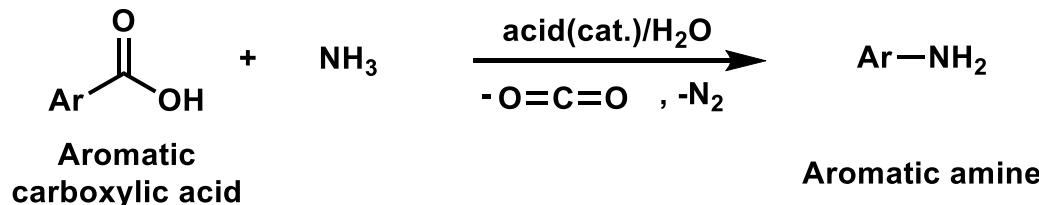


# Catalytic Ester and Amide to Amine Interconversion: Nickel-Catalyzed Decarbonylative Amination of Esters and Amides by C-O and C-C Bond Activation

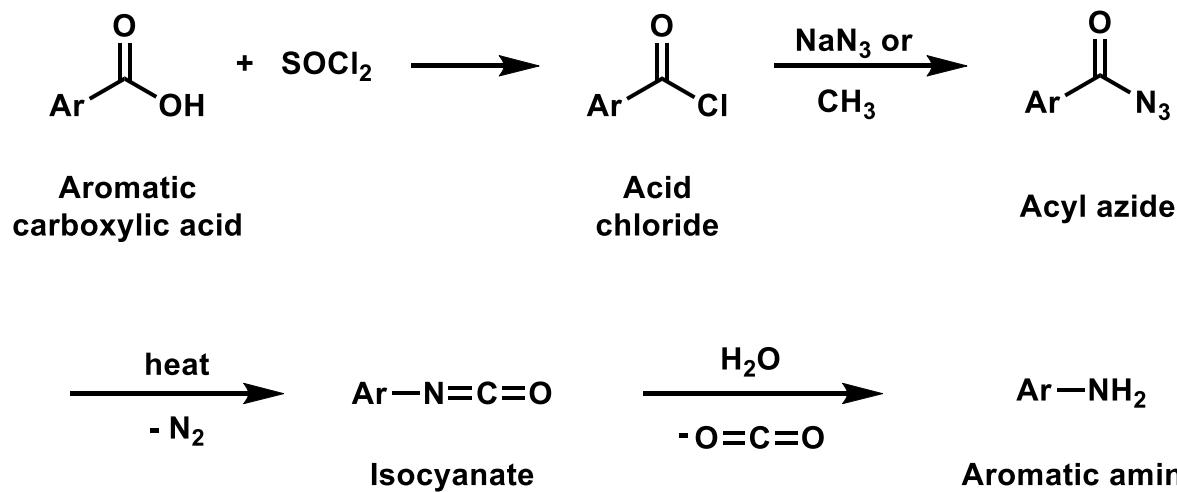
Reporter: Feifei Song  
Supervisor: Prof. Yong Huang  
2017. 04. 24

# Classical carboxylic acid to amine interconversions

## ➤ Schmidt reaction



## ➤ Curtius rearrangement

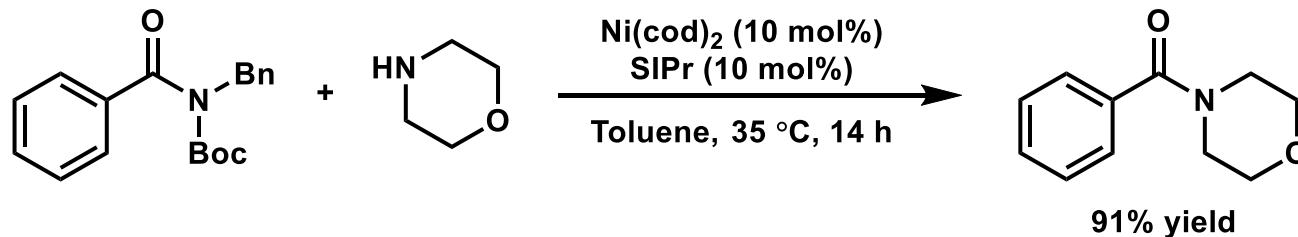
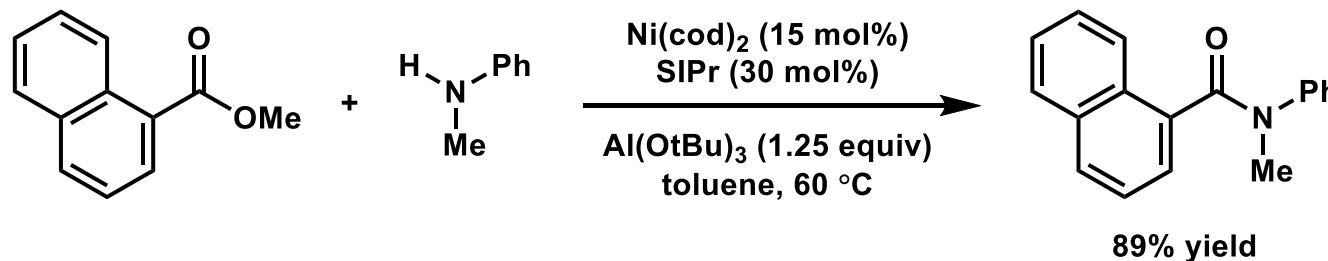


