Nickel(0)/Dihydroimidazol-2-ylidene Complex Catalyzed Coupling of Aryl Chlorides and Amines

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A general and simple nickel-catalyzed coupling of aryl chlorides and amines is reported. The scope and limitations of the coupling process using Ni(0), 1,3-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidene, and NaO-*t*-Bu as base were investigated. Secondary cyclic and acyclic amines and anilines provided the arylamine coupling products in good to excellent yields. Compared to palladium-catalyzed aminations, this procedure offers an alternative route to *N*-substituted anilines starting from readily available aryl chlorides.

Aromatic amines are attractive targets for chemical synthesis because of their prevalence and wide utility as pharmacological agents, fine chemicals, dyes, and polymers.[1] There is thus a considerable interest in developing efficient synthetic protocols for the construction of aryl−nitrogen bonds.

The palladium-catalyzed carbon−nitrogen bond formation using aryl halides has been an area of intense research in recent literature.[2,3] The groups of Buchwald and Hartwig have detailed the palladium-catalyzed formation of aryl−nitrogen bonds using primary and secondary amines, hydrazines, anilines, imines, and nitrogen-containing heterocycles. General, reliable, and practical *N*-arylations using both electron-rich and electron-deficient aryl halides have thus been achieved. These studies have all shown that a well-tailored metal−ligand catalyst system is crucial for successful aryl carbon−nitrogen bond formation. In the search for ligands that provide highly active catalysts, improvements have been made using bidentate phosphines,[4] aminophosphines,[5] and bulky electron-rich phosphines.[6]

By contrast, nickel-catalyzed amination reactions have received less attention. Buchwald first reported the use of $Ni(cod)_2$ (cod = cyclooctadiene) associated with 1,1′-bis(diphenylphosphino)ferrocene (dppf) or 1,10-phenanthroline for the synthesis of arylamines.[7] Bolm extended this *N*-arylation method for the coupling of sulfoximines with aryl tosylates using $Ni(cod)_2$ liganded with 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl (BINAP).[8] A heterogeneous Ni(0)/C catalyst liganded with dppf was also recently developed by Lipshutz.[9] For our part, we have reported the use of a catalyst combination of in situ generated colloidal Ni(0) associated with 2,2′-bipyridine and NaO-*t*-Am-activated sodium hydride, which provided an efficient route to substituted anilines.[10] Some advantages of this nickel-catalyzed approach were that the coupling reactions occurred under fairly mild conditions and were effective with inexpensive and readily available aryl chlorides. In addition, the Ni/2,2′-bipyridine catalyst

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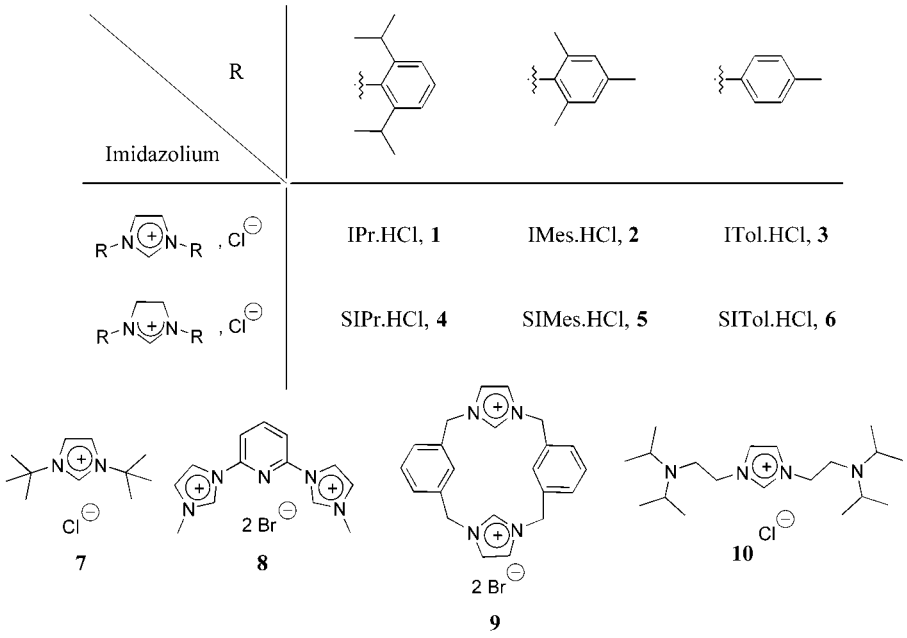
Scheme 1. Carbene Precursors



has also been shown to be effective for a wide variety of carbon−nitrogen bond forming processes including *N*-monoarylation of piperazine[11] and polyamination or selective monoamination of aryl di- and trichlorides.[12]

However, the scope of our Ni/2,2′-bipyridine was somewhat limited. Indeed, fast and clean amination reactions could only be achieved in the presence of a stoichiometric amount of sodium hydride. The strong basicity of the catalytic system limits the functional group tolerance of the process and the nature of the amine which could be used as coupling partner. For example, primary amines and anilines were readily deprotonated by NaO-*t*-Am- *or* NaO-*t*-Bu-activated NaH and the aryl amination products were obtained as mixtures of regioisomers resulting from a competing benzyne pathway.

