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Synthesis of dihydroisoquinolinone-4-methylboronic esters *via* domino Heck/borylation using a structurally characterized palladacycle as a catalyst †

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Synthesis of dihydroisoquinolinone-4-methylboronic esters from *N*-allylcarboxamides and $B_2(Pin)_2$ *via* domino Heck/borylation approach is reported. A quinoxaline-based NHC-palladacycle $[Pd(C\wedge C)(PPh_3)Cl]$, which has been structurally characterized, is used as a catalyst. The scope of the substrate with a wide range of substituents is explored. In addition to the synthesis of title compounds, a few examples of methylboronic esters of indoline and benzofuran motifs have also been prepared using the same protocol.

Introduction

Compounds containing dihydroisoquinolinone core have been found to be highly biologically active.¹ They have widespread applications as drugs in various therapies including cancer treatment.² Owing to the importance of the dihydroisoquinolinone motif there has been a plethora of synthetic methodologies reported in the literature, which have been reviewed in detail recently.³ Most of these methods do not directly lead to the synthesis of targeted drug, necessitating the building of the remaining parts of the drug. Hence, the synthesis of easily functionalizable dihydroisoquinolinone core is very important.⁴ Recent advances in Pd-catalyzed domino reactions demonstrate an intramolecular carbopalladation followed by the trapping of the alkyl-Pd species by various nucleophiles.⁵ Boronic ester moiety is one of the best tools for constructing C–C, C–N, C–O and C–halogen bonds.⁶ Incorporation of such an indispensable moiety into the isoquinolinone core can make it a valuable building block in the synthesis of drugs and natural products.⁷ Recently, Vachhani and Eycken have demonstrated the synthesis of indolinone-3-methylboronic esters *via* domino Heck/borylation reactions of acryl amide and bis(pinacolato)diborane $B_2(Pin)_2$ (Scheme 1a).⁸ In spite of potential hurdles such as direct Miyaura-type borylation, hydroarylation of the alkene and the cross-coupling products of the targeted boronic ester as detailed in the article, the

authors were quite successful in obtaining the desired indolinone-3-boronic esters.

Motivated by this work we designed a strategy for the synthesis of dihydroisoquinolinone-4-methylboronic esters. Most recently, Qu and Chen have reported the synthesis of indolinone-3-ethylboronic esters from alkene substituted carbamoyl chloride and 1,1-[bis(pinacolato)boryl]methane and successfully transformed the boronic ester moiety into various functional groups without affecting the indolinone core (Scheme 1b).⁹ While preparing the manuscript we have also come across a report on the synthesis of dihydroisoquinolinones using a similar strategy that we used in this work (Scheme 1c).¹⁰ However, the synthesis of dihydroisoquinolinone-4-methylboronic esters, which can be further functionalized easily on sp^3 carbon, is more challenging and important. Herein we report their synthesis using a structurally characterized palladacycle as a catalyst in a domino Heck/borylation approach.

Result and discussion

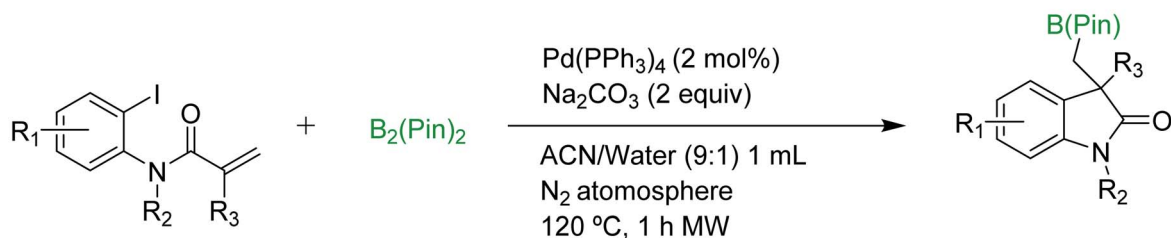
We have recently reported the synthesis of zwitterionic palladium complexes and their catalytic efficiency in Suzuki–Miyaura cross coupling (SMC) reactions.¹¹ In order to explore the mechanistic details of those reactions two quinoxaline based NHC-palladacycles were synthesized. It was found that these palladacycles were less efficient than the precursor imidazolium zwitterionic complexes in catalyzing the SMC reactions.^{11a} However, with a slight modification we were able to successfully utilize them as catalysts for the synthesis of dihydroisoquinolinone-4-methylboronic esters. The palladacycle $[Pd(C\wedge C)(PPh_3)Cl]$ has been prepared as shown in Scheme 2 and characterized thoroughly using NMR and

