

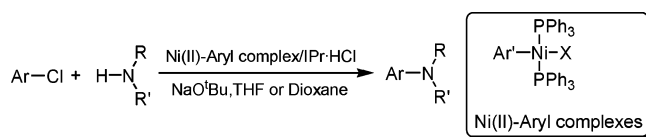
## Ni(II)–( $\sigma$ -Aryl) Complex: A Facile, Efficient Catalyst for Nickel-Catalyzed Carbon–Nitrogen Coupling Reactions

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*trans*-Haloarylbis(triphenylphosphine)nickel(II), a type of air- and moisture-stable Ni(II)–( $\sigma$ -aryl) complex, was examined as catalyst precursor in the C–N coupling reaction. This type of Ni(II) pre-catalyst, associated with *N*-heterocyclic carbene ligands, is found to easily produce the catalytically active Ni(0) species in situ without the aid of external reductants and allows for the efficient amination of aryl chlorides with secondary cyclic amines and anilines under mild conditions.

Nickel-catalyzed carbon–carbon<sup>1–7</sup> and carbon–nitrogen<sup>8</sup> bond-forming reactions have become important and powerful tools in organic syntheses during the past decades. Compared to the corresponding Pd catalyst systems,<sup>9</sup> the major advantages

of Ni-based catalysts are their much lower cost and increased reactivity toward readily available and inexpensive aryl chlorides.<sup>10</sup> In Ni-catalyzed cross-couplings, both Ni(0) and Ni(II) reagents are employed as Ni catalyst sources, but the Ni(0) species is generally regarded as being catalytically active. Although utilizing Ni(0) reagents, such as Ni(COD)<sub>2</sub>, Ni(PPh<sub>3</sub>)<sub>4</sub>, etc., as catalysts is the simplest and most direct route, such nickel sources would be difficult to handle and manipulate because of their high air sensitivity and thermal instability. By contrast, Ni(II) compounds, readily available and conveniently handled, as pre-catalysts are more preferred from a practical point of view. Certainly, the Ni(II) as pre-catalyst needs to first be activated (i.e., converted in situ to zerovalent nickel) in reaction systems because the active Ni(0) species is essential for Ni-catalyzed processes. Different from the Pd(II), however, the added ligands, solvents, or bases in reaction systems are normally insufficient to reduce Ni(II) to Ni(0).<sup>11</sup> In some coupling reactions with organometallic reagents as partners, such as the Kumada–Corriu reaction,<sup>5</sup> Negishi reaction,<sup>6</sup> and Suzuki reaction,<sup>7f–i</sup> Ni(0) species could be formed from the Ni(II) via the homocoupling of the organometals used. However, for the other processes not involving the organometals (e.g., typically in the Ni(II)-catalyzed arylation), in situ generation of Ni(0) species would be problematic. Therefore the treatment of Ni(II) precatalysts with external reductants has been an inevitable step. The reported modes included addition of zinc dust<sup>7a,b</sup> and pretreatment of butyllithium or the Grignard reagent<sup>7c–e</sup> and NaH.<sup>8d–h</sup> Also, the Ni(0)-on-charcoal from Ni(II) pretreated with *n*-BuLi was elaborated for the C–C<sup>6e,7j</sup> and C–N<sup>8c</sup> couplings.

Recently we were interested in exploring new Ni(II)-catalyzed protocols for C–N bond-forming reactions, where the use of external reducing agents would be obviated. A type of isolatable *trans*-haloarylbis(triphenylphosphane)nickel(II) attracted our great attention. An intensive investigation of Ni(II)–( $\sigma$ -aryl)

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<sup>†</sup> Institute of Chemistry, Chinese Academy of Sciences.

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(1) For the Heck reaction, see: (a) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *14*, 2320–2322. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066.

