

# Nickel Catalyzed Cross-Couplings of Amino Acid Derivatives via C-N Bond Activation

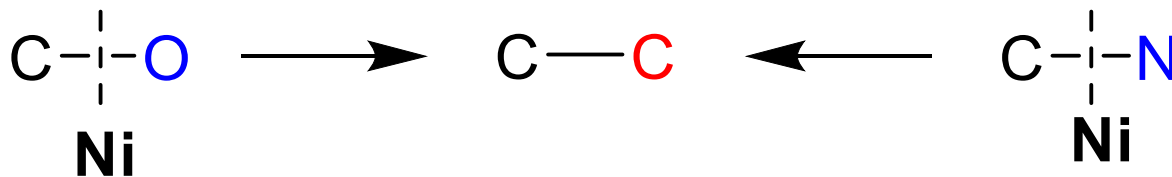
Earl Bampo

M. Watson Group



# MPW Research:

## Cross Couplings of Amine and Alcohol-derived Electrophiles

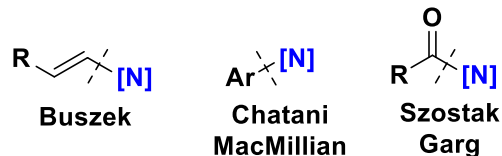


Our research is focused on the development of Transition Metal catalyzed cross-coupling reactions to form Carbon-Carbon bonds from Carbon-Nitrogen and Carbon-Oxygen derived electrophiles.

# Prior Art: Known Cross-Coupling Reactions via C-N Activation

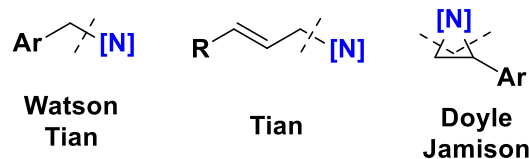
- Limitations in previous examples of C-N bond activation in cross-coupling reactions
- Previous work on C<sub>sp3</sub>-N bond cleavage rely on either electronic or strain activation

## A. C<sub>sp2</sub>-N bonds



Buszek, K. R.; Brown, *N. Org. Lett.* **2007**, 9, 707-710.  
 Tobisu, M.; Nakamura, K.; Chatani, N. *J. Am. Chem. Soc.* **2014**, 136, 5587-5590.  
 Blakey, S.; MacMillan, D. *J. Am. Chem. Soc.* **2003**, 125, 6046-6047.  
 Meng, G.; Szostak, M. *Org. Lett.* **2016**, 18, 796-799.  
 Hie, L.; Baker, E. L.; Anthony, S. M.; Desrosiers, J.-N.; Senanayake, C.; Garg, N. K. *Angew. Chem., Int. Ed.* **2016**, 55, 15129-15132.

## B. C<sub>sp3</sub>-N bonds

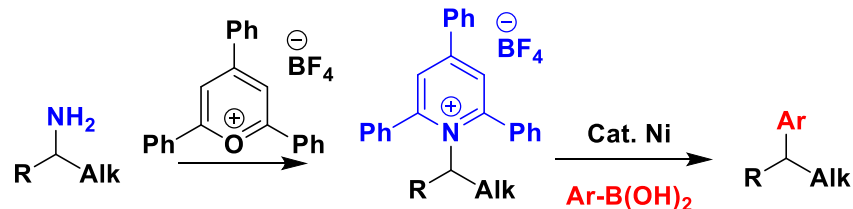


*electronically activated*      *strain activated*

Basch, C. H.; Cobb, K. M.; Watson, M. P. *Org. Lett.* **2016**, 18, 136-139.  
 Li, M.-B.; Wang, Y.; Tian, S.-K. *Angew. Chem., Int. Ed.* **2012**, 51, 2968-2971.  
 Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, 134, 9541-9544.  
 Jensen, K. L.; Standley, E. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2014**, 136, 11145-11152.

