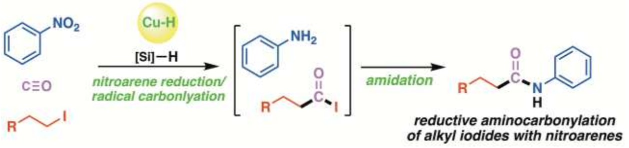
Synergistic Copper-Catalyzed Reductive Aminocarbonylation of Alkyl Iodides with Nitroarenes

Siling Zhao and Neal P. Mankad*

Department of Chemistry, University of Illinois at Chicago, 845 W. Taylor St., Chicago, IL 60607

Supporting Information Placeholder

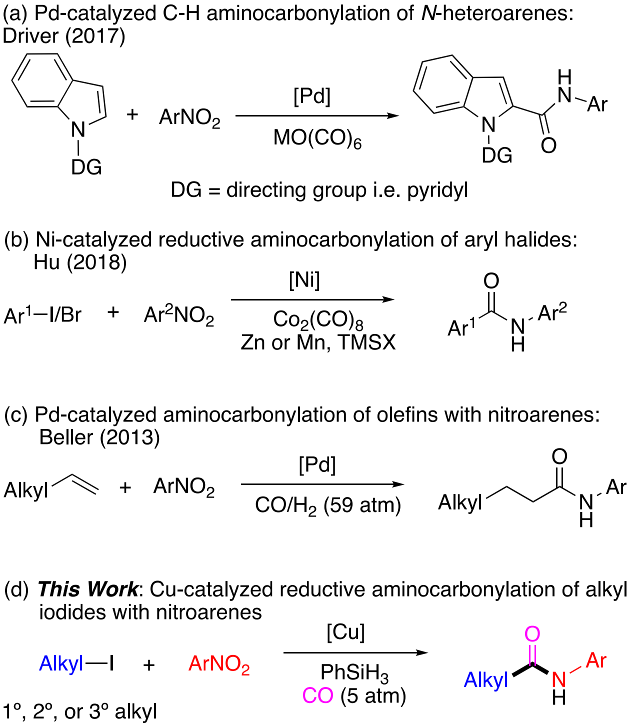


ABSTRACT: We have developed a Cu-catalyzed reductive aminocarbonylation of alkyl iodides using nitroarenes as the nitrogen source. The reaction proceeds with a single copper catalyst playing dual roles of synergistically mediating both carbonylation of alkyl iodides and reduction of nitroarenes, providing acyl iodides and anilines as possible reactive intermediates that then do amide coupling spontaneously. A diverse range of secondary *N*-aryl alkylamides are accessible from a variety of primary, secondary, and tertiary alkyl iodides using this method.

Amides are among of the most important chemical units in all of organic and biology chemistry,[1] and so the synthetic community has maintained an interest in developing different, complementary synthetic methods to target diverse amide compounds.[2] For example, the classic Ritter reaction involves protonation of an alcohol or alkene and *in-situ* trapping of the resulting carbocation with a nitrile nucleophile;[3] thus, only *N*-alkyl amides are accessible. Similarly, amidation of esters or transamidation between amides and amines typically only produce *N*-alkyl amides except in rare cases.[4] An efficient method for *N*-aryl amide synthesis is aminocarbonylation of aryl halides with anilines under CO atmosphere;[5] here use of alkyl electrophiles has proven challenging and limits the scope of accessible products to arylamides.

Nitroarenes can act as surrogates for anilines under reductive conditions, in some cases exhibiting orthogonal functional group tolerance to classical amine nucleophiles in various coupling reactions.[6] However, there are only a few reports of successful reductive aminocarbonylation using nitroarenes as the nitrogen source, none of which involve C(sp^3)-hybridized electrophiles. Driver reported a Pd-catalyzed reductive aminocarbonylation of aromatic C-H bonds with $Mo(CO)_6$ serving as both reducing agent and CO source, producing *N*-aryl arylamides as long as the substrate contained an *ortho*-pyridyl directing group (Scheme 1a).[7] Additionally, recent advances by Hu, Wu, and others have enabled Ni-catalyzed reductive aminocarbonylation of aryl halides (Scheme 1b), esters, and aryl boronic acids.[8] The only example of alkylamide synthesis by reductive aminocarbonylation was reported by Beller, who disclosed a Pd-catalyzed coupling of terminal alkenes with nitroarenes under *syn*-gas pressure to provide *N*-aryl alkylamides (Scheme 1c).[9] Here, the range of accessible products was limited by the fact that only monosubstituted alkenes were amenable to coupling. Recently, Hu also furnished alkylamides through reductive transamidation between nitroarenes and amides.[10] Although C(sp^3)-X electrophiles have not been investigated in reductive aminocarbonylation, they have been used in aminocarbonylation with amine nucleophiles,[11] including a recent report by Alexanian of stereospecific aminocarbonylation with alkyl tosylates with primary and secondary amines.[12]

