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Nickel-catalyzed aminocarbonylation of aryl halides using carbamoylsilane as an amide source†

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The nickel-catalyzed aminocarbonylation of aryl halides using carbamoylsilane as an amide source is developed. The procedure can prepare both tertiary and secondary amides, and is applicable to various carbamoylsilanes and aryl halides containing different functional groups. The types and the relative position of substituents on the aryl ring impact the coupling efficiency.

Amides are very important functional groups in the synthesis of organic molecules, and play a significant role in biological systems, and the fields of natural products, polymers, and pharmaceuticals.[1] In the past decades, a great number of methods for the synthesis of amides have been developed.[2] Among the developed methods, the palladium-catalyzed aminocarbonylation is an important and the most frequently used procedure for the selective and direct synthesis of aryl amides starting from aryl halides, amines and carbon monoxide.[3] Since the pioneering work of Heck in 1974,[4] various improved protocols for amino-carbonylation have emerged using CO as a carbonyl source.[5] However, the troublesome handling, transport, and storage of hazardous CO, the reaction setup requiring high-pressure reactors, high temperature and harsh reaction conditions restrict its applications in lab-scale synthesis.[6] Therefore, a simple and newer CO-free procedure for the aminocarbonylation to amides using an easy to handle carbonyl source would obviously be of great interest to synthetic chemists.[6b,7] Previously, various carbamoylsilanes had been synthesized in good yields,[8] which can be used as amides source to introduce into an organic substrate, for example, addition of carbamoylsilane to the C=N bond of imines,[9] addition of carbamoylsilane to the C=O bond of α-ketoesters or α-ketoamides,[10] and the aminocarbonylation of acid chlorides.[11] Cunico *et al.* had reported aminocarbonylation of aryl halides with carbamoylsilane catalyzed by palladium complexes.[12] Drawbacks of the method are the high cost and toxicity of palladium catalysts, and the need to dispose toxic byproducts. We have reported the direct functionalization of aromatics by carbamoylsilanes leading to formation of amides.[13] However, the scope is limited to electron-deficient aromatics. Recently, we found that nickel complexe could be used as catalyst in the aminocarbonylation of aryl halides using carbamoylsilanes as

amides source, which is inexpensive and low toxic compared to palladium catalyst. To the best of our knowledge, aminocarbonylation of aryl halides with carbamoylsilane catalyzed by nickel complexe have never been reported. One example of amides synthesized catalyzed by nickel complexe is the aminocarbonylation of aryl halides using formamide derivatives as amides source. This reaction must undergo in the presence of strong base.[14] Herein, we report a general Ni-catalyzed process for the conversion of aryl halides to aryl amides that can be carried out under mild reaction conditions by using various carbamoylsilanes as amides source.

First, the aminocarbonylation of bromobenzene with *N,N*-dimethylcarbamoyl(trimethyl)silane catalyzed by [(Ph)$_3$P]$_4$Ni(0) was chosen as a model reaction to investigate the effects of solvents and temperature. When a range of solvents often used for cross-coupling reactions were tested, the reaction proceeded smoothly in tested solvents except dichloromethane. As shown in Table 1, we observed: when the reaction was carried out in toluene, the highest yields of product was achieved, and the reaction time was short (Table 1, entry 4), while in dichloromethane the reaction could not be conducted. Several other tested solvents, including benzene, THF, and acetonitrile, gave inferior results compared to toluene (Table 1, entries 2–5). The temperature study shows that 75 °C is the optimum temperature to obtain a higher yield of coupling product. Increase or decrease in reaction temperature led to reduce in yield of coupling product (Table 1, entries 6–9). Next, model reaction was run in toluene at 75 °C to examine the effect of catalyst loading, which reveled that 2 mol% of [(Ph)$_3$P]$_4$Ni (relative to bromobenzene) was essential for best results. When the amount of catalyst used was less than 2 mol%, low yields of the desired products were obtained, while increasing the catalyst loading results also in slightly lower yields (Table 1, entries 10–12).