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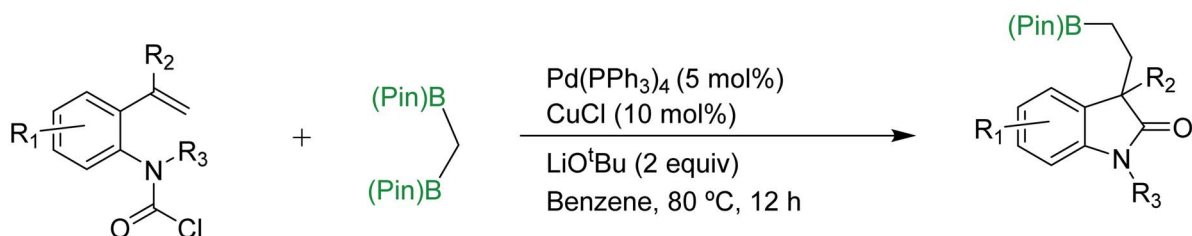
† Electronic supplementary information (ESI) available: Experimental details. Crystal data for $[Pd(C\wedge C)(PPh_3)Cl]$ and **2o** CCDC 2087488 and 2087489, 1H and ^{13}C NMR spectra of all new compounds. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d2ra00389a



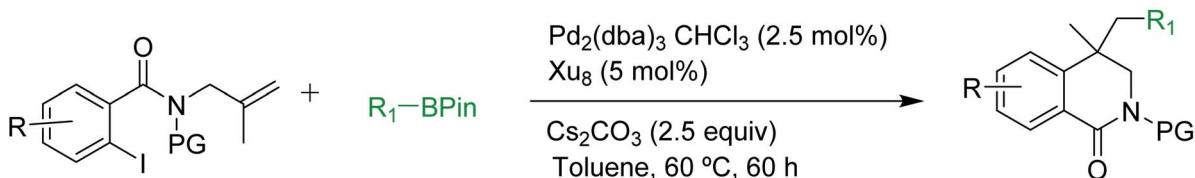
a) Vachhani and Eycken (2015): Pd-catalyzed domino Heck/borylation of acrylamides.⁸



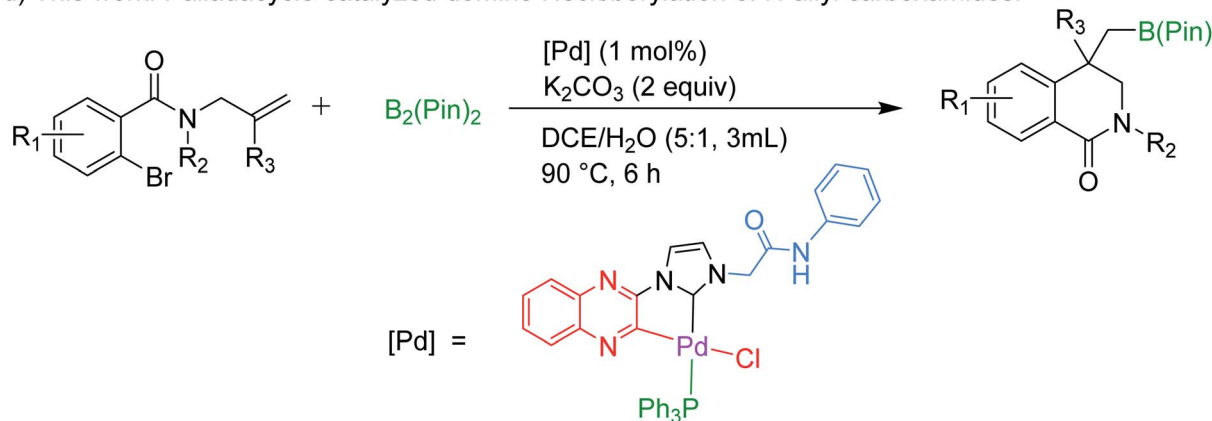
b) Qu and Chen (2020): Pd/Cu-catalyzed domino cyclization/deborylation of alkenes.⁹



c) Zhang (2021): Pd-catalyzed domino cyclization/Suzuki reaction of N-allyl carboxamides.¹⁰



d) This work: Palladacycle-catalyzed domino Heck/borylation of N-allyl carboxamides.



Scheme 1 Pd-catalyzed domino Heck/borylation of alkenes.

single crystal X-ray techniques (Fig. 1) supported by elemental analysis and ESI mass spectral data (see ESI†).

A model reaction was probed between an N-allylcarboxamide **1a** and bis(pinacolato)diboron (B₂(Pin)₂) using [Pd(CAC:)(PPh₃)Cl] as a catalyst, and K₂CO₃ as a base in water at 90 °C under nitrogen. After 6 h the desired borylated product **2a** was obtained in 16% yield. Optimization studies for a suitable solvent revealed that dichloroethane (DCE) was the best among all the solvents probed (Table S1, ESI†). Hence, further optimization reactions such as employing

commercially available Pd reagents as catalysts and screening of various bases, and controlled experiments were conducted in DCE. The results of these reactions, which are listed in Tables 1 and S1 (ESI†), suggest that the best combination is [Pd(CAC:)(PPh₃)Cl] as catalyst and K₂CO₃ as base in DCE as a solvent at 90 °C under nitrogen atmosphere, which gave 91% yield of **2a** (Table 1, entry 3). The yields were further improved when a mixture of DCE and water in 5 : 1 ratio was used instead of neat DCE (94%, entry 4). Among the commercially available Pd complexes only Pd(PPh₃)₂Cl₂ afforded good yield

