Amination

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

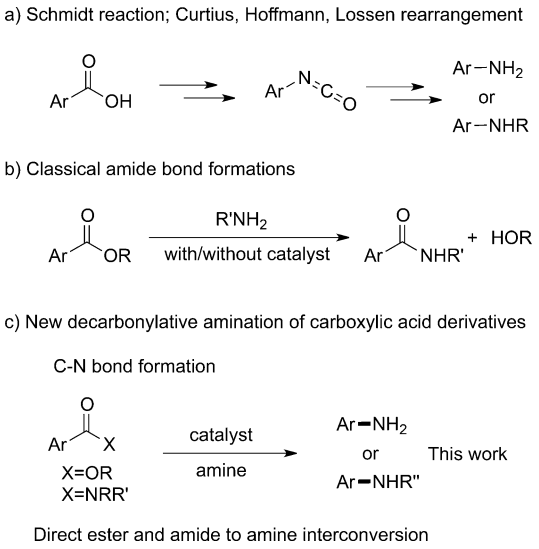
*Huifeng Yue, Lin Guo, Hsuan-Hung Liao, Yunfei Cai, Chen Zhu, and Magnus Rueping**

Dedicated to Professor Lutz F. Tietze on the occasion of his 75th birthday

Abstract: *An efficient nickel-catalyzed decarbonylative amination reaction of aryl and heteroaryl esters has been achieved for the first time. The new amination protocol allows the direct interconversion of esters and amides into the corresponding amines and represents a good alternative to classical rearrangements as well as cross coupling reactions.*

Aromatic amines are important synthetic building blocks in chemistry because of their application in the preparation of pharmaceuticals, biologically active molecules, natural products, polymers, as well as functional materials.[1] Accordingly, the development of new methodologies to access these valuable molecules continues to be of great importance in synthetic organic chemistry.[1] Conventionally, the palladium-catalyzed Buchwald–Hartwig reaction represents a valuable C(sp^2)–N bond-formation method which makes a great contribution to this field.[2] Although palladium is dominating the field, and a considerable number of powerful catalytic systems for the conversion of aryl (pseudo) halides into aromatic amines has been reported, recent efforts are devoted to the disclosure of improved protocols based on nonprecious metal catalysts. Particular attention has been drawn to the use of inexpensive and earth-abundant nickel catalysts,[3] along with easily available and versatile C(sp^2)–O electrophiles.[4–8] Despite the advances in this field, it is still highly desirable to further explore different electrophilic coupling partners for metal-catalyzed amination reactions with the aim of developing protocols based on cheaper, more-stable, and readily available substrates. Considerable progress has been achieved in metal-catalyzed decarboxylative and decarbonylative cross-coupling reactions using carboxylic acids and its derivatives.[9–12]

However, to the best of our knowledge, metal-catalyzed C(sp^2)–N bond formations by a decarbonylative process with carboxylic acid derivatives as substrates have not been realized before. Traditionally, either acids or ester derivatives are transformed into amines using multistep sequences, and involve classical rearrangements (Scheme 1 a).



Scheme 1. a) Classical carboxylic acid to amine interconversions by rearrangements. b) Classical amide-bond formations by ester amine coupling. c) Direct transformation of either esters or amides into amines.

Amides are typically rather stable functional groups, part of peptides and proteins, and are less prone to hydrolysis, when compared to ester derivatives. They can simply be prepared by the reaction of esters with amines, and many different protocols, including a recent nickel-catalyzed protocol[13] for the amide formation, have been described (Scheme 1 b).

Given the enormous interest in efficient protocols for the preparation of amines and limitations associated with the classical rearrangement reactions, we became interested in developing a direct catalytic amination of aryl and heteroaryl esters, in which the ester moiety would be replaced by an amine to yield aromatic amines in a one-step process (Scheme 1 c). Herein, we report an unprecedented decarbonylative amination protocol for the direct interconversion of esters, as well as amides, into aryl amines (Scheme 1 c). To prevent the undesired amide-bond formation when reacting esters with amines (Scheme 1 b), we decided to use imines as nucleophiles instead. This approach would also allow further

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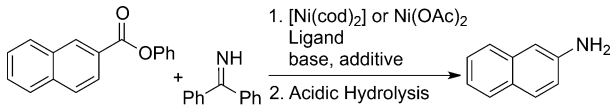
functionalization, as well as direct access to primary aromatic amines.

