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The Scope and Limitation of Nickel-Catalyzed Aminocarbonylation of Aryl Bromides from Formamide Derivatives

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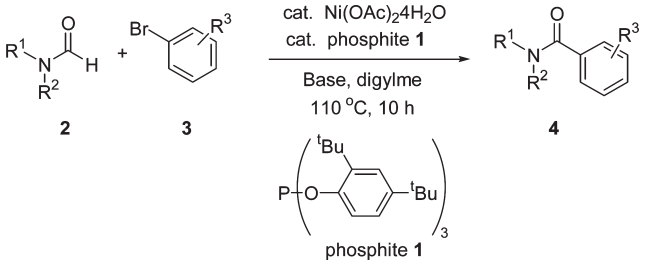

Nickel-catalyzed aminocarbonylation of aryl halides is described. A well-defined air-stable nickel−phosphite catalytic system ($Ni(OAc)_2 \cdot 4H_2O$/phosphite **1**) effectively promoted the aminocarbonylation of aryl bromides with a range of formamides to give the corresponding aryl amide products in moderate to good yields. The less hindered formamide required lower catalytic loading for full conversion and produced higher yields than the more hindered one. It also exhibited base-dependent activity toward formamides.

The amide is a very important functional group in organic compounds. Some amide derivatives exhibit biological activities such as antibacterial and antifungal effects.[1] Several useful synthetic methods have been reported.[2] Among them, palladium-catalyzed aminocarbonylation, which was developed by Heck, is a powerful method for the synthesis of amides from the reaction of aryl halides and amines in the presence of carbon monoxide, and is one of the most frequently used in organic synthesis.[3] This transformation has been used for the synthesis of simple building blocks and bioactive materials.[4] The reaction mechanism of palladium-catalyzed aminocarbonylation was well established, and carbon monoxide was employed as the carbonyl source.

However, the use of carbon monoxide requires instruments such as high-pressure vessels, and is cumbersome in the organic laboratory. To address the handling of toxic carbon monoxide gas, a variety of other sources such as $Mo(CO)_6$ and formamides have been reported. Larhed et al. reported the use of $Mo(CO)_6$ as a carbon monoxide source in the aminocarbonylations of aryl halides.[5] They showed that $Cr(CO)_6$ and $W(CO)_6$ were also able to be employed as surrogates.[5c] Despite their suitability for high-throughput organic synthesis, these inorganic materials are relatively expensive. Carbamoylstanne[6] and carbamoylsilane[7] were reacted with aryl halides in the presence of a palladium catalyst to afford the product to which the corresponding carbamoyl group directly bonded. However, they are not commercially available, and are limited to the synthesis of only the *N*,*N*-dimethyl-substituted amide derivatives. In addition, carbamoylstanne is thermal unstable. DMF decomposes to release carbon monoxide in the presence of strong base at high temperature and has been utilized for the preparation of inorganic metal−carbonyl complexes.[8] Hallberg et al. employed DMF as a CO surrogate in the palladium-catalyzed aminocarbonylation.[9] They showed that the addition of amine to the reaction mixture delivered the corresponding aryl amides. However, imidazole was required as an additive and the reaction temperature was very high (180−190 °C). Hiyama et al. reported aminocarbonylation using DMF as an amide source.[10] Although their method offered the advantage of functional group tolerance,

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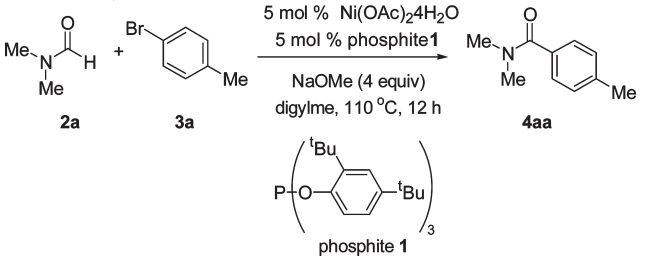
TABLE 1. The Minimum Amount of DMF for Nickel-Catalyzed Aminocarbonylation[a]



entry	DMF	yield (%)[b]
1	1 mL (excess)	99
2	20 equiv	98
3	10 equiv	98
4	8 equiv	82
5	5 equiv	42

[a]Reaction conditions: 0.3 mmol of 4-bromotoluene (**3a**) was employed. [b]Yield determined by GC with an internal standard.

