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Grace Ahlgrim

Ethan Heyboer

Trey Pankratz

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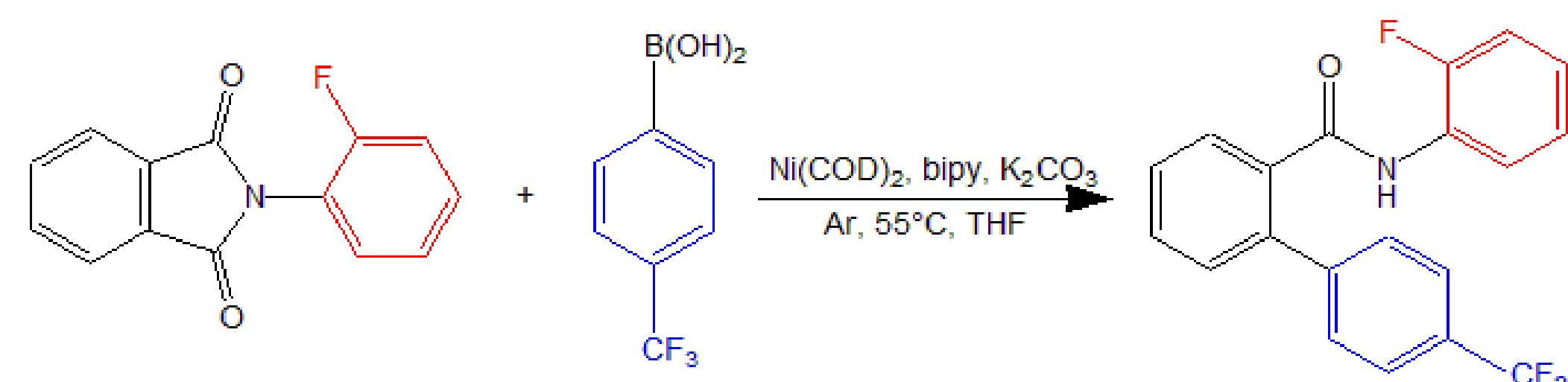
Synthesis of Ortho-Substituted Benzamides through Decarbonylative Cross-Coupling of Phthalimides

Grace C. Ahlgrim, Trey C. Pankratz, Ethan M. Heyboer, Kimberly S. DeGlopper, Mason D. Yoder, Megan Kwiatkowski, Jeffrey B. Johnson*
Department of Chemistry, Hope College, Holland, MI 49423

For more information, contact:
Jeffrey B. Johnson
Hope College
(616)395-7118
jjohnson@hope.edu

Background

The development of nickel-mediated catalysis has progressed to the decarbonylation of phthalimides for cross-coupling with boronic acids to form ortho-substituted benzamides. Research is focused on isolating these desired products. However, many reactions produce a byproduct in which a carbon-hydrogen bond forms in the position of the boronic acid substituent, making isolation of the desired product through column chromatography difficult.

