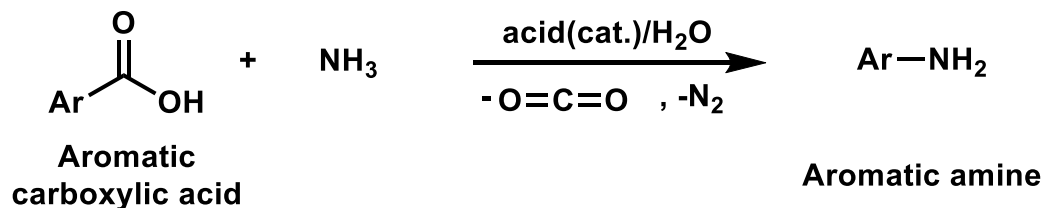


Catalytic Ester and Amide to Amine Interconversion: Nickel-Catalyzed Decarbonylative Amination of Esters and Amides by C-O and C-C Bond Activation

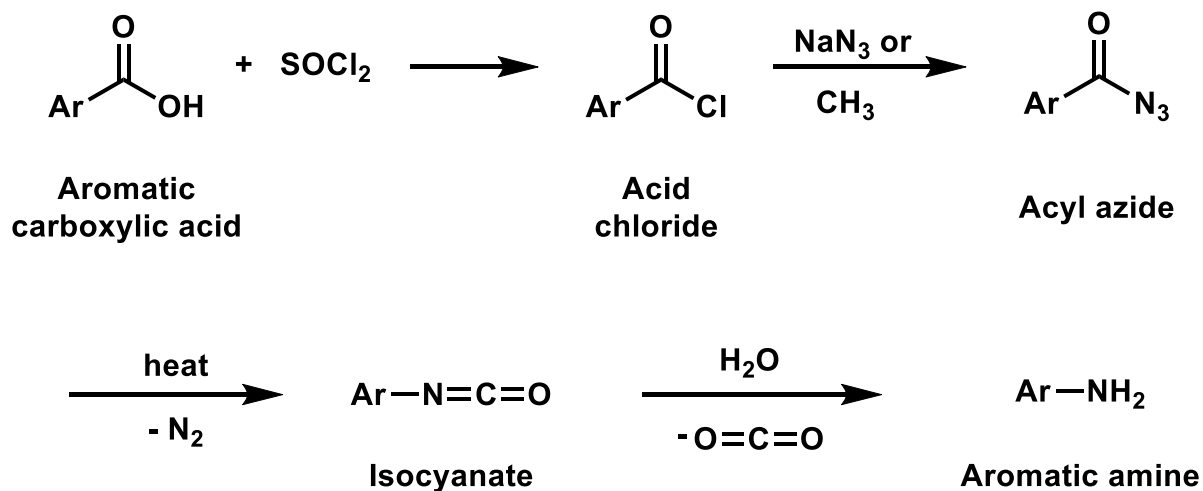
Reporter: Feifei Song
Supervisor: Prof. Yong Huang
2017. 04. 24

Classical carboxylic acid to amine interconversions

➤ Schmidt reaction



➤ Curtius rearrangement

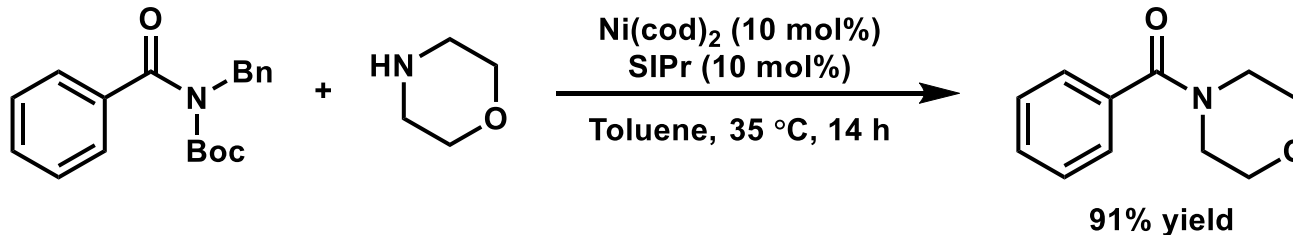
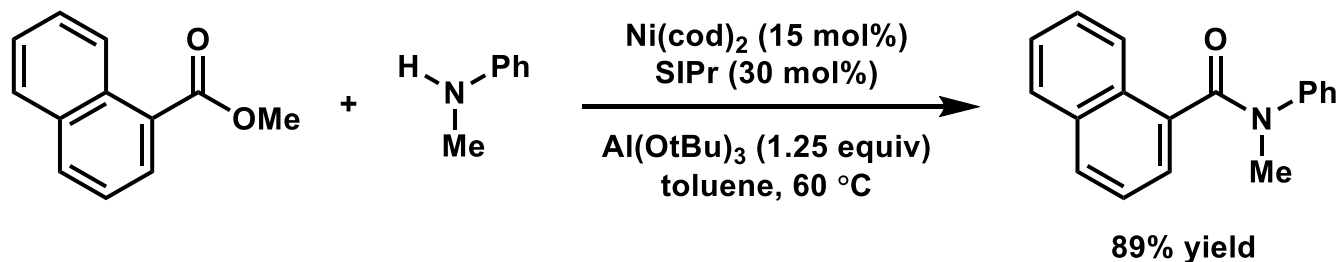


