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Synthesis of *ortho*-arylated and alkenylated benzamides by palladium-catalyzed denitrogenative cross-coupling reactions of 1,2,3-benzotriazin-4(3*H*)-ones with organoboronic acids†

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An efficient palladium-catalyzed denitrogenative Suzuki–Miyaura type cross-coupling of 1,2,3-benzotriazin-4(3*H*)-ones with organoboronic acid is described. The reaction is compatible with various aryl and alkenyl boronic acids affording *ortho*-arylated and alkenylated benzamides in good to high yields. Heteroaromatic boronic acids were also successfully employed. Along with this, a coupling reaction was established by using phenyl boronate ester as the coupling partner. The reaction is believed to proceed *via* a five-membered aza-palladacyclic intermediate. DFT calculations were studied comparing the reactivity of palladium and nickel complexes in the five-membered aza-metallacycle formation from 1,2,3-benzotriazin-4(3*H*)-ones. The application of the reaction was successfully demonstrated by converting *ortho*-alkenylated products to *ortho*-alkylated products in high yields *via* a reduction reaction.

Introduction

A transition-metal catalyzed cross-coupling reaction remains one of the robust protocols to construct carbon–carbon and carbon-hetero bonds in organic synthesis.[1] In particular, palladium-catalyzed cross-coupling reactions have played a vital role in the preparation of molecules having potential applications in the areas of pharmaceuticals, agriculture, agrochemicals, and so on.[2] A variety of palladium-catalyzed reactions, including Heck coupling, cross-coupling (Kumada, Stille, Negishi, Suzuki–Miyaura, Hiyama), Tsuji–Trost allylation, and Buchwald–Hartwig amination reactions have been well established.[3,4] Of these cross-coupling reactions, the Suzuki–Miyaura reaction between aryl boronic acids and aryl halides is, arguably, one of the most efficient transformations for the synthesis of biaryl molecules in organic synthesis.[5] This methodology has numerous advantages, including mild reaction conditions, good functional group compatibility, low toxicity of the organoboron compounds, and commercial availability of many aryl boronic acids.[6] The significance of this cross-coupling reaction was also successfully demonstrated by employing carbon–oxygen[7–9] and carbon–nitrogen[10] compounds as the electrophilic counterparts. Despite being effective, formation of a stoichiometric amount of (pseudo) halides as waste during the reaction is inevitable.[11] Therefore, the development of newer, more efficient methodologies for the synthesis of biaryls with minimum waste generation is still in high demand.

Significant efforts have been devoted towards the synthesis of biaryls in a step and atom economical fashion. Representative examples include transition-metal catalyzed C–H bond functionalization reactions,[12] and metal-catalysed decarboxylative,[13] decarbonylative,[14] and denitrogenative[10] cross-coupling reactions. In this context, the transition metal-catalyzed denitrogenative arylation reaction of 1,2,3-triazoles has emerged as an attractive strategy for the synthesis of biaryls.[15] Mechanistically, the reaction proceeds *via* a metallocarbene or five-membered metallacycle intermediate with the extrusion of an environmentally friendly molecular nitrogen as a by-product.[15] Even though a variety of metal-catalyzed denitrogenative transannulations of 1,2,3-triazoles has been well established,[16] only a few reports are available in the literature employing them as the electrophilic counterpart for the biaryl synthesis (Fig. 1). In 2017, Tang *et al.* reported a palladium-catalyzed denitrogenative Suzuki and carbonylative Suzuki coupling reaction of benzotriazoles with organoboronic acids to prepare structurally diverse *ortho*-amino-substituted biaryl and biaryl ketone derivatives.[15a] Recently, our group[15b] and Cheng *et al.*[15c] independently reported

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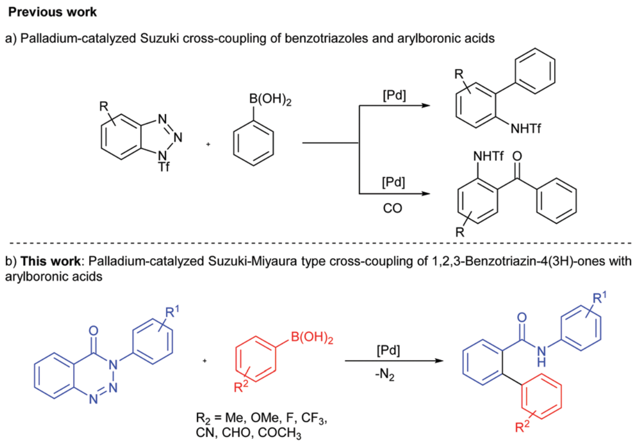
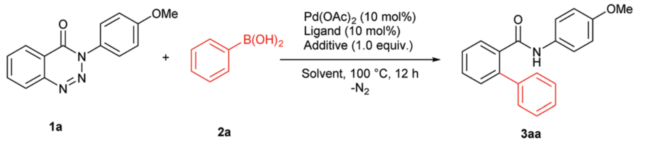


Fig. 1 Palladium-catalyzed denitrogenative arylation reactions of 1,2,3-triazoles.

