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Nickel-Catalyzed Denitrogenative Cross-Coupling Reaction of 1,2,3-Benzotriazin-4(3*H*)-ones with Organoboronic Acids: An Easy Access to *Ortho*-Arylated and Alkenylated Benzamides

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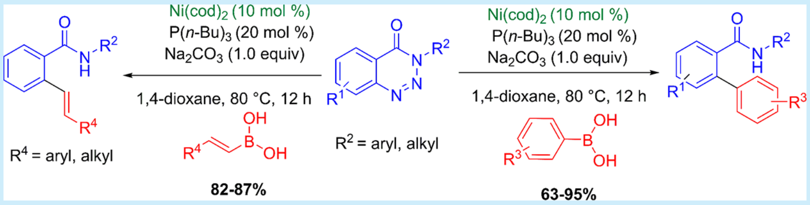
Supporting Information



ABSTRACT: A novel nickel-catalyzed approach to synthesize *ortho*-arylated and alkenylated benzamides in good to high yields via a denitrogenative cross-coupling reaction of 1,2,3-benzotriazin-4(3*H*)-ones with organoboronic acids is described. The reaction proceeds through a five-membered azanickelacyclic intermediate with the extrusion of a nitrogen molecule. Moreover, the resulting *ortho*-arylated benzamides were successfully converted into synthetically useful substituted fluorenones and *ortho*-arylated benzylamine derivatives in high yields.

Biaryls are important motifs that are present in various agrochemicals, dyes, organic materials, and pharmaceutically relevant compounds.[1] Consequently, significant attention has been paid toward the synthesis of these scaffolds for more than a century.[2] One of the classical methods to create such motifs is transition-metal-catalyzed coupling reaction of aryl halides (or pseudo halides) with organometallic reagents.[3] These reactions, however, need preactivation of both aryl rings, which is intrinsically uneconomical since it demands the installation and later disposal of the stoichiometric activating agent.[2c] On the other hand, transition-metal-catalyzed directing group assisted C−H bond activation of substituted aromatics with organometallics or aryl halides (pseudo halides) provides an excellent alternate way to prepare biaryl molecules in a step- and atom-economical fashion.[4,5] Mechanistically, these reactions proceed via a key metallacycle intermediate[4] and, notably, require less functionalization of coupling partners. Apparently, this strategy is not only advantageous in minimizing the reaction steps but also reduces byproduct (waste) formation. However, to perform this transformation, a stoichiometric amount of (metal) oxidant and, in most cases, the higher reaction temperature is always necessary. Despite these significant advances, there is always a demand for development of a new methodology toward the synthesis of biaryl molecules under mild reaction conditions with minimum waste generation.

In recent years, 1,2,3-triazoles such as pyridotriazoles, *N*-sulfonyl-1,2,3-triazoles, 1,2,3-benzotriazinones, and *N*-aroylbenzotriozoles have been recognized as useful substrates to synthesize various azaheterocycles via metal-catalyzed denitrogenative transannulation reactions.[6] In this context, Murakami et al. demonstrated a series of nickel-catalyzed transannulation reaction of 1,2,3-benzotriazinones with various π-components such as alkyne, alkene, allene, benzyne, and isocyanides to prepare isoquinolones and isoindolinones.[7a−f] Recently, Liu et al. also demonstrated the asymmetric denitrogenative transannulation reaction of 1,2,3-benzotriazinones by synthesizing axially chiral isoquinolones in high yields with high enantioselectivity.[7g] Interestingly, these reactions proceed through a five-membered aza-nickelacycle intermediate **I**[7] (Figure 1) which is in sharp contrast to rhodium- and palladium-catalyzed reactions of other 1,2,3-triazoles such as pyridotriazoles, *N*-sulfonyl-1,2,3-triazoles, and *N*-aroylbenzotriazoles that proceed via a metallocarbene intermediate.[6]

Inspired by the literature reports on metallacycle-triggered cross-coupling reactions by a nickel catalyst,[8] we set out to perform a cross-coupling reaction of 1,2,3-benzotriazin-4(3*H*)-ones by trapping the aza-nickelacycle with organometallics to prepare biaryl scaffolds. It is important to mention that cross-coupling reactions of 1,2,3-triazoles with organometallics are scarcely studied.[9] In fact, cross-coupling reactions with 1,2,3-benzotriazinones are yet to be developed. In 2012, Fokin and co-workers displayed a stereoselective arylation of *N*-sulfonyl-1,2,3-triazoles with organoboronic acids using rhodium complex as the catalyst to synthesize 2,2-diaryl enamines at ambient temperatures.[9a] Very recently, Tang et al. reported a palladium-catalyzed denitrogenative Suzuki and carbonylative