Classical amide-bond formations

➤ Ester amine coupling



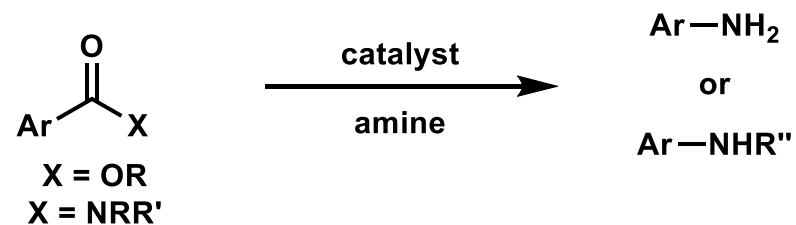
➤ Recent nickel-catalyzed protocol



This work

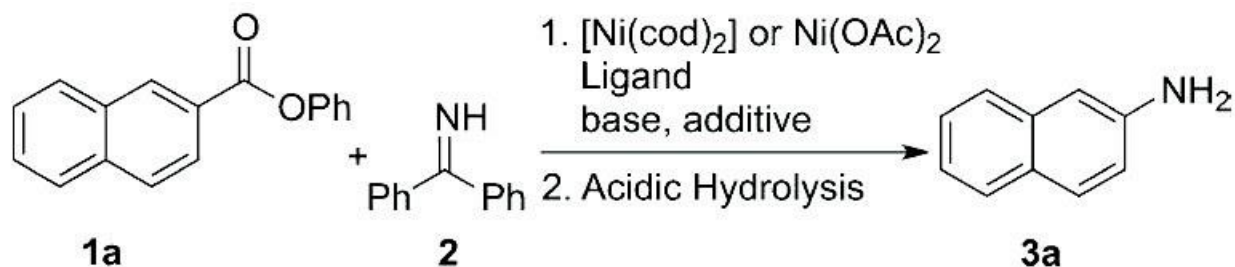
➤ Direct transformation of ester or amides into amines

C-N bond formation



New decarbonylative amination of carboxylic and derivatives.

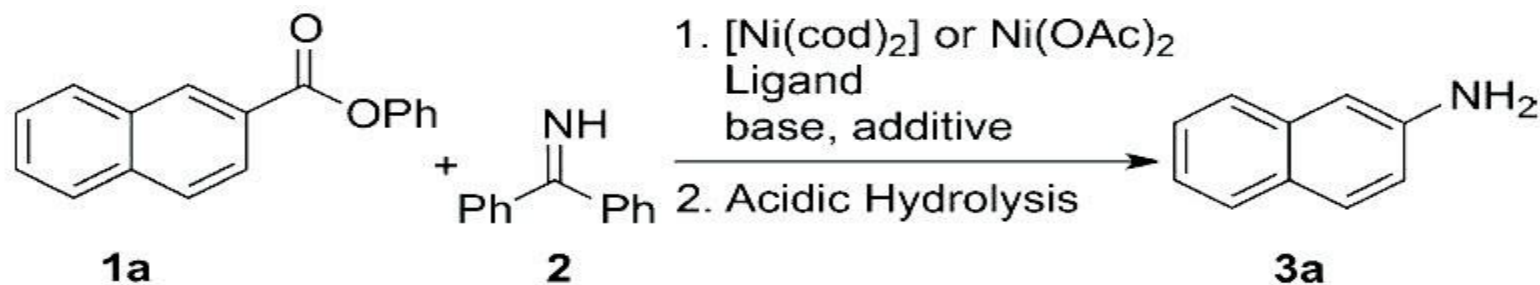
Optimization of the reaction conditions



Entry	[Ni]	Ligand (x mol %)	Base (2 equiv)	Additive (2 equiv)	Yield [%] ^[b]
1	$[\text{Ni}(\text{cod})_2]$	IPr·HCl (20)	Cs_2CO_3	—	0
2	$[\text{Ni}(\text{cod})_2]$	P^nBu_3 (20)	Cs_2CO_3	—	0
3	$[\text{Ni}(\text{cod})_2]$	PCy_3 (20)	Cs_2CO_3	—	0
4	$[\text{Ni}(\text{cod})_2]$	dcype (10)	Cs_2CO_3	—	14
5	$[\text{Ni}(\text{cod})_2]$	dcypf (10)	Cs_2CO_3	—	trace
6	$[\text{Ni}(\text{cod})_2]$	dcype (20)	Cs_2CO_3	—	17
7	$[\text{Ni}(\text{cod})_2]$	dcype (20)	Li_2CO_3	—	21
8	$[\text{Ni}(\text{cod})_2]$	dcype (20)	K_2CO_3	—	31
9	$[\text{Ni}(\text{cod})_2]$	dcype (20)	Na_2CO_3	—	31
10	$[\text{Ni}(\text{cod})_2]$	dcype (20)	K_3PO_4	—	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), $[\text{Ni}(\text{cod})_2]$ (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

