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Nickel-Catalyzed Amination of Aryl Fluorides with Primary Amines

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The Ni-catalyzed cross-coupling reaction between aryl fluorides and primary amines was enabled by the 1,2-bis(dicyclohexylphosphino)benzene (DCYPBz) or 1,2-bis(dicyclohexylphosphino)ethane (DCYPE) ligands. Both *N*-alkyl- and *N*-aryl-substituted primary amines participated in the selective reaction to form secondary amines. This protocol would potentially be useful for late-stage diversification of fluorinated compounds with complex structures for the synthesis of functionally interesting aniline derivatives.

Compounds with F-substituted aryl groups are widely available from reagent suppliers, and their structural diversity in pharmaceuticals and functional materials is significant.¹ Thus, the transformation of C–F bonds in these compounds is expected to be a useful strategy to create large-scale biased compound libraries.² However, the intrinsic inertness of C–F bonds limits their utility as a functional group for chemical transformations.³ Therefore, development of new ways for transforming C–F bonds of aryl fluorides is highly desirable.

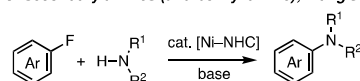
Transition metal catalyzed cross-coupling reactions of aryl halides are powerful tools for C–C and C–heteroatom bond formation.⁴ Since the seminal report by Tamao, Kumada and a co-worker,⁵ Ni catalysis has been recognized as a favorable strategy for derivatization of aryl fluorides through C–F bond activation. Recent progress in this field has been spectacular.⁶ However, compared to C–C bond formation reactions using nucleophilic organometallic reagents,⁷ C–heteroatom bond formation reactions have been less developed.⁸ For C–N bond forming reactions to prepare arylamines,⁹ Wang and a co-worker disclosed Ni catalysis for amination of aryl fluorides using a bulky *N*-heterocyclic carbene ligand (NHC), IPr (Scheme 1, top).¹⁰ While various *N*-dialkyl- or *N*-alkylaryl secondary amines participated in this transformation, its applicability toward primary amines has not been well-demonstrated despite the importance of secondary arylamines as handles for further *N*-

functionalizations leading to various derivatives such as tertiary amines and amides.

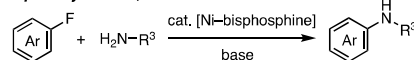
Here, we report the Ni-catalyzed cross-coupling between aryl fluorides and primary amines enabled by 1,2-bis(dicyclohexylphosphino)benzene (DCYPBz),¹¹ which features a rigid backbone connecting two dicyclohexylphosphino moieties, as a ligand (Scheme 1, bottom). Both *N*-alkyl- and *N*-aryl-substituted primary amines successfully participated in this transformation, giving secondary arylamines in high yields.

Specifically, the reaction between an electron-rich aryl fluoride, 4-fluoroanisole (**1a**, 0.25 mmol), and *N*-octylamine (**2a**, 1.5 equiv) in the presence of [Ni(cod)₂] (5 mol%), DCYPBz (7.5 mol%) and NaOtBu (1.5 equiv) in toluene at 120 °C over 20 h occurred cleanly and gave the secondary amine product **3a** in 94% isolated yield (Scheme 2). Importantly, the corresponding tertiary amine was not detected in the crude product. Even with an excess amount of **1a** (**1a**/**2a** 1.5:1), **3a** was the sole product (94% NMR yield). IPr and PCy₃, which have often been employed as effective ligands in Ni-catalyzed C–F bond transformations,^{7,8,10} induced no reaction.

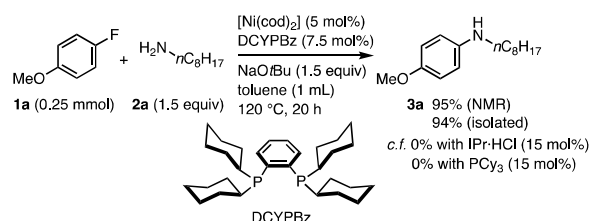
For secondary amines (and benzyl amine); Wang's work



For primary amines; This work



Scheme 1 Ni-catalyzed amination of aryl fluorides.