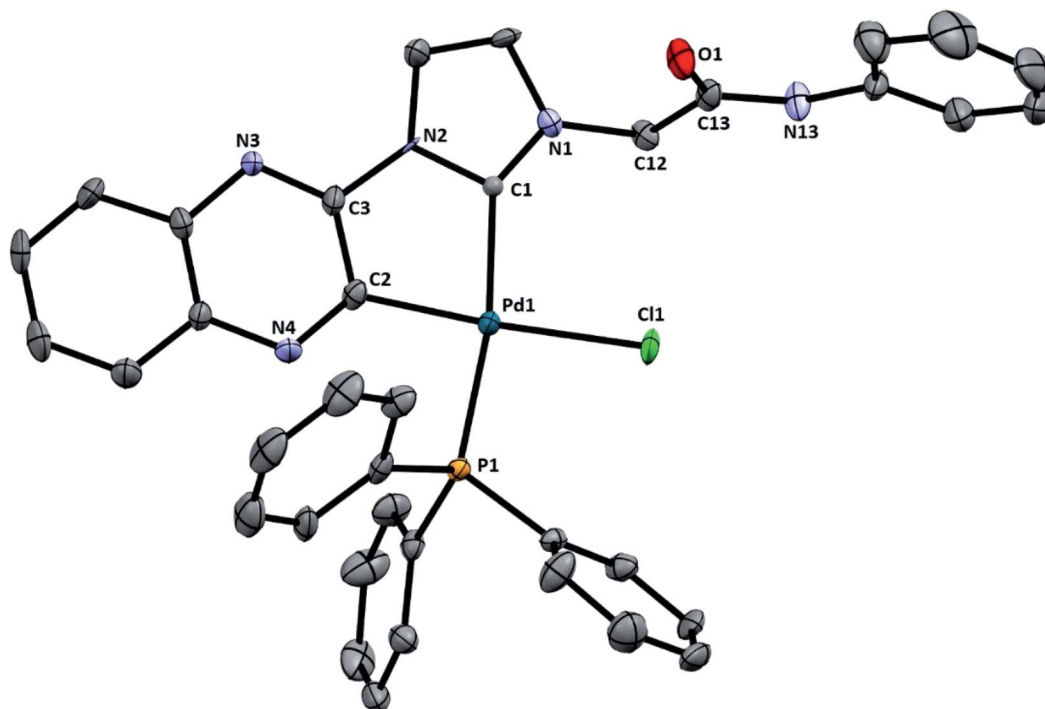
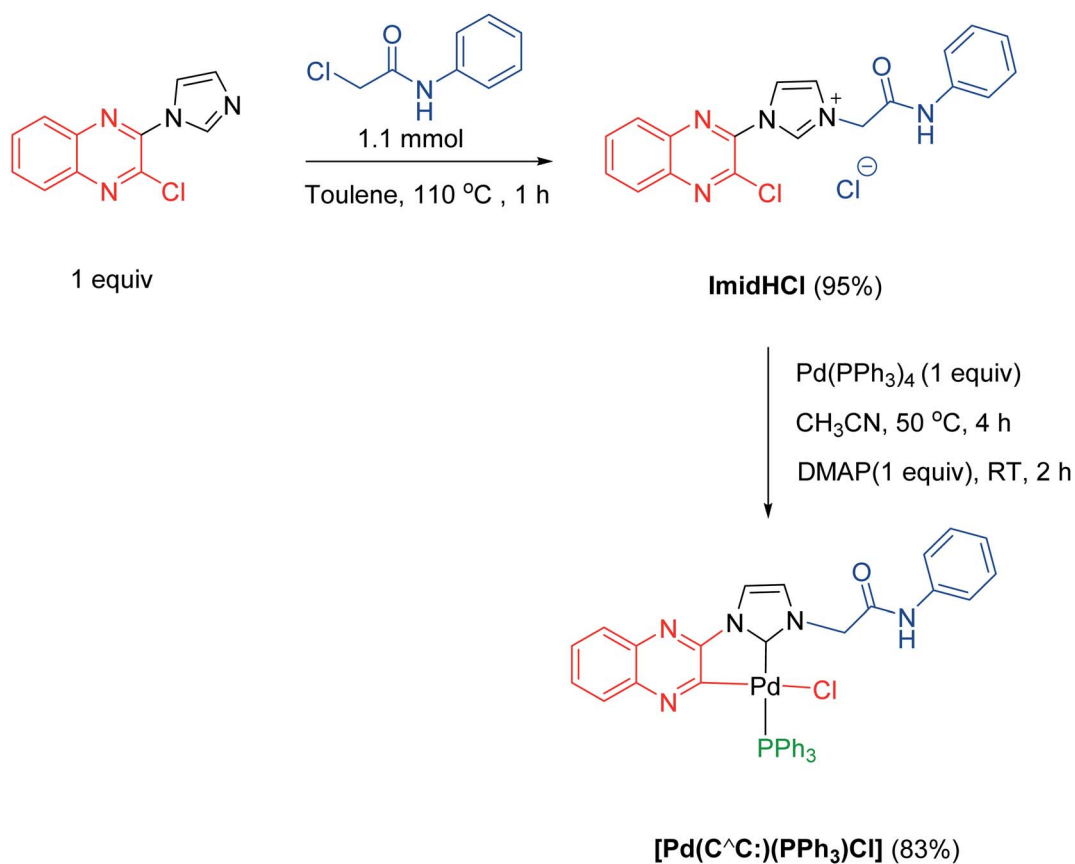