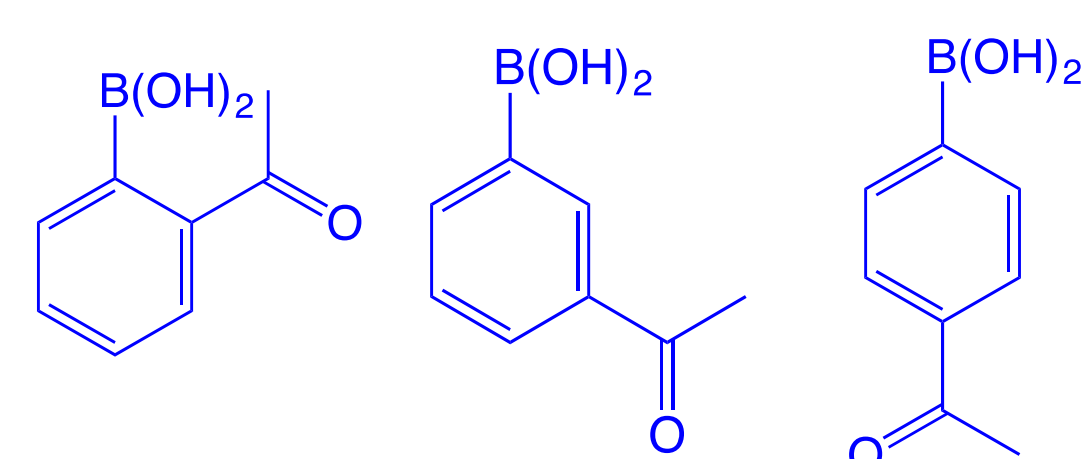


Additional research focuses on manipulating the variables of the above reaction to determine if the nickel can be used catalytically rather than stoichiometrically. Isolation of the desired product and development of a catalytic cycle are the main goals as the scope of the project is expanded.

