

Breaking Amide Bonds using Nickel Catalysis

Dander, J.E. and Garg, N. K.

ACS Catalysis. **2018**. 7 (2), 1413-1423

Austin Durham

Wipf Group

Current Literature 8/11/18



Overview

- Introduction
 - Nickel: Advantages, Applications, and Prospects
 - The Prevalent Amide: Peptide to Synthon
- Carbon-Heteroatom
 - Amide to Ester
 - Transamidation
- Carbon-Carbon
 - Carbonyl-Aryl
 - Carbonyl-Alkyl (Negishi)
- Bringing it to the Benchtop
- Summary, Future Directions, and Questions

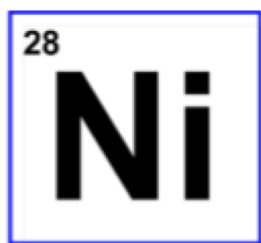
Nickel

- \$0.47 / oz vs. \$720 / oz for Pd
- 500 ug/ day vs. 100 ug/ day for Pd

A periodic table of elements with Nickel (Ni) highlighted in orange. The table shows elements from Hydrogen (H) to Oganesson (Og). Nickel is located in the 10th column and 4th row of the main body of the table.

Potential cost benefits

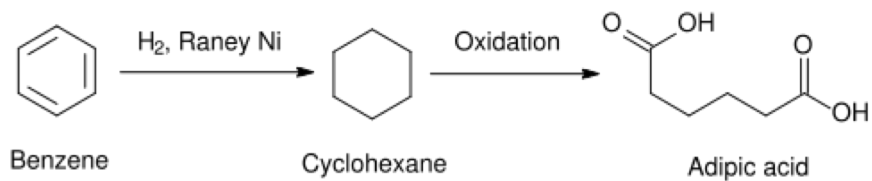
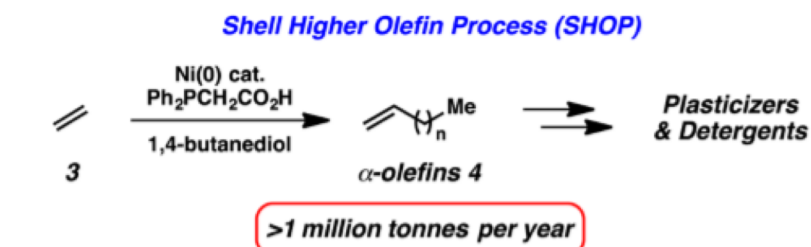
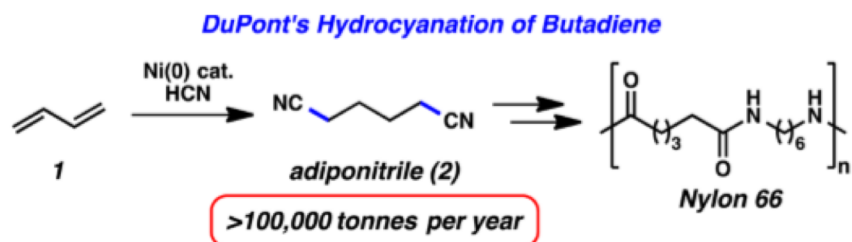
*Low CO₂ footprint
and toxicity*



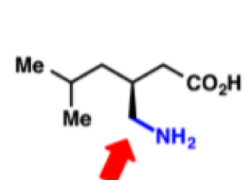
New reactivity

*New transformations for
use in chemical synthesis*

Nickel – Current Applications

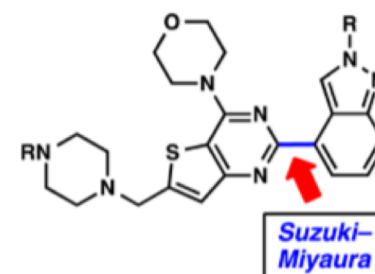


Nickel Catalysis in the Synthesis of Pharmaceuticals



Lyrica (5)
treatment of epilepsy,
pain, and anxiety

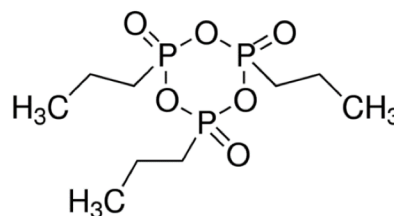
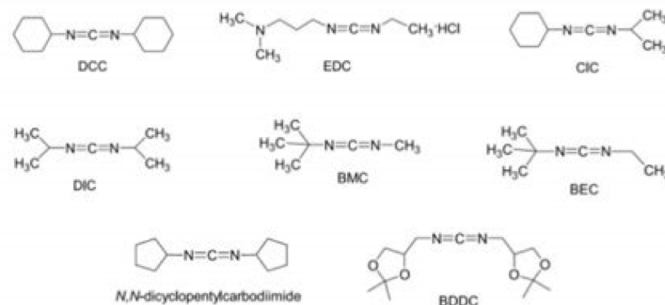
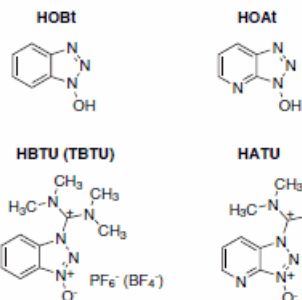
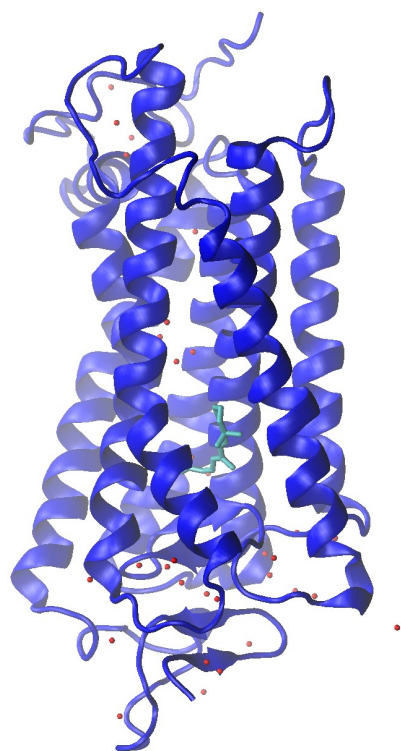
>2 tonne scale



6
PI3K
inhibitor

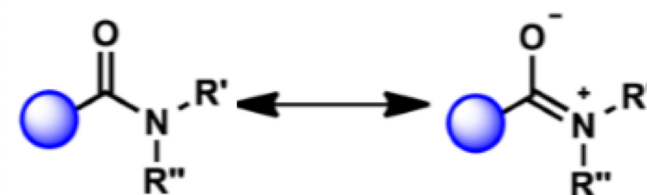
>50 kg scale

The Amide Bond



Amide Stability

- acidic and basic conditions
- reduction and oxidation
- palladium catalysis
- thermal conditions

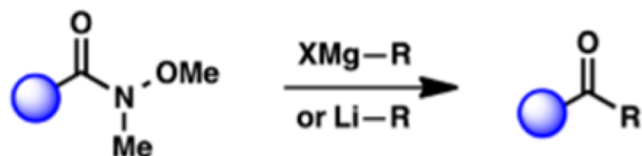


Amide Resonance Stabilization

barrier to rotation = 15–20 kcal/mol
resonance energy = 19–26 kcal/mol
C–N bond length = ~1.33 Å

