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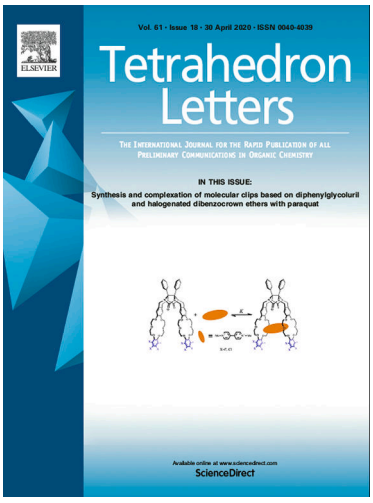

Nickel-Catalyzed Aminocarbonylation of Aryl/Alkenyl/Allyl (pseudo)halides with Isocyanides and H_2O

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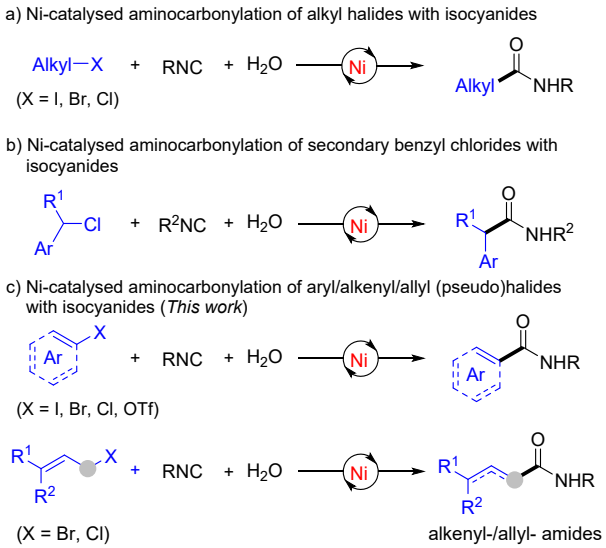
Abstract:

Herein described is a nickel-catalyzed aminocarbonylation of aryl/alkenyl/allyl (pseudo)halides with isocyanides, providing aryl/alkenyl/allyl amides in 41% to 92% yields. Functional groups such as F, Cl, OMe, and heteroaromatic rings are compatible in the reaction. A Ni(0)/(II) catalytic cycle is proposed based on preliminary experiments and previous literature. The reaction features readily available nickel catalysis, broad functional group tolerance, and simple reaction conditions.

The amide is ubiquitous in nature and plays unique role particularly in proteins, agrochemicals, pharmaceuticals, and polymers.[1-2] Amides also serve as versatile building blocks to access a variety of useful organic compounds through traditional transformations or transition metal-catalyzed C-C or C-N bond activation.[3] In this regard, the development of useful methods for amide preparation is highly desirable. Although the condensation of carboxylic acid derivatives with amines is routinely employed as the most robust process, transition metal-catalyzed aminocarbonylation of aryl/alkyl (pseudo)halides, CO, and amines has been extensively investigated over the past several decades.[4] In addition, the reductive coupling reaction of isocyanates also provides a direct pathway for the amide synthesis.[5] Notably, isocyanide, as a serviceable C1 synthon is susceptible to the multicomponent reactions or one-pot cascade reactions with nucleophiles, electrophiles, and radicals.[6] Thus, one promising way to construct amide bond can be achieved through the transition metal-catalyzed aminocarbonylation of aryl/alkyl (pseudo)halides, isocyanides, and H_2O.[7] It should be mentioned that precious metals such as palladium hold a dominant position for the synthesis of aromatic/allyl amides[8] while those reactions catalyzed by base metals[9] are far less developed.

Nickel salt has gained intense attention due to its rich abundance in earth crust and unique catalytic reactivity of single electron transfer (SET) process which may not be readily accessible with palladium analogs.[10-11] The application of nickel catalysis to the amide synthesis using isocyanide as a carbonyl source has been reported more recently.[12] For example, Qu and Chen group[12a] disclosed a nickel-catalyzed aminocarbonylation of alkyl halides, isocyanides, and H_2O (Scheme 1a). This reaction characterizes a broad substrate scope and excellent yields at 100 ^oC. However, an air-sensitive $Ni(COD)_2$ was employed as a catalyst and alkyl iodines were used as electrophile in most cases. Soon later, Qu and Chen group[12b] again described a nickel-catalyzed aminocarbonylation of secondary benzyl chlorides with isocyanides in which halides (-I, -Br, -Cl) and heteroaromatic rings such as pyridine and pyrazine were fairly compatible (Scheme 1b). Despite that alkyl halides have been successfully employed as vital electrophiles, the aryl and allyl