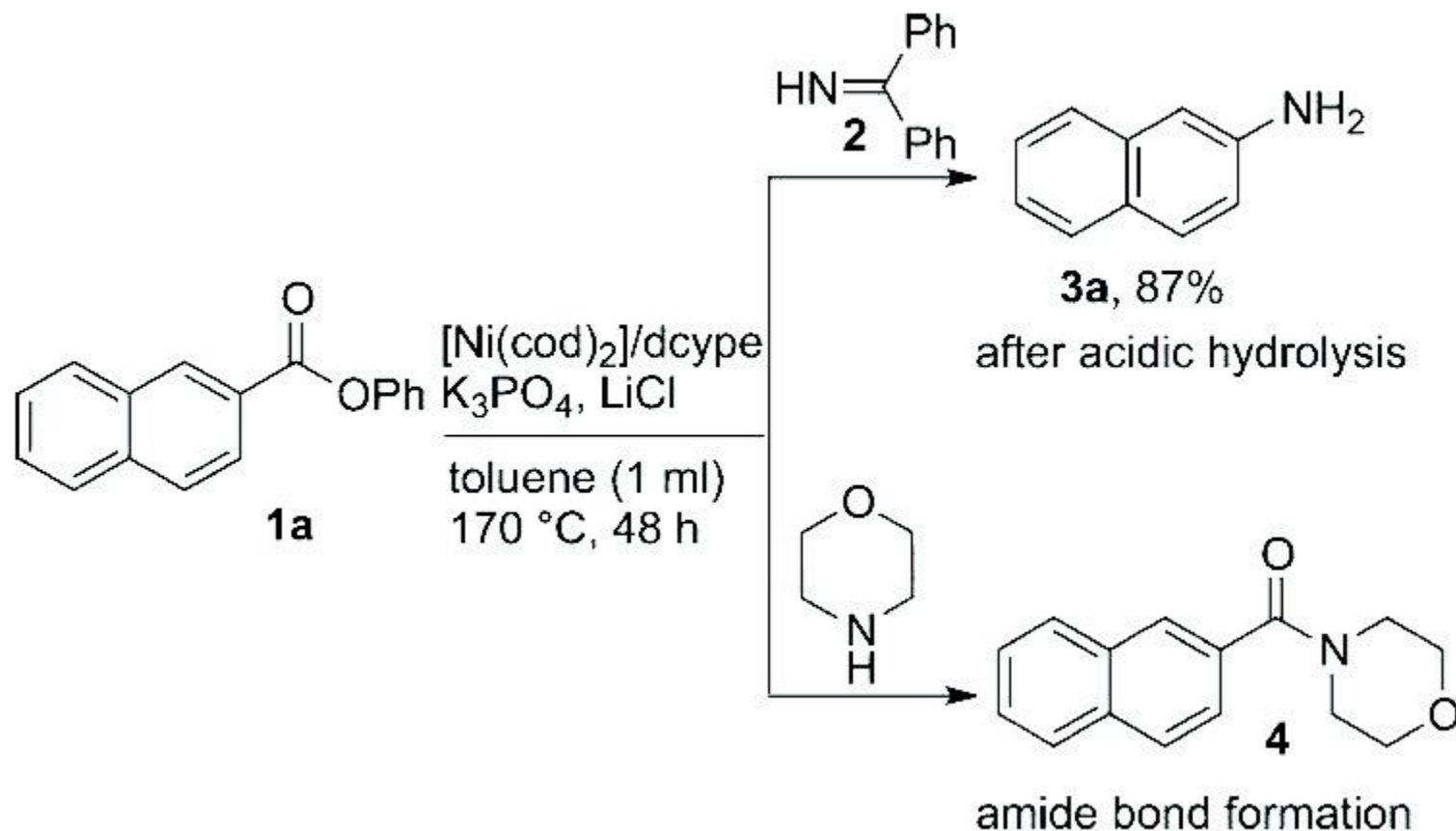
Optimization of the reaction conditions



Entry	[Ni]	Ligand (x mol %)	Base (2 equiv)	Additive (2 equiv)	Yield [%] ^[b]
11	$[\text{Ni}(\text{cod})_2]$	dcype (20)	NaO^tBu	—	0
12 ^[c]	$[\text{Ni}(\text{cod})_2]$	dcype (20)	K_3PO_4	—	56
13 ^[c]	$[\text{Ni}(\text{cod})_2]$	dcype (20)	K_3PO_4	LiCl	63
14 ^[c,d]	$[\text{Ni}(\text{cod})_2]$	dcype (20)	K_3PO_4	LiCl	84
15 ^[c-e]	$[\text{Ni}(\text{cod})_2]$	dcype (20)	K_3PO_4	LiCl	87
16 ^[c-e]	$[\text{Ni}(\text{cod})_2]$	—	K_3PO_4	LiCl	0
17 ^[c-e]	—	dcype (20)	K_3PO_4	LiCl	0
18 ^[c-e]	$\text{Ni}(\text{OAc})_2$	dcype (20)	K_3PO_4	—	80
19 ^[c-e]	$\text{Ni}(\text{OAc})_2$	dcype (20)	K_3PO_4	$\text{Mn}^{[f]}$	63
20 ^[c-e]	$\text{Ni}(\text{OAc})_2$	dcype (20)	K_3PO_4	$\text{Et}_3\text{SiH}^{[g]}$	77