Scheme 1. Reductive aminocarbonylation with nitroarenes


(a) Pd-catalyzed C-H aminocarbonylation of *N*-heteroarenes: Driver (2017)

DG = directing group i.e. pyridyl

(b) Ni-catalyzed reductive aminocarbonylation of aryl halides: Hu (2018)

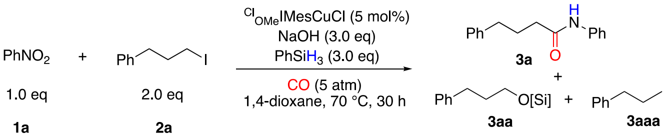
(c) Pd-catalyzed aminocarbonylation of olefins with nitroarenes: Beller (2013)

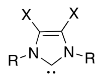
(d) ***This Work***: Cu-catalyzed reductive aminocarbonylation of alkyl iodides with nitroarenes

1°, 2°, or 3° alkyl

Our group has reported several examples of carbonylative coupling reactions involving single-electron transfer activation of alkyl halides mediated by *N*-heterocyclic carbene (NHC) copper catalysts in the presence of reducing agents such as hydrosilanes.[13,14] Thus, we wondered whether this methodology could be extended to reductive aminocarbonylation with nitroarenes as pro-nucleophiles (Scheme 1d), with the copper catalyst playing dual roles of synergistically mediating nitroarene reduction and alkyl halide carbonylation. To our knowledge, copper catalysts have not been explored previously for reductive aminocarbonylation.[15] Nonetheless, Beller has successfully reduced nitroarenes to anilines using copper hydrides,[16] and Yin recently showed that copper catalysis is appropriate for reductive C-N coupling with nitroarenes using hydrosilane reductants.[17] However, to realize our goal that involves controlling a complex sequence of reduction, radical carbonylation, and amidation steps, several challenges would need to be overcome: potential multiple CO insertion,[18] high energy activation of substrates,11[d] competing reduction of alkyl halides by the copper hydride catalyst,[19] and competing hydroxymethylation via reduction of carbonylated intermediates by the copper hydride rather than by the nitrogen nucleophile.[20]

Table 1. Reaction Optimization for Copper-Catalyzed Reductive Aminocarbonylation of Alkyl Iodides[a,b]





IPr R = 2,6-(diisopropyl)phenyl X = H
IMes R = 2,4,6-trimethylphenyl X = H
^{Cl}IMes R = 2,4,6-trimethylphenyl X = Cl
^{Br}IMes R = 2,4,6-trimethylphenyl X = Br
$^{Cl}_{OMe}$IMes R = 4-methoxy-2,6-dimethylphenyl X= Cl

entry	change from optimized conditions	yield of **3a** [%]	yield of **3aa** [%]	yield of **3aaa** [%]
1	None	78	40	12
2	No catalyst	0	0	0
3	IPrCuCl catalyst	38	50	24
4	IMesCuCl catalyst	61	34	14
5	^{Cl}IMesCuCl catalyst	59	32	0
6	^{Br}IMesCuCl catalyst	38	39	23
7	LiOH base	18	22	18
8	LiOMe base	13	25	22
9	Ph_2SiH_2 as silane	0	0	0
10	2.0 eq. $PhSiH_3$	28	18	3
11	10 mol% catalyst	62	64	12
12	60 °C	51	39	10
13	3 atm CO	30	31	6

[a]Reactions were done on 0.1-mmol scale. [b]Yields relative to **1a** were determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard.