# Classical amide-bond formations

## ➤ Ester amine coupling



## ➤ Recent nickel-catalyzed protocol

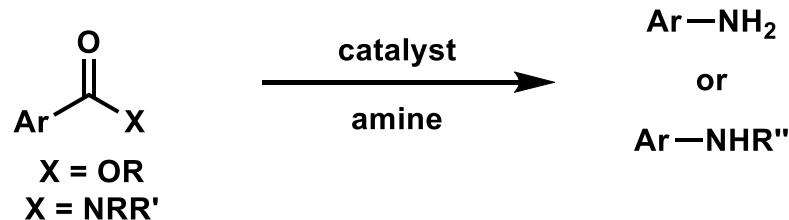


# This work

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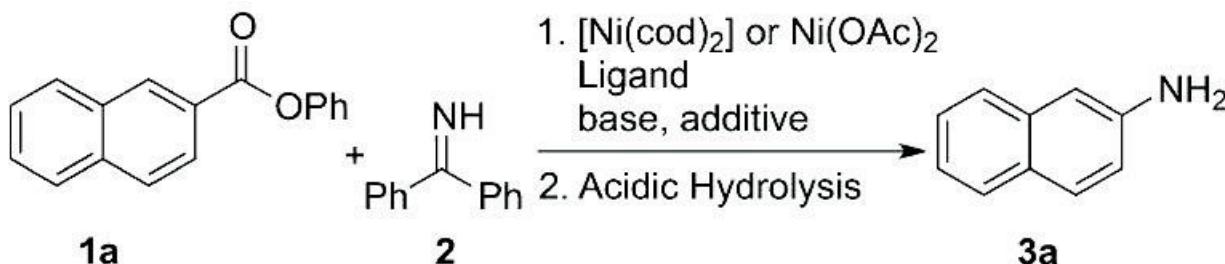
- Direct transformation of ester or amides into amines

C-N bond formation



New decarbonylative amination of carboxylic and derivatives.

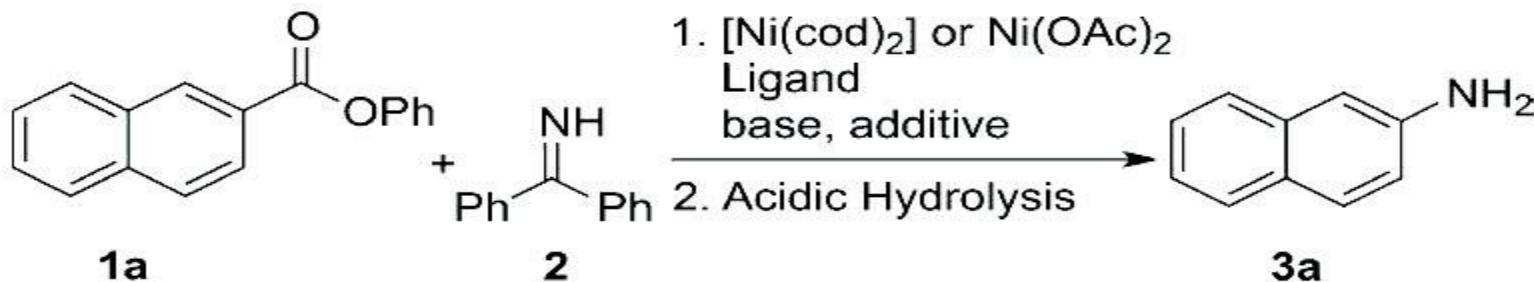
# Optimization of the reaction conditions



Entry	[Ni]	Ligand (x mol %)	Base (2 equiv)	Additive (2 equiv)	Yield [%] <sup>[b]</sup>
1	[Ni(cod) <sub>2</sub> ]	IPr·HCl (20)	Cs <sub>2</sub> CO <sub>3</sub>	—	0
2	[Ni(cod) <sub>2</sub> ]	P <sup>n</sup> Bu <sub>3</sub> (20)	Cs <sub>2</sub> CO <sub>3</sub>	—	0
3	[Ni(cod) <sub>2</sub> ]	PCy <sub>3</sub> (20)	Cs <sub>2</sub> CO <sub>3</sub>	—	0
4	[Ni(cod) <sub>2</sub> ]	dcype (10)	Cs <sub>2</sub> CO <sub>3</sub>	—	14
5	[Ni(cod) <sub>2</sub> ]	dcypf (10)	Cs <sub>2</sub> CO <sub>3</sub>	—	trace
6	[Ni(cod) <sub>2</sub> ]	dcype (20)	Cs <sub>2</sub> CO <sub>3</sub>	—	17
7	[Ni(cod) <sub>2</sub> ]	dcype (20)	Li <sub>2</sub> CO <sub>3</sub>	—	21
8	[Ni(cod) <sub>2</sub> ]	dcype (20)	K <sub>2</sub> CO <sub>3</sub>	—	31
9	[Ni(cod) <sub>2</sub> ]	dcype (20)	Na <sub>2</sub> CO <sub>3</sub>	—	31
10	[Ni(cod) <sub>2</sub> ]	dcype (20)	K <sub>3</sub> PO <sub>4</sub>	—	42

[a] IPr·HCl=1,3-bis(2,6-diisopropylphenyl)imidazolium chloride, dcype=1,2-bis(dicyclohexylphosphino)-ethane, dcypf=1,1'-bis(dicyclohexylphosphino) ferrocene. Reaction conditions: phenyl naphthalene-2- carboxylate (**1a**; 0.2 mmol), benzophenone imine **2** (0.3 mmol), [Ni-(cod)<sub>2</sub>] (0.02 mmol), ligand (0.02 mmol or 0.04 mmol), base (0.4 mmol) in toluene (1 mL) at 160 °C, 12 h. [b] Yield of isolated products. 5