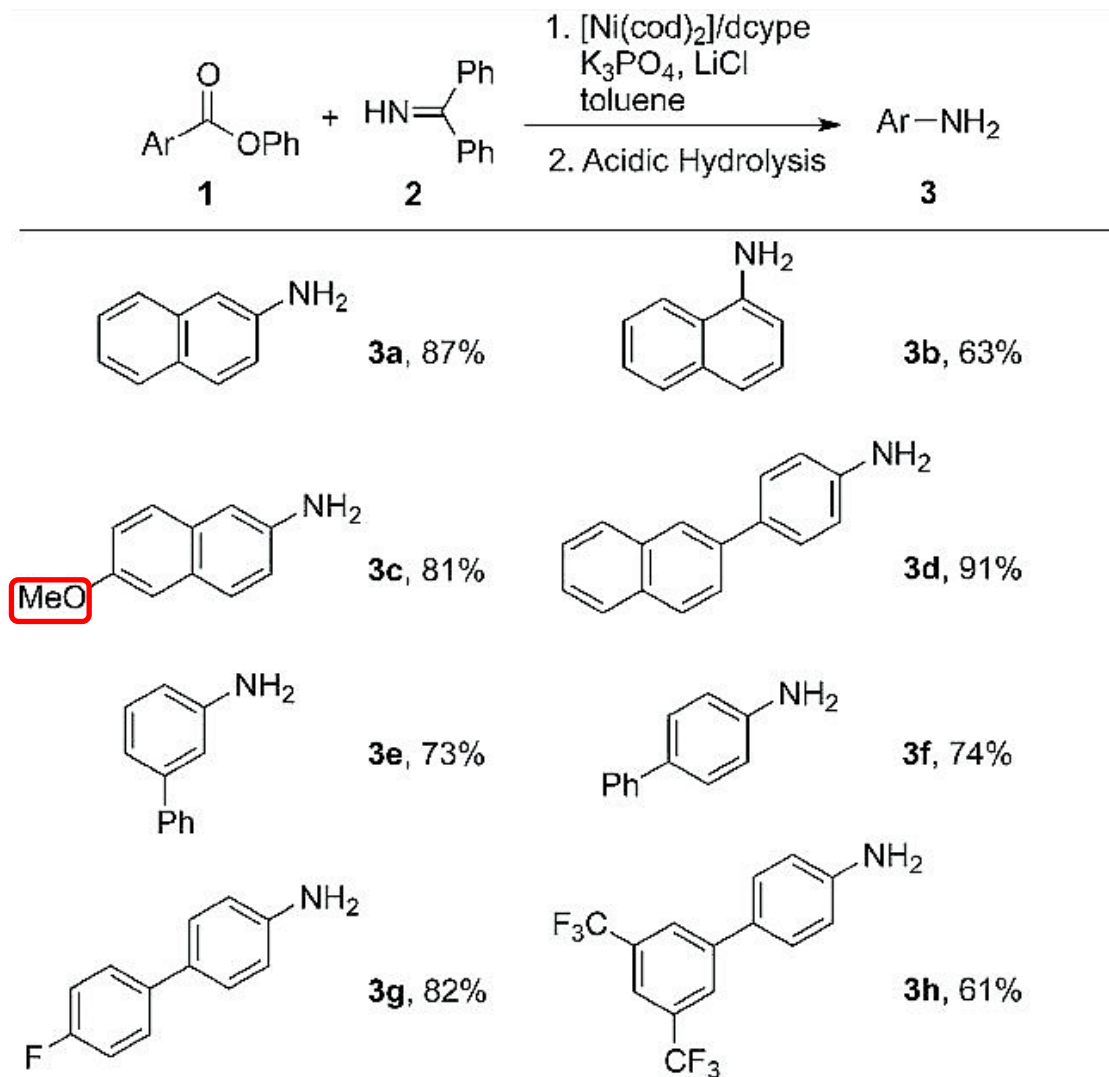
[c] Benzophenone imine **2** (2 equiv), K_3PO_4 (3 equiv). [d] 48 h. [e] 170°C.
 [f] Mn powder (1.5 equiv). [g] Et_3SiH (20 mol%). cod=1,5-cyclooctadiene.

Decarbonylative amination of the naphthyl ester



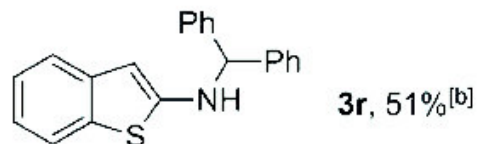
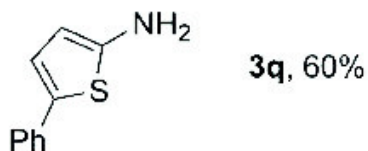
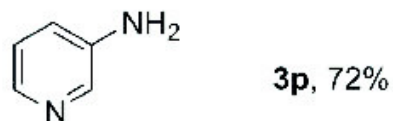
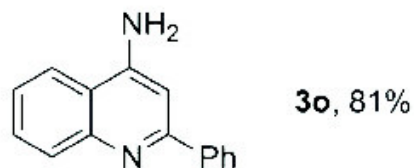
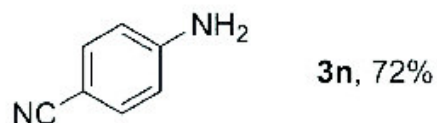
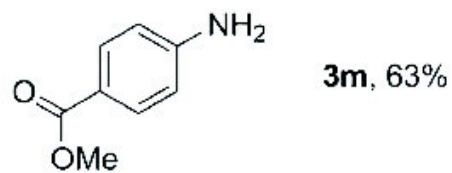
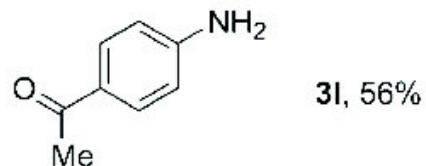
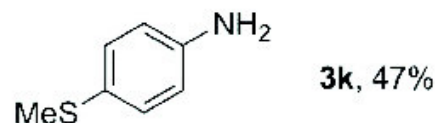
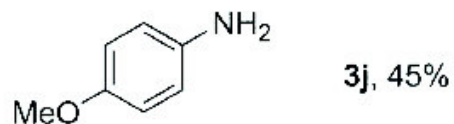
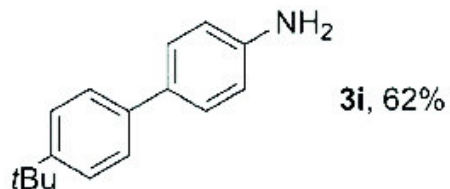
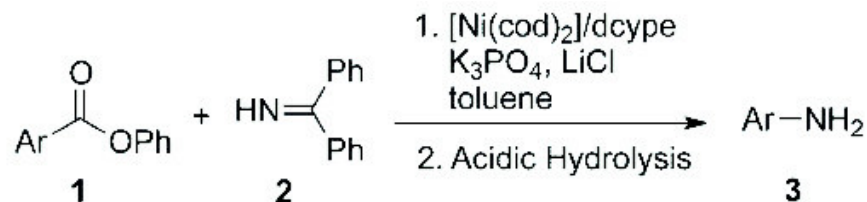
Other esters such as methyl and benzyl esters were not suitable for this transformation as it allows for a chemoselective amination of differently protected ester.

