A Journal of the Gesellschaft Deutscher Chemiker
Angewandte Chemie
International Edition
www.angewandte.org

Accepted Article

Title: The Discovery of A Pd(II)-Initiated Borono-Catellani Reaction

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201803865
Angew. Chem. 10.1002/ange.201803865

Link to VoR: http://dx.doi.org/10.1002/anie.201803865
http://dx.doi.org/10.1002/ange.201803865

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The Discovery of A Pd(II)-Initiated Borono-Catellani Reaction

Shuqing Chen†, Ze-Shui Liu†, Tao Yang, Yu Hua, Zhiyu Zhou, Hong-Gang Cheng and Qianghui Zhou*

Dedicated to Prof. Xiyan Lu on the occasion of his 90th birthday

Abstract: We report a novel Pd(II)-initiated Catellani-type reaction that utilizes widely accessible aryl boronic acids as the substrates instead of aryl halides, thereby greatly expanding the existing paradigm of this powerful transformation. This tentatively called "Borono-Catellani reaction" was promoted by a cooperative catalysis of Pd(OAc)$_2$ and the inexpensive 5-norbornene-2-carbonitrile. Practicality is the striking feature of the reaction: it is run at ambient temperature under air while no phosphine ligand is needed. This mild, chemo-selective, and scalable protocol is compatible with a large range of readily available functionalized aryl boronic acids, bromides as well as terminating olefins (50 examples, 39-97% yields). Moreover, the orthogonal reactivity between the Borono-Catellani and classical Catellani reaction was demonstrated. This work is expected to open up new avenues for developing novel Catellani-type reactions.

One of the central tasks in modern organic synthesis is to develop efficient strategies for C-C bond construction. The sequential activation of C-H bond and construction of C-C bond is an appealing but particularly challenging pathway.[1] Nevertheless, the Catellani reaction is one of the most promising approaches to accomplish these processes.[2-3] It utilizes cooperative palladium and norbornene catalysis to facilitate sequential *ortho* C–H functionalization and *ipso* coupling of aryl iodide, thereby allowing the simultaneous functionalization of both *ortho* and *ipso* positions to permit the expeditious syntheses of highly substituted arenes with high efficiencies and selectivities.[4] During the twenty years of development, the substrates utilized for the Catellani-type reactions are mainly limited to aryl halides,[3] and a Pd(0) initiated cooperative catalysis mechanism was suggested.[4] Recently, the Bach group revealed a novel Catellani-type reaction applying substituted 1-H-indole and 1-H-pyrrole as the substrates, which was believed to be promoted by Pd(II)-initiated cooperative catalysis.[5] Later, the Yu group[6] and others[7] developed a *meta*-C-H functionalization strategy of substituted arenes *via* a directed *ortho*-C-H activation and a Pd(II)/norbornene cooperative catalysis relay mechanism. As can be seen, the emerging Pd(II)-initiated cooperative catalysis behaved quite differently from the classical Pd(0) version, thus opening a new avenue for this field.