Scheme 2 Ni-catalyzed amination of **1a** with **2a**.

Screening of chelating bisphosphines identified DCYPBz as the most effective ligand for the reaction between **1a** and **2a** (Scheme

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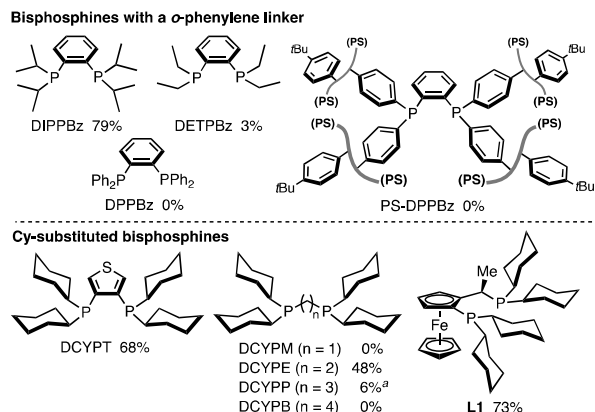
E-mail: iwai-t@sci.hokudai.ac.jp (T.I.)E-mail: sawamura@sci.hokudai.ac.jp (M.S.)Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data and copies of ¹H, ¹³C and ³¹P NMR spectra. See DOI: 10.1039/x0xx00000x

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3).¹² Among bisphosphines having a rigid *o*-phenylene linker between the two P atoms, less-hindered *P*-alkyl-substituted bisphosphines such as DIPPBz and DETPBz were less effective. A perarylated bisphosphine DPPBz gave no catalytic activity. Thus, steric bulk and strong electron-donation of the bisphosphines were crucial. The polystyrene-cross-linking bisphosphine PS-DPPBz,¹³ which allowed controlled bisphosphine monochelation to metals, was also ineffective.

Effects of linkers between two dicyclohexylphosphino moieties were also investigated (Scheme 3). The thiophene-based ligand DCYPT^{11b} was less effective than DCYPBz, giving **3a** in 68% yield. DCYPE having a flexible ethylene (C2) linker showed similar performance to DCYPT (48%), while product yields dropped for ligands with C1, C3 and C4 linkers (DCYPM, DCYPP and DCYPB, respectively; 0–6%). The *P,P,P',P'*-tetracyclohexyl-substituted Josiphos-type ligand **L1** gave a moderate yield (73%), but did not improve the yield obtained with DCYPBz.

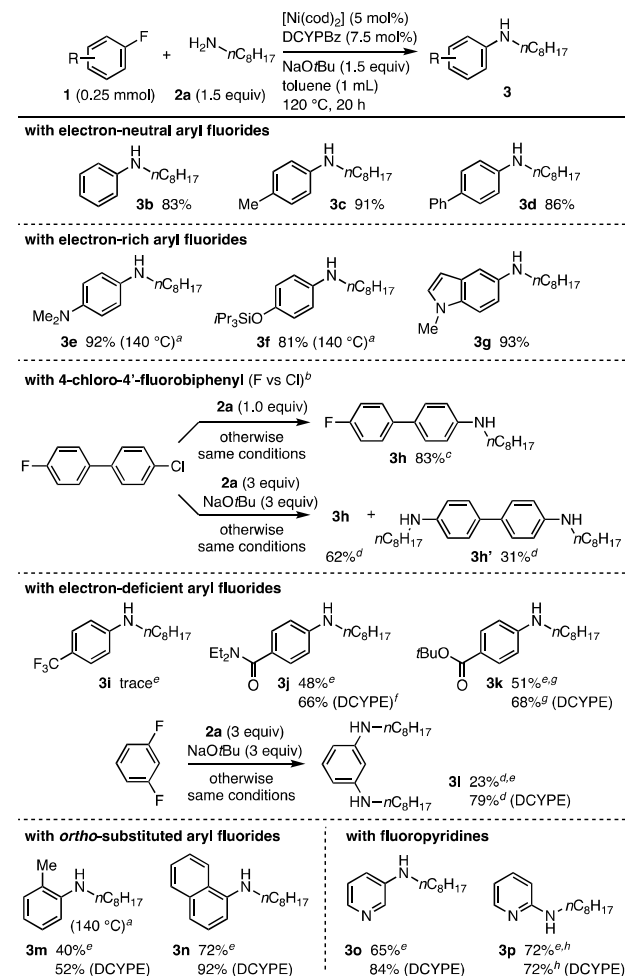
The use of NaOtBu as a base was also important for the efficient amination of **1a** with **2a** in the presence of the DCYPBz-Ni system (5 mol% Ni, 120 °C for 20 h). LiOtBu (20%), KOtBu (17%), and NaHMDS (22%) were much less effective. Aprotic solvents such as CPME (82%) and octane (75%) could be used, but gave slightly lower yields than toluene. Aprotic polar solvents such as DMA (0%) or protic solvents such as *t*-AmOH (5%) were not suitable. A lower reaction temperature (in toluene with NaOtBu) decreased the yields (62% and 15%, at 110 °C and 100 °C, respectively). Removal of either the Ni complex or ligand from the conditions shown in Scheme 2 resulted in no reaction. Thus, the possibility of a nucleophilic aromatic substitution reaction pathway was excluded.¹⁴



