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Pd(II)-Catalyzed Catellani-Type Domino Reaction Utilizing Arylboronic Acids as Substrates

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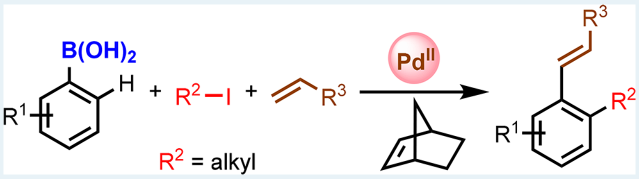
Supporting Information

ABSTRACT: The Catellani reaction provides a facile and efficient method for the synthesis of multifunctionalized arenes. However, the use of Pd(0) catalysts restricts the scope of accessible products. We have developed a Pd(II)-catalyzed, Catellani-type reaction utilizing arylboronic acids as the substrates for the first time. The arylboronic acids can be mono- or dialkylated at the *ortho* positions with alkyl iodides and olefinated at the *ipso* positions with olefins, producing various multifunctionalized aromatic compounds. This work should open new avenues for developing novel Catellani reactions, in particular those using new electrophiles.

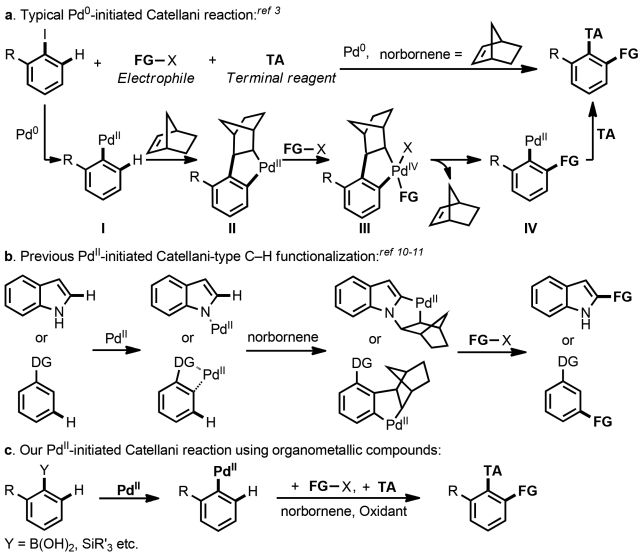


KEYWORDS: *Catellani reaction, arylboronic acid, palladium catalysis, C−H activation, arene*

The functionalization of arenes is a fundamental transformation in organic synthesis. Transition-metal catalysis plays significant role in this field. While traditional transition-metal-catalyzed reactions rely on the use of prefunctionalized arene substrates, direct aryl C−H functionalization overcomes this shortcoming.[1] However, directing groups have to be used to achieve high regioselectivity for the majority of current transition-metal-catalyzed C−H functionalizations, which restricts the scope of accessible products. To circumvent this drawback, removable directing groups have gained considerable interest, in particular those that can be removed or transformed in situ.[2] Catellani reaction represents a desirable example of this type of reaction.[3] A typical Catellani reaction starts from aryl halides. With the aid of norbornene, the *ortho*-C−H bonds and *ipso* positions of arylhalides are functionalized in a well-defined sequence, which provides a facile and efficient method for the synthesis of multifunctionalized arenes. Mechanistically, the catalytic cycle of the Catellani reaction starts with the oxidative addition of aryl halides to Pd(0) (Scheme 1a).[3a,b] The migratory insertion of the resulted arylPd(II) complex **I** to norbornene and subsequent intramolecular C−H activation form arylnorbornylpalladacycle **II**. **II** undergoes oxidative addition with an electrophile to give Pd(IV) intermediate **III**. The subsequent reductive elimination and deinsertion of norbornene yield arylPd(II) intermediate **IV**. **IV** could be captured by a terminal reagent, affording the final *ortho*- and *ipso*-bisfunctionalized product. The selective oxidative addition of aryl halides to Pd(0) and electrophiles to palladacycle **II** is crucial for the catalytic sequence.