Fig. 1 ORTEP diagram of the palladacycle $[\text{Pd}(\text{C}^{\text{A}}\text{C}:)(\text{PPh}_3)\text{Cl}]$. All hydrogen atoms and solvent molecules have been omitted for clarity. Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths [Å]: Pd1–Cl1 2.378(2), Pd1–P1 2.334(2), Pd1–C1 2.099(7), Pd1–C2 2.013(8), C2–C3 1.441(11), C2–N4 1.291(10), C3–N3 1.307(10), C3–N2 1.408(10), C1–N2 1.354(9), C1–N1 1.308(9). Selected bond angles [°]: P1–Pd1–Cl1 93.97(8), P1–Pd1–C1 169.7(2), P1–Pd1–C2 89.5(2), Cl1–Pd1–C1 95.8(2), Cl1–Pd1–C2 176.2(2), and C1–Pd1–C2 80.7(3).



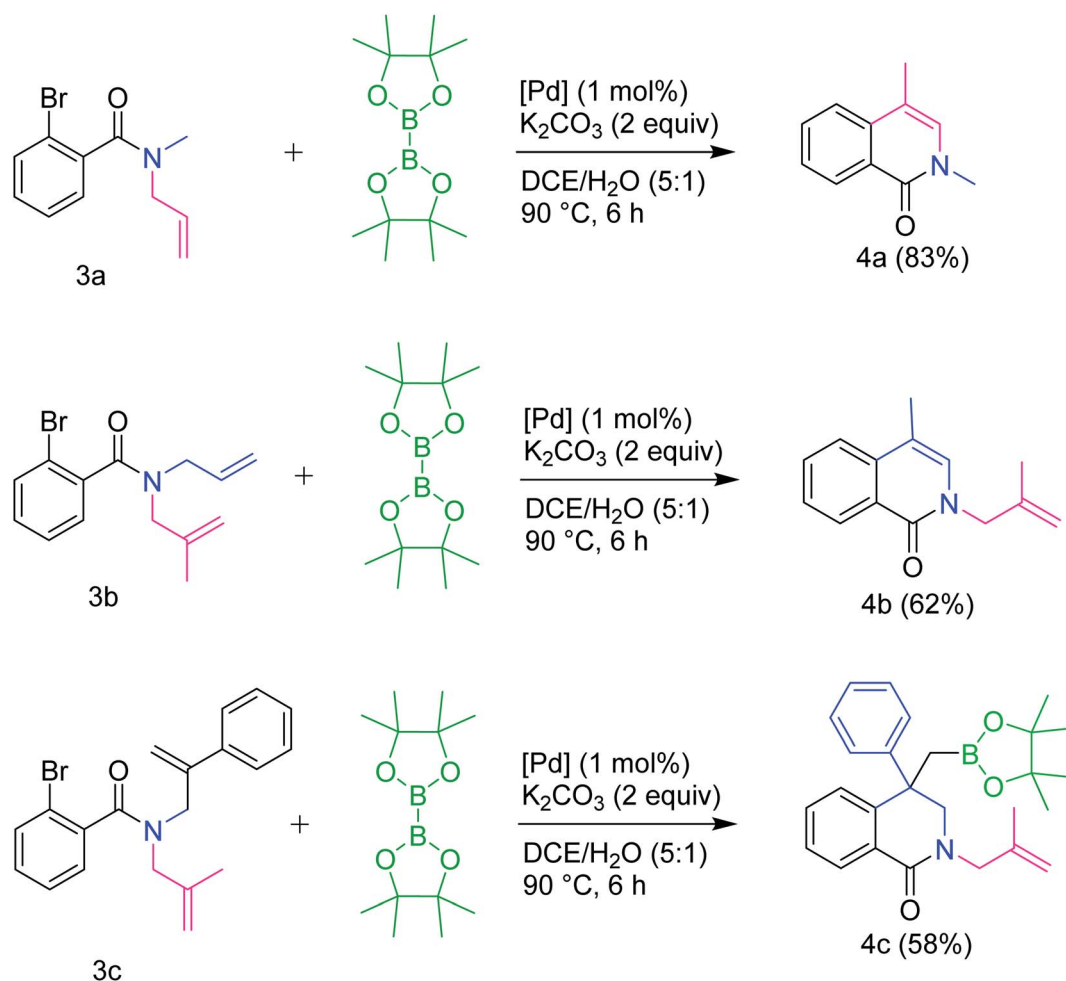
Scheme 2 Synthesis of palladacycle $[\text{Pd}(\text{C}^{\text{A}}\text{C}:)(\text{PPh}_3)\text{Cl}]$.