Table 1 Optimization studies[a]



Entry	Ligand	Solvent	Additive	Yield[b] (%)
1	Xantphos	DMF	Na_2CO_3	95 (93)[c]
2[d]	PPh_3[g]	DMF	Na_2CO_3	35
3	dppm[g]	DMF	Na_2CO_3	20
4	dppe[g]	DMF	Na_2CO_3	21
5	dppp[g]	DMF	Na_2CO_3	15
6	TFP[g]	DMF	Na_2CO_3	17
7	Xantphos	DMF	Na_2CO_3	51[e]
8	Xantphos	Toluene	Na_2CO_3	41
9	Xantphos	THF	Na_2CO_3	11
10	Xantphos	DMF	K_2CO_3	83
11	Xantphos	DMF	NaOAc	53
12	Xantphos	DMF	—	41
13[f]	Xantphos	DMF	Na_2CO_3	—
14	—	DMF	Na_2CO_3	—
15[h]	Xantphos	DMF	Na_2CO_3	90

[a] Unless otherwise mentioned, all reactions were carried out using **1a** (0.10 mmol), **2a** (0.15 mmol), $Pd(OAc)_2$ (10 mol%), ligand (10 mol%), Na_2CO_3 (0.10 mmol), solvent (2.0 mL), 100 °C, 12 h under argon atmosphere. [b] GC yields. [c] Isolated yield. [d] 20 mol% of ligand has used. [e] Reaction was carried out at 50 °C. [f] Reaction was carried out without palladium acetate. [g] dppm = bis(diphenylphosphino)methane; dppe = bis(diphenylphosphino)ethane; dppp = bis(diphenylphosphino)propane, TFP = Tri(2-furyl)phosphine. [h] The reaction was carried out with 3.0 equivalent of water.

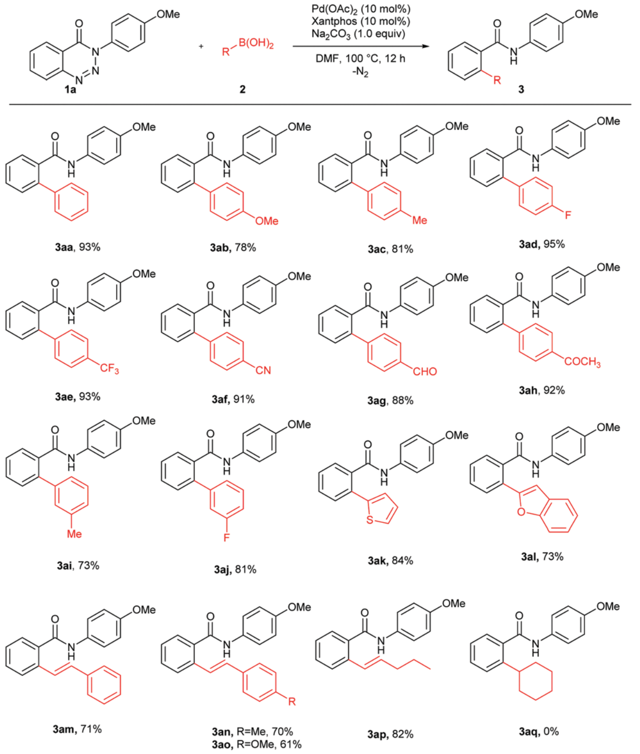
a nickel-catalyzed denitrogenative cross-coupling reaction between 1,2,3-benzotriazin-4(3*H*)-ones and organoboronic acids to prepare *ortho*-arylated and alkenylated benzamides.

