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Nickel-Catalyzed Suzuki-Miyaura Cross-Coupling Involving C–O Bond Activation

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Dedicated to Professor E. Peter Kündig on the occasion of his 75th birthday.

An efficient *Suzuki-Miyaura* cross-coupling reaction of *ortho*-phenoxy-substituted aromatic amides with aryl boronates is described. The use of LiO^tBu is crucial for the success of the reaction. An amidate anion, which is formed through deprotonation of the amide NH bond by LiO^tBu, functions as a directing group to activate a C–O bond.

Keywords: amides, C–O activation, nickel, organoboron, Suzuki-Miyaura cross-coupling.

Introduction

Organic synthesis involves the breaking of an existing bond and the formation of a new one to convert simple, small compounds into large and complex organic molecules by C--C bond and C--heteroatom bond formation. The use of reactive chemical bonds has long been the primary focus of organic synthesis. However, reactions of various unreactive chemical bonds, such as C-H, C-C, C-F, C-O, and other bonds are now beginning to be the focus of interest in organic transformations, thus providing new possibilities for developing new synthetic methodologies. Chelation assistance is one of the more reliable strategies for the activation of C–H bonds.^[1–5] A wide variety of chelation-assisted systems has been designed and have been used in developing new transformations involving C-H activation.^[6] Chelation systems that are applicable to the activation of various unreactive bonds, however, such as C-O, C-N, C-F, and other unreactive bonds continue to be an undeveloped area. In 2017, we reported that the Nicatalyzed C-H/N-H annulation of aromatic secondary amides with alkynes in the presence of KO^tBu results

in the formation of isoquinolinone derivatives (*Scheme 1*, X=H).^[7] A key to the success of this reaction is the use of a base, which functions to abstract a proton from an aromatic amide to form an amidate anion species, which acts as a chelation-assisted directing group. The amidate anion coordi-



Scheme 1. Ni-catalyzed transformations involving the activation of unreactive bonds.

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nates to the Ni(0) complex to give the nickel ate species A in which the nickel center is located in close proximity to the ortho C-H bond, which is selectively activated.^[8] Encouraged by this reaction, we were prompted to apply this protocol to the activation of other unreactive bonds. Surprisingly, the strategy was found to be applicable to the activation of other unreactive bonds, such as C-F,^[9] C-O, C-S, and C-CN.^[10] In all cases, no ligand was required. We also recently applied this protocol to the Ni-catalyzed cross-electrophile coupling of 2-fluoro-substituted aromatic amides with aryl chlorides^[11] and the Nicatalyzed Suzuki-Miyaura coupling reaction of 2-fluorosubstituted aromatic amides with aryl boronates.^[12] In all cases, anionic nickel ate species A appears to be a key species. We wish to report herein the Ni-catalyzed Suzuki-Miyaura cross-coupling reaction of orthophenoxy-substituted aromatic amides with aryl boronates, which involve the activation of C-O bonds.^[13–17]

Results and Discussion

We first carried out the reaction of 2-phenoxy-Nphenylbenzamide (1a) with tolylboronic acid neopentylglycol ester **2a** (3 equiv.), Ni(cod)₂ (10 mol-%), Me₄Phen (3,4,7,8-tetramethyl-1,10-phenanthroline: 5 mol-%), KO^tBu (1 equiv.), and CsF (1 equiv.) in DMF (1 mL) at 100 °C for 20 h. The reaction gave the expected arylation product **3a** in 59% GC yield, along with 4a in 6% and 5a in 16% yields as byproducts (Scheme 2). The formation of 5a appears to proceed through an S_NAr mechanism. Thus, the KO^tBu abstracts a proton from **1a** to generate an amidate anion **B**. The nitrogen anion in **B** then attacks at the *ipso*-carbon to give the Meisenheimer intermediate C, from which a phenyl group migrates from an O-atom to a N-atom to gives **D**. The protonation of **D** then gives **5a**. An alternative pathway involves the oxidative addition of a Ph–O bond in E give F, which gives 5a through reductive elimination followed by protonation.

To suppress possible side reaction through an S_N Ar-like mechanism to give the undesired product **5a**, an electron-donating group such as 4-methoxyphenoxy group was used as a leaving group as in **1b** in place of a phenoxy group. As expected, the reaction of **1b** with **2a** gave the desired arylated product **3a** in 85% GC yield and **5b** was not formed (*Scheme 3*). Among the bases that were examined, LiO^tBu gave a slightly higher product yield compared to NaO^tBu (76% yield) and KO^tBu (59%). The reaction





Scheme 2. Ni-catalyzed reaction of reaction of **1a** with **2a** and the possible pathways for the formation of byproduct **5a**.