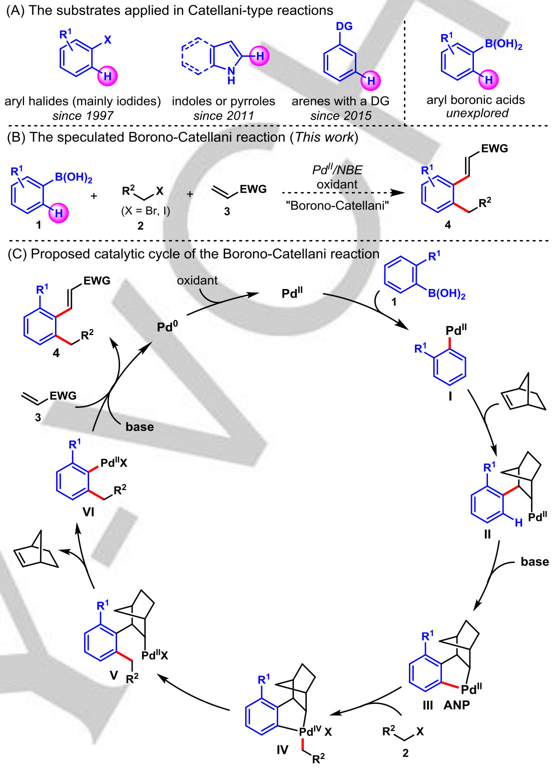

Figure 1. Pd(0)- and Pd(II)-catalyzed Catellani reactions

Aryl boronic acids and their derivatives are widely accessible and useful organic reagents,[8] which have been extensively applied as cross coupling partners,[9] catalysts[10] and so on. In classical Catellani-type reactions, aryl boronic acids and their derivatives mainly act as terminating reagents.[11] Nevertheless, the innovative research from the Bach and Yu groups inspired us to pursue a tentatively called "Borono-Catellani reaction" as illustrated in Figure 1B, applying these readily available reagents as the substrates. Prior to the start of this project, applying them as the substrates instead of aryl iodides in Pd/NBE cooperative catalysis had not been reported. Until very recently, Zhang and co-workers reported a similar reaction.[12] As shown in Figure 1C, we envisioned that the reaction would be initiated by a Pd(II) catalyst, which reacts with aryl boronic acid **1** to afford arylPd(II) intermediate **I** *via* transmetallation. The migratory insertion of norbornene and subsequent *ortho*-C–H activation in the presence of a base to form the key aryl/norbornene palladacycle complex (ANP) **III**. The oxidative addition of alkyl halide **2** to **III** gives palladium(IV) complex **IV**, which then undergoes reductive elimination and subsequent extrusion of norbornene to afford Pd(II) species **VI**. **VI** can be captured by the olefin **3** to provide the Catellani product **4** and release a Pd(0) species, which is then oxidized to regenerate the Pd(II) catalyst. Although the above process is mechanistically feasible, the challenge is two-fold. Firstly, the direct oxidative Heck reaction between **1** and **3** will be a strong competitive process.[13] Secondly, the oxidant applied to regenerate the Pd(II) may not be compatible with aryl boronic acid **2**, which will result in various side reactions including homo-

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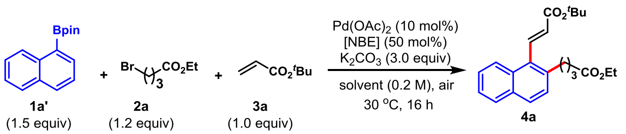
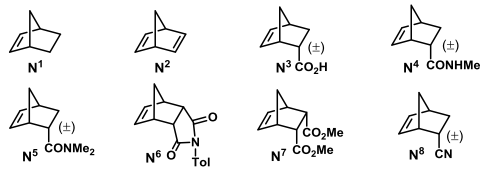
Supplementary information for this article is given via a link at the end of the document.

10.1002/anie.201803865

Table 1. Optimization of reaction conditions.[a]



Entry	[NBE]	Solvent	Yield [%][b]
1	**N1**	NMP	40
2	**N2**	NMP	14
3	**N3**	NMP	38
4	**N4**	NMP	27
5	**N5**	NMP	21
6	**N6**	NMP	59
7	**N7**	NMP	43
8	**N8**	NMP	70
9	**N8**	toluene	0
10	**N8**	MeCN	0
11	**N8**	DMF	73
12	**N8**	DMA	79
13[c]	**N8**	DMA	89
14[d]	**N8**	DMA	99
15[d,e]	**N8**	**DMA**	**99 (91)[f]**



[a] All reactions were performed on 0.2 mmol scale. [b] GC yield with biphenyl as an internal standard. [c] 1.0 equiv of **N8** was applied. [d] 1.5 equiv of **N8** was applied. [e] 2.0 equiv of K_2CO_3 was applied. [f] Isolated yield in parentheses, which is calculated based on the olefin. NMP: *N*-methyl-2-pyrrolidinone, DMF: N,N-dimethylformamide, NMA: N,N-dimethylacetamide.

