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Nickel-Catalyzed Amination of Aryl Phosphates through Cleaving Aryl C–O Bonds

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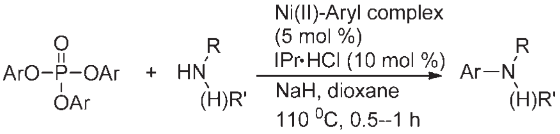
ABSTRACT



The amination of triaryl phosphates was achieved using a Ni(II)–(σ-Aryl) complex/NHC catalyst system in dioxane at 110 °C in the presence of NaH as base. Electron-neutral, -rich, and -deficient triaryl phosphates were coupled with a wider range of amine partners including cyclic and acyclic secondary amines, aliphatic primary amines, and anilines in good to excellent yields.

Transition-metal-catalyzed amination reactions have become a powerful tool for the formation of aromatic C–N bonds which are ubiquitous in pharmaceuticals, agrochemicals, and materials.[1] In these transformations, aryl halides represent the most widely employed type of electrophilic substrates. On the other hand, phenolic derivatives as potential electrophiles have been receiving considerable attention due to their ease of preparation and handling, pronounced stability, low toxicity, and low cost.[2] Although this is a challenging task because phenol-derived compounds are traditionally regarded as "inert" substrates, several successful examples have been achieved in palladium-catalyzed aminations of aryl triflates[3] and sulfonates.[4,5] In recent years, efforts to explore catalytic cross-coupling reactions of these "unusual" electrophiles have focused on nickel-based catalysts[6] because nickel systems possess the advantages of cheapness and high reactivity toward relatively inert electrophiles without the use of specially tailored ligands. In 2000, Bolm reported the first example of Ni(0)-catalyzed amination of tosylates with sulfoximines.[7] Subsequently, our group found that aryl tosylates were aminated effectively with amines/anilines using a Ni(II) complex as a precatalyst.[8] Tobisu and Chatani established anisoles and aryl carboxylates as effective electrophiles in the nickel(0)-catalyzed amination.[9]

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(2) For a leading reference, see: *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1997.

(3) Pd-catalzed aminations of aryl triflates: (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1264. (b) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268.

(4) Pd-catalyzed aminations of aryl tosylates and benzenesulfonates: (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (b) Huang, X.-H.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (c) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704. (d) Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 13848.

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(6) For a recent review on Ni-catalyzed cross-couplings involving C–O bonds, see: Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346.

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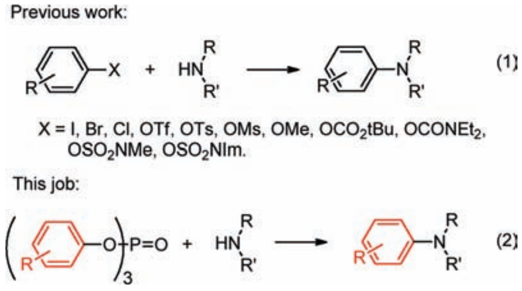
Most recently, Garg[10] and Ackermann[11] independently performed the amination of aryl sulfamates based on the nickel(0) catalyst.

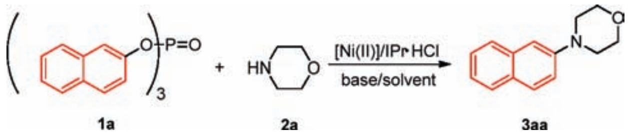
As ongoing work along this line, we desired to explore the possibility of utilizing other types of electrophiles in catalytic C–N couplings. Aryl phosphates, also derived from phenols, have advantages similar to those of other classes of phenolic derivatives and, moreover, are more benign. Aryl phosphates have been employed as an electrophile in the nickel-catalyzed Suzuki–Miyaura reaction.[12] However, they have not yet been established as effective substrates for the catalytic aminations. Herein, we wish to report our findings about nickel-catalyzed amination of triaryl phosphates as electrophilic partners through the cleavage of aromatic carbon–oxygen bonds (Scheme 1, eq 2).