We began our study with nitrobenzene (**1a**) and 1-iodo-3-phenylpropane (**2a**) as substrates, targeting amide compound **3a** (Table 1). After screening with different NHC ligands, we found that while direct reduction of alkyl iodides (**3aaa**) can be avoided by the choice of ligands (Table 1, entry 5), hydroxymethylation (**3aa**) cannot be avoided completely. In order to compensate the loss of iodide substrate consumed by hydroxymethylation, we employed 2.0 equivalents of **2a** in the reaction (see SI for more information). Based on further investigation, we noticed that the electronegativity of ligand is crucial to improve the yield of **3a**. For example, while IMes and ^{Cl}IMes provided almost the same yields (Table 1, entries 4-5), ^{Br}IMes decreased yield (Table 1, entry 6) and $^{Cl}_{OMe}$IMes boosted the yield up to 78% (Table 1, entry 1). The choice of NaOH as the base and $PhSiH_3$ as the hydrosilane are necessary for the successful transformation (Table 1, entries 7—9). It is worth noting that the use of LiOMe favored the hydroxymethylation side reactions described above, which is in agreement with our previous work (Table 1, entry 8).[20] Reducing the amount of hydrosilane or raising catalyst loading both diminished the desired reaction (Table 1, entries 10-11). Finally, we observed moderate yields at lower temperature and pressure (Table 1, entries 12-13). Use of alkyl bromide in place of alkyl iodide resulted in only trace conversion, but use of alkyl bromide + KI produced the corresponding amide in 52% yield.

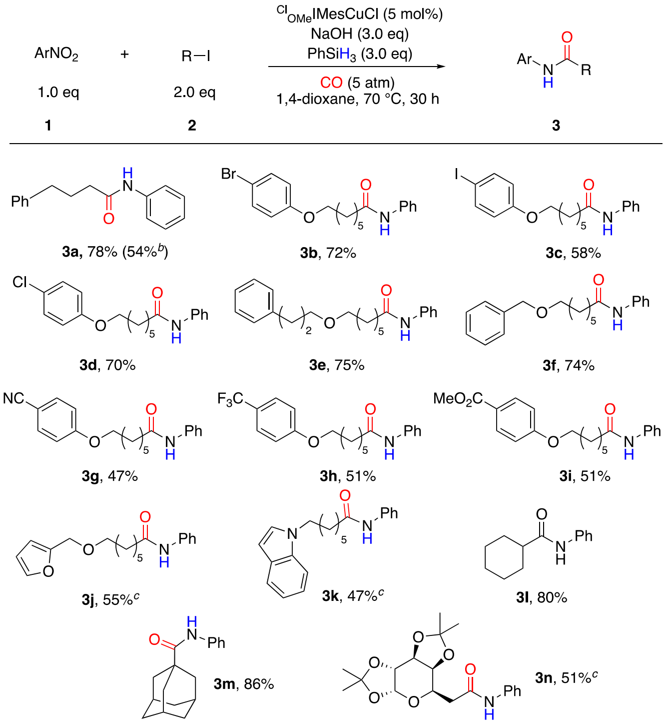


Figure 1.[a] Scope of Alkyl Iodides. [a]Reactions were done on 0.1-mmol scale. All yields are isolated yields relative to **1** and average two parallel experiments. [b]Reactions were done on 1-mmol scale, reported as average isolated yield relative to **1** from two parallel experiments. [c]The ^{Cl}IMes ligand was used instead of $^{Cl}_{OMe}$IMes.

With the optimized conditions in hand, we started to test the scope of alkyl iodides (Figure 1). Simple primary (**3a**), secondary (**3l**), and tertiary (**3m**) alkyl iodides underwent the transformation smoothly. Substrate containing aryl halides were efficiently converted to target amides (**3b—3d**), implying that this methodology is orthogonal to classical Pd-catalyzed couplings. Synthetically important moieties, such as ether (**3e**), cyano (**3g**) and trifluoromethyl (**3h**) are all compatible. To our delight, some base-sensitive groups including benzyl ether (**3f**) and methyl ester (**3i**) survived under these conditions. Heterocyclic groups such as furan (**3j**) and indole (**3k**) gave modest yields and required use of ^{Cl}IMes in place of $^{Cl}_{OMe}$IMes. This method can also be applied to complex carbohydrate substrates (**3n**).

