Breaking Amide Bonds using Nickel Catlysis

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

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

Austin Durham

Wipf Group

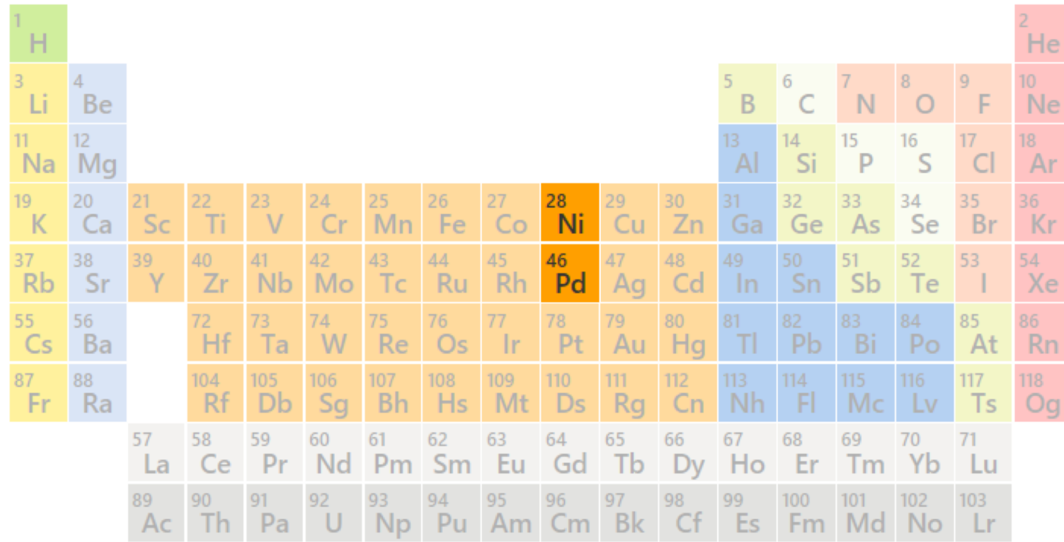
Current Literature 8/11/18

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

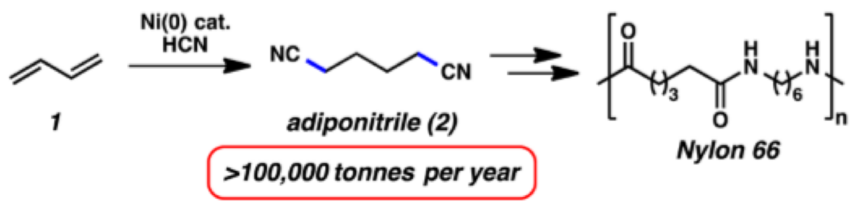
Nickel

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

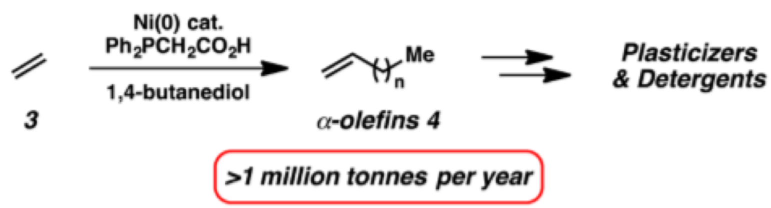


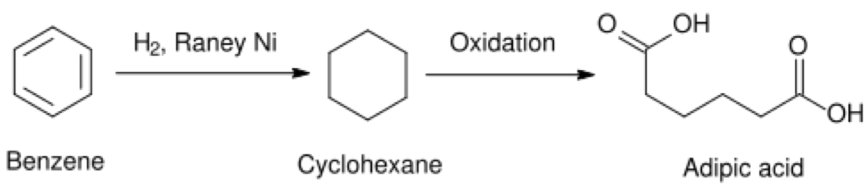
Nickel – Current Applications

DuPont's Hydrocyanation of Butadiene

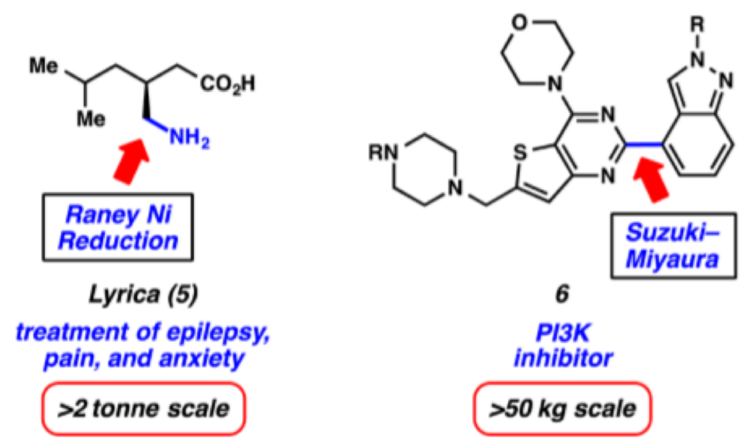


Shell Higher Olefin Process (SHOP)

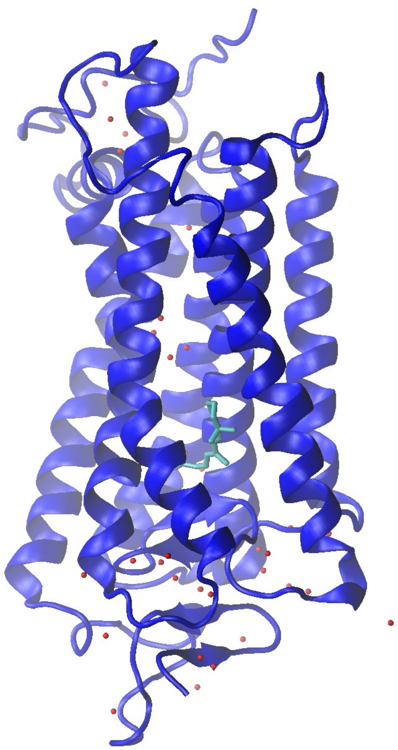


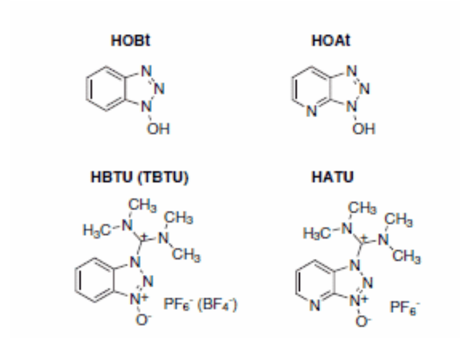


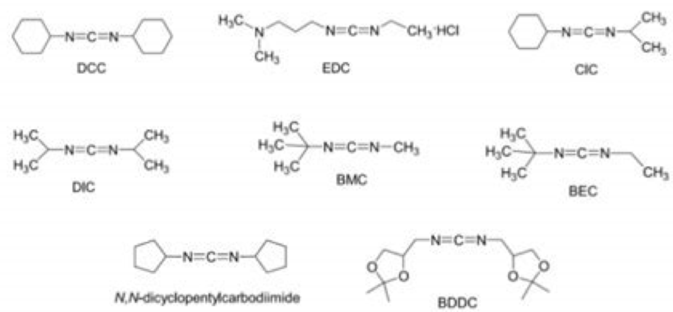
Nickel Catalysis in the Synthesis of Pharmaceuticals