Scheme 1



The coupling of tri(2-naphthyl) phosphate (**1a**) with morpholine (**2a**) was performed as a model reaction. Ni(II) sources were preferentially selected as catalyst precursors because they are readily available, cheap, and conveniently treated due to their air and moisture stability. Since *N*-heterocyclic carbenes (NHCs) have proven to be favorable ligands for the nickel-catalyzed amination of phenol-derived electrophilic substrates,[8–11] we chose easily available 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) as the ligand precursor which may free an NHC ligand under basic conditions. Some experimentation (mainly involving bases, solvents, and temperatures) was conducted for the optimal conditions (Table 1). Common nickel(II) sources, such as $NiCl_2\cdot 6H_2O$, Ni(acac)$_2$, and $NiCl_2(PPh_3)_2$, were found to be ineffective for the desired C–N coupling (Table 1, entries 1–3), where only small amounts of 2-naphthol were detected, which resulted from the decomposition of the phosphate **1a** through the base-promoted O–P bond cleavage. The reason why the common Ni(II) precatalysts are ineffective was presumably that those Ni(II) species are difficult to convert into the catalytically active Ni(0) in the reaction system without the aid of additional reductants. Then, we began to examine another nickel(II) source, *trans*-NiCl(1-naphthyl)$(PPh_3)_2$ (**C-1**),[13] which has successfully been utilized in the catalytic amination of aryl chlorides[14] or tosylates[8] and was believed to be capable of generating the Ni(0) species in the reactions without the need for additional reductants. To our pleasure, the **C-1**/IPr·HCl system was able to catalyze the amination reaction in toluene at 110 °C in the presence of NaO^tBu with a high yield of 82% (entry 4). The reaction proceeded quickly (completed within 30 min), but a small amount of 2-naphthol byproduct remained observed. An attempt to reduce reaction temperatures failed (entry 5). The choice of bases seemed to be crucial. For example, weaker K_2CO_3 (entry 6) did not work and stronger KO^tBu (entry 7) led to a complete decomposition of **1a** into 2-naphthol. Ethereal solvents seemed better than toluene for this reaction (entry 8 vs 4; entry 9 vs 5). In view of the fact that the reaction needs deprotonating agents but is sensitive to a strongly basic environment, NaH was used in place of NaO^tBu to perform this reaction, where an almost quantitative yield of the aminated product was afforded (entry 10). Finally, our standard conditions were set up as entry 10 in Table 1.

Table 1. Screening of Conditions[a]



entry	[Ni(II)]	base	solvent	temp [°C]	yield [%][b]
1	$NiCl_2\cdot 6H_2O$	NaO^tBu	toluene	110	0
2	Ni(acac)$_2$	NaO^tBu	toluene	110	0
3	$NiCl_2(PPh_3)_2$	NaO^tBu	toluene	110	0
4	**C-1**[c]	NaO^tBu	toluene	110	82
5	**C-1**	NaO^tBu	toluene	80	0
6	**C-1**	K_2CO_3	toluene	110	0
7	**C-1**	KO^tBu	dioxane	110	0[d]
8	**C-1**	NaO^tBu	dioxane	110	87
9	**C-1**	NaO^tBu	THF	70	61
10	**C-1**	NaH	dioxane	110	95(0[e])

[a] Conditions: tri(2-naphthyl) phosphate (1 mmol), morpholine (1 mmol), [Ni(II)] (0.05 mmol), IPr·HCl (0.1 mmol), base (2 mmol), solvent (10 mL), 0.5 h. [b] Isolated yield. [c] **C-1**: NiCl(1-naphthyl)$(PPh_3)_2$. [d] The phosphate **1a** was completely decomposed. [e] In the absence of IPr·HCl as ligand.

With the optimal conditions in hand, we examined the scope of triaryl phosphates in this reaction (Table 2). Generally, electron-neutral (**3aa**, **3ba**, and **3ca**), -rich (**3da**, **3ea**, **3ha**, and **3ia**), and -deficient (**3ja**, **3ka**, **3la**, and **3ma**) aryl phosphates were all suitable electrophilic substrates,

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(13) *trans*-NiCl(1-naphthyl)$(PPh_3)_2$ (**C-1**) belongs to Ni(II)-(σ-aryl) complexes and is easily prepared from $NiCl_2\cdot 6H_2O$, 1-chloronaphthene, PPh_3, and zinc dust in ethanol according to the literature procedure. See: Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer: New York, 1998; p 3.