Considering the major effect of the ligands in palladium-catalyzed carbon−nitrogen bond forming processes, we wondered whether the scope of our nickel-catalyzed amination reactions could be improved and extended to primary amines and anilines by the help of a judiciously selected ligand, yielding a catalyst combination which does not require sodium hydride.

In recent years, it has become clear that *N*-heterocyclic carbenes (NHCs) can offer an interesting alternative class of ligands to the ubiquitous phosphines for catalytic applications. Various reactions involving imidazolium salts as precursors to NHCs have recently been reported. These include copolymerization of ethylene and CO,[13] hydrogenation,[14] and alkene metathesis.[15] Palladium-catalyzed protocols using NHCs have also been shown to offer a significant advantage for a range of synthetically valuable coupling processes such as carbon−carbon[16] or carbon−nitrogen[17] bond forming reactions. These reports have all demonstrated that such thermally stable and strong electron-donating ligands can be incorporated into the catalysts and that an excess of ligand is not required to prevent aggregation of the metal.

A preliminary account of nickel-catalyzed amination reactions performed with Ni(0)/NHC catalysts associated with NaO-*t*-Bu-activated NaH has appeared.[18] Herein, we disclose the results of a detailed study of NHCs in nickel-catalyzed aryl amination processes performed without NaH demonstrating that the scope of the reaction could be extended to aromatic and primary alkylamines with this catalyst combination.

Results and Discussion

Influence of the Carbene Ligand. To select the most effective ligand, chlorobenzene and morpholine were considered as appropriate substrates for the aryl amination coupling, and this combination was tested with various mono- and bidentate imidazolium or dihydroimidazolium salts (Scheme 1) associated with Ni(0) to

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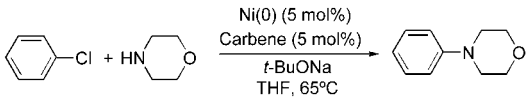
Table 1. Evaluation of Imidazolium Salts for Nickel-Catalyzed Coupling of Chlorobenzene with Morpholine[a,b]



entry	ligand	yield (%)	entry	ligand	yield (%)
1		0	7	SIMes·HCl, **5**	20
2	2,2-bipyridine	25[c]	8	SITol·HCl, **6**	8
3	IPr·HCl, **1**	90	9	**7**	44[d]
4	IMes·HCl, **2**	12	10	**8**	0
5	ITol·HCl, **3**	5	11	**9**	27
6	SIPr·HCl, **4**	94	12	**10**	14

[a] Reaction conditions: 10 mmol of chlorobenzene, 15 mmol of morpholine, 0.5 mmol of Ni(0), 0.5 mmol of imidazolium salt, 18 mmol of *t*-BuONa, 12 mL of THF, 65 °C. [b] Yields were determined by GC and are the average of two runs. [c] Reaction performed using 2 equiv of 2,2′-bipyridine relative to Ni(0). [d] Reaction performed using 4 equiv of imidazolium chloride relative to Ni(0).

determine the optimal conditions for the catalytic *N*-arylation.

A variation on the preparation of the Ni(0) complex was first investigated. Instead of employing stoichiometric amounts of NaH for the cross-coupling of amines with aryl chlorides, the aryl amination reactions were performed in the presence of NaO-*t*-Bu. The amount of NaH used for the preparation of the catalyst was therefore exactly adjusted to reduce the starting Ni(II) to Ni(0) and to convert *t*-BuOH into NaO-*t*-Bu. This variation was found to be effective, and a slight excess of NaH was not necessary to maintain the Ni(0) catalyst in the lowest oxidation state. The catalysts were all in situ generated by stirring a mixture of $Ni(acac)_2$ (5 mol %), the imidazolium carbene precursor, and NaH in refluxing THF followed by the addition of *t*-BuOH and morpholine. These Ni/carbene catalysts were used after 1/2 h at 65 °C for the amination of chlorobenzene.

The role of the in situ generated NaO-*t*-Bu is 2-fold during the preparation of the starting NHC liganded Ni(0) complex: (i) it initially activates sodium hydride used to reduce the Ni(II) salt to Ni(0) ; (ii) it deprotonates the imidazolium salt to form the carbene ligand which coordinates to the metal.

As expected, the coupling without using ligand resulted in no detectable reaction products (entry 1, Table 1). It was also of interest to run a control reaction with 2,2′-bipyridine, which has led to good results when the reactions were performed with stoichiometric amounts of NaH.[10−12] Using the new protocol, this ligand afforded only a moderately active catalyst, and *N*-phenylmorpholine was obtained in a modest 25% yield (entry 2, Table 1).

A screening of representative NHC ligands is summarized in Table 1. After some experimentation, we first found that with monodentate carbenes **1**−**6** and **10**, biscarbene **9**, or tridentate ligand **8**, a 1/1 ratio of carbene to Ni gave the best catalyst combination. Using 1,3-di(*tert*-butyl)imidazolium **7**, a Ni/ligand ratio of 1/4 gave improved yields of *N*-phenylmorpholine (10% when Ni/L = 1/1 compared to 44% when Ni/L =1/4).

