

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

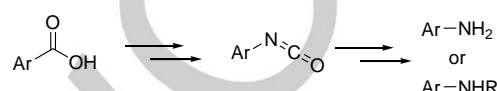
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**Abstract:** An efficient nickel catalyzed decarbonylative amination reaction of aryl and heteroaryl esters has been achieved for the first time. The new amination protocol allows the direct interconversion of esters and amides into the corresponding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

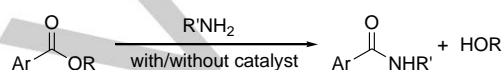
Aromatic amines are important synthetic building blocks in chemistry due to their application in the preparation of pharmaceuticals, biologically active molecules, natural products, polymers, as well as functional materials.<sup>[1]</sup> Accordingly, the development of new methodologies to access these valuable molecules continues to be of great importance in synthetic organic chemistry.<sup>[1]</sup> Conventionally, Pd-catalyzed Buchwald-Hartwig reaction represents a valuable C(sp<sup>2</sup>)-N bond formation method which makes a great contribution to this field.<sup>[2]</sup> Although Pd 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 non-precious metal catalysts. Particular attention has been drawn to the use of inexpensive and earth abundant nickel catalysts,<sup>[3]</sup> along with easily available and versatile C(sp<sup>2</sup>)-O electrophiles.<sup>[4-8]</sup> 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 derivatives.<sup>[9-12]</sup>

However, to the best of our knowledge, metal catalyzed C(sp<sup>2</sup>)-N bond formations via a decarbonylative process with carboxylic acid derivatives as substrates have not been realized before. Traditionally, acids or ester derivatives are transformed to amines following a multi-step sequences and involve classical rearrangements (Scheme 1a).

## a) Schmidt reaction; Curtius, Hoffmann, Lossen rearrangement

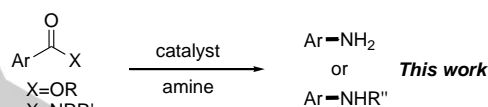


## b) Classical amide bond formations



## c) New decarbonylative amination of carboxylic acid derivatives

### C-N bond formation



### Direct Ester and Amide to Amine Interconversion

**Scheme 1.** a) Classical carboxylic acid to amine interconversions via rearrangements; b) Classical amide bond formations via ester amine coupling; c) Direct transformation of esters or amides to amines.

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

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 yielding aromatic amines in a one step process (Scheme 1c). Herein, we report an unprecedented decarbonylative amination protocol for the direct interconversion of esters as well as amides to aryl amines (Scheme 1c). In order to prevent the undesired amide bond formation when reacting esters with amines (Scheme 1b), we decided to apply imines as nucleophiles instead. This would also allow the further 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

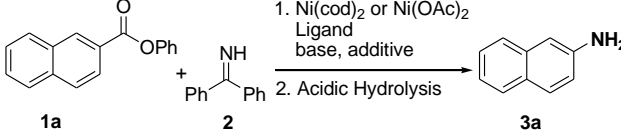
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transformation. No reaction occurred when IPr·HCl was applied as ligand (entry 1). The use of monodentate phosphine ligands such as P(*n*-Bu)<sub>3</sub> and PCy<sub>3</sub> gave also no desired product (entries 2 and 3).