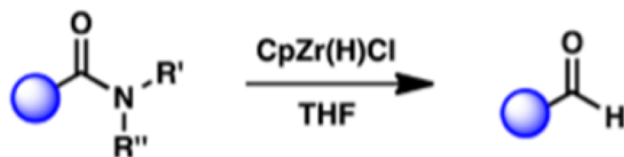
Amide Cleavage Precedence

Ketones from Weinreb Amide Displacement



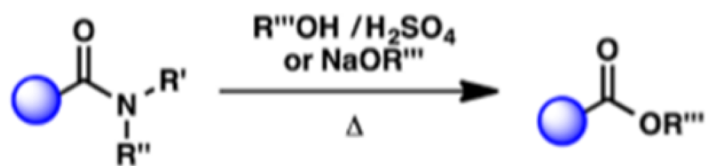
**Pyrophoric/Basic
Reagents Required**

Aldehydes from Tertiary Amides using Schwartz Reduction



**Stoichiometric
Precious Metal Complex**

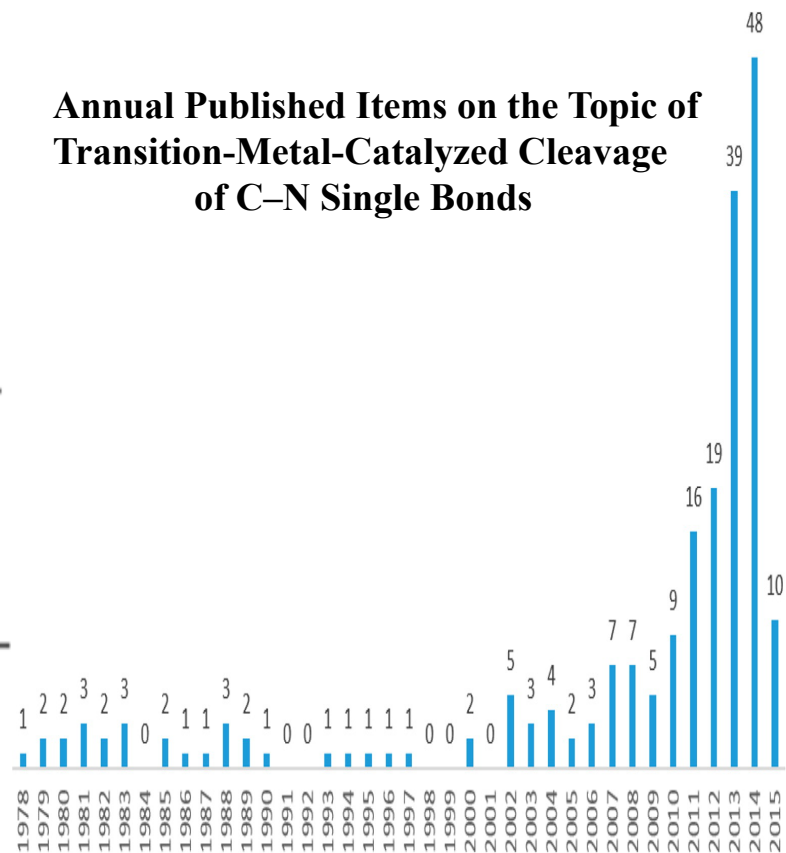
Carboxylic Acids or Esters by Amide Hydrolysis



**Harshly Basic/Acidic
Reaction Conditions**

Common Synthetic Methods for Amide C–N Bond Cleavage

Annual Published Items on the Topic of Transition-Metal-Catalyzed Cleavage of C–N Single Bonds



Breaking Amides

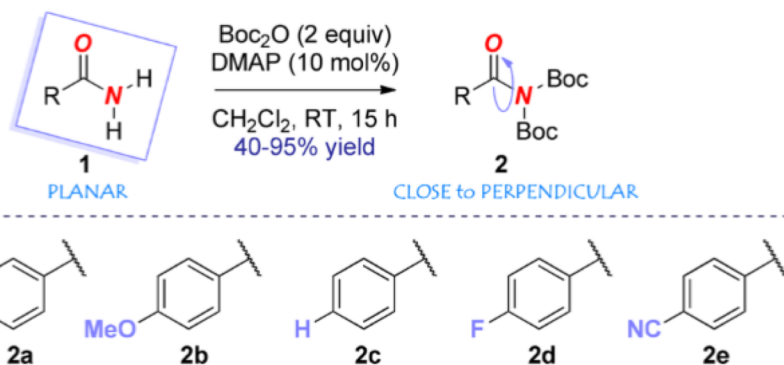
A: N-Acyl-glutarimides in amide bond cross-coupling



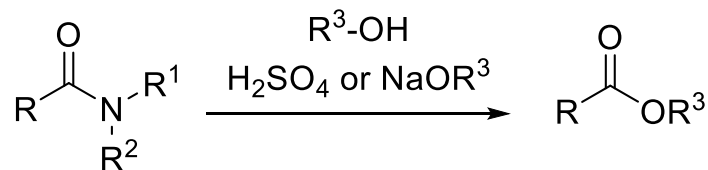
B: Acyl, decarbonylative and reductive cross-coupling of N-acyl-glutarimides



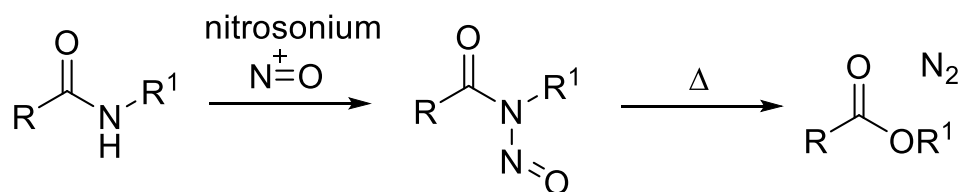
Figure 1. A) General pathways in amide N-C bond activation. B) N-Acyl-glutarimides in N-C amide bond cross-coupling: the most reactive amides and privileged scaffolds for reaction discovery.



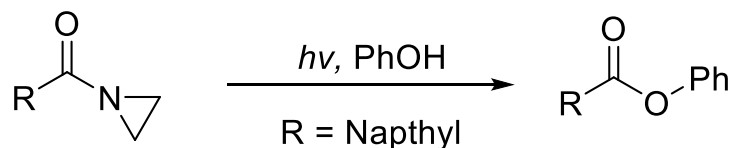
Amide to Ester Precedence



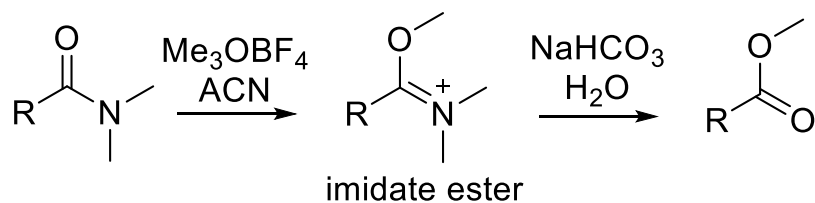
Direct Hydrolysis
Requires Strong Acid/ Base
Often High Heat



