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Palladium(II)-Catalyzed Regioselective *syn*-Hydroarylation of Disubstituted Alkynes Using a Removable Directing Group

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Supporting Information Placeholder

ABSTRACT: A palladium(II)-catalyzed regioselective *syn*-hydroarylation reaction of homopropargyl amines has been developed, wherein selectivity is controlled by a cleavable bidentate directing group. Under the optimized reaction conditions, both dialkyl and alkylaryl alkyne substrates were found to undergo hydroarylation with high selectivity. The products of this reaction contain a 4,4-disubstituted homoallylic amine motif that is commonly seen in drug molecules and other bioactive compounds.

INTRODUCTION

Substituted alkenes are common structural motifs found in natural products, drug molecules, and organic materials. They are also important synthetic intermediates that participate in a wide range of organic transformations. Transition-metal-catalyzed hydroarylation of alkynes with organometallic reagents is a powerful method to synthesize substituted alkenes.¹ Various classes of organometallic reagents have been applied in this reaction, including organoboron, -silane, -stannane, -magnesium, -zinc, -lithium and -copper reagents.² Among these, organoboron reagents have attracted significant attention because they are operationally convenient to handle and have low toxicity.³ In this context, Hayashi and coworkers reported the first example of rhodium-catalyzed alkyne hydroarylation with arylboronic acids.⁴ Later, Oh found that the combination of palladium(0) catalyst, aryl boronic acid, and HOAc could promote alkyne hydroarylation via an HOAc oxidative addition/hydroarylation sequence.⁵ Since then, transition-metal-catalyzed hydroarylation has emerged as a powerful technique to synthesize di- and trisubstituted olefins.^{6–8} Most examples of metal-catalyzed alkyne hydroarylation give *syn*-stereoselectivity, affording a single product when symmetrical alkynes are used as substrates. When unsymmetrically substituted alkyne substrates are employed, however, two regioisomeric products are formed, and the regioselectivity is typically low (Scheme 1a). For example, in Hayashi's initial publication, a 3:1 mixture of α and β regioisomers was obtained in the hydroarylation of 1-phenylpropyne.⁹

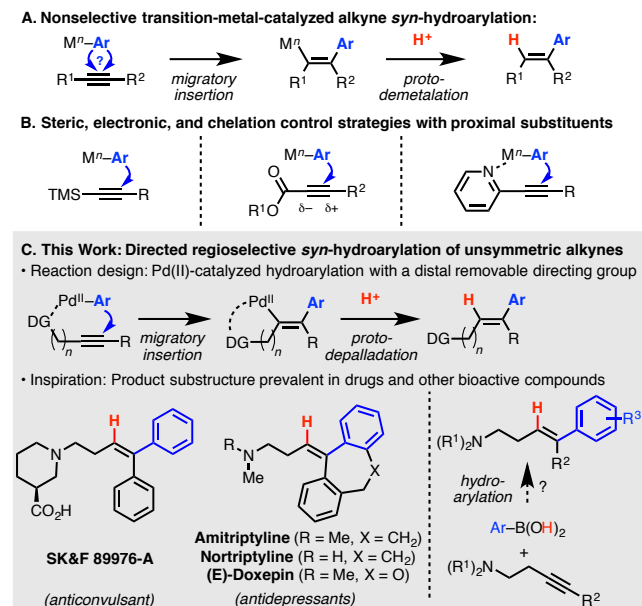
To overcome this issue, several different strategies have been pursued. One approach has been to introduce a sterically bulky group (e.g., TMS) to block one of the two possible addition sites.^{6d,7a} A second strategy, as demonstrated by Hayashi, has been to employ a polarized alkyne containing an electron-withdrawing group (e.g., an ester) in conjugation with the π -system to promote selective arylmetalation.^{4,8b} Lastly, Lautens and others have reported the use of non-removable functional groups (e.g., a 2-pyridyl moiety) to improve selectivity through chelation and/or electronic effects (Scheme 1b).^{2g,6a,6b,6f,7a,7c,7d}

Despite this progress, these strategies possess limitations. Firstly, these reactions can exhibit variable selectivity as the substitution patterns on the arylboronate and alkyne substrate change. Secondly,

they require proximal substituents that can be difficult to modify downstream, which limits overall synthetic flexibility. As a result, applications of alkyne hydroarylation in organic synthesis remain rare.