Scheme 3 Ligand effects in the reaction between **1a** and **2a**. Conditions: **1a** (0.25 mmol), **2a** (0.375 mmol), [Ni(cod)₂] (5 mol%), ligand (7.5 mol%), NaOtBu (0.375 mmol), toluene (1 mL), 120 °C, 20 h. ¹H NMR yields are shown. ^a DCYPP was generated in situ from DCYPP-2HBF₄.

With the optimal conditions in hand, the scope of the aryl fluorides was investigated using **2a** as a representative primary amine substrate (Scheme 4). Electronically neutral aryl fluorides (fluorobenzene, 4-fluorotoluene and 4-fluorobiphenyl) underwent efficient amination, giving the corresponding *N*-octylanilines **3b–3d** in high yields. Amination of electron-rich aryl fluorides having *N,N*-dimethylamino (**3e**) or triisopropylsiloxy (**3f**) groups at the *para* position occurred at 140 °C. 5-Fluoro-1-methylindole, an electron-rich heteroaryl fluoride, served as a suitable substrate (**3g**). In the

reaction between 4-chloro-4'-fluorobiphenyl and 1 equiv of **2a** at 120 °C, the C–Cl amination product **3h** was obtained as the sole product, indicating that the C–Cl bond underwent the amination preferentially over the C–F bond. The use of 3 equiv of **2a** gave a mixture of **3h** and diamination product **3h'**, which formed through the consecutive C–Cl and C–F amination.



Scheme 4 Scope of aryl fluorides. Conditions: **1** (0.25 mmol), **2a** (0.375 mmol), [Ni(cod)₂] (5 mol%), DCYPBz (7.5 mol%), NaOtBu (0.375 mmol), toluene (1 mL), 120 °C, 20 h. Isolated yields are shown. ^a 140 °C in *m*-xylene. ^b The substrate 4-chloro-4'-fluorobiphenyl (~96% purity) was contaminated with inseparable 4,4'-dichlorobiphenyl. ^c **2a** (0.25 mmol). The isolated product **3h** contained *N*-octyl-[1,1'-biphenyl]-4-amine (4%). ^d **2a** (0.75 mmol) and NaOtBu (0.75 mmol). ^e ¹H NMR yields. ^f *N,N*-Diethylbenzamide (ca. 10%) was detected in the ¹H NMR spectrum of the crude product. ^g The *t*Bu ester cleavage product of **3k** was observed in the crude mixture using DCYPBz (22%) or DCYPE (6%). ^h The tertiary amine product was observed in the crude mixture using DCYPBz (4%) or DCYPE (5%).

