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Palladium-catalyzed prenylation of (hetero)aryl boronic acids

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ABSTRACT

Prenyl or dimethylallyl groups are common structural motifs in natural products and small molecule therapeutics. In this report, we describe a palladium-catalyzed method for the cross-coupling of aryl and heteroaryl boronic acids with prenyl alcohol. Catalyst systems based on dialkylbiaryl phosphines were highly active for this transformation. These supporting ligands provided opportunities for tuning the efficiency and regioselectivity of carbon–carbon bond formation. In addition, this method was further extended to the cross-coupling of symmetrical allylic alcohols with aryl boronic acids.

Introduction

Prenylation reactions provide a unique method for Nature to establish molecular complexity. This feature is eloquently showcased in transformations that covalently attach hydrophobic isoprene units to secondary metabolites [1,2]. In turn, prenyl (3,3-dimethylallyl) or reverse-prenyl (1,1-dimethylallyl) groups are found in bioactive terpenes, terpenoids, flavonoids, and related alkaloids (Fig. 1) [3–5]. Analogous processes can also afford polyisoprene chains (e.g. geranyl and farnesyl), and these structural motifs are accordingly observed in a myriad of natural products [6].

Guided by our recent synthetic efforts [7–9], we were interested in developing a palladium-catalyzed method that promoted the prenylation of aryl boronic acids. These nucleophiles are ideal as they generally lack toxicity and possess a high degree of functional group tolerance [10]. Aryl boronic acids have also proven successful as cross-coupling partners in palladium catalysis with symmetrical allylic electrophiles including allylic halides, acetates, and alcohols (Fig. 2A) [11–16]. Despite these advantages, the reaction of aryl boronic acids with unsymmetrical allylic electrophiles remains challenging, as two regioisomers may be produced. To circumvent this issue, previous reports have generally employed aryl-substituted allylic electrophiles, which bias the transformation to yield a single product (Fig. 2A) [17–23]. The cross-coupling reaction of prenyl electrophiles with aryl boronic acids can similarly result in two regioisomers: linear (prenyl) or branched (reverse-prenyl). However, carbon–carbon bond formation almost entirely favors the linear product versus establishing the quaternary carbon center found in the branched regioisomer [12,20,24–27].

In this study, we sought to define a palladium-based catalyst system for the cross-coupling of aryl boronic acids with a prenyl electrophile (Fig. 2B). In addition, given the difficulties associated with obtaining the reverse-prenyl group, we concurrently wanted to determine key factors that may overcome the inherent substrate bias of prenyl electrophiles and thereby increase branched product formation. This method would offer a complementary approach to elegant studies employing prenyl organoboranes [28,29]. Moreover, advancing these dual objectives would potentially provide new synthetic strategies to access prenyl-containing natural products.

Results and discussion

We examined two nucleophiles for the transformation: 3-methoxyphenyl boronic acid (**1a**) and 3-methoxyphenyl pinacol boronate ester (**1b**). These organoboranes were reacted with several electrophiles including prenyl alcohol (**2a**), chloride (**2b**), bromide (**2c**), and acetate (**2d**). However, no cross-coupling product was initially observed (Table 1, entries 1–8). A supporting ligand can increase catalyst stability and activity; therefore, each electrophile was resubjected to the reaction conditions in the presence of $P(2\text{-furyl})_3$ (Table 1, entries 9–12). In these experiments, **2b-2d** remained ineffective, whereas **2a** successfully furnished the desired carbon–carbon bond. The alcohol-based electrophile provided a 20% combined yield of the branched (**3B**) and linear (**3L**) products. Consistent with the literature, **3L** was favored in this

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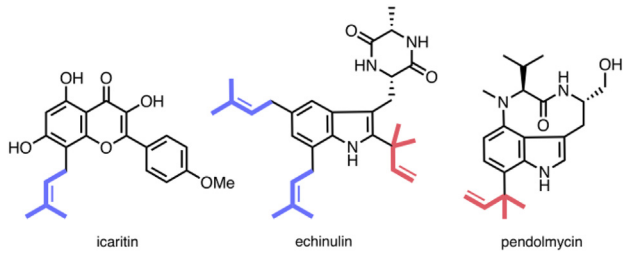


Fig. 1. Representative examples of bioactive natural products that integrate prenyl (blue) and/or reverse prenyl (red) groups.

