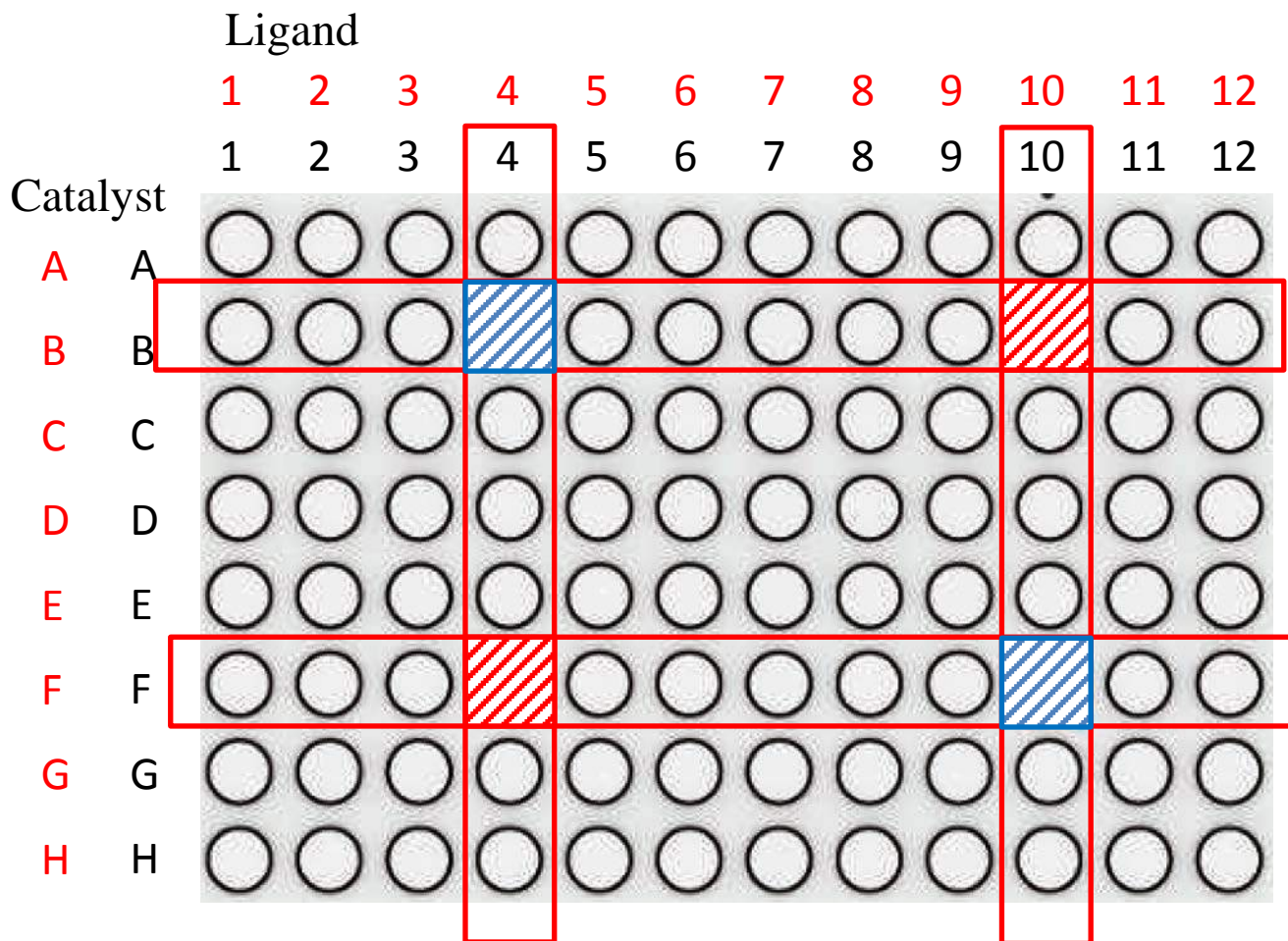


➤ The identity of this product was not obvious from the mass spectrum.