The bulky 1,3-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidene, generated from SIPr·HCl (**4**), was found to be the most effective NHC precursor, leading to *N*-phenylmorpholine in a 94% yield (entry 6). 1,3-Disubstituted imidazolium salts **2**, **3**, and **5**−**10** led to the formation of moderately active catalysts and allowed low conversion of the starting materials (entries 4, 5, and 7−12), while the use of IPr·HCl (**1**) led to *N*-phenylmorpholine in 90% yield. The differences in activity displayed by the ligands might be attributed to the effectiveness of NaO-*t*-Bu in the imidazolium salt deprotonation step or, once the carbene is generated, to steric and electronic effects affecting the performances of the nickel species in the course of the aryl amination process. However, one general feature needs to be noted. Dihydroimidazolium carbenes, more σ-donating than imidazolium-based carbenes,[19] increased the activity of the catalysts, and *N*-phenylmorpholine was obtained in substantial increased yields using these ligands (compare entries 3−5 to entries 6−8, respectively).

In addition, a number of Ni(II) precursors were screened in the coupling between morpholine and chlorobenzene in refluxing THF using 1,3-bis(2,6-diisopropylphenyl)-dihydroimidazol-2-ylidene as supporting ligand. $Ni(acac)_2$ was found to be the best Ni(0) source. $Ni(OAc)_2$ can also be used (81% yield after 6 h of reaction time), while the reaction proceeded, respectively, in only 53% and 35% yield using $NiCl_2$ and $NiBr_2$. A variety of reaction conditions were also examined, and we found that the base NaO-*t*-Bu gave significantly higher isolated yields than either the lithium or potassium analogue (respectively, 19% and 4%). Finally, either THF or dioxane at reflux appeared suitable as solvent, while the use of a nonpolar solvent such as toluene resulted in a slower conversion (43% after 15 h) and significant reduction of chlorobenzene to benzene via β-hydride elimination followed by reductive elimination from the intermediate nickel−amido complex.

Arylation of Secondary Cyclic and Acyclic Alkylamines. To further investigate the scope of this new method, we studied the nickel-catalyzed coupling of secondary cyclic and acyclic amines with aryl chlorides using **4** as carbene precursor and NaO-*t*-Bu as base. Table 2 describes the results of these couplings using structurally and electronically diverse aryl chlorides. Using the optimal conditions described above (5 mol % Ni, 5 mol % SIPr·HCl, NaO-*t*-Bu (1.5 equiv relative to the aryl chloride), THF, 65 °C), the Ni-catalyzed couplings of aryl or heteroaryl chlorides with secondary amines provided a general route to the corresponding arylamines. The only side product observed was the arene resulting from reduction of the starting aryl chloride. Electron-poor aryl chlorides generally gave the amination product in good to excellent yields (entries 7−13, 20−23, and 25, Table 2), while lower yields were obtained with electron-rich aryl chlorides (entries 14 and 15).

Surprisingly, while morpholine and pyrrolidine were efficiently coupled with 3-chloroanisole in high yields (entries 7 and 9), the reaction with piperidine gave a large amount of reduced side product, and *N*-phenylpiperidine was obtained in a modest 55% yield. Such a limitation was previously observed with the Pd/BINAP[20] catalyst and is, for the moment, difficult to explain.

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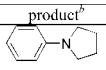
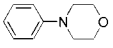
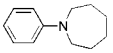
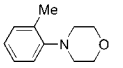
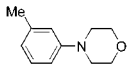
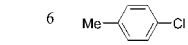
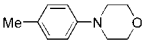
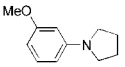
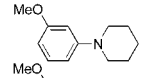
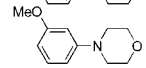
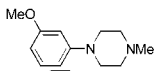
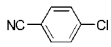
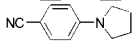
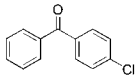
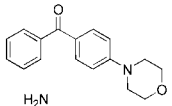
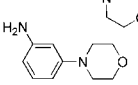
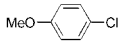
Table 2. Nickel-Catalyzed Coupling of Secondary Amines with Aryl Chlorides[a]

entry	aryl chloride	amine	product[b]	yield (%)[c]
1				92
2				94
3				60
4				69
5				91
6				91
7				96
8				55
9				95
10				93
11				71
12				99
13				68
14				55
15				53
16				92[d]
17				81[d]
18				79[e]
19				83[f]
20				82
21				88
22				54[d]
23				87[g]
24				86[h]
25				89[h]

[a] Reaction conditions: 10 mmol of aryl halide, 15 mmol of amine, 18 mmol of NaO-*t*-Bu, 0.5 mmol of Ni(0), 0.5 mmol of SIPr·HCl, 12 mL of THF, 65 °C, 5−10 h (reaction times have not been minimized). [b] All products were characterized by ^{1}H and ^{13}C NMR, IR, and GC/MS spectroscopy methods. [c] Yields are for isolated compounds estimated to be >95% pure by ^{1}H and ^{13}C NMR, GC, and EA and are an average of two runs. [d] A 1 mmol sample of Ni(0), a 1 mmol sample of SIPr·HCl, and a 20 mmol sample of amine were used, and dioxane was used as solvent. [e] A 20 mmol sample of piperazine was used, and dioxane was used as solvent. [f] A 30 mmol sample of chlorobenzene and a 10 mmol sample of piperazine were used. [g] A 28 mmol sample of NaO-*t*-Bu was used. [h] A 10 mmol sample of aryl halide, a 30 mmol sample of amine, a 36 mmol sample of NaO-*t*-Bu, a 1 mmol sample of Ni(0), and a 1 mmol sample of SIPr·HCl were used.