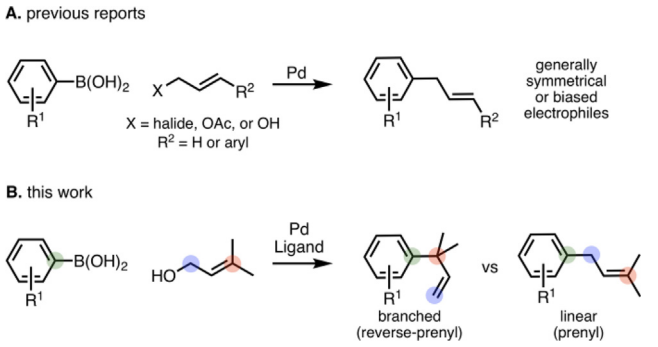


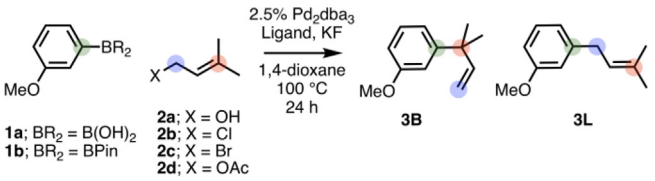
Fig. 2. (A) Brief overview of literature reports for the Pd-catalyzed allylation of aryl boronic acids. (B) General reaction for this study on the prenylation of aryl boronic acids.

initial reaction. Interestingly, the **3B**:**3L** ratio of 35:65 provided greater selectivity for the branched product than described in previous reports with prenyl alcohol, where 0–8% reverse-prenyl was observed [26,27]. These preliminary results suggested that (1) a supporting ligand would increase catalyst activity as well as reaction efficiency and (2) the ligand may influence the product distribution.

A focused library of monophosphine and diphosphine ligands was examined in the cross-coupling reaction of **1a** with **2a** (Table 1). Monophosphine ligands were more successful than their diphosphine counterparts. Specifically, no product was detected in reactions employing BINAP, DPPF, DPEphos, or XantPhos (Table 1, entries 17–20). In contrast, $P(OPh)_3$ displayed a comparable yield and product ratio as $P(2\text{-furyl})_3$ (Table 1, entry 13). $P(o\text{-tolyl})_3$ and P^tBu_2Me resulted in < 5% of the cross-coupling product (Table 1, entries 14–15). Interestingly, PPh_3 favored **3B** over **3L**, demonstrating a significant reversal of regioselectivity typically found for prenyl electrophiles (Table 1, entry 16). The reaction with PPh_3 remained low yielding (17%) though; therefore, a series of monophosphines were examined to determine whether branched selectivity could be maintained, while increasing reaction efficiency.

Dialkylbiaryl phosphines have proven highly effective in cross-coupling reactions employing aryl boronic acids [30–32]. In this study, we investigated a variety of these ligands for the cross-coupling reaction of **1a** with **2a** (Table 1) [33]. Several di-*tert*-butyl-derived ligands (i.e., JohnPhos, TrixiePhos, tBuXPhos) were initially examined, but minimal improvements to reaction yield or **3B**:**3L** ratio was observed (Table 1, entries 21–23). In contrast, catalyst systems based upon dicyclohexylbiaryl phosphines provided appreciable levels of the cross-coupling product (Table 1, entries 24–30). For example, DavePhos afforded a 42% yield with a **3B**:**3L** ratio of 57:43. Moreover, the nature of the ligand was found to substantially adjust the reaction efficiency and product distribution, as

Table 1
Optimization of reaction conditions Pd-catalyzed prenylation reaction.[a]