A Simple, Multidimensional Approach

Example: reaction selected from HTS

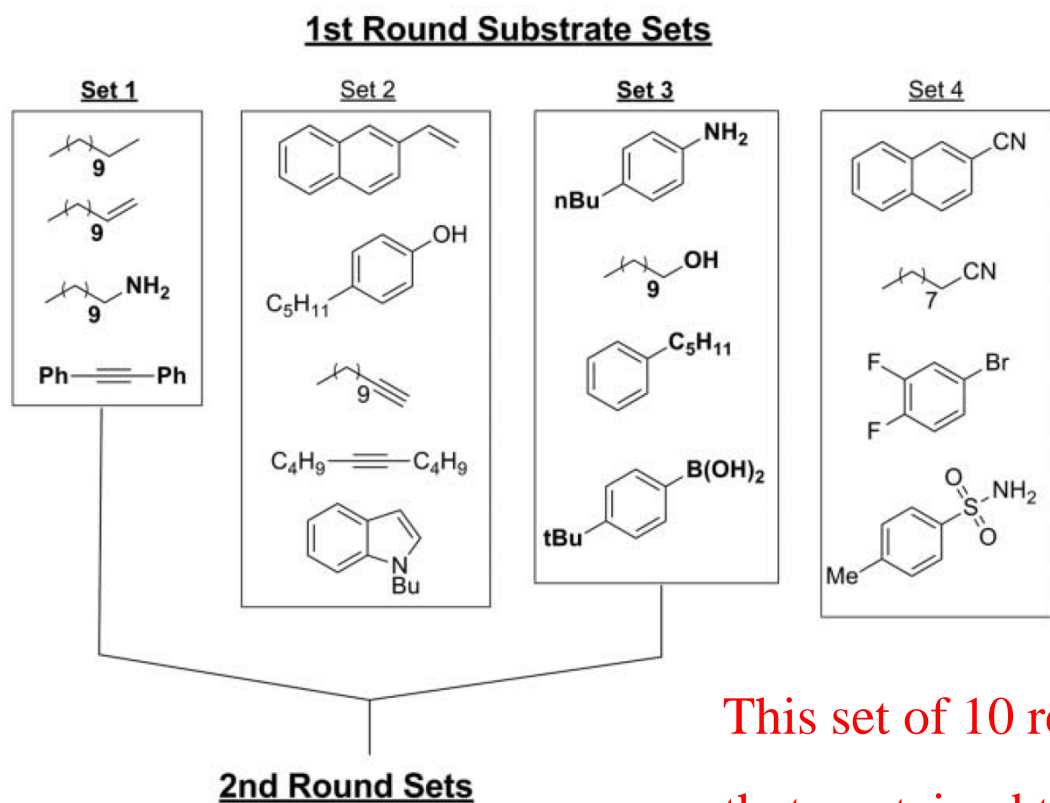


➤ This peak was observed in the wells containing the combination of $\text{Ni}(\text{cod})_2$ or $\text{NiCl}_2\text{-dme}$ and several phosphine ligands and an NHC.