Therefore, our initial experiments in developing the new decarbonylative amination started with phenyl naphthalene-2-carboxylate (**1a**) and commercially available benzophenone imine (**2**; Table 1). Among the different metals tested, nickel complexes proved to be good catalysts for the decarbonylation. The nature of the ligand critically affected the efficiency of our transformation. No reaction occurred when IPr·HCl was applied as a ligand (entry 1). The use of monodentate phosphine ligands such as P(*n*-Bu)$_3$ and PCy$_3$ also gave no desired product (entries 2 and 3). However, bidentate phosphine ligands were suitable for this reaction and 14% yield was obtained when 1,2-bis (dicyclohexylphosphino)ethane (dcype) was used. Increasing the ratio of nickel to bidentate phosphine ligand from 1:1 to 1:2 was beneficial for this transformation (entry 4 versus 6). Various bases were next examined and K_3PO_4 was found to be the optimal choice. Reactions in the presence of other bases gave either lower yields (Li_2CO_3, K_2CO_3, Na_2CO_3), or even no desired product (NaO^{t}Bu), and indicated that the base plays a crucial role in this reaction (entries 6–11). The yield of the coupling product increased to 56% when 2 equivalents of benzophenone imine and 3 equivalents of K_3PO_4 were used (entry 12).

Table 1: Optimization of the reaction conditions.[a]

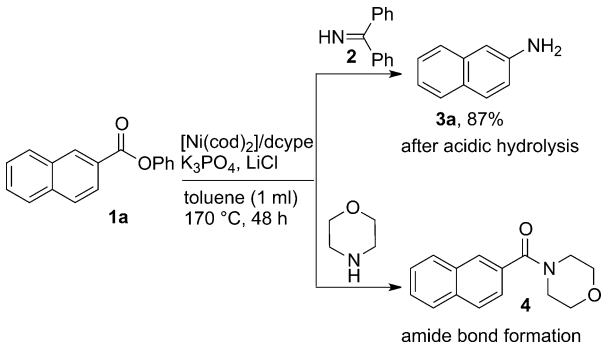


1a **2** **3a**

Entry	[Ni]	Ligand (*x* mol%)	Base (2 equiv)	Additive (2 equiv)	Yield [%][b]
1	[Ni(cod)$_2$]	IPr·HCl (20)	Cs_2CO_3	–	0
2	[Ni(cod)$_2$]	P^{n}Bu$_3$ (20)	Cs_2CO_3	–	0
3	[Ni(cod)$_2$]	PCy$_3$ (20)	Cs_2CO_3	–	0
4	[Ni(cod)$_2$]	dcype (10)	Cs_2CO_3	–	14
5	[Ni(cod)$_2$]	dcypf (10)	Cs_2CO_3	–	trace
6	[Ni(cod)$_2$]	dcype (20)	Cs_2CO_3	–	17
7	[Ni(cod)$_2$]	dcype (20)	Li_2CO_3	–	21
8	[Ni(cod)$_2$]	dcype (20)	K_2CO_3	–	31
9	[Ni(cod)$_2$]	dcype (20)	Na_2CO_3	–	31
10	[Ni(cod)$_2$]	dcype (20)	K_3PO_4	–	42
11	[Ni(cod)$_2$]	dcype (20)	NaO^{t}Bu	–	0
12[c]	[Ni(cod)$_2$]	dcype (20)	K_3PO_4	–	56
13[c]	[Ni(cod)$_2$]	dcype (20)	K_3PO_4	LiCl	63
14[c,d]	[Ni(cod)$_2$]	dcype (20)	K_3PO_4	LiCl	84
15[c–e]	[Ni(cod)$_2$]	dcype (20)	K_3PO_4	LiCl	87
16[c–e]	[Ni(cod)$_2$]	–	K_3PO_4	LiCl	0
17[c–e]	–	dcype (20)	K_3PO_4	LiCl	0
18[c–e]	Ni(OAc)$_2$	dcype (20)	K_3PO_4	–	80
19[c–e]	Ni(OAc)$_2$	dcype (20)	K_3PO_4	Mn[f]	63
20[c–e]	Ni(OAc)$_2$	dcype (20)	K_3PO_4	Et$_3$SiH[g]	77

[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)$_2$] (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. [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$_3$SiH (20 mol%). cod = 1,5-cyclooctadiene.