Inspired by earlier precedents of directed carbometalation of alkynes with organometallic species (e.g., Grignard reagents),¹⁰ we envisioned that by temporarily masking a distal functional group with a removable Lewis basic auxiliary, high regioselectivity could be achieved in catalytic hydroarylation with otherwise unbiased alkyne substrates. In this design, regioselectivity would be controlled principally by the directing group, which could then be removed after the reaction, allowing access to biologically important product classes (Scheme 1c). Though it has been less frequently studied, we elected to focus on hydroarylation catalyzed by palladium(II).^{7e,f} In doing so, we reasoned that because palladium(II) is known to promote addition a diverse range of nucleophiles to unsaturated C–C bonds, we could potentially extend the insights from this study to other reaction types in the future.

Scheme 1. Background and Project Synopsis

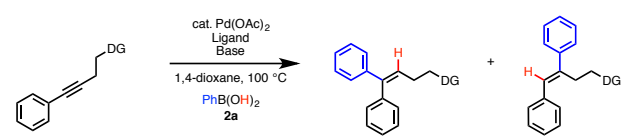


RESULTS AND DISCUSSION

To reduce this idea to practice, substituted homopropargyl amines (e.g., **1a**) were selected as the first class of substrates to investigate. We were attracted to these substrates because the resultant products would contain a 4,4-diaryl homoallylic amine motif, which is commonly found in drug molecules and their analogs (Scheme 1c).¹¹ Optimization of the reaction conditions and directing group was carried out in parallel (Table 1). After initial screening revealed that a

picolinamide (PA) directing group (as in **1a**)¹² provided the highest yield and selectivity, reaction conditions were optimized with this substrate and phenylboronic acid (**2a**) (Table 1). We were pleased to find that by using 5 mol % Pd(OAc)₂ as the catalyst and PCy₃•HBF₄ as the ligand, trisubstituted olefin **3a** was observed as the major product, with minimal formation of the minor isomer **4a** (**3a/4a** = 15:1) (entry 3). The addition of PCy₃ as ligand was critical for the success of the reaction, as only 9% yield was observed without ligand (entry 1). We believe that the ligand lowers the rate of transmetalation, suppressing undesired homocoupling of the arylboronic acid, which generates catalytically unreactive Pd(0). Various inorganic bases were tested (entries 6–8), and among them KOAc was found to be optimal, providing up to 64% yield with excellent regioselectivity (**3a/4a** = 30:1) (entry 8). KF provided slightly higher product yields but poor selectivity (entry 6). Finally, we found that by decreasing the reaction temperature and reducing the ligand loading to 1 equiv relative to palladium, formation of **4a** was almost entirely suppressed, and **3a** was generated in 80% yield (78% isolated) (entry 9).