**Table 1.** Optimization of the reaction conditions.<sup>[a]</sup>



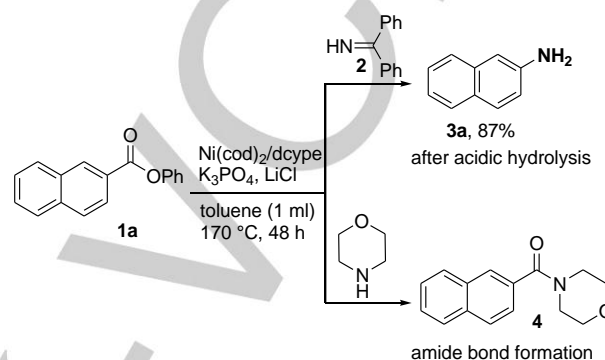
Entry	[Ni]	Ligand (x mol%)	Base (2 equiv.)	Additive (2 equiv.)	Yield (%) <sup>[b]</sup>
1	Ni(cod) <sub>2</sub>	IPr·HCl (20)	Cs <sub>2</sub> CO <sub>3</sub>	-	0
2	Ni(cod) <sub>2</sub>	P <sup><i>n</i></sup> Bu <sub>3</sub> (20)	Cs <sub>2</sub> CO <sub>3</sub>	-	0
3	Ni(cod) <sub>2</sub>	PCy <sub>3</sub> (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
11	Ni(cod) <sub>2</sub>	dcype (20)	NaO <sup><i>t</i></sup> Bu	-	0
12 <sup>[c]</sup>	Ni(cod) <sub>2</sub>	dcype (20)	K <sub>3</sub> PO <sub>4</sub>	-	56
13 <sup>[c]</sup>	Ni(cod) <sub>2</sub>	dcype (20)	K <sub>3</sub> PO <sub>4</sub>	LiCl	63
14 <sup>[c,d]</sup>	Ni(cod) <sub>2</sub>	dcype (20)	K <sub>3</sub> PO <sub>4</sub>	LiCl	84
15 <sup>[c-e]</sup>	Ni(cod) <sub>2</sub>	<b>dcype (20)</b>	<b>K<sub>3</sub>PO<sub>4</sub></b>	<b>LiCl</b>	<b>87</b>
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>	-	dcype (20)	K <sub>3</sub> PO <sub>4</sub>	LiCl	0
18 <sup>[c-e]</sup>	Ni(OAc) <sub>2</sub>	dcype (20)	K <sub>3</sub> PO <sub>4</sub>	-	80
19 <sup>[c-e]</sup>	Ni(OAc) <sub>2</sub>	dcype (20)	K <sub>3</sub> PO <sub>4</sub>	Mn <sup>[f]</sup>	63
20 <sup>[c-e]</sup>	Ni(OAc) <sub>2</sub>	dcype (20)	K <sub>3</sub> PO <sub>4</sub>	Et <sub>3</sub> SiH <sup>[g]</sup>	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)<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. [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%).

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 vs 6). Various bases were next examined and K<sub>3</sub>PO<sub>4</sub> was found to be the optimal choice. Reactions in the presence of other bases gave lower yields (Li<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>) or even no desired product (NaO<sup>*t*</sup>Bu), which 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 equiv. of benzophenone imine and 3 equiv. of K<sub>3</sub>PO<sub>4</sub> were used (entry 12).

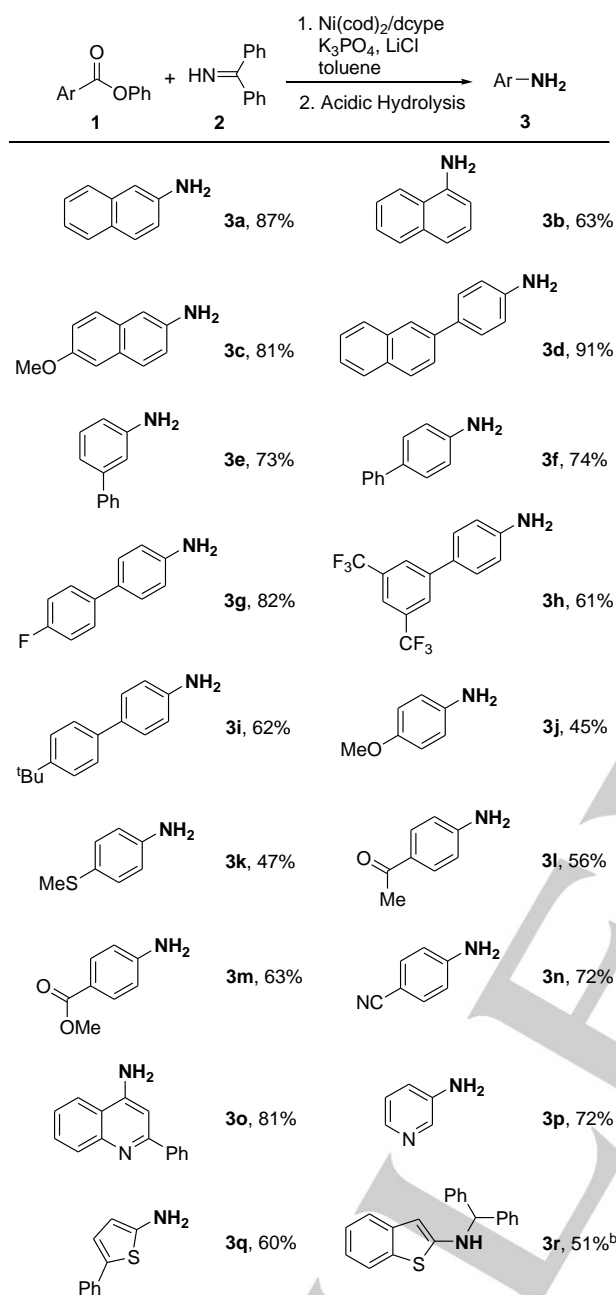
LiCl as Lewis acid additive was found to have a beneficial effect on our decarbonylative amination which may be due to coordination to the carbonyl group (entry 13). Extending the reaction time and increasing slightly the temperature, improved