During the past 20 years, a number of Catellani reactions have been developed.[3−9] In these reactions, efforts were mostly focused on the diversity of terminal reagents, including alkenes, alkynes, organoboronic acids, cyanides, heteroarenes, amines, amides, and reductive reagents.[3−5] In comparison, electrophiles to functionalize *ortho*-positions are restricted to several kinds of reagents with quite weak oxidizability, including alkyl/aryl halides,[3a,b,4a−c,6] *O*-benzoyl hydroxyamines,[5a−e,7] anhydrides,[8] acyl chlorides,[9] and thioesters.[5f] One main obstacle is that electrophilic reagents could oxidize Pd(0) catalyst rather than the arylnorbornylpalladacycles.[5a,8b,c] A feasible solution is to develop Pd(II)-initiated Catellani reactions. Actually, there have been several examples of Catellani-type reactions initiated by Pd(II), including 2-C−H functionalization of indole and

Scheme 1. Pd(0)- and Pd(II)-Initiated Catellani Reactions



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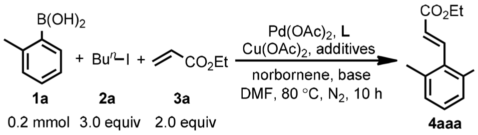
pyrrole,[10] and *meta*-C−H functionalization of arenes bearing directing groups (Scheme 1b).[11] It should be mentioned that Yu has realized chlorination and alkynylation of *meta*-C−H bonds,[11f,g] which may provide an evidence for the feasibility of this strategy. However, Pd(II)-initiated Catellani reactions are still at an early stage of development and remain to be developed. Organometallic compounds are very common substrates in Pd(II)-initiated reactions.[12] Thus, our efforts were focused on developing Pd(II)-initiated Catellani-type reactions starting from organometallic compounds such as arylboronic acids, arylsilanes et al. (Scheme 1c). Herein, we have realized this idea by utilizing arylboronic acids as the substrates, which are difunctionalized by alkyl iodides and alkenes. To the best of our knowledge, the reaction represents the first example of Pd(II)-initiated Catellani reaction using organometallic compounds. The success should open new avenues for developing new Catellani reactions using other electrophiles.

As the catalytic cycle was expected to start with Pd(II) and end with Pd(0), oxidants should be necessary and crucial for the reaction. Thus, we initiated the attempt by searching for an efficient oxidant for the reaction of *o*-tolylboronic acid **1a**, *n*-butyl iodide **2a**, and ethyl acrylate **3a**. After extensive screening of oxidants, we found that 4% desired difunctionalized product **4aaa** was formed in the presence of $Cu(OAc)_2$ (Table 1, entry 1). The addition of 20 mol % PPh_3 as ligand promoted the reaction, and the yield was enhanced to 16% (entry 2). Next, a range of inorganic bases were screened, and KOAc proved to be the most efficient (entry 3). Reducing the temperature to 80 °C led to a slightly higher yield (45%), while the yield decreased to 37% when the temperature was further reduced to 60 °C (entries 4 and 5). Surprisingly, the addition of 2.0 equiv of water could promote the transformation (entry 6). The reason remains to be investigated. The yield was further improved to 65% by the addition of 0.25 equiv of BQ (entry 7). Considering the great impact of P-ligand on Catellani reaction,[3e,f] diverse P-ligands were examined. Gratefully, a yield of 80% was obtained when PCy_3 was used (entry 8). The quantity of norbornene was also screened, and the optimal result (85%) were obtained with 1.0 equiv of norbornene (entry 9). Notably, a yield of 71% was still obtained when the reaction was scaled up to 1.5 mmol. Finally, the reactions failed to give the target product **4aaa** in the absence of $Pd(OAc)_2$ (entry 10), which indicated the crucial role of $Pd(OAc)_2$. (For the detailed optimization table, see the Supporting Information).

