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Regioselective Cross-Coupling of Allylboronic Acid Pinacol Ester Derivatives with Aryl Halides via *Pd-PEPPSI-IPent*

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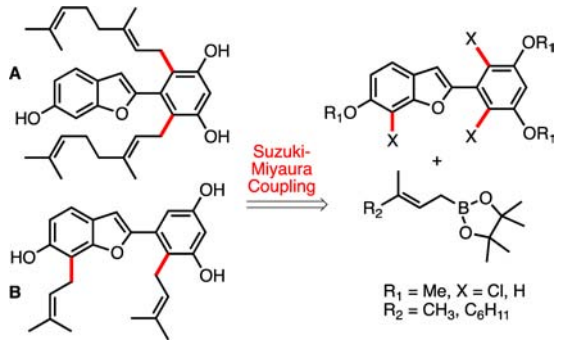
Supporting Information

ABSTRACT: The cross-coupling reactions of allylboronic acid pinacol ester derivatives with aryl and heteroaryl halides occurred with high selectivity (>97%) at the α-carbon of the allylboron reagent in the presence of *Pd-PEPPSI-IPent* precatalyst and 5 M KOH in refluxing THF. In the case of trisubstituted allylboronates with different substituents on the olefin, minor olefin geometry isomerization was observed ($E/Z \approx 80/20$).

Isoprenylated arenes are found in the structure of many natural products, several of which demonstrate biological and pharmacological activities.[1] Among these compounds are cathafurans A and B (Scheme 1), which have antimicrobial,

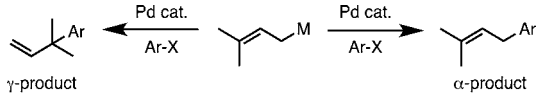
Scheme 1. Synthetic Approach to Cathafurans A and B



antioxidative, anti-inflammation, and cytotoxic activities.[2] The retrosynthetic route that we have developed to prepare these compounds is based on the introduction of prenylated side chains to an advanced benzofuran building block via Suzuki–Miyaura cross-coupling (Scheme 1).

While cross-coupling has proven to be one of the most powerful and direct methods for introducing prenyl and geranyl side chains into aromatic systems, controlling the regioselectivity has proven challenging. The catalyst ligand and structure of the organometallic reagent employed impacts this selectivity (Scheme 2).[3−5,14−16] Despite the many advantages of organoboron reagents, including air and moisture stability and low toxicity, few studies have yielded high and reliable regioselectivity with allylic derivatives. While Miyaura[5a−c] and Szabó[5d−f] have developed conditions using phosphine ligands to achieve high selectivity for the branched product (i.e., the γ-isomer) with allyltrifluoroborates and allylboronic acids, respectively, no catalyst system that is selective for the linear

Scheme 2. Formation of α- and γ-Coupling Products via Pd-Catalyzed Cross-Coupling Reactions



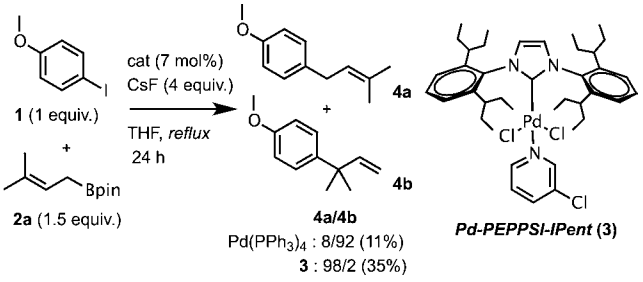
Ar = aryl; X = OTf, Br, I; M = Mg, Zn, B, Si, Zr, Cu

product (i.e., the α-isomer) has been developed to date. This is unfortunate since most natural products contain prenyl and geranyl side chains attached at the α-carbon. Armed with this information, we set out to find conditions that would be selective for the linear product, thus providing access to cathafurans A and B.