Scope with respect to the aryl esters



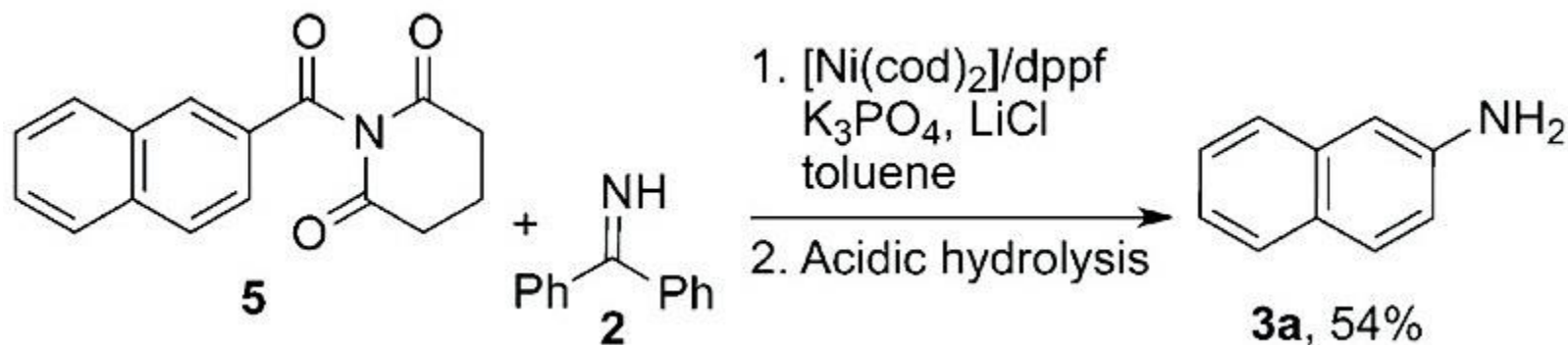
[a] Reaction conditions: aryl ester **1a–r** (0.2 mmol), benzophenone imine **2** (0.4 mmol), $[\text{Ni}(\text{cod})_2]$ (0.02 mmol), dcype (0.04 mmol), K_3PO_4 (0.6 mmol), LiCl (0.4 mmol) in toluene (1 mL) at 170°C , 48 h. [b] Work up: reduction by NaBH_4 (10 equiv) in methanol (5 mL).

Scope with respect to the aryl esters



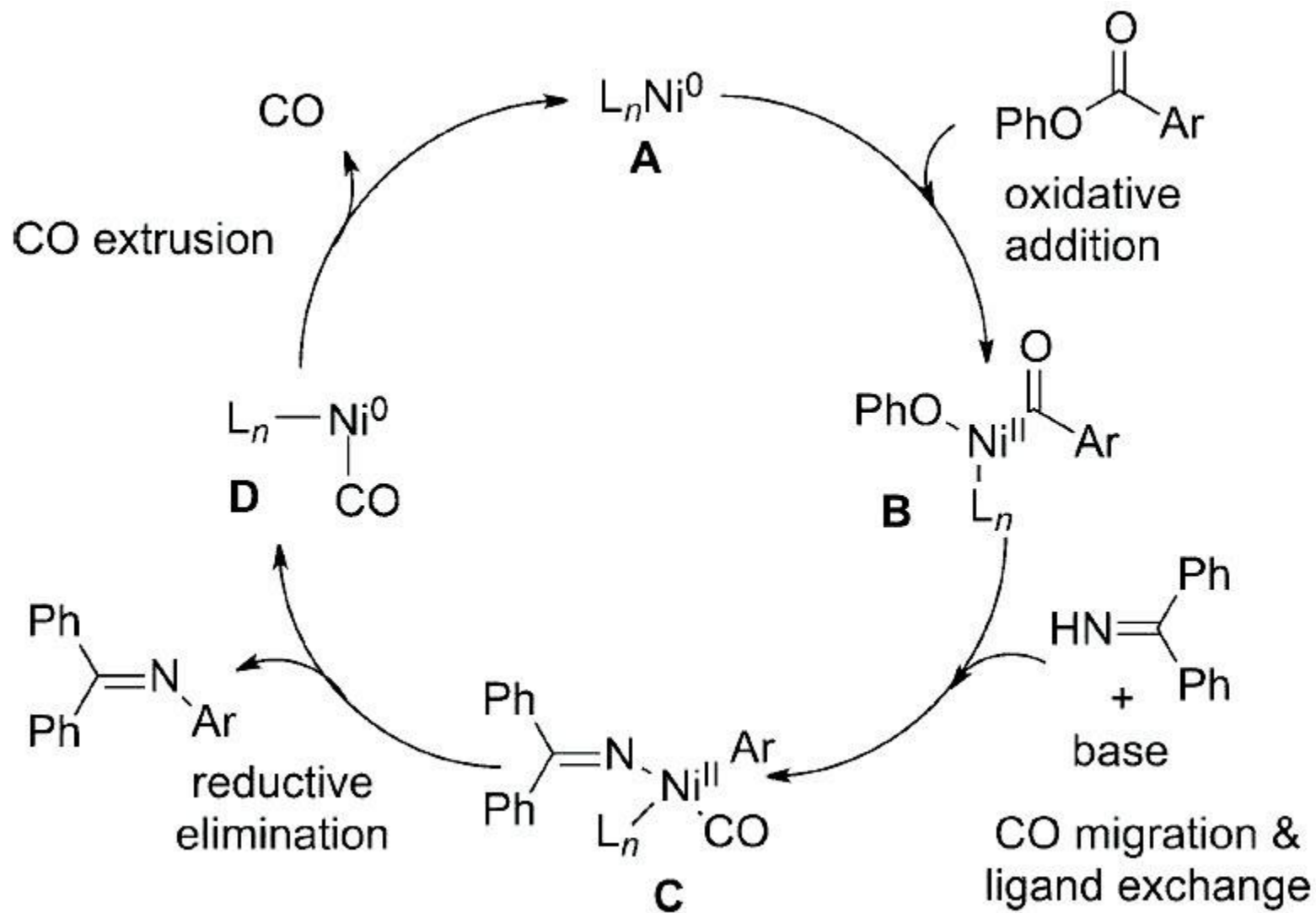
[a] Reaction conditions: aryl ester **1a–r** (0.2 mmol), benzophenone imine **2** (0.4 mmol), [Ni(cod)₂] (0.02 mmol), dcype (0.04 mmol), K₃PO₄ (0.6 mmol), LiCl (0.4 mmol) in toluene (1 mL) at 170°C, 48 h. [b] Work up: reduction by NaBH₄ (10 equiv) in methanol (5 mL).