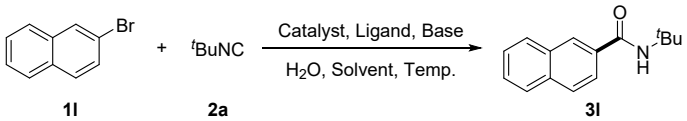
ha re still underdeveloped. We herein present a nickel-catalyzed aminocarboxylation of aryl/alkenyl/allyl (pseudo)halides with isocyanides and H_2O (Scheme 1c). Utilizing $NiBr_2$ as a catalyst and NHC as a ligand, aryl, alkenyl, and allyl amides could be easily obtained in moderate to excellent yields, which provide a novel strategy to construct the amide bond.



Scheme 1. Nickel-catalyzed aminocarbonylation using isocyanide as a C1 source

At the beginning, we commenced the model reaction of 2-bromonaphthalene **1l**, *tert*-butyl isocyanide **2a**, and H_2O under the conditions of $Ni(dme)Cl_2$ (10 mol%), **L1** (20 mol%), NaO^tBu (2 equiv), and toluene (1 ml) at 150 °C for 20 h. To our delight, the desired product **3l** was isolated in 32% yield (Entry 1, Table 1). Other nickel salts were then examined and it was found that $NiBr_2$ was the most efficient catalyst (Entries 2-5, Table 1). Control experiments indicated that nickel salt and ligand were critical to the catalytic cycle (Entries 6-7, Table 1). Next, tuning the volume ratio of H_2O to toluene further improved the yield to 90% (Entries 8-12, Table 1, see Supporting Information for details). Ligand screening revealed that **L1** remained the best one compared with other NHC salts (Entries 13-17, Table 1). Neither phosphine nor nitrogen ligands could promote the reaction (see Supporting Information for details). Different kinds of base were investigated and the yields were inferior to that of NaO^tBu (Entries 18-21, Table 1). Finally, either halving the amount of nickel salt or lowing the reaction temperature resulted in a sharp decrease in yield (Entries 22-23, Table 1).

Table 1. Reaction parameter screening



L1 L2 L3 L4 L5 L6

Entry	Catalyst (mol%)	Ligand	Base	H_2O : toluene (*v*/*v*, ml)	Temp./°C	Yield/%
1	$Ni(dme)Cl_2$ (10)	**L1**	NaO^{t}Bu	0.1 ml: 1.0 ml	150	32
2	$Ni(acac)_2$ (10)	**L1**	NaO^{t}Bu	0.1 ml: 1.0 ml	150	64
3	$Ni(cod)_2$ (10)	**L1**	NaO^{t}Bu	0.1 ml: 1.0 ml	150	57
4	$NiCl_2$ (10)	**L1**	NaO^{t}Bu	0.1 ml: 1.0 ml	150	30
5	$NiBr_2$ (10)	**L1**	NaO^{t}Bu	0.1 ml: 1.0 ml	150	72
6	$NiBr_2$ (10)	-[b]	NaO^{t}Bu	0.1 ml: 1.0 ml	150	0
7	-[c]	**L1**	NaO^{t}Bu	0.1 ml: 1.0 ml	150	0
8	$NiBr_2$ (10)	**L1**	NaO^{t}Bu	0.3 ml: 1.0 ml	150	76
9	$NiBr_2$ (10)	**L1**	NaO^{t}Bu	0.5 ml: 1.0 ml	150	65
11	$NiBr_2$ (10)	**L1**	NaO^{t}Bu	0.3 ml: 0.3 ml	150	80
12	$NiBr_2$ (10)	**L1**	NaO^{t}Bu	0.1 ml: 0.3 ml	150	90
13	$NiBr_2$ (10)	**L2**	NaO^{t}Bu	0.1 ml: 0.3 ml	150	43
14	$NiBr_2$ (10)	**L3**	NaO^{t}Bu	0.1 ml: 0.3 ml	150	65
15	$NiBr_2$ (10)	**L4**	NaO^{t}Bu	0.1 ml: 0.3 ml	150	0
16	$NiBr_2$ (10)	**L5**	NaO^{t}Bu	0.1 ml: 0.3 ml	150	37
17	$NiBr_2$ (10)	**L6**	NaO^{t}Bu	0.1 ml: 0.3 ml	150	40
18	$NiBr_2$ (10)	**L1**	LiO^{t}Bu	0.1 ml: 0.3 ml	150	32
19	$NiBr_2$ (10)	**L1**	KO^{t}Bu	0.1 ml: 0.3 ml	150	76
20	$NiBr_2$ (10)	**L1**	Na_2CO_3	0.1 ml: 0.3 ml	150	31
21	$NiBr_2$ (10)	**L1**	NaOH	0.1 ml: 0.3 ml	150	45
22	$NiBr_2$ (5)	**L1**	NaO^{t}Bu	0.1 ml: 0.3 ml	150	60
23	$NiBr_2$ (10)	**L1**	NaO^{t}Bu	0.1 ml: 0.3 ml	130	67