To explore the scope and limitation of the nickel-catalyzed aminocarbonylation of aryl halides using carbamoylsilane as an amide source, a series of aryl halides were screened to react with carbamoylsilane 2 in toluene solvent under 2 mol% of catalyst at 75 °C. Results are displayed in Table 2. Initially, aminocarbonylation of various halogen substituted benzene

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Table 1 Optimization of nickel-catalyzed aminocarbonylation of aryl halides using carbamoylsilane as an amide source[a]

Entry	Cata. (mol%)	Solvent	Temp (°C)	Time[b] (h)	Yield[c,d] (%)
1	2	Dichloromethane	35	80	0
2	2	Acetonitrile	75	50	32
3	2	THF	65	44	36
4	2	Toluene	75	38	68
5	2	Benzene	75	41	58
6	2	Toluene	60	48	49
7	2	Toluene	90	34	64
8	2	Toluene	100	31	56
9	2	Toluene	110	70	20
10	1	Toluene	75	46	39
11	3	Toluene	75	37	60
12	5	Toluene	75	36	54

[a] Catalyst: tetrakis(triphenylphosphine)nickel(0). [b] To complete consumption of carbamoylsilane. [c] Isolated yield after chromatography on silica gel based on bromobenzene. [d] 1 : 1.2 mol ratio of bromobenzene and carbamoylsilane.

were performed. We found that chloro-, bromo- and iodo-benzene reacted with carbamoylsilane **2** smoothly in the presence of [(Ph)₃P]₄Ni(0), to give corresponding *N,N*-dimethylbenzamide directly, bromobenzene exhibited faster reaction rate and higher yield than others (Table 2, entries 1–3). However, fluorobenzene (**1d**) did not undergo the coupling reaction with carbamoylsilane **2** under the same conditions (Table 2, entry 4).

Next, aryl halides containing different functional groups were tested to investigate the effect of electronic property and relative position of substituents on the aryl ring. A comparison of the results obtained from **1e–h** indicates that the electronic properties of the substituent in the phenyl ring influenced both the reaction time and yields of aminocarbonylation. Aryl bromides possessing an electron-withdrawing group, such as a nitro or chloro, reacted faster and gave higher isolated yields than that possessing electron-donating group, such as a methyl or methoxy group. The stronger electron-withdrawing the substituent, the faster the process and the higher the yield was (Table 2, entries 5–8). For aryl halides containing Br and Cl simultaneously, the aminocarbonylation only selectively occurred at the bromo-terminal, such as 4-bromo-chlorobenzene (**1f**) gave exclusively 4-chloro aryl amide **3f**. The reaction results of aryl bromides **1i** and **1j** indicate that the coupling reaction is highly sensitive to the relative position of substituent on the phenyl ring. Substrate **1i**, the relatively minor steric impediment of an *ortho* methyl inhibiting the coupling reaction, afforded product **3i** in low yield, whereas *ortho* dimethyl completely inhibits the coupling reaction, **1j** gave no desired product due to big steric hindrance (Table 2, entries 9 and 10). Fluoro substituted aryl bromide at *ortho* (an electron-withdrawing group) also led to low yield of product (Table 2, entries 11). As expected, an electron-deficient heteroaryl (pyridyl) bromides and chlorides possessing fluoro, trifluoromethyl or nitro (**1l**, **1m** or **1n**) gave the coupling reaction products in

good yield. However, fluoropyridine **1o** bearing two electron-withdrawing groups proved to be totally inert even at 75 °C for 3 days. 2-Bromonaphthalene (**1p**) provided a moderate yield of desired product **3p**. Aryl bromide **1q** containing an electron-rich heteroaryl was also reactivity with carbamoylsilane **2** to give product **3q** in good yield.

This approach is an easy and practical method for the aminocarbonylation of aryl halides, suitable for the formation of tertiary amides. For more application within different areas, secondary amides need to be synthesized, for example, the synthesis of heterocyclic compounds.[15] We must further develop this method towards the preparation of secondary amides. Therefore, carbamoylsilanes containing an amino protecting group are expected to solve this problem. Considering this, the *N*-methoxymethyl-*N*-methyl-carbamoyl(trimethyl)silane was selected as an amide source to synthesize secondary amides under same reaction conditions, wherein methoxymethyl group was used as an amino protecting group. To our surprise, all reactions proceeded smoothly and most of reactions afforded secondary amides directly in good yields, the methoxymethyl group could be hydrolyzed in the separation process. As shown in Table 3, we observed that aryl halides **1a**, **1e**, **1g**, and **1h**, bearing different functional groups, gave the corresponding secondary amides in good yields, while hetero aryl halide **1n** afforded the methoxymethyl-protected amide **5n** in 73% yield (Table 3, entry 5).