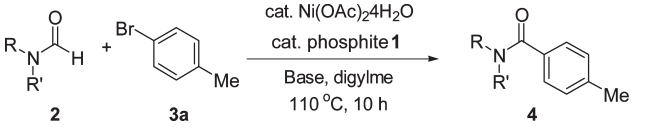
it suffered from the limited scope of aryl halide and required a long reaction time. All these reactions were carried out in the presence of palladium as the catalyst. Recently, we reported the nickel-catalyzed aminocarbonylation of aryl halides using DMF as the amide source.[11]

The use of the nickel−phosphite **1** catalytic system afforded a more practical and inexpensive method for the synthesis of arylamide derivatives. It was the first use of nickel as a catalyst in aminocarbonylation. In our previous paper, DMF was employed as an amide source and a solvent, and reacted with aryl halides to afford the corresponding aryl *N*,*N*-dimethylamides. Here, we expand the scope of the substrates and optimize the condition for the coupling of formamide derivatives.

In our previous report, we used an excess of DMF with cosolvent. First, we investigated the limited amount of DMF for this transformation. 4-Bromotoluene and DMF were reacted in the presence of 4 equiv of NaOMe with diglyme cosolvent (Table 1). When we attempted to reduce the amount of DMF from 10 equiv to 8 equiv, we obtained the product in a lower yield, indicating that at least 10 equiv of DMF was required for satisfactory reaction yield. In addition, both 1,4-dioxane and diglyme were effective as the solvent. Diglyme was chosen as the solvent for the high reaction temperature.

To expand the scope of the formamides, we carried out the coupling reaction of 4-bromotoluene and a variety of formamides. The results are summarized in Table 2. First, *N*,*N*-disubstituted formamide derivatives were tested for the coupling reactions. The screening reactions were performed with respect to a variety of bases and the amount of formamides. In the case of 1-formylpiperidine (**2b**) and 4-formylmorpholine (**2c**), 5 equiv of formamides was required for full conversion. In the case of **2b**, among the bases screened, the use of NaOMe did not completely convert 4-bromotoluene to the desired product and afforded a yield of only 9%. However, KOMe showed full conversion and 68% yield (entries 1 and 2). The 2.5 mol % catalytic loading did not show the complete conversion (entry 3) and gave 27% product yield. We found that the reaction required at least 5 mol % of nickel/phosphite catalytic loading. In addition, 3 equiv of base did not show full conversion (entry 4). We found that 4 equiv of base was required to obtain a satisfactory yield. In the case of 4-formylmorpholine (**2c**), KOMe showed a better result than NaOMe, but a lower yield than that of 1-formylpiperidine (**2b**) (entries 5 and 6). We then attempted to apply this method to the more sterically demanding substrates such as *N*,*N*-diethylformamide (**2d**) and *N*,*N*-diisopropylformamide (**2e**), which consist of

TABLE 2. Optimization of Nickel-Catalyzed Aminocarbonylation for Formamides[a]



entry	Foramide	(eq)	Ni/L[b] (mol %)	Base (eq)	Conv. (%)[c]	Prod. yield (%)	
1		5	5	NaOMe (4)	14	**4ba**	9
2		5	5	KOMe (4)	100	**4ba**	68
3		5	2.5	KOMe (4)	48	**4ba**	27
4	**2b**	5	5	KOMe (3)	72	**4ba**	43
5		5	5	NaOMe (4)	31	**4ca**	18
6	**2c**	5	5	KOMe (4)	94	**4ca**	51
7	**2d**	10	5	NaOMe (4)	57	**4da**	-[d]
8	**2e**	10	5	KOMe (4)	3	**4ea**	-[d]
9		3	1	NaOMe (2)	100	**4fa**	92
10	**2f**	3	1	KOMe (2)	85	**4fa**	62
11		4	2	NaOMe (3)	100	**4ga**	35
12	**2g**	4	2	KOMe (3)	100	**4ga**	89
13	**2h**	4	2	KOMe (3)	100	**4ha**	72[e]
14[f]	**2i**	10	10	KOMe (4)	-	**4ia**	-[d]
15[g]	**2j**	5	5	KOMe (4)	50	**4je**	24
16	**2k**	10	5	NaOMe (4)	-	**4ka**	-[d]