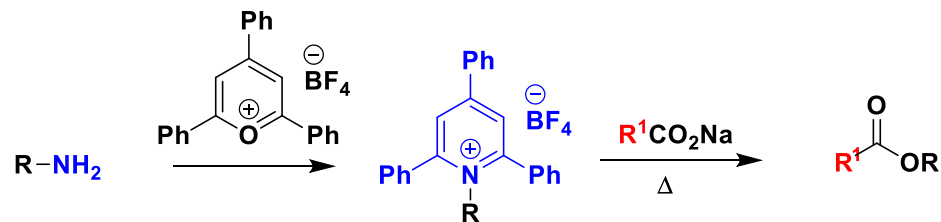
# Prior Art: Pyridinium Formation

- To enable cross coupling of unactivated alkyl amines, our group developed methods demonstrating pyridinium salts as great electrophiles for Nickel Catalyzed Suzuki reactions.



Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P. *J. Am. Chem. Soc.* 2017, 139,5313-5316.

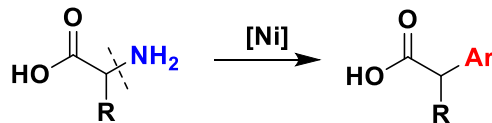
- First example of cross-coupling via C-N bond cleavage of alkyl amines with unactivated alkyl groups.



Katritzky, A. R.; Gruntz, U.; Kenny, D. H.; Rezende, M. C.; Sheikh, H. J. *Chem. Soc. Perkin Trans.* 1979, 1, 430  
Bapat, J. B.; Blade, R. J.; Boulton, A. J.; Epszajn, J.; Katritzky, A. R.; Lewis, J.; Molina-Buendia, P.; Nie, P.-L.; Ramsden, C. A. *Tetrahedron Lett.* 1976, 31, 2691

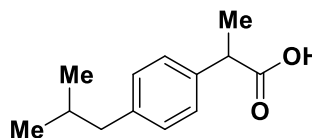
Katritzky, A. R.; Marson, C. M. *Angew. Chem. Int. Ed.* 1984, 23, 420

# This Work

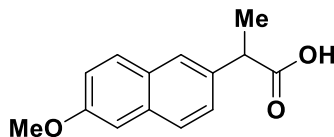


*Why are these products interesting?*

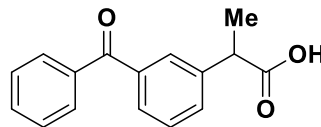
- Products structurally similar to known Bioactive molecules (NSAIDs)



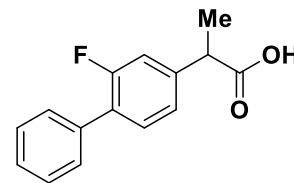
Ibuprofen



Naproxen



Ketoprofen

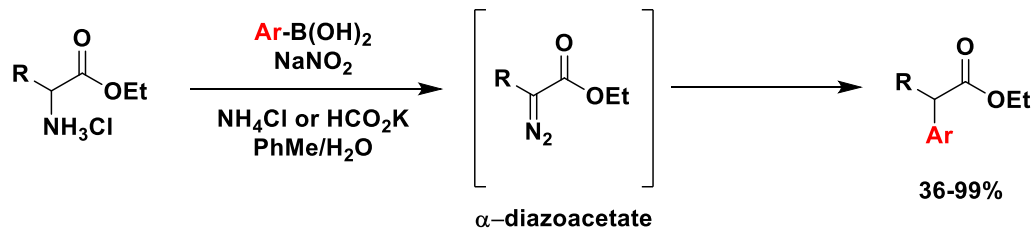


Flurbiprofen

*Non-Steroidal Anti-inflammatory Drugs*

## Metal Free $\alpha$ -aryl ester formation

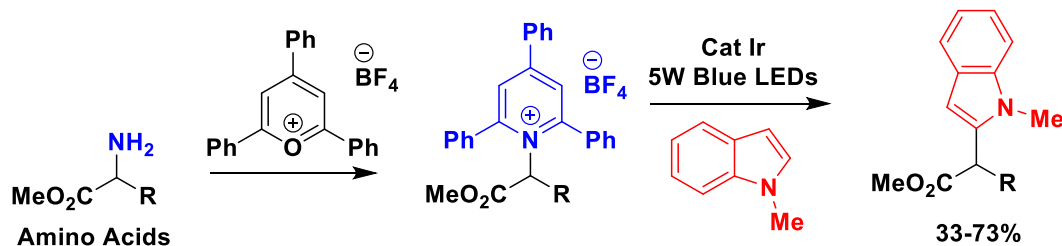
Wang



Wu, G.; Deng, Y.; Wu, C.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2014**, 53, 10510