The Ni(0)/SIPr·HCl catalyst was only slightly sensitive to an *ortho*-substitution of the aryl chloride. 2-Chlorotoluene reacted with morpholine in 69% yield (entry 4, Table 2), while 3- and 4-chlorotoluene reacted with the amine without difficulty (entries 5 and 6). Contrary to other Ni(0) catalysts,[21] nitriles (entry 11) and nonenolizable ketone groups (entry 12) were well tolerated. Moreover, substrates containing functional groups that might be problematic in a palladium-catalyzed methodology such as a primary aromatic (entry 13) or an alkene (entry 15) were transformed in good yields.

The reaction of acyclic secondary amines occurred in refluxing dioxane using 10 mol % catalyst with rates that were comparable to those of cyclic secondary amines. *N*-Methylbenzylamine and *N*-methylaminoacetaldehyde dimethyl acetal reacted with chlorobenzene to give the desired arylamines in, respectively, 92% and 81% yield (entries 16 and 17), and even the sterically hindered dibenzylamine reacted with 3-chloropyridine to give the coupled product in 54% yield (entry 22).

The Ni(0)/SIPr·HCl catalyst was also effective for the arylation of piperazine. Using a 2-fold excess of amine relative to the aryl chloride and performing the reaction in dioxane, chlorobenzene coupled with piperazine to form the *N*-arylated product in 79% yield (entry 18, Table 2). Higher temperatures than those used for secondary cyclic monoamines were however necessary. It must also be underlined that the formation of the bisarylated product was observed in less than 7% yield. Using an excess of chlorobenzene (3 equiv) relative to piperazine, the symmetrically *N*,*N*′-biphenyl substituted diamine could be isolated in 83% yield (entry 19).

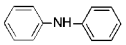
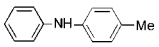
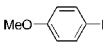
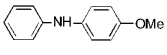
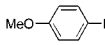
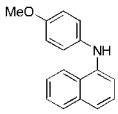
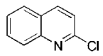
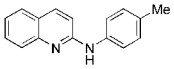
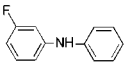
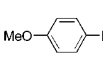
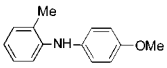
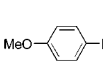
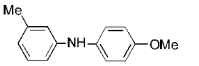
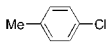
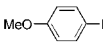
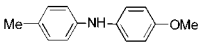
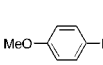
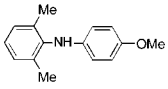
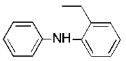
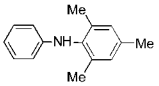
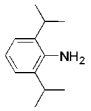
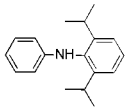
Amination of aryl dichlorides was finally investigated. Diaminated products were formed exclusively and in good yields when 1,3-dichlorobenzene or 4,4′-dichlorobenzophenone was treated with morpholine using 5 mol % Ni(0)/SIPr·HCl catalyst combination per carbon−chlorine functionality (entries 24 and 25, Table 2).

Arylation of Anilines. Given the success of the Ni(0)/SIPr·HCl combination for the arylation of secondary cyclic and acyclic amines, we were interested to extend the scope and generality of this system to the arylation of anilines.

Under standard conditions using typically 5 mol % nickel and 5 mol % SIPr·HCl and preparing the Ni(0) catalyst in the presence of the amine, aniline was coupled in a poor 21% yield with chlorobenzene even after extended reaction times. Initial studies revealed first that premixing the aryl chloride and the amine and adding

(20) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem*. **2000**, *65*, 1144.
(21) (a) Garcia, J. J.; Jones, W. D. *Organometallics* **2000**, *19*, 5544. (b) Miller, A. J. *Tetrahedron Lett*. **2001**, *42*, 6991.