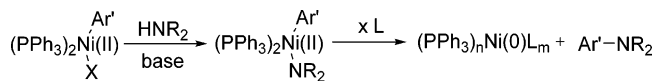
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**SCHEME 1. Possible Pathway for Activation of Ni(II)–( $\sigma$ -Aryl) Complexes**


complexes was conducted by Kochi et al., focusing mainly on insight into the nature and mechanism of nickel-catalyzed processes.<sup>12</sup> However, such complexes have very rarely been employed as catalysts to form general synthetic methods in cross-coupling reactions.<sup>13</sup> The previous studies<sup>5a,7a,8b</sup> have demonstrated that Ni-catalyzed cross-couplings might undergo a possible mechanism that follows a catalytic cycle of the Ni(0)–Ni(II) shuttle involving sequential oxidative addition, transmetalation, and reductive elimination. Accordingly, the Ni(II)–( $\sigma$ -aryl) complex may formally be regarded as an intermediate (oxidative adduct) in the catalytic cycle and hence has the possibility for generating Ni(0) species in situ by attack of nucleophiles and subsequent reductive elimination prior to the normal catalytic cycle (Scheme 1). If so, it would produce a new, facile protocol for Ni-catalyzed C–N couplings. Herein we wish to report our results on using Ni(II)–( $\sigma$ -aryl) complexes as catalysts in the amination of aryl chlorides.

Four Ni(II)–( $\sigma$ -aryl) complexes used in this study, Ni(PPh<sub>3</sub>)<sub>2</sub>–(1-naph)Cl (**1**), Ni(PPh<sub>3</sub>)<sub>2</sub>(*o*-tol)Cl (**2**), Ni(PPh<sub>3</sub>)<sub>2</sub>(1-naph)Br (**3**), and Ni(PPh<sub>3</sub>)<sub>2</sub>(phenyl)Br (**4**), were readily prepared from NiCl<sub>2</sub>·6H<sub>2</sub>O in ethanol according to the literature procedures.<sup>14</sup> Associated with ancillary ligands, they were evaluated as catalyst systems in the amination of aryl chlorides. The coupling of chlorobenzene and morpholine was selected as a model reaction (Table 1). The combination of Ni(PPh<sub>3</sub>)<sub>2</sub>(1-naph)Cl and PPh<sub>3</sub> did not mediate the reaction (entry 1), although such a catalytic system was highly effective in the Suzuki reaction.<sup>13b</sup> It might be because PPh<sub>3</sub> is not bulky enough to drive the reductive elimination to produce the active Ni(0). After all, the formation of C–N bonds is much harder than that of C–C bonds. Nitrogen-based bidentate ligands 1,10-phenanthroline (phen) and 2,2'-bipyridine (bpy), reported to be excellent in the Ni(COD)<sub>2</sub><sup>8a</sup> or Ni(II)–NaH systems,<sup>8d–f</sup> also played no role in the reaction (entries 2 and 3). Then we turned to another class of ligands, *N*-heterocyclic carbenes (NHC), which can conveniently be formed in situ from deprotonation of the corresponding imidazolium salts.<sup>15</sup> After some experimentation, a 1:1 ratio of IPr·HCl to Ni(PPh<sub>3</sub>)<sub>2</sub>(1-naph)Cl was found to give a nearly

(12) (a) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7547–7560. (b) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319–6332. (c) Morrell, D. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 7262–7270. (d) Parshall, G. W. *J. Am. Chem. Soc.* **1974**, *96*, 2360–2366. (e) Cramer, R.; Coulson, D. R. *J. Org. Chem.* **1975**, *40*, 2267–2273.

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(14) For the preparation of nickel–( $\sigma$ -aryl) complexes, see: (a) Cassar, L.; Ferrara, S.; Foá, M. *Advances in Chemistry Series*; American Chemical Society: Washington, DC, 1974; Vol. 132, p 252. (b) Brandsma, L.; Vasilevsky, S. F.; Verkruisje, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer: New York, 1998; pp 3–4.

(15) Two imidazolium salts were chosen: 1,3-bis(2,6-diisopropylphenyl)-imidazolium chloride (IPr·HCl) and 1,3-bis(2,6-diisopropylphenyl)-dihydroimidazolium chloride (SIPr·HCl). For their preparation, see: (a) Arduengo, A. J., III; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523–14534. (b) Grasa, G. A.; Viciu, M. S.; J. Huang; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729–7737.