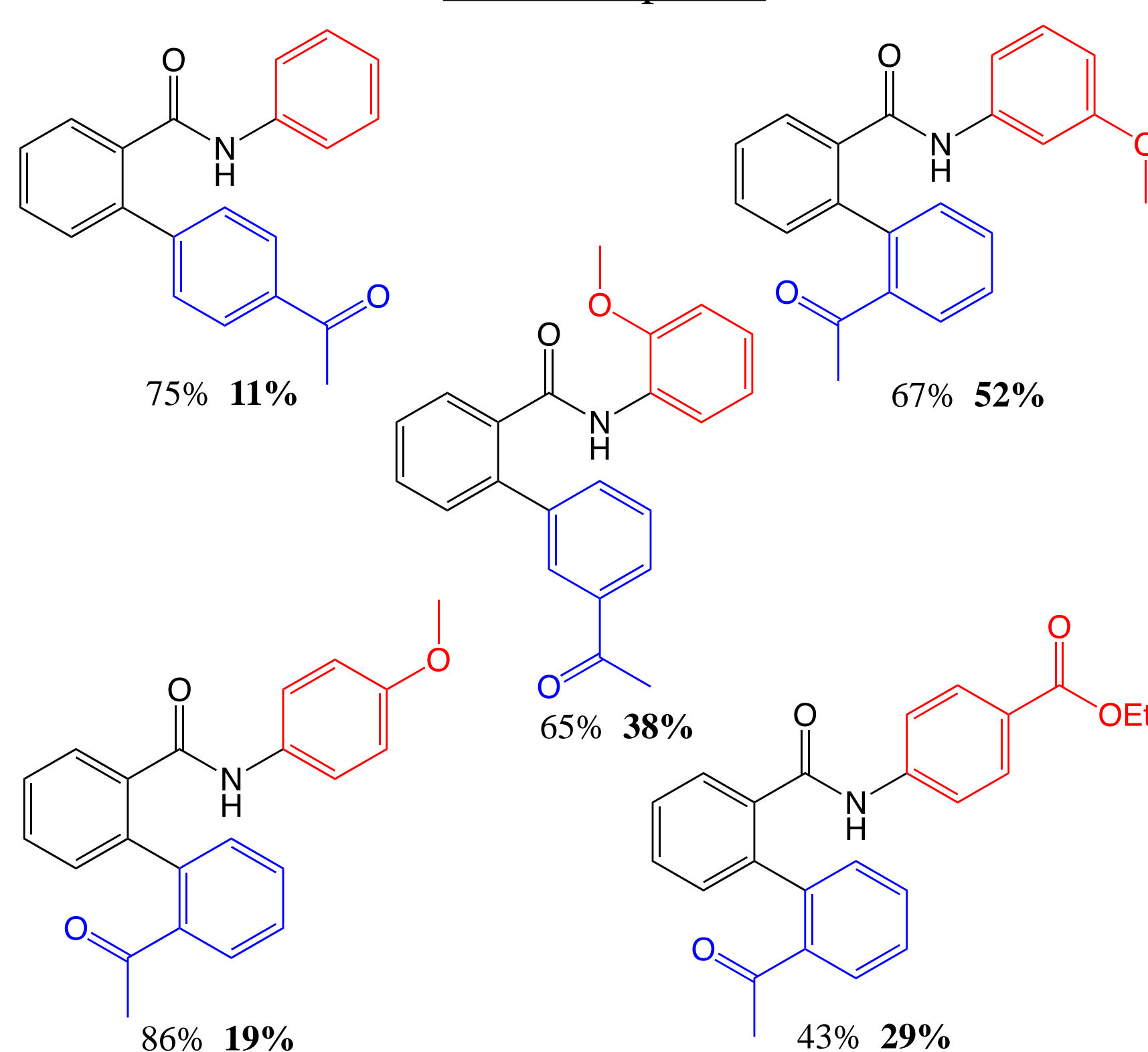
Isolation of Desired Product

Efforts to isolate the desired product are limited by the reduction product's propensity to have a R_f value to the desired product. In an effort to alleviate this situation, acetylphenyl boronic acids are being used to create a more polar desired product for easier separation via column chromatography.