Table 3. Nickel-Catalyzed Coupling of Anilines with Aryl Chlorides[a]

entry	aryl chloride	amine	product[b]	yield (%)[c]
1				92
2				99
3				97
4				82
5				82
6				83
7				99
8				91
9				83
10				86
11				96
12				91
13				55
14				58[d]
15				59[d]
16				59[d]
17				63[d]
18				84
19				93
20				99
21				47
22				84[e]

[a] Reaction conditions: 10 mmol of aryl halide, 15 mmol of amine, 18 mmol of NaO-*t*-Bu, 1 mmol of SIPr·HCl, 0.5 mmol of Ni(0), 12 mL of dioxane, 100 °C, 5−10 h (reaction times have not been minimized). [b] All products were characterized by ^{1}H and ^{13}C NMR, IR, and GC/MS spectroscopy methods. [c] Yields are for isolated compounds estimated to be >95% pure by ^{1}H and ^{13}C NMR, GC, and EA and are an average of two runs. [d] A 2 mmol sample of SIPr·HCl and a 1 mmol sample of Ni(0) were used. [e] A 10 mmol sample of aryl dihalide, a 30 mmol sample of amine, a 36 mmol sample of NaO-*t*-Bu, a 2 mmolsample of Ni(0), and a 4 mmol sample of SIPr·HCl were used.

these reagents simultaneously to the liganded Ni(0) catalyst was essential for a high catalytic activity. These results support the fact that these nickel-catalyzed aryl aminations proceed via intermediates in which the nitrogen−nickel interaction is important. Presumably, adding simultaneously the aryl chloride and the amine to the catalyst allowed the coordination of aniline toward the nickel center to be avoided, thereby permitting the oxidative addition of the aryl chloride.

We also reevaluated the relative importance of the ligand/metal ratio and solvent on the reaction yields using diphenylamine as a model substrate. Reaction rates were markedly increased using a 2/1 ratio of ligand to metal and using dioxane as solvent. A slight excess of the amine was also necessary.

The scope of the reaction of anilines with aryl chlorides is presented in Table 3. An excess of aniline (1.5 equiv relative to the aryl chloride) was used in all these couplings to ensure short reaction times. However, we found that reactions could also be performed using 1.2 equiv of the amine without a significant decrease of reaction yields. It is also worth noting that no double arylation products were observed using either 1.5 or 1.2 equiv of amine relative to the aryl chloride.

The amination technology based on the Ni(0)/SIPr·HCl combination is applicable to a wide range of anilines and aryl or heteroaryl chlorides. In general, the substrate scope for arylation of anilines was similar to that for reactions performed with secondary cyclic or acyclic amines. Excellent results for the arylations of aniline, *p*-toluidine, or *p*-anisidine with aryl chloride were obtained using the Ni(0)/SIPr·HCl catalyst. For example, the reaction of *p*-toluidine with chlorobenzene proceeded to completion in 5 h to afford the desired product in 99% yield (entry 2, Table 3). Using *ortho* (entry 7), *meta* (entries 6 and 8), or *para* (entries 9 and 20) substituted aryl halides, the corresponding amines were obtained in good to excellent yields. Even *ortho*,*ortho* disubstituted substrates such as 2,6-dimethylchlorobenzene reacted with *p*-anisidine to give the diarylamine in 86% yield (entry 10), indicating that a high degree of steric hindrance on the aryl chloride does not impede the reaction.

We next screened a variety of anilines to determine the effect of the substitution pattern on the reaction yield. *Ortho* substitution of the aniline was well tolerated (entries 11, 16, and 17, Table 3). Reactions performed with sterically hindered anilines afforded the desired products in moderate to good yields. Chlorobenzene reacted with 2,4,6-trimethylaniline (entry 12) in 91% yield, and even 2,6-diisopropylaniline provided the diarylamine product in 55% yield when combined with chlorobenzene (entry 13). However, the Ni(0)/SIPr·HCl catalyst system was found to be less effective for the arylation of anilines bearing electron-withdrawing sub-

stituents (entries 14−16, Table 3). For example, the coupling between chlorobenzene and 3-fluoroaniline gave only 59% *N*-(3-fluorophenyl)-*N*-phenylamine (entry 15), while aniline reacted with 3-fluorochlorobenzene to give the desired arylamine in 83% yield (entry 6). Using such substrates, reaction times were increased and aryl amination was depressed. Arylations of anilines substituted by electron-withdrawing substituents were possible, although fairly high catalyst loadings (10 mol % Ni) were required (entries 14−16). This may be a consequence of the reduced nucleophilicity of these amines, which inhibits the coordination to the nickel(II) center, which is necessary for their deprotonation. An alternative explanation is that their reduced nucleophilicity inhibits the substitution of the chlorine atom on the intermediate aryl nickel(II) complex, which is necessary for the transamination step. This relative drawback can however easily be overcome by inverting the substitution pattern of the aniline and the aryl chloride (compare entries 6 and 15).

Surprisingly, the introduction of an *o*-methoxy group on the aromatic ring resulted in an incomplete reaction even after extended reaction times (24 h), and the coupling between chlorobenzene and *o*-anisidine afforded *N*-(2-methoxyphenyl)-*N*-phenylamine in only 63% yield (entry 17, Table 3). We speculate that the decrease of efficiency of the Ni(0)/SIPr·HCl catalyst might result from a coordination of the nickel center at the nitrogen and oxygen atoms of *o*-anisidine.

