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Nickel-Catalyzed Amination of Aryl 2-Pyridyl Ethers via Cleavage of the Carbon−Oxygen Bond

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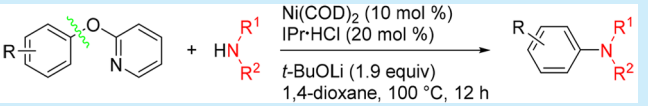
Supporting Information

ABSTRACT: Reaction of aryl 2-pyridyl ethers with amines was carried out via Ni-catalyzed C−O_{Py} bond cleavage, giving aniline derivatives in reasonable to excellent yields. Both electron-rich and electron-poor aryl 2-pyridyl ethers and a wide range of amines can be used in the transformation. The method provides a conversion way for the 2-pyridyloxy directing group in the C−H bond functionalization reactions.



2-Pyridyloxy (OPy) group is an excellent *ortho* directing group in transition-metal-catalyzed C−H bond functionalization reactions because of the strong coordination ability of its sp^2 nitrogen atom and its stability under various synthetic conditions.[1,2] On the other hand, developing methodology to remove or convert the OPy group after directing C−H functionalization is also an important topic. In an earlier publication Wu et al. reported a method to convert the directing group via a successive two-step reaction. Thus, aryl 2-pyridyl ether was treated with MeOTf and subsequently sodium methoxide to give corresponding phenol via cleavage of the C_{Py}−O bond.[2] More recently Chatani et al. reported catalytic protocols of directly converting an OPy group into boryl group with rhodium[3] or nickel[4] as the catalyst, which expanded the synthetic utility of the OPy directing group. Methods to convert the C−O_{Py} bond of the aryl 2-pyridyl ethers to a C−C bond or other C−heteroatom bonds except the C−B bond mentioned above are unavailable.

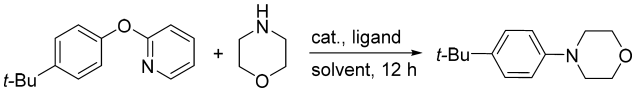
Aniline derivatives are ubiquitous in drug molecules and natural products.[5] Transition-metal-catalyzed amination reactions were considered one of the most powerful approaches to achieve these compounds.[5,6] Although aminations of aryl halides and reactive phenolic derivatives, such as aryl triflates, tosylates, and carboxylates, are well-established,[6−8] converting phenolic derivatives with unactivated C−O bonds into aniline derivatives are still challenging. Chatani et al. carried out Ni-catalyzed amination of (hetero)aryl methyl ethers via C_{sp2}−OMe bond cleavage. However, the substrate scope was mainly limited to π-extended aromatic systems, such as 2-naphthyl methyl ethers and electron-deficient heteroaryl methyl ethers.[9]

With all the considerations above, we initiated a study on transition-metal-catalyzed amination of aryl 2-pyridyl ethers via C−O_{Py} bond cleavage.

We screened reaction conditions by choosing 2-(4-*tert*-butylphenoxy)pyridine and morpholine as the model substrates and nickel as the catalyst because nickel was reported to be the most effective catalysts for the inactive C−O bond cleavage.[7−9]

A combination of $Ni(COD)_2$ and PCy_3 was first examined.[7] However, no cross-coupling product was detected (Table 1, entry 1). We thought that perhaps K_3PO_4 was a too weak base

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

entry	[Ni] (mol %)	ligand (mol%)	solvent	yield (%)[b]
1[c]	$Ni(COD)_2$ (5)	PCy_3 (10)	1,4-dioxane	none
2	$Ni(COD)_2$ (5)	PCy_3 (10)	1,4-dioxane	trace
3	$Ni(COD)_2$ (5)	BINAP (5)	1,4-dioxane	trace
4	$Ni(COD)_2$ (5)	Dcype (5)	1,4-dioxane	trace
5	$Ni(COD)_2$ (5)	SIPr·HCl (10)	1,4-dioxane	14
6	$Ni(COD)_2$ (5)	IMes·HCl (10)	1,4-dioxane	55
7	$Ni(COD)_2$ (5)	IPr·HCl (10)	1,4-dioxane	87
8	$Ni(COD)_2$ (5)	ICy·HCl (10)	1,4-dioxane	trace
9	$Ni(COD)_2$ (5)	IPr·HCl (5)	1,4-dioxane	73
10	$Ni(COD)_2$ (5)	IPr·HCl (10)	toluene	55
11	$Ni(COD)_2$ (5)	IPr·HCl (10)	THF	trace
12	$Ni(COD)_2$ (5)	IPr·HCl (10)	DMF	57
13[d]	$Ni(COD)_2$ (5)	IPr·HCl (10)	1,4-dioxane	85
14[e]	$Ni(COD)_2$ (5)	IPr·HCl (10)	1,4-dioxane	35
15	$NiCl_2$(dme) (5)	IPr·HCl (10)	1,4-dioxane	trace
16	$Ni(acac)_2$ (5)	IPr·HCl (10)	1,4-dioxane	29
17	$Ni(COD)_2$ (10)	IPr·HCl (20)	1,4-dioxane	99(90[f])
18[g]	$Ni(COD)_2$ (10)	IPr·HCl (20)	1,4-dioxane	90