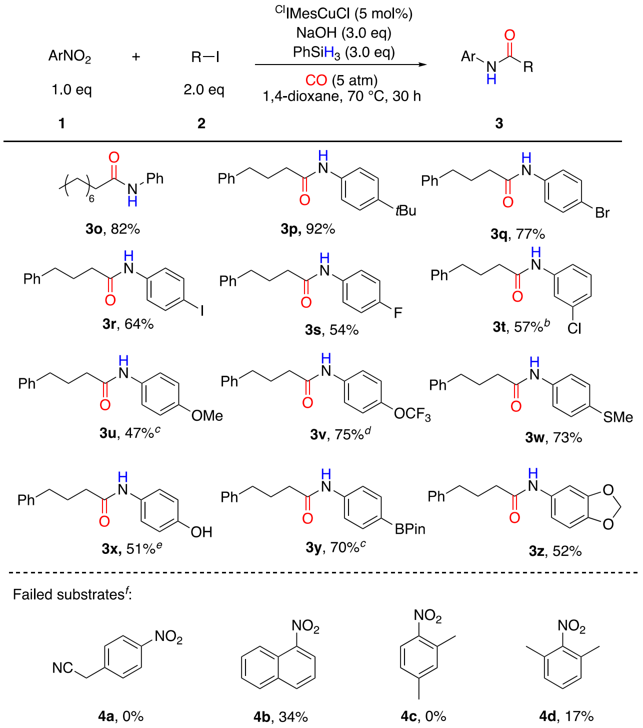
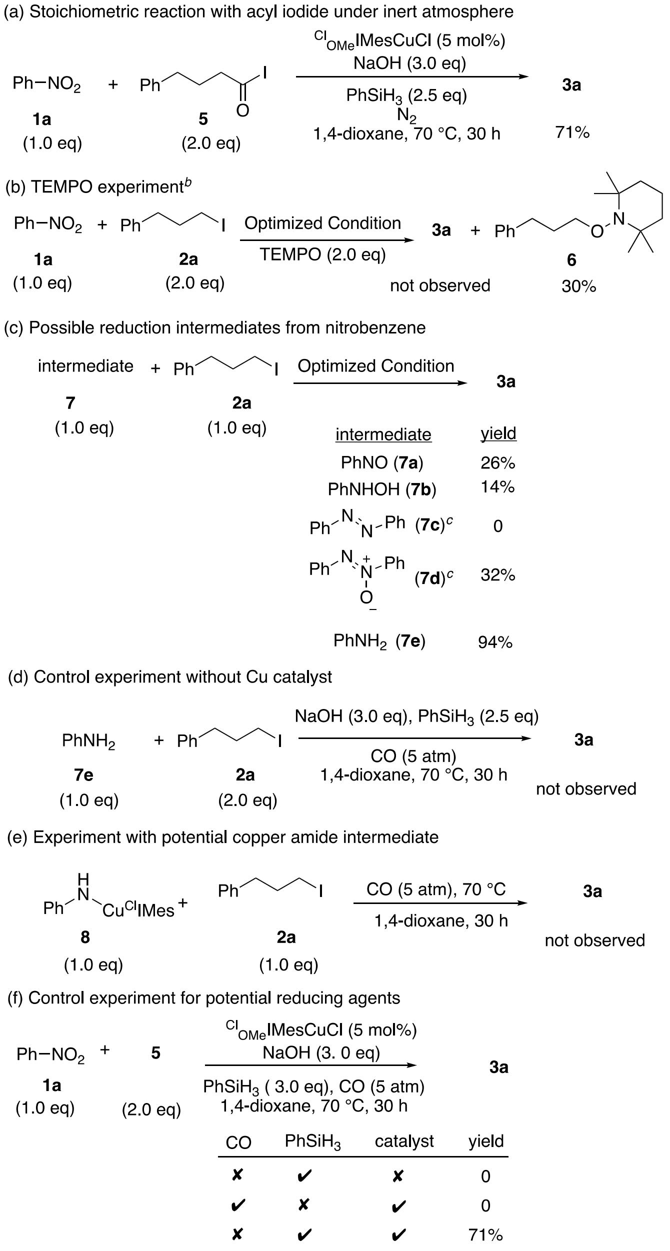


Figure 2.[a] Scope of Nitroarenes. [a]Reactions were done on 0.1-mmol scale. All yields are isolated yields relative to **1** and average two parallel experiments. [b]Product was isolated with 10% inseparable impurities. [c]The IPr ligand was used instead of ^{Cl}IMes. [d]The $^{Cl}{}_{OMe}$IMes ligand was used instead of ^{Cl}IMes. [e]Phenolic group was protected as its pivalic ester and underwent deprotection during the reaction. [f]Yields were NMR yields relative to **1** against 1,1,2,2-tetrachloroethane as internal standard.

Next, we investigated the substrate scope with respect to nitroarenes (Figure 2). We found ^{Cl}IMes performed better than $^{Cl}{}_{OMe}$IMes in this transformation with substituted nitroarenes. Aryl halide (**3q-3t**) and thioether (**3w**) substituents posed no problem in the transformation, whereas protected phenols (**3x**) and heterocyclic groups (**3z**) gave moderate yields. Use of IPr as ligand allowed for smooth conversion with nitroarenes containing boronic esters (**3y**) and anisole (**3u**), while $^{Cl}{}_{OMe}$IMes was required for trifluoromethoxyl substituted nitroarenes (**3v**) to give good yield. However, cyanide groups on the nitroarene (**4a**) inhibited the reaction, and a polyaromatic nitroarene (**4b**) performed poorly in this reaction. We also found this method is highly sensitive to steric environment on the nitrobenzene partner (**4c** and **4d**).