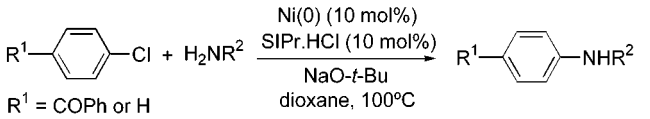
N-Methylaniline was also efficient in cross-coupling with various aryl chlorides (entries 18−20 and 22). As shown in Table 3, the reaction proceeded to completion in less than 10 h, affording the desired products in yields ranging from 84% with chlorobenzene (entry 18) to 99% with the activated 4-chlorobenzophenone (entry 20). Changing the substitution on the nitrogen atom from Me to a simple Et group provided the diarylamine in a modest 47% yield (entry 21). This experiment demonstrates that the steric bulk on the nitrogen atom plays an important role in the outcome of the reaction using the Ni(0)/SIPr·HCl catalyst and explains why diarylamines were obtained selectively without formation of the corresponding triarylamines.

It should be noted that diphenylamine, a sterically hindered aromatic amine, and α- or *β*-naphthylamine (experiments not reported), did not provide any coupling product when reacted with chlorobenzene. By contrast, *N*-naphthyl-*N*-phenylamine could be obtained in 82% yield by coupling *p*-anisidine and 1-chloronaphthalene (entry 4, Table 3).

Additionally, the Ni-catalyzed arylation reaction has been successfully employed for the polyamination of aryl dichlorides. 4,4′-Dichlorobenzophenone reacted with 3 equiv of *N*-methylaniline in the presence of an excess of NaO-*t*-Bu in dioxane at 100 °C to give bis[4-(methylanilino)phenyl]methanone in 84% yield (entry 22, Table 3).

Arylation of Primary Alkylamines. Finally, in the case of primary alkylamines, acceptable yields could only be realized with activated aryl chlorides. 4-Chlorobenzophenone was efficiently coupled with *n*-hexylamine or cyclohexylamine to give the desired products in 65% and 85% yield, respectively. Using a neutral substrate such as chlorobenzene, the reaction rate was slower and a substantial amount of dehalogenated product was observed (Scheme 2). The lower reactivity of primary

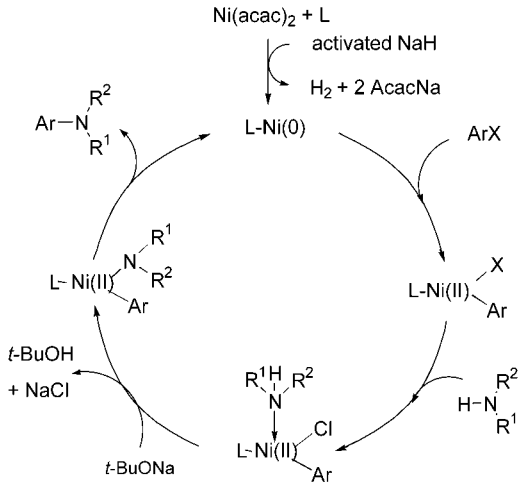
Scheme 2



alkylamines relative to other amines used in this study may be due to the formation of catalytically inactive nickel species such as bis-amido-bridged complexes or bis-(amine) complexes as observed in the palladium-catalyzed aryl amination reaction.[3a,22]

Mechanistic Considerations. There is little mechanistic information about couplings conducted with the Ni(0)/SIPr·HCl/NaO-*t*-Bu catalyst combination, but the catalytic cycle for the amination reaction is presumably similar to that postulated for the palladium-catalyzed amination of aryl halides using Pd/carbene systems.[17] The first step involves formation of Ni(0) by reduction of $Ni(acac)_2$ with NaO-*t*-Bu-activated sodium hydride followed by coordination of the carbene generated from SIPr·HCl to the metal center. Transmission electron microscopy coupled energy-dispersive X-ray spectra of the Ni/carbene catalyst thus obtained revealed a homogeneous distribution of uniformly sized amorphous and subnanometrical Ni(0) particles. The strong electron-donating property of the carbene ligand facilitates the oxidative addition of the aryl chloride to Ni(0). From results obtained with anilines and primary alkylamines, it seems apparent that aryl amido nickel species are involved in the second step of the catalytic cycle. Finally, the steric bulk of the carbene generated from SIPr·HCl may accelerate the carbon−nitrogen bond forming reductive elimination. On the basis of these observations, a likely pathway for carbon−nitrogen couplings mediated by the Ni(0)/SIPr·HCl/NaO-*t*-Bu catalyst is depicted in Scheme 3.

Scheme 3. Proposed Mechanism for the Amination of Aryl Chlorides



(22) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534.

(23) (a) Arduengo, A. J., III. U.S. Patent 5 077 414, 1991. (b) Arduengo, A. J., III; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523−14534.

Conclusion

In summary, we have developed a novel protocol for the amination of aryl chlorides which is based on nickel/*N*-heterocyclic carbene cross-coupling methodology. The Ni(0)/SIPr·HCl catalyst combined with NaO-*t*-Bu proved to be efficient and high yielding for the arylation of secondary cyclic or acyclic amines and anilines. The reaction is widely applicable to a variety of electron-rich, electron-poor, and neutral aryl chlorides as well as heterocyclic halides. Good to excellent yields were obtained regardless of the substitution pattern of the aryl chloride. Studies are under way to further expand the scope of this methodology to primary alkylamines as well as to understand the mechanistic pathway of the nickel-catalyzed process.