significantly the yield (entries 14-15). 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)<sub>2</sub>·4H<sub>2</sub>O as catalyst (entry 18). Control experiments showed that no amination product was observed in the absence of Ni(cod)<sub>2</sub> or dcype ligand (entries 16-17). When secondary amines such as morpholine was used, aminolysis reaction of the ester substrate occurred, affording the undesired amide product **4**.<sup>[13]</sup> Other esters such as methyl and benzyl esters were not suitable for this transformation which allows for a chemoselective amination of differently protected esters.



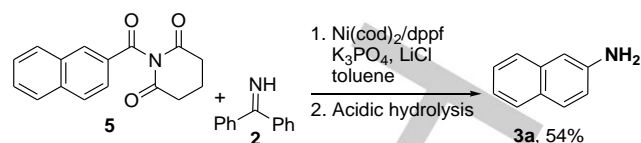
**Scheme 2.** Nickel catalyzed decarbonylative amination of naphthyl ester **1a**.

With the optimized reaction conditions in hand, the scope with respect to the aryl esters was subsequently examined (Table 2). The results show that a range of aromatic and heteroaromatic esters bearing various substitution patterns were tolerated in this newly developed ester to amine transformation, 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 C-OMe bond under nickel catalysis have been reported,<sup>[4]</sup> 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**), or tertiary butyl substituents (**1i**) efficiently underwent this transformation. Simple phenyl derivatives are more challenging substrates than  $\pi$ -extended systems.<sup>[3f]</sup> 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 illustrated by the fact that sensitive functional groups such as methoxy, methylthio, ketone, ester and cyano on the phenyl ring were perfectly accommodated, 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, 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.

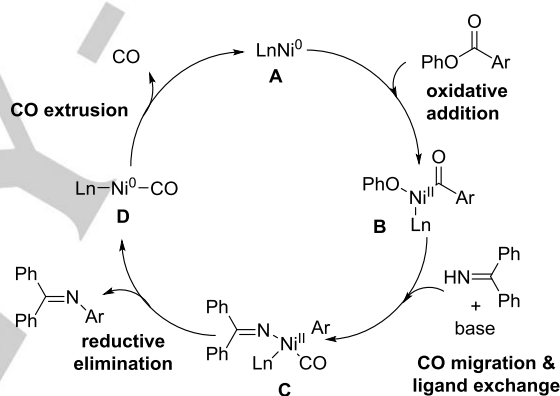
**Table 2.** Scope of the aryl esters.<sup>[a]</sup>

[a] Reaction conditions: aryl ester **1a-r** (0.2 mmol), benzophenone imine **2** (0.4 mmol), Ni(cod)<sub>2</sub> (0.02 mmol), dcype (0.04 mmol), K<sub>3</sub>PO<sub>4</sub> (0.6 mmol), LiCl (0.4 mmol) in toluene (1 ml) at 170 °C, 48 h. [b] Work up: reduction by NaBH<sub>4</sub> (10 equiv.) in methanol (5 ml).

In order 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 conditions by changing the ligand from dcype to dppf allowed the decarbonylative amination of amide **5** with benzophenone imine to proceed, showing the great potential of our amination protocol in the development of versatile aryl compounds as electrophiles (Scheme 3).

