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Amination Methods

Nickel-Catalyzed Amination of Aryl Pivalates by the Cleavage of Aryl C–O Bonds**

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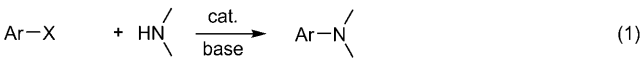
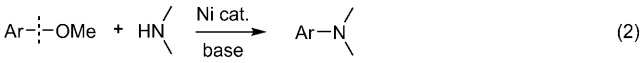
The prevalence of aniline derivatives in the pharmaceutical, agrochemical, and electronic industries has prompted the development of new, general, and efficient methods for the formation of aromatic carbon–nitrogen bonds.[1] Since the pioneering work by Migita and co-workers,[2] significant advancements have been made in palladium-catalyzed C–N bond-forming reactions. In particular, contributions from the research groups of Buchwald and Hartwig have established the powerful nature of this method by achieving the cross-coupling of aryl halides with amines in the presence of a suitable base [Eq. (1)].[3] Numerous publications have



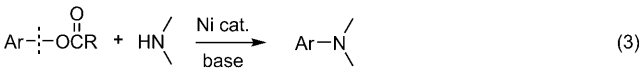
(1)

reported palladium-catalyzed amination reactions, however, the possibility of using electrophilic coupling partners other than halides and sulfonates is yet to be disclosed. During the course of our studies on the development of nickel-catalyzed cross-coupling reactions, through the cleavage of carbon–oxygen bonds in aryl methyl ethers,[4,5] we found that aryl methyl ethers can be aminated directly [Eq. (2)].[4b,6] This study demonstrates the potential utility of aryl methyl ethers



(2)

as aryl halide surrogates in catalytic amination reactions. However, the reaction proceeds efficiently only with fused aromatic substrates, such as 2-methoxynaphthalenes, and thus limits its broad synthetic application. On the other hand, the research groups of Shi and Garg independently reported the use of aryl carboxylates as effective electrophiles in cross-coupling reactions with organometallic reagents (i.e. the Suzuki–Miyaura,[7a–c] Negishi,[7d] and Kumada–Tamao–Corriu[7e] reactions). Inspired by their studies, we envisaged that aryl carboxylates could be employed as more reactive, halogen-free electrophiles in the catalytic amination reaction. Herein, we report this unprecedented catalytic amination of aryl carboxylates [Eq. (3)].



(3)

Although the feasibility of the reaction described in Equation (3) was supported, in part, by the results of Shi and Garg,[7] the success of the amination chemistry was uncertain owing to the inherent susceptibility of the carbonyl carbon atom towards nucleophilic attack by amines, which would eventually lead to the undesired fission of the acyl–O bond. Indeed, this undesired pathway occurred exclusively when aryl pivalate **1a** was treated with morpholine (**2a**) and NaO*t*Bu in the absence of the catalyst (phenol was formed in 49% yield; Table 1, entry 1). On the other hand, the amination reaction proceeded smoothly under the reaction conditions suitable for aryl methyl ethers,[4b] that is, [Ni(cod)$_2$)] as a catalyst, IPr·HCl (1,3-bis(2,6-diisopropylphenyl)imidazolium chloride) as the ligand, and NaO*t*Bu as an external base (Table 1, entry 2). Consistent with our expectations, the use of **1a** resulted in significantly milder reaction conditions. In comparison to those conditions required for aryl methyl ethers,[4b] our conditions were milder in terms of reaction temperature, time, catalyst loading, and the quantity of amine substrate (Table 1, entry 3). Notably, the use of PCy_3, which has been reported as the most effective ligand in nickel-catalyzed C–C bond formation of aryl carboxylates,[7] resulted in a lower yield of **3a** under these conditions (Table 1, entry 4). In addition, the use of a nickel(II) complex (a bench stable catalyst) led to the undesired fission of the acyl–O bond. (Table 1, entry 5). The choice of the substituent on the acyl group in **1** is crucial for this catalytic amination to proceed. When phenyl acetate (**1b**) was subjected to the catalytic conditions, no aminated product was observed, even though **1b** was almost completely

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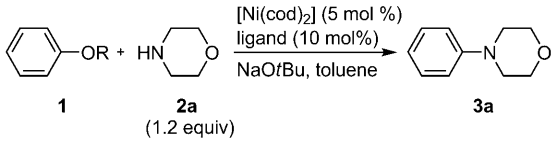
Table 1: Optimization of reaction conditions.[a]