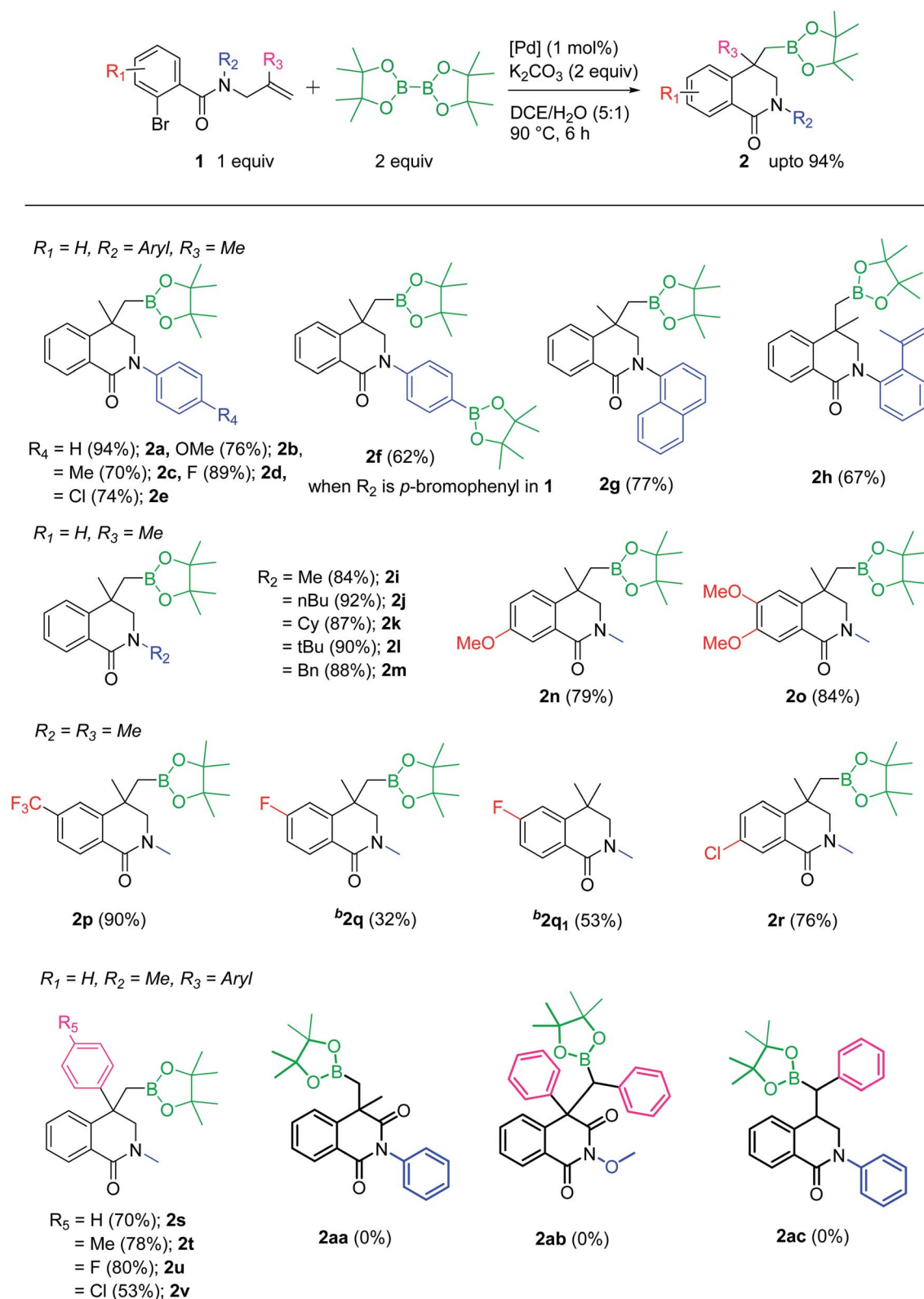
Table 1 Optimization of the reaction conditions^a

entry	[Pd]	Solvent	Yield ^b (%)
1	No catalyst	DCE	0
2	[Pd(C^A/C:)(PPh3)Cl] without K2CO3	DCE	0
4	[Pd(C^A/C:)(PPh3)Cl]	DCE/H2O	94
5	Pd(PPh3)4	DCE/H2O	30
6	Pd2(dba)3	DCE/H2O	0
7	Pd(OAc)2	DCE/H2O	0
8	Pd(PPh3)2Cl2	DCE/H2O	82
9	PdCl2	DCE/H2O	43
10	[Pd(C^A/C:)(PPh3)Cl] Br replaced by H in 1a	DCE/H2O	0

^a Reaction conditions: **1** (0.5 mmol), B₂(Pin)₂ (1.0 mmol), [Pd] (1 mol%), K₂CO₃ (1.0 mmol), and DCE (3 mL) or DCE/H₂O (5 : 1; 3 mL) at 90 °C under N₂ for 6 h. ^b Isolated yield.



Scheme 3 Substituted vs. unsubstituted allyl groups on the nitrogen. Reaction conditions: **3a–c** (0.5 mmol), B₂(Pin)₂ (1.0 mmol), [Pd] = [Pd(C^A/C:)(PPh3)Cl] (1 mol%), K₂CO₃ (1.0 mmol), and DCE/H₂O (5 : 1, 3 mL) at 90 °C under N₂ for 6 h.

Table 2 Substrate scope of the reaction^a

^a Reaction conditions: **1** (0.5 mmol), B₂(Pin)₂ (1.0 mmol), [Pd] = [Pd(C[∧]C)(PPh₃)Cl] (1 mol%), K₂CO₃ (1.0 mmol), and DCE/H₂O (5 : 1, 3 mL) at 90 °C under N₂ for 6 h. ^b A mixture of compounds **2q** and **2q₁** (1 : 2) were obtained.