**Scheme 3.** Nickel catalyzed decarbonylative amination of naphthyl amide.

Based on our results and previous studies,<sup>[14-15]</sup> a mechanism for this new Ni-catalyzed decarbonylative amination reaction is proposed (Scheme 4). Oxidative addition of the LnNi<sup>0</sup> 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 aryl-imine nickel(II) intermediate **C**. Reductive elimination produces a L<sub>n</sub>Ni<sup>0</sup>CO **D** and the amination product. Finally, extrusion of CO from **D** regenerates the active LnNi<sup>0</sup> catalyst **A**.

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

In summary, we have developed the first catalytic decarbonylative amination protocol which allows for the first time to transfer 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 Ni(cod)<sub>2</sub>/dcype catalytic system or the use of a Ni(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 or CN groups 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.

## Acknowledgements

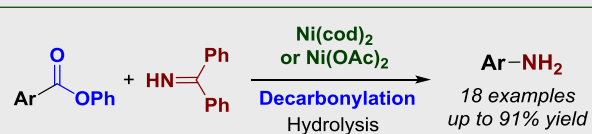
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**Keywords:** Amination • Decarbonylation • Aryl Ester • Benzophenone Imine • Nickel Catalysis

- [1] a) Ricci, A., Ed. *Amino Group Chemistry: From Synthesis to the Life Sciences*; Wiley-VCH: Weinheim, **2008**; b) S. A. Lawrence, *Amines: Synthesis, Properties and Applications*, Cambridge University, Cambridge, **2004**; c) B. R. Brown, *The Organic Chemistry of Aliphatic Nitrogen Compounds*, Cambridge University, Cambridge, **2004**; d) Rappoport, Z., Ed. *The Chemistry of Anilines, Parts 1 and 2*; John Wiley & Sons: New York, **2007**; e) M. Kienle, S. R. Dubbaka, K. Brade, P. Knochel, *Eur. J. Org. Chem.* **2007**, 4166-4176; f) M. Liang, J. Chen, *Chem. Soc. Rev.* **2013**, *42*, 3453-3488.
- [2] a) J. P. Wolfe, S. Wagaw, J. F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805-818; b) J. F. Hartwig, *Acc. Chem. Res.* **1998**, *31*, 852-860; c) J. F. Hartwig, *Angew. Chem. Int. Ed.* **1998**, *37*, 2046-2067; d) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131-209; e) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534-1544; f) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 6338-6361; g) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27-50.
- [3] a) Y. Tamaru, *Modern Organonickel Chemistry*, Wiley-VCH, Weinheim, Germany, **2005**; b) V. B. Phapale, D. J. Cárdenas, *Chem. Soc. Rev.* **2009**, *38*, 1598-1607; c) J. Yamaguchi, K. Muto, K. Itami, *Eur. J. Org. Chem.* **2013**, 19-30; d) F.-S. Han, *Chem. Soc. Rev.* **2013**, *42*, 5270-5298; e) M. Tobisu, N. Chatani, *Acc. Chem. Res.* **2015**, *48*, 1717-1726.
- [4] a) Tobisu, M.; Shimasaki, T.; Chatani, N. *Chem. Lett.* **2009**, *38*, 710-711; b) M. Tobisu, A. Yasutome, K. Yamakawa, T. Shimasaki, N. Chatani, *Tetrahedron* **2012**, *68*, 5157-5161.
- [5] T. Shimasaki, M. Tobisu, N. Chatani, *Angew. Chem. Int. Ed.* **2010**, *49*, 2929-2932; *Angew. Chem.* **2010**, *122*, 2991-2994.
- [6] a) T. Mesganaw, A. L. Silberstein, S. D. Ramgren, N. F. Fine Nathel, X. Hong, P. Liu, N. K. Garg, *Chem. Sci.* **2011**, *2*, 1766-1771; b) L. Hie, S. D. Ramgren, T. Mesganaw, N. K. Garg, *Org. Lett.* **2012**, *14*, 4182-4185.