In order to study the synthetic potential and general applicability of developed methodology, carbamoylsilanes having different alkyls were selected as amides source, such as *N*-methoxymethyl-*N*-propylcarbamoyl(trimethyl)silane (**6**) and *N*-methoxymethyl-*N*-cyclohexylcarbamoyl(trimethyl)silane (**8**), to react with aryl halides bearing different functional groups (**1a**, **1e**, **1g**, **1h** and **1n**) under same reaction conditions. Experimental results are displayed in Table 4. We

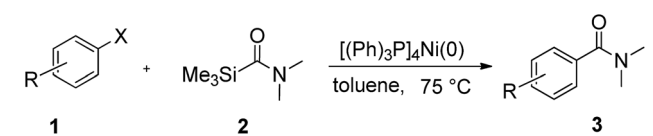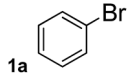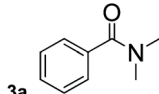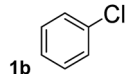**Table 2** Aryl amides **3** from *N,N*-dimethylcarbamoyl(trimethyl)silane and aryl halides[a]
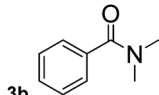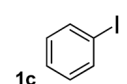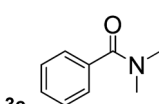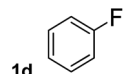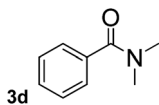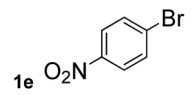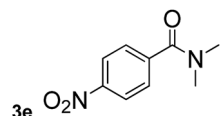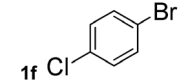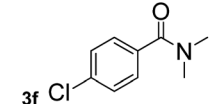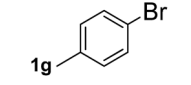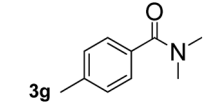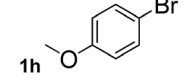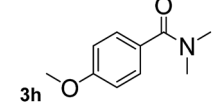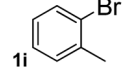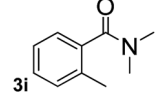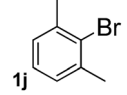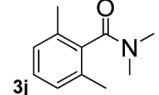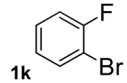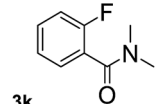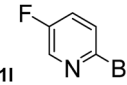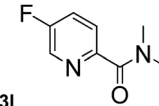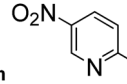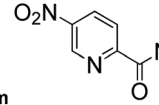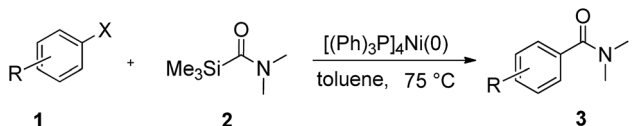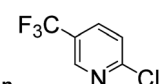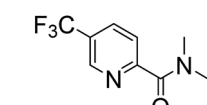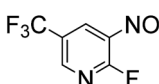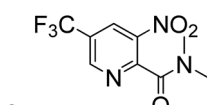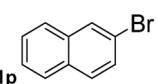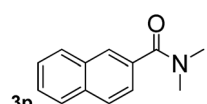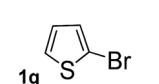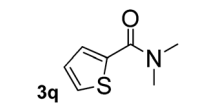
Entry	Aryl halide	Product	Time (h)	Yield[b,c] (%)
1	**1a**	**3a**	38	68
2	**1b**	**3b**	40	58
3	**1c**	**3c**	47	35
4	**1d**	**3d**	50	0
5	**1e**	**3e**	27	75
6	**1f**	**3f**	36	71
7	**1g**	**3g**	48	58
8	**1h**	**3h**	39	69
9	**1i**	**3i**	46	42
10	**1j**	**3j**	52	0
11	**1k**	**3k**	39	57
12	**1l**	**3l**	28	62
13	**1m**	**3m**	15	67
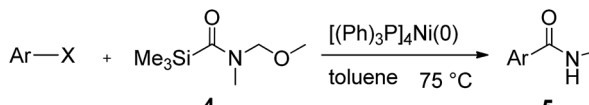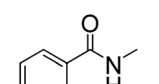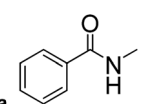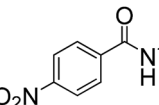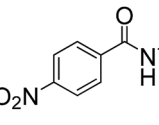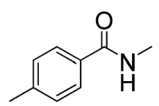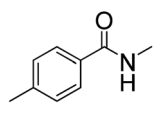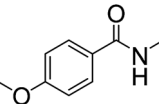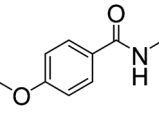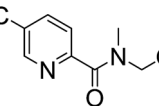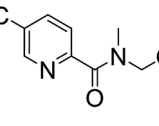
Table 2 (*Contd.*)

Entry	Aryl halide	Product	Time (h)	Yield[b,c] (%)
14	1n	3n	28	78
15	1o	3o	72	0
16	1p	3p	36	68
17	1q	3q	28	62

[a] 2 mol% of tetrakis(triphenylphosphine)nickel(0). [b] Isolated yield after chromatography on silica gel based on aryl halides. [c] 1 : 1.2 mol ratio of aryl halides and carbamoylsilane.