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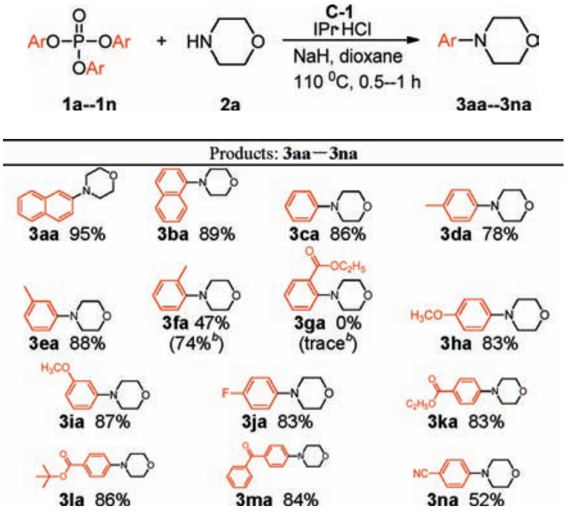
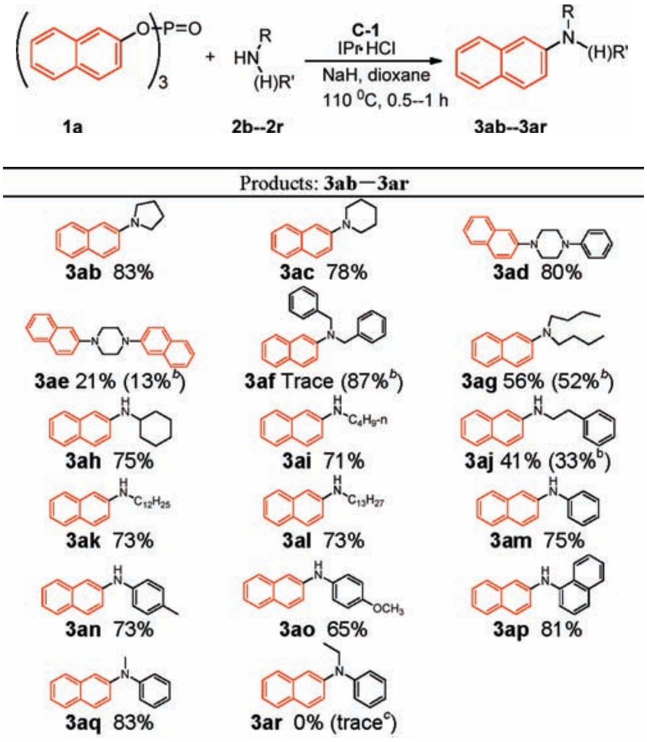
Table 2. Nickel-Catalyzed C−N Couplings of Triaryl Phosphates with Morpholine[a]



[a] Reaction conditions: triaryl phosphate (1 mmol), morpholine (1 mmol), **C-1** (5 mol %), IPr·HCl (10 mol %), NaH (2 mmol), dioxane (10 mL), 110 °C, 0.5−1 h; isolated yield. [b] IPr·HCl was replaced with SIPr·HCl.

giving the desired products in good to excellent yields; fluoride, ester, carbonyl, and cyano functionalities were tolerated under the reaction conditions. The phosphates with electron-withdrawing groups (**3ia**, **3ja**, **3ka**, **3la**, and **3ma**) were slightly more reactive than those with electron-donating groups (**3da** and **3ha**). An exception is that, in the case of tri(*p*-cyanophenyl) phosphate (**3na**), a lower yield of the coupled product was obtained likely because the overstrongly electron-withdrawing effects of the cyano group led to a more facile side reaction of the O−P cleavage. On the other hand, the steric factors of the phosphate substrates would be unfavorable for this reaction: the ortho-substituted aryl phosphates led to a significantly reduced yield (**3fa**) or even no product (**3ga**). When the ligand IPr·HCl was replaced by its saturated counterpart 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (SIPr·HCl), the amination of the *o*-methyl substituted substrate (**3fa**) proceeded with 74% yield, but the sterically overhindered *o*-ethoxycarbonyl substrate was intact (**3ga**).[15]

Table 3. Nickel-Catalyzed C−N Couplings of Amines with Tri(2-naphthyl) Phosphate[a]



[a] Conditions: tri(2-naphthyl) phosphate (1 mmol), amine (1 mmol), **C-1** (5 mol %), IPr·HCl (10 mol %), NaH (2 mmol), dioxane (10 mL), 110 °C, 0.5−1 h; isolated yield. [b] NaH was replaced by NaO^{t}Bu. [c] IPr·HCl was replaced by SIPr·HCl.

