The Application of MAOS to Medicinal Chemistry and Drug Discovery

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Why Use MAOS?

- Accelerated reaction kinetics
- Increased conversion of starting materials to products
- Reaction mixtures are often cleaner than conventional synthesis
- Small to large scalability
- Auto-sampler allows for overnight runs
- Extremely easy to operate

Why is MOAS Important for Nanosyn?

Nanosyn is a contract research organization (CRO)

- Multiple projects with multiple customers at any given time
- Chemistry constantly changes from one day to the next
- Non-trivial synthesis: heterocyclic ring formation, C-C and C-N bond formation, multi-step (10-12 steps)
- Synthetic method development needs to be completed in a very short time frame—typically 1-2 days

How Often is MAOS Applied at Nanosyn?

- MAOS is used almost daily by every chemist at Nanosyn
- During the last 4 years, chemists used MAOS an average of 1.3 times per day
- The microwave is typically the first place we start when investigating a new chemical synthesis or method development

What Types of Chemistry Have Been Applied to MAOS at Nanosyn?

- Palladium catalyzed reactions
  Suzuki, Stille, Buchwald, Sonogashira
- Nucleophilic aromatic substituiton reactions
- Reductive amination
- Amide bond formation
- Heterocycle formation

We have applied MAOS to almost every type of reaction possible

What Types of Chemistry Have Been Applied to MAOS at Nanosyn?

- Multi-step scaffold synthesis
- Multi-step single compound synthesis
- Mg to multi-gram synthesis
- Predominantly C-C and C-hetero-atom and heterocyclic chemistry