Entry	Nuc	Elec	Ligand	GC Yield (%)[b]	**3B**:**3L**[d]
1	**1a**	**2a**	—	0	—
2	**1a**	**2b**	—	0	—
3	**1a**	**2c**	—	0	—
4	**1a**	**2d**	—	0	—
5	**1b**	**2a**	—	0	—
6	**1b**	**2b**	—	0	—
7	**1b**	**2c**	—	0	—
8	**1b**	**2d**	—	0	—
9	**1a**	**2a**	$P(2\text{-furyl})_3$	20	35:65
10	**1a**	**2b**	$P(2\text{-furyl})_3$	0	—
11	**1a**	**2c**	$P(2\text{-furyl})_3$	0	—
12	**1a**	**2d**	$P(2\text{-furyl})_3$	0	—
13	**1a**	**2a**	$P(OPh)_3$	21	33:67
14	**1a**	**2a**	$P(o\text{-tolyl})_3$	<5	—
15	**1a**	**2a**	$PtBu_2Me$	<5	—
16	**1a**	**2a**	PPh_3	17	53:47
17	**1a**	**2a**	BINAP	0	—[e]
18	**1a**	**2a**	DPPF	0	—[e]
19	**1a**	**2a**	DPEphos	0	—[e]
20	**1a**	**2a**	XantPhos	0	—[e]
21	**1a**	**2a**	JohnPhos	7	57:43
22	**1a**	**2a**	TrixiePhos	<5	—
23	**1a**	**2a**	tBu-XPhos	31	34:66
24	**1a**	**2a**	CyJohnPhos	17	66:34
25	**1a**	**2a**	DavePhos	42	57:43
26	**1a**	**2a**	CPhos	24	62:38
27	**1a**	**2a**	RuPhos	29	58:42
28	**1a**	**2a**	BrettPhos	17	45:55
29	**1a**	**2a**	XPhos	89	34:66
30	**1a**	**2a**	SPhos	48	52:48
31	**1a**	**2a**	SPhos	60[c]	52:48[f]
32	**1a**	**2a**	SPhos	77[c]	60:40[f,g]

[a]Reaction Conditions: nucleophile (1.0 equiv), electrophile (10 equiv), KF (2.0 equiv), 1,4-dioxane (2 mL/mmol nucleophile), Pd_2dba_3 (0.025 equiv), Ligand:Pd = 2:1. [b]Combined GC yield of **3B** and **3L**; average of two experiments. [c]Combined isolated yield of **3B** and **3L**; average of two experiments. [d]Ratio of **3B**:**3L**. [e]Reaction conducted with Ligand:Pd = 1:1. [f]Reaction performed in toluene instead of 1,4-dioxane. [g]Reaction conducted at 80 °C instead of 100 °C.

the use of XPhos resulted in an 89% yield with selectivity for the linear product (Table 1, entry 29).

From these initial optimized conditions, Pd_2dba_3 with SPhos provided the highest activity among all catalyst systems that favored **3B** (Table 1, entry 30). In addition, an increase in yield to 60% was observed when the reaction was conducted with toluene as the solvent (Table 1, entry 31). The transformation was further found to be sensitive to temperature. At lower temperatures, Pd_2dba_3/SPhos resulted in an increased selectivity for **3B** but with concomitant loss of overall yield. Specifically, a 6% yield with a **3B**:**3L** ratio of 66:34 was observed at 60 °C. In contrast, elevated temperature (120 °C) resulted in a 75% yield but with opposing regioselectivity (**3B**:**3L** ratio of 43:57). Through further optimizations of reaction temperature and time, we determined that conducting the reaction at 80 °C for 72 h provided the highest yield (77%), while still favoring **3B** (Table 1, entry 32). These results with the Pd_2dba_3/SPhos catalyst system represent a promising advancement for overcoming the substrate bias found in the cross-coupling of prenyl electrophiles.

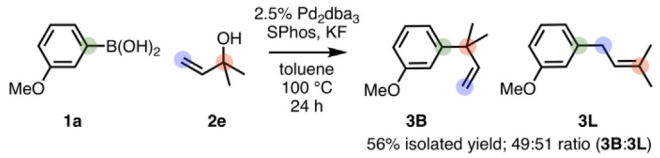
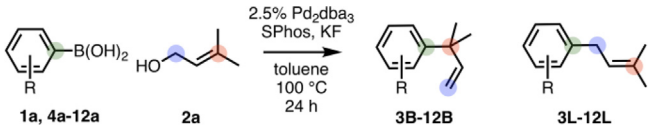