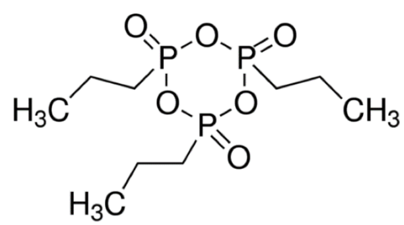


The Amide Bond



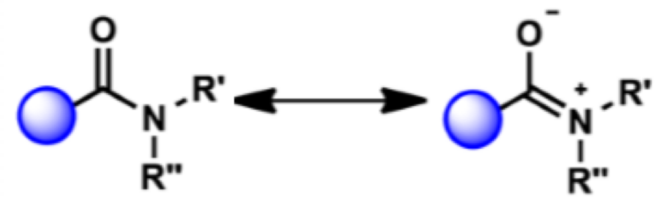






Amide Stability

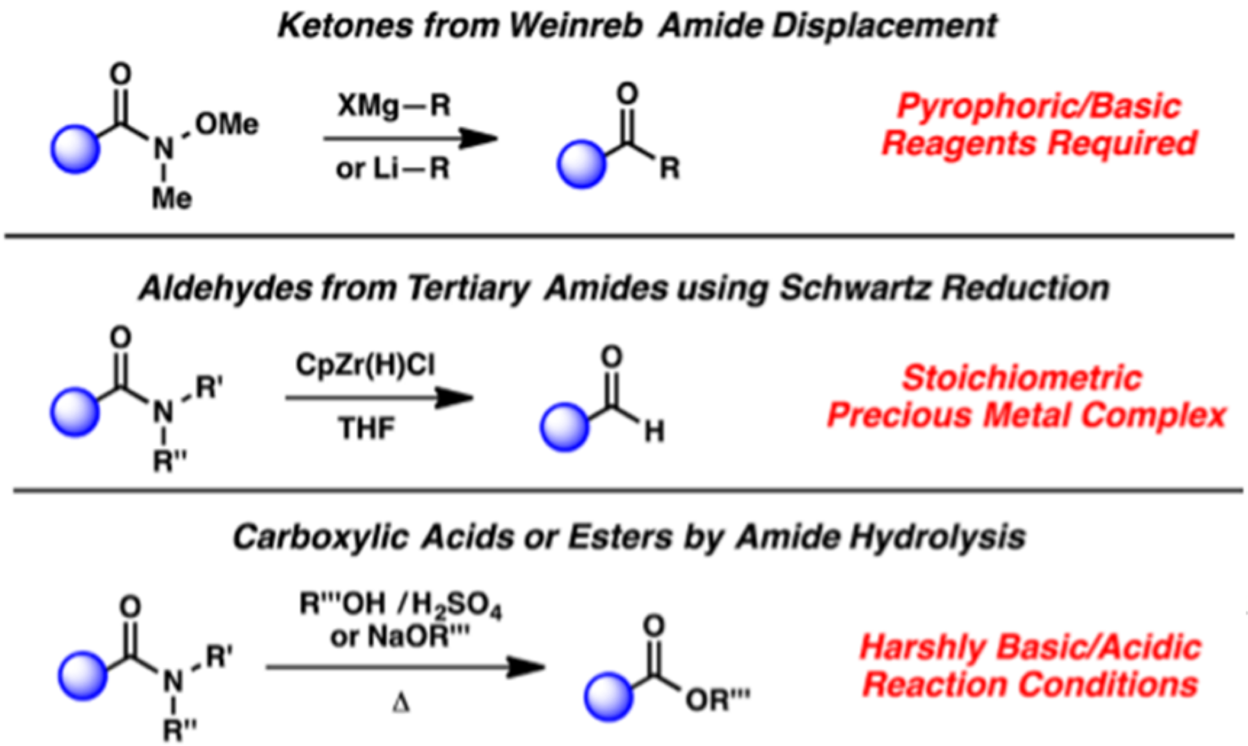
- *acidic and basic conditions*
- *reduction and oxidation*
- *palladium catalysis*
- *thermal conditions*



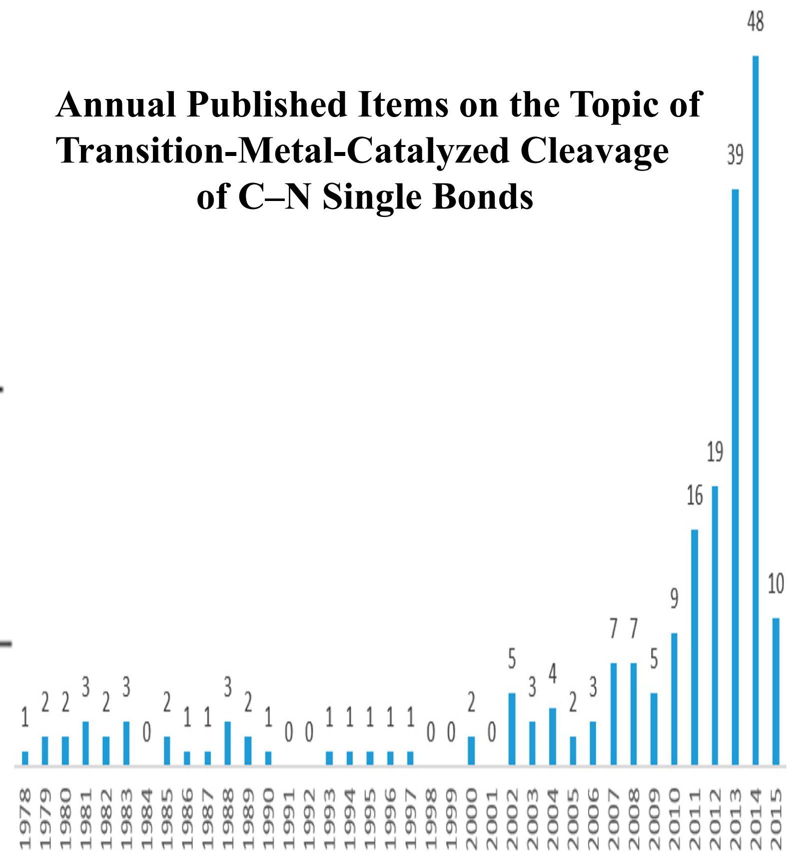
Amide Resonance Stabilization

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

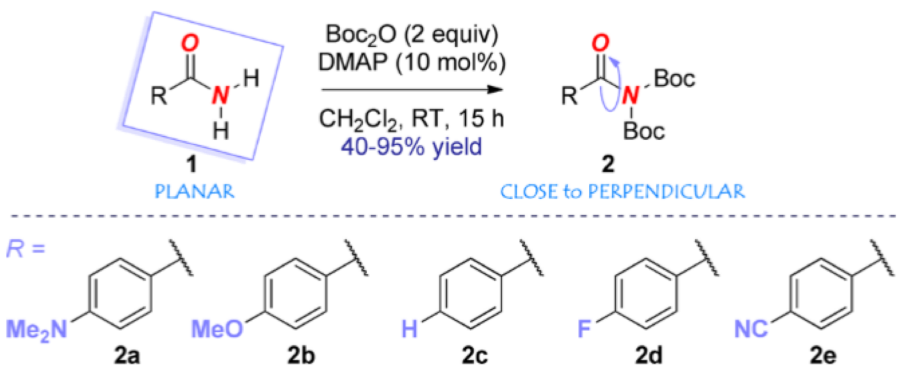
Amide Cleavage Precedence



Common Synthetic Methods for Amide C–N Bond Cleavage



Breaking Amides



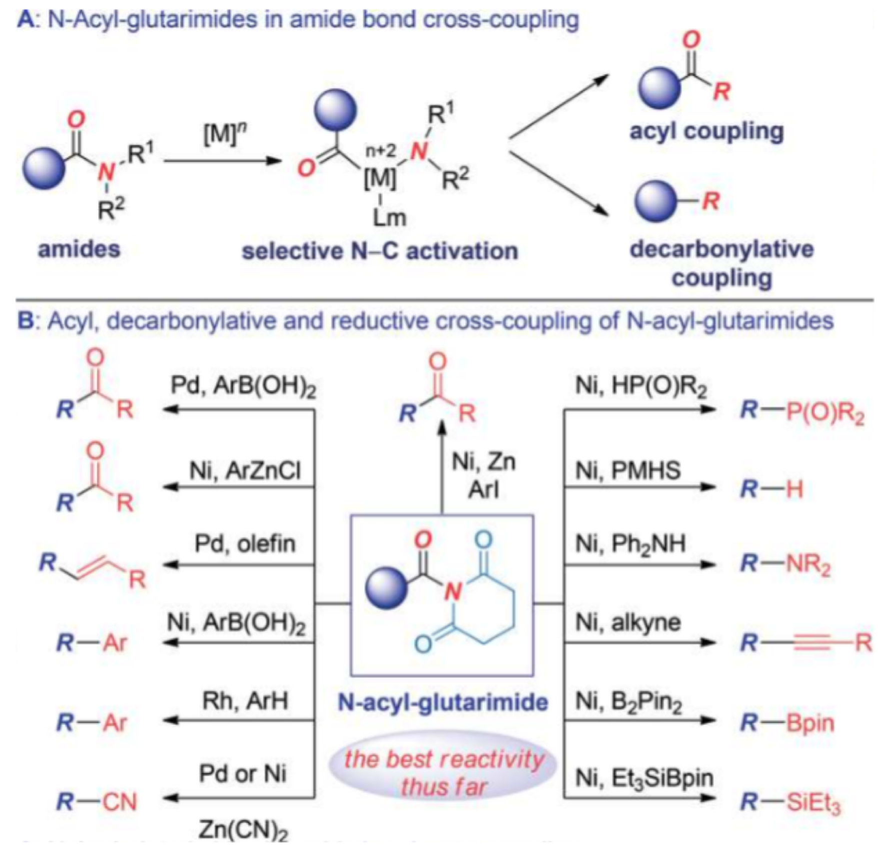
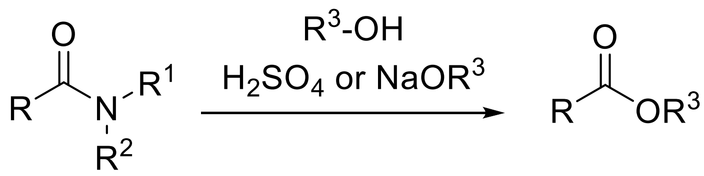
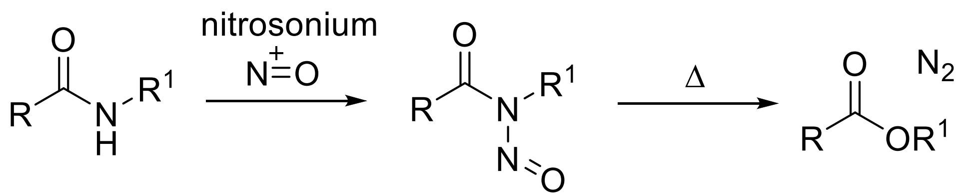


Figure 1. A) General pathways in amide N–C bond activation. B) *N*-Acyl-glutarimides in N–C amide bond cross-coupling: the most reactive amides and privileged scaffolds for reaction discovery.