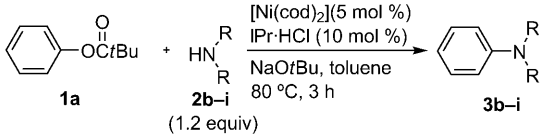


1 **2a** (1.2 equiv) **3a**

Entry	**1** (R)	Ligand	*T* [°C]	*t* [h]	Yield [%][b]
1[c]	**1a** (CO*t*Bu)	none	120	12	0
2[d]	**1a**	IPr·HCl	120	12	>99
3	**1a**	IPr·HCl	80	3	91
4[e]	**1a**	PCy_3	80	3	51
5[f]	**1a**	none	80	3	0
6[g]	**1b** (COMe)	IPr·HCl	80	3	0
7[h]	**1c** (COPh)	IPr·HCl	80	3	26
8	**1d** ($CONEt_2$)	IPr·HCl	80	3	>99

[a] Reaction conditions: To a sealed tube was added **1** (0.5 mmol), **2a** (0.6 mmol), $[Ni(cod)_2]$ (0.025 mmol), IPr·HCl (0.05 mmol), NaO*t*Bu (0.7 mmol), and toluene (2.5 mL). [b] Yield of isolated product based on **1**. [c] In the absence of $[Ni(cod)_2]$, phenol was formed in 49% yield (as determined by GC analysis). [d] Reaction conditions: **2a** (0.75 mmol), $[Ni(cod)_2]$ (0.05 mmol), IPr·HCl (0.1 mmol) and NaO*t*Bu (0.9 mmol). [e] Used PCy_3 (0.1 mmol). [f] Used $[NiCl_2(PCy_3)_2]$ (0.025 mmol) as a catalyst. [g] Phenol was formed in 30% yield (as determined by GC analysis). [h] Phenol was formed in 27% yield (as determined by GC analysis). cod = cycloocta-l,5-diene, Cy = cyclohexyl.

Table 2: Nickel-catalyzed cross-coupling of phenyl pivalate **1a** with amines.[a]



1a **2b–i** (1.2 equiv) **3b–i**

Entry	Amine	Product	Yield [%][b]
1	**2b** (*n*=1)	**3b**	87[c]
2	**2c** (*n*=2)	**3c**	74
3[d]	**2d** (*n*=3)	**3d**	56
4	**2e**	**3e**	95
5	**2f**	**3f**	74
6	**2g**	**3g**	87
7	**2h**	**3h**	79
8	**2i**	**3i**	75
9[e]	**2j**	**3j**	60

[a] Reaction conditions: To a sealed tube was added **1a** (0.5 mmol), **2** (0.6 mmol), $[Ni(cod)_2]$ (0.025 mmol), IPr·HCl (0.05 mmol), NaO*t*Bu (0.7 mmol), and toluene (2.5 mL). [b] Yield of isolated product. [c] The yield was determined by GC analysis. [d] Used $[Ni(cod)_2]$ (0.05 mmol) and IPr·HCl (0.1 mmol). [e] Used **2j** (1.0 mmol), $[Ni(cod)_2]$ (0.05 mmol) and IPr·HCl (0.1 mmol) for 12 h.

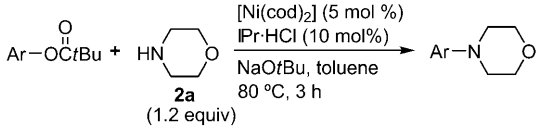
consumed (phenol was formed in 30% yield; Table 1, entry 6). On the other hand, the use of a benzoyl group (as in **1c**) afforded **3a** in a much lower yield compared to **1a** (Table 1, entry 1 vs. entry 7). This lower yield resulted from significant cleavage of the acyl–O bond (phenol was formed in 27% yield). Importantly, these catalytic conditions have also been applied to the direct amination of carbamate **1d** (Table 1, entry 8), thus enabling possible application to tandem *ortho*-directed functionalization/cross-coupling reactions.[8]

Having optimized the reaction conditions, we next examined the scope of this reaction with respect to the amine nucleophile (Table 2). The pivaloyl moiety in **1a** was replaced with a wide range of secondary amines under our catalytic conditions. The use of five- to seven-membered cyclic amines afforded the corresponding aromatic amines efficiently (Table 2, entries 1–4). In addition to simple monobasic amines, those amines bearing multiple basic sites were also employed successfully (Table 2, entries 5 and 6). Moreover, bicyclic *trans*-decahydroisoquinoline (**2h**) efficiently underwent the amination (Table 2, entry 7). Acyclic secondary amines also served as appropriate nucleophiles for this catalytic amination (Table 2, entries 8 and 9). Cyclohexylamine and *N*-methylaniline did not afford the corresponding arylated products under the present reaction conditions, this may be a consequence of their lower nucleophilicity.

