

Aminocarbonylation of Aryl Halides Using a Nickel Phosphite Catalytic System

Jinhun Ju,[†] Miso Jeong,[†] Jeongju Moon,[†] Hyun Min Jung,[‡] and Sunwoo Lee^{*,†}

Department of Chemistry, Chonnam National University, 300 Yongbong-dong, Buk-gu, Gwangju 500-757, Republic of Korea, and Advanced Materials Division, Korea Research Institute of Chemical Technology, 100 Jang-dong, Yuseong-gu, Daejeon 305-600, Republic of Korea

sunwoo@chonnam.ac.kr

Received August 30, 2007

ABSTRACT



The nickel and phosphite catalytic system with sodium methoxide enables a very efficient aminocarbonylation reaction to be performed between aryl iodides or bromides and *N,N*-dimethylformamide (DMF). Phosphite ligand 1, which is very stable to air and moisture and, furthermore, inexpensive, afforded the highest reaction yield.

Heck reported the first formation of palladium-catalyzed amides from aryl halides by reaction with carbon monoxide and primary or secondary amines.¹ Carbon monoxide is generally employed in this reaction as a source of carbonyl groups.² To eliminate the cumbersome handling of toxic carbon monoxide gas,³ a variety of surrogates have been used, including Ni(CO)₄,⁴ Mo(CO)₆,⁵ carbamoylstannanes,⁶ carbamoylsilanes,⁷ and dimethylformamide (DMF).⁸

However, each substitute has its own drawbacks, including thermal instability,⁶ reagent cost, the limited scope of aryl halides,^{8b} the necessity of using a microwave,^{8a} or the fact that the ligand alkylphosphine^{8a,b} is unstable in air. In addition, all of these choices rely on palladium as a catalyst.

Only a few results have been reported for the use of DMF as a source of carbon monoxide or amide.⁸

Therefore, we focused on optimizing the process conditions to give a more practical and inexpensive catalytic system. Recently, we reported that phosphites can be used as ligands in palladium-catalyzed Hiyama cross-coupling reactions.⁹ In this paper, we report the first nickel-catalyzed aminocarbonylation of aryl halides using DMF as an amide source and phosphite as a ligand (Figure 1). To the best of our knowledge, nickel has never been reported as a catalyst in this transformation.¹⁰

[†] Chonnam National University.

[‡] Korea Research Institute of Chemical Technology.

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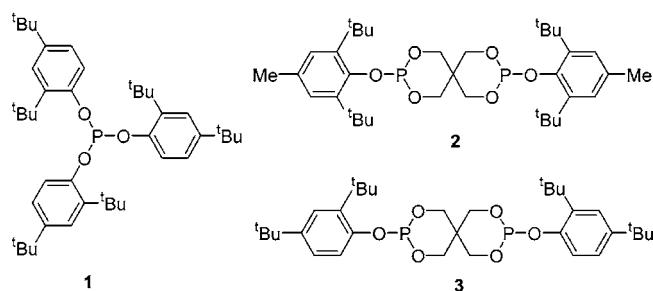


Figure 1. Phosphite ligands.

To investigate the activity of nickel as a catalyst, we first screened four different nickel sources and ligands in the aminocarbonylation of 4-bromotoluene with DMF in the presence of base. As shown in Table 1, $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ was

Table 1. Screening of Nickel Sources and Ligands^a

entry	Ni catalysts	ligands	yield ^b (%)
1	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	1	99
2	NiCl_2	1	79
3	$\text{Ni}(\text{acac})_2$	1	52
4	$\text{Ni}(\text{COD})_2$	1	40
5	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	2	90
6	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	3	87
7	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	P^tBu_3	89
8	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	PCy_3	23
9	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	$\text{P}(\text{OEt})_3$	0
10	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	PPh_3	12
11	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	DPPF ^c	14
12	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	Xantphos ^d	43
13	$\text{Pd}_2(\text{dba})_3$	1	0 ^e