Optimal conditions for α-selective allylation with $Pd(PPh_3)_4$ have been reported by Podestá and co-workers for the cross-coupling of aryl iodides with prenylboronic acid pinacol ester (**2a**).[5g,6] Using this as a starting point, we wanted to evaluate our most active Pd–NHC complex, *Pd-PEPPSI-IPent* (**3**), in the coupling of 4-iodoanisole (**1**). While **3** has performed well in sp^2–sp^2 and sp^3–sp^3 Suzuki–Miyaura[7] and Negishi[8] cross-coupling reactions, its application in sp^2–sp^3 coupling reactions involving allylic metals with aryl and/or alkenyl electrophiles has not yet been explored. Interestingly, in our hands $Pd(PPh_3)_4$ actually generated the branched (γ) product almost exclusively, rather than the linear (α) one as we anticipated. However, **3** did show very high selectivity for the linear product (Scheme 3).

While the selectivity was very high with **1**, reduction of the iodide and homocoupling were unavoidable, leading to a low yield of allylated products **4**. Consequently, we opted to conduct further studies using an aryl bromide instead. 1-

Scheme 3. Comparison of $Pd(PPh_3)_4$ and *Pd-PEPPSI-IPent* (3) in the Allylation of 1 with 2a



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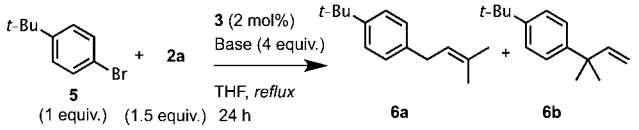
Bromo-4-*tert*-butylbenzene (**5**) and **2a** were chosen to optimize the reaction conditions and to study the kinetics for this transformation because **5** showed no steric or electronic bias[9] and was suitable for analysis by GC/MS. A short base/solvent optimization study (Table 1) showed that 5 M KOH (4 equiv)

Table 1. Optimization of Suzuki–Miyaura Reaction Conditions: Base Study



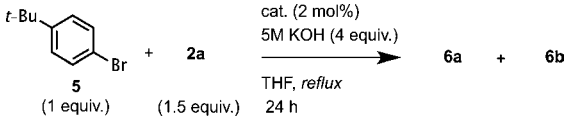
entry	base	conv. (%)[a]	6a/6b
1	KF	0	0
2	CsF	42.5	98/2
3	TBAF	<4	100/0
4	K_2CO_3	<4	100/0
5	KOH	10	100/0
6	KO^{t}Bu	0	0
7	2 M K_2CO_3	18.5	96/4
8	5 M KOH	81	97/3

[a]Determined by GC/MS using a calibrated internal standard (undecane); reactions were performed in duplicate.

in tetrahydrofuran (THF) provided optimal results (entry 8); under anhydrous conditions, the conversion was poor (entries 1–6). Although CsF was better than KF, switching to tetrabutylammonium fluoride (TBAF), which was fully soluble, led to poorer conversion (entries 1–3). Interestingly, K_2CO_3, one of the most common bases used in a variety of Suzuki–Miyaura cross-coupling applications, led to poor conversion both with (entry 7) and without (entry 4) water.

To be certain that the *IPent* ligand was responsible for the observed regioselectivity, we screened several other ligands reported to produce the α-isomer preferentially (Table 2).

Table 2. Effect of Ligands



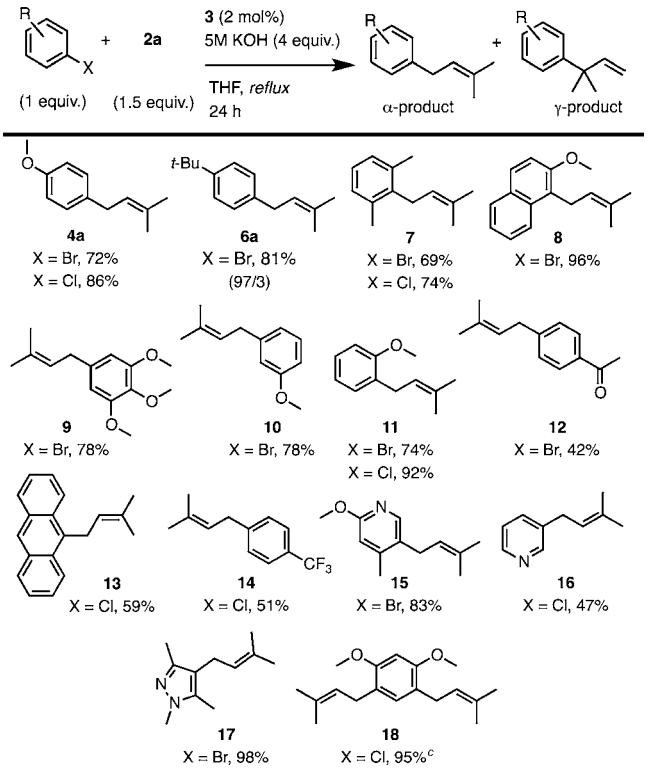
entry	cat	conv. (%)[a]	6a/6b
1	$Pd(OAc)_2$/dppe	90	56/44
2	$Pd(OAc)_2$/dppp	76	54/46
3	$Pd(PPh_3)_4$	90	5/95
4	*Pd-PEPPSI-IPr*	86	93/7
5	*Pd-PEPPSI-IPent* (**3**)	81	97/3