## Light Mediated $\alpha$ -Aryl Ester Formation

Glorius



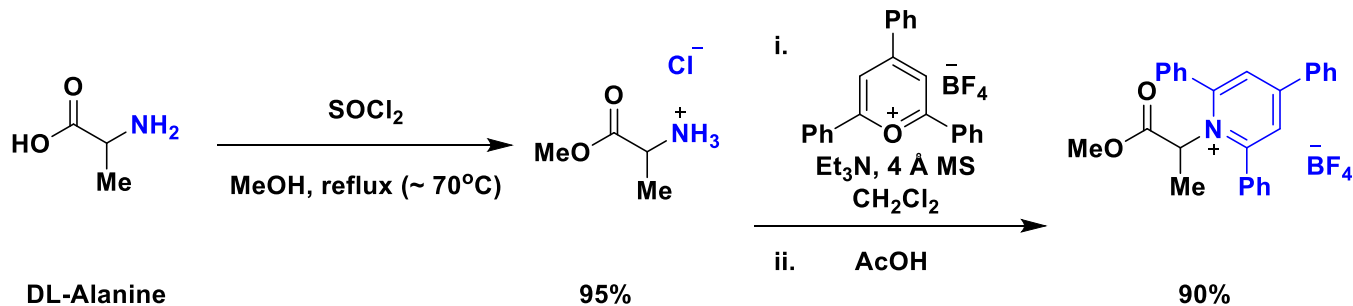
Limitations:

Used only 4 amino acids

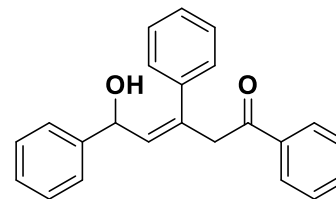
Very specific heteroaryl coupling groups

Klauck, F. J. R.; James, M. J.; Glorius, F. *Angew. Chem. Int. Ed.* **2017**, 56, 12336

# Substrate Synthesis

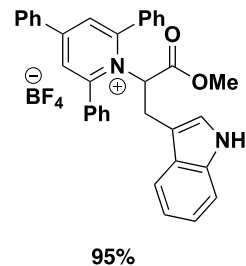
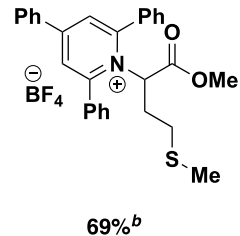
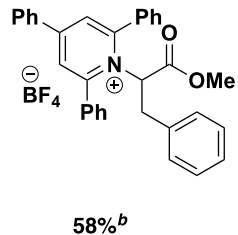
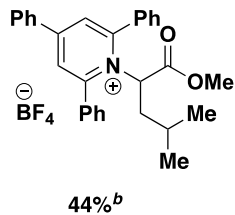
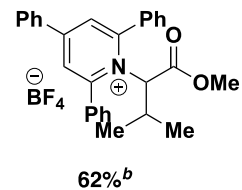
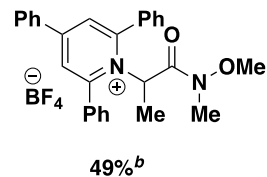
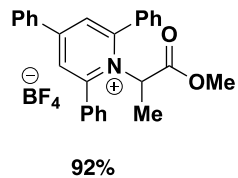
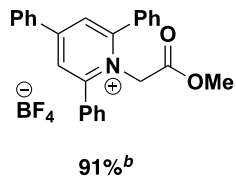
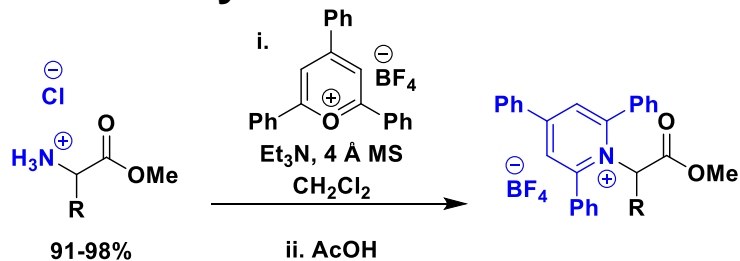


- Methyl Esters made in high yields
- Pyridinium formation with one by-product
- Pyridinium salts purified by column chromatography