^a Reaction conditions: 1.0 mmol of aryl halide, 4.0 mmol of NaOMe, 0.5 mL of DMF, 3 mL of 1,4-dioxane, 5 mol % of nickel, and 5 mol % of ligand were reacted at 110 °C for 12 h. ^b Yield was determined by GC by comparison to an internal standard (naphthalene). ^c 1,1'-Bis(diphenylphosphino)ferrocene. ^d 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. ^e No product and 33% of homocoupling product of 4-bromotoluene.

the best nickel source (entry 1). The use of other nickel catalysts, such as NiCl_2 , $\text{Ni}(\text{acac})_2$, and $\text{Ni}(\text{COD})_2$, gave very low reaction yields (entries 2–4). Among the ligands examined, phosphite **1** gave the highest yield. Sterically hindered phosphites and P^tBu_3 afforded good yields of more than 87% (entries 5–7). However, PCy_3 afforded a poor yield, and $\text{P}(\text{OEt})_3$ showed no activity, possibly due to the small substituent on the phosphite (entries 8 and 9). Wang

(10) For a recently reported nickel/phosphite catalytic system for coupling reactions, see: (a) Ho, C.-Y.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 782–785. (b) Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Org. Lett.* **2005**, *7*, 4871–4874. (c) Wang, Y.; Marrocco, M. L., III; Trimmer, M. S. WO 9639455 A1, 1996.

et al. reported that small substituents favor dimeric nickel species, which may not be catalytically active.^{10c} Mono and chelating arylphosphine ligands gave low yields (entries 10–12). Noticeably, the homocoupling of aryl halides was not detected in the nickel-catalyzed reactions; this side reaction gave rise to the major products in palladium-catalyzed reactions which afforded no amide-coupled product (entry 13).

We next examined the effects of solvents, bases, temperatures, and the molar ratios of nickel and ligand in the model reaction. The results are summarized in Table 2.

Table 2. Optimization of Aminocarbonylation with Phosphite **1** and $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ ^a

entry	Ni/L	mol %	base	solvent	yield ^b (%)
1	1:1	5	NaOMe	dioxane	99
2	1:1	5	NaO ^t Bu	dioxane	56
3	1:1	5	KOMe	dioxane	56
4	1:1	5	KO ^t Bu	dioxane	19
5	1:1	5	n-BuLi	dioxane	0 ^c
6	1:1	5	NaHMDS	dioxane	0 ^c
7	1:1	5	Na_2CO_3	dioxane	0 ^c
8	1:1	5	Na_3PO_4	dioxane	0 ^c
9	1:1	5	NaOMe	dioxane	25 ^d
10	1:1	5	NaOMe	dioxane	60 ^e
11	1:1	5	NaOMe	diglyme	93
12	1:1	5	NaOMe	DMA	77
13	1:1	5	NaOMe	NMP	70
14	1:1	5	NaOMe	DMF	97
15	1:1	5	NaOMe	<i>p</i> -xylene	8
16	1:1	2.5	NaOMe	dioxane	82
17	1:1	1	NaOMe	dioxane	78
18	1:1	0.1	NaOMe	dioxane	18
19	1:2	5	NaOMe	dioxane	60
20	1:0.5	5	NaOMe	dioxane	72

^a Reaction conditions: 1.0 mmol of 4-bromotoluene, 4.0 mmol of base, 0.5 mL of DMF, 3 mL of solvent, 5 mol % of **1**, and 5 mol % of $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ were reacted at 110 °C for 12 h. ^b Yield was determined by GC by comparison to an internal standard (naphthalene). ^c No reaction: only starting materials appeared in GC. ^d 2 equiv of NaOMe was used. ^e 3 equiv of NaOMe was used.