# Optimization of the reaction conditions

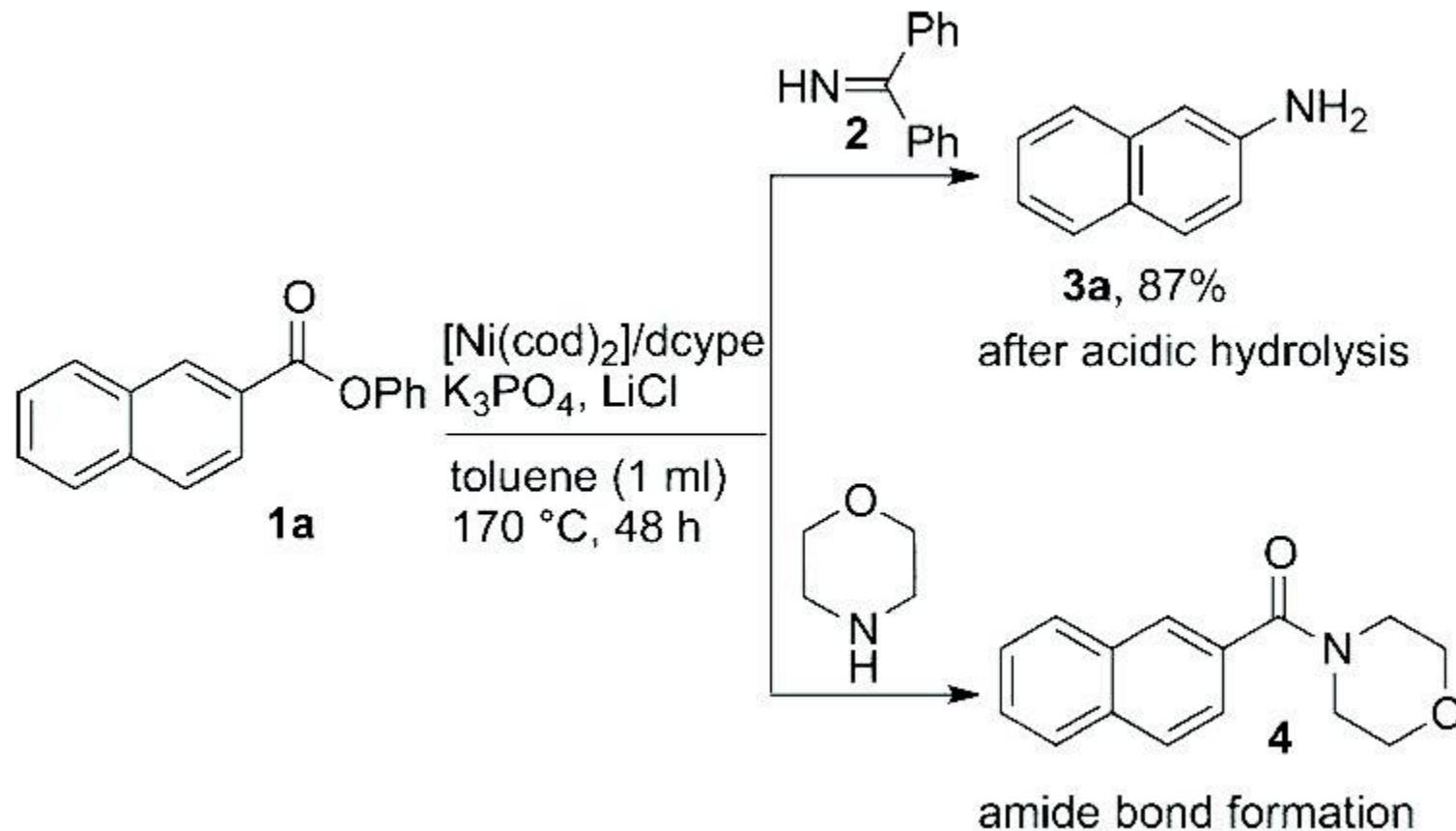


Entry	[Ni]	Ligand (x mol %)	Base (2 equiv)	Additive (2 equiv)	Yield [%] <sup>[b]</sup>
11	[Ni(cod) <sub>2</sub> ]	dctype (20)	NaO <sup>t</sup> Bu	—	0
12 <sup>[c]</sup>	[Ni(cod) <sub>2</sub> ]	dctype (20)	K <sub>3</sub> PO <sub>4</sub>	—	56
13 <sup>[c]</sup>	[Ni(cod) <sub>2</sub> ]	dctype (20)	K <sub>3</sub> PO <sub>4</sub>	LiCl	63
14 <sup>[c,d]</sup>	[Ni(cod) <sub>2</sub> ]	dctype (20)	K <sub>3</sub> PO <sub>4</sub>	LiCl	84
15 <sup>[c–e]</sup>	[Ni(cod) <sub>2</sub> ]	dctype (20)	K <sub>3</sub> PO <sub>4</sub>	LiCl	87
16 <sup>[c–e]</sup>	[Ni(cod) <sub>2</sub> ]	—	K <sub>3</sub> PO <sub>4</sub>	LiCl	0
17 <sup>[c–e]</sup>	—	dctype (20)	K <sub>3</sub> PO <sub>4</sub>	LiCl	0
18 <sup>[c–e]</sup>	Ni(OAc) <sub>2</sub>	dctype (20)	K <sub>3</sub> PO <sub>4</sub>	—	80
19 <sup>[c–e]</sup>	Ni(OAc) <sub>2</sub>	dctype (20)	K <sub>3</sub> PO <sub>4</sub>	Mn <sup>[f]</sup>	63
20 <sup>[c–e]</sup>	Ni(OAc) <sub>2</sub>	dctype (20)	K <sub>3</sub> PO <sub>4</sub>	Et <sub>3</sub> SiH <sup>[g]</sup>	77

[c] Benzophenone imine **2** (2 equiv), K<sub>3</sub>PO<sub>4</sub> (3 equiv). [d] 48 h. [e] 170 °C.