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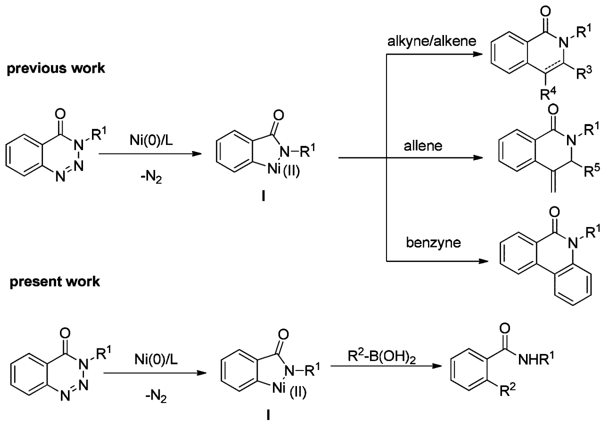
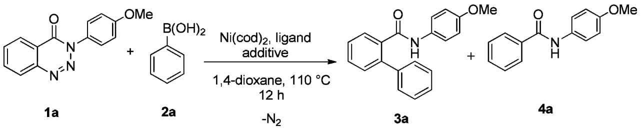


Figure 1. Nickel-catalyzed denitrogenative reactions of 1,2,3-benzotriazinones.

Suzuki coupling reactions of benzotriazoles with organoboronic acids to prepare structurally diverse *o*-amino-substituted biaryl and biaryl ketone derivatives.[9b] Herein, we report a nickel-catalyzed denitrogenative cross-coupling reaction between 1,2,3-benzotriazin-4(3*H*)-ones and organoboronic acids to prepare *ortho*-arylated benzamides.[10]

1,2,3-Benzotriazin-4(3*H*)-ones **1** are readily prepared from commercially available methyl anthranilates and their corresponding anilines via diazotization and cyclization reactions.[7] After preparing the starting materials, we began our investigation by treating **1a** with phenylboronic acid (**2a**) in the presence of 10 mol % of Ni(cod)$_2$ as the catalyst with 1,4-dioxane as solvent at 110 °C. After 12 h, the reaction afforded the desired product **3a** in 20% yield along with *N*-(4-methoxyphenyl)benzamide (**4a**) as the byproduct in 10% yield. To suppress the formation of byproduct and to improve the reaction efficacy, we investigated the reaction with various ligands and additives under similar reaction conditions. After extensive screening, we found that the catalytic system comprising of 10 mol % of Ni(cod)$_2$ as the catalyst, 20 mol % of P(*n*-Bu)$_3$ as the ligand, and Na$_2$CO$_3$ (1.0 equiv) as an additive was the most effective, affording the desired product **3a** in 96% GC yield. It is also noteworthy to mention that **3a** was obtained in 88% yield when water was employed as an additive. The choice of solvent is also crucial in obtaining the desired product in high yield (see the Supporting Information). Among the solvents that we tested, 1,4-dioxane, and THF were the best, producing **3a** in 95 and 91% yields, respectively. Other solvents including 1,2-dichloroethane (DCE), toluene, and acetonitrile were less useful, giving **3a** in 43–54% yields. Delightfully, a decrease in the reaction temperature from 110 to 80 °C afforded **3a** in 92% isolated yield (Table 1, entry 14). However, further lowering the temperature led to moderate yield due to poor conversion of **1a**.

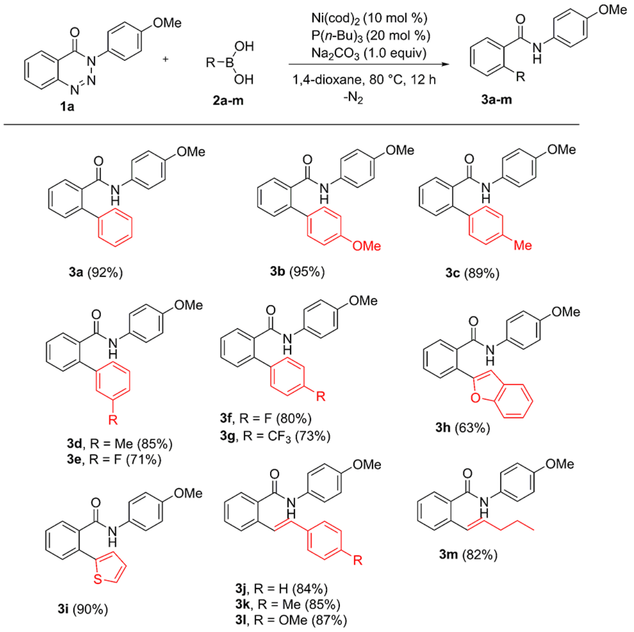
Table 1. Optimization of Reaction Conditions[a]