Table 1. Optimization of the Reaction Conditions^a



Entry	DG	Ligand	Base	Pd/L (mol%)	3 (%) ^b	4 (%) ^b	Selectivity (3/4) ^c
1	A (NHPA)	none	K ₂ CO ₃	—	9	—	—
2	A (NHPA)	(±) BINAP	K ₂ CO ₃	5/5	trace	—	—
3	A (NHPA)	PCy ₃ •HBF ₄	K ₂ CO ₃	5/10	55	3.7	15:1
4	A (NHPA)	XPhos	K ₂ CO ₃	5/10	34	3.8	8.9:1
5	A (NHPA)	<i>N</i> -Acetylglycine	K ₂ CO ₃	5/10	29	10	2.8:1
6	A (NHPA)	PCy ₃ •HBF ₄	KF	5/10	77	12	6.3:1
7	A (NHPA)	PCy ₃ •HBF ₄	K ₃ PO ₄	5/10	10	2.5	25:1
8	A (NHPA)	PCy ₃ •HBF ₄	KOAc	5/10	64 (60)	2.1	30:1
9 ^d	A (NHPA)	PCy ₃ •HBF ₄	KOAc	5/5	80 (78)	—	>50:1
10 ^d	B	PCy ₃ •HBF ₄	KOAc	5/5	76	13	5.8:1
11 ^d	C	PCy ₃ •HBF ₄	KOAc	5/5	82	10	8.0:1
12 ^d	D	PCy ₃ •HBF ₄	KOAc	5/5	89	4.9	18:1
13 ^d	E	PCy ₃ •HBF ₄	KOAc	5/5	78	7.1	11:1
14 ^d	F	PCy ₃ •HBF ₄	KOAc	5/5	80	14	5.6:1
15 ^d	G	PCy ₃ •HBF ₄	KOAc	5/5	14	3.5	7.4:1
16 ^d	H	PCy ₃ •HBF ₄	KOAc	5/5	27	3.1	9.6:1
17 ^d	I	PCy ₃ •HBF ₄	KOAc	5/5	74	8.1	9.1:1
18 ^d	J	PCy ₃ •HBF ₄	KOAc	5/5	72	11	6.7:1

DG = **A** (NHPA) **B** **C** **D** **E**

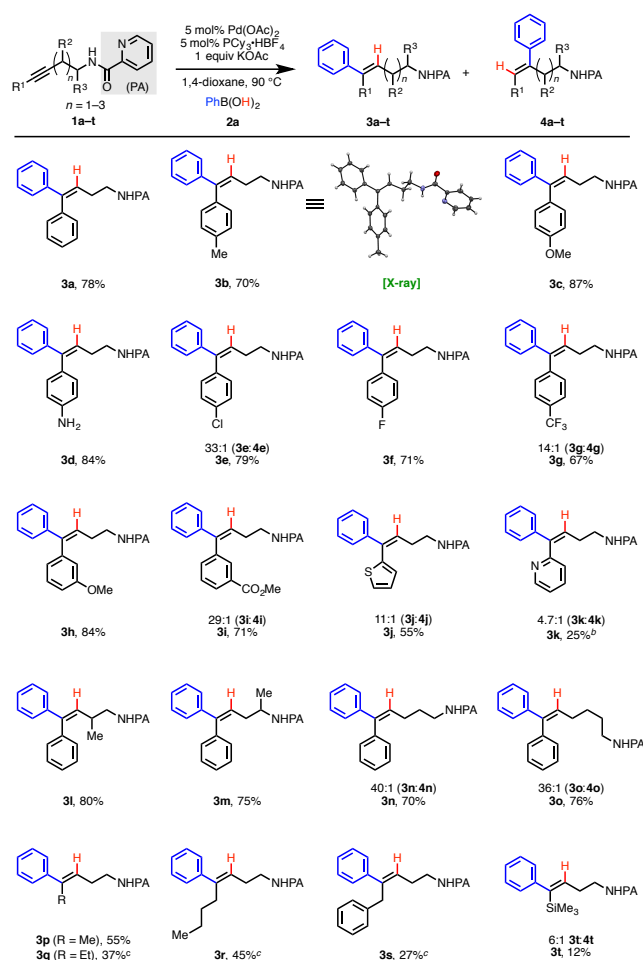
F **G** **H** **I** **J**

^aReaction conditions: **1a** (0.1 mmol), **2a** (0.18 mmol), Pd(OAc)₂ (5–10 mol %), ligand (5–10 mol %), base (1 equiv), dioxane (0.4 mL), 100 °C, N₂, 4–5 h. ^bYields were determined by ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as an internal standard. Values in

parentheses correspond to isolated yields. ^cDetermined by ¹H NMR analysis. ^d90 °C.