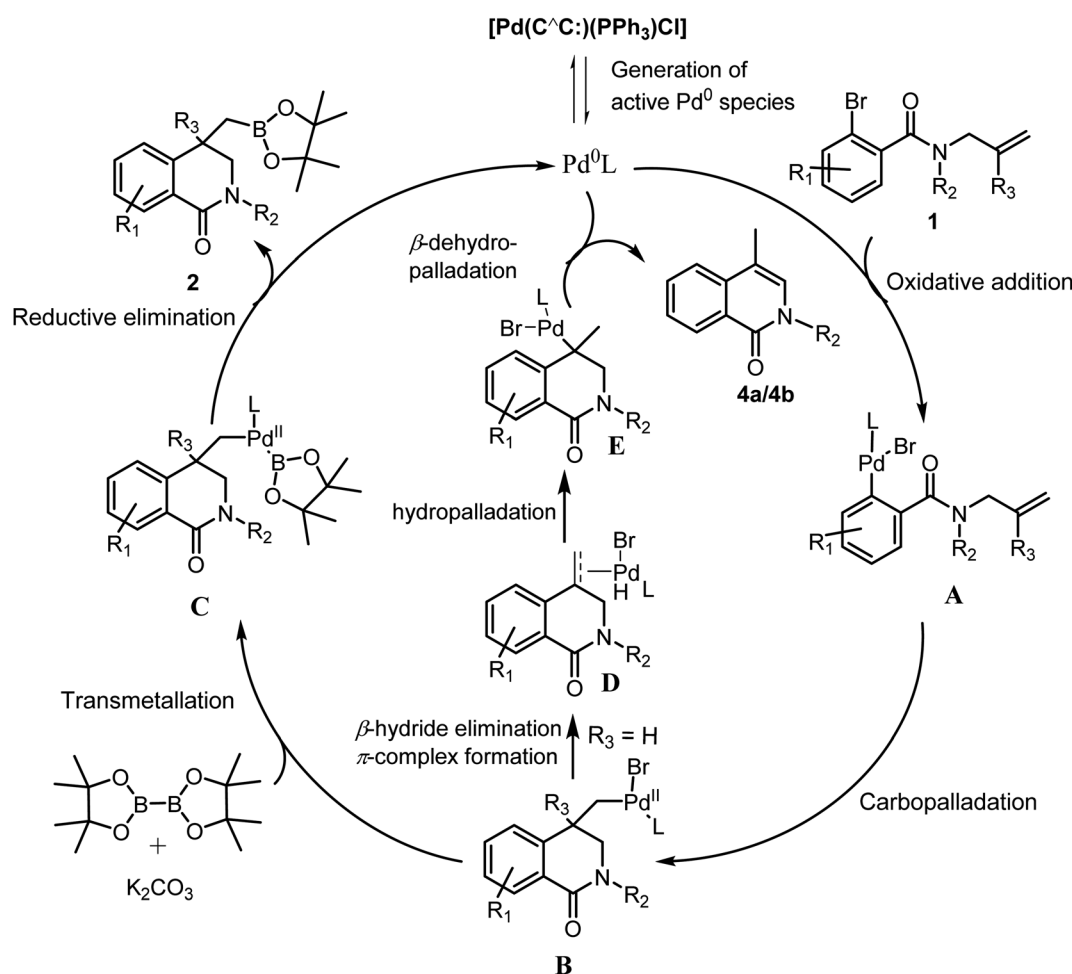


(82%). The others either gave low yields (entries 5 and 9) or were not active at all (entries 6 and 7). We also probed for a possible C–H activation by employing a carboxamide without Br (Br replaced by H in **1a**), which resulted in no reaction (entry 10). Controlled experiments (entries 1 and 2) disclosed the importance of the catalyst and the base. Reaction between **1a** and $B_2(Pin)_2$ was also probed using various bases and found that K_2CO_3 and Na_2CO_3 performed equally good and better than the other bases. The detailed results are listed in Table S1, ESI.†

After optimizing the reaction conditions, substrate scope of the reaction was explored by varying R_1 , R_2 and R_3 . Both aryl and alkyl substituents on the *N*-allyl carboxamide were well tolerated and the corresponding products (**2a–e** and **2g–m**) were obtained in good to excellent yields. However, in case of *N*-*p*-bromophenyl substitution, a diborylated product **2f** was obtained in 62% yield. Even when one equivalent of $B_2(Pin)_2$ was used the formation of only **2f** was observed. It is noteworthy that the additional alkenyl substitution in **1h** is intact and the desired dihydroisoquinolinone-4-methylboronic ester **2h** was produced in 67% yield. Further studies on the substrate scope by changing the substituents (R_1) on the bromobenzoyl moiety of carboxamides (**1n–r**) were

carried out and observed the facile formation of **2n–r** (Table 2). The molecular structure of **2o** was determined by single crystal X-ray technique and an ORTEP diagram is given in Fig. 2. Though a slight difference in the yields based on electron withdrawing or donating nature of the substituents can be seen, it is not enough to draw any conclusions. Unexpectedly, in case of fluoro substitution (**1q**) a mixture of the targeted boronic ester (**2q**) and a product of hydroarylation of alkene (**2q₁**) was formed in 1 : 2 ratio (based on NMR of the crude product). The isolated yields were 32% and 53% respectively). Aromatic substitution having either electron donor or acceptor groups on C2 carbon of the allyl group (R_3) was also found to be highly compatible and afforded the corresponding products **2s–v** in moderate to good yields (53–80%).