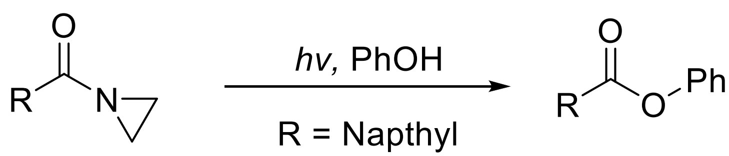
Amide to Ester Precedence



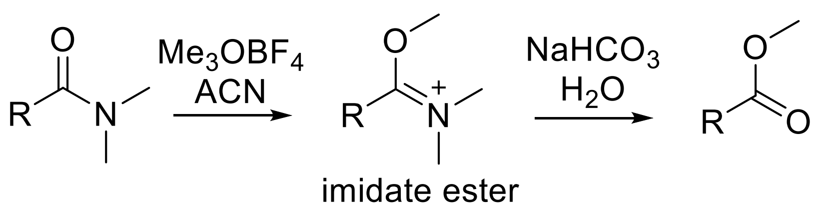
Direct Hydrolysis
Requires Strong Acid/ Base
Often High Heat



Nitrosation and Rearrangement
NO donor often Nitric Acid
Strong Electrophile



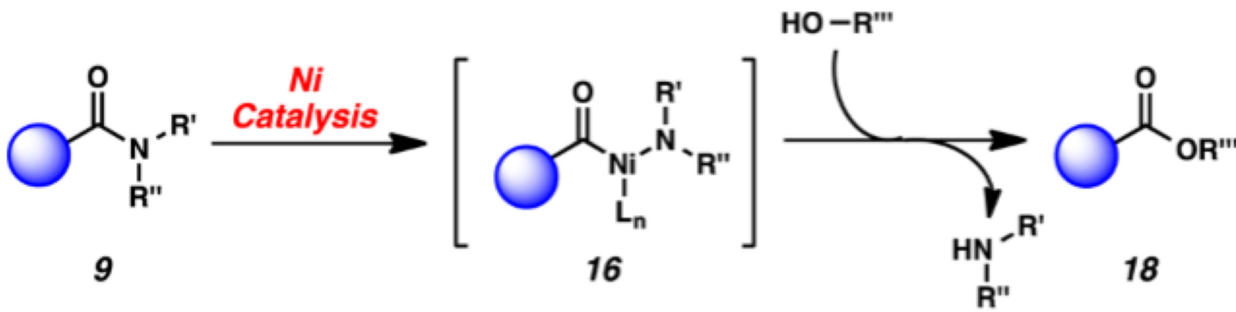
N-Acyl Aziridines
Limited Scope



Keck Methylation/Hydrolysis
Trimethyl Oxonium /
Strong Electrophile

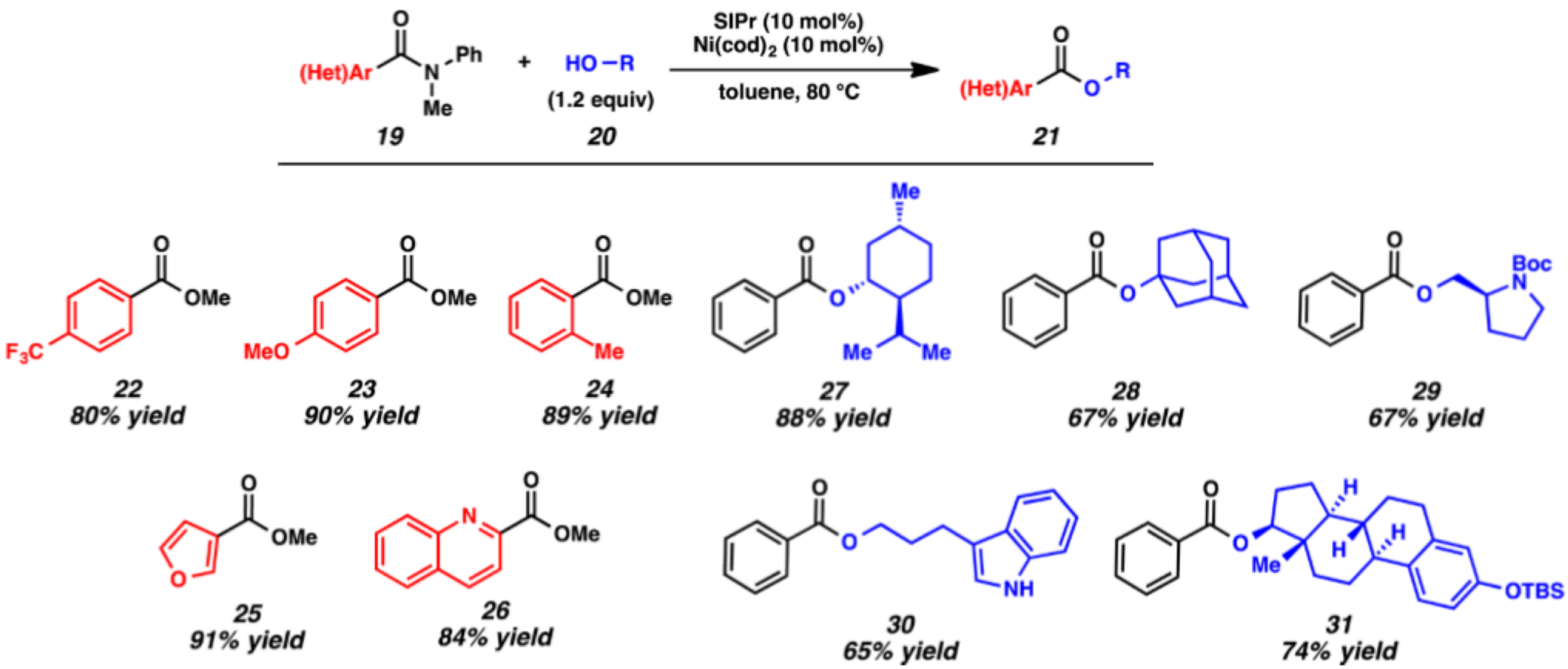
J. Am. Chem. Soc. **1977**, 22, 6011-6014
Bull. Chem. Soc. Jpn. **1982**, 55, 1484−1488.
Tetrahedron. **2000,** 56, 9875−9883.

Amide to Ester

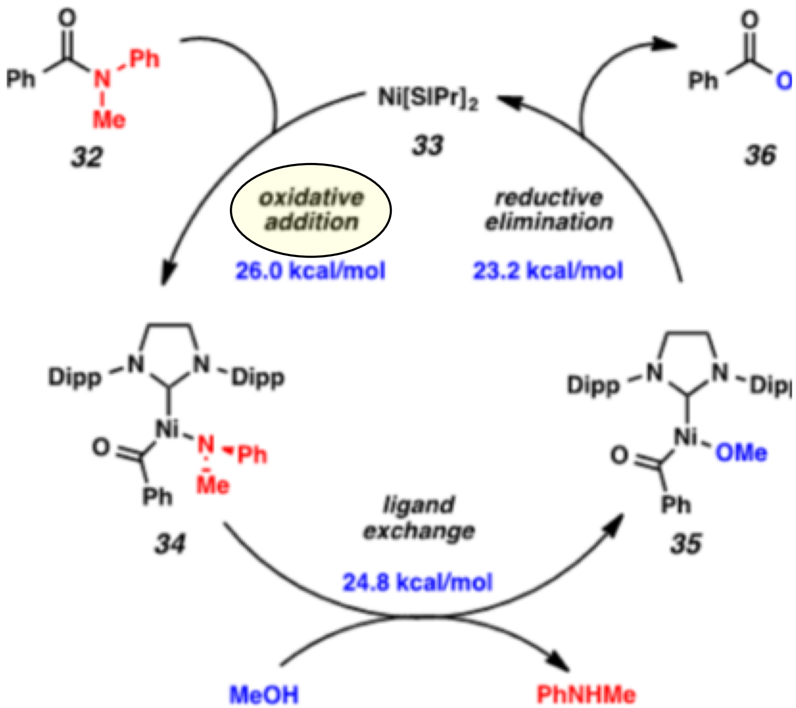


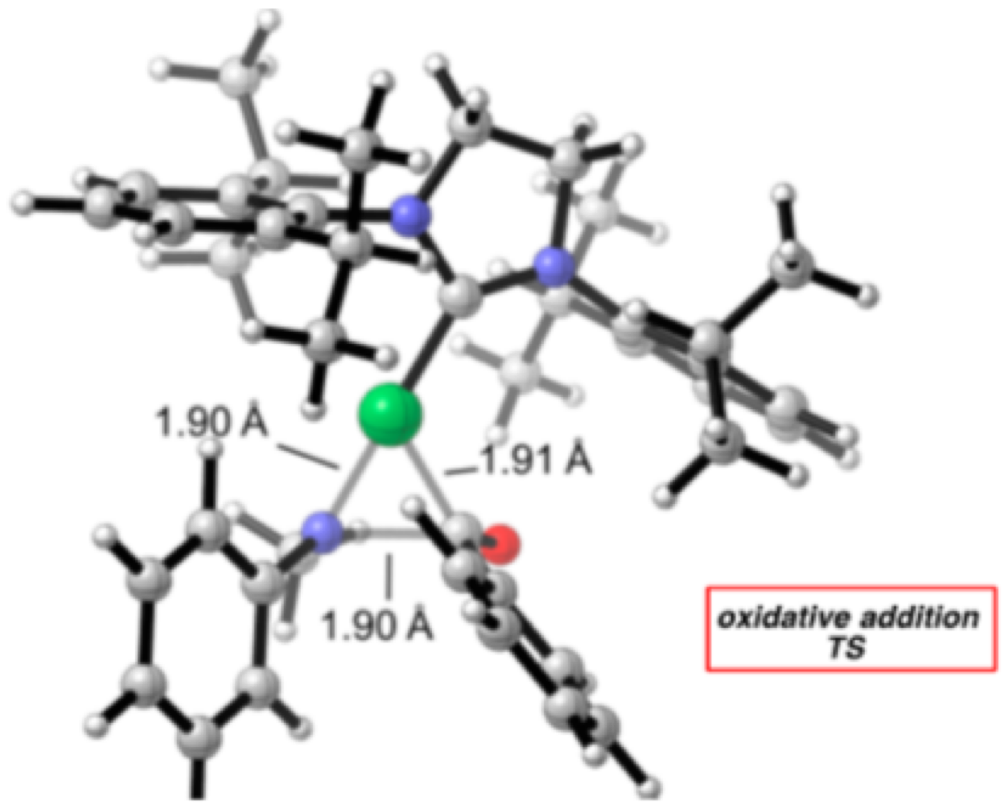
- *Underdeveloped transformation*
- *Amide activation via Ni catalysis*
- *Use of amides as synthons*