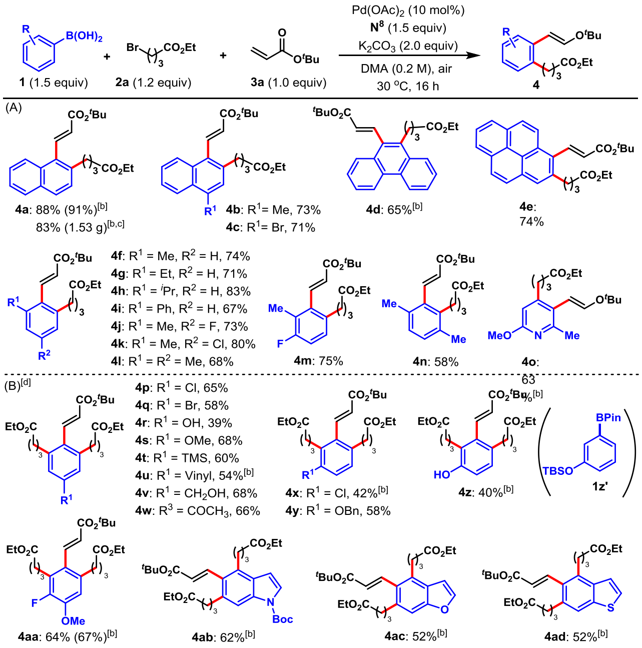
coupling,[14] oxidation to phenols,[15] and protolytic deboronation.[15]

To address the aforementioned challenges, our efforts commenced with the model reaction using readily available 1-naphthylboronic acid pinacol ester (**1a'**), ethyl 4-bromobutanoate (**2a**) and *tert*-butyl acrylate (**3a**) as the reactants (Table 1). $Pd(OAc)_2$ was initially chosen as the catalyst (10 mol%), K_2CO_3 as the base (3.0 equiv), and NMP as the solvent, while the reaction was allowed to run at ambient temperature (30 °C) under air (as the mild oxidant)[16] to minimize possible side reactions. To our delight, the reaction with 50 mol% NBE (**N1**) did furnish the desired product **4a** in 40% yield (entry 1). In attempt to improve the reaction efficiency, various readily available norbornene derivatives were then examined, including 2,5-norbornadiene (**N2**), 5-norbornene-2-carboxylic acid (**N3**) [17] and the Dong mediator (**N4**)[18] (entries 2-4), which did not improve the efficiency of this process. Gratifyingly, the inexpensive NBE derivative 5-norbornene-2-carbonitrile **N8** was identified as the optimal mediator,[19] affording **4a** in a significantly improved yield (70%) (entry 8). Following studies focused on screening reaction solvent, which plays a critical role in this process. The switching of NMP for toluene or acetonitrile led to no product formation (entries 9-10). In contrast, the amide-type solvent DMF behaved similarly to NMP (Entry 11), while the use of DMA increased the yield of **4a** to 79% (Entry 12). Thus, DMA was selected as the optimal reaction solvent. Further optimization indicated that the amount of the mediator **N8** had a positive effect on the reaction. For instance, increasing the loading of **N8** to 1.0 equivalent and 1.5 equivalents provided **4a** in 89% and 99% yield respectively (entries 13-14). Additional optimization of the base, palladium catalyst and the oxidant did not provide significant improvement in the efficiency (see the Supplementary Information (SI) for details). Finally, the optimal conditions involved the reduction of the base to 2.0 equivalents, which furnished **4a** in 99% yield (91% isolated yield) (entry 15).[20] It is worth mentioning that the current reaction has several advantageous aspects, such as the fact that it uses a green oxidant (air) and does not require any phophine ligand[21] (**N8** may act as a ligand as well as mediator). Additionally, the reaction proceeds well in an open flask at ambient temperature. These practical features make this reaction amenable for process chemistry.