Acetylphenyl Boronic Acids



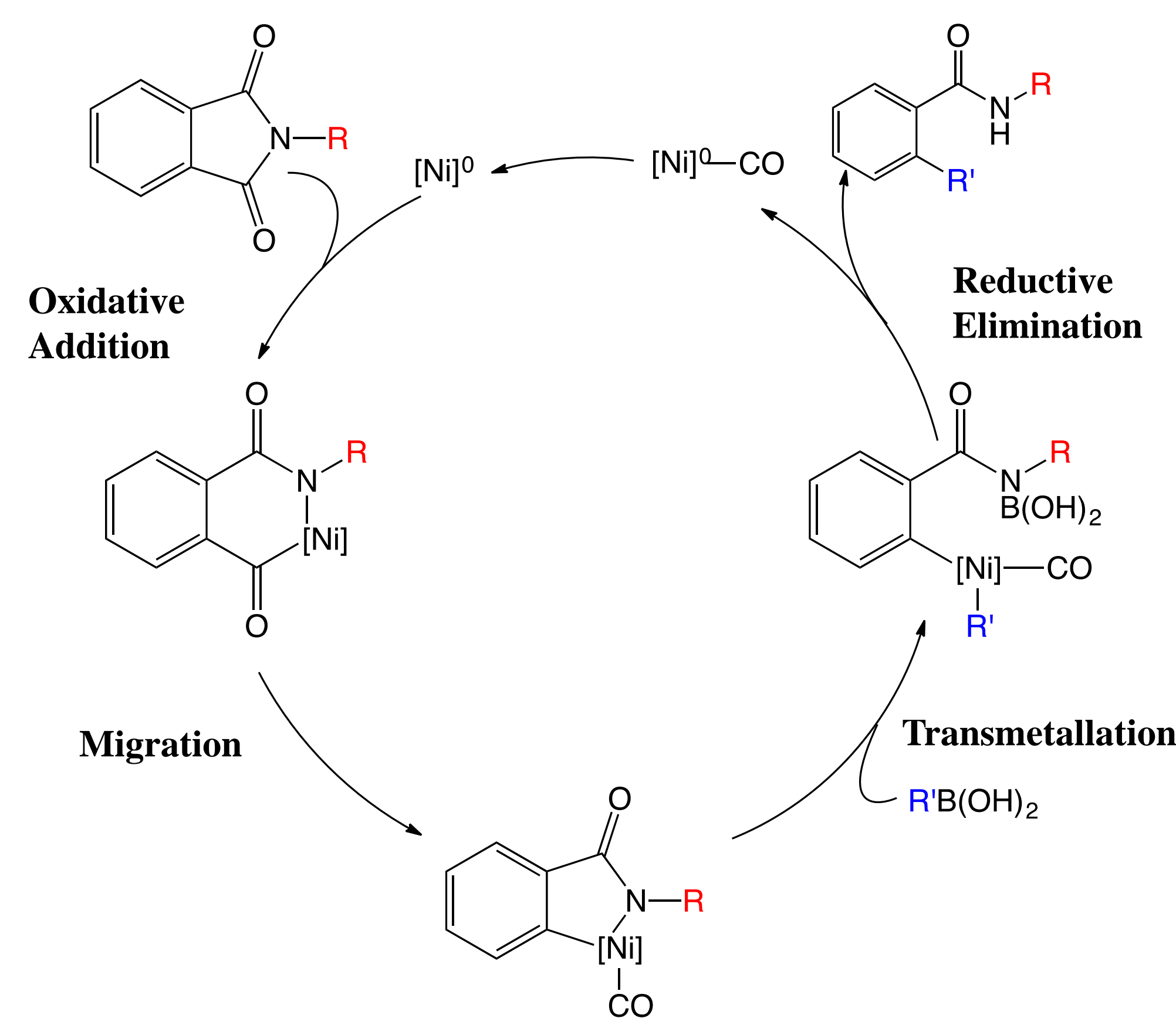
Isolated Species



A variety of products have been able to be isolated with high levels of purity, showing this method works for *ortho*-, *meta*-, and *para*- acetylphenyl boronic acids and various electronic and steric conditions in the phthalimide substituent.