The data from our directing group optimization effort shed light on structure–activity relationships in this reaction (entries 9–18), revealing that both the electronic properties of the auxiliary and the geometry of the metal binding sites significantly impact selectivity. More electron-deficient amides (that have N–H bonds with lower pK_a values) gave better selectivity (entries 11 and 12). Bidentate auxiliaries (entries 9 and 15–18), which to our knowledge have not been previously explored in catalysis on alkyne substrates, afforded higher selectivity than their monodentate counterparts (entries 9 versus 10 and 17 versus 14). Taken together, these data are consistent with a mechanism in which the auxiliary binds in an LX bidentate mode during the 1,2-migratory insertion step.

Table 2. Homopropargyl Picolinamide Scope^a



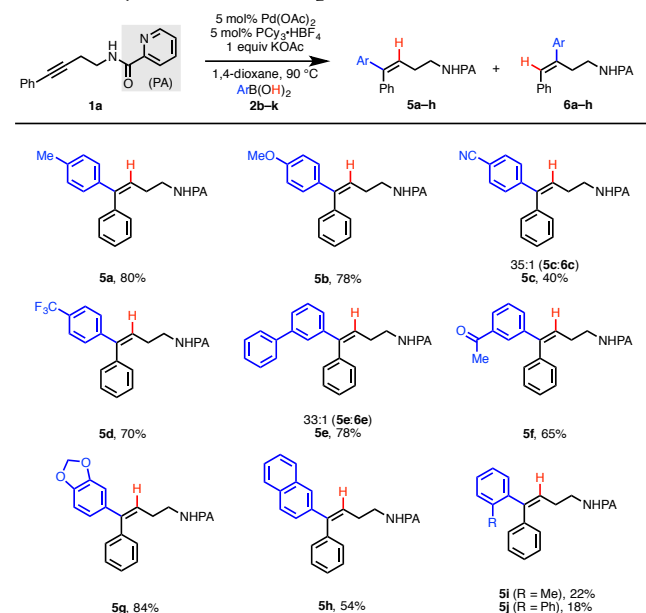
^aReaction conditions: **1a–t** (0.1 mmol), **2a** (0.18 mmol), Pd(OAc)₂ (5 mol %), PCy₃•HBF₄ (5 mol %), KOAc (1 equiv), dioxane (0.4 mL), 90 °C, N₂, 4–5 h. Percentages represent isolated yields of the major regioisomer. The ratio of the two regioisomers was determined by ¹H NMR analysis of the crude reaction mixture. ^b10 mol % PCy₃•HBF₄. ^c5 mol % PPh₃, 1 equiv of K₂HPO₄, 12–20 h. ^dYield determined by ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as internal standard.

Having optimized the reaction conditions, we next investigated the substrate scope of this palladium(II)-catalyzed alkyne hydroarylation reaction. First, various substituted homopropargyl amine derivatives

were tested with phenylboronic acid (**2a**) as the coupling partner (Table 2). Aryl substituents with different electronic properties were examined, providing the corresponding products in moderate to good yield with excellent selectivity (**3b–i**).¹³ In only a few cases was the minor regioisomer detected (**3e**, **3g** and **3i**). Notably, a free amino group was compatible (**3d**). Additionally, a chloride group was tolerated, presenting the opportunity for subsequent diversification via cross-coupling. Heteroaryl substituted alkynes, namely those containing 2-thiophenyl (**1j**) and 2-pyridyl (**1k**) groups, showed a competing directing effect with the picolinate auxiliary, as evidenced by the measurably lower regioselectivity in these cases (**3j** and **3k**) compared to examples with simple aryl groups. Nevertheless, these results demonstrate that the picolinate auxiliary has a stronger directing effect than these monodentate heterocycles, since **3j** and **3k** were still the major products. In the case of **3k**, this preference is opposite to what Lautens previously observed with 2-pyridylacetylene substrates.^{6a} Homopropargyl amines containing alkyl branching (**1l** and **1m**) also performed well in the reaction, leading to products **3l** and **3m** as the only detectable regioisomers. Interestingly, starting materials containing a more distal directing group could also be hydroarylated in good yield with only a slight decrease in selectivity (**3n** and **3o**) demonstrating that products containing different carbogenic skeletons can be accessed with this method (*vide infra*). Collectively, these results establish that alkynes containing one aryl and one alkyl group, which are typically insufficiently differentiated to give high selectivity in non-directed hydroarylation, can be regioselectively functionalized using a removable directing group strategy.