[a]Reaction condition: 4-bromotoluene (0.3 mmol), formamide **2**, $Ni(OAc)_2 \cdot 4H_2O$, phosphite **1**, diglyme (0.3 M) at 110 °C for 10 h; reaction time was not optimized. [b]The ratio of Ni/L is 1/1. [c]Conversion of 4-bromotoluene was determined by GC analysis with internal standard. [d]No major product was found in ^{1}H NMR. [e]~90% purity was determined by ^{1}H NMR. [f]Reaction temperature was 150 °C. [g]4-*tert*-Butylbromobenzene was employed instead of 4-bromotoluene.

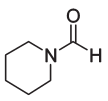
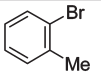
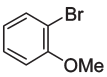
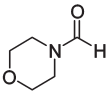
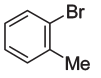
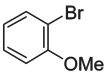
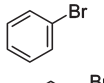
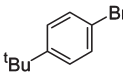
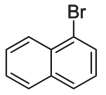
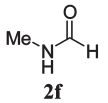
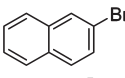
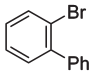
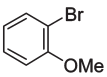
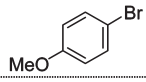
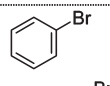
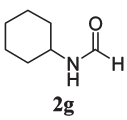
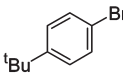
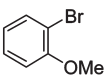
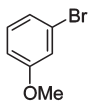
(11) Ju, J.; Jeong, M.; Moon, J.; Jung, H. M.; Lee, S. *Org. Lett.* **2007**, *9*, 4615–4618.

noncyclic substituents (entries 7 and 8). Unfortunately, they did not afford the desired products even though the reactions were carried out with phosphine ligands, such as P^tBu_3, xantphos, and biphenylP^tBu_2, in excess formamides. Longer reaction times did not produce the coupled product in any case. In the reaction with *N*,*N*-diethylformamide, the conversion of 4-bromotoluene was 57%. However, no major product was found in ^{1}H NMR (entry 7). In *N*,*N*-disubstituted formamides, only the cyclic substituted substrates showed reactivities in aminocarbonylation.

Next, we investigated the catalytic applicability toward the aminocarbonylation of *N*-monosubstituted formamides, which are less sterically demanding. Therefore, we expected that the amounts of formamides would be less than those of the *N*,*N*-disubstituted ones. *N*-Methylformamide (**2f**), which has a less steric demanding group, required only 1 mol % of catalytic loading for full conversion. In addition, it showed the best yield when 3 equiv of formamide and 2 equiv of NaOMe were employed (entry 9). In the case of *N*-cyclohexylformamide (**2g**), 2 mol % catalytic loading was needed for full conversion with the desired coupled product in 89% yield (entry 12). Under the same reaction condition, *N*-hexylformamide (**2h**), which has a longer alkyl chain, gave the desired coupled product **4ha** in 72% yield (entry 13). However, we failed to isolate the product in pure form. As the base, KOMe afforded a higher yield than NaOMe. Unfortunately, *N*-*tert*-butylformamide (**2i**) failed to produce the desired product, even though 20 mol % of catalyst was employed at 150 °C (entry 14). The absence of any activity for **2i** was attributed to the sterically bulky group of formamide. Next, we attempted to apply this transformation in the coupling reaction of *N*-phenylformamide (**2j**) with 4-*tert*-butylbromobenzene (**3e**). Potassium *tert*-butoxide afforded the coupled product in 24% yield (entry 15). However, the major product was aniline, which was dissociated from the reaction of *N*-phenylformamide and alkoxide base. The dissociation process occurred at over 90 °C in the presence of alkoxide base without nickel catalyst. When the more sterically bulky formamide is employed, a much larger amount of substrate and stronger base are required.[12] However, formamide (**2k**) was not converted to the desired product (entry 16). In addition, for all cases of *N*-alkylformamides, no *N*-arylated formamides were found.[13]

