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Communication

Room-temperature nickel-catalyzed amination of heteroaryl/aryl chlorides with Ni(II)–(σ-Aryl) complex as precatalyst

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ABSTRACT

The room-temperature cross-coupling of heteroaryl and aryl chlorides with secondary cyclic amines can be effected using Ni(II)-(σ-aryl) complex as pre-catalyst. Some useful aromatic and heteroaromatic amine derivatives were readily synthesized in moderate to good yields in the presence of the Ni(II)-(σ-aryl) complex/NHC/KO^{t}Bu/toluene system.

1. Introduction

(Hetero)aryl amines constitute an important class of building blocks extensively used in the synthesis of pharmaceuticals, agrochemicals and chemical materials, etc [1]. Therefore, the development of efficient and practical methods for the formation of aromatic C–N bonds (the Buchwald–Hartwig reaction) is of particular interest to synthetic chemists. In catalytic amination reactions, palladium-based systems certainly represent the most widely used class of catalysts that allow (hetero)aryl halides/pseudohalides to be effectively aminated under mild reaction conditions [2,3]. On the other hand, the choice of nickel complexes as alternatives has been attracting considerable interest due to their low cost and potential high reactivity towards easily-available but relatively inert substrates (e.g., aryl chlorides and sulfonates) without the use of specially tailored ligands.

Buchwald in 1997 first reported the nickel-catalyzed amination of aryl chlorides in the presence of Ni(0)/DPPF or 1,10-phenanthroline [4]. Bolm provided the example for the amination of aryl tosylates with sulfoximines by employing BINAP as ligand for Ni(0) [5]. Fort developed the Ni(II)–NaH–bipyridine [6–9] and Ni(II)–NaH–NHC [10] systems as efficient catalysts for the couplings of aryl and heteroaryl chlorides with various nitrogen-containing substrates. Lipshutz extended this methodology by using a heterogeneous Ni(0)-on-charcoal catalyst [11]. In view of the facts that air-sensitive Ni(0) sources are difficult to handle and the pre-treatment of Ni(II) precursors with strong reducing reagents such as *n*-BuLi, Grignard reagents or NaH could decrease compatibility of the reactions with functional groups, Knochel utilized polymethylhydrosiloxane (PMHS) as a mild and effective reductant in the Ni(II) precatalyst with excellent results [12]. Our group explored a more facile protocol for aromatic C–N bond-forming reactions by employing stable arylnickel(II) halides complexes as catalyst precursors, where the Ni(II) precursor, in conjunction of NHC ligands, could be 'self-activated' to the Ni(0) species without the need of additional reducing agents [13,14]. Very recently, Nicasio revealed the first room-temperature nickel-catalyzed amination of (hetero)aryl chloride utilizing a preformed organonickel(II) complex, [(NHC)Ni(allyl)Cl], as easily-activated precatalyst [15].

From a synthetic point of view, room-temperature transformations represent a highly desirable process. However, room-temperature nickel-catalyzed aminations have been extremely rare, and the diverse protocols for this goal remain to urgently be needed. Based on our previous studies [13,14] and inspired by Nicasio's work [15], we were interested in exploring the possibility of room-temperature nickel-catalyzed aromatic aminations by utilizing a special class of Ni(II) complexes, *trans*-haloarylbis(triphenylphosphine)nickel(II), as

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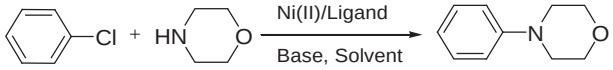
catalyst precursors, which have successfully been applied in some catalytic C–N [13,14,18] and C–C [16,17] coupling reactions. The Ni(II)–(σ-aryl) complexes are easily prepared from cheap starting materials and insensitive to air and moisture, making them highly preferred catalyst precursors [19]. Herein, we wish to disclose our preliminary findings concerning nickel-catalyzed aminations of aryl and heteroaryl halides at room temperature.

2. Results and discussion

A catalytic room-temperature amination of chlorobenzene with morpholine was performed to screen the optimal reaction conditions (Table 1). In an initial trial, we found that a combination of $Ni(PPh_3)_2$(1-naphthyl)Cl (**C-1**), IPr·HCl and NaO^{t}Bu, which was effective for the same reaction under the heating conditions [13], did not cause any conversion to occur (Table 1, entry 1), but the desired product can be obtained in almost quantitative yield if NaO^{t}Bu is replaced with KO^{t}Bu (entry 2). The reason is likely that the basicity of NaO^{t}Bu is weak so that it is unable to free an effective IPr ligand from its hydrochloric salt precursor IPr·HCl. This was further confirmed when IPr·HCl was not added to the reaction system (entry 3). The use of another Ni(II)–(σ-aryl) complex, $Ni(PPh_3)_2$(1-naphthyl)Br (**C-2**), offered an excellent outcome similar to **C-1** did (entry 4), but commonly used Ni(II) sources such as $Ni(acac)_2$ and $Ni(PPh_3)_2Cl_2$ were ineffective for this reaction (entries 5 and 6), indicating that the catalytically active Ni(0) species was not produced from these Ni(II) precursors under these mild conditions. It was found that a 1:0.5–2 molar ratio of **C-1** to IPr·HCl seemed to be a suitable range for giving excellent results (entries 2, 7 and 8 vs. entry 9). Among other ligands used, PCy_3·HBF_4 (entry 10), PPh_3 (entry 11) and 2,2′-bipyridine (entry 12)