Arguably an even greater challenge is regioselective hydroarylation of dialkylalkynes. Thus, it was gratifying to observe that homopropargyl picolinamides containing terminal alkyl groups (**1p–s**) could also be converted into hydroarylated products **3p–s** with high selectivity (only one regioisomer detected), albeit in moderate yield. Installation of a sterically bulky SiMe₃ group on the alkyne led to 6:1 selectivity, with 12% isolated yield of the major product **3t**.

Table 3. Arylboronic Acid Scope^a

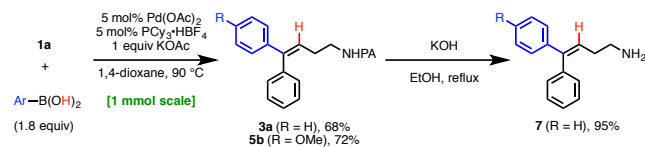


^aReaction conditions: **1a** (0.1 mmol), **2b–k** (0.18 mmol), Pd(OAc)₂ (5 mol %), PCy₃·HBF₄ (5 mol %), KOAc (1 equiv), dioxane (0.4 mL), 90 °C, N₂, 4–5 h. Percentages represent isolated yields of the major regioisomer. The ratio of the two regioisomers was determined by ¹H NMR analysis of the crude reaction mixture.

Next, the scope of arylboronic acids was studied using homopropargyl picolinamide **1a** as a representative alkyne (Table 3). An array of substituted arylboronic acids containing substituents on the *para* or *meta* position participated in the reaction, providing the corresponding hydroarylated products in moderate to high yields (**5a–5h**). Arylboronic acids with *ortho*-substituents were also competent coupling partners but gave lower yields (**5i** and **5j**). The selectivity for the desired products **5a–j** was consistently high and did not depend on the electronic properties of the organoboron coupling partner. In only two cases was the minor regioisomer observed, and in both instances, the product ratio was >33:1 (**5c** and **5e**). The regio- and stereoselectivity of this transformation were confirmed by nOe measurements of **5g** (see Supporting Information) and X-ray crystallographic analysis of **3b**.

An attractive aspect of this method is that the 4,4-diaryl homoallylic amine products can be obtained with complete control of alkene stereochemistry. Aryl-substituted homopropargyl picolinamide starting materials **1a–k** are conveniently prepared in one step via Sonogashira coupling. Thus, the ultimate stereochemistry of the product can be controlled by choosing which of the two aryl groups is introduced by Sonogashira coupling and which is introduced by hydroarylation (*e.g.*, **3b/5a** and **3c/5b**). As a more general comment, the majority of the examples in Tables 2 and 3 were prepared in two steps from a common starting material (homopropargyl picolinamide), which speaks to the potential utility of this method as tool in divergent synthesis for medicinal chemistry applications.

Scheme 2. Large-Scale Synthesis of Trisubstituted Olefins **3a**, **5b** and Removal of the Picolinyl Group

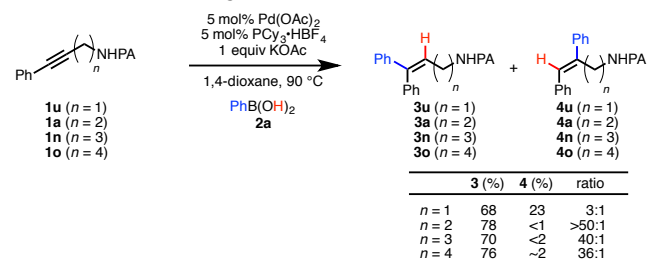


To demonstrate the practicality and operational simplicity of this Pd(II)-catalyzed alkyne hydroarylation method, we performed two representative examples on larger scale (Scheme 2). Electron-neutral and -rich arylboronic acids were both tested on 1 mmol scale under the reaction conditions described in Table 4, and the yields in these experiments were similar to the smaller scale trials. After hydroarylation, the PA directing group could be conveniently cleaved to reveal the free amine. As an example, product **3a** was hydrolyzed under aqueous conditions to give primary amine **7** in 95% yield.