[a]Reaction conditions: **1l** (0.2 mmol), **2a** (0.2 mmol), catalyst, ligand (20 mol%), base (2 equiv), H_2O, toluene, at an indicated temperature for 20 h. [b]No ligand. [c]No catalyst.

With the optimized conditions in hand, we started to evaluate the substrate scope of aryl halides (Scheme 2). Phenyl halides were first examined and bromobenzene exhibited a superior reactivity over chloro/iodo analogs (**3a**, Scheme 2). A series of bromobenzenes with electron varied functional groups at

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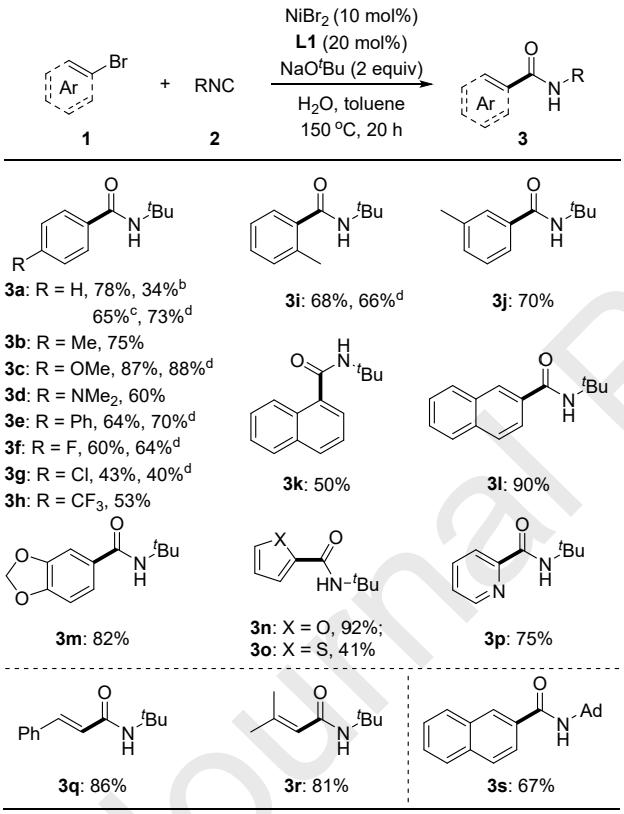
bearing the electron donating group at phenyl ring. Note that the reaction of 1-bromo-4-chlorobenzene gave a single product **3g** albeit in a low yield, which suggested a good chemo-selectivity. Relatively lower yields of **3i** (*vs* **3b**, **3j**) and **3k** (*vs* **3l**) implied a steric hindrance effect on product outcome. It should be mentioned that heteroaromatic bromides bearing pyridinyl, furyl, and thienyl were compatible with the reaction conditions (**3n**-**p**, Scheme 2). In addition of aryl halides, alkenyl bromide was employed as an electrophile as well. Both (E)-(2-bromovinyl)benzene and 1-bromo-2-methylprop-1-ene gave the desired products in 86% and 81% yield, respectively (**3q**-**r**, Scheme 2). Aryl triflates instead of aryl halides exhibited a comparable reactivity (**3a**, **3c**, **3e**-**g**, **3i**, Scheme 2). We next examined the scope of isocyanide. Expectedly, 1-adamantane isocyanide reacted with 1-bromonaphthalene and H_2O generating the corresponding product in 67% yield (**3s**, Scheme 2). However, aryl and butyl isocyanides failed to deliver the amides even for the prolonged reaction time.