[a]Determined by GC/MS using a calibrated internal standard (undecane); reactions were performed in duplicate.

Dppe and dppp were unselective despite their difference in bite angles (entries 1–2). This was surprising since other groups have found significant differences between these two ligands in other Pd-catalyzed cross-couplings.[3–5] Once again, $Pd(PPh_3)_4$ showed high selectivity for the γ-isomer **6b**, while both the *IPr* and *IPent* ligands displayed high selectivity for α-isomer **6a**, with *IPent* providing slightly higher α selectivity.[10]

With optimization completed, **3** was evaluated in the allylation of a variety of aryl and heteroaryl halides with **2a** (Table 3). The reactions proceeded smoothly under these

Table 3. Allylation of Aryl Halides with 2a Catalyzed by 3[a,b]



[a]Yields of isolated products following silica gel chromatography (averages of two runs) are reported. [b]Product ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures and were >99/1 (α/γ) unless otherwise indicated. [c]3 equiv of **2a** and 8 equiv of 5 M KOH were used.

conditions regardless of how sterically or electronically deactivated the aryl halide. Since the aryl bromides showed good reactivity, attention was then focused on aryl chlorides, as there are no such couplings reported in the literature. The reactions proceeded smoothly and in most cases were higher-yielding than the corresponding reactions with aryl bromides, which we attribute to less reduction. We were also pleased to see that the reaction conditions could be extended to dihaloarenes such as **18**. In all cases, heterocyclic halides coupled uneventfully.

While the exact mechanism by which allylboranes are transmetalated remains unclear, there is evidence to support either addition–elimination[5f] or an inversion (S_E2') process[5c] for γ-selective coupling reactions. An S_E2' mechanism would be promoted by bulky phosphine ligands that could facilitate fast reductive elimination to give the observed γ-regioselectivity. In both cases, the formation of a (π-allyl)palladium(II) intermediate, (e.g., **26** in Scheme 4) which would lead to α-coupling, was ruled out.[5c,f]

To examine the possible formation of **26**, we carried out a classical allylic substitution reaction of prenyl bromide (**19**) with **20** in the presence of $Pd(PPh_3)_4$ or **3** (eq 1). Both catalysts provided marginal regioselectivity, which was surprising since other Suzuki-type allylations have been reported to proceed preferentially to give the linear product (e.g., **4a**).[11] The results in eq 1 could be interpreted to indicate that following ionization, the less hindered σ complex is slightly favored in the equilibrium because of steric interactions with the ligands. If it is assumed that reductive elimination is