To better understand the influence of directing group distance/geometry on reaction outcome, we compared substrates with different tether lengths between the alkyne and the picolinamide directing group (Scheme 3). In all four cases that were examined, the reaction proceeds in >70% yield under the standard conditions. Interestingly, with propargyl substrate **1u**, containing the smallest tether length, the reaction gave only a 3:1 ratio of the two regioisomers **3u** and **4u**, compared to >50:1 with substrate **1a**. Systematically introducing additional methylene units (**1n** and **1o**), led to only a moderate erosion of selectivity from 40:1 to 36:1. The finding that **1a** gave the highest selectivity is likely due to the formation of a stable 5-membered palladacycle upon *syn*-carbopalladation with this substrate. For substrates **1n** and **1o**, with more distal PA directing groups, the attenuation of selectivity could be due to the formation of less stable 6- and 7-membered palladacycles following *syn*-carbopalladation. The origin of the more dramatic loss of selectivity with propargyl substrate **1u** is likely due to the fact that putative 4-membered palladacycle formed via *syn*-carbopalladation is

prohibitively unstable, causing the system to default to more inherent non-directed selectivity. While transition state inductive effects¹⁴ could also explain the trend from **1a** ($n = 2$) to **1n** ($n = 3$) to **1o** ($n = 4$), the selectivity with **1u** ($n = 1$) would not be consistent with this model.

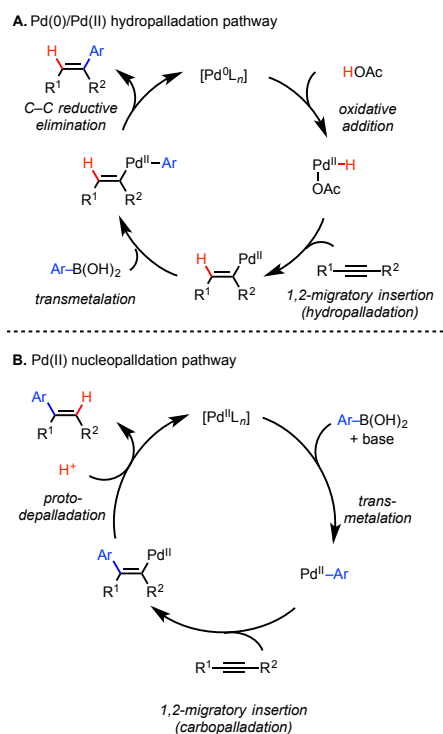
Scheme 3. Comparison of Alkynyl Picolinamides with Different Tether Lengths



MECHANISTIC ANALYSIS

With palladium as the catalyst, two main mechanistic paradigms have been proposed for alkyne hydroarylation with arylboronic acids, each operating under different reaction conditions (Scheme 4). The first type, as invented by Oh,⁵ involves palladium(0) as the catalyst, generally in combination with a phosphine ligand and in an acidic solvent medium (e.g., HOAc) (Scheme 4a).^{7a-c,7f} To generate the catalytically active species in these systems, a palladium(0) precatalyst, such as $\text{Pd}_2(\text{dba})_3$, can be employed directly or a palladium(II) precatalyst, such as $\text{Pd}(\text{OAc})_2$, can be reduced in situ. In the proposed sequence of events, the $[\text{Pd}(0)\text{L}_n]$ species oxidatively adds to HOAc,¹⁵ to generate a $[\text{Pd}(\text{II})-\text{H}]$ intermediate, which adds across the alkyne in a 1,2-migratory insertion (hydropalladation) event to give a vinylpalladium(II) species. This intermediate then undergoes transmetalation with the aryl boronate, followed by C–C reductive elimination to form the product and regenerate $\text{Pd}(0)$, thereby closing the catalytic cycle.

