

Carbon—Carbon Formation via Ni-Catalyzed Suzuki—Miyaura Coupling through C—CN Bond Cleavage of Aryl Nitrile

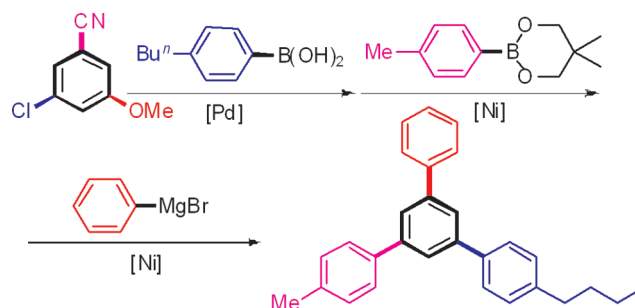
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ABSTRACT



The Suzuki—Miyaura coupling of aryl nitriles with aryl/alkenyl boronic esters is reported. With this method, the cyano group could be applied as a protecting group of arenes and finally as a leaving group to further construct polyaryl scaffolds.

Carbon—carbon bond formation is a main task of synthetic chemists. Generally, the construction of a C—C bond is initiated from C—X (X = halides, OR, etc.) of functionalized molecules through group transfer. For example, cross couplings have been well developed starting from aryl halide and its equivalents, with different organometallic reagents.¹ Recent studies also advanced this field by “inert” C—O and

C—H activations.² Recently, C—C cleavage drew much attention due to its high challenging features.³ It not only provides an efficient pathway to reorganize the organic scaffolds through the cleavage and reunion of organic species but also offers the method to understand the intrinsic reactivity of a C—C bond, which was generally considered

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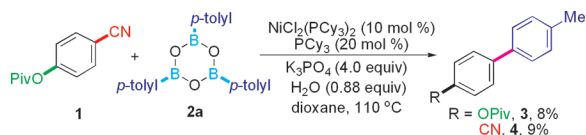
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as an inert reaction partner. In this field, the structural specific substrates are the first choices, and many relative transformations have been developed through the skeleton reorganization.⁴ Many efforts have also been made to the cleavage and transformation of nitriles due to their availability and stability.⁵

Previous studies also indicated that the CN group could be applied as a leaving group in cross couplings with more active Grignard reagents and organo zinc reagents via Ni catalysis.⁶ During those transformations, active organometallic reagents first played the critical role to reduce the Ni(II) to Ni(0) to initiate the catalytic cycle as a reducing reagent other than a coupling partner. However, cross coupling of aryl nitriles with relatively unreactive organo species, such as organoboronic species, has never been reported. Not only does it arise from the difficulty of transmetalation between the unreactive organometallic species and organonickel intermediates but also the poor reductivity of unreactive species may not reduce Ni(II) species to initiate the oxidative addition.⁷

To our interest, when we studied Ni-catalyzed C–O cleavage of aryl carboxylate to cross couple with boroxine **2a**,⁸ in the presence of a cyano group on substrate **1**, two different coupling products were isolated in comparable yields (Scheme 1). It implied that the same condition not

Scheme 1



only activated the aryl C–O bond but also induced the cross coupling between aryl nitriles and phenylboroxine. This observation also showed the potential ability of aryl boroxine to reduce Ni(II) to Ni(0) to initiate the oxidative addition of

C–CN for the further cross coupling. We set out to further explore the reactivity of aryl nitriles in the presence of different aryl boronic species to facilitate the construction of the C–C bond.

2-Naphthyl nitrile **1a** was first chosen as a studying objective. After the screening, we found that the best base for this transformation was *t*-BuOK, in the presence of CuF₂ as an additive. On the other hand, aryl boronic ester **2b** seems to be the best partner for this cross coupling (Table 1). It is

Table 1. Cross Coupling between **1a** with Phenyl Boronic Acid Derivatives^a

entry	2	yield (%) ^b
1 ^c		54
2 ^d		68
3		43
4		46
5		<5

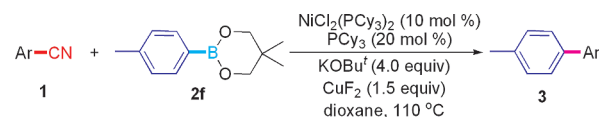
^a All the reactions were carried out in 0.2 mmol scale of **1a** with 4.0 equiv of **2**. ^b GC yields with *n*-dodecane as an internal standard. ^c 1.3 equiv of **2a** was used. ^d Isolated yield.

pointed out that only Ni catalyst is sufficient for this transformation, and Pd, Fe, and the other transition metal species were tested but failed. The efficiency was further promoted by the addition of excess PCy₃ (please refer to Table S1, Supporting Information).

Different aryl nitriles were further surveyed (Table 2). Other than the naked naphthyl group, both the electron-donating group and the electron-deficient group on the naphthyl skeleton did not obviously affect the efficiency. The good reactivity of the phenyl derivative showed a broad generality of the substrate scope. Similarly, the electron-withdrawing group and electron-donating group survived well. The presence of the MeO, PhO, ester, and amide group offers the great chance to further functionalize the products with developed methods. It is noteworthy that the heterocyclic substrates showed even better reactivity, which expanded the substrate scope much broader.