Decarbonylative amination of naphthyl amide

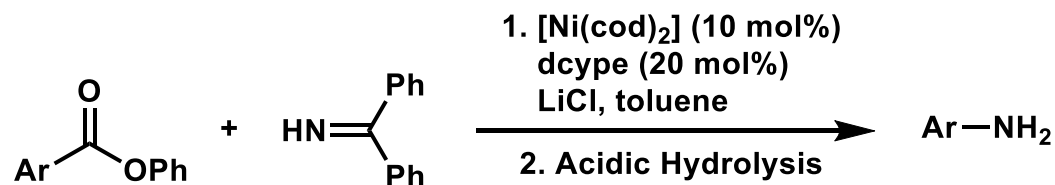


An aryl amide was also used as a different electrophile.

Proposed mechanism



Summary

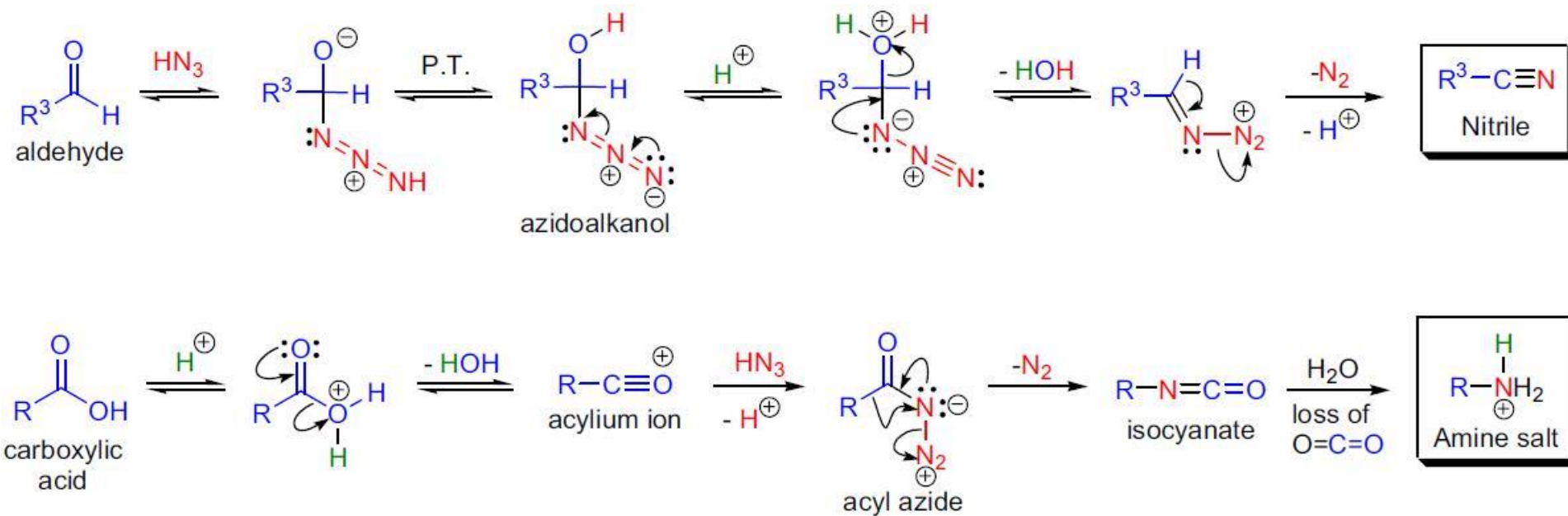


- The first decarbonylative amination for the direct interconversion of esters;
- Nickel catalyzed a new and efficient route to aryl amines;
- Good chemoselectivity and good tolerance of functional groups.