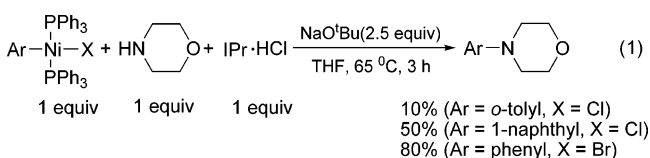
**TABLE 1. Screening of Conditions for C–N Coupling with Amine Catalyzed by Ni(II)–Aryl Complexes<sup>a</sup>**

entry	catalyst (mol %)	ligand (mol %)	base	time (h)	isolated yields (%)
1	<b>1</b> (5)	PPh <sub>3</sub> (10)	NaO <sup>t</sup> Bu	10	no reaction
2	<b>1</b> (5)	bpy (5)	NaO <sup>t</sup> Bu	10	trace
3	<b>1</b> (5)	phen (5)	NaO <sup>t</sup> Bu	10	trace
4	<b>1</b> (5)	IPr·HCl (5)	NaO <sup>t</sup> Bu	5	99
5	<b>1</b> (5)	IPr·HCl (10)	NaO <sup>t</sup> Bu	5	no reaction
6	<b>1</b> (5)	SIPr·HCl (5)	NaO <sup>t</sup> Bu	5	26
7	<b>1</b> (5)	IPr·HCl (5)	KO <sup>t</sup> Bu	5	84
8	<b>1</b> (5)	IPr·HCl (5)	CsCO <sub>3</sub>	10	no reaction
9	<b>2</b> (5)	IPr·HCl (5)	NaO <sup>t</sup> Bu	5	15
10	<b>3</b> (5)	IPr·HCl (5)	NaO <sup>t</sup> Bu	5	99
11	<b>4</b> (5)	IPr·HCl (5)	NaO <sup>t</sup> Bu	5	99
12	<b>1</b> (3)	IPr·HCl (3)	NaO <sup>t</sup> Bu	5	5
13	<b>1</b> (3)	IPr·HCl (3)	NaO <sup>t</sup> Bu	5	56 <sup>b</sup>
14	<b>3</b> (3)	IPr·HCl (3)	NaO <sup>t</sup> Bu	5	25
15	<b>4</b> (3)	IPr·HCl (3)	NaO <sup>t</sup> Bu	1	99
16	<b>4</b> (1)	IPr·HCl (1)	NaO <sup>t</sup> Bu	10	trace

<sup>a</sup> Reaction conditions: chlorobenzene (1.0 equiv), morpholine (1.2 equiv), base (1.3 equiv), THF (65 °C). <sup>b</sup> Dioxane (100 °C).













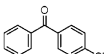







quantitative yield (entry 4). Further increase in the ratio of IPr·HCl was detrimental to the reaction (entry 5). The more  $\sigma$ -donating SIPr·HCl, a saturated counterpart of IPr·HCl that is highly effective in the Ni(acac)<sub>2</sub>–NaH system,<sup>8g,h</sup> was modest in this study (entry 6). For the bases used, KO<sup>t</sup>Bu (entry 7) was a little inferior to NaO<sup>t</sup>Bu and Cs<sub>2</sub>CO<sub>3</sub> (entry 8) was entirely ineffective. Among the other Ni(II)–( $\sigma$ -aryl) complexes, Ni(PPh<sub>3</sub>)<sub>2</sub>(1-naph)Br (entry 10) and Ni(PPh<sub>3</sub>)<sub>2</sub>(phenyl)Br (entry 11) displayed excellent activity comparable to that of Ni(PPh<sub>3</sub>)<sub>2</sub>–(1-naph)Cl under the same conditions with 5 mol % of Ni loadings, whereas Ni(PPh<sub>3</sub>)<sub>2</sub>(*o*-tol)Cl (entry 9) performed rather poorly. Interestingly, attempts to decrease their loadings to 3 mol % caused a dramatic decrease of yields for either Ni(PPh<sub>3</sub>)<sub>2</sub>–(1-naph)Cl (entry 12 vs entry 4) or Ni(PPh<sub>3</sub>)<sub>2</sub>(1-naph)Br (entry 14 vs entry 10), and even at elevated reaction temperatures the increase of yield was rather limited (entry 13). By contrast, Ni(PPh<sub>3</sub>)<sub>2</sub>(phenyl)Br worked well with no loss of its catalytic activity under the condition of 3 mol % Ni(II) loading, with the reaction proceeding to completion within 1 h at 65 °C (entry 15). Unfortunately, continuing to reduce the loading to 1 mol % led to loss of activity (entry 16).