Experimental Section

General Considerations. All reactions were carried out using standard Schlenk techniques under an atmosphere of nitrogen. Gas chromatographic analyses were performed on a capillary gas chromatograph fitted with an "Optima 5" column (22 m × 0.25 mm i.d. × 0.25 μm). All quantifications of reaction constituents were achieved by gas chromatography using a known quantity of decane as reference standard. Melting points were taken on a Tottoli apparatus and are uncorrected. The ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded at 400.13, 235.0, and 100.40 MHz using $CDCl_3$ as solvent. IR spectra were recorded using NaCl cells or a mixture of compound/KBr. Compounds previously described were characterized by ^{1}H and ^{13}C NMR, and their purity was confirmed by GC analysis. The characterization data of these compounds are given in the Supporting Information. All new compounds were fully characterized by ^{1}H and ^{13}C NMR, IR, and elemental analysis.

THF and dioxane were distilled under nitrogen from sodium benzophenone ketyl. *tert*-Butyl alcohol was distilled from sodium before use. Sodium hydride (65% in mineral oil) was purchased from Fluka and used after two washings with THF under nitrogen. Aryl halides were purchased from commercial sources and used without further purification. Amines were purchased from commercial sources and distilled or passed through alumina before use. Nickel(II) acetylacetonate was purchased from Acros and used as received. All imidazolium salts were synthesized according to literature procedures.[1,2]

General Procedure for the Arylation of Secondary Cyclic Amines. A 50 mL Schlenk tube was loaded with degreased NaH (16 mmol), $Ni(acac)_2$ (0.5 mmol, 5 mol %), SIPr·HCl (0.5 mmol, 5 mol %), and 6 mL of solvent (THF or dioxane), and the mixture was heated to reflux. A solution of *t*-BuOH (15 mmol) in 3 mL of THF or dioxane was then added dropwise followed by the amine (15 mmol), and the mixture was further stirred for 1/2 h. A solution of the aryl chloride (10 mmol) in 3 mL of THF or dioxane was then added, and the reaction was monitored by GC. After complete consumption of the aryl chloride, the mixture was cooled to room temperature and adsorbed onto silica gel. The crude reaction mixture was purified by silica gel chromatography.

3-Morpholinoaniline (Table 2, Entry 13). The general procedure was used to couple 3-chloroaniline and morpholine. The reaction was conducted at 65 °C in THF with 5 mol % Ni(0) and 5 mol % SIPr·HCl. The title compound was isolated as a brown oil (68%). IR (NaCl, cm^{-1}): ν_{NH} 3349. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.04−6.99 (m, 1H), 6.31−6.29 (m, 1H), 6.19−6.17 (m, 2H), 3.79−3.77 (m, 4H), 3.55 (br s, NH_2), 3.06−3.04 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.17, 147.23, 129.62, 107.00, 105.96, 102.20, 66.59, 48.99. MS: m/z 178. Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39, H, 7.92, N, 15.72. Found: C, 67.4, H, 7.9, N, 15.9.

4-(4-Vinylphenyl)morpholine (Table 2, Entry 15). The general procedure was used to couple 4-chlorostyrene and morpholine. The reaction was conducted at 65 °C in THF with 5 mol % Ni(0) and 5 mol % SIPr·HCl. The title compound was isolated as a yellow oil (53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 6.64 (dd, J = 16.0, 12.0 Hz, 1H), 5.60 (d, J = 16.0 Hz, 1H), 5.09 (d, J = 12.0 Hz, 1H), 3.87−3.84 (m, 4H), 3.18−3.14 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.81, 136.22, 129.43, 127.08, 115.34, 111.03, 66.80, 49.05. MS: m/z 189. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16, H, 7.99, N, 7.40. Found: C, 76.3, H, 8.1, N, 7.3.

***N,N*-Dibenzyl-3-pyridinamine (Table 2, Entry 22).** The general procedure was used to couple 3-chloropyridine and *N,N*-dibenzylamine. The reaction was conducted at 65 °C in THF with 10 mol % Ni(0), 10 mol % SIPr·HCl, and 20 mmol of *N,N*-dibenzylamine. The title compound was isolated as a light yellow oil (54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 1.8 Hz, 1H), 7.90 (d, J = 4.0 Hz, 1H), 7.33−7.15 (m, 12H), 4.62 (s, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.59, 137.54, 137.21, 134.57, 128.51, 126.93, 126.25, 123.31, 118.77, 53.89. MS: m/z 274. Anal. Calcd for $C_{19}H_{18}N_2$: C, 83.18, H, 6.61, N, 10.21. Found: C, 83.3, H, 6.3, N, 10.4.

General Procedure for the Arylation of Anilines. A 50 mL Schlenk tube was loaded with degreased NaH (16 mmol), $Ni(acac)_2$ (0.5 mmol, 5 mol %), SIPr·HCl (1 mmol, 10 mol %), and 6 mL of dioxane, and the mixture was heated to 100 °C. A solution of *t*-BuOH (15 mmol) in 3 mL of dioxane was then added dropwise, and the mixture was further stirred at 100 °C for 1/2 h. A solution of the aryl chloride (10 mmol) and the amine (15 mmol) in 3 mL of dioxane was then added dropwise, and the reaction was monitored by GC. After complete consumption of the aryl chloride, the mixture was cooled to room temperature and adsorbed onto silica gel. The crude reaction mixture was purified by silica gel column chromatography.