Amide to Ester Scope



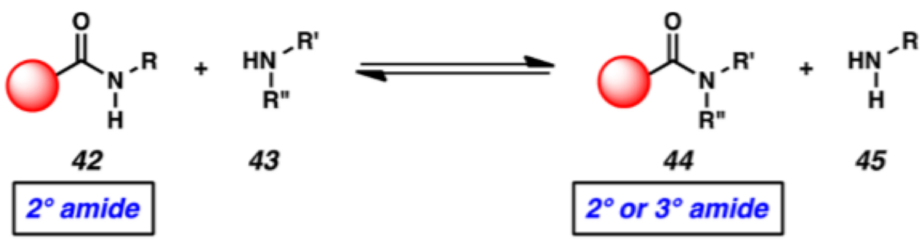
Amide to Ester Examined



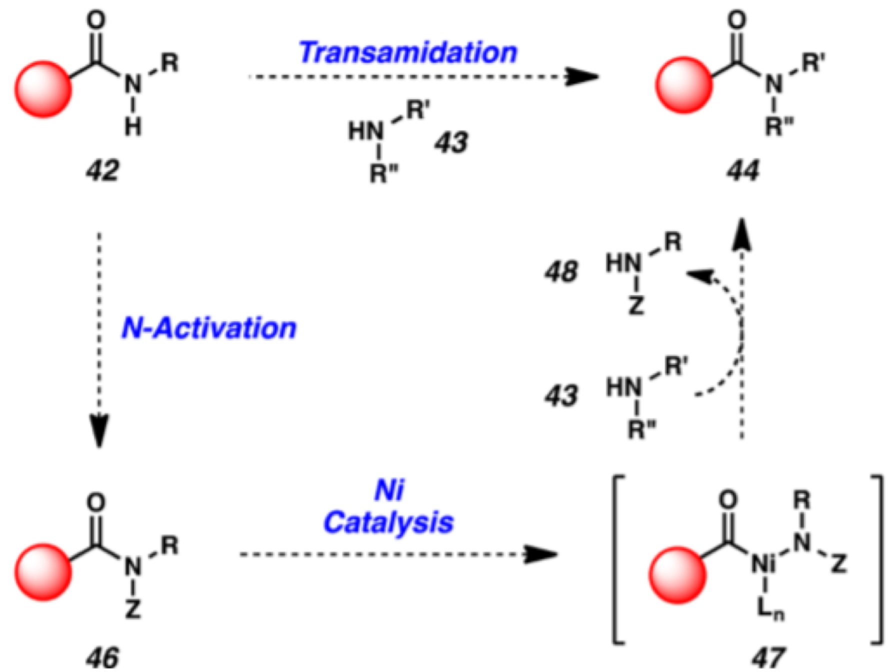


Transamidation Strategy

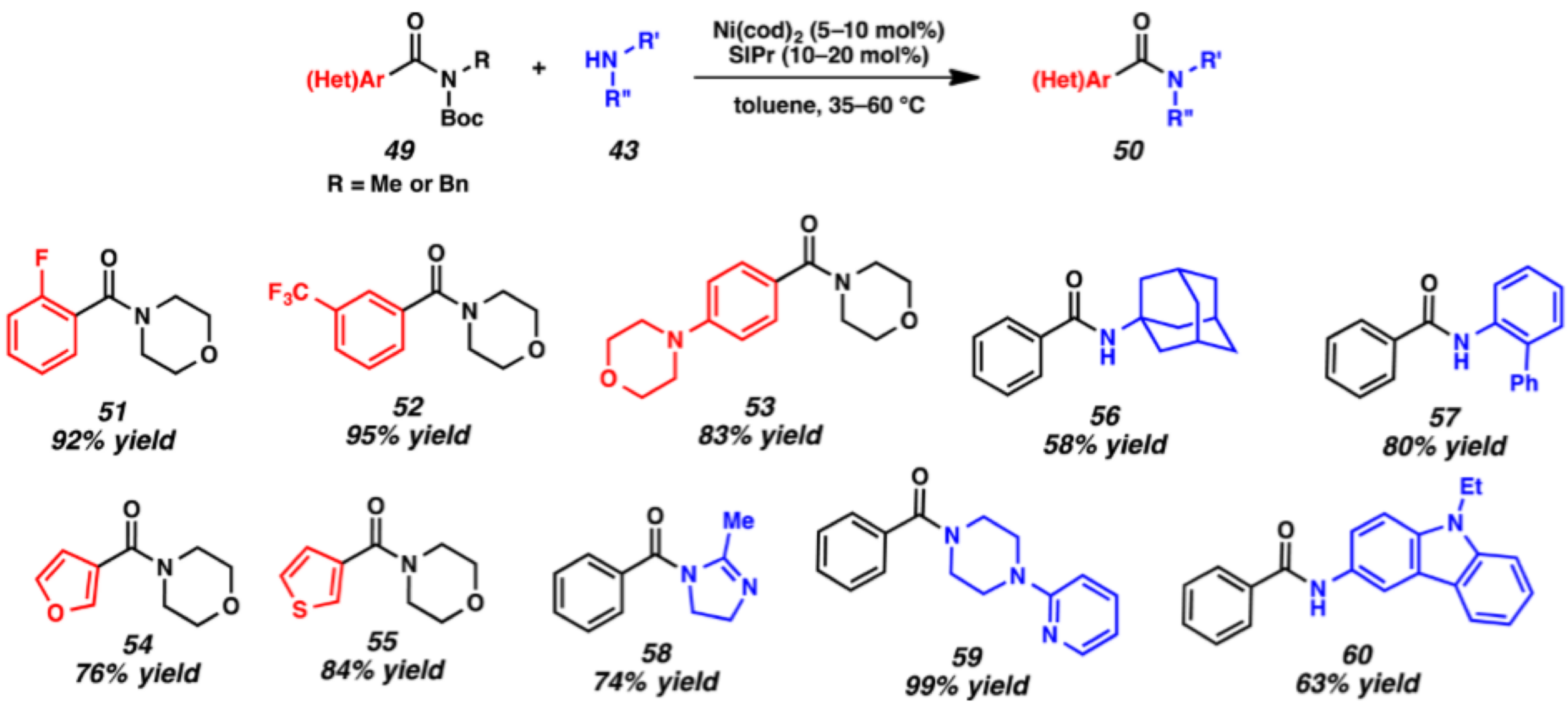
- Requires *Activation* of Amide
- Generally **Thermoneutral**



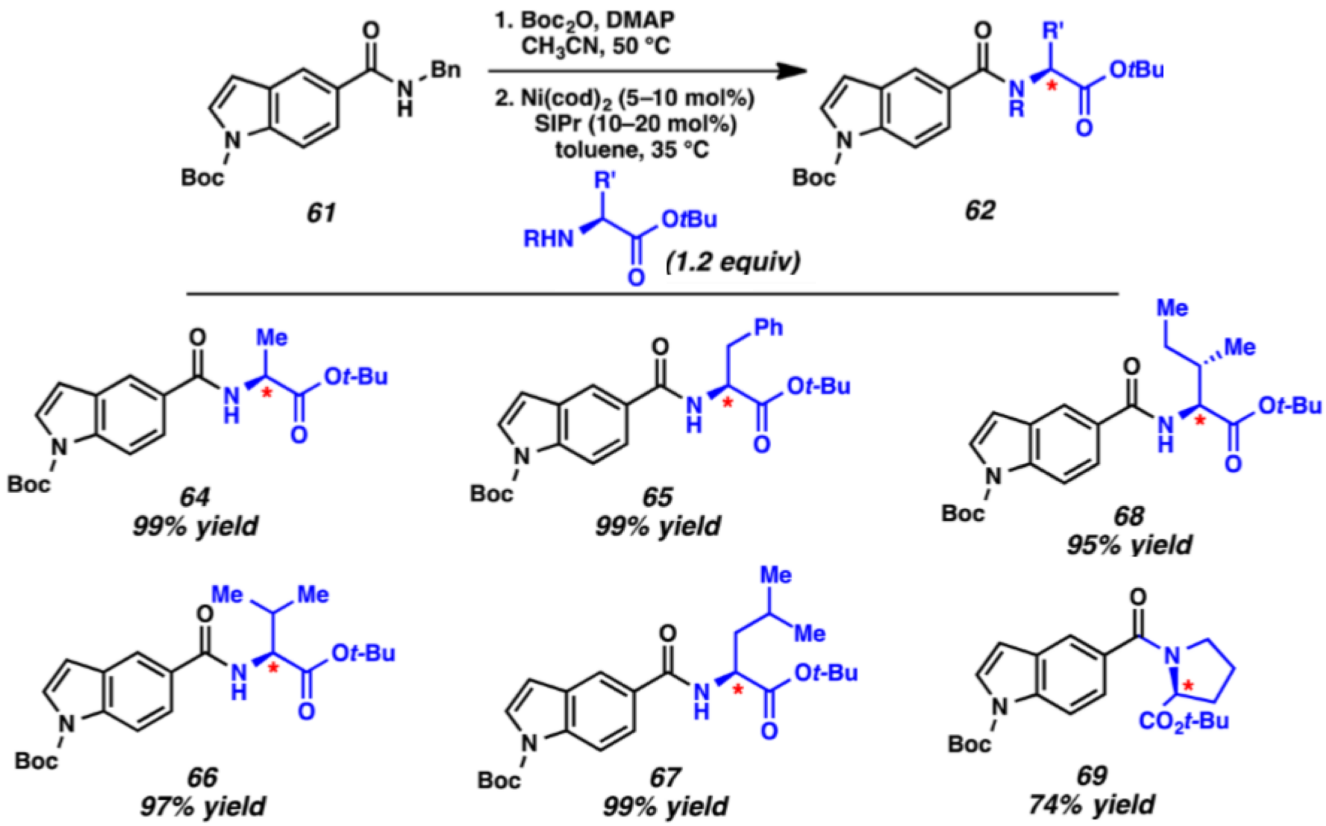
- *High activation barrier due to amide resonance stability*
- *Unfavorable thermodynamics/thermoneutral process*



