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Pd-Catalyzed Hydroborylation of Alkynes: A Ligand Controlled Regioselectivity Switch for the Synthesis of α- or β-Vinylboronates

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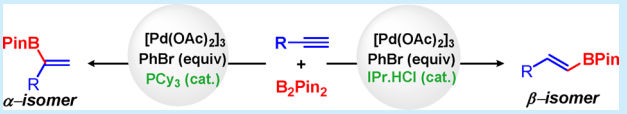
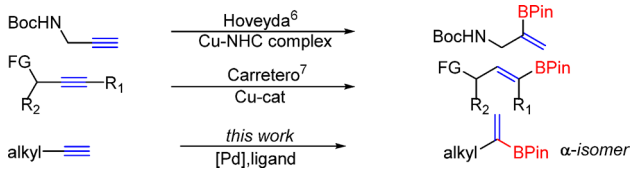
Supporting Information

ABSTRACT: A ligand controlled selective hydroborylation of alkynes to α- or β-vinylboronates has been developed using a Pd catalyst. The high α-selectivity displayed by this reaction can be switched to furnish β-vinylboronates by altering the ligand from a trialkylphosphine to N-heterocyclic carbene. A variety of terminal alkynes are shown to furnish the corresponding α- or β-vinylboronates in good to excellent selectivity and yield. The mechanistic studies suggest that the solvent is the proton source and bromobenzene functions as an important additive in driving this reaction forward.



The hydroborylation of alkynes is one of the fundamental reactions for the synthesis of vinylboron compounds in organic chemistry. Vinylboronate esters are an important class of intermediates used in a variety of organic transformations,[1] such as Suzuki−Miyaura coupling, Chan−Lam coupling, Petasis reaction, Hayashi−Miyaura conjugate addition, and stereospecific C−C bond forming reactions.[2−4] Studies on hydroborylation of alkynes have resulted in the discovery and use of various metal catalysts such as Cu, Rh, Ni, Co, etc., to accompolish the synthesis of vinylboron species.[3,4] A vast majority of these hydroborylations furnish the corresponding β-isomers,[5] whereas reports of selective formation of α-borylated products are limited. Synthesis of α-vinylboronates requires a multistep reaction sequence, and these utilize vinyl halides as precursors. Therefore, direct one-step synthesis of α-vinylboronates using alkynes as a precursor is necessary, but it is a challenging task. The only method for selective hydroborylation of terminal alkynes to α-vinylboronates was reported by Hoveyda in 2011, by employing NHC−Cu complexes (Scheme 1). However, α-vinylboronates can also be obtained using

Scheme 1. Regioselective Hydroboration of Alkynes



aliphatic allenes.[6] Further, using a directing group strategy, Carretero's group has documented the Cu-catalyzed selective borylation of internal alkynes (Scheme 1).[7] Nevertheless, until now a direct method for selective hydroboration of alkynes to obtain α-vinylboronates using Pd catalysts has not been reported.

The metal catalyzed hydroborylations of alkynes proceed in a three-step process: (i) formation of a metal-BPin species; (ii) addition of a metal-Bpin species across the alkynes, generating an organometallic species; and (iii) quenching of the organometallic species with electrophiles. The regioselectivity observed in the addition M-Bpin species is governed by the steric and electronics factors of both metal complex and alkyne substitutions. In continuation of our work on Pd-catalyzed reactions,[8] and based on the literature precedence on borylation of alkenes,[4i] we envisioned borylation reactions of alkynes using an aryl halide and Pd catalyst. Thus, herein we reveal an unprecedented Pd-catalyzed hydroborylation of terminal alkynes to selectively furnish α- or β-vinylboronates wherein the ligand plays a decisive role in the regioselectivity of the reaction.

The optimization studies were initiated with nonyne (**1a**) and B_2Pin_2 by employing various ligands. After evaluating several palladium catalysts, ligands, and additives, we found that a combination of $[Pd(OAc)_2]_3$ (5 mol %), PCy_3 (10 mol %), CF_3CH_2OH, and bromobenzene in toluene furnished the product **2a** in 85% yield with excellent regioselectivity (90% α-selectivity, entry 1, Table 1). The aryl bromide was found to furnish phenylboronic acid pinacol ester (**4**) as the byproduct in almost quantitative yields.