Our attempts to synthesize isoquinoline-1,3-dionemethylboronic esters **2aa** and **2ab** under similar reaction conditions were unsuccessful. When an *N*-allylcarboxamide with phenyl substitution on the terminal alkene carbon was employed, in order to make the boronic ester **2ac**, the reaction did not occur. Surprisingly, not even the Heck coupling product was formed though $R_3 = H$. Synthesis of compound **2a** was also accomplished in gram-scale, which demonstrates the



Scheme 4 Plausible mechanism of the transformations.

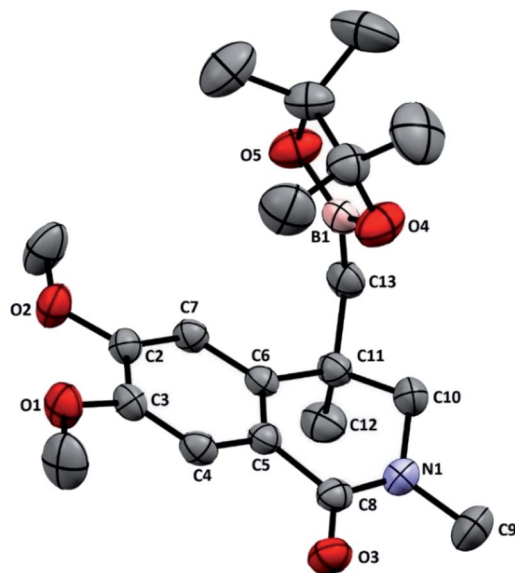
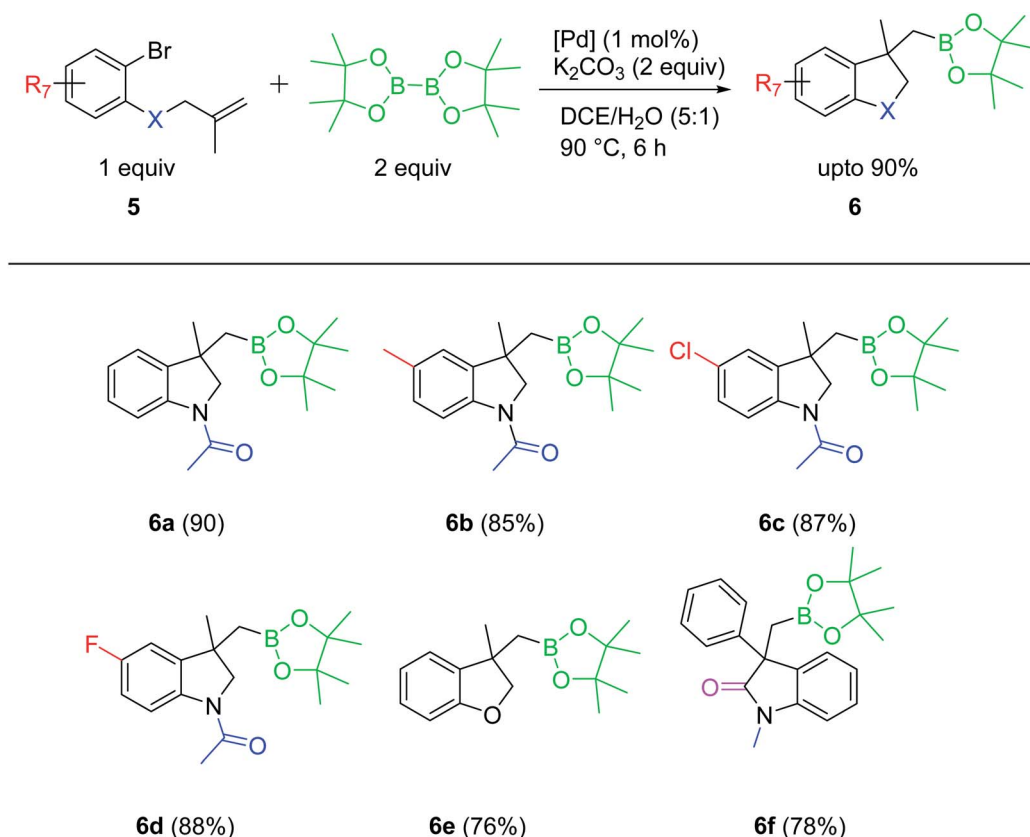


Fig. 2 ORTEP diagram of **2o**. All hydrogen atoms and solvent molecules have been omitted for clarity. Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths [Å]: N1–C8 1.342(2), C8–O3 1.250(2), N1–C10 1.480(2), N1–C9 1.449(2), C10–C11 1.539(2), C5–C6 1.412(2), C11–C13 1.556(2), C13–B1 1.561(3), B1–O4 1.374(2), B1–O5 1.354(2). Selected bond angles [°]: C5–C8–O3 121.96(15), C5–C8–N1 114.92(14), O3–C8–N1 123.09(16), C8–N1–C10 121.54(14), C8–N1–C9 118.60(16), N1–C10–C11 113.49(14), C10–C11–C6 107.24(13), C10–C11–C12 110.30(15), and C10–C11–C13 109.04 (14).