Hydrolysis by-product

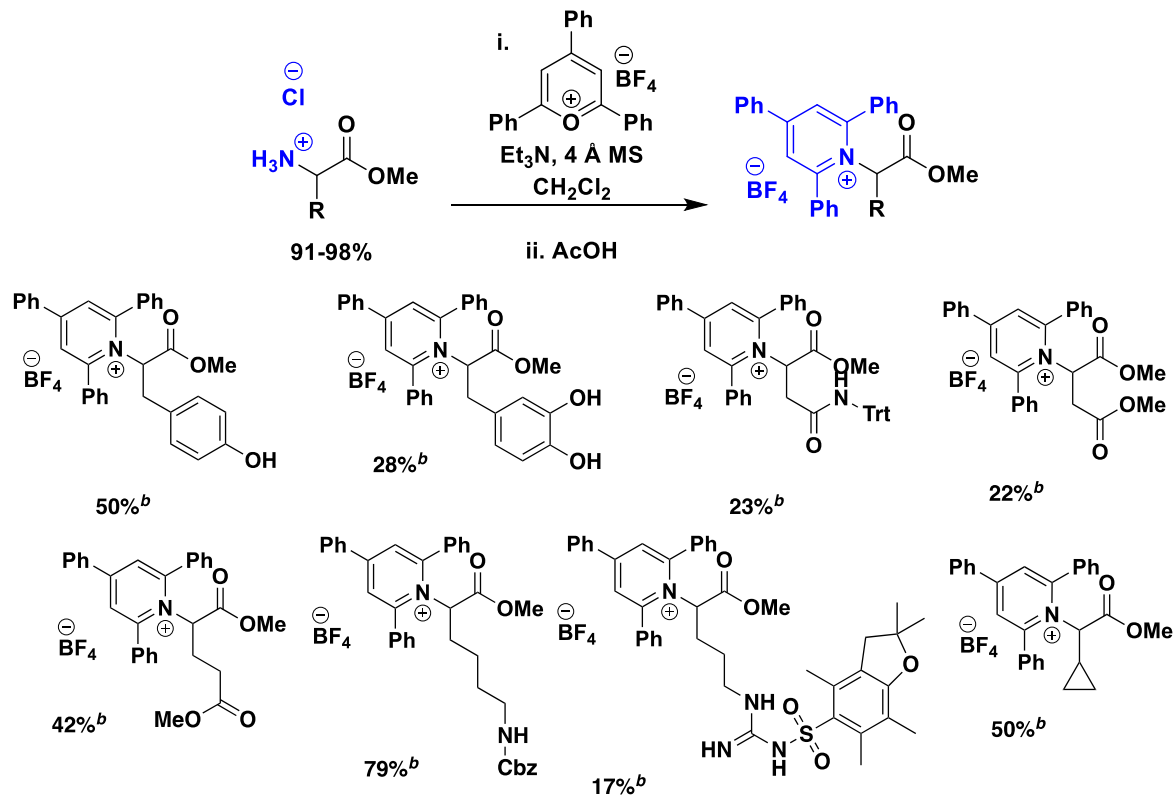
# Pyridinium Salts



<sup>b</sup> Purified by Column Chromatography

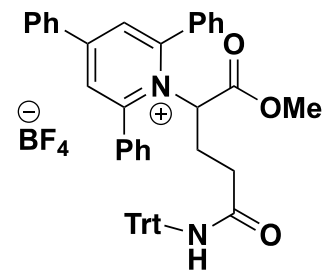
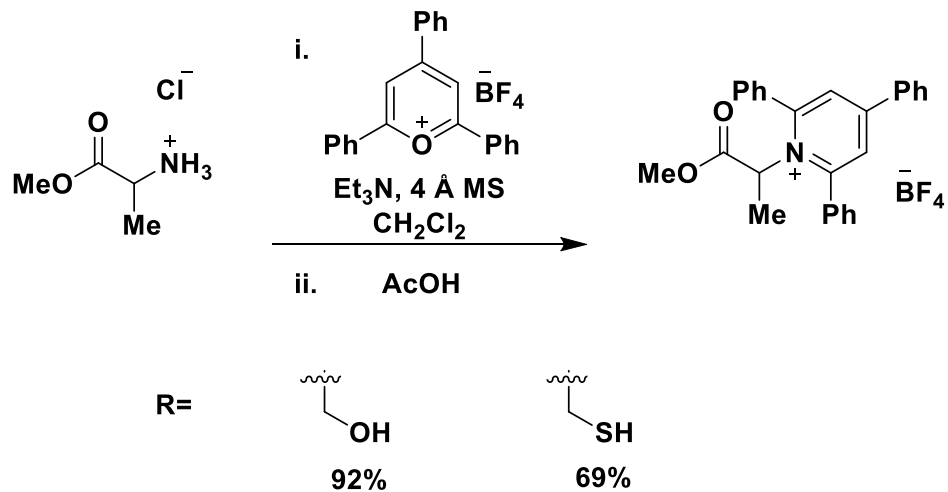