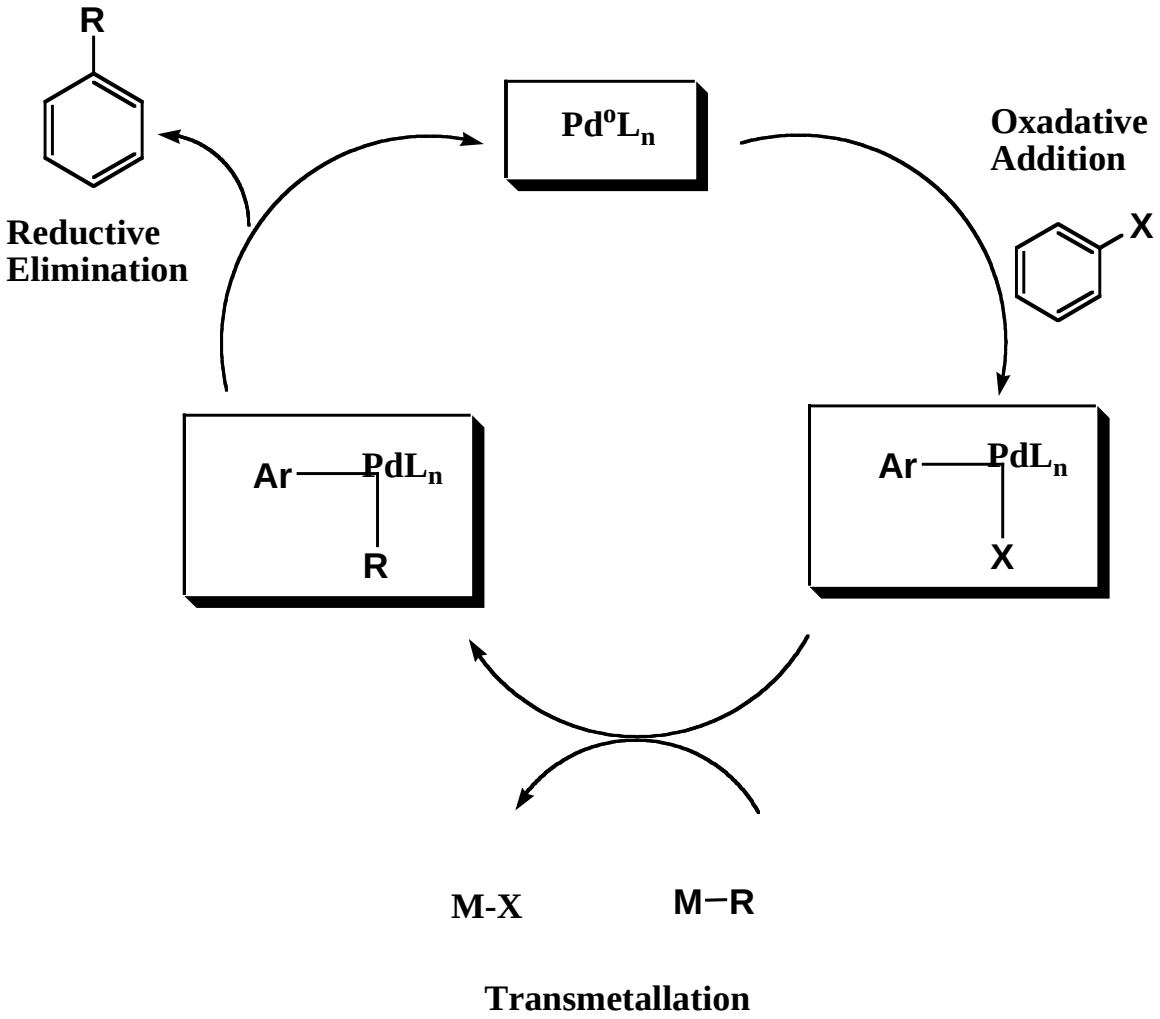
Challenging, diverse chemistry

Palladium Catalyzed Reactions

Suzuki type reactions:

- One of most important class of contemporary carbon-carbon bond forming reactions
- Require boronic acid and aryl halide or aryl triflate coupling partner
- Not all boronic acids are commercially available
- Conventional conditions require heating at ~100^{o}C for 24 hours

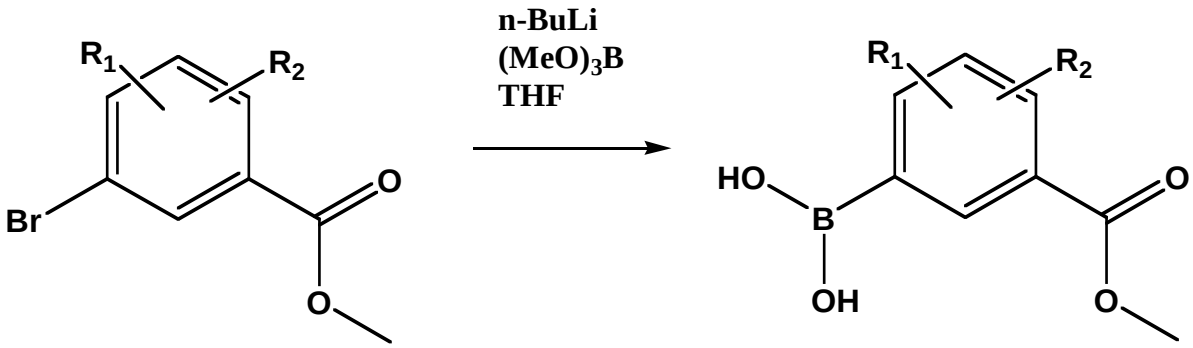
Palladium Catalyzed Reactions



How does MAOS Help In Applying the *Suzuki* to MedChem?

The boronic acid is not commercially available

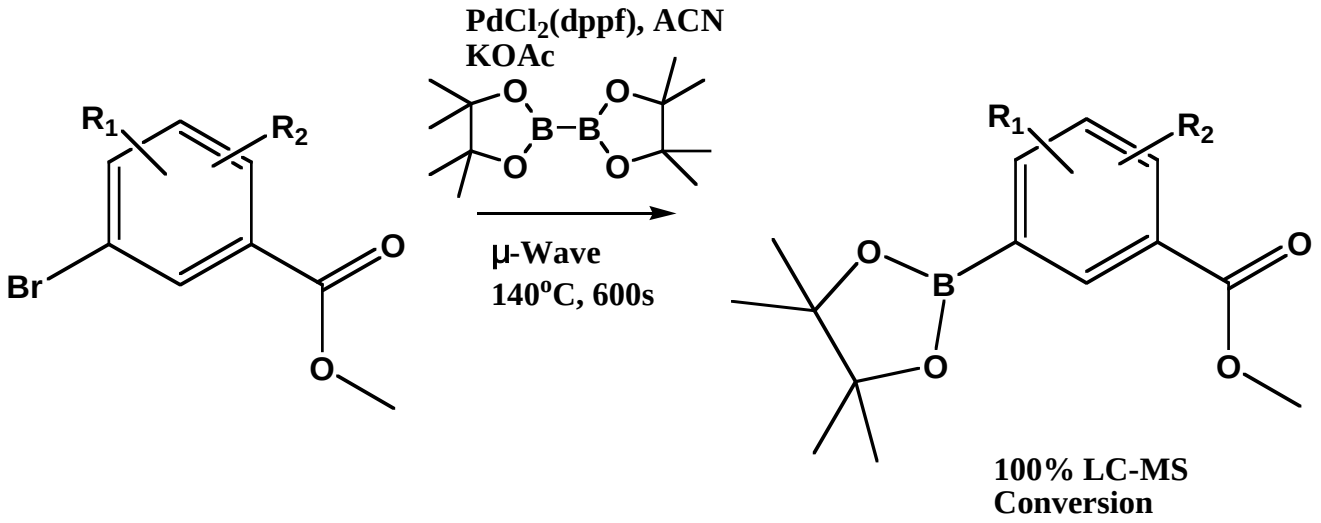
- Conventional boronic acid synthesis:



Drawbacks:

- Ester functionality makes n-BuLi use difficult

MOAS Boronic Ester Synthesis

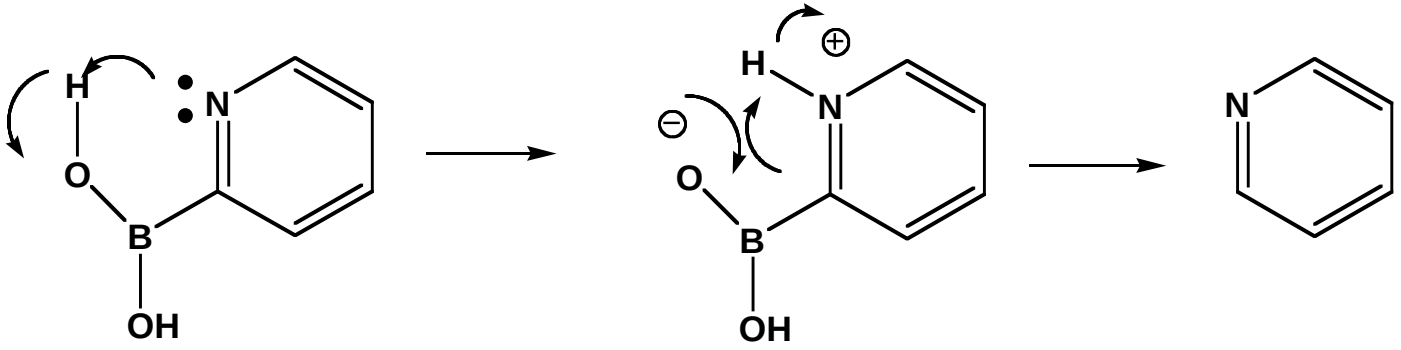


- Fast and convenient boronic ester synthesis
- Tolerates many functionalities
- Works well with Br-, I-, and OTf derivatives

MAOS to Provide Access to Unaccessible Substrates

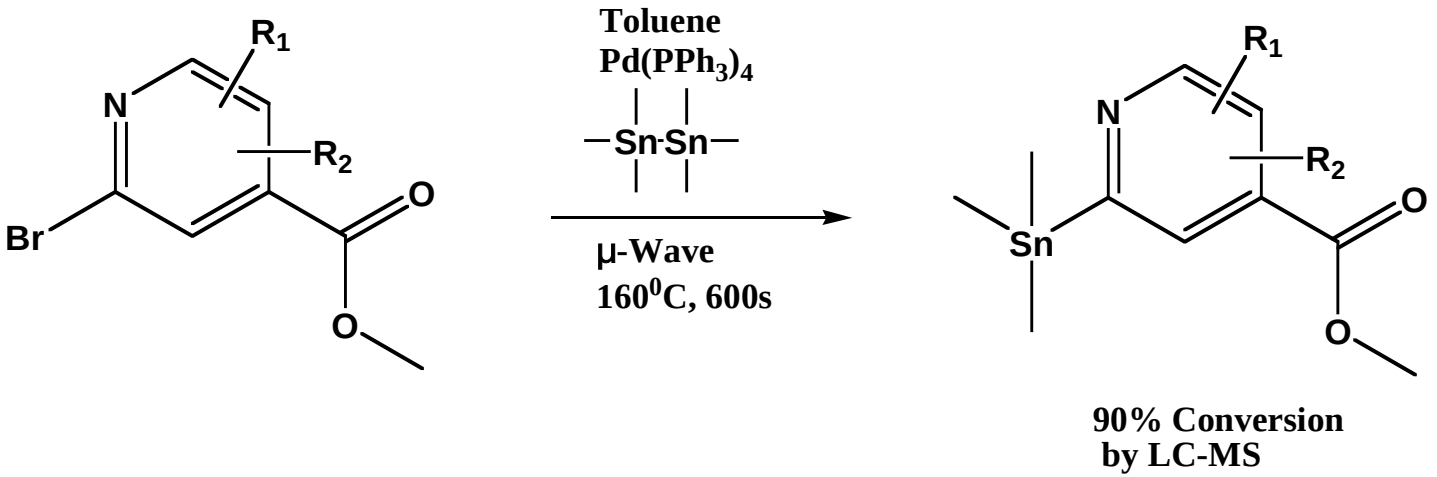
- 2-Substituted pyridyls:

  2-pyridyl boronic acids are not commercial available due to proto-deboronation



Simple Method for Preparing 2-Pyrdyl Substrates

- Stannane in the 2-position is stable



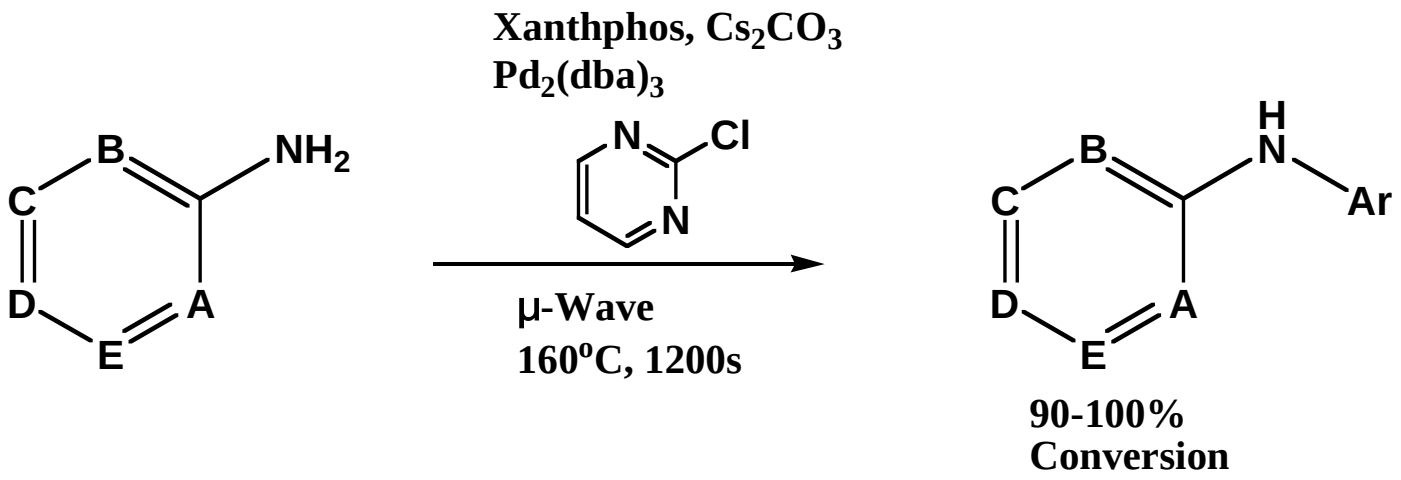
90% Conversion by LC-MS

Buchwald/Hartwig Reaction

- Works very well for simple substrates
- Complicated substrates require tedious and difficult optimization
- Very sensitive to temperature, catalyst, base solvent and ligand

  MAOS can be very useful for *Buchwald optimization*
- Multiple conditions can be easily performed
- Excellent control of temperature

Buchwald/Hartwig Reaction



- Works well with simple substrates
- Heteroaryl amines and halides pose issues
- MAOS can work well when conventional Buchwald fails