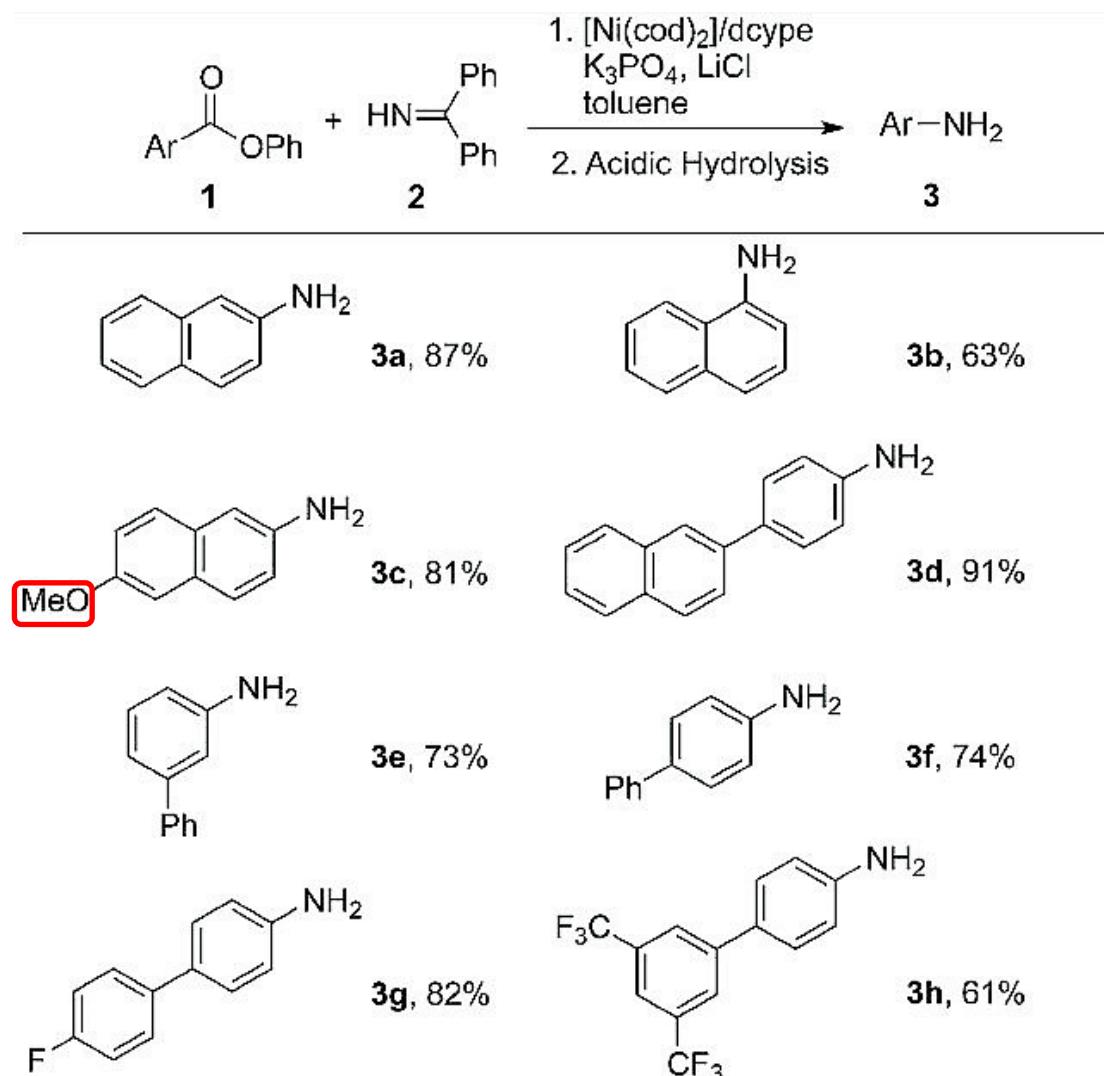
[f] Mn powder (1.5 equiv). [g] Et<sub>3</sub>SiH (20 mol%). cod=1,5-cyclooctadiene.

# Decarbonylative amination of the naphthyl ester



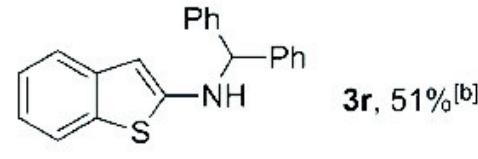
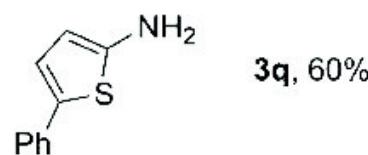
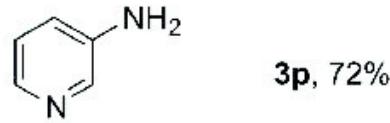
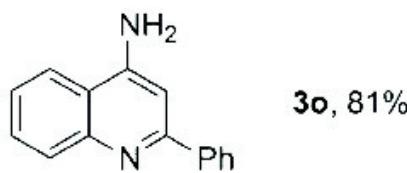
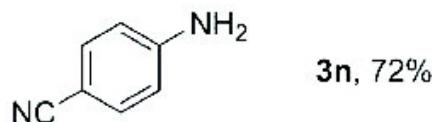
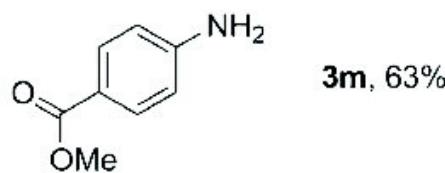
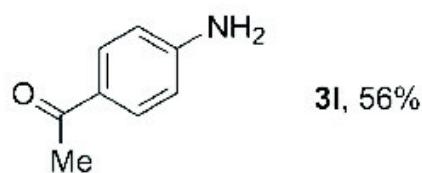
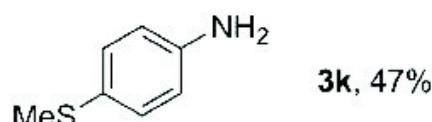
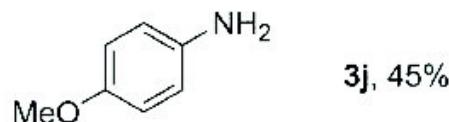
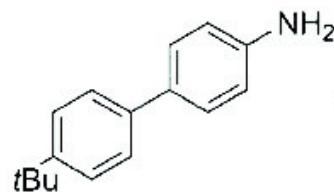
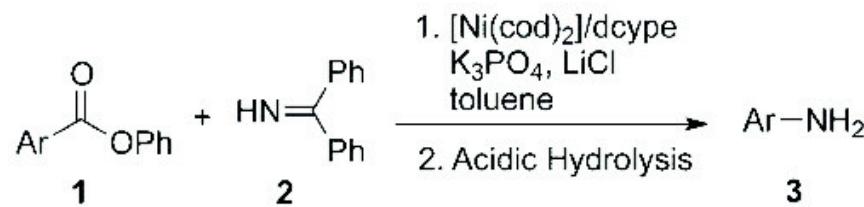
Other esters such as methyl and benzyl esters were not suitable for this transformation as it allows for a chemoselective amination of differently protected ester.