Having successfully demonstrated the viability of the Ni $(OAc)_2 \cdot 4H_2O$/phosphite-catalyzed coupling reaction of formamides and aryl bromides in the presence of alkoxide base, we then proceeded to test the scope and limitation of this transformation by applying the optimized reaction conditions of Table 3. In the reactions of *N*,*N*-disubstituted formamides, which are a more sterically demanding substrate, the 1-formylpiperidine afforded somewhat higher yields than the 4-formylmorpholine in all cases. Aryl bromides bearing an ortho substituent were also successfully applied to this system (entries 1−4). For the *N*-methylformamide (**2f**), we observed that the coupling of bromobenzene, 4-bromo-*tert*-butylbenzene, 1-bromonaphthalene, and 2-bromonaphthalene proceeded smoothly to give the corresponding coupled products in 99%, 94%, 81%, and 82% yields, respectively (entries 5−8). The aryl bromide bearing *o*-phenyl group afforded higher yield than the one bearing the *o*-methoxy group (entries 9 and 10). The para substituent provided 68% yield of the corresponding coupled product (entry 11). The coupling of *N*-cyclohexylformamide (**2g**) with aryl bromides produced the desired products in moderate to good yields. They all required 2 mol % catalytic loading for full conversion.

TABLE 3. The Scope of Nickel-Catalyzed Coupling Reactions of Formamides and Aryl Bromides[a]

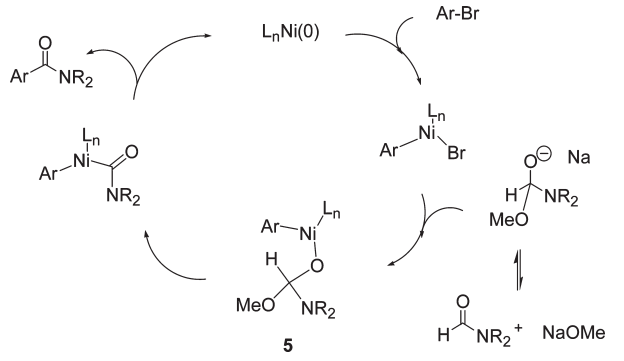
entry	Formamide	ArBr		Cond.[b]	Prod.	Yield (%)[c]
1	 **2b**		**3b**	A	**4bb**	58
2			**3c**	A	**4bc**	41
3	 **2c**		**3b**	A	**4cb**	42
4			**3c**	A	**4cc**	35
5			**3d**	B	**4fd**	99
6			**3e**	B	**4fe**	94
7			**3f**	B	**4ff**	81
8	 **2f**		**3g**	B	**4fg**	82
9			**3h**	B	**4fh**	82
10			**3c**	B	**4fc**	53
11			**3i**	B	**4fi**	68
12			**3d**	C	**4gd**	65
13	 **2g**		**3e**	C	**4ge**	94
14			**3c**	C	**4gc**	56
15			**3j**	C	**4gj**	43

[a]All reactions were carried out in diglyme at 110 °C for 10 h. [b]Reaction condition A: 5 mol % of Ni/phosphite **1**, ArBr (1.0 equiv), formamide (5.0 equiv), KOMe (4.0 equiv). Reaction condition B: 1 mol % of Ni/phosphite **1**, ArBr (1.0 equiv), formamide (3.0 equiv), NaOMe (2.0 equiv). Reaction condition C: 2 mol % of Ni/phosphite **1**, ArBr (1.0 equiv), formamide (4.0 equiv), KOMe (3.0 equiv).