Acknowledgment

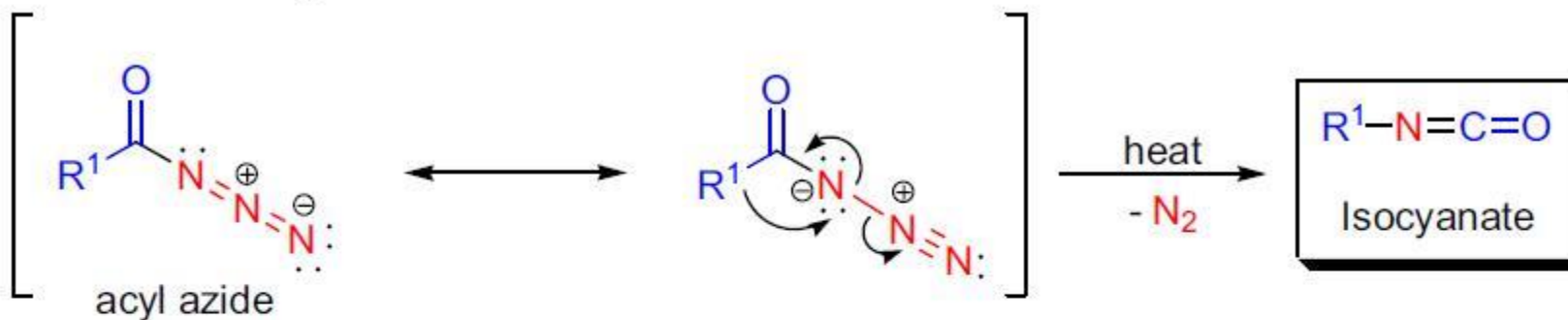
Thanks for your attention!

➤ **Schmidt reaction mechanism:**

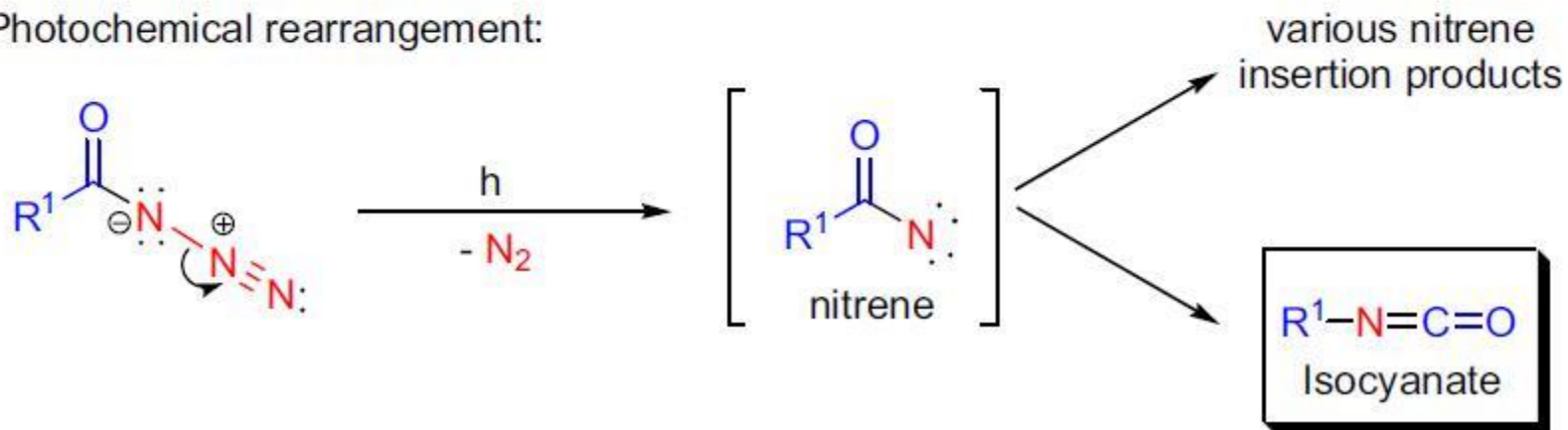


➤ Curtius rearrangement mechanism:

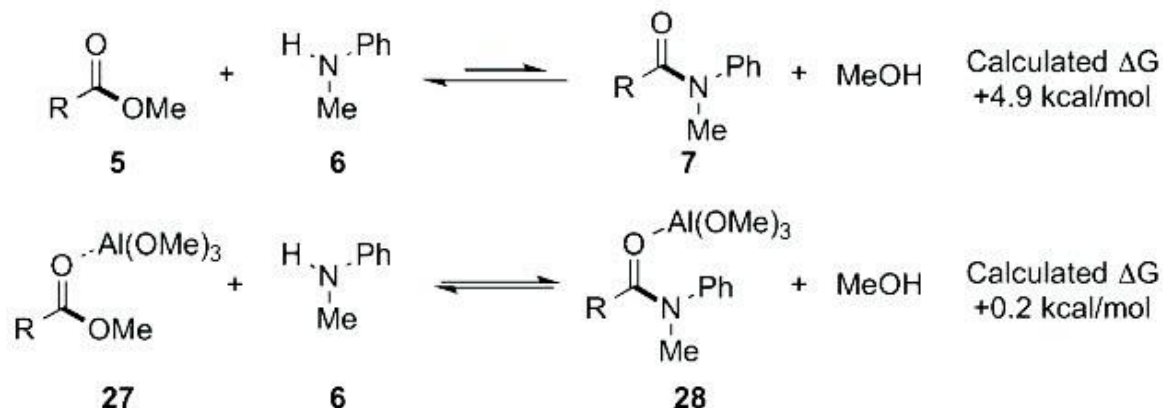
Thermal rearrangement:



Photochemical rearrangement:



Al(OR)₃ Additive Renders Amidation More Thermodynamically Feasible



Al(OR)₃ Additive Lowers Kinetic Barrier for Oxidative Addition

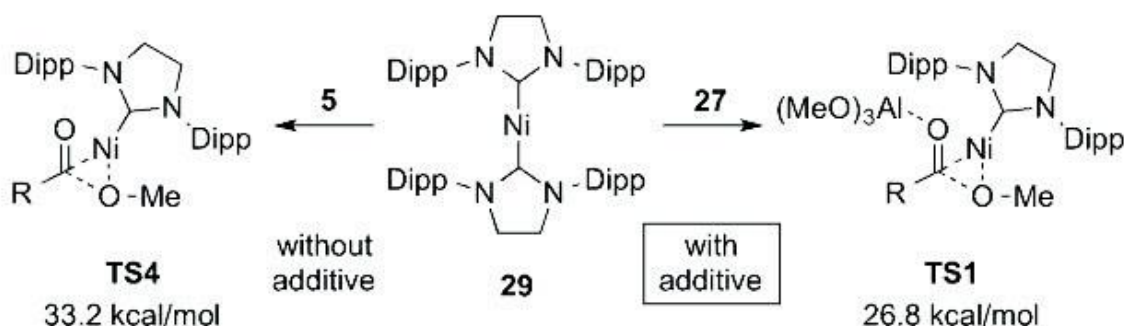
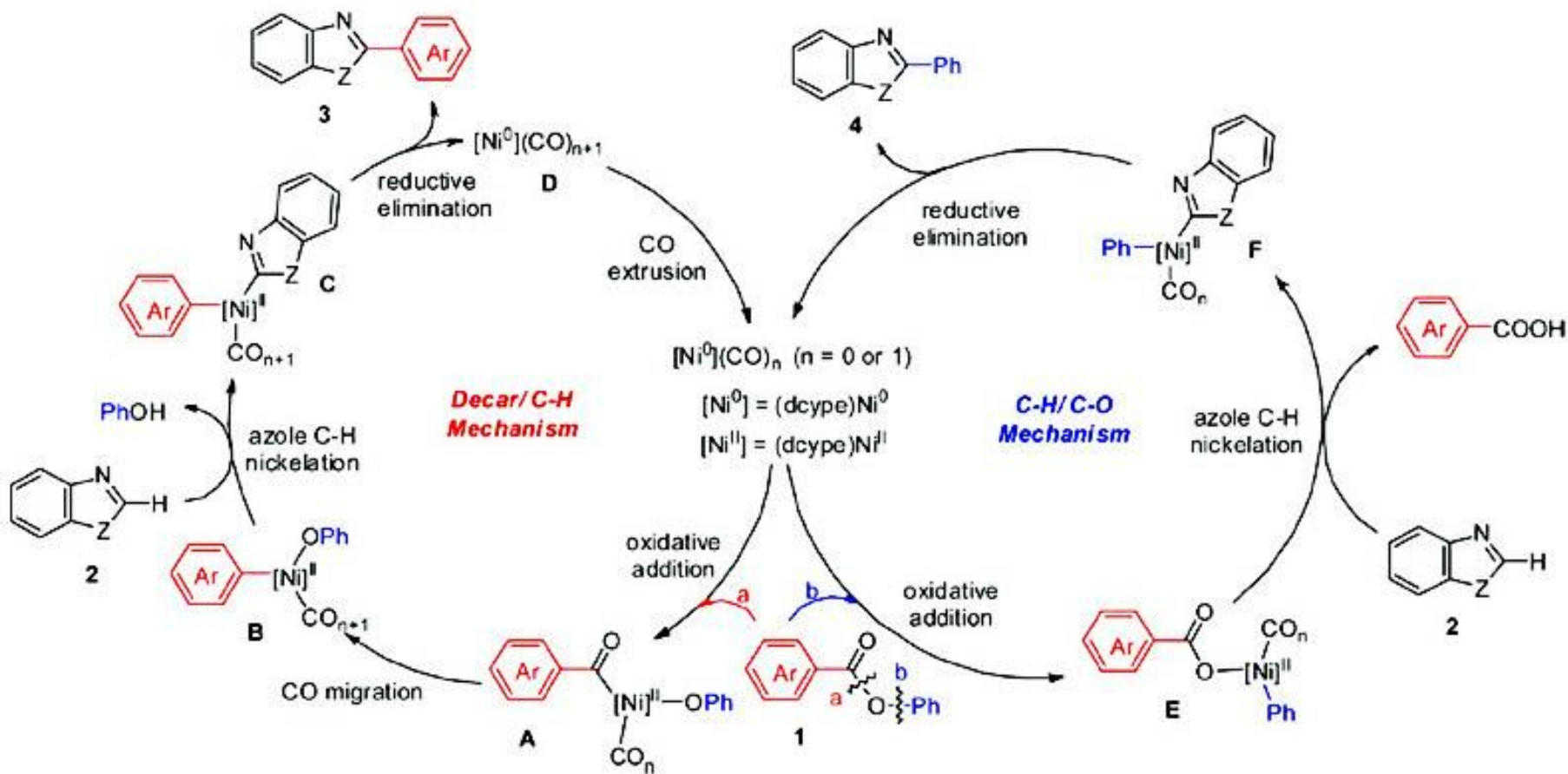


Figure 5. Effect of the additive on the thermodynamics of amidation and the kinetic barrier for oxidative addition as determined by DFT calculations. Al(OMe)₃ is used as a model for Al(OtBu)₃ and R = 1-naphthyl.

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 [Ni(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.