Next, the scope of this reaction was examined with respect to aryl pivalates (Table 3). Both electron-rich (Table 3, entry 1) and -deficient (Table 3, entry 2) aryl pivalates afforded the aminated products in good yields. Although nickel-catalyzed substitution reactions of aryl fluorides have previously been reported,[5d,7d,9] fluoride functionalities survived under the present reaction conditions (Table 3, entry 3). Also, a styryl substituent on the aryl pivalate was tolerated (Table 3, entry 4). Several other aryl substituents, acetals (Table 3, entry 5) and amines (Table 3, entry 6), were tolerated under these amination conditions. In addition, the chloride moiety was aminated at a faster rate than pivalates under the present catalytic conditions (see the Supporting Information for details). The pivaloyl groups bonded to fused aromatic rings, such as naphthalene (Table 3, entries 7 and 8) and phenanthrene (Table 3, entry 9), were efficiently aminated. The pivalates of heteroaromatic derivatives also underwent the catalytic amination (Table 3, entry 10).

The difference in reactivity between aryl methyl ethers and aryl carboxylates in the nickel-catalyzed C–O bond functionalization provides a new strategy for the sequential elaboration of the aromatic framework (Scheme 1). The pivalate group in **24** was aminated under the catalytic conditions with the methoxy group remaining intact. The methoxy group in **25** was arylated through our previously reported cross-coupling reaction using an organoboron reagent and furnished **26**.[4a]

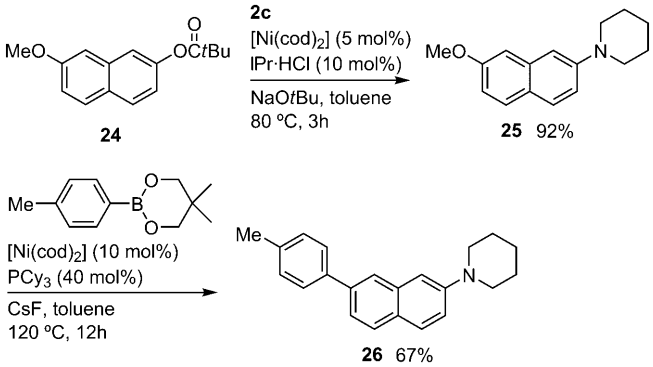
Table 3: Nickel-catalyzed amination of aryl pivalates with **2a**.[a]



Entry	Aryl pivalate	Product	Yield [%][b]
1	**4**, R = OMe	**5**	71
2	**6**, R = CF_3	**7**	73
3	**8**, R = F	**9**	73
4	**10**, R = (*E*)-styryl	**11**	87 (*E* only)
5	**12**	**13**	81
6	**14**	**15**	87
7	**16**	**17**	99
8	**18**	**19**	91
9	**20**	**21**	80
10	**22**	**23**	66

[a] Reaction conditions: To a sealed tube was added **1** (0.5 mmol), **2a** (0.6 mmol), [Ni(cod)$_2$] (0.025 mmol), IPr·HCl (0.05 mmol), NaO*t*Bu (0.7 mmol), and toluene (2.5 mL). [b] Yield of isolated product.

In summary, we have shown that aryl carboxylates can serve as suitable electrophilic coupling reagents in catalytic aromatic amination reactions. In view of the widespread utility of the catalytic amination in industrial settings,[10] these results should provide a meaningful opportunity for process development, in particular in avoiding the use of halides and sulfonates. In addition, the diversity of the electrophiles in the catalytic amination reactions would allow an orthogonal-functionalization strategy of aromatic compounds.[11] Additional studies to further expand the scope of the nickel-catalyzed C–O bond functionalization are ongoing.



Scheme 1. Tandem C–O bond transformations.

Experimental Section

Typical procedure for the nickel-catalyzed amination of aryl pivalates (Table 1, entry 3): Catalyst [Ni(cod)$_2$] (6.9 mg, 0.025 mmol), IPr·HCl (21.3 mg, 0.05 mmol), NaO*t*Bu (67.3 mg, 0.7 mmol), **1a** (89.1 mg, 0.5 mmol), **2a** (52.3 mg, 0.6 mmol) and toluene (2.5 mL) were added to a vial (10 mL) with a teflon sealed screwcap in a glovebox filled with nitrogen. The reaction mixture was stirred at 70 °C for 3 h. After cooling to room temperature, the crude mixture was purified by flash column chromatography on silica gel (eluent: *n*-hexane/CH_2Cl_2 4:1), and afforded 4-phenylmorpholine as a colorless oil (74.6 mg, 91 %).

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