Table 1. Optimization of Reaction Conditions[a]



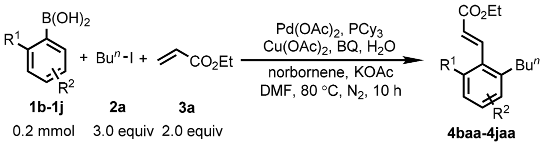
entry	L (mol %)	additive (equiv)	base (equiv)	yield/%[b]
1[c]	-	-	K_2CO_3 (3.0)	4
2[c]	PPh_3 (20)	-	K_2CO_3 (3.0)	16
3[c]	PPh_3 (20)	-	KOAc (3.0)	43
4	PPh_3 (20)	-	KOAc (3.0)	45
5[d]	PPh_3 (20)	-	KOAc (3.0)	37
6	PPh_3 (20)	H_2O (2.0)	KOAc (3.0)	50
7	PPh_3 (20)	H_2O (2.0), BQ (0.25)	KOAc (3.0)	65
8	**PCy_3 (20)**	**H_2O (2.0), BQ (0.25)**	**KOAc (3.0)**	**80**
9[e]	**PCy_3 (20)**	**H_2O (2.0), BQ (0.25)**	**KOAc (3.0)**	**85 (82) (71%[g])**
10[f]	PCy_3 (20)	H_2O (2.0), BQ (0.25)	KOAc (3.0)	0

[a]Reaction condition: **1a** (0.2 mmol), **2a** (3.0 equiv), **3a** (2.0 equiv), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (2.0 equiv), norbornene (1.5 equiv), ligand, additive, base, DMF (1.5 mL), N_2, 80 °C, 10 h. [b]The yields were determined by ^1H NMR analysis of crude reaction mixture using $CHCl_2CHCl_2$ as the internal standard; Isolated yield in parentheses. [c]100 °C. [d]60 °C. [e]1.0 equiv of norbornene. [f]without $Pd(OAc)_2$. [g]1.5 mmol of **1a**.

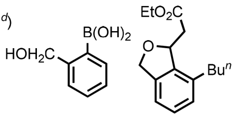
With the optimal condition in hand, we then explored the substrate scope of the arylboronic acid-based Catellani-type reaction. First, we examined the compatibility of various phenylboronic acids bearing one *ortho*-substituent, which would give monobutylated products at the other *ortho* positions. As shown in Table 2, the substrates bearing a trifluoromethyl, trifluoromethoxy, ethoxycarbonyl, and even sterically hindered isopropyl group at the *ortho* position could react with *n*-butyl iodide and ethyl acrylate in sequence, furnishing the Catellani products in moderate or good yields. The reaction was also scalable, and the yield almost remained unchanged (**4caa**). The reactivity of substrates bearing additional substituents at other positions was also examined, and we found that both fluoro and chloro groups at 4- or 5-positions were well-tolerated. Furthermore, 1-iodonaphthalene could also be difunctionalized at the *ipso* and *ortho* positions in 71% yield (**4jaa**). Notably, 2-hydroxymethyl phenylboronic acid was suitable under the reaction condition. However, the product underwent intramolecular cyclization to generate compound **4kaa**.

Next, we examined the performance of phenylboronic acids without *ortho*-substituents (Table 3). Just as classical Catellani reaction starting from aryl halides, dialkylated products were formed in the reactions. A variety of common functional groups were tolerated, such as methyl, methoxy, fluoro, chloro, bromo, trifluoromethyl, cyano, carbonyl, ester, and even vinyl groups.