# Scope with respect to the aryl esters



[a] Reaction conditions: aryl ester **1a–r** (0.2 mmol), benzophenone imine **2** (0.4 mmol),  $[\text{Ni}(\text{cod})_2]$  (0.02 mmol), dcype (0.04 mmol),  $\text{K}_3\text{PO}_4$  (0.6 mmol),  $\text{LiCl}$  (0.4 mmol) in toluene(1 mL) at  $170^\circ\text{C}$ , 48 h. [b] Work up: reduction by  $\text{NaBH}_4$  (10 equiv) in methanol (5 mL).

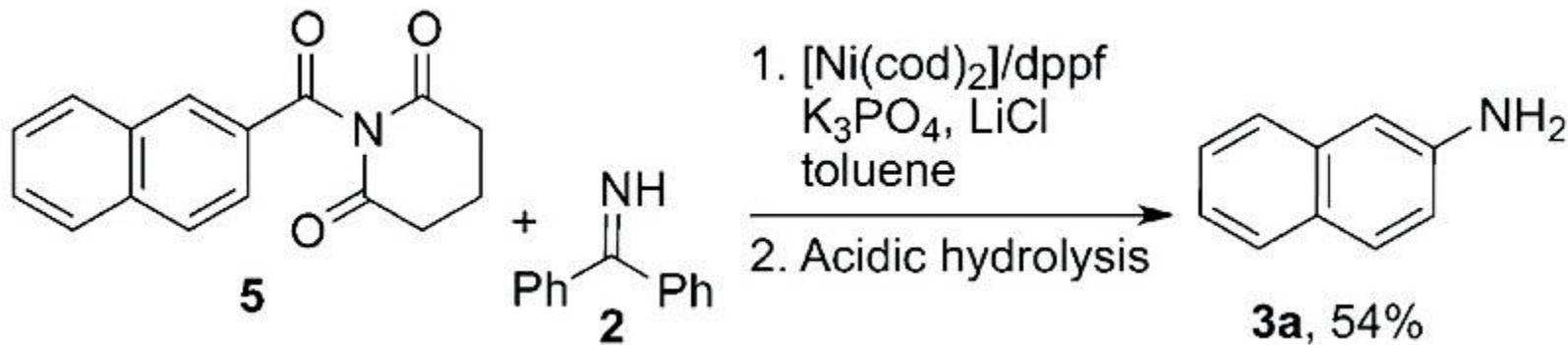
# Scope with respect to the aryl esters



[a] Reaction conditions: aryl ester **1a–r** (0.2 mmol), benzophenone imine **2** (0.4 mmol),  $[\text{Ni}(\text{cod})_2]$  (0.02 mmol), dcype (0.04 mmol),  $\text{K}_3\text{PO}_4$  (0.6 mmol),  $\text{LiCl}$  (0.4 mmol) in toluene (1 mL) at  $170^\circ\text{C}$ , 48 h. [b] Work up: reduction by  $\text{NaBH}_4$  (10 equiv) in methanol (5 mL).

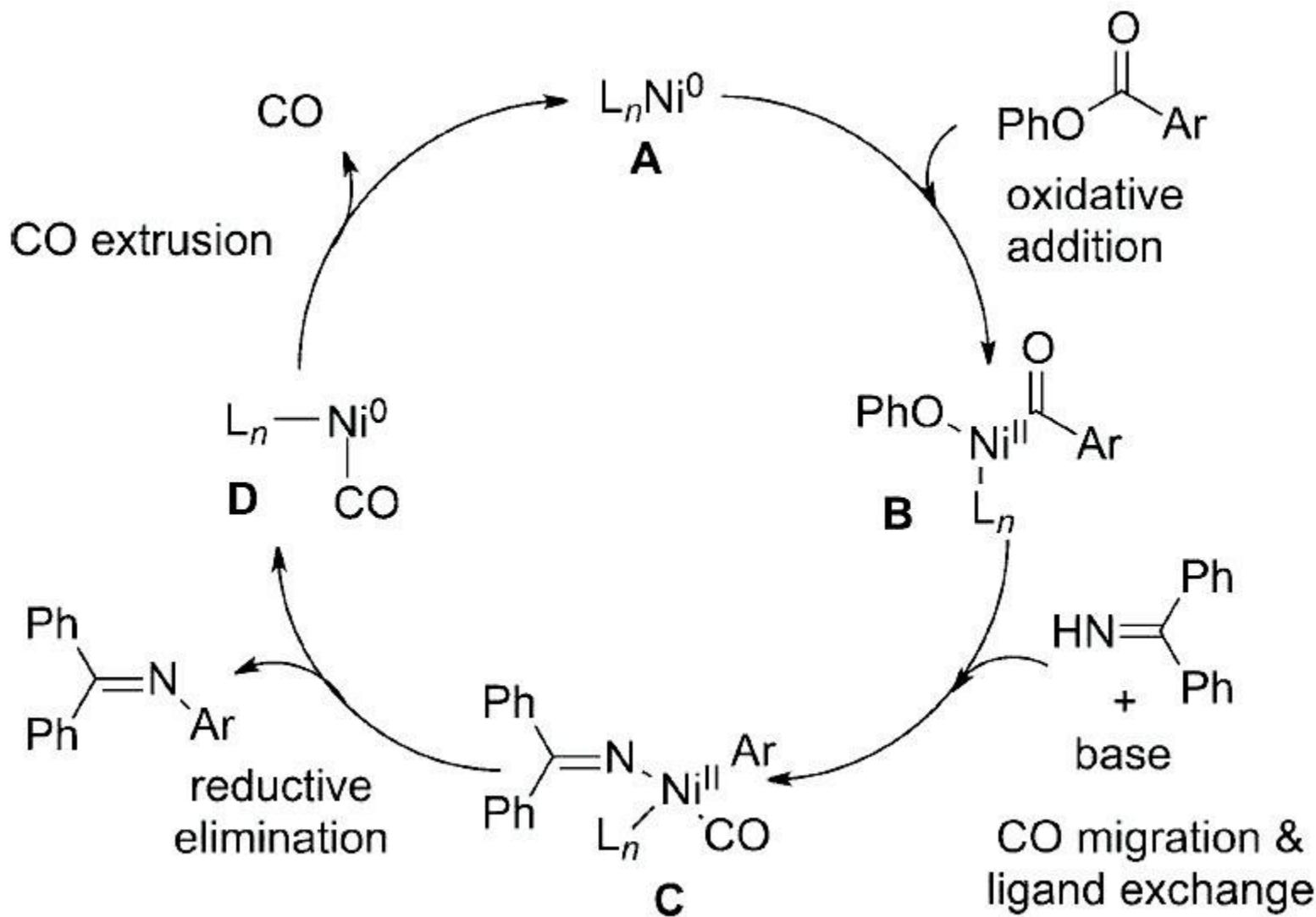
# Decarbonylative amination of naphthyl amide