Nitrosation and Rearrangement
NO donor often Nitric Acid
Strong Electrophile

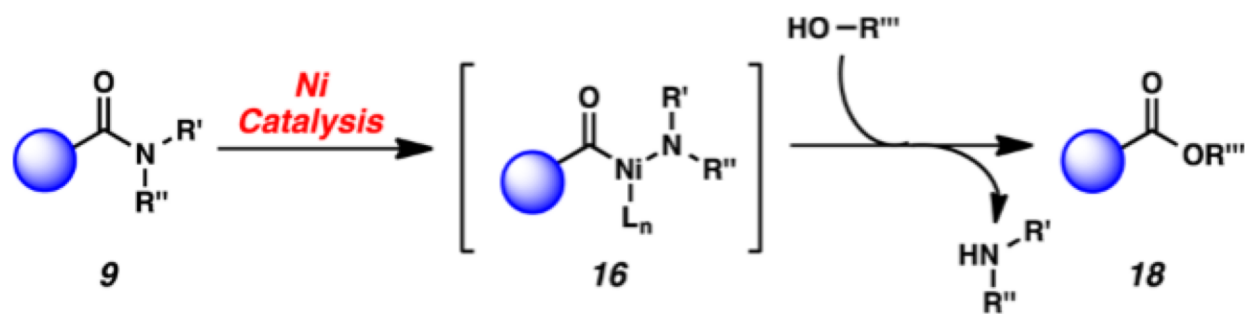


N-Acyl Aziridines
Limited Scope



Keck Methylation/Hydrolysis
Trimethyl Oxonium /
Strong Electrophile

Amide to Ester



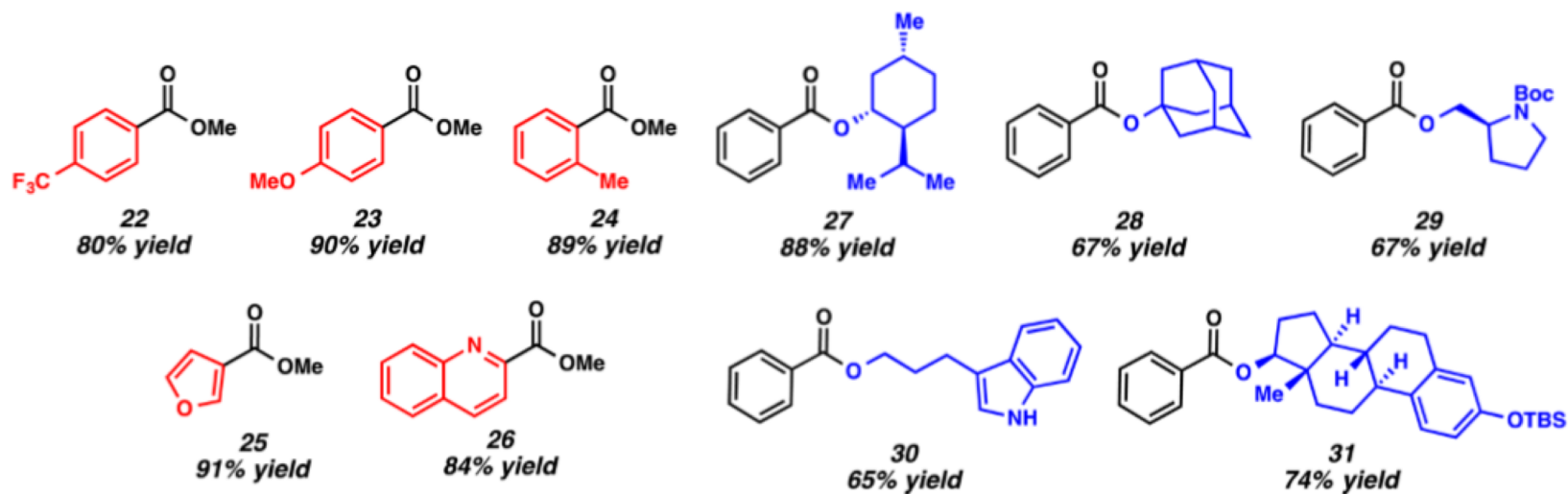
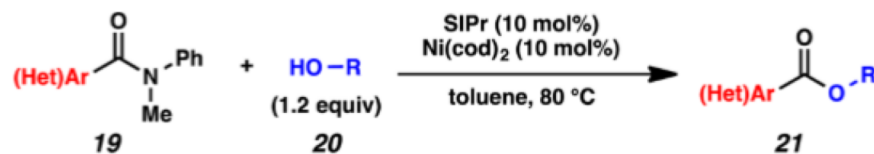
Amide



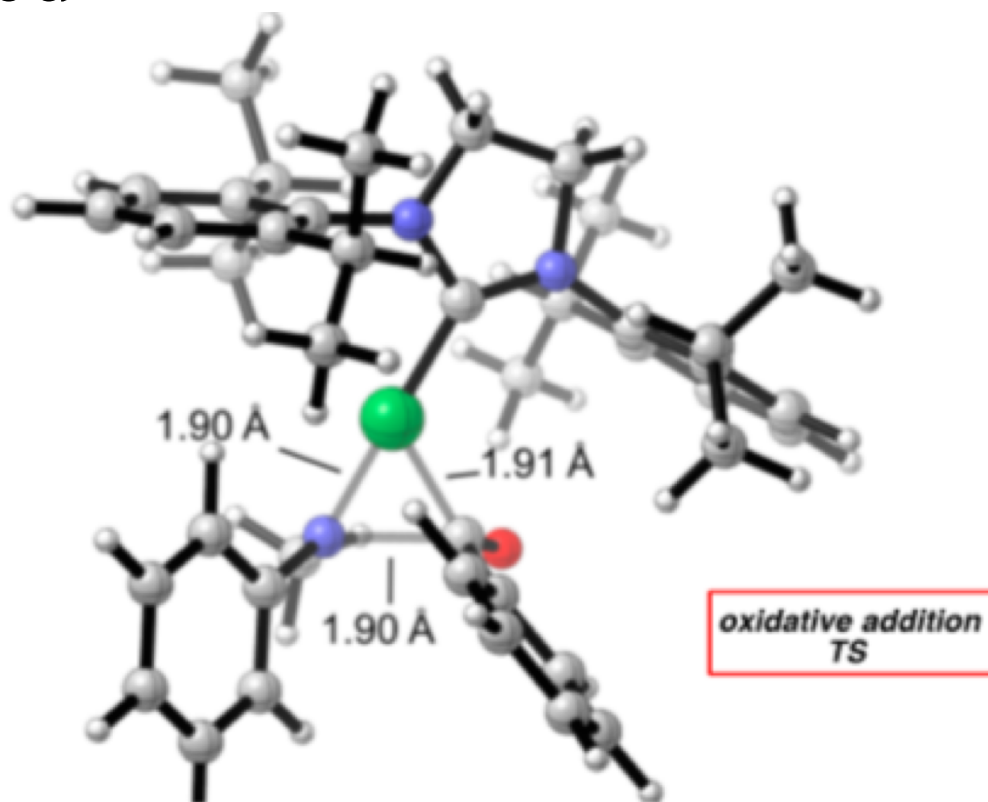
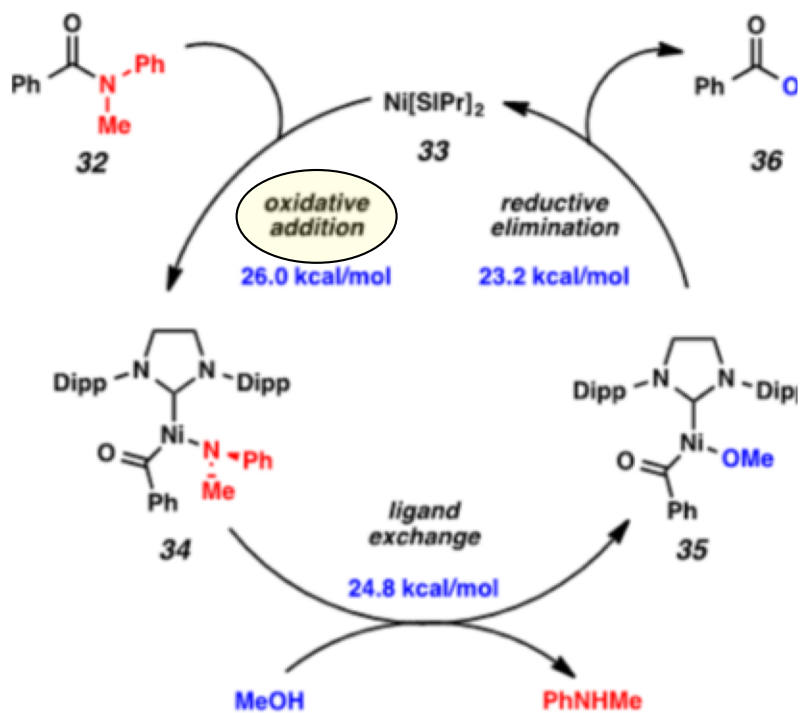
Ester

- Underdeveloped transformation
- Amide activation via Ni catalysis
- Use of amides as synthons