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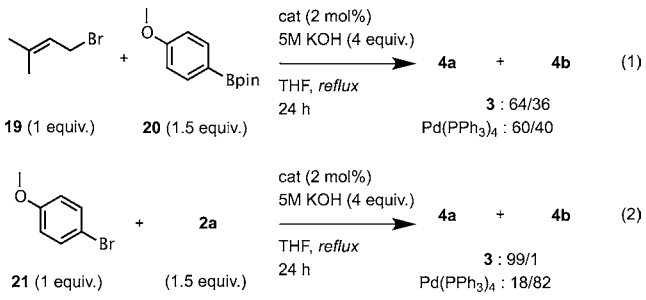
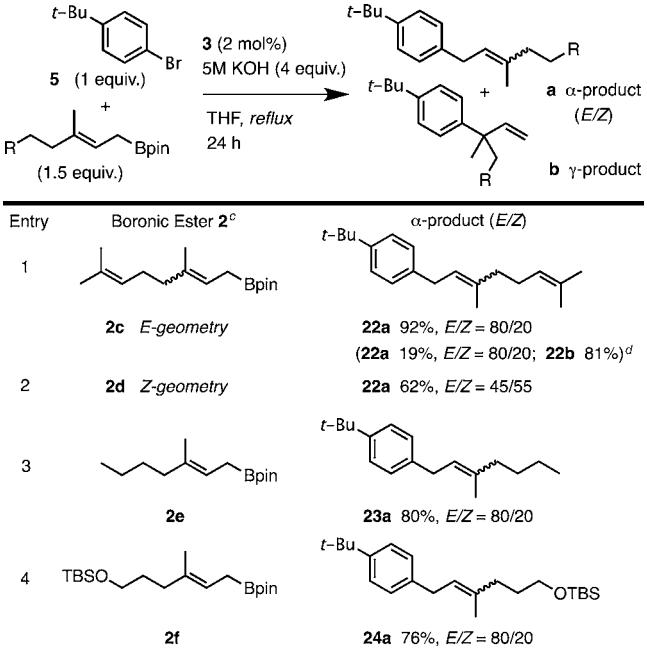


relatively fast with both catalysts, the α- and γ-isomers would be produced in the same ratio as their corresponding Pd σ complexes. In other words, while there is $\sigma-\pi-\sigma$ interconversion following ionization of the bromide that leads to an equilibrium of σ complexes, there is no such interconversion following transmetalation, which would be consistent with proposals by Miyaura[5c] and Szabó.[5f] However, the results of eq 1 are in stark contrast to those of eq 2, which formed identical products through similar if not identical intermediates. Here $Pd(PPh_3)_4$ gave primarily the γ-product (**4b**) while **3** gave exclusively the α-product (**4a**), as was the case for all earlier examples in the manuscript.

To probe further the existence of a post-transmetalation π-allyl complex resembling **26**, we substituted one of the methyl groups on **2a** with different groups and different olefin geometries to look for scrambling of the olefin stereochemistry (Table 4). Indeed, there appeared to be a small amount of

Table 4. Allylation of 5 with Allylboronic Acid Pinacol Ester Derivatives Catalyzed by 3[a,b]



Entry	Boronic Ester **2**[c]	α-product (*E*/*Z*)
1	**2c** *E-geometry*	**22a** 92%, *E*/*Z* = 80/20 (**22a** 19%, *E*/*Z* = 80/20; **22b** 81%)[d]
2	**2d** *Z-geometry*	**22a** 62%, *E*/*Z* = 45/55
3	**2e**	**23a** 80%, *E*/*Z* = 80/20
4	**2f**	**24a** 76%, *E*/*Z* = 80/20

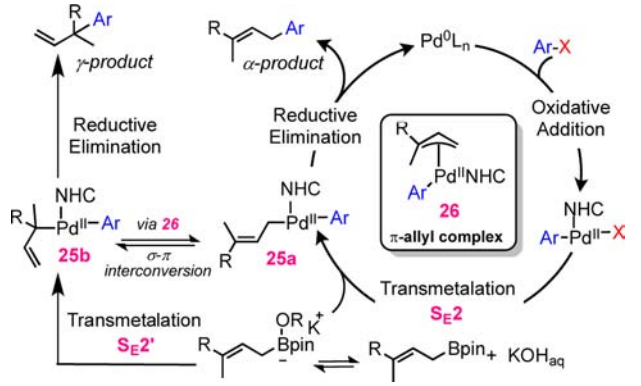
[a]Yields of isolated products following silica gel chromatography (averages of two runs) are reported. [b]Product ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixtures and were >99/1 (α/γ) unless otherwise indicated. *E*/*Z* product ratios were determined by 1D and 2D NMR spectroscopy [see the Supporting Information (SI)]. [c]For the preparation of allylboronates **2c** and **2d**, see refs 6 and 13, respectively. For the preparation of **2e** and **2f**, see the SI. [d]The yields and isomer ratio obtained using $Pd(PPh_3)_4$ are given in parentheses. The yield of the combined products was 93%.