With the above optimal conditions identified, we first examined the scope of aryl boronic acids, with bromide **2a** and olefin **3a** as the reaction partners (Table 2). First, we explored the compatibility of *ortho*-substituted aryl boronic acids, which would give mono-alkylated products. As shown in Table 2A, polycyclic aryl boronic acids (**4a**-**e**), as well as substrates bearing a methyl (**4f**, **4j**-**n**), ethyl (**4g**), phenyl (**4i**) and even sterically hindered isopropyl group (**4h**) at the *ortho* position were suitable substrates, furnishing the Catellani products in moderate to good yields (58-88%). Other substituents including fluoro (**4j** and **4m**), chloro (**4k**) and bromo (**4c**) at 3- or 4-positions were well-tolerated. Notably, heteroaryl boronic acid also reacted well to afford the desired product (**4o**) in 63% yield. We further investigated the practicality of this protocol on a larger scale (5 mmol), which led to a gram-scale preparation of product **4a** (1.53 g, 83% yield).

Next, the reactivity of aryl boronic acids without *ortho*-substitution were examined (Table 2B). Gratifyingly, these substrates containing either electron-donating or -withdrawing groups proved to be competent substrates, providing the

Table 2. Reaction scope with respect to the aryl boronic acid.[a]



[a] All reactions were performed on a 0.2 mmol scale. Reported yields are for the isolated products, , which are calculated based on the olefin. [b] Ar-Bpin was used instead of Ar-$B(OH)_2$. [c] on 5.0 mmol scale. [d] 2.4 equiv of alkyl bromide and 3.0 equiv of K_2CO_3 were applied.

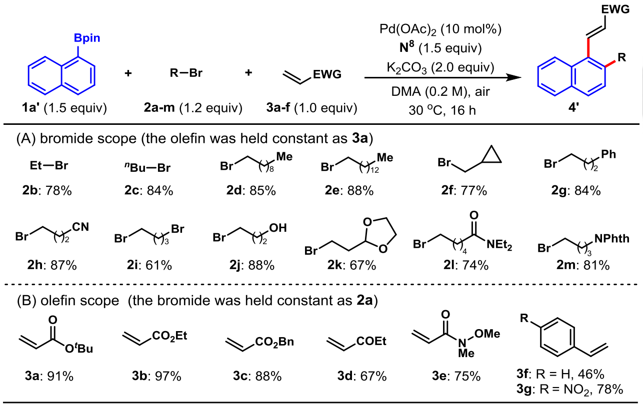
dialkylated products in moderate to good yields. Notably, the reaction system also exhibited high chemo-selectivity: various functional groups were tolerated, including fluoride (**4aa**), chloride (**4p** and **4x**), bromide (**4q**), hydroxy (**4r** and **4v**), methoxy (**4s** and **4aa**), benzyloxy (**4y**), TMS (**4t**), vinyl (**4u**) and acyl (**4w**), providing handles for further product diversifications. Interestingly, when the pinacol ester **1z'** was tested, the TBS deprotected product **4z** was obtained in 40% yield, indicating the TBS group isn't compatible with the reaction conditions. Lastly, it's found that the pinacol ester of heteroaryl boronic acids (**4ab-ad**) were also suitable substrates to deliver the desired products in moderate yields.

Due to improved stability or ease of preparation, some cases in Table 2 utilized the corresponding pinacol ester as substrate instead of the boronic acid,[22] for example, **4d**, **4o**, **4u**, **4x**, **4z** and **4ab-ad**. As to case **4a** and **4aa**, both the boronic acids and the corresponding pinacol esters were tested, and the later were found to give slightly higher yields.

Then, the scope of bromides **2** was examined (Table 3A).[23] Alkylation with simple ethyl bromide (**2b**), *n*-butyl bromide (**2c**), alkyl bromides with a long aliphatic chain (**2d-e**), as well as the cyclopropyl and phenyl substituted alkyl bromides (**2f-g**) gave the desired products in good to excellent yields (77-88%). Bromides containing an array of functional groups including cyano (**2h**), bromo (**2i**), acetal (**2k**), amide (**2l**), and protected amino (**2m**) gave good to excellent yields (61-87%). It is noteworthy that a free hydroxyl group (**2j**) was also compatible with this protocol.