[a]Unless otherwise stated, the reactions were run at 100 °C for 12 h; 0.2 mmol of 2-(4-(*tert*-butyl)phenoxy)pyridine, 1.5 equiv of morpholine, and 1.8 equiv of *t*-BuOLi were employed. [b]NMR yield. [c]K_3PO_4 as base. [d]*t*-BuONa as base. [e]*t*-BuOK as base. [f]Isolated yield. [g]Reaction was run at 80 °C.

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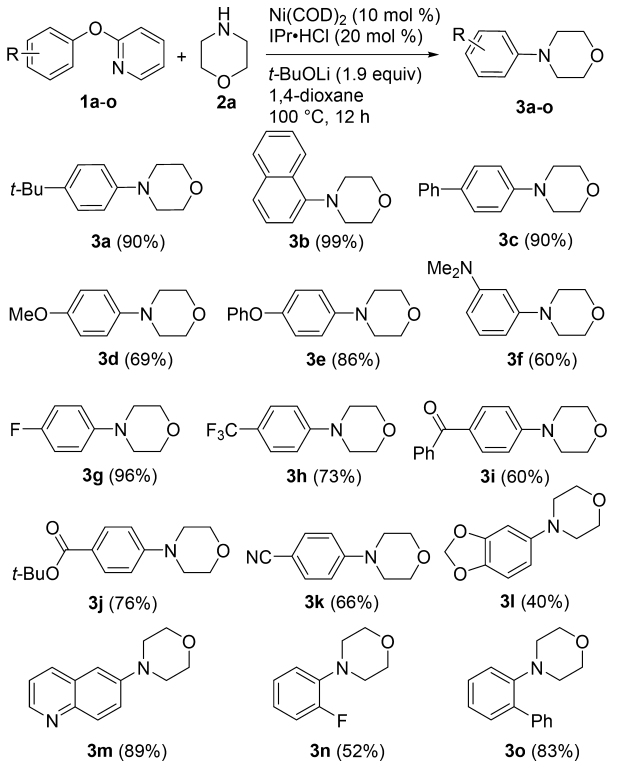
to complete the reaction. Then a stronger base, *t*-BuOLi, was used to replace K_3PO_4. A trace amount of product can be observed (Table 1, entry 2). These enlightened us that *t*-BuOLi might be suitable, while PCy_3 might not. So we kept *t*-BuOLi as the base and screened a series of ligands which were commonly used in transition-metal-catalyzed C−O bond cleavage (Table 1, entries 3−8), including *rac*-BINAP (2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl), dcype (1,2-bis(dicyclohexylphosphino)ethane), SIPr·HCl (1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolinium chloride), IMes·HCl (1,3-bis(2,4,6-trimethylphenyl)-1*H*-imidazolium chloride), IPr·HCl (1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazolium chloride), and ICy·HCl (1,3-bis(cyclohexyl)imidazolium chloride). The results showed that ligands exerted a tremendous influence on the reaction, only N-heterocyclic carbene ligands gave practical yields and IPr·HCl performed best. The use of 5 mol% of IPr·HCl led to a slight decrease of the yield (Table 1, entry 9), implying that the reactivity is not a result of a monoligated carbene-nickel complex. Next we examined the effect of solvents and bases. Toluene, THF, and DMF were respectively tested and the results showed that each of them was less effective than 1,4-dioxane. Both toluene and DMF gave moderate performance and THF led to only a trace amount of product (Table 1, entries 10−12). Two alternative bases, *t*-BuONa and *t*-BuOK, were tested. *t*-BuONa performed almost the same well as *t*-BuOLi (Table 1, entry 13). However, *t*-BuOK performed far worse than *t*-BuOLi (Table 1, entry 14). Two air-stable nickel sources, $NiCl_2$(dme) and $Ni(acac)_2$, were used to replace $Ni(COD)_2$ (Table 1, entries 15 and 16). However, the Ni(II) species exhibited much lower catalytic activity than the Ni(0) probably due to lacking effective reducing agents. We also found that in the reaction with the currently optimized conditions there still existed a little starting material and some phenol as side product. So we increased the catalyst loading to 10 mol% and found that all the ether were consumed and gave an excellent result (Table 1, entry 17). Expanding reaction scale 10 times to 2 mmol gave similar isolated yield (85%). Finally, attempts to lower the reaction temperature to 80 °C (Table 1, entry 18) or reduce the amount of amine to 1.2 equiv led to inferior results.