To investigate the activation ability of Ni(II)–( $\sigma$ -aryl) complexes, a stoichiometric reaction of Ni(II)–( $\sigma$ -aryl) complexes with morpholine was carried out as in eq 1. The



efficiency of producing Ni(0) species in situ from the arylnickel(II) complexes may to a certain degree be reflected by the yields of *N*-arylmorpholine. It was found that the yield of *N*-arylmorpholine follows the order Ni(PPh<sub>3</sub>)<sub>2</sub>(phenyl)Br > Ni(PPh<sub>3</sub>)<sub>2</sub>(1-naph)Cl > Ni(PPh<sub>3</sub>)<sub>2</sub>(*o*-tol)Cl. Considering Ni(0)-generating efficiency and the factor of the decomposition of Ni(0) species due to no immediate ligation, decoordination of

**TABLE 2.** Coupling of Aryl Chlorides with Amines Catalyzed by Ni(II)–Aryl Complexes<sup>a</sup>

entry	ArX	amine	solvent (temp.)	yield (%)
1			THF(65)	99
2			THF(65)	93
3			THF(65)	43
4			Dioxane (80)	96
5			Dioxane (80)	72
6			Dioxane (80)	84 <sup>b</sup>
7			THF(65)	95 <sup>c</sup>
8			THF(65)	93
9			THF(65)	72 <sup>c</sup>
10			Dioxane (80)	82 <sup>b</sup>









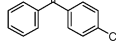













<sup>a</sup> Reaction conditions: chlorobenzene (1.0 equiv), cyclic amine (1.2 equiv), **4** (3 mol %), IPr•HCl (3 mol %), base (1.3 equiv), 1–3 h. <sup>b</sup> Cyclic amine (2.4 equiv). <sup>c</sup> **4** (5 mol %), IPr•HCl (5 mol %).

the ligand, and adventitious traces of air in the reaction media, we could roughly account for the difference of Ni(II)–(σ-aryl) complexes in the catalytic performance and capability.

The coupling of various aryl chlorides with secondary cyclic amines was examined under the optimal conditions (Table 2). For aryl chlorides, the electronic factors seemed to produce no significant effect: electron-neutral and -deficient aryl chlorides were coupled smoothly (entries 1, 2, and 6–8), and electron-rich aryl chlorides could obtain good yields (entries 3 and 4) simply by elevating reaction temperatures (by changing reaction solvent from THF to dioxane). Under our reaction conditions *p*-dichlorobenzene was doubly aminated in high yields (entries 5 and 9); this is one sole positive result in this case reported until now.<sup>8f</sup> On the other hand, the reaction is very sensitive to the steric hindrance of aryl chlorides: the reaction of *o*-chlorotoluene and 1-cholophenyl with morpholine gave low yields of 20% and 26%, respectively (unlisted in Table 2). The other advantage of our protocol is that shorter reaction times were required. In most cases, the reaction was completed within 3 h using 3 mol % of catalyst loading and 1.2 equiv of amine.

Next, we turn to *N*-arylation of aromatic amines. Under the above standard conditions using 5 mol % Ni(PPh<sub>3</sub>)<sub>2</sub>(1-naph)Cl with a 1:1 ratio of Ni(II) to IPr•HCl, the coupling of chlorobenzene with aniline was coupled in a poor yield of 20%, and the yield was not improved even after prolonged reaction times or at elevated temperatures. The yield increased with increase in the ratio of ligand to Ni(II). The desired yield was up to about 90% when performing the reaction in dioxane at 100 °C using a 1:2 ratio of Ni(PPh<sub>3</sub>)<sub>2</sub>(1-naph)Cl to IPr•HCl. It must be pointed out that the desired products were always contaminated with a trace of unidentified and hard-to-eliminate byproducts when utilizing Ni(PPh<sub>3</sub>)<sub>2</sub>(1-naph)Cl as pre-catalyst and also when using Ni(PPh<sub>3</sub>)<sub>2</sub>(phenyl)Br. The reason might presumably be related to the activation process of the Ni(II) complexes, for different phenomena were observed in the course of reaction with amine and with aniline, respectively. For the purpose of

**TABLE 3.** Coupling of Aryl Chlorides with Anilines Catalyzed by Ni(II)–Aryl Complexes<sup>a</sup>

entry	ArX	amine	yield (%)
1			99
2			78
3			80
4			92 <sup>b</sup>
5			90
6			96
7			99
8			98
9			92
10			69
11			66

<sup>a</sup> Reaction conditions: chlorobenzene (1.0 equiv), aniline (1.2 equiv), **5** (5 mol %), IPr•HCl (10 mol %), base (1.3 equiv), Dioxane (100 °C), 3–6 h. <sup>b</sup> Dioxane (120 °C).