To examine the mechanism of this reductive aminocarbonylation, a stoichiometric reaction was carried out by subjecting acyl iodide **5** to the standard reaction in place of **2a** under N_2 atmosphere (Scheme 2a). The expected amide **3a** was obtained in 71% yield, implying that acyl iodide might serve as the carbonylated intermediate during catalysis. Then the radical nature of this transformation was confirmed by the addition of radical scavenger TEMPO to the standard reaction. The target amide **3a** was not observed; instead the TEMPO adduct compound **8** was isolated in 30% yield (Scheme 2b).

Scheme 2. Mechanistic Studies



[a]Reactions were done on 0.1-mmol scale, and yields were determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard. [b]Isolated yield. [c]0.5 eq. intermediates were added instead of 1.0 eq.

To gain insight into the reactive nitrogen nucleophile during catalysis, several possible intermediates resulting from nitroarene reduction were tested under catalytic conditions (Scheme 2c).[21] No amide product was detected with azobenzene (**7c**), and nitrosobenzene (**7a**), *N*-phenyl hydroxyamine (**7b**) and azoxybenzene (**7d**) gave low yields. Only aniline (**7e**) gave quantitative yield (94%) under the standard reaction conditions. Thus, we propose that aniline might be the major reactive intermediate for C-N bond formation. However, we cannot rule out a potential role of other intermediates such as hydroxylamine serving as nitrogen sources by minor pathways (see SI for more information).

Then the aniline intermediate (**7e**) was subjected to condition shown in Scheme 2d without the presence of copper catalyst.

Surprisingly, amide **3a** or other carbonylated compounds were not detected. This indicates that the carbonylation is a copper-mediated radical process rather than a radical chain-type atom transfer carbonylation.[22] Another potential copper amide intermediate **8** was also tested under optimized conditions shown in Scheme 2e. The absence of targeted **3a** help to eliminate the possible route of a copper amide intermediate mediating radical carbonylation.

To probe the reducing reagent responsible for nitroarene reduction, several control experiments were conducted. Since carbon monoxide, hydrosilanes, and metal hydrides have all been shown to reduce nitroarenes,[23,7] each of them was eliminated individually. According to the results shown in Scheme 2f, we can conclude that only (NHC)CuH intermediates are competent to reduce nitroarenes under these conditions.

Collectively, there is definitive evidence that the copper catalyst plays a dual role of synergistically mediating both alkyl iodide carbonylation and nitroarene reduction. While the detailed mechanism of each step requires more study, we propose that the dual roles of the copper catalyst produce the two reactive intermediates, acyl iodide and aniline, which then engage in C-N coupling via a rapid, uncatalyzed step.

In conclusion, we have developed a copper-catalyzed reductive aminocarbonylation from simple nitroarenes and alkyl iodides. This methodology has shown good tolerance with variety of functional groups and serves as the only reductive aminocarbonyation method for C(sp^3)-hybridized electrophiles. Mechanistic studies suggested that NHC copper catalyst serves a dual function in the tandem process: a copper catalyzed carbonylation of alkyl iodides followed by amidation with *in-situ* generated anilines resulting from nitroarenes reduction catalyzed by the same copper catalyst.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, supplementary results, and spectral data (PDF)

AUTHOR INFORMATION

Corresponding Author

* npm@uic.edu

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

Funding was provided by NSF (CHE-1664632).

REFERENCES

[1] a) Greenberg, A.; Breneman, C. M. & Liebman, J. F. (ed.) *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Material Science*; Wiley: New York, 2000). b) Dunets, J. R.; Magano, J.; Weisenburger, G. A. Large-Scale Application of Amide Coupling Reagents for the Synthesis of Pharmaceuticals. *Org. Process Res. Dev*. **2016**, *20*, 140.c) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem*. **2011**, *54*, 3451.