Amide to Ester Scope

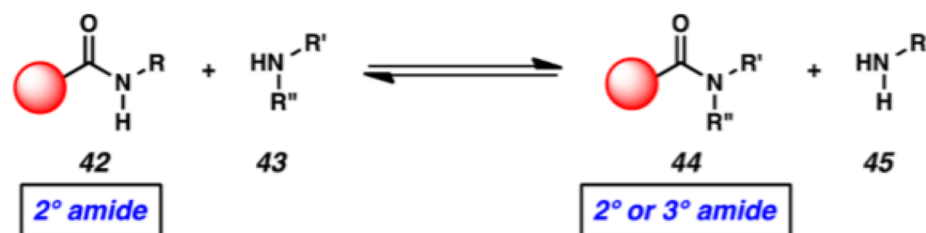


Amide to Ester Examined

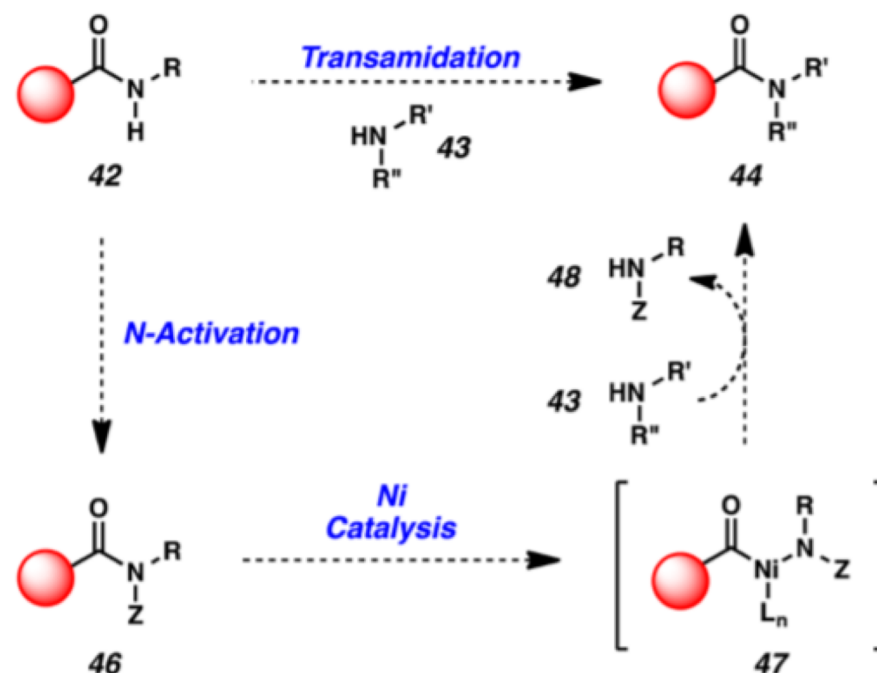


Transamidation Strategy

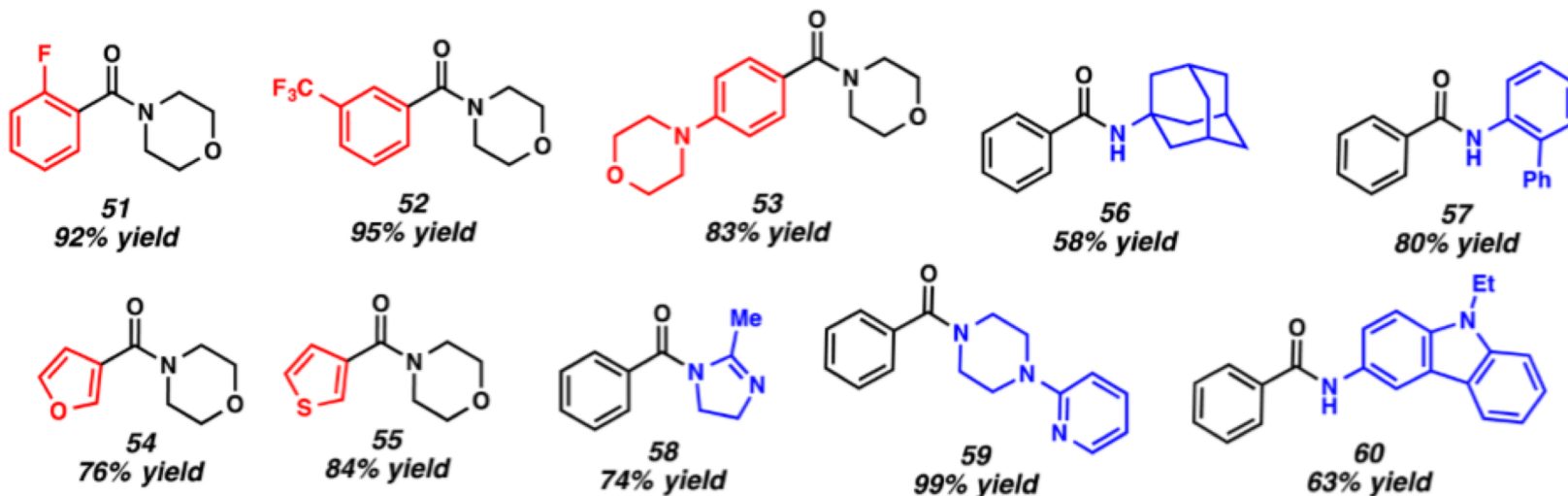
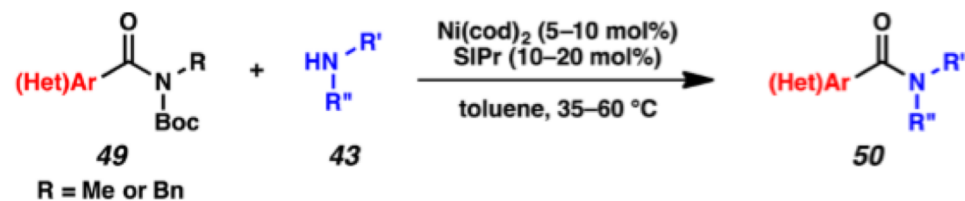
- Requires *Activation* of Amide
- Generally **Thermoneutral**



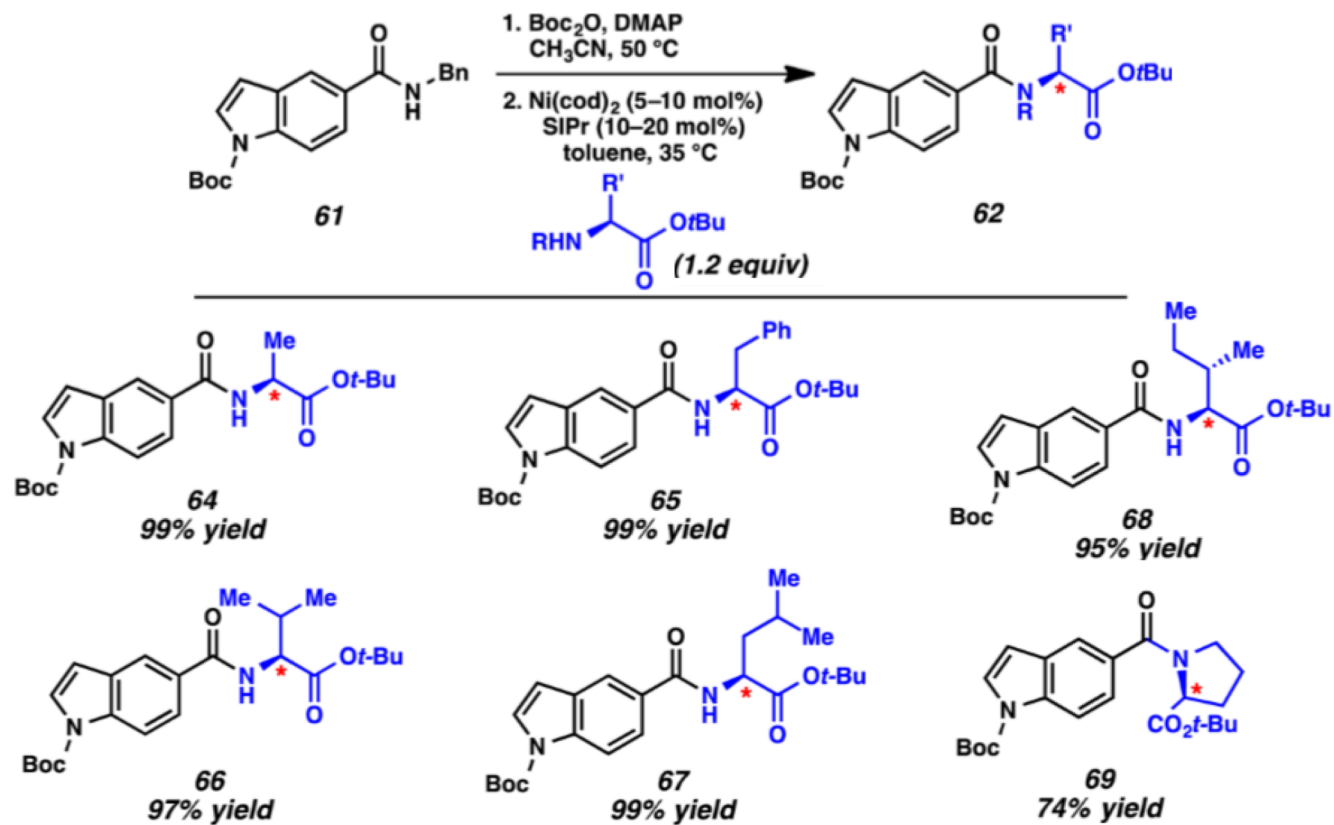
- High activation barrier due to amide resonance stability
- Unfavorable thermodynamics/thermoneutral process