Scheme 3. Ni-catalyzed *Suzuki-Miyaura* coupling reaction of 1b with 2a.

proceeded, even in the absence of CsF (58% yield). The use of PPh₃ (20 mol-%) in place of Me_4Phen also gave **3a** in 70% yield.

The scope of this arylation was investigated with respect to amides and boronates (*Figure 1*). To examine electronic effects, the reaction of *meta*-substituted aromatic amides that contain a 4-methoxyphenoxy



Figure 1. Scope of products of the Ni-catalyzed *Suzuki-Miyaura* coupling reaction of **1** with **2**. Reaction conditions: amide **1** (0.5 mmol), arylboronate **2** (1.5 mmol), Ni(cod)₂ (0.05 mmol), Me₄Phen (0.025 mmol), LiO^tBu (0.5 mmol), and CsF (0.5 mmol) in DMF (1 mL) at 100 °C for 20 h. Yields after isolation with MPLC are given.

group as a leaving group was examined. The use of an electron-withdrawing group gave the arylated products in higher yields (**3c**-**3e**). We next examined the scope of arylboronic esters using **1b** as a substrate. The presence of an electron-donating group on the arylboronic esters showed a higher reactivity, irrespective of the position of the substituents. Thus, methoxy-substituted arylboronic esters gave higher product yields, as in **3g** and **3j** compared to trifluoromethyl-substituted arylboronic esters, as in **3i** and **3m**. Although a C–OMe bond is known to participate in *Suzuki-Miyaura* cross-coupling reactions,^[13-19] the C–OMe bond remained intact under the reaction conditions employed, as in **3g**, **3j**, and **3o**. In addition,

a C–F bond remained unreactive, as in **3d**, indicating that chelation-assistance is involved in the activation of the C–O bond. It was found that *N*-aryl-substituted amides gave the corresponding products **3b**, **3o** and **3p** in good yields.

A proposed mechanism for the cross-coupling reaction is shown in *Scheme 4*. Deprotonation of the amide **1** by LiO^tBu forms the amidate anion **G**, which coordinates to Ni(0) to give the Ni(0) ate complex **H**.¹ Activation of the C–OAr bond in **H** gives the fivemembered azanickelacycle **I** with the elimination of LiOAr. Transmetalation between complex **I** and the arylboronic ester **2** gives the Ni intermediate **J**. An arylated product **K** is then obtained by reductive elimination from **J** with the regeneration of Ni(0) and the final product **3** is then obtained after workup. The addition of CsF was not crucial for the reaction to proceed since LiOAr, which can activate an aryl boronate in place of CsF, is generated during the reaction.



Scheme 4. A proposed mechanism.

¹A similar nitrogen-based Ni(0) ate complex was proposed.^[20] An alkoxy anion-substituted Ni(0) ate complex, which facilitates the rate determining C–O activation step, was proposed as a key catalytic species in the Ni-catalyzed hydrogenolysis of aryl ethers.^[21]





Conclusions

We report herein on a Ni-catalyzed *Suzuki-Miyaura* cross-coupling that involves the activation of a C–O bond, in which an amidate anion functions as a directing group. The present protocol using an amidate directing group is a promising strategy for activating various strong bonds, such as C–O, C–F, C–CN, and C–S bonds.^[9–12] Studies directed to the use of this methodology are currently underway and will be reported in due course.

Experimental Section

General Procedures

To an oven-dried 5 mL screw-capped vial in a glove box, Ni(cod)₂ (14.0 mg, 0.05 mmol), Me₄Phen (6.0 mg, 0.025 mmol), and DMF (0.5 mL) were added in this order and the mixture was stirred at room temperature for 2 min. LiO^tBu (40.0 mg, 0.5 mmol), CsF (77.1 mg, 0.5 mmol), 2-(4-methoxyphenoxy)-N-phenyl-5-(trifluoromethyl)benzamide (195.1 mg, 0.5 mmol), 4-(5,5dimethyl-1,3,2-dioxaborinan-2-yl)methylbenzene (2a, 306.7 mg, 1.5 mmol), and DMF (0.5 mL) were then added in sequential order. The mixture was stirred at 100 °C for 20 h and then cooled to room temperature. The resulting mixture was washed with 5 MNaOH aq. (20 mL) and then 1 м HCl aq. (20 mL), and extracted with AcOEt. The combined organic layers were filtered through an alumina column and the filtrate concentrated in vacuo. The product was purified by MPLC (Medium-pressure Liquid Chromatography: eluent: 9% AcOEt in hexane) to afford the product 3e (140.4 mg, 79%) as a white powder.

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Author Contribution Statement

N. C. conceived this work. *Y. I.* and *N. C.* designed the experiments and analyzed the data. *A. M., Y. I.,* and *N. C.* discussed the results and *N. C.* wrote the manuscript. *A. M.* performed the experiments described in this manuscript.

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