[2] a) Pattabiraman, V. R. & Bode, J. W. Rethinking Amid Bond Synthesis. *Science* **2011**, *480*, 471. b) Peng, J.-B.; Wu, F.-P.; Li, D.; Geng, H.-Q.; Qi, X.; Ying, J.; Wu, X.-F. Palladium-Catalyzed Regioselective Carbonylative Coupling/Amination of Aryl Iodides with Unactivated Alkenes: Efficient Synthesis of β-Aminoketones. ACS Catal. **2019**, *9*, 2977. c) Han, J.; Wang, N.; Huang, Z.-B.; Zhao, Y.; Shi, D.-Q. Ruthenium-Catalyzed Carbonylation of Oxalyl Amide-Protected Benzylamines with Isocyanate as the Carbonyl Source. J. Org. Chem. **2017**, *82*, 6831. d) Review of "nonclassical" amide syntheses: de Figueiredo, R. M.; Suppo, J.-S.; Campagne, J.-M. Nonclassical Routes for Amide Bond Formation. Chem. Rev. **2016**, *116*, 12029.

[3] Review of the Ritter reaction: Jiang, D.; He, T.; Ma, L.; Wang, Z. Recent Developments in Ritter Reaction. *RSC Adv*. **2014**, *4*, 64936.

[4] Guo, H.; Wang, Y.; Du, G.-F.; Dai, B.; He, L. N-Heterocyclic Carbene-catalysed Amidation of Vinyl Esters with Aromatic Amines. *Tetrahedron* **2015**, *71*, 3472.

[5] For selected reviews: a) Brennfuhrer, A.; Neumann, H.; Beller, M. Palladium-Catalyzed Carbonylation Reactions of Aryl Halides and Related Com-pounds. *Angew. Chem. Int. Ed.* **2009**, *48*, 4114. b) Allen, C. L.; Williams, J. M. J. Metal-Catalysed Approaches to Amide Bond Formation. *Chem. Soc. Rev*., **2011,** *40*, 33405.

[6] Selected recent examples: a) Gui, J.; Pan, C-M.; Jin, Y.; Qin, T.; Lo, J. C.; Lee, B. J.; Spergel, S. H.; Mertzman, M. E.; Pitts, W. J.; La Cruz, T. E.; Schmidt, M. A.; Darvatkar, N.; Natarajan, S. R.; Baran, P. S. Practical Olefin Hydroamination with Nitroarenes. *Science* **2015**, *348*, 886. b) Cheung, C. W.; Hu, X. Amine Synthesis via Iron-Catalyzed Reductive Coupling of Nitroarenes with Alkyl Halides. *Nat. Commun.* **2016**, *7*, 12494. c) Zhu, K.; Shaver, M. P.; Thomas, S. P. Chemoselective Nitro Reduction and Hydroamination Using an Single Iron Catalyst. *Chem. Sci*., **2016**, *7*, 3031. Chemoselective Nitro Reduction and Hydroamination Using an Single Iron Catalyst. *Chem. Sci*., **2016**, *7*, 3031.

[7] Zhou, F.; Wang, D.-S.; Guan, X.; Driver, T. G. Nitroarenes as Nitrogen Source in Intermolecular Palladium-Catalyzed Aryl C-H Bond Aminocarbonylation Reactions. Angew. Chem. Int. Ed. 2017, 56, 4530.

[8] a) Cheung, C. W.; Ploeger, M. L.; Hu, X. Amide Synthesis via Nickle-Catalysed Reductive Aminocarbonylation of Aryl Halides with Nitroarenes. *Chem. Sci.* **2018**, *9*, 655. b) Cheung, C. W.; Ploeger, M. L.; Hu, X. Direct Amidation of Esters with Nitroarenes. *Nat. Commun*. **2017**, *8*, 14878. c) Peng, J.-B.; Li, D.; Geng, H.-Q.; Wu, X.-F. Palladium-Catalyzed Amide Synthesis via Aminocarbonylation of Arylboronic Acids with Nitroarenes. *Org. Lett.* **2019**, *21*, 4878. d) Yin, Z.; Zhang, Z.; Soulé, J-F.; Dixneuf, P. H.; Wu, X.-F. Iron-catalyzed Carbonylative Alkyl-acylation of Heteroarenes. J. Catal. **2019**, *372*, 272. e) Shen, N.; Cheung, C. W.; Ma, J.-A. Direct Amide Synthesis via Ni-mediated Aminocarbonylation of Arylboronic Acids with CO and Nitroarenes. *Chem. Commun.* **2019**, *55*, 13709. f) Qi, X.; Zhou, R.; Peng, J-B.; Ying, J.; Wu, X.-F. Selenium-Catalyzed Carbonylative Synthesis of 2-Benzimidazolones from 2-Nitroanilines with TFBen as the CO Source. *Eur. J. Org. Chem.* **2019**, 5161. g) Peng, J.-B.; Geng, H.-Q.; Wu, F.-P.; Li, D.; Wu, X.-F. Selectivity Controllable Divergent Synthesis of -unsaturated Amides and Maleimides from Alkynes and Nitroarenes via Palladium-Catalyzed Carbonylation. *J. Catal.* **2019**, *375*, 519. h) Geng, H-Q.; Peng, J.-B.; Wu, X.-F. Palladium-Catalyzed Oxidative Carbonylative Coupling of Arylallenes, Arylboronic Acids, and Nitroarenes. *Org. Lett.* **2019**, *21*, 8215.