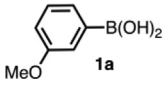
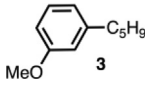
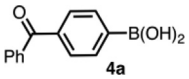
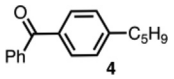
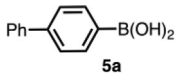
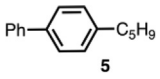
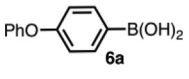
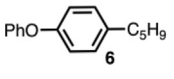
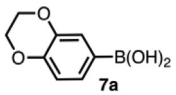
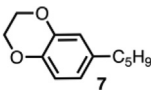
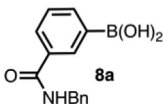
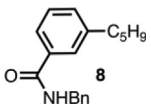
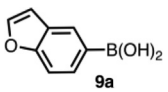
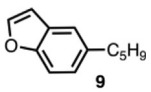
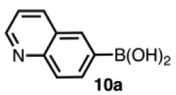
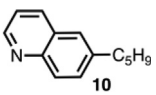
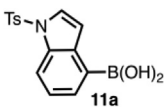
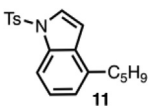
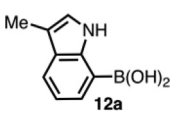
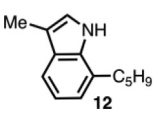
Fig. 3. Prenylation of **1a** with alcohol **2e**.

Our studies identified prenyl alcohol (**2a**) as a suitable electrophile for the prenylation of aryl boronic acids. However, because **2a** is a linear 1° alcohol, this starting material could be partially biasing the product distribution towards the linear regioisomer **3L**. To test this hypothesis, analogous experiments were conducted with 2-methylbut-3-en-2-ol (**2e**), a 3° alcohol that could directly lead to branched regioisomer **3B**. The Pd_2dba_3/SPhos catalyst system displayed comparable yields and product distributions with electrophiles **2a** and **2e** (Fig. 3). These experiment suggested that interconversion via a π-allyl intermediate was readily occurring during the catalytic cycle and therefore the outcome of the cross-coupling reaction was independent of the starting alcohol.

The substrate scope of Pd_2dba_3/SPhos catalyst system was examined with a variety of aryl and heteroaryl boronic acids (Table 2). Shorter reaction times are typically more practical in laboratory settings, so standard conditions of 100 °C for 24 h were adopted for evaluation of this methodology. The transformation was effective for aryl boronic acids possessing electronic properties ranging from electron-rich to -poor. For example, nucleophile **4a**, which possesses an electron-withdrawing ketone, displayed an enhanced yield of 86% (Table 2, entry 2). In addition, electron-neutral (**5a**) and -rich (**6a**) aryl boronic acids provided consistently high yields of 74% and 73%, respectively (Table 2, entries 3–4). The process proved to be less efficient for **7a**, a nucleophile with multiple electron-donating groups (Table 2, entry 5). The method was applicable to aryl boronic acids with reactive functional groups, and **8a**, which has a 2° amide bearing a free NH, success-

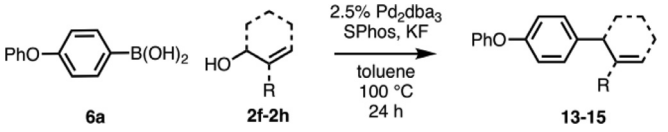
Table 2
Substrate scope of the Pd-catalyzed prenylation reaction.[a]



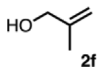
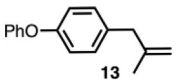
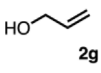
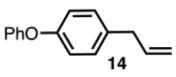
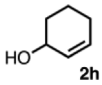
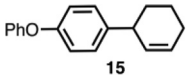
Entry	Nucleophile	Product	Yield (%)[b]	B:L[c]
1	 **1a**	 **3**	60	52:48
2	 **4a**	 **4**	86	48:52
3	 **5a**	 **5**	74	56:44
4	 **6a**	 **6**	73	46:54
5	 **7a**	 **7**	38	40:60
6	 **8a**	 **8**	63	45:55
7	 **9a**	 **9**	62	42:58
8	 **10a**	 **10**	69	46:54
9	 **11a**	 **11**	77	22:78
10	 **12a**	 **12**	32[d]	21:79

[a]Reaction Conditions: nucleophile (1.0 equiv), **2a** (10 equiv), KF (2.0 equiv), toluene (2 mL/mmol nucleophile), Pd_2dba_3 (0.025 equiv), SPhos:Pd = 2:1. [b]Combined isolated yield of **B** and **L**; average of two experiments. [c]Ratio of **B**:**L**. [d]Reaction conducted with Pd_2dba_3 (0.05 equiv).