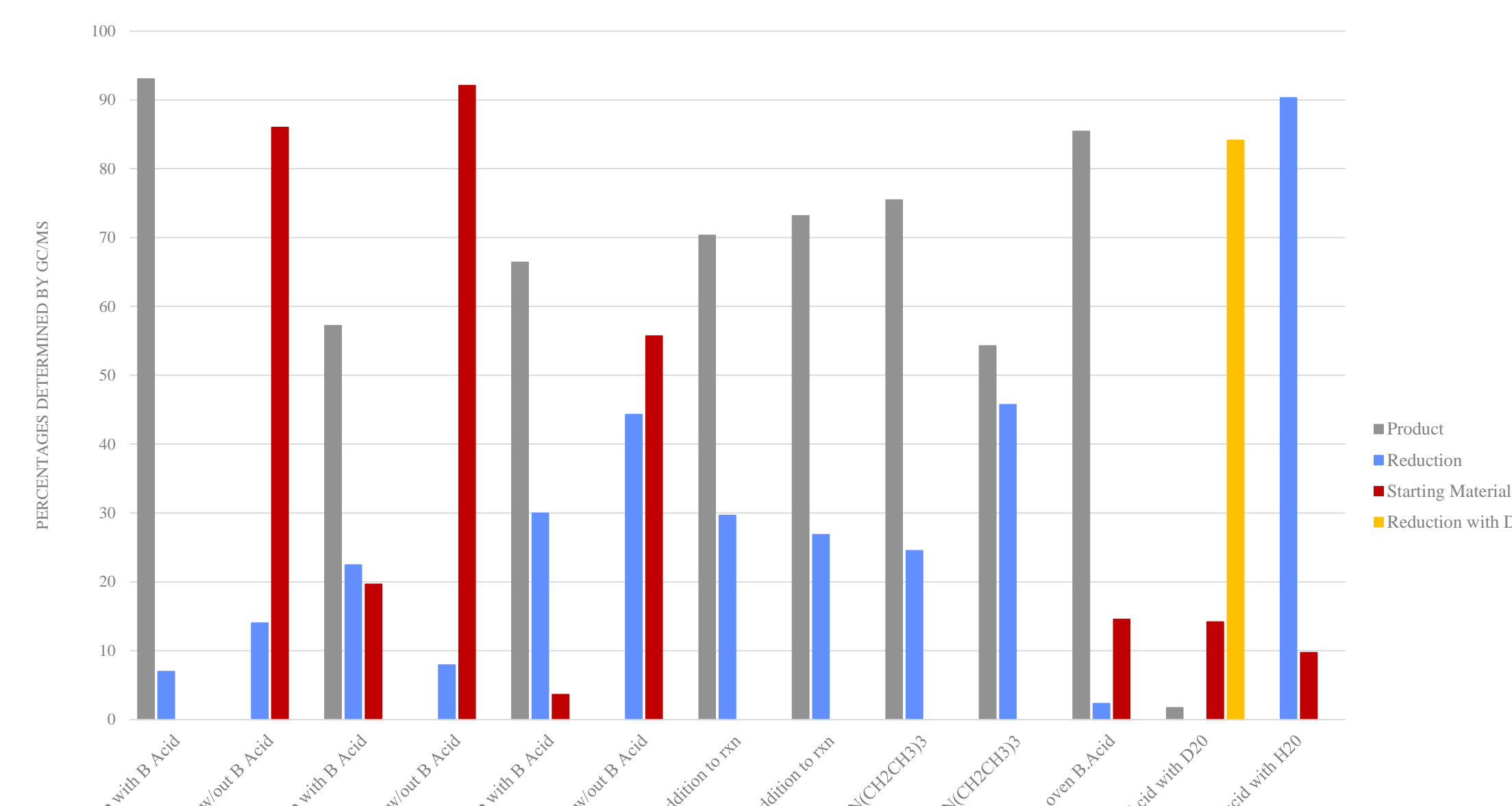
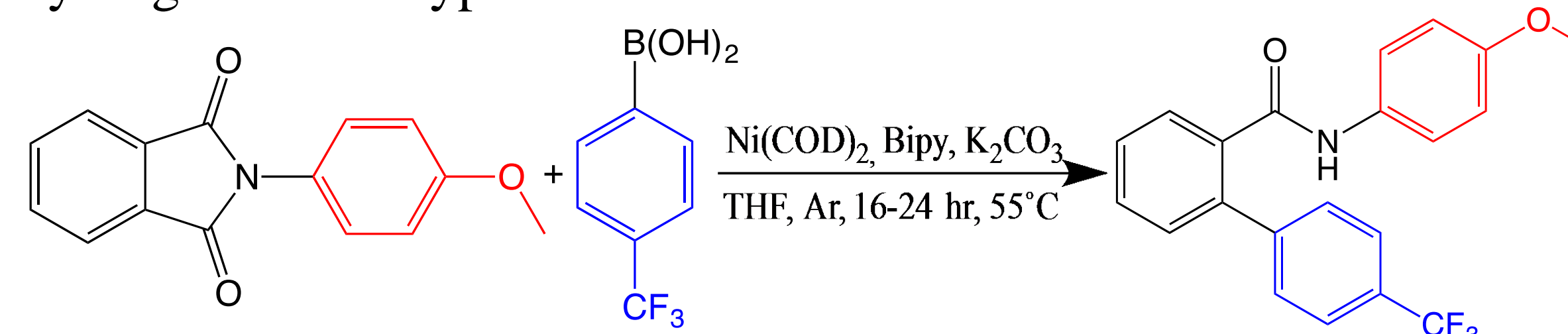
*GC/MS Yield, Isolated Yield