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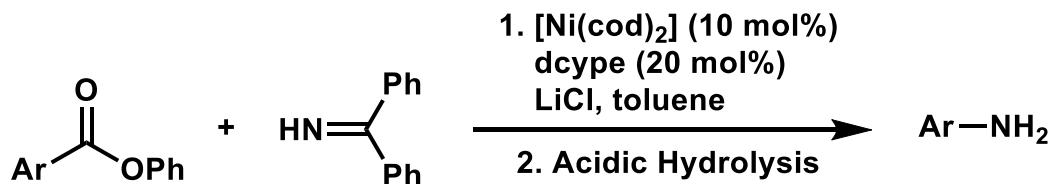
An aryl amide was also used as a different electrophile.

# Proposed mechanism



# Summary

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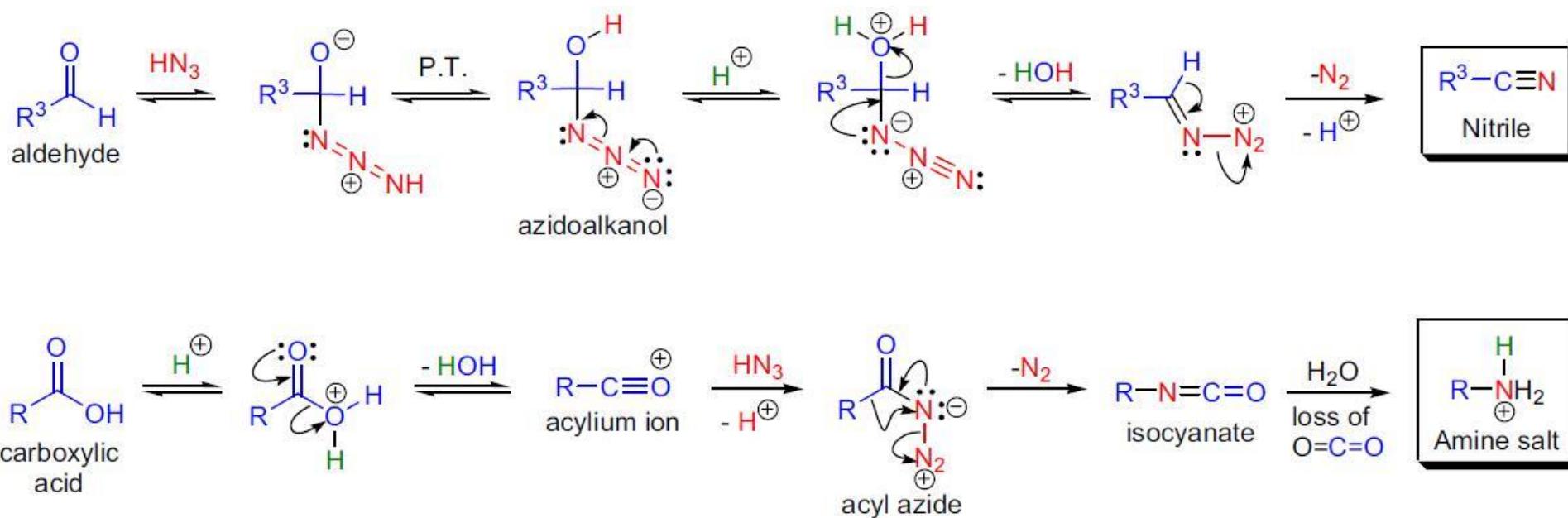
- The first decarbonylative amination for the direct interconversion of esters;
- Nickel catalyzed a new and efficient route to aryl amines;
- Good chemoselectivity and good tolerance of functional groups.