In contrast to electron-neutral and electron-rich aryl fluorides, electron-deficient aryl fluorides underwent less efficient amination with the DCYPBz-Ni system. Most typically, the reaction between 1-fluoro-4-(trifluoromethyl)benzene and **2a** at 120 °C in toluene over 20 h produced only a trace amount of **3i** (Scheme 4). The reaction of *N,N*-diethyl-4-fluorobenzamide produced **3j** in only 48% yield (NMR). However, the use of DCYPE instead of DCYPBz

improved the yield to 66%. ^1H NMR and GC-MS analysis of the crude product showed formation of *N,N*-diethylbenzamide (ca. 10%), probably through protonation of a putative Ar-Ni(II)-F oxidative addition intermediate,¹⁵⁻¹⁷ indicating lower efficiencies of transmetalation and/or subsequent reductive elimination. Although the reaction of *t*-butyl 4-fluorobenzoate competed with the cleavage of the *t*Bu ester moiety, the use of DCYPE provided a better yield of **3k** compared to DCYPBz. Double C–F amination of 1,3-difluorobenzene with **2a** (3 equiv) proceeded smoothly with the DCYPE-Ni system, giving the corresponding diaminobenzene **3l** in 79% yield.¹⁸ The reasons for the higher performance of DCYPE than DCYPBz in these cases are unclear at present. Similar ligand effects were observed in the reactions of *ortho*-substituted substrates such as *o*-tolyl fluoride (**3m**) and 1-naphthyl fluoride (**3n**), and fluoropyridine such as 2- and 3-fluoropyridines (**3o** and **3p**).

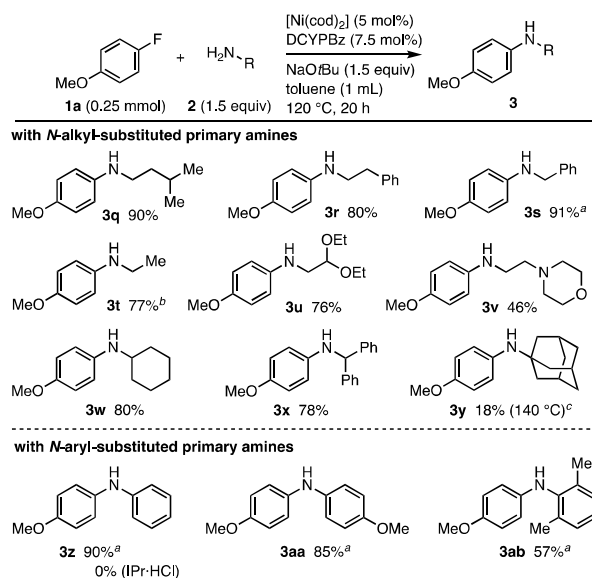
The DCYPBz-Ni system was applicable to the C–F amination with various primary amines. The results are summarized in Scheme 5. Isoamyl- and 2-phenylethyl amines reacted with **1a** at 120 °C, giving the secondary amines **3q** and **3r**, respectively, in high yields. In the reaction of benzylamine, 3 equiv each of the amine and NaOtBu were used for obtaining the coupling product **3s** in high yield. Ethylamine hydrochloride served as an amine source (in CPME), giving **3t** in a useful yield. Diethyl acetal (**3u**) and morpholine (**3v**) moieties were tolerated in the primary alkylamines. *N*-Secondary-alkyl-substituted amines such as cyclohexylamine and benzhydrylamine were also suitable substrates (**3w** and **3x**). An *N*-tert-alkyl-substituted primary amine, 1-adamantylamine, induced less efficient amination even at a higher temperature (**3y**, 140 °C in *o*-xylene, 18%).

Primary arylamines also participated in the amination of aryl fluorides (Scheme 5). The reaction of **1a** with aniline (3 equiv) occurred using 3 equiv of NaOtBu at 120 °C, giving diaryl amine **3z**. The use of IPr in place of DCYPBz induced no catalytic activity as in the case of the reaction with *N*-octylamine (Scheme 2). *p*-Methoxy-substituted aniline also served as a suitable substrate (**3aa**), while *p*-CF₃-substituted aniline gave no amination product (data not shown). Sterically demanding 2,6-dimethylaniline coupled with **1a**, giving **3ab** in an acceptable yield.