Transamidation Scope

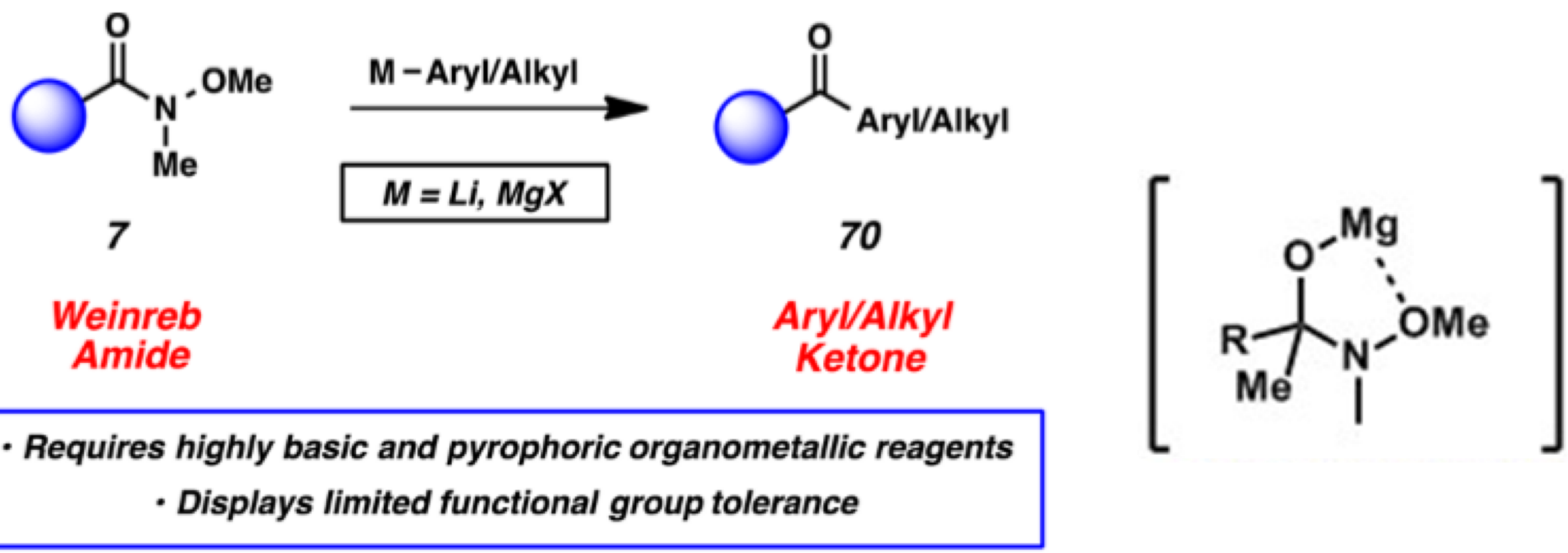


Two-Step Transamidation

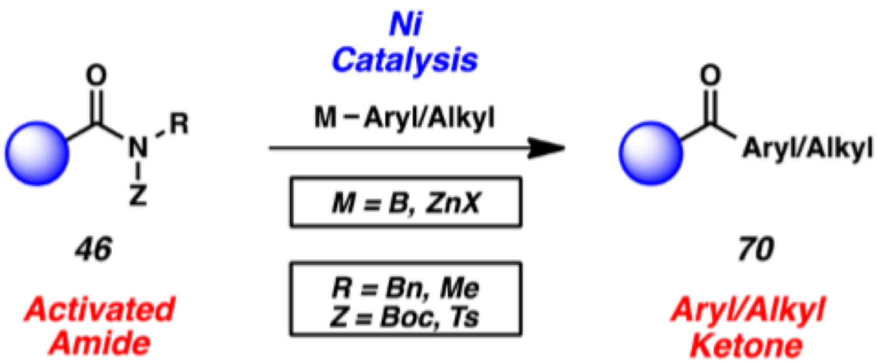


Carbon-Carbon Bond Formation

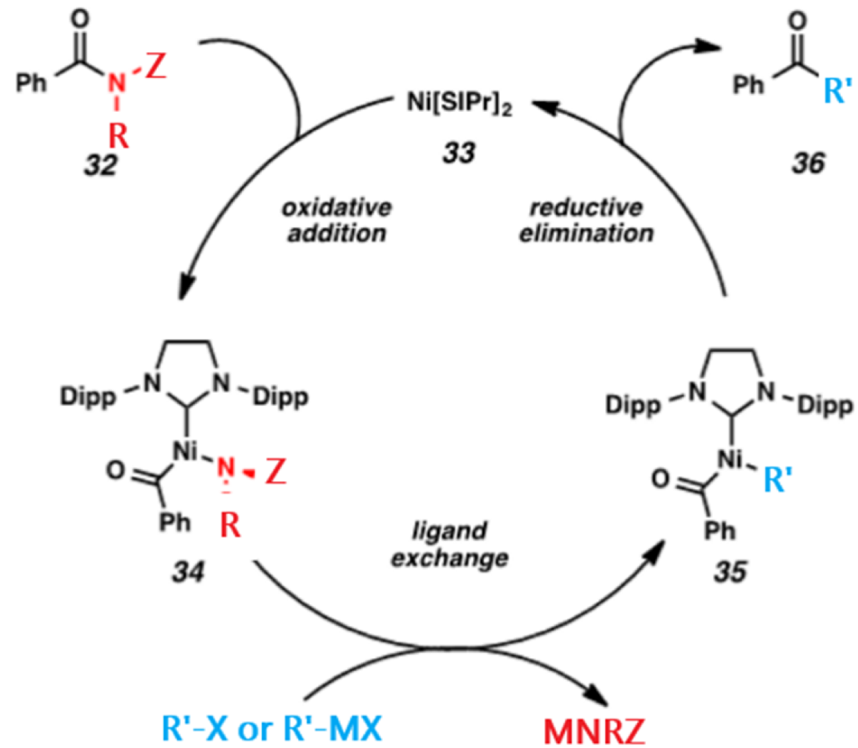
- Weinreb-Amide (Amide to Ketone)