Transamidation Scope

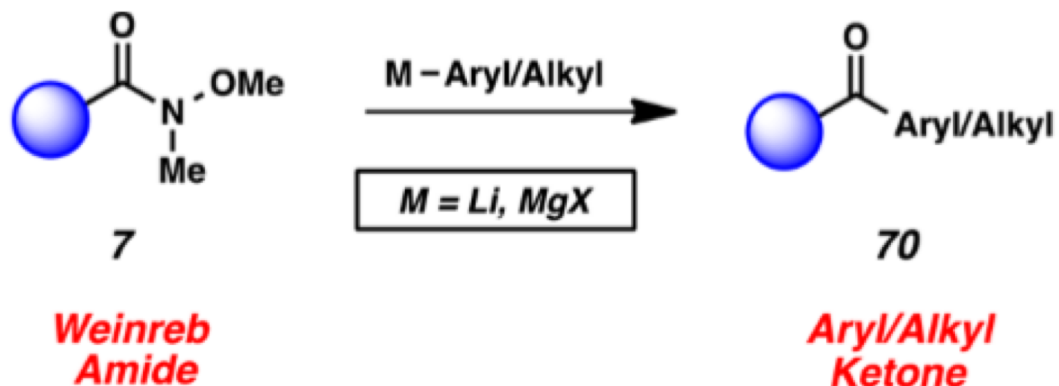


Two-Step Transamidation

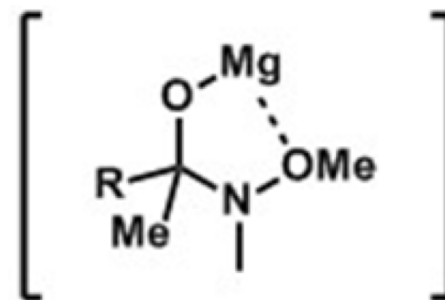


Carbon-Carbon Bond Formation

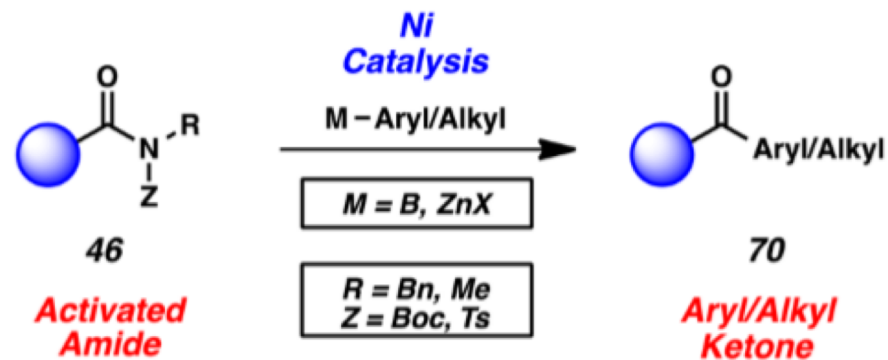
- Weinreb-Amide (Amide to Ketone)



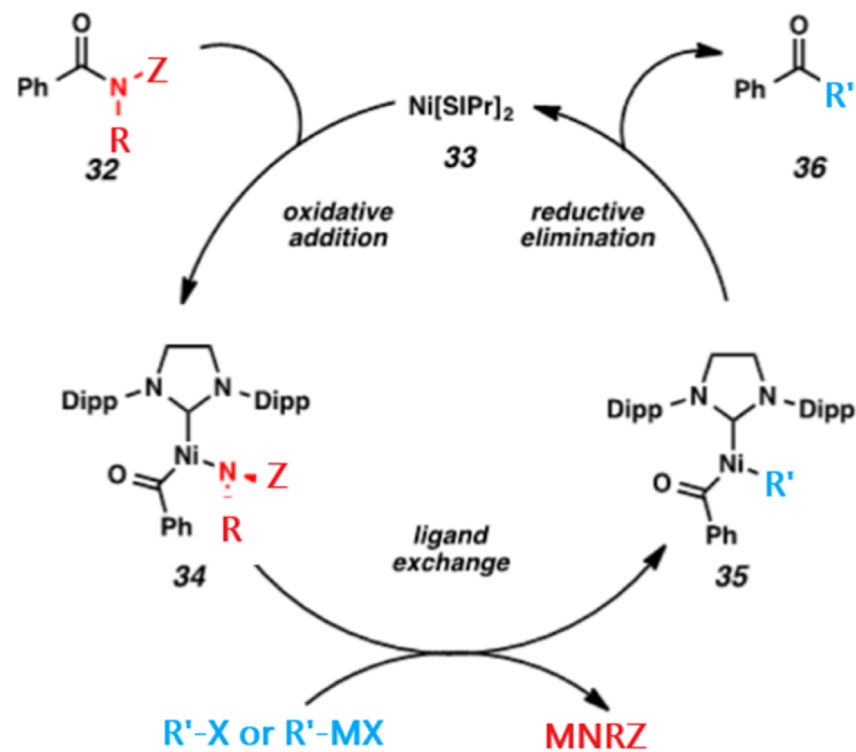
- Requires highly basic and pyrophoric organometallic reagents
- Displays limited functional group tolerance



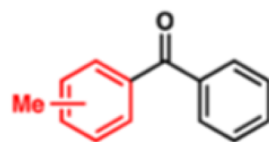
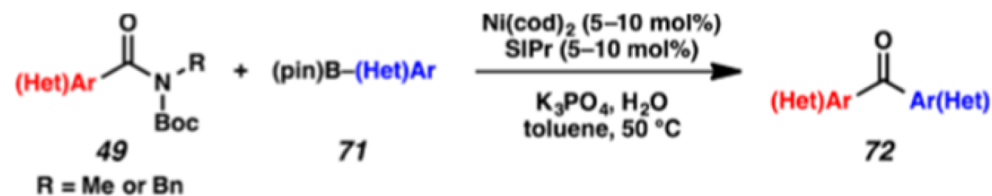
Carbon-Carbon Bond Formation



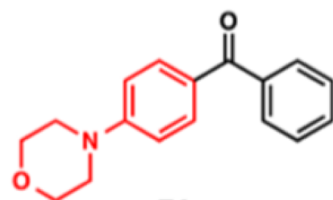
- Non-precious metal catalyst
- Mild reaction conditions
- Broad functional group tolerance



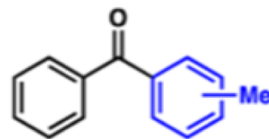
Carbonyl-Aryl Bond Formation



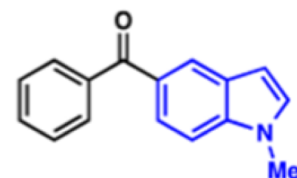
73a–c
(ortho) 51% yield
(meta) 91% yield
(para) 92% yield



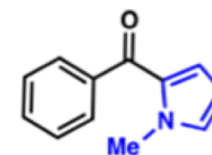
74
81% yield



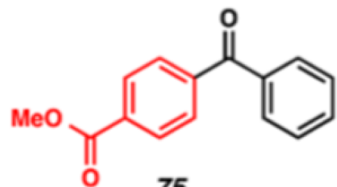
78a–c
(ortho) 66% yield
(meta) 80% yield
(para) 73% yield