The scope of olefins **3** was also explored.[24] As shown in Table 3B, an array of *mono*-substituted olefins with electron-withdrawing groups are suitable substrates (**3a-e**), providing the desired products in good to excellent yields (67-97%). Interestingly, simple styrene (**3f**) and 4-nitro-styrene (**3g**) were also suitable substrates to afford the products in 46% and 78% yields, respectively.

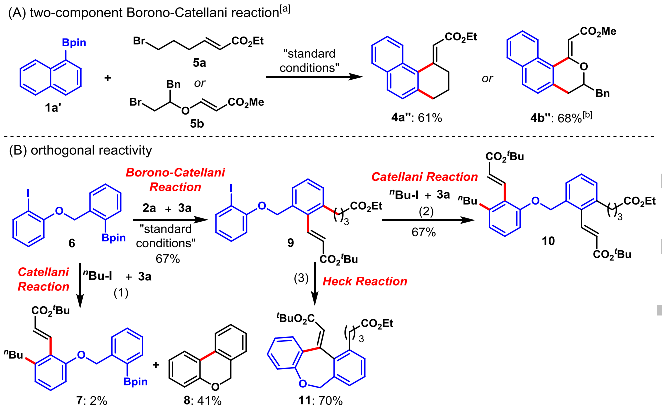
Table 3. Reaction scope with respect to the alkyl bromide and olefin.[a]



[a] All reactions were performed on a 0.2 mmol scale. Reported yields are for the isolated product, which are calculated based on the olefin.

To further illustrate the synthetic utility of this protocol, an annulation process was explored based on a speculated two-component Borono-Catellani process (Scheme 1A). It was found that **1a'** reacted with the bifunctional reagent **5a**[25a] and **5b** bearing a bromide and an olefin group, to afford the benzo-fused products **4a''** and **4b''** in 61% and 68% yields, respectively. A higher reaction temperature was needed for the latter to obtain a reasonable yield. Thus, the two-component Borono-Catellani process provides an attractive method complementary to the existing Catellani-type annulations.[25]

Compared to the classical Catellani reactions, the different reaction mechanism and the extremely mild reaction conditions of the current Borono-Catellani process prompted us to investigate the possible orthogonal reactivity[26] between them. The readily available bifunctional reagent **6** containing an iodo and a Bpin group was chosen as the model substrate. Under classical Catellani reaction conditions,[27] only trace amount of the Catellani product **7** was obtained, alongside the intramolecular Suzuki coupling product **8** as the major component. In sharp contrast, **6** was able to react with **2a** and **3a** under the standard Borono-Catellani reaction conditions to afford the Borono-Catellani product **9** in good yield (67%) with no classical Catellani product observed, which further demonstrated the excellent chemo-selectivity of this process. The intact iodo group in **9** enabled a conventional Catellani reaction to provide the product **10** in 67% yield. Thus, the orthogonal reactivity between the two types of Catellani reactions was evidently demonstrated. In addition, **9** could undergo a microwave promoted intramolecular Heck reaction[28] to form the complex polycyclized product **11** in good yield. Efforts are underway to utilize this strategy in the preparation of complex natural products and important therapeutics.



Scheme 1. Synthetic applications. [a] All reactions were performed on a 0.2 mmol scale. Reported yields are for the isolated products, which are calculated based on the olefin. [b] reaction temperature was 70 °C. Reagent and conditions: (1) Pd(OAc)$_2$, Ph$_3$P, NBE, Cs$_2$CO$_3$, CH$_3$CN, 90 °C, Ar, 1 h; (2) Pd(OAc)$_2$, Ph$_3$P, NBE, Cs$_2$CO$_3$, CH$_3$CN, 90 °C, Ar, 12 h; (3) Pd(OAc)$_2$, NaHCO$_3$, Bu$_4$NCl, DMF, 130 °C, mw, 40 min.