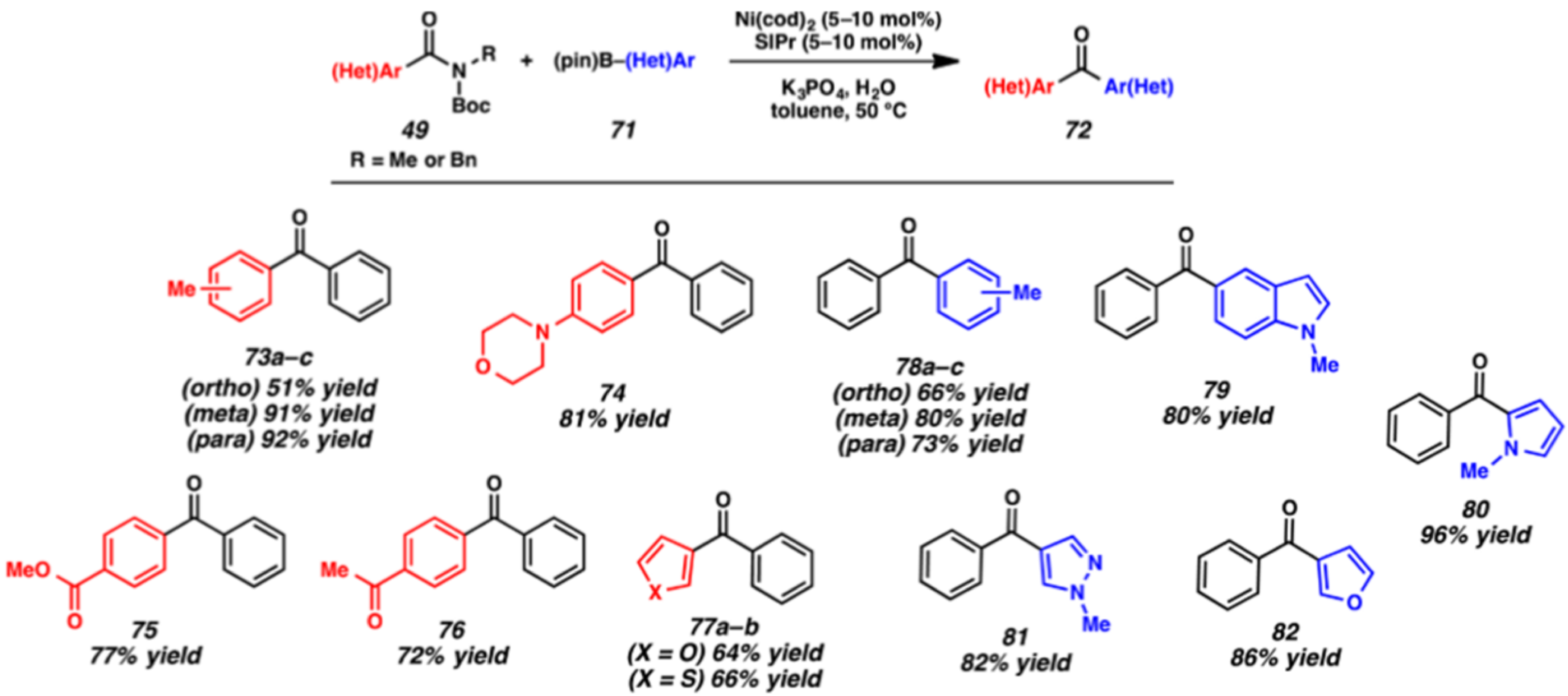
Carbon-Carbon Bond Formation



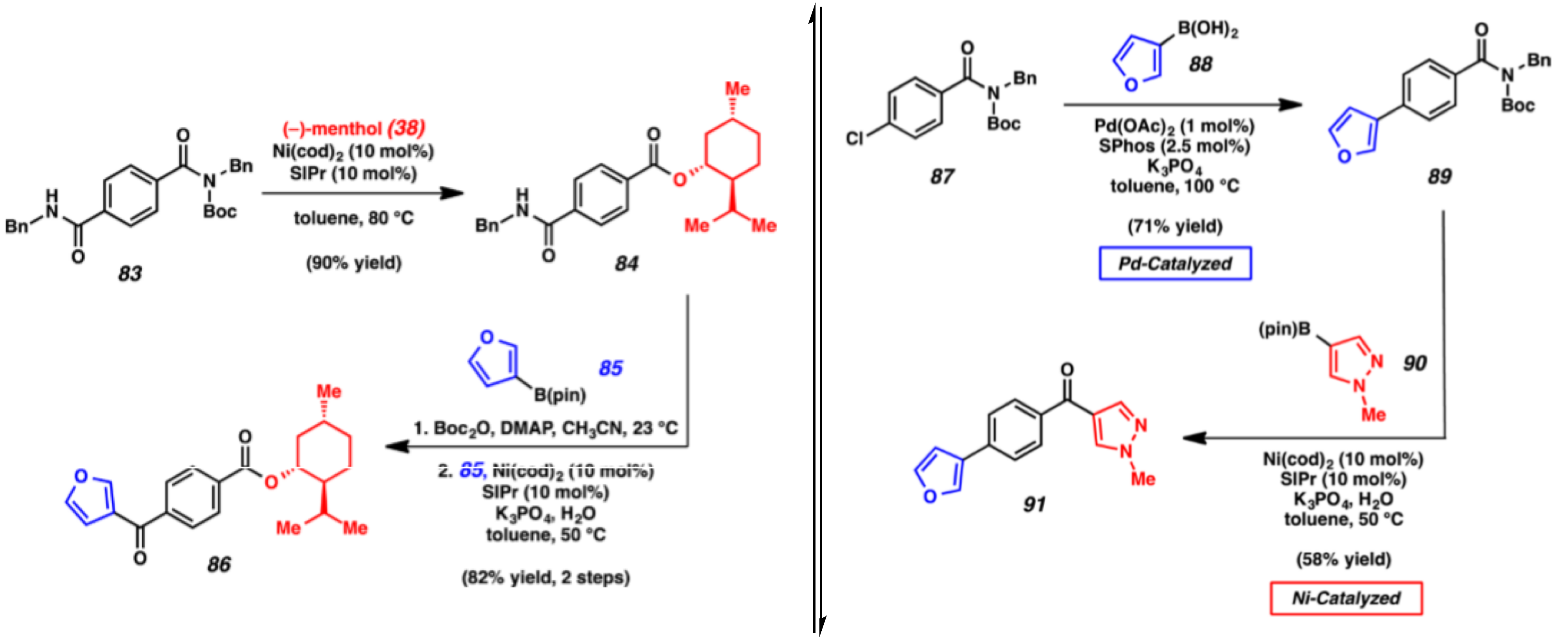
- Non-precious metal catalyst
- Mild reaction conditions
- Broad functional group tolerance