Proposed Mechanism



Reduction Product

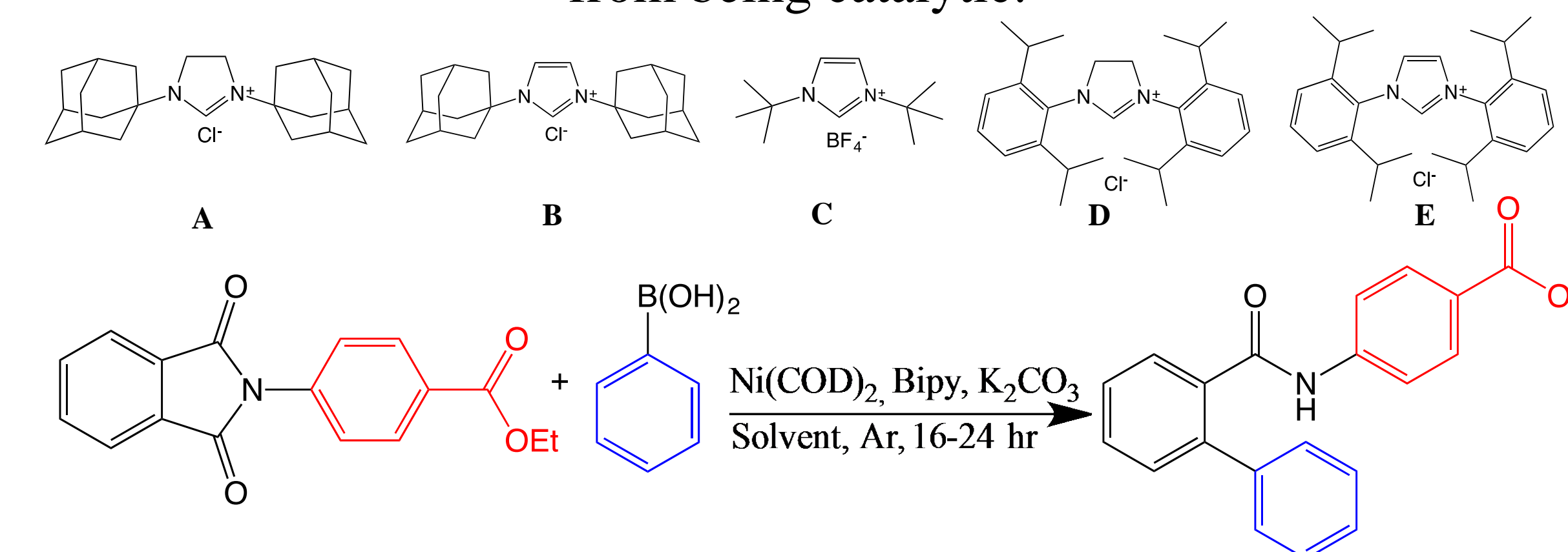
The reduction product has similar polarity to the desired product, hindering the isolation process. This byproduct started to form once boronic acids became the source of cross-coupled substituent, and was initially theorized as the source of the unexpected hydrogen on the byproduct.



- The reduction product is not likely to form from the workup as seen with no reduction with Deuterium when using a D_2O
- The pretreatment of the boronic acid with H_2O and D_2O indicated higher percentages of reduction product giving evidence of the hydrogen coming from wet boronic acid

Catalysis Prospects

N-heterocyclic ligands have been recently shown to complete the catalytic cycle of nickel. These ligands coordinate with the nickel to weaken the nickel-carbonyl bond that is preventing this process from being catalytic.



Entry	Catalyst	Ligand	Base	Solvent	Yield*
1	Ni(COD) ₂	A	K ₂ CO ₃	THF	0%
2	Ni(COD) ₂	B	K ₂ CO ₃	THF	9.65%
3	Ni(COD) ₂	C	K ₂ CO ₃	THF	29.05%
4	Ni(COD) ₂	D	K ₂ CO ₃	THF	0%
5	Ni(COD) ₂	E	K ₂ CO ₃	THF	32.37%
6	Ni(COD) ₂	B	K ₂ CO ₃	Dioxane	0%
7	Ni(COD) ₂	C	K ₂ CO ₃	Dioxane	10.71%
8	Ni(COD) ₂	E	K ₂ CO ₃	Dioxane	0%
9	Ni(COD) ₂	B	K ₂ CO ₃	Acetonitrile	0%
10	Ni(COD) ₂	C	K ₂ CO ₃	Acetonitrile	0%
11	Ni(COD) ₂	E	K ₂ CO ₃	Acetonitrile	0%

* Determined through GC/MS

• No reduction product was produced as indicated by GC/MS

Future Work

Isolation of the ortho-substituted benzamides

Continue to explore the N-heterocyclic ligands to establish the Ni catalysis and optimize the reaction with base and solvent manipulations.

Explore alternatives to boronic acids and phthalimides

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