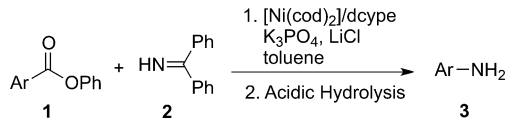
LiCl as a Lewis acid additive was found to have a beneficial effect on our decarbonylative amination, and may be due to coordination to the carbonyl group (Table 1, entry 13). Extending the reaction time and increasing the temperature slightly, significantly improved the yield (entries 14 and 15). Under the optimized reaction conditions the desired product was isolated in 87% yield upon acidic hydrolysis. A slightly lower yield (80%) was obtained with Ni(OAc)$_2$·4H$_2$O as the catalyst (entry 18). Control experiments showed that no amination product was observed in the absence of [Ni(cod)$_2$] or dcype ligand (entries 16 and 17). When secondary amines, such as morpholine were used, the aminolysis reaction of the ester substrate occurred, thus affording the undesired amide product **4**.[13] Other esters such as methyl and benzyl esters were not suitable for this transformation as it allows for a chemoselective amination of differently protected esters (Scheme 2).

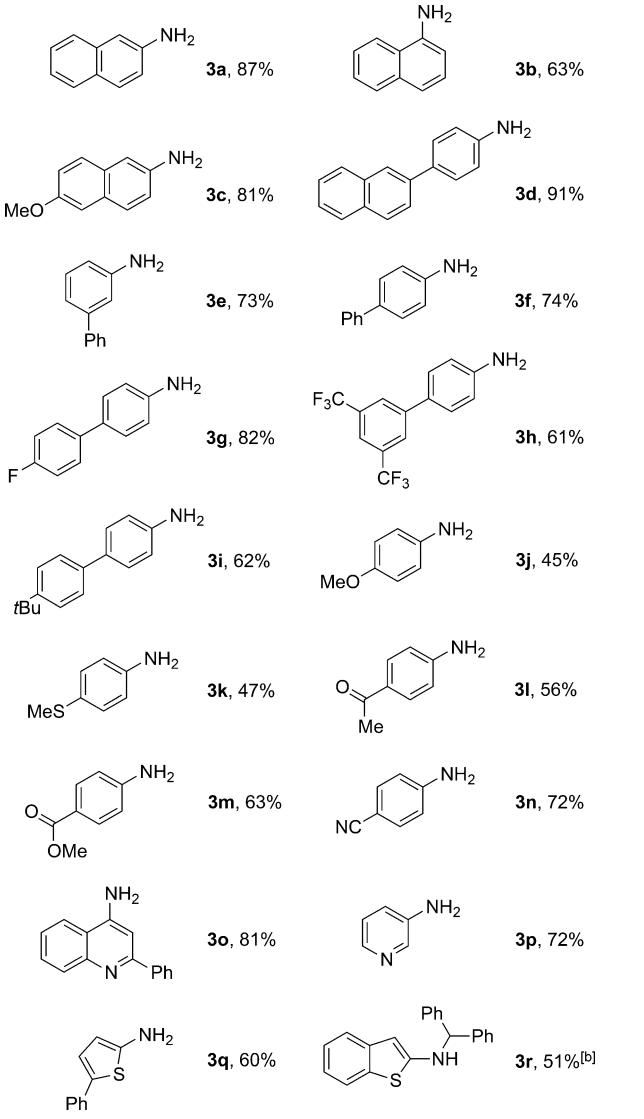


Scheme 2. Nickel-catalyzed decarbonylative amination of the naphthyl ester **1a**.

With the optimized reaction conditions in hand, the scope with respect to the aryl esters was examined (Table 2). The results show that a range of aromatic and heteroaromatic esters having various substitution patterns were tolerated in this newly developed ester to amine transformation, thus giving the corresponding primary amines in moderate to high yields. As anticipated, naphthyl esters (**1a–c**) underwent this decarbonylative amination protocol in good to high yields. Although protocols for the amination of the C–OMe bond under nickel catalysis have been reported,[4] we were pleased to find that methoxy groups are well tolerated in our amination protocol (**3c** and **3j**). Furthermore, not only simple biphenyl ester gave the desired products (**3e** and **3f**) in good yields, but also a series of biphenyl ester derivatives possessing fluoro (**1g**), trifluoromethyl (**1h**), and tertiary butyl substituents (**1i**) efficiently underwent this transformation. Simple phenyl derivatives are more challenging substrates than π-extended systems.[3e] However, we were pleased to find that under our catalytic system, simple phenyl ester derivatives, possessing either electron-donating or electron-withdrawing functional groups, could be converted into the corresponding amines in moderate to good yields. The chemoselectivity of this new amination protocol was nicely

Table 2: Scope with respect to the aryl esters.[a]

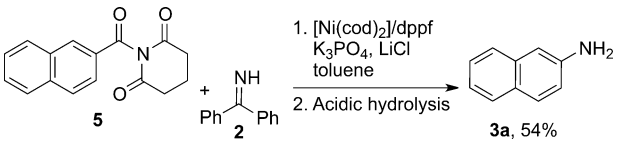




[a] Reaction conditions: aryl ester **1a–r** (0.2 mmol), benzophenone imine **2** (0.4 mmol), [Ni(cod)$_2$] (0.02 mmol), dcype (0.04 mmol), K_3PO_4 (0.6 mmol), LiCl (0.4 mmol) in toluene (1 mL) at 170 °C, 48 h. [b] Work up: reduction by $NaBH_4$ (10 equiv) in methanol (5 mL).