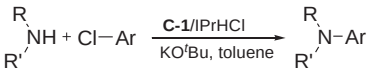
Table 1
Screening of conditions for Ni(II)-catalyzed amination of chlorobenzene. [a]

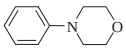
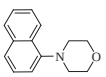
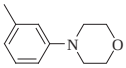
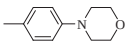
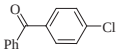
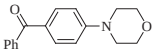
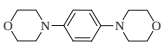
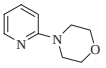
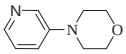
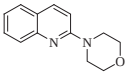
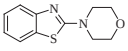
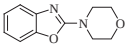
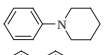


Entry	[Ni(II)] [b] (mol%)	Ligand (mol%)	Base	Solvent (5 mL)	Yield[c] (%)
1	**C-1** (5)	IPr·HCl [d] (5)	NaO^{t}Bu	toluene	0
2	**C-1** (5)	IPr·HCl (5)	KO^{t}Bu	toluene	99
3	**C-1** (5)	none	KO^{t}Bu	toluene	0
4	**C-2** (5)	IPr·HCl (5)	KO^{t}Bu	toluene	97
5	$Ni(acac)_2$ (5)	IPr·HCl (5)	KO^{t}Bu	toluene	0
6	$Ni(PPh_3)_2Cl_2$ (5)	IPr·HCl (5)	KO^{t}Bu	toluene	0
7	**C-1** (5)	IPr·HCl (10)	KO^{t}Bu	toluene	99
8	**C-1** (5)	IPr·HCl (2.5)	KO^{t}Bu	toluene	99
9	**C-1** (5)	IPr·HCl (1.25)	KO^{t}Bu	toluene	50
10	**C-1** (5)	PCy_3·HBF_4 (10)	KO^{t}Bu	toluene	0
11	**C-1** (5)	PPh_3 (10)	KO^{t}Bu	toluene	0
12	**C-1** (5)	Bipy [e] (5)	KO^{t}Bu	toluene	0
13	**C-1** (5)	DPPF [f] (5)	KO^{t}Bu	toluene	60
14	**C-1** (5)	Phena [g] (5)	KO^{t}Bu	toluene	27
15	**C-1** (5)	IPr·HCl (5)	KO^{t}Bu	dioxane	22
16	**C-1** (5)	IPr·HCl (5)	KO^{t}Bu	THF	23
17	**C-1** (3)	IPr·HCl (6)	KO^{t}Bu	toluene	95
		IPr·HCl (3)			80
		IPr·HCl (1.5)			44

[a] Reaction conditions: chlorobenzene (1.0 mmol), morpholine (3.0 mmol), base (4.0 mmol), toluene (5 mL), room temperature (ca. 23 °C), 24 h.
[b] **C-1**: $Ni(PPh_3)_2$(1-naphthyl)Cl; **C-2**: $Ni(PPh_3)_2$(1-naphthyl)Br.
[c] Isolated yield.
[d] IPr·HCl: 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride.
[e] Bipy: 2,2′-bipyridine.
[f] DPPF: 1,1′-bis(diphenylphosphino)ferrocene.
[g] Phena: 1,10-phenanthroline.

Table 2
Room-Temperature Ni(II)-Catalyzed Amination of Aryl/Heteroaryl chloride. [a]



Entry	Amine	Cl–Ar	Product	Yield[b](%)
1				99
2				92
3				98
4				90
5				70[c]
6				82[d]
7				88
8				98
9				80
10				99
11				90
12				50
13				69
14				63
15				72
16				80
17				70
18				79
19				52[e]
20				trace
21				trace
22	n-$C_{12}H_{25}NH_2$			23 11

[a] Reaction conditions: the chloride (1 mmol), amine (3 mmol), **C-1**(0.05 mmol), IPr·HCl (0.05 mmol), KO^{t}Bu (4 mmol), toluene (5 mL), room temperature (ca. 23 °C), 24 h.
[b] Isolated yield.
[c] **C-1** (0.15 mmol), IPr·HCl (0.15 mmol).
[d] Morpholine (6 mmol), **C-1** (0.10 mmol), IPr·HCl (0.10 mmol), KO^{t}Bu (8 mmol), toluene (10 mL).
[e] Chlorobenzene (3 mmol), piperazine (1 mmol), **C-1**(0.10 mmol), IPr·HCl (0.10 mmol).

did not promote the reaction at all, and DPPF (entry 13) and 1,10-phenanthroline (entry 14) worked poorly. Apparently, toluene was the solvent of choice and far superior to ethereal solvents like dioxane (entry15) and THF (entry 16). In attempts to reduce the catalyst loadings, we found that although it was feasible for the reaction to use only 3 mmol% the Ni(II) complex associated with 2 equiv IPr·HCl, a reduced ratio of ligands would substantially affect the yields (entry 17). Thus, our standard reaction conditions were finally selected according to entry 2 of Table 1.