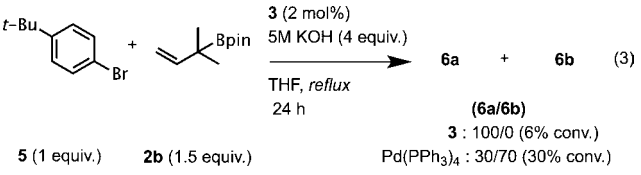
leakage of olefin stereochemistry that presumably must have taken place through the formation of a Pd–π-allyl complex. In all cases starting with the (*E*)-allylboronate, the same 80/20 *E*/*Z* ratio was observed. However, the results in entries 1 and 2 are instructive. Whereas the (*E*)-geranylborane gave 80/20 *E*/*Z* **22a**, the *Z* isomer led to only 45% scrambling of the *Z* stereochemistry (i.e., *Z* to *E*). These results show that limited $\sigma-\pi-\sigma$ interconversion occurs via π-allyl complex **26** with catalyst **3**, as the two different boronate isomers do not reach equilibrium before reductive elimination occurs. This experiment did confirm that reductive elimination with catalyst **3** is relatively fast.

As this manuscript focuses primarily on the regioselectivity aspect of this allylation with allylboronates, it is noteworthy that the more complex substrates in Table 4, some of which possessed coordinating functionality, still rigorously provided α-selectivity with **3**; no γ-isomer was observed. To this point, when $Pd(PPh_3)_4$ was used (entry 1), the primary product was again the γ-isomer, further demonstrating the unique selectivity that can be achieved with catalyst **3** relative to any other catalyst in the literature.

The remaining issue that we tried to clarify was the mechanism of transmetalation itself. Since **3** has been shown to facilitate fast reductive elimination in other cross-coupling reactions because of its bulky nature,[8] we believe that transmetalation proceeds without allylic transposition (S_E2) (Scheme 4). To investigate this, we reacted **2b**[12] with **5** in the

Scheme 4. Proposed Mechanism





presence of **3** and obtained very little product (eq 3). This suggests that transmetalation, at least with the *IPent* ligand on Pd, does not proceed by an S_E2' mechanism. One might expect that if transmetalation first involves olefin coordination, then **2b** might actually transmetalate as fast or faster than **2a**. That it scarcely reacted suggests that transmetalation with **3** is S_E2 in nature and that the borane is simply too hindered to allow it to be activated. This also suggests that coordination of the olefin in **2a** to the catalyst metal during transmetalation is not likely, as the olefin in **2b** is sterically less hindered than **2a**. In contrast, a different outcome was obtained in the reaction with

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$Pd(PPh_3)_4$, which proceeded to ~30% conversion (eq 3). Thus, while the reaction with $Pd(PPh_3)_4$ did not go to completion, it proceeded significantly farther than that with **3**. Taken together, these results suggest that transmetalation with **3** proceeds by an S_E2 mechanism but in the case of $Pd(PPh_3)_4$ may well proceed by an S_E2' pathway.

In conclusion, sterically bulky *Pd-PEPPSI-IPent* (**3**) has shown to be extremely reactive in the metal-catalyzed allylation of allylboronate derivatives. The higher α-selectivity demonstrated by **3** in comparison with all other Pd catalysts in the Suzuki–Miyaura cross-coupling of prenylboronic acid pinacol ester **2a** with a variety of aryl halides illustrates that this process can now be used with high reliability to produce such allylated aromatics. This is especially important because isomeric allylated products typically cannot be separated. We attribute the observed regioselectivity primarily to both the significant steric bulk of the NHC ligand and the substitution of the allylboronic ester. This new protocol will serve to complement the useful γ-selectivity demonstrated by Miyaura[5a−c] and Szabó.[5f] While reactive allylmetal species formed from metals such as Mg,[14] Zn,[15] and In[16] can be coupled under mild conditions, those systems have failed to demonstrate high selectivity in metal-catalyzed allylation. Furthermore, while allylstannanes[4] have demonstrated good linear selectivity, the coupling requires harsh conditions and confronts the chemist with tin waste and purification problems that the boronate system does not.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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