With the optimized conditions in hand, we first examined the scope of aryl 2-pyridyl ethers. Substrates **1b**−**1o** were found to be suitable reaction partners with morpholine to provide corresponding anilines as shown in Scheme 1. The extended π-conjugated aromatic substrates 2-(naphthalen-1-yloxy)pyridine (**1b**) and 2-(biphenyl-4-yloxy)pyridine (**1c**), were successfully coupled with morpholine to afford products **3b** and **3c**, respectively, in excellent yields. Electron-rich aryl 2-pyridyl ethers (**1d**-**1f**) presented slightly lower reactivity and gave good to excellent yields (60−90%). Activated substrate 2-(4-fluorophenoxy)pyridine resulted in an excellent yield leaving fluoro substituent intact (**3g**).[10] Meanwhile, a series of the functional groups on the aromatic rings, such as F, CF_3, COPh, COO*t*-Bu, and CN (**3g**−**3k**), as well as other alkoxy groups, such as OMe and OPh, were well tolerated. Furthermore, acetal also remained intact with moderate yield probably due to strong deactivated effect (**3l**). Heteroaromatic substrate like 6-(pyridin-2-yloxy)quinoline performed smoothly with an excellent result (**3m**). Importantly, *ortho*-substituents were acceptable, allowing for further amination to occur after directed C−H functionalization (**3n**, **3o**).[2]

Next we examined the scope of amines using 2-(biphenyl-4-yloxy)pyridine (Scheme 2). Reactions with 4-methylpiperidine

Scheme 1. Scope of Aryl 2-Pyridyl Ethers[a,b]



[a]Unless otherwise stated, the reactions were performed with 0.2 mmol of aryl 2-pyridyl ethers and 0.3 mmol of morpholine in 1,4-dioxane (2 mL) according to the conditions indicated by the above equation. [b]Isolated yield.

and decahydroisoquinoline afforded the cross-coupling products in excellent yields (**3p**, **3r**). 2-Methylpiperidine gave a lower yield (**3q**) probably due to steric hindrance in 2-methylpiperidine. Pyrrolidine with low boiling point performed excellently demanding an extra equivalent (**3s**). Reaction with acyclic amines performed almost as well as cyclic amines (**3t**). Even primary aliphatic amines went smoothly (**3u**). Furthermore, primary anilines performed even better than aliphatic amines. Substituents with various electron delivery property and steric hindrance all gave excellent results (**3v**−**3y**). Even less reactive substrate containing methoxy group at *ortho* position, 2-(2-methoxyphenoxy)pyridine, also gave excellent yield of cross-coupling product (**3z**).

To further demonstrate the utility of this method for organic synthesis, the sequential OPy-directed *ortho* C−H functionalization and amination of the directing group were carried out (Scheme 3). It is known that a pyridine-based directing group is stable under oxidative conditions, which allows it to function smoothly in various kinds of oxidative *ortho* C−H transformations. For example, it was reported that 2-phenoxypyridine underwent palladium-catalyzed oxidative *ortho* fluorination to form **1n**,[2] which can subsequently be converted to the aniline product **3n** through the removal of the OPy group under our conditions. The OPy directing group can also promote *ortho* arylation of 2-phenoxypyridine to form **1o**,[2] then led to the aminated product **3o** eventually.

To gain preliminary mechanistic information about this transformation, several control experiments were carried out under the standard conditions. We observed that *in situ* formed IPr_2Ni can catalyze cross-coupling of 2-(biphenyl-4-yloxy)