Table 3
Pd-catalyzed allylation reaction with symmetrical alcohols.[a]



6a 2f-2h 13-15

Entry	Electrophile	Product	Yield (%)[b]
1	 2f	 13	65 (67)[c]
2	 2g	 14	40 (29)[c]
3	 2h	 15	59 (70)[c]

[a]Reaction Conditions: 6a (1.0 equiv), electrophile (10 equiv), KF (2.0 equiv), toluene (2 mL/mmol nucleophile), Pd_2dba_3 (0.025 equiv), SPhos:Pd = 2:1. [b]Isolated yield; average of two experiments. [c]Isolated yield for XPhos shown in parentheses.

fully furnished the cross-coupling product in 63% yield (Table 2, entry 6). For these substrates, the branched product consistently comprised 46–56% of the **B**:**L** ratio, which remained higher in terms of branched regioselectivity than comparable methods for the coupling of prenyl electrophiles with aryl boronic acids [26,27].

Heterocycles are structures of fundamental importance to the pharmaceutical industry and natural product synthesis [34]; therefore, we explored the applicability of this methodology to several heteroaryl boronic acids. Electron-rich 5-benzofuran boronic acid (**9a**) smoothly furnished the desired cross-coupling product in 62% yield with a **9B**:**9L** ratio of 42:58 (Table 2, entry 7). In addition, quinoline-6-ylboronic acid (**10a**) successfully provided a 69% yield with a similar product distribution (Table 2, entry 8). Indole-based boronic acids were also examined. The *N*-protected indole (**11a**) provided a high yield (77%), whereas the free-NH substrate (**12a**) displayed a decrease in reaction efficiency even with elevated catalyst loadings (Table 2, entries 9–10). Linear selectivity was found for both of these nucleophiles. This observation could be attributed to the fact that each substrate possesses *ortho*-substitution, which may further shift the product distribution towards the linear regioisomer. Importantly, the Pd_2dba_3/SPhos catalyst system remained highly active for both aryl and heteroaryl boronic acids.

To further illustrate the applications of this methodology, we also sought to demonstrate that the catalyst remained active for standard allylic alcohols. Experiments were conducted with 4-phenoxyphenylboronic acid (**6a**) and several symmetrical allylic alcohols: 2-methylprop-2-en-1-ol (**2f**), prop-2-en-1-ol (**2 g**), and cyclohex-2-en-1-ol (**2 h**) (Table 3). The Pd_2dba_3/SPhos system maintained consistently high yields (65% and 59%, respectively) for alcohols **2f** and **2 h**, whereas electrophile **2 g** was less efficient (Table 3, entries 1–3). The standard conditions require the reaction to be conducted slightly above the boiling point of alcohol **2 g**, which may contribute to the lower observed yield.

The reactions of **2f**-**2 h** should produce symmetrical π-allyl systems; therefore, we hypothesized that XPhos would be beneficial in these studies, as Pd_2dba_3/XPhos was highly active during initial optimization. Indeed, employing XPhos as the supporting ligand provided an increase in yield of cross-coupling products **13** and **15** (Table 3, entries 1 and 3). No further improvements were found for electrophile **2 g** though. Importantly, these results collectively demonstrated that the substrate scope of the cross-coupling reaction could be extended to both prenylations as well as direct allylations using symmetrical electrophiles. The latter fact is key, as this methodology could prove generally applicable to a variety of molecular targets in organic synthesis.

Conclusion

In summary, we have developed a palladium-based cross-coupling method that allows for the prenylation of aryl and heteroaryl boronic acids in moderate to good yield (32–86%). Prenyl alcohol was identified as the ideal electrophile for the transformation. Catalyst systems based upon dicyclohexylbiaryl phosphines were most effective for promoting carbon–carbon formation, and Pd_2dba_3/SPhos provided increased levels of reverse-prenyl product relative to previous reports employing prenyl electrophiles. This method was further demonstrated with symmetrical allylic alcohols. Future studies will focus on application of this methodology to the synthesis of therapeutically relevant natural products.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152800.

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