

Ni⁰-catalyzed Direct Amination of Anisoles Involving the Cleavage of Carbon–Oxygen Bonds

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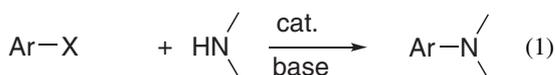
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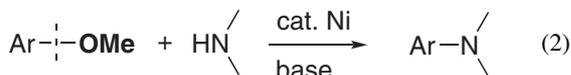
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Ni⁰-catalyzed cross-coupling of aryl methyl ethers with amines is described. The use of an *N*-heterocyclic carbene as a ligand and NaOt-Bu as a base promotes the amination of anisole derivatives via the cleavage of normally unreactive aryl carbon–oxygen bonds.

In 1983, Kosugi and Migita reported on the palladium-catalyzed cross-coupling of tin amides with aryl halides to form anilines.¹ Stimulated by this report, Buchwald and Hartwig independently reported more practical protocols for the cross-coupling of amines with aryl halides in the presence of a base (eq 1).² These palladium-catalyzed methods have rapidly become important tools in organic synthesis, pharmaceuticals, and materials science. Although this reaction has seen significant advancement over the last decade, the electrophilic coupling partner for use remains limited to organic halides and sulfonates. We report herein a nickel-catalyzed cross-coupling of amines with anisole derivatives, wherein a carbon–oxygen bond is cleaved (eq 2).³

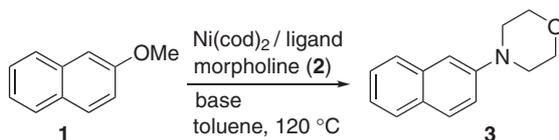


X = I, Br, Cl, OTf, OTs, etc



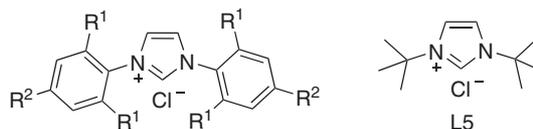
Based on our studies on the nickel-catalyzed cross-coupling of aryl methyl ethers with aryl boronic esters,^{4,5} we initially examined the reaction of 2-methoxynaphthalene (**1**) with morpholine (**2**) in the presence of a catalytic amount of Ni(cod)₂ and PCy₃ (Table 1). Similar to the catalytic amination of halides,⁶ the choice of base proved to exert a critical impact on the reaction. While the use of BuLi or KOt-Bu as a base failed to promote the desired amination reaction (Entries 1 and 2), the expected product **3** was formed in promising yield by employing NaOt-Bu (Entries 3 and 4). With NaOt-Bu as a base, we next investigated the effect of ligands. A significant decrease in yield was observed with other phosphine ligands, such as P(*t*-Bu)₃, P(*i*-Pr)₃, (biphenyl-2-yl)dicyclohexylphosphine, and dppf, as we have encountered a similar trend in the cross-coupling with boronic esters.⁴ On the other hand, it was found that the addition of some *N*-heterocyclic carbene ligands also furnished the amination product **3** (Entries 5–9). Yields were improved by increasing a steric demand of the ligand (L1 < L2 < L3), whereas the catalytic amination did not proceed when a highly bulky ligand L4 was used. With L3 as an optimal ligand, the yield of **3** was

Table 1. Optimization studies^a



Entry	Ligand	Base	Time/h	Yield/% ^b
1	PCy ₃	BuLi	12	complex
2	PCy ₃	KOt-Bu	12	0
3	PCy ₃	NaOt-Bu	12	24
4	PCy ₃	NaOt-Bu	48	31
5	L1	NaOt-Bu	48	13
6	L2	NaOt-Bu	48	37
7	L3	NaOt-Bu	48	56
8	L4	NaOt-Bu	48	0
9	L5	NaOt-Bu	48	22
10 ^c	L3	NaOt-Bu	48	89

^aReaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), Ni(cod)₂ (0.05 mmol), ligand (0.10 mmol), base (1.5 mmol), toluene (1.5 mL) at 120 °C in a sealed tube. ^bIsolated yield of **3**. ^c**2** (2.5 mmol), Ni(cod)₂ (0.1 mmol), L3 (0.2 mmol), and NaOt-Bu (3.0 mmol) were used.