Once the optimal conditions were established, an intensive screening study was performed to validate the reaction conditions. The reaction in the absence of a palladium catalyst did not furnish any product, whereas the reaction in the absence of ligands was ineffective (entries 2−3, Table 1). Use of other monophosphine ligands, such as XPhos, *t*-Bu-XPhos, and P(*o*-tolyl)$_3$, furnished the expected product **2a** in only trace amounts (entries 4−6). The use of a *bis*-phosphine ligand, *rac*-BINAP, also proved to be completely ineffective (entry 7). Interestingly, the use of an N-heterocyclic carbene precursor, IPr·HCl, as a ligand with a catalytic amount of *tert*-BuOK (12 mol %) was found to completely reverse the selectivity of the reaction, furnishing β-vinylboronate **3a** in high selectivity and good yield (83% selectivity and 80% yield, entry 9). Using the Pd(dppf)Cl_2

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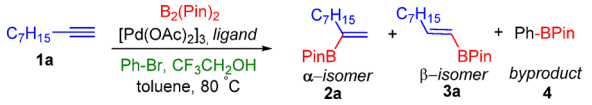
Table 1. Optimization Studies[a,b]



entry	reagents and conditions	yield[c] (%)	α:β
1	B_2Pin_2, $[Pd(OAc)_2]_3$ (5 mol %), PCy_3 (10 mol %), PhBr (1.1 equiv), TFE (2 equiv), toluene, 80 °C	85	**90:10**
Deviations from the standard condition			
2	*w/o* $[Pd(OAc)_2]_3$	NR	–
3	in the absence of ligands	trace	–
4	XPhos instead of PCy_3	10	60:40
5	^{t}BuXphos instead of PCy_3	NR	–
6	P(*o*-tol)$_3$ instead of PCy_3	15	65:35
7	*rac*-Binap instead of PCy_3	30	70:30
8	1,10-Phen instead of PCy_3	NR	–
9	**IPr·HCl instead of PCy_3**	**80**	**17:83**[d]
10	$Pd(dppf)Cl_2$ instead of $[Pd(OAc)_2]_3$	NR	–
11	*w/o* PhBr	NR	–
12	PhI instead of PhBr	22	–
13	MeOH instead of TFE	38	71:29

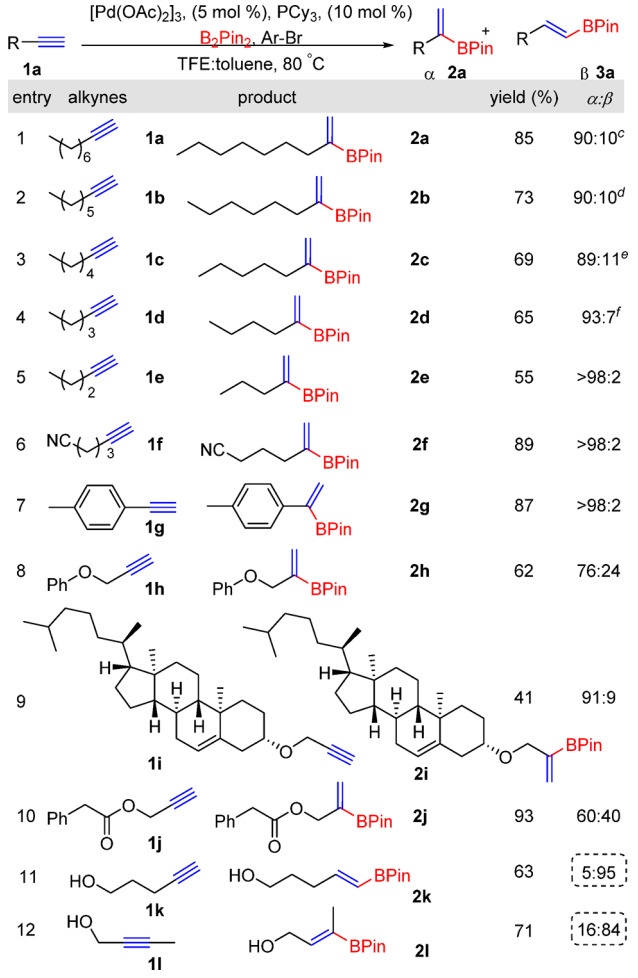
[a]Reaction conditions: **1a** (1 mmol), B_2Pin_2 (1.1 equiv), toluene (1.5 mL), 12 h. [b]TFE: trifluoroethanol. [c]Isolated yields. [d]*tert*-BuOK (12 mol %). NR = No reaction.