We have been interested in the metal-catalyzed denitrogenative cross-coupling reaction of 1,2,3-triazoles, particularly involving 1,2,3-benzotriazinones as the electrophilic counterpart. In this context, we have recently described a denitrogenative alkylidenation and *ortho*-alkynylation of 1,2,3-benzotriazinones by using a palladium/copper catalyst.[17] Literature reports reveal that the generation of the aza-palladacycle intermediate from 1,2,3-benzotriazinones using a palladium catalyst is relatively unknown compared to nickel-catalyzed denitrogenative transannulation and coupling reactions.[17,18] Considering the versatility of a palladium catalyst in Suzuki–Miyaura reactions and the importance of 1,2,3-benzotriazinones as the electrophilic counterpart, we are delighted to perform a denitrogenative cross-coupling reaction of 1,2,3-benzotriazin-4(3*H*)-ones and organoboronic acids to prepare biaryl motifs. Herein, we disclose the first palladium-catalyzed direct Suzuki–Miyaura type cross-coupling of 1,2,3-benzotriazinones with aryl boronic acids for the synthesis of valuable biaryl motifs. It is well known that biaryls and heterobiaryls are essential motifs present in pharmaceuticals, natural products, and organic materials.[19]

Results and discussion

Treatment of 1,2,3-benzotriazin-4(3*H*)-ones (**1a**) and phenylboronic acid (**2a**) with 10 mol% of $Pd(OAc)_2$, 10 mol% of xantphos, and 1.0 equiv. of sodium carbonate in DMF at 100 °C for 12 hours afforded the desired *ortho*-arylated product **3aa** in 93% isolated yield (Table 1, entry 1). Control experiments revealed that no desired product was formed in the absence of either palladium or xantphos (entries 13 and 14). Switching the ligand from xantphos to other phosphine ligands, such as PPh_3, tri(2-furyl)phosphine (TFP), dppe, and dppp, led to **3aa** only in low yield (entries 2–6). Moreover, the reaction yield decreased significantly when other additives, such as potassium carbonate (entry 10) and sodium acetate (entry 11), were used, or the reaction was performed at a lower temperature (entry 7). The solvent used played a vital role in obtaining **3aa** in high yield. Among the solvents that we screened, DMF appeared to be the best, affording the desired product in 93% yield, whereas other solvents, such as toluene and THF, provided **3aa** in 41% and 11% yields respectively (entries 8 and 9). Other palladium precursors, including $PdCl_2(PPh_3)_2$ and $Pd(TFA)_2$, were also effective, furnishing the desired product in 81% and 90% yields, respectively (see the ESI†). The effect of water on the present reaction conditions was examined (see the ESI†) and we found that the reaction can tolerate 2 equivalents of water without a significant drop in the product yield. However, the presence of an excess amount of water (>2.0 equiv.) during the reaction led to the formation of *N*-(4-methoxyphenyl)benzamide as the by-product and decreased the desired product yield (entry 15).

Having the optimized reaction conditions in hand, we studied the scope of the *ortho*-arylation reaction with different organoboronic acids (Scheme 1). The reaction of **1a** with electron-rich boronic acids **2b** and **2c** gave the arylated products **3ab** and **3ac** in 78% and 81% yields, respectively. Similarly, aryl boronic acids (**2d–h**) possessing electron-withdrawing groups like –F, $-CF_3$, –CN, –CHO, and $-COCH_3$ in the para position of the phenyl ring furnished the corresponding products **3ad–3ah** in slightly higher 88% to 95% yields. These results are in contrast with our earlier reported nickel catalyst system, where the electron-donating group substituted aryl boronic acids afforded better yields than electron-withdrawing ones.[15b] The coupling of 3-substituted-phenylboronic acids, **2i** and **2j**, with

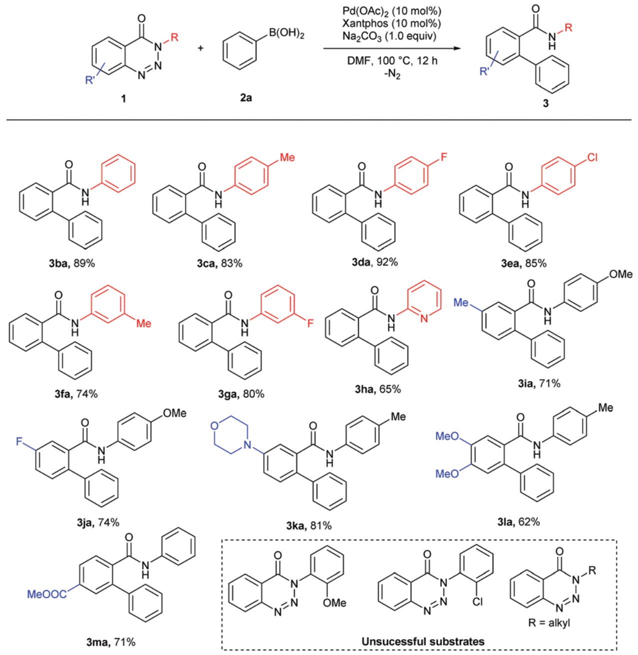


Scheme 1 Scope of organoboronic acids. Reaction conditions: **1a** (0.40 mmol), **2** (0.60 mmol), Pd(OAc)$_2$ (10 mol%), Xantphos (10 mol%), Na$_2$CO$_3$ (1.0 equiv.) in dry DMF (2.0 mL), 100 °C, 12 h. Isolated yields.