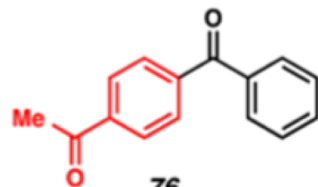
79
80% yield



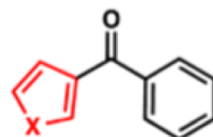
80
96% yield



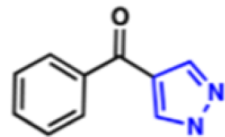
75
77% yield



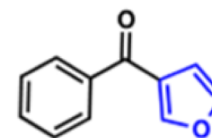
76
72% yield



77a–b
(X = O) 64% yield
(X = S) 66% yield

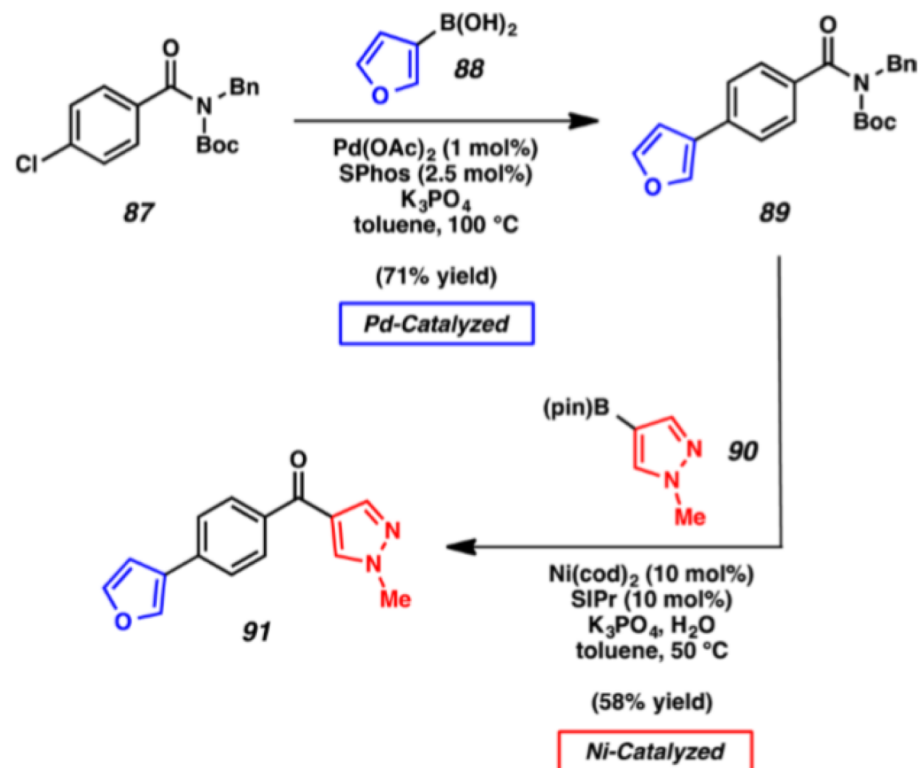
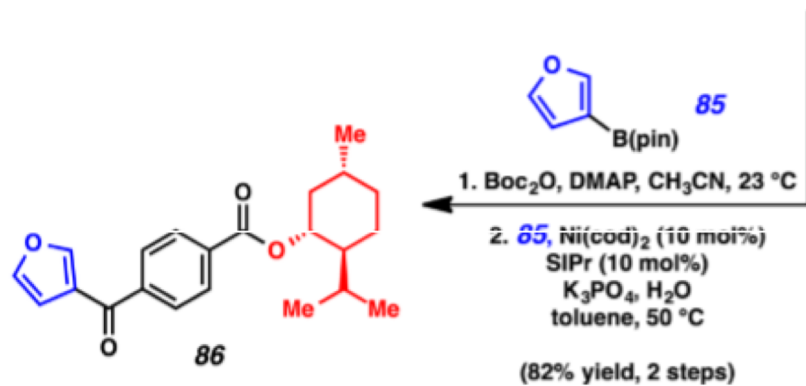
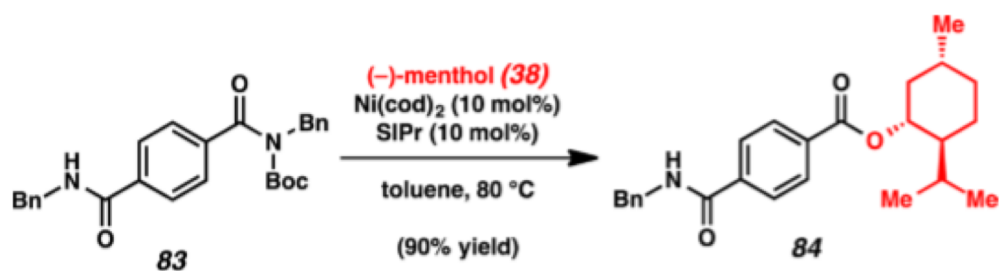


81
82% yield



82
86% yield

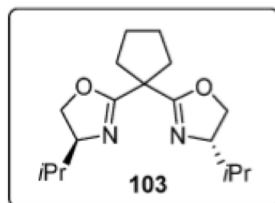
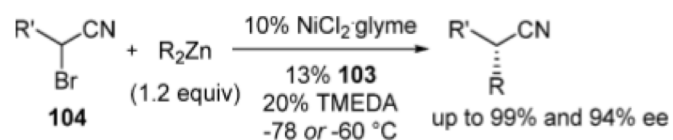
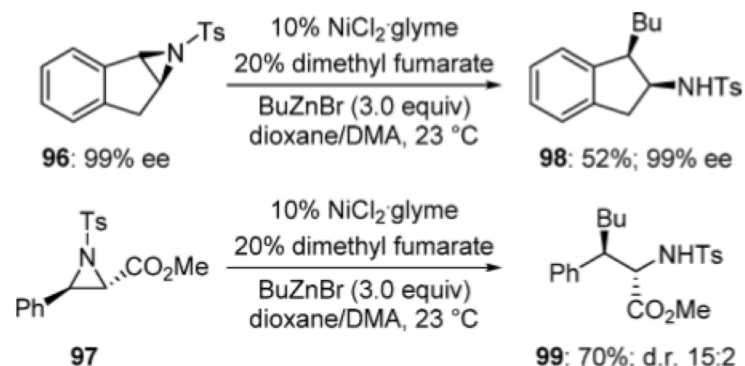
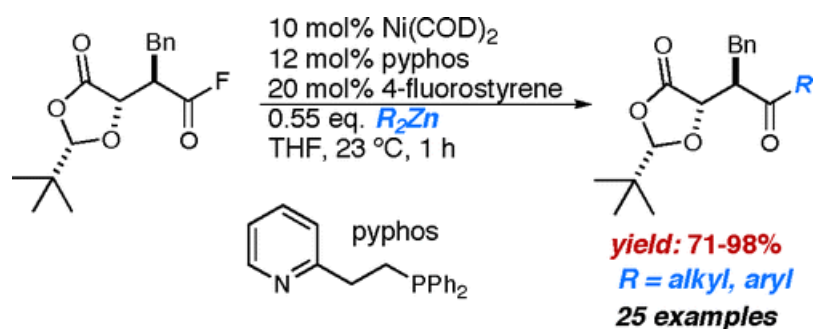
Carbonyl-Aryl Bond Formation



Carbonyl-Alkyl Bond Formation - Negishi

- Their Carbonyl-Aryl (Suzuki-Miyaura) conditions not applicable
- Negishi conditions using **organozinc** reagents
 - Tolerate crosslinking of sp²/sp³ hybridization; stereoretention with some Pd systems
 - Do **not** tolerate air/moisture
 - Preparation via direct metalation (Zn⁰) or via transmetallation (RMgBr)

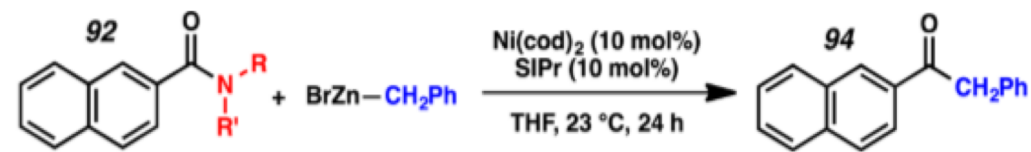
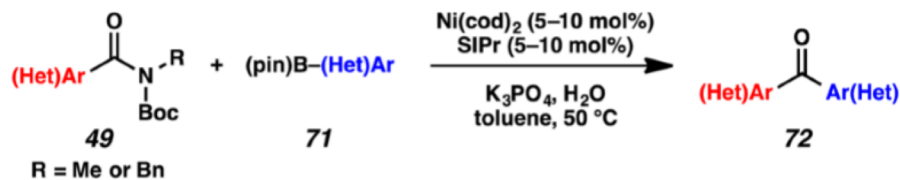
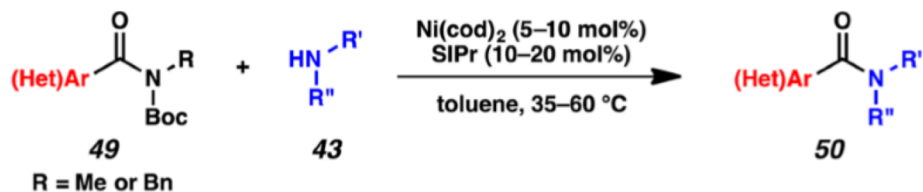
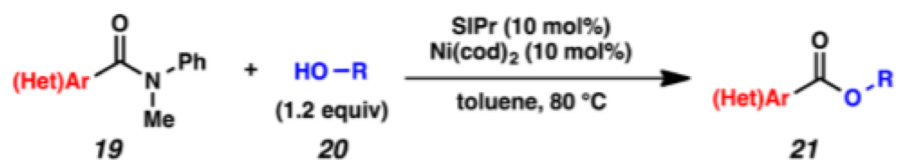
Some Negishi Precedence with Nickel Catalysis