[9] Fang, X.; Jackstell, R.; Beller, M. Selective Palladium-Catalyzed Aminocarbonylation of Olefins with Aromatic Amines and Nitroarenes. *Angew. Chem. Int. Ed.* **2013**, *52*, 14089.

[10] a) Cheung, C. W.; Ploeger, M. L.; Hu, X. Nickle-Catalyzed Reductive Transamidation of Secondary Amides with Nitroarenes. *ACS Catal*. **2017**, *7*, 7092. b) Cheung, C. W.; Ma, J.-A. Hu, X. Manganese-

Mediated Reductive Transamidation of Tertiary Amides with Nitroarenes. *J. Am. Chem. Soc.* **2018**, *140,* 6789.

[11] a) Yuan, H.; Liu, Z.; Shen, Y.; Zhao, H.; Li, C.; Jia, X.; Li, J. Iron-Catalyzed Oxidative Coupling Reaction of Isocyanides with Simple Alkanes towards Amide Synthesis. *Adv. Synth. Catal*. **2019**, *361*, 2009. b) Serrano, E.; Martin, R. Nickel-Catalyzed Reductive Amidation of Unactivated Alkyl Bromides. *Angew. Chem. Int. Ed*. **2016**, *55*, 11207. c) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. Carbonylation Reactions of Alkyl Iodides through the Interplay of Carbon Radicals and Pd Catalysts. *Acc. Chem. Res*. **2014**, *47*, 1563. d) Chow, S. Y.; Odell, L. R.; Eriksson, J. Low-Pressure Radical ^{11}C-Aminocarbonylation of Alkyl Iodides through Thermal Initiation. *Eur. J. Org. Chem.* **2016**, *36*, 5980.

[12] Sargent, B. T.; Alexanian, E. J. Cobalt-Catalyzed Aminocarbonylation of Alkyl Tosylates: Stereospecific Synthesis of Amides. *Angew. Chem. Int. Ed*. **2019**, *58*, 1.

[13] a) Cheng, L.-J.; Mankad, N. P. Cu-Catalyzed Hydrocarbonylative C-C Coupling of Terminal Alkynes with Alkyl Iodides. *J. Am. Chem. Soc*. **2017**, *139*, 10200. b) Cheng, L.-J.; Islam, S. M.; Mankad, N. P. Synthesis of Allylic Alcohols via Cu-Catalyzed Hydrocarbonylative of Alkynes with Alkyl Halides. *J. Am. Chem. Soc.* **201**8, *140*, 1159. c) Cheng, L.-J.; Mankad, N. P. Cu-Catalyzed Borocarbonylative Coupling of Internal Alkynes with Unactivated Alkyl Halides: Modular Synthesis of tetrasubstituted β-Borylenones. *Angew. Chem., Int. Ed.* **2018**, *57*, 10328.

[14] A review of metal-catalyzed radical carbonylation reactions: Zhao, S.; Mankad, N. P. Metal-Catalysed Radical Carbonylation Reactions. *Catal. Sci. Tech.* **2019**, *9*, 3603.

[15] a) A review of current methodology for reduction of nitroarenes: Kadam, H. K.; Tilve, S. G. Advancement in Methodologies for Reduction of Nitroarenes. *RSC Adv*., **2015**, *5*, 83391. Recent review on carbonylation: b) Peng, J.-B.; Wu, F.-P.; Wu, X.-F. First-Row Transition-Metal-Catalyzed Carbonylative Transformations of Carbon Electrophiles. *Chem. Rev*. **2019**, *119*, 2090. c) Peng, J-B.; Geng, H.-Q.; Wu, X.-F. *Chem*, **2019**, *5*, 526.