C-N Forming Reactions

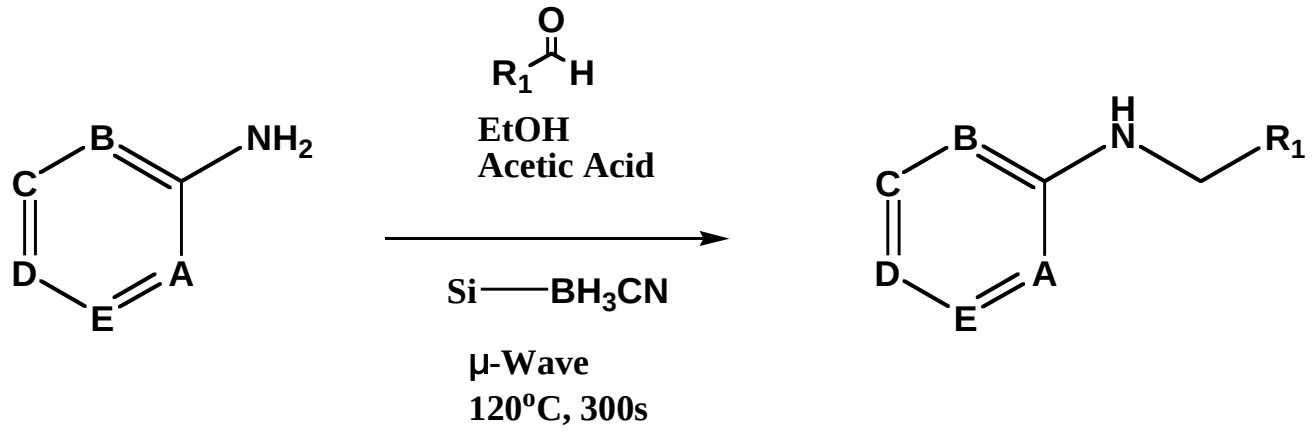
Reductive amination:

- Excellent method for alkylating amines
- Major drawback for multiple/parallel reactions is work up

Combination of MAOS and silica bound cyanoborohydride

Reductive Amination

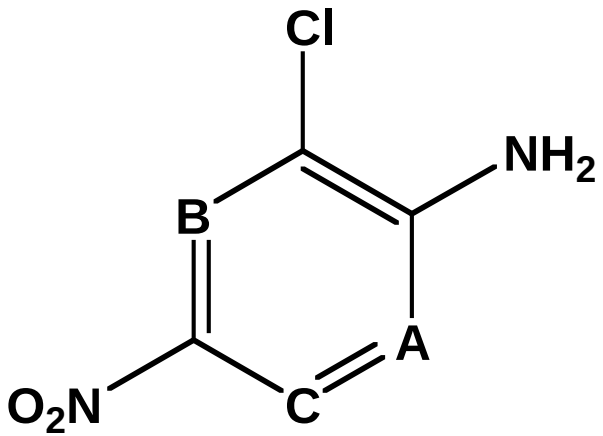
- Fast
- Easy to work-up; centrifuge, decant, evaporate



MAOS Applied to *Simple* Chemistry

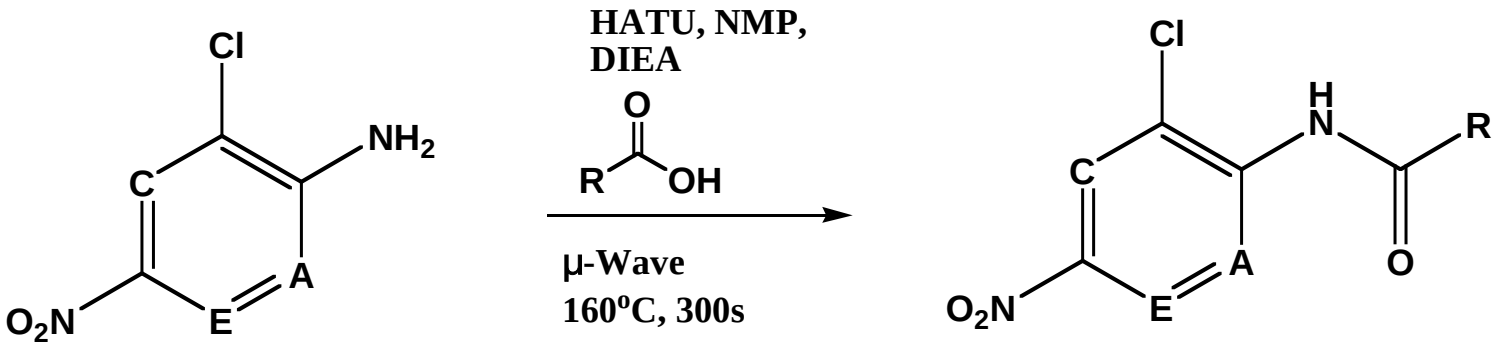
Amide bond formation

- *Supposed* to be *simple*
- What about cases with extremely deactivated anilines?



Amide Bond Formation

- Conventional heating will give only traces of product



50-60% Conversion

Conclusions

- MAOS has wide applicability to industry oriented medicinal chemistry
- MAOS has changed how Nanosyn's approach synthetic and medicinal chemistry
- MAOS has become indispensable to our method development
- Combining MAOS with excellent synthetic and medicinal chemists is a true formula for success in drug discovery