Further, the scope of amines was surveyed in this reaction (Table 3). Cyclic secondary amines (**3ab**, **3ac**, and **3ad**) were coupled smoothly with the phosphate (**1a**) in good yields. But the double coupling of piperazine gave only poor results (**3ae**). Acyclic secondary amines seemed to be complicated. Dibenzylamine gave only a trace of the product under the standard conditions, but interestingly the yield increased significantly upon the replacement of NaH with NaO^{t}Bu (**3af**); however, di(*n*-butyl)amine always gave modest yields whether or not the base was changed (**3ag**). To our surprise, aliphatic primary amines, a difficult class of nucleophilic substrates in usual catalytic aminations, worked well in this reaction (**3ah**, **3ai**, **3ak**, and **3al**). In other words, a β-hydrogen elimination side reaction of aliphatic amines could be suppressed significantly under our reaction conditions. In the case of phenylethylamine, good yields were not provided (**3aj**), for which we cannot make a clear explanation at present. Aromatic amines are also efficient nucleophiles in the reaction. Anilines (primary aromatic amines) were coupled in good yields (**3am**, **3an**, **3ao**, and **3ap**), where the electron-donating groups produced a slightly adverse influence (comparing **3am** and **3ap** to **3an** and **3ao**). In addition, the performance of *N*-alkylanilines (secondary aromatic amines) might depend mainly on the steric factors: relatively less hindered *N*-methylaniline (**3aq**) reacted very well, but more bulky *N*-ethylaniline (**3ar**) did not undergo the reaction. The phenomenon may, to some degree, explain the reason why monoarylation of primary amines (**3ah**, **3ai**, **3ak**, **3al**, **3am**, **3an**, **3ao**, and **3ap**) proceeds

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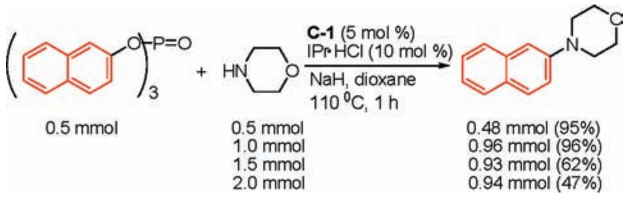
[15] Note: In all experiments there always exists a small amount of the *N*-(1-naphthyl)morpholine byproduct generated from the precatalyst Ni(II)−(1-naphthyl) complex. In most cases, the byproduct does not cause difficulty in the separation of the desired products due to a pronounced difference in their R_f values in chromatography. In a few cases, the byproduct may be removed easily by recrystallization because of its low content. In the case of the 1-naphthyl substrate, the yield reported was determined after subtracting the contribution from the Ni(II)−(1-naphthyl) complex used, based on an estimate that [(1-naphthyl)Ni(PPh$_3$)$_2$Cl] would be completely converted.

selectively without the formation of the corresponding diarylated products.

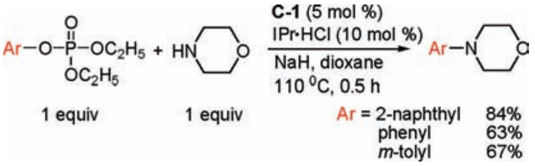
Scheme 2. An Investigation into the Aryl-Transfering Capability of Triaryl Phosphates (Yields Based on Morpholine)



Since the substrate triaryl phosphate contains three aryl groups, we were interested in knowing how many of these aryls are able to be transferred onto the nitrogen atom of the amine in the cross-coupling reaction. As shown in Scheme 2, a set of experiments was carried out under our standard conditions, and the results suggested that at least two of three aryl groups in the triaryl phosphate may be employed effectively. Whether or under which conditions all three aryls in the phosphate can be utilized should be an interesting subject, and further study is needed.

As shown in Scheme 3, diethyl aryl phosphates, another class of phosphate electrophiles which have been used in the Suzuki–Miyaura coupling reaction,[12] also seemed to be the substrates applicable in this amination reaction. Several cases preliminarily demonstrated that the corresponding coupling reaction occurred with reasonable yields.

Scheme 3. Amination of Diethyl Aryl Phosphates with Morpholine



In conclusion, we have first demonstrated that aryl phosphates can be utilized as electrophiles in nickel-catalyzed amination reactions. This reaction has a wider scope of substrates with respect to both the phosphate and amine coupling partners. The use of the phosphate, the Ni(II), rather than the Ni(0), as a catalyst precursor and a faster reaction process make this protocol convenient, cheap, and efficient. Further work is underway in our laboratory to improve reaction conditions, expand the scope of substrate types, and clarify the detailed reaction mechanism.

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Supporting Information Available. Experimental procedures and characterization data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.