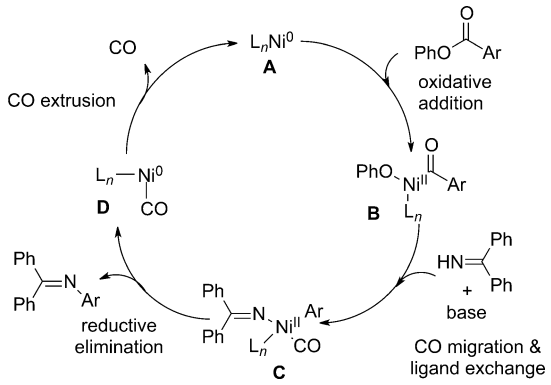
illustrated by the fact that sensitive functional groups such as methoxy, methylthio, ketone, ester, and cyano on the phenyl ring were perfectly accommodated, thus providing opportunities for further functionalization (**3j–n**). Gratefully, our decarbonylative amination transformation could be readily extended to heterocyclic esters derived from quinoline, pyridine, and thiophene, thus affording the corresponding heteroaryl primary amines in moderate to high yields (**3o–q**). It is noteworthy that the corresponding secondary amine **3r** could also be obtained by reductive hydrogenation of the ketimine intermediate instead of acidic hydrolysis.

To demonstrate the applicability of this newly developed amination methodology, an aryl amide was also used as a different electrophile. Minor modification of the standard reaction conditions by changing the ligand from dcype to dppf allowed the decarbonylative amination of the amide **5** with benzophenone imine to proceed, thus showing the potential of our amination protocol in the development of versatile aroyl compounds as electrophiles (Scheme 3).



Scheme 3. Nickel-catalyzed decarbonylative amination of naphthyl amide. dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

Based on our results and previous studies,[14,15] a mechanism for this new nickel-catalyzed decarbonylative amination reaction is proposed (Scheme 4). Oxidative addition of the



Scheme 4. Proposed mechanism for the new nickel-catalyzed decarbonylative amination of aryl esters.

[LnNi^0] complex **A** into the C(acyl)–O bond of aryl ester gives an acyl nickel(II) intermediate (**B**), which subsequently undergoes CO migration and ligand exchange with benzophenone imine, with the assistance of a base to afford an arylimine nickel(II) intermediate **C**. Reductive elimination produces a [L_nNi^{0}CO] (**D**) and the amination product. Finally, extrusion of CO from **D** regenerates the active LnNi^0 catalyst **A**.

In summary, we have developed the first catalytic decarbonylative amination protocol which allows, for the first time, the transfer of a series of readily available aryl and heteroaryl esters, and even amides, to the corresponding amines. In contrast to classical multistep rearrangement procedures, the method relies on the use of either [Ni(cod)$_2$]/dcype catalytic system or the use of a nickel(II) salt to directly provide the desired amines. Considering the substrate scope of this protocol, the method provides a new and efficient route to aryl amines from readily available esters. The protocol shows good chemoselectivity, and functional groups including C–OMe, C–SMe, C–F, and CN moieties,

previously used in cross-couplings, remain intact. Since aryl and heteroaryl amines are highly valuable products for many different applications this new ester to amine interconversion will be of value and may become a good alternative to aryl halides amination reactions. Efforts to investigate the mechanism and broaden the scope further are currently ongoing in our laboratories and will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amination · arenes · esters · nickel · reaction mechanisms

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Communications

Amination

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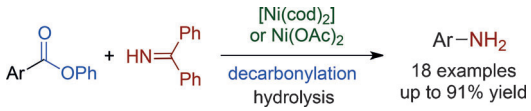

An efficient nickel-catalyzed decarbonylative amination reaction of readily available aryl and heteroaryl esters has been developed. This new amination protocol shows high tolerance towards a variety of aryl and heteroaryl esters, thus providing a practical and versatile access to valuable primary amines. cod = 1,5-cyclooctadiene.