catalyst instead of the standard catalyst in the reaction did not furnish the expected product (entry 10). Moreover, the reaction in the absence of phenyl bromide did not furnish any product (entry 11) indicating that the oxidative oxidative insertion of an aryl halide is a necessary process for the reaction to initiate. The utility of phenyl iodide was found to be detrimental, as the reaction furnished a quantitative amount of Suzuki product **4** along with the borylated product **2a** in low yield (22%, entry 12). It was also found that MeOH as a protonating source was not effective in improving the yield of the product **2a** (38%, entry 13).

With these optimized conditions, we started examining the scope of the hydroboration reaction with a variety of alkynes with varying reactivity (Table 2). Terminal aliphatic alkynes having linear hydrocarbon chains furnished the corresponding borylated products (**2a**–**2e**) in high regioselectivity (>90% α-selectivity) and in good yields (entries 1–5, Table 2).[9] The high α-selectivity observed for the hydroborylation of *n*-alkyl substituted acetylenes is rare, and to the best of our knowledge such a transformation requires a multistep reaction sequence.[10] Further we explored the potential of the present strategy by subjecting substrates which possess reactive functional groups. Thus, the reaction of substrate with a nitrile functional group such as 5-cyanopentyne (**1f**), under the optimal catalytic conditions, furnished exclusively the α-vinylboronate (**2f**, >98:2) in excellent yield (89%, entry 6, Table 2). Considering the coordinating ability of a cyano group with Pd, the selectivity observed in this hydroborylation reaction is unique.[11] An aryl acetylene, 1-ethynyl-4-methylbenzene (**1g**), under the optimal reaction conditions afforded the corresponding α-borylated product **2g** in excellent yield with high regioselectivity (87% yield and 98% α-selectivity, entry 7).

Propargyloxy functional groups are sensitive substrates due to their intrinsic ability to form π-allyl complexes with palladium.[12] Moreover, it is well-known that heteroatoms coordinate to a nearby metal atom, affecting the regioselectivity of the reactions and yields. Surprisingly, under the present reaction conditions,

Table 2. Synthesis of α-Vinylboronates[a,b]



entry	alkynes		product		yield (%)	α:β
1		**1a**		**2a**	85	90:10[c]
2		**1b**		**2b**	73	90:10[d]
3		**1c**		**2c**	69	89:11[e]
4		**1d**		**2d**	65	93:7[f]
5		**1e**		**2e**	55	>98:2
6	NC	**1f**	NC	**2f**	89	>98:2
7		**1g**		**2g**	87	>98:2
8	Ph–O	**1h**	Ph–O	**2h**	62	76:24
9		**1i**		**2i**	41	91:9
10	Ph	**1j**	Ph	**2j**	93	60:40
11	HO	**1k**	HO	**2k**	63	5:95
12	HO	**1l**	HO	**2l**	71	16:84

[a]Reaction conditions: **1a** (1 mmol), B_2Pin_2 (1.1 equiv), PhBr (1.1 equiv), [Pd] (5 mol %), ligand (10 mol %), TFE (2 equiv), toluene (1.5 mL), 80 °C, 12 h. [b]Isolated yields. [c]**3a** (*E*/*Z* 65:35). [d]**3b** (*E*/*Z* 50:50). [e]**3c** (*E*/*Z* 25:75). [f]**3d** (*E*/*Z* 70:30).

propargyl substrates such as phenyl propargyl ether (**1h**) and *O*-propargyl ether of cholesterol (**1i**) underwent a facile hydroborylation reaction to furnish the corresponding α-vinylboronates **2h** and **2i** in good yields (entries 8 and 9) and moderate to high regioselectivity. Further, the propargyl ester of phenyl acetic acid also underwent facile reaction to furnish the corresponding α-vinylboronates in moderate selectivity (60:40) but high yields (93%, entry 10, Table 2).