N-Substitution allows for Negishi Coupling

- N-Tosyl Amides gave max conversion

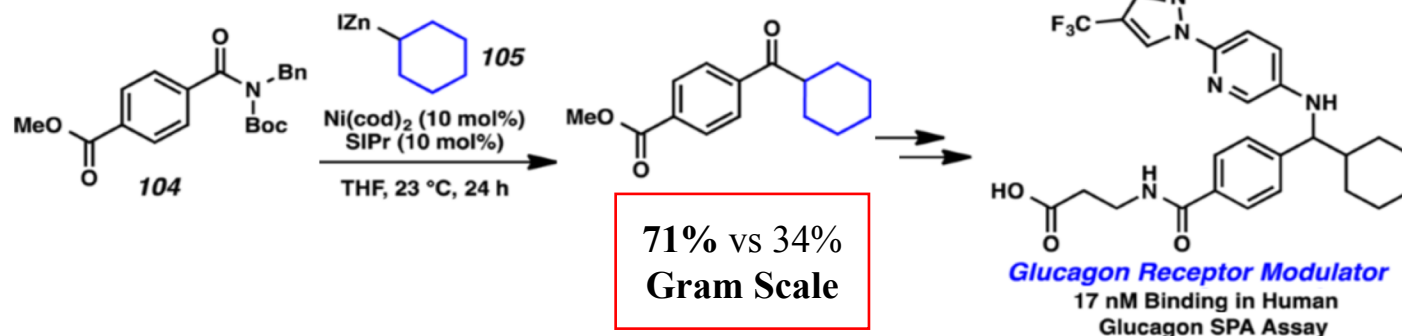
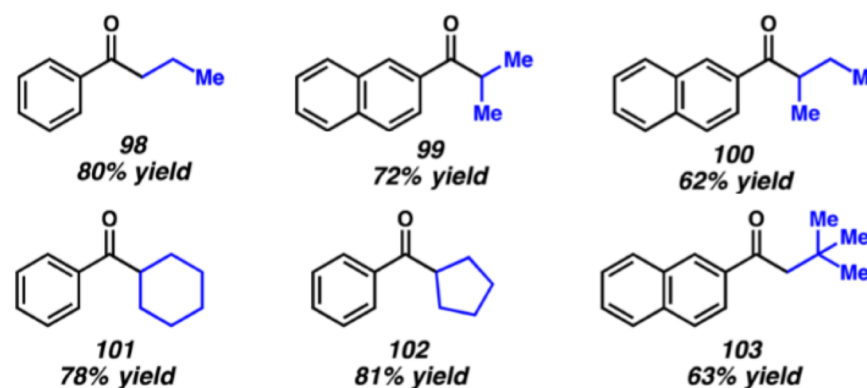
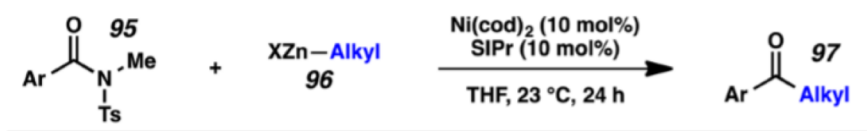
Previously,



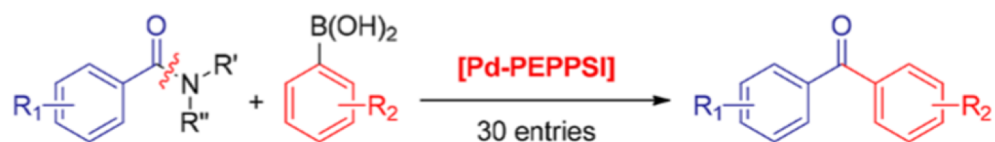
Entry		Recovered 92	Yield of Ketone 94
1		100%	0%
2		40%	60%
3		17%	81%

Amide Negishi Coupling

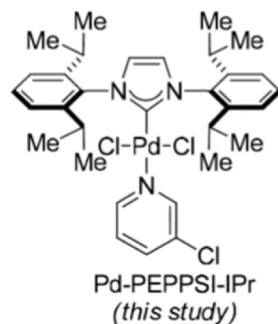
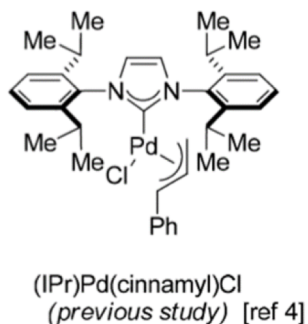
- Scope of Alkylzinc Reagent
- Tolerates Arene Substitution
 - -NMe₂, -CF₃, -F, -OMe
- **Application** towards a Pfizer GRM
 - Tolerates Aryl Ester



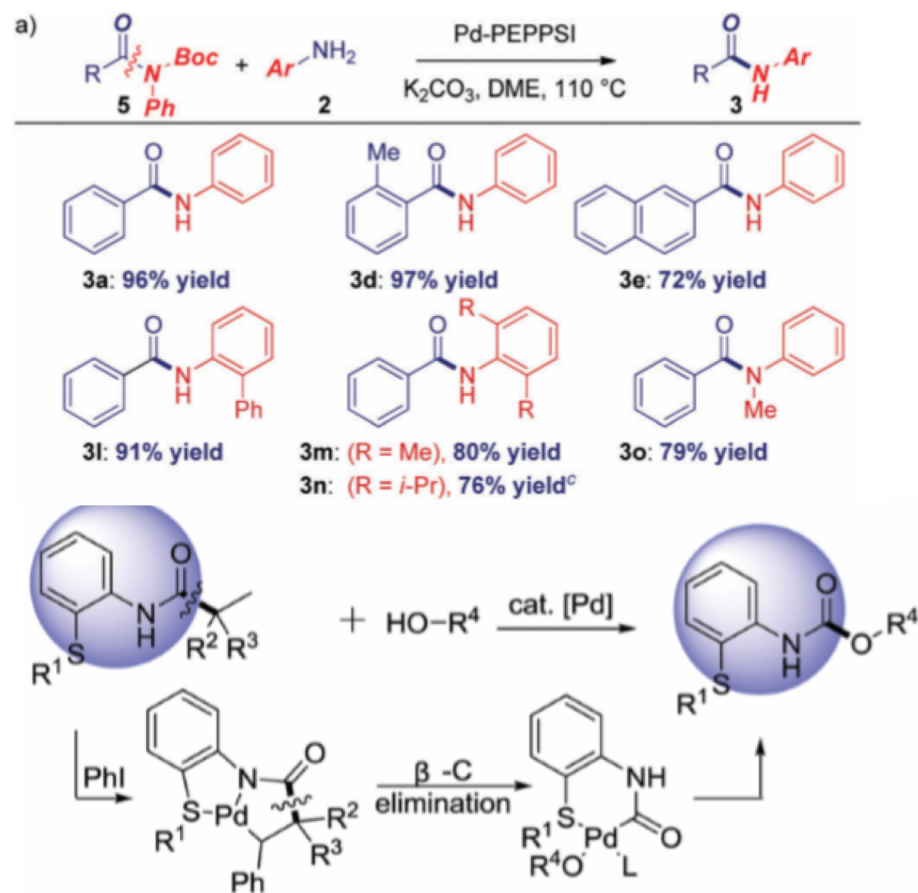
So what about Palladium?