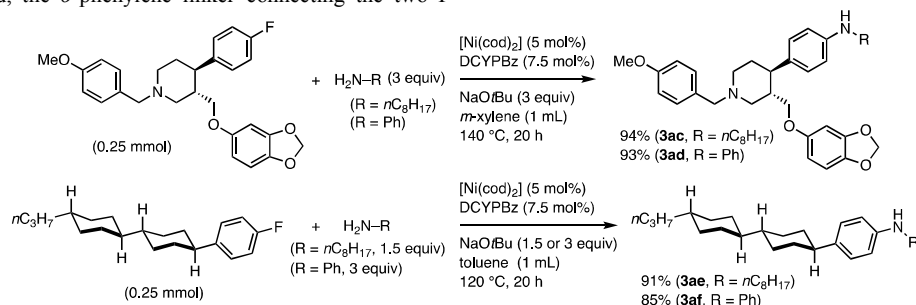
The effectiveness of DCYPBz in the Ni-catalyzed amination of aryl fluorides with primary amines can be summarized as follows. First, the electron-donating *P*-alkyl substituents increase electron density of the Ni(0) species, assisting oxidative addition of the C–F bond.¹⁵⁻¹⁷ Second, the steric demand of the ligand is beneficial to form a bisphosphine-monochelated monomeric Ni(0) species, which would be highly active due to the coordinative unsaturation of the metal center. Third, the *o*-phenylene linker connecting the two P

atoms is favorable for a rigid metal chelation, which may suppress undesired ligand exchange by primary amine substrates. The latter two points are supported by Hartwig's mechanistic studies on a bisphosphine-Ni system for amination of aryl chlorides with *N*-alkyl-substituted primary amines¹⁹ and by our own study with polystyrene-cross-linking bisphosphine PS-DPPBz.¹³

Finally, utility of the DCYPBz-Ni system was demonstrated in the derivatization of fluorinated compounds, including a bioactive molecule and a functional material (Scheme 6). The C–F amination of an *N*-*p*-methoxybenzyl-protected form of paroxetine,²⁰ an antidepressant of the selective serotonin reuptake inhibitor class, occurred with 3 equiv of octylamine or aniline (5 mol% Ni loading in *m*-xylene at 140 °C for 20 h), affording **3ac** or **3ad**, respectively, in high yields. *Trans,trans*-4-(4-fluorophenyl)-4'-propylbicyclohexyl, which is a fluorinated liquid crystal material,²¹ was converted to the corresponding C–F amination products **3ae** and **3af** (in toluene at 120 °C). As demonstrated by these transformations, the present Ni-catalyzed C–F amination reaction would serve as a means for late-stage diversification of complex molecules, taking advantage of the masked reactivity of the C–F bond.



Scheme 5 Scope of *N*-primary amines. Conditions: **1a** (0.25 mmol), **2** (0.375 mmol), [Ni(cod)₂] (5 mol%), DCYPBz (7.5 mol%), NaOtBu (0.375 mmol), toluene (1 mL), 120 °C, 20 h. Isolated yields are shown. ^a 3 equiv. each of amine and NaOtBu were used. ^b 3 equiv. of EtNH₂·HCl and 6 equiv. of NaOtBu were used in CPME (1 mL). ^c 140 °C in *o*-xylene.



Scheme 6 C–F Amination of *N*-PMB-protected paroxetine (top) and a fluorinated liquid crystal material (bottom).

In summary, Ni-catalyzed amination of aryl fluorides with primary amines was enabled by using 1,2-bis(dicyclohexylphosphino)benzene (DCYPBz) as a ligand. The reaction is selective for the formation of secondary amines over tertiary amines. The electron-donating, sterically demanding, and rigid properties of DCYPBz seem to be favorable to form catalytically active Ni species. A broad substrate scope covering various types of *N*-alkyl- and *N*-aryl-substituted primary amines was achieved with the complementary use of the nickel catalyst systems with DCYPBz or DCYPE bisphosphine ligands. The C–F amination of a paroxetine derivative and a fluorinated liquid crystal demonstrated the utility of the present protocol for late-stage diversification of broadly available fluorinated compounds with complex structures. Further studies for developing highly active C–F transformation catalysts are ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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