A Simple, Multidimensional Approach

Example: Deconvolution strategy



Set combinations tested

1-2 1-3

1-4 2-3

2-4 3-4

1-2-3 1-2-4

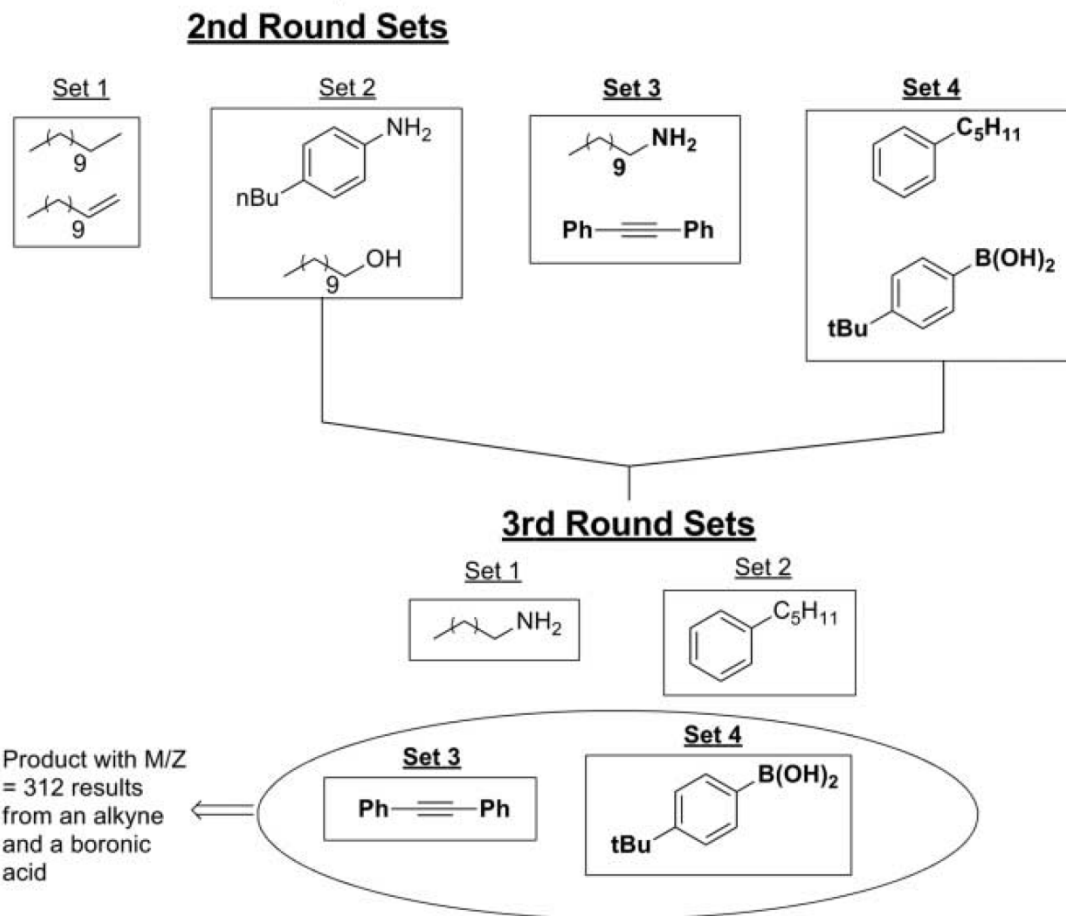
1-3-4 2-3-4

This set of 10 reactions identified the two sets that contained the reactants that formed the unknown product.