Table 2. Substrate Scope with Respect to *ortho*-Substituted Phenylboronic Acids[a]



substrate		product	yield[b]
R^1 = 2-CF_3	R^2 = H	**4baa**	80%[c]
2-OCF_3	H	**4caa**	71% (69%[d])
2-CO_2Et	H	**4daa**	68%
2-Pr^i	H	**4eaa**	60%[e]
2-Me	4-F	**4faa**	51%
2-Me	5-F	**4gaa**	82%[c]
2-CF_3	4-Cl	**4haa**	63%
2-CF_3	5-F	**4iaa**	53%
1-naph	H	**4jaa**	71%



1k **4kaa**, 41%

[a]Reaction condition: **1a** (0.2 mmol), **2a** (3.0 equiv), **3a** (2.0 equiv), $Pd(OAc)_2$ (10 mol %), PCy_3 (20 mol %), Cu $(OAc)_2$ (2.0 equiv), norbornene (1.0 equiv), BQ (0.25 equiv), H_2O (2.0 equiv), DMF (1.5 mL), N_2, 80 °C, 10 h. [b]Isolated yields. [c]BQ (1.0 equiv), $Cu(OAc)_2$ (3.0 equiv). [d]1.5 mmol of **1c**. [e]without H_2O.

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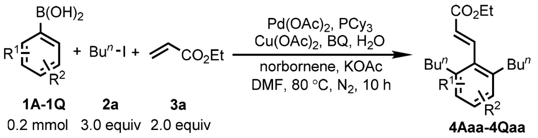
Table 3. Substrate Scope with Respect to Phenylboronic Acids without *ortho*-Substituents[a]



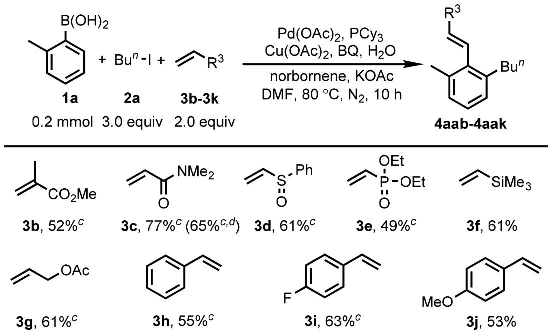
substrate		product	yield[b]	substrate		product	yield[b]
R^1 = 4-Me	R^2 = H	**4Aaa**	52%[c]	R^1 = 4-CHO	R^2 = H	**4Jaa**	54%[d]
4-OMe	H	**4Baa**	54%[c]	3-CHO	H	**4Kaa**	67%[d]
4-F	H	**4Caa**	56%[d]	4-CO_2Me	H	**4Laa**	78%[d]
4-Cl	H	**4Daa**	60%[d]	4-vinyl	H	**4Maa**	57%[c]
3-Cl	H	**4Eaa**	60%	3-F	5-F	**4Naa**	93%[d] (75%[d,f])
4-Br	H	**4Faa**	50%[e]	3-Cl	4-Cl	**4Oaa**	72%
4-CF_3	H	**4Gaa**	66%[d]	3-Cl	4-F	**4Paa**	80%
4-CN	H	**4Haa**	47%[d]	2-naph	H	**4Qaa**	76%[c]
4-Ac	H	**4Iaa**	66%[d]				

[a]Reaction condition: as in Table 2. [b]Isolated yield. [c]$Pd(OAc)_2$ (20 mol %), PCy_3 (40 mol %), without H_2O. [d]without H_2O. [e]$Pd(OAc)_2$ (20 mol %), PCy_3 (40 mol %). [f]1.5 mmol of **1N**.

Disubstituted phenylboronic acids including **4N−4P** were also compatible, affording multisubstituted arenes as the products. Even for 2-naphthalenylboronic acid with 1-carbon hindered, 1,3-dibutylated product (**4Qaa**) was still generated. However, the reaction conditions had to be reoptimized slightly to achieve reasonable yields for some substrates.

The scope of alkenes was also investigated (Table 4). Therefore, a variety of terminal alkenes were allowed to react with *o*-tolylboronic acid **1a** and *n*-butyl iodide **2a**. Sterically encumbered methyl methacrylate (**3b**) could furnish the desired product in a yield of 52%. A range of terminal alkenes bearing different electron-withdrawing or electron-donating groups, such as amide, sulfonyl, phosphate, and trimethylsilyl, were effective olefinating reagents. Allyl acetate **3g** could also undergo the new Catellani reaction without compromising the acetate group, affording the olefinated product in 61% yield. Styrene **3h** and its derivatives **3i** and **3j** were also suitable, and the corresponding Catellani products were formed in moderate yields, which provides a new method for the synthesis of variously substituted unsymmetrical stilbenes. It should be noted that 3.0 equiv of alkenes had to be used to achieve optimal yields for alkene **3b**, **3c**, **3d**, **3e**, **3g**, **3h**, and **3i**.