L1: R¹ = R² = Me L3: R¹ = *i*-Pr, R² = H
L2: R¹ = Et, R² = H L4: R¹ = R² = *t*-Bu

finally increased to 89% by increasing the catalyst loading (20 mol %) and amount of amine (5 equiv). It is important to note that no amination product was formed in the absence of a nickel catalyst under otherwise identical conditions, indicating that base-promoted nucleophilic aromatic substitution⁷ is not operative in this reaction. The use of NiCl₂ as a nickel source also afforded **3**, albeit in significantly lower yield.

Having optimized conditions in hand, we next explored the scope of this reaction with respect to the amine component (Table 2). Various cyclic amines, such as pyrrolidine (**4**), piperidines **5–7**, and piperazines **8** and **9**, underwent the nickel-catalyzed cross-coupling with **1** to successfully construct important structural motifs commonly found in pharmaceutical substances. The larger the ring size, the lower the yield, indicating the sensitivity of the reaction to the steric factor of the amines (compare **4**, **5**, and **10**). Acyclic amines, as in **11** and **12**, can also be applied to this catalytic amination reaction. On the other hand, pri-

Table 2. Ni⁰-catalyzed cross-coupling of **1** with various amines^a

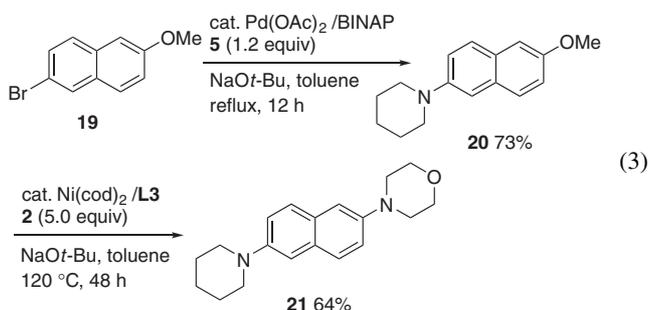
Entry	Amine	Yield/% ^b	Entry	Amine	Yield/% ^b
1		89	6		59
2		91	7		53
3		70	8		51
4		59 ^c	9		42
5		55	10		51

^aReaction conditions: **1** (0.5 mmol), amine (2.5 mmol), Ni(cod)₂ (0.1 mmol), L3 (0.2 mmol), and NaOt-Bu (3.0 mmol), toluene (1.5 mL) at 120 °C for 48 h in a sealed tube. ^bIsolated yield based on **1**. ^cNi(cod)₂ (0.05 mmol) and L3 (0.1 mmol) were used.

mary amines and anilines did not afford the corresponding coupling products under these conditions.

Table 3 illustrates the scope of the nickel-catalyzed amination with respect to the anisole component. While 2-methoxynaphthalenes, as in **1** and **13**, proved to be good substrates, 1-methoxy isomer **14** resulted in a significant loss of yield probably due to the steric hindrance. As is observed in the cross-coupling with boronic esters,⁴ the reaction of anisole **15** with **2** did not proceed under these conditions. However, introduction of electron-withdrawing groups, such as Ph **16**, CF₃ **17**, and CO₂Me **18** groups, significantly enhanced the reactivity toward this catalytic amination to form the corresponding amines in modest yields. The exclusive formation of the ipso substituted products in these cases indicates that an aryne-type intermediate is not involved in this catalysis.⁸ The applicability of relatively unactivated anisole **16** is in contrast to our previous results.⁹

Diaminonaphthalene **21** can be synthesized through the sequential aminations of halide and methyl ether moieties in **19** by palladium and nickel catalysts, respectively (eq 3).



In summary, we have developed a nickel-catalyzed amination of anisole derivatives which proceeds through the cleavage

Table 3. Ni⁰-catalyzed amination of anisole derivatives^a

Entry	Anisole derivative	Yield/% ^b
1		89
2		78
3		30
4		0
5		43
6		44
7		43 ^c

^aReaction conditions: **1** (0.5 mmol), **2** (2.5 mmol), Ni(cod)₂ (0.1 mmol), L3 (0.2 mmol), and NaOt-Bu (3.0 mmol), toluene (1.5 mL) at 120 °C for 48 h in a sealed tube. ^bIsolated yield based on anisole derivatives. ^cThe product was morpholino(4-morpholinophenyl)methanone.

of carbon–oxygen bonds.¹⁰ Although the reaction efficiency and the substrate scope require further improvements, these studies clearly indicate that anisoles can be employed as a synthetic surrogate of aryl halides in transition-metal catalysis. Studies along this line are currently underway.

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