Scheme 2. Substrate scope of aryl/alkenyl (pseudo)halides. [a]Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), $NiBr_2$ (10 mol%), **L1** (20 mol%), NaO^tBu (2 equiv), H_2O (0.1 ml), toluene (0.3 ml), at 150 °C for 20 h. [b]From aryl chloride. [c]From aryl iodine. [d]From aryl triflate.

To our surprise, allyl bromide was also viable substrate providing an isomerized alkenyl amide **3t** as major product in 60% yield under the standard reaction conditions. The yield of **3t** was further improved to 68% if the reaction was conducted under the Conditions A. Notably, allyl chloride could give a comparable yield (71%) with higher regio-selectivity (**3t**, Scheme 3). In contrast, other selected allyl halides reacting with **2a**

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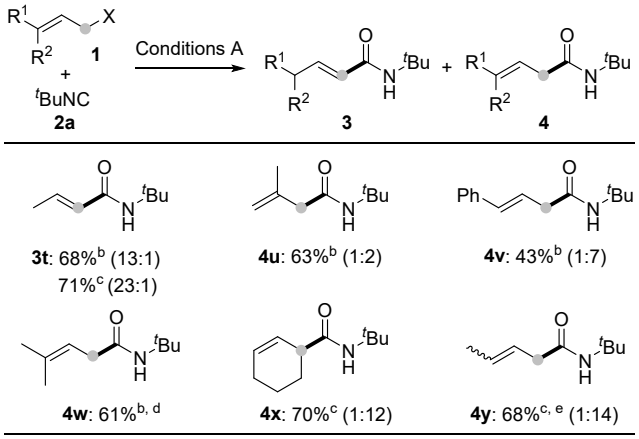
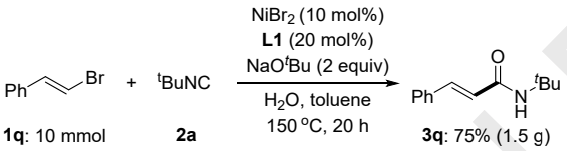


Scheme 3. Substrate scope of allyl halides. [a]Conditions A: **1** (0.2 mmol), **2a** (0.2 mmol), Ni(dppp)Cl_2 (10 mol%), base (2 equiv), H_2O (0.3 ml), MeCN (0.5 ml), at 150 °C for 12 h. The ratio of **3** to **4** was determined by crude ^{1}H NMR analysis and given in the parenthesis and major isomer was shown in Scheme 3. [b]X = Br. [c]X = Cl. [d]Single isomer. [e]The Z/E ratio of **4y** could not be determined by the crude ^{1}H NMR analysis.

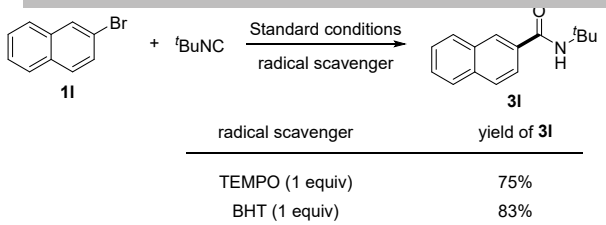
A gram-scale reaction of (E)-(2-bromovinyl)benzene **1q** with *tert*-butyl isocyanide **2a** was performed under the standard reaction conditions (Scheme 4). Delightedly, the product **3q** was isolated in a synthetically useful yield. This result indicated that the nickel-catalyzed aminocarbonylation reaction might be practically useful for the amide synthesis.



Scheme 4. Gram-scale reaction

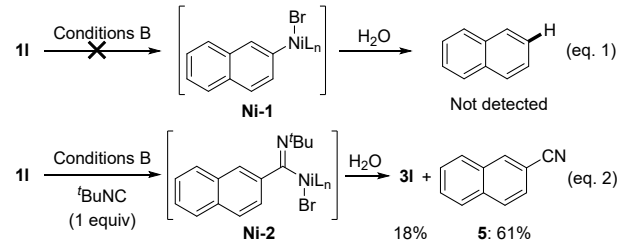
To clarify the possible reaction mechanism, we first conducted the radical trapping experiment (Scheme 5). TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) and BHT (butylated hydroxytolueneand) were respectively chosen as radical scavenger and subjected to the model reaction. As a result, these reactions proceeded smoothly providing the product in good yields (Scheme 5a). It could be inferred that a radical process might not be involved in the catalytic cycle. Next, stoichiometric experiments were carried out. The model substrate **1l** was treated with stoichiometric nickel salt, ligand, and base in toluene at 150 °C for 3 h (Scheme 5b, eq. 1). Unfortunately, naphthalene could not be detected and the starting material **1l** was recovered. Then we conducted the similar reaction under the Conditions B with extra addition of *tert*-butyl isocyanide **2a**. The product **3l** and 2-naphthonitrile **5** were isolated in 18% and 61% yield, respectively (Scheme 5b, eq. 2). These results indicated that **Ni-2** might be the key intermediate in the aminocarbonylation reaction.