Carbonyl-Aryl Bond Formation



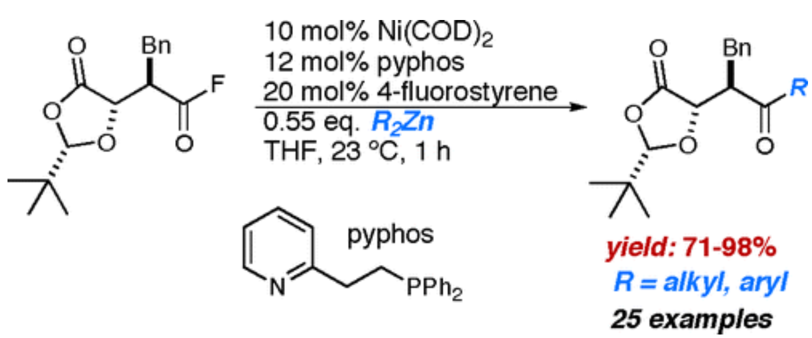
Carbonyl-Aryl Bond Formation

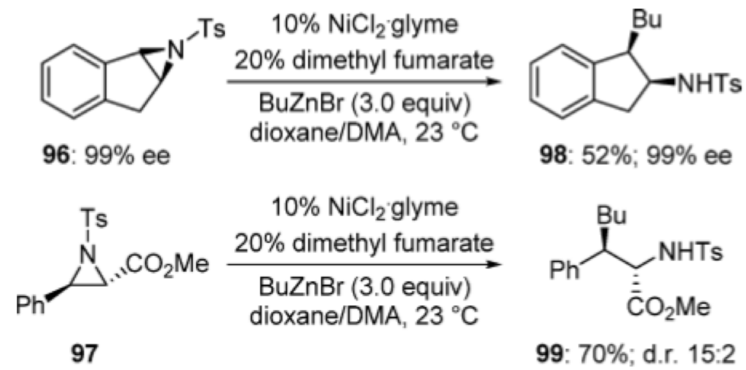


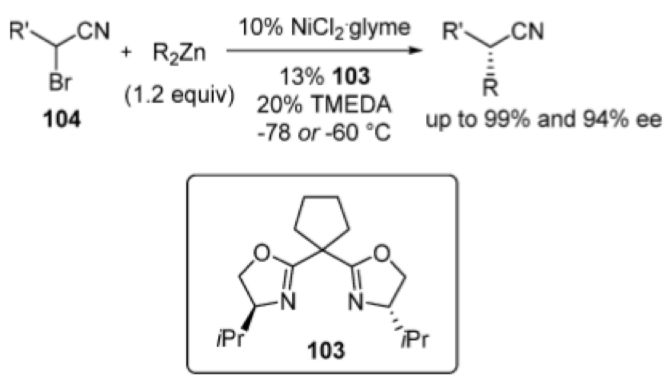
Carbonyl-Alkyl Bond Formation - Negishi

- 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



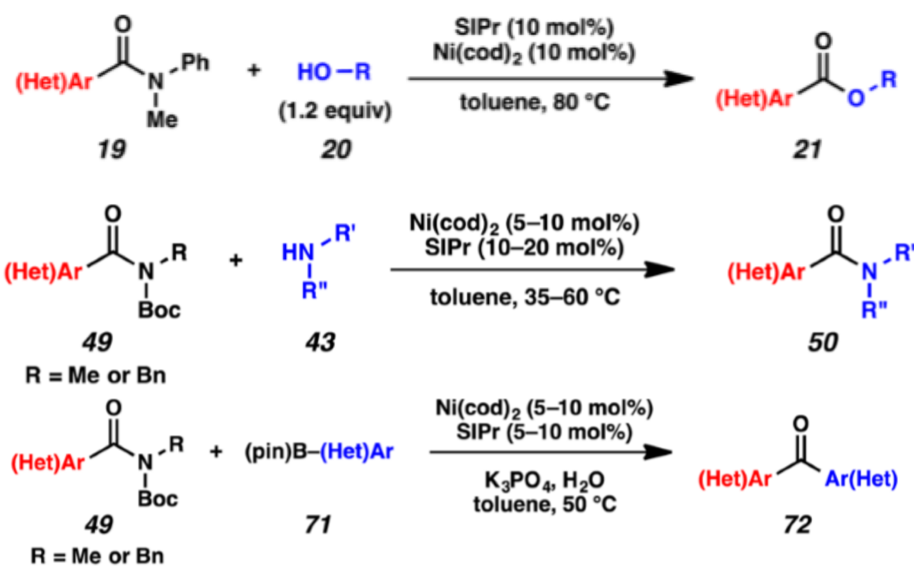


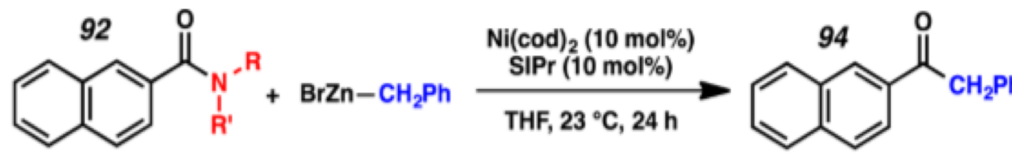


N-Substitution allows for Negishi Coupling

- N-Tosyl Amides gave max conversion

Previously,

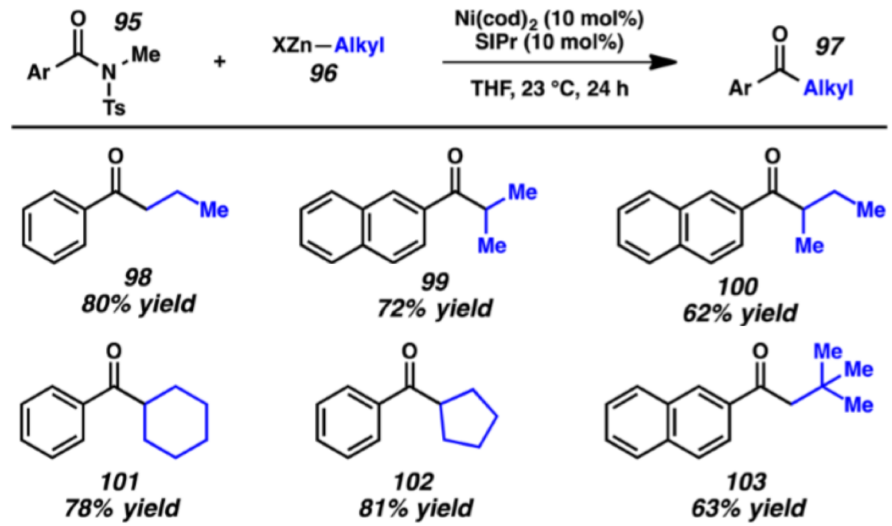


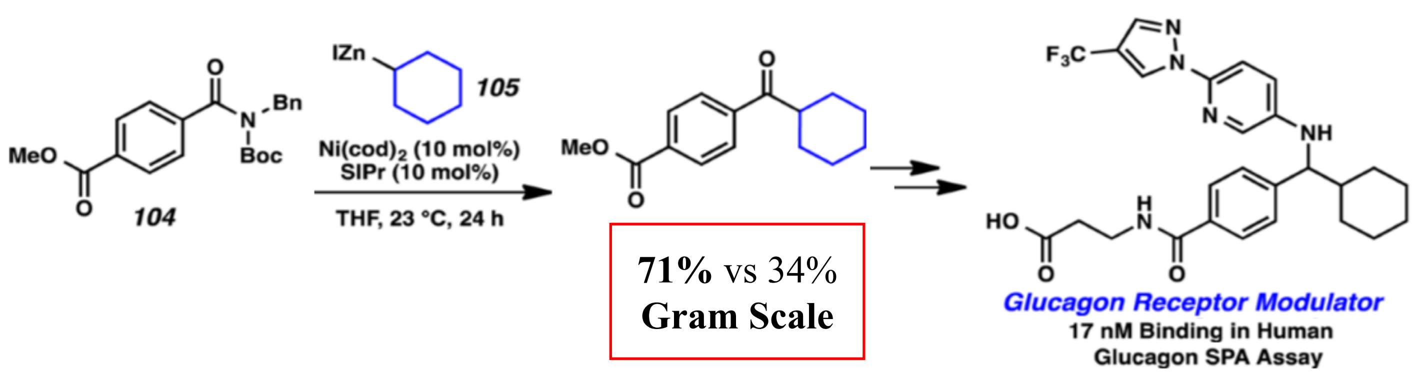


Entry	N(R)R'		*Recovered 92*	*Yield of Ketone 94*
1	N(Me)Ph	*92a*	*100%*	*0%*
2	N(Bn)Boc	*92b*	*40%*	*60%*
3	N(Me)Ts	*92c*	*17%*	*81%*

Amide Negishi Coupling

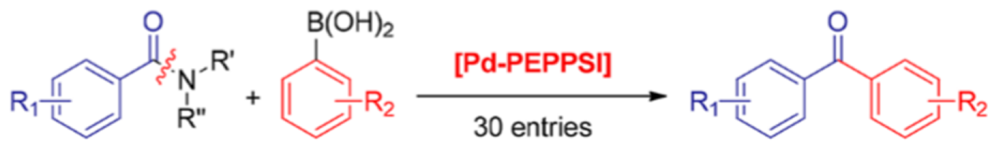
- Scope of Alkylzinc Reagent
- Tolerates Arene Substitution
  - $-NMe_2$, $-CF_3$, -F, -OMe
- **Application** towards a Pfizer GRM
  - Tolerates Aryl Ester



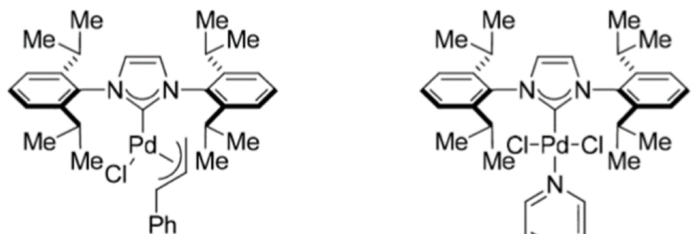


71% vs 34%
Gram Scale

So what about Palladium?



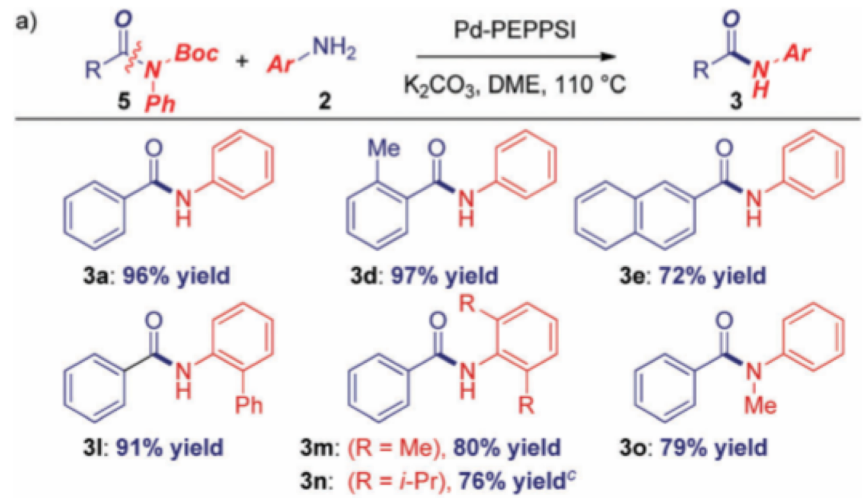
- general Pd-NHC catalyst for amide coupling
- high catalytic efficiency
- high reactivity for *N*-Boc-carbamates

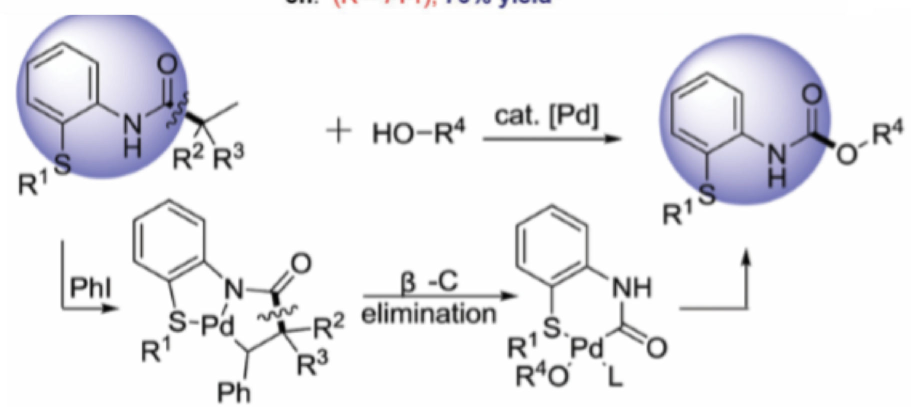


(IPr)Pd(cinnamyl)Cl *(previous study)* [ref 4]