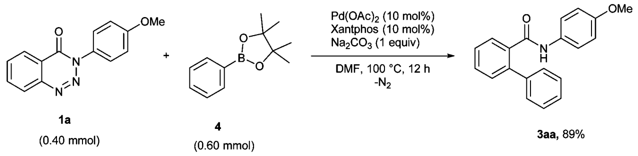
1a furnished products **3ai** and **3aj** in 73% and 81% yields respectively. Pleasingly, heteroaryl boronic acids, such as thiophene boronic acid (**2k**) and benzofuranboronic acid (**2l**), successfully participated in the reaction and afforded the products **3ak** and **3al** in 84% and 73% respectively. To our delight, alkenyl boronic acids, such as styryl boronic acid (**2m**) and its derivatives **2n** and **2o**, afforded the *ortho*-alkenylated products **3am–3ao** in 61% to 71% yields. Satisfyingly, *n*-pentenyl boronic acid (**2p**) also provided **3ap** in 82% yield. It is noteworthy to mention that alkyl boronic acid failed to participate in the reaction.

The scope of 1,2,3-benzotriazin-4(3*H*)-ones with **2a** is shown in Scheme 2. In general, 1,2,3-benzotriazin-4(3*H*)-ones having *N*-aryl substituents participated successfully and gave the *ortho*-arylated products **3ba–3ha** in good to high yields (65% to 92%). On the other hand, reactions involving 1,2,3-benzotriazin-4(3*H*)-ones bearing *N*-alkyl substituents were unsuccessful. The present catalytic reaction exhibited good tolerance of the functional groups–like methyl, fluoro, methoxy, morpholine, and ester–on the backbone aromatic ring of 1,2,3-benzotriazin-3(*H*)-one and furnished the expected products **3ia–3ma** in 62% to 81% yields. To our delight, phenyl boronate ester **4** successfully participated in this reaction with **1a** and afforded **3aa** in 89% yield (Scheme 3).

To overcome the incompatibility of alkylboronic acid in the present catalytic reaction, a reduction reaction of *ortho*-alkenylated benzamide was performed. Thus, the reaction of **3am** and **3ap** in the hydrogen atmosphere using Pd/C as the catalyst in glacial acetic acid at room temperature gave *ortho*-alkylated benzamides **5a** and **5b** in high yields (Scheme 4). A gram scale reaction of **1a** and **2a** was also demonstrated using 5 mol% of Pd(OAc)$_2$ to prepare *ortho*-arylated benzamide **3aa** in 89% yield.

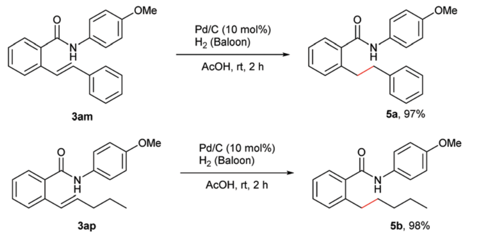


Scheme 2 Scope of 1,2,3-benzotriazinones. Reaction conditions: **1** (0.40 mmol), **2a** (0.60 mmol), Pd(OAc)$_2$ (10 mol%), Xantphos (10 mol%), Na$_2$CO$_3$ (1.0 equiv.) in dry DMF (2.0 mL), 100 °C, 12 h. Isolated yields.

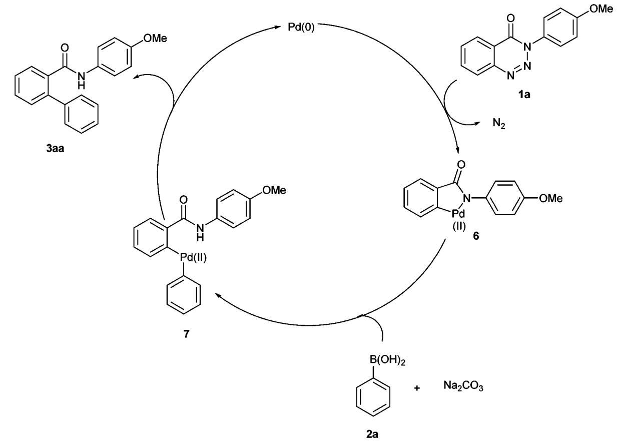


Scheme 3 Arylation reaction of **1a** with phenylboronate ester (**4**).