achieving clean products with excellent yields, we tested Ni(PPh<sub>3</sub>)<sub>2</sub>(1-naphth-Ac)Cl (**5**) (1-naph-Ac = 1-(*p*-acetylnaphthyl)), which is considered as the modified Ni(PPh<sub>3</sub>)<sub>2</sub>(1-naph)Cl (**1**) bearing an electron-withdrawing group on the naphthyl moiety. Indeed, the pre-catalyst **5** facilitated the activation process and made the reaction completed within 3 h in nearly quantitative yield of 99%. More satisfyingly, the varied Ni(II) catalyst effected a very clean transformation, where the annoying byproduct disappeared. Finally, the optimal conditions were set up using dioxane as solvent and NaO<sup>t</sup>Bu as base in the presence of 5 mol % Ni(PPh<sub>3</sub>)<sub>2</sub>(1-naphth-Ac)Cl with a 1:2 ratio of Ni to IPr•HCl.

With the optimal conditions in hand, a range of cross-couplings between various anilines and aryl chlorides was carried out (Table 3). The reaction was sensitive to the steric and electronic effects of aryl chlorides. The coupling of *o*-chlorotoluene with aniline and 2,6-dimethylaniline gave only 78% and 69% yield, respectively (entries 2 and 9), whereas the corresponding reaction of chlorobenzene gave high yields of 99% and 92%, respectively (entries 1 and 8). Similarly, the reaction of *p*-chlorotoluene needed to be run at 120 °C to obtain a high yield of 92% (entry 3), whereas *p*-chlorobenzophenone reacted easily with aniline at 100 °C in 90% yield (entry 4). On the part of anilines, the reaction of primary aromatic amines appeared rather insensitive to both the steric and electronic effects (entries 5–8). Conversely, the steric bulk on the nitrogen atom (i.e., in the case of secondary aromatic amines) remarkably affected the outcome of the reaction. For example, *N*-methylaniline was coupled with chlorobenzene to give a lower yield

of 66% (entry 10), whereas diphenylamine did not react with chlorobenzene under the conditions (unlisted in Table 3).

Compared to the Ni(acac)<sub>2</sub>/SIPr/NaH system<sup>8g,h</sup> where 5 mol % catalyst loadings and 1.5 equiv of amine were needed to enable fast reaction (5–10 h), our method appeared more efficient, especially for the *N*-arylation of amines. In our protocol, the Ni(0) species coligated with (IPr + PPh<sub>3</sub>) might finally be produced. There the existence of PPh<sub>3</sub> would substantially enhance the catalytic activity of the coligated Ni(0) by accelerating the reductive elimination step. The analogous coligand effects were observed in palladium-<sup>16</sup> and nickel-catalyzed<sup>17</sup> coupling reactions.

In conclusion, Ni(II)–( $\sigma$ -aryl) complexes have first been employed as catalysts in C–N coupling reactions and allowed for the efficient amination of aryl chlorides. These complexes are readily available and easy to manipulate as a result of their stability toward air and moisture. Most distinctively, Ni(II)–( $\sigma$ -aryl) complexes could be activated without the need of additional reducing agents. This new protocol provides an extremely convenient, highly efficient, and less expensive alternative for the synthesis of *N*-substituted arylamines. Studies

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are underway in our laboratory to further expand the scope of this methodology as well as to ascertain mechanistic details of this process.

## Experimental Section

### Representative General Procedure for *N*-Arylation of Amines.

An oven-dried 100-mL three-necked flask was charged with NaO<sup>t</sup>-Bu (1.3 mmol, 125 mg), Ni(PPh<sub>3</sub>)<sub>2</sub>(phenyl)Br (3 mol % relative to aryl chloride, 22 mg) and IPr·HCl (3 mol % relative to aryl chloride, 13 mg). The aryl chloride (1.0 mmol) was added at this time if solid. The flask was evacuated and backfilled with nitrogen, with the operation being repeated twice. Aryl chloride (1.0 mmol) if liquid and secondary cyclic amine (1.2 mmol) were added via syringe. The dried THF or dioxane (3 mL) was added via syringe. The reaction mixture was heated in an oil bath at 65 °C (in THF) or 80 °C (in dioxane) for 1–3 h. The reaction mixture is allowed to cool to room temperature and filtered through a pad of silica gel. The silica gel pad was washed with ethyl acetate (20 mL × 3). Then the combined organic phases were evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel with hexane/ethyl acetate to give the desired product.

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**Supporting Information Available:** Experimental procedures, characterization data, and references to the known compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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