Scheme 4. Comparison of Two Commonly Invoked Mechanistic Paradigms

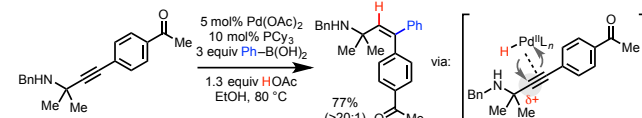


In the second type, palladium(II) is the active catalyst, and the reaction is run under basic conditions (generally with inorganic base) and typically in the presence of phosphine ligand (Scheme 4b).^{7d,e} The proposed sequence begins with transmetalation between palladium(II) and the aryl boronate. 1,2-Migratory insertion (carbopalladation) followed by protodepalladation then generates the product and closes the catalytic cycle.

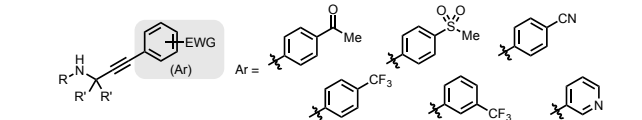
The reaction conditions in the present alkyne hydroarylation reaction appear to fall into the latter category ($\text{Pd}(\text{II})$ -catalyzed nucleopalladation). Nevertheless, we were interested in more precisely elucidating the reaction mechanism and examining potential differences in reactivity/selectivity between these two palladium-catalyzed pathways with homopropargyl amine substrates. To begin, we first took note of relevant literature precedents. Using a $\text{Pd}(0)/\text{PCy}_3/\text{HOAc}$ system, Marinelli and coworkers, have previously demonstrated hydroarylation of 3-arylpropargyl amines in 43–85% yields and >20:1 selectivity favoring Ar group transfer to the alkynyl carbon atom distal from the amine (Scheme 5).^{7c} The authors report 9 examples, all of which contain electron-withdrawing substituents on the arene. Based on analysis of reactivity trends and computed charge distribution in putative intermediates, the authors conclude that the regioselectivity is due to electronic bias in the alkyne, with the hydride of the $[\text{Pd}(\text{II})-\text{H}]$ species reliably attacking the alkynyl carbon atom with the highest partial positive charge in the π -alkene complex.¹⁶

Scheme 5. Relevant Literature Precedent Involving $\text{Pd}(0)/\text{PCy}_3/\text{HOAc}$ Catalysis to Effect Hydroarylation of 3-Arylpropargyl Amines and Attempted Application of this Catalytic System to 4-Arylhomopropargyl Amine Substrates

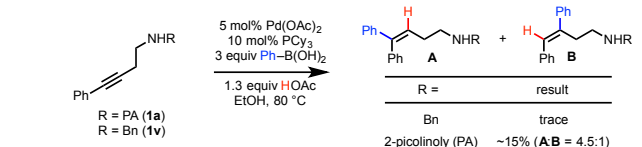
A. Hydroarylation under $\text{Pd}(0)/\text{PR}_3/\text{HOAc}$ conditions (Ref. 7c) and authors' proposal for electronic control.



B. Reactive 3-arylpropargyl amine substrates in Ref. 7c (9 total examples bearing the 6 aryl groups below).



C. *N*-Protected 4-phenylhomopropargyl amine substrates under $\text{Pd}(0)/\text{PR}_3/\text{HOAc}$ conditions from Ref. 7c.