entry	ligand	additive	yield[b] (%) 3a	yield[b] (%) 4a
1			20	10
2	P(*n*-Bu)$_3$		81	19
3	P(*n*-Bu)$_3$	H$_2$O	88	3
4	PPh$_3$	H$_2$O	81	8
5	TFP[f]	H$_2$O	62	0
6	dppe	H$_2$O	64	26
7	dppp	H$_2$O	75	25
8	2,2′-bipyridine	H$_2$O	4	4
9	P(*n*-Bu)$_3$	NaOAc	74	26
10	P(*n*-Bu)$_3$	KOH	89	10
11	P(*n*-Bu)$_3$	Na$_2$CO$_3$	96	4
12	P(*n*-Bu)$_3$	K$_2$CO$_3$	92	4
13	P(*n*-Bu)$_3$	NaHCO$_3$	95	5
14[d]	P(*n*-Bu)$_3$	Na$_2$CO$_3$	95 (92)[c]	5
15[e]	P(*n*-Bu)$_3$	Na$_2$CO$_3$	80	4

[a] All of the reactions were carried out using **1a** (0.40 mmol), **2a** (0.60 mmol), Ni(cod)$_2$ (0.04 mmol), P(*n*-Bu)$_3$ (0.08 mmol), additive (0.40 mmol), and solvent (dry) at mentioned temperature and 12 h under N$_2$. [b] GC yields. [c] Isolated yield. [d] Reaction was carried out at 80 °C. [e] Reaction was carried out at 50 °C. [f] TFP = tri(2-furyl)phosphine.

Scheme 1. Scope of Organoboronic Acids[a,b]

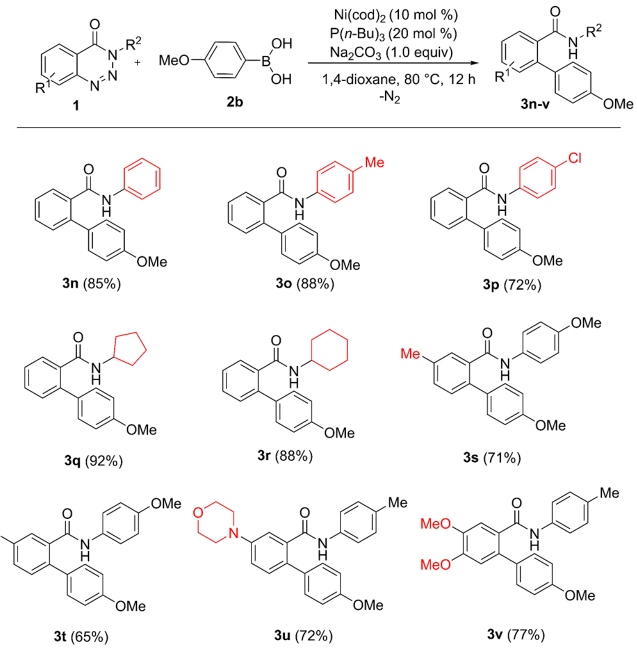


[a] All the reactions were carried out using 1,2,3-benzotriazin-4(3*H*)-one **1a** (0.40 mmol), organoboronic acid **2** (0.60 mmol), Ni(cod)$_2$ (0.04 mmol), P(*n*-Bu)$_3$ (0.08 mmol), and Na$_2$CO$_3$ (0.40 mmol) for 12 h. [b] Isolated yields.

With the optimized reaction conditions in hand, we have investigated the scope of the denitrogenative cross-coupling reaction of **1a** with various organoboronic acids (Scheme 1). From Table 1, it is clear that aryl boronic acids bearing electron-rich substituents on the phenyl ring afforded the cross-coupling products **3** in higher yield than electron-deficient aryl boronic acids. Thus, the reaction of *p*-methoxy- (**2b**) and *p*-tolylboronic acids (**2c**) with **1a** gave the products **3b** and **3c** in high yields. Similarly, 3-methyl-substituted boronic acid **2d** furnished the respective products in good yield. However, when the reaction was carried out with 3-fluoro- (**2e**), 4-fluoro- (**2f**), and 4-trifluoromethyl-substituted (**2g**) arylboronic acids, the desired products were obtained in 71, 80, and 73% yields, respectively. Correspondingly, benzofuran-2-ylboronic acid (**2h**) and thiophene-2-ylboronic acid (**2i**) afforded **3h** and **3i** in 63 and 90% yields, respectively. Delightfully, alkenyl boronic acids, **2j−m**, also successfully participated in the reaction providing the corresponding coupling products **3j−m** in high yields.