***N*-(4-Methoxyphenyl)-2,6-dimethylaniline (Table 3, Entry 10).** The general procedure was used to couple 2,6-dichlorotoluene and *p*-anisidine. The reaction was conducted at 100 °C in dioxane with 5 mol % Ni(0) and 10 mol % SIPr·HCl. The title compound was isolated as a light yellow solid (86%). Mp: 53 °C. IR (NaCl, cm^{-1}): ν_{NH} 3406. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11−7.01 (m, 3H), 6.75 (d, J = 8.0 Hz, 2H), 6.50 (d, J = 8.0 Hz, 2H), 3.74 (s, 3H), 2.20 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.08, 139.23, 134.85, 128.56, 128.44, 124.99, 124.87, 123.58, 115.26, 114.83, 114.68, 55.70, 18.36. MS: m/z 227. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26, H, 7.54, N, 6.16. Found: C, 79.1, H, 7.4, N, 6.3.

***N*-(2-Ethylphenyl)aniline (Table 3, Entry 11).** The general procedure was used to couple chlorobenzene and 2-ethylaniline. The reaction was conducted at 100 °C in dioxane with 5 mol % Ni(0) and 10 mol % SIPr·HCl. The title compound was isolated as a light yellow oil (96%). IR (NaCl, cm^{-1}): ν_{NH} 3399. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15−7.23 (m, 4H), 7.09 (td, J = 8.0, 2.0 Hz, 1H), 6.95 (td, J = 8.0, 2.0 Hz, 1H), 6.88−6.80 (m, 3H), 5.30 (s, NH), 2.55 (q, J = 8.0 Hz, 2H), 1.19 (t, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.43, 140.36, 134.71, 129.15, 128.81, 126.53, 122.51, 120.05, 120.01, 116.87, 24.15, 13.77. MS: m/z 197. Anal. Calcd for $C_{14}H_{15}N$: C, 85.24, H, 7.66, N, 7.10. Found: C, 85.4, H, 7.3, N, 7.3.

***N*-Methyl-*N*-phenylaniline (Table 3, Entry 18).** The general procedure was used to couple chlorobenzene and *N*-methylaniline. The reaction was conducted at 100 °C in dioxane with 5 mol % Ni(0) and 10 mol % SIPr·HCl. The title compound was isolated as a light yellow oil (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (t, J = 8.0 Hz, 4H), 7.01 (d, J = 8.0 Hz, 4H), 6.92 (td, J = 8.0, 2.0 Hz, 2H), 3.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.97, 129.13, 121.20, 120.39, 40.18. MS: m/z 183. Anal. Calcd for $C_{13}H_{13}N$: C, 85.21, H, 7.15, N, 7.64. Found: C, 85.3, H, 7.0, N, 7.7.

***N*-Ethyl-*N*-phenyl-3-pyridinamine (Table 3, Entry 21).** The general procedure was used to couple 3-chloropyridine and *N*-ethylaniline. The reaction was conducted at 100 °C in dioxane with 5 mol % Ni(0) and 10 mol % SIPr·HCl. The title compound was isolated as a light yellow oil (47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (br s, 1H), 8.11 (br s, 1H), 7.34 (t, J = 8.0 Hz, 2H), 7.20−7.18 (m, 1H), 7.13−7.10 (m, 4H), 3.80 (q, J = 8.0 Hz, 2H), 1.25 (t, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.29, 144.02, 140.28, 140.04, 129.59, 124.68, 123.49, 123.39, 123.34, 46.23, 12.37. MS: m/z 198. Anal. Calcd

for $C_{13}H_{14}N_2$: C, 78.75, H, 7.12, N, 14.13. Found: C, 78.7, H, 7.3, N, 14.0.

Bis[4-(methylanilino)phenyl]methanone (Table 3, Entry 22). The general procedure was used to couple 4,4′-dichlorobenzophenone and *N*-methylaniline. The reaction was conducted at 100 °C in dioxane with 10 mol % Ni(0), 20 mol % SIPr·HCl, 10 mmol of 4,4′-dichlorobenzophenone, 30 mmol of *N*-methylaniline, and 36 mmol of NaO-*t*-Bu. The title compound was isolated as a yellow solid (84%). Mp: 112 °C. IR (NaCl, cm^{-1}): ν_{CO} 1629. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.8 Hz, 4H), 7.93 (t, J = 8.0 Hz, 4H), 7.26−7.16 (m, 6H), 6.81 (d, J = 8.8 Hz, 4H), 3.38 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.86, 151.83, 147.56, 131.81, 129.71, 128.21, 125.52, 125.03, 113.91, 40.20. MS: m/z 392. Anal. Calcd for $C_{27}H_{24}N_2O$: C, 82.62, H, 6.16, N, 7.14. Found: C, 82.4, H, 6.0, N, 7.1.

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

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