Further studies also showed the wide range of boronic ester derivatives for this transformation (Table 3). Electron-donating groups facilitated this transformation well, and desired cross coupling products were isolated in good yields (entries 1–4 and 6–7). It is important to note that the steric

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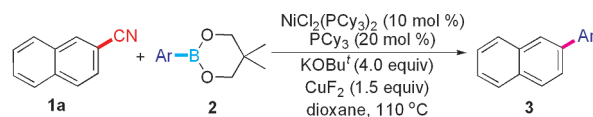
Table 2. Cross Coupling between 4-Tolylboronic Ester **2f** with Different Aryl Nitriles^a

entry	Ar (1)	3	yield (%) ^b
1		1a 3af	68
2 ^c		R = Me, 1b 3bf	60
3 ^c		R = Ph, 1c 3cf	58
4		1d 3df	65
5		1e 3ef	55
6		1f 3ff	55
7 ^d		1g 3gf	63
8 ^e		1h 3hf	57
9		1i 3if	82
10		1j 3jf	70

^a Reaction conditions: 0.4 mmol of aryl nitrile **1**, 1.6 mmol of **2f**, 0.04 mmol of NiCl₂(PCy₃)₂, 0.08 mmol of PCy₃, 1.6 mmol of KOBu⁺, and 0.6 mmol of CuF₂ in 2 mL of dioxane at 110 °C for 20 h. ^b Average isolated yields of two runs. ^c These reactions were carried out for 30 h. ^d Bu ester was obtained by ester exchange. ^e This reaction was carried out at 120 °C.

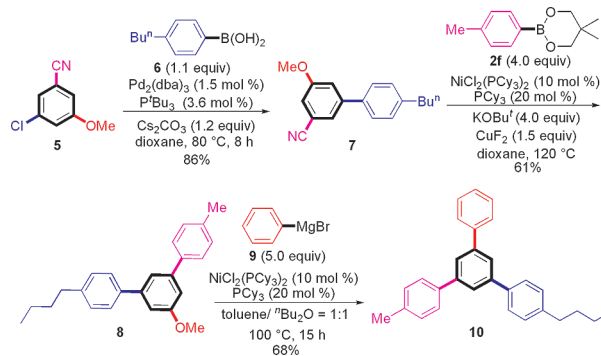
hindrance played a very important role, and the *o*-methoxyl substituent induced much lower efficiency (entry 5). In contrast, the electron-withdrawing groups slightly decreased the yields with 2,2'-binaphthyl as a byproduct, which may arise from the lower rate at the transmetalation stage (entry 8). Importantly, alkenylboronic ester showed good reactivity (entry 10). Moreover, the heterocyclic boronic esters showed the even better reactivity (entries 11 and 12).

Due to the relatively “inert” property of C–CN, it might be applied as a good “protecting” group in many transformations. To explore the potential application, the sequential cross coupling was designed to construct polyarenes (Scheme 2). Initiated from the general Suzuki–Miyaura coupling, the first substituted phenyl group was introduced on the central benzene by cleavage of C–Cl.⁹ With our method, the second phenyl group was equipped through C–CN activation with

Table 3. Cross Coupling between **1a** with Different Boronic Esters^a

entry	Ar (2)	3	yield (%) ^b
1		2f 3af	68
2		2g 3ag	60
3		2h 3ah	51
4		2i 3ai	64
5		2j 3aj	31
6		2k 3ak	67
7		2l 3al	62
8		2m 3am	45
9		2n 3an	59
10		2o 3ao	59
11		2p 3ap	82
12		2q 3aq	74

^a Reaction conditions: 0.4 mmol of 2-naphthyl nitrile **1a**, 1.6 mmol of **2**, 0.04 mmol of NiCl₂(PCy₃)₂, 0.08 mmol of PCy₃, 1.6 mmol of KOBu⁺, and 0.6 mmol of CuF₂ in 2 mL of dioxane at 110 °C for 20 h. ^b Average isolated yields of two runs.

Scheme 2. Sequential Cross-Coupling to Construct Polysubstituted Benzene

untouching of the C–OMe group. Further, Kumada coupling offered the good efficiency for the last group transforma-

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tion.^{2b} The polyfunctionalized benzene might show the unique optical and electronic property, which is further under investigation.

In summary, we demonstrated Ni-catalyzed Suzuki–Miyaura coupling of aryl nitriles with aryl/alkenyl boronic esters. The studies of the generality of both nitriles and boronic esters showed a broad range of substrate scope. With these studies, CN might be applied as a good protecting group and finally as a leaving group to further construct biaryl and polyarene scaffolds. Further studies to unveil more reactivities of nitriles and application of this method are underway.

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Supporting Information Available: Brief experimental detail and other spectra data for products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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