## Acknowledgment

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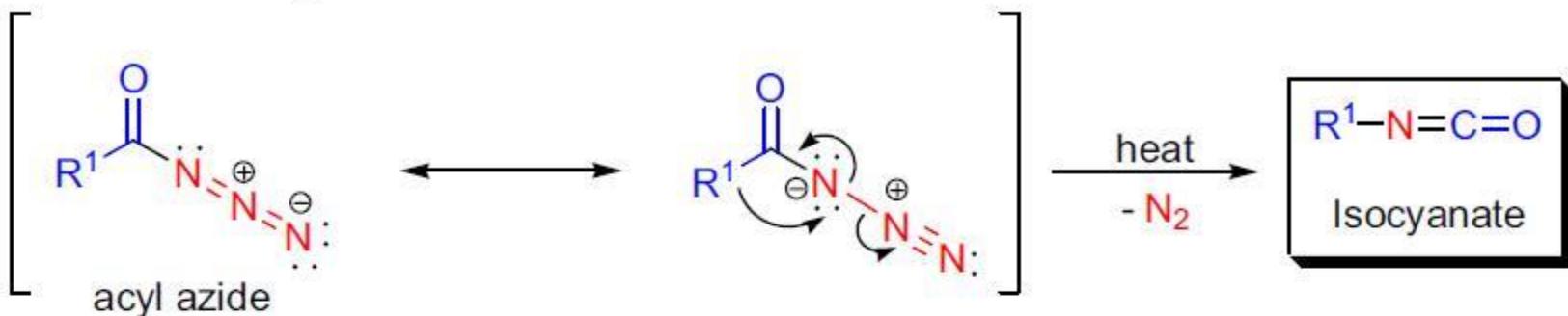
***Thanks for your attention!***

## ➤ Schmidt reaction mechanism:

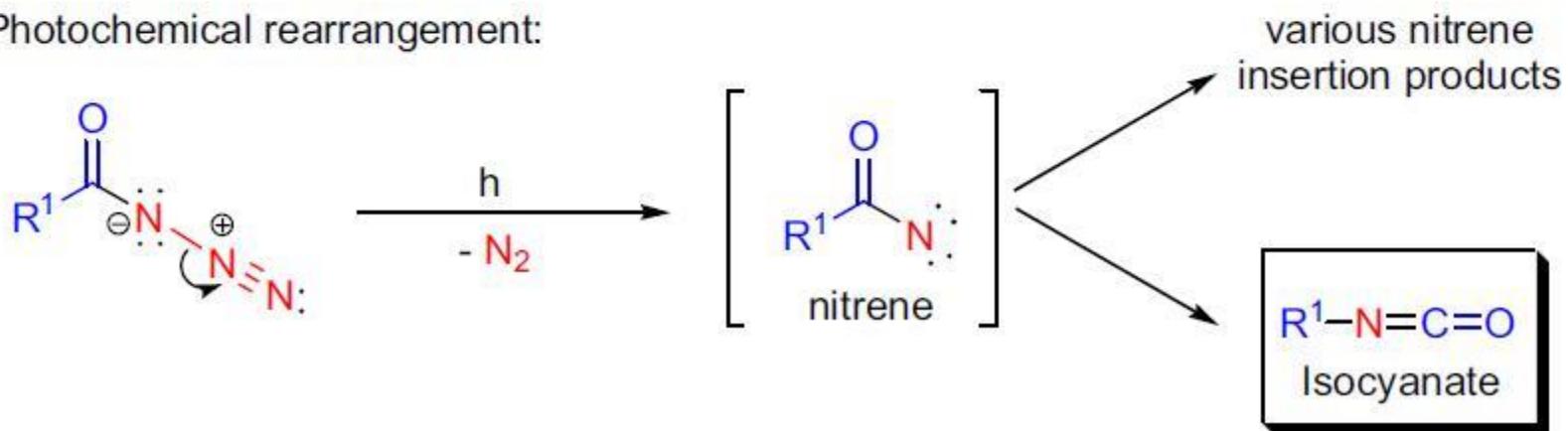


➤ Curtius rearrangement mechanism:

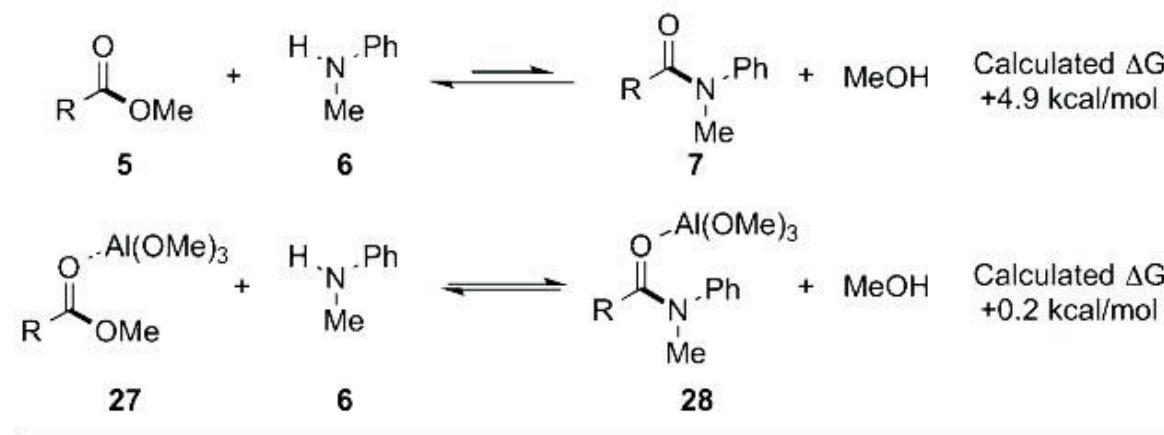
Thermal rearrangement:



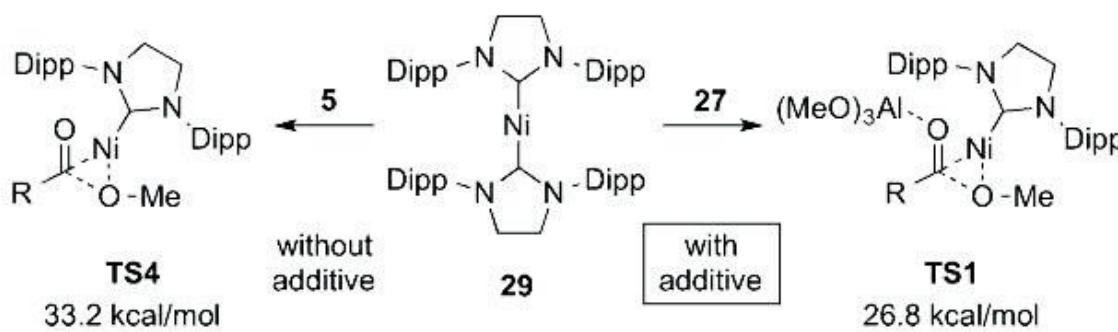
Photochemical rearrangement:



*Al(OR)<sub>3</sub>* Additive Renders Amidation More Thermodynamically Feasible

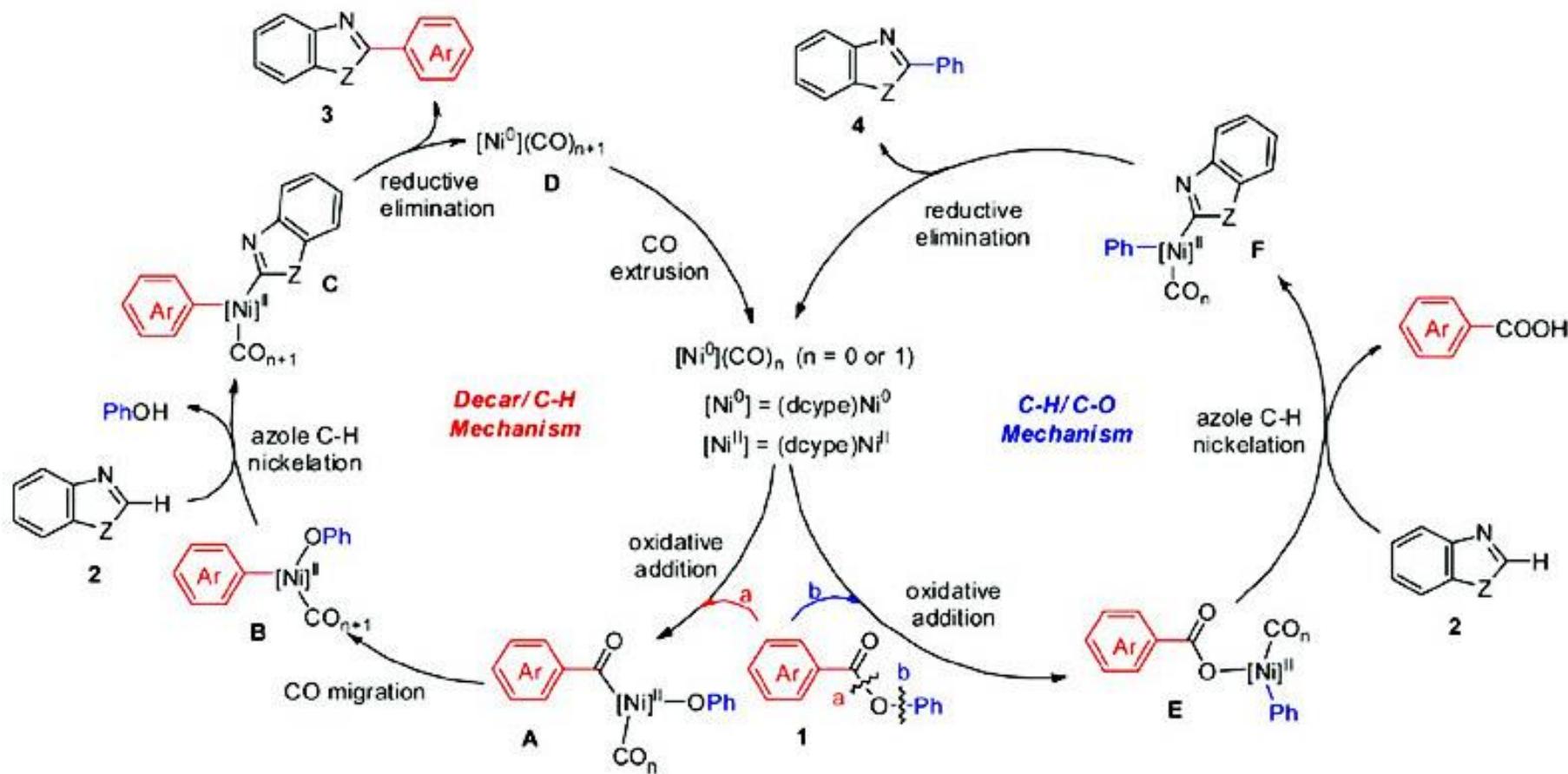


*Al(OR)<sub>3</sub>* Additive Lowers Kinetic Barrier for Oxidative Addition



**Figure 5.** Effect of the additive on the thermodynamics of amidation and the kinetic barrier for oxidative addition as determined by DFT calculations.  $\text{Al}(\text{OMe})_3$  is used as a model for  $\text{Al}(\text{OtBu})_3$  and  $\text{R} = 1\text{-naphthyl}$ .

This is due to the greater Lewis basicity of the carbonyl oxygen atom of the amide compared to that of the ester, which therefore drives the equilibrium towards amide complex **28**. The additive is also thought to have a beneficial kinetic influence with regard to the rate-determining oxidative-addition step. In the absence of the additive, the kinetic barrier for oxidative addition is computed to be 33.2 kcal/mol relative to  $[\text{Ni}(\text{SIPr})_2]$  **29**. With the additive, however, the oxidative addition becomes significantly more facile, with a kinetic barrier of 26.8 kcal/mol.



It was found that the impact of different aryl esters on the decarbonylative C-H coupling mechanism is greater than that on the C-H/C-O coupling mechanism. We concluded that the less-bulky substituted electrophiles favors the decarbonylative C-H coupling reaction, while bulky substituted electrophiles favors the C-H/C-O coupling reaction.