While propargyl ethers exhibit very good α-selectivity, the reactions of ω-hydroxy alkynes under the same reaction conditions, surprisingly furnished the β-borylated products. This complete reversal of selectivity may be attributed to the coordination of the catalytic species to the free-hydroxyl groups in the molecule or on the basis of hydroxyl directed oxidative metalation across the alkyne.[13] Thus, the reactions of pent-4-yn-1-ol and but-2-yn-1-ol under the optimal conditions furnished the β-borylated products **2k** and **2l** in good yields (63% and 71%, Table 3) with excellent β-selectivity (95% and 84%, respectively). Hydroboration of terminal aliphatic alkynes using metal complexes of Rh, Ti, Ir, Cu, and Zr which lead to the formation of β-vinylboronates is known in literature.[14] However, such reactions are unknown with Pd complexes. We explored a few representative *n*-alkyl acetylenes to check the generality of the

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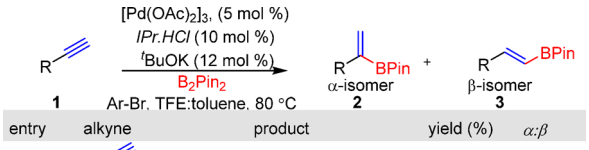
Table 3. Synthesis of β-Vinylboronates[a,b]



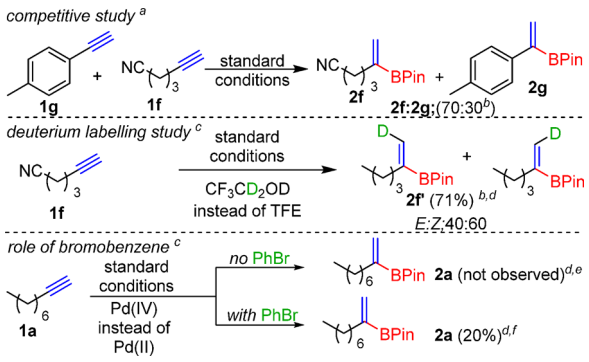
entry	alkyne	product	yield (%)	α:β
1	**1a**	**3a**	80	15:85
2	**1b**	**3b**	76	8:92
3	**1c**	**3c**	85	9:91
4	**1m**	**3d**	81	2:98

[a]Reaction conditions: **1a** (1 mmol), B_2Pin_2 (1.1 equiv), PhBr (1.1 equiv), [Pd] (5 mol %), ligand (10 mol %), tBuOK (12 mol %), TFE (2 equiv), toluene (1.5 mL), 80 °C, 12 h. [b]Isolated yields.

selectivity switch. Accordingly, we used IPr·HCl (N-heterocyclic carbene precursor) as a ligand in the presence of a base, *tert*-BuOK, with non-1-yne (**1a**), and this reaction resulted in an efficient β-borylation (84:16) to form **3a** in good yield (80% yield, entry 1, Table 3). A similar outcome was also observed with octyne (**1b**) and heptyne (**1c**) to obtain the corresponding borylated products **3b** and **3c** in good yields (76% and 85%) with high β-selectivity (92% and 91%, respectively, entries 2 and 3). An arylacetylene, phenyl acetylene, was also tested under similar reaction conditions, which afforded the expected product **3d** in 81% yield with excellent β-selectivity (98%, entry 4).

A competitive experiment was undertaken to determine if the electronic nature of the alkyne has any role in the reaction. Accordingly, a reaction of 1-ethynyl-4-methylbenzene (**1g**) and 5-cyanopentyne (**1f**) under standard reaction conditions resulted in the formation of the corresponding products, **2f** and **2g**, in the ratio 70:30 (Scheme 2). As expected, this shows that aliphatic