A Simple, Multidimensional Approach

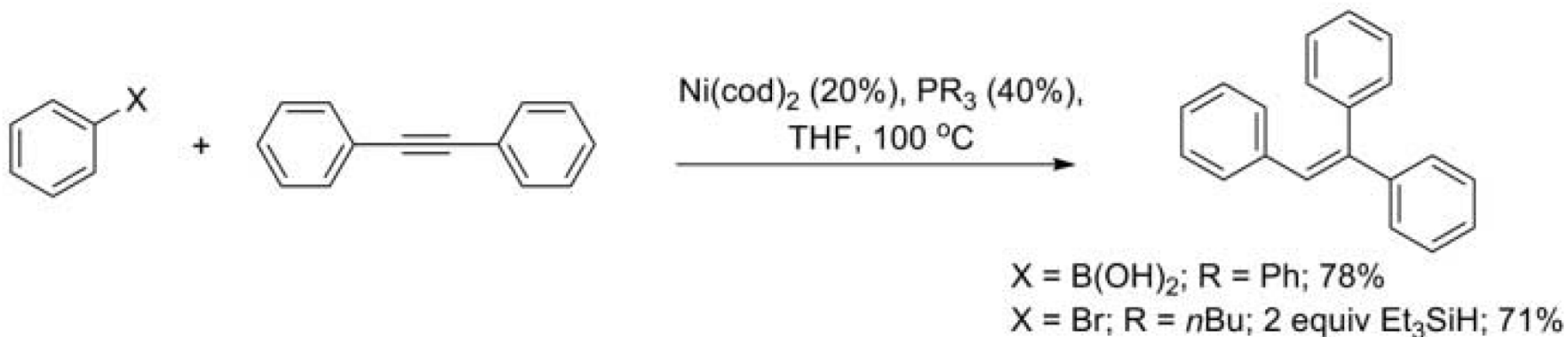
Example: Deconvolution strategy





A Simple, Multidimensional Approach

Example: Deconvolution strategy



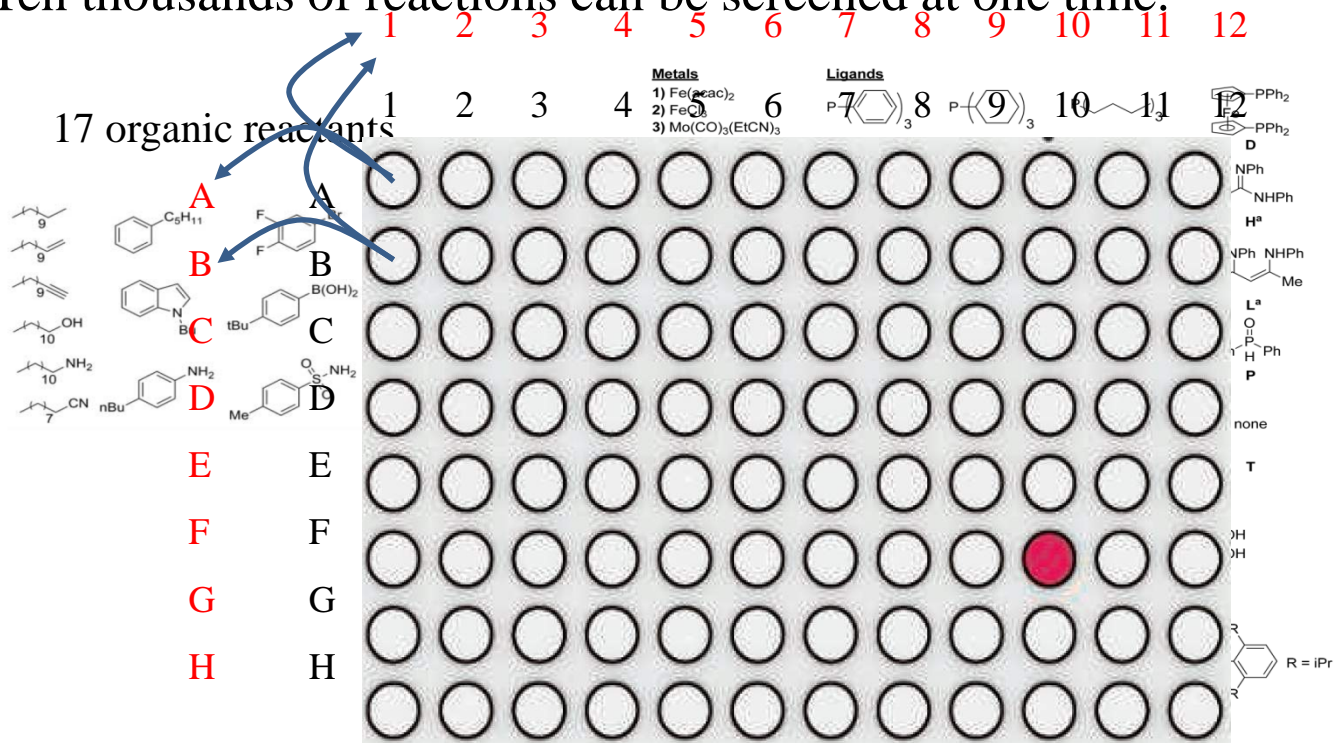
- ✓ This transformation of arylboronic acids has been reported most commonly with rhodium and palladium catalysts, which contain costly precious metals.
- ✓ Identified the reactants
- ✓ Identified the catalyst and ligand



Summary

A multi-dimensional high throughput screening method of chemical reactions.

- ✓ Only 20 spectra on each 96-well plate are needed.
- ✓ Ten thousands of reactions can be screened at one time.

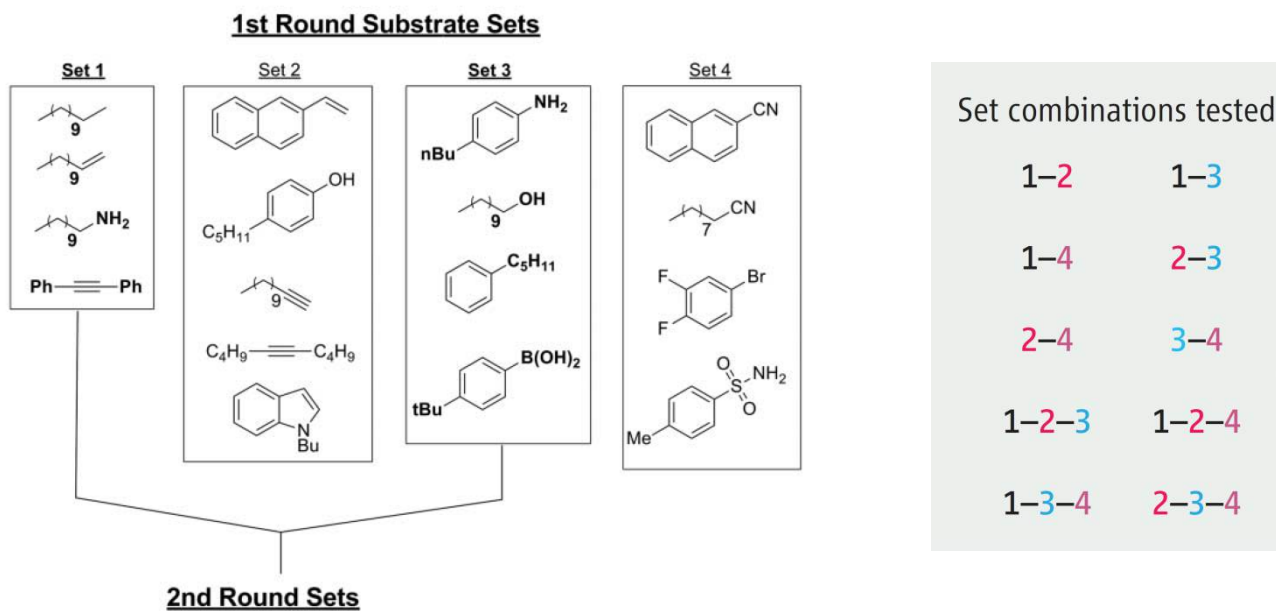




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- ✓ A deconvolution strategy was developed to identify unknown products.





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- ✓ A deconvolution strategy was developed to identify unknown products.



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Thanks for your attention!