Next, a wide range of (hetero)aryl chlorides and some cyclic secondary amines were examined under the optimized reaction conditions. As shown in Table 2, morpholine were *N*-arylated with both electron-neutral (entries 1 and 2) and -rich (entries 3 and 4) chloroarenes in excellent yields; in the case of the substrate bearing ketone group (entry 5), good yield was achieved when the catalyst loadings were increased; and *p*-dichlorobenzene can be doubly aminated in a higher yield (entry 6). Particularly, heteroaryl chlorides seem to be a class of eletrophilic substrates very suitable for the coupling reaction. 2-Chloropyridine (entry 7), 3-chloropyridine (entry 8), 2-chloroquinoline (entry 9), 2-chlorobenzothiazole (entry 10) and 2-chlorobenzoxazole (entry 11) were well coupled with morpholine, giving high yields of 80–99%. For two other amines piperidine and pyrrolidine, they did not react very well with aryl chlorides. For example, the reaction of piperidine and chlorobenzene afforded only a medium yield of 50% (entry 12), and that of pyrrolidine almost gave no product (trace amounts of the desired product, unlisted in Table 2). Generally, heteroaryl chlorides could react with piperidine (entries 13 and 14) or pyrrolidine (entries 15–18) with good yields. Double arylation of piperazine could proceed with an acceptable yield of 52% (entry 19). In addition, some other kinds of amines were also tested in this study. Acyclic secondary amine gave only a trace amount of the product (entry 20); almost no reaction took place for aniline as well (entry 21). Interestingly, for primary amine (e.g., 1-dodecanamine), both mono- and di-coupled products were produced with lower yields (entry 22), and upon increasing the molar amount of 2-chloroquinoline to 3-fold that of the amine, 45% yield of the di-coupled product could be achieved, with the mono-coupled product being a yield of only 7%.

As shown in Fig. 1, the catalytically active species might be the Ni(0) species that could be formed in-situ from the reaction of Ni(II)–(σ-aryl) complex with the amine (i.e., by transmetalation of the nucleophilic reactant and subsequent reductive elimination prior to the normal reaction). We presumed that the mechanism might follow a catalytic cycle of the Ni(0)–Ni(II) shuttle involving sequential oxidative addition, transmetalation, and reductive elimination. The rate-determining step of the amination reaction is unclear at present. With the help of base, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride frees HCl and offers 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, a strongly σ-donating *N*-heterocyclic carbene, as ligand which can effectively stabilize the Ni(0) species. Interestingly, morpholine displayed the best reactivity among all the secondary amines used, but the reason cannot be explained clearly at present and further work will be needed.

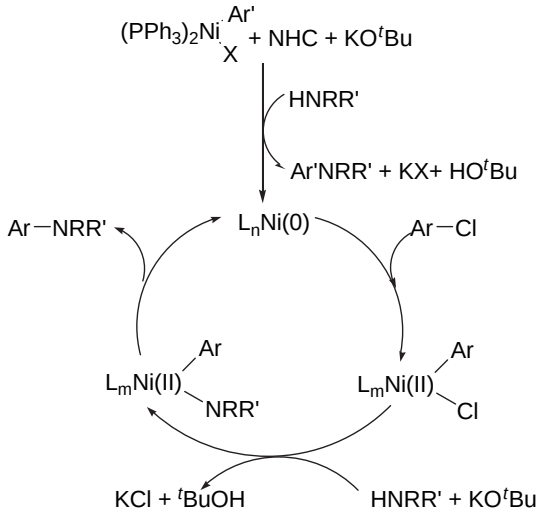


Fig. 1. A possible mechanistic pathway for the amination reaction.

3. Conclusions

In summary, we have disclosed a simple, efficient protocol for the room-temperature aromatic C–N cross-coupling reaction utilizing the Ni(II)–(σ-aryl) complex/NHC/KO^{t}Bu system, and some arylamine and particularly heteroaryl amine derivatives can be readily synthesized under very mild conditions. Further study to expand the scope of both substrates is ongoing in our laboratory.

4. Experimental section

General procedure for the room-temperature amination of (hetero) aryl halides catalyzed by the Ni(II)–(σ-aryl) complex/NHC/KO^{t}Bu. An oven-dried 25-mL three-necked flask was charged with KO^{t}Bu (4 mmol), Ni(PPh$_3$)$_2$(1-naphthyl)Cl (**C-1**) (0.05 mmol) and IPr·HCl (0.05 mmol). Then the aryl or heteroaryl halide (1 mmol) if solid and amine if solid (3 mmol) were added. The flask was evacuated and backfilled with nitrogen, with the operation being repeated twice. The halide and amine if liquid, dried toluene (5 ml) were added via syringe at this time. The reaction mixture was stirred at room temperature for 24 h, and filtered through a silica-gel pad that was washed with ethyl acetate. The combined organic phases were evaporated under reduced pressure and the residue purified by silica-gel column chromatography to give the desired product.

Acknowledgments

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