The type of base was the most important factor in this reaction. An excellent yield was obtained with NaOMe as base (entry 1), while other alkoxide or hydroxide bases such as NaO^tBu, KOMe, and KO^tBu showed low yields (entries 2–4). However, the non-alkoxide-type, strong bases failed to give the desired product (entries 5 and 6). With weak inorganic bases, no desired product was isolated (entries 7 and 8). Four equivalents of base was required to reach the highest yield. When using 2 or 3 equiv of NaOMe, the yield was 25% and 60%, respectively (entries 9 and 10). We then turned our attention to the cosolvent used with DMF. Hiyama's research group described that Pd-catalyzed aminocarbonylation was carried out in DMF without any other cosolvents.^{8b} Dioxane was proven to be the best cosolvent, while diglyme, possessing an ether group like dioxane, also showed a high yield (entry 11). The reactions with other amide-type cosolvents resulted in moderate yields (entries

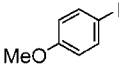
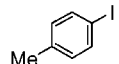
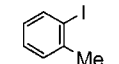
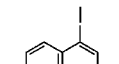
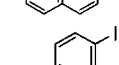
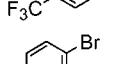
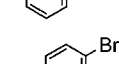
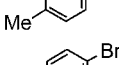
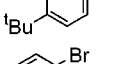
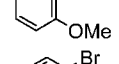
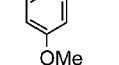
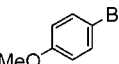
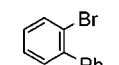
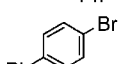
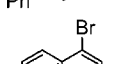
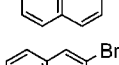
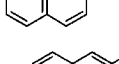
12 and 13). However, *p*-xylene, which was a good solvent in the Hiyama reaction with phosphite, was not suitable for the coupling reactions (entry 15). When the amount of catalyst used was less than 1 mol %, very low yields of the desired products were obtained (entry 18). A 1:1 ratio of catalyst to ligand was proven to form the most active catalytic system, whereas systems with other nickel to phosphite ratios such as 1:2 or 1:0.5 produced inefficient catalysis for this reaction (entries 19 and 20).

To explore the scope of this reaction system, we screened the aminocarbonylation of representative aryl halides with DMF (Table 3). Aryl iodides possessing an electron-donating group, such as a methoxy or methyl group, gave the desired coupling product in high yield (entries 1 and 2). 2-Iodo-toluene, bearing a sterically hindered group, afforded the coupling product in moderate yield (entry 3). 1-Iodonaphthalene and 4-iodobenzotrifluoride possessing an electron-withdrawing group afforded the coupling product in low yield and produced dehalogenated product in 38% and 45% yields, respectively (entries 4 and 5). We conclude that, in general, aryl bromides possessing an electron-donating group gave a better yield than those having an electron-withdrawing group. Among the bromoanisoles, the *o*-bromoanisole, which is sterically hindered, showed almost quantitative yield (99%) (entry 9). However, use of the meta version of this molecule decreased the yield to 82% (entries 10 and 11). Bromobiphenyl substrates showed good to excellent yields (entries 12 and 13). The coupling yield of 1-bromonaphthalene was 64% (entry 14) and that of 2-bromonaphthalene, a less sterically hindered variant, was 72% (entry 15). Bromonaphthalene, having methoxy as an electron-donating group, yielded 97% (entry 16). Half (51%) of the 2-bromothiophene was converted to give the desired product in 50% yield, whereas the yield was dramatically increased to 94% by running the reaction using 10 mol % catalyst (entry 17).

To understand the reaction mechanism, comparable reactions were carried out on the basis of reaction mechanisms suggested by palladium-catalyzed aminocarbonylation. The influence of the electronic properties of the aryl group and of the base used in the catalytic reactions were investigated. First, based on the mechanism proposed by Halberg of adding imidazole and benzylamine as external amine sources,^{8a} we obtained neither the imidazole amide form nor the benzylamide form under microwave or thermal heating conditions. Therefore, our nickel-catalyzed reaction may not proceed through Halberg's proposed mechanism of direct involvement of carbon monoxide from the decomposition of DMF. Second, the influence of the electronic property of the aryl substrate was clearly shown by the fact that the reaction yielded an amide-coupled product. Aryl halides bearing electron-donating groups showed higher reactivities than aryl halides bearing electron-withdrawing groups, and the latter produced dehalogenated arene as a major side product. This implies that the pathway of β -hydride elimination is competing with the reductive elimination pathway to produce amide coupling. Based on this reaction tendency and side product formation, two competing pathways were proposed, as shown in Scheme 1.