Table 3 The reaction of carbamoylsilane **4** with aryl halides

Entry	Aryl halide	Product	Time (h)	Yield[a,b] (%)
1	1a	5a	26	67
2	1e	5e	22	70
3	1g	5g	31	58
4	1h	5h	27	61
5	1n	5n	16	73

[a] Isolated yield after chromatography on silica gel based on aryl halides.
[b] 1 : 1.2 mol ratio of aryl halides and carbamoylsilane.

observed that both carbamoylsilanes reacted smoothly and afforded the corresponding amides in moderate yields. Aryl halides bearing an electron-withdrawing and electron-donating group were tolerated. Aryl halides **1e** and **1n** gave the methoxymethyl-protected amides **7e**, **9e** and **9n** in 56%, 60% and 62% yields respectively (Table 4, entries 2, 7 and 10), while others directly afforded secondary amides in good yields.
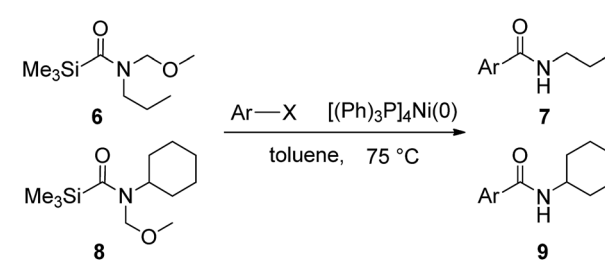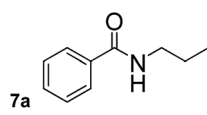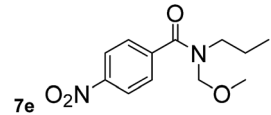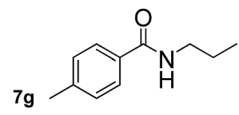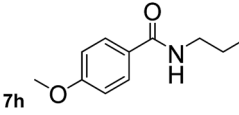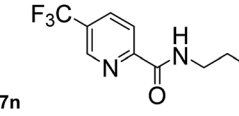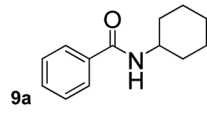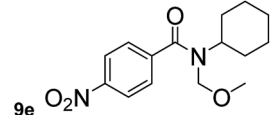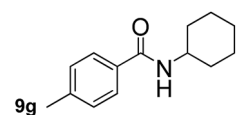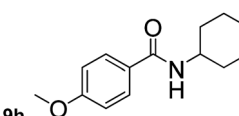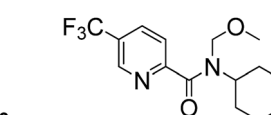
In summary, a novel nickel-catalyzed aminocarbonylation method of aryl halides using carbamoylsilanes as amides source has been developed. The protocol could prepare both tertiary and secondary amides, and tolerate a broad range of aryl halides bearing different functional groups to provide good yields of the products under mild reaction conditions. The mild and simple procedure, the easy availability of aryl halides and the low toxity of reagents provide a valuable method for the preparation of various aryl amides. We believe that the current methodology will prove to be an attractive alternative to the reported methods for aminocarbonylation reactions due to utilizing carbamoylsilanes used as amides source instead of a toxic CO source.

Conflicts of interest

There are no conflicts to declare.

Table 4 The reaction of carbamoylsilanes **6** and **8** with aryl halides

Entry	Aryl halide	Product	Time (h)	Yield[a,b] (%)
1	1a	7a	30	60
2	1e	7e	24	56
3	1g	7g	33	52
4	1h	7h	30	54
5	1n	7n	21	63
6	1a	9a	29	59
7	1e	9e	36	60
8	1g	9g	31	52
9	1h	9h	28	56
10	1n	9n	26	62

[a] Isolated yield after chromatography on silica gel based on aryl halides. [b] 1 : 1.2 mol ratio of aryl halides and carbamoylsilane.

Acknowledgements

Notes and references

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