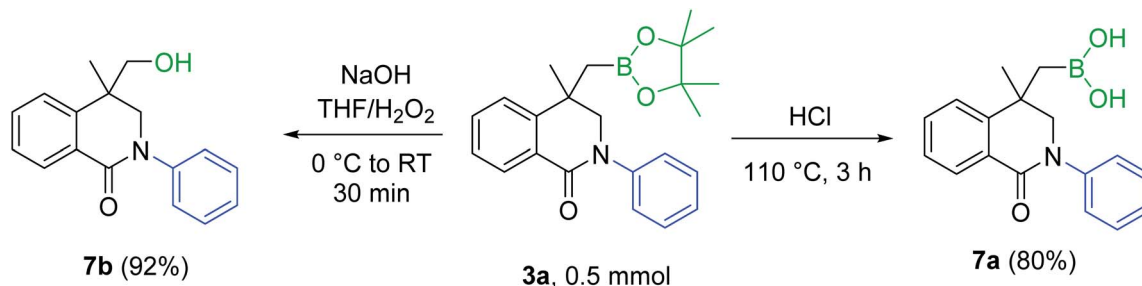
importance of this protocol in large scale preparation of readily functionalizable dihydroisoquinolinone-4-methylboronic esters.

Interestingly, when there was a competition between methyl and phenyl substituted allyl groups on the N (basically when there were two allyl groups, one with phenyl substitution and another with Me substitution, present on the N), only the allyl group with phenyl substitution on C2 carbon was found to undergo carbopalladation producing the boronic ester **4c** in 58% yield (Scheme 3). This can be explained in terms of the stability of the Pd-alkene π -complex involved in the transition state, which is more stable when phenyl substitution is present due to delocalization. The trapping of σ -alkylpalladium intermediate with boronic ester moiety did not occur when a simple allyl group is present on the N as in **3a** and **3b**. Instead, the corresponding intramolecular Heck coupling products **4a** and **4b** were formed in 83% and 62% yields respectively. This behavior can be attributed to the facile 1,2-Pd migration, which is possible only in case of allyl group ($R_3 = H$), followed by β -dehydropalladation. A detailed plausible mechanistic path for all these transformations is given in Scheme 4. After carbopalladation, the resultant alkyl-Pd species undergoes 1,2-Pd migration *via* a sequence of β -hydride elimination/ π -complex formation/hydropalladation. The isomerized alkyl-Pd finally undergoes β -dehydropalladation to give **4a** and **4b**. It is noteworthy that allyl



Scheme 5 Synthesis of indoline and benzofuran-3-methylboronic esters. Reaction conditions: **5** (0.5 mmol), $B_2(Pin)_2$ (1.0 mmol), [Pd] = $[Pd(C\wedge C)(PPh_3)Cl]$ (1 mol%), K_2CO_3 (1.0 mmol), and DCE/ H_2O (5 : 1, 3 mL) at 90 °C under N_2 for 6 h.





Scheme 6 Further functionalization of a dihydroisoquinolinone-4-methylboronic ester.

group undergoes carbopalladation preferentially over 2-methylallyl group.

Encouraged by these results, this protocol was also applied to access methylboronic esters of indoline and benzofuran motifs, which are well known for their biological activity and their applications in pharmaceutical industry. The indoline-3-methylboronic esters **6a–d** were prepared from corresponding *N*-(2-bromoaryl)-*N*-(2-methylallyl) acetamide and the 2-oxindoline-3-methylboronic ester **6f** was obtained by employing *N*-(2-bromophenyl)-*N*-(methyl)-2-phenylacrylamide (Scheme 5). All these compounds were produced in very good yields. Under similar conditions, 2-methylallyl-2-bromophenylether afforded benzofuran-3-methylboronic ester **6e** in good yield. These results clearly emphasize the versatility and efficiency of the palladacycle [Pd(CAC:)(PPh₃)Cl] as a catalyst in domino Heck/borylation approach for the synthesis of heterocyclic methylboronic esters.

Transformation of methylboronic ester moiety into various functional groups has been reported in the literature.^{8,9} As shown in Scheme 6, **3a** was converted to dihydroisoquinolinone boronic acid **7a** and hydroxymethyl-substituted dihydroisoquinolinone **7b** in good yields.

Conclusion

We have synthesized and structurally characterized a palladacycle [Pd(CAC:)(PPh₃)Cl], which has been found to be an efficient catalyst in domino Heck/borylation reactions leading to the synthesis of dihydroisoquinolinone-4-methylboronic esters. The reaction protocol, which works with aryl bromides, involves mild reaction conditions and requires less catalyst loading (1 mol%). Tolerance to a wide range of *N*-allylcarboxamides and employability in the synthesis of indoline and benzofuran derivatives demonstrate the versatility of the method.

Conflicts of interest

There are no conflicts to declare.

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