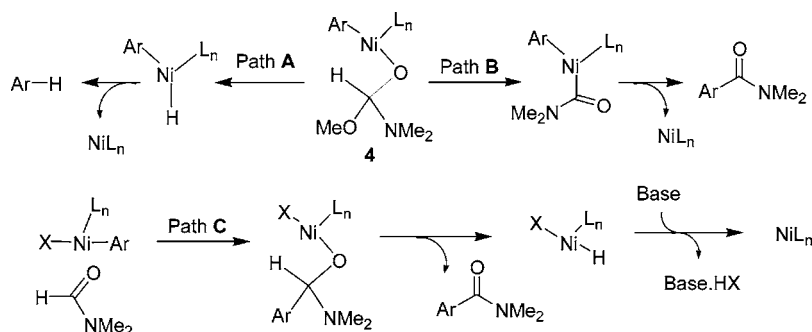
Both proposed paths proceed through the nickel-coordinated alkoxide–DMF adduct **4**, although it is not clear

Table 3. Nickel-Catalyzed Aminocarbonylation of Aryl Halides^a

entry	Arl	conversion(%) ^b	yield(%) ^c
1		100	99
2		100	98
3		100	68 (8 ^d)
4		100	45 (38 ^d)
5		100	11 (45 ^d)
6		100	98
7		100	99
8		100	93
9		100	99
10		100	82
11		100	62
12		100	87
13		90	85
14		100	64
15		100	72
16		100	97
17		50(100)	51(94)

^a Reaction conditions: 1.0 equiv of aryl halides, 5 mol % of **1**, 5 mol % of Ni(OAc)₂·4H₂O, 4 equiv of NaOMe, DMF (0.5 mL), 1,4-dioxane (3.0 mL). ^b Determined by GC. ^c Isolated yields of compounds. ^d Yield of dehalogenated arene. ^e 10 mol % of **1** and 10 mol % of Ni(OAc)₂·4H₂O were used.

whether the alkoxide–DMF adduct is formed first and then coordinated to a nickel complex or whether nickel-coordinated DMF is attacked by alkoxide. The electronic properties of the aryl substrate are a primary means of determining the pathway of this reaction. One pathway (path A) is the nonproductive β -hydrogen elimination pathway, using an electron-deficient nickel center with an electron-withdrawing aryl group to favor nickel hydride formation

Scheme 1. Proposed Mechanism

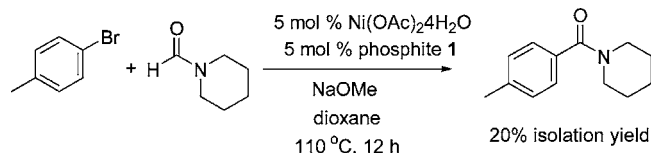
and subsequent production of the reduced arene. The second pathway relies on a nickel amido intermediate (path B) to give an amide product through reductive elimination. Alternatively, this product might be produced by aryl group insertion to nickel-coordinated DMF, followed by β -hydrogen elimination (path C). However, considering the strong tendency of base species to yield amide products, the role of the base is likely a nucleophilic attack on the carbonyl carbon in DMF (path A) rather than simple absorption of the HX on nickel complex (path C).

On the basis of mechanistic studies, we tested the feasibility of the universal use of nickel-catalyzed aminocarbonylations. When employing 10 equiv of 1-formylpiperidine as the DMF replacement, the coupled product was obtained with 20% yield (Scheme 2). This is much lower than the

yield obtained using DMF, but nevertheless implies that 1-formylpiperidine may be useful in catalytic aminocarbonylation reactions. Further mechanistic elucidation and studies of this aminocarbonylation protocol are in progress in our laboratory.

In summary, the first synthetically useful, convenient, and cost-effective nickel-catalyzed aminocarbonylation is presented here. The relatively inexpensive catalyst and ligand systems used in this reaction confirm this method's superiority over other existing processes.

Acknowledgment. This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, Basic Research Promotion Fund) (KRF-2006-003-C00178).

Scheme 2. Aminocarbonylation of 1-Formylpiperidine

Supporting Information Available: Reaction procedures and spectral and analytical data for reaction products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL702058E