# Pyridinium Salts



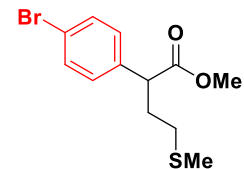
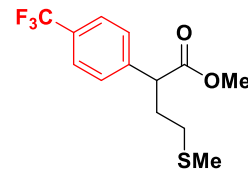
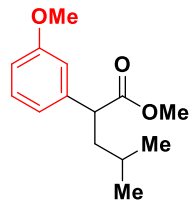
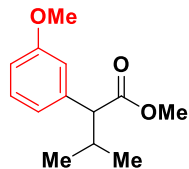
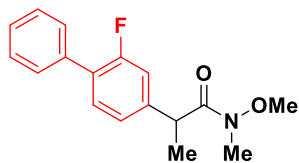
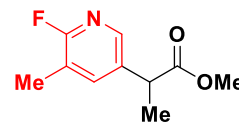
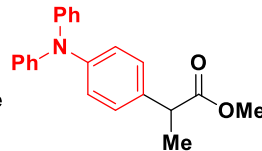
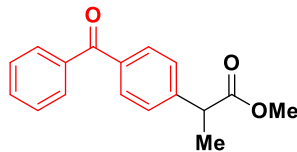
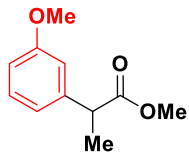
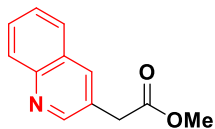
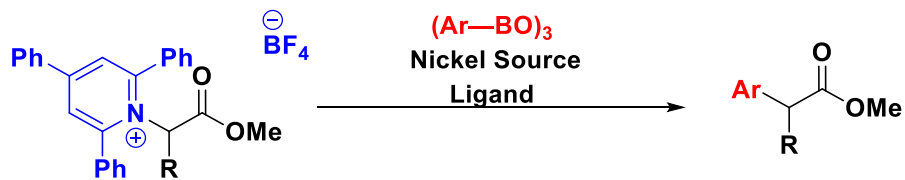
<sup>b</sup> Purified by Column Chromatography

# Limitations in Substrate Synthesis



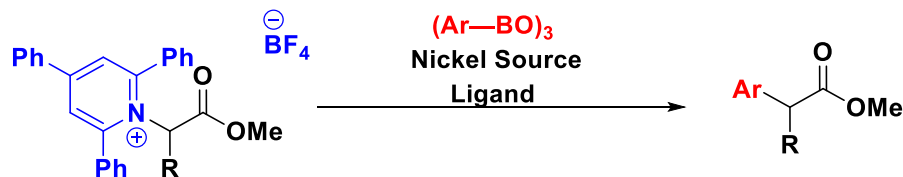
Gln  
15%  
Still contains an impurity

## Reaction Scope





## Summary



- Variety of amino acids and aryl boroxines to form  $\alpha$ -aryl amino acid esters in moderate to high yields
- Air stable nickel source
- Readily available ligand

# Acknowledgements



**MPW group:**  
**Post Docs:**  
 Dr. Sarah Pound  
 Dr. Shane Plunkett

**Grad Students:**  
**Corey Basch**  
 Jennie Liao  
 Javon Rabb-Lynch  
**Megan Hoerrhner**  
 Weiye Guan  
 Jianyu Xu  
**Kristen Baker**

**Undergrads:**  
 Alana Duke  
 Winnie Cheung



University of Delaware  
 Research Foundation



R01GM111820-01  
 COBRE#P20GM104316  
 COBRE#P20GM103541



AstraZeneca

Donation of Chemicals

Zondlo Lab