[16] a) Junge, K.; Wendt, B.; Shaikh, N.; Beller, M. Iron-Catalyzed Selective Reduction of Nitroarenes to Anilines using Organosilanes. *Chem. Commun*., **2010**, *46*, 1769. Other examples of catalytic reduction of nitroarene: b) Vanier, G. S. Simple and Efficient Microwave-Assisted Hydrogenation Reactions at Moderate Temperature and Pressure. *Synlett*, **2007**, *1*, 131. c) Rahaim, R. J.; Jr. Maleczka, R. E. Pd-Catalyzed Silicon Hydride Reduction of Aromatic and Aliphatic Nitro groups. *Org. Lett*. **2005**, *7*, 5087. d) Hanaya, K.; Muramatsu, T.; Kudo, H.; Chow, Y. L. Reduction of Aromatic Nitro-Compounds o Amines with Sodium Borohydride-Copper (II) Acetylacetonate. *J. Chem. Soc. Perkin Trans. I.* **1979**, *1*, 2409. e) Jain, S. K.; Kumar, K. A. A.; Bharate, S. B.; Vishwakarma, R. A. Facile Access to Amides and Hydroxamic Acids Directly from Nitroarenes. *Org. Biomol. Chem*, **2014**, *12*, 6465. Examples of noncatalytic reduction of nitroarene: f) Saha, A.; Ranu, B. Highly Chemoselective Reduction of Aromatic Nitro Compounds by Copper Nanoparticles/Ammonium Formate. *J. Org. Chem*. **2008**, *73*, 6867. g) Li, G.; Wang, X.; Tian, C.; Zhang, T.; Zhang, Z.; Liu, J. Rapid Access to Multi-Substituted Pyrimido-[4,5-b][1,4]diazepine-2,4,6-trione and Pyrimido-[4,5-b][1,4]diazepine-2,4-dione as Novel and Versatile Scaffolds for Drug Discovery. *Tetrahedron Lett*., **2012,** *53*, 5193.

[17] Peng, H.; Ma, J.; Duan, L.; Zhang, G.; Yin, B. CuH-Catalyzed Synthesis of 3-Hydroxyindolines and 2-Aryl-3H- indol-3-ones from o-Alkynylnitroarenes, Using Nitro as Both the Nitrogen and Oxygen Source. *Org. Lett.* **2019,** *21*, 6194.

[18] a) T Fukuyama, T, Nishitani, S.; Inouye, T.; Morimoto, K.; Ryu, I. Effective Acceleration of Atom Transfer Carbonylation of Alkyl Iodides by Metal Complexes. Application to the synthesis of the Hinokinin Precursor and Dihydrocapsaiin. *Org. Lett*. **2006,** *8*, 1383. b) Fukuyama, T.; Inouye, T.; Ryu, I. Atom Transfer Carbonylation Using Ionic Liquids as Reaction Media. *J. Organomet. Chem*. **2007**, *692*, 685. c) Fusano, A.; Sumino, S.; Nishitani, S.; Inouye, T.; Morimoto, K.; Fukuyama, T.; Ryu, I. Pd/Light-Accelerated Atom-Transfer Carbonylation of Alkyl Iodides: Applications in Multicomponent Coupling Process Leading to Functionalized Carboxylic Acid Derivatives. *Chem. Eur. J.* **2012**, *18*, 9415.

[19] Dang, H.; Cox, N.; Lalic, G. Copper-Catalyzed Reduction of Alkyl Triflates and Iodides: And Efficient Method for the Deoxygenation of Primary and Secondary Alcohols. *Angew. Chem. Int. Ed*. **2014**, *53,* 752.

[20] Zhao, S. Mankad, N. P. Cu-Catalyzed Hydroxymethylation of Unactivated Alkyl Iodides with CO to Provide One Carbon Extended Alcohols. *Angew. Chem., Int. Ed*. **2018**, *57*, 5867.

[21] a) Blaser, H.-U. A Golden Boost to an Old Reaction. *Science* **2006**, *313*, 312. b) Zhu, K.; Shaver, M. P.; Thomas, S. P. Chemoselective Nitro Reduction and Hydroamination Using an Single Iron Catalyst. *Chem. Sci*., **2016**, *7*, 3031.

[22] a) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. Chemistry of Acyl Radicals. *Chem. Rev.* **1999**, *99*, 1991. b) Ryu, I. Radical Carboxylations of Iodoalkanes and Saturated Alcohols using Carbon Monoxide. *Chem. Soc. Rev.* **2001**, *30*, 16.

[23] Tafesh, A. M, Weiguny, J. A Review of the Selective Catalytic Reduction of Aromatic Compounds into Aromatic Amines, Isocyanates, Carbamates, and Ureas Using CO. *Chem. Rev.* **1996**, *96*, 2035.