After successfully establishing the scope of the reaction with organoboronic acid, we next investigated the denitrogenative cross-coupling reaction with various 1,2,3-benzotriazin-4(3*H*)-ones **1b−j** (Scheme 2). First, the effect of substituent on the nitrogen atom was examined. Both *N*-aryl- and *N*-alkyl-substituted 1,2,3-benzotriazin-4(3*H*)-ones **1b−f** participated well in the reaction, affording the respective *ortho*-arylated benzamide derivatives in 85−92% yield. However, an *N*-aryl ring bearing chloro substituent (**1d**) gave **3p** in 72% yield. Similarly, 1,2,3-benzotriazin-4(3*H*)-ones **1g−j** with different substituents on the benzene ring also provided the corresponding products **3s−v** in 71%, 65%, 72%, and 77% yields, respectively. It is important to mention that in all the denitrogenative cross-coupling reactions 5−10% yields of the corresponding amide **4** was observed.

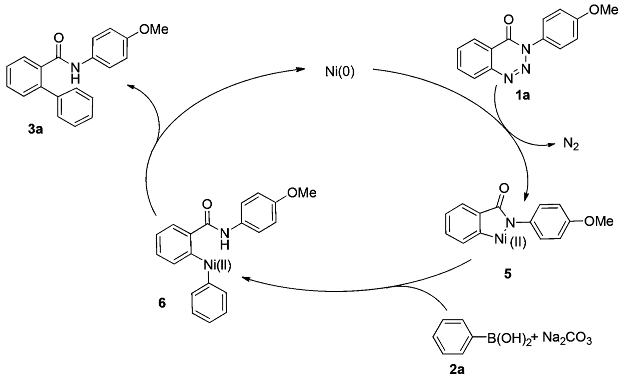
Scheme 2. Scope of 1,2,3-Benzotriazin-4(3*H*)-ones[a,b]



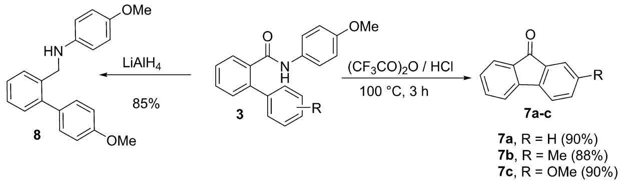
[a] All of the reactions were carried out using **1a** (0.40 mmol), organoboronic acid **2** (0.60 mmol), $Ni(cod)_2$ (0.04 mmol), $P(n\text{-}Bu)_3$ (0.08 mmol), and Na_2CO_3 (0.40 mmol) for 12 h. [b] Isolated yields.

A possible catalytic reaction mechanism is proposed based on the reported nickel-catalyzed denitrogenative reaction of 1,2,3-benzotriazin-4(3*H*)-ones[7] in Scheme 3. Oxidative addition of nickel(0) to 1,2,3-benzotriazin-4(3*H*)-ones affords five-membered aza-nickelacyclic intermediate **5**.[7d] Transmetalation of **5** with boronic acid **2** gives intermediate **6**. Subsequent reductive elimination affords **3a** and regenerates the Ni(0) for the further catalytic cycle. In the present catalytic reaction, it is believed that sodium carbonate facilitates the transmetalation step by cleaving the boronic acid moiety.

Scheme 3. Proposed Mechanistic Pathway



Scheme 4. Synthesis of Fluorenones and *Ortho*-Arylated Benzylamine



The synthetic utility of the present catalytic reaction is shown in Scheme 4. Substituted fluorenones **7** are important scaffolds in natural products and bioactive molecules. Such molecules were readily synthesized in good yields by treating **3** in the presence of trifluoroacetic anhydride and hydrochloric acid at 100 °C for 3 h.[10c] A reduction reaction of **3** was also performed in the presence of lithium aluminum hydride to obtain **8** in 85% yield.[11]

In conclusion, we have successfully described the first denitrogenative cross-coupling reaction of 1,2,3-benzotriazin-4(3*H*)-ones with organoboronic acids using a nickel complex as the catalyst. The present catalytic reaction provides a mild and convenient method for the preparation of synthetically useful *ortho*-arylated and alkenylated benzamides in good to high yields. The reaction is compatible with both aryl and alkenyl boronic acid and proceeds through a five-membered azanickelacyclic intermediate with the extrusion of a nitrogen molecule. The synthetic utility of the current methodology was also demonstrated by synthesizing substituted fluorenones and *ortho*-arylated benzylamine derivatives in high yields. Currently, cross-coupling reactions with different coupling partners are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01401.

Experimental procedures and characterization of all products (PDF)

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Notes

The authors declare no competing financial interest.

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