- [7] a) S. D. Ramgren, A. L. Silberstein, Y. Yang, N. K. Garg, *Angew. Chem. Int. Ed.* **2011**, *50*, 2171-2173; *Angew. Chem.* **2011**, *123*, 2219-2221; For further examples, see: b) L. Ackermann, R. Sandmann, W. Song, *Org. Lett.* **2011**, *13*, 1784-1786; c) N. F. Fine Nathel, J. Kim, L. Hie, X. Jiang, N. K. Garg, *ACS Catal.* **2014**, *4*, 3289-3293; d) N. H. Park, G. Teverovskiy, S. L. Buchwald, *Org. Lett.* **2014**, *16*, 220-223.
- [8] Examples For the amination of fluorosulfonates, phosphates, tosylates, mesylates and triflates, see: a) P. S. Hanley, T. P. Clark, A. Krasovskiy, M. S. Ober, J. P. O'Brien, T. S. Staton, *ACS Catal.* **2016**, DOI: 10.1021/acscatal.6b00865; b) J.-H. Huang, L.-M. Yang, *Org. Lett.* **2011**, *13*, 3750-3753; c) C.-Y. Gao, L.-M. Yang, *J. Org. Chem.* **2008**, *73*, 1624-1627; d) M. J. Iglesias, J. F. Blandez, M. R. Fructos, A. Prieto, E. Álvarez, T. R. Belderrain, M. C. Nicasio, *Organometallics* **2012**, *31*, 6312-6316; f) ref. 7d.
- [9] New trends in cross-coupling: Theory and applications, T. J. Colacot Ed., RSC: Cambridge, UK, **2015**.
- [10] For a recent review, see: W. I. Dzik, P. P. Lange, L. J. Goofsen, *Chem. Sci.* **2012**, *3*, 2671-2678.
- [11] C-C-bond formations: K. Amaike, K. Muto, J. Yamaguchi, K. Itami, *J. Am. Chem. Soc.* **2012**, *134*, 13573-13576; b) K. Muto, J. Yamaguchi, D. G. Musaev, K. Itami, *Nat. Commun.* **2015**, *6*, 7508-7515.
- [12] C-B-bond and C-Si bond formations: a) L. Guo, M. Rueping, *Chem. Eur. J.* **2016**, *22*, 16787-16790; b) J. Hu, Y. Zhao, J. Liu, Y. Zhang, Z. Shi, *Angew. Chem. Int. Ed.* **2016**, *55*, 8718-8722; c) L. Guo, A. Chatupheeraphat, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, *55*, 11810-11813.
- [13] For representative reports on the nickel-catalyzed formation of amides from aryl compounds, see: a) L. Hie, N. F. F. Nathel, X. Hong, Y. F. Yang, K. N. Houk, N. K. Garg, *Angew. Chem. Int. Ed.* **2016**, *55*, 2810-2814; b) E. L. Baker, M. M. Yamano, Y. Zhou, S. M. Anthony, N. K. Garg, *Nat. Commun.* **2016**, *7*, DOI: 10.1038/ncomms11554.
- [14] a) M. Leiendecker, C. C. Hsiao, L. Guo, N. Alandini, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 12912-12915; b) L. Guo, M. Leiendecker, C. C. Hsiao, C. Baumann, M. Rueping, *Chem. Commun.* **2015**, *51*, 1937-1940; c) M. Leiendecker, A. Chatupheeraphat, M. Rueping *Org. Chem. Front.*, **2015**, *2*, 350-353; d) X. Liu, C.-C. Hsiao, I. Kalvet, M. Leiendecker, L. Guo, F. Schoenebeck, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, *55*, 6093-6098; e) L. Guo, X. Liu, C. Baumann, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, *55*, 15415-15419; f) L. Fan, J. Jia, H. Hou, Q. Lefebvre, M. Rueping, *Chem. Eur. J.* **2016**, *22*, 16437-16440; g) L. Guo, C.-C. Hsiao, H. Yue, X. Liu, M. Rueping, *ACS Catal.* **2016**, *6*, 4438-4442.
- [15] a) X. Hong, Y. Liang, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 2017-2025; b) Q. Lu, H. Yu, Y. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 8252-8260.

Layout 2:

## COMMUNICATION



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, providing a practical and versatile access to valuable primary amines.

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