a) R



radical scavenger	yield of **3l**
TEMPO (1 equiv)	75%
BHT (1 equiv)	83%

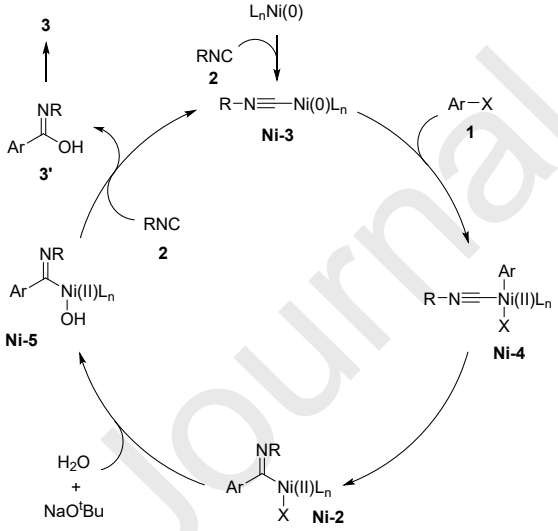
b) Stoichiometric experiments



Conditions B: $NiBr_2$ (1 equiv), **L1** (1 equiv), NaO^tBu (1 equiv), toluene, 150 °C, 3 h.

Scheme 5. Mechanistic experiments

Based on the mechanistic experiments and previous literature,[13] we proposed a possible reaction mechanism shown in Scheme 6. The catalytic reaction might be initiated by an *in situ* formed Ni(0) species which coordinated with isocyanide to form **Ni-3**. An oxidative addition reaction of **Ni-3** with aryl halide resulted in the formation of aryl nickel species **Ni-4**, followed by a 1,1-migratory insertion into C-Ni bond generating imidoyl nickel species **Ni-2**. The resulting **Ni-2** reacted with H_2O in the presence of base giving the intermediate **Ni-5**. Finally, a reductive elimination reaction took place to regenerate **Ni-3** and release the intermediate **3'** which fast tautermerized to stable aryl amide **3**.



Scheme 6. Plausible reaction mechanism

In conclusion, we have developed a nickel-catalyzed aminocarboxylation reaction for the synthesis of aryl/alkenyl/allyl amides. Aryl/alkenyl/allyl halides and aryl triflates are all competent to furnish this reaction affording the amides in moderate to excellent yields. A variety of functional groups as well as heteroaromatic rings such as pyridinyl, furyl, and thienyl were tolerated under the optimized conditions. The further exploration of nickel-catalyzed aminocarbonylation involving isocyanide insertion is still

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary material containing experimental procedures, characterization data and scanned copies of the NMR spectra of all new compounds is provided.

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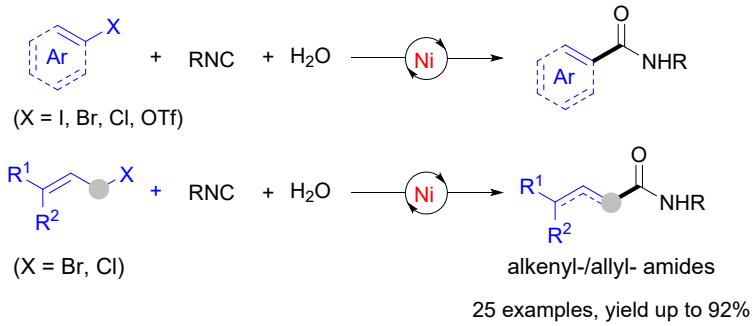
Graphical abstract



Highlights:

- A nickel-catalyzed aminocarbonylation is reported.
- Aryl/alkenyl/allyl (pseudo)halides are viable substrates.
- A Ni(0)/Ni(II) catalytic cycle is proposed.