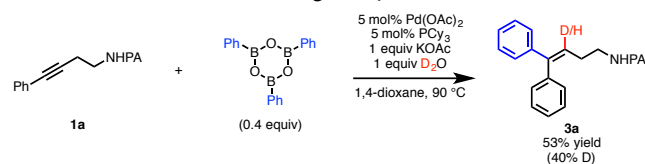
Given that Marinelli's $\text{Pd}(0)/\text{PCy}_3/\text{HOAc}$ conditions gave a product with similar connectivity to that obtained under our conditions, we questioned whether this catalytic system would be effective in a reaction with a 4-phenylhomopropargyl amine derivative, our standard substrate. To probe this, we exposed our standard PA-protected 4-phenylhomopropargyl amine substrate **1a** and Bn-protected analog **1v** to Marinelli's reactions conditions (Scheme 5c). In the case of **1a**, hydroarylation took place in only 15% yield, with a 4.5:1 of regioisomers. Though Marinelli had previously demonstrated reaction compatibility with *N*-Bn-protected 3-arylpropargyl amines, with homopropargyl amine **1v**, only trace product was formed. The poor reactivity in both cases could be due to the fact that the arene is not sufficiently electron-poor to allow for facile hydropalladation, while the poor selectivity in the case of **1a** could be due to competing

electronic and chelation effects on the putative $[Pd(II)-H]$ species. These data show that the mechanism of our system is likely distinct from the Marinelli system and related $Pd(0)$ cycles.

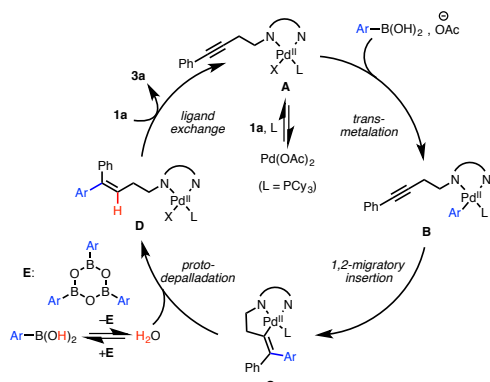
Next, to confirm the source of the hydrogen atom in our reaction, a deuterium labeling study was performed under reaction conditions that were slightly modified to minimize the amount of H^+ in solution (Scheme 6). Upon addition of 1 equiv D_2O , 40% deuterium was observed exclusively at the vinylic position, with the remaining non-deuterated product presumably arising from the NHPA group. This result is consistent with the vinylic hydrogen in the product arising from the boronic acid or the NHPA group under the standard reaction conditions. This experiment also rules out the possibility of $[1,4]$ -palladium migration from vinylic position to an *ortho*-aryl position prior to protodepalladation, since no deuterium incorporation was detected on the aromatic ring.

A plausible mechanism for this $Pd(II)$ -catalyzed alkyne hydroarylation reaction is proposed in Scheme 7. Initially, the palladium catalyst, $Pd(OAc)_2$, coordinates with the PCy_3 ligand and picolinate directing group to generate $Pd(II)$ species **A**. With the assistance of base, intermediate **A** undergoes transmetalation with the arylboronic acid to generate aryl palladium complex **B**, which can undergo *syn*-1,2-migratory insertion (carbopalladation) to form bicyclic palladacycle intermediate **C**. Complex **C** reacts via protodepalladation¹⁷ to afford palladium complex **D**, which can undergo ligand exchange with a new substrate molecule to release the product and regenerate $Pd(II)$ species **A**. It is also possible that the active $Pd(II)$ species first participates in transmetalation to generate an arylpalladium(II) complex prior to coordination of the picolinamide directing group of the substrate.

Scheme 6. Deuterium Labeling Study



Scheme 7. Proposed Reaction Mechanism



CONCLUSION

In conclusion, we have reported a regioselective *syn*-hydroarylation of non-symmetrical disubstituted alkyne substrates using a removable picolinamide (PA) directing group. This reaction was found to be highly regio- and stereoselective, allowing for nearly exclusive formation of a single product isomer in most cases. Moreover, the reaction proceeded effectively with both dialkyl and alkylaryl disubstituted alkyne substrates, including those containing more distal directing groups. The reaction was amenable to scale up (1.0 mmol

scale), and clean removal of the PA directing group via hydrolysis was demonstrated. Future investigation will focus on elucidating the reaction mechanism and developing other regioselective hydrofunctionalization reactions of alkenes and alkynes using a removable directing group strategy. These results will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experiment details, spectra data, copies of 1H and ^{13}C NMR spectra, and X-ray crystallographic data. These materials are 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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TOC Image