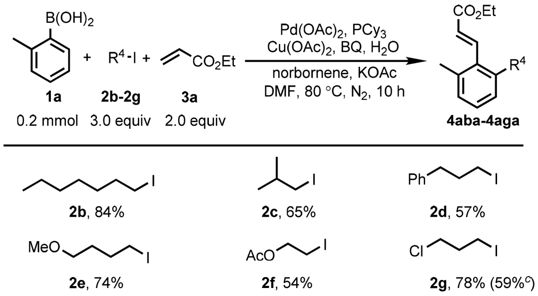
Table 4. Substrate Scope with Respect to Alkenes[a,b]



[a]Reaction condition: as in Table 2. [b]Isolated yield. [c]3.0 equiv of olefin. [d]1.5 mmol of **1a**.

Finally, we examined the reactivity of other alkyl iodides. As depicted in Table 5, *n*-heptyl iodide showed similar reactivity to *n*-butyl iodide and isobutyl iodide was also reactive, albeit in a lower yield. Various functional groups including phenyl, methoxy, acetoxy, and chloro at the terminal positions of alkyl iodides were tolerated, and the corresponding alkylated products were formed in the yields ranging from 54% to 78%.

Table 5. Substrate Scope with Respect to Alkyl Iodides[a,b]



[a]Reaction condition: as in Table 2. [b]Isolated yield. [c]1.5 mmol of **1a**.

The mechanism of this new Catellani reaction is proposed (Figure 1). The catalytic cycle is initiated by Pd(II), which reacts with arylboronic acids to afford arylPd(II) intermediate **V**. The migratory insertion of norbornene and subsequent *ortho*-C−H activation form palladacycle intermediate **VII**. The oxidative addition of alkyl iodides to **VII** yields palladacycle **VIII**, which then undergoes reductive elimination and deinsertion of norbornene to afford Pd(II) species **X**. **X** can be captured by alkenes to provide the final Catellani products

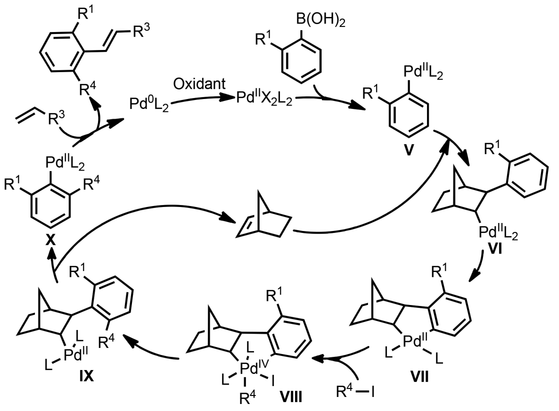


Figure 1. Proposed mechanism.

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and release Pd(0) species, which is oxidized to regenerate Pd(II) catalyst.

In conclusion, we have developed an efficient protocol for Pd(II)-initiated Catellani-type reaction utilizing arylboronic acids as the substrates for the first time. A range of multifunctionalized arenes can be synthesized by the domino reaction with alkyl iodides and olefins. Unlike the classical Pd(0)-initiated Catellani reaction starting from aryl halides, this reaction may avoid the competitive reaction of Pd(0) with the electrophiles and should therefore be compatible with new electrophilic coupling partners, especially oxidative ones. This work should open new avenues for developing new Catellani-type reactions. Further studies on developing other reactions of this type, in particular those using electrophiles that have not been used in the Pd(0)-catalyzed Catellani reaction, are underway in our lab.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b00637.

> Experimental procedures, detailed screening of reaction conditions, and spectral data for all the new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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