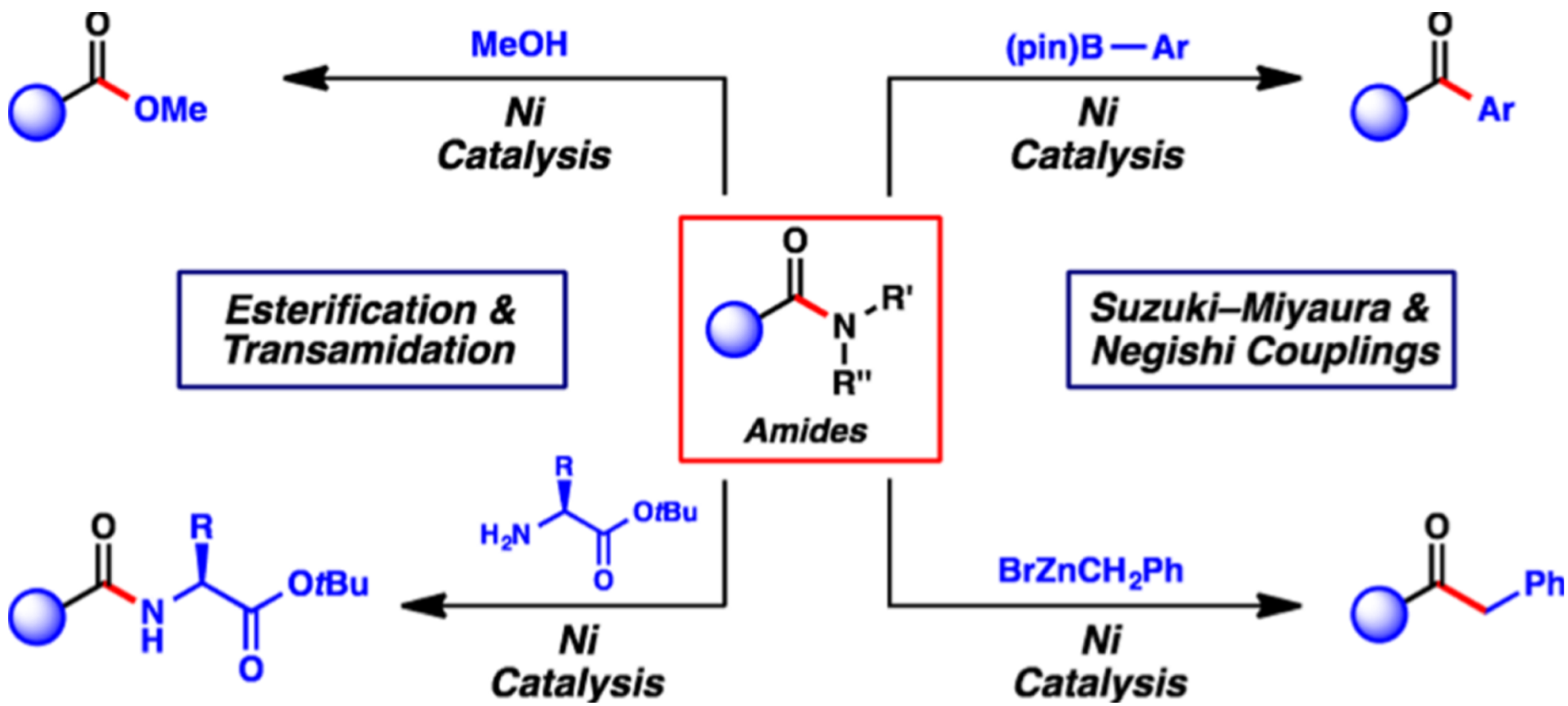
Pd-PEPPSI-IPr *(this study)*

Michal Szostak Group, Rutgers





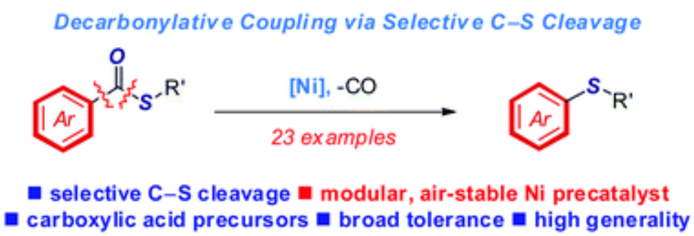
Summary



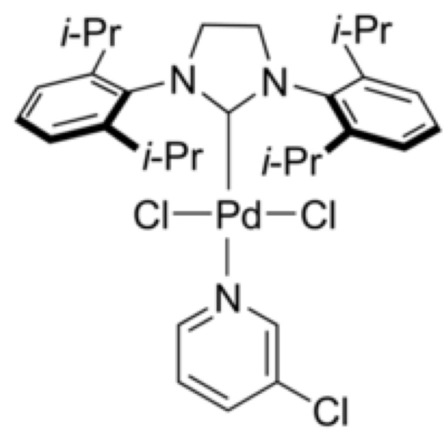
MeOH
Ni
Catalysis
OMe
(pin)B—Ar
Ni
Catalysis
Ar
Esterification &
Transamidation
R'
N
R''
Amides
Suzuki–Miyaura &
Negishi Couplings
R
H2N
OtBu
Ni
Catalysis
N
H
OtBu
BrZnCH2Ph
Ni
Catalysis
Ph

Questions?

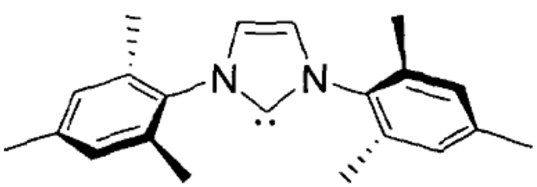
Extra I



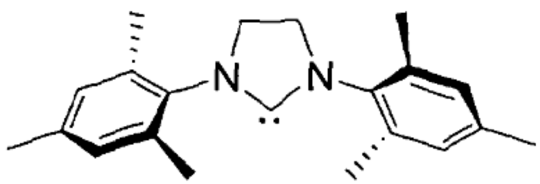
Chem. Commun., 2018, 54, 2130--2133



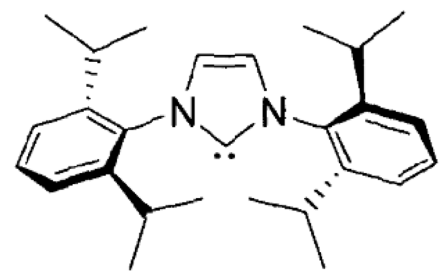
PEPPSI™-SIPr catalyst



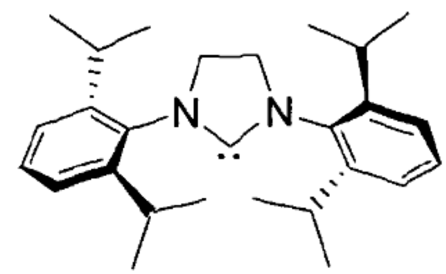
IMes



SIMes

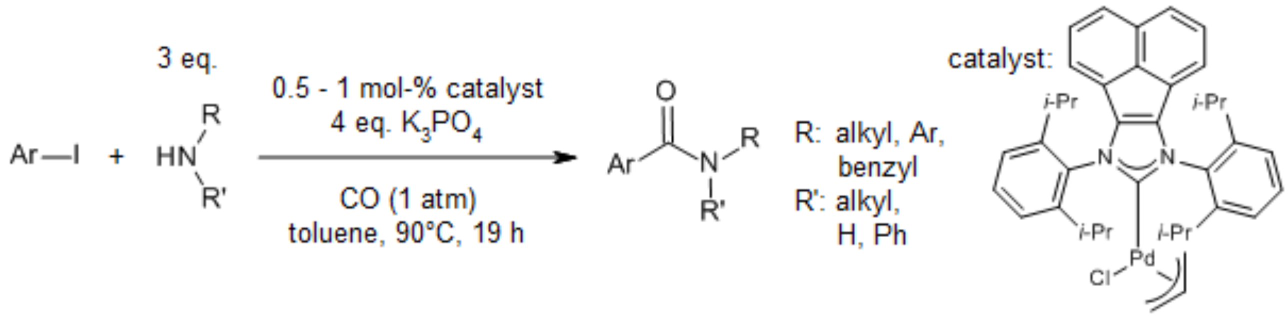


IPr



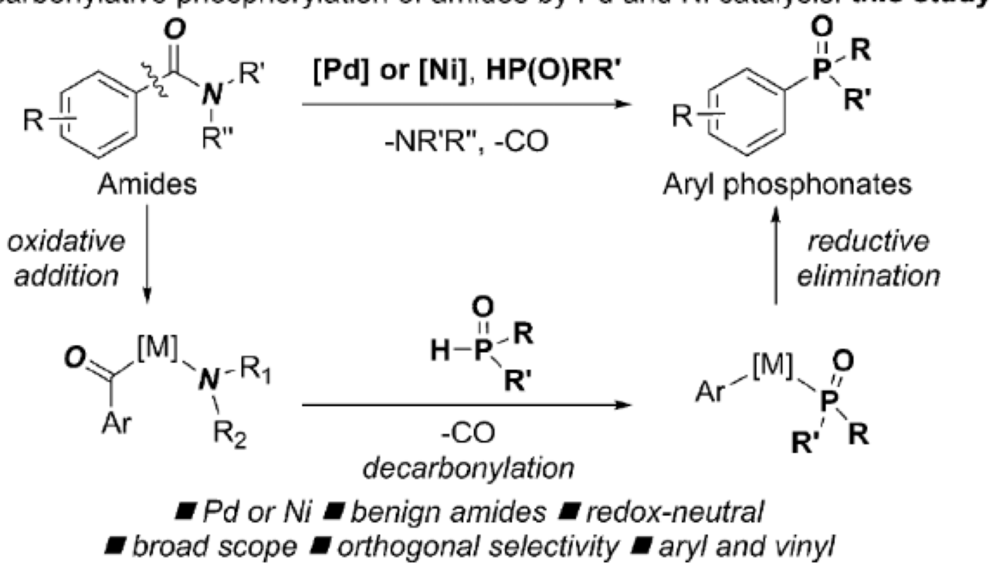
SIPr

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***



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

Extra III