A plausible mechanism for the present catalytic reaction is shown in Scheme 5, based on the reported metal-catalyzed denitrogenative reaction of 1,2,3-benzotriazin-4(3*H*)-ones. The reaction proceeds *via* oxidative addition of Pd(0) to 1,2,3-benzotriazin-4(3*H*)-ones affording a five-membered azapalladacyclic intermediate and followed by transmetallation



Scheme 4 Synthesis of *ortho*-alkylated benzamides **5**.



Scheme 5 Proposed mechanism.

of phenylboronic acid with **6** to give **7**. Reductive elimination of **7** affords the desired product **3aa** and regenerates the Pd(0) for the further catalytic cycle.

A literature survey on metal-catalyzed denitrogenative reactions of 1,2,3-benzotriazin-4(3*H*)-ones discloses that nickel complexes are the frequently employed catalyst system.[16] Conversely, only a few reports are available in the literature with palladium as the catalyst. To understand the reactivity of nickel and palladium complexes in the denitrogenative reactions of 1,2,3-benzotriazinones, density functional theory-based calculations were performed on the extrusion of a N_2 molecule and metal insertion reactions using Ni–$(PMe_3)_2$ and Pd–$(PMe_3)_2$ complexes. The energy barriers and free energies of these two reactions are compared and shown in Fig. 2.

As shown in Fig. 2, the first step involves the formation of a seven-membered ring (Ni–Ph2 and Pd–Ph2) intermediate *via* a transition state. In the case of the Ni–$(PMe_3)_2$ based complex, we have observed significantly less activation energy barrier ($\sim$0.2 kcal mol^{-1}), whereas in the case of Pd–$(PMe_3)_2$, the same value increased to 12.55 kcal mol^{-1}. The next step involves the cleavage of a C–N bond and formation of a M–C (M = Ni and Pd) bond *via* the second transition state to give the five-membered complex M–Ph_3 (M = Ni and Pd). The calculated activation energy barriers for Ni and Pd complexes are 16 kcal mol^{-1} and 32 kcal mol^{-1} respectively. These results reveal that the metal insertion reaction to form a five-membered aza-metallacycle intermediate using a palladium complex is indeed possible. Meanwhile, the high energy barriers for transition states Pd-TS1 and Pd-TS2 justify the requirement of a higher reaction temperature for the palladium-catalyzed reaction in the denitrogenative reactions of 1,2,3-benzotriazinones. The overall free energies of Ni-based and Pd-based reactions are more or less the same. The optimized geometries of reactants, transition states, intermediates, and products are shown in the ESI.†

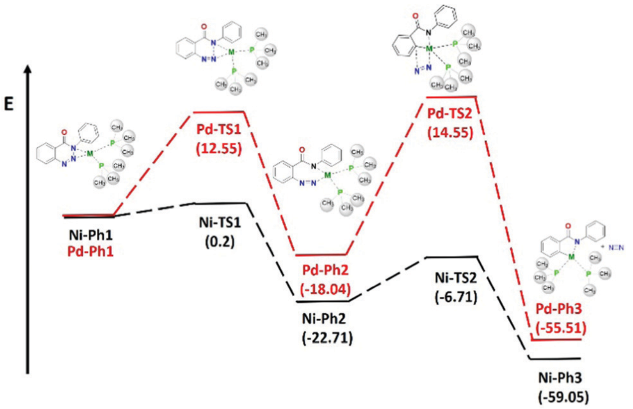


Fig. 2 Calculated free energy profiles of Ni-$(PMe_3)_2$ (shown in black color) and Pd-$(PMe_3)_2$ (shown in red color) catalyzed denitrogenative process as determined using the M06L/6-311G** U SDD basis set. All values are given in kcal mol^{-1}.

Conclusions

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 palladium as the catalyst. The reaction is compatible with various aryl and alkenyl boronic acids affording *ortho*-arylated and alkenylated benzamides in good to high yields. Together with our previous report,[15b] the present catalytic system is successful for the carbonyls and cyanide substituted aryl boronic acids. DFT calculations were performed, for the first time, comparing the reactivity of palladium and nickel complexes in the five-membered aza-metallacycle formation from 1,2,3-benzotriazin-4(3*H*)-ones. A detailed mechanistic study of the arylation reaction is under way in our laboratory. Overall, the present catalytic system could serve as an excellent complement and alternative to the Suzuki–Miyaura cross-coupling reaction to synthesize *ortho*-arylated biaryls.

Conflicts of interest

There are no conflicts to declare.

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