In summary, we have developed a Pd(II)-initiated Borono-Catellani reaction utilizing the widely accessible aryl boronic acids and derivatives as the substrates instead of aryl halides, thereby greatly expanding the existing paradigm of this powerful transformation. The inexpensive reagent 5-norbornene-2-carbonitrile is used as the mediator for the first time. Practicality is the salient feature of this Borono-Catellani reaction. It is run under air at ambient temperature while no phosphine ligand is needed. This mild, chemo-selective, and scalable protocol is compatible with a large range of readily available functionalized aryl boronic acids, bromides as well as terminating olefins. Moreover, the orthogonal reactivity between the Borono-Catellani and classical Catellani reactions was demonstrated. We believe this work should open up new avenues for developing novel Catellani-type reactions.

Acknowledgements

We are grateful to the National Key Research and Development Program of China (No. 2016YFB0101203), the National “1000-Youth Talents Plan”, the Innovation Team Program of Wuhan University (Program No. 2042017kf0232) and start-up funding from Wuhan University for financial support. We thank Prof. Wen-Bo Liu (Wuhan University) for sharing the instruments, Prof. P. Andrew Evans (Queen’s University) for helpful discussions, Prof. Wenjun Tang (Shanghai Institute of Organic Chemistry) and Dr. Ming Yan (Fish & Richardson) for assistance with the preparation of the manuscript.

Keywords: Catellani reaction • norbornene • cooperative catalysis • aryl boronic acid • air • orthogonal reactivity

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[19] **N⁸** is an inexpensive reagent, and the price is just 1.5 $/gram (from Energy Chemical).

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[22] The reactivity of various ary boronic acid derivatives, including the Molander salt was checked, and the results were described in SI, part 10.

[23] Reactions with secondary alkyl bromide suffered from low yields or even no reactivity under the current conditions.

[24] Some suitable olefins in Zhang’s work (Ref. 12), like phenyl vinyl sulfone, and allyl acetate suffered from low yields under the current conditions, which may result from the low reaction temperature.

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10.1002/anie.201803865

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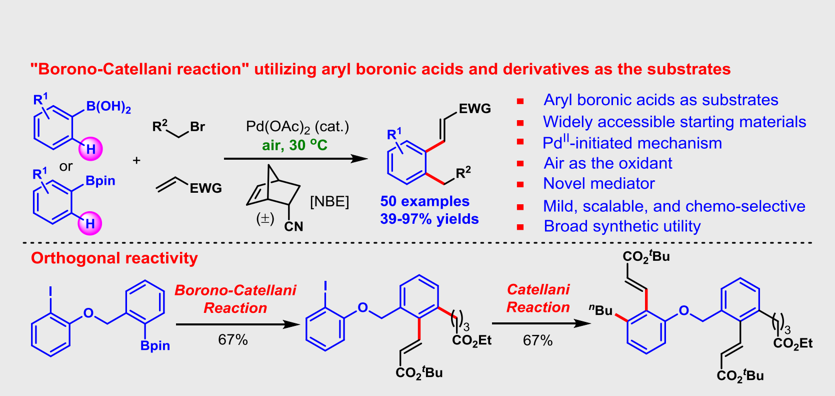

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The Discovery of A Pd(II)-Initiated Borono-Catellani Reaction

A Pd(II)-initiated Borono-Catellani reaction utilizing widely accessible aryl boronic acids as the substrates instead of aryl halides was developed. The reaction was promoted by cooperative catalysis of Pd(OAc)$_2$ and the inexpensive 5-norbornene-2-carbonitrile. Practicality is the salient feature of this reaction: It is run under air at ambient temperature while no phosphine ligand is needed. This mild, chemo-selective, and scalable protocol is compatible with a large range of readily available functionalized aryl boronic acids, bromides as well as terminating olefins (50 examples, 39-97% yields). Moreover, the orthogonal reactivity between the Borono-Catellani and classical Catellani reaction was demonstrated.