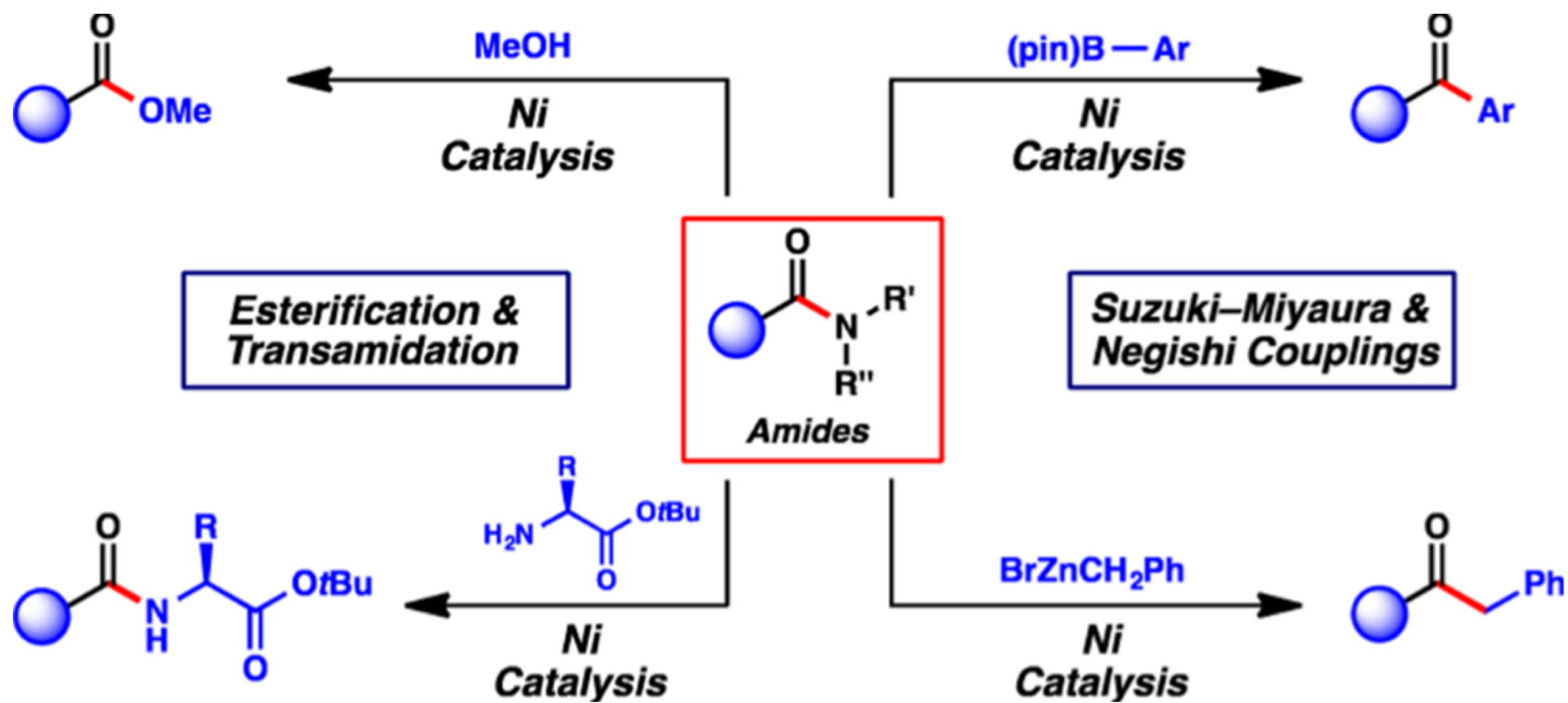
- general Pd-NHC catalyst for amide coupling
- high catalytic efficiency
- high reactivity for N -Boc-carbamates



Michal Szostak Group, Rutgers



Summary

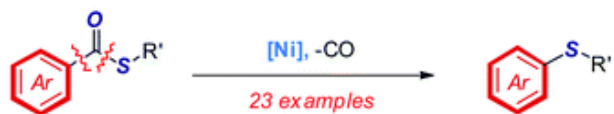


Questions?



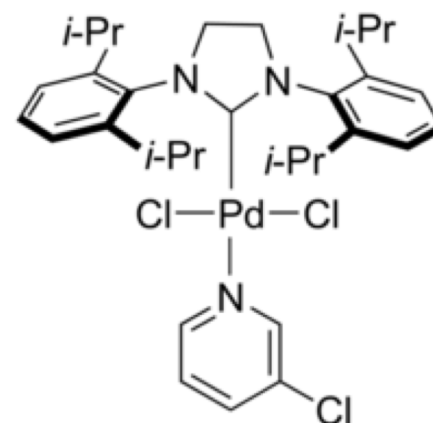
Extra I

Decarbonylative Coupling via Selective C-S Cleavage

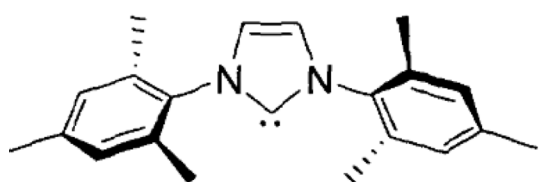


- selective C-S cleavage
- modular, air-stable Ni precatalyst
- carboxylic acid precursors
- broad tolerance
- high generality

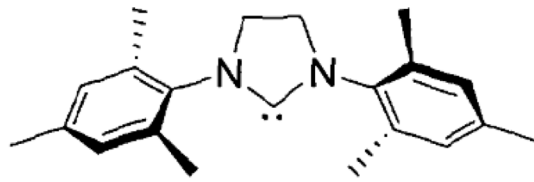
Chem. Commun., 2018, 54, 2130--2133



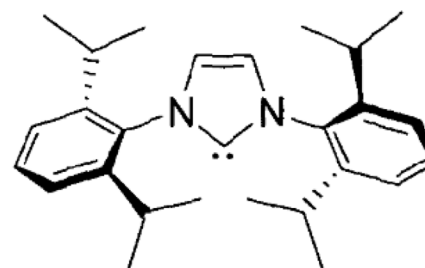
PEPPSI™-SIPr catalyst



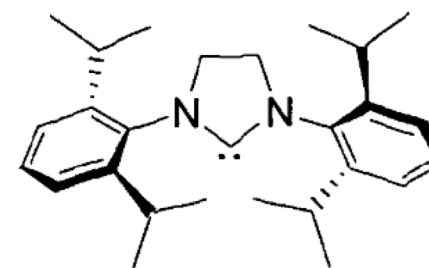
IMes



SIMes

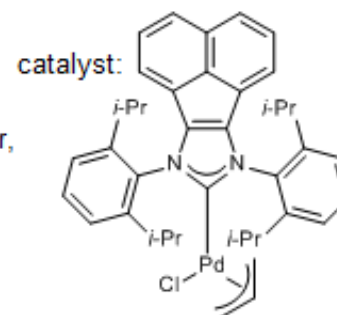
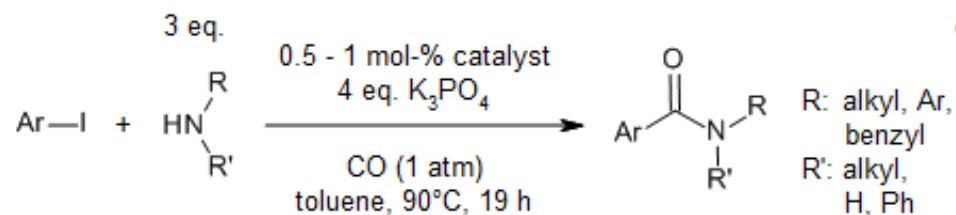


IPr



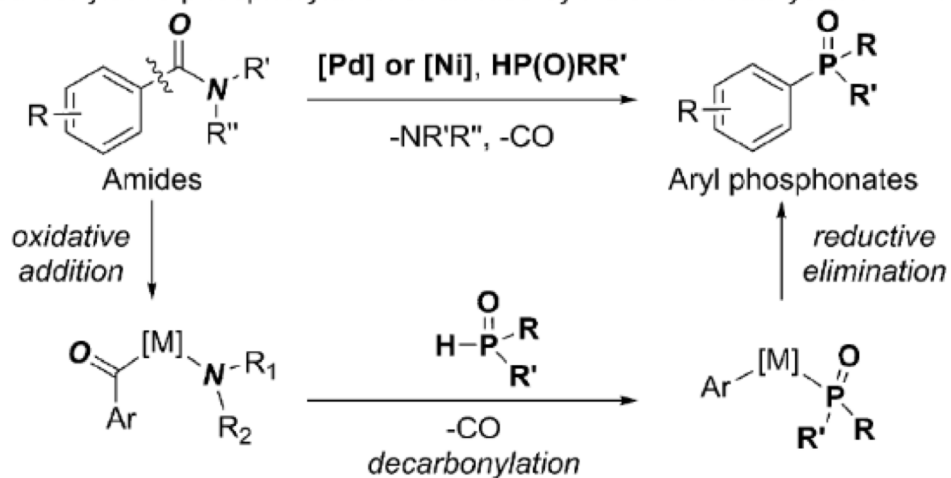
SIPr

Extra II



W. Fang, Q. Deng, M. Xu, T. Tu, *Org. Lett.*, **2013**, *15*, 3678-3681.

C) Decarbonylative phosphorylation of amides by Pd and Ni catalysis: **this study**



- Pd or Ni ■ benign amides ■ redox-neutral
- broad scope ■ orthogonal selectivity ■ aryl and vinyl

Angew.Chem.Int. Ed. 2017, *56*,12718-22

Extra III