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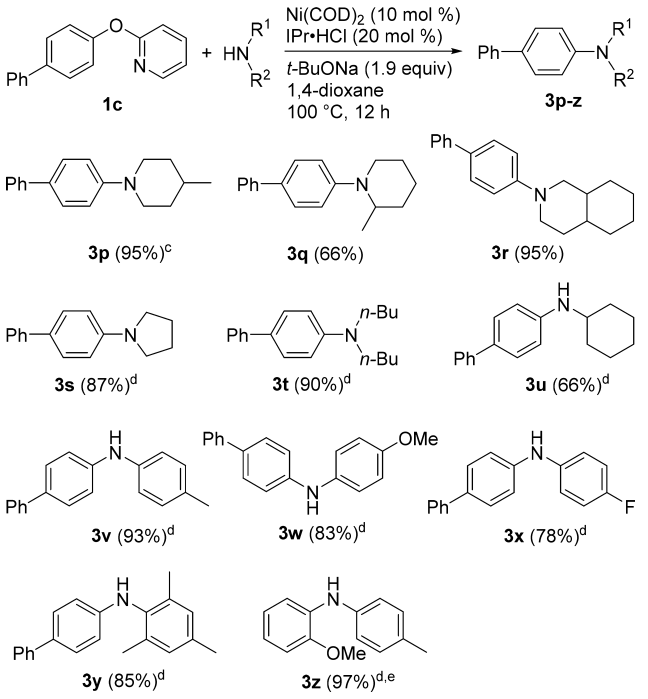
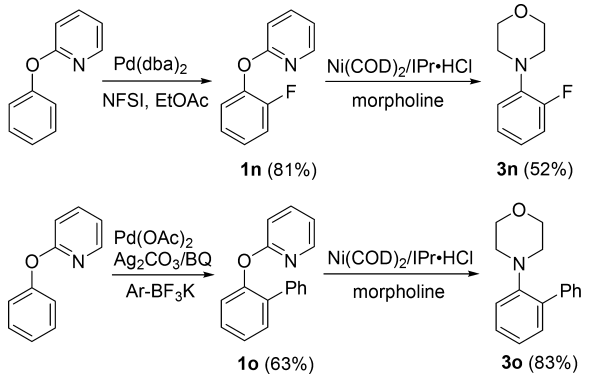
Scheme 2. Scope of Amines[a,b,c,d,e]



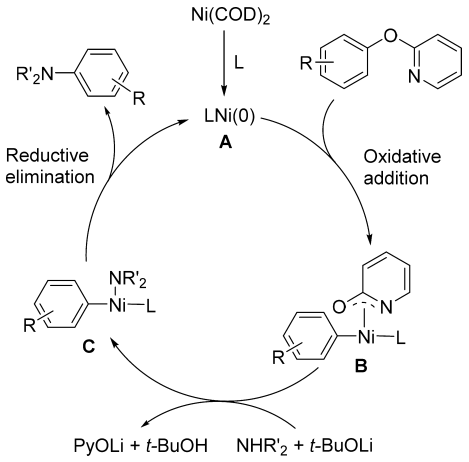
[a]Unless otherwise stated, the reactions were performed with 0.2 mmol of 2-(biphenyl-4-yloxy)pyridine and 0.3 mmol of amines in 1,4-dioxane (2 mL) according to the conditions indicated by the above equation. [b]Isolated yield. [c]*t*-BuOLi as base. [d]Two equiv of amines and 2.4 equiv of bases were employed. [e]2-(2-Methoxyphenoxy)pyridine was employed to replace 2-(biphenyl-4-yloxy)pyridine.

Scheme 3. Sequential Reaction



pyridine (**1c**) with morpholine in the presence of *t*-BuOLi (82%). And the *in situ* reaction products of 2-(biphenyl-4-yloxy)pyridine (0.1 mmol), $Ni(COD)_2$ (0.1 mmol), IPr·HCl (0.2 mmol) and *t*-BuOLi (0.2 mmol) can couple with morpholine (0.15 mmol) in the presence of *t*-BuOLi (0.15 mmol) to afford aminated product in 73% yield. It seems apparent that an aryl nickel species was formed in this step and then transformed into an arylamido nickel intermediate. The arylamido nickel species underwent reductive elimination to form arylamine and regenerate active Ni(0) catalyst. This process is consistent with that of Ni(0)/SIPr complex-catalyzed coupling of aryl chlorides with amines reported by Fort et al.[11] As for the mechanism about the cleavage of the $Ar-O_{Py}$ bond, Chatani et al. have proposed two possible pathway.[3] One is that $C_{aryl}-O$ bond activation is initiated by the Lewis acid/base interaction between the boryl ligand and the 2-pyridyl moiety via a six membered cyclic transition state, which can be ruled out in our reaction. The other is direct oxidative addition pathway, which may be facilitated by the coordination of the pyridine ring to the metal center. Based on the above-mentioned experimental facts and literature information, a possible mechanism is outlined in Scheme 4.

Scheme 4. Proposed Catalytic Cycle



In conclusion, we have performed nickel-catalyzed amination of aryl 2-pyridyl ethers through cleavage of the $C-O_{Py}$ bond. The method displays a broad scope of substrates, including electron-rich and electron-poor aryl 2-pyridyl ethers and various amines. The reaction gives reasonable to excellent yields and exhibits good compatibility of functional groups. We believe that the methodology is a valuable complement to Buchwald–Hartwig reaction involving phenol derivatives and provides a subsequent conversion way for the 2-pyridyloxy directing group in the C–H functionalization reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01549.

Experimental details of the coupling reaction, characterization data, and the copies of NMR spectra of the cross-coupling products (PDF)

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Notes

The authors declare no competing financial interest.

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