Scheme 2. Mechanistic Studies

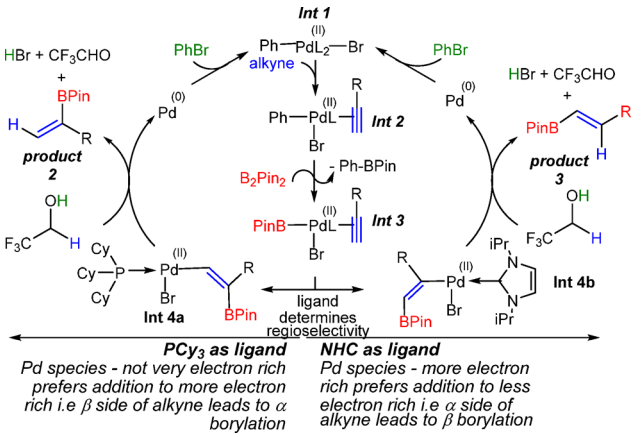


[a]Reaction conditions: **1g** (0.5 mmol). **1f** (0.5 mmol). [b]Isolated yield. [c]CF_3CD_2OD (2 equiv). [d]Yield based on ^1H NMR. [e]**1a** (1 mmol), no PhBr, K_2PdCl_6 (5 mol %) instead of $[Pd(OAc)_2]_3$. [f]**1a** (1 mmol), PhBr (1.1 equiv), K_2PdCl_6 (5 mol %) instead of $[Pd(OAc)_2]_3$.

alkynes, which are inherently electron rich, are more favorable as substrates in comparison to aryl alkynes. Further, to confirm that trifluoroethanol (TFE) is the source of the proton, a deuterium labeling experiment was carried out using deuterated TFE (CF_3CD_2OD). Indeed, this reaction has shown the deuterium incorporation in the product (Scheme 2) at the terminal end with an E/Z ratio of 40:60.

Using a premade commercially available Pd(IV) source, K_2PdCl_6, we reacted non-1-yne (**1a**) under the optimal conditions in the presence of PhBr and in the absence of PhBr. We found borylated product **2a** only in the presence of PhBr (20%, Scheme 2). We believe that, as shown in Scheme 2, that PhBr is essential for the recycling of the metal catalyst. Based on these observed facts, we propose a tentative mechanism (Scheme 3). The reaction starts with Pd(0) and undergoes oxidative

Scheme 3. A Plausible Reaction Mechanism



insertion into PhBr, to form a Pd(II) species, **Int 1**.[15] The ligand in **Int 1** exchanges with alkyne to form the π-coordinated intermediate **Int 2**. Subsequently, B_2Pin_2 reacts with **Int 2**, to eliminate Ph-BPin, generating the active reactive species **Int 3**,[16] which undergoes migratory insertion into the alkyne. This migratory insertion is dictated by the ligands around the Pd center. Although, we have not provided any evidence, we believe that, because NHCs are better electron donors than phosphine ligands, **Int 4a** is formed with the boron insertion at the α-position and the palladium species is formed at the β-position. Similarly, with phosphine as the ligand the **Int 4a** is formed with boron insertion at the β-position and Pd species at the α-position. Further, these species undergo a protonative demetalation to release the corresponding products, regenerating the Pd(0) catalysts via an alcohol oxidation process.[17] The reason for this ligand directed divergence in regioselectivity is still unknown, and studies are underway in our laboratory to further understand their roles.[18]

To conclude, a Pd-catalyzed hydroborylation of a range of terminal alkynes to synthesize their α-vinylboronates in excellent selectivity has been uncovered. This selectivity can be reversed by using N-heterocyclic carbene ligands to obtain β-vinylboronates. A mechanistic study was undertaken to elucidate the reaction pathway of the catalytic borylation process. These studies have suggested that the solvent CF_3CH_2OH is the proton source for the reaction. Additionally, it was also found that bromobenzene is essential for the reaction and is an important driving force for this reaction. Further studies are underway for the hydroborylation of other classes of alkynes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03416.

Experimental procedures, characterization data and spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(9) The trace amount of β-borylated products was obtained in both *E* and *Z* mixtures (Table 2). **3a** (*E*/*Z* 65:35), **3b** (*E*/*Z* 50:50), **3c** (*E*/*Z* 25:75), **3d** (*E*/*Z* 70:30).

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(18) We believe that the metal center prefers the most electron-rich carbon in contrast to the competitive boron atom attack. Thus, in a later study with electron-rich NHC ligands, which stabilizes the metal, the boron moiety transfer may predominate over the palladium to the terminal site which may result in a switch in site selectivity.

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