(12) The basicity of potassium methoxide is greater than that of sodium methoxide.

(13) For Pd-catalyzed *N*-arylation of formamides, see: (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048. For Cu-catalyzed *N*-arylation of formamides, see: (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.

SCHEME 1. Proposed Mechanism



However, meta-substituted aryl halides such as 3-bromoanisole showed lower yield than the others (entry 15). Its yield was not improved even though 5 mol % of catalyst was loaded. We attempted to run the coupling reaction of heteroaromatic bromides such as bromothiophene and bromopiperidine with *N*-methylformamides under the same conditions, but failed. A complicated compound mixture was found with a trace amount of the desired coupling product as detected in GC-MS spectral analysis.

Recently, the C−H bond in DMF was reported to be activated by Ni(0) catalyst in an oxidative addition manner.[14] We conducted the coupling reactions of 4-bromotoluene and DMF with nickel catalyst in the presence of Lewis acid instead of strong base; however, the desired product was not obtained. Considering the steric effect between the formamide and base, the role of the base might be a nucleophilic attack on the carbonyl carbon in the formamide. On the basis of this reaction tendency, we proposed the mechanism as shown in Scheme 1. The nickel-coordinated alkoxide-formamide adduct is formed after the oxidative addition of ArBr to Ni(0). The adduct **5** is converted to the nickel-amido intermediate, and give the amide product through reductive elimination. The mechanism of this reaction is not clear to us and further mechanistic studies are needed.

We have investigated the scope and limitation of the nickel-catalyzed coupling of aryl bromides and formamides. We found that the most important factor was the steric bulkiness of formamides. The less hindered formamide required lower catalytic loading for full conversion and produced higher yields than the more hindered one. In addition, NaOMe was a good base for the less hindered formamide, and KOMe were good bases for the more hindered one. We first showed the direct coupling reaction of formamide derivatives with aryl bromides using a nickel−phosphite catalytic system.

(14) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 5070–5071.

Experimental Section

General Procedure for Nickel-Catalyzed Coupling Reactions of *N*-Methylformamide with Aryl Bromides. $Ni(OAc)_2 \cdot 4H_2O$ (7.5 mg, 0.03 mmol), phosphite **1** (19.5 mg, 0.03 mmol), and aryl bromide (3.0 mmol) were combined with NaOMe (324 mg, 6.0 mmol) in a small round-bottomed flask. Diglyme (9.0 mL) and *N*-methylformamide (531.6 mg, 9.0 mmol) were added, and the flask was sealed with a septum. The resulting mixture was placed in an oil bath at 110 °C for 10 h. The reaction was poured into 20 mL of saturated aqueous ammonium chloride and extracted (3×20 mL) with Et_2O. The combined ether extracts were washed with brine (60 mL), dried over $MgSO_4$, and filtered. The solvent was removed under vacuum, and the resulting crude product was purified by flash chromatography on silica gel. The product was eluted with 70% ethyl acetate in hexane.

***N*,4-Dimethylbenzamide (4fa).** 4-Bromotoluene (513.1 mg, 3.00 mmol) was coupled with *N*-methylformamide (531.6 mg, 9.0 mmol) to give 411.2 mg (2.76 mmol, 92%) of **4fa** as a white solid after chromatography. Recrystallization from Et_2O gave a white solid (mp 143−145 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (dd, J = 8.1, 1.8 Hz, 2H), 7.20 (dd, J = 8.1, 1.8 Hz, 2H), 6.17 (br s, 1H), 3.04 (d, J = 4.8 Hz, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.14, 141.68, 131.77, 129.17, 126.78, 26.75, 21.39; FTIR (KBr, cm^{-1}, peak intensity) 3338 (m), 3067 (w), 2937 (w), 1636 (s), 1551 (s), 1508 (s), 1304 (m), 751 (m); MS (EI, m/z, rel intensity) 149 (M^+, 32), 119 (100), 91 (85), 65 